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Bridging the Gap: From Bench to Bedside

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Letter from the Editors: Forging Ahead

The McGill Journal of Medicine (MJM) is overjoyed to introduce the latest issue of our student-run medical journal - *Bridging the Gap: From bench to bedside* - a compilation of insightful articles that reflect the dedication and passion of the medical community in striving for excellence in patient care and medical practice to meet the ever-evolving needs of patients and practitioners alike.

As we dive into the pages of this issue, we are met with a wealth of knowledge and innovation that truly embodies the spirit of our theme. This issue calls for a concerted effort to address disparities in healthcare; ranging from variances in vaccine effectiveness across ethnic groups to barriers to women's reproductive health. Furthermore, it delves into the continuous pursuit of knowledge and mastery in medicine. Our authors have contributed articles that highlight the value of refining our skills as medical professionals, be it related to a modern suturing curriculum for medical students, or using online media to teach the neurological exams, among others. Ultimately, our common goal as medical practitioners is to improve patient outcomes. This issue features articles that discuss approaches to common medical issues, perioperative complications, and compelling case reports.

As a student-run medical journal, we take pride in the diverse perspectives and ideas that our contributors bring to the table. We are committed to providing a platform for emerging researchers, students, and healthcare professionals to share their experiences and contribute to the advancement of medical knowledge. This platform extends beyond our editorial publications and includes the workshops we hold to educate our readers, as well as two podcast series that discuss medical board exam topics and showcase research taking place within McGill University and beyond.

We are pleased to announce the promotion of Meryem Talbo and Aïnhoa Olazabal to Managing Editors, Print, where they will take over from Brandon Arulanandam and Divleen Malhi who have graduated from McGill University with MDCM degrees and moved on to pursue further residency training.

In closing, we would like to extend our heartfelt appreciation to all the authors, reviewers, and MJM team members who have worked tirelessly to bring this issue to fruition. Your dedication to upholding the highest standards of academic integrity and your invaluable feedback have allowed us to preserve the excellence of this journal.

As we continue to grow and evolve, we welcome your suggestions and contributions to help shape the future of our journal. Together, let us strive to create a healthcare landscape that values innovation, inclusivity, and a steadfast commitment to improving patient outcomes. We hope this issue will inspire and empower you in your medical or scientific journey.

Sincerely,

Sera Whitelaw, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
MD Candidate

Bennet Desormeau, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
MD Candidate

Foreword: Dr. Fraser Moore

This issue of the Journal aims to explore the evolution of medical education, but what exactly is "medical education?" At its essence it is, and always has been, about promoting understanding and developing skills. It is a key part of every physician's role, whether they are affiliated with medical school/residency programs, teaching junior colleagues/other health professionals in clinical practice, or teaching patients and families about their diagnoses. We want our students and patients to learn from us because their greater understanding will lead to better care.

My personal interest in medical education evolved gradually. As a senior resident, I taught junior residents and did small group teaching with medical students. As a junior staff, I began giving lectures to medical students. This led to roles in curriculum design as a Block leader in the Fundamentals of Medicine and Dentistry course and then a residency program director. Along the way I joined the McGill Centre for Medical Education (CME), which became the Institute for Health Sciences Education (IHSE) in 2019. I learned about the expanding interest in medical education scholarship. As Peter McLeod, a previous director of the CME, would always say, "If you are working on a project in medical education, think how you can turn it into a *research* project.".

The evolution of medical education and interest in scholarship is reflected in the increasing number of journals dedicated to health sciences education research. In my own field, this past year saw the launch of the new "Neurology: Education" journal. Looking forward, the CanMEDS 2025 project aims to revise and refine the current CanMEDS frameworks; one of the four stated goals of this revision is to "contribute to the strategic direction of medical education" (1). The transformation of the Centre for Medical Education to the Institute for Health Sciences Education, the active role of McGill medical students in the anti-racism and diversity curriculum review, and the previous MJM Nursing issue are all examples of positive strategic efforts already undertaken here at McGill.

The theme of this issue, *Bridging the Gap: From bench to bedside*, continues these efforts. The articles presented here are evidence that McGill provides tremendous opportunities for students to develop their own interests and innovations in health sciences education. For example, the "Foundations in Medical and Health Sciences Education" elective offered by the IHSE allows learners to "develop essential knowledge and skills in curriculum design, teaching and learning, assessment, program evaluation, and educational research and scholarship.". The IHSE also provides opportunities for research electives or even Masters and PhD training in health sciences education. The Steinberg Centre for Simulation and Interactive Learning is more than just a place for OSCE's! It provides a setting for education, research, and innovation, with a priority of translating this to improved patient care.

I began this foreword by saying that we want our students and patients to learn from us because their greater understanding will lead to better care. That has always been the first gap in health sciences education; how can the teacher transfer their understanding and skills to the student or patient? When I give a lecture to a class of 200+ students I try my best to tailor it to the class and their needs. The difficulty is that a class is composed of different individuals with different learning styles. My best results and greatest impact are often not in teaching large groups

of students but in teaching the individual student or patient who is struggling to understand. Thinking about how to get the message across, trying different approaches, and observing carefully to see if I have been successful are, for me, the essence of education. When it works your reward is seeing their understanding; the light coming on in their eyes or the change in expression on their face.

I hope that the ideas and innovations described in this issue of the Journal will inspire you to think about health sciences education, to get involved, to try new things, and to consider how you might turn that idea into a research project. Above all, don't forget that you are now all educators; I hope that you will see the proof in the eyes of your learners.

Fraser Moore, MD
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Associate Member, McGill Institute of Health Sciences Education
Competency Committee Chair, McGill Adult Neurology Residency Program

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EDITORIAL

EDITORIAL
McGill Journal of Medicine

Non-Invasive Prenatal Testing (NIPT): A Call for Change in Reporting Practices

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ABSTRACT

The use of non-invasive prenatal testing (NIPT) technology has revolutionized the practice of prenatal screening. The assay's validity and reliability have been demonstrated in both low- and high-risk pregnancies. Despite its excellent screening parameters, its reliability is often overestimated due to confusing and incorrect terminology that appears in private NIPT reports. Herein, we provide a brief explanation of the potential implications at two different levels: patient and provider. We conclude with a call to redesign the way in which information is presented on NIPT reports to avoid stressing patients, enhance transparency in clinical counselling, and perhaps most critically, to prevent medical decisions that may not be warranted solely based on the NIPT results.

KEYWORDS
NIPT, aneuploidy, screening, age-adjusted PPV, reporting practices

1 | INTRODUCTION

The use of non-invasive prenatal testing (NIPT) technology, which detects the presence of cell free fetal DNA (cfDNA) in maternal blood, has revolutionized the practice of prenatal screening and modern obstetrics. (1) Though originally reserved for primarily high-risk pregnancies, its validity and reliability have been demonstrated in both low- and high-risk pregnancies as well. (2) Not surprisingly, NIPT now represents the primary method used for prenatal screening in North America. Despite its excellent screening parameters, with sensitivity and specificity estimates over 90-99% for most conditions tested, its reliability is often overestimated due to confusing and incorrect terminology that appears in private NIPT reports.

2 | THE ISSUE

In these authors' experience, most NIPT reports include a table that lists each tested condition with an estimate of risk or probability. Often, this risk or probability is reported as either inferior to 1/10,000 (0.01%) when the test is negative, and depending on the condition, as greater than 99/100 (99%) "probability" when the test is positive. This estimate is considered as a high-risk result and flagged for subsequent diagnostic testing. The diagnostic test in this case is amniocentesis or chorionic villous sampling (CVS), and both procedures carry the risk of serious complications.

What is a layperson to make of the word "probability" in the context of a positive NIPT result? The word translates colloquially to a chance of greater than 99% for carrying an affected pregnancy. Yet, this assumption is incorrect. A brief explanation follows.

3 | SENSITIVITY AND POSITIVE PREDICTIVE VALUE

The NIPT test is marketed as the best and most accurate method to screen for fetal aneuploidy during pregnancy. Statements like "over 99% accurate" often figure in the marketing of these assays. While the superior performance of NIPT over the maternal serum screen (MSS, nuchal translucency) is undisputed, all screens are faced with the obstacle that is Bayes' theorem.

Bayes' theorem dictates that prevalence (or pre-test probability in an individual) influences the positive predictive value (PPV) obtained. Put simply: the more common a condition is, the more reliable a screen for it is, and hence, PPV is higher with increasing prevalence (and vice versa). The prevalence of trisomies is low in the population, so even among individuals considered to be at highest risk of Trisomy 21 (Down syndrome), the PPV will always be lower than the sensitivity. Sensitivity is defined as our ability to detect true positive results and answers this question, "among patients with a disease, how many will have a positive test?" Therefore, the 99% "probability" reflects the sensitivity, and not the PPV. The PPV asks the more important question in this context which is: "among the positive screening tests, how many will end up having the condition?"

4 | THE PATIENT

Many expecting parents are eager to discover fetal sex and to ascertain fetal health early in pregnancy. Patients may resort to private companies for NIPT screening because the assay is not typically covered by the public healthcare system in most North American jurisdictions. Most of these companies provide a copy of results to the patient regardless of its findings. While access to health information is fundamental, the way in which the information is presented can have a significant impact on how it is received. The nature of private NIPT means that many individuals will access this assay as a first line test. Pre-test probability is low; therefore, many parents are subjecting their pregnancies to overscreening. Moreover, Canadian prenatal screening programs usually reserve NIPT as the follow-up test for an abnormal result from a less specific screen, and this practice is endorsed by the Society of Obstetricians and Gynaecologists of Canada. (1) Often, patients will receive the abnormal screening result without explanation and are directed to diagnostic testing. This process can be unnecessarily anxiety-inducing and render the experience of pregnancy more stressful. Little to no research has studied parental anxiety in the interval between a positive NIPT screen and subsequent diagnostic testing. (3) In addition to psychological distress, the clinical risks of overscreening include false positive results and the medical complications inherent to the diagnostic testing. The latter include premature rupture of membranes, clubbed feet, placental hemorrhage, and fetal demise.

5 | THE PROVIDER

A basic understanding of sensitivity and PPV is critical when engaging in clinical counselling with patients. We must be mindful that the NIPT is not intended to be a diagnostic test. The NIPT has an excellent negative

predictive value of over 99%. (2) Yet, PPV values may fall below 50%. The NIPT technology yields a significant number of false positives because the low prevalence of trisomic conditions falls well below the prevalence threshold. (4) The prevalence threshold varies by test and is defined as the "prevalence level below which the PPV declines most sharply relative to disease prevalence." The prevalence threshold for NIPT is 7% and trisomic conditions have a prevalence of 0.2%. (5)

When facing a patient with a positive result, the provider can use a clinical tool to calculate age adjusted PPV such as the NIPT/Cell Free DNA Screening Predictive Value Calculator (6) provided by the [American] National Society of Genetic Counselors and the Prenatal Quality Foundation. Some of these calculations have been simulated and are presented in Table 1 for reference. Subsequently, for all expecting parents with an abnormal result, the provider should refer the patient on to local genetic counsellors and possible diagnostic testing.

6 | CONCLUSION

In the context of screening, words like "risk" and "probability" as they appear on NIPT reports may be misleading to the lay public and carry significant undue stress for patients. Because NIPT reports are often made directly available to consumers, these authors propose that laboratories offering direct-to-consumer prenatal screening by cfDNA (i) clearly indicate these tests are meant for screening and not for diagnostic purposes and (ii) report age-adjusted PPV and NPV as the "probability" of results in lieu of sensitivity to provide a more accurate calculation of true risk. When a healthcare provider is confronted with one of these reports, these values can be simply calculated using a medical calculator as presented. (6) We hope that, ultimately, these changes would reduce parental anxiety and the medical and economic impacts of overtesting following NIPT.

	Sensitivity	Specificity	Age 25		Age 30		Age 35		Age 40	
			PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
Trisomy 21	99.2	99.91	51	99	61	99	79	99	93	99
Trisomy 18	96.3	99.87	15	99	21	99	39	99	69	99
Trisomy 13	91	99.87	7	99	10	99	21	99	50	99

PPV = positive predictive value; NPV = negative predictive value.

These values were calculated using the tool available at: https://www.perinatalquality.org/Vendors/NSGC/NIPT. (5)

TABLE 1 PPV of NIPT by condition as a function of maternal age

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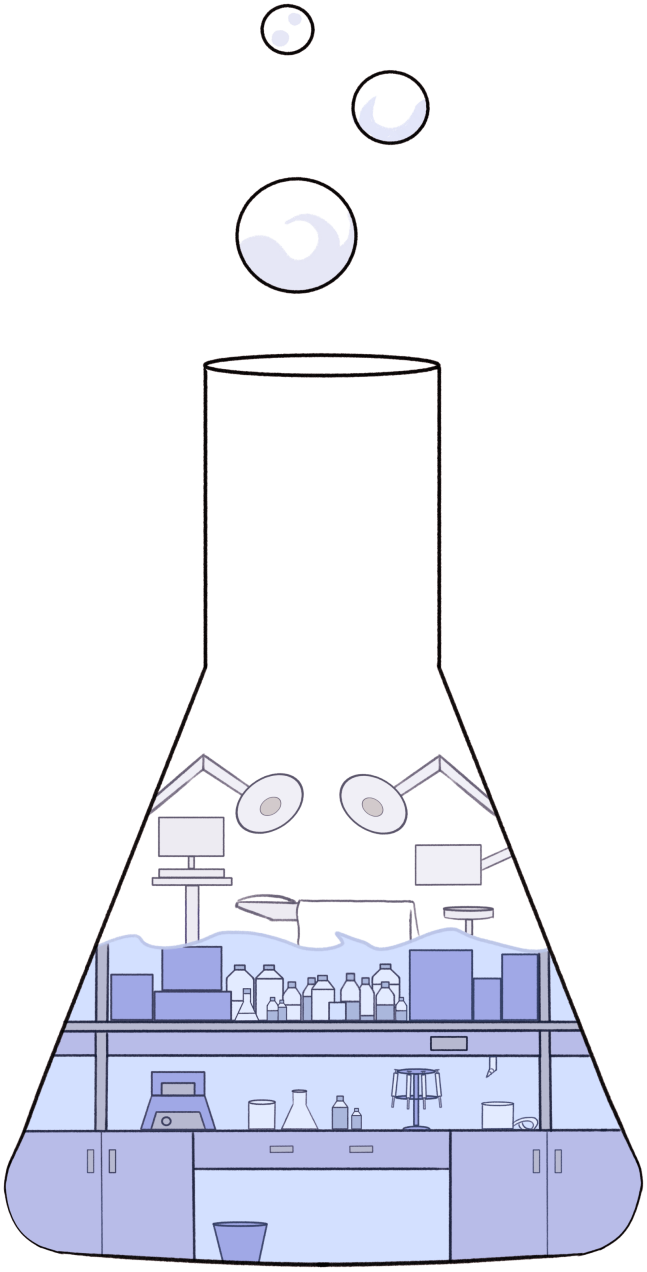
ORIGINAL RESEARCH



ORIGINAL RESEARCH
McGill Journal of Medicine

SARS-CoV-2 Epitope Presentation by Class II HLA Genotypes Common in North American Populations: A Proposed Computational Approach for Vaccine Efficacy Evaluation

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ABSTRACT

Background: Human Leukocyte Antigen (HLA) gene polymorphisms between ethnic groups have been shown to play a role in the heterogeneity of response to SARS-CoV-2, in terms of COVID-19 disease severity and susceptibility, in addition to socioeconomic factors. It was predicted that this finding may extend to vaccine responsiveness.

Purpose: To the best of our knowledge, this study was the first that aimed to predict and evaluate the effectiveness of four COVID-19 vaccines across North American ethnic groups, in terms of their ability to trigger CD4+ T cell help, based on class II HLA allele frequencies.

Methods: Various databases including the Immune Epitope Database (IEDB) were used in this computational approach. The number of peptide-HLA high-affinity pairs between the most common HLA II haplotypes and SARS-CoV-2 peptides in various vaccine types were retrieved and compared between ethnicities. From this, the efficiency of antigen presentation to CD4+ T cells was evaluated, a crucial component in the context of vaccination for cellular immunity and support in antibody generation.

Results: Multiple discrepancies in vaccine effectiveness for ethnic minorities relative to the Caucasian group, overrepresented in vaccine clinical trials, were highlighted. Recommendations were issued in terms of which vaccine types could be most effective for particular ethnicities.

Conclusion: There exists a genetic basis for differential responses to vaccines among ethnic groups in North America. However, given the multifactorial nature of vaccine responsiveness and limitations of computational methods, this study offers future research directions to undertake before the findings can be transferred to clinical and public health settings.

KEYWORDS
HLA antigens, Vaccines, Ethnicity, COVID-19, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for causing Coronavirus disease 2019 (COVID-19) with infections ranging from asymptomatic to fatal. Structural proteins encoded within its genome are spike (S), envelope (E), membrane (M) and nucleocapsid (N). (1) SARS-CoV-2-specific antibodies, CD4+ T cells, and CD8+ T cells are at the core of the adaptive immune response against SARS-CoV-2. The focus of this study was on CD4+ T cells only, as they play a crucial role in natural infection and vaccination in terms of T cell help in antibody generation. They are also critical in maintaining long-term memory B cells and humoral immunity. (2)

The four main types of COVID-19 vaccines contain: whole virus (inactivated), the spike protein, the receptor-binding domain (RBD) of the spike protein, as well as spike and nucleocapsid proteins. (3-5) Most vaccine developers focus exclusively on the spike protein as it is the main target of neutralizing antibodies. (2) Yet, it has been shown that the generation of antibodies against spike relies on CD4+ T cells recognizing any component of the SARS-CoV-2 genome. (6) Grifoni et al. demonstrated via an ex vivo T cell assay that a SARS-CoV-2-specific CD4+ T cell response, correlated with antibody generation, may be triggered against almost all SARS-CoV-2 proteins. Thus, they recommended including more structural proteins in vaccines to better represent the infection observed in COVID-19. (7) This may amplify CD4+ T cell responses, in turn reinforcing humoral immunity through T cell help in generating antibodies.

CD4+ T cells recognize SARS-CoV-2 peptide-Human Leukocyte Antigen II (HLA II) complexes on the surface of antigen presenting cells to become activated and differentiate into their effector subsets. (8) The major HLA class II genes are HLA-DPA, HLA-DPB, HLA-DRA, HLA-DRB, HLA-DQA, and HLA-DQB. They encode highly polymorphic proteins, whose allele frequencies vary between ethnic groups, based on historical exposure to different pathogens. Each allele has varying binding affinity and can only bind a portion of the processed viral peptides, affecting the efficiency of antigen presentation. (9) Consequently, HLA alleles can either confer susceptibility or protection to infection or disease severity, as shown by epidemiological analyses and small-scale cohort studies of HLA typed individuals. (10-16) Heterogeneity in infection susceptibility and disease outcome can also be predicted by computational HLA and SARS-CoV-2 peptide association studies. Barquera et al. observed in a computational approach that the frequencies of strongest and weakest binders to various coronaviruses differ among populations from different geographic regions worldwide. (17) In the case of SARS-CoV-2, Copley et al. predicted similar protective CD4+ cellular immunity potential, based on HLA II haplotypes, across 25 human populations of different ethnicities in the United States. (18)

Other computational studies aiming to design the most effective multi-epitope COVID-19 vaccines predicted heterogeneity in vaccine response based on ethnicity. He et al. found that their designed vaccine may confer less protection for people of African descent based on HLA coverage. (19) Remarkably, Liu et al. designed vaccines predicted to have high coverage for Asian, Black, and White ancestry individuals. (20)

Ethnic minorities in North America are disproportionately affected by COVID-19, both in terms of risk of infection and mortality. (21) Socioeconomic factors have been extensively reported to explain such disparities, but the role of genetic factors remains understudied. (22-25) Further, participants from ethnic minorities are unjustifiably underrepresented in vaccine clinical trials. (26)

The rate of reported cases of COVID-19 on Indigenous reserves is 183% higher than in the general Canadian population. (27) Since geographically isolated Indigenous communities are not protected by the herd immunity of urban centers and may have a higher susceptibility to COVID-19, assessing vaccine effectiveness is critical.

Real-world, post-hoc vaccine effectiveness studies that have started to emerge mainly focus on the general population. While elderly or healthcare workers, for example, have been part of distinct subgroup analyses,

ethnic groups have not. (28)

The underrepresentation of ethnic minorities in clinical trials may persist in vaccine effectiveness studies. Computational tools have proven extremely useful in SARS-CoV-2 vaccine development and may provide a solution by predicting vaccine effectiveness for special populations. (29)

A particularly relevant example is Liu et al.'s analysis of the Moderna, Pfizer-BioNTech, and AstraZeneca vaccines. They showed that African Americans and Asians could have a slightly increased risk of vaccine ineffectiveness in silico, but the findings remain to be confirmed clinically. (30)

Hence, evidence for the implication of HLA polymorphism and varying allele frequencies in COVID-19 heterogeneity is provided in the literature. This means different HLA haplotypes could also influence responsiveness to vaccines through presentation of different HLA II immunopeptidomes to CD4+ T cells. The purpose of this study is to predict and evaluate vaccine effectiveness in terms of the ability to trigger the CD4+ T cell help required in antibody generation, based on the HLA II haplotypes common in ethnically diverse North American populations.

2 | METHODS

2.1 | Retrieving allele frequencies

The Allele Frequency Net Database (AFND) stores gene frequencies in the form of alleles, haplotypes, or genotypes from worldwide populations. (31) The "HLA classical allele frequency search" tool was used to retrieve the most common HLA II alleles in Canada and the United States (i.e., North American populations) for the HLA-DPA1, -DPB1, -DQA1, -DQB1, -DRB1 class II loci (Supplemental Material 1).

2.2 | Grouping by principal component analysis (PCA) and computing weighted averages

To determine if the raw data for the individual populations in each ethnic group sample could be merged based on variance, PCAs were performed using R software 4.0.3 (R Core Team, Vienna, Austria) for each ethnic group separately. (32) From the resulting PCA biplots, pools or groups of populations were created based on the Euclidean distance in a plot of the first and the second component. The weighted averages of the allele frequencies based on sample sizes of the populations were computed for the various pools or groups. The weighted average frequencies of the most common alleles were summed to reach a minimum of 70% total coverage of the population, in line with the principle of herd immunity. In certain cases, multiple combinations were made, when alleles were particularly common. Finally, a merged list of alleles for all ethnic groups was created (Supplemental Material 2, 3).

2.3 | Haplotype associations

HLA-DP and -DQ must be considered as haplotypes in the Immune Epitope Database (IEDB), while only the beta chain of HLA-DR alleles may be specified because the alpha chain is invariable. Thus, haplotypes were retrieved from AFND and the literature (Supplemental Material 1). (31, 33-39)

2.4 | Retrieving COVID-19 vaccine contents and protein sequences

Four vaccine types (whole virus, spike, RBD and spike and nucleocapsid) were selected for analysis and their protein sequences were retrieved in FASTA format from the NCBI GenBank (Accession number: MN908947.3) (Supplemental Material 4). (40)

2.5 | Using IEDB's MHC II binding prediction tool

Using the bioinformatics tool Split FASTA, (41) the various protein sequences were separated into peptides of 15 amino acids in length, with an overlap of 10 amino acids, to reduce redundancy in the results. (42) The protein sequences and the HLA haplotypes were inputted into IEDB's MHC II Binding Prediction Tool to predict peptide-HLA binding affinities and immunogenicity. (39, 42) The prediction method selected was "IEDB recommended 2.22" to ensure the best predictor or algorithm for each allele was used. To compare the binding affinities obtained from various algorithms, IEDB outputs a percentile rank for each peptide-HLA "hit." Lower percentile ranks suggest higher peptide-HLA affinity (Supplemental Material 4). (43)

2.6 | Calculating weighted counts, total counts, and plotting count histograms

Weighted counts were computed by multiplying the number of peptide-HLA hits or score for each allele/haplotype by their frequency. Sums of the weighted counts for each ethnic group were then calculated, for each type of vaccine according to their protein contents, to arrive at total counts of the number of peptide-HLA hits for both top 1^{st} and top 10^{th} percentiles. The top 10^{th} percentile data for all vaccine types except RBD (i.e., less relevant than other types) were distributed along percentile intervals. Count histograms were plotted from the sum of weighted counts along each interval (Supplemental Material 4).

This is a descriptive report that presented estimates of the HLA II and SARS-CoV-2 proteome affinities based on pre-existing data, without attempting to compare them. Thus, statistical analyses were not performed.

3 | RESULTS

3.1 | Population definitions

HLA allele frequencies in population samples from all sources were subjected to PCA to determine how they could be pooled. It was not necessarily possible to pool together all samples from different sources named after the same ethnicity. For example, since the Indigenous Canada population samples appeared as two distinct clusters in the PCA biplot, they were separated into two groups, Indigenous Canada #1 and #2 (Table 1).

3.2 | Certain minority ethnic groups were predicted to have fewer peptide-HLA hits within the top 1^{st} percentile

Results for the top 10^{th} and top 1^{st} percentile peptide-HLA hits were tabulated (Table 1). The reference group used to highlight major discrepancies were Caucasian, as it is the most studied ethnicity. As expected, it was one of the top scoring groups across all four vaccine types, showing high total counts of predicted peptide-HLA hits. Overall, the biggest discrepancies between ethnicities occurred within the top 1^{st} percentile (i.e., the strongest peptide-HLA bindings). In fact, the bottom five scores for each type of vaccine were lower than the Caucasian score by at least a factor of 2, and up to a factor of 8 in the RBD vaccine.

An underestimate of the true total counts arose for African American #1 group because the coverage of the population only amounted to 40% instead of the set minimum of 70%, due to the unavailability of some data. Since African American #1 has a sample size of around 4,900 compared with approximately 480,000 for African American #2, the latter group was deemed more representative.

Percentile	Whole virus		Spike		RBD		Spike and nucleocapsid	
	Top 10th	Top 1st	Top 10th	Top 1st	Top 10th	Top 1st	Top 10th	Top 1st
Indigenous Canada #1	113	6.10‡	15.6	0.980‡	1.95	0.00‡	19.2	0.980‡
Indigenous Canada #2	142	14.3	19.1	1.95	3.80	0.697	21.7	2.09
Indigenous US #1	95.2	5.29‡	10.6	0.315‡	1.78	0.00‡	13.3	0.426‡
Indigenous US #2	177	18.7	22.8	2.97	5.24	0.779	25.5	2.97
Indigenous US + Canada #1	177	18.6	22.7	2.97	5.23	0.778	25.5	2.97
Indigenous US + Canada #2	95.2	5.29‡	10.6	0.315‡	1.78	0.00‡	13.3	0.426‡
African American #1*	63.9*	5.55*	8.06*	0.635*	1.59*	0.173*	9.59*	0.668*
African American #2	137	10.7	14.7	0.579‡	2.34	0.544	17.1	0.886‡
Caucasian†	167†	19.4†	18.6†	2.23†	4.59†	0.813†	20.7†	2.23†
Polynesian	131	9.85	16.7	1.89	2.87	0.987	19.9	1.89
Asian (General)	111	9.14	16.2	1.28	1.80	0.102‡	19.5	1.46
South Asian	115	11.0	17.4	1.36	3.93	0.290	20.3	1.59
East Asian	109	9.42	15.9	1.34	2.88	0.417	18.2	1.66
Southeast Asian #1	125	13.9	18.7	1.91	4.66	0.655	21.0	2.16
Southeast Asian #2	130	11.8	16.4	1.05	2.20	0.766	18.8	1.05
Hispanic #1	108	8.48‡	15.7	1.01	3.01	0.171	18.3	1.25
Hispanic #2	96.4	5.32‡	10.7	0.302‡	1.72	0.00‡	13.5	0.411‡
Mestizo #1	198	25.9	21.9	3.24	6.69	1.30	22.5	3.24
Mestizo #2	113	8.69	16.2	1.07	3.10	0.149	18.9	1.27
Mixed	167	17.0	19.2	1.92	3.98	0.654	21.8	2.14
Arab	108	9.30	14.0	1.27	3.10	0.264	17.1	1.71

Abbreviations: RBD = receptor-binding domain * Underestimate † Reference group ‡ Discrepancy relative to Caucasian reference group (for top 1st percentile only)

TABLE 1 Total counts of peptide-Human Leukocyte Antigen (HLA) hits for all vaccine types

3.3 | Increased counts of peptide-HLA hits among the lower percentiles may suggest better antigen presentation

Although an ethnic group may have scored low within the top 1st percentile, it may have additional peptide-HLA hits with sufficient binding affinities for successful antigen presentation, for example, between the 1st and 5th percentiles. Thus, the distributions of peptide-HLA hits across the top 10th percentile were plotted in count histograms (Figures 1-3) for whole virus, spike, and spike and nucleocapsid vaccines, for the groups with the discrepancies identified in Table 1 (refer to Supplemental Material 4 for the rest of the data and RBD vaccine).

Patterns of distribution showing increased counts of peptide-HLA hits among the lower percentiles may suggest a greater amount of potentially stronger peptide-HLA hits, while increased counts among the higher percentiles (i.e., closer to the 10th percentile) could suggest a greater amount of weaker peptide-HLA hits. Most importantly, the former, most advantageous pattern of distribution may augment antigen presentation efficiency for the lowest-scoring groups in Table 1.

Caucasians showed high counts of peptide HLA-hits compared with ethnic minorities. This reflects that Caucasians could be, generally, more responsive to the four vaccine types.

The four groups that showed major discrepancies across all vaccine types (Indigenous Canada #1, Indigenous US #1, Indigenous US + Canada #2, and Hispanic #2) could be particularly less responsive to RBD vaccines, as they showed a score of 0 for RBD in top 1st per-

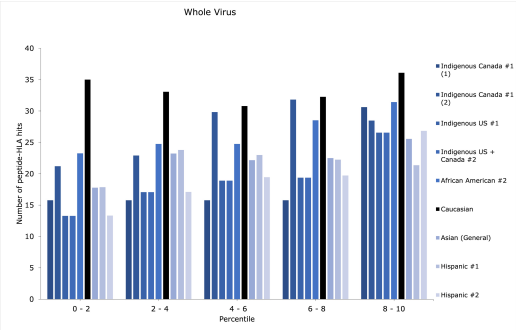

FIGURE 1 Distributions of total counts of peptide-Human Leukocyte Antigens (HLA) hits along the top 10th percentile for whole virus vaccine in combined count histograms for the groups showing discrepancies compared with the Caucasian reference in Table 1.

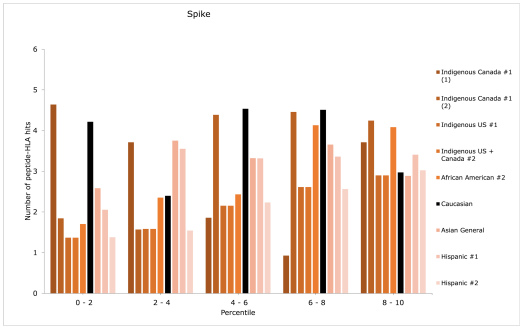

FIGURE 2 Distributions of total counts of peptide-Human Leukocyte Antigens (HLA) hits along the top 10th percentile for spike vaccine in combined count histograms for the groups showing discrepancies compared with the Caucasian reference in Table 1.

centile (Table 1). Out of them, only allele combination #1 in the Indigenous Canada #1 group showed a pattern of distribution predicted to potentially augment the efficiency of antigen presentation for spike and spike and nucleocapsid vaccines, with slightly increased counts of low percentile values (Indigenous Canada #1 (1) in Figures 2 and 3). This could be indicative of enhanced effectiveness for two vaccine types for Indigenous peoples in Canada with the first combination of alleles. Overall, the type of vaccine to prioritize for the four low-scoring groups could be whole virus, for which the discrepancies in the top 1st percentile compared with Caucasian were less important than with other vaccine types (Table 1).

For African American #2, when looking at the spike as compared to spike and nucleocapsid vaccines, the addition of nucleocapsid enhanced the number of successfully predicted peptide-HLA hits as the gap with the Caucasian count was reduced. However, the top 10th percentile distributions were not deemed advantageous in providing additional successful peptide-HLA hits in both vaccine types (Figures 2 and 3). Instead, the difference in counts of peptide-HLA hits between African American #2 and Caucasian was less for the RBD vaccine than for whole virus. Thus, an RBD vaccine might provide stronger responses for African American #2 (Table 1).

For Asian (General) group, the opposite was predicted. The RBD only vaccine could be the least effective, and a more advantageous option could be the spike and nucleocapsid vaccine, providing less of a discrepancy with the Caucasian score (Table 1).

For Hispanic #1, whole virus was the lowest scoring vaccine. However, its top 10th percentile distribution seemed quite evenly distributed (Figure 1). This could suggest that strong peptide-HLA hits found among the lowest percentiles could provide enough response to the whole virus vaccine. The same cannot be said Hispanic #2, for which the spike and nucleocapsid vaccine may be preferable. Again, this can be explained by the smaller difference in counts between Caucasians and Hispanic #2 for this type of vaccine, compared with other types (Table 1).

4 | DISCUSSION

In this computational approach to assess vaccine effectiveness across North American ethnic groups, it was proposed that differences in allele frequencies may result in different HLA II immunopeptidomes being presented to CD4+ T cells. In turn, this was thought to possibly translate to population-level differences in effective anti-SARS-CoV-2 immunity between ethnic groups, resulting in disparities in vaccine responsiveness. Barquera et al. compared the binding affinities in silico of HLA class I and II to SARS-CoV-2 peptides and found

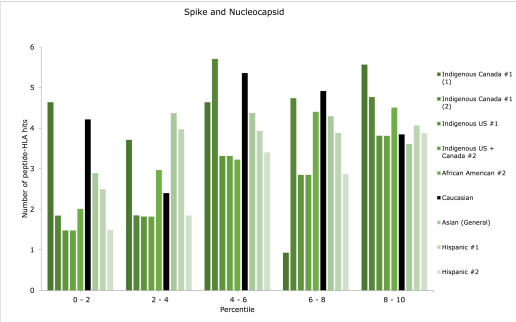

FIGURE 3 Distributions of total counts of peptide-Human Leukocyte Antigens (HLA) hits along the top 10^{th} percentile for spike and nucleocapsid vaccine in combined count histograms for the groups showing discrepancies compared with the Caucasian reference in Table 1.

that the large majority do not bind HLA I molecules, whereas a proportion do bind HLA II molecules. (17) Furthermore, because CD4+ T cells are crucial in natural infection and vaccination for antibody generation, our COVID-19 vaccine effectiveness analysis focused solely on HLA II molecules. (2, 18) Complementary studies could investigate the role of HLA I.

Thus, vaccine effectiveness was evaluated in terms of counts and patterns of distribution of peptide-HLA hits, based on the interpretation that lower percentile peptide-HLA hits should provide the strongest bindings. More peptide-HLA hits within the top 1^{st} percentile were predicted to offer better antigen presentation to CD4+ T cells, thereby improving effector response, support in antibody generation, and vaccine responsiveness. Less peptide-HLA hits within the top 1^{st} percentile (or proportionally more hits within higher percentiles) were predicted to correlate with reduced vaccine responsiveness.

This hypothesis was based on an approach that we designed and proposed as a part of this manuscript and that has not yet been validated experimentally. The field of research on the immunological response to COVID-19 and its pathways is still evolving. The true implications of such predictions on antigen presentation and CD4+ cellular immunity cannot be adequately confirmed without in vitro and in vivo studies. Furthermore, although peptide-HLA hits are necessary for antigen presentation by HLA molecules, they may not be sufficient for T cell recognition. Nonetheless, Copley et al. validated their theoretical data by comparing to a dataset of experimentally determined T cell epitopes and demonstrating that their in silico approach did not overestimate the number of immunogenic epitopes. (18) The general method and prediction algorithm (NetMHCIIpan) used in latter study are similar to those in our present approach.

4.1 | Comparison of vaccine efficacy predictions with other studies

Regarding African American #2, He et al.'s multi-epitope vaccine design was also predicted to confer less protection for people of African descent based on HLA coverage, although the specific vaccine content differed from the ones tested here. (19)

While three Indigenous ethnic groups scored lower than Caucasians, the three other Indigenous groups (Indigenous Canada #2, Indigenous US #2 and Indigenous US + Canada #1) generally scored close to or higher than the Caucasian reference (Table 1). This finding is supported by Barquera et al., who showed that Indigenous peoples in America could have particularly protective HLA haplotypes in some instances and against a range of multiple viruses including coronaviruses. (17) One possible reason for having both low-scoring and high-scoring Indigenous groups could be due to the different degrees of admixture with ethnicities that are better equipped to respond to COVID-19 vaccines, like European descent admixture. Further studies analyzing genome-wide association studies (GWAS) data could confirm or refute this conjecture. Alternatively, natural selection may have favored the strongest HLA binders in those Indigenous groups following European colonization and the introduction of new infectious diseases. (17)

In opposition to Copley et al.'s conclusion that all ethnic groups have similar HLA II antigen presentation potential, (18) the findings presented here demonstrated variability in vaccine effectiveness based on different

antigen presentation patterns for all vaccine types investigated. This discrepancy may result from differences in methodology. Copley et al. only used the NMDP/Be The Match registry to extract HLA haplotype data, while we combined multiple sources from the AFND as registries are notoriously incomplete for ethnic minorities. Further, they restricted their peptide-HLA binding affinities analysis to the NetMHCIIpan-4.0 algorithm and their results to a percentile rank threshold of ≤ 2, whereas our analysis included but was not limited to the NetMHCIIpan-4.0 algorithm, and it covered results up to the top 10^{th} percentile.

As previously suggested by Liu et al., African American and Asian populations, in general, scored lower than the Caucasian group when looking at the spike vaccine. In addition, the present study evaluated more vaccine types and a wider range of ethnic groups, including Indigenous populations, filling the gaps in Liu et al.'s work. (30)

Our results supported the recommendations by Zelba et al. and Grifoni et al. to include more proteins in vaccines than just spike or RBD. (6-7) Indeed, for certain ethnic groups and their characteristic HLA haplotypes, the whole virus, or the spike and nucleocapsid vaccines were predicted to be more effective.

4.2 | Methodological limitations and future research directions

In addition to the limitation related to the purely predictive basis of potential antigen presentation, before the recommendations issued from this evaluation can be transferred to the clinical and public health settings, the methodological limitations must also be acknowledged. Although computational methods provide rapid and cost-effective approaches, the prediction of peptide-HLA hits is an imperfect science due to the nature of predictive algorithms based solely on chemical structure and lack consideration for the actual in vivo environment in antigen presentation. In addition, populations were defined by visual interpretation of the various PCA pools, which would sometimes overlap and were not necessarily clearly defined. Also, HLA II binding predictions are known to be more challenging and less accurate than HLA class I, but their accuracy has greatly improved in the last decade. (42) Nonetheless, the limitation of using pre-existing HLA allele frequency data to predict viral infection outcomes could be alleviated by integrating HLA typing in vaccine clinical trials to clinically evaluate vaccine effectiveness for various HLA genotypes and ethnicities. A review paper by Sohail et al. on the performance of computational methods in the context of COVID-19 offered promising evidence of their practical significance but warned that improvements must be made before predictions can apply to real-world vaccine developments. (44)

Predictions may nonetheless impel researchers to validate such data with experimental and immunogenicity testing, and to undertake larger-scale epidemiological and clinical studies. Investigating new variants of SARS-CoV-2 in the approach used here could elucidate the consequences of mutations on HLA binding and thereby on vaccine effectiveness. Finally, the investigation of other biological factors such as the effects of polymorphisms in genes like ACE2 and TMPRSS2, (45) blood groups, hormonal balances, and co-morbidities, (46) in relation to ethnicity and vaccine effectiveness, are equally important perspectives for future research directions.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. HLA II Allele Frequencies for Canadian Populations of Various Sample Sizes:
`https://mjm.mcgill.ca/article/view/907/868`

Supplementary Material 2. Sample PCA Code for Indigenous Canada:
`https://mjm.mcgill.ca/article/view/907/868`

Supplementary Material 3. PCA Biplots for Ethnic Groups with 3 or More Variable:
`https://mjm.mcgill.ca/article/view/907/868`

Supplementary Material 4. Haplotype Inputs for the Immune Epitope Database (IEDB) Analysis:
`https://mjm.mcgill.ca/article/view/907/868`

ORIGINAL RESEARCH
McGill Journal of Medicine

Major Perioperative Complications of Benign Gynecologic Procedures at a University-Affiliated Hospital

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ABSTRACT

Background: With the increasing use of minimally invasive techniques for gynecologic procedures, women are at a low risk for perioperative complications. The purpose of this study was to determine the incidence of and risk factors for major intra or postoperative complications among women undergoing benign gynecologic surgeries.

Methods: We conducted a retrospective observational study of all women who underwent benign gynecologic surgery in 2016-2017 at a University-Affiliated community hospital. Pregnant women, malignancy cases, and hysteroscopic or minor vulvar procedures were excluded. Primary outcome was composite intraoperative and/or 30-day postoperative complications requiring medical or surgical management. Logistic regression identified significant patient, peri-operative and surgeon risk factors associated with complications.

Results: Of 975 patients included, 53 patients experienced major intra or postoperative complications (5.4%). Mean age was 47.7 ± 13.8 years. Mean BMI was 27.1 ± 5.8 kg/m2. Prior abdominal surgery (laparotomy or laparoscopy) (adjusted odds ratio [OR]= 2.01, 95%CI 1.05-3.83) and emergency surgery (adjusted OR= 19.54, 95%CI 2.99-127.54) were significantly associated with major complications. Surgeon volume of 1-2 operative days per month (adjusted OR=0.30, 95%CI 0.10 - 0.87) and age 40-64 years (adjusted OR=0.24, 95%CI 0.11- 0.56) had a protective effect on the risk of major complications.

Conclusion: Among patients in our sample, 5.4% experienced major complications from a benign gynecologic surgery. Complications from benign gynecologic surgery are rare, even in the absence of robotic equipment. Center-specific data and a discussion of the increased morbidity associated with with prior abdominal surgery and emergency surgery should be considered for pre-operative patient counselling.

KEYWORDS

Gynecologic surgical procedures, Postoperative complications, Intraoperative complications, Minimally invasive surgery, Benign gynecology

1 | INTRODUCTION

Major complications are infrequent after gynecological procedures, and are occurring less commonly as minimally invasive techniques are increasingly being used. (1) Minimally invasive techniques also improve recovery times and shorten hospital stays. (2) In fact, composite major intra and postoperative complications rates in laparoscopic and vaginal hysterectomies were estimated at 1.4% and 1.9%, respectively. (3) Similarly, the frequency of major intraoperative complications in laparoscopic adnexal surgery has been evaluated at 0.8% among women who had not previously undergone a hysterectomy. (4) Although rare, major complications such as hemorrhage, bowel or urinary tract injuries and vaginal cuff dehiscence still arise and often require additional surgical or pharmacological interventions, resulting in higher morbidity and mortality risks. (5-7)

Risk factors for complications include multiple surgeon and center-specific factors. Surgeon volume has repeatedly been found to be a predictive factor, as surgeries performed by high-volume surgeons are usually associated with shorter hospitalizations, fewer perioperative complications, and fewer conversions to laparotomy. (8, 9) In addition, complication rates per center can vary due to access to various minimally invasive equipment types and by center condition expertise. For example, access to robotic equipment for benign gynecologic surgery is limited to non-existent in most Canadian centers, with only a few facilities benefiting from these technologies. (10, 11) When discussing complication rates for preoperative patient counseling, center-specific data would be optimal, as it encompasses all these technical factors. However, this can be difficult to collect and provide. Quality improvement programs frequently perform departmental audits and can provide a tool to collect such information.

Few recent studies describe overall major intra or postoperative complications risk of benign gynecologic surgery. The Canadian context with limited robotic surgery access in most centers may differ from other published North American rates. We aimed to determine the incidence of major intra or postoperative complications in women undergoing benign gynecologic procedures at a Canadian university-affiliated hospital. Secondly, we sought to evaluate the association between patient, surgeon and operative factors and surgical complications at our center.

2 | METHODS

We performed a retrospective chart review of all women who underwent benign gynecological surgeries at a Canadian university-affiliated center, in 2016 and 2017. Patients were excluded for pregnancy, undergoing hysteroscopic or minor vulvar procedures, or malignancy. The sample size was determined by the number of cases meeting inclusion criteria during the period studied. We classified cases by diagnosis, procedure and approach (vaginal, laparoscopic or laparotomy). We collected patients' age, body mass index, birthplace, smoking status, comorbidities, prior surgeries, surgeon, admission type, conversion of approach, operative time, pre-operative hemoglobin, peri-operative prophylactic antibiotics administration, thromboprophylaxis (in the form of heparin or low molecular weight heparin received pre-operatively +/- post-operatively), and diagnosis severity. Surgeon volume for the 20 surgeons at our center was determined based on compiled data, and subdivided into 3 categories (high, medium and low volume) based on the mean number of operative days per month per surgeon. We used the Charlson Comorbidity Index (CCI) to report on comorbidities. (12) Formal approval by the local Research Ethics Committee was obtained prior to the start of the study.

Risk factors were categorized. Age was grouped into young adults (18-39), middle-aged (40-64) and senior adults (65 years old or greater). Obesity was defined as a body mass index higher or equal to 30 kg/m2 . (13) Smoking history was divided as current cigarette smoker vs. non-smoker or ex-smoker. The CCI was used to measure the significance of patient comorbidities. (12) Operative time longer than 180 minutes was considered a risk factor. (6, 14) Anemia was defined as a hemoglobin level lower than 120 g/L. (15) A large uterus and/or fi-

Characteristics	Values	# missing values
Pre-operative patient factors		
Age (years), mean (SD)	47.7 (13.8)	0
Place of birth, n (%)		2
Canada	515 (52.9)	
Elsewhere	458 (47.1)	
BMI*, mean (SD)	27.1 (5.8)	107
Current smoker, n (%)	109 (11.5)	26
Charlson Comorbidities Index, mean (SD)	0.8 (1.2)	23
At least one prior pelvic surgery, n (%)	401 (42.0)	21
At least one non-gynecological prior abdominal surgery, n (%)	249 (26.2)	26
Peri-operative factors		
Admission type, n (%)		0
Planned	948 (97.2)	
Emergency	27 (2.8)	
Approach of surgery, n (%)		0
Vaginal approach	261 (26.8)	
Laparoscopy	542 (55.6)	
Laparotomy	172 (17.6)	
Conversion to laparotomy from laparoscopy or vaginal approach, n (%)	19 (2.4)	
Operative time (minutes), median (IQR)	87 (50, 147)	
Pre-operative hemoglobin (g/L), mean (SD)	130.4 (14.3)	61
Prophylactic antibiotics, n (%)		4
Recommended, received	581 (59.8)	
Recommended, not received	83 (8.6)	
Not recommended	307 (31.6)	
Received Thromboprophylaxis, n (%)	462 (47.6)	4
Main diagnosis (1 to 7) and severity		
1-Fibroids, n (%)	261 (26.8)	
Weight of pathology specimen (g), median (IQR)	347 (178, 690)	7
2-Endometriosis, n (%)	52 (5.3)	
Stage, median (IQR)	4 (3, 4)	13
3-Prolapse, n (%)	231 (23.7)	
Stage, median (IQR)	3 (2, 3)	16
4-Ovarian cyst	114 (11.7)	
Size (cm), mean (SD)	4.1 (2.5)	4
5-Stress urinary incontinence, n (%)	62 (6.4)	
6-Family planning, n (%)	103 (10.6)	
7-Other, n (%)†	152 (15.6)	

Data is presented as n (%), mean (SD=Standard Deviation); or median (IQR=Inter-quartile range, 1st and 3rd quartiles) *BMI=Body Mass Index † The 'other' diagnosis group includes adenomyosis, abnormal bleeding (without concurrent diagnosis, fibroids or adenomyosis), chronic pelvic pain and history of cancer/prophylaxis.)

TABLE 1 Patient and surgery characteristics (n=975)

Procedures:	N	Intraoperative complications n (%)	Postoperative complications n (%)	Overall rate of complications n (%)
Prolapse repair without hysterectomy (any route) (with or without incontinence procedure)	139	1 (0.7)	3 (2.2)	4 (2.9)
Prolapse repair with hysterectomy (any route)	89	0 (0.0)	4 (4.5)	4 (4.5)
Incontinence procedure alone (without prolapse repair)	59	1 (1.7)	0 (0.0)	1 (1.7)
Laparoscopic hysterectomy	144	4 (2.8)	10 (6.9)	14 (9.7)
Vaginal hysterectomy without prolapse indication	4	1 (25.0)	0 (0.0)	1 (25.0)
Abdominal hysterectomy	104	8 (7.7)	6 (5.8)	13 (12.5)
Laparoscopic myomectomy	17	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal myomectomy	49	3 (6.1)	6 (12.2)	7 (14.3)
Laparoscopic adnexal surgery (includes family planning procedures)	280	0 (0.0)	1 (0.4)	1 (0.4)
Open adnexal surgery	10	2 (20.0)	1 (10.0)	3 (30.0)
Resection of endometriosis	25	1 (4.0)	1 (4.0)	1 (4.0)
Diagnostic laparoscopy	13	0 (0.0)	0 (0.0)	0 (0.0)
Other *	62	1 (1.6)	3 (4.8)	4 (6.5)

Some patients had multiple complications *The 'other' surgeries group includes procedures such as pelvic abscess drainage, rectovaginal fistula repair, urinary fistula repair and periurethral cyst removal.

TABLE 2 Rates of complications by procedure type

broids was defined as weighing more than 500 g. (16) Case complexity was defined as endometriosis stage 3-4, fibroids >500 g or adnexal cyst size >10 cm. Finally, surgeon volume was categorized based on the number of operative days per month into low (<1 day), medium (1-2 days) and high (>2 days) volume using observed tendencies in our sample. The majority of surgeons in the sample operate exclusively at this center, thus the volume recorded is representative of overall operative time. The number of OR days was used to represent both surgical case volume as well as expertise in complexity. Some surgeons perform more complex surgeries or operate on patients with more comorbidities which can limit the number of cases in one day.

The primary outcome was composite major intraoperative and/or 30-day postoperative complications. The Clavien-Dindo classification was used to define major complications, more generally as grade II and above. (17) Therefore, major complications were defined as requiring transfusions, administration of drugs other than antiemetics, antipyretics, analgesics, diuretics and electrolytes, surgical intervention or intensive care unit management, or resulting in mortality. (17) Hemorrhage was considered a major complication if it required a blood product transfusion, or if radical measures were used such as an artery ligation, prolonged pelvic packing, or re-operation. (2) Major infections, including wound infections, pelvic abscesses, pneumonia and sepsis, were included if they required antibiotics or abscess drainage; simple urinary tract infections were excluded. (18) Major bowel injury and rectovaginal fistula were defined as requiring intraoperative or postoperative surgical intervention and/or antibiotics. (6, 19) Small bowel obstructions were also considered major complications. (20) Urinary tract injuries or urogenital tract fistulas were considered if they required a nephrostomy tube,

Complications	Vaginal (n=261)	Laparoscopy (n=542)	Laparotomy (n=172)	All approaches (n=975)
Overall	11 (4.2)	18 (3.3)	24 (14.0)	53 (5.4)
Intraoperative complications				
Any complication	2 (0.8)	6 (1.1)	14 (8.1)	22 (2.3)
Hemorrhage	1 (0.4)	2 (0.4)	8 (4.7)	11 (1.1)
Bowel injury	1 (0.4)	0 (0.0)	4 (2.3)	5 (0.5)
Urinary tract injury	0 (0.0)	4 (0.7)	3 (1.7)	7 (0.7)
Postoperative complications				
Any complication	9 (3.5)	12 (2.2)	14 (8.1)	35 (3.6)
Hemorrhage	1 (0.4)	6 (1.1)	4 (2.3)	11 (1.1)
Bowel injury (not recognized intraoperatively)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract injury (not recognized intraoperatively)	1 (0.4)	0 (0.0)	1 (0.6)	2 (0.2)
Pelvic abscess	2 (0.8)	1 (0.2)	1 (0.6)	4 (0.4)
Wound infection	1 (0.4)	1 (0.2)	3 (1.8)	5 (0.5)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Sepsis or septic shock	1 (0.4)	1 (0.2)	0 (0.0)	2 (0.2)
Deep vein thrombosis	0 (0.0)	1 (0.2)	1 (0.6)	2 (0.2)
Pulmonary embolus	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Urogenital tract fistula	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Rectovaginal fistula	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Small bowel obstruction	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Vaginal cuff dehiscence	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)
Other	2 (0.8)	0 (0.0)	2 (1.2)	4 (0.4)

Note: mortality, hernia, myocardial infarction, stroke, coma, cardiac morbidity, respiratory morbidity and renal morbidity did not occur *some patients had multiple complications

TABLE 3 Rates of each complication by approach

a ureteral stent, or intraoperative or postoperative surgical intervention. (21, 22) Thus, bladder perforations requiring no intervention were not included (as in anti-incontinence procedures). Vaginal cuff dehiscence was defined as needing surgical repair. (2) Renal morbidity was defined as acute or progressive, requiring dialysis or a creatinine rise of more than 2 mg/dL. (18) Respiratory and cardiac morbidity (other than myocardial infarction) were included if they required an intensive care unit stay. (18) Pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, comatose state longer than 24 hours, and mortality were also considered to be major complications. (18)

Descriptive statistics were used to report the results. The rate of each binary outcome (1-Intraoperative complication, 2-Postoperative complication, 3-Overall complication) was computed for 17 potential baseline risk factors. These factors were divided in 3 blocks of variables: 1) pre-operative patient variables, 2) peri-operative variables, and 3) surgeon volume. For the 'Overall complication' outcome, logistic regression was performed for each risk factor. (23) Multivariable logistic regression was performed for each block of variables, and the Bayesian Information Criterion (BIC) was used to select the best model by minimizing the BIC. (24) The final multivariable logistic model included the variables retained in each block. A sensitivity analysis was also performed to capture the multilevel aspect of the data

(patient nested in surgeon). The Generalized Estimating Equations (GEE) approach was used to handle the correlation; surgeon was treated as a random intercept. (25) The Intra-class Correlation Coefficient (ICC) was computed to measure the proportion of the outcome's total variance explained by the surgeon. (26) For all models, Odds Ratios (OR) and 95% Confidence Intervals (CI) were computed from the estimates of the model. A subanalysis including only hysterectomies (all approaches included) was also performed. Statistical analysis was performed using SAS University Edition (SAS Institute Inc, North Carolina).

Missing values were accounted for in different ways depending on their frequency. If there were less than 10 missing values (<1%), those were imputed with the mode. If there were 10 or more missing values, those were coded as a 'missing' category and included in the regression model. Missing BMI values were coded as normal (<30 kg/m2 category) as high BMIs are generally recorded in the operative report for physician billing purposes. Thus, it is reasonable to assume charts recording no BMI correspond to women with a BMI <30 kg/m2. Similarly, missing hemoglobin values were coded as normal (>120 g/L category). For low-risk procedures such as tubal ligation or small adnexal cysts removal in women below the age of 40 without significant medical history, the patient is considered healthy and does not get assessed at the pre-operative clinic, which would include blood work. Therefore, if no pre-operative hemoglobin value was measured, we assumed that the patient's hemoglobin is likely greater than 120 g/L.

3 | RESULTS

1757 women underwent gynecologic surgery at our tertiary care hospital in 2016 and 2017. 782 were excluded for pregnancy, malignancy and hysteroscopic or minor vulvar procedures. 975 patients were included in the final analysis. Patient demographics are presented in Table 1. A majority of procedures were performed laparoscopically (55.6%) (26.8% vaginal and 17.6% laparotomy). The most common comorbidities were diabetes, chronic kidney disease, chronic obstructive pulmonary disease and hepatic disease. Overall, 53 women (5.4%) had a surgical complication. Table 2 shows complication rates by procedure type. The most common intraoperative complications included hemorrhage (1.1%), bowel injury (0.5%), and urinary tract injury (0.7%). Postoperative complications were most frequently hemorrhage (1.1%), wound infection (0.5%), and pelvic abscess (0.4%). Mortality, hernia, myocardial infarction, stroke, coma, cardiac morbidity, respiratory morbidity, and renal morbidity did not occur. Table 3 shows the rates of each complication by approach.

Univariate and multivariate analyses of risk factors and their impact on complication rates are shown in Table 4. Univariate analysis of the primary outcome (composite intraoperative and/or 30-day postoperative complications) showed prior abdominal surgery (OR= 2.06, 95%CI 1.16-3.67), admission through emergency (OR= 3.19, 95%CI 1.06-9.59), laparotomy approach (OR= 3.69, 95%CI 1.76-7.74), conversion to laparotomy (OR= 8.93, 95%CI 3.25-24.53), and complexity (OR=2.98, 95%CI 1.60-5.52) to be significant factors when treated independently. None of the missing values categories showed an association to the outcome. BMI and hemoglobin showed higher percentage of missing data (11% and 7%). Four variables showed a rate of 3% of missing data and three variables showed a rate less than 1%. BMI was not significant when obesity was defined as a BMI higher or equal to 30 kg/m2. The extreme obesity cut-off of 40 kg/m2 did not return a significant result either, although this sample contained few patients.

For the multivariate analysis (Table 4), age, smoking status, comorbidities (CCI>0), prior abdominal surgeries, surgeon volume, admission type, approach, conversion to laparotomy, peri-operative prophylactic antibiotics, thromboprophylaxis, and complexity were included in the final multivariate model. This model showed that prior abdominal surgery (laparotomy or laparoscopy) (adjusted OR=2.01, 95%CI 1.05- 3.83), and emergency surgery (adjusted OR=19.54, 95%CI 2.99-127.54) were significantly associated with increased risk of major complications. Of note, 4/27 (14.8%) of emergency surg-

eries resulted in complications, compared to 49/948 (5.2%) of planned procedures. Age of 40-64 years had a protective effect on complication rates (adjusted OR= 0.24, 95%CI 0.11- 0.56), compared to both younger and older women. The relationship between surgeon volume and complications was U-shaped, with surgeons operating 1 to 2 days per month having the lowest complication rates (adjusted OR= 0.30, 95%CI 0.10 - 0.87). The sensitivity analysis (GEE model, data not shown) reveals similar findings, the proportion of the variation explained by adding the surgeon as a random intercept variable in the final multivariable model was weak and non-significant (ICC=1%). Finally, the sub-analysis of only hysterectomies (all approaches included) did not return significant risk factors. Of note, hysterectomies are mainly performed when medical management failed.

4 | DISCUSSION

We reported an overall risk of major intra- or postoperative complication of 5.4% after benign gynecologic surgery at a university-affiliated center, with a majority of procedures being performed via minimally invasive approach. Prior abdominal surgery and emergency surgery were unsurprisingly associated with an increased complication risk. The rates measured appear to be consistent with prior literature on gynecologic surgical complications.

In Erekson's large scale study on postoperative complications following gynecologic surgery based on American College of Surgeons National Surgical Quality Improvement Program (ASC-NSQIP) data on over 22,000 women, the frequency of complications from benign procedures ranged from 1.7% for prolapse procedures to 3.5% for benign hysterectomies, with an overall 3.7% rate of major postoperative complications. (18) We similarly found 3.6% postoperative complications. However, some of our outcome definitions differed, as Erekson's study did not include urinary tract injuries, which accounted for 5.7% of our reported post-operative complications. (18) In addition, the authors did not mention how many surgeries were robotically-assisted; but similar to our population, a large number of surgeries were performed via minimally invasive techniques. Another study, by Margulies et al., of close to 110,000 hysterectomies based on retrospective ASC-NSQIP data, found a rate of postoperative complication of 6% after laparoscopic and 14% after abdominal hysterectomy. (1) These authors do report that laparoscopy and robotic procedure codes used for their analysis cannot be distinguished, hence a significant proportion of their laparoscopic cases may have been robotically-assisted. (1) Despite the lack of robot use at our center, we similarly found a postoperative complication rate of 9.7% after laparoscopic and 12.5% after abdominal hysterectomy. Moreover, the laparotomy approach has been associated with an increased risk of complications in previous literature and was not a surprising finding in our univariate analysis, although it became non-significant in the multivariate analysis. (1, 2, 18)

Although it has been observed, the association between emergency surgery and increased risk of perioperative complications in benign gynecology has not been, to our knowledge, studied extensively. It has been reported for emergency general surgery. (18, 27) Havens' study on the complications of urgent general surgery concluded that emergency surgery is an important risk factor for complications. (27) They also reported that pre-operative patient characteristics such as comorbidities and physiological status do not solely explain the high complication rates in urgent cases. (27) Surgeries in comorbid patients may be delayed for medical optimization or trial of conservative management, contributing to the increased morbidity. (28) Havens et al. concluded that emergency general surgery should be a target for quality improvement programs. (27) Likewise, as highlighted in our study and reinforced by literature, surgical history is an important determinant of complication risk, notably because it can distort pelvic anatomy and cause adhesions. (2, 5, 29)

In our study, patients aged 40 to 64 years were less likely to get complications from their surgeries than younger and older patients. In prior literature, increasing age is generally associated with higher complication rates (18, 30) and longer operative times. (1) Surgeries

on older patients are also less likely to be done via minimally invasive techniques. (8) One hypothesis as to why younger patients in our sample had more complications than middle-aged patients is that the 18-39 year old group underwent more myomectomies and laparotomies, which are procedures that resulted in more complications. For example, 18.5% of patients aged 18-39, compared to 4.4% of patients aged 40-64, underwent myomectomies. In the younger group, 19.9% had a laparotomy compared to only 10.3% in the middle-aged group. We also hypothesize that the senior adult group was more likely to have a complication from their comorbidities than from the type of surgery. These hypotheses could not be verified in our study.

The finding of a U-shaped relationship between surgeon volume and complication was unexpected. This finding does not seem to be related to a hypothesis of high-volume surgeons performing more complex procedures. By defining complex procedure as a diagnosis of endometriosis stage 3-4, fibroids/uterus $\geq$500g or adnexal cyst size $\geq$10 cm, high-volume surgeons performed 30.8% of complex procedures, which cannot solely explain the association. Nonetheless, 82.9% of procedures on women aged 65 and over and 87.7% of operations on women with comorbidity scores $\geq$3 were performed by high-volume surgeons. Thus, high-volume surgeons seem to have operated on older patients with more comorbidities who were more likely to have complications, which explains their higher complication rates than medium-volume surgeons. Surgeon training and experience could not be assessed in our study.

Sub-specialization fellowship training and high surgical volume have previously been linked to improved gynecological surgical outcomes. (33-35) Conversely, this additional training narrows a physician's scope of practice and, on a larger scale, could limit access to routine or preventive health care from general Obstetricians Gynecologists. (36) Many surgeons in our study are subspecialty-trained in urogynecology and/or minimally invasive surgery, which may have contributed to our overall low rates of complications. However, surgeon training and/or experience was not a factor assessed in this study.

Our study has a few limitations. Most importantly, as the data was collected retrospectively, incomplete patient files lead to missing values which may have disturbed the measured associations of risk factors on outcomes. BMI values were missing most commonly (11% of charts). In addition, patients may have presented to another center with postoperative complications, which our data collection method would not have recognized. Moreover, some factors, notably socio-economic factors, were not studied and could impact outcomes. (8) Lastly, reliable information on the use of medications for pre-operative optimization was not available to us, and thus could not be included in the study. For example, preoperative use of gonadotropin-releasing hormone agonist to reduce fibroid size and iron supplements to improve anemia have been shown to reduce blood transfusions and postoperative complications in gynecologic surgery. (40, 41) Therefore, the administration of these medications likely influenced outcomes, but it could not be measured in this study.

In conclusion, the rate of major intra- or postoperative complications related to benign gynecologic procedures at a university-affiliated urban hospital was 5.4%. Prior abdominal surgery (laparotomy or laparoscopy) and emergency surgery were significantly associated with increased risk of major complications. Future research could explore quality improvement targets for emergency surgeries specifically, such as patient comorbidities, prioritization of these procedures, and associated delays. Our findings also demonstrate that complications arising from benign gynecologic surgery are rare, even in the absence of robotic equipment. Surgeons should consider the use of center-specific data and of these factors when counseling patients about the risk of adverse outcomes.

	Intra or post operative complications	
	Univariate logistic models	Multivariable logistic model
Variables	**OR [95% CI]**	**OR [95% CI]**
Pre-operative patient factors		
Age (years)		
18-39	1.00	1.00
40-64	**0.53 [0.29, 0.96]**	**0.24 [0.11; 0.56]**
≥65	0.66 [0.29, 1.51]	0.49 [0.10;2.42]
Born outside Canada		
No	1.00	
Yes	1.01 [0.58, 1.76]	
BMI*		
<30 kg/m2	1.00	
≥30 kg/m2	0.98 [0.51; 1.90]	
Current smoker		
No	1.00	1.00
Yes	0.46 [0.14, 1.51]	0.49 [0.13; 1.76]
Charlson Comorbidities Index (CCI)		
CCI = 0	1.00	1.00
CCI = 1, 2	0.59 [0.29, 1.20]	0.61 [0.24; 1.58]
CCI ≥ 3	0.67 [0.26, 1.75]	0.33 [0.06; 1.79]
Prior pelvic surgeries		
No prior pelvic surgery	1.00	
≥ 1 prior pelvic surgery	1.01 [0.58, 1.78]	
Non-gynecological prior abdominal surgeries		
No prior abdominal surgery	1.00	1.00
≥ 1 prior abdominal surgery	**2.06 [1.16, 3.67]**	**2.01 [1.05; 3.83]**
Surgeon factors		
Surgeon volume† (OR days per month)		
Low (<1)	1.00	1.00
Medium(1 - 2)	0.41 [0.16; 1.02]	**0.30 [0.10; 0.87]**
High(>2)	0.93 [0.42; 2.07]	1.35 [0.51; 3.56]
Peri-operative factors		
Admission type		
Planned	1.00	1.00
Emergency	**3.19 [1.06, 9.59]**	**19.54 [2.99; 127.54]**
Approach of surgery		
Vaginal approach	1.00	1.00
Laparoscopy	0.78 [0.36, 1.68]	1.58 [0.64; 3.90]
Laparotomy	**3.69 [1.76, 7.74]**	2.75 [0.89; 8.45]

Variables	Intra or post operative complications Univariate logistic models OR [95% CI]	 Multivariable logistic model OR [95% CI]
Conversion to laparotomy	**8.93 [3.25, 24.53]**	2.75 [0.75; 10.10]
Operative time ≥ 180 minutes	1.44 [0.72, 2.86]	
Pre-operative hemoglobin ≥ 120 g/L	1.75 [0.93, 3.30]	
Peri-operative prophylactic antibiotics when recommended		
Recommended, received	1.00	1.00
Recommended, not received	1.56 [0.73, 3.34]	2.09 [0.85; 5.10]
Not recommended	**0.08 [0.02, 0.35]**	**0.08 [0.01; 0.45]**
Thromboprophylaxis		
Received	1.00	1.00
Not received	0.38 [0.21, 0.69]	0.46 [0.21; 1.01]
Complexity (endo 3-4, fibroids 500g+, cyst 10+)		
No	1.00	1.00
Yes	**2.98 [1.60; 5.52]**	2.20 [0.91; 5.32]
Main diagnosis and severity		
Other	1.00	
Fibroids	1.36 [0.65, 2.84]	
Endometriosis	0.79 [0.21, 2.93]	
Prolapse	0.58 [0.24, 1.40]	
Ovarian cyst	0.47 [0.14, 1.50]	
Stress Incontinence	na	
Family planning	na	

OR=Odds Ratio; ORs are in Bold font are significant
*BMI: Body Mass Index †Surgeon volume was treated as a random effect

TABLE 4 Univariate and multivariable analysis of risk factors and their impact on complication rates (n=975)

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ORIGINAL RESEARCH
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Teaching Medical Students to Suture: Evaluation of a Modern Medical School Curriculum

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ABSTRACT

Background: Medical students are traditionally introduced to suturing in a simulated environment using animal products or synthetic materials. However, there is little evidence to support this pedagogy. Our study explored whether a modern suturing curriculum adequately prepares medical students and examined student preference for learning suturing skills.

Methods: Suturing performance was recorded and assessed by expert raters. Students also completed a survey that inquired about self-perceived knowledge and confidence in suturing, and preferred pedagogical methods.

Results: The majority (79%) of students that completed our suturing curriculum demonstrated competence in basic suturing techniques. There was no correlation between objective abilities and self-perceived knowledge or confidence. Students reported being significantly more confident suturing anesthetized patients and in simulated environments. Students reported a desire for earlier introduction to suturing and more frequent simulation training.

Conclusion: A modern medical school suturing curriculum, comprising online modules and in-person simulation-based learning, adequately develops basic suturing techniques. .

KEYWORDS
Suturing, Education, Curricula, Medical students

1 | INTRODUCTION

Medical students are introduced to procedural skills, such as suturing, during their preclinical years in preparation for their surgical and emergency medicine rotations during clerkship. (1) Learning to suture entails observation and deliberate practice, both in a real or simulated setting. (2, 3) Although it has taken many forms over the years, surgical skills training has gradually shifted away from learning on-the-job towards simulation-based training. (4) At present, there is no established standardized suturing curriculum or consensus regarding best curricular design. (5) While previously, medical students were taught to suture by the "see one, do one, teach one" adage, modern instruction utilizes animal products or synthetic materials in a simulation-based teaching environment. (1, 5-13)

Online modules or simulation-based training can positively impact learners' self-efficacy and objective proficiency in suturing abilities. (14-16) However, studies do not illustrate the effect of patient awareness on performance. In other words, it is unknown if learners will be more proficient when suturing a patient who is awake versus sedated. Such information can effectively guide the medical school curriculum to invest resources appropriately and, thus, supply medical students with the necessary environment for optimized learning. Furthermore, investigating the synergism of online modules and simulation-based exercises used in conjunction to train medical students and assess their level of confidence may be beneficial for the academic community.

The goal of the present study is to determine the effectiveness of a modern suturing curriculum, comprising of both online modules and in-person simulation-based learning, by discerning objective suturing competence, and self-perceived confidence and knowledge in suturing. Additionally, we aimed to elucidate medical students' perspectives on the benefit of each teaching modality, and to evaluate whether there is an association between self-efficacy and suturing abilities. Lastly, we sought to explore whether a patient's state of awareness has significant effects on a learner's ability to successfully complete a suturing task. The results of this study are intended to inform educational leaders on how best to improve medical students suturing skills.

2 | METHODS

Second-year medical students at the University of British Columbia medical school were recruited via email in the spring of 2019. Participants were offered a small monetary incentive for participating in the study. Students were anonymized upon enrolment and excluded if they were involved in the workings of the study. The experimental protocol was approved by local research ethics boards. All participants provided informed consent.

The suturing curriculum consisted of two 3-hour in-person hands-on teaching sessions and associated online learning modules, administered 2 months apart, prior to clerkship. The philosophy of such a curriculum is to introduce early and deliberate practice in which students can enhance their confidence and have the flexibility to practice at home via online modules. (10) Furthermore, the online modules can pose a solution to challenging logistical problems facing a traditional curriculum, such as recruiting facilitators and instructors. (17) These sessions were taught by clinical faculty from surgery, emergency medicine and family medicine departments. The initial in-person session introduced students to the basics of suturing, including equipment, tissue handling and basic suturing techniques, such as simple interrupted. The second session focused on more advanced suturing techniques, including vertical mattress, horizontal mattress, and running subcuticular. The majority of the second session was dedicated to having faculty observes learners' techniques and provide direct feedback.

Upon completion of this curriculum, participants were recorded completing both a simple interrupted (SI) and vertical mattress (VM) suture on pork hock with unlimited time under video recording. Their performance was scored using the modified 12-criteria OSATS by two senior surgical residents. The participants were concealed from the surgical residents; participant names,

genders and whether they had completed modules or not, for instance, were unbeknownst to the evaluators. The OSATS assesses the ability to safely, appropriately, and technically complete basic suturing skills using a combination of task-specific checklists and global rating scales. (18-20) OSATS were scored from 0-24 with a higher score indicating better performance.

Additionally, participants completed two surveys inquiring about suturing experience, confidence, knowledge, and preparedness. One survey was distributed after completion of the suturing curriculum but prior to clerkship and the second survey was distributed upon completion of 12 weeks of clerkship consisting of core surgical and medical rotations. Incomplete surveys were excluded from analysis.

Participant descriptive data and survey responses are reported in the standard format. We compared the mean (± standard deviation) OSATS score between SI and VM sutures. Using a paired sample t-test, we compared participants' confidence and knowledge between SI and VM sutures, confidence suturing awake versus anesthetized patients, and pre- and post-clerkship confidence. Using Chi-Square tests, we compared whether participant's confidence differed between simulated and clinical settings. The correlation between participants' perceived knowledge and confidence for SI and VM sutures were reported with R-square. We calculated Pearson correlation between SI and VM for perceived knowledge and confidence. Effect sizes were calculated using Cohen's d. (21) Qualitative survey analysis was completed via narrative analysis methods. All data analyses were conducted in SPSS Statistics (version 23.0, IBM Corp., Armonk, NY). Significance was set a priori at $p<0.05$. No corrections were made for multiple comparisons.

3 | RESULTS

Twenty-four second-year medical students (26.8 ± 3.0 years old) enrolled in the study and completed the objective evaluation of their suturing skills. An additional 39 students were involved in the survey aspects of the study but declined having their suturing skills assessed (total enrolment rate, 21.9%; pre-clinical survey, n=63; post-clinical survey, n=14).

In our video analysis, students were significantly better at performing SI (OSATS = 19.2 ± 1.9) than VM (OSATS = 18.2 ± 2.0) sutures ($p = 0.022$, Cohen's $d = 0.51$). Pearson's correlation was significant ($r = 0.58$, $p=0.003$) between participant performance on SI and VM sutures. There was no significant correlation between self-reported suturing confidence and/or knowledge and objective performance in SI or VM sutures (Figure 1). Students most commonly lost points on their OSATS score from the following aspects of evaluation: safe mounting of needle on driver, mounting and orientation of needle in driver, trajectory of needle through tissues, suture tension, and avoiding handling needle.

The vast majority (93.4%) of students reported at least one exposure to suturing prior to clerkship, however, only 20.5% reported having sutured a patient (Table 1). After completing the suturing curriculum, students reported a "moderate" mean preparedness (3.0 ± 0.8 out of 5) and a "moderate" mean overall confidence of (2.8 ± 0.8 out of 5). Participant's perceived knowledge and confidence was significantly ($p<0.001$) higher for SI than VM sutures (Figure 2).

Before starting clerkship, students were significantly more confident suturing an anesthetized patient compared to an awake patient ($p<0.001$, Cohen's $d = 0.86$), and were significantly more confident suturing in a simulated, rather than clinical, environment ($p=0.018$; Figure 2). The majority (94.7%) of students who stated they were unsure or not confident in performing SI sutures in a clinical setting were confident in a simulated setting. Similar results (81.2%) were found for VM sutures.

In our post-clerkship survey, we found no significant difference in overall confidence in suturing after 12 weeks of clerkship experience ($p=0.726$; Table 2). Participant's self-reported confidence in suturing was both "moderate" pre-clerkship (3.2 ± 0.9 out of 5) and post-clerkship (3.1 ± 0.7 out of 5).

When asked about their preferred methods of learning, students rated online videos as significantly ($p=0.009$) more beneficial than suture kits. There was no

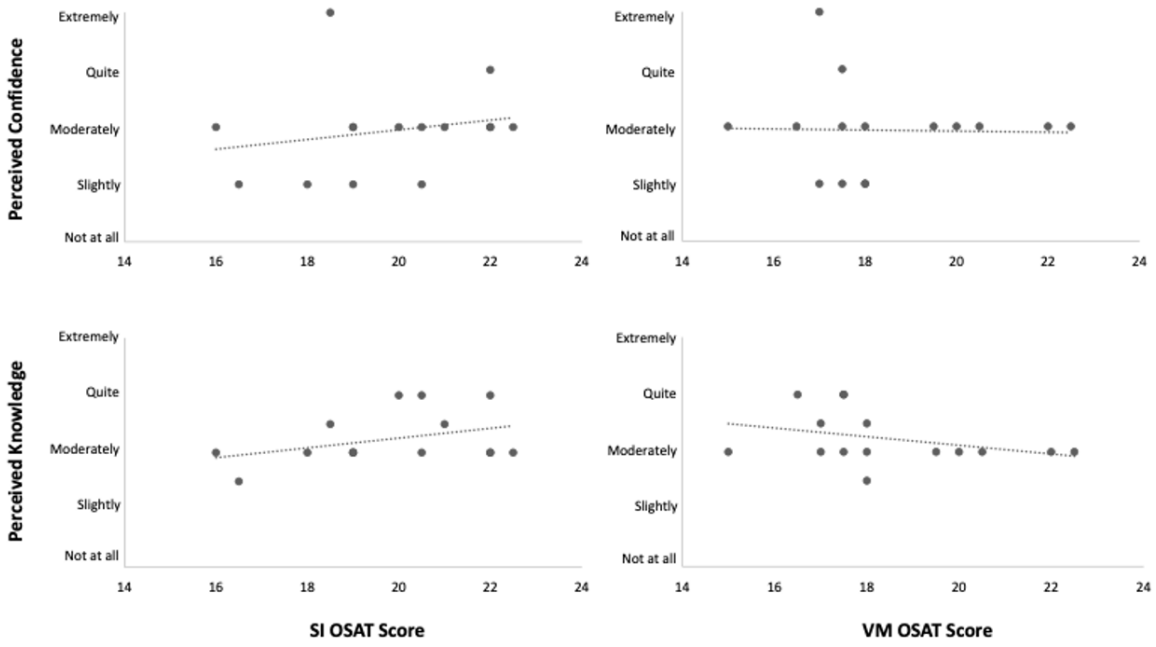

FIGURE 1 Correlation between objective suturing abilities (OSAT score) and self-reported confidence and knowledge for simple interrupted (SI) and vertical mattress (VM) sutures for medical students after completion of a modern suturing curriculum, comprising online modules and in-person simulation-based learning.

significant difference between teaching sessions and online videos (p=0.101) or suturing kits (p=0.157). Themes that emerged from qualitative data include preference for earlier suturing training, additional in-person teaching, advanced technical training opportunities, and practice tools. Students reported uncertainty about the transition from a simulated to clinical environment, yet viewed patients as the ideal learning model.

4 | DISCUSSION

This study assessed the effectiveness of a modern suturing curriculum in preparing medical students for clerkship and explored medical students preferred methods of learning suturing techniques. After completion of simulation-based suturing and online modules, the majority (79%) of students were competent in basic suturing techniques. Interestingly, there was no correlation between objective suturing abilities and students' self-perceived knowledge or confidence in suturing. Factors that increased student confidence while suturing included suturing in a simulated setting and suturing an anesthetized patient. In regards to pedagogy, students preferred in-person teaching sessions, online educational videos and early exposure to suture training during pre-clerkship years. These findings suggest that, although a suturing curriculum comprising online modules and in-person simulation-based learning adequately prepares students for clerkship, improvements can be made to increase student confidence in suturing. This is pertinent as student are frequently asked to suture during their clinical rotations and uncertainty in medical care is seen as detrimental to the physician-patient relationship. (22)

When suturing skills were objectively measured, we found no correlation between measurable suturing performance and self-reported knowledge or confidence suturing, indicating that subjective self-assessments were not reliable predictors of objective performance. Physician overconfidence increases diagnostic and medical management errors, which are associated with poor

Pre-clerkship Suturing Exposure						
Previous Experience (%)	**Nil**	**1-3 Occasions**	**4-6 Occasions**	**7+ Occasions**		
	6.6	60.7	26.0	6.6		
Previous Experience (%)	**Mandatory Teaching**	**Supplementary Teaching**	**Online Videos**	**Shadowing**	**Patient**	**Practice Material**
	60.3	34.2	67.1	42.5	20.5	64.4
Experience Outside Curriculum (%)	**Nil**	**Little Bit**	**Moderate**	**Significant**	**Majority**	
	27.9	55.7	9.8	3.3	3.3	
Preparedness (%)	**Not at All**	**Slightly**	**Moderately**	**Quite**	**Extremely**	
	0.0	32.8	44.3	18.0	4.9	
Overall Confidence (%)	**Not at All**	**Slightly**	**Moderately**	**Quite**	**Extremely**	
	3.3	27.8	52.5	13.1	3.3	

TABLE 1 Medical students' exposure to and self-perceived knowledge and confidence in suturing prior to clerkship.

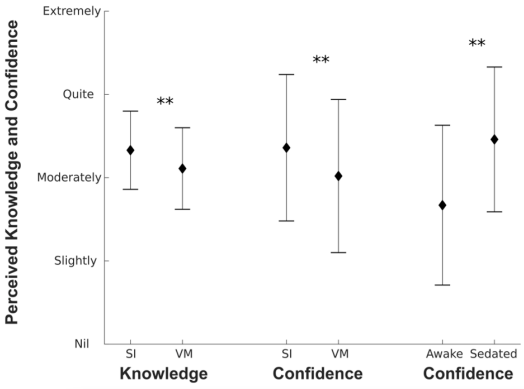

FIGURE 2 Medical students self-perceived knowledge and confidence in suturing simple interrupted (SI) and vertical mattress (VM) sutures, and in suturing awake and anesthetized patients, after completion of a modern suturing curriculum, comprising online modules and in-person simulation-based learning.

Benefit	Teaching Sessions	Suturing Kit	Online Videos
Nil (%)	0.0	0.0	0.0
Minimal (%)	7.7	45.5.	23.1
Moderate (%)	15.4	54.5	69.2
High (%)	76.9	0.0	7.7

TABLE 2 Medical students perceived benefit of different teaching modalities.

patient outcomes. (23, 24) Given the importance of accurate feedback in managing overconfidence and reducing the likelihood of future errors, providing medical students with objective feedback of suturing ability prior to clerkship may lead to greater self-awareness and less patient harm. (25)

Two themes emerged regarding where students most frequently made errors while suturing. Firstly, errors were commonly made in domains related to safety, such as mounting and orientation of needle in driver and avoiding handling needle. Secondly, errors were common in domains related to tissue handling, specifically the trajectory of needle through tissues and suture tension. In the clinical setting, errors in these domains can cause harm to both patients and students, through needlestick injuries or tissue damage and associated adverse healing. Students are more likely to damage tissue and are at increased risk of sharp injuries without proper

teaching. (26-29) Given that students are expected to suture patients during their clinical years, it is imperative that they have access to adequate training prior to clerkship to reduce risk of harm to patients or self.

Medical students were more confident suturing in a simulated, compared to a clinical, environment. Of those students who were unsure or lacked confidence suturing in a clinical environment, more than 80% stated they were confident in a simulated environment. Reduced confidence in a clinical setting is likely multifactorial, including limited supervision or feedback, concerns about causing poor patient outcomes, or concerns about preceptors' style of teaching. (26, 30, 31) Learning to suture in a clinical environment is stressful. It may lead to reduced skill acquisition, decreased confidence, and ultimately an avoidance of suturing in the future. (10, 32, 33) To reduce the likelihood of discontinued practice, medical schools should ensure ample opportunity to practice suturing in a supportive, simulated environment with adequate supervision and instruction. (10, 11, 32) A desire to learn suturing earlier in pre-clerkship training and having additional in-person training sessions were common themes that emerged from students. These themes complement previous literature that found medical students who learn suturing earlier in medical school and receive more training sessions report higher levels of confidence and have greater technical competence. (10, 11)

Within the clinical environment, medical students' confidence in suturing was impacted by the patients' level of consciousness. Students felt significantly more confident suturing an anesthetized, compared to an awake, patient. Malpas et al. (34) explain that there are two distinct components of completing a procedure: performing the technical aspect and communicating effectively with the patient. When suturing an anesthetized patient, medical students may feel that they can focus all of their attention on the task itself without the additional stress of exhibiting adequate relational skills. Although an anesthetized patient is ideal for offering an opportunity to focus solely on the technical task, it is crucial to consider the ethical implications of this, such as ensuring informed consent is obtained from the patient. (34-36) Suturing is a core competency of medical education, and suturing an anesthetized patient allows medical students to focus solely on improving their technique. (5) However, as highlighted by recent attention regarding pelvic examinations on anesthetized patients, to foster trust between patient and physicians, it is imperative that patients are informed that medical students may participate in their care. (37)

Medical students perceived in-person teaching sessions as the most beneficial teaching modality, and online educational videos to be more beneficial than suturing kits. Online educational videos provide an accessible, cost-effective and efficient alternative to in-person teaching. (30) However, frequent and deliberate practice in a simulated setting with direct observation remains the gold-standard during the skill acquisition phase of suturing. (10, 11, 38) Medical students rated suturing kits to be the least important tool for learning basic suturing skills; nonetheless, every student stated that they want access to a suturing kit. Suturing kits provide an important adjunct tool to reinforce foundation skills learned in education videos and in-person teaching sessions through dedicated practice outside of curricular time. (3)

A considerable limitation of this study is the lack of a Global Rating Scale (GRS) in objectively assessing students' performance. While students may score well on the OSATS, a novel GRS may be a better reflection of overall technical competence. For instance, this could take into consideration the number of attempts prior to success as well as other factors that the OSATS does not include. (39) Furthermore, although the OSATS assessment tool has been widely used, it has not undergone formal validation. (20, 40) Other limitations involve the inability to control for potential confounding variables such as prior medical training of varied forms.

In conclusion, we found that a modern suturing curriculum comprising online modules and in-person simulation-based learning adequately prepares medical students for clerkship. There was no correlation between objective suturing abilities and self-reported knowledge or confidence in suturing thereby emphasizing the importance of objective feedback prior to clerk-

ship in order to improve student self-awareness and reduce the risk of patient harm. Students were more confident while suturing an anesthetized patient which raises important ethical issues regarding informed consent within a teaching hospital or clinic. To improve medical students suturing curricula we recommend the use of online teaching videos as an adjunct teaching resource, early introduction to suturing, and simulation training prior to suturing in a clinical setting. Early and recurrent simulation training with direct expert feedback remains the gold-standard method to develop suturing skills.

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APPENDIX

Modified OSATS

Please rate the trainee's performance in the following areas **(1 – LOWEST, 5 – HIGHEST)**

Pre-procedure preparation				
1	2	3	4	5
Needed to be instructed on equipment gathering and patient positioning		Gathered equipment and helped position patient with some guidance; imperfect positioning		Assembled all equipment and positioned patient with no guidance required
Wound anesthesia				
1	2	3	4	5 N/A
Needed prompting and directed guidance to achieve wound anesthesia		Generally competent but somewhat inefficient and/or incomplete in anesthesia		Anesthetized wound completely and efficiently
Wound irrigation				
1	2	3	4	5
Needed frequent prompting and directed guidance to irrigate wound		Irrigated wound correctly with some prompting or is somewhat inefficient		Irrigated wound completely and efficiently without prompting or intervention
Use of Instruments				
1	2	3	4	5
Tentative or awkward positioning of instruments; poor use of instruments		Competent use of instruments but occasionally appears stiff or awkward		Fluid moves with instruments and no awkwardness
Time and motion				
1	2	3	4	5
Highly tentative, unsure of movements		Efficient, but somewhat tentative, with some unnecessary moves		Clear economy of movements and maximum efficiency
Needle Insertion and bite sizes				
1	2	3	4	5
Inappropriate needle positioning and bite sizes resulting in poor suture placement		Generally appropriate techniques with some room for correction		Appropriate needle angle and size and distance of bites every time
Knot tying				
1	2	3	4	5
Ties knots incorrectly, or needs frequent prompting on appropriate technique		Generally competent but somewhat inefficient and/or imperfect technique		Always tied knots efficiently using correct technique
Self-correction				
1	2	3	4	5
Oblivious to obvious deficiencies in repair, needs prompting to identify		Identifies imperfections in repair but unsure of how to correct		Performs perfect repair or independently and efficiently corrects imperfections
Overall Knowledge of Procedure				
1	2	3	4	5
Deficient knowledge. Needed specific instruction at most steps		Knew all important steps of procedure		Demonstrated familiarity with all aspects of procedure
Independence				
1	2	3	4	5
Needs frequent prompting and correction		Mostly independent needing only occasional guidance		Performs procedure with near-total independence
Overall performance				
1	2	3	4	5
Major intervention necessary to avoid cosmetic imperfection		Some prompting and redirection required to obtain acceptable cosmetic outcome		Outstanding cosmetic outcome achieved with minimal guidance
Post-procedure				
1				5
Needles and biohazards ignored or improperly discarded				Appropriately disposes of all hazardous materials & refuse

The Modified Objective Structured Assessment of Technical Skills (OSATS).

ORIGINAL RESEARCH
McGill Journal of Medicine

Evolving a Conceptual Framework and Developing a New Questionnaire for Usability Evaluation of Blended Learning Programs in Health Professions Education

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ABSTRACT

Background: Blended learning programs (BLPs) have been widely adopted across health professions education (HPE). To bolster their impact on learning outcomes, the usability of BLPs should be rigorously evaluated. However, there is a lack of reliable and validated tools to appraise this dimension of BLPs within HPE. The purpose of this investigation was to evolve a conceptual framework for usability evaluation in order to initially develop the Blended Learning Usability Evaluation – Questionnaire (BLUE-Q).

Methods: After the completion of a scoping review, we conducted a qualitative descriptive study with seven purposefully selected international experts in usability and learning program evaluation. Individual interviews were conducted via videoconferencing, transcribed verbatim, and analyzed through thematic analysis.

Results: Three themes were identified: (1) *Consolidation of the multifaceted ISO definition of usability in BLPs within HPE*; (2) *Different facets of usability can assess different aspects of BLPs*; (3) *Quantitative and qualitative data are needed to assess the multifaceted nature of usability*. The first theme adds nuance to a previously established HPE-focused usability framework, and introduces two new dimensions: 'pedagogical usability' and 'learner motivation.' The latter two provide guidance on structuring BLP evaluations within HPE. From this followed the development of the BLUE-Q, a new questionnaire that includes 55 Likert scale items and 6 open-ended questions.

Conclusion: Usability is an important dimension of BLPs and must be examined to improve the quality of these interventions in HPE. As such, we developed a new questionnaire, solidly grounded in theory and the expertise of international scholars, currently under validation.

KEYWORDS

Blended learning, Health professions education, Program evaluation, Questionnaire design, Usability

1 | INTRODUCTION

This article documents the second of three phases for the development and preliminary validation of the Blended Learning Usability Evaluation – Questionnaire (BLUE-Q), specifically conceived to appraise the usability of blended learning programs (BLPs) in health professions education (HPE).

Traditionally, blended learning has been defined as a pedagogical approach that utilizes both face-to-face teaching and information technology. (1-3) To ascribe limits to this broad definition, scholars indicate that learning is truly blended when education is provided through online learning methods for approximately 30 to 79% of the program. (4) Any less than 30% of technology use would refer to technology-assisted learning and any more than 79% would refer to online learning. (4) As technology continues to advance, new models of teaching and learning such as hybrid or hyflex have been developed and have pushed us to reconsider what blended learning is. (5-9) However, to our understanding, what is common among recent definitions of BLPs from around the world is that the blend being referred to is not necessarily about "in person" and "technology-facilitated" learning, but rather about the use of both synchronous and asynchronous learning modalities in a program.

Despite heterogeneity in definitions, BLPs have been demonstrated as beneficial for learners as they enable them to tailor their educational experiences to their needs, and to some extent, provide learners with the opportunity to control the pace, time, and location of their learning. (1, 10-17) BLPs empower learners and educators by using learning management systems, which can enable meaningful monitoring of learner progress. (2, 10, 11, 17) Additionally, BLPs can provide a cost-saving potential for institutions. (16) With these benefits in mind, BLPs have been adopted at an increasing rate across HPE faculties and departments over the last decade. (17-20)

The COVID-19 pandemic and its related lockdown measures have accelerated this trend as some learners have been unable to receive traditional classroom education. (21-26) Interestingly, institutional willingness to continue adopting and developing their BLPs in HPE faculties and departments exists to some extent, even as pandemic-related distancing measures ease-out. (27, 28) This is coupled with the increased acceptance of BLPs among HPE learners and their willingness to continue utilizing BLPs beyond the context of the pandemic. (27, 29)

Though BLPs are valuable, relatively well-accepted, and are being increasingly adopted, these educational interventions must be evaluated routinely in their entirety to ensure that they are effective and systematically improved. (1, 30, 31) This is especially necessary as new knowledge is developed in the teaching and learning domain, and innovative technologies become more readily available for use in educational systems. However, the lack of a common lexicon of evaluative terminology, frameworks, and methods to evaluate BLPs in HPE has been noted as a major threat to the comparability, generalizability, and overall systematicity of evaluation for BLPs, particularly in HPE. (32, 33) In the general field of education, a diversity of frameworks and models to evaluate BLPs exist – the vast majority of which, however, are focused on evaluating the technology involved in BLPs, and not necessarily the entirety of the program. (34) Additionally, scholars highlight that BLP evaluations are often unique across programs – but consistently unique evaluations of similar programs within and across institutions may hinder the rigorous comparison of the potential effects of BLPs on learners. (31, 34) Within HPE specifically, a lack of incorporation of consistent evaluative terms and frameworks was seen through a 2021 scoping review which included 80 studies from across 25 countries. (33) Interestingly, the vast majority of studies (86%) utilized questionnaires to evaluate their programs. (33) However, these questionnaires were developed to measure specific concepts such as "communication" or "learning" in general, and not specifically within the context of BLPs. Moreover, no questionnaire was identified that specifically evaluated the usability of BLPs within HPE. (33)

Several authors have suggested that *usability* is an instrumental pillar for BLP evaluation. (35, 36) Usability,

as discussed by the International Organization for Standardization (ISO), is a multidimensional concept that measures the "extent to which a system, product or service can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use". (37) Across the field of education, usability has traditionally been viewed as "ease-of-use" of a technology and has been implemented in the evaluation of e-learning modalities. (33, 38-40) However, this limited understanding and application of usability does not adequately reflect the construct's multifaceted nature and depth. (33)

1.1 | Developing the BLUE-Q

In this context, we conceived a research program with three consecutive phases to rigorously construct an instrument to evaluate usability of BLPs in HPE. Phase 1 consisted of a scoping review which aimed at understanding how usability has been conceptualized and evaluated for in HPE. (32, 33) Phase 1 results highlight that usability has been implicitly utilized across all evaluation studies and that explicit application of this construct can facilitate the adoption of a shared lexicon for BLP evaluations. (33) Through a deductive analysis, we developed a conceptual map of usability and its application in BLPs within HPE that: (1) depicts the three major pillars of usability (i.e., effectiveness, efficiency, and satisfaction); (2) includes two newly identified concepts that are often used interchangeably with usability (i.e., accessibility and user experience); and (3) lists 22 subconcepts that exist across HPE BLP evaluations. (33) This conceptual map provides an understanding of potential items that can be included in a questionnaire to evaluate usability in BLPs within HPE.

Our purpose in Phase 2, reported here, was to further deepen the previously developed HPE-focused conceptual framework for usability by exploring the perspectives of learning program evaluation experts, with the ultimate goal of developing a new questionnaire to systematize usability evaluations in BLPs across HPE. This approach to evolving conceptual frameworks generated from scoping reviews adheres to recommendations made by methodologists for ensuring that results from such knowledge syntheses are refined through consultation with relevant stakeholders. (41)

2 | METHODS

2.1 | Ethics

Ethics approval to conduct this study was received from the McGill University Faculty of Medicine and Health Sciences' Institutional Review Board (Study Number: A06-E42-18A). All participants reviewed and signed consent forms prior to their interview.

2.2 | Research Question and Methodology

The question that guided this research endeavor was: how do experts conceptualize usability and perceive its application in evaluating BLPs within HPE? To answer this question, we adopted a qualitative descriptive methodology. (42)

2.3 | Participant Selection

Adopting a purposeful sampling approach, (42, 43) participants were international experts in usability and learning program evaluation. Usability evaluation in the context of BLPs, particularly in HPE, is an emerging domain of inquiry. Thus, few experts exist in this area. However, a greater number of experts can be found that assess usability for other learning pedagogies such as e-learning and Massive Open Online Courses. Therefore, to identify experts, authors with Google Scholar profiles were primarily searched. Several reasons for this exist: (1) Google Scholar allowed for easy searching with regards to author interests (i.e. authors that have interests in 'usability' AND 'blended learning' can be efficiently identified); (2) Google Scholar allowed for easy reference to author publications and author influence (i.e., h-index and i10-index scores) which assisted in identifying their expertise in the current context; and lastly, (3) Google Scholar provided an indication of author primary

affiliations, which ultimately allowed for easier contact with potential experts.

Maximum variation may be advantageous when utilizing purposeful sampling to identify experts.(43) As such, experts were identified from across different continents and levels of expertise. Google Scholar searches consisted primarily of key words such as [(usability OR "human centred-design") AND ("blended learning" OR e-learning OR "online learning" OR "hybrid learning" OR "flipped classroom") AND "program evaluation"]. The first author compiled a list of potential scholars to contact based on their geographic location and number of their relevant publications. This list included a total of 14 experts, of which two were early-career investigators, six were mid-career experts, and six were senior-level experts. The list was reviewed and consolidated with co-authors. Based on discussions with the team 9 experts were contacted and 7 agreed to be interviewed.

2.4 | Data Collection and Analysis

An interview guide (see supplementary materials) was developed initially by the first author and was then refined by the co-authors in subsequent research meetings. The first author conducted individual interviews via Zoom videoconferencing software. Interviews lasted approximately 30 minutes on average. The first author transcribed verbatim the audio and video recordings with the aid of two assistants. All transcriptions were imported into QSR's NVIVO 12. Semantic thematic analysis, guided by Braun and Clarke's framework, (44) was conducted independently by the first and fourth authors. A hybrid approach to analysis was taken whereby codes were: (a) initially grouped based on a previously developed usability evaluation framework for BLPs in HPE, (33) and (b) inductively developed after each interview. The two reviewers met at three times during the coding process: after coding one transcribed interview, after coding four, and after coding all seven transcribed interviews. Initial themes were generated from the discussions between these two researchers, and were then revised and validated through meetings with the entire research team. Thematic data saturation "relates to the degree to which new data repeat what was expressed in previous data". (45) No new themes were identified beyond the fourth interview. Thus, thematic data saturation was indeed reached with seven participants and no more participants were recruited beyond this sample.

3 | RESULTS

The experts who participated in this study originated from and worked in Australia, Brazil, England, Greece, Indonesia, Italy, and the United States. Two were women and five were men. Their professional roles included: an Associate Dean, a Full Professor, an Associate Professor, two Academic Faculty Members, an Industry Lead, and a PhD Student. Through thematic analysis, three themes were identified: the first focusing on consolidating the framework of usability and the latter two focusing on the actual process of evaluating usability. Refer to tables 1-3 to see illustrative excerpts from interviewees for each sub-theme within the three themes.

3.1 | Theme 1: Consolidation of the Multifaceted ISO Definition of Usability in BLPs within HPE

In defining usability and its application in BLP evaluations within HPE, four of the seven experts explicitly referred to the ISO definition. Using their experiences, each expert also provided a nuanced understanding of the specific facets of usability.

3.1.1 | Accessibility and Organization of the Learning System

In the scoping review, accessibility was identified as synonymous to usability and was comprised of two sub-concepts: ease of access and access across time and space. (33) The experts nuanced this finding by indicating that accessibility is a sub-component of usability and that in BLPs it must address the fact that some learners may experience technological limitations (i.e., low internet bandwidth), may have special needs (i.e.,

visual impairments), or may have low technological literacy (i.e., possibly elderly learners). As such, when designing a BLP, experts highlighted the critical importance of understanding the learner population, specifically their challenges and needs, in order to optimize the educational program. One expert explained:

"… all our teaching materials [must be] highly accessible – things like particular fonts that you're using; not using italics because if you've got dyslexia, it's difficult to read ... So all those need to be thought through because … as you start using technology, what it does is foregrounds and heightens all these things …" (Participant #1).

Beyond recognizing issues of accessibility, experts indicated that system organization is a critical feature that must be planned in advance to ensure that accessibility needs are met appropriately. System organization refers to the clear, logical, and easy-to-navigate aspects of the content and learning systems, with a particular focus on e-learning environments (i.e., learning management systems).

3.1.2 | Effectiveness and Ease-of-use

Ease-of-use is a critical concept discussed by all experts. In fact, one of the three experts that did not refer to the ISO framework based their definition of usability strictly on ease-of-use:

"For me, usability is ease-of-use of a product. How easy is that product to use. So, it's a bit like [when I go to] one of our local coffee shops … [they've] got some little coffee cups … [and the handle is] really difficult to hold between your finger and your thumb. And you think 'it's got no usability'. Therefore, is it useful? No, it's not useful" (Participant #1).

Multiple experts indicated that the reason why ease-of-use is such a critical concept in the context of BLPs within HPE is because:

"…there are studies that point out that if a platform is not useable enough, students will take more time to try to understand how the platform works instead of learning the content that is being provided by this platform" (Participant #4).

Though ease-of-use was frequently discussed by the experts, this concept was almost always directly related to effectiveness. For example, one expert mentioned, "... making the platform easier would make the learning process more effective" (Participant #4). Interestingly, whereas the scoping review we conducted provides 10 specific sub-concepts that fall under the usability facet of effectiveness, the experts centered their definition of effectiveness around two specific sub-concepts: (1) gaining knowledge and (2) gaining skills.

3.1.3 | Efficiency

In the scoping review, efficiency was found to be comprised of four sub-concepts: time management; engagement with program content, materials, and faculty; cost-benefit analysis; and initial labour investment by faculty versus long-term results. (33) The experts provided nuance to this understanding of efficiency, with a focus on the first two sub-concepts. With respect to time management, the experts discussed time in relation to flexibility in learning, as well as the effort required to learn the material and navigate the learning platform. With respect to engagement, the experts discussed the importance of reflecting on and evaluating the resources available to learners (e.g., one-on-one time with instructors, self-paced modules, etc.).

3.1.4 | Satisfaction and Learner Motivation

Satisfaction was discussed similarly by the experts to the way it was analyzed in the scoping review. Satisfaction was often described as positive or negative perceptions of the content, and of the synchronous and asynchronous aspects of BLPs. However, an interesting addition to this description, highlighted by one expert was 'motivation to learn' as a major indicator of satisfaction and overall usability of the BLP. The expert explained:

"… I proposed in my [previous] work that intrinsic motivation to learn should be the fourth pillar when we measure usability … because I think that motivation to learn is probably the most important parameter for a

qualitative type of, you know, learning situation ..." (Participant #2).

When asked to provide more detail on what is meant by intrinsic motivation, the expert explained that:

"… when we say intrinsic motivation, we refer to things that … exclude tangible rewards. … Intrinsic motivation comes from inside. When we are pleased with things, when we are deeply satisfied, we tend to become intrinsically motivated to keep doing what we are doing, in this case to keep learning ... Not because we are told to do this, not because someone has promised a good payment when we do it, but because we really really like it and we think this is valuable for us" (Participant #2).

To note, though other experts did not explicitly refer to intrinsic motivation, they did hint at the overall idea of being motivated to take part in a BLP through describing the value or purpose of the learning environment, as well as learner expectations with the program at hand.

3.1.5 | User Experience

In the scoping review, user experience was identified as a synonymous term to usability and was found to focus on the perspectives of learners, faculty, and staff (i.e., teaching assistants), and how these perspectives changed over time. (33) The experts nuanced this finding by suggesting that user experience is a subcomponent of usability and that it deals with the emotions and feelings of learners. For example, one expert explains that:

"User experience also covers other types of aspects, such as emotions, feelings. Not just satisfaction, overall satisfaction, of the user. So how user felt when using the platform? Did he feel anxious? Tired? Or another type of feeling that he or she may feel during the interaction?" (Participant #4).

Importantly, another expert explained that although user experience is an important measurement to gauge usability, it is still only one facet of this multidimensional construct and must be considered in tangent with the other facets to truly apprehend the overall impact of BLPs. The expert explained:

"… experience measures [are] not measures of learning. You know, people can have a good experience at something and not learn something, so we have to be mindful of using these kinds of things in evaluation programs. Just like any good, you know, research process, you should triangulate your sources of data … forming your opinion on as to whether the program is successful or not" (Participant #7).

3.1.6 | Pedagogical Usability

The experts suggested a differentiation between the usability of the learning environment (i.e., asynchronous and synchronous learning modalities) and the content being taught. Two experts referred to this idea as 'pedagogical usability.' One expert explained:

"I would distinguish the container from the content … the possibility to organize content, the possibility to set-up both synchronous and asynchronous sessions, the possibility to link different sections of the material according to special information needs ..." (Participant #5).

To evaluate pedagogical usability (i.e., the usability of the content of BLPs and its delivery), experts highlighted several factors to consider: relevance of the content to learners, its reliability (i.e., how accurate and true the content appears), if the content is understandable, adherence of the educator to the syllabi, possibility for learners to choose personal paths, options to engage learners with different learning preferences, and how well the BLP is delivered by the instructor(s).

3.2 | Theme 2: Different Facets of Usability Can Be Used to Assess Different Aspects of BLPs

Moving beyond definitions, experts explained how usability could and should be evaluated in the context of BLPs. A primary recommendation here was that the content being taught in BLPs, the synchronous learning components, and the asynchronous learnings environment and activities should all be evaluated separately.

It was noted that the first five facets of usability as defined by the experts (i.e., accessibility and organiza-

tion, effectiveness and ease-of-use, efficiency, satisfaction and learner motivation, and user experience) are essential in the evaluation of the asynchronous and synchronous learning environments in particular. Whereas for the content being taught in the BLP, though the first five facets of usability are important, the sixth facet (i.e., pedagogical usability) is the most critical.

3.3 | Theme 3: Quantitative and Qualitative Data Is Needed to Assess the Multifaceted Nature of Usability

The experts highlighted the need to adopt both closed and open-ended questions. Experts noted that multiple-choice questions can help program evaluators garner an overall perspective of the usability of BLPs, and that short answer questions can help better understand learners and their context. Additionally, pre-post testing was also recommended by some experts. Such evaluations shed light to changes in subjective perceptions or objective GPA scores.

When asked how the experts would evaluate usability in BLPs within HPE, each expert discussed different tools and frameworks. Their suggestions included: the *E-learning Usability Scale*, the *Technology Acceptance Model*, the *System Usability Scale*, and the *Kirkpatrick Model*. Furthermore, some experts discussed the importance of interviews, whereas others discussed the importance of observing the interaction of learners with learning management systems.

3.4 | Towards the Blended Learning Usability Evaluation – Questionnaire (BLUE-Q)

Using the learnings and recommendations generated from the three themes, we evolved our previously developed conceptual map stemming from our previously published scoping review to further elucidate the various elements for evaluating usability in BLPs within HPE (Figure 1).

The first theme helped us pair accessibility and organization in one sub-category, introduced pedagogical usability as a sub-concept for specifically evaluating the content and materials of BLPs, and indicated that user experience and accessibility/organization are sub-components of usability (illustrated via unidirectional arrows). The second theme helped us establish four main pathways by which BLP usability evaluations can take place (i.e., that BLP evaluations can focus on the different components of the program or can evaluate the program in its entirety). The third theme assisted in consolidating the sub-components of the various domains of usability (e.g., sub-components of effectiveness are now limited to gaining knowledge, gaining skills and ease-of-use). Moving forward, the evolved concept map can serve as an essential pillar in guiding usability evaluations across BLPs within and potentially even beyond the field of HPE.

Through these themes and the evolved concept map, an initial version of an instrument to evaluate BLPs in HPE was developed and called the BLUE-Q. Preliminary face validity was assessed through research team and stakeholder engagement meetings. This initial version of the instrument currently includes 55 Likert scale items and six open-ended questions. The preliminary version of the questionnaire is currently under validation.

4 | DISCUSSION

To strengthen the usability, generalizability, and rigour of BLPs within HPE, both a new framework and instrument are needed to guide evaluations. Through this study, a more nuanced understanding of usability and its applicability in BLP evaluations within HPE was generated via analysis of interview data from seven international experts – which in turn enabled (1) the evolution of a previously developed conceptual map depicting a framework for evaluating the usability of BLPs within HPE; and (2) the development of the initial version of the BLUE-Q.

Four critical additions are made to the usability framework we previously developed through our scoping review. (33) Firstly, the usability facet of accessibility was

expanded to consider learner limitations with respect to using technology. Adding to this, experts also suggested that BLP developers and evaluators must consider the organization of the learning content and environment, concordant to accessibility. Secondly, the relationship between ease-of-use and effectiveness is clarified in this study. In the scoping review, ease-of-use was analyzed as *synonymous* to effectiveness. The experts, however, explain that ease-of-use *leads* to effectiveness of a BLP. Thirdly, learner motivation was deemed to be a critical aspect of usability and related directly to satisfaction. The experts explain that if learners do not feel motivated to learn the content or engage with the learning platform, the overall perception of usability would be negatively affected. Finally, pedagogical usability, was also added to group evaluations specific to the content and material being taught and utilized in the BLP.

It is important to note that, whereas the number of participants in this study might seem limited, they were experts recruited from around the world. Their similar conceptualizations of usability (data saturation) both validated and enhanced our framework for usability. Furthermore, each expert provided unique methods, frameworks, and tools to evaluate the usability of BLPs within HPE. This finding validates the fact that there is currently no unanimously agreed upon method or instrument to evaluate usability in BLPs within HPE, even among experts. See the supplementary materials for tables that present raw data to outline the themes.

In conclusion, thematic analysis of in-depth interviews from seven international experts in usability and program evaluation assisted in strengthening a framework for usability that we previously developed through a rigorous scoping review. Researchers can use this revised usability framework, depicted in Figure 1, to structure their HPE-based BLP evaluations. Additionally, this framework was used to develop a new instrument, coined the BLUE-Q, which will be useful in ascertaining the comparability, rigour, and systematic improvement of BLPs across the field of HPE – all of which are necessary to ensure that such programs are well designed, well received by learners, and genuinely facilitate learning. (46, 47) Moving forward, the BLUE-Q's psychometric properties will be evaluated using Bayesian factor analysis and seminal guidelines for content validation to ensure it is viable for use by scholars across the field of HPE. (48-50)

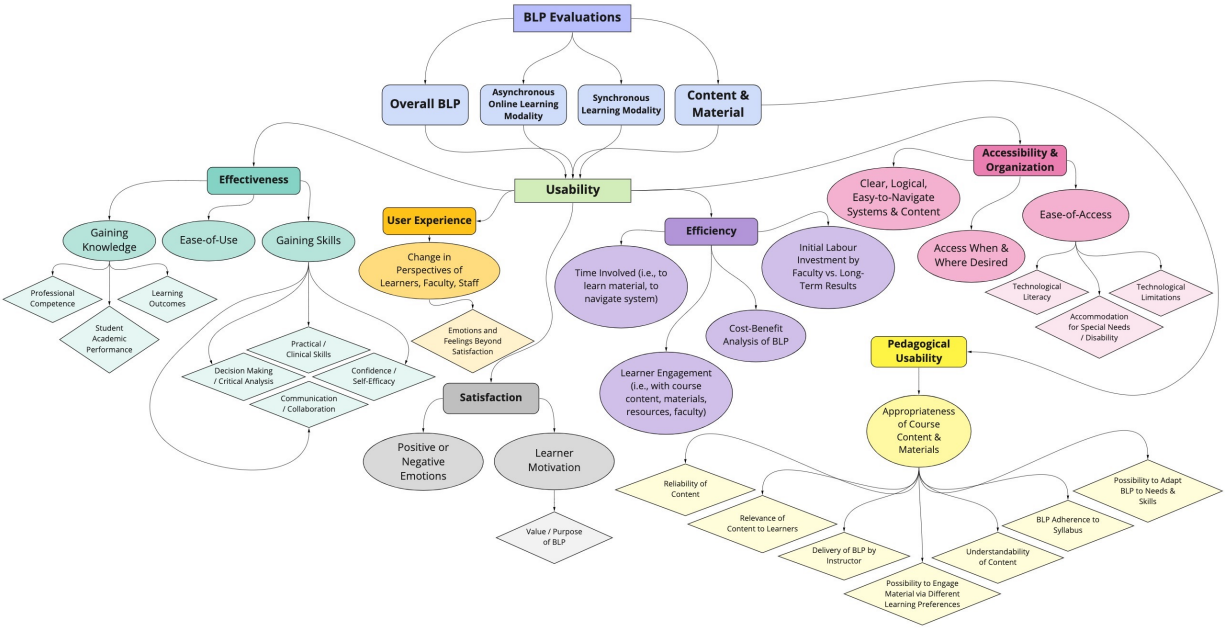

FIGURE 1 Revised conceptual framework depicting the application of usability in BLP evaluations within HPE, evolved via thematic analysis of interview transcripts with learning program evaluation experts.

TABLE 1 Theme 1 – Consolidation of the multifaceted ISO definition of usability in BLPs within HPE

Sub-Theme	Illustrative Quotations from Interviews
Usability (General)	"Well, I'm going to repeat my beloved definition of ISO standard which means that usability uhh is the extent that uhh people, certain people, can use certain products, systems, applications, platforms, etc. with specific goals in a specific context, with effectiveness, efficiency, and satisfaction are the three most basic usability dimensions… Well the one that I have already said before, it is an old definition, but uhh, there is no definition on usability by ISO. There is a newer definition on UX on user experience, but user experience is a larger concept. So when we are talking about usability, I think, if I remember well, nothing has changed I mean regarding the definition of usability, the basic pillars of usability are these three…It's just that we have to start from the basics, that's why I'm always referring to the basic three pillars – effectiveness, efficiency, and satisfaction… intrinsic motivation to learn is another important usability dimension, not just instructional design." – Participant 2 "Well, usability is how the user can perform the tasks with effectiveness and efficiency, during a real time, for example. How well the platform supports users to perform tasks and accomplish these tasks. Right. So, usability is really well related to easiness of use, how well the platform is easy to use in simple terms… Well usually I use the definition of ISO, I think it is one of the most used definitions and it covers well the main points of usability I think… I use the latest definition of ISO because it involves also the emotions and experiences that are being considered user experience." – Participant 4 "Usability is not such a short concept because it en-encompasses – uh – different aspects. For example – uh – you know, the classical definition is efficiency, effectiveness and satisfaction, and we can say that – uh – actually, these are the most important, the most important issues, the, the student must not spend more effort in using the platform or the blended – uh – system than learning the content. This is the, the golden rule of any educational system. So the system must be easy enough to be used not to distract the, the student from the study. Uh – and so, in this case, efficiency and effectiveness are quite related. Of course, satisfaction. But, even the user, the, the overall experience – uh – of the user is important because notwithstanding – uh – the good features, it is important to take the student involved, even emotionally involved and – uh – interested, and this may go beyond usability for a learning system. A, a, a, a, a usable system could be boring, let's say, while for a learning system, engagement is, is of paramount importance. So, in, in, in the case of a learning system, I would add engagement to the typical – uh – items." – Participant 5

Accessibility and Organization of the Learning System	"If you are using a flip chart and people can't read your writing and so people can't use it. Using handouts with small fonts or videos that are flickering too much are also, in my institution, and I expect your institution, at the moment we got a whole raft of directives recently about making uhm all our teaching materials highly accessible – things like particular fonts that you're using; and not using italics because if you've got dyslexia it's difficult to read; about background – using things you're not using like certain colours. So all those need to be thought through because what happens if you've got red-green colour blindness and you've gotta traffic light system and it's not very explicit. So having just colour icons is not a good idea. And you need -microsoft has got whole pages of this now so all those are – the problem is with technology, if you're using technology e-learning whatever you wanna call it, soon as you start using technology what it does is foregrounds and heightens all these things because you have to think about it." – Participant 1 "…if you, if you're talking about the basics of usability for learning environments, you want to make it so that how you design it does not impede learning… So, that blended learning environment, sometimes we take things for granted because we might be in face-to-face and be like 'Oh they can figure it out,' but we have to be much more intentional about how we organize information, the assignments and instructions." – Participant 3 "Usability and also accessibility; accessibility that means usability also for users with special needs – uh – with special needs and also with different technical skills. This is somehow important, especially important for learning systems because – uh – even students, learners with the most special technical skills, should should not left, should not be left behind. Because in some contexts – uh – the distance, distance part of learning is – uh – to get more insights into topics. And so it is – uh – necessary to assure these to, to everybody." – Participant 5
Effectiveness and Ease-of-use	"Was it useful? Have you learned anything new? Have you not learned anything new? Is at those levels. But actually, what you would like to know is whether they've made a change, a sustained change in the way they think things, and have that transformation, transformation of self, transformation of others, and transformation particularly clinically." – Participant 1 "So making the platform easier would make the learning process more effective for example. Well if they need to understand how to use the platform they will, they will be distracted I think , yeah. Trying to learn it before learning the content, right." – Participant 4

	"So, usability should be something that, I suppose, if something is usable then, the user doesn't really need to think too much about how to use it. They could just use it. Um, if you think about modern interfaces like maybe Facebook, for example, there are not too many people that are not able to use Facebook. Well, at least in its earlier days when it was more simple to use um.." – Participant 7
Efficiency	"…people spend a lot of time developing resources. As soon as you decide to go down the route of using technology, you are committing time, money, a whole range of things to that resource." – Participant 1 "…this part of learning to use the platform may have a learning curve right. At the beginning they will have some difficulties, but after they will use it more smoothly without thinking too much about how to use the platform to perform the tasks, right. But if we could minimize this learning curve, it will be better so we can learn faster and not bother with the platform." – Participant 4 "… If you think about usability in the sense of a HCI human computer interaction style research or more set of ironed out theories of course it's important. We know that usability costs us a lot when it's not done right. Um, in educational space it would cost the students, it would costs students the ability to learn easily, um, its costs frustration. So, you know, and from an academic or teacher's point of view, if we have to deal with systems that are not really usable it costs them time and again frustration that they probably don't have." – Participant 7
Satisfaction and Learner Motivation	"…intrinsic motivation to learn should be the fourth pillar when we measure usability of e-learning environments to courses, applications. Because I think that motivation to learn is probably the most important parameter for a qualitative type of you know learning uhh situation. I mean even if it is traditional education, or e-learning, or something else. I mean any kind of education, or any kind of educational product, or any kind of learning module must have the you know, quality to provoke users in a very good manner and I mean to make them intrinsically motivated to learn … when we say intrinsic motivation, we refer to things that, you know, they are not as, I mean which would exclude uhh tangible rewards. I mean, I'm not intrinsically motivated to learn when someone says "hey [removed name to retain anonymity], if you are going to succeed with this e-learning course you are going to get paid $1,000." No. It's obvious that this is not intrinsic motivation. Intrinsic motivation comes from inside. When we are pleased with things, when we are deeply satisfied we tend to become intrinsically motivated to keep doing what we are doing, in this case to keep learning and keep using and interacting with an e-learning environment. Not because we are told to do this, not because someone has promised a good payment when we do it, but because we really really like it and we think this is valuable for us. Valuable, this is very important word which is directly related to intrinsic motivation to learn. When we are intrinsically motivated to learn, we strongly believe that this is a valuable thing to us. Valuable, once again, not in terms of financial terms or tangible rewards – no no." Participant 2

	"Does it provide a positive experience or a negative experience?" – Participant 4 "…the classical definition is efficiency, effectiveness and satisfaction, and we can say that – uh – actually, these are the most important, the most important issues" – Participant 5
User Experience	"User experience also covers another types of aspects, such as emotions, feelings. Not just satisfaction, overall satisfaction of the user. So how user felt when using the platform? Did he feel anxious? Tired? Or another type of feeling that he or she may feel during the interaction? So it is not just – Well I'm fine with the platform or I'm satisfied it – but also the emotions." – Participant 4 "Uhh I have a belief that the more useable the product, it yield to a good user experience. So, if the usability focus more on the product, the UX or the user experience focus more the on experience of the user. So it means that we need to build a good product, high usability of the product to, so that, in that way we expect that the user will have a better experience in using it." – Participant 6 "It is often difficult to measure those kind of things I think um. The role of things like participant evaluation sheets, in my opinion, should be borderline their happy sheets, they use their experience um measures their not measures of learning um, you know people can have a good experience at something and not learn something so, we have to be mindful of using these kind of things in evaluation programs" – Participant 7
Pedagogical Usability	"The design of content which means how we design the learning material or you know how the instructional design has been transferred and you know packaged into an e-learning course." – Participant 2 "Okay, of course the content must be as – um – must be complete, must be reliable, must be – uh – well understandable and provide many examples, many practical cases – uh – and also open-ended exercises because I, I, I do not trust much – uh – what is usually exploited, that is the multiple answer questions." – Participant 5 "Should be able also to follow personal paths. For example, some students may already have some previous acquired skills, so maybe they could – some, some students could avoid a linear path because maybe they have already acquired, in some way – uh – skills that are required to follow-up." – Participant 5

TABLE 2 Theme 2 – Different facets of usability can be used to assess different aspects of BLPs

Sub-Theme	Illustrative Quotations from Interviews
Evaluating the Overall Learning Program	"You know the the bigger perspective of evaluation is quite tough. It has, it includes many things. It is multi-level. You have to evaluate always the content, the methodology, the training staff – the professors or the trainers, their ability– that's very very important. I mean their ability to perform in e-learning situations because you know it's not easy. I mean you can, there are many people and colleagues out there that are very good and and and experts in their field, but sometimes they are not so good in e-learning courses." – Participant 2 "Ok! Well the evaluation is very complex, right? So, the main point is that it is difficult to evaluate the platform by separating the content that is provided by professor and the platform itself. So students, when you ask students to evaluate the platform, the learning management system for example, they usually evaluate the content that is provided by the platform, rather than the platform itself. So, most of the times, they, they, for example, if the professor does not provide a content that is interesting for them, or is not well explained, then the students are more likely to evaluate the platform more negatively when actually the platform is not so bad at all. So, it is a difficult point to evaluate this type of platform… So, yeah they evaluate for example, whether their content is well – is updated. They evaluate some aspects that try to understand how well the platform supports learning to learn remotely, right." – Participant 4 "I would distinguish the container from the content. So, evaluating the container – uh – is somehow 'generical' to any kind of topic, so that's usability, the possibility to organize content, the possibility to set-up both synchronous and asynchronous sessions, the possibility to link different sections of the material according to special information needs. And this is about the container and these are general requirements, notwithstanding the kind of topic…." – Participant 5
Focusing Evaluations on the Asynchronous & Technological Features	"Well, usability is very important when we are talking about the digital aspects. I mean uhh how can we transfer usability into a face-to-face learning situation? I'm not sure about that. I think it is clear to me that we have to be clear that usability is about the design of digital things. I mean, okay, there are several economic factors and human factors that we have to take into account when we design other kinds of things, but I want to be clear in order, you know, to frame the situation, when we are talking about usability, we are talking about the digital design, the design of digital uhh systems. Not forms. So usability is very important in the design of blended learning regarding the aspect of how we design and deliver the e-learning aspect of the blended learning thing. Okay?" – Participant 2

	"I mean, e-learning poses several difficulties, it has several specific you know obstacles, that you have to overcome, it's not so easy to do. So you have to evaluate the infrastructure, the content, the instructional design, the ability of trainers and instructors, when it comes to e-learning you have to evaluate the design and usability of e-learning application, or the usability of the learning management system tool that maybe used in this kind of situation. Uhm what else? I think that these are the most important ones." – Participant 2
Focusing Evaluations on the Synchronous & Traditional Face-to-face Features	"So, that blended learning environment, sometimes we take things for granted because we might be in face-to-face and be like "Oh they can figure it out," but we have to be much more intentional about how we organize information, the assignments and instructions. So it's very important." – Participant 3 "So it's not just the learning management system, it could be the content or in-person content, so I think that can be the product." – Participant 6
Focusing Evaluations on the Content and Materials (Pedagogical Usability)	"But you know in both cases, I mean face-to-face and e-learning contexts, the key, the king, is always the content. I mean, we have to provide a very good content to the learners even if it is face-to-face or e-learning. Uhh I, I know this is not something knew, we are already aware of that, but we should stress this kind of parameter, I suppose" – Participant 2 "So, so, there's two levels to that evaluation too, like, if you're looking at the summative evaluation, you're actually looking at what did they learn or what they're able to achieve based on the course. But if you're looking at more of the formative evaluation, which looks at the pedagogical usability, so then you know that that is good and does not impact how they learn. It's two different levels. Or two different time frames when you do that." – Participant 3 "Something that is – uh – in the middle between the container and the content is the possibility to provide the same content in different forms according to different learning styles – uh – because, for example, some students prefer to have all the material in one chunk, other students prefer to have sections, some students prefer to have the assessment at the end, other students prefer to have assessment in the middle – uh – and so, this is both related to the kind of content, the way the content is organized, but also to the possibility provided by the platform." – Participant 5

TABLE 3 Theme 3 – Quantitative and qualitative data is needed to assess the multifaceted nature of usability

Sub-Theme	Illustrative quotations from interviews
Questionnaires	"Questionnaire as well, it is always a method which is valid." – Participant 2 "Oh right right, just one thing, well, uh, I think that one of the problems of the questionnaires that are already seen in the literature is that they are very quantitative for this field. And I think that the, obtaining, gathering, qualitative data would be much more interesting. Well, in our last study, we obtained some better insights when trying to understand, trying to extract information from the qualitative data obtained provided by the students in the questionnaires, through the open-ended questions for example. Right so combining quantitative and qualitative data will be better for evaluating these types of platforms, not just using questionnaire with Likert scales for example." – Participant 4 "If you think about what a student experience survey is, it's a usability survey, it's a user experience survey and that necessarily means that there has to be some form of meeting of minds of the teacher and the students in terms of how the learning is structured how the teaching is done um" – Participant 7
Pre-post Testing / Evaluation over time	"So it's a challenge, evaluating e-learning and it needs to be done, but overall, it's understanding the process of e-learning which is about usability, and longer term, which is about transfer. How does it actually change practice? How does it change overtime? Because it might have stimulated people, I've got a PhD student … who's looking at impact of health professional education training courses. One of them really really, I think one of the really important aspects that we need to think about very seriously is about how the people interact – who have they spoken to, what influences, as it stimulating them to read more, to do more, to look into it more, and they're the types of questions, that we need, you know following what up after a course and then maybe 3 months later, following people, checking in has that course changed your ability to practice but also has that course stimulated to read more. Cause that's really important information, because in fact there is no change in knowledge scores -because we did a control trial and saw that it didn't really increase knowledge scores before and after – it didn't increase knowledge, but what it did do is stimulate curiosity – and surely that is education." – Participant 1

	"but in order to go more, to go farther, and deeper, I would propose to you know to evaluate the participants after some months after the program has ended and, you know, try to observe them while they are doing the job. I mean, the best way and when it comes to medical education [laughs] for instance, the most important thing is, you know, not the conceptual uh kind of knowledge, but the experiential one. I mean a good doctor has to perform, not only to to to have the knowledge in his mind. [Laughs]. I mean, it is very important that that that every every doctor has to to to perform and interact very well with a patient and be able to apply his or her knowledge. It's not that okay I got it, I can do perfectly fine in a test and that's it. No no. We have to go beyond the basic and or imagine we are talking about surgeons, [laughs] we have to see them in specific operations. I mean, how they do it? This is so important! In order to evaluate if their training was effective one or good one. Uhh, well as I said, you know, evaluation in general has many many many levels." – Participant 2
Interviews	"When it comes to the direction of an e-learning kind of thing, of the blended learning, uhh some methods would be usability testing, uhh user interviews – I mean you have to context some interviews with the learners. Uhh okay, we also use some kinds of questionnaires, questionnaires are always helpful, but uhh that would be in addition to the usability testing sessions. I mean first of all, usability testing sessions uhh which would be accompanied by usability interviews and questionnaires." – Participant 2 "Uhh regarding the non-digital thing of the non-blended learning, okay aaah evaluation could be in the form – once again – interviews could be a very useful way – a speak with the participants and ask them face-to-face and ask them about the quality of the program they are participating in." – Participant 2 "There is this idea of, I guess, a community of learners and those people who are able to get involved in the discussion um. If you think about it's a usable situation." – Participant 7
Observations	Uhh another kind of method would be to observe how people use this kind of e-learning applications, in a natural way, if it is possible… Uhh when I say to observe, I mean if it would be possible for the researcher to you know to spend some time with the learner or spend some days with the learner when they use the e-learning systems of the blended learning." – Participant 2

	"but in order to go more, to go farther, and deeper, I would propose to you know to evaluate the participants after some months after the program has ended and, you know, try to observe them while they are doing the job. I mean, the best way and when it comes to medical education for instance, the most important thing is, you know, not the conceptual uh kind of knowledge, but the experiential one. I mean a good doctor has to perform, not only to to to have the knowledge in his mind. I mean, it is very important that that that every every doctor has to to to perform and interact very well with a patient and be able to apply his or her knowledge. It's not that okay I got it, I can do perfectly fine in a test and that's it. No no. We have to go beyond the basic and or imagine we are talking about surgeons, we have to see them in specific operations. I mean, how they do it? This is so important! In order to evaluate if their training was effective one or good one." – Participant 2
Usability testing	"When it comes to the direction of an e-learning kind of thing, of the blended learning, uhh some methods would be usability testing, uhh user interviews – I mean you have to context some interviews with the learners. Uhh okay, we also use some kinds of questionnaires, questionnaires are always helpful, but uhh that would be in addition to the usability testing sessions. I mean first of all, usability testing sessions uhh which would be accompanied by usability interviews and questionnaires." – Participant 2 "Um if we, if we talked about the technology side of it that, again it's about thinking about how you present you materials and your activities and making sure that they are... I suppose you still have to go through some form of user testing regime to figure out whether what you're doing is understandable by others but um." – Participant 7 "I'd probably go back to the old fashioned way of doing usability tests with a target audience. Um, I mean, It's often difficult to do it in the education sense because you might not be able to obtain access to the potential students in advance, but you can always get colleagues to look at things." – Participant 7
Triangulation of methods	"Well, I don't know if I, I use one specific tool. I actually use different things related to instructional design paradigms that I know and it's based on problem-based learning." – Participant 3 "Yeah, so if I can revise what I suggested, I said that there probably you can use two, probably three, the generic one, and the e-learning usability scales, and then the program evaluation, the medical subjects." – Participant 6 "…um just like any good, you know, research process you should triangulate your sources of data are about what forming your opinion on as to whether the program is successful or not." – Participant 7
Tools and frameworks to guide BLP evaluations	"…the latest Kirkpatrick evaluation model that's out has many many more process questions in it…" – Participant 1

	"Well there's the technology acceptance model by Davis, and that talks about – there's an intention to use something is dependent on the perception of usefulness and the perception of ease of use." – Participant 1 "I suggest that we can use the usability instruments. So measuring the usability of the product in general, so because we have the generic usability instrumentation, for example the system usability scales – I think it's a very well known instruments in this field, but I think we need to have additional instruments which focus more on the field, for example if we have engineering online course, I think we need to prepare a specific instrument to measure the engineering aspect. But if we measure the medical, I think we need to have additional instruments, so not only measuring the generic usability of the product, but also the medical education program itself. So I think we can use two type of instruments of measurements. So the instrument in generic – so it covers the technology aspect. But we also need to add the usability in terms of let's say the blended learning usability. I just found that I think a researcher came up with the e-learning usability scale, so it's not just system usability scales which can be used for any program, but I just found that there is e-learning usability scales which focus more on the e-learning software usability. And I think we also need to evaluate the educational program itself." – Participant 6

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ORIGINAL RESEARCH
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Access to Immunoglobulin Treatment for CIDP Patients During the COVID-19 Pandemic

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ABSTRACT

Background: Immunoglobulin supplies are limited; their access for patients diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may have been difficult during the COVID-19 pandemic.

Methods: A retrospective cross-sectional study was conducted with CIDP patients (n=16, 68.8% female, mean age 60.4±11.3) recruited from three Montreal tertiary care institutions. Inclusion criteria were patients over 18 years old who were receiving immunoglobulin treatment as of March 1st, 2020. Patients were asked to complete a questionnaire inquiring about changes in their immunoglobulin treatment during the pandemic and about their quality of life. Their charts were reviewed by an independent investigator. We used weighted chi-squared statistical tests and Cramer's V correlation ratios to measure associations with treatment change.

Results: Eighteen months after the pandemic started, 50% of patients were receiving the same treatment, 25% were receiving immunoglobulin treatment at a different frequency, 6.3% were receiving a different dose, 12.5% were receiving a different dose and frequency, and 6.3% were receiving a different treatment. Reasons associated with treatment change were worsening of neurological condition (18.8%; Cramer's V=0.480; p-value=0.055), improvement of neurological condition (25%; Cramer's V=0.577; p-value=0.021) and reduced availability of treatment (6.3%; Cramer's V=0.258; p-value=0.302). There were no significant correlations between lower quality of life (p-value=0.323) or lower Rasch-built Overall Disability Scale score (p-value=0.574) and treatment change.

Conclusion: Difficulty accessing immunoglobulin treatment was infrequent and not significantly associated with treatment change for CIDP patients during the COVID-19 pandemic. A larger multicentre study across multiple sites might identify other treatment access problems resulting from the pandemic.

KEYWORDS

COVID-19, CIDP, Neuromuscular diseases

1 | INTRODUCTION

Access to care for some patients with neuromuscular conditions has become a challenge during the COVID-19 pandemic (1). Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy defined by clinical progression for more than 2 months, and electrodiagnostic evidence of peripheral nerve demyelination (2). Immunoglobulin treatment is considered a first-line treatment for patients with CIDP (3). Various factors may have limited access to immunoglobulin during the pandemic including social distancing, cancellation of blood drives (4, 5), reduced donor availability, reduced availability of personnel trained to collect and manufacture blood products (6, 7), and reallocation of healthcare resources (8). Reduced blood product inventory has been reported both in Canada (9) and in the United States (4) during the pandemic. Patients themselves may have been reluctant to attend healthcare facilities due to fear of contracting COVID-19. Patients with CIDP have reported similar concerns (10), and some patients have tried to discontinue or change their treatment course for safety reasons (11). Finally, a proposition to promote patient-administered subcutaneous over intravenous immunoglobulin treatment was recommended during the pandemic to help reduce the movement of people and the potential spread of the virus (11). The goal of this study was to determine whether the pandemic was associated with changes in immunoglobulin treatment access for CIDP patients.

2 | METHODS

2.1 | Study Design

After institutional ethics board approval, we conducted an observational cross-sectional study of CIDP patients treated with immunoglobulin. We followed the STROBE guideline in reporting our findings to help in bias identification (12).

2.2 | Patient identification and inclusion criteria

Sixteen patients were recruited with convenience sampling from three academic tertiary care institutions in Montreal, QC, Canada: the Jewish General Hospital, the Montreal Neurological Institute, and the Montreal General Hospital. Patients were identified from lists maintained by the treating neurologists. All patients meeting inclusion criteria were invited to participate by their treating physicians.

Inclusion criteria were: age 18 years old; diagnosis of CIDP; and active treatment with immunoglobulin (subcutaneous or intravenous) as of March 1st, 2020. Patients were invited to participate by their treating physician or by phone by a member of the research team after physician referral.

2.3 | Data collection

Eligible patients were invited to complete an in-person or online questionnaire inquiring about treatment changes 18 months after the start of the pandemic (September 1st, 2021). The questionnaire collected basic information about patient characteristics and demographics, treatment change compared to the beginning of the pandemic (March 1st, 2020), and reasons for treatment change if applicable. We used the linearly weighted R-ODS (Rasch-built Overall Disability) scale to collect information on activity and social limitations during the COVID-19 pandemic. The scale asks about a wide range of activities and has been used with patients with different levels of functional limitations due to Guillain-Barré Syndrome (GBS), CIDP, and Monoclonal Gammopathy of Underdetermined Significance (MGUSP) (13). We also collected information on the patient's reported quality of life (greatly impaired (1), slightly impaired (2), average (3), good (4), and excellent (5)) and on the patient's reported level of physical activity (low (1), moderate (2), and high(3)) as both are direct or indirect predictors of overall function (14). Patient charts were reviewed by an independent investigator not directly involved in patient care, who then

completed a physician questionnaire.

2.4 | Data analysis

Our primary objective was to determine whether changes in treatment occurred during the COVID-19 pandemic and what the reasons for these changes were. Our secondary objectives were to identify if overall disability (R-ODS score), reported quality of life, and level of physical activity were associated with treatment change and with reasons for treatment change. If an association was established, our third objective was to evaluate the strength of such association with correlation coefficients.

To analyze associations between the dichotomous dependent variable "treatment change" and the independent categorical variable "reasons for treatment change", we used the chi-squared statistical test (χ^2). We used the Cramer's V correlation ratio to evaluate the strength of established associations (15). We used the chi-squared statistical test and the Cramer's V correlation ratio to evaluate associations between other categorical variables (reported quality of life and level of physical activity) and our main outcome "treatment change", and we used the point-biserial correlation coefficient (r_{PB}) to evaluate its association with the continuous variable overall disability (R-ODS score) (16). We defined statistical significance as a p-value <0.05 and conducted our analyses with IBM SPSS Statistics v.28.0 (IBM Corp., Armonk, New York, United States) (17).

3 | RESULTS

Twenty-seven patients were identified from the treating neurologists' lists. Seven patients were excluded by the independent investigator due to failure to meet inclusion criteria after further chart review (e.g., patients were started on intravenous immunoglobulin (IVIG) after March 1st, 2020), two patients refused to participate or were unable to participate, and two patients could not be reached. Sixteen patients were included for analysis.

Characteristics of our study population were: 68.8% female, age 60.38 ± 11.31, mean quality of life 2.75 ± 1.39, mean level of physical activity 1.5 ± 0.63, mean R-ODS score 33.75 ± 9.11, mean motor conduction velocity of the right ulnar nerve at original diagnosis 41.15 ± 16.79 m/s, and mean CSF protein value at original diagnosis 1.21 ± 0.56 g/L. Comorbidities included end-stage renal disease (1 patient), hypothyroidism (3 patients), vitamin B12 deficiency (2 patients), cancer treated with chemotherapy (2 patients), and diabetes (2 patients) (Table 1).

Eighteen months after the pandemic started (using a start date of March 1st, 2020, for our region), 8 patients (50%) were receiving the same treatment, 4 patients (25%) were receiving immunoglobulin treatment at a different frequency, 1 patient (6.3%) was receiving a different dose of immunoglobulin treatment, 2 patients (12.5%) were receiving a different dose and a different frequency, and 1 patient (6.3%) was receiving a treatment other than immunoglobulin therapy (Figure 1). Reasons associated with treatment change were worsening of neurological condition (18.8%; Cramer's V=0.480; p-value=0.055), improvement of neurological condition (25%; Cramer's V=0.577; p-value=0.021) and reduced availability of treatment (6.3%; Cramer's V=0.258; p-value=0.302) (Table 2).

We analyzed associations between R-ODS score, quality of life, and level of physical activity with treatment change and reasons for treatment change. No statistically significant associations were found (Table 3).

4 | DISCUSSION

We found no association between changes in immunoglobulin treatment for CIDP patients during the COVID-19 pandemic and reduced availability or difficulty accessing immunoglobulin. We also found no significant association between R-ODS score, level of physical activity, or quality of life with reasons for treatment change.

Although reduced inventory of blood products including immunoglobulin was reported during the pan-

demic, most of the decline in blood product collection in Canada was between February 2020 and May 2020, with a robust recovery by December 2020. Pre-pandemic, 70,000 donors were able to attend donor centres compared to 54,738 donors in May 2020, and 72,853 by December 2020 (9). By the fourth quarter of 2020, whole blood collections were almost back to pre-pandemic levels: 190,000 collections compared to the pre-pandemic baseline of 200,000 collections (18). Therefore, rapid adaptations of blood centres to public health measures, ongoing commitment to blood donation during the pandemic, and changes in donor selection criteria (such as reducing the hemoglobin threshold acceptable for donation) could explain why our patients did not experience reduced immunoglobulin treatment availability (9).

One patient did report reduced availability of IVIG as a reason for change in treatment. After chart review, the actual reason for treatment change was improvement of neurological condition. Fears about suspected impacts of the pandemic may have contributed to our patient's misconception; news reports of decreased blood product reserves were common during the first few months of the pandemic (9). A study with 29 adult CIDP patients reported pronounced psychological distress during the COVID-19 outbreak, with 27% of patients reporting concerns about drug availability and 20% reporting concerns about hospital accessibility (10). Another study reported increased anxiety and feelings of loneliness for patients with neuromuscular diseases (19).

Patients with other chronic neurological conditions also faced impaired access to their care during the pandemic and resulting consequences: patients with migraines have been facing difficulty in accessing care and increased headache frequency (20); patients with epilepsy with high seizure frequency and difficulty obtaining proper medical care reported depressive symptoms (21); and patients with dementia experienced worsening cognitive, behavioral and psychological symptoms with disruption of their care (22). Therefore, while immunoglobulin accessibility has not been directly affected, it is still possible that patients with CIDP faced difficulties and alterations in their normal care access in association with the pandemic. Examples include the development of concomitant COVID-19 infection, global safety measures affecting access to physical rehabilitation, mandatory social isolation (1), and the increasing use of telemedicine (23, 24).

Although our study showed no significant association between R-ODS score, level of physical activity, or quality of life with treatment change, other studies have shown that the COVID-19 pandemic did impact quality of life for CIDP patients and others. The pandemic was negatively associated with CIDP patients' daily activities and associated with lower sleep quality (10) which is a predictor of quality of life (25). An international survey with thirty-five research organizations across the world showed that home confinement had a negative effect on physical activity level for people in general and led to increased daily sitting time (26). Physical activity is associated with better quality of life, lower sensory impairment, and reduced disability measured by R-ODS score for CIDP patients (14); it is possible that CIDP patients had reduced activity levels and therefore a lower overall quality of life during the pandemic.

Our study features two main strengths: the risk of selection bias was reduced by referring all patients expected to meet inclusion criteria prior to looking for treatment change in their charts, and reporting bias was reduced by reporting all findings, including not statistically significant findings. Our study's main limitation is the small sample size that may have led to an underestimation of the true association between treatment changes and reduced availability of treatment (27). In fact, due to a significant sampling bias, our small group of patients may not be fully representative of treatment issues experienced by all CIDP patients during the pandemic. Similarly, while our study included patients from three academic tertiary care institutions, all institutions were in the same city (Montreal, QC, Canada), undermining potential treatment access difficulties experienced by patients in more remote areas or different cities. Our study focused solely on patients treated with immunoglobulin and how their immunoglobulin treatment was affected; we did not try to detect other associations between the pandemic and impaired access

to care for CIDP patients. Finally, patients newly diagnosed during the pandemic were excluded because achieving successful treatment may take some time for new CIDP patients and require multiple changes that would have influenced our main objective, that is to evaluate how the pandemic affected patients already under treatment. Hence, it is possible that CIDP patients encountered greater barriers to treatment.

In conclusion, difficulty accessing immunoglobulin treatment was infrequent in our population and not significantly associated with treatment change for CIDP patients during the COVID-19 pandemic. We found no association between quality of life, physical activity, or R-ODS score and reasons for treatment change. Our study highlights important points to learn from the COVID-19 pandemic: a reduced inventory of blood products including immunoglobulin was reported during the pandemic, patients reported concerns about drug availability during the pandemic, patients with neurological conditions faced impaired access to their care during the pandemic, and studies have shown that the COVID-19 pandemic impacted the quality of life of CIDP patients. A larger multicentre study across multiple sites could identify treatment access difficulties not limited to immunoglobulin, and further evaluate associations between patients' quality of life and treatment access difficulties. This could help justify providing them with greater resources, if needed.

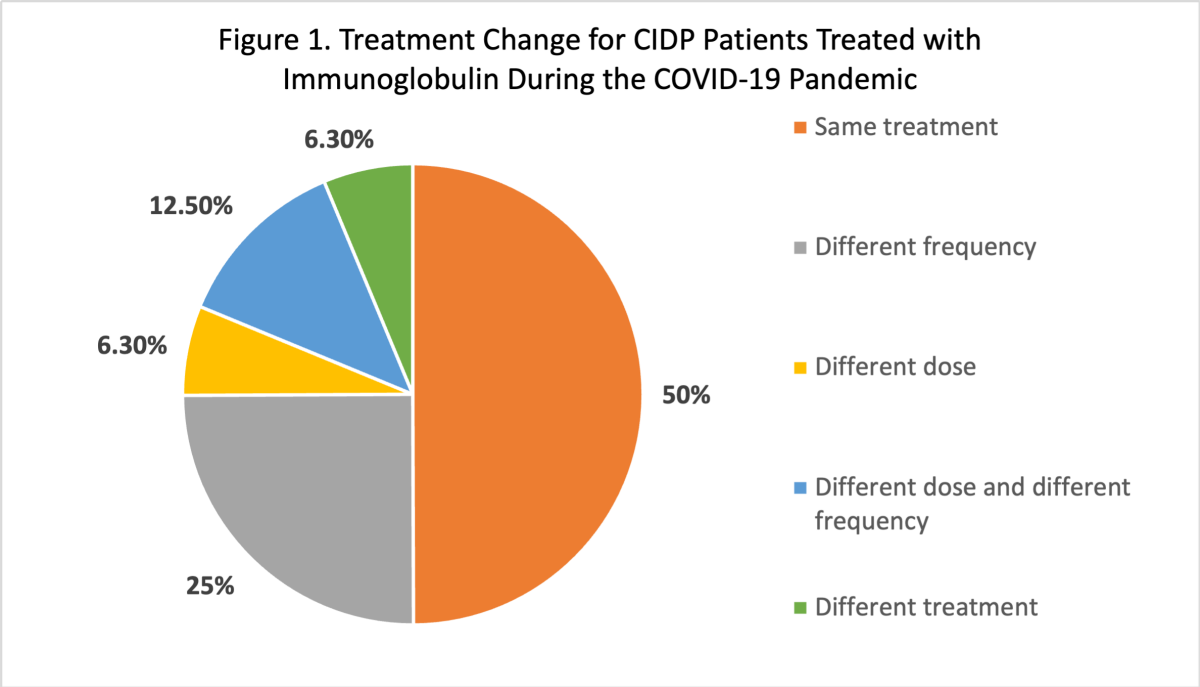

FIGURE 1 Treatment Change for CIDP Patients Treated with Immunoglobulin During the COVID-19 Pandemic.

	Mean	SD
Gender (%)		
Male	31.25	-
Female	68.75	-
Age (years)	60.38	±11.31
Quality of life	2.75	±1.39
Level of physical activity	1.50	±0.63
R-ODS Score	33.75	±9.11
Mean Cv* of right ulnar nerve at diagnosis (m/s)	41.15	±16.79
Greatest reduction in Cv at diagnosis (m/s)	21.85	±10.56
Mean CSF** protein value (g/L)	1.21	±0.56
Comorbidities (number of patients)		
ESRD***	1	-
Hypothyroidism	3	-
Vitamin B12 deficiency	2	-
Cancer treated with chemotherapy	2	-
Diabetes	2	-

TABLE 1 Characteristics of our Study Population.
* Cv: conduction velocity.
**CSF: cerebrospinal fluid.
***ESRD: End-stage renal disease.

Reason	% of our population	p-value	Cramer's V
Worsening of neurological condition	18.8	0.055	0.480
Improvement of neurological condition	25	0.021	0.577
Reduced availability of treatment	6.3	0.302	0.258

TABLE 2 Reasons Associated with Treatment Change.

	Quality of life		Physical activity		R-ODS score	
	p-value	Cramer's V	p-value	Cramer's V	p-value	r_{PB}*
Treatment change	0.323	0.54	0.411	0.333	0.835	0.057
No treatment change	0.323	0.54	0.411	0.333	0.835	-0.057
Worsening of neurological condition	0.123	0.673	0.853	0.141	0.333	-0.259
Improvement of neurological condition	0.695	0.373	0.196	0.451	0.429	0.213
Reduced availability of immunoglobulin	0.525	0.447	0.660	0.228	0.570	0.154
Change to a different treatment	0.777	0.333	0.660	0.228	0.235	-0.315

TABLE 3 Associations Between Quality of Life, Physical Activity, and R-ODS Score and Treatment Change and Reasons for Treatment Change.

*r_{PB} = point-biserial correlation coefficient.

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ORIGINAL RESEARCH
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Advance Care Directives: A Herzl Clinic Quality Improvement Project

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ABSTRACT

Background: Advance Care Planning has benefits for patients and is often optimal when done in the primary care setting. Unfortunately, it does not occur frequently or routinely. The goal of this project was to understand the challenges and barriers that residents at a Family Medicine training site face in initiating and discussing Advance Care Directives.

Methods: An online survey was conducted among 50 Family Medicine residents at the Herzl clinic. Participants were asked about their experience, their comfort level, and their challenges with Advance Care Planning discussions.

A focus group with 12 Family Medicine residents further probed, through open-ended questions, the specific challenges they have faced during Advance Care Planning and ideas to address them.

Results: The online survey and focus group identified that most residents perceived a lack of time, inadequate training, and poor uptake of available tools as barriers to have Advance Care Planning discussions in a community setting. Residents also felt that patients were inadequately prepared for these discussions. For improvement, most residents suggested to increase the variety of teaching modalities, to dedicate time for these discussions and to prioritize in-person discussions.

Conclusion: The residents in Family Medicine face many challenges and barriers to having Advance Care Directives discussions with their patients but were able to provide avenues for improvement.

KEYWORDS

Advance care planning; Advance care directives; Family Medicine; Medical education; Quality Improvement; Physicians, family; Ethics

1 | INTRODUCTION

Advance Care Planning (ACP) includes the exploration of patient's values, desires, and wishes for end-of-life decisions. It also involves considering a surrogate medical decision maker in case of loss of capacity, and indicating the desired level of care and goals of treatment. ACP discussions and documentation are considered a best practice of medical care. Clearly identified and documented ACP is a priority for the Ministry of Health in Quebec, Canada. La Loi concernant les soins de fin de vie recognizes the importance and primacy of a person's clearly and freely expressed wishes regarding care, notably through the establishment of the system of Advance Care Directives (ACD). (1)

ACP has been shown to have clear benefits for patients and their families. It helps ensure that the patient's consent is respected should the patient be judged incapable of participating in treatment decisions. (2) It allows patients to have better end-of-life care, focused on improving their quality of life. (2, 3, 4) It also reduces unwanted aggressive treatments. (2, 4, 5) Clear ACD benefit patients' family members, lessening the burden of the bereavement process which can be accompanied by much guilt, anxiety, and depression if their beloved one's wishes were felt to not be respected at end of life. (2, 3)

Primary care is an optimal setting for discussing ACD with patients. (6) In many studies, the patients have stated that they prefer to have these conversations in an outpatient setting and with their primary care physician, with whom they already have an established relationship. (6, 7) This minimizes the urgent or life-sustaining treatment decisions that must be made by a physician who doesn't know the patient's values and wishes. (8) It also allows for continuing discussions that happen over time. (9)

Unfortunately, ACP does not occur regularly and frequently, particularly in an outpatient or primary care setting. (4, 6, 9) The greatest barrier brought up by family physicians include a perceived lack of time, discomfort with the topic, and a need for more training and resources. (5, 7, 9, 10, 11, 12). Barriers to ACP for patients and their families include their reluctance to have these discussions, as well as their lack of knowledge. (7, 11)

The current literature on medical education has identified some similar barriers among resident physicians to implement ACP with patients. These include a perceived lack of time during the encounter, a reluctance to have these discussions with a healthy patient or during an acute care visit, as well a lack of training. (7, 13 14)

This quality improvement project was developed to further explore trainee's perspective on the initiation of ACP discussions with patients in primary care. The overarching objective is to understand the challenges and barriers that Family Medicine residents face when discussing ACD, and what can be done to optimize these discussions with their patients.

2 | METHODS

The Herzl Family Medicine Practice clinic is a McGill Family Medicine teaching unit where the mandate is to train residents in the competencies enumerated by the College of Family Physicians of Canada. One such competency is the ACP or planning for end-of-life decisions. (15) Herzl clinic trains about 50 residents who are either in their first and second year of training. Residents follow 2 home care patients in their resident patient practice throughout their 2 years of training.

The Herzl Home Care program had previously developed several resources for residents including an annual 60 minute didactic presentation, an electronic medical record (EMR)- integrated teaching algorithm tool to guide the discussion of ACD (2018), 2 different forms to document ACD ("Advance Directive Living Will" and the "Capacity and Level of Care"), and a resource page in the EMR with multiple resources on the legal procedures and implications of ACD. However, it was recognized that the ACD discussion and form was infrequently or partially documented (<10%) among our 85+ home care patients' charts.

The primary outcome of this study was to identify the challenges and barriers Family Medicine residents at the

Herzl clinic face when initiating and discussing ACD. The secondary outcomes were to identify why the resources provided were ineffective and what measures can be implemented to facilitate their use. A descriptive analysis was done for data collected through an online survey and a focus group discussion.

2.1 | Online survey

An online survey was developed to probe the experience of residents as well as their level of comfort with discussing ACD with their patients, whether in an outpatient or inpatient setting. (See Table 1) The survey was administered and hosted by the authors, supervised by MSc candidate Dominic Chu and project supervisor Dr. Hersson-Edery. The email invitation to participate was sent to the 50 Family Medicine residents based at the Herzl clinic. The 12 item survey used a mix of multiple-choice answers and 4-5 point Likert scales. It was available from March 24th 2021 to May 4th 2021. The survey was not pre-tested. No monetary incentive was offered to participants.

The survey began with two questions that explored the frequency and context of ACP. The third question assessed the residents' comfort in discussing ACD with their patients. The following seven questions explored the level of teaching, supervision, role modeling, and timing of ACD discussions. The twelfth question, open-ended, was about any additional comments or other barriers to discussing ACD. Finally, participants were asked if they were willing to participate in a focus group to further discuss the subject.

2.2 | Focus group

A 30-minute virtual focus group was organized with interested and available Family Medicine residents, to discuss the specific challenges and barriers they might have faced when having discussions regarding ACD, as well as their suggestions to facilitate these conversations. This focus group took place on May 5th 2021. Participants were invited to respond to the following open-ended questions.

1. What were your personal experiences having discussions about ACD at the Herzl clinic and what challenges did you face?
2. What are factors that made you more or less comfortable discussing ACD with your patients?
3. What resources have you used to help with these discussions?
4. What teaching modalities did you find most helpful in preparing to engage in these discussions with patients and family members? Has exposure in palliative care had an impact on your ability to have these discussions?
5. What could be done to further facilitate these discussions at the Herzl clinic? Do you feel a need for some training earlier in residency (Academic Half-Day, seminar, reading material, videos, etc.)?

3 | RESULTS

3.1 | Online survey

3.1.1 | Characteristics of survey respondents

25 out of 50 residents in Family Medicine from the Herzl clinic participated in the online survey. Of those residents, 60% were in their first year of residency and 40% were in their second year of residency.

3.1.2 | Experience with having ACD discussions

A total of 12 (48%) responders rarely had and 7 (28%) responders never had any ACD discussions in an outpatient context. In an inpatient context, all residents had ACD discussions at least 3 times, with 20 (80%) responders having had these discussions multiple times in rotations such as Palliative Care and Geriatrics.

3.1.3 | Comfort level when discussing ACD

16 (64%) residents felt somewhat comfortable, while none of them felt very uncomfortable.

3.1.4 | Resources available in the EMR for ACD discussions

Most residents were either not aware of the available resources in the EMR (n=11, 44%) or were aware that they were available but had never used them (n=8, 32%). 5 (20%) residents had used them and found them helpful. One resident stated that the form in Myle was "very complicated". Finally, 14 (56%) residents didn't know where to access these resources in Myle.

3.1.5 | Teaching and supervision on ACD

Only 4 (16%) residents responded never having received any teaching on ACD, although the majority (n=15, 60%) answered that the amount of teaching was very limited. 9 (36%) residents had received didactic teaching and 9 (36%) residents had received bedside teaching.

14 (56%) residents never had supervision while having ACD discussions with patients, although 13 (52%) of them felt that they would have the same level of comfort having these discussions regardless of supervision.

Finally, 14 (56%) residents agree that they have had limited teaching on how to conduct ACD discussions.

3.1.6 | Barriers to having ACD discussions

15 (60%) responders agree and 6 (24%) of them strongly agree that they don't have enough time during clinical encounters to have an ACD discussion.

As outlined in Table 2, residents mention difficulties with understanding the legal aspects of ACD and the difference with Levels of Intervention. Residents also perceived that patients were either unwilling, unprepared or surprised when residents initiated discussions on ACP and ACD.

3.2 | Focus Group

3.2.1 | Characteristics of participants

The participants for the focus group were recruited through the online survey. A total of 12 residents out of the 25 who answered the survey agreed to participate in the focus group. All the participants were in their first year of residency.

A summary of the answers collected from the focus group questions are outlined below, as well as illustrative quotes reported by residents.

1. What were your personal experiences having discussions about ACD at the Herzl clinic and what challenges did you face?
   Multiple residents brought up the lack of time when in an outpatient clinical setting, the difficulty of bringing up another discussion topic in addition to the many other health issues that need to be addressed at the visit, as well as the lack of experience with these discussions in an outpatient context.
   - *"I tried to do a Level of Care discussion… brought it up with the patient's daughter and we planned to have an appointment to discuss this only. At the next visit other things were more urgent and it was brushed to the side…"*
   - *"Our Herzl patients are complex at times and medical issues take up most of the time, usually not on my radar…"*
2. What are factors that made you more or less comfortable discussing ACD with your patients?
   Multiple residents expressed that it was not ideal to bring up this discussion during their clinical encounters via telemedicine, which was more prevalent at that time due to the Covid pandemic.
   - *"It was really, really awkward. When you are doing it in person it's very different. Body language is reassuring. Can't see how they are reacting, what they are thinking, if they have any questions."*
   - *"I had to do it over the phone… it felt impersonal. It's such a vulnerable conversation."*
   - *"I think it's not a good idea to do it on the phone."*
3. What resources have you used to help with these dis-

cussions?

Some residents found the Serious Illness Conversation Guide helpful, which is introduced in hospital-based Palliative Care rotations, while others found it was too rigid. While Herzl had developed several resources in the EMR to aid ACD discussions, none of the residents had used the resources, either because they were unaware of their existence or did not find them to be useful.

4. What teaching modalities did you find most helpful in preparing to engage in these discussions with patients and family members? Has exposure in palliative care had an impact on your ability of having these discussions? The residents who had completed their Palliative Care rotation expressed having felt significantly more prepared and more comfortable addressing end of life decisions.
   - *"I think what helped me most was not so much the structure, but how to bring up the topic with patients and their families…"*

   Although not many residents expressed the need to have staff supervision when having this conversation, all of them said they found it beneficial to watch, at least once, an attending physician having this discussion with a patient and family members.
5. What could be done to further facilitate these discussions at the Herzl clinic? Do you feel a need for some training earlier in residency (Academic Half-Day, seminar, reading material, videos, etc.)?

   Most residents expressed the need for training earlier in residency, as they anticipated needing these skills in an inpatient hospital setting rather than an outpatient community setting. Discussions around end-of-life decisions were perceived to be less prioritized in patients with stable or chronic illnesses. Many residents identified physicians outside of Family Medicine or Family Physicians working in inpatient domains of care as potential resources, rather than clinic-based physicians.

   Participants commented on the desired content of additional education. Content suggestions were often related to timing of ACP discussions. Desired timing-related topics included: when to introduce the ACP discussions in a family medicine practice, when to revisit the ACP conversation, and whether or not every home-care visit should include an ACD conversation. A few residents expressed interest in doing scenario-type activities to learn different ways to introduce the topic. A few also expressed a desire to learn some of the language that is better received by patients and encourages more openness. Finally, many residents were wondering how this documented discussion or the ACD would be transferred to the new treating team if the patient were to be hospitalized.

4 | DISCUSSION

The current literature is clear about the advantages of Advance Care Planning (ACP) for patients and families. People who engage in ACP are more likely to receive medical care that in congruent with their values and personal goals of care. The literature is less clear about why the engagement with ACP directives, uptake of ACP tools and discussions of ACP is low among primary care physicians and especially primary care residents.

This Quality Improvement project helped to identify the main barriers that Family Medicine residents face when having ACP discussions in an ambulatory setting and their suggestions to facilitate these discussions. This confirmed some of the findings in other studies and added to our knowledge of trainees' attitudes towards ACP, their perceptions of confidence, and barriers to ACP in an ambulatory clinical setting.

The survey results demonstrated that most residents had ACP discussions with patients during an acute hospitalized illness or hospitalization for palliative care at end of life, but very few had these discussions in an outpatient context. Much of the resources identified by residents were introduced to them in their hospital-based Palliative Care rotations. The survey and focus group results show that ACP discussions are more difficult for residents to initiate in the outpatient context compared to the hospitalized context.

Focus group discussions helped gather more details

on the specific barriers that residents faced with ACP discussions in both initiation and completion thereof. Challenges included the perceived lack of time during clinical visits, the barrier of telemedicine platform, discomfort with the initiation and maintenance of discussions as well as a poor understanding of how to make sure the ACP documentation will be honored throughout transfer of patient care.

These barriers are reflected in the literature by trainees in other programs and include perceived lack of time during a clinical encounter, the reluctance to bring up ACP discussions and a lack of a standardized process to prepare the patient for the visit. (7, 12, 13 ,16) Most trainees will feel more comfortable when they have had prior exposure to ACP conversations and the opportunity to practice having these conversations. (13, 16, 17)

Despite the availability of tools and resources at Herzl, residents were largely unaware of their existence and were not adequately exposed to supervisors or colleagues modeling their use. The uptake of tools into clinical practice is a well-known challenge in clinical medicine.

This Quality improvement study adds to the literature on trainee-generated proposals for improvement of ACP implementation, especially in primary care medical education. Residents proposed various avenues including providing diverse methods of teaching on ACP, such as didactic modules, simulations, and role modeling. As many residents in this study brought up simulations and role modeling to be methods of teaching they would be interested in, it is suggested that trainees acquire communication competence with practice and feedback. (18, 19) This is reflected in other studies that support experiential teaching methods to acquire competence in ACP. Pottash et al (2020) had residents participate in education on serious illness conversation through videos and role plays, followed by a supervised serious illness conversation. (13) All of the residents reported that they found this intervention to be helpful. (13) In another study, Internal medicine residents' comfort levels were significantly improved after they participated in a simulation-based ACP discussion with a standardized patient. (20) Finally, Detering et al (2014) demonstrated that, among general physicians and trainees, the physicians' self-confidence in having ACP discussions was subjectively improved following a multimodal educational program which included didactic teaching and an interactive patient simulation workshop. (2) Family Medicine residents suggested other practical strategies. These include that timing of discussions could be addressed with in-person, dedicated appointments. A visible reminder to initiate or complete the discussion on the electronic medical record could be helpful. Furthermore, there was a perception among residents that their patients were unprepared for or unwilling to pursue ACP discussion. A better understanding of patients' perspective on the initiation and preparation for discussions would be contributory.

One limitation of our study is the incomplete response rate among the Family Medicine residents at the Herzl clinic. Half of them answered the online survey and about 25% of them participated in the focus group. The focus group consisted exclusively of first year residents; second year residents have had a greater length of training and clinical exposure. There could also be a selection bias, as only participants with an interest in the topic might have answered the survey or participated in the focus group. The survey was released during a time when telemedicine was very prevalent at the Herzl Family Medicine clinic, which could have decreased the number of home-care visits and in-person visits where these discussions usually take place.

This study advances our understanding of the challenges that Family Medicine residents perceive in initiating and discussing ACP with their patients in the outpatient setting. Barriers included limited knowledge of existing tools and resources, a lack of variety of teaching and role modeling of the use of resources, low comfort level with ACP in outpatient settings, competing with other clinical priorities, and patient reluctance to discuss ACP.

Primary care medical education will need to employ multiple strategies to address the competence of trainees to initiate, conduct, maintain, and document ACD discussions. This quality improvement initiative study provides multiple avenues to explore and

advances our understanding of the challenges in ensuring that effective ACP is provided to individual patients, their families and the population served by Family Medicine trainees.

TABLE 1 Online survey distributed to family medicine residents at the Herzl clinic.

1. How many times have you had an Advance Care Directives discussion in an outpatient (clinic) context?
- Never (0)
- Rarely (1-3)
- A few times (3-10)
- Multiple times (10+)

2. How many times have you had an Advance Care Directives discussion in an inpatient (hospital) context?
- Never (0)
- Rarely (1-3)
- A few times (3-10)
- Multiple times (10+)

3. How comfortable are you discussing Advance Care Directives with your patients?
- Very uncomfortable
- Somewhat comfortable
- Neither comfortable nor uncomfortable
- Very comfortable

4. How familiar are you with the resources for Advance Care Directives discussions on MYLE?
- Not at all, I'm not sure what they are
- I'm aware they're available, but I never used them
- I've used them and found them helpful
- I've used them and I found them unhelpful

5. Do you know where in MYLE you can access the Advance Care Directives documents?
- Yes
- No

6. Did you receive teaching on Advance Care Directives?
- Never
- Didactic teaching (lectures)
- Bedside teaching
- Self-teaching

7. If you have had teaching regarding Advance Care Directives, how much?
- None
- Very limited
- Moderate
- Extensive

8. Have you ever had supervision while discussing Advance Care Directives with a patient?
- Yes
- No

9. If you were supervised while discussing Advance Care Directives with a patient, would you feel:

- More comfortable
- Less comfortable
- Same level of comfort as if I was unsupervised
- I have not previously discussed Advanced Care Directives

10. I have found that I have had limited professional education on how to conduct Advance Care Directives.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

11. I don't have enough time during clinical encounters to have an Advance Care Directives discussion.

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

12. Additional comments, or other barriers to discussing advanced care directives you may have encountered:

13. Would you be willing to participate in a focus group discussion on Advanced Care Directives?

- Yes
- No

TABLE 2 Results of the online survey distributed to family medicine residents at the Herzl clinic.

Questions	N = 25 (%)
1. How many times have you had an Advance Care Directives discussion in an outpatient (clinic) context?	
Never (0)	7 (28%)
Rarely (1-3)	**12 (48%)**
few times (3-10)	6 (24%)
Multiple times (10+)	0
2. How many times have you had an Advance Care Directives discussion in an inpatient (hospital) context?	
Never (0)	0
Rarely (1-3)	0
A few times (3-10)	5 (20%)
Multiple times (10+)	**20 (80%)**
3. How comfortable are you discussing Advance Care Directives with your patients?	
Very uncomfortable	0
Somewhat comfortable	**16 (64%)**
Neither comfortable nor uncomfortable	4 (16%)
Very comfortable	5 (20%)
4. How familiar are you with the resources for Advance Care Directives discussions on MYLE?	
Not at all, I'm not sure what they are	**11 (48%)**
I'm aware they're available, but I never used them	8 (32%)
I've used them and found them helpful	1 (4%)
I've used them and I found them unhelpful	5 (20%)
5. Do you know where in MYLE you can access the Advance Care Directives documents?	
Yes	11 (44%)
No	**14 (56%)**
6. Did you receive teaching on Advance Care Directives?	
Never	4 (16%)
Didactic teaching (lectures)	**9 (36%)**
Bedside teaching	**9 (36%)**
Self-teaching	3 (12%)

7. If you have had teaching regarding Advance Care Directives, how much?	
None	2 (8%)
Very limited	**15 (60%)**
Moderate	8 (32%)
Extensive	0
8. Have you ever had supervision while discussing Advance Care Directives with a patient?	
Yes	11 (44%)
No	**14 (56%)**
9. If you were supervised while discussing Advance Care Directives with a patient, would you feel:	
More comfortable	10 (40%)
Less comfortable	2 (8%)
Same level of comfort as if I was unsupervised	**13 (52%)**
I have not previously discussed Advanced Care Directives	0
10. I have found that I have had limited professional education on how to conduct Advance Care Directives.	
Strongly agree	1 (4%)
Agree	**14 (56%)**
Neutral	7 (28%)
Disagree	3 (12%)
Strongly disagree	0
11. I don't have enough time during clinical encounters to have an Advance Care Directives discussion.	
Strongly agree	6 (24%)
Agree	**15 (60%)**
Neutral	2 (8%)
Disagree	2 (8%)
Strongly disagree	0
12. Additional comments, or other barriers to discussing advanced care directives you may have encountered:	
"Understanding legal aspects of advanced care directions and legal jargon."	
"Difficult to discuss in an outpatient encounter. Some teaching on how best to have these conversations would be appreciated"	
"The majority of these patients are 'healthy,' and are therefore surprised to even have this conversation."	

"Patients not being ready, not having heard of them before, patient been uncomfortable with these discussions... In an inpatient setting it is a lot easier to explain the need for these discussions, whereas in the outpatient setting it is more difficult to explain the importance of these discussions."
"Main barrier is differentiating between Advanced Care Directives, Level of Intervention, serious illness discussion. [There is a] mandatory great teaching from pallium Canada online resources"
"Very complicated form in Myle"
"Topic rarely breached beforehand with patient. Being first time it is brought up, patient often reluctant to make decision right away."

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ORIGINAL RESEARCH
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Advance Care Directives: A Herzl Clinic Quality Improvement Project on Patients' Perspectives

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ABSTRACT

Background: Advance Care Planning (ACP) is beneficial to patients by ensuring their values and wishes regarding end-of-life care are respected. Despite the primary care setting being optimal for ACP discussions with tools available to facilitate these discussions, the initiation and documentation of Advanced Care Directives (ACD) in patients' medical files were low and resident physicians perceived that patients were unwilling or unprepared for ACP discussions. The goal of this project was to understand the challenges and barriers that patients and their caregivers face in initiating and discussing ACD with their primary care team.

Methods: An online survey was conducted among 78 patients who are part of the Home Care program at the Herzl clinic. Participants were asked about the value placed on ACP and their preferences on various aspects surrounding the initiation of ACD discussions.

Results: 25 of 78 possible responses were received. This included survey responses from 6 patients, 13 caregivers, 4 family members and 2 physicians. Our results show that patients and their caregivers value Advance Care Planning discussions (>80%). Additionally, they endorse multiple benefits of ACP for themselves, their care teams, and families. Patients and caregivers prefer that medical professionals initiate and facilitate the discussions (70-80%) and are open to receive educational material to prepare for these discussions (68%).

Conclusion: Patients in a frail population are willing and open to discuss advance care planning with their primary care team. Family Medicine teaching clinics can support patients' desire to engage in ACP by providing access to education material and initiating these discussions.

KEYWORDS

Advance Care Planning, Advance Care Directives, Patients

1 | INTRODUCTION

Advance care planning (ACP) is a proactive approach designed to facilitate comprehensive discussions and decisions regarding patients' values and wishes regarding end-of-life-care. This process involves an open discussion between patients, their families, and their physician aiming to determine the desired level of care, goals of treatment and a surrogate medical decisions maker in case of loss of capacity. The s-32.0001 law (*La Loi concernant les soins de fin de vie*) is a Quebec law which underlines the importance of patients' agency with regards to end-of-life care through the establishment of the system of Advanced Care Directives (1). The Quebec Ministry of Health considers ACP a priority, making ACP discussions and documentation an integral part of the best practice of medical care.

ACP has been demonstrated to improve patients' end-of-life care, by respecting their consent and ensuring their quality of life should there be a loss of capacity (2). For example, it has been shown that a significant number of patients die in a medical setting, such as an Intensive Care Unit, despite a vast majority of people reporting that they would ideally prefer their death take place in their home (3). With well documented ACP, patients are able to dictate their preferences regarding end-of-life care, including the setting, lowering the risk of death in an unwanted setting. Additionally, ACP also benefits patients' families and surrogate decision maker, lightening the weight of certain medical decisions and lessening the burden of the bereavement process which can be turbulent, particularly if the patient's wishes were not felt to be respected.

In multiple studies, participants have stated their preferences regarding the discussion of ACP as being in the outpatient setting, with either their primary care physician or another healthcare professional they already had an established therapeutic relationship (4). These studies underline the fact that primary care is an optimal setting for ACP discussions. Discussed and well documented ACP minimizes urgent and invasive life-sustaining treatments that would otherwise be the default standard of care (5).

Many studies have looked at effective interventions to improve Advance Care Planning discussions in the primary care setting (2,4,7). The most successful intervention is to pursue an interactive discussion, that often extends over multiple visits as the patient's disease or life situation changes (2,4,7). Including the patient's family in these discussions, if possible, can improve the patient's end of life care and decrease anxiety regarding their family members' wishes not being respected (4). Unfortunately, multiple studies have shown that ACP does not occur regularly nor frequently (4).

Herzl clinic is a McGill Family Medicine teaching unit mandated to train residents in the competencies outlined by the College of Family Physicians of Canada. One such competency is Advance Care Planning or planning for end-of-life decisions (8). Herzl clinic trains about 23 residents per cohort and has about 50 residents combined between first and second-year residents, as well as third-year fellows. Herzl Clinic cares for over 30,000 patients of which approximately 80 are in the home care program due to their frailty. Residents follow two home care patients in their resident patient practice during the two years of their training program.

The Herzl Home Care program had previously developed several educational and clinical resources for residents, including two different forms to document Advance Care Directives. However, it was recognized that the Advance Care discussions and forms were infrequently or only partially documented among our home care patients' charts.

A 2021 Quality Improvement study at Herzl, using survey and focus group data, explored barriers to ACP discussions amongst resident physicians (9). Barriers identified by residents included their perceived lack of education, opportunity, and time during clinical visits, as well as a perception that patients were unwilling or unprepared for advance care discussions.

Literature looking at patients' perspectives on ACP in the outpatient setting support that patients prefer having these discussions in the aforementioned setting (10). Most participants preferred earlier ACP, when patients are non-frail and are able to participate in these discussions themselves. (10,11). An adult general prac-

tice population indicated their preference was to initiate the discussion themselves (10). Interestingly, our population did not often initiate end-of-life care discussion with residents (9). However, the literature indicates that there is a portion of the population who consider ACP very important and would prefer that their family physician initiates the discussion (10). Preference for their family doctor to initiate the discussion correlated to the importance they gave to ACP discussions. Other studies have suggested that other health professionals such as nurses are well placed to initiate ACP discussions (12).

This quality improvement (QI) project was developed to better understand our home care patients' perspectives on initiation of ACP discussions.

2 | METHODS

2.1 | Online survey

A nine-question online survey was developed to probe the patients' perspectives on ACP in our home care setting. Caregivers and family members were invited to answer the questionnaire if the patient was unable to do so autonomously. The survey was administered and hosted on the Qualtrics platform by the Quality Assurance Team at the CIUSSS Centre-Ouest health authority in Montreal. Ethics review and approval was granted by the same team. 78 Home care patients were invited to participate. An email invitation was sent to the patients who had a contact email in the medical record. A paper version of the survey was sent to patients who did not have an email address. 2/25 surveys were completed on the paper version. A follow up email was sent 2 weeks later. A final attempt at increasing participation included phone calls to potential participants.

The 9-item survey used a mix of multiple-choice answers and 5-point Likert scales. It was available from February 2022 through April 2022. The survey was not pre-tested, and no monetary incentive was offered to participants.

The survey defined the components of ACP and ACD (the 'what') and explored the value respondents placed on ACP (the 'why'). The following questions explored the process of initiating ACP discussions (by whom, when, where, and how).

The project was carried out by Drs Adrienne Poitras and Zhou Fang, residents in the Department of Family Medicine, McGill and supervised by Dr Hersson-Edery and Dr Keith Todd. Support was provided by Alexandru Ilie.

3 | RESULTS

3.1 | Characteristics of survey respondents

Survey response rates were 32% (25/78), among which 6 respondents are Herzl patients themselves. Barriers to completion of the survey included hearing and vision impairment, or declining cognitive function. The largest group of respondents were patients' caregivers (13/25). Family members and physicians answered for the patients in 6/25.

96% of responders agreed that it is important to discuss ACP with healthcare professionals, yet more than half (54%) had not heard about ACP prior to this survey (Fig. 1A), and less than 25% have discussed ACP at Herzl.

A majority of respondents (24/25) answered 'agree' or 'strongly agree' to the statement "It is important to discuss Advance Care Planning with a health professional" (Fig. 1A). Six of the remaining respondents agreed and one individual was neutral. The reasons for placing this value were multiple. Some reasons included a desire to understand the choices around end-of-life interventions, to prepare for end-of-life decisions, to pre-emptively make decisions to avoid burdening family members, to ensure that their wishes will be respected, and to ensure dignity at end of life. Most respondents (70%) indicated that ACD could help reduce disagreements between family members and health teams.

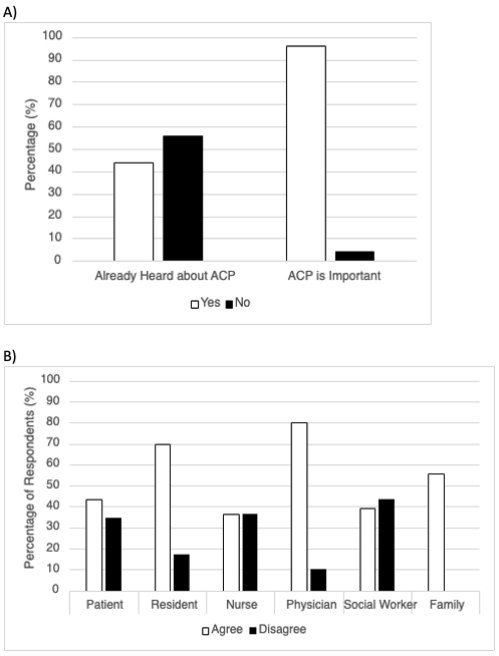

FIGURE 1 A) Percentage of respondents who had heard of advance care planning and who believe ACP is important. B) percentage of respondents who agreed or disagreed with different individuals initiating discussions on ACP.

3.2 | Timing and How ACP discussions should happen

Respondents showed a clear preference towards retaining autonomy on when to initiating discussions. Another large proportion indicated they would want an invitation to discuss ACP when there is a change in their health status (16/25), whether there is a new diagnosis or deterioration in health status. Less than half of participants (10/25) indicated that they would want this discussion on a yearly basis, such as when a new resident physician took over care, or if they are healthy.

More than 50% of respondents indicated a preference for informal initiation of ACD during a previously scheduled medical visit, rather than a separately scheduled visit, an email or a phone invitation. Additionally, (15/25) 68% of respondents were open to receiving preparatory medical information on ACD or medical interventions such as CPR, intubation, or dialysis, either through paper or digital format, or for this information to be provided to their family or caregiver. A single participant indicated that they preferred to receive preparatory information via a website.

3.3 | Who Should Discuss ACP

Participants expressed a stronger preference for the resident, staff physician or family member to bring up the ACP discussion, rather than a nurse or a social worker or themselves (Fig. 1B). 16 out of 25 respondents agreed or strongly agreed that a resident or staff physician should initiate the discussion.

4 | DISCUSSION

This quality improvement initiative adds important insights into how people think about advance care directives and their planning. Our results were somewhat surprising in that, although one would expect some knowledge of ACP amongst a frail population such as the one surveyed here, fewer than half had heard of ACP prior to the survey. Unlike a larger survey in Canada (13), our results are not focused on the term per se, since a definition was provided to ensure understanding. The work by Teixeira et al. (13), however, illustrated that many Canadians are engaging in these informal discussions with family members, which did not seem to be the case with our patients.

Our study confirms findings in the medical literature that patients prefer having physicians initiate discussions regarding end-of-life care in addition to facilitating the discussion when the patient brings it up or when there is a change is health status (10,11,12). The preference for involvement of a medical doctor may reflect a familiarity with these members of the care team since in our context since they are the professionals making the home care visits. However, it is quite likely that for other patients who were more familiar with other members of the health care team, such as a nurse or social worker, that these individuals would be the preferred contact person for these discussions (12).

The surprisingly small proportion of people who were

aware of ACD and who had participated in discussions highlights the need for more patient education. This seems not to be unique to our population as survey administered across Canada found that only 16% of people were aware of the term and only 20% had a written advance care plan (13). Interestingly, the residents' perception that patients, their caregivers, and their family members are reluctant to prepare and discuss end-of-life care in the outpatient setting (9) was not supported in our iterative follow-up quality improvement project. Our survey did reveal an openness by patients and families to receive educational material prior to discussions. This gives us clear opportunity and focus for changing patient awareness to facilitate more frequent ACP discussions. Patients and family members also indicated a preference for individual, in-person visits with their physician and family members, while there was little interest in group discussions on ACP. This also clarifies where we need to focus our implementation strategies.

Considering the limitations posed by the frailty and other possible barriers such as communication, auditory or cognitive difficulties, of our patient population we hope to extend this survey to the general older adult population at Herzl Clinic to see if their experience and perspectives on the initiation of Advance Care Planning and Directives differ.

4.1 | Limitations of study

The low response rate of 32% was likely multifactorial. In addition to the fact that our Home Care patients form a frail population in which varying degrees of cognitive, language or hearing barriers are not uncommon, many do not have or use email, and some would have difficulty understanding how to access an online survey. Only 6 out of 25 respondents were the patients themselves and family members answered the survey in 4/25 surveys.

Due to these anticipated barriers, the authors followed up with phone calls and offered to administer the survey by phone, which increased our response rate considerably. Most of our respondents were caregivers (13/25), who despite knowing their care recipient well, do not necessarily have the same values and beliefs as their care recipient, and therefore may not always respond to the survey in the same way the patients would themselves. Indeed, caregivers did include their care recipient in answering the survey questions, when possible, but it is unclear how well the responses reflected the patients' perceptions. We did not capture the prevalence of significant cognitive and sensory barriers to participating in this survey among our population.

In conclusion, this study advances our understanding of the challenges patients, caregivers, and family members in a frail Home Care population perceive in the initiation and discussion of Advance Care Directives with their physicians in the outpatient setting. Patients identified several areas of improvement that will be addressed in future iterations of this quality improvement project in order to improve the frequency and quality of Advance Care Planning discussions between Family Medicine residents or staff physicians, and their patients.

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CASE REPORT

CASE REPORT
McGill Journal of Medicine

Methadone Maintenance Therapy after Aneurysmal Subarachnoid Hemorrhage: A Case Report

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ABSTRACT

There is limited information on the effects of continued methadone maintenance therapy (MMT) following aneurysmal subarachnoid hemorrhage (aSAH). However, with the increasing incidence of opioid use disorder (OUD) in the US, there is a need to define best practices for the management of pain and prevention of acute withdrawal syndrome in patients with pre-existing OUD who develop aSAH. In this case report, we describe the use of MMT in a patient with aSAH and discuss important considerations, including sedation or confusion that might mimic acute neurologic changes seen in cerebral vasospasm or delayed cerebral ischemia, cardiac complications related to QTc prolongation, and liver or kidney interactions associated with aSAH routine treatment. Our patient recovered from her aSAH without any adverse events and, with increased monitoring and collaborative team-based care including input from those with expertise in OMD or aSAH, we believe MMT can be safely continued in most aSAH patients.

LEARNING POINTS

- Methadone maintenance therapy (MMT) may cause sedation that mimics the acute neurologic changes seen in cerebral vasospasm, a severe complication of aneurysmal subarachnoid hemorrhage (aSAH).
- Sedation can be differentiated from acute neurologic changes due to aSAH complications by the absence of radiologic or angiographic changes on computed tomography (CT) or digital subtraction angiography (DSA) and by the reversal of sedative effects when sedative agents are discontinued or when specific sedative antagonists (e.g. naloxone for opioids) are administered.
- Both aSAH and MMT may increase the QTc interval. T his combination may therefore significantly increase the risk of QTc prolongation and Torsades de Pointes. Continuous EKG monitoring is recommended during the first few days of MMT in aSAH patients.
- Methadone is primarily metabolized by CYP2B6, a CYP450 family enzyme, and may significantly alter the metabolism of some medications. Although most medications traditionally used in aSAH care are not affected, pharmacy consultation is recommended in aSAH patients who undergo continuation of their MMT after aSAH.

KEYWORDS

Subarachnoid hemorrhage, Opioid withdrawal syndrome, Prolonged QTc syndrome

1 | INTRODUCTION

Opioid use disorder (OUD) is an important public-health problem, affecting over 15 million people worldwide and over 2 million in the United Sates alone. (1) Methadone, a long-acting mu-receptor agonist, is sometimes used in patients with OUD as an oral opioid replacement for heroin, fentanyl or other intravenously-injected illicit opioids. Daily methadone maintenance therapy (MMT), prescribed and overseen by an approved methadone clinic, has been associated with reduced symptoms of drug withdrawal, drug craving, and relapse compared to opioid abstinence alone. It has also been associated with a reduced risk of viral or bacterial bloodstream infection and illegal drug and money-seeking behaviors compared to continued intravenous illicit opioid use. (2)

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating form of hemorrhagic stroke, resulting from acute rupture of an intracranial aneurysm, that causes a significant risk of mortality and long-term neurologic disability. (3) Approximately 1% of aSAH patients will also have a diagnosis of OUD at the time of their aneurysm rupture and may be receiving MMT as a part of their OUD treatment. (4) The safety and efficacy of MMT after aSAH is unknown. In this case report, we describe a patient with a history of MMT in the setting of OUD who developed aSAH. We also highlight potential complications of MMT in aSAH patients and provide recommendations for continuing MMT in aSAH patients.

2 | CASE DESCRIPTION

A 32-year-old female presented to hospital with acute onset of severe headache and lethargy shortly after awakening. A non-contrast computed tomography (CT) scan of her head demonstrated diffuse subarachnoid hemorrhage (SAH). The patient was placed on a nicardipine infusion to reduce her blood pressure and was transferred to our hospital. On arrival, she underwent a repeat non-contrast CT of the head and CT angiography (CTA) of the head and neck. These scans revealed diffuse SAH, an 8mm right posterior inferior cerebellar artery (PICA) aneurysm, and moderate hydrocephalus. On examination, she was lethargic with a Glasgow Coma Score =13 (Eye=3, Motor=6, Verbal=3) and Hunt and Hess Score = 3. Her medical history was significant for recent pregnancy, daily MMT, and a remote history of intravenous opioid use more than 1 year prior to aneurysm rupture. Unfortunately, more detail regarding her MMT, OUD, and other medication history was not obtainable from the patient at that time.

Due to worsening lethargy, she was intubated for airway protection and an extraventricular drain (EVD) was placed. Propofol and hydromorphone infusions were initiated for sedation and analgesia, respectively. The hydromorphone infusion was also used to prevent opioid withdrawal symptoms (OWS) until more details about her OUD and MMT could be obtained. Later that day, she underwent diagnostic angiography. A left posterior inferior cerebellar artery aneurysm was identified and endovascular coils were placed for aneurysm obliteration. On post-bleed day 1 (PBD1), the patient was significantly more alert and was successfully extubated. Of note, both her propofol and hydromorphone infusions were discontinued at that time. Following extubation a more detailed medical history was conducted, and the patient reported that her daily methadone dose was 95 mg/day and this dose was subsequently confirmed with the prescribing physician. After an electrocardiogram (EKG) demonstrated no QTc prolongation, 95 mg of methadone was given orally on the morning of PBD1 and this dosage was continued daily throughout her hospitalization. Continuous bedside telemetry and formal EKG on PBD5 were used to monitor for QTc prolongation. After aneurysm obliteration, she was treated per our routine aSAH protocol, including scheduled nimodipine therapy, daily transcranial Doppler (TCD) assessment, blood pressure control, and serum sodium monitoring. Her EVD was left open to drain at 0 cm H20 and on PBD9, as the patient had had no evidence of cerebral vasospasm (CV) or delayed cerebral ischemia (DCI), her EVD was weaned per protocol. The EVD was removed on PBD11 and she was discharged from the ICU later that day.

Throughout her hospitalization, the patient received appropriate ancillary care, including treatment for pain (primarily headache), constipation and electrolyte abnormalities. The patient's pain scores, stool frequency, and serum electrolytes were continuously monitored per protocol throughout her ICU stay. After extubation, the patient reported 10/10 pain due to headache. This was treated with scheduled acetaminophen-codeine. Despite this therapy, she continued to report significant headache pain through PBD4 that significantly improved to less than 2/10 through the rest of her hospitalization. Bowel function was monitored throughout her hospitalization and constipation was successfully treated on PBD6 with oral polyethylene glycol and bisacodyl with no additional reoccurrence of constipation during hospitalization. Her serum electrolytes were replaced per routine hospital protocol to ensure they remained within a normal range via oral and intravenous routes, as appropriate.

The patient was discharged from hospital to an acute rehabilitation facility on PBD16. At the time of her discharge, she remained on 95 mg/day of methadone and was scheduled to continue this regimen throughout her rehabilitation. At routine clinical follow-up on PBD90, she was recovering well. Her only complaint was minimal persistent headaches and she remained on MMT through her pre-existing provider. The patient provided written consent to publish this case report.

3 | DISCUSSION

This case report highlights the safe and effective early re-initiation of chronic MMT to prevent OWS in a patient with aSAH. In the care of this patient, we were not able to identify relevant published literature on the use of MMT in aSAH patients. For this reason, we discussed the potential complications and considerations, including concerns that early initiation of MMT might result in sedation or confusion that could mimic acute neurologic changes similar to those seen in cerebral vasospasm, that MMT could cause cardiac complications related to QTc prolongation, and that MMT could cause liver or kidney interactions with other medications routinely used in patients with aSAH. Although we did not detect any of these issues in our patient, they were important potential complications that were considered during her hospitalization.

Methadone is an opioid-agonist primarily active at the opioid mu receptor. It is used to prevent OWS in opioid-dependent patients and to treat acute and chronic pain in certain patient populations. (5) Daily MMT is used to blunt the distressing components of OWS, including anxiety, nausea, sweating, vomiting, abdominal pain, and diarrhea, that can occur with abrupt discontinuation of opioids in opioid-dependent patients. This patient did not develop any OWS-related symptoms; this was likely attributable to the early use of a hydromorphone infusion during sedation and then re-initiation of oral MMT in a timely manner.

The ability to conduct accurate serial neurological exams is critical after aSAH to detect the subtle acute neurological changes that portend potentially devastating sequelae, such as cerebral vasospasm and/or delayed cerebral ischemia. While we were concerned that MMT may cause inappropriate sedation or confusion, we believed that, with appropriate communication and discussion, we could balance the potentially conflicting goals of neurologic monitoring and continued opioid therapy. Our plan in the setting of new or unexplained mental status changes was to evaluate the patient, use early non-invasive radiographic imaging including computed tomography (CT) or computed tomography angiography (CTA) and, if needed, perform invasive digital subtraction angiography (DSA) to exclude organic brain disease. If radiographic testing did not explain the neurologic changes, we would then temporarily discontinue MMT and monitor for improvements in her neurologic status. Because methadone has a very long half-life (up to 59 hours), MMT discontinuation alone would have taken a prolonged period to see resolution of neurologic symptoms. (6) For this reason, emergent opioid antagonist therapy (naloxone) was also considered; however, because emergent naloxone likely would have precipitated OWS, it was only to be used after direct discussion of the risks and benefits between the neurosurgery and

critical care attendings.

One of our concerns was the possibility of prolonged QTc syndrome, which has been linked to mortality through Torsade de Pointes (TdP). Because both aSAH and methadone are known to prolong the QTc interval, the combination of chronic MMT and aSAH may therefore significantly prolong the QTc and increase the risk of TdP. (7, 8) In aSAH patients, the development of prolonged QTc syndrome is most likely to occur in female patients and in patients with serum hypokalemia. (9) Other variables, including age, aSAH severity, aneurysm site and other serum electrolyte abnormalities were not associated with an increased risk of prolonged QTc syndrome. Our patient was continuously monitored through bedside cardiac telemetry and formal 12-lead EKGs obtained on PBD1 and PBD5 did not exhibit a significantly prolonged QTc. These time points were chosen, after consultation with the clinical pharmacist. The former represents the baseline state before re-initation of therapy; the latter represents the state after 5 dosing intervals had passed, a time when serum methadone steady-state had likely been achieved.

Another concern was the possibility of unique drug interactions that may exist between methadone and various medications frequently used in patients with aSAH. Methadone is primarily metabolized to an inactive metabolite, known as EDDP, by CYP2B6 in the liver. (10) Other CYP450 enzymes including CYP3A4, CYP2C19, CYP2D6, CYP2C9, and CYP2C8 are involved in methadone metabolism to a lesser degree.(11) As such, we were concerned about potential drug interactions; however, none of the medications used, including antibiotics, nicardipine, nimodipine, or levetiracetam, are known to be metabolized by or affected by this hepatic metabolic pathway based on reviews of the published literature. Further review of the literature revealed no significant CYP2B6 inducer and inhibitor agents frequently used in the treatment of aSAH, alleviating some our concerns regarding the inclusion of MMT in this patient's treatment plan.

In summary, this case report describes the successful re-initiation of MMT in a patient with aSAH. Although continued MMT introduced the potential for additional sedation, mental status abnormalities, cardiac complications and drug interactions, we believed the potential benefits of continuing MMT, included mitigation of OWS symptoms and the continued blunting of opioid cravings, outweighed the potential risks. The patient recovered well and had no apparent complications from this treatment. Figure 1 highlights a potential clinical pathway for future patients with aSAH who are being considered for re-initiation of their chronic MMT therapy. We recommend that the neurologic status and other organ systems or complications be evaluated and stabilized prior to consideration of MMT. When stable and appropriate, we recommend pharmacist consultation to evaluate for potential drug interactions with methadone and to provide alternative safer recommendations, if appropriate. We also recommend careful

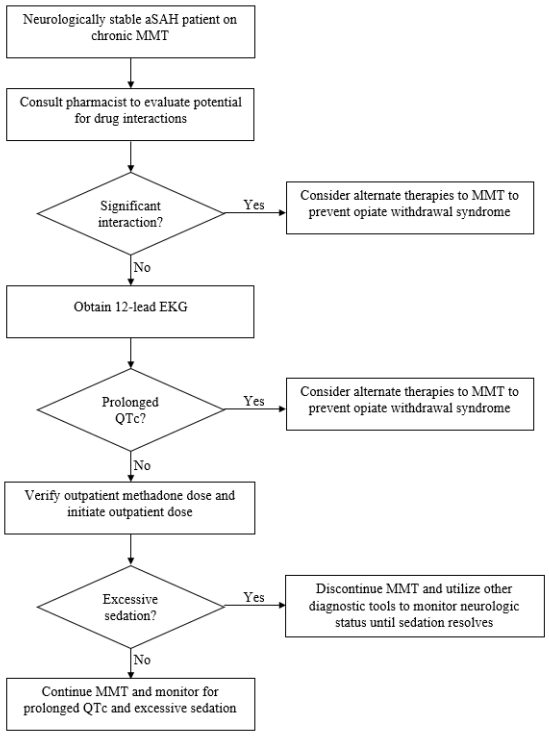

FIGURE 1 Care pathway for re-initiation of methadone maintenance therapy (MMT) in patients with aneurysmal subarachnoid hemorrhage (aSAH). CT = computed tomograph scan, CTA = computed tomography angiography scan, DSA = digital subtraction angiography.

QTc monitoring for, at least, the first few days as the normal cardiac abnormalities from aSAH subside and methadone serum concentrations reach steady state. (12) Formal 12-lead EKG is warranted prior to the first dose of MMT after aSAH and may be considered after 5 doses when methadone has achieved serum steady-state concentration; however, for most patients, continuous telemetry monitoring is likely adequate unless other therapies known to prolong QTc are added. In the event of increasing or prolonged QTc, alternate opiate therapies without the risk of QTc prolongation should be used to prevent complications of acute OWS. These alternatives should be discussed with the pharmacist and cardiology consultation may be considered. Finally, we recommend careful monitoring for excessive sedation, which may be confused with altered mental status, and the development of an evaluation and management plan with the neurosurgical team prior to MMT, including the use of earaly radiography or angiographic tests to exclude the possibility of organic brain disease. Following this protocol, we were able to re-initiate MMT after aSAH with no apparent related adverse effects. We believe MMT may be considered for patients on chronic MMT, without obvious exclusionary conditions, at the time of aneurysm rupture.

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CASE REPORT
McGill Journal of Medicine

A Case of Organizing Pneumonia Following Azacitidine Treatment for Myelodysplastic Syndrome

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ABSTRACT

Organizing pneumonia (OP) is a lung pathology mainly affecting distal lung structures. Its etiology is often unknown, in which case it is termed cryptogenic organizing pneumonia (COP). In cases of OP with an identified cause, the usual culprits include infections, medications, and radiation therapy. In this report, we present the case of a 73-year-old female on azacitidine, a pyrimidine analogue, used for treatment of myelodysplastic syndrome (MDS). The patient presented with fever, productive cough, and pleuritic chest pain. A CT scan of the chest, bronchoalveolar lavage, and transthoracic biopsy were performed, and the findings were consistent with OP, thought to be induced by azacitidine. The patient was treated with prednisone and showed significant improvement. Although rare, this case underlines the importance of considering OP in the context of non-resolving pulmonary infiltrates, particularly when there is a potentially relevant exposure.

LEARNING POINTS

- Organizing pneumonia denotes a distinct pathologic pattern involving the distal terminal bronchioles, alveolar ducts, and alveoli. The associated clinical syndrome is termed cryptogenic organizing pneumonia when no clear cause can be identified.
- The typical associated radiographic pattern is one of patchy, subpleural airspace disease.
- The development of organizing pneumonia has been reported with the use of hypomethylating agents such as azacitidine.
- Low dose azacitidine is used in the treatment of myelodysplastic syndrome and inhibits DNA methylation.

KEYWORDS

Organizing pneumonia, Myelodysplastic syndrome, Azacitidine

1 | INTRODUCTION

Organizing pneumonia (OP) is a lung condition characterized by non-infectious, plug-like lesions of fibroblastic tissue that primarily affect the alveoli and to a lesser extent, the alveolar ducts and terminal bronchioles. (1) While the exact pathogenesis of OP is not fully understood, it is believed to develop following injury to the alveolar epithelium, leading to the leakage of plasma proteins and inflammatory cells into the alveolar airspaces, which then promotes repair and fibrosis. (1) Many etiologies for OP have been established, including infectious agents (e.g., *Mycoplasma pneumoniae*, cytomegalovirus, SARS coronavirus-2), medications (e.g., bleomycin, methotrexate), radiation therapy, connective tissue disorders (e.g., scleroderma, dermatomyositis-polymyositis), and inflammatory bowel diseases (e.g., Crohn's, ulcerative colitis). (2) These causes should be considered when a new diagnosis of OP is made. In many instances, no injurious agent or event can be identified, in which case the associated clinical syndrome is termed cryptogenic organizing pneumonia (COP). (1)

Histopathological features consistent with OP include the presence of fibroblastic tissue in the distal airspaces and mild chronic interstitial inflammation, with preserved lung architecture. (1) Clinical manifestations may include dyspnea, cough, fever, and crackles heard on auscultation while patchy areas of consolidation are common imaging findings. (1)

Adverse reactions to many medications, including hypomethylating agents such as azacitidine, have been linked to the development of various forms of OP and other interstitial lung diseases (ILD). (3) Notably, in one reported case, OP was reported following administration of azacitidine for myelodysplastic syndrome (MDS). (3) While this toxicity reaction appears to be rare, heightened clinical suspicion in patients treated with hypomethylating agents for MDS who present with respiratory symptoms is important to ensure timely diagnosis, treatment, and optimal outcomes. More generally, inflammatory lung conditions such as OP (with or without a putative inciting agent) should be considered in immunosuppressed patients who fail to respond to antibiotic treatment despite presenting with signs and symptoms suggestive of an infectious lung process – even more so if focused investigations such as bronchoscopic sampling do not yield an infectious cause. We describe the case of a female with MDS who developed clinical and radiographic findings compatible with OP after administration of azacitidine. The patient has provided written informed consent to review and share her case information.

2 | CASE DESCRIPTION

We present the case of a 73-year-old female with essential thrombocytosis (ET) progressed to a JAK2-mutated myelodysplastic syndrome (MDS). She began azacitidine treatment for her MDS in March 2019, with monthly cycles involving 7 consecutive daily doses. The patient also had a history of stasis dermatitis, nummular eczema, rosacea, a previously resected squamous cell carcinoma of the nose and scalp, sciatica, Sweet syndrome, and irritable bowel syndrome. Home medications included pregabalin, pantoprazole, and valacyclovir, none of which is known to be associated with lung disease, including OP. (4)

Shortly after administration of the 23rd cycle of azacitidine, the patient developed a fever and experienced chills and rigors. The symptoms persisted for seven days, after which the patient presented to the hospital, reporting fever, chills, productive cough, and right-sided pleuritic chest pain. Physical examination was significant for a temperature of 38.4°C, heart rate of 125 beats per minute, and mild bilateral basilar crackles on lung auscultation.

A chest x-ray demonstrated right-sided abnormalities, including an upper lobe para-mediastinal opacity, nodular opacities at the base, and a small pleural effusion. Moreover, an initial CT scan of the chest (Figure 1a) revealed bilateral, predominantly subpleural, irregular solid nodules with ground glass halos in addition to a mild small right pleural effusion. Cultures of the patient's blood and urine failed to grow any pathogens. Cytomegalovirus (CMV) DNA was undetectable in the

serum, and serum antigen testing for Cryptococcus, Galactomannan, Blastomycosis, Mycoplasma were all negative. The patient also tested negative for SARS-CoV-2. Other notable laboratory findings included an elevated C-reactive protein (CRP) of 68.7 mg/L, slightly elevated absolute neutrophil count, a microcytic anemia, with leukocytes and platelet counts within the normal range. Given the patient's suppressed immune state in conjunction with the clinical, laboratory, and imaging findings, pneumonia potentially related to an opportunistic pathogen was initially considered the most likely diagnosis. Hence ceftriaxone, azithromycin, and isavuconazole were started empirically.

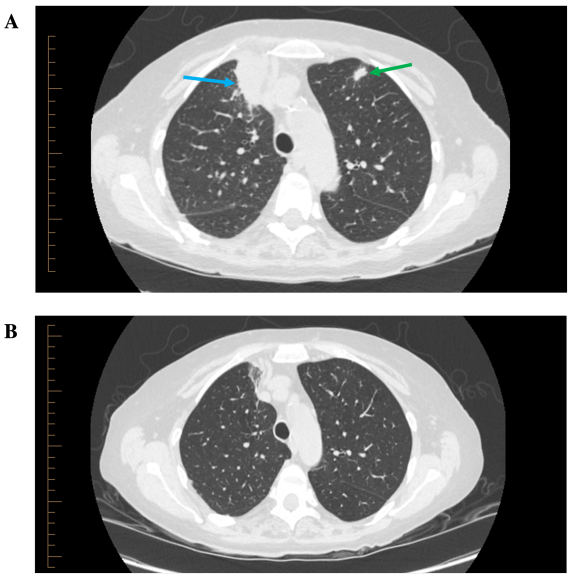

FIGURE 1 CT of the chest before and after treatment with prednisone.

(A) Representative CT chest image on admission. The image shows a dense, subpleural mass-like lesion in the right upper lobe in paramediastinal location (blue arrow), as well as a small nodular opacity in the left upper lobe (green arrow). The right upper lobe lesion was biopsied. (B) CT chest image from same level, one month after initiation of prednisone. The right paramediastinal mass-like lesion has substantially decreased in size and density. The left upper lobe lesion is no longer visible.

As the patient did not improve clinically, further investigations were conducted, including a bronchoalveolar lavage (BAL) and a CT-guided transthoracic lung biopsy of the right upper lobe. The BAL cellular analysis showed mainly inflammatory cells and minimal T-lymphocytes. The tissue biopsy only showed inflammatory changes, without the presence of neoplastic cells (Figure 2). As depicted in Figure 2, the tissue obtained from the biopsy was stained with hematoxylin and eosin and displayed polypoid fibroblastic aggregations in alveolar sacs (as indicated by the arrows) in addition to reactive changes in the alveolar epithelium. Neither specimen showed *Pneumocystis jiroveci* or any other fungal or viral organisms.

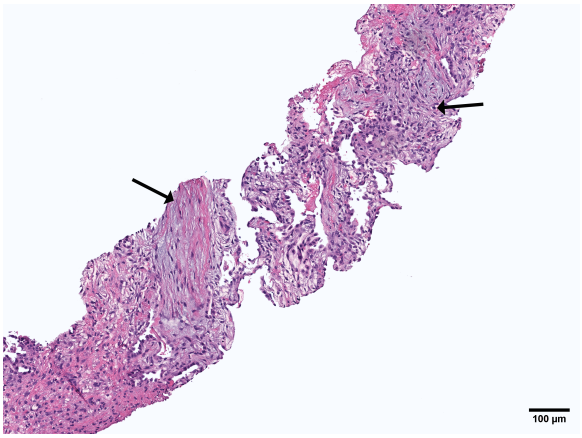

FIGURE 2 Hematoxylin and eosin-stained tissue from patient's transthoracic lung biopsy of the right upper lobe.

The lumens of the alveoli and alveolar sacs are filled with polypoid fibroblastic aggregations (arrows). The lung alveolar epithelial cells show reactive changes. Digital images are prepared using the Aperio AT2 scanner at a 200X magnification.

Based on the new findings, an ongoing infectious process was deemed unlikely, and with input from respiratory consultants, a provisional diagnosis of drug-induced organizing pneumonia was suggested. The patient was started on 50 mg of oral prednisone daily, with rapid symptomatic and radiographic improvement. A repeat CT of the chest (Figure 1b), obtained four days after the start of prednisone treatment, showed partial regression of the parenchymal lung disease. The patient was subsequently discharged and followed up in the respirology outpatient clinic, with gradual tapering of her prednisone. Her organizing pneumonia syndrome was attributed to the azacitidine, which was consequently stopped and replaced with decitabine-cedazuridine, an

alternative treatment for MDS.

3 | DISCUSSION

In the past two decades, hypomethylating agents (HMA) such as azacitidine have become the preferred treatment option for patients with high-risk MDS who are not eligible for more aggressive chemotherapy or stem cell transplantation. (5) At the low doses prescribed for the treatment of MDS, azacitidine acts as a nucleoside analogue that inhibits DNA methyltransferase, leading to DNA hypomethylation. (5) These molecular events activate tumor suppressor genes, which are thought to be silenced via hypermethylation, creating a favourable tumor-suppressing environment. (6) While azacitidine is generally safe, adverse events have been associated with its use. (7) Unlike other chemotherapeutic agents, these side effects do not result from cumulative dosage, but are most frequent and severe following treatment initiation, with marked improvement over time. (7) The most common hematologic toxicity is cytopenia, while the most common non-hematologic side-effects are related to the gastrointestinal system. (7) Mild fever and fatigue can also occur. (7) Rarer toxicities, such as respiratory dysfunction and necrotizing fasciitis, have been reported. (8, 9) Alnimer et al. reported a patient who developed respiratory symptoms one week after receiving their second cycle of azacitidine and was diagnosed with organizing pneumonia, similar to our patient. (3) They also discussed six other known patients who developed OP following administration of HMAs. (3) Of note, four of them developed symptoms within the first two cycles of treatment. (3) Toxicities and adverse events after prolonged use of azacitidine are sparsely reported in the literature. One rare instance shows clinical progression of ischemic heart disease following 60 cycles of azacitidine. (10)

To our knowledge, this is the first patient reported to have developed symptoms and signs of organizing pneumonia after a long course (23rd cycle) of azacitidine. The following elements support a diagnosis of azacitidine-induced OP including exclusion of infectious, neoplastic, and medication-induced causes, temporal relationship between symptom onset and HMA administration, radiographic findings (multiple subpleural irregular nodules), histopathological results, and a favourable response to prednisone. Importantly, as there is no consensus on the optimal number of azacitidine cycles needed to treat MDS, treatment duration varies widely in the literature. One study examining patients with high-risk MDS found that a median of 14 cycles was necessary for those who responded positively to treatment. (6) While most patients showed a favourable response early on (after 6 cycles), optimal response was achieved only with continued use. (6) As such, continuous management of MDS with azacitidine is recommended for patients with strong response who do not experience adverse effects. (6)

We recognize that many of the side effects associated with HMAs typically occur early in the treatment course and that short courses of pharmacotherapy are responsible for most drug-induced cases of OP. (11) However, it is possible that the development of respiratory symptoms seen early in azacitidine treatment reflects an immediate, idiosyncratic injury and reaction, while the events in our patient resulted from cumulative toxicity, eventually reaching a threshold sufficient to cause pulmonary injury. We hypothesize that prolonged use of azacitidine may lead to gradual tissue accumulation and late toxicity. Delayed lung toxicity has been observed with other drugs. (12) In one case, a 64-year-old female was diagnosed with an OP secondary to amiodarone treatment, a medication she had taken for four years to treat atrial fibrillation. (13) Similarly, following long-term prophylactic treatment with nitrofurantoin for urinary tract infections, a 82-year-old female developed OP which improved after cessation of the antibiotic. (14) However, the potential for toxicity resulting from tissue accumulation after chronic azacitidine use has yet to be clarified. A phase-1 study reported no toxicity following azacitidine administration, although it included only 29 patients who had completed a median of six cycles for MDS, so the possibility of later, dose-related toxicity could not be excluded on this basis.

Another study examined mononuclear cells ex-

tracted from the bone marrow of patients newly diagnosed with MDS at baseline and after the fourth and eighth courses of azacitidine treatment. (16) Following treatment, the extracted mononuclear cells exhibited azacitidine-induced autophagy, a regulated, lysosome-dependent cellular degradation mechanism that plays an important role in acute and chronic inflammatory lung processes. (16) For instance, autophagy-associated proteins have been shown to be highly expressed in patients diagnosed with hypersensitivity pneumonitis. (17) To our knowledge, the specific role of autophagy in OP particularly in the context of azacitidine treatment has yet to be explored, but it represents a plausible mechanism of tissue injury that merits further investigation.

4 | CONCLUSION

We present a case of azacitidine-induced pulmonary toxicity in the context of MDS treatment. We posit that the destruction of alveolar epithelium leading to the development of OP following azacitidine treatment may conceivably reflect different mechanisms, including toxic accumulation and autophagy. This case highlights the importance for clinicians to remain vigilant for this rare but toxic side effect. More generally, physicians should bear in mind the potential for non-infectious etiologies, including drug-induced inflammatory conditions, when patients with apparent pneumonias do not evolve as expected.

5 | CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

6 | AUTHOR'S CONTRIBUTIONS

All authors read and approved the final manuscript.

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REFLECTION

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Healthcare in Her Shoes

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ABSTRACT

Women's reproductive health has been the subject of debate for decades and the surrounding controversy does not appear to be dissipating any time soon. Thousands of articles are published annually on the topics of abortion, female sterilization, their associated ethical dilemmas, and the disparities that women face in the healthcare system. Although we have made great strides towards equitable healthcare, I would argue that women still face a disproportionate degree of stigmatization, bias, and unethical policy when it comes to their reproductive health. This essay highlights fictional but realistic examples to illustrate this ongoing discrimination, followed by an evidence-based discussion which proposes the potential roots of the discrimination and describes the harms associated with stigma and bias in this setting. Broadcasting these issues and encouraging medical professionals to think about them allows disparities to be more greatly recognized, and more readily dismantled.

KEYWORDS
Reproductive Health, Abortion, Sterilization, Women

1 | EMMA & STERILIZATION

Emma is a 25-year-old graduate student from a rural community in Canada. Emma's personal interests include art, baking, and philosophy. She has many plans for her future, some of which include travelling to Europe, writing a novel, and pursuing her dream career of becoming a lawyer. Emma has two sisters and a current long-term relationship – a boyfriend of four years to whom she hopes to one day be engaged. She has always known that she does not want children. She is sexually active and takes an oral contraceptive pill daily to prevent pregnancy but finds she often forgets to take it, and this produces a great deal of stress for her. Though she has consulted with her physician about her options, she is not open to the available contraceptive alternatives. Other contraceptive options include an intramuscular injection, an intravaginal ring, or an intrauterine device, but they all seem too invasive to Emma. Additionally, she does not feel comfortable using condoms or other barrier methods as her sole method of contraception. At this time, Emma reports being tired of the worry and fear surrounding unwanted pregnancy, and mentions she is not comfortable with the idea of having to undergo an abortion in the event she does become pregnant. Thus, following a long period of careful thought, Emma sched-

ules an appointment with her family doctor to discuss tubal ligation.

Tubal ligation is also an invasive procedure, but Emma thinks it will be worth it to not have to worry about contraceptive medications or their side effects, and to know that she will not become pregnant if she continues to have sex with her boyfriend. Emma called her doctor's office and obtained a consultation appointment for later that month. Emma's doctor, Dr. Matthews, is a general practitioner in his late 40s and has been overseeing Emma's health since she was a teenager. It is evident to Emma that Dr. Matthews cares about her well-being and she has always felt he provided her with the best possible care. Several weeks went by and the date of Emma's appointment rolled around. Emma stepped into the doctor's office and was greeted warmly by Dr. Matthews before jumping into their discussion on tubal ligation.

"Do you understand that tubal ligation is often irreversible?" Dr. Matthews inquired gently. Emma began nodding in understanding before her doctor had even finished his sentence. She responded, "I have done my research into this quite thoroughly".

Dr. Matthews hesitated before presenting his next question: "can you tell me a little bit about how you came to this decision?". Emma was prepared for this question too and promptly responded that the worry and stress of possible pregnancy often affected her ability to study and impaired her sleep.

Dr. Matthews listened intently as Emma spoke, but the confusion that remained on his face suggested that his question had not entirely been answered. "I mean, how did you come to decide that you don't want children?", he rephrased. Before Emma could counter, the doctor went on to question how thoroughly she had thought about this decision. Emma felt that it was a fair question as the procedure is potentially permanent, but admittedly did not anticipate being asked about how she came to her decision about children. She replied that she had always known. Dr. Matthews remained perplexed; he leaned toward his patient with concern in his eyes, "Emma, I don't think you understand the gravity of the decision you are trying to make here".

Now, it was Emma's turn to be confused. "I've always known that I don't want children. I simply don't want them – what more is there to it?", she asked. Dr. Matthews leaned back in his chair and sighed in mild frustration, "but how can you know that?". At this point, Emma did not know what to say. Dr. Matthews continued, "I mean, you're so young, how could you possibly know with certainty that you don't want kids?". It was clear to Emma that this question was rhetorical. Dr. Matthew's tone continued to exemplify concern for his patient, but the nature of his questions suggested resistance to Emma's request for sterilization. Advocating for herself, Emma transitioned the conversation towards the medical consultation she had hoped for and asked if the procedure was unsafe for her to undergo. "Is there another reason I shouldn't be considering this?", she asked. At this question, the doctor sat upright in his seat and in clear exasperation, implored "have you talked to your boyfriend about what he wants? How would your future husband feel about this?".

The case of 25-year-old Emma seeking tubal ligation is representative of the experiences of many women who are denied tubal ligation by their doctors. Reasons for rejection often include age (women are judged as being too young to make a decision of this nature), fear of regret, or concern for a future partner's desire to have children. (1, 2) A case series of women seeking tubal ligation conducted by two Ontario physicians found that many women were referred from their initial point of contact (abortion clinics, primary care providers, and gynaecologists) to other providers on the basis of hospital limitations or personal conscience. (3) The study patient's records documented that many women had experienced prior difficulty in obtaining the sterilization procedure. (3) If we go back in time a mere 50 years in the United States, obstetrician-gynaecologists would multiply a woman's age by her parity to determine if she could qualify for sterilization. (4) If the product was less than 120, the woman was deemed ineligible. (4) At this time, several states required spousal consent for a woman to obtain sterilization, meaning that a woman could not access any kind of tubal ligation procedure without the permission and signature of her husband (if she was

unmarried, her father's signature could have been required). (5) The double-standard seems flagrant here. To this day, the stigma surrounding male sterilization is arguably minimal compared to that of female sterilization. One might contend that this is because vasectomies are reversible procedures where tubal ligation is permanent, but this is not entirely correct. While rates of pregnancy following reversal are generally higher with vasectomies, a study assessing rates of successful pregnancy in women (mean age of 32) following tubal ligation reversal found the rate to be over half at 56%. (6) A separate study assessing rate of pregnancy in women (mean age of 31) whose partners had undergone vasectomy reversal found the rate of pregnancy to be 72.2%. (7) Evidently, successful pregnancy following tubal ligation reversal is possible, and despite the common misconception, pregnancy following vasectomy reversal is not a guarantee. That is not to say that physicians should not carefully consider the appropriateness of tubal ligation in their patients, or that it is unreasonable for a doctor to present the risks and potential for regret to their patients seeking this procedure. A discussion of this nature should certainly be had, but provided that there are no contraindications, a woman should not be denied sterilization because she is, for example, currently without children, or because her future partner(s) may object. Further, a woman's decision to become pregnant and have a child or not should be her own to make. Her partner's opinion may be of considerable value to her in making this decision, but such matters are for her to manage personally, and not the responsibility of her healthcare provider. The eligibility policies mentioned above have since changed, but significant barriers to a woman obtaining sterilization still exist. Many physicians continue to be apprehensive about performing tubal ligation, and the causes for their hesitation reflect age-old ideas about a woman's value to society, and more specifically her role in childbearing.

The fictional scenario that I have presented through the character of Emma illustrates the unconscious bias at play that hinders a woman's access to sterilization. Why is the doctor hesitant to agree to Emma's wish to undergo tubal ligation? The doctor raises concern around Emma's age and suggests she is too young to know that she does not want to have kids. Emma is 25 years old. A 25-year-old in this country does not face any age-related limitations in any setting – a 25-year-old can rent a car or a hotel room, hold more than one university degree, independently move to a new country, choose a life partner under the eyes of the law and, her health and other variables permitting, can then decide to give birth to as many children as she wishes. Why is it that when a 25-year-old declares she is ready for marriage and children that she is met with societal praise, but when she declares she is certain that a life with children is not what she wants, she is met with disbelief? The age need not be set at 25 either – people do not doubt young girls or teenagers when they claim that they are sure they will one day want kids. A double standard clearly exists here. It may be thought that the younger a woman is, the greater the risk that she may regret her decision to undergo sterilization later in life – an appropriate consideration. This segues into the ethical dilemma surrounding regret in women undergoing sterilization procedures. Research has been conducted regarding how often women are regretful of their decision to undergo tubal ligation. One study found the overall 14-year cumulative probability of a woman obtaining tubal ligation reversal to be 1.1% (8). The researchers also determined the 14-year cumulative probability of a woman requesting information on tubal ligation reversal to be 14.3%. (8) This data suggests the majority of women do not regret their decision to undergo tubal ligation. Notably, the study observed that the younger a woman was when she underwent tubal ligation, the greater the likelihood that she would later request information about reversal. (8) Therefore, it would be reasonable for clinicians to consider that the potential for regret is greater in younger women and to counsel their patients accordingly. However, a woman should not be denied the procedure based purely on age. It would make little sense to force a woman to wait until she is in her mid 30s or 40s, for example, to access sterilization, at which point her most fertile years would be behind her. On the subject of regret, consider that a similar argument surrounding a change of heart could be applied

to a woman electing to undergo other irreversible surgeries (such as cosmetic surgery, for example). While sterilization cannot be equated to other surgical procedures, I propose this comparison to highlight the disproportionate fixation on the potential for regret that exists in the setting of female sterilization. If a woman is knowledgeable of the risks, understands her options, and wishes to proceed (i.e. has made an *informed* decision), to deny her sterilization on the grounds that she may regret her decision later in life is not only paternalistic, but beyond medical purview. In the setting of other irreversible medical procedures, the informed decision to follow through ultimately lies with the patient. Why should it be different in the context of female sterilization? As I have mentioned, it is important to counsel patients on the potential for regret and to possibly be prepared to offer psychological support in the event that regret occurs, but this exaggerated apprehension in providing women with access to sterilization may serve as a barrier to care.

The issue that remains in Canada is predominantly that of an unconscious bias rendering physicians reluctant to provide women with sterilization procedures. Personal physician bias should cease to play a role in a woman's access to reproductive healthcare, and a woman who otherwise qualifies should not be denied access to sterilization on the basis of perceived naivety.

2 | CARRIE & ABORTION

I now move to the example of Carrie, an 18-year-old woman from the city of Birmingham in Alabama, USA. Carrie recently graduated high school and will soon be attending the University of Alabama where she will be majoring in biomedical sciences. She is hoping to one day work in healthcare but is not yet decided on which profession she would like to pursue. She will be paying for her university education exclusively through a line of credit and government loans. Carrie was raised by a single mother and has one older brother. She has a large friend group that she graduated high school with which further bolster her support system, and although she is not currently in a relationship, she identifies as heterosexual. In the summer, Carrie works at a coffee shop in the city. Her shifts begin quite early in the morning and over the past few weeks, Carrie has noticed that she has been feeling nauseous when she gets up to get ready for work, even vomiting a couple of times. Three weeks prior to the onset of her nausea, on the night of her prom, she had sex for the first time and did not use protection. This morning, she couldn't keep her breakfast down before work and it dawned on her that there was a real possibility that she could be pregnant. She decided to stop at the drugstore nearest her house on her way home from work to pick up a pregnancy test.

Carrie began to feel very uncomfortable as she entered the women's health section of the drugstore. A wave of anxiety washed over her as she scanned the aisle for the test that would best apply to her. She was confused by all the different boxes, labels, and timeframes for the tests, but did not feel comfortable asking the pharmacist for help. When a front store worker passed her in the aisle, she reflexively ducked her head in shame and skittered away from the area where the pregnancy tests were located; she grabbed a box of tampons off the shelf and tucked them under her arm. The worker didn't seem to notice Carrie's odd behaviour and turned the corner into another aisle. Carrie darted back down the aisle and grabbed the first pregnancy test she could find; she noted the test read "early response" and felt that was good enough. She rushed to the self-checkout and, still quite embarrassed, scanned her items and tossed them in a bag as quickly as she possibly could. When she got home, she hurried up the stairs to the bathroom without saying hello to her mother. She threw the plastic grocery bag on to the floor at her feet, and felt her heart begin to beat rapidly in her chest. Her breathing quickened as she contemplated the prospect of pregnancy, what it would mean for her future, and what her mother may think. She knew that she would not be able to afford a baby, and that her family did not have the resources to help her. She carefully followed the directions written on the pamphlet that came with the pregnancy test. The instructions stated that it may take a few minutes for her results to become clear. She lowered herself onto the cold laminate floor and

watched the analog clock in the corner of her bathroom anxiously. At the end of the wait period, she picked the test up from the bathroom counter and closed her eyes tightly before looking at the test result. After a painful 30 seconds, Carrie opened her eyes. The test result was very clearly positive. She quietly wept on her bathroom floor before slinking away to her bedroom and crawling under the covers of her bed. She went on to cry herself to sleep as she embraced what she perceived to be the beginning of her terribly bleak future.

The *Human Life Protection Act* was enacted in 2019 in the state of Alabama, USA. (9) This bill was passed in both chambers of the Alabama Legislature, and states that any physician who performs an abortion could be subject to life in prison. (9) The bill bans abortions at any stage of pregnancy and fails to recognize its necessity under even extreme circumstances. (9) A preliminary injunction has delayed its implementation, but were it to be implemented, women like Carrie would not be able to access abortion at all and would be forced to carry out their pregnancies. (10) States like Alabama are not alone in their pursuit to ban abortion access. Extreme abortion bans are being proposed all over the United States of America, among other countries around the globe. (11) The leak of a draft decision by the supreme court of the United States which occurred just this past month serves as concrete evidence of this very fact. (12) The draft outlines the supreme court's intention to overturn the landmark Roe v. Wade – a law that has protected a woman's right to an abortion since 1973. Evidently, an extreme abortion ban is on the horizon in Canada's neighbouring country. This is a reality that cannot be ignored by Canadians; American policies are not without influence in our country and conceivably set a precedent within Canada. (12) What could a lack of access to abortion mean? Limiting access to abortion may actually lead to a rise in unsafe abortions. One study from 2009 found an association between restrictive abortion laws and the rate of unsafe abortions. Researchers observed that abortion related deaths are much higher in countries with laws that restrict access to abortion, and that when abortion laws are relaxed, the rate of unsafe abortions drops dramatically. (13) For example, in South Africa, following legalization of abortion in 1998, the abortion mortality ratio dropped by 91% in just 3 years. The study reports that similar trends were observed in other countries. (13) The evidence suggests that restricting access to safe abortion creates an increase in abortions which are associated with greater physical harm. Of note, the methods through which women complete unsafe abortions involve the ingestion of toxins, infliction of abdominal injury, or direct trauma to the vagina, while the most common causes of death related to unsafe abortion were found to be genital trauma, sepsis, hemorrhage, infection, and necrotic bowel. (13)

Carrie represents one of many different types of women who may reasonably seek an abortion. She is 18 years old with desires to pursue a higher education and, while she may one day want a family, strongly feels that now is not the time for her to raise a child. Financial stressors mean that it is not feasible for Carrie to follow through with her current pregnancy. A 2013 study which sampled nearly 1000 women from 30 abortion facilities in the United States found that the two most common reasons to seek an abortion were financial stressors and timing. (14) Thus, I chose to share the story of Carrie because I feel it is representative of a realistic and prevalent case in which a person could want to terminate a pregnancy. However, it is important to acknowledge that there are many different circumstances that may lead a woman to seek an abortion. Consider the case of a young girl who is molested and raped by a relative, only to become pregnant with his child. Under the US laws proposed in 2019, any doctor who agrees to conduct an abortion for the victim of rape and incest could be subject to life imprisonment. (9)

Abortion is certainly a controversial subject, and there understandably exists a spectrum of opinions surrounding when it is reasonable to access abortion. The safety of these procedures at various time points throughout pregnancy should be considered, and the decision to undergo abortion should involve some contemplation. However, provided that a woman has discussed the benefits and risks with her healthcare team, deliberated the decision carefully, and decided to move forward with abortion, provider bias and politics should

not stand in the way of her right to this form of healthcare. This is an issue of bodily autonomy; when it can safely be avoided, women must not be forced to follow through with unwanted pregnancies. I would argue it is unethical for our governments to restrict which healthcare is and is not accessible to women when we have the professional and financial resources to provide this care.

If nothing else, the stigma surrounding abortion must end. Despite being a commonly sought procedure – around 73 million induced abortions are performed every year worldwide – abortions are a clandestine topic. (15) Women who undergo abortions are pitied, and judged, and the air of controversy that surrounds the procedure likely contributes to some of the misinformed perspectives of the public and our policy makers. For many women, the decision to get an abortion is not cut and dry. For some, it is a very stressful experience requiring days and weeks of contemplation. To add insult to injury, abortion clinics are notoriously riddled with protestors, making a potentially overwhelming appointment almost unbearable. What other medical procedure is so heavily stigmatized? This stigma likely contributes to unconscious bias among the public and the healthcare community which creates a barrier to abortion access.

3 | IN CONCLUSION

There are many other disparities that exist between men and women in the context of healthcare. Though they may not be immediately apparent, the issues exist and have real consequences for women in Canada, USA, and other countries around the world. Access to sterilization and abortion are only two examples, which I have selected to highlight because they are a major part of modern public debates and effectively demonstrate the issues of stigmatization, unethical law making, and unconscious bias that exist in our medical systems today. Understandably, these subjects are complex and difficult to navigate. My aim is to validate the frustrations of the real women who, like the fictional characters of Emma and Carrie, have struggled to navigate the healthcare system, and to raise awareness of these issues to health providers so that they may recognize their own biases in their pursuit to provide the best possible care. Women should experience a healthcare system that is as ethical, unbiased, and unprejudiced as is realistically possible.

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REFLECTION
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Reflections on Medical Education: An Innovative Near-Peer Led Initiative Using Online Media to Teach the Neurological Exam

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ABSTRACT

The move to virtual learning due to the COVID-19 pandemic has resulted in fewer opportunities for medical students to participate in bedside teaching and encounter patients presenting with characteristic clinical findings of various neurological disorders. We describe an interactive, peer-taught learning-session on Zoom teleconference wherein upper-year students developed learning cases using online videoclips of neurological examinations and corresponding findings. A post-session survey revealed an overwhelmingly positive response, especially regarding the sessions' case-based and peer-taught structure. Overall, considering the dual benefits of peer-teaching, and the opportunity to see a wide range of findings from the videos, this initiative may be a valuable supplemental learning activity for existing undergraduate neurology rotations.

KEYWORDS
Medical Education, Neurological Exam, Videos

The move to virtual learning due to the ongoing COVID-19 pandemic has resulted in fewer opportunities for medical students to participate in bedside teaching and encounter patients presenting with characteristic clinical findings of various neurological disorders. The use of video clips demonstrating positive examination findings has significant advantages in medical education. In addition to providing an experiential component to learning when in-person opportunities are limited, (1) incorporating videos into lectures has been found to help students better visualize concepts, apply knowledge, and increase acquisition of clinical skills.

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(2) In neurology education, supplementing face-to-face teaching sessions with blended learning that makes use of videos showing examination techniques has been effective in teaching the neurological examination to medical students. (3) The use of videoclips integrated into learning modules and lectures have also improved trainees' ability to identify epileptic seizures, read electroencephalograms, and enhance knowledge of various movement disorders while providing standardized virtual exposure to patients and learning. (4–6) Peer-teaching has been shown to be effective in promoting learning in various components of medical neuroscience courses and neurology clerkship, while also having a dual effect whereby student-teachers benefit academically from doing the teaching. (7, 8)

At McGill University, second-year medical students complete a 2-week neurology course in which they refine their neurological examination skills and develop an approach to diagnosing common neurological problems. In response to learning gaps created by the pandemic, we developed a peer-taught online learning activity using video clips of patients aimed at providing students with opportunities to observe components of the neurological examination, identify abnormalities, and develop hypotheses for lesion localization. We designed and delivered case-based learning sessions over Zoom teleconference for 180 second-year medical students using videos of the neurological examination performed on patients with detectable abnormalities. Videos were selected from public sources (e.g. YouTube) by two third-year medical students and reviewed for quality and accuracy of examination technique by a staff neurologist. Videos were then categorized and corresponding interactive cases were created using the Medical Council of Canada learning objectives (e.g. Diplopia, Stroke, Ataxia, Seizures, etc.) as a content blueprint. A total of 8 topics were divided across two 2-hour learning sessions for approximately 60 students at a time. The topics presented included seizures, vertigo, diplopia, weakness, sensory disturbance, ataxia, movement disorders, speech, and language disorders. During these sessions, the student-tutors presented cases with corresponding videos and encouraged students to share their observations using the chat function and attempt to localize lesions based on the identified abnormalities. The staff neurologist was present to provide expert opinion to supplement the student-tutors' explanations. Following the sessions, we invited students to share their feedback via an anonymous voluntary survey.

We received 39 out of 180 possible responses. Most students agreed that the peer-learning aspect was effective (85%), that the videos were useful in case-based

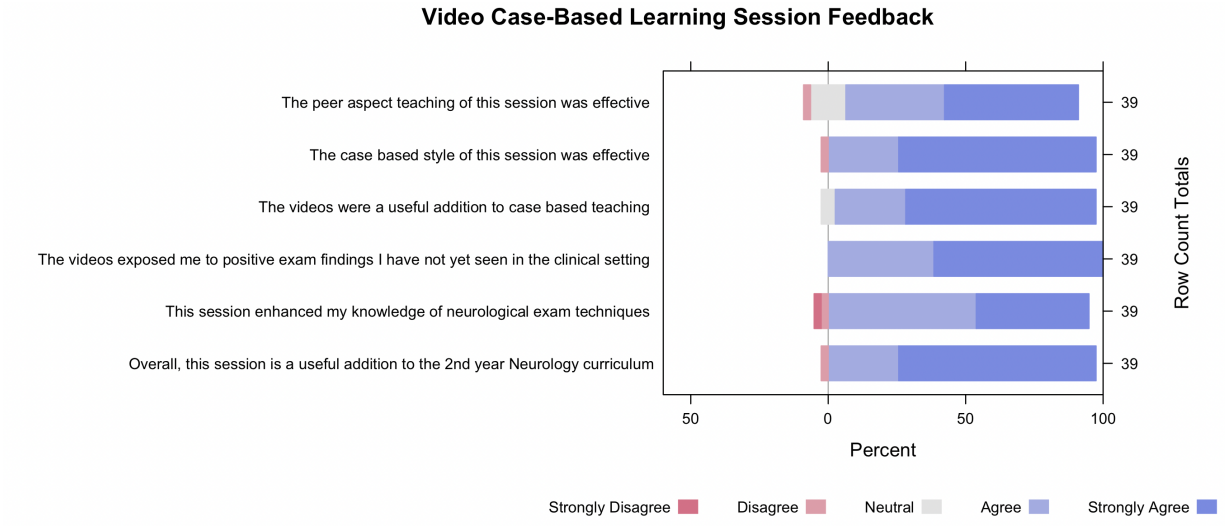

FIGURE 1 Session feedback survey responses for N = 39 participants

teaching (95%), and that the sessions enhanced their knowledge of examination techniques (95%) (Fig. 1). All respondents indicated that the videos exposed them to findings they had not yet seen in the clinical setting (Fig. 1). Overall, this format to teach neurological examination and neuroanatomical localization received positive feedback from students and was successful at enriching the clinical learning experience. While this session cannot replace the hands-on experience gained during in-person clinical rotations, it did provide certain advantages. It offered a baseline standardized experience for all students, whereas exposure to different neurological disorders may otherwise have varied based on chance and site-related characteristics. Students had the opportunity to observe a complete range of common and "rarer" findings, from hyperreflexia to internuclear ophthalmoplegia. The peer-teaching format allowed for information to be presented in a relatable manner appropriate to the students' training level. The ability to replay the videos with commentary and expert insight, a feature not necessarily available in the clinical setting, was valued greatly. Given this teaching format's simplicity and the public availability of materials used, it can be cost-effectively implemented as a supplemental learning activity for existing undergraduate neurology education programs, especially those intending to maintain a hybrid (on-line/on-site) educational format in the post-COVID era. It may also be of particular value for those programs that lack mandatory clinical neurology rotations. Future directions may include using videos filmed at individual academic institutions to further enhance and ensure quality of materials.

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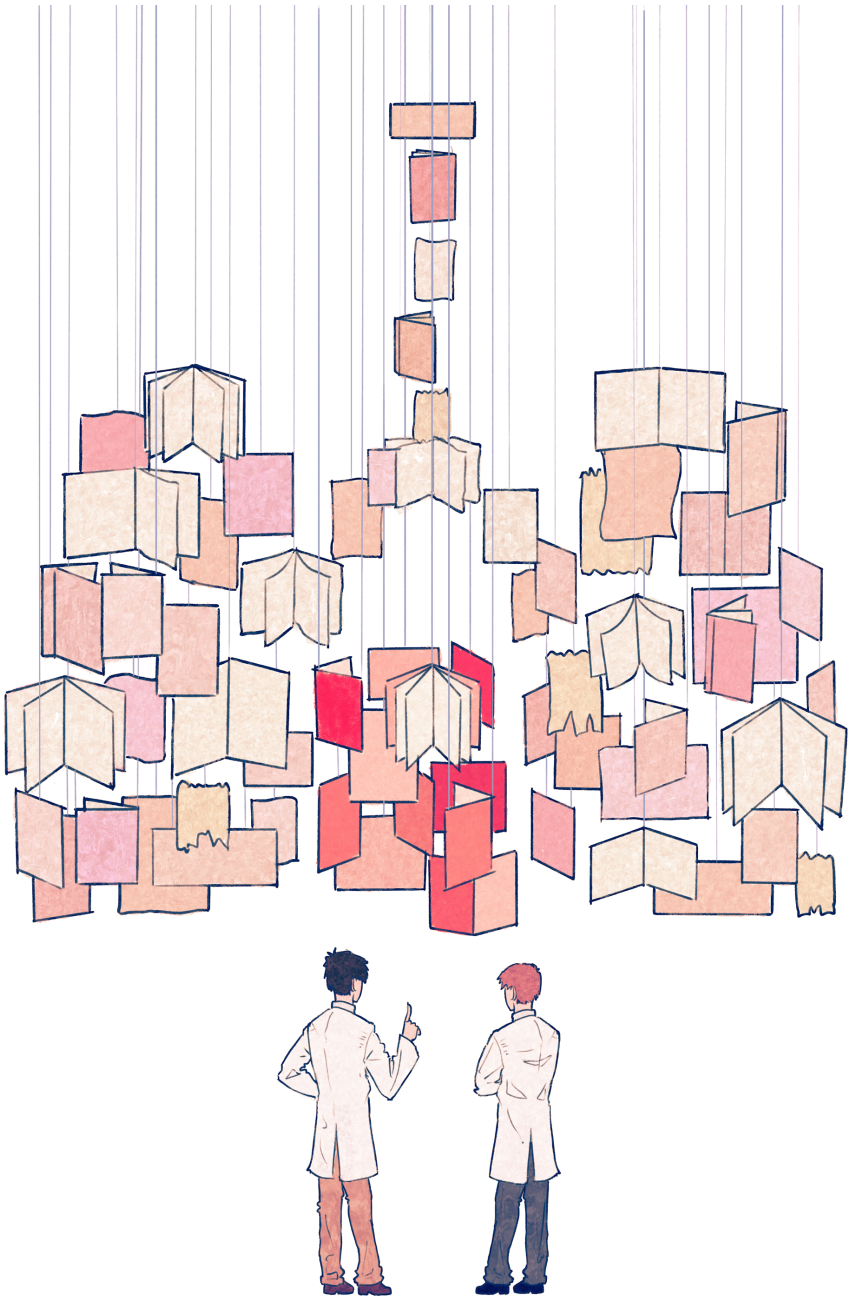
NARRATIVE REVIEW



NARRATIVE REVIEW
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Effects of Visual, Auditory, and Combined Cues on Human Movement and Brain Regions Involved in Perception Action

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ABSTRACT

Background: Sensory stimuli such as visual and auditory cues are important to perceive our surroundings accurately. The effects of visual, auditory, or combined cues to modulate human movements such as walking are well-reported in the neuroscience literature. To date, no comprehensive report has summarized these findings.

Objective: The primary aim of this narrative review is to synthesize the literature on the interaction of visual, auditory, and combined cues of movement, as well as to present specific brain regions involved in perception-action.

Methods: A comprehensive review of the literature of published scientific work was conducted using PubMed and Google Scholar. Only English language articles that reported on visual, auditory, or combined cues and human movements were selected. Literature that included biofeedback was excluded.

Results: The literature suggests that visual and auditory cues have the potential to induce deviation in human movements. The posterior superior temporal sulcus and mirror neuron networks are shown to be critical in multimodal sensory integration.

Conclusion: This review presents some important theoretical models and outlines the brain regions involved in sensorimotor synchronization in human movement. Individual visual, auditory, or combined cues may have the potential to develop therapeutic interventions in the rehabilitation of movement disorders.

KEYWORDS

Visual cue, Auditory cue, Synchronization, Mirror neuron network

1 | INTRODUCTION

Humans function within a multisensory environment, where sound often accompanies action (clapping, crushing a can, or hammering). The most common sensory stimuli are visual and auditory signals, which, when combined, amplify the perception of surrounding objects and movement. (1) It is well established that the response (or reaction) is optimal with multisensory stimulation instead of individual stimulus. (2) Multisensory integration involves complex sensory interactions that help to perceive the environment more accurately. (3) The perceptual system integrates the audiovisual information to provide a comprehensive picture for optimal functioning within multisensory surroundings, evident by a decrease in reaction time to multisensory stimulation. (4, 5) Additionally, multisensory signals provide information about the environment that would be insufficient when obtained from anyone sensory signal in isolation. (6)

The perceptual-motor system has been studied for over half a century. This narrative review will present the interaction of sensory cues and movement as well as brain areas involved in perception-action. The review will also provide an overview of the literature on unintentional synchronization. This comprehensive review is divided into three sections: Section 1 will present the effects of visual, auditory, and combined cues on human movement; Section 2 will highlight brain region activation in response to sensory cues and the mirror neuron network, and Section 3 will discuss unintentional synchronization.

2 | METHODS

Only the English language literature related to sensory cues and human movement was searched in PubMed and Google Scholar. A pragmatic search strategy approach using a saturation matrix typically used in qualitative research was deployed, whereby the search was terminated once the same articles appeared. The aim of this work is not to present a reproducible search but to present the breadth of information on a topic. Literature in the field of biofeedback was excluded.

3 | EFFECT OF INDIVIDUAL SENSORY CUES ON MOVEMENT

3.1 | Visual Cue

Visual stimulus is the most dominant and ecologically salient source of information during walking. (7-10) Johansson et al. (1973) conducted a pioneer study to determine the ability of the visual system to recognize biological motion. In his study, the visual stimulus was constructed using a point-light attached to human joints the observers were asked to identify. (11) The study demonstrated the ability to interpret visual signals related to human movements in order to make meaningful inferences using past knowledge. We are constantly exposed to real multisensory stimuli complex scenes , so the perception of envirnonment complex scenes would differ from the relatively simple point-light design in the study. Moreover, it is shown that complex visual scenes result in distributed activations of different brain regions. The ventral temporal cortex (lateral and medial fusiform) is activated in response to video displays as opposed to point-light images. (12) The ventral temporal cortex is also responsive to static and moving human stimuli and objects (such as a saw or hammer) in motion. In contrast, the lateral temporal cortex is specifically responsive to moving complex stimuli such as articulated human motion. (12) This differential neural activation arose from the additional information in video display, such as form, color and texture that was absent in point-light display. Furthermore, the perception of motion is also affected based on the observer's position. It is shown that the perception of motion of the point-light images differs between a static observer posture (standing on a treadmill or sitting on a static bicycle) and dynamic self-motion, such as healthy individuals walking on a treadmill. (13) The perception of point-light images is least accurate when the observer walks than when sitting. (13) In research and clinical practice, visual cues such as laser light and stride length markings on the floor are often

used as a strategy to improve walking performance in people with Parkinson's. (14) Recently, a trial studied the use of visual cues such as steppingstones for the rehabilitation of post-stroke walking. (15, 16) The use of steppingstones displays as a visual cue in healthy elderly subjects was reported to positively affect gait parameters. (17) The steppingstone visual display was compared to metronome beats among adults during a treadmill walking task and showed that the visual information resulted in quick gait recovery in response to perturbations compared to auditory beats. (17) Visual cue displayed over the treadmill determines step length (and consequently step frequency within a range of walking speeds) and directs spatial position for foot placement. The disadvantage of visual cues such as steppingstones, flashlights, or stripes on the floor, is that the cues have no ecological meaning.

3.2 | Auditory Cue

Auditory system is a fast-processing sensory system that rapidly captures and extracts meaning from the received signals. (18, 19) Reaction time to auditory cues is faster by 20-50 milliseconds compared to visual or tactile cues. (18, 19) External auditory cues, such as metronome beats and music, are shown to have beneficial effects on walking in various neurological populations such as stroke, Parkinson's, Huntington's conditions. (14, 20-28) Unpredictable changes in auditory cue frequency provided by the metronome are shown to induce perturbation during walking in patients with stroke. (29, 30) This suggests that changes in the frequency of metronome sequences produces direct frequency entrainment capable of triggering instantaneous gait adjustments.

The critical aspect of rhythmic auditory cueing is the underlying rhythmicity or periodicity that enables auditory-motor interaction and also determines the strength of those interactions. (31) The auditory system is sensitive to time information and builds precise, stable time traces that acts as a motor template and helps individuals sync their movements. (31) The rhythmicity of the cue serves as an anticipatory and continuous external frame of reference. If the beats occur at regular intervals, there is a strong tendency to anticipate the next stimulus. This 'anticipation tendency' guides subsequent movement in advance. A stable auditory-motor synchronization is indicated by minimal variability in timing between the movement and the external cue. Steady-state auditory-motor synchronization is shown to occur within 2 to 3 repetitions of exposure to rhythmic metronome beats during finger tapping. (32) This ability of the sensory information from auditory cues helps to establish a stable synchronization pattern rapidly.

Monotonous metronome beats provide periodicity; this is in contrast to musical cues that are rich in other information such as melodicity. Auditory entertainment cues such as musical rhythms during a walking task in healthy young adults (33) and elderly individuals (34) resulted in reduced variability in synchronization compared to a metronome. Acoustic stimuli delivered as rhythmic music resulted in increased stride length and gait velocity compared to no cue stimuli or metronome conditions. (34) There is evidence that music-supported therapy has a beneficial effect in people post-stroke, as it provides an opportunity for the repetitive movement practice. (35)

Auditory-motor synchronization is well reported in the field of musical performance. Musical performance is a complex process that requires fast feedforward and feedback loops to rapidly process auditory, visual, and motor signals while referencing the learned sequence of musical output. (36, 37) Professional musicians are known to display precise auditory-motor synchronization. (36) Imaging studies in skilled musicians show brain activation in response to either auditory stimuli or passive finger movements, suggesting a co-activation phenomenon. (36) Auditory-motor coupling is defined as co-activation of cortical auditory and sensorimotor hand regions in either pure auditory or silent motor tasks. (38) Auditory-motor coupling is suggested to activate similar cortical networks both in trained and naïve musicians within 20 minutes of practice. (39-41) This suggests that music is able to establish a relatively fast coupling effect within a short span of exposure.

In addition, professional musicians display involuntary auditory-to-motor (listening to music – purely acoustic) and motor-to-auditory co-activation (silent finger movements – purely motor). (37, 38, 42-46) Similar brain activation is also seen with imagery of sound or music playing motor action (non-acoustic). (47-49) A well-trained pianist showed involuntary, without actual finger movements, activation of the motor cortex (M1)(42), bilateral supplementary motor area (SMA), the primary motor cortex (PMC), anterior cingulate gyrus and parietal cortex(50-52), on listening to piano music, compared to a non-trained musician; this suggests a strong coupling between perception and action. Recent studies showed activation in posterior superior temporal gyrus (pSTS) and ventral premotor cortex during entrainment of motor responses with auditory cues in non-musicians. (53)

3.3 | Combined Visual and Auditory Cues

Human visual and auditory systems are tele-receptive senses. This can be defined as a sensory system that receives and processes information from near and distant external environments and defines the origin of these sensations. (54-55) Perception of a scene depends on the concordance between the visual and auditory stimuli and should be temporally congruent in order to have a coherent percept, known as the Unity assumption. In other words, the more different sensory signals arise from a single source, the greater likelihood that the inputs would be combined to provide a coherent percept. For instance, women walkers produce a the sound of footsteps that suggest a feminine gender. (56-60) At the single neuron level, multisensory integration is defined as a statistically significant difference between the number of impulses evoked by a cross-modal combination of stimuli and the number evoked by the most effective of these stimuli individually. (61) The temporal congruency of visual and auditory stimuli is necessary for neural potentiation and is reflected in the magnitude of synaptic potential for congruent stimuli. (62) Thus, auditory and visual signals need to be meaningfully linked to each other and be temporally congruent for a coherent perception.

Sound signals can influence the perception of visual stimuli. A study presented variation in footstep sounds to young adults, resulting in an alternation of visual depth-perception of the point-light walker. The study showed that looming sounds paired with orthographic (facing the viewer) point-light walkers appear more looming, and similarly point-light walkers appear more receding (facing away from the viewer) when paired with receding sounds, compared to no-sound and stationary sound conditions. (55) Another study demonstrated decreased reaction time to the presence of a coherent point-light walker when auditory motion travelled in the same direction as the walker and increased reaction time when auditory and point-light walker motions travelled in the opposite direction. (59) Another group of researchers designed a task in which observers had to decide whether a periodically moving point-light walker had the same temporal frequency as a series of auditory beeps, which in some cases coincided with the footsteps of the walker. Performance in this task was consistently better for upright point-light walkers compared to inverted or scrambled walkers. (63) This suggests that individual auditory or visual stimuli can influence the the other stimulus's perception and that combined stimuli improve perception.

Among the various meaningful sounds in the environment, the sound of footsteps has a clear acoustic signal. Walking involves two distinct phases; a stance and swing phase, which are repeated periodically. The stance phase, which consists of heel strike and foot flat events has a distinct acoustic signal, while the swing phase has no acoustic signal. (64, 65) Human bipedal locomotion generates a stable regular footstep rhythm and a periodic motion of arms, trunk, and lower limb during normal gait. (66, 67) Besides, the sound of human footsteps carries a rich pattern of social information such as source - gender (68, 69), emotional state(68) and posture of the walker(70), walking surface(71), sole of footwear(68) as well as the temporal and spatial origin of sounds. (72) Also, footstep sound provides information about a dynamic human group, such as people walking in synchrony or one leading the other in pairs. (73)

Given these qualities, the sound of footsteps is termed as footsteps' acoustic signature in the literature.

Sensorimotor synchronization is a referential behaviour in which a motor action is performed in sync with an external predictable stimulus or event known as the 'referent'. (74) There are two possible aspects to external cueing; first, the external stimuli are isochronous in time (fixed interstimulus interval) and therefore stable and predictable; second, the interstimulus interval is altered (progressive up or down ramp-like changes or random) and therefore unpredictable. In the variable frequency beats, there is an increase in synchronization error, and thus a deliberate and conscious action on the part of the individual is necessary in order to sustain a stable synchronization state. (75) Synchronized state is said to occur when the response sequence of movement has the same time interval as the external stimulation with no phase deviation. (75) However, during a sensory-motor synchronization, there exists variability in movement performance which necessitates a continuous adjustment to an external rhythm. The error-correction can be brought about by modulating movement in-phase and period duration. (75) Rhythmic auditory stimulation provides an effective timing mechanism, based on individuals' ability to focus on the rhythm, detect time interval of external rhythm, process time information and consciously integrate it in ongoing movement sequence. It also involves the ability to detect errors during synchronization and take corrective measures. (76) For example, walking to a fixed-paced metronome, which is isochronous, involves the ability to predict the subsequent beat, plan movement in anticipation of the beat, and closely match movement to external beat pace. In case of asynchrony or an error, a correction of the next movement is consciously considered in the subsequent movements. Furthermore, sensorimotor synchronization is also dependent on the motor effector. For instance, finger or foot tapping involves muscle force, movement amplitude, and degrees of freedom that are small and limited. In contrast, walking involves large muscle activity with many degrees of freedom that need to be constrained with additional postural and balance demands to match the external rhythm.

4 | BRAIN ACTIVATION IN RESPONSE TO SENSORY STIMULI

The effect of the visual and auditory cue on movement is supported by neuroimaging research that has identified activation of certain brain regions in response to sensory stimulation. (77-89)

4.1 | Supra-spinal Regions

Multisensory neurons, specifically in the superior colliculus and cerebral cortex, have a receptive field that needs the stimuli to be congruent and in a close time frame in order to have an accentuated or super-additive effect (non-linear enhancement) that is, stronger than the sum of unimodal response. (3) Perception of congruent audio-visual biological motion (point-light walker and sound of footsteps) stimuli is reflected as activation in the posterior extend of the posterior superior temporal sulcus (pSTS), inferior parietal sulcus (IPS), (77-83) and premotor cortex. (84, 85) A study by Wuerger et al. (2012) demonstrated the role of ventral premotor cortex activation for congruent (same motion direction in auditory and visual modalities) than incongruent (different motion direction) biological auditory (footsteps sound) and visual motion (point-light walker). (86) Alaerts et al. in healthy adults using auditory (crushing of plastic bottle) and visual (action of crushing) cues, using transcranial magnetic stimulation, showed an increase in motor evoked potentials in the primary motor cortex to congruent audio-visual stimuli compared to unimodal and incongruent actions. (87) In addition to these regions, neurons in the superior colliculus also display a super-additive effect for simultaneous visual and auditory stimuli in animals. (2, 88) There appears to be a continuum in pSTS regions where neurons that respond to vision, auditory, and combined sensory signals(89) are activated in response to action versus non-action related stimulus. (90) Area pSTS is delineated as a robust structure in the perception of biological motion across most human(83) and primate studies. (91) The super-additive effect is also seen for social context and complex visual and auditory signals. (92) This may indicate its role in

deriving meaning from the biologically relevant events. The role of pSTS and premotor cortex in biological motion perception is also supported by a study in people with chronic unilateral stroke, which showed that lesions in superior temporal and inferior frontal (premotor) regions play a causal role in biological motion perception (walking, jogging, throwing activities) compared to age-matched controls. (77) The response in the premotor and parietal cortex is enhanced when the observer intends to perform the movement compared to passive observation. (93) There is yet another brain region that could explain the effect of sensory cues on movement: the mirror neuron network.

4.2 | Mirror Neuron Network (MNN)

A group of visuomotor neurons in the primate ventral premotor cortex (f5) and inferior frontal cortex, called mirror neurons, are activated on observation and execution of goal-directed hand actions like grasping objects as well as listening to action-related sound. (94, 95) In humans, MNN is shown to be present in the ventral premotor cortex, precentral gyrus, posterior part of inferior frontal gyrus, Broca's area, and intraparietal area, which activates in response to action observation and sound related to actions such as crushing of plastic bottle or ripping of paper. (79, 85, 96-100) This led to the hypothesis that perception-induced activation of movements may obey a 'whole-or-nothing' principle(96). For example, the perception of tearing paper evokes the action irrespective of whether it is heard, seen, or both, and is modality-independent(96). An alternate hypothesis is the shared 'modality-dependent' action representations, where the mechanism of perception-induced action retrieval is based on the simultaneous input of vision and sound describing the same movement. (101) Neuroimaging suggests that seeing actions activates the frontoparietal neural network, which is also active when performing those same actions(102, 103). There is evidence of motor cortex activation (increased motor evoked potentials) in the observer when viewing an action execution (for example, grasping an object) compared to seeing the object alone or movement alone. (104) The MNN activity occurs in response to action-associated sound, and this area is more likely to respond to ecological stimuli, such as the sound of footsteps than the metronome. The MNN is also hypothesized to be the site for self-agency, defined as a feeling of being in control and being the author of one's movement. (105) The network is implicated in its ability to differentiate voluntary induced self-motion from external action in environment. (105, 106) Lastly, observing someone's actions allows one to predict the possible movement pattern that one would have to generate in order to achieve a similar end outcome, which in other words, provides a first-person grasp of the motor goals(106). From the ideomotor perspective, the neural representation of action generated through observation is similar to that required to execute the same action. (107, 108) Moreover, mirror neurons and observation of gait share a similar neural substrate as motor execution, including the premotor cortex, SMA, basal ganglia, and cerebellum. (109-111) This suggests that sensorimotor tasks based on action observation, imitation, or execution involve complex activation patterns and goes beyond the activation of the cortex and subcortical structures. Therefore, by a mere act of observing an action, it is possible to bring about compatible effects in subsequent action execution.

The cerebellum plays an important role in motion detection and has been recently highlighted in neuroimaging studies. The rhythmic motor synchronization of finger tapping to progressively increased external rhythm shows activation in cerebellar regions (anterior cerebellar lobe, thalamus, cingulate area) and cerebral (intraparietal sulcus, lateral prefrontal, and bilateral dorsolateral prefrontal) regions in a positron emission tomography (PET) study(112). Also, finger tapping to random sequence rhythmic cues showed activation in parieto-thalamic and premotor activity. (112) This suggests that these cerebro-cerebellar connections play a possible role during rhythmic motor synchronization. Lastly, the cerebellum also has a connection to pSTS and possibly plays a role in motion perception. (113)

5 | UNINTENTIONAL SYNCHRONIZATION (SPONTANEOUS OR UNINSTRUCTED)

The studies that used external rhythmic auditory cueing strategy during walking tasks asked the participants to match their heel-strike to auditory cues as precisely as they could, thereby consciously engaging them to synchronize movement to the auditory stimuli. (21, 28, 30) As opposed to this conscious synchronization, there is literature supporting unintentional imitation in humans that is exhibited in daily life and thought to be necessary for social interaction and interpersonal communication. (114, 115) The unintentional imitation, mimicry or a sense of similarity occurs automatically without any intention or awareness. (116, 117) During an unintentional imitation of an action, the consequence of execution or feedback is not registered. Studies have shown that it is possible to influence the task performance during an unintentionally synchronized movement (finger tapping) by changing external rhythm (auditory cue that was modulated at 3%, 7%, and 20% of the interstimulus interval from baseline). (118, 119) In order for unintentional synchronization to remain below the level of conscious perception, the modulation of the external rhythm needs to be subtle and progressive, or else the modulated stimulus reaches a conscious level when the motor adaptations switch to the active response mode. (118) Neuroimaging using PET showed a switch in the activation areas from the ventral medial prefrontal cortex at 3% and dorsolateral prefrontal cortex at 20% modulation (when conscious perception occurs). (118) Similarly, a study by Oullier et al. (2008) involving spontaneous synchronization between partners during rhythmic finger movements showed that the movements become unintentionally coupled as soon as the visual information is available and that the synchronization persists when the visual input of the other's movements is occluded. (120) Thus, subtle modulation in external sensory cues not only influences the ongoing task, but the effect continues even after the external cue is removed. Similarly, several other studies have demonstrated subconscious modulation in motor sequence. A visual-motor conflict study presented participants with their own full-body real-time images as an avatar. The avatar was programmed to deviate during a goal-directed locomotion task. This manipulation showed that the individuals induce compensatory correction without conscious perception when the deviation was within 10-15° but beyond this threshold, conscious correction kicked in. (105, 121) Another study using auditory cues manipulated footsteps and footsteps-related sound by introducing a temporal delay in real-time and demonstrated that the stepping correction occurred without conscious awareness with delays less than 120 milliseconds. (122) Furthermore, it has been suggested that energy cost may play a role in unintentional entrainment. (123) The subconscious negotiation of a shared stepping pattern between partners was demonstrated during a side-by-side treadmill walking task in healthy adults. This supports unintentional interpersonal synchronization in the absence of conscious effort compared to forced entrainment; however, the effect was transient and weak. (123) A similar effect was demonstrated during an overground walking task involving pairs that walked side-by-side while holding hands (tactile), visual (presence of another person), and auditory (sound of heel strike). (124, 125) Thus, external cue appears to affect one's behaviour without conscious perception. Unintentional synchronization shows activation in the orbitofrontal, ventrolateral, ventral prefrontal cortex, and lateral cerebellar hemispheres; whereas conscious adaptation activates the dorsolateral prefrontal cortex, anterior cingulate gyrus and premotor cortex(118), and these sites share some common regions with the mirror network. (126)

6 | CONCLUSION

This review summarised both the theoretical and brain mechanisms that underlie the effects of visual and auditory cues separately and when presented together. The use of combined visual and auditory cues that are biological in nature as well as unintentional synchronization may have a potential application in the field of rehabili-

tation.

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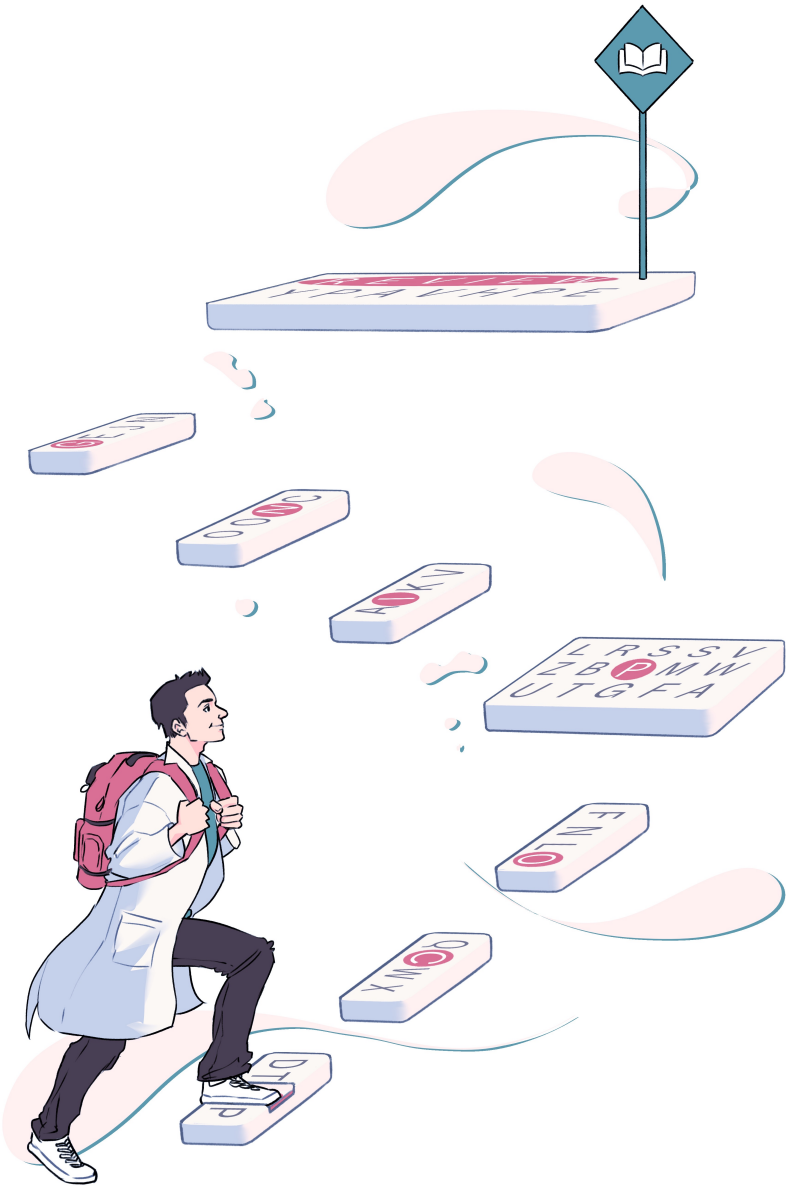

SCOPING REVIEW
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Children's Health-Related Experiences in India: A Scoping Review

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ABSTRACT

Background & Objectives: The perspectives of children have becoming increasingly emphasized in healthcare research and practice in order to facilitate children's inclusion, participation, and decision-making in matters related to their health. In India, however, little is known about children's views regarding their health despite the various health challenges and ethical concerns they may face, such as poverty, malnutrition, and gender inequalities. The aim of this scoping review is to explore children's health-related experiences from their own perspectives in India from 2000 to 2020.

Methods: Five online databases were searched. Three independent reviewers screened articles for inclusion. Included texts were analyzed using thematic synthesis, which involved extracting and descriptively coding data, categorizing/grouping codes by similar topics, and comparing and contrasting topics to generate descriptive themes. The scoping review was reported using the PRISMA-ScR checklist.

Results: Fifty-two articles were included, and five descriptive themes were identified. The articles typically overlapped in themes, which related to children's health-related experiences (n=38), emotions (n=19), and knowledge (n=15); the impact of illness on children's lives (n=41); and children's ability to communicate their needs (n=12).

Interpretation & Conclusions: We identified the need to tailor research designs to better elicit children's perspectives and provide comprehensive health education for children and families in India. This scoping review helped to highlight gaps in healthcare policy, practice, and research, providing a starting point for more focused investigation into children's health-related experiences in India.

KEYWORDS

India, Children's healthcare, Scoping review, Child ethics, Lived experience

1 | INTRODUCTION

Childhood ethics is an emerging field of inquiry with a paucity of research examining health-related experiences from the child's perspective. (1) A child's perspective is defined as a direct view on "conditions, experiences, perceptions and actions, based on what he or she finds important". (2) Children's perspectives are being increasingly utilized to promote their participation, inclusion, and agency within fields such as education, health, and law. (1) According to the World Health Organization, (3) health extends beyond the simple absence of disease and encompasses physical, mental, and social well-being. The concept of whole person well-being involves various domains of one's life, including physiological and psychological processes, as well as physical, sociocultural, and spiritual environments. (4) Therefore, an individual's well-being can be deeply affected by their interpretation of day-to-day events, which may align with or go against personal values and beliefs. (5)

Ethics play an integral role in health care and services as healthcare providers must make decisions in patients' best interests by seeking to reduce harm and maximize benefit. The act of genuinely hearing, acknowledging, and addressing a patient's voice is therefore critical toward understanding a child's particular experiences, aspirations, and concerns. This helps to inform an individualized determination of their best interests, which should orient treatment decision-making and is particularly relevant for children who are vulnerable given their development, status as minors and limited legal decision-making capacities within healthcare contexts. (6) However, children with chronic illness have reported being excluded from decisions, discussions, and actions related to their care. This compromises clinicians' and parents'/caregivers' abilities to understand children's perspectives and in turn, their best interests, while leading to feelings of frustration, anger, and fear in children. (7) Nonetheless, young people have clear ideas regarding how their treatment can be improved (8) and have expressed desires for their voices to be heard in healthcare settings. (9) Given that self-management capacities and self-efficacy are positively correlated with health-related quality of life for children with chronic illness, (10) eliciting children's perspectives during care may support a sense of control over their health, improve their care, and enhance their quality of life. For these reasons, seeking to understand and render children's perspectives visible in health-related literature is an important step towards advancing the field of childhood ethics. Despite increasing recognition of the children's voices in healthcare research and practice, research related to this topic has been geographically limited. In turn, children's perspectives regarding their health are still unclear in many low- and middle-income countries such as India. India has the largest child population (0 to 18 years) in the world but is also disproportionately affected by poverty, malnutrition, poor access to healthcare, gender inequalities, and other health and ethical concerns. (11–13)

This study presents a scoping review of health-related literature from the child's perspective in India. This review was conducted by VOICE (Views on Interdisciplinary Childhood Ethics), a group of researchers and community partners committed to advancing the field of childhood ethics and global child health. The goals of this scoping review are to: a) improve our understanding of children's health-related experiences by exploring the perspectives of children in India with illness, disability, and/or physical symptoms within empirical studies; and b) identify areas for further empirical research and examination of ethical concerns.

2 | METHODS

2.1 | Study design

We conducted a scoping review, also known as a knowledge synthesis design, allowing us to summarize a range of evidence and identify the key concepts underpinning a complex, new, or unfamiliar research topic. (14) The approach of a scoping review is broad and uses purposive sampling to identify evidence and gaps in the literature without a quality appraisal step. (15) The six steps of the scoping review framework are: (a) identifying the research question; (b) identifying relevant stud-

ies; (c) study selection; (d) charting the data; (e) collating, summarizing, and reporting the results; and (f) consultation. (14) Our results were reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR; 16) checklist which can be found as a Supplemental Material (File S1).

2.2 | Identifying the research question

The objective of this scoping review was to explore the existing knowledge about children's health-related experiences from their own perspectives in India. We aimed to answer the research question: What do we know about children's health-related experiences in India?

2.3 | Identifying relevant studies and study selection

For this review, the term 'children' referred to individuals between 3 and 17 years of age. Seventeen years was selected as the upper limit for the age range as the age of majority in India is 18 years (i.e., when an individual ceases being a minor). (17) Only empirical studies examining children's health-related experiences from their own perspective were included (e.g., outlining findings in the child's own words). No language restrictions were implemented, but the studies were limited to those entirely conducted or at least partly conducted in India and by publication date from 2000 to June 2020. This time period was selected because the interdisciplinary interest in childhood studies emerged recently around the year 2000 (1), yielding an increase in literature exploring children's voices, agency, and perspectives. Thus, the current literature was seen as providing a synopsis of the state of knowledge on the topic.

Studies that were excluded were opinion papers or studies that were normative in focus (i.e., recognized norms defined by legal, ethical and/or professional practice standards). Moreover, data from infants (0-12 months), toddlers (12-36 months), and children giving opinions on health topics, illnesses, or conditions for which they were not afflicted with were excluded. However, studies with some participants over 18 years of age but which fulfilled the rest of the inclusion criteria were included if most participants in the respective study were under 18 years of age, as these articles still contained valuable knowledge regarding children's perspectives.

2.4 | Search strategy

The search strategy paralleled the three-step process outlined by Peters et al. (18) whereby (a) an initial search was run in CINAHL and MEDLINE, (b) a second, comprehensive search was run using keywords derived from the initial search, consultation with a research librarian, and a target article. Then five online databases were searched: CINAHL (1937-2020), Global Health (1973-2020), MEDLINE (1949-2020), PsycINFO (1597-2020), and Web of Science (1900-2020); and (c) reference and citation searching was used to supplement the results from the reference lists in the included studies. (18) Keywords such as "child*", "India", "perception*", and "experience*" were searched within titles and abstracts, reducing the number of irrelevant retrieved articles. The detailed search strategy for MEDLINE can be found in File S2. Endnote X7 software was used to store, organize, and retrieve the search results. Additionally, interlibrary loans were used to locate articles not retrievable in the university collection. Following article retrieval, three independent reviewers screened titles, abstracts, and full-text articles to determine study inclusion.

2.5 | Charting the data then collating, summarizing, and reporting results

Selected articles were read in full and summarized in a data extraction sheet outlining the: year; study setting; study design and methodology (research type, sample size, data collection methods and tools); population demographics (age range, illnesses/symptoms, healthcare context); qualitative and/or quantitative findings and outcome measures related to children's perspectives, reports, or understandings of their health-related

experiences; and any additional comments or discussion points (e.g., key takeaways, article discussion summary, recommendations and research implications, reviewer questions). The data extraction sheet was created by the first authors (YWW and JB) and tested by charting data from sample articles. The sheet was then reviewed by co-authors and refined in collaboration with the research team to ensure that the contents permitted standardized charting and aligned with our research question. Three authors (YWW, JW, SJ) charted the data. They met regularly with our research team to share their data extraction sheets; discuss and address questions, uncertainties, and concerns; and ensure the charting process remained consistent between the three authors.

The framework for collating and summarizing the results was based on recommendations for enhancing the consistency of scoping review methodologies (19), which includes conducting a descriptive numerical analysis and qualitative thematic analysis guided by our review question. Data analysis was led by the first authors (YWW and JB) in close collaboration with the research team who permitted for member checking and debriefing (i.e., obtaining feedback on data interpretations and analysis); provided input during quantitative and qualitative analysis; and vetted, gave feedback, and provided consensus on generated themes and findings. The descriptive numerical analysis for this scoping review consisted of numerically summarizing the characteristics of the included studies, such as the number of included studies, population demographics, and study designs. (14,19)

A thematic synthesis was conducted whereby the research question guided categorization of the codes and generation of descriptive themes. (20) Data analysis was iterative, inductive, continuous, (1) and conducted in three phases. The first phase included initial open coding, in which data relevant to the review question were extracted from the data extraction sheet and descriptively coded, generating units of analysis or codes. (21) In the second phase, we looked for similarities and differences between codes and grouped similar codes together to form topics, which captured the meaning of the initial code groups. Examples of topics include "impacts of illness on children's lives", "children's physical sensations and symptoms", and "children's understanding of their health and illness". The third phase included relating topics to each other (axial coding), organizing individual topics into themes (thematic analysis), and drawing connections between themes (comparative analysis). (22) This allowed us to generate an understanding of children's health-related experiences in India and identify areas for further empirical research and ethical examination.

3 | RESULTS

3.1 | Sample and Study Characteristics

The initial search yielded 11,304 articles. Once duplicates were removed, 10,547 articles were screened based on the inclusion criteria, after which 134 articles remained and were read and assessed in full for eligibility. Finally, 52 studies were included for analysis and summarized in a PRISMA flow diagram (Figure 1). This review synthesized the perspectives of 15,996 children between 3 and 21 years old (inclusive), and was comprised of 37 quantitative studies, 9 qualitative studies, and 6 mixed-methods studies, which were conducted in schools, communities, hospitals, rehabilitation centers, and clinics in both rural and urban settings. Seven studies included some participants above the age of majority (18 to 21 years). Participants had various illnesses and symptoms including asthma, cancer, renal disease, thalassemia, visual impairments, dental issues, leprosy, HIV/AIDS, menstrual symptoms, somatic symptoms, substance-use, depression, musculoskeletal pain, cleft-lip, pregnancy, and mobility impairments/disability.

3.2 | Thematic Analysis

The 52 studies in this review are summarized in Table 1. Five main themes were identified along with 11 subthemes from the extracted codes (Table 2). Each theme was salient to the understanding of children's health-

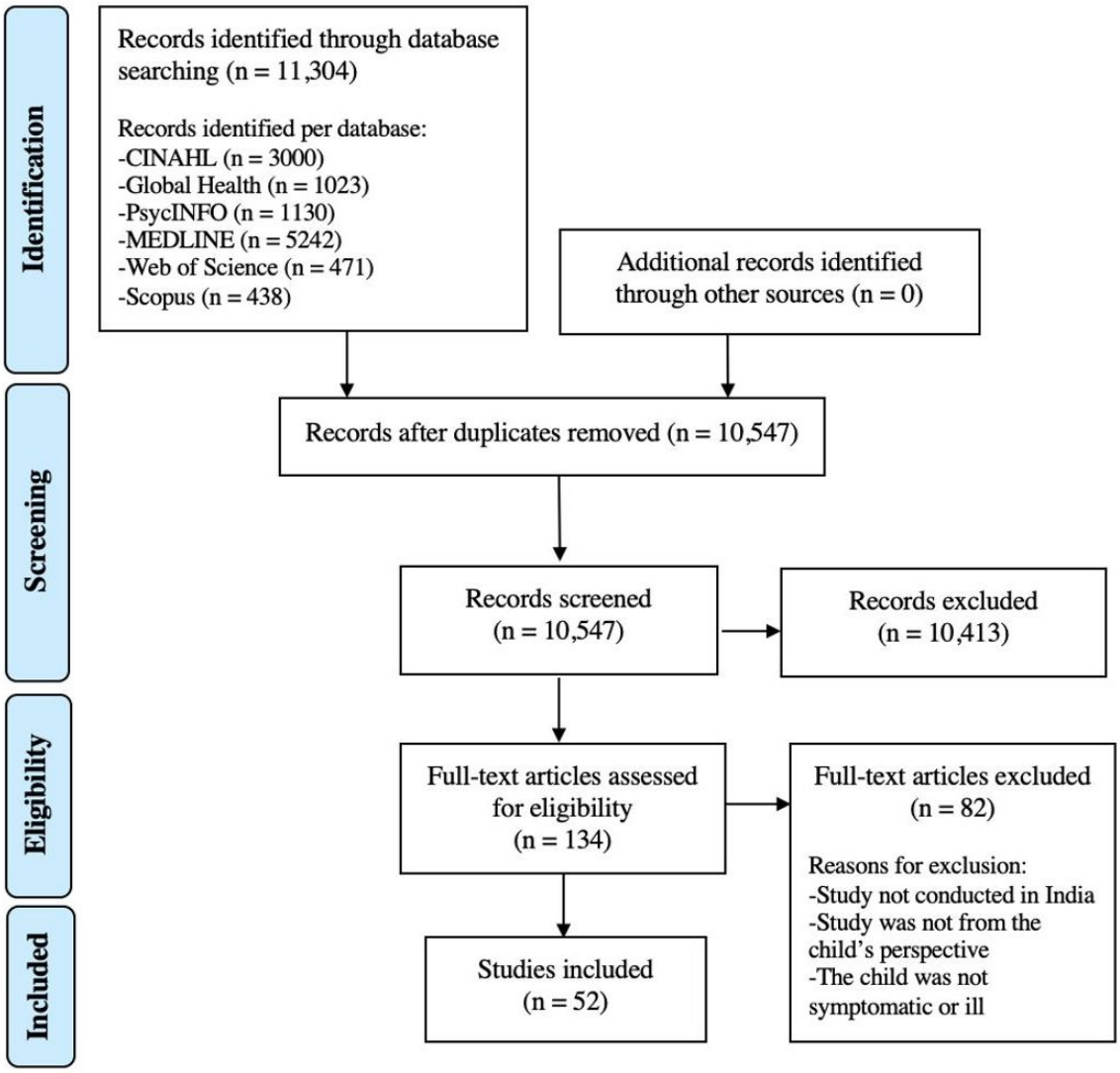

FIGURE 1 PRISMA (*preferred reporting items for systematic reviews and meta-analyses*) Flow Diagram

related experiences and are presented below.

3.3 | Children recalled detailed health-related experiences in healthcare facilities and communities.

Thirty-eight studies showcased children's abilities to recall and reflect on their health-related experiences. A key similarity between studies was that children were able to describe detailed memories of favourable and unfavourable events related to their medical care, interactions with healthcare staff, and within healthcare facilities. For example, youth living with HIV recounted how discourteous service from healthcare staff left negative impressions of the clinic (23) while adolescents with cancer talked about the debilitating effects of treatment (e.g., oral ulcers, nausea, pain). (24) Conversely, children in PICU recounted comforting actions of nurses and doctors such as speaking nicely and painless injections. (25) Children's recollections also extended be-

yond themselves as they described witnessing the experiences of other ill children in the PICU undergoing invasive procedures, injections, and even death. (25)

Within the community, however, children mostly recounted negative experiences related to health barriers and social exclusion. Post-menarche girls, for example, reported having limited access to hygienic facilities at school (e.g., soap, clean water, toilets), prompting them to miss classes during menstruation. (26–29) Children living with HIV/AIDS reported experiencing discriminatory actions from family members including refusals to share food, avoidance, and propagation of misgivings. (23) Finally, children also reported experiencing bullying, teasing, and/or negative judgement from peers due to their symptoms and illness, contributing to absenteeism and treatment non-compliance. (29,30)

3.4 | Children expressed both positive and negative emotions related to their health.

Nineteen studies highlighted children's expression of positive and negative emotions related to their health. Using interviews, questionnaires, and focus groups, researchers showed that children experienced emotions such as fear, hope, anxiety, hopelessness, insecurity, appreciation, guilt, and sadness towards their health. In general, children's negative emotions—particularly fear and anxiety—stemmed from unpleasant physical symptoms (e.g., pain, discomfort, nausea), uncertainty about their health and future, and limitations due to dependence on caregivers, activity restrictions, and socioeconomic status. (31–33) Despite the psychological impacts of illness, pediatric PICU patients (25) and children with HIV/AIDS, (34) leprosy, (35) and asthma (36) also reported positive feelings, such as hope and contentment. Examples of when primarily positive emotions arose were when children had a positive outlook on life, (34,36) were knowledgeable about their illness, (35) and felt supported by healthcare providers. (25) While children's emotions varied with the severity and nature of their illness, their interpersonal experiences, access to resources in healthcare facilities, and communities also contributed to their positive and negative emotions. For example, social exclusion and discrimination led to negative emotions, (29,30) while support and comfort from healthcare providers and family helped to attenuate the negative effects of illness (25, 34-36).

3.5 | Children had varying levels of knowledge regarding their health, treatment, and the consequences of illness.

Fifteen studies showed that children had varying levels of knowledge regarding their health. Children's beliefs and understanding of their illness and symptoms were shaped by their sociocultural backgrounds. Differences in health-related knowledge were particularly evident in children with thalassemia (37) and post-menarche girls. (32) For example, educated Hindu youth with thalassemia attributed their illness to medical causes, such as lack of prenatal screening. (37) Conversely, Muslim respondents (regardless of education level) believed that their illness was caused by a "sinful past". (37) For post-menarche girls, perceptions of menstruation varied by maternal education, such that adolescents from rural areas, where women's educational attainment was typically low, had significantly worse attitudes towards menstruation than their urban counterparts. (32) In particular, rural adolescents were less inclined to ask questions about and discuss menstruation, contributing to a poor understanding of menstrual symptoms, inability to identify organs involved in menstruation, and negative emotions such as feeling "ugly" or "gross". (32) Regarding other illnesses, such as those with HIV/AIDS or sickle cell hemoglobinopathy, most youth had some knowledge related to medication, treatment, and/or prevention. (34,38,39)

Overall, family, teachers, and friends played the greatest role in children's health-related knowledge and attitudes. Post-menarche girls, for example, often learned about menstruation from their mothers, (26–28,40). Youth who used tobacco, areca nut (a type of nut with similar properties as nicotine which is usually chewed and can be harmful to one's health), and other drugs were influenced by friends and/or by wit-

nessing family members use substances. (41–43) These different sources of knowledge influenced the accuracy and scope of children's health knowledge, as well as their understanding of the importance of treatment and consequences of untreated illness. Although most children understood the severity and impact of their various illnesses, most had incomplete knowledge regarding their symptoms and treatment, which negatively affected treatment seeking, medication compliance, and quality of life. For example, children with asthma commonly reported poor understanding of their disease, contributing to medication resistance. (44) Similarly, children with poor spectacle compliance reported that their parents did not understand their vision problems and that they themselves did not know what "normal" vision was (30) Although post-menarche girls commonly reported experiencing abnormal menstrual symptoms such as UTIs, infections, and lacerations, the vast majority did not seek medical treatment. (45,46)

3.6 | The impacts of health and illness extended beyond children's physical well-being.

Forty-one studies showcased how the impacts of health and illness extended beyond children's physical well-being. Children's various health statuses impacted their physical, emotional, and developmental well-being regardless of illness type and severity. Moreover, children's well-being varied with age, gender, and socioeconomic status (SES) such that girls, youth 12 years and older, and children with low SES tended to report greater physical and emotional burden and lower quality of life. (32,33,47,48) Although all children reported negative physical sensations such as discomfort, pain, or weakness, they tended to speak more about the impacts of health on their daily activities. Thus, children with health problems (e.g., vision deficits, dental issues, thalassemia, HIV/AIDS) generally reported lower quality of life than their healthy counterparts. (23,42,48,49)

One of the most common issues reported by children was the negative effect of illness on their schooling and relationships with peers. This was particularly salient for children with dental problems, (47) vision impairments, (30) thalassemia, (37) sickle cell hemoglobinopathy, (38) HIV/AIDS, (34) musculoskeletal pain, (50) and unpleasant menstrual symptoms. (29) Children often complained of school absences due to physical symptoms, lack of support, and inadequate facilities to accommodate their health needs. (29,34,50,51) For example, children with sickle cell hemoglobinopathy and thalassemia expressed a lack of support from teachers. (37,38) Children with spectacles reported being teased by school peers (30) and post-menarchal adolescent girls reported having to cope with unhygienic, poorly equipped bathroom facilities that lacked privacy. (29)

Children's health also impacted their self-perceptions, such that youth with thalassemia, (37) cancer, (24) and sickle cell hemoglobinopathy (38) perceived their diagnosis as a psychological and economic burden for their family and society. Negative self-perceptions usually arose due to feelings of dependence, (24,37) disablement, and guilt. (38) Children's concerns also revolved around their self-image and desires to be like their "healthy" peers. (44,52–54) While some children with dental fluorosis reported that they liked the appearance of their teeth, others were worried about their appearance. (52) For children with vision impairments, appearance was an important contributing factor towards spectacle non-compliance, particularly amongst girls. (30,55)

3.7 | Children had the capacity to identify and communicate their health-related needs.

Twelve studies highlighted children's capacity to identify and communicate their health-related needs. Despite the physical and psychosocial challenges associated with ill-health, children were able to identify and communicate their health-related needs when their voices were elicited during interviews, focus groups, or self-report questionnaires. For example, adolescents with thalassemia, (37) cancer, (24) and leprosy (53) demonstrated understanding of their coping needs by expressing their desires for better access to counselling and

psychological support. Children's desires also extended beyond their personal needs: when asked what can be done to improve the intensive care unit, PICU patients suggested implementing "more beds so that more sick children can be in intensive care". (25)

Although few studies examined children's communication with healthcare providers, Tiwari et al. (56) found that children with end-stage renal disease were able to ask questions and talk to doctors, nurses, and other staff about their health. Children also revealed the most insight towards their health in group settings with other youth having similar health conditions. For example, results from a focus group study by Narayanan et al. (30) showed that youth with vision deficits had several ideas to encourage spectacle-compliance such as implementing science clubs to deliver education, emphasizing teachers' roles in the education and encouragement of spectacle-use, and providing trendy frames. Similarly, adolescents with various disabilities (e.g. hearing and vision impairments, and poliovirus) who participated in a community-based rehabilitation programme with other youth, with and without disabilities, provided several insights toward their experiences, desires, and needs. (57) The adolescents reported wanting more education, freedom to engage in day-to-day activities (e.g. social interactions, play, and going outside), and having someone to talk to about their emotions. (57) Despite their restrictions, the youth with disabilities viewed the group setting as a fun and effective way to engage with their community, assume control over their rehabilitation, and take charge of their lives. (57)

4 | DISCUSSION

The purpose of this scoping review was to examine children's health-related experiences in India, including children's participation, perceptions, knowledge, and decision-making capacities in matters concerning their health, as well as to identify gaps in the current literature. Despite children's various health statuses and India's pluralistic society, (58) children often reported similar health-related experiences, some of which paralleled circumstances in Western societies. (7-10) Overall, the studies were diverse in scope, topic, and focus, consisting of various methodologies and study tools such as self-report questionnaires, focus groups, interviews, participant observations, and children's drawings. In turn, this scoping review revealed a range of topics related to children's perspectives such as their recollections, feelings and emotions, and knowledge about their illnesses/symptoms. These aspects shed light on children's unique perspectives of their health in India, which can serve to enrich our understanding of their best interests. Rendering children's perspectives visible can influence how healthcare providers and other adults understand and address children's best interests in the provision of care, which is rooted in childhood ethics.

Most children had clear recollections of their health experiences regardless of illness, symptoms, and surroundings (school, hospital, community). Children and youth were particularly attuned to healthcare providers' actions, contributing to positive and negative attitudes towards health. For example, children recounted receiving discourteous service from healthcare staff, (23) but also being treated nicely by PICU nurses and doctors. (25) Researchers examining nurse-patient interactions with hospitalized children in Spain reported similar findings, such that children evaluated their treatment based on their perceptions of nurses' affect, interest, and sympathy towards them. (59) Youth used nurses' behavioural signals to distinguish between their preferred healthcare providers, contributing towards their treatment compliance and adaptation to hospitalization. (59) Additionally, Ullán et al. (60) found that unlike adults, children appeared to be more sensitive to the "symbolic" aspects of hospitalization, such as the emotional processes, needs, preferences, and behaviours of hospital users. Similarly, the studies in this scoping review highlighted that: a) children were observant of healthcare staff's behaviours towards themselves and others; and b) their observations directly impacted their emotions and perceptions regarding their health-related experiences.

In the Indian context, parents and peers influenced children's health-related attitudes, knowledge, and prac-

tices. Common challenges including medical non-compliance, poor psychosocial well-being, and lack of health knowledge were often exacerbated by low SES and inadequate support from family, teachers, and friends. These findings align with recent research by Olsen et al., (61) who found that European adolescents who had undergone ulcerative colitis surgery reported feeling "deserted, misunderstood, and ignored" by family and friends due to personal physical changes and school absences. In addition, researchers from Canada and the United States explained that children with a low SES are less likely to have access to medical care, nutrition, and environmental stimuli, increasing the likelihood of injury, mental and physical illness, and developmental delay. (62– 64) Despite some similarities, there were notable differences between children's health experiences in India and Western countries, particularly related to menstruation and areca nut chewing. For example, American girls/females appeared to be more knowledgeable and accepting of menstruation, (65,66) had greater access to menstrual products (e.g., pads, tampons), (67) and adhered to less strict social restrictions (e.g., being able to attend school and family/religious events) (67) compared to girls from low and middle-income countries. In addition, research on areca nut chewing was limited to South Asia likely due to where it is grown, with only one study conducted in Europe that showed that children who used areca nut were exclusively South Asian. (68)

Finally, although only 16 out of 52 studies elicited children's health-related opinions via interviews or focus groups, the qualitative and mixed-methods studies showed that children recognized their needs and desires, were insightful when suggesting healthcare changes, and appeared to be more engaged in health discussions in groups settings with other youth. Similarly, Livesley and Long (69) found that hospitalized children in England actively resisted passive roles in healthcare settings and worked hard to assert their competence, knowledge, and capabilities. The notion that peer groups are effective in promoting well-being, knowledge-acquisition and exchange, and collaboration is well supported in research. (70,71) In an overview of loneliness across the lifespan, Qualter et al. (72) described how children increasingly value peer acceptance, intimacy, and social standing as they age. Consequently, disruptions in social functioning by poor health can contribute to feelings of rejection, negative attitudes towards health, and low self-esteem, which were all common issues in this scoping review. The utilization of focus groups to elicit children's voices therefore supported young people's psychosocial well-being by providing an safe environment to communicate health concerns and interact with peers. (72–74)

4.1 | Gaps and limitations

Although we have identified research examining children's health-related experiences from their perspectives in India, we limited the evidence to empirical studies. Thus, further research into normative standards is required to examine the how notions of participation, inclusion, agency, consent, and assent are viewed in the Indian context, what practices are recommended based upon these views, and if the evidence summarized in this review reflects the adoption of practices. Next, studies were excluded from the review if they examined the health-related knowledge, attitudes, and beliefs of children who were not symptomatic or diagnosed with an illness (e.g., perception of boys towards menstruation). Given the importance of peer relations towards children's health-related experiences, we recommend an extensive examination of the public health literature. This would provide a more comprehensive understanding of how children perceive their health in India. In terms of methodology, 36 out of 52 studies included in this review used only quantitative methods (e.g., questionnaires, objective medical examinations) to explore children's health-related experiences, mostly related to quality of life. Although questionnaires are a quick, economic, and effective way to determine individuals' perceptions regarding a specific topic, questionnaire-use may also lead to bias or reflect the preconceptions of the researcher instead, thus failing to truly capture the participants views, experiences, and voice. (75) Finally, the studies featured in this scoping

review were heterogeneous in terms of participant sociodemographic background, illnesses, methodologies, and findings, which precluded our ability to showcase potential relationships between children's sociodemographic characteristics and contexts (e.g., religion, socioeconomic background, gender/sex) and their health experiences. However, delving into these potential relationships through further empirical studies may help researchers and healthcare providers better understand the unique healthcare needs of children in India.

4.2 | Future directions and implications for practice

Through this scoping review, we have identified a need for more qualitative, interview-based, and child-centric methodologies (e.g., art, play) in conducting research with children. This will help to fully capture their health-related experiences, promote their inclusion in care, and support the provision of ethical care by healthcare providers. In terms of practice, this review highlighted the clear need for family-centred interventions that focus on providing health education to parents of children with health conditions, as well as enhancing health education in school settings. Furthermore, young people expressed insightful suggestions to improve care, showcasing the need for healthcare providers to elicit young people's voices and recognize the impact that clinicians may unconsciously have on children's health experiences. Future researchers may consider conducting a more focused review of the literature pertaining to specific ethical concerns or consequences impacting children. In all, this review provides a foundational body of evidence to serve as a starting point for continued research in the area of children's perspectives towards their health in India.

5 | CONCLUSIONS

The themes identified from this review demonstrated that ill and symptomatic children in India often expressed similar health-related experiences, views, and needs across several domains of life despite their various health statuses, experiences, and backgrounds. These domains were not restricted to their immediate medical milieu, but rather extended to children's relationships, schooling, and activities of daily living. This scoping review identified key areas for improvement in children's healthcare including the need to elicit children's voices during care, provision of adequate psychosocial support, enhancing health education, and training healthcare providers to recognize the impact of their behaviours on children's health experiences while taking actions to provide appropriate, sensitive care. Given the widespread impacts of health services on other areas of children's lives, research in healthcare and childhood ethics play an integral part in insuring that these impacts are known and considered by those who make healthcare decisions in children's best interests. By highlighting this link, our scoping review contributes to children's healthcare and childhood ethics research. Although more research is needed to fully understand children's health-related experiences in India, the development of an ongoing dialogue between researchers, healthcare providers, as well as children and families can promote the inclusion of children in their own care and lead to improved health research and practices that are suitable for young people in India.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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Author	Setting	Age (years)	Sample Size	Study Design	Data Collection Tools	Illness/ Symptom	Main Findings	Relevant Theme(s)*
(Christy et al., 2002)	Rehabi-litation center	3-10	n=50	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions)	Visual impairment	• Children with visual impairment expressed their emotions and needs, but had difficulty expressing sympathy due to visual conditions, backgrounds, experiences, and age	5
(Karande et al., 2005)	Pediatric intensive care unit (PICU) in tertiary care public hospitals	5-12	n=50	Qualitative, Phenomeno-logical	Semi-structured interviews	Various severe illnesses (e.g., dengue shock syndrome, malaria, etc.)	• Positive recollections of PICU stay related to aspects of medical care, personal factors, environmental factors • Negative recollections of PICU stay were personal, such as being restrained in bed or seeing a dead body	1, 2, 5
(John et al., 2005)	Hospital in Kolkata	10-20	n=258	Qualitative, Phenomeno-logical	Focus group discussions, interviews	Leprosy	• Adolescents were dependent on parents to seek care for their symptoms • Children felt ashamed of their disabilities, despair, helplessness, and insecurity • Expressed desire for support to cope	1, 2, 5
(Patel & Pathan, 2005)	Regional Hemo-globino-pathy Center (Urban)	8-14	n=52	Quantitative, Quasi-experimental, Descriptive, Cross-sectional	Self-report questionnaire (quality of life [QOL])	Sickle cell anemia (SCA) and sickle cell anemia trait	• Children with SCA had greater restriction of physical activities • Expressed feelings of sadness or disinterest, lack of support, intensity of weakness and pain, and realization of being affected by a major illness	1, 2, 4
(Roy & Chatterje, 2007)	Various community locations	9-17	n=36	Qualitative, Phenomeno-logical	Interviews	Thalassemia	• Culture and education important in the construction of meanings • Consequences of illness has been stressful, tedious, painful and causing psychological distress	1, 2, 3, 4, 5
(Kumar et al., 2008)	Health clinic	Mean=15.7	n=360	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	General health problems	• For health problems boys consulted mainly friends/peers (48%) while girls consulted their mothers (63%)	3
(Singh & Ghai, 2009)	School providing integrated education	11-16	N=14	Qualitative, Participatory action research	Semi-structured interviews, focus groups, discussions, drawings made by participants	Mobility impairment/ disabilities	• Findings illuminated immense variation and fluidity in children's understanding of 'disability' • Children desired to appear similar to 'non-disabled' children • Most attributed 'disability' to existential causes	1, 2, 3, 4

(Raval et al., 2010)	Suburbs of Ahmedabad	6-8	n=120	Mixed methods, Embedded, Cross-sectional	Child emotion vignettes, interview questions, questionnaire for mothers to complete (child behaviour)	Children with internalizing, externalizing, and somatic symptoms, and children with no symptoms	• The internalizing and externalizing groups considered their expressions of anger and sadness uncontrollable and reported crying and utilizing aggressive behaviors, respectively, more than the control group • The somatic complaints group considered emotions trivial and reported withdrawing more than the control group	1, 2
(Gulati et al., 2011)	A comm-unity based rehabi-litation program in the urban slums	12-18	n=42 (21 youth with disability, 10 youth without, 10 staff)	Qualitative, Critical ethnography	Participant observations focus group discussion. audio-visual data, field notes	Various disabilities (e.g., polio, hearing impairments, vision impairments)	• Adolescents viewed the group setting as the most fun and effective way of getting involved • Four central themes informed the framework: group participation, group demonstration, group recognition and the socio-cultural environment's interaction with disability • Adolescents with disabilities expressed desires to negotiate and engage in meaningful age-appropriate occupations with their peers	1, 2, 4, 5
(Dandi et al., 2011)	School in both urban and rural comm-unities	12	n=2250	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (experiences)	Dental pain	• Children expressed higher need for dental care when pain was severe, continuous, and/or aggravated on thermal stimuli • Daily living was affected by dental pain • Not all children with dental pain expressed their need to seek dental care	1, 4, 5
(Khan et al., 2012)	Urban in-patient oncology unit	Mean =16.7	n=7	Qualitative, Phenomeno-logical	Semi-structured interviews	Cancer	• Children expressed mixed perception about cancer, reported uncertain and bleak future, and physical and psychological distress • Children reported that their parents were the strongest source of support • There is still stigma attached to cancer despite awareness programs	1, 2, 4, 5
(Bansal et al., 2013)	Dr. B.R.A Institute Rotary Cancer Hospital	5-18	n=120 (40 youth with cancer, 40 siblings, 40 healthy youth)	Quantitative, Descriptive, Cross-sectional, Comparative	Self-report questionnaire (QOL)	Acute lymphoblastic leukemia (ALL)	• The quality of life (QOL) of children with ALL was significantly poorer than that of their siblings and the healthy children in physical, emotional, social, and school health domains • There was no significant difference in the QOL of siblings and healthy children in all domains of health	1, 4
(Grover et al., 2013)	Two hospitals in New Delhi	7-12	n=20	Qualitative, Grounded theory	Semi-structured interviews	Asthma	• Major reported issues included poor child understanding of disease and medication • Child self-image, resistance to medication use and lack of responsibility in medication taking	1, 3, 4

							were themes that emerged from child interviews	
(Jodalli et al., 2013)	Schools in rural areas	12-15	n=316	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, knowledge, concerns), teeth assessment	Dental fluorosis	• Negative perceptions regarding dental fluorosis increased with the severity of fluorosis • Children expressed feelings of distress, worry, embarrassment and hindrance from smiling • Children were aware of the presence of fluoride and the health effects of fluorosis	1, 2, 4
(Verma & Verma., 2013	Schools	12-16	n=200	Quantitative, Correlational, Cross-Sectional	Self-report questionnaire (QoL, coping, symptoms)	Asthma	• Symptom severity affected overall and positive QoL, both directly and indirectly via coping • Positive reappraisal, and information seeking was related to increased QoL, whereas hiding asthma and worrying was related to lower QoL	1, 4
(Siluvai et al., 2015)	Urban comm-unity clinic	13-19	n=900	Quantitative, Descriptive, Cross-sectional	Screening tool, self-report questionnaire (QOL, practices/habits)	Dental malocclusion	• There was a positive association between malocclusion and impact on children's quality of life	4
(Tiwari et al., 2015)	In-patient and out-patient unit of pediatric hospital	5-18	n=55	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (QOL), parent proxy report	End stage renal disease	• Kidney transplant group had better health related quality of life in comparison to maintenance dialysis group • Kidney transplant group did not have difficulty in telling their parents and health care providers how they felt or to ask questions	1, 4, 5
(Batra et al., 2016)	Dr. B. R. A. Institute Rotary Cancer Hospital	5-21	n=122	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (QOL)	Retinoblastoma	• Overall QOL was significantly poorer in retinoblastoma survivors as compared with controls • Difficulties in maintaining friendships and competing were reported in the social health domain and the school health domain showed significantly higher absenteeism	1, 4
(Govind-haraj et al., 2016)	Leprosy Mission Hospital	8-18	n=65	Mixed methods, Explanatory sequential, Cross-sectional	Self-report questionnaire (attitude towards health), interview	Leprosy	• The results indicate that the children and adolescents had a positive attitude towards having leprosy. However, one-third of the participants experience internalised stigma	1, 2, 4
(San-jeeva et al., 2016)	HIV clinic	10-18	n=362	Mixed methods, Cross-sectional	Structured questionnaire (perceptions,	HIV/AIDS	• Although about 60% of children were disclosed about their HIV, only one-third	1, 2, 3

					experiences), interview		were fully disclosed (know the name and treatments associated with HIV/AIDS) • 62% of children were disclosed via an informal process (e.g., non-parental, peers, self-disclosure) • Children experienced a range of emotions and actions upon disclosure (e.g., silence, asking questions)	
(Mehta et al., 2016)	HIV clinic	10-18	n=24	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (knowledge, perceptions, experiences), social desirability questionnaire	HIV/AIDS	• Most participants reported that they still had good relationships with family and friends, could overcome challenges in school, and had a positive outlook on their future; school absenteeism was common reported problem • Disclosure was met with acceptance by one-third of the children, but 67% reported that they felt upset • Despite disclosure, some children had incomplete knowledge about HIV	1, 2, 3, 4
(Rani et al., 2016)	Urban, rural, and slum comm-unities of Chan-digarh	11-18	n=300	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences, practices, beliefs, symptoms)	Post-menarche girls with menstruation related symptoms	• Most girls reported pain and unhappiness during menstruation, but only 11.3% consulted a physician for dysmenorrhea • Most of the girls in urban areas gained information about it through the teachers, whereas girls in rural and slum areas gained information from their mother • Lack of accommodations and physical symptoms were major reasons for absenteeism	1, 2, 3, 4
(Bhad et al., 2016)	Tertiary de-addiction centre	13-18	n=23	Quantitative, Descriptive, Cross-sectional	Semi-structured questionnaire (perceptions, experiences)	Adolescent males seeking treatment for inhalation drug use	• Reasons for inhalant drug use were: curiosity and experimentation (39.13%), peer pressure (26.08%), anger toward family members (17.4%), boredom (8.69%), just for fun (4.34%), and to impress their friends (4.34%)	1
(Dhirar et al., 2016)	Thalas-semia Day Care Centre	2-18	n=241	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (QOL), medical records	Thalassemia	• Factors improving the quality of life were control of iron overload and adverse effects of ICTs, management of comorbidities and fewer hospital visits	1, 2
(Chauhan & Kodnani, 2016)	Community	14-19	n=100	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	Post-menarche girls with dysmenorrhea	• There was significant association between dysmenorrhea and school absenteeism, school performance, daily activities, and social relations • Girls experienced unpleasant physical and psychological symptoms, but only 5% consulted a doctor	1, 3, 4

(Prem Kumar et al., 2016)	Orphanages in Hyderabad	12-16	n=400	Quantitative, Descriptive, Comparative	Self-report questionnaire (anxiety, strengths and difficulties)	HIV/AIDS	• Children orphaned due to HIV/AIDS experience the highest average levels of anxiety, conduct problems, and peer relationship issues; girls also experienced worse symptoms • Being an AIDS orphan and being a girl had the strongest effect on generalized anxiety	2, 4
(Malhotra et al., 2016)	Three Uttar Paresh districts	10-19	n=1800	Quantitative, Descriptive, Cross-sectional	Self-report questionnaires (perceptions and experiences)	Post-menarche girls with menstruation related symptoms	• Girls with more media exposure had greater knowledge about menstruation • They commonly reported challenges with finding a place to dispose menstruation pads and washing cloths	1, 4, 5
(Dhawan et al., 2016)	Community	< 18	n=509	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	Injection drug using (IDU) children	• IDU children reported regular contact with drug-using peers, familial conflict, and abuse • Most IDU children reported experiencing sadness and anxiety and 66% felt that life was stressful and difficult	1, 2, 4
(Seeni-vasan et al., 2016)	Schools	12-17	n=500	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	Post-menarche girls with menstruation related symptoms	• Most of the girls felt scared on first menstruation (59%)	1, 2, 3, 4
(Das, Detels, Javan-bakht, et al., 2017)	Community	8-15	n=34 (20 caregivers, 14 children)	Qualitative, Phenomeno-logical	Interviews, focus group discussions	HIV/AIDS	• Common issues shared by caregiver and children include concerns about illnesses, medications, HIV-related discrimination, health as a state of mind, available health services and satisfaction and grievances about them. • Many participants reported poor accessibility due to distance, unpleasant experiences (discourteous service, and negative side-effects of drugs	1, 4
(Das, Detels, Afifi, et al., 2017)	Community	8-15	n=393 (199 caregivers, 194 children)	Quantitative, Correlational	Self-report questionnaire (QOL)	Children diagnosed with HIV or affected by HIV	• HIV infection was associated with poorer scores in all QOL domains except 'discrimination.' • Being on ART was not associated with any QOL domains but was found to be associated with poorer scores in the 'discrimination'	4
(Sharma et al., 2017)	Pediatric day care centre & out-patient depart-	2-18	n=155	Quantitative, Cross-sectional, Comparative	Self-report questionnaire (QOL), parent proxy survey	Thalassemia	• Children with thalassemia had worse QoL than their healthy counterparts	4

	ment							
(Sharma et al., 2017)	Schools	14-19	n=816	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	Children who use tobacco	• Peer influence was the major reason for initiation of smoking. Parental smoking was the second most important influencing factor in this research • Majority of the students thought that teachers (70.6%) and parents (65.2%) were the most important source of information about the hazards of tobacco use	1, 3
(Gopa-kumar et al., 2017)	Anti-retroviral therapy (ART) center	5-18	n=144	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (QOL)	Children with HIV	• Children with HIV reported good QOL and better physical QOL than their psychosocial QOL	4
(Kumar et al., 2017)	Schools	5-16	n=165	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (sleep, perceptions, experiences), physical assessment	Chronic, idiopathic musculoskeletal pain	• Children with IMSP had pain at multiple body sites and psychosocial difficulties such as sleep disturbances, absenteeism, and sadness • IMSP significantly occurred more in lower socio-economic class in comparison to upper and middle and was more prevalent in children with lower maternal education	1, 4
(Mathi-yalagen et al., 2017)	School	12-18	n=242	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (knowledge, attitude, practices)	Post-menarche girls with menstruation related symptoms	• Most girls reported experiencing abdominal pain, reproductive tract problems (but few sought medical care), and were restricted from attending religious events, going to school, and/or had to sleep separately • Although most girls knew that menstruation was a natural process, few could identify the correct/relevant physiological features involved	1, 3, 4
(Singh et al, 2017)	Districts of Uttarak-hand	9-15	n=423	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (impact on life), physical assessment	Visually impaired children and dental problems	• Participants >12 years of age had severe impact of poor oral health on their day-to-day activities as compared to those <12 years of age • Children who presented with dentofacial deformities, dental caries, and traumatic injuries reported greater impact on daily life • Visually impaired individuals showed a higher prevalence of dental caries, traumatic dental injuries, and dentofacial anomalies	1, 4
(Rajag-opal &	Community and schools	10-20	n=270	Mixed methods, Triangulation, Cross-	Focus groups, interviews, and self-report questionnaires	Post-menarche girls with menstruation	• Common perceptions include "menstrual blood is the accumulated dirt that flows out of the body every month"	1, 3, 4, 5

Mathur, 2017)				sectional	(perceptions and experiences)	related symptoms	• Girls stated that there was a lack of clean washrooms in homes/schools • Girls using cloths also stated that usage of cloth led to laceration and discomfort. Most girls did not take any medication for these problems or consult a doctor	
(Naray-anan, Kumar, & Ramani., 2017)	Schools	13-17	n=64 (32 parents, 32 children)	Qualitative, Phenomeno-logical	Focus groups	Adolescents who need vision correction	• Adolescents generally did not like wearing their spectacles and reported judgements and teasing from peers • They reported poor understanding of normal vision, preventing them from enjoying the benefits of their spectacles • Adolescents wanted fun/interesting spectacle educations sessions (e.g., cartoons, famous personalities, other adolescents wearing spectacles, science clubs)	1, 2, 3, 4, 5
(Chor-diya et al., 2018)	Hospital	8-18	n=93	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (QOL)	Transfusion-dependent thalassemic children	• Mean PedsQL score was higher in 8-12 y age group as compared to 13-18 y • Lowest mean score was observed in School functioning • Children with one transfusion per month had better QoL compared to children visiting 3-4 times a month for transfusion	4
(Singhal et al., 2018)	Schools	13-18	n=120	Quantitative, Quasi-experimental, Non-randomised controlled trial	Self-report questionnaires (symptoms, stress, coping, etc.)	Subclinical depression	• The intervention group evidenced clinically significant reductions in depressive symptoms, negative cognitions, and academic stress, and increased social problem solving and coping skills, at both post-intervention and follow-up	4
(Dudeja et al., 2018)	Urban slums	6th-12th grade	n=250	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (knowledge, practices)	Post-menarche girls with menstruation related symptoms	• Only 56.4% of girls had knowledge about menarche pre-menarche; most reported gaining knowledge from their mothers • 90% of the girls faced health complaints (e.g., dysmenorrhoea) and had restrictions in place due to menstruation including religious, physical and social restrictions • All reported dissatisfaction with toilets and handwashing facilities on the school premises	1, 3, 4, 5
(Vashisht et al., 2018)	Schools	8th-12th grade	n=600	Mixed methods, Triangulation, Cross-sectional	Focus groups, self-report questionnaires (perceptions, practices)	Post-menarche girls with menstruation related symptoms	• Most students (65.5%) reported that menstruation affected their school functioning as they were not allowed to attend school during their periods and lacked accommodations	1, 4

(Gupta et al., 2019)	Urban and rural Delhi comm-unities	13-18	n=200	Quantitative, Descriptive, Comparative	Self-report questionnaire (attitudes)	Post-menarche girls with menstruation related symptoms	• Girls in rural areas experienced worse negative feelings and experiences related to menstruation than urban adolescents • Mother's educational and occupation status significantly affected adolescents' menstrual attitudes	3, 4
(Verma et al., 2019)	Schools	8-14	n=500	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (practices), health examination	Tobacco use	• Friends (78.04%) were most common influencing factor for tobacco use, followed by family members (12.2%) and media (9.7%)	1
(T. K. Singh et al., 2019)	Dental clinics/ hospitals	12-15	n=520	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	Adolescents with orthodontic treatment	• Females felt more self-conscious, less fit to work/function, and more worried due to their teeth in comparison to males • Both genders felt embarrassed due to their teeth	1, 2, 4
(A. Singh et al., 2019)	Districts of Uttarak-hand	9-15	n=250	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences)	Hearing impairments	• Hearing-impaired children with dental problems reported higher impact scores • Children >12 years had higher impact scores and lower QOL than younger children • Hearing-impaired children had maximum difficulty in maintaining personal hygiene due to oral health problems	4
(Nagap-pan et al., 2019)	Hospital	8-16	n=160	Quantitative, Descriptive, Comparative	Self-report questionnaire (perceptions, experiences), health examination	Cleft-lip	• Children with orofacial clefts had statistically significantly lower QOL than control for Functional Well-being, Social/Emotional Well-being, and School Environment subscales	4
(Mor-jaria et al., 2019)	Schools	11-15	n=460	Noninferiority randomized clinical trial, Mixed methods, Explanatory sequential	Interviews, observations, health examination	Vision impairments	• The two most frequent reasons for spectacle non-compliance in this cohort were teasing or bullying by peers and lost, forgotten, or stolen spectacles • Girls reported parental disapproval as a reason for non- wear more frequently than boys	1, 4
(Deepa Lak-shmi et al., 2020)	Schools	8-15	n=628	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (QOL, perceptions, experiences), health examination	Permanent anterior teeth fractures	• All children with tooth fractures reported negative oral health related quality of life • 54% reported negative QOL; this was higher amongst children > 13 years	4

Major Themes	Sub-themes
Children recalled detailed health-related experiences in healthcare facilities and communities	Children had vivid memories of favourable and unfavourable events in the healthcare setting and community
Children expressed both positive and negative emotions related to their health	Negative emotions primarily arose when children experienced uncomfortable symptoms, uncertainty, and health-related limitations
	Positive emotions primarily arose when children were knowledgeable about their health, felt supported, and/or maintained a positive outlook
Children had varying levels of knowledge regarding their health, treatment, and the consequences of illness	Children's health-related knowledge and attitudes were influenced by their sociocultural backgrounds
	Family and peers were the most commonly reported sources of health-related information which influenced the accuracy and scope of children's health-related knowledge
	Most children had incomplete knowledge regarding their illness/symptoms, contributing to distress, confusion, and poor treatment compliance
The impacts of health and illness extended beyond children's physical well-being	Illness significantly disrupted children's schooling, social relationships, and day-to-day activities such that children reported unwanted school absences, exclusion from peers and family, difficulties with activities of daily living, and other social and physical limitations and restrictions
	Illness impacted children differently depending on gender, age, and background
Children had the capacity to identify and communicate their health-related needs to clinicians and researchers	Children understood the additional stressors associated with illness, expressed their need for more psychosocial support, and took into consideration the needs of other ill children when making suggestions to improve care
	Children spoke openly about their health-related needs and desires when their voices were elicited
	Children were most empowered in collaborative group settings with healthy peers and youth who have similar conditions

TABLE 2 Summary of main themes and subthemes

(Gupte et al., 2020)	Schools	11-18	n=166	Qualitative, Phenomeno-logical	Focus groups	Areca-nut chewing, tobacco use	• Adolescents reported witnessing family members and adults using the substances and felt that it was not fair when they were told not to use it; they perceived tobacco to be stress-relieving and expressed curiosity towards cannabis and alcohol • Key influencing factors in initiation include normalization, curiosity, attraction, critical situations (e.g., pressure from an adult), easy access and affordability	1
(Gothwal et al., 2020)	LV Prasad Eye Institute	8-18	n=309	Quantitative, Descriptive, Cross-sectional	Self-report questionnaire (perceptions, experiences, functioning)	Children with glaucoma	• School-aged children treated for Primary Congenital Glaucoma during early childhood experience significantly better vision function and QOL than those treated for secondary glaucoma	4	

*Theme 1: Children were able to recall and reflect on their health-related experiences
Theme 2: Children expressed both positive and negative emotions related to their health
Theme 3: Children had varying levels of knowledge regarding their health
Theme 4: The impacts of health and illness extended beyond children's physical well-being
Theme 5: Children had the capacity to identify and communicate their health-related needs

TABLE 1 Brief summary of articles included in the scoping review.

APPROACH TO

APPROACH TO
McGill Journal of Medicine

Venous Thromboembolism

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1 | QUESTION

A 75-year-old man presents to the emergency room with a one-day history of new-onset dyspnea and right calf pain and swelling. Review of systems was notably negative for chest pain, palpitation, and fever. He is known for metastatic small cell lung carcinoma, hypertension and dyslipidemia. His medications include codeine, amlodipine and atorvastatin, and his chemotherapy regimen includes cisplatin and etoposide. He denies any allergies. He is normotensive (142/80), tachycardic at 111 beats per minute, tachypneic (22 breaths/min) with good oxygen saturation (96% on room air). His physical examination is remarkable for unilateral swelling of the right lower extremity and a positive Homans's sign. An ECG done in triage shows sinus tachycardia, and nonspecific T-wave inversions unchanged from previous ECGs. You already have the following laboratory values:

Hemoglobin: 100 g/L (normal: 130-170 g/L)
Platelet count: 380 x 109/L (normal: 130-400 x 109/L)
White blood cell count: 7 x 109/L (normal: 4-10 x

109/L)
Sodium: 136 mmol/L (normal 136–146 mmol/L)
Potassium: 4 mmol/L (normal 3.5–5.1 mmol/L)
Chloride: 98 mmol/L (normal 98–100 mmol/L)
Bicarbonate: 26 mmol/L (normal 21–32 mmol/L)
Creatinine: 64 µmol/L (normal: 49–93 µmol/L)

What is the next best step?

A. Order a Chest X-Ray (CXR), Troponins, D-dimer
B. Order a D-dimer and Whole-leg ultrasound
C. Order a CT pulmonary angiogram (CTPA) and start anticoagulation
D. Order an echocardiogram then a V/Q lung scan

2 | ANSWER

C. Order a CTPA and start anticoagulation

This patient has a history of malignancy, received chemotherapy within the last 6 months, had clinical signs and symptoms of deep vein thrombosis (pain, swelling, erythema, positive Homans's sign), he is tachycardic and pulmonary embolism is the most likely diagnosis (PE). (1) Given his presentation, this patient's Wells score is above 4.5 which puts him in the likely PE risk category. (1) A high-sensitivity D-dimer is most useful to rule out PE when it is unlikely. (1) Certain centres may also choose to order a CXR and troponins to investigate other differential diagnoses, however the most important given his high-risk is to undergo a CTPA to confirm the diagnosis of PE. A V/Q lung scan can be considered in patients with renal dysfunction or contrast allergy for example; however, this study is best suited for patients that do not have intraparenchymal lung pathologies. (1) An echocardiogram can be helpful especially when a patient is too unstable to undergo CTPA, but does not provide a definitive diagnosis of PE. (1) Anticoagulation should be started especially if this study cannot be done within 4 hours and if there are no contraindications. (2)

3 | INITIAL APPROACH

With an annual incidence of 45,000 Canadians, venous thromboembolisms (VTEs) can manifest as a spectrum of diseases and complications, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), as a consequence of hypercoagulability, endothelial damage and/or venous stasis. (3, 4) Mirroring Virchow's triad, the risk factors of VTEs include prolonged immobilization, hormonal therapy, surgery, trauma, as well as malignancy, pregnancy, myeloproliferative disorders and inherited thrombophilia. (3) Nonetheless, 50% of PEs presenting for the first time are idiopathic. (1)

DVTs can present as localized pain, heaviness, swelling and/or discoloration of the affected extremity. Signs may vary from unilateral edema (with a difference $\geq$2cm in the circumference of the limb), dilatation of superficial nonvaricose veins, a palpable cord or a positive Homans's sign (tenderness with dorsiflexion of the foot). (3, 5) Upper extremity DVT, which may arise in the context of venous catheter, Paget-Schroetter syndrome and other conditions, is however less common. (4) Although only 25% to 50% of PEs present with clinical evidence of DVT, PEs are commonly a complication of proximal DVTs. (1) Symptoms of PE include acute or worsening shortness of breath, pleuritic chest pain, hemoptysis and/or syncope, while physical examination may be remarkable for tachycardia and tachypnea. (6) In submassive or massive PEs, ECG may show a right bundle branch block, T-wave inversion of precordial leads or a S1Q3T3 Pattern, which are manifestations of right ventricular strain. (6) However, the most common ECG finding remains sinus tachycardia. (6) CXR is most useful in assessing for other potential diagnoses as the Hampton hump (wedge-shaped opacification) or Westermark sign (decreased vascularity distal to the PE), which are signs suggestive of PE, but that are rarely seen. (6)

Given their non-specificity, using these signs and symptoms alone allows for poor differentiation between VTEs and other differential diagnoses, such as cellulitis and superficial thrombophlebitis for DVTs, or pericarditis and congestive heart failure for PEs. (5) This review will focus on a multi-step diagnostic tree allowing for evidence-based interpretation of tests following a determined pre-test probability (PTP).

4 | DEEP VENOUS THROMBOSIS

4.1 | Pre-test Probability (PTP)

The Wells clinical prediction rule for DVT (Figure 1) is a validated model that stratifies patients based on their risk for DVT. (7) Taking into account their risk factors and presentation, the score given will determine the risk category of the patient. For example, a score of 0 corresponds to a PTP of 5.0% (95% CI, 4.0%-8.0%) but a score higher than 3 corresponds to a PTP of 53% (95% CI, 44%-61%) of DVT. (7, 8) A score of 0 or 1 implies that DVT is unlikely, whereas a score of 2 and above means that DVT is likely.

4.2 | D-Dimer

D-dimer assays measure the product of fibrin degradation. They are highly sensitive but poorly specific as they can be elevated in other inflammatory conditions, such as malignancy or following surgery. (7) A high-sensitivity D-dimer assay is helpful in the unlikely DVT risk group to "rule out" a VTE if normal, while an elevated D-dimer would warrant further investigations. (4, 8) In the likely DVT risk category, the D-dimer result, whether elevated or not, would not change your likelihood sufficiently to rule out DVT given its high initial PTP, which is why ultrasound imaging is directly the next step.

4.3 | Venous Compression Ultrasound

Thrombosis Canada recommends proximal leg compression ultrasound (CUS) for evaluation of DVT, as non-compressibility of the deep veins below the deep fascia suggests a high likelihood of DVT. (4) In patients with a high PTP, a repeat proximal CUS should be sought 5-7 days following a negative CUS, given that 20% of distal DVTs may extend proximally. (4) Limitations of this study include distinguishing an acute clot from a chronic clot and operator variation. (3) Whole-leg ultrasound (including distal veins) is used in some centres, in which case a repeat CUS is not warranted if negative. (4, 9) Another less common imaging modality is CT Venography, which can be useful with proximal iliac DVTs or in May Thurner syndrome. (3)

5 | PULMONARY EMBOLISM

Given certain patients may present with complications of PE, it is important to first assess the hemodynamic stability of the patient. If the patient is stable with a blood pressure >90/60 mmHg, starting with determining the pre-test probability is best. A moderate or large PE can lead to right heart failure and subsequent cardiogenic shock. In fact, in a patient with massive PE, CTPA may not be possible as they may be too unstable. (3) In such scenarios, an urgent echocardiogram may give clues of massive PE with the presence of signs of right heart overload, presence of right ventricle or main pulmonary artery embolus and elevated pulmonary artery systolic pressure. (1, 6) If so, treatment should be started, especially if there are no alternative diagnoses. (1) The diagnosis should still be confirmed when the patient is able to tolerate CTPA. (1, 9)

5.1 | Pre-test Probability (PTP)

The Wells clinical prediction rule for PE (Figure 2) is a validated model, initially used in the emergency population, that stratifies patients based on their risk of PE. (10, 11) PE is unlikely with a score of 0-4, which corresponds to a PTP of 12.1% (95% CI, 10.7%-13.5%). (12) In the emergency room setting, meeting all criteria for the PE Rule-out Criteria (PERC) rules out PE without the need for D-dimer testing. (1, 9, 12) PERC criteria are met if a patient is less than 50 years old, not tachycardic (heart rate less than 100 beats/min), not hypoxemic (with oxygen saturation higher than 94%), does not have a history of surgery or trauma in the last 4 weeks, a history of VTE or estrogen use, and does not present with unilateral leg swelling or hemoptysis. (11, 12) A patient is likely to have PE with a Wells score of 4.5 and above, with PTP of 37.1% for that risk category (95% CI, 34.2%-40.0%). (12)

5.2 | D-Dimer

Once again, high sensitivity D-dimer assays may be used in patients in the unlikely risk category as they rule out PE if normal given their high negative predictive value. (12) Age-adjusted D-dimer cut-offs have been validated for PE such that the cut-off increases after 50-years-old by their age x 10ng/L. Its use is institution-dependent and was found to be as safe as standard cut-off when used in the outpatient setting. (1, 9) If the high-sensitivity D-dimer is positive or elevated, further investigations are necessary. (1)

5.3 | Multidetector Computed Tomography Pulmonary Angiogram (CTPA/CTPE)

With its high sensitivity and specificity, multidetector CTPA is the next step in likely PE patients as well as the unlikely risk group with a positive high-sensitivity D-dimer. (1) It has largely replaced pulmonary angiography given it is less invasive. (3) Following intravenous contrast injection, PE is identified by pulmonary arteries filling defects. (3) Follow-up with venous CUS or V/Q lung scan may be considered in patients with high clinical suspicion despite a negative CTPA and is recommended by the ASH guideline panel. (1, 9)

5.4 | Ventilation-perfusion (V/Q) Lung Scan

Given the risk of contrast nephropathy, contrast allergy and radiation exposure associated with CTPA, a V/Q lung scan study may be chosen in certain patients and is recommended by the ASH guideline panel for the unlikely risk group. (1, 9) Pulmonary arterial filling defects are identified by any mismatches in ventilation to perfusion following radioisotope administration. (3) This study has a high sensitivity and specificity for patients without significant lung disease. A V/Q scan may be nondiagnostic in older patients and those with pre-existing lung pathologies (such as COPD), in which case serial venous CUS or even CTPA can be undertaken as a next step to aid in the diagnosis. (9)

6 | TREATMENT

As a first step, it is important to address any signs of instability patients may present, such as hypoxemia or hypotension. For high-risk patients with more than four hours of delay for their diagnosis, it is important to consider a rapidly acting anticoagulant while waiting for imaging or other tests, unless there are contraindications (such as active bleeding). (5) While most DVTs can be managed in an outpatient setting, PEs should be risk stratified. Two tools are available from Thrombosis Canada: The Pulmonary Embolism Severity Index [PESI], which has 5 classes of severity, and the Simplified PESI. (2) Patients with low or very low-risk scores by the PESI can be managed as outpatients, while the following characteristics should generally prompt inpatient treatment instead: severe renal dysfunction, high bleeding risk, history of cancer or of cardiopulmonary disease, hypotension, hypoxemia, tachycardia or age above 80-years-old. (2, 6)

Once a diagnosis of VTE is established, there are 3 general principles of initial treatment (Figure 3). First, monotherapy is available by the administration of the direct-acting oral anticoagulants (DOACs) apixaban or rivaroxaban, unfractionated heparin (UFH) or low molecular weight heparin (LMWH). (2, 5) UFH is mostly useful in patients with severe renal failure and unstable patients who may require interventions (thrombolytic therapy or inferior vena cava filter placement) given the short half-life and easy reversibility, while the inhibitor of factor Xa fondaparinux can be used in heparin-induced thrombocytopenia for example. Second, the DOACs dabigatran and edoxaban have been shown to have lower bleeding risk in non-cancer patients, but treatment should start by LMWH for 5-10 days, before switching to these specific DOACs. (2, 5) Finally, warfarin, a vitamin K antagonist, can be also used for the treatment of VTE but requires to be started with LMWH for at least 5 days, as the international normalized ratio (INR) should be above 2.0 for two consecutive days prior to warfarin monotherapy. (13) The LMWH counteracts the initial prothrombotic effect of warfarin. (3) A fourth

treatment option, thrombolysis, is considered for massive PEs but has significant morbidity given its high risk of bleeding and hemorrhagic stroke and its discussion is beyond this review. (9) Finally, if a patient with an acute proximal DVT or acute PE has any contraindications for anticoagulation therapy, the possibility of using a vena cava filter should be raised. (2)

Duration of treatment is a balancing act between the risk of recurrence and of bleeding. This complication occurs mostly during the first 3 months of treatment and the highest risk factors are: cancer, thrombocytopenia, chronic kidney or liver disease and antiplatelet therapy. (5, 14) As a general principle, patients with a VTE provoked by a transient resolved risk factor (such as surgery in the last 3 months, reduced mobility, hormonal therapy, pregnancy) can stop their anticoagulant treatment after a minimum of 3 months. (9, 14) In patients with unprovoked VTE, anticoagulation therapy should be pursued for at least 3 months, and further therapy should be discussed. (14) Patients with persistent strong risk factors, such as active cancer, antiphospholipid antibody positivity or high-risk thrombophilia, may require lifelong anticoagulation. (14)

7 | BEYOND THE INITIAL APPROACH

This section covers an introduction to the approach to VTE in special populations.

7.1 | Pediatrics

Pediatric VTEs often present secondary to a multitude of risk factors from surgery, central lines, inherited thrombophilic conditions and more. (15) In fact, central-access vascular catheters are related to 90% of neonatal VTEs. (15) Because clinical decision tools or markers such as the Wells score and D-dimer assays have not been validated in pediatrics, diagnosis of DVT can be sought by CUS and doppler while PE needs to be confirmed with CTPA or even magnetic resonance venography (MRV). (15) The use of DOACs is not yet approved in pediatrics, as such UFH, LMWH and warfarin are first-line for anticoagulation therapy, for a duration of at least 3 months if provoked, or longer depending on the clinical scenario. (15)

7.2 | Pregnancy

The incidence of VTEs, commonly occurring from peripartum to 6-12 weeks postpartum, is about 1.5 per 1,000 pregnancies in Canada. (16) Most present as isolated iliofemoral DVT of the left lower extremity, and it can be difficult to distinguish DVT or PE symptoms given dyspnea and leg swelling are common in pregnancy. The LEFt rule is a risk stratification strategy that can be used for DVTs where points are allocated when the patient presents during the first trimester, with left leg symptoms and/or edema of the leg (with a 2 cm difference). However, venous CUS remains the first diagnostic choice. (16, 17) For PE diagnosis, although CTPA has less risk of radiation to the foetus (below 50mGy for both CTPA and V/Q scan), there is higher concern for breast irradiation cancer risk. (16) Of note, V/Q lung scan can affect breastmilk up to 48 hours after the study. (16) The Pregnancy-Adapted YEARS Algorithm can be used according to Thrombosis Canada. (16) Because warfarin can cross the placenta and DOACs have not been approved for use in pregnancy, and the first-choice therapy stays LMWH or UFH. (2, 13)

7.3 | Thrombophilias

Although the initial diagnostic tree will be similar, it is important to recognize when to do thrombophilia testing, such as in patients with a strong family history of VTE, recurrent VTEs or spontaneous VTE in young patients or at unusual sites unexplained by other causes. (4, 15) The most common, heterozygosity for factor V Leiden or prothrombin G20210A mutations, are considered low-risk thrombophilia and generally do not require longer anticoagulation therapy. (14, 15) Deficiency for antithrombin, protein C or protein S is however more potent and may require lifelong anticoagulation. (14, 15)

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APPROACH TO
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Bleeding

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ABSTRACT

This article presents a basic approach to the bleeding patient and is intended for medical students in their pre-clinical and clerkship years. Easy bruising and abnormal bleeding are relatively common symptoms, and may present as excessive bleeding post-injury, epistaxis, menorrhagia, prolonged bleeding after surgery or spontaneous bleeding. Identification and appropriate medical management of abnormal bleeding and bruising can decrease associated morbidity and mortality.

KEYWORDS
Bleeding, Coagulation, Hemostasis

1 | QUESTION

A 24-year-old women came to the urgent walk-in clinic due to continuous gum bleeding after a mouth injury the day prior. She was playing frisbee and was accidentally struck on her bottom lip when her friend threw the disc without warning. The patient had a history of bruising easily and of heavy menstruation with crampy lower abdominal pain. She had no significant medical history and took no medications other than occasional Advil. The patient did not use tobacco or illicit drugs, and had 2-3 alcohol drinks per week with her friends. She was a recreational athlete and ate a balanced diet. She reported that her mother also had a history of "bleeding issues." Her blood pressure was 117/73 mm Hg and her pulse was 78/min. Oropharyngeal examination showed blood oozing from a gum abrasion. A fading bruise was present on the left arm, but there were no other skin abnormalities. The remainder of the physical examination was normal. Initial investigation results were as follows:

Hemoglobin 107 (Normal: 120-160)
MCV 76 (Normal: 80-100)
Platelets 180,000 (Normal: 150,000-400,000)
PT 12 (Normal: 11-15)
INR 1 (Normal: <1.1)

PTT 39 (24-32)

Which of the following conditions is most likely in this patient?

A) Hemophilia A
B) Von Willebrand Disease
C) Hemophilia B
D) Bernard-Soulier Syndrome
E) Disseminated Intravascular Coagulation (DIC)
F) Advanced liver cirrhosis
G) Glanzmann's Thrombasthenia
H) Warfarin ingestion

2 | ANSWER

B, This patient's presentation is consistent with Von Willebrand Disease (VWD), an inherited disorder of platelet adhesion that is estimated to affect approximately 1% of the worldwide population. (1) Most individuals with VWD are asymptomatic, however, a minority of patients have easy bruising, skin bleeding and mucosal bleeding. (2) This patient's normal platelet count effectively rules out a quantitative platelet disorder as a cause of her prolonged mucosal bleeding. As well, her normal PT and INR suggest that her extrinsic coagulation pathway is intact, making entities such as Warfarin ingestion (H), fat-soluble vitamin deficiencies and advanced liver cirrhosis unlikely (F).

VWD is associated with impaired quality/quantity of von Willebrand factor (vWF), a glycoprotein produced by endothelial cells and platelets. (2) VWF contributes to platelet-endothelial binding and platelet aggregation, as well as acts as a carrier protein for coagulation factor VIII. (3) Therefore, individuals with VWD may have a slightly prolonged PTT due to degradation of factor VIII, as well as a prolonged bleeding time due to platelet dysfunction, however, PT/INR would typically be unaffected. (2)

A normal PTT would be expected in conditions such as Glanzmann's Thrombasthenia (G) and Bernard-Soulier Syndrome (D), which are inherited platelets disorders. (4) Hemophilia tends to present with deep tissue bleeding, such as spontaneous hemarthroses, and is much more common in males than females (A,C). (5) Disseminated intravascular coagulation would be associated with a prolong PT and PTT due to coagulation factor consumption (E). (6)

3 | INITIAL APPROACH

The initial investigation of a patient presenting with bleeding that is considered to be abnormal begins with a thorough history and physical exam. A detailed history should characterize the onset, course, duration, precipitating events and alleviating factors of the current bleeding episode. As well, inquiring about the presence of any constitutional symptoms (potentially concerning for malignancy), in addition to obtaining a detailed personal bleeding history, family history and medication history (with emphasis on anticoagulant and antiplatelet agents) is vital. (5) When assessing a patient with bleeding, symptoms such as pallor, dizziness and perceived tachycardia/palpitations may help characterize potential blood volume loss. In addition, a thorough physical examination may identify information regarding the origin and severity of the bleeding and can help tailor further investigations. Obtaining accurate vital signs along with an assessment of volume and perfusion status (such as checking distal pulses and capillary refill) is important for initial assessment. In addition, a complete head-to-toe examination is needed to identify any present signs of bleeding. For example, mucocutaneous bleeding (such as epistaxis, petechiae and gingival bleeding) tend to be more suggestive of platelet disorders. (4, 7) On the contrary, spontaneous hemarthroses, and muscle hemorrhages are commonly associated hemophilia or other congenital coagulopathies. (8) Initial laboratory evaluations should include a complete blood count, prothrombin time (PT) and partial prothrombin time (PTT) along with liver and renal function testing. (8) These basic laboratory parameters can indicate possible disorders affecting platelets and/or the clotting cascade, thus narrowing the differen-

tial diagnosis (Figure 1). A normal PT and PTT imply that the coagulation cascade is intact, suggesting a possible platelet source of bleeding. (8)

3.1 | Prothrombin Time/International Normalized Ratio

The prothrombin time (PT) is used to evaluate the function of the extrinsic and final common pathway of the coagulation cascade (Figure 2), with a prolonged PT indicating dysfunction of these processes. (9) As such, a prolonged PT may indicate deficiencies or inhibitors of clotting factors affecting the extrinsic and final common pathways. (10) A prolonged PT in the clinical setting is often due to the use of Warfarin, a commonly prescribed anticoagulant with effects on factor VII activity. (9) Other causes of PT prolongation include liver failure, vitamin K deficiency and consumptive coagulopathies (such as disseminated intravascular coagulation). (8) The International Normalized Ratio (INR) is often used in clinical practice to overcome interlaboratory variation within measured PT. It is a mathematical conversion of a patient's measured PT that accounts for variability in reaction reagents used in the different laboratory settings. (8) As such, a prolonged INR should be interpreted as would a prolonged PT.

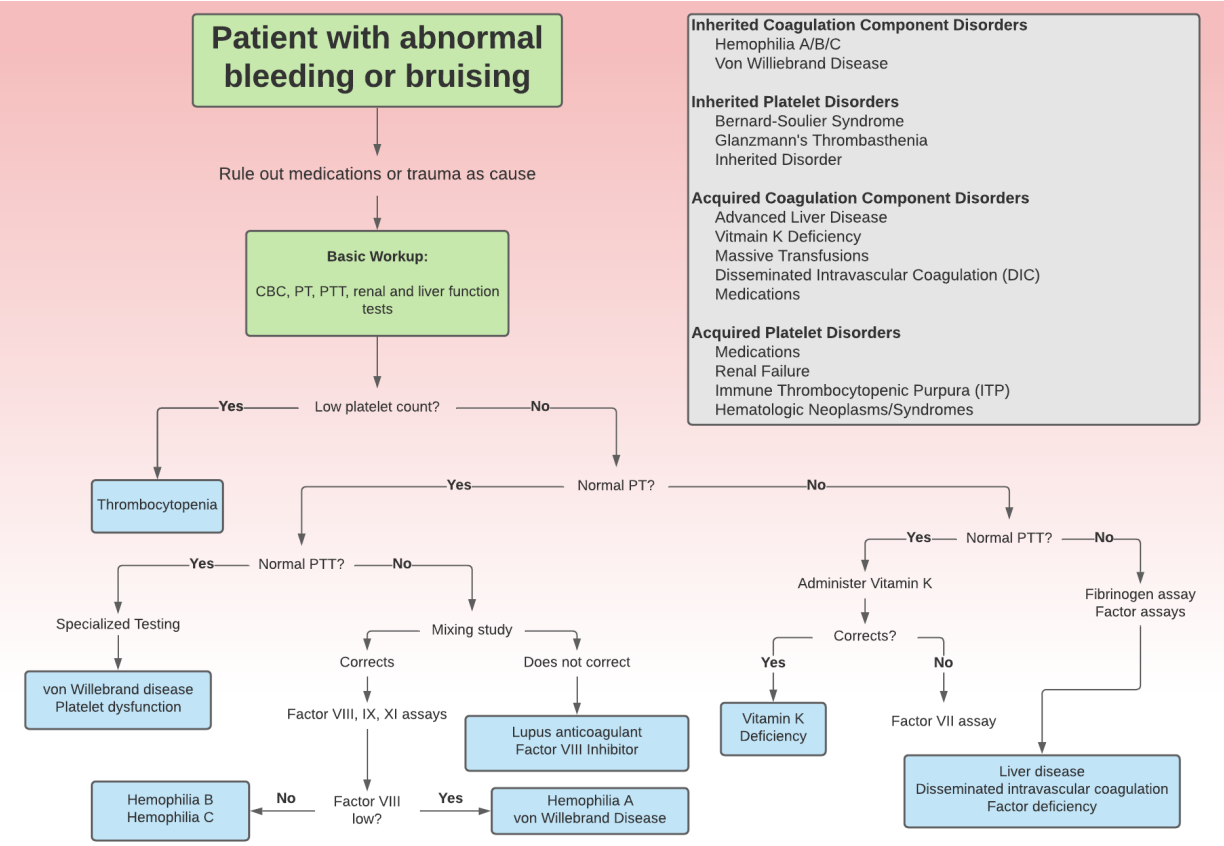

FIGURE 1 Initial approach to abnormal bleeding. Systematic approach to the evaluation of abnormal bleeding. Adapted from: Neutze D, Roque J. Clinical Evaluation of Bleeding and Bruising in Primary Care. Am Fam Physician. 2016;93(4):279-86.

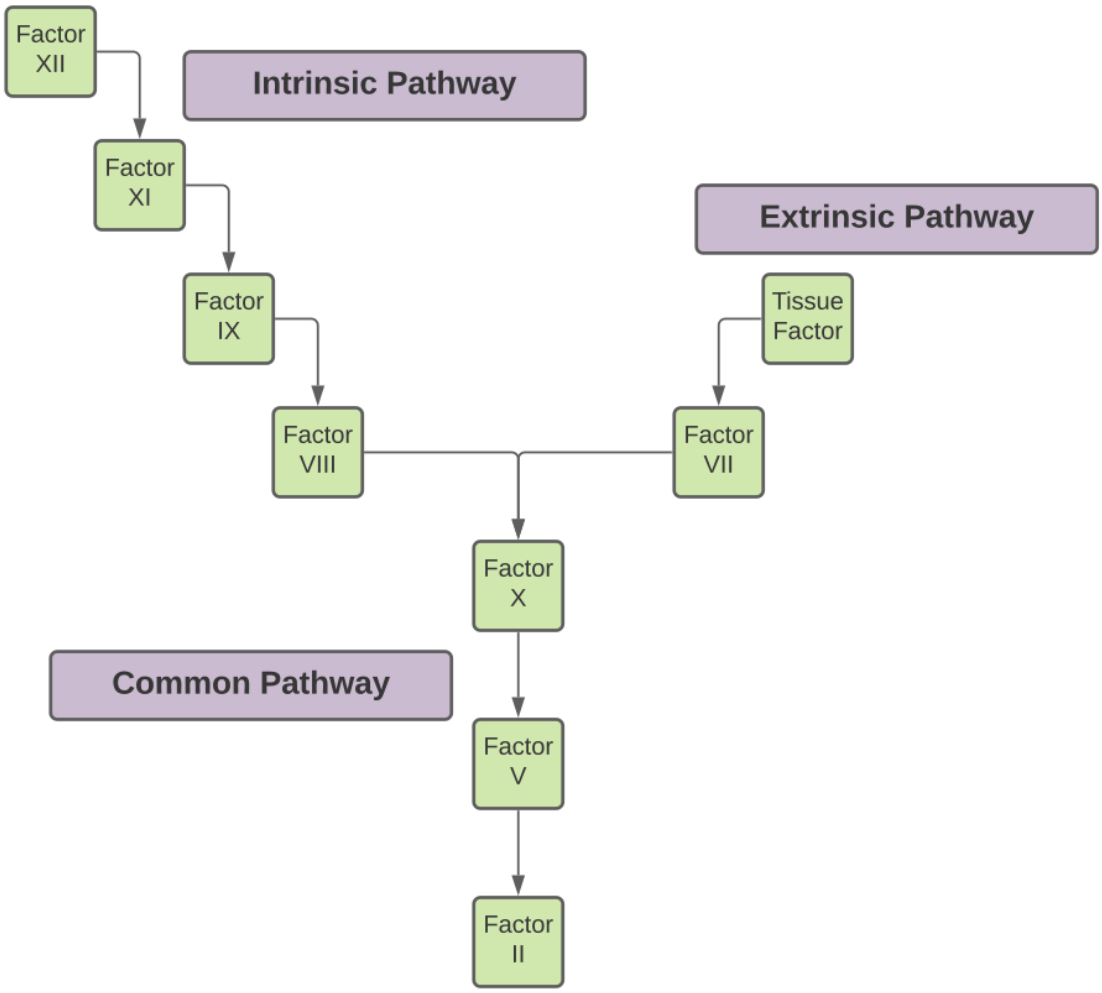

FIGURE 2 Simplified coagulation cascade. Adapted from: Kruse-Jarres R, Singleton TC, Leissinger CA. Identification and basic management of bleeding disorders in adults. J Am Board Fam Med. 2014;27(4):549-64.

3.2 | Partial Thromboplastin Time (PTT)

To evaluate the function of the intrinsic and final common pathway of the coagulation cascade, the partial thromboplastin time (PTT) is used (Figure 2). (9) Similarly to the PT, deficiencies or inhibitors of clotting factors within the extrinsic and final common pathways result in prolongation of the PTT. (8) In the clinical setting, PTT is used to monitor response to heparin, an anticoagulant that works on factors II (thrombin) and factor X. (10) Other causes of PTT prolongation include congenital factor deficiencies (such as in Hemophilia), decrease in certain coagulation factors (such as VIII in VWD) and consumptive coagulopathies (such as disseminated intravascular coagulation). (8, 11)

3.3 | Other Laboratory Testing

When evaluating a patient with abnormal bleeding, it is often relevant to obtain complete blood counts, as well

as renal and liver function tests, to evaluate for underlying systemic disease. (5) Peripheral blood smears may also be of value, to help confirm the presence/absence of thrombocytopenia as well as to evaluate platelet morphology and possible hematologic malignancies or hyperproliferation conditions. (8) Classically, measurement of a patient's bleeding time was used to assess platelet function. This involved the creation of a standardized skin incision in order to record the time until bleeding ceased, however, this has now been mostly replaced with modern alternative platelet function analyzers. (12) Specialized laboratory testing for specific underlying causes of abnormal bleeding can be used once the differential diagnosis has been narrowed by the use of more preliminary measures as above. These specialized investigations include assays to assess specific coagulation factor titers (such as assays for factors VIII, IX or XI), procoagulant particle activity (von Willebrand factor antigen quantification/activity) or the presence of certain coagulation factor inhibitors (lupus anticoagulant detection). (10)

4 | BEYOND THE INITIAL APPROACH

In this section, commonly described causes of bleeding are discussed in more detail.

4.1 | Inherited Disorders

4.1.1 | Hemophilia A and B

Hemophilia A and B are inherited bleeding disorders due to the deficiency of factors VIII and IX, respectively. (5, 11) These disorders are passed along via an X-linked recessive inheritance pattern, as such, males are more affected than females. (8) Patients affected by these disorders can experience profound bleeding after surgeries as well as spontaneous bleeding into deep tissues (causing entities such as spontaneous hemarthroses). (5)

4.1.2 | Von Willebrand Disease (VWD)

VWD is due to a defect in Von Willebrand factor (VWF), which is a glycoprotein produced by platelets which functions to facilitate platelet adhesion and aggregation. (3) VWF also acts as a carrier for factor VIII. As such, individuals with VWD may have a prolonged PTT. (10) Treatment for this disease is possible without the use of blood products, as tranexamic acid and desmopressin have been seen to be helpful in correcting bleeds. (3) However, when indicated, factor VIII concentrates and other plasma products can be used to overcome bleeding. (5)

4.1.3 | Inherited Platelet Disorders

Several blood disorders associated with dysfunctional platelets can result in a bleeding diathesis due to defective primary hemostasis. Many inherited thrombocytopathies have been characterized and each can be classified into abnormal platelet adhesion, activation or aggregation, or a combination thereof. (4) While many of these disorders are quite rare, Bernard-Soulier syndrome (BSS) and Glanzmann's thrombasthenia (GT) are more commonly described. (5) BSS is caused by a qualitative or quantitative defect of the GPIbIX/V complex on the platelet membrane, which often leads to a severe bleeding disorder. (13) This complex is the major receptor for VWF and mediates both platelet agglutination and adhesion. (4) Meanwhile, GT is caused by a qualitative or quantitative deficiency of the platelet GPIIb/GPIIIa complex, which can lead to severely impaired platelet aggregation. (13)

4.2 | Acquired Disorders

4.2.1 | Medications

Drug-induced bleeding disorders can be classified according the mechanisms in which they disrupt bleeding. This includes drugs that 1) are anticoagulants themselves 2) potentiate the action of other anticoagulants 3) inhibit the activity of platelets 4) decrease the quantity of circulating platelets and 5) increase vascular fragility.

(4, 5, 8, 9, 13) Many commonly used medications are implicated in these processes, although medications most commonly associated with bleeding include anticoagulants (particularly warfarin, heparin, enoxaparin, dabigatran, apixaban, and rivaroxaban), anti-platelet agents (such as clopidogrel, aspirin), corticosteroids, and non-steroidal anti-inflammatory drugs. (8)

4.2.2 | Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) describes the widespread activation of coagulation, leading to intravascular formation of fibrin and thrombotic occlusion of small and midsize vessels. (6) The resulting depletion of platelets and coagulation proteins resulting from the ongoing coagulation can cause a severe bleeding diathesis. (8) As such, deep tissue bleeding is often the presenting symptom in a patient with DIC. DIC is associated with many clinical conditions, although bacterial infections, widespread trauma, malignancies, obstetrical complications, reactions to toxins and immunologic disorders are often implicated. (6, 14) The development of DIC is associated with unfavourable outcomes and has been shown to be an independent predictor of mortality. (6)

4.2.3 | Acquired Platelet Disorders

Acquired platelet disorders are relatively common in clinical practice, in contrast to congenital platelet disorders. (4, 7) As discussed above, medications such as aspirin have well-documented anti-platelet activity and are commonly used in patients with cardiovascular disease. However, these patients may be at increased risk of subsequent bleeding. Other medications with possible anti-platelet activity include some anti-inflammatory drugs and herbal remedies. (8) Systemic medical disorders may also disrupt platelet quality/quantity including uremia due to renal failure, anti-platelet antibodies (in conditions such as systemic lupus erythematosus and idiopathic thrombocytopenic purpura) and hematologic disorders (such as myeloproliferative neoplasms, leukemias and myelodysplastic syndromes). (15) Other causes of acquired thrombocytopenia include viral infections (such as Epstein-Barr virus, parvovirus B19 and cytomegalovirus), autoimmune syndromes (such as idiopathic thrombocytopenic purpura) and splenic sequestration. (16)

4.2.4 | Liver Disease

Individuals with liver disease can have a bleeding diathesis that is often multifactorial. The liver is responsible for synthesizing many of the major coagulation factors, which may be affected in states of liver pathology. (10) Reduced levels of factors II, V, VII, IX, X and XI are commonly seen in advanced liver failure. (5) As such, prolonged PT/INR and PTT can be seen. (10) In addition, liver disease can lead to thrombocytopenia, as portal hypertension contributes to the splenic sequestration of platelets. (5)

4.2.5 | Vitamin K Deficiency

Several key coagulation factors (II, VII, IX, X) depend upon sufficient Vitamin K for carboxylation in the liver. (5) As such, a vitamin K deficiency (or intrinsically impaired carboxylase activity in the liver) may lead to ineffective coagulation. (8) This would prolong the PT/INR, much in the same way that administration of warfarin would. Oral or parental vitamin K should be given if deficiency is suspected. (5)

4.2.6 | Massive Transfusion

Classically, a massive transfusion is defined as a replacement of a patient's total blood volume in 24 hours. (5) As transfusions of packed red blood cells (PRBCs) do not contain significant levels of clotting factors and can cause a dilutional coagulopathic state, regular infusion of coagulation factors in the forms of fresh frozen plasma or platelet rich plasma should be given throughout the transfusion protocol. (17)

4.3 | Conclusion

Easy bruising and abnormal bleeding are relatively common symptoms experienced by patients. Proper identification and appropriate medical management of such presentations can decrease associated morbidity and mortality. Physicians should be prepared with an approach to patients with abnormal bleeding to identify and address common underlying etiologies. Ultimately, the implementation of basic clinical method, guided by a thorough history and physical exam, is an essential starting point to initially asses such patients as well as to guide further investigations.

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APPROACH TO
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Concussion in the adult athlete

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ABSTRACT

Concussions are common in the athlete population. They occur after a trauma to the head and can lead to a loss of consciousness. Patients suffering from a concussion commonly present with confusion, amnesia, and headache in the context of a recent head trauma. The approach to this pathology consists of making a clinical diagnosis, ruling out life-threatening complications such as fractures and intracranial hemorrhages, and educating the patient on a safe recovery and return-to-play. Patients who do not have worrisome symptoms can be discharged home with a responsible adult that has been informed of when to seek medical care in case of a complication. After a short rest period, they should be advised to gradually resume their cognitive and physical activities. After a period of minimum 10 days and in the absence of symptoms, the patients can undergo a progressive return-to-play plan.

KEYWORDS
Sport Medicine, Concussion, Athlete, Return to Play, Traumatic Brain Injury

1 | QUESTION

A 22-year-old soccer player presents to the emergency room complaining of a headache after being accidentally hit in the head by a ball during practice. He describes feeling the ball hit the side of his head and falling immediately on the ground after the impact. He denies losing consciousness. On further questioning, he has no past medical history, takes no medications, but recalls a similar event happening two years ago that forced him to miss school for two weeks due to headaches and difficulty focusing in class. On physical examination, there is a 3 × 2 cm mildly tender ecchymosis on the side of his head. Neurological examination shows mildly impaired attention but is otherwise normal. After making the diagnosis, what recommendations should be made to this patient?

A) Stop all contact sports to avoid another concussion
B) Full cognitive and physical rest for at least two weeks after the injury.

C) Avoid non-steroidal anti-inflammatory (NSAID) medications for 7–10 days due to the risk of intracranial bleeding
D) Rest for 24–72 hours before resuming non-contact physical activity as tolerated

2 | ANSWER

D, the correct answer is to resume physical activity gradually after a short period of physical and cognitive rest. Patients should not be told to stop all contact sports but a discussion with the family should be had to reduce the risk of additional injuries. NSAIDs are first-line medications for treating post-concussion headaches. Prolonged cognitive and physical rest has been shown to slow the recovery and lead to longer post-concussion symptoms. Persistent post-concussive symptoms (PPCS) are defined by symptoms lasting longer than the natural post-injury course. Patients with PPCS may present clusters of vestibulo-ocular, cervicogenic, migrainous and psychological symptoms. (1)

3 | OVERVIEW OF CONCUSSIONS

3.1 | What Is a Concussion?

Concussions, also called mild traumatic brain injury (mTBI) are a common medical condition in both the athlete and the general population. Concussions may be caused by a direct blow to the head or by any force on another part of the body that is transmitted to the head. Many definitions of concussion exist as there are multiple mechanisms of injury and a large range of symptoms associated with concussions. The American Academy of Neurology defined concussions as “a clinical syndrome of biomechanically induced alteration of brain function typically affecting memory and orientation, which may involve loss of consciousness.” (2) Although not fully elucidated, the pathophysiology includes a sudden release of excitatory neurotransmitters inducing a glycolytic hypermetabolic state and lactate production which impairs neuronal function. (3)

3.2 | Epidemiology

Approximately 1.2% of the Canadian population sustain a mTBI every year. (4) The prevalence of mTBI varies depending on the population observed. In the general population, men are at least two times more likely to sustain a concussion than women. (5, 6) However, women are more likely to sustain a mTBI while playing sports, regardless of their level. (7) The sports most associated with mTBI are football, ice hockey, soccer, boxing, and rugby. (8) It is common for athletes to refuse disclosing a potential concussion. These situations are dangerous as they increases the risk of second impact syndrome . (9) Second impact syndrome is defined as a second brain trauma occurring on a previously injured brain that has not fully recovered.(10) Although not fully understood, it is postulated that it results in a rapid brain swelling that can lead to herniation and catastrophic neurological damage.(11)

4 | INITIAL APPROACH

The goals of the initial approach to this condition are to make the diagnosis, rule out life-threatening conditions with additional tests when indicated, and to advise the patient on behaviour modification and recovery strategies.

4.1 | Clinical Presentation and Diagnosis

Signs and symptoms of a concussion may take up to 48 hours to manifest. The hallmark symptoms of concussion are confusion and amnesia. (12, 13) Other common symptoms include new or worsening difficulty thinking or concentrating, new or worsened headaches, dizziness, light and sound sensitivity, and emotional symptoms such as nervousness and emotional lability. (14) (Table 1) The diagnosis of mTBI is clinical.

Many tools are available to assess concussions. They can be categorized as screening and confirmatory tools.

(15) The most common screening tools are the Standardized Assessment of Concussion (SAC). Screening tools can be used to assess the risk of concussion immediately after an injury to remove an athlete from the game. Other tools, such as the SCAT5 (Sport Concussion Assessment Tool 5th Edition) and the impact (immediate post-concussion assessment and cognitive testing), are more extensive and used in a clinical settings as they provide a more in-depth assessment of the athlete's condition and allow follow-up testing. The SCAT5 is the most common validated tool that can assist the clinician in diagnosing a concussion in the acute setting. This evaluation tool combines a symptom evaluation, cognitive and gross neurological function assessment. It has been demonstrated as especially useful before the 3-5 days post injury to aid in the diagnosis. (16)

The physician must take a complete history, physical and neurological examination to associate a head trauma

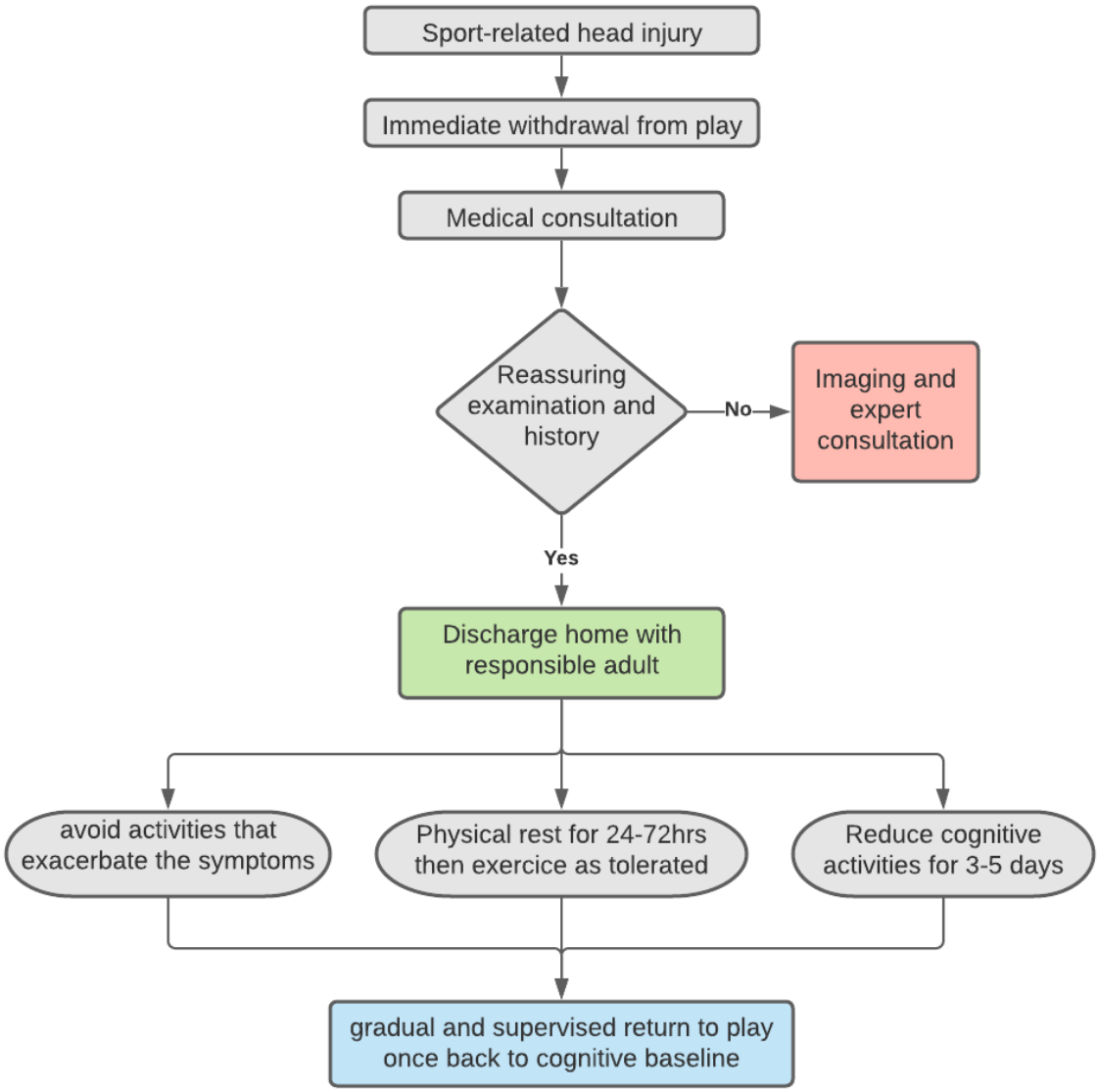

FIGURE 1

with an above-mentioned symptom and make the diagnosis. On history it is essential for the physician to clearly understand the mechanism of injury to determine the severity of the head and associated injuries. Some factors associated with a more severe injury are high speed or high energy injuries – where the brain could be exposed to a greater force of impact inside the cranium. Whiplash injuries are associated with cervical and vestibular injuries in addition to brain injuries. (17) The patients should be questioned on previous head injuries (including possible undiagnosed concussions), medication use (particularly medications that increase the risk of bleeding) and associated injuries such a neck or back pain. At any time if an injury to the cervical spine is suspected, the patient should be immobilized until a fracture can be ruled out.

The physical examination should be focused on identifying fractures, cerebrospinal fluid leaks and other injuries. To do so, the physician should carefully palpate the patient's head, look for otorrhea or rhinorrhea and complete a head-to-toe examination to rule out other injuries. A complete neurological examination should be done on the first assessment. It should include a baseline mental status exam, cognitive assessment, and a thorough examination of the cranial nerves. It should also look for neurological deficits and signs of increased intracranial pressure such as headache, vomiting and visual changes. Acute and mild impairment in cognition might be normal but focal neurological deficits, worsening neurological status or mental status are worrisome features that warrant further investigation. Laboratory tests and imaging are not routinely used but might be useful when life-threatening complications such as fractures of intracranial bleed are suspected.

4.2 | Complications

Most mTBI are uncomplicated, but 6–10% are associated with cerebral contusions that can lead to intracerebral, subdural, epidural or subarachnoid hemorrhages. (18) It is essential for the physician to recognize these complications rapidly since they can be life-threatening and are associated with a poor functional prognosis. (19)

Worrisome symptoms that warrant urgent imaging are a suspicion of fractures, worsening neurological status, worsening level of consciousness, cerebrospinal fluid otorrhea or rhinorrhea, severe headaches, repeated vomiting, and seizures (Table 2). If a bleed or fracture is suspected, the patient should receive an urgent computed tomography (CT) of the head without contrast and be referred to a neurosurgeon.

4.3 | Treatment

The treatment of an uncomplicated sport-related concussion consists of outpatient observation if the patient has a Glasgow coma scale (GCS) of 15, which indicates intact cognitive function (the patient is responsive with optimal eye, verbal and motor responses), a normal examination or CT and no risk factors for bleeding such as anticoagulation, or a genetic disorder. (20) After possible complications and life-threatening conditions have been ruled out, the patient can be discharged home if accompanied and supervised by a responsible adult. It is essential to educate the patient and their caregiver on when and how to seek medical attention if a complication occurs. Parents should seek immediate attention if there is a change in the mental status, level of arousal, significant increase in headache, or visual changes.

Symptoms such as impaired attention, difficulty concentrating and sleepiness will improve with time. Post-concussive headache symptoms can be managed effectively with simple analgesics such as NSAIDs. If not effective, triptans can be used for headaches with migrainous features. (3) Multiple new treatment modalities are currently being studied. Transcranial pulsating low-frequency electromagnetic stimulation (21) and hyperbaric oxygen therapy (22) has been studied in small groups of patients with long-lasting concussion symptoms.

Worrisome Symptoms	Common Symptoms
• Worsening mental status • Worsening neurological status • Seizure • Visual disturbances • Severe neck pain • Repeated or severe vomiting • Focal neurological deficit • Incontinence • Impaired consciousness • Severe balance problems	• Confusion • Amnesia • Headache • Dizziness • Light and sound sensitivity • Emotional lability • Nervousness • Difficulty concentrating

TABLE 1 Common and Worrisome symptoms (Red flags) of a concussion

5 | BEYOND THE INITIAL APPROACH

5.1 | Patient Counselling

Traditional advice was to avoid all physical and cognitive activities for a prolonged period after a concussion. It has been demonstrated that moderate cognitive activity is equivalent to complete cognitive rest. (23) Patients should be advised to reduce significantly their cognitive activity for 3–5 days after the injury and then scale up as tolerated. (3) Contrary to previous advice, recent studies have shown that early physical activity following a concussion is beneficial and leads to lower rates of persistent post-concussive symptoms. Patients should be advised to rest for 24–72 hours and then exercise as tolerated. (3, 14) The goal is that following a short period of rest, patients should gradually reintegrate cognitive and physical activity without exacerbating their symptoms.

5.2 | Returning to Sport Following a Concussion

Return to sport following a concussion should be gradual and may vary upon the injury sustained by the patient. For a uncomplicated sport-related injury, the athlete should not engage in physical activity for the first 48 hours following the concussion. After 48 hours post-injury, the patient may gradually return to physical and intellectual activities. This gradual return to activities has multiple steps separated by a minimum of 24 hours. To progress to the next step, the patient needs to be able to complete the activity without an increase in the number or intensity of their symptoms. If symptomatic, the patient needs to wait another 24 hours and return to the previous step . (24) A concussed player should only return to high-intensity training (with or without the team) once there has been a complete return to normal cognitive activities such as school or work. (24) To reduce the risks of second-impact syndrome which can be catastrophic (25) patients should not undergo any activities that put them at risk of head injury before a minimum of 10 days after the injury. (3, 26)

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APPROACH TO
McGill Journal of Medicine

Headaches

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ABSTRACT

Headaches are one of the most common reasons for visiting a family physician. The estimated lifetime prevalence of a headache is about 66%. (1) They pose a significant burden on the patient's quality of life, and in fact contribute to about 20% of work absences. (2) Fortunately, most cases are benign. The following article presents an approach to headaches with a focus on migraines. The article aims to differentiate between benign and worrisome causes of headaches and describe the management.

KEYWORDS
Headaches, Migraines, Imaging, Family Medicine

1 | QUESTION

J is a 27-year-old female university student who works part-time as a waitress. She presents to a family physician office with an 11-month history of intermittent severe headaches. Her past medical history is unremarkable. She has no allergies, and occasionally takes Ibuprofen to which she claims does not help anymore. Her father is diabetic, and her mother is known for high blood pressure.

She began to have headaches at the start of exams last semester. She experiences about 2-3 every month and they each last about 7 hours. Sometimes she stays home from school as because the headaches are so severe. During a headache episode she feels a unilateral throbbing pain around her head, she also feels nauseous and has even vomited on occasion. During the attack she gets very irritable to any loud sound. Fortunately, lying down and closing her eyes helps ease the pain.

On physical exam her BP is 130/86, heart rate 65/min, respiratory rate 15/min. Oral temperature is 37 degrees. No papilledema was identified. No pain was reproduced

upon sinus palpation.

The patient denies recent trauma, fever, neck stiffness, night sweats, fatigue, or weight loss. The patient denies any syncope, vertigo, light-headedness, tremor, weakness, paresthesia or speech difficulty. Patient is alert, attentive and oriented. Neurology exam including cranial nerves, motor strength, reflexes, sensation and coordination were within normal limits.

J's grandfather recently died from cancer and this is causing her to worry that her headaches may be indicative of a harmful underlying condition.

As the family physician, what would be the next best course of action?

A. Order an MRI stat to rule out malignancy

B. Prescribe a high dose NSAID

C. Referral to neurology to evaluate for brain damage

D. Reassure the patient and discuss other possible medications

2 | ANSWER

D. The case is of a young student who is juggling multiple potential stressors. She reports no head trauma, lack of coordination, or numbness and is otherwise in good health. Her headache presented several months ago and has maintained in frequency. The case is a typical presentation of a migraine. While headaches are commonly benign, it is important to complete a thorough history and physical exam to exclude any serious secondary causes. Once the diagnosis with migraines is made, the patient will explore the avenues of treatment and the physician should reassure her that the condition is not life-threatening.

3 | INITIAL APPROACH

3.1 | Definition of Primary and Secondary Headaches

Headaches are divided into two classes, primary and secondary. Primary headaches describe disorders in which the cephalalgia is not due to an underlying lesion. Secondary headaches describe disorders in which the pain is from another underlying cause. Despite 66% of the population experiencing primary headaches at one point in their lives, the etiology is poorly understood. (3) The most widely accepted theory describing primary headaches is that there is sensitization of nociceptive neurons. The long-lasting activation and sensitization of these neurons triggers a headache attack. This can be further explained as a form of disinhibitory sensitization with dysfunction of descending modulatory pathways; a similar mechanism to what occurs in allodynia. The peripheral sensitization of trigeminal nociceptive afferents innervating the dural meninges was seen to be playing the leading role. (3) Specifically, the local release of inflammatory markers were responsible for activating the trigeminal nociceptors. (4)

3.2 | Important Causes of Secondary Headaches

While primary headaches constitute 98% of all headaches, it is important to recognize secondary headaches as they can potentially be life threatening. (5) Secondary headaches are those that arise from an underlying structural lesion to the brain and/or the surrounding structures. Etiologies include vascular, infectious, neoplastic, or traumatic causes. Vascular causes include hemorrhages such as subdural hemorrhage, incracerebral hemorrhage and subarachnoid hemorrhage which presents as a sudden severe onset headache is termed a "thunderclap headache." (6) Subdural hemorrhage and intracerebral hemorrhage are included too. Vascular disorders also include arteriovenous malformations, cerebral venous sinus thrombosis (CVST), collagen vascular disease, carotid artery dissection, arteritis, and others. Infectious causes typically include meningitis and sinus infections. Mass lesions can present with systemic symptoms, seizures and headaches. Trauma to the neck and head can cause direct/indirect structural lesions – namely contusions, skull fracture and edema which can lead to headaches as well. The clinical presentation of

secondary headaches will be discussed in further detail.

3.3 | Red Flags for Headaches

While performing the history it is important to keep in mind the most common and most worrisome causes of headaches. The most common being benign such as a tension-type headache while the most worrisome being a subarachnoid hemorrhage or a hypertensive emergency. Signs such as systemic symptoms, neurological symptoms, sudden onset, onset at older age, and change in pattern are **red flags** that require prompt evaluation for a serious cause. A concise summary of the red flags is shown in Table 1.

When a patient presents with pain, such as a headache, it is often instinctual to order imaging tests. Meanwhile, in the case where there are no red flags, imaging is rarely helpful. (7) Utilizing clinical skills can help avoid the risks and the high cost associated with imaging. Having an established clinical approach does not only alleviate the burden on the imaging department but also helps avoid unnecessary tests on the patients.

3.4 | History and Physical Exam

Most headache diagnoses can be made entirely from the patient history and physical exam. A Flowchart summarizing the approach to headaches is found on Flowchart 1. The history should focus on the location, quality, severity, provoking and alleviating factors and length of the headache. Associated symptoms that occur with the headache should be asked as well such as nausea, vomiting or photophobia. The physical exam should focus on the head and neck along with a full neurological exam. The head is examined for any skin changes, bruising and deformities. The scalp should be examined for tenderness and swelling which can be signs of trauma. The conjunctiva and fundi are each examined. The head and neck are palpated for any lesions or lymphadenopathy.

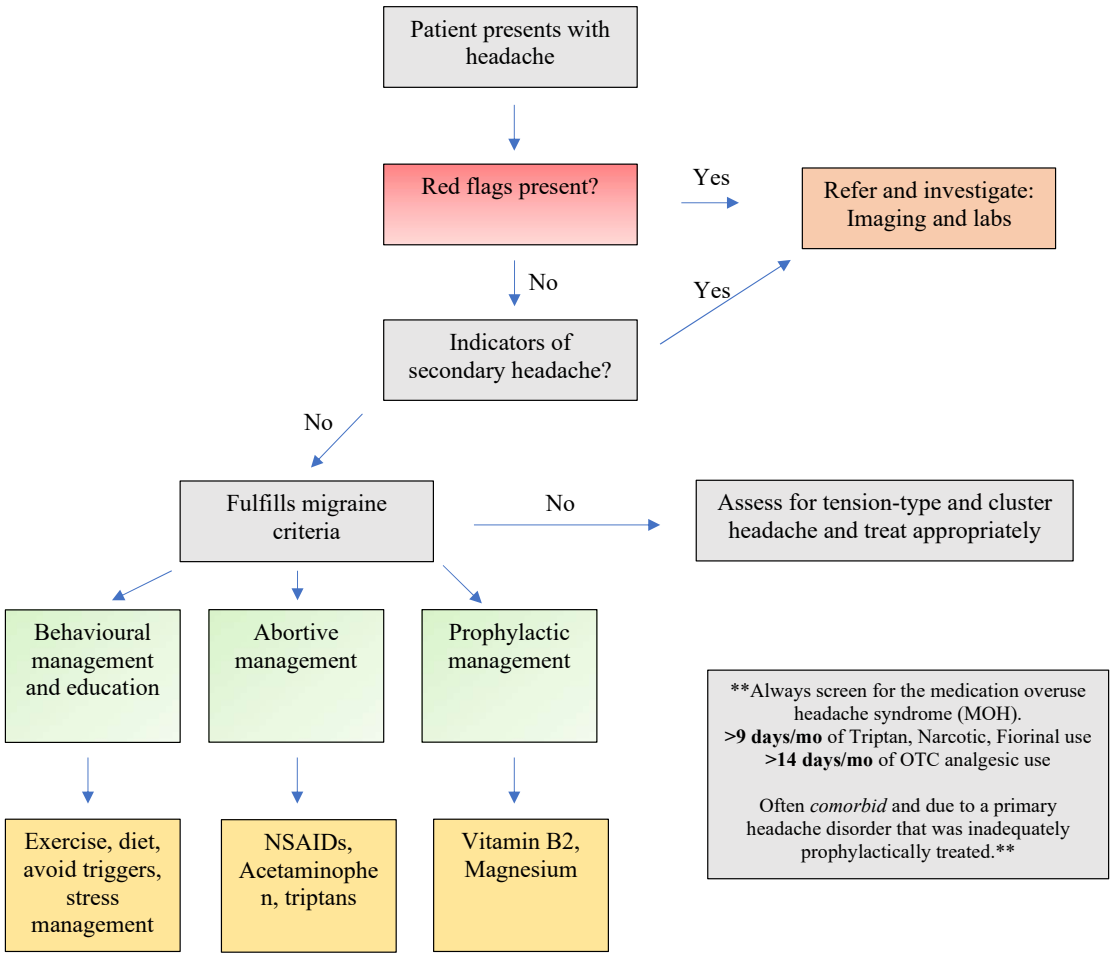
Neurological exam should include a cursory overview of the mental status and language. Cranial nerve exam should include a minimum screening of visual fields, fundoscopy, pupillary light reflexes and visual acuity. Extraocular motility and presence of pathological nystagmus should also be commented on. Lower cranial nerves are to be examined for facial asymmetries, facial sensory loss or hearing impairment (i.e, with finger rub, Weber and Rinne testing). The remainder of the neurological exam should be aimed at identifying if any (presence of) motor asymmetries, limb weakness, changes in tone, or objective anatomically based regions of sensory loss. Abnormal or asymmetrical deep tendon reflexes can help distinguish UMN from LMN, which may facilitate localization to the PNS or CNS. Gait and coordination should be commented on, and is expected to be normal.

Other signs to look out for are especially important to help rule out secondary or worrisome causes of headaches. Some of the common infectious, vascular, neoplastic, and drug-induced aetiologies will be described, divided into broad categories.

Infectious: Headache with fever, nuchal rigidity, photophobia and sometimes mental status change can indicate a headache secondary to meningitis. (8) Meningi-

Systemic symptoms: Fever, night sweats, weight loss
Neurological symptoms
Sudden severe onset: Need to r/o Thunderclap headache
Onset age over 50
Change in Pattern
Progressive worsening
Other: precipitated by Valsalva, postural aggravation, papilledema

TABLE 1 Red flags for headaches
Adapted from (1)



FLOWCHART 1 Flowchart summarizing approach to headache and management.

tis can also be associated with headache and change in personality or mental status. Sinusitis can also lead to headaches, which is why it may be useful to palpate the sinuses on physical exam to evaluate for any reproducible pain.

Vascular: The temporal artery and temporomandibular joints are palpated to evaluate for temporal artery arteritis; a recognizable cause of blindness. Sudden onset with maximal intensity within minutes can indicate a sub-arachnoid hemorrhage. An acute headache with a gradual worsening can point more towards a subdural headache. New onset headache in pregnancy or postpartum can point to cranial venous sinus thrombosis, carotid artery dissection or pituitary apoplexy. (9)

Neoplastic: Papilledema on a fundoscopy exam can indicate signs of increased cranial pressure resulting from hemorrhage or a tumor such as glioblastoma. (10) In severe cases masses can also cause herniation leading to focal neurological signs. Systemic symptoms such as night sweats, fatigue, and weight loss can also be present. Lastly, age is generally an important factor when suspecting a malignancy.

Drug/poisoning: Medication overuse with NSAIDs or acetaminophens has been shown to cause rebound headaches. (11) Carbon monoxide poisoning classically presents with a sudden onset severe headache. (12)

3.5 | Investigations to Exclude Secondary Causes of Headaches

Laboratory investigations are not diagnostic in the context of primary headaches but help in the suspicion of secondary headaches. *Blood investigations:* A complete blood count, thyroid function, and erythrocyte sedimentation rate (ESR) should be performed when relevant. A basic metabolic panel including glucose, electrolytes, and kidney function can be ordered. Thyroid function tests are performed as there are increasing studies linking hypothyroidism to headaches. (13) ESR is a marker of inflammation and can increase suspicion of giant cell arteritis, classically in individuals over 50 with new onset headaches. Lastly, in a clinical context of arthritis and headaches antinuclear antibody and rheumatoid factor can be performed. *Lumbar tap (LP):* an LP would be performed if there is a high clinical suspicion of an infection or subarachnoid hemorrhage. An increasing red cell count would indicate a hemorrhage while a high white cell count points towards infection. *Imaging:* as with any investigation, imaging should only be ordered in the proper clinical context. X-ray should be considered in a trauma setting, for example to detect skull fractures. X-rays provide 2D images primarily used to see bones, tumors, and pneumonias. Computed tomography (CT) creates a 2D image which can help better visualize soft tissue and organs. CT without contrast is necessary to diagnose a subarachnoid hemorrhage or ischemic stroke. CT and X-rays are not without risks, there is small dose of radiation which can slightly increase the risk of cancer especially if the images add up over time. (14) Magnetic resonance imaging (MRI) offers a 2D image without radiation and is particularly useful to visualize the brain and spine, however it is not as readily available. While imaging can be useful it may also identify incidental findings which can lead to even more testing and patient anxiety. Choosing Wisely Canada in collaboration with the American College of Radiologists discourage the use of imaging unless red flags are present. (15)

3.6 | Description of Primary Headaches

When being presented with patients having headaches, the OPQRST mnemonic (onset, provocation, quality, radiation, severity, and time) will be especially important when assessing the type. A concise classification for the types of primary headaches are described and summarized in Table 2:

Migraines: predominantly unilateral in adults with a pulsating pain. Associated with nausea and sensitivity to sound or light. Often follow emotional stress, hormonal changes, physical exercises, irregular sleeping and eating patterns, or schedule changes. The duration can last from hours to days. Treatment includes ibuprofen, acetaminophen and amitriptylne. (16)

Tension headaches: episodic, occurring from one to multiple days a month. Bilateral pain described as tightness around the forehead with a fluctuating/pulsating inten-

Primary headache	Duration	Location	Pain intensity	Quality of pain	Associated symptoms
Migraine	4-72 hours	Unilateral	Moderate	Pulsating	Nausea, vomiting, photophobia, Phonophobia
Tension-type	<4 hours	Bilateral (band-like fashion)	Moderate	Pressure	Migraine features notably absent
Cluster	<2 hours	Unilateral; orbital, supraorbital	Severe	Stabbing	Lacrimation, congestion, rhinorrhea, sweating, miosis, ptosis.

TABLE 2 Primary headaches. Adapted from: Miłowska K, Grabowska K, Gabryelak T. Zastosowanie promieniowania elektromagnetycznego w medycynie [Applications of electromagnetic radiation in medicine]. Postepy Hig Med Dosw (Online). 2014 May 8;68:473-82. Polish. doi: 10.5604/17322693.1101572. PMID: 24864099.

sity. Pain is not localized, nor severe. There is no aggravation by physical activity. The duration being 30 minutes to 7 days. Responds well with analgesia (ex, ibuprofen, or acetaminophen). (17)

Cluster: Unilateral pain around eye or temple. Symptoms involve the trigeminal nerve, including runny nose, Horner's syndrome, sweating and pallor. Has a quick onset to a deep and excruciating pain. Lasts minutes to hours and occurs in cycles of a few days: hence, 'cluster'. Acutely treated with 100% O2, and Triptans Prophylactic treatment may include verapamil, lithium and valproic acid. (18)

4 | BEYOND THE INITIAL APPROACH

4.1 | Management of Primary Headaches

The management of primary headaches, specifically migraine headaches as seen in the patient above will be described. The management for secondary headaches involves treatment of the underlying cause.

Approximately half of patients that are treated for headaches will have a 50% reduction in headache frequency. (18) Recurrences are likely to occur in greater numbers due to the poor understanding of headache etiology and side effects of drugs leading to decreased compliance. While there is a high prevalence of headaches amongst the population there is no "one size fits all" approach. Having a patient-centered approach to treating headaches will result in a greater response to therapy.

The management of migraines can be divided into non-pharmacological and pharmacological types. The non-pharmacological treatments have moderate quality evidence in headache prevention and include proper sleep, stress management, and avoidance of triggers such as skipping meals, dietary (dark chocolate, red wine), excessive stress, and weather changes. (19)

Pharmacological treatment includes abortive and prophylactic choices. Abortive management is medication taken at the headache onset. First line therapy includes NSAIDs or acetaminophen. Second line includes triptans which are migraine specific. (19) While medication may work in the context of few headaches per month, medication-overuse headaches (MOH) are a serious concern in patients with higher frequency headaches. MOH can be triggered when abortive medication is taken greater than 9 days per month for triptans and 14 days per month with NSAIDs or acetaminophen. (20) In these patients, it is important

to stop the medications and explore other avenues of treatments. Prophylactic management with low level evidence includes options such as vitamin B2 (riboflavin) and magnesium. (21) Other common options include tricyclic anti-depressants, beta-blockers and anticonvulsants (i.e., Topiramate or gabapentin) or anti-hypertensive agents (ARB or ACEi such as candesartan or lisinopril respectively). Certain aspects to consider are well-educating and reassuring the patient, medication side-effect profile, medication cost, patient values and preferences. With proper treatment and management, the frequency can be greatly reduced. It is worth noting that there is also an increased likelihood for patients with recurring headaches to have comorbid depression. (22) Thus, in addition to patient education concerning headaches, it is as important to provide patients with the proper tools and education to best look after their mental health.

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APPROACH TO
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Rotator Cuff Pathology

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ABSTRACT

Shoulder pain is a common problem and the third most common musculoskeletal symptom for which patients seek medical care. Rotator cuff tendinosis is a frequent cause of this pain and can be diagnosed clinically with a careful history and physical exam. Treatment consists of a trial of pain management and physiotherapy and imaging modalities are often not required. However, imaging can be highly valuable for other pathologies. This article guides the reader through key elements to include in a history and physical exam of the shoulder, and how and when to select an appropriate imaging modality.

KEYWORDS
Rotator cuff tendinopathy, Shoulder pain, Imaging, Best practice

1 | QUESTION

You are a family medicine resident in a clinic. Your next patient is Mr. D, a 54-year-old accountant who enjoys playing baseball as a left-handed pitcher. He comes in with a 3-month history of insidious onset left shoulder pain.

He rubs the supero-lateral aspect of his deltoid as he describes a 5/10 diffuse pain that worsens with pitching, lifting objects, starting the lawn mower, and lying on that side. He has not tried any treatment for the pain. Mr. D denies weakness or limited range of motion. He denies shoulder injury and has had no previous surgeries or shoulder problems. His review of systems is unremarkable. He has a body mass index of 29 and has been diagnosed with hypertension and diabetes mellitus type 2 which are well-managed with Enalapril and metformin. Mr. D is otherwise in good health, and denies smoking, drinking or drug use.

In your physical exam, you do not note any asymmetry, swelling, erythema, atrophy or deformities in your thorough inspection and palpation of the shoulder. Mr. D has full active and passive range of motion of the shoulder. There is some tenderness in the musculature around the greater tubercle of the humerus and below the scapular spine.

You then perform a series of special orthopedic tests including the external and internal rotation resistance

tests and the drop arm test. Mr. D does not demonstrate weakness when performing these tests but reports that it is painful to perform resisted external rotation.

What is the next best step in managing this patient?

A) Plain radiographs of the shoulder
B) Ultrasound (US)
C) Magnetic resonance imaging (MRI)
D) Magnetic resonance arthrography (MRA)
E) 6-week trial of pain management physiotherapy

2 | ANSWER

E. Mr. D's case is typical of a rotator cuff tendinosis which usually does not require any imaging for diagnosis. In fact, there is a weak correlation between positive imaging findings and the presence of symptoms. (1) Management should include a 6-12 week trial of pain management, relative rest, and physiotherapy. (1, 2, 16) If symptoms do not improve after this trial, imaging modalities can then be considered and selected according to the patient's history and physical exam findings.

2.1 | Background

2.1.1 | Problem

Shoulder pain is a common problem with a self-reported prevalence of 16-26% in the general population. It is the third most common musculoskeletal symptom for which patients seek medical care, followed by low back and knee pain. (3) Shoulder injury is associated with a delay in return to work and an increased frequency of sick leave. (4) Among the many etiologies of shoulder pain, rotator cuff (RC) disease - which includes tendinosis, impingement, and tears - is the most common. (5)

2.1.2 | Anatomy

The RC includes the supraspinatus, infraspinatus, teres minor and subscapularis muscles. These muscles act as dynamic stabilizers of the glenohumeral joint. (5) The supraspinatus originates in the supraspinous fossa of the scapula, inserts on the greater tubercle of the humerus, and acts to abduct the shoulder. The infraspinatus and teres minor originate from the infraspinous fossa and inferior lateral border of the scapula, respectively, and both insert on the greater tubercle of the humerus. These muscles act to externally rotate the shoulder. Finally, the subscapularis originates from the subscapular fossa and inserts on the lesser tubercle of the humerus, acting to internally rotate the shoulder. See Figure 1 for the anatomy. (5)

2.1.3 | Etiology of RC Pathology

Multiple factors including over- or under-loading, age over 40 years, genetics, vascular changes, and an impinging acromion may lead to cumulative injury and degeneration which contribute to RC disease. (1, 6, 7, 9)

A distinction must be made between RC tendinosis and RC tears as they may require different treatment. Tendinosis is treated with pain management and physical therapy. (1) However, in the case of a traumatic full-thickness RC tear, it is important to treat early with surgery. Untreated full-thickness tears may enlarge and the muscle may atrophy, predisposing the individual to recurrent tears. (3) Furthermore, if the tear becomes too large or is left too long without repair, intrinsic changes to the tendon may make it inoperable at a later date. (3)

2.2 | History

When taking the patient's history, it is first important to determine whether there was any trauma to the shoulder as this will influence further management. (3, 12) Once trauma is ruled out, the physician must then ascertain whether the issue is indeed musculoskeletal in origin by doing a review of systems to rule out referred pain from other areas including the neck, diaphragm, gallbladder, and heart.

A detailed history on the nature and location of the pain will then help narrow down the diagnosis. RC tendinosis usually presents as atraumatic shoulder pain at the tip of the shoulder and supero-lateral aspect of the deltoid. The pain may worsen with activities such as reaching, punching, pulling, lifting, or lying on that side. (10)

The presentation of a RC tear differs in that there may be weakness (e.g., with external rotation or abduction of the shoulder) in the affected muscle. (1, 10) Other examples of causes of non-traumatic shoulder pain include adhesive capsulitis, glenohumeral osteoarthritis, labral tears, biceps tendinopathy, avascular necrosis, and bone tumors. (8, 10)

Attention to risk factors for these shoulder pathologies should also be investigated. Risk factors that increase the likelihood of RC disease include: age, tissue over- or under-loading, an occupation or sport with overhead activity, diabetes mellitus, hypertension, high body mass index, and smoking. (1, 6)

2.3 | Physical Examination

The physician should begin with observation of the patient. (12) They should note their posture, arm position, and the use of compensating accessory muscles. The physician should then inspect for swelling, erythema, atrophy, deformities, and any asymmetries between the shoulders and scapulae. (12) The physician should then proceed to palpate for any pain or deformities in the bony and muscular structures of the shoulder and surrounding joints. Next, they should assess the patient's active and passive range of motion. (12)

Special orthopedic tests should then be employed to narrow down the diagnosis. Examples of these tests include the belly press test (sensitivity 28%, specificity 94%) and lift off test (sensitivity 19%, specificity 95%) for the subscapularis; Hornblower (sensitivity 17%, specificity 96%) for the infraspinatus; and Jobe's test (sensitivity 88%, specificity 62%) and full can tests (sensitivity 7-% and sensitivity 81%), for the supraspinatus. (10, 12, 13) However, a combination of special orthopedic tests must be used to increase diagnostic accuracy (17) as none of these tests alone reliably isolate separate structures given their close proximity to one another. (1) Normal strength in a series of tests may point the physician toward a tendinosis whereas weakness may allow the physician to diagnose a RC tear. (1, 12, 14)

2.4 | Treatment for RC Tendinosis

2.4.1 | Pain management

Adequate pain management and a prompt return to work are important components of the recovery process. (2, 15) Non-pharmacological measures such as ice, heat, and massage as well as pharmacological agents including acetaminophen or nonsteroidal anti-inflammatory

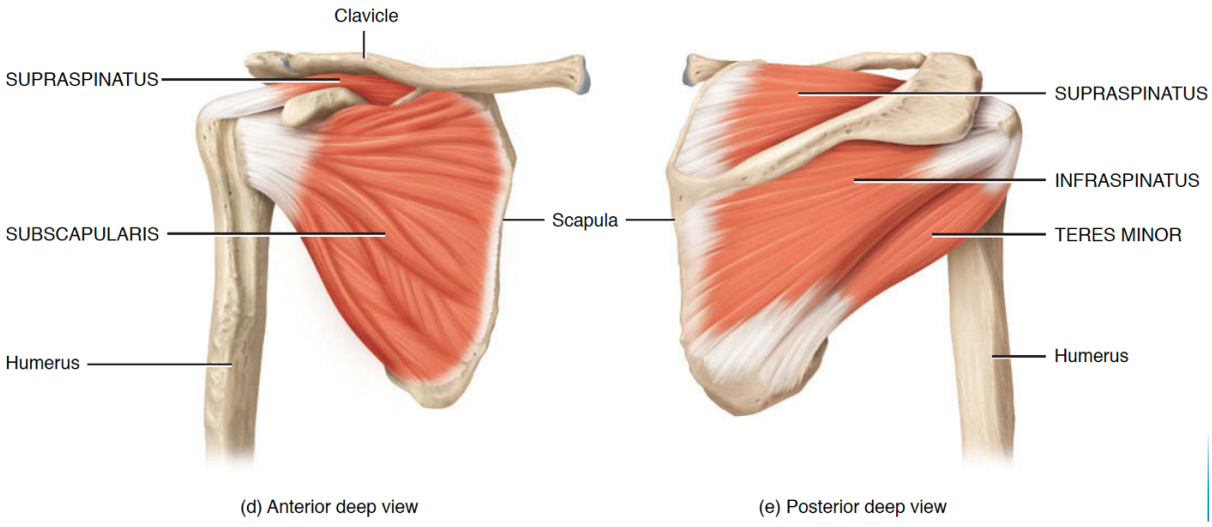


FIGURE 1 Anatomy of the rotator cuff. (10)

drugs should be employed for pain relief. (2, 15) If these pain management measures plus exercise programs are not effective in relieving pain, cortisone or local anesthetic injections may provide some temporary analgesia. (1, 2, 17)

2.4.2 | Physical Therapy

Fortunately, RC tendinosis can be managed with physical therapy which has a 75% success rate. (16) These exercise programs include three stages: shoulder mobility, building strength and flexibility, and integration towards sports or occupation-specific activities such as a return-to-work program. (15, 18) Pain and function usually improve after just 6 to 12 weeks of a rehabilitation exercise program. (16) Treatment should involve relative rest from or modification of painful activities, adjusting posture, avoiding sleeping on the sore shoulder, controlled reloading, sustained isometric contractions, and progression from simple to complex shoulder movements. (1, 2) Compared with surgery, this rehabilitative approach brings the additional benefit of implementing exercise, minimizing sick leave with a faster return to work, and reducing costs to the healthcare system. (1) Likewise, for non-traumatic partial thickness tears, surgery has no better outcome than an exercise program. (1, 17) In fact, exercise programs are beneficial even in large inoperable RC tears. (1, 17)

However, despite the benefits of exercise, surgery may still be warranted in traumatic, full-thickness tears as there is a risk that the size of the tear, fatty infiltration and muscle atrophy may all increase over time (3,6). Without prompt surgery on these acute tears, the tissue may be inoperable and unable to recover with conservative management. (3)

3 | BEYOND THE INITIAL APPROACH

3.1 | Imaging

Although imaging can be a critical diagnostic tool for shoulder pathologies, it must be used wisely and the modality must be chosen carefully based on the patient's history and physical exam findings. (3) With RC tendinosis in particular, there is a very weak association between symptoms and structural changes found on imaging, which challenges the validity of using imaging to justify that structural abnormalities lead to pain in RC tendinosis. (1) See Flow Chart 1 for a decision tree regarding selection of imaging modalities.

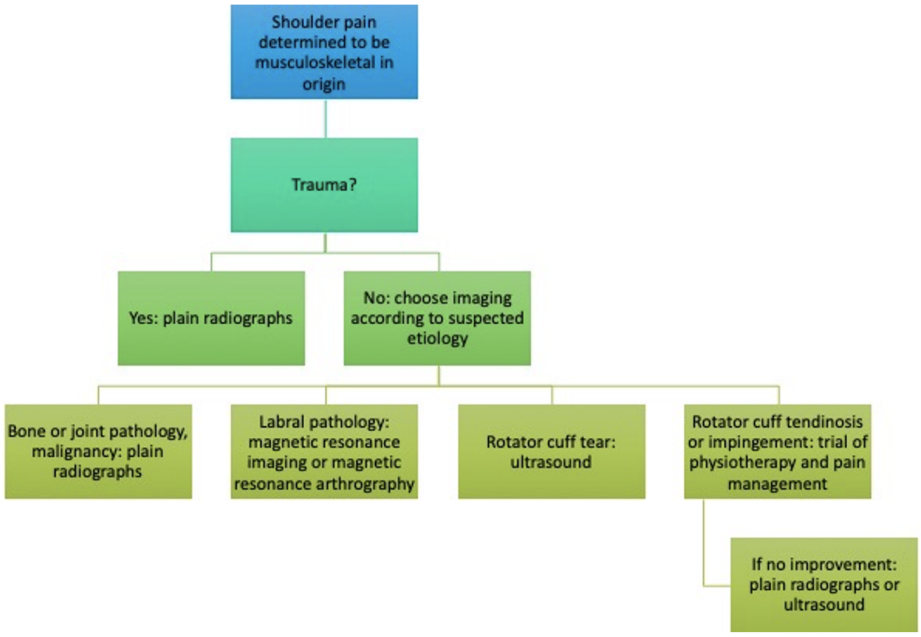
3.1.1 | Utility of Plain Radiographs

Although plain radiographs of the shoulder may not be necessary in the initial investigation of non-traumatic shoulder pain, they should be the first imaging modality in acute trauma, especially given their ease of access and low cost. (19) X-rays can provide information about pathologies such as fractures, osteoarthritis, malignancy, dislocation, Hills-Sachs lesions, and Bennett Lesions to name a few. (3, 9, 14, 19) Although plain radiographs can also detect abnormalities related to impingement, such as osteophyte formation or a down sloping acromion, these findings are commonly present in asymptomatic patients as well and must be interpreted with caution. (9, 14)

3.1.2 | Utility of US, MRI, and MRA

Since chronic partial RC tears and tendinosis are treated similarly, whereas acute traumatic full thickness tears may require timely surgery for the best prognosis, it is most important to choose a modality that can accurately detect a full-thickness tear in a timely manner. (3, 11) US, MRI, and MRA perform equally well in the detection of full-thickness tears. (3, 11) Ultrasound should be the first-line imaging of choice over MRI or MRA given its low cost, portability, availability, real-time imaging, short scan times, and greater patient satisfaction. Furthermore, MRI and MRA have contraindications such as metal implants or claustrophobia, which ultrasound avoids. (3, 9, 11, 19) If ultrasound imaging remains inconclusive, the patient should then undergo MRI or MRA. (3)

Although ultrasound carries the above benefits, it



FLOWCHART 1 Decision tree for selecting an imaging modality for shoulder pain.

does have some shortcomings. One major disadvantage of ultrasound is the necessity of personnel trained in ultrasound imaging of the RC. (19) When it comes to evaluating partial thickness tears, MRA may be the best imaging modality for this pathology given its superior sensitivity compared to US or MRI. (11) Finally, ultrasound has a limited ability to provide information about labrum, ligamentous, and osseous abnormalities; (3, 9) here, MRI or MRA would be the first-line imaging choice,(3) especially in younger populations less than 40 years of age where labral injuries are more common. (9)

3.2 | Summary

RC disease is the most common etiology of shoulder pain and includes a continuum of pathologies including tendinosis, tears, and impingement. RC disease can often be diagnosed clinically with a history and physical exam. (1) In the case of traumatic full thickness tears, prompt surgery is recommended. (3) For tendinosis, if symptoms do not improve after a 6-12 week (16) course of conservative treatment, imaging may be indicated. The modality of choice should be carefully selected based on the suspected etiology according to the patient's presentation. In general, plain radiographs are best used to assess bone and joint pathology, ultrasound is best for RC or bursal pathology, and MRI or MRA are best for labral pathology. (20)

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APPROACH TO
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The Glaucoma Patient

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KEYWORDS
Intraocular pressure, Open-angle glaucoma, Closed-angle glaucoma, Ocular hypertension, Physiologic cupping

1 | QUESTION

A 62-year-old male presents to the ophthalmology service following a referral from his optometrist regarding dilated fundus exam abnormalities. The patient denies ocular symptoms and feels that his vision is normal. His past medical history is significant for type 2 diabetes mellitus, coronary artery disease, alcoholic liver disease, and no past ocular history. On exam, his best corrected visual acuity is 20/25 bilaterally. His intraocular pressure (IOP) is 16mmHg in the right eye and 12 mmHg in the left eye. He states that his pressures are “always around there” during visits to his optometrist’s office. His pupils are equal, round, and reactive to light and accommodation. Anterior segment examination is normal and the patient is phakic. On gonioscopy, there are open angles in both eyes and no synechiae or abnormal pigmentation. Dilated fundus exam shows a cup-to-disc ratio of 0.75 in both eyes and a right eye disc hemorrhage inferotemporally. There is peripapillary atrophy and inferoretinal neuroretinal rim

thinning bilaterally, more severe in the right eye than the left. The macula is flat and there is no retinal tear or detachment. Visual field testing shows peripheral vision loss in the superior nasal quadrants (mean deviation -4-49 dB in the right eye and -2.01 dB in the left eye). Optical coherence tomography (OCT) of the macula is normal, although there is significant inferotemporal thinning of the retinal nerve fiber layer and ganglion cell complex thinning, more pronounced in the right eye compared to the left eye. Corneal thickness is within normal limits. The patient's mother, grandmother, and aunt have glaucoma. What is the most likely diagnosis?

A. Physiologic cupping
B. Primary open-angle glaucoma
C. Normal tension glaucoma
D. Primary angle-closure glaucoma
E. Secondary angle-closure glaucoma

2 | ANSWER

C. Given the patient's history and clinical examination findings, normal tension glaucoma is the most likely diagnosis. More specifically, findings such as bilateral nerve cupping, chronic visual loss, thinning retinal nerve fiber layer, normal IOP, and normal gonioscopy make this the most likely diagnosis. Notably, a diagnosis of glaucoma cannot be made with a single reading of IOP, and looking for progression through follow-up is of utmost importance. Physiologic cupping is not likely in this case given the glaucomatous vision loss and retinal nerve fiber layer changes. Primary open-angle glaucoma is less likely as well given that the IOP is within the normal range, although some sources consider normal tension glaucoma as a subtype of primary open-angle glaucoma. Primary and secondary angle-closure glaucoma are unlikely diagnoses in this case as gonioscopy showed open angles, and acute angle-closure would also present with significantly increased IOP.

3 | INITIAL APPROACH

Intraocular pressure (IOP) is considered one of the "vital signs" of ophthalmology and is a key parameter to assess and follow in an initial approach to glaucoma. Normal mean IOP is 15 mmHg to 16 mmHg with a standard deviation of 3 mmHg (1). Elevated IOP is typically recognized as being the only modifiable risk factor for optic nerve damage, also known as glaucoma (1). The Early Manifest Glaucoma trial showed that a 25% reduction in IOP can decrease glaucoma progression by up to 50% (2). Beyond IOP, there are a number of other risk factors for the development of glaucoma including, but not limited to, age, ethnicity, and corneal thickness. Notably, one of the most important ophthalmological emergencies is acute angle-closure glaucoma, which if left untreated, can lead to rapid irreversible vision loss.

The "angle" of the eye refers to the space between the posterior cornea and the iris. This space contains the trabecular meshwork which allows aqueous humour to drain from the eye (3). More specifically, the aqueous humour clears into the trabecular meshwork, passes through Schlemm's canal and the collector channels, drains into the episcleral venous plexus, and ultimately enters the venous system. Aqueous humour is produced by the ciliary body and fills the anterior chamber, thereby contributing to IOP.

There are important elements of the patient's medical history that need to be elicited when a patient is presenting with an elevated IOP. Importantly, the patient should be asked about relevant past ocular history, including but not limited to past ophthalmic surgeries, uveitis, or trauma (4). Additionally, the clinician should determine the patient's general past medical history, ethnicity, current medications, eyedrop use, as well as family history of glaucoma and other ocular conditions (4). A particular emphasis should be placed on any steroid and hypotensive medications alongside any history of diabetes mellitus, autoimmune conditions, sleep apnea, migraines, or Raynaud's disease. The majority of patients with primary open-angle glaucoma, which is the most common form of glaucoma, are asymptomatic and incidentally diagnosed; however, it is important to ask about any self-perceived changes to patients' visual acuity as well.

The most relevant clinical exam maneuver is the measurement of IOP. The gold standard of measurement is

the Goldmann Applanation tonometer, although there are other tools such as the Tonopen and iCare which are typically used for screening (1, 5). The anterior segment slit lamp examination can provide important information regarding glaucoma etiology. For example, a Krukenberg spindle and transillumination (i.e. pigment dispersion syndrome), signs of pseudoexfoliation, or iris neovascularization secondary to diabetes can all provide vital information in diagnosis. The patient's lens status is also an important consideration as cataracts can be a predisposing factor for glaucoma.

Next, gonioscopy is the gold standard for determining whether the angle is open or closed (1). It is important to note that myopic eyes are at increased risk of open-angle glaucoma and reduced risk for angle-closure glaucoma. Further, dilated fundus exam is essential, specifically in determining the optic nerve cup-to-disc ratio and inspecting for disc hemorrhages (1). Contrasting the cup-to-disc ratio between eyes and examining the peripheral retina to are also key investigations for ruling out other pathologies that could contribute to elevated IOP, such as retinal detachment or uveitis. When analyzing the optic nerve head, a common "5 R's" mnemonic can prove useful: observing the scleral ring to determine the limits of the optic disc size, identifying the rim size, inspecting the retinal nerve fiber layer, assessing for regions of peripapillary atrophy, and looking for disc or retinal hemorrhages.

Relevant investigations of IOP typically include optical coherence tomography (OCT) of the macula and optic nerve head, with a particular focus on the retinal nerve fiber layer and ganglion cell complex thickness. Ganglion cell thinning typically occurs first, followed by retinal nerve fiber layer thinning and, although the exact pathogenesis is not well established, oxidative stress is hypothesized to play a role (6). Visual field loss can be inversely correlated to the location of thinning (7). Visual field testing is insurmountably important in quantifying vision loss and is typically done in an outpatient setting. Data obtained from visual field testing can be cross-referenced with OCT retinal nerve fiber layer changes. Note that a thinner central corneal thickness (CCT) is an independent risk factor for glaucoma, so measuring corneal thickness is typically done with pachymetry in an outpatient setting as well. In some centers, ultrasound biomicroscopy or OCT can also be used to evaluate the anterior angle.

4 | BEYOND THE INITIAL APPROACH

This section provides further information about open-angle and closed-angle glaucoma and is further divided into primary and secondary glaucoma. Primary glaucoma does not have a defined cause, whereas secondary glaucoma has a known underlying cause. Ocular hypertension and physiologic cupping are also discussed briefly in this section.

4.1 | Ocular Hypertension and Physiologic Cupping

Ocular hypertension is defined as elevated IOP without glaucomatous optic nerve head changes or visual field changes, while physiologic cupping is the presence of an increased cup-to-disc ratio with normal IOP and visual fields. Neither of these diagnoses are pathological, although patients with ocular hypertension have an increased risk of developing glaucoma in the future and should be monitored closely (8). The Ocular Hypertension Treatment Study outlined several risk factors for progression of ocular hypertension to primary open-angle glaucoma including age, greater vertical and horizontal cup-disc ratio, pattern standard deviation, higher intraocular pressure, and thinner CCT (9). Many online calculators have been created based on the findings of this study to assess the risk of progression from ocular hypertension to glaucoma, which can be found on websites such as MDCalc (10).

4.2 | Primary open-angle glaucoma

Primary open-angle glaucoma is the most common type of glaucoma in the Western World and is a problem of idiopathic reduced trabecular outflow (11). Risk factors include increased age, male sex, hypertension, diabetes mellitus, and African or European ethnicity (9, 12). Pri-

mary open-angle glaucoma is a chronic condition characterized by peripheral vision loss and can be monitored using visual field testing with perimetry, cup-to-disc ratio measurement, and retinal nerve fiber layer thickness (12). Screening for primary open-angle glaucoma is crucial, with over 50% of glaucoma cases being hypothesized to remain undiagnosed (12).

4.3 | Normal tension glaucoma

Normal tension glaucoma is a type of open-angle glaucoma where there is glaucomatous damage, but the IOP is within normal range. Some sources consider normal tension glaucoma as a subtype of primary open-angle glaucoma (11). Visual field defects, retinal nerve fiber layer thinning, or cupping of the nerve alongside normal IOP would raise suspicion for normal tension glaucoma (13). Although risk factors remain poorly understood, this condition is hypothesized to be related to vascular degeneration and neurodegenerative processes; associated conditions include Alzheimer's dementia, migraines, Raynaud's phenomenon, low blood pressure, and sleep apnea (13).

4.4 | Secondary open-angle glaucoma

Secondary open-angle glaucoma includes several conditions; however, this subsection will focus on the most common ones. Pseudoexfoliation glaucoma is not fully understood but results in the production of white, fibrillary deposits in the anterior segment of the eye leading to clogging of the trabecular meshwork (14). Zonular weakness, higher IOP at presentation, and aggressive progression are characteristics of this disease (15). Pigmentary dispersion syndrome occurs secondary to pigment separating from the iris which, similar to the mechanism pseudoexfoliation glaucoma, prevents outflow through the trabecular meshwork (14). Pigmentary dispersion syndrome generally presents in younger patients with transillumination defects, Krukenberg spindles in the corneal endothelium, and significant pigmentation of the trabecular meshwork. In uveitic glaucoma, anterior chamber cells interfere with aqueous outflow. Notably, IOP is decreased in many types of uveitis (e.g. herpes simplex virus uveitis). Prolonged corticosteroid use plays a key role in cases of elevated IOP associated with uveitis (14). Steroid-induced glaucoma is an important secondary cause of glaucoma to make note of as many medical conditions are treated with systemic or topical steroids. Monitoring IOP after initiation of a topical steroid is essential, and IOP typically decreases shortly after the termination of steroid medication (14).

4.5 | Primary angle-closure glaucoma

Primary angle closure (PAC) occurs when there is occlusion of the anterior angle of the eye preventing aqueous outflow through the trabecular meshwork without a predisposing secondary cause. Primary angle closure glaucoma (PACG) is defined as PAC with damage to the optic nerve. A primary angle closure suspect (PACS) is someone who has narrow angles as determined through gonioscopy. Hyperopia, female sex, and Inuit or Asian ethnicity are all risk factors for angle-closure glaucoma (16). Acute angle-closure leads to dramatic increases in IOP and can cause symptoms such as decreased visual acuity, halos, glare, headaches, nausea, vomiting, and a sensation of retro-orbital pressure. Chronic angle-closure refers to gradual narrowing of the angle leading to progressive glaucomatous damage (17). Patients with a narrow iridocorneal angle are at risk for periodic angle-closure attacks and can have chronic, progressive damage to their optic nerves as well. Over time, iridotrabecular synechiae may be observed (17).

4.6 | Secondary angle-closure glaucoma

Secondary angle-closure can be further subdivided based on the presence or absence of pupillary block. Secondary pupillary block occurs when the iris moves posteriorly or the lens moves anteriorly and blocks communication between the posterior and anterior chamber, leading to a dramatic increase in IOP (16). Pupillary block can also be caused by posterior synechiae in the context of uveitis, or by iris and angle neovascularization in the context of diabetes mellitus (i.e. neovas-

cular glaucoma). In neovascular glaucoma, the chronic contraction and proliferation of blood vessels leads to angle-closure glaucoma (17).

Drug-induced angle closure glaucoma with or without pupillary block is also possible. Adrenergic agonists, anticholinergics, and medications with anticholinergic side effects have been associated with angle-closure glaucoma with pupillary block (16). Sulfonamides, anticoagulants, and cholinergics have been associated with angle-closure glaucoma without pupillary block, mostly caused by anterior movement of the lens-iris diaphragm (16).

4.7 | Management

Medical (ie. non-surgical) management of open-angle glaucoma is standard for the treatment of glaucoma, with the four most common classes of topical medications used being prostaglandin analogues, beta-blockers, cholinergic agonists, and carbonic anhydrase inhibitors (12). Given that the majority of patients are asymptomatic and do not feel any direct benefits of treatment, compliance remains one of the biggest challenges in glaucoma treatment (19). Selective laser trabeculoplasty to increase aqueous outflow has become commonplace in newly diagnosed open-angle glaucoma patients. In severe cases, surgical management options are considered including trabeculectomy, placement of a glaucoma drainage device, cataract surgery, or minimally invasive glaucoma surgery such as placement of intraocular stents (12). Angle-closure glaucoma is managed by resolving angle closure using laser peripheral iridotomy immediately or, in some cases, with clear-lens extraction (17, 20). Notably, a patient with unilateral acute angle closure has an increased likelihood of experiencing angle closure in the contralateral eye. Thus, peripheral iridotomy is typically performed in the contralateral eye as well. Prophylactic peripheral iridotomy was first explored by He et al. (2019) in the ZAP trial and is commonplace in many practices for patients with narrow anterior angles (21). Pilocarpine and oral carbonic anhydrase inhibitors can also be used for acute lowering of IOP.

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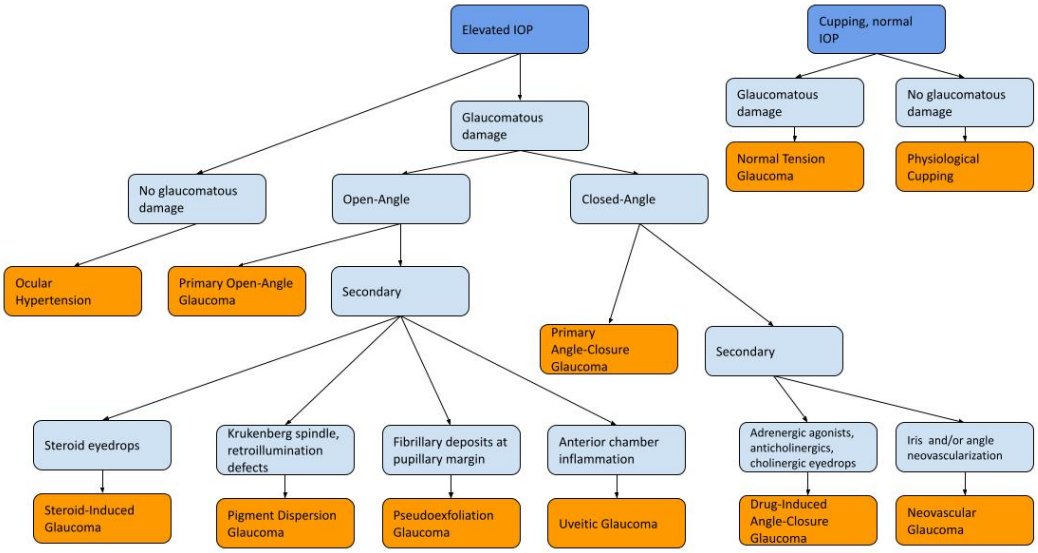
5 | FLOWCHARTS



FLOWCHART 1 Algorithm for glaucoma classification and diagnosis, based on history and physical exam findings.

APPROACH TO
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The Patient with a Palpable Breast Mass

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ABSTRACT

A palpable breast mass is a common reason for presenting to the primary care, emergency, or obstetrics and gynecology clinical settings. Although most palpable masses are benign, patients may experience anxiety due to the risk of malignancy. To ensure a comprehensive evaluation, a systematic approach to history-taking, clinical breast examination, and imaging is crucial.

This article aims to provide medical students with a stepwise approach to the evaluation and diagnosis of palpable breast masses. Considering the wide spectrum of diseases associated with palpable masses, this paper does not cover the differential diagnosis and management. Nonetheless, we will touch upon the breast cancers most commonly associated with breast masses and briefly mention their respective treatments.

KEYWORDS
Breast Mass, Breast Lump, Breast Cancer

1 | QUESTION

A 29-year-old (y/o) African American woman presents to her family doctor after noticing a new left-sided breast lump during self-examination one month ago. The lump has been gradually increasing in size over time and she reports a new onset of bloody nipple discharge as of yesterday. She denies systemic symptoms such as weight loss, fever, or chills and her appetite is preserved. She has not experienced any abdominal pain, nausea, jaundice, dyspnea, cough, or bone pain.

Given her positive family history of breast cancer (both her mother and maternal aunt were diagnosed prior to menopause), she admits to being quite concerned. She is overall healthy, with a body mass index of 28 (i.e., overweight). She denies previous surgeries, smoking, alcohol consumption, or recreational drug use. Her age at menarche was 10y/o; she is nulliparous and has been on the oral contraceptive pill for the last seven years. Her last menstrual period was two weeks ago.

On physical exam, a 1.5cm rubbery, mobile, painless mass is observed above the patient's left nipple. There is no erythema, thickening, or dimpling of the overlying skin. The rest of her physical examination is unremark-

able.
The initial laboratory workup shows:

- Complete Blood Count (CBC) within normal limits
- C-Reactive Protein (CRP) within normal limits
- ß-HCG < 0.5 mIU/mL

What is the best next step for managing this patient?

A. Watchful waiting with clinical follow-up.
B. Ultrasound.
C. Mammography.
D. MRI.
E. PET scan.
F. Biospy.

2 | ANSWER

The correct answer is (**B**). For patients under 30 years of age, ultrasound is the preferred initial imaging modality. In fact, breasts tend to be denser with a lower proportion of fatty tissue, which decreases the accuracy and ability to detect microcalcifications in mammography (1). Ultrasound proves to be effective in distinguishing between cystic (i.e., benign finding) from solid masses while having no associated contraindications and being safe during pregnancy.

This patient's ultrasound reveals a hypoechoic well-circumscribed, round, macrolobulated mass, which, when considered alongside the clinical picture, suggests a diagnosis of fibroadenoma. Fibroadenomas are benign breast tumors most commonly found in women aged 20-30, composed of both glandular and connective tissue. The majority of fibroadenomas can be observed and typically regress over time. In cases where they become symptomatic or increase in size, treatment options such as lumpectomy or cryoablation may be considered.

3 | INITIAL APPROACH

3.1 | History and Physical Examination

A thorough history and physical examination are crucial for guiding clinical reasoning and level of suspicion for malignancy. Elements that should be elicited include:

3.1.1 | Onset and Fluctuations

Determining the onset of a patient's breast mass can be challenging; they are most frequently discovered incidentally upon routine screening as no established guidelines recommend self-examination or clinical breast screening for breast cancer detection (2). Moreover, it is essential to identify preceding events (such as blunt trauma, infection, menstruations, medications, etc.) and monitor fluctuations in mass size.

3.1.2 | Associated Symptoms

- **Pain**: Painful masses may suggest mastitis, cysts, abscesses, or a breast hematoma with fat necrosis secondary to trauma. Tenderness in fibrocystic breast changes is common but less localized (3). Malignant breast masses are less likely to be tender, although this finding should not rule out malignancy from the differential diagnosis.
- **Systemic symptoms**: The presence of systemic symptoms should raise suspicion of malignancy. The most common metastatic breast cancer sites are the bones, liver, and lungs. Symptoms including but not limited to weight loss, bone pain, dyspnea, cough, chest pain, abdominal pain, nausea, and jaundice may suggest disseminated disease with the presence of metastases (4).
- **Nipple discharge**: The risk of malignancy is higher in patients with unilateral spontaneous non-milky (i.e. clear or bloody) nipple discharge (5). However, benign papilloma and duct ectasia remain the leading causes of pathologic nipple discharge (6).

3.1.3 | Medical History

Patient risk factors raising suspicion for breast cancer should be identified. For instance, a personal and/or family history of breast cancer, whether accompanied by genetic mutations or not, increases a patient's risk (7). Furthermore, it is essential to consider causes of in-

creased estrogen exposure, such as number of pregnancies, age at menarche and menopause, oral contraceptives, or hormonal therapy. In addition, radiation exposure and lifestyle habits, such as alcohol and smoking, should be explored as they are associated with a higher risk of breast cancer (8).

3.1.4 | Physical Examination

A thorough clinical breast examination should be performed (9) with a physical examination of other body systems if warranted by the clinical history. A chaperone is recommended to ensure patient comfort.

Inspect the breasts in an upright position for asymmetry, mass, skin dimpling, erythema, nipple retraction, inversion, or discharge. If discharge is not obvious upon inspection, consider asking the patient if they have noticed any on self-observation.

Skin changes, including erythema, warmth, and tenderness, may indicate an infectious etiology such as mastitis or cellulitis. Inflammatory breast cancer can present similarly, or with additional ridging and pitting (similar to an orange peel). Paget's disease of the breast should also be considered in cases presenting with persistent eczematous nipple changes.

Examine the patient supine with raised arms; palpate both breasts systematically for masses using either concentric circles, a radial approach, or vertical stripes. Then assess for lymphadenopathy in the nipples, the axillae, and the supraclavicular regions. If present, document the location, size, consistency, tenderness, mobility, and margins.

Benign masses typically exhibit smoothness, mobility, and well-defined margins, while malignant ones are often firm, non-mobile, and fixed to the surrounding skin and soft tissue with irregular margins. However, variations exist, and the physical examination cannot be used as a stand-alone diagnosis; for instance, mobile masses may be cancerous.

3.2 | Imaging

Ultrasound and mammography are the most commonly used imaging modalities for breast pathologies, often used in combination to improve accuracy. Moreover, MRI is significantly effective as an additional diagnostic tool for women with dense breasts.

3.2.1 | Patients < 30 y/o

Ultrasound is the preferred initial imaging modality for women under 30y/o and men presenting with a palpable breast mass (1). (Figure 1)

3.2.2 | Patients > 40 y/o

Mammography is the first line modality for women over 40 y/o presenting with a palpable breast mass (1). Mammography should be performed before biopsy to assess for other suspicious areas or calcifications in the breast. (Figure 1)

3.2.3 | Patients 30 < X < 40 y/o

Either ultrasound or mammography can be performed; oftentimes, both modalities will be needed to enhance accuracy (1). (Figure 1)

3.2.4 | Breat Imaging-Reporting and Data Systesm (BI-RADS)

The BI-RAD is a tool developed by the American College of Radiology to provide a unanimous reporting schema for breast imaging. It applies to ultrasound, mammography, and MRI (10). The radiology report assigns the scan results to one of the seven defined categories (Table 1), which guides the management plan.

3.3 | Pathology

Diagnostic breast imaging should always precede breast biopsy. Patients with concerning breast abnormalities on imaging (BI-RADS 4 or 5) should undergo breast

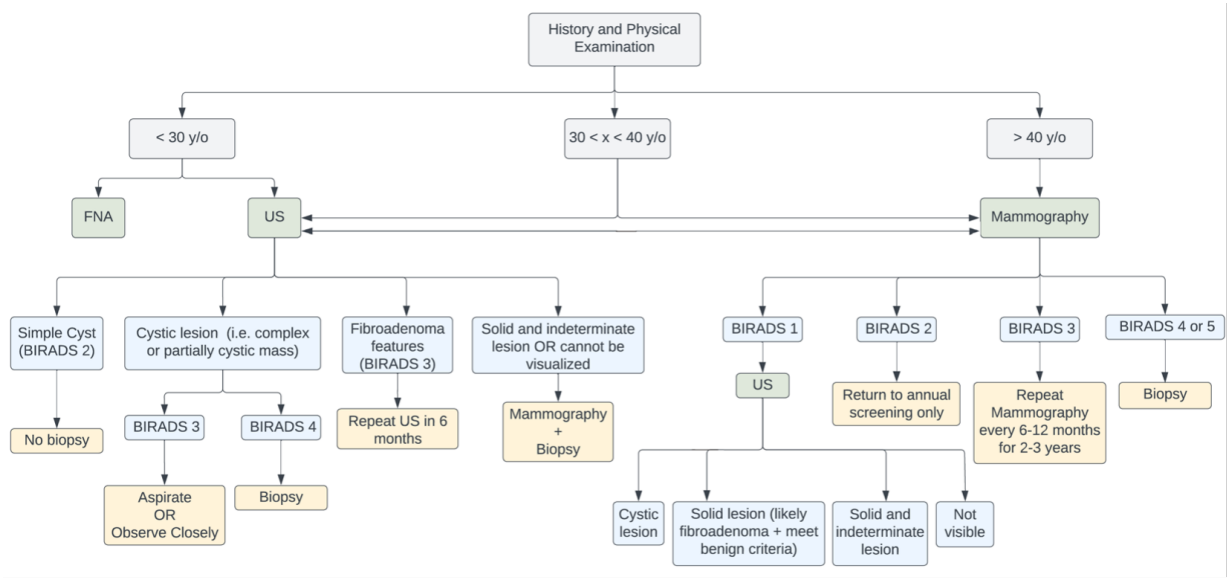


FIGURE 1 Approach to adrenal mass flowchart

Abbreviations used: y/o, years old; US, ultrasound; BIRADS, Breast Imaging Reporting and Data System.

Information provided above is based on Esserman LJ, Joe BN. Diagnostic Evaluation of Suspected Breast Cancer. In: UpToDate. Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 06, 2023.)

biopsy. However, a biopsy may be needed despite negative imaging in patients with a clinically suspicious palpable breast mass (11).

3.3.1 | Biopsy Methods

Most biopsies are performed under image guidance. Core needle biopsy (CNB) is the preferred initial approach due to its ability to provide larger tissue samples, offering more accurate histopathological information and reducing false-negative outcomes compared to fine needle aspiration (FNA) (12). Though FNA with intraprocedural cytopathology may expedite patient management (providing an immediate preliminary diagnosis), it risks non-diagnostic or inconclusive results due to smaller samples and limited architecture preservation. Surgical biopsy is rarely a first-line approach but may investigate unclear or inconclusive percutaneous biopsy results (13) and is typically performed under conscious sedation or general anesthesia. For anticoagulated patients, radiologists should be informed; if feasible, suspend anticoagulation for CNB or consider FNA or open biopsy for bleeding control (14).

3.4 | Additional Investigations

Other investigations are available for breast mass analysis, depending on the likely differential and available resources. Baseline blood tests, typically suggested for surgical patients, encompass hemoglobin, bone profile, and liver function tests for suspected hepatic metastases. Inflammatory markers and blood cultures should be considered when a breast abscess is suspected. Tumor markers such as Ca27.29 and Ca15-3 have limited screening and diagnostic utility but are used for prognostication and monitoring for recurrence (15).

Alongside these tumor markers, hormone receptor status assessment (ER, PR, HER2) is crucial for directing treatment strategies, such as hormonal or targeted therapies (16), and determining prognosis as well as specific treatment response.

Nuclear medicine scanning assists in staging, while genetic testing caters to individuals with hereditary breast and ovarian cancer risk factors (17).

Category	Recommended action	Likelihood of cancer
BI-RADS 0: incomplete (need additional imaging evaluation: mammographic views or ultrasound and/or for mammography, obtaining previous images not available at the time of the study)	Additional imaging required	N/A
BI-RADS 1: negative (symmetrical and no masses, architectural distortion, or suspicious calcifications)	Routine screening	Essentially 0% probability of malignancy
BI-RADS 2: benign	Routine screening	Essentially 0% probability of malignancy
BI-RADS 3: probably benign	Short interval follow-up suggested	-<2% probability of malignancy
BI-RADS 4: suspicious for malignancy	Biopsy should be considered	2-94% probability of malignancy For mammography and ultrasound, these can be further divided into: ▪ BI-RADS 4A: low suspicion for malignancy (2-9%) ▪ BI-RADS 4B: moderate suspicion for malignancy (10-49%) ▪ BI-RADS 4C: high suspicion for malignancy (50-94%)
BI-RADS 5: highly suggestive of malignancy	Appropriate action should be taken	>95% probability of malignancy
BI-RADS 6: known biopsy-proven malignancy	Appropriate action should be taken	N/A

TABLE 1 The Breast Imaging Reporting Data System (BI-RADS)

Abbreviations used: N/A; not applicable

Information provided above is based on Eghtedari M, Chong A, Rakow-Penner R, Ojeda-Fournier H. Current status and future of BI-RADS in multimodality imaging, from the AJR special series on radiology reporting and data systems. Am J Roentgenol. 2021;216(4):860–873. https://doi.org/10.2214/AJR.20.24894

4 | BEYOND INITIAL APPROACH

This section discusses common malignant causes of breast masses in more detail (Table 2).

4.1 | Non-invasive Breast Cancer

Ductal Carcinoma in Situ (DCIS) is caused by the proliferation of epithelial cells contained within breast ducts. DCIS may present as a palpable breast mass, although most cases are non-palpable and detected on screening mammography (18). Treatment includes lumpectomy with wide excision margins and radiation therapy or simply mastectomy if a larger area of disease is present. Lobular Carcinoma in Situ (LCIS) is another benign breast cancer in which neoplastic cells are contained within the breast lobule. However, LCIS does not present as a palpable mass.

4.2 | Invasive Breast Cancer

The most common malignant palpable breast mass is invasive ductal carcinoma (IDC) in which neoplastic cells originating from the ductal epithelium infiltrate the supporting stroma. Conversely, invasive lobular carcinoma (ILC) usually presents as a diffuse thickening rather than a discrete mass (19). Finally, approximately half of patients with Paget's disease of the breast may present

with a palpable lump.

Treatment of invasive breast cancer is complex and depends on factors such as molecular subtype, tumor size, nodal status, and presence or absence of metastases. Therapeutic approaches can be classified into general categories: endocrine therapy, targeted therapy (e.g., Herceptin), chemotherapy, immunotherapy (in triple-negative breast cancer), and radiation therapy.

In early-stage breast cancer, regardless of molecular subtype, locoregional treatment involves surgery (lumpectomy or mastectomy) and axillary lymph node management. Postoperative therapies rely on tumor size and molecular expression. For instance, estrogen receptor (ER)-positive patients receive endocrine treatment, while those at high risk undergo chemotherapy. Triple-negative breast cancers or those with human epidermal growth factor receptor 2 (HER2)-overexpressing cancers are administered neoadjuvant systemic therapy tailored to the specific subtype before surgery. Intensified systemic treatment may be considered if a pathological complete response (pCR) is not achieved (20).

In locally advanced and metastatic cancer, locoregional and systemic therapies are combined. Treatment

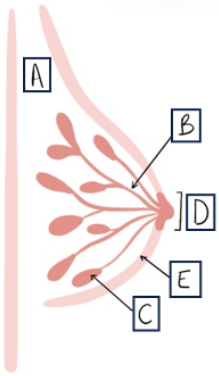
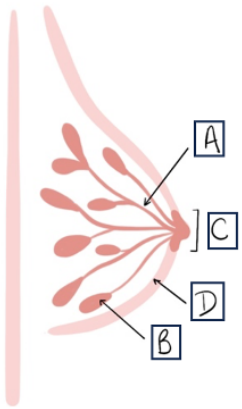
	Breast Anatomy	Pathology
Benign Breast Conditions 	**A** | Breast Tissue, Connective Tissue, Fat Tissue	Fibroadenoma Fibrocystic breast changes Cyst Lipoma Abscess Fat necrosis (trauma)
	B | Ducts	Galactocele Usual ductal hyperplasia
	C | Lobules	Sclerosing adenosis Atypical lobular hyperplasia
	D | Nipple and Areola	Nipple adenoma
	E | Blood Vessels	Haemangioma
Malignant Breast Conditions 	**A** | Ducts	Ductal Carcinoma in Situ Invasive Ductal Carcinoma
	B | Lobules	Invasive Lobular Carcinoma
	C | Nipple and Areola	Paget Disease of the nipple

TABLE 2 Benign and malignant breast conditions leading to palpable breast masses (non-exhaustive list).

for invasive breast cancer should be tailored to individual disease characteristics and preferences. More specifically, in luminal-like conditions, endocrine therapy, sometimes combined with targeted treatment, precedes chemotherapy. Consecutive monotherapy is advised upon chemotherapy initiation. Chemotherapy remains the primary treatment for triple-negative diseases; however, PD-L1-expressing tumors may qualify for initial immunotherapy. In HER2-positive cases, a series of anti-hHER2 agents and chemotherapy are used; ER-positive, HER2-positive diseases may also benefit from endocrine and anti-HER2 therapy combinations, preferably as maintenance therapy. Germline BRCA mutation carriers may consider PARP inhibitors as an additional treatment option.

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APPROACH TO
McGill Journal of Medicine

Adrenal Mass

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ABSTRACT

Adrenal masses are a common incidental finding in imaging. Although most are benign, they should be thoroughly investigated to rule out malignancy and hormone hypersecretion. This article provides an approach to evaluating these adrenal masses, delving into the various differential diagnoses and special management considerations.

KEYWORDS
Adrenal Mass, Adrenal Incidentaloma, Imaging, Hormones, Endocrinology

1 | CLINICAL SCENARIO

A 68-year-old male presents to the emergency room with right flank pain and is found to have a non-complicated obstructing kidney stone. On the non-contrast computed tomography (CT) scan of the abdomen, a left adrenal mass is also noted.

The patient is known for poorly controlled hypertension, type II diabetes mellitus, and spinal stenosis. He denies any personal or family history of adrenal cancer and recent malignancy. He does not have any recent weight loss, night sweats, or fatigue. He denies headaches, palpitations, and diaphoresis. Upon physical exam, he appears to have flank pain, proximal weakness on power testing, an elevated BMI, and 2-cm-wide red-purple lines (striae) on his thighs.

On the radiology report, the adrenal mass is described as unilateral left 2.4 cm x 3.6 cm, homogeneous with smooth border, and 6 HU (Hounsfield units). His complete blood count (CBC) is normal and electrolytes show hypokalemia at 3.3 mEq/L.

1.1 | Question

Once renal colic is resolved, which of the following investigations would you complete?

a) 24-hour urine fractioned metanephrines and catecholamines

b) Dexamethasone suppression test

c) Aldosterone-renin ratio

d) Dehydroepiandrotestosterone (DHEAS)

e) CT scan of the abdomen with contrast

f) Adrenal fine needle aspiration biopsy (FNA)

Which tests would you choose?

1. a), b), and e)

2. a), b), c), d), and e)

3. a), b), e), and f)

4. a), b), and c)

5. e) and f)

1.2 | Answer

4. is the correct answer. All adrenal masses should be investigated for pheochromocytoma with 24-hour urine fractioned metanephrines and catecholamines or plasma fractioned free metanephrines. Cushing's syndrome should be evaluated using the dexamethasone suppression test or late-night salivary cortisol testing, given findings of Cushing's upon examination (striae, high BMI, proximal weakness). Additionally, this patient is presenting with a history of hypertension and hypokalemia which suggests possible hyperaldosteronism and requires additional aldosterone-renin ratio testing. DHEAS testing is only warranted if the patient presents with symptoms of sex hormone excess, which is not the case here. The described imaging findings (smooth border, homogeneous, <4 cm, <10 HU) suggest that the mass is benign; therefore, a CT scan with contrast is not required at this stage. CT scans with contrast are used to measure contrast washout to differentiate benign and malignant masses when initial non-contrast CT features are suspicious (heterogeneous, irregular margins, necrosis, >10 HU attenuation, >4 cm in size). Lastly, FNA biopsies are not usually done as they do not differentiate between malignant and benign masses.

2 | INITIAL APPROACH

Adrenal masses are often accidentally discovered when a patient undergoes imaging studies for other medical reasons and are called incidentalomas. They have a mean prevalence of 2.3% at autopsy with a prevalence range from 1%-9%. A higher number of cases are found in older, white, obese, diabetic, and hypertensive people. (1) The majority of adrenal incidentalomas are benign non-functioning adenomas or lipomas. However, approximately 10%-15% are functional and result in the hypersecretion of cortisol (Cushing's syndrome) or of other hormones (pheochromocytoma, hyperaldosteronism). Some cases can represent malignant primary tumours (2%-5%) or metastasis (1%-2.5%). (2) Incidentalomas require imaging and biochemical workups to rule out malignancy or hormone hypersecretion.

3 | EVALUATION FOR MALIGNANCY

When evaluating a mass, malignancy should always be on the differential. Patients may report having a recent or active cancer, which could lead to possible metastasis of the adrenal gland. The most common metastatic sources are lung, breast, colon, stomach, lymphoma, melanoma, and renal cancers. (3) It is also important to ask about constitutional symptoms (weight loss, fever, night sweats, appetite loss, fatigue) and family history of malignancy.

A non-contrast abdominal CT scan is the main modality used to investigate adrenal masses for malignancy. The National Italian Study Group on adrenal tumours evaluated adrenal incidentaloma hospital records to retrospectively identify characteristics that suggest malignancy. Ascertained features include a larger size (>4 cm), irregular borders, heterogeneous masses, calcifications, and necrosis. (3-6) Additionally, on non-contrast CTs, radiographic attenuation of the mass is evaluated by Hounsfield units (HU). Malignant masses have higher HU (>10) as they absorb more X-rays than benign lipid-rich tissues, as was determined by Delivanis

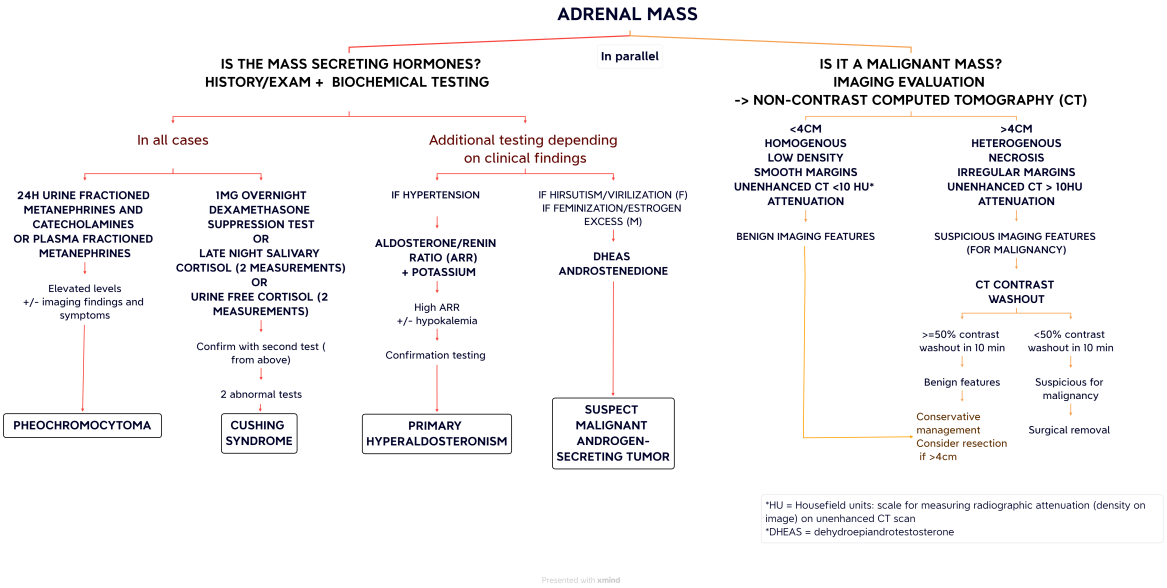

FIGURE 1 Approach to adrenal mass flowchart

et al. (2018) in a retrospective cohort study, amongst others. (4,7) If the mass has a suspicious appearance on a non-contrast CT scan, an adrenal contrast washout CT protocol should be done. Adrenocortical carcinomas and other malignant masses commonly have decreased washout percentages (<40% relative enhancement loss at 15 minutes), whereas adenomas (benign masses) have higher washouts. (5) Pheochromocytomas can have similar characteristics to malignant masses on imaging. (8) Thus, it is important to rule out pheochromocytomas as described below.

If metastasis is suspected or the aforementioned imaging techniques are inconclusive, an FDG-PET (fluorodeoxyglucose positron emission tomography) scan can help assess for malignant features in indeterminate masses. In a prospective study by Guerin et al. (2017), MRIs were shown to aid in investigating the mass and distinguish pheochromocytomas. (9) Fine needle aspiration biopsy is not commonly done as it does not differentiate between benign and malignant adrenal tissue. However, it can help differentiate metastatic, extra-adrenal and primary adrenal malignancy, and allow to histological description of the tumour. If it is done, pheochromocytoma needs to be ruled out prior to avoid precipitating a pheochromocytoma crisis. (10,11)

4 | EVALUATION FOR HORMONE HYPERSECRETION

Although most adrenal masses are non-functional, hormone hypersecretion needs to be ruled out by a thorough patient history, physical examination, and biochemical testing, as most patients are asymptomatic.

4.1 | Cortisol Excess

ACTH (adrenocorticotropic hormone) independent cortisol excess or Cushing's syndrome, is the most common presentation of a functioning adrenal mass. (4) In most cases, functional incidentalomas present with mild autonomous cortisol secretion (MACS), known as subclinical Cushing's syndrome and have a prevalence of up to 20% amongst adrenal incidentalomas. (5) Patients with MACS lack the usual clinical findings associated with Cushing's syndrome (menstrual changes, lethargy, bruising, hirsutism, round face, dorsal fat pad, striae, decreased libido, proximal muscle weakness, etc.) Instead, they may display the effects of cortisol hypersecretion

in the form of hypertension, diabetes, dyslipidemia, obesity, atherosclerosis, and osteoporosis. (4,12). To assess for cortisol hypersecretion in an incidentaloma, the standard test is a 1 mg (low dose) overnight dexamethasone suppression test (DST). Alternatively, two measurements of late-night salivary cortisol or two measurements of urine-free cortisol can be done to assess for Cushing's syndrome. If the first laboratory investigation is abnormal, another test, amongst the above-mentioned three tests, should be conducted to confirm the diagnosis of Cushing's syndrome. (3,5)

4.2 | Catecholamine Excess

Pheochromocytomas account for 3% of incidentalomas and are another entity to rule out. (4) Although most pheochromocytomas are symptomatic, up to 15% of individuals may have normal blood pressure. (3) Clinical findings of pheochromocytoma catecholamine hypersecretion may include headache, sweating, tachycardia, palpitations, and hypertension. Before biochemical testing, certain medications (e.g., levodopa, adrenergic receptor agonists, TCAs, psychoactive agents, amphetamine, ethanol, etc.) should be discontinued if possible as they may cause false positives. Testing consists of 24-hour urine metanephrines and catecholamines or plasma-fractioned metanephrines. Metanephrines are products of catecholamine metabolism, and are, as a result, elevated in the context of catecholamine hypersecretion. (5)

4.3 | Aldosterone Excess

Hypertensive patients with incidentalomas should also be screened for primary hyperaldosteronism (Conn's syndrome). These patients may have unexplained hypokalemia and a family history of hyperaldosteronism or early-onset cerebrovascular accidents. Aldosteronomas are best tested by the plasma aldosterone-renin ratio. A high plasma aldosterone concentration to plasma renin activity ratio is abnormal and suggests primary hyperaldosteronism. (5,13) Certain medications, such as mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can affect test results. One of several downstream tests (oral sodium loading, saline infusion, fludrocortisone suppression test, captopril challenge) confirms the diagnosis. (14)

4.4 | Sex Hormone Excess

Sex hormone-secreting adrenal tumors are rare and usually malignant. Sex hormone testing is only indicated if signs of unexpected virilization or excess estrogen are present without other symptoms of glucocorticoid excess. Testing is also done when there is a suspicion of adrenocortical carcinoma. (8) Symptoms of virilization include new onset hirsutism, acne, and deepening of voice in females. Estrogen hypersecretion in females results in irregular uterine bleeding and breast tenderness, while in males it is characterized by decreased libido, testicular atrophy, and gynecomastia. (5) Biochemical tests include dehydroepiandrotestosterone (DHEAS) and androstenedione.

5 | BEYOND INITIAL APPROACH

This section details further considerations and management options.

5.1 | Bilateral Adrenal Incidentalomas

Bilateral adrenal incidentalomas are found in 10%-15% of cases of incidentalomas and are estimated to have a prevalence of 0.3%-0.6% in the general population. (15) They can be found in the event of metastases, primary bilateral macronodular adrenal hyperplasia (PBMAH), bilateral cortical adenomas, congenital adrenal hyperplasia (CAH), amyloidosis, hemorrhage, granulomas, infiltrative disease, pheochromocytoma, Cushing's syndrome, and primary hyperaldosteronism. (4,5)

The initial approach towards bilateral masses is as described above. However, bilateral masses are most likely to present with hormone hypersecretion compared to unilateral masses. Bilateral masses should be

investigated for adrenal insufficiency if they appear to be hemorrhagic or infiltrative, as infiltration or destruction of adrenals can result in adrenocortical hyposecretion. (5) This is done by measuring fasting morning cortisol and ACTH levels, followed by an ACTH stimulation test. Adrenal insufficiency is present when cortisol increase is incomplete in response to ACTH injection. (16) With bilateral masses, late-onset CAH, specifically 21-hydroxylase deficiency, should be ruled out by measuring morning 17-hydroxyprogesterone levels. Very elevated levels are diagnostic, while moderate elevation requires ACTH stimulation testing to confirm the diagnosis. (5)

5.2 | Management

Management of adrenal incidentalomas depends on biochemical and imaging findings. Masses >4 cm, those suspicious of malignancy and hyperfunctioning masses should be considered for resection. Adrenalectomies are usually conducted laparoscopically; however, open surgery is sometimes necessary. As per the latest European Society of Endocrinology guidelines, non-functioning benign-appearing masses below 4 cm, do not necessitate follow-up imaging. (5,17) On the other hand, the American Association of Clinical Endocrinologists recommends up to 5 years of radiological follow-up for all non-resected masses. (18) More recent European guidelines recommend that non-surgically removed masses >4 cm should be followed radiologically to monitor for stability, usually at 6-12 months. If there is a 5 mm and 20% size increase, surgical removal is recommended. (5,8) Repeat biochemical testing for hypersecretion should be done if a patient with initially non-functioning incidentaloma develops signs and symptoms of hormone hypersecretion. (5)

Of note, pheochromocytomas need to be promptly resected to avoid cardiovascular complications. Their removal is complicated by the risk of hypertensive crises, arrhythmias, and multiorgan failure. To prevent these complications, patients require pre-operative alpha-adrenergic blockade followed by beta-adrenergic blockade and subsequent high sodium diet. Beta-adrenergic blockade should never be given before alpha blockade in these patients. (19) As for subclinical Cushing's syndrome-associated adrenal mass removal, it is important to test for adrenal insufficiency post-operatively using the ACTH stimulation test. Due to cortisol hypersecretion, the hypothalamic-pituitary-adrenal (HPA) axis is suppressed by negative feedback. When the cortisol-secreting mass is removed, the axis remains suppressed for some time resulting in a lack of adrenal stimulation by ACTH to release cortisol, leading to hypocorticolism. In the event of adrenocortical hypofunction, patients need to be given glucocorticoid replacement until the HPA axis recovers. (4)

In summary, adrenal incidentalomas are incidental findings of adrenal masses on imaging that require a workup to rule out hormone hypersecretion and malignancy. This entails evaluating imaging findings for features of malignancy, as well as testing for cortisol and catecholamine excess in all patients. Further testing is catered based on clinical presentation.

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APPROACH TO
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Ptosis

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KEYWORDS
Ptosis, Droopy eyelid, Third nerve palsy

1 | QUESTION

A 75-year-old male presents to the emergency room with a drooping left upper eyelid. Upon further questioning, he states that he feels his visual acuity has deteriorated in the left eye, but only in the dark. On testing his best corrected visual acuity is 20/25 in the right eye and 20/30 in the left eye. His pupils are equal, round, and reactive to light and accommodation. His intraocular pressures are 14mmHg bilaterally. His past medical history is significant for type 2 diabetes mellitus, hypertension, hypercholesterolemia, and obesity. He states that he first noticed his eyelid drooping this morning, and it does not get better or worse during the day. He also states that he has been experiencing some horizontal diplopia since this morning. Your clinical examination reveals no significant ocular misalignment, but extraocular movements of the patient's left eye are limited in upward, downward, and inward gaze. His margin to reflex distance (distance between corneal light reflex and

upper eyelid) is 2mm and he is unable to raise his eyelid more than 1mm, suggesting a decreased levator function. His ESR and CRP are within normal limits. At his 6-week follow-up appointment, his symptoms have almost entirely resolved. Given the patient's clinical presentation, what is the most likely diagnosis?

A) Third nerve palsy
B) Myasthenia gravis
C) Congenital ptosis
D) Horner syndrome
E) Aponeurotic ptosis

2 | ANSWER

A. Given the patient's history and clinical examination, the most likely diagnosis is a third cranial nerve palsy. Furthermore, given his positive systemic risk factors (obesity, diabetes mellitus, hypertension, hypercholesterolemia) and absence of pupillary involvement, an ischemic third nerve palsy is favoured. Typically, ischemic third nerve palsies are self-limited and the patient can be scheduled for follow-up in 4-6 weeks with management of vascular risk factors. Pupillary involvement or lack of improvement at follow-up are indications for head imaging with CT angiography to rule out an aneurysm or other compressive etiologies. In this case, since the ptosis does not worsen as the day goes on, there is no fatigable ptosis on upgaze, and symptoms do not improve after rest, myasthenia gravis is unlikely. Congenital ptosis is also unlikely in this case as it would present in the first years of life. Horner syndrome would include miosis and facial anhidrosis alongside the ptosis. Aponeurotic ptosis (a result of normal aging) is a possible diagnosis; however, it is less likely in this patient given that the ptosis is not isolated and is accompanied by incomplete upward, downward, and inward gaze of the ipsilateral eye.

3 | INITIAL APPROACH

Ptosis, also referred to as blepharoptosis, is defined as the lowering of the upper eyelid below the typical resting position. Generally, if the upper eyelid drops more than 1mm from the superior limbus, a diagnosis of ptosis can be made. (1) History taking should be focused on eliciting whether the ptosis is unilateral or bilateral, the time of onset, whether it was acute or progressive, whether it fluctuates during the day, pertinent family history, and any other ocular symptoms. Understanding the impact on daily functioning as well as the psychosocial impact are also relevant to the initial approach. It is particularly important to determine whether there are any other symptoms outside of the dropping eyelid for patients presenting with acute onset ptosis. Childhood photographs can help elicit the duration of ptosis. Past cancer history, risk factors, or constitutional symptoms should also be considered due to the possibility of an intracranial mass impeding on the innervation pathway or an eyelid mass physically weighing down the eyelid. In pediatric patients, head posture is another element to observe and ask caregivers about. (1) The clinical exam should focus on determining the margin-to-reflex distance (MRD), quantifying levator function, checking pupillary function, and assessing extraocular movements. There are three types of MRDs, however MRD 1 is typically the most clinically relevant, MRD 1 measures the corneal light reflex to the center of the upper eyelid margin and can quantify the degree of upper eyelid retraction. A normal MRD1 is greater than 2.5 mm, typically 4-5 mm. (1,2) In patients with vertical strabismus, this measurement is not as useful. Levator function can be assessed by measuring the distance that the center of the upper eyelid margin travels between downgaze and upgaze, while the frontalis muscle is held in place. Normal levator function is 10mm or greater. (1) As well, MRD 1 and levator function between the two eyes should be compared. It should be noted that proptosis in one eye may lead to an incorrect diagnosis of ptosis in the contralateral eye. Binocular Esterman visual field testing can help objectively determine the amount of visual compromise caused by ptosis. Depending on the suspected cause, specific investigations can be ordered such as serum acetylcholine receptor antibody levels, ice pack testing, CT or MRI of the head with or without angiography, or genetic testing. (1)

Lastly, eyelid palpation should be done in an effort to detect any palpable mass weighing the eyelid down.

4 | BEYOND THE INITIAL APPROACH

This section outlines common causes of ptosis and is subdivided into two categories of ptosis: congenital and acquired (Figure 1). Treatment is also briefly discussed as a separate subsection.

4.1 | Pseudoptosis

Some conditions can be mistaken for ptosis and this phenomenon is referred to as pseudoptosis. Dermatochalasis, a term for excessive redundant upper eyelid skin, can overlie the upper eyelid mimicking ptosis. Unilateral proptosis can cause the contralateral eyelid to appear ptotic due to ipsilateral lid retraction. Unilateral vertical strabismus can cause a ptotic appearance, specifically when the patient is looking down.

4.2 | Congenital Ptosis

Patients presenting with a drooping eyelid within the first years of life are considered to have congenital ptosis. Although congenital ptosis is typically idiopathic, other causes including malignancy, autoimmune conditions, and hereditary disorders such as Duane syndrome or blepharophimosis syndrome should be ruled out. (3,4) In congenital ptosis, there is fibrous and fatty infiltration of the levator palpebrae superioris with a poorly developed levator palpebrae superioris. (3) Left untreated, congenital ptosis can lead to occlusion amblyopia. (4)

4.3 | Acquired Ptosis

4.3.1 | Aponeurotic

The most common form of acquired ptosis, aponeurotic ptosis (also referred to as involutional ptosis), occurs due to the normal aging process and is a clinical diagnosis. The levator aponeurosis connects the levator palpebrae superioris to the upper eyelid tarsal plate. Disinsertion or dehiscence of the levator aponeurosis causes aponeurotic ptosis. Typically, levator function remains strong. (5)

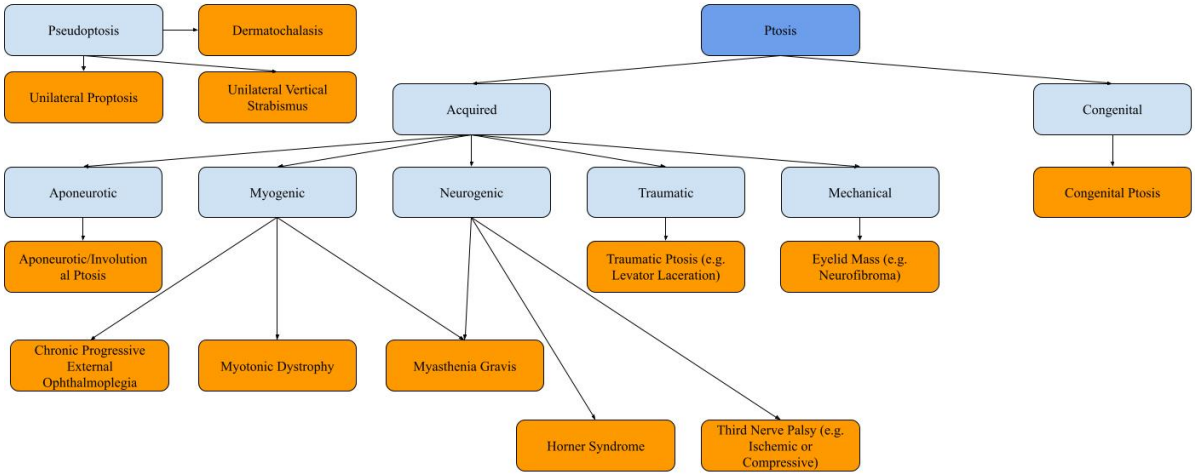

FIGURE 1 **Flowchart.** Ptosis diagnoses categorization flowchart.

4.3.2 | Myogenic

Myogenic ptosis is characterized by the weakening of the levator palpebrae superioris muscle, leading to ptosis. A common example is myasthenia gravis, an autoimmune condition characterized by elevated postsynaptic acetylcholine receptor antibodies at the neuromuscular junction leading to progressive muscle weakness. (6) Notably, myasthenia gravis is sometimes classified as neurogenic ptosis given that its mechanism is localized to the neuromuscular junction. The most common presenting symptom of myasthenia gravis is ptosis, which can be accompanied by diplopia or blurred vision. These symptoms worsen with increased muscle use and therefore become worse as the day progresses and improve with rest. (6,7) While ocular symptoms can be present in isolation, 50% of cases will progress to generalized myasthenia gravis. (8) Determining whether the patient has difficulty with chewing or swallowing, proximal limb weakness, or respiratory muscle can also be useful when considering a diagnosis of myasthenia gravis. Ptosis improvement after the sleep test or ice test are also useful signs. (6) These tests work as they reduce acetylcholine breakdown and therefore transiently improve ptosis caused by myasthenia gravis. Chronic progressive external ophthalmoplegia (a mitochondrial disorder), oculopharyngeal muscular dystrophy, and myotonic dystrophy are other examples of myogenic ptosis. Muscle biopsy, genetic testing, and looking at family photos are additional parts of the diagnostic approach.

4.3.3 | Neurogenic

Neurogenic ptosis refers to ptosis that occurs as a result of dysfunction of the nerves innervating the eyelid muscles. The most common example is a third cranial nerve palsy, in which the clinical examination would also typically show the eye positioned inferior and lateral, limited adduction, infraduction, and/or supraduction of the eye, and occasionally a fixed dilated pupil. This is because the oculomotor nerve innervates the levator palpebrae superioris, superior rectus, inferior rectus, medial rectus, and inferior oblique muscles. (9) The innervation to the pupil travels along the exterior portion of the oculomotor nerve, so pupil-sparing third nerve palsies typically have an ischemic cause that has only compromised the core of the oculomotor nerve. (9) Notably, a third nerve palsy can be complete or partial, and it is possible for a partial third nerve palsy to present only with mild ptosis. (10) Uncommonly, bilateral third nerve palsy can be present. (11) If there is misalignment between the eyes, diplopia is a common chief complaint. The differential diagnosis for a third nerve palsy is vast, but can be generally stratified into compressive, vascular, neoplastic, or traumatic etiologies. (10) Typically, ischemic third nerve palsies are self-resolving. Imaging such as a CT angiogram arch to vertex is often done to rule out a compressive vascular etiology which can have significant consequences. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are typically done as well to rule out giant cell arteritis. Another example of neurogenic ptosis is Horner syndrome which constitutes the characteristic triad of miosis, ptosis, and facial anhidrosis. (12) Horner syndrome is always observed secondary to an underlying cause that disrupts the sympathetic innervation to the eye at the level of the head or neck. The causes can be stratified depending on the location of sympathetic innervation disruption has taken place: first-order neuron causes are typically intracranial, second-order neuron causes are in the thoracic region, and third-order neuron causes are typically near the cavernous sinus. (13) Pseudo-enophthalmos, or the appearance that the eye has been posteriorly displaced in the orbit, may also be observed. (13)

4.3.4 | Traumatic

Traumatic ptosis includes a vast array of causes and occurs following a traumatic injury to the upper eyelid that disrupts the function of the levator palpebrae superioris. Traumatic ptosis can be further categorized into the neurogenic, myogenic, aponeurotic, or mechanical ptosis depending on the mechanism. For example, laceration of the levator muscle by a knife would be myogenic whereas excessive stretching of the eyelid leading to levator aponeurosis dehiscence would be aponeurotic.

4.3.5 | Mechanical

Mechanical ptosis refers to drooping of the upper eyelid caused by the weight of the eyelid. A neoplastic eyelid mass, large hematoma in the eyelid, or excessive dermatochalasis are examples of mechanical ptosis.

4.4 | Management

For ptosis associated with a treatable secondary cause, treatment of the underlying condition is the main objective. For patients with ptosis that does not have an underlying condition and is not bothersome to the patient, no treatment is necessary. Pediatric patients are followed more closely to monitor for signs of amblyopia. (4) Levator muscle resection and frontalis suspension are common surgical procedures used for the treatment of ptosis. (14)

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