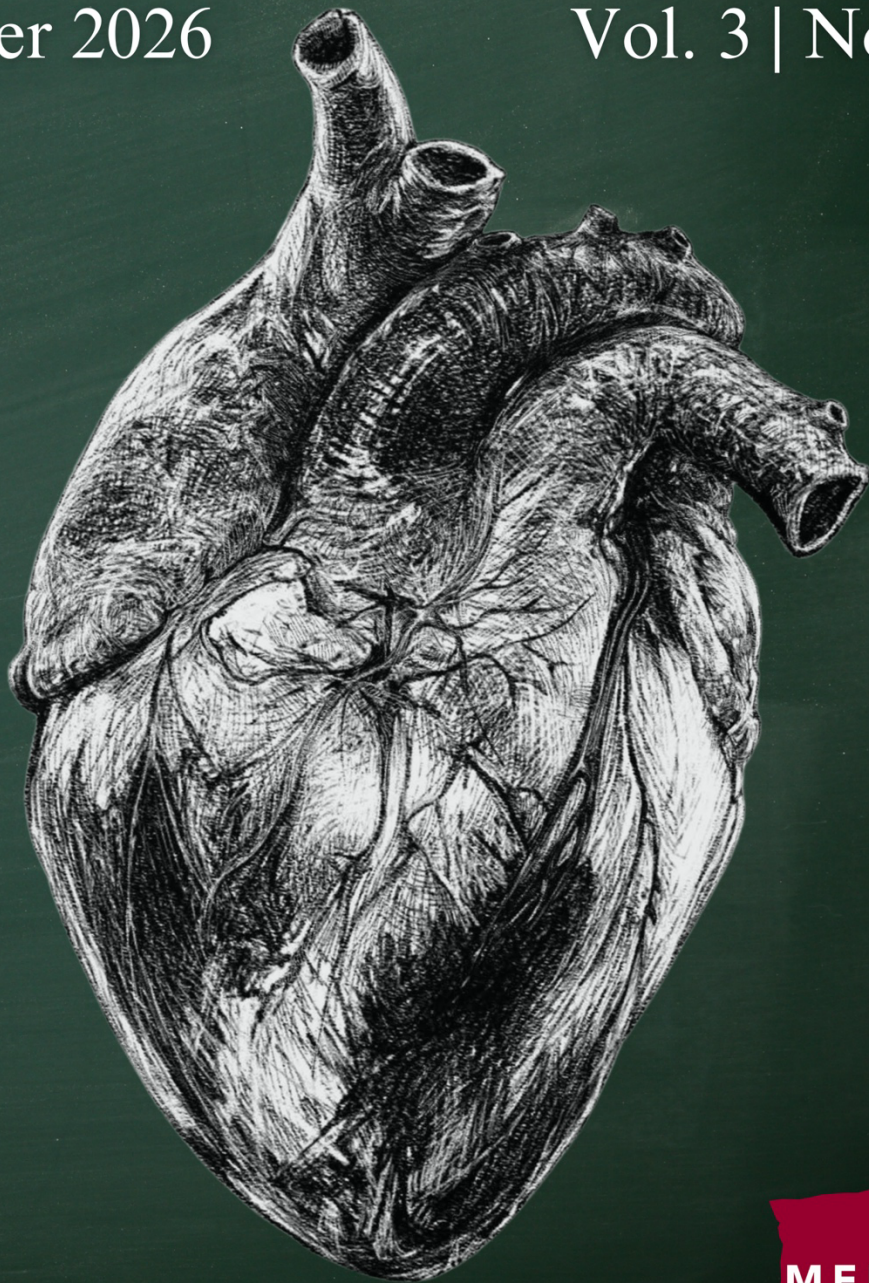


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Land Acknowledgement



We respectfully acknowledge the territory in which we gather as the ancestral homelands of the Beothuk, and the island of Newfoundland as the ancestral homelands of the Mi'kmaq and Beothuk. We would also like to recognize the Inuit of Nunatsiavut and NunatuKavut and the Innu of Nitassinan, and their ancestors, as the original people of Labrador. We strive for respectful relationships with all the peoples of this province as we search for collective healing and true reconciliation and honour this beautiful land together.

Artificial intelligence in radiology: Risks and the need for residency education

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Keywords: Artificial Intelligence, Radiology, Residency Training, Medical Education

The intersection of radiology and artificial intelligence (AI) is a rapidly evolving development in modern medicine. AI has the potential to enhance diagnostic accuracy, improve workflow efficiency, and support clinical decision-making^{1,2}, positioning it as a powerful adjunct to radiology. At the same time, the integration of AI into radiology introduces complex risks that require critical oversight. In particular, algorithmic bias, automation bias, and AI interpretability represent some of the risks associated with modern AI systems. Despite the increasing adoption of AI within radiology, AI education has not been widely incorporated into radiology residency training programs^{3,4}. By examining these three challenges of AI in radiology, this discussion highlights the growing need for formal AI education to ensure future radiologists can appropriately assess and safely integrate these technologies into clinical practice.

Algorithmic bias in the context of radiology and AI is defined as systematic errors or prejudices in AI algorithms⁵. Because AI models are trained on large medical imaging datasets⁶, the quality and composition of these datasets directly influence how AI systems perform. Simply put, AI systems become efficient at recognizing patterns within the data on which they are trained. However, medical imaging datasets frequently contain demographic imbalances, often underrepresenting certain groups based on factors such as race, ethnicity, sex, or socioeconomic status⁷. These imbalances may reflect existing healthcare disparities, unequal access to care, or limited demographic reporting within datasets themselves^{7,8}. As a result, AI systems can learn and reproduce these biases, leading to performance disparities that disproportionately disadvantage historically underrepresented populations⁹. For example, a study evaluating racial bias in a cardiac MRI segmentation AI model found significant differences in model performance across racial groups when trained on the UK Biobank dataset, which consisted predominantly of White patients (81%). The authors concluded that the observed racial bias was likely related to imbalance within the training data itself, highlighting how non-representative datasets can contribute to inequitable AI performance¹⁰. This raises significant concerns that AI may perpetuate, or even exacerbate, existing healthcare inequities. Identifying AI algorithmic bias is further complicated by inconsistent demographic reporting within medical image databases^{11,12}. The Canadian Association of Radiology (CAR) has recognized both the risk of algorithmic bias and the challenges associated with identifying these biases,

emphasizing the important role that physicians and data scientists play in recognizing, evaluating, and mitigating them⁹. As AI becomes increasingly integrated into radiology, radiologists must be equipped with the knowledge to identify and evaluate algorithmic bias to ensure that AI systems do not perpetuate existing healthcare inequities.

Automation bias is another risk associated with the integration of AI into radiology and has been widely discussed in the literature. It refers to the tendency of individuals to place excessive trust in AI-generated outputs while disregarding or underutilizing their own clinical judgment and critical thinking skills¹³. Literature suggests that the risk of automation bias increases with task complexity and time constraints, making radiology particularly susceptible^{14,15}. This overreliance on AI systems in radiology may contribute to missed or incorrect diagnoses¹⁶. In a study evaluating AI-assisted mammography interpretation, radiologists across all experience levels were more likely to assign an incorrect Breast Imaging Reporting and Data System (BI-RADS) classification when the AI system also provided an incorrect classification¹⁷. Because BI-RADS classifications are used to estimate malignancy risk and guide patient management, these findings are of major concern, as they demonstrate how radiologists may become susceptible to automation bias, which may negatively influence clinical decision-making and patient care. Importantly, the way AI is integrated into radiology workflows may further compound the risk of automation bias. In many radiology workflows that incorporate AI, AI outputs are directly integrated into Picture Archiving and Communication Systems (PACS) with limited opportunity for radiologist interaction or modification.⁹ This passive integration of AI outputs may encourage overreliance without sufficient independent evaluation by radiologists, potentially contributing to diagnostic errors. Furthermore, incorrect AI interpretations accepted without sufficient scrutiny may reinforce future AI model inaccuracies and contribute to repeated diagnostic errors over time¹⁵. Given this, formal AI education within radiology residency programs is essential to prepare future radiologists to critically engage with AI systems and reduce the risk of automation bias influencing clinical decision-making.

In addition to algorithmic and automation bias-related risks, the interpretability of AI systems remains a major concern in radiology. AI interpretability refers to the ability to understand how an AI system arrives at its conclusions.

However, many AI systems function as “black boxes”, meaning they may generate conclusions without providing a clear understanding of how those conclusions were reached¹⁸. As a result, radiologists may have limited insight into how AI outputs are produced. This can be problematic, as AI systems may occasionally produce unexpected or unreliable outputs that do not align with conventional clinical reasoning¹⁹, and the “black box” nature of these systems makes AI-related errors difficult to detect²⁰. This creates significant challenges for radiologists who are expected to assess the reliability of AI-generated recommendations in clinical practice. Closely related to these interpretability challenges is the susceptibility of AI systems to adversarial inputs. Adversarial AI refers to techniques that manipulate AI models through subtle alterations in input data intended to deceive the system²¹. The potential impact of adversarial AI in radiology has been demonstrated in the literature. For example, one study demonstrated that adversarial AI attacks could add or remove evidence of lung cancer on CT imaging, thereby altering clinical interpretation²². This represents only one of many ways adversarial AI attacks may impact radiology practice. Because many AI systems function as “black boxes,” adversarial AI can be challenging to recognize or understand. Consequently, these attacks may contribute to missed diagnoses, inappropriate or unnecessary treatments, and delayed urgent care^{21,23}. Therefore, education regarding AI interpretability and the potential for adversarial AI is essential to ensure radiologists recognize the vulnerabilities and limitations of AI systems and maintain appropriate oversight²¹.

Despite the increasing integration of AI into radiology practice and the risks associated with its use, formal AI education within radiology residency programs remains limited and inconsistent. This is particularly problematic given the scale of AI adoption in medicine. Over 1,000 FDA-cleared AI algorithms have been approved for clinical use as of 2025, with many of them designed for radiology tasks²⁴. Given this, there is a responsibility to prepare radiology residents to critically evaluate and safely work with AI. However, in a 2023 study in the United States, nearly one-quarter of radiology residents reported having no AI or machine learning educational offerings within their residency program³. Similar concerns have been recognized in Canada. A 2023 study evaluating a pilot AI workshop within a Canadian radiology residency program noted that it represented one of the first formal AI educational initiatives integrated into radiology residency training in Canada²⁵. Initiatives such as these demonstrate growing recognition of the importance of AI education. Despite this progress, there remains no standardized AI curriculum for radiology residents²⁵. Furthermore, many of the existing AI educational opportunities remain external to residency curricula and rely on extracurricular learning²⁵. As a result, AI education remains inconsistent across residency programs²⁵ and may be difficult to incorporate alongside residents’ demanding

clinical and academic responsibilities^{26,27}. Importantly, evidence suggests that structured AI education can be effective. A systematic review published in 2025 found that roughly 93% of studies showed that AI training improves radiology residents’ AI knowledge and diagnostic performance²⁸, suggesting that AI education is beneficial to radiology residency curricula. Overall, these findings make a compelling case that while AI education is limited, its integration into radiology residency curriculums can positively influence their training. Such a curriculum should not only address the foundations of AI, but also prepare residents to critically assess and mitigate challenges associated with its integration into radiology practice.

As AI becomes increasingly integrated into radiology, radiologists will be expected not only to use these technologies, but also to recognize their limitations and apply them responsibly to clinical practice. While AI shows significant potential in the field, it also introduces a wide range of risks, including algorithmic bias, automation bias, and limited AI interpretability. Without sufficient education regarding the risks of AI systems, patient safety may be compromised. Therefore, radiologists cannot function as passive users of AI. Instead, they must be equipped with the knowledge necessary to responsibly integrate AI into radiology practice, underscoring the need for formal AI education within radiology residency programs.

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Investigating the clinical utility of three protocols of hepatobiliary iminodiacetic acid scans in gallbladder dyskinesia

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ABSTRACT

Purpose: Stimulated hepatobiliary iminodiacetic acid (HIDA) scans assess gallbladder function by measuring gallbladder ejection fraction (GBEF) to help diagnose biliary dyskinesia, a functional disorder causing biliary-type pain with no structural abnormalities on ultrasound. Various HIDA protocols use different stimulants and imaging times, but their comparative clinical utility and impact on patient outcomes remain unclear. This study aimed to compare GBEF values, surgical intervention rates, pathology, and symptom resolution across three common HIDA protocols.

Methods: A retrospective review of 525 patients with abdominal pain, normal biliary ultrasound, and abnormal HIDA scans (GBEF $\leq 40\%$ or radiologist opinion) from 2018–2022 was performed. Protocol 1 used intravenous sincalide with imaging at 30 minutes; Protocols 2 and 3 used oral stimulants (Ensure® and fatty meal, respectively) with imaging at 60 minutes. Demographic and clinical variables were compared using ANOVA, Welch's ANOVA, Chi-square, and Fisher's exact tests.

Results: Protocol 1 included 318 patients (60.6%), Protocol 2 had 175 (33.3%), and Protocol 3 had 32 (6.1%). Protocol 1 showed significantly lower mean GBEF values ($60.7\% \pm 30.6$) compared to Protocol 2 ($74.9\% \pm 19.0$; $p < 0.001$), with greater variability. Cholecystectomy rates were higher in Protocol 1 (21.4%) versus Protocol 2 (9.7%; $p = 0.004$). Symptom resolution post-surgery was similar across groups (63.6% for Protocol 1, 78.6% for Protocol 2; 80.0% for Protocol 3; $p = 0.839$), as was final pathology ($p = 0.485$).

Conclusion: Despite protocol differences affecting GBEF values and surgery rates, patient outcomes were comparable. Protocol 1 remains the gold standard, but Protocols 2 and 3 could serve as reasonable alternatives; prospective studies with standardized imaging times are needed to validate these findings.

Keywords: *Hepatobiliary Iminodiacetic Acid Scan, Gallbladder Ejection Fraction, Biliary Dyskinesia, Cholecystectomy, Nuclear Medicine, Radiology.*

Biliary dyskinesia is defined as a functional disorder of the gastrointestinal tract, presenting with a reduced gallbladder ejection fraction (GBEF) without another identified cause for biliary-type pain.¹ One diagnostic technique is the stimulated hepatobiliary iminodiacetic acid (HIDA) scan in nuclear medicine, often used when the first-line imaging modality - ultrasound - provides little diagnostic clarity.² Sequential images are captured with a gamma camera using radioactive tracers to evaluate bile flow through the hepatobiliary system into the small intestine, approximating the system's function.^{3,4} The GBEF can then be calculated, which is often reduced in calculous and acalculous biliary diseases.³ While the technique is well understood, there are inconsistencies in the literature regarding its clinical utility and the optimal imaging protocol.

Generally, the hepatobiliary system is first imaged for 60 minutes using a radiotracer.^{5–8} The scan should be performed using either ^{99m}Tc-disofenin or ^{99m}Tc-mebrofenin as the radiotracer, which is injected intravenously. The radiotracer dose varies from 66.6 to 370 MBq, but most commonly

ranges from 148 to 185 MBq of mebrofenin. In the gold-standard protocol (referred to as Protocol 1 in this study), sincalide, a cholecystokinin (CCK) synthetic, is given intravenously at 0.02 $\mu\text{g/kg}$ and infused over 30–60 minutes (preferably 60 minutes) once the gallbladder is proven to be filled with radiotracer. A CCK synthetic is an ideal choice because it is a hormone responsible for gallbladder contraction.⁹ The biliary system is then imaged with a gamma camera to track the flow of bile.^{4,5,10} Some studies image for 20 minutes^{10,11} or 30 minutes^{12,13} post-infusion, while others image for up to 60 minutes or more.^{4,6–8,13} Other studies^{6,8} have concluded that Ensure® (Regular formulation) or a fatty meal administered orally may be employed as alternatives for stimulating gallbladder contractions in HIDA scanning when sincalide is not available. Several studies have also explored the potential impact of adding morphine post-treatment if the gallbladder is unable to be visualized, or pre-treatment pre-emptively, which has shown promise.¹⁴

The values used for a normal GBEF vary throughout the literature. Some studies have used 38% as the lower limit of

normal when using a 60-minute sincalide infusion, as per the 2010 guidelines by the Society of Nuclear Medicine (SNM).¹⁵ However, others have arbitrarily defined cut-off values for the normal range of GBEF, such as >40%.¹⁶ Another study proposed a lower limit of normal of GBEF as high as 41% with a 60-minute sincalide infusion.¹⁷ Others have accepted GBEF limits as low as 35% for the lower limit of normal.^{4,7,10–12,18–20}

Many have suggested that GBEF is a useful tool in determining who will benefit from a cholecystectomy. One study found that the use of a HIDA scan in addition to an abdominal ultrasound significantly increased the sensitivity for diagnosing chronic cholecystitis.² It has been found that patients with an abnormally low GBEF have symptom improvement post-cholecystectomy.^{16,19} A correlation has also been identified between low GBEF and histopathological changes in the gallbladder.^{11,16} It has been reported that most patients with abnormal HIDA scans and abnormal pathologies had symptom resolution post-cholecystectomy.^{11,20} Further, pain provocation during the sincalide infusion could be useful in determining which patients may have successful outcomes post-cholecystectomy.²¹ Meanwhile, other studies have found no significant correlation between low GBEF, reproducible pain during the sincalide infusion, and resolution of symptoms post-surgical intervention.^{4,7}

While the HIDA scan is a well-understood technique, there is still much controversy surrounding its utility and predictive value. Regardless, many authors agree that it is a useful tool for investigating chronic biliary dyskinesia and pain symptoms. The purpose of this study was to compare the diagnostic utility and clinical predictive value of each of the three protocols. Based on the current literature, it was hypothesized that all three protocols would likely produce equivalent findings regarding GBEF values and patient outcomes, which may help to inform clinicians' practice and choice of protocol.

METHODS

This study utilized data collected as part of a larger study (Kerr et al., unpublished data, 2024) exploring the value of HIDA scans in biliary dyskinesia. The study received full ethical approval by the local Health Research Ethics Board (file #20240629). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This was a retrospective chart review including all patients who had undergone HIDA scans at a single institution from January 2018 to December 2022. The inclusion criteria included all patients with abdominal pain, normal biliary ultrasound findings, and abnormal HIDA scan findings as defined by GBEF $\leq 40\%$ or radiologist opinion. The exclusion criteria specified patients with abnormal ultrasound findings (including cholelithiasis, pericholecystic fluid, gallbladder wall thickening, or sludge) and patients

undergoing HIDA scans for indications other than abdominal pain in the context of normal biliary ultrasound findings. The local electronic medical records database, Meditech (Medical Information Technology Inc., Westwood, Massachusetts, USA), was used for the collection of relevant patient data, including age, sex, past medical and surgical history, date and indication for the HIDA scan, radiological impression and diagnosis, date of cholecystectomy, and final pathology report. Clinic notes were also searched to include data on preoperative symptoms and symptom resolution post-operatively.

Of note, at the institution during the study period, Protocol 1 imaging was conducted at the 30-minute mark post-sincalide infusion, reflecting historical practice at the time. Protocols 2 and 3, using oral gallbladder stimulants, employed imaging at the 60-minute mark, consistent with published protocols for these methods and allowing sufficient time for gallbladder contraction. This was a retrospective protocol which was the standard at the institution at the time of data collection. Since the completion of data collection, the institutional practice has become standardized for imaging to occur at 60 minutes across all protocols, reducing variability and improve comparability of GBEF measurements.

Statistical analysis of the final dataset was performed using R version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as means $\pm$ standard deviations, and categorical variables as frequencies and percentages. The distribution of patients across protocols was evaluated using a Chi-square goodness-of-fit test, with standardized residuals calculated to identify deviations from expected frequencies. Normality of residuals and homogeneity of variance for continuous variables were assessed using the Shapiro-Wilk test and Levene's test, respectively. One-way Analysis of Variance (ANOVA) was used for age comparisons, given that these assumptions were sufficiently met. Due to violations of these assumptions for GBEF, comparisons of GBEF across protocols were conducted using Welch's ANOVA to account for unequal variances, and post-hoc pairwise comparisons were performed using the Games-Howell test with adjustment for multiple comparisons. Categorical variables such as sex, comorbidities, surgical intervention rates, and pathology findings were analyzed using Chi-square tests of independence or Fisher's exact tests when expected cell counts were less than five. Significant results were followed by pairwise comparisons with Bonferroni correction to adjust for multiple tests. The threshold for statistical significance was set at a p-value of <0.05 for all analyses.

RESULTS

Of the 585 patients in the original sample, 60 were excluded (3 due to absence of gallbladder stimulation and 57 due to non-numeric GBEF values), leaving 525 patients for analysis.

Since data collection, the study's institution has changed Protocol 1 imaging to occur at the 60-minute mark; however, these data are not included, as this change occurred after the study period. Of these patients, 318 (60.6%) underwent Protocol 1, 175 (33.3%) Protocol 2, and 32 (6.1%) Protocol 3. This distribution differed significantly from equal distribution ($p < 0.001$), with Protocol 1 overrepresented and Protocol 3 underrepresented (see Table 1).

Table 1. Baseline patient demographics by protocol.

Patient Demographic	Protocol 1	Protocol 2	Protocol 3	p-value
Number of Patients (%)	318 (60.6%)	175 (33.3%)	32 (6.10%)	$< 2.20 \times 10^{-16}$ (*)
Mean Age in Years (SD)	48.1 (16.5)	50.0 (15.7)	45.6 (15.2)	0.255
Female (%)	241 (75.8%)	126 (72.0%)	26 (81.3%)	0.449
Comorbidities (%)				
Dyslipidemia	15 (22.1%)	1 (20.0%)	0 (0%)	1.00
Type 2 diabetes mellitus	12 (17.6%)	1 (20.0%)	0 (0%)	1.00
Gastroesophageal reflux disease	31 (45.6%)	1 (20.0%)	1 (100.0%)	0.262
Hypertension	14 (20.6%)	2 (40.0%)	0 (0%)	0.452
Non-alcoholic steatohepatitis	2 (2.94%)	2 (40.0%)	0 (0%)	1.00
Chronic obstructive pulmonary disease	2 (2.94%)	0 (0%)	0 (0%)	1.00
Asthma	4 (5.88%)	1 (20.0%)	0 (0%)	0.353
Obstructive sleep apnea	2 (2.94%)	0 (0%)	0 (0%)	1.00
Alcohol Use (%)	15 (28.8%)	1 (33.3%)	0 (0%)	1.00
Smokers (%)	10 (19.2%)	1 (33.3%)	0 (0%)	0.594

Percentage proportions are based upon the total number of patients in each protocol with follow-up data available for the listed parameter. P-values are from Chi-square tests for categorical variables, Fisher's exact tests where appropriate, and one-way ANOVA for continuous variables. Follow-up data were available for N=74 patients (comorbidities), N=56 (alcohol/smoking). (*) indicates a statistically significant p-value.

There were no significant differences in baseline demographics, including age and sex, across protocols (all $p > 0.05$; see Table 1). Data on comorbidities, alcohol use, and smoking were limited but similarly showed no significant differences between groups (all $p > 0.05$; see Table 1). Common comorbidities included dyslipidemia (DLD), type 2 diabetes mellitus (T2DM), gastroesophageal reflux disease (GERD), hypertension (HTN), non-alcoholic steatohepatitis (NASH), chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea (OSA). Eight patients (1.52%) had alternative diagnoses other than biliary dyskinesia documented, all in Protocol 1, including 4 diagnosed with irritable bowel syndrome (IBS), 1 diagnosed with Crohn's disease, 2 diagnosed with gastritis, and 1 diagnosed with abdominal pain not yet determined (NYD).

Mean GBEF differed significantly across protocols ($p < 0.001$), with higher values observed in Protocol 2 compared to Protocol 1 (Welch's ANOVA; mean difference=14.2%, 95% CI 8.9–19.5). However, no significant differences were observed between Protocols 1

and 3 or Protocols 2 and 3 ($p = 0.107$ and $p = 0.116$, respectively).

The distribution of GBEF categories (hypokinetic [0–40%], dyskinetic [41–79%], hyperkinetic [80–100%]) also differed significantly across protocols (Chi-square test of independence, $p < 0.001$). Protocol 1 demonstrated a higher proportion of hypokinetic values compared to Protocols 2 and 3. However, visual inspection of GBEF distributions suggested similar patterns of values below the abnormal threshold ($\leq 40\%$) across protocols (see Figures 1-4).

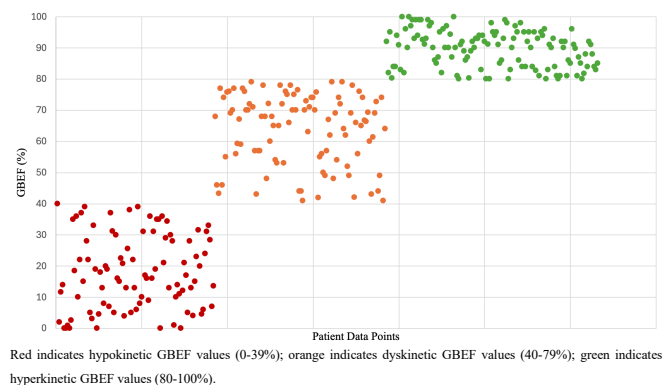


Figure 1. Scatter plot showing individual gallbladder ejection fraction (GBEF) data points for Protocol 1.

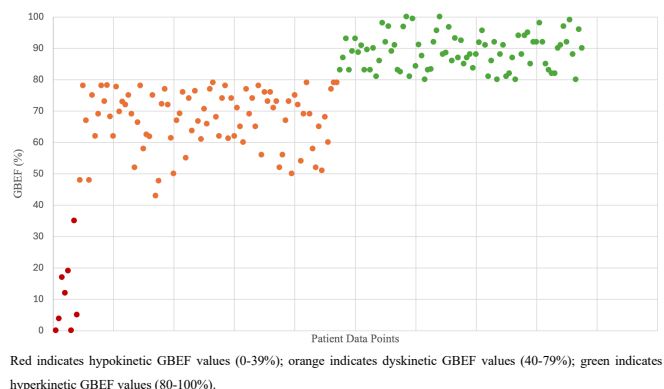


Figure 2. Scatter plot showing individual gallbladder ejection fraction (GBEF) data points for Protocol 2.

A total of 91 patients (17.3%) underwent surgical intervention via cholecystectomy. Surgical rates differed significantly across protocols, with higher rates observed in Protocol 1 compared to Protocol 2 (Chi-square test of independence, $p = 0.00436$; see Table 2). Reasons for not undergoing surgery were documented for 44 patients (8.38%), and included clinical judgement (31.8%), loss to follow-up or no surgical assessment (22.7%), awaiting surgery (11.4%), and patient refusal (11.4%). Reasoning did not differ significantly between protocols (all $p > 0.05$; see Table 2).

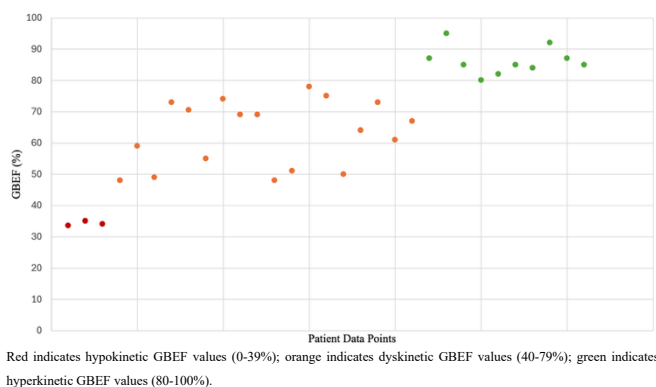


Figure 3. Scatter plot showing individual gallbladder ejection fraction (GBEF) data points for Protocol 3

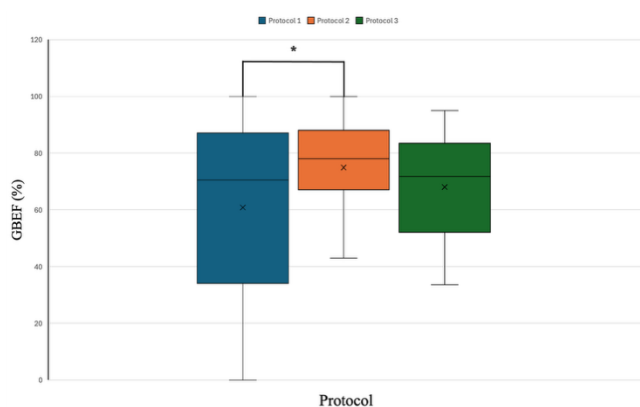


Figure 4. Box and whisker plot depicting the distribution and means of the gallbladder ejection fraction (GBEF) values in each protocol.

Table 2. Patient outcomes by protocol.

Patient Outcome	Protocol 1	Protocol 2	Protocol 3	p-value
Surgical Intervention (%)	68 (21.4%)	17 (9.71%)	6 (18.8%)	0.00436 (*)
Pathology				
Chronic acalculous cholecystitis	41 (62.1%)	1 (50.0%)	0 (0%)	0.485
Other	25 (37.9%)	1 (50.0%)	1 (100%)	
Pain Resolution Post-Operatively (%)	42 (63.6%)	11 (78.6%)	4 (80.0%)	0.839
Reason for No Surgical Intervention (%)				
Patient declined	4 (10.3%)	1 (25.0%)	0 (0%)	1.00
Awaiting surgery	5 (12.8%)	0 (0%)	0 (0%)	
Surgeon clinical judgment	12 (30.8%)	1 (25.0%)	1 (100%)	
Lost to follow-up / no surgical assessment	8 (20.5%)	2 (50.0%)	0 (0%)	

Percentage proportions are based upon the total number of patients in each protocol with follow-up data available for the listed parameter. P-values are from Chi-square tests for categorical variables, Fisher's exact tests for small sample sizes, and post-hoc pairwise Fisher's exact tests

Among those who underwent surgery, pathology data were available for 69 patients, classified as chronic acalculous cholecystitis or other pathologies (e.g., chronic calculous cholecystitis, cholesterolosis, polyps, adenomyosis, benign cholelithiasis). No significant differences in pathology were found across protocols (Fisher's exact test, $p=0.485$; see Table 2).

Similarly, data on pain and/or symptom resolution were available for 85 patients (16.2%). The majority reported symptom resolution, with no significant differences between protocols (63.6% for Protocol 1, 78.6% for Protocol 2, 80.0% for Protocol 3; Fisher's exact test, $p=0.839$; see Table 2).

DISCUSSION

This study has addressed a clinically relevant issue, given that multiple protocols exist for HIDA scanning without clear data on whether clinical outcomes differ with each. The patients in this sample did not differ significantly on demographic characteristics such as age, sex, alcohol use, smoking rates, or presence of comorbidities. This indicates that significantly lower GBEF values observed in Protocol 1 are more likely attributable to the specific technique employed rather than demographic characteristics.

Despite this, the most relevant finding was that no significant differences were observed in clinical outcomes at follow-up appointments post-cholecystectomy, regardless of protocol used or GBEF values. Most patients fared very well, with approximately 60-80% of people across each protocol endorsing pain resolution post-operatively. Although significant differences were found in GBEF values across different protocols, this did not appear to have any clinical implications for patients in the long term.

While intravenous gallbladder stimulation is traditionally considered the gold standard, the present study's methodological limitations - including differing imaging time points, lack of within-subjects comparisons, and unequal sample sizes - warrant caution in interpreting direct comparisons between protocols. Our findings suggest that Protocols 2 and 3 may offer clinically comparable outcomes, but prospective, controlled studies are needed to confirm their equivalence. If the use of Ensure[®] or a fatty meal administered orally were found in such future studies to produce relatively equal outcomes clinically, these may serve as equivalents to sincalide in scenarios such as shortages.²² Therefore, intravenous gallbladder stimulation remains the recommended first-line method where available, with alternative protocols available for consideration when deemed appropriate.

The differences in GBEF values found in this study are conflicting findings as compared to the existing literature. In one retrospective study, no significant differences in GBEF

values were reported when using 60-minute protocols of sincalide versus Ensure®.²³ Further, another study found no significant differences in mean GBEF values when using sincalide versus Ensure®.²² However, an important limitation of this study is the difference in imaging time points across protocols; imaging at 60 minutes generally yields higher and more stable GBEF values than earlier time points, such as 30 minutes, which can affect comparisons across protocols.¹⁵ This variability is reflected in the current data, where Protocol 1 (imaged at 30 minutes) demonstrated a notably higher standard deviation in GBEF values (30.6%) compared to Protocols 2 and 3 (19.0% and 17.4%, respectively; see Table 2); meanwhile, some previously referenced studies imaged at 60 minutes when using intravenous gallbladder stimulation.²² Existing literature posits that 60-minute imaging produces more consistent and diagnostically accurate values.²⁴⁻²⁷ Given these findings and the variability observed, a 60-minute imaging time point may be the preferred default choice. This limitation should be considered when interpreting the results, as variability in GBEF measurements related to timing may affect the strength of conclusions regarding the equivalence of protocols. As well, given that the institutional technique for imaging time in Protocol 1 has been updated following data collection, future research may warrant a comparison between the prior and updated methods.

Significantly more surgical interventions were completed for patients in Protocol 1 versus Protocol 2. Overall, the most common reason cited for not pursuing surgical intervention was the clinical judgment of the attending physician, which is likely multifactorial and informed by individual opinions and experience.²⁸ As discussed, the Protocol 1 group contained significantly lower GBEF values than Protocol 2, which may be related to the use of intravenous gallbladder stimulation versus Ensure®, and could have led clinicians and patients to decide with more objectivity that surgical intervention was warranted. After plotting all individual GBEF values for patients in each protocol, distinct categories of GBEF values were visualized (see Figures 1-3). Most patients had values clearly above or below the abnormal threshold of $\leq 40\%$; this supports the appropriateness of this cut-off in our population. Despite these findings, no significant differences were observed between the three protocols regarding pain and symptom resolution at follow-up appointments. This aligns with the findings of a study where post-cholecystectomy pain outcomes did not differ in patients with normal versus decreased GBEF values; thus, GBEF should be considered as one of many tools in decisions surrounding surgical management.²⁶

All patients with alternative diagnoses had undergone Protocol 1. The majority of these were eventually diagnosed with IBS, with the remainder diagnosed with Crohn's disease, gastritis, or abdominal pain not yet determined. Each of the listed conditions displays much symptom overlap with diseases of the biliary tract and gallbladder dyskinesia, and

HIDA scanning is generally expected to narrow the differential diagnosis.²⁹ As well, no significant differences were found regarding the final pathology between protocols, whether chronic acalculous cholecystitis or other. Therefore, differences in GBEF, number of cholecystectomies performed, and symptom resolution are less likely to be attributable to different underlying disease processes as a confounding factor and more likely due to implications surrounding the protocol itself.

This study utilized a retrospective, between-subjects design in which each patient underwent only one of the HIDA scan protocols. While this reflects real-world clinical practice, it limits the ability to directly compare protocols within the same individuals and control for inter-patient variability or the patient distribution across protocols. The uneven distribution of patients reflects real-world practice patterns during the study period but limits the statistical power and confidence in findings related to Protocol 3, increasing the risk of a type II error and decreasing generalizability. Accordingly, conclusions involving Protocol 3 should be interpreted with this consideration in mind, and future studies with larger and more balanced cohorts are warranted. Nevertheless, our findings contribute valuable comparable data from a large clinical cohort and highlight important considerations for protocol selection.

Finally, the follow-up data for parameters such as comorbidities, alcohol use, smoking rates, reasoning for no surgical intervention, and final pathology were limited. This incomplete data reduces the statistical power to detect potential differences between protocols in these areas and the generalizability of these results, and may introduce bias. Again, future studies would benefit from a more comprehensive prospective design.

CONCLUSION

This study reinforces the clinical relevance of HIDA scans in diagnosing and managing biliary dyskinesia. These findings suggest that, despite differences in GBEF values between protocols, patient outcomes were largely similar across all three protocols. While Protocol 1 remains the recommended first-line approach as the current gold standard, it is possible that Protocols 2 and 3 may serve as adequate alternatives when necessary. Imaging at the 60-minute mark appears to reduce variability in GBEF measurements compared to earlier imaging times, given the variability observed with 30-minute imaging. Due to the retrospective design of the study and limited follow-up data, future prospective studies with larger cohorts are warranted to validate these findings and better inform HIDA protocol selection in clinical practice.

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Family medicine residency program simulation survey

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ABSTRACT

Introduction: Simulation-based education is a rapidly growing field within medical training and has been shown to be superior to traditional didactic and clinical training in achieving and retaining medical skills. It allows learners the opportunity to develop their clinical decision-making skills in a realistic environment while focusing on learning rather than the busy demands of a service. This study explores simulation-based medical education utilization within Canadian Family Medicine residency training programs and determines perceived barriers to implementation of simulation.

Methods: Two cross-sectional surveys were developed, for site leads and residents, using a previously developed survey created by Dr. Andrew Koch at Queen's University to assess simulation-based education in emergency medicine training programs. The survey questions were adapted to be applicable to Family Medicine with the permission of the author. Ethics was approved by Newfoundland and Labrador Health Research Ethics Board. The surveys were anonymous and delivered using Qualtrics.

Results: The survey results found 62% of urban training sites have formal simulation curriculums compared to 36% of rural training sites ($p = 0.274$). Barriers included limited access to equipment and limited protected faculty time. Although 72% of resident respondents felt the addition of allied health professionals is beneficial in simulation, only eight sites participate in multidisciplinary simulation. While all sites agreed simulation is very valuable to residents training, 43% of the programs have four or less sessions a year.

Conclusion: These findings suggest a need for greater integration of simulation-based education across Canadian Family Medicine training programs to meet the learning needs of Family Medicine residents.

Simulation-based education is a rapidly growing field within medical education. Medical learners at both the undergraduate and postgraduate level have the opportunity to practice and develop skills in a realistic environment, without risk to patients, and to work with interprofessional team members to improve communication skills. It mirrors real-world clinical scenarios which allows them to further develop their clinical decision-making skills.^(1,2) Simulation training encompasses a wide variety of methods. These include high-fidelity mannequins, which can be programmed to have dynamic vital signs replicating real clinical conditions, procedural task trainers which allow learners to practice specific procedural skills and standardized patients, who are individuals trained to act as real patients allowing learners to enhance their communication skills. Virtual simulation and other online learning models are increasing in popularity to aid in the development of clinical decision making skills for learners who may not have access to high-fidelity mannequins or are training in rural or remote locations.⁽³⁾ A meta-analysis published by McGaghie, et al. demonstrated that simulation-based medical education was superior to traditional didactic and clinical training in achieving and retaining medical skills.⁽⁴⁾

Simulation allows residents to focus on learning rather than the busy demands of a service and provides a safe

environment to learn by trial and error. More importantly, it allows dedicated time for debrief and reflection to set future learning goals for areas of improvement.⁽³⁾ In addition to offering a higher standard of training, simulation is also shown to positively affect patient care practices and improve patient outcomes.^(1,2,5) Simulation has also become an effective form of assessment to monitor students' progress and perform competency assessments which are adaptive to the level of the learner.^(1,2,5)

Family physicians maintain a broad scope of practice, requiring Family Medicine residents to acquire extensive clinical knowledge and procedural competency within a two-year training program as Canada has one of the shortest Family Medicine training programs.^(6,7) A recent study showed that Canadian Family Medicine residency graduates do not feel adequately prepared for clinical activities outside of office-based Family Medicine, including emergency-care hospitals and obstetrics.⁽⁸⁾ With the CFPC's planned transition to a three-year training program, simulation based-education can be incorporated in the curriculum to facilitate the development of these diverse clinical and procedural skills.⁽⁸⁾ It provides the opportunity to gain hands-on experience in a realistic yet controlled environment to allow residents to learn and refine their skills to develop the confidence to perform in these clinical settings.⁽⁹⁾

A call was put forward in 2011 by the Future of Medical Education in Canada Postgraduate Project for postgraduate training programs to implement simulation into their residency curriculums.⁽¹⁰⁾ To date there have been no studies performed to assess the status of simulation-based education in Family Medicine residency training programs in Canada despite similar research by other postgraduate specialty programs that showed considerable variability in simulation utilization across programs.⁽¹¹⁾ A study characterizing simulation within Emergency Medicine programs found that the frequency of simulation ranged from weekly to once or twice per year and only 52% of residents felt their time dedicated to simulation met their needs despite the vast majority stating simulation improved their ability to care for patients in the clinical setting.⁽¹¹⁾ The objective of this study is to characterize the current state of simulation-based education in participating English-language Family Medicine residency programs across Canada and assess how simulation is delivered. It also seeks to determine site leads perceived barriers to its implementation, gain insight to current practices, and explore residents' opinions on simulation.

METHODS

Ethics approval for this study was obtained from The Newfoundland and Labrador Health Research Ethics Board on June 15th, 2022. The reference number is 2022.081 and the research porter file number is 20230072.

Survey Design

The study design included developing two cross-sectional surveys - one for Family Medicine residency training program site leads and one for Family Medicine residents in Canada. A previously developed survey created by Dr. Andrew Koch at Queen's University which assessed simulation-based education in postgraduate Emergency Medicine training programs across Canada was used.⁽¹⁰⁾ The survey questions were adapted to be applicable to Family Medicine residency programs with the permission from Dr. Koch. The survey questions were divided into sections which included demographics, instructional format, content, resident assessments, benefits, and barriers. The survey contained a combination of likert scale, multiple choice, and short answer questions.

Survey Administration

The survey was delivered using the online survey platform Qualtrics® and responses were anonymous. The site lead survey was conducted from September 6th to September 30th, 2022 with a second opportunity to participate from January 4th to February 17th, 2023. The resident survey was conducted from November 4th to December 2nd, 2022, with a second opportunity to participate from January 4th to February 17th, 2023. Program administrators were contacted to determine if

their school was interested in participating. Interested residency programs were provided with the Qualtrics survey link and study information to distribute to site leads and residents.

Analysis

Microsoft Excel® and Qualtrics® were used to analyze the data. Descriptive statistics was used to calculate frequencies and proportions. To analyze the comparison between simulation curriculums in urban and rural sites a Pearson's Chi-squared test of Independence with Yates' continuity correction was performed. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographics

Seven universities participated in the survey, which constitutes ~41% of the 17 Family Medicine residency training programs in Canada. A total of 35 site leads responded to the survey, ~33% of the 107 site leads for English Family Medicine residency programs in Canada. A total of 108 residents responded - 29 in their first year of Family Medicine residency and 31 in their second year, with 48 others who did not specify. The population-base at the training sites ranged from less than 10,000 to more than 1,000,000 with 13 of the 35 (37%) site leads classified their location as urban and 22 (63%) sites considered rural (Table 1).

Program Characteristics

The results showed that 16 of the 35 (46%) sites have a formal simulation curriculum while 16 (46%) do not and 3 (9%) did not specify (Table 1). When comparing urban versus rural sites, 8 of the 13 (62%) urban sites have a formal simulation curriculum within their residency training programs, while only 8 of the 22 (36%) rural sites do ($p = 0.274$). Of the 16 sites without a formal simulation curriculum, 3 stated they are in the process of developing a curriculum, 6 sites are considering adding a simulation curriculum, and 4 sites currently have no plan to introduce a simulation curriculum (Table 1).

Instructional Format

Most simulation is occurring in a formal simulation lab - either hospital-based or within a medical school. Other sites included the emergency department, other clinical environments in-situ simulation, and off-site simulation labs (Table 1). The frequency of simulation sessions ranged from once per year to as frequent as monthly (Table 1). Both the site leads and residents reported the most common simulation modality being used is high-fidelity mannequins (35% (16

and 43% (67) respectively), followed by procedural task trainers (26% (12) and 21% (33) respectively) (Figure 1).

Table 1. Summary of site lead survey results

	Sites, n (100%)	Chi-square (p<0.05)
Program Location		
Urban	13 (37%)	
Rural	22 (63%)	
Formal Simulation Curriculum		p = 0.274
Yes	16 (46%)	
No	16 (46%)	
Unanswered	3 (9%)	
Urban site formal curriculum	8 (62%)	
Rural site formal curriculum	8 (36%)	
In the process of developing a simulation curriculum	3 (23%)	
Considering adding a simulation curriculum	6 (46%)	
No plan to introduce a simulation curriculum	4 (31%)	
Simulation Location		
Hospital or medical school simulation lab	13 (39%)	
Emergency department	4 (12%)	
In-situ simulation	5 (15%)	
Off-site simulation labs	3 (9%)	
Other	8 (24%)	
Frequency		
2 or less sessions a year	7 (30%)	
3-4 sessions a year	3 (13%)	
6-10 sessions a year	8 (34%)	
Monthly	3 (13%)	
Multidisciplinary Simulation		
Yes	8 (23%)	
No	15 (43%)	
Unanswered	12 (34%)	
Designated Simulation Lead		
Yes	12 (34%)	
No	4 (11%)	
Unanswered	19 (54%)	
Simulation Lead Incentives		
Protected Time	7 (58%)	
Monetary Compensation	3 (25%)	
Assessment		
Formative Assessment	2 (8%)	
Summative Assessment	1 (4%)	

Only 8 of the 35 sites (23%) participate in multidisciplinary simulation with various interprofessional team members, most commonly nurses and staff physicians (Figure 2). Many residents reported the addition of allied health professionals was helpful in simulation training with 41 (45%) residents agreeing and 25 (27%) strongly agreeing, while only 2 (2%) disagreeing. Interestingly, for those who do not have multidisciplinary simulation, 10 (67%) sites said they would like to see it at their site (Figure 3).

When assessing who is responsible for running the simulation curriculum, 12 of the 35 sites (34%) have simulation leads, 7 (58%) of which have protected time and 3 (25%) are provided monetary compensation (Table 1). A paid position for a dedicated simulation technician to program the equipment was available at 10 sites, while no sites have a volunteer simulation technician. Finally, defined and recurring simulation curriculums were developed by faculty simulation directors/leads at 7 sites and other faculty/physicians at 2 sites.

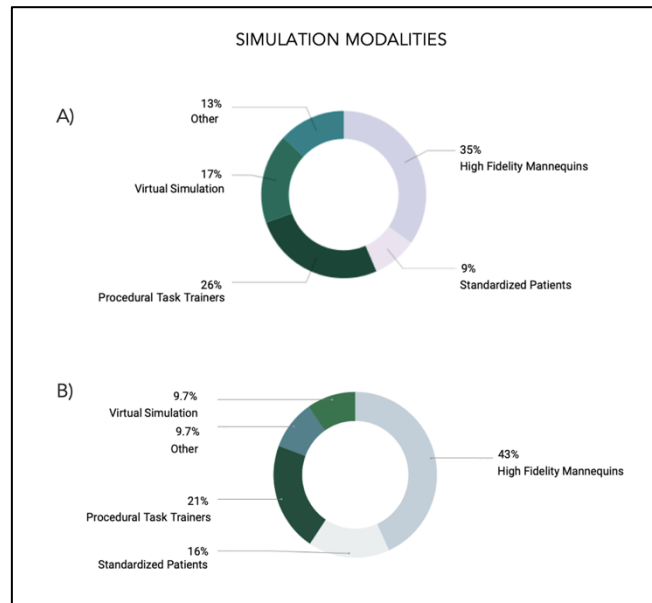


Figure 1. Simulation modalities utilized in the simulation curriculum (A) Site Lead Survey (B) Resident Survey

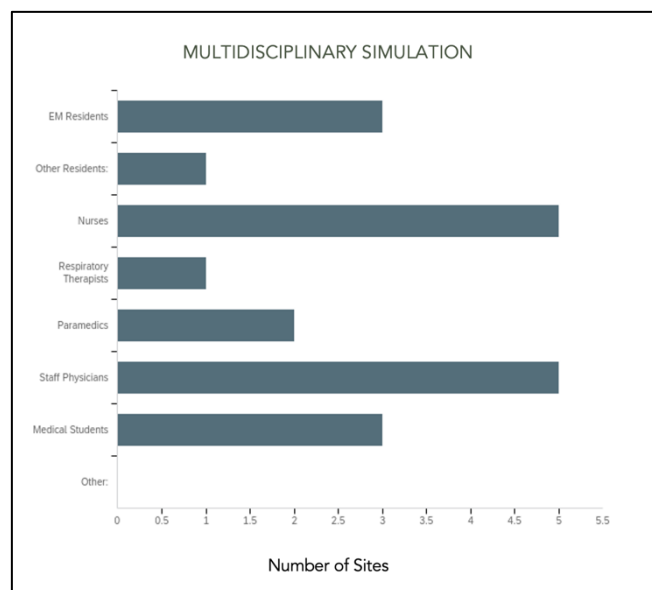


Figure 2. Site lead responses for multidisciplinary involvement in simulation

Content

Scenarios incorporated into the site's simulation curriculum are shown in Figure 4, with the most common being both adult and pediatric ER/resuscitation scenarios, cardiac arrest, and airway cases. Figure 5 demonstrates the scenarios site leads believe are important to incorporate into Family Medicine residents' simulation program.

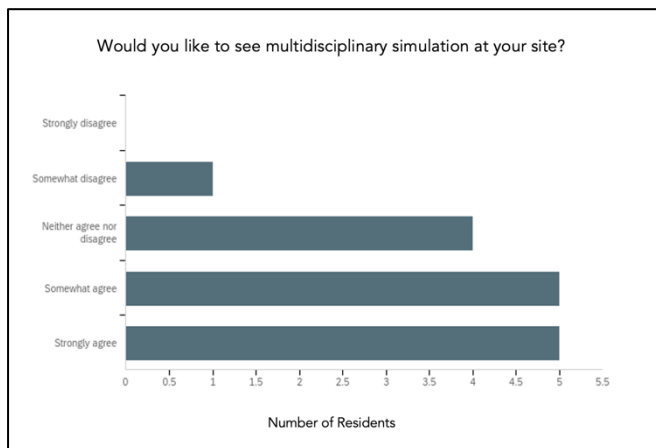


Figure 3. Resident opinions towards the incorporation of multidisciplinary simulation (N=15).

Some scenarios, such as breaking bad news and office based emergencies, are underrepresented within the curriculum, despite an interest in these experiences. No programs had breaking bad news scenarios in their current simulation curriculum but 31%, 11 of the 35 site leads report it is important to Family Medicine resident's training. Similarly, only 6%, 2 of the 35 programs have office-based emergency scenarios incorporated into their program but 40%, 14 of the 35 site leads report it is important to incorporate as well. Table 2 lists the procedures and scenarios incorporated into the simulation curriculum at select residency programs.

Resident Assessment

Only 6%, 2 of the 35 sites use simulation as a method of formative assessment of residents and only 3%, 1 of the 35 sites uses simulation for summative assessment (Table 1). Interestingly, 40%, 14 of the 35 site leads said simulation should not be used for assessment (Figure 6). Similarly, 44 (53%) resident respondents stated they would prefer if their performance during simulation was not assessed. However, only 22 (27%) residents stated they do not feel comfortable being assessed in a simulation environment, while 43 (52%) said they did feel comfortable.

Benefits

The most common perceived benefits by site leads included the opportunity to practice procedural skills, 57% (20 of 35 site leads), providing a safe learning environment to develop clinical reasoning skills, 54% (19 of 35 site leads), improving residents' abilities to care for patients, 51% (18 of 35 site leads) and allowing the opportunity for residents to gain exposure to cases/procedures not commonly seen at their site, 51% (18 of 35 site leads) (Figure 7). 82 of the 83 (99%) resident respondents felt all Family Medicine Residency programs should have simulation training and 80%, 40 of 50 question respondents reported their ability to care for real patients has improved because they have practiced similar situations in simulation training. Only 25 (50% of resident respondents) reported the time dedicated to simulation-based activities met their educational needs.

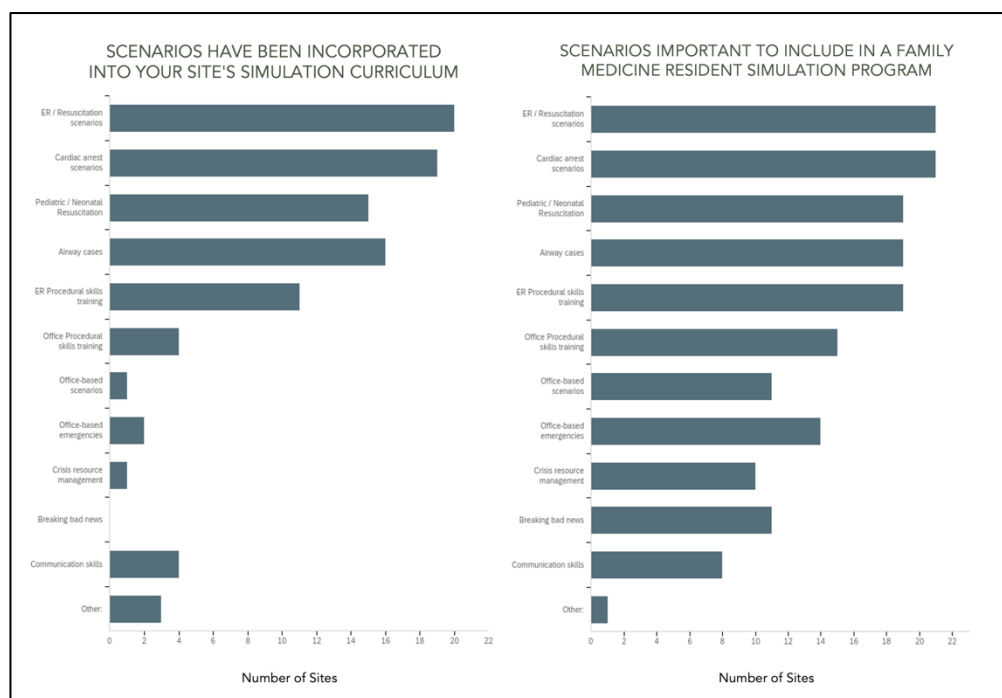


Figure 4. Scenarios incorporated in current simulation curriculum (N=35).

Figure 5. Scenarios important to resident training (N=35).

Barriers

Most commonly perceived barriers by site leads to developing a simulation curriculum within their residency training program included limited faculty time, 46% (16 of 35 site leads), limited access to equipment, 40% (14 of 35 site leads), and limited protected time in the current curriculum, 37% (13 of 35 site leads) (Figure 8). When asked how to improve simulation within their programs, the common themes amongst resident responses included: increasing frequency of simulation by having regularly scheduled time such as during academic half days, having prepared scenarios (including office based scenarios) and incorporating more allied healthcare professionals.

Table 2. Current procedures and scenarios incorporated into simulation curriculums as listed by site leads and residents.

PROCEDURES	SCENARIOS
Chest tubes	Cardiac arrest/ACLS
Paracentesis	Shock
Central lines	DKA and Thyroid Storm
Intubation	Anaphylaxis
IUD insertion	Altered LOC
Endometrial biopsy	Toxicology
Deliveries	Drowning
Perineal repairs	Respiratory Distress
Excisional and punch biopsies	MVAs/Trauma/ATLS
Laceration repairs	Sepsis
Casting	Seizures
Reductions	GI Bleeds
Joint injections	PALS
IOs	NRP
IVs	Ectopic
Tourniquets	ALARM

DISCUSSION

Numerous studies have highlighted the importance of simulation-based medical education in residency training programs.^(1,2,4,5) Based on our survey, only 46% of Family Medicine residency training programs included in the study had a formal simulation curriculum. The survey results found 62% of urban training sites have formal simulation curriculums compared to 36% of rural training sites.

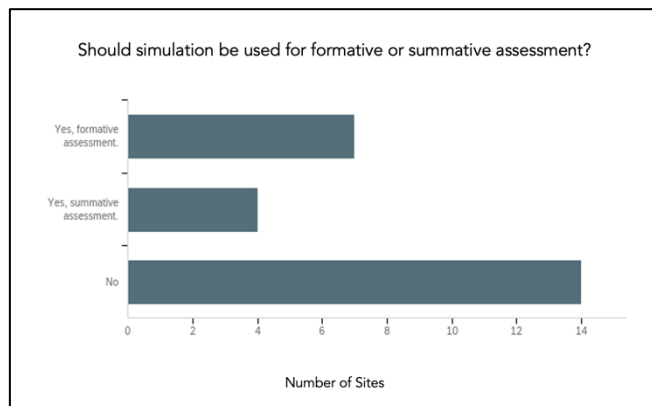


Figure 6. Site leads' opinion on simulation use for assessment (N=25).

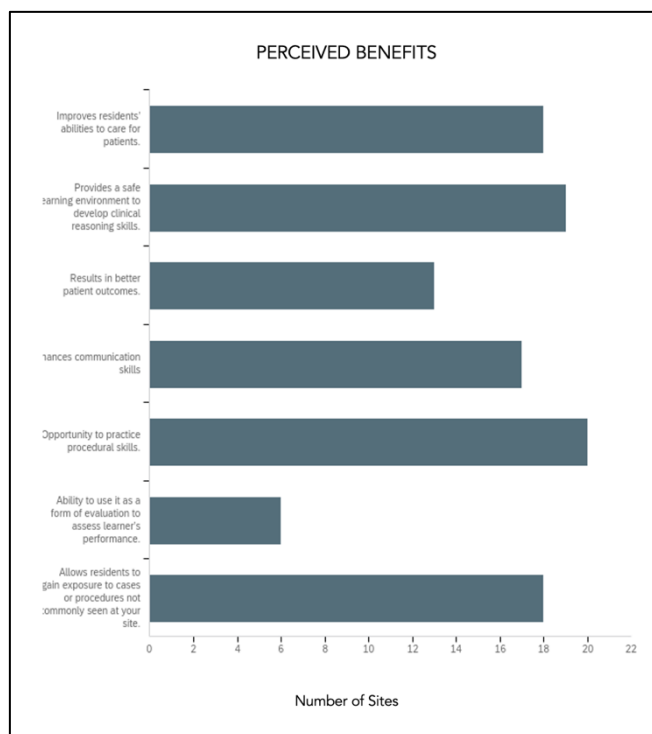


Figure 7. Benefits of simulation to Family Medicine resident training (N=35).

Multidisciplinary simulation is valuable in developing communication, leadership, and teamwork skills required to provide comprehensive, patient-centered care.⁽¹²⁾ It also expands resident knowledge of other healthcare providers' scope of practice.⁽¹²⁾ However, only 8 of the 35 sites surveyed participate in multidisciplinary simulation. Programs that did offer multidisciplinary simulation have opportunities to expand the number of interprofessional team members participating. Of those that did not offer it, many expressed an interest for increased interprofessional involvement.

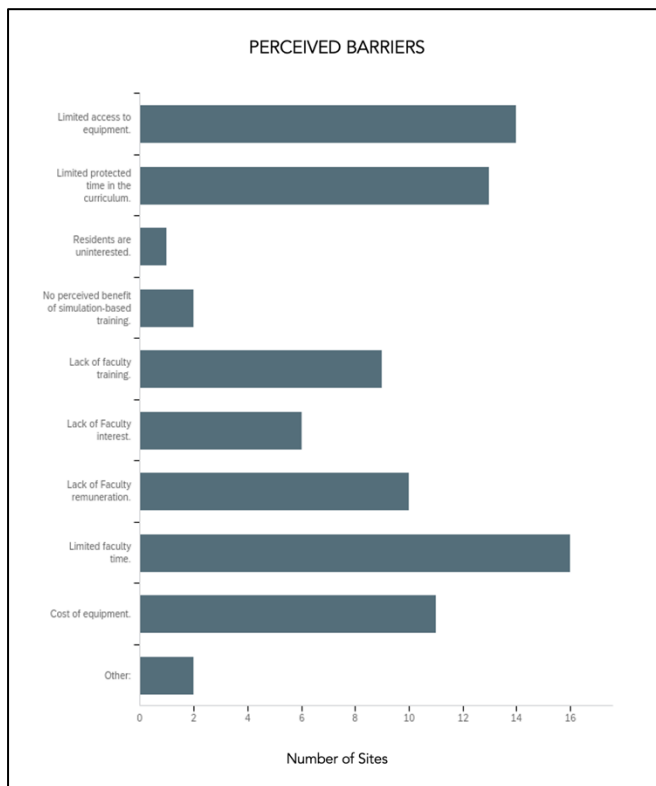


Figure 8. Barriers to incorporating a simulation curriculum (N=35).

Although there were mixed opinions on whether simulation should be used as a form of assessment amongst both site leads and residents, many site leads believe simulation-based medical education is valuable to Family Medicine residents training. Identified benefits included providing a safe learning environment to develop clinical reasoning skills, and providing opportunities to practice procedural skills and gain exposure to cases not commonly seen at their site. This corresponds with 99% of resident respondents who felt all Family Medicine Residency programs should have simulation training and 80% reporting their ability to care for real patients has improved because of simulation. However, many programs offering simulation have only a few sessions a year and only 50% of resident respondents reported the time dedicated to simulation-based activities in their program meets their educational needs.

Barriers to delivering simulation-based education included limited access to equipment and limited protected faculty time which correlates with only 7 sites having protected time for simulation leads and only 3 providing monetary compensation. Implementing a simulation curriculum can be financially challenging as it involves purchasing and maintaining specialized equipment and trained faculty. However, with the advancement of technology, virtual simulation is becoming more common and can be useful in limited resource areas.⁽¹²⁾ Other cost effective methods in

areas with limited access to specialized equipment include the utilization of standardized patients which have been shown to enhance learners' communication skills and clinical decision making skills.⁽¹²⁾

Finally, some scenarios, such as breaking bad news and office based emergencies, are underrepresented within the simulation curriculums, despite being deemed important to resident learning by site leads. This survey, in addition to the current literature supporting simulation-based medical education, aims to help Family Medicine residency programs advocate for access to the equipment and the protected time for faculty required to develop a simulation curriculum at their site to meet the learning needs of Family Medicine residents.

LIMITATIONS

Only 35 site leads and 108 Family Medicine residents in Canada responded to the survey therefore this may affect the validity of the results. Additionally, French programs were excluded in the survey, thus, including them may have improved response rates. As well, programs with an interest in simulation may have been more likely to respond. Finally, PGY1s had limited exposure to simulation at the time the survey was completed. As such, the results may not be an accurate reflection of their yearly simulation curriculum and may be more representative of the PGY2's simulation curriculum within their residency training.

CONCLUSION

This study explores simulation-based medical education utilization across Canadian Family Medicine residency training programs. Additionally, it highlights several barriers facing simulation delivery. Our aim is to encourage programs to incorporate simulation-based education into their residency training programs, adapt their curriculum to meet the evolving learning needs of Family Medicine residents and learn from best practices of established simulation curricula. Participating simulation programs included a mixture of simulation modalities and provided the investigators with lists of current procedures and scenarios. This may help inform future development of a national simulation curriculum that shares standardized cases among all Family Medicine training programs in Canada, which is the future aim for this study.

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The case for widening the scope of Alzheimer's disease models and biomarkers

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder primarily associated with amyloid-beta and tau, but numerous other mechanisms, such as vascular injury, oxidative stress, mitochondrial dysfunction, and inflammation—among many others—also contribute but are comparatively less integrated into dominant research frameworks or biomarker classification systems. This paper builds on existing critiques of the amyloid-and tau-centric research paradigm by focusing on how this limited scope is reflected in both animal model usage and biomarker classification frameworks. While essential, many animal models chosen to investigate individual mechanisms fail to capture the full complexity of AD's pathology, limiting their ability to accurately model disease progression and translate findings to humans. In parallel, biomarker classification systems and therapeutic development remain largely centered on a narrow set of pathological features. Addressing these limitations requires a shift toward more comprehensive approaches, such as the combined use of complementary animal models, as well as the validation and integration of emerging multi-domain biomarker frameworks that incorporate diverse pathological processes. Such strategies may better capture disease heterogeneity and support biomarker-driven patient stratification, helping to link AD's diverse pathological processes to more targeted therapeutic approaches.

Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid-beta peptides (A β) in the form of neuritic plaques and an increase in the hyperphosphorylation of tau protein resulting in bundles of neurofibrillary tangles, ultimately leading to cerebral atrophy.¹⁻² AD is classified into two prominent types: familial (FAD) and sporadic (SAD). FAD often arises early and can be linked to well-known genetic mutations (APP, PSEN1, PSEN2, etc.), but it accounts for only 5-10% of cases.³ In contrast, while SAD typically arises later in life and is associated with genetic factors that may increase the risk, such as the APOE e4 allele, it accounts for up to 95% of cases and has multiple pathways to its presentation.³

Over the past decade, the conceptualization of AD has evolved considerably. For example, advances in plasma biomarkers, such as phosphorylated tau isoforms, now allow for earlier and less invasive detection of AD pathologies.⁴⁻⁵ Furthermore, updated classification systems emphasize the biological definition of AD over clinical symptomatology, allowing for a more individualized understanding of disease progression.⁶⁻⁷ However, despite these key developments, significant challenges remain in translating this evolving framework into effective, widespread therapeutic strategies. These challenges are particularly rooted in the inherently heterogeneous nature of AD, as emerging systems-level and network-based models suggest that AD progression reflects dynamic interactions between various mechanistic pathways and selectively vulnerable neural networks, rather than isolated pathological processes.⁸⁻¹⁰ This evolving perspective highlights the inherent difficulty in accurately modeling and designing AD therapeutics through traditional, reductionist approaches.

Accordingly, although many obstacles impede the development of more effective AD therapies, two key challenges are a) limitations with animal models and b) a persistently narrow scope within research and treatment conceptualization, as reflected in the continued focus of biomarkers and their classification. This opinion piece is informed by a targeted review of the literature, focusing on key studies related to AD pathophysiology, animal models, and biomarker development, with an emphasis on widely cited frameworks and representative examples rather than a systematic review.

From 1995-2010 alone, over 300 interventions were shown to reduce the neuropathology or cognitive deficits of AD in mouse models.¹¹ Despite these findings, translation to effective human therapies has remained limited.¹² This discrepancy is often attributed, at least in part, to challenges in translating findings from animal models—particularly rodents—to humans.¹³⁻¹⁴ Animal models refer to non-human species used to study selected biological processes or diseases found in humans, either naturally occurring or transgenically engineered.¹⁵ Because AD is a complex and heterogeneous disease that animals do not naturally replicate, AD models are most commonly transgenically engineered to express human AD mutations such as APP or PSEN1.¹⁶ Historically, transgenic AD models have evolved from a reductionist approach that isolated a single pathological feature, such as amyloid, toward comprehensive models that incorporate both amyloid and tau—although reductionist approaches are often still used to interrogate individual mechanisms.¹⁷

However, while it might be expected that combining amyloid and tau would approximate the disease, even models incorporating both pathologies often fail to exhibit the

neurodegeneration characteristic of AD.^{12,18} Furthermore, inserting aspects of the disease may have unintended effects that complicate interpretation. For instance, overexpressing the amyloid precursor protein (APP) gene results in elevated levels of other, non-related APP fragments that could have either neuroprotective or neurotoxic effects.¹⁹

As AD involves numerous interacting mechanisms ongoing throughout its progression, inserting the most prominent features at a given stage of development is unlikely to capture the full complexity of the disease and instead may represent only a partial model.²⁰⁻²¹ This challenge is particularly pronounced for SAD as it is not strongly related to specific mutations to the same degree as FAD and encompasses many possible pathways to a disease state, therefore making it inherently difficult to model.^{16,22} Due to this, ongoing work includes the development of more sophisticated transgenic models and complementary human-derived systems, such as organoids, to better capture disease complexity.²³⁻²⁴

Despite these limitations, and acknowledging the ethical considerations inherent in animal research, current animal models remain essential for advancing our understanding of AD and developing effective treatments. Progress can be achieved by using the most complete pathological representation of AD possible, while focusing on specific components of disease progression to better understand how targeted interventions may translate to humans.²⁰ For example, studies in mice have shown that reducing A β is insufficient to rescue memory function once downstream processes are underway.¹¹ This finding was later confirmed in humans, contributing to the shift toward potential treatments targeting A β earlier in the disease pathogenesis.²⁵

To this end, while it is a simplistic notion, this animal model-based roadblock could be partially mitigated by adopting a broader perspective in the choice of animal models. One step in this direction could involve using a reductionist tau-only or amyloid-only model in combination with a more pathologically comprehensive model, such as 3xTg mice—which exhibit both tau and A β pathology—in studies that are investigating solely tau- or amyloid-based mechanisms.^{21,26} While tau- or amyloid-only models may allow for clearer mechanistic interrogation, the additional use of 3xTg mice may help determine how the effects being investigated manifest within a more accurate pathological environment. Therefore, this dual model approach allows a balance between mechanistic isolation and construct validity, providing greater insight into the interrogated mechanisms within a systems-level context than the use of either model alone. However, it must be acknowledged that implementing this approach at scale is constrained by the practical consideration of the associated cost and time to maintain multiple transgenic colonies and run parallel experiments. Furthermore, distributing limited resources across multiple models may reduce sample size, thereby decreasing statistical

power and limiting the ability to detect significant effects. Regardless, a more integrative approach to model selection may help improve the contextualization and translational potential of preclinical findings, despite the practical limitations involved.

Regarding the scope of research and treatment, while A β and tau are the most well-known features of AD, other pathological mechanisms such as inflammation, immune dysregulation, vascular injury, oxidative stress, mitochondrial dysfunction, and calcium-mediated excitotoxicity also contribute but receive comparatively less attention.²⁷⁻³² Numerous studies have shown that AD is a multifactorial disease process with complex, bidirectional interactions and heterogeneity in pathology, genetics, and molecular mechanisms.^{10,33-37} Importantly, these interactions between pathological mechanisms reflect systems-level dynamics. Therefore, perturbations in one aspect, such as vascular dysfunction, can propagate through interconnected molecular and cellular pathways to influence other processes, including neuroinflammation and synaptic dysfunction.¹⁰ This perspective aligns with the framework of AD as a disorder of network degeneration, in which pathology within selectively vulnerable neural systems, such as the hippocampal-entorhinal memory network, leads to progressively altered widespread neural connectivity patterns.⁸⁻⁹ Therefore, heterogeneity in clinical presentation may stem from differences in how these interacting molecular processes influence one another and how degeneration spreads across neural networks in individual patients, rather than from variation in any single pathological substrate.

Despite this, most disease modifying treatments focus primarily on amyloid, with relatively little investigation into other pathological substrates.^{12,38-42} Furthermore, even though in preclinical studies the portfolio of targets for treatment is broader, the percentage of A β targeting therapies relative to all other approaches is almost double the percentage of that in clinical studies.⁴³⁻⁴⁴ This comes despite it being well established that amyloid deposition alone does not cause the disease to reach the symptomatic stage without tau and other secondary pathologies contributing.⁴⁵⁻⁴⁶ Therefore, although recent developments in the amyloid disease modifying therapies Lecanemab and Donanemab have shown promising results, combination therapies targeting multiple mechanisms will likely be necessary.⁴⁷⁻⁴⁹

This narrow focus is especially evident in the use of biomarkers for diagnosis and treatment. While biomarkers exist for many traditional AD substrates, there is a lack of them for many other critical aspects, such as mitochondrial injury or calcium-mediated excitotoxicity.^{12,41-42} Consequently, only a subset of AD's components are monitored when assessing patient outcomes or progression. Given the individual variability in pathogenesis, and the fact that a patient's position on the pathogenic continuum greatly

determines their potential for treatment— as disease modifying therapies function best in early AD cases— this represents a significant limitation to effective treatment.^{4-5,37,50-52}

This limited scope is best reflected in the National Institute on Aging and Alzheimer's Association (NIA-AA) A/T/N classification system, which categorizes AD based on three biomarkers: amyloid (A), tau (T), neurodegeneration (N).⁵³ Although there is significant heterogeneity among patients with the same clinical phenotype in terms of the degree, distribution, and progress of pathologies, the A/T/N system excludes other pathologies for which biomarkers currently exist.²⁸ Furthermore, considering most patients exhibit mixed pathologies, using this limited classification system complicates patient comparison.⁴³ For example, vascular disturbances can exacerbate A β and tau aggregation and therefore, may directly contribute to neurodegeneration.⁵⁴ Therefore, given that approximately 50-80% of aging and AD brains have varying degrees of vascular pathology, patients with the same A/T/N status may have vastly different underlying disease processes.⁵⁴⁻⁵⁵

One approach to addressing this limitation is the integration of emerging biomarker frameworks that capture multiple pathological mechanisms simultaneously to create a more comprehensive representation of disease state. For example, emerging multi-omic plasma biomarker panels could integrate a) proteomic markers of amyloid- β and phosphorylated tau, b) metabolomic signatures reflecting measures such as lipid dysregulation and oxidative stress (e.g. sphingolipids and N,N-dimethylglycine), and c) genomic risk scores capturing pathologic pathways such as inflammation (e.g. APOE-associated risk).^{52, 56-57}

However, in contrast to the traditional A/T/N markers, these emerging multi-omic panels are less established and require a combination of multiple markers to generate a meaningful signal.⁵⁷⁻⁵⁸ Therefore, these non-A/T/N markers are more difficult to standardize into a simple classification framework, which creates barriers to widespread adoption.⁵⁷⁻⁵⁸ Regardless, machine learning-based clustering of this multidimensional plasma biomarker data in combination with imaging data has the potential to identify AD subtypes that more accurately reflect the underlying pathophysiology of individual patients.⁵⁸ By incorporating these diverse, comprehensive biomarkers into the classification system we may better capture the heterogeneity of the disease across patients. This approach has the potential to enable more accurate patient stratification based on their unique pathological signature, facilitating the eventual design of personalized treatment plans once the necessary combination of disease modifying therapies becomes available.²⁸ However, while this personalized approach using non-A/T/N biomarkers is conceptually promising, its routine implementation remains limited, as many non-A/T/N

biomarkers still lack standardized thresholds and are not routinely available due to the cost of the necessary multi-omic assays and computational infrastructure.⁵⁹ Therefore, ongoing research into the development and validation of these panels is vital for facilitating their eventual clinical translation and integration into standardized diagnostic frameworks.

In conclusion, while the road to an effective treatment for AD remains complex, progress will depend on aligning research approaches with the multifactorial nature of the disease. Moving forward, AD research would greatly benefit from focusing on a) the combined use of reductionist and comprehensive models to allow isolated mechanisms to be properly contextualized and b) the validation and integration of emerging multi-omic biomarker panels into classification systems. By shifting to this comprehensive approach, AD research will be better positioned to translate mechanistic insight into therapies that target the heterogeneous nature of this disease.

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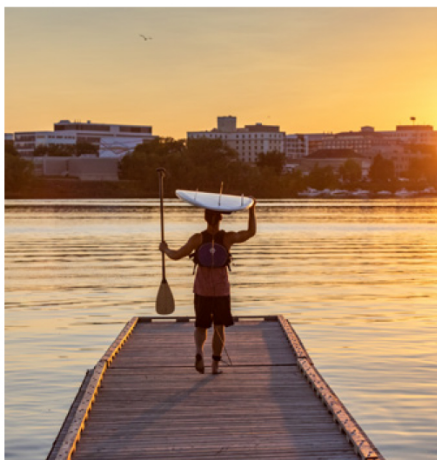
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The research race in medical school: An Atlantic medical student's perspective

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The pressure to contribute to research begins even before medical school begins. Pre-medical students are often convinced that a research publication offers a critical “one-up” in the competitive admissions process.¹ However, this belief is not universally accurate across Canadian medical schools. For example, compared to other Canadian medical schools, Memorial University of Newfoundland (MUN) adopts a holistic admissions approach which considers academics in addition to other components such as work experience and extracurricular activities including “volunteer work, health-related activities, community involvement, sports activities, and any other activities/information.”² Interestingly, they do not explicitly list research as a required criterion. In contrast, schools such as the University of Toronto emphasize research under their “Scholar” domain, which evaluates applicants based on their “awards, conference presentations, publications and scholarships.”³ It is therefore, unsurprising that research experience may differ among applicants matriculating to different medical schools across Canada. Yet regardless of how they arrive, most quickly learn that medical school is just the beginning and the pressure to publish is far from over. Unfortunately, this pressure may be contributing to research output that presents an opportunity for students to advance their careers without developing a true appreciation for the scientific principles of research and scholarly inquiry, as per the CanMEDs Scholar role. As a result, in this opinion piece, I will explore the factors contributing to this pressure to publish, its impact on the quality and purpose of medical student research and strategies to help shift toward a more meaningful and equitable approach to scholarly work.

After medical school, students match into residency, and depending on the specialty of choice, they may complete fellowships and further studies. The competition is steep and research resumes are believed to make or break a match. According to data from the US National Resident Matching Program, matched students had a higher average number of research abstracts, presentations and publications compared to their unmatched peers across all specialties, with the exception of Pediatrics.⁴ Of note, competitive specialties such as neurological surgery and plastic surgery had more than double the number of abstracts, presentations and publications.⁴ It is important to err on the side of caution with these results as this is just correlation, not causation. Interestingly, an analysis of the CaRMS database from 2013-2019 showed that applicants who engaged in more research activities were less likely to match to their first choice discipline in the first iteration of the match.⁵ Furthermore, the

number of publications did not have a significant impact on the likelihood of matching in the first or second iteration.⁵ This contrast in Canadian and American data can be attributed to differences in the evaluation focus of residency applications between the two countries.^{6,7} According to El Galad et al.,⁸ over 95% of Canadian programs in internal medicine, family medicine, pediatrics, anesthesia, general surgery and psychiatry required or considered scholarly work in their selection process.

Despite this contradiction, the research output from medical students continues to climb. Between 2008 and 2022, the number of publications with medical students as authors has increased from less than 50 to more than 300.⁹ On the surface, this seems admirable and may suggest that medical students are fulfilling the CanMEDS role of a Scholar and contributing to the creation and dissemination of knowledge and practices applicable to health.¹⁰ But a closer look reveals a more complex and less flattering reality.

According to Elliott and Carmody (2023),⁹ the most common types of publications by medical students in PubMed-indexed journals were review articles, cross-sectional studies and case reports, which are arguably less rigorous compared to other types of publications. Alarming, 59.1% have never been cited subsequently.⁹ This statistic raises questions about whether students are producing meaningful science or simply checking boxes.

In essence, we are witnessing a “research arms race” —where quantity is outpacing quality, and the pressure to publish is being driven more by securing a residency spot than by a genuine desire to advance medicine. According to the CanMEDS framework, as Scholars, physicians must contribute to the application, dissemination, translation, and creation of knowledge and practices applicable to health and health care.¹⁰ Research prompts the development of life-long learners with self-directed independent learning skills, critical thinking and writing skills, and an understanding of the scientific method.¹¹ When physicians engage in research, patient outcomes improve because their research is informed by clinically-relevant insights that allows them to make breakthroughs like smallpox vaccines, and immunotherapy for cancer treatments.^{12,13} However, these outcomes are less likely when the process is rushed or transactional. Many medical schools, including MUN, have implemented a mandatory research project as a part of their undergraduate medical curriculum. The purpose of the project is “to learn the basics of conducting research” and does not “mandate

publication.”¹⁴ Yet the hidden curriculum often speaks louder than the formal one.

Forty-three percent of respondents across three medical schools in Ontario agreed that the main reason for participation in research during medical school was to improve their chances of acceptance into a residency program.¹⁵ This sentiment echoes a question posed by Dr. Agrawal, a clinician scientist: “Are we truly driven by passion and good faith in helping patients or are we simply churning out papers after papers for our own interest and greed?”¹⁶ This answer may be yes, given that 2022 data from the US Physician Workforce Data Dashboard reported that research is the major professional activity for only 1.2% of physicians.¹⁷ This begs the question: Are we overemphasizing research as a ticket to residency, when for most, it won’t remain a meaningful part of their medical careers?

There’s no doubt that research is important. Without it, we would not have eradicated polio, understood the neurobiology of schizophrenia or improved stroke outcomes. The benefit of research speaks for itself. However, the issue isn’t whether research matters—but whether we’re creating conditions for it to be meaningful and accessible for all students.

Many students report barriers to conducting research such as a lack of time, limited availability of mentors and under-recognition of their research efforts.¹⁸ In the context of MUN, the shortage of clinician-scientist mentors may be a particularly significant barrier to medical students’ participation in research. Few MUN faculty juggle clinical practice and research and this lack of mentorship may contribute to a lack of interest in scholarly work. However, solutions exist. Studies conducted at Queens University and Stanford University show that increased interaction with research faculty can contribute to increased research engagement among students.^{19–20} Perhaps expanding mentorship opportunities at MUN could help foster research engagement as well. Encouragingly, the Canadian Atlantic Medical Students Association recently launched a regional research database which provides Atlantic medical students with a resource that lists all the research being conducted at various institutions across Atlantic Canada. This grassroots effort could be a step toward rebalancing the system and empowering students from smaller, less well-connected institutions.

Ultimately, we need to ask ourselves: What is the purpose of research in medical education? Is it a tool for personal advancement or a platform for collaborative discovery? According to the CanMeds Scholar role, physicians’ scholarly abilities should “allow them to contribute to the application, dissemination, translation, and creation of knowledge and practice applicable to health and health care.”¹⁰ However, these goals are often forgotten in the race to publish to secure a spot in medical school, residency and beyond. Solutions

such as limiting applicants to list only 3-5 research publications may give students the incentive to prioritize quality over quantity.⁹ Doing this would require addressing some significant barriers to medical student research participation. One that I did not mention previously would be equal opportunity. Depending on the institution and students’ personal networks, research opportunities may be limited particularly at smaller institutions like MUN with fewer research faculty in various specialties of interest. For example, at MUN, there are two surgical specialties offered; general surgery and orthopedic surgery for which research involvement is quite high as listed on the website²¹; but there are no opportunities listed for research in other surgical specialties like cardiac surgery, thoracics, ENT or plastics. As a result, developing a standardized method for student research involvement may help reduce this disparity. Similar to the establishment of the AFMC portal²² by the Canadian Federation of Medical Students and the AFMC Standing Committee on Undergraduate Medical Education for students planning away electives, a portal should be developed to support students navigating research opportunities. In conclusion, research is an integral component to evidence-based practice and its benefits are far-reaching. With systems level changes in admission policies and research opportunities, we can help inspire future physicians to engage in research that is driven by curiosity rather than career advancement.

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Beyond the skin: A case report of Merkel cell carcinoma involving the external auditory canal and parotid gland

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumour most often arising from sun-exposed skin in elderly Caucasian patients, with high rates of local invasion, distant metastasis, and recurrence. A rare case of infiltrative MCC is described in a 73-year-old Caucasian female with two enlarging lesions in the left external auditory canal (EAC) and parotid gland. Due to this rare clinical presentation, MCC was not considered in the initial differential diagnosis. However, histopathological analysis demonstrated a high-grade neuroendocrine carcinoma with immunohistochemical findings supporting MCC, despite an atypical staining profile. Imaging revealed rapid progression with regional nodal metastases. Despite MCC's grave prognosis, the patient achieved a complete metabolic response to chemotherapy and is currently undergoing adjuvant radiotherapy. This case highlights an uncommon presentation with a wide differential diagnosis, emphasizing the critical role of radiologic and pathologic evaluation alongside a high index of suspicion for MCC in atypical head and neck lesions.

Keywords: Merkel cell carcinoma; Neuroendocrine tumour; Chemotherapy; Radiotherapy; Radiology; Oncology.

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine tumour commonly arising in sun-exposed areas of the skin.¹ Its global incidence is approximately 0.1-1.6 cases per 100,000 annually and is highest in Australia; however, incidence increased by 95% in the United States between 2000-2013.² Although the cause of this increase is unclear, proposed explanations, including population aging, increased UV exposure, immunosuppressive medication use, and improved immunohistochemical detection, mirror established risk factors such as sun exposure, Caucasian ethnicity, immunosuppression, and advanced age.^{3,11} MCC most commonly occurs on sun-damaged skin of the head and neck in elderly Caucasian patients.² Notably, a novel polyomavirus of the Polyomaviridae family was found to be associated with the development of MCC: Merkel cell polyomavirus (MCPyV).³ A Pan-Canadian Merkel Cell Cancer Collaborative cohort study found five-year overall survival (OS) rates for head and neck MCC ranging from 49.8% for stage 1 to 18.5% for stage 4.⁴

This report describes an extremely rare case of infiltrative MCC involving the left parotid gland and external auditory canal (EAC) in a 73-year-old Caucasian female.

CASE PRESENTATION

A 73-year-old female with a history of hypertension, atrial fibrillation, pacemaker placement, dyslipidemia, hypothyroidism, and recurrent transient ischemic attacks presented to her family physician with a 2-month history of a progressively enlarging palpable mass in the left EAC and a one-month history of firmness in the left preauricular area (anterior to the auricle). She was subsequently referred to

otolaryngology. Physical examination revealed a firm 1-cm mass involving the left conchal bowl (central depression of the auricle) and a palpable small firm nodule involving the left parotid gland. Given the rarity of MCC involving the EAC and parotid region, the initial differential diagnosis included cystic basal cell carcinoma (BCC) or unusual-appearing squamous cell carcinoma (SCC). A 4-mm punch biopsy was performed on the left conchal bowl mass, and a fine-needle aspiration was performed on the left parotid gland mass; both specimens were sent urgently.

Histopathologically, both lesions demonstrated features consistent with a high-grade neuroendocrine carcinoma. Immunohistochemical staining revealed strong paranuclear dot-like positivity for pankeratin and neurofilament, as well as positivity for synaptophysin, supporting neuroendocrine differentiation. The Ki-67 proliferative index was elevated, suggesting aggressive tumour behaviour. Patchy weak chromogranin positivity was observed in the parotid sample. Both specimens were negative for cytokeratin 20 (CK20), thyroid transcription factor-1 (TTF-1), cytokeratin 7 (CK7), chromogranin (in the conchal bowl mass), S100, human melanoma black-45 (HMB-45), cluster of differentiation 99 (CD99), and leukocyte common antigen (LCA). Nine days following the two biopsies, contrast-enhanced computed tomography (CT) of the head and neck was performed, and the patient was referred to the local Cancer Centre.

Contrast-enhanced CT of the head and neck demonstrated a $3.0 \times 1.6 \times 3.4$ cm soft tissue mass in the left preauricular region, showing heterogeneous enhancement, extending both superiorly and inferiorly to the external auditory canal (see Figure 1). The medial border of the mass was in direct contact

with the muscular attachments at the mandibular head, raising concern for minimal invasion. Internal neovascularity was noted within the lesion, which extended inferiorly into the superior aspect of the left parotid gland, suggesting direct contiguous spread. Superiorly, the mass was in direct contact with the temporalis muscle, with possible extension into the temporal fossa (superior to the auricle). Laterally, the lesion reached the skin surface.

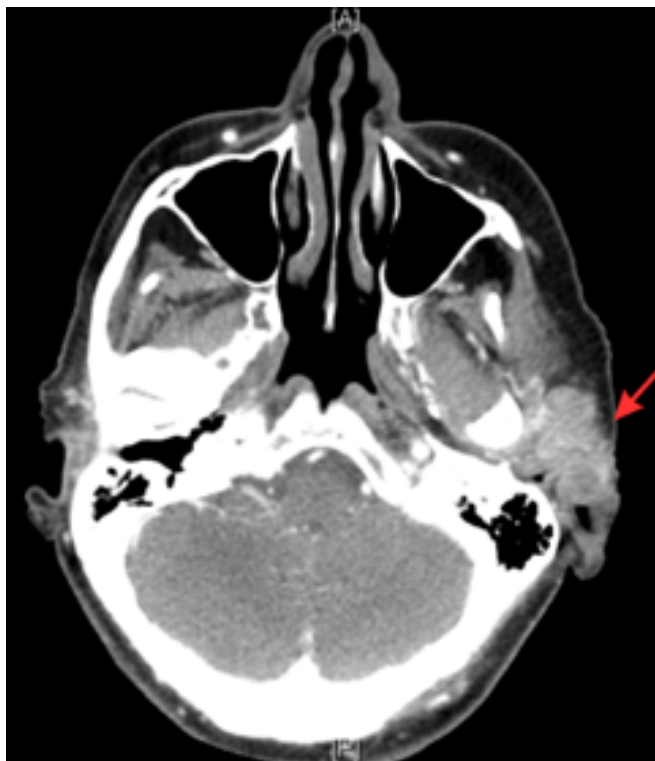


Figure 1. An enhancing mass is seen within the left preauricular subcutaneous soft tissues, extending both above and below the external auditory canal (EAC), and inferiorly into the superior aspect of the left parotid gland (red arrow).

A 1.4 x 1.2 cm enhancing, slightly irregularly contoured soft tissue mass was identified within the inferior portion of the left parotid gland and was noted to be suspicious for metastatic lymphadenopathy (see Figure 2). An additional 1.3 x 1.1 cm enhancing lymph node in the left level II cervical region (upper jugular lymph node group) was also concerning for nodal metastasis (see Figure 3).

No additional pathologically enlarged lymph nodes were identified. The remaining salivary glands, upper aerodigestive tract mucosa, cervical spine, and intracranial structures were unremarkable. The differential diagnosis in the radiology report (completed after histopathological diagnosis) considered “basal cell carcinoma of the EAC, squamous cell carcinoma, or even Merkel cell carcinoma”, indicating MCC’s uncommon presentation in this clinical context.



Figure 2. A slightly irregularly contoured, enhancing soft tissue mass is seen within the left parotid gland (red arrow).

Following initial discussion with the local Multidisciplinary Tumour Board, it was determined that primary surgery with likely adjuvant radiation therapy would be most appropriate, and a fluorodeoxyglucose positron emission tomography / computed tomography (FDG PET/CT) scan was ordered pre-operatively for staging. However, this imaging demonstrated a rapidly enlarging, intensely FDG-avid left preauricular mass with extension into the superior aspect of the parotid gland, now measuring 2.8×2.4 cm. A separate component extending outward from the inferior left conchal bowl region of the left ear measured 1.7×1.3 cm. The intense FDG avidity (reflecting increased FDG uptake) indicates high metabolic activity, consistent with aggressive tumour behaviour in this context. Both lesions had increased in size since the initial CT (see Figure 4).

Multiple FDG-avid lymph nodes were identified, including within the left parotid gland and ipsilateral cervical lymph node levels 2A, 3, 4, and 5 in the neck, raising concern for regional nodal metastases. Notably, a right-sided level II lymph node anterior to the styloid process was also intensely

FDG-avid and suspicious for contralateral nodal spread. A small focus of moderate-grade FDG avidity in segment 5 of

the liver, with a corresponding subtle hypoattenuating area on CT, raised concern for distant hepatic metastasis. However, follow-up imaging later demonstrated this lesion to be a stable, longstanding benign finding. Additional FDG avidity was observed in the C1–C3 vertebrae, bilateral acromioclavicular joints, lumbar spine, left hip, and bilateral knees. However, these findings were favoured to reflect degenerative changes, rather than metastatic disease. No concerning pulmonary nodules or aggressive osseous lesions were identified. Given these extensive, rapidly progressive findings, the decision was made to forego surgical intervention and proceed with systemic chemotherapy (4 rounds of carboplatin and etoposide) with palliative intent.

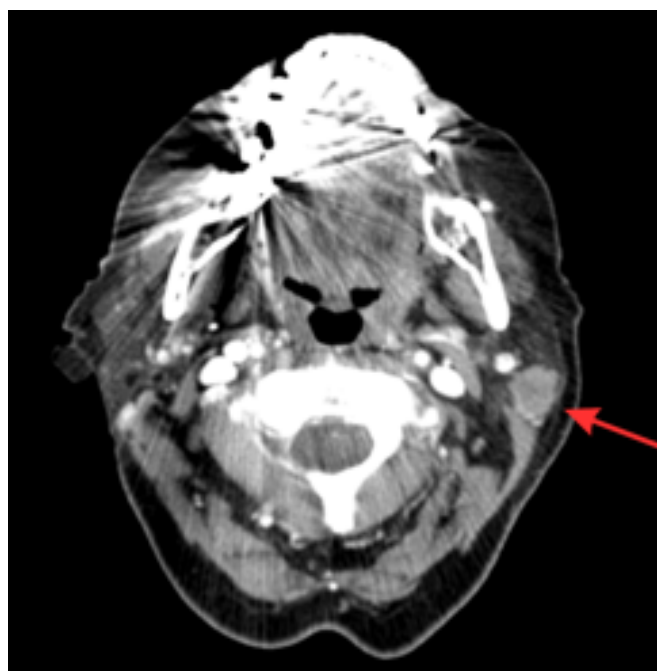


Figure 3. A pathologically enlarged left level 2 cervical lymph node with mild enhancement is seen, concerning for nodal metastasis (red arrow).

A follow-up FDG-PET/CT scan performed approximately 3-4 months after the initial diagnosis showed complete metabolic response to therapy, with marked reduction in the size and FDG avidity of the primary lesion in the left ear and previously involved left cervical lymph nodes. Only minimal residual low-grade FDG avidity remained, with no evidence of new or progressive disease. The previously FDG-avid liver lesion was no longer visualized, and a follow-up CT one month later confirmed no evidence of hepatic metastasis. No new FDG-avid lesions were identified in the chest, abdomen, or skeleton. A small, stable right neck lymph node with moderate FDG avidity remained unchanged and was favoured to represent a benign lesion. Adjuvant radiotherapy was recommended, which the patient is currently undergoing. A follow-up FDG-PET/CT scan is scheduled after

radiotherapy to assess response and potential need for immunotherapy.

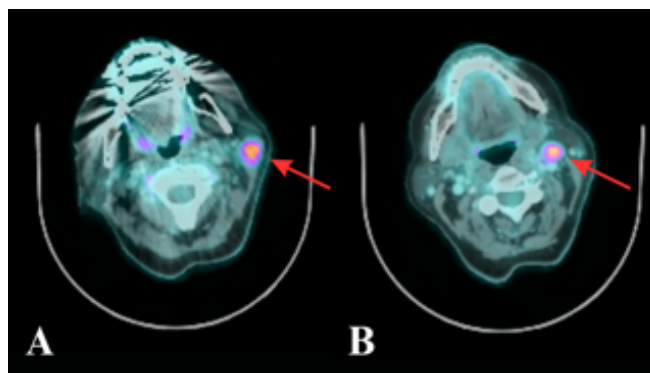


Figure 4. A very intensely FDG-avid mass is centred within the left preauricular soft tissues, extending into the superior aspect of the left parotid gland, located just below the skin surface (red arrow) (A). A second, smaller, nodular/mass-like component extends outward from the inferior portion of the left ear, just inferior to the external auditory canal (EAC) (red arrow) (B).

DISCUSSION

MCC is a rare, aggressive neuroendocrine carcinoma typically arising in elderly Caucasian patients.⁵ This report details an unusual presentation with infiltrative involvement of the EAC and parotid gland, as MCC normally arises from sun-exposed areas of skin on the head or neck in up to 43% of cases and accounts for less than 1% of skin cancers.⁵ MCC involving the EAC, and the ear region more generally, is rare and largely described in case reports.¹²⁻¹⁴ A population-based analysis identified 210 cases of external ear MCC between 2000-2019 and found that these tumours retain the aggressive behaviour characteristic of MCC despite their rarity.⁸

MCC can be difficult to distinguish from other carcinomas on imaging alone. Here, the differential diagnosis within the radiological reports also included BCC and SCC, with MCC being considered as the rarest possibility. This reflects the non-specific imaging appearance of MCC, particularly in unlikely areas, and highlights the critical role of radiologists in considering such rare malignancies. Given this, immunohistochemistry is often viewed as the cornerstone of MCC diagnosis. However, this case is also particularly rare given that the tumour was negative for numerous stains that are normally positive. In one report, it was noted that as many as 15% of MCCs may be negative for CK20 (which stains positive in approximately 95% of cases) but are normally still CK7 positive, though the tumour described in this case was double-negative.⁶⁻⁷ The suspicious liver lesion is an important teaching point to emphasize that some FDG-avid findings may represent benign entities, while still keeping a high index of suspicion for malignancy for truly concerning findings.

In keeping with its aggressive nature, this case revealed findings of metastatic disease and bilateral cervical nodal involvement. Despite this extensive spread, the patient experienced a complete metabolic response to chemotherapy. Generally, surgical excision with clear gross (<1-cm) and wide (>1-cm) margins is considered the optimal treatment for overall survival, especially in localized disease.⁸ However, treatments such as chemotherapy or radiotherapy may be considered for advanced metastatic or unresectable cases within the ear, though one population-based analysis showed no significant differences in outcomes.⁸ Immunotherapy is becoming an increasingly popular option, with one analysis citing improvement in mean overall survival for patients with stage 4 MCC compared to chemotherapy.⁹ First-line options that have been shown to have positive response rates include pembrolizumab, avelumab, nivolumab, and more.¹⁰

CONCLUSIONS

Given the favourable response in this case, the value of multidisciplinary treatment of advanced metastatic MCC cannot be understated. Early recognition and an index of suspicion by healthcare providers remain essential for rare, aggressive tumours such as MCC - even with atypical imaging or immunohistochemical findings - to yield the best possible patient outcomes.

PATIENT CONSENT

Complete written informed consent was obtained and documented from the patient in this case for the preparation of this manuscript and publication of its contents, as well as the associated images, data, and anonymized information.

DISCLOSURE

All authors agree with the following statement: Neither I nor my immediate family members have a financial relationship with a commercial organization that may have a direct or indirect interest in the content stated, and there are no disclosures on my behalf. There are no funding sources to disclose in association with this content.

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COVID-19 and head, neck, and thyroid cancer diagnoses in Newfoundland and Labrador: Changes in incidence and severity

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ABSTRACT

Purpose: This study examined the changes in diagnosis patterns of head, neck, and thyroid cancers in Newfoundland and Labrador before, during, and after the onset of the COVID-19 pandemic.

Methods: A retrospective population-based study analyzed new diagnoses from April 2019 to March 2022, divided into pre-COVID (2019–20), peak-COVID (2020–21), and post-COVID (2021–22) periods. Chi-square tests evaluated differences in cancer type and stage, Poisson regression compared population-adjusted advanced cancer incidence, and Kruskal-Wallis testing compared monthly case distribution differences.

Results: Among 592 patients, monthly case counts remained stable across periods ($p = 0.423$). The proportion of thyroid cancers decreased significantly over time ($\chi^2(2) = 8.55$, $p = 0.014$), dropping from 58.1% pre-COVID to 46.1% post-COVID; however, year-to-year differences were not statistically significant. Non-thyroid head and neck cancer proportions were stable ($p = 0.593$). The proportion of advanced-stage cancers rose significantly during the pandemic compared to the previous year ($\chi^2(1) = 6.54$, $p = 0.011$), but population-adjusted incidence rates of advanced cancers showed no significant change (IRR 1.28; 95% CI 0.84–1.93; $p = 0.245$).

Conclusions: Head, neck, and thyroid cancer diagnoses remained overall stable during the pandemic. Delays mainly affected early-stage detection, while advanced cases were prioritized. Maintaining timely diagnostic access and public education during disruptions is critical. Future studies should examine long-term outcomes and barriers to care during healthcare crises.

Keywords: COVID-19; Oncology; Head and neck cancer; Thyroid cancer; Cancer diagnosis; Newfoundland and Labrador.

COVID-19, a novel coronavirus not previously identified in humans, was discovered in Wuhan, China, early in 2019.¹ The virus is primarily transmitted in humans through respiratory droplets and typically presents as an acute respiratory syndrome, causing fever, cough, and fatigue.^{2,3} The virus was declared a global pandemic in April 2019 and had many economic, social, and healthcare implications, provoking prompt multi-level government and healthcare authority action responses to manage the spread of the virus.^{4,5} Due to the unexpected rate of global spread, lack of preparedness, and risk to healthcare providers and the public, many health authorities implemented measures in an attempt to reduce transmission and protect the public.^{6,7} These measures included the reduction of staff volume to “essential operation” levels and a reduction of in-person, outpatient, and non-urgent services.^{6,7} As such, these measures resulted in an overall decrease in the provision of public healthcare as well as decreased rates of emergency room patient attendance.^{8–10}

The Centers for Disease Control and Prevention (CDC) cited an overall decline in emergency department visits of approximately 42%, even with significantly increased numbers of patients with COVID-19.¹¹ Similar declines were observed in Newfoundland and Labrador (NL), Canada; cumulative monthly visits in the capital city, St. John's,

decreased by nearly 50% from March to June of 2020.¹² One survey from Johns Hopkins University in Baltimore, Maryland, indicated that 41% of respondents had forgone medical care from March to July of 2020, as compared to 79% of respondents who indicated that they required care.¹³

Due to significant reductions in emergency department and primary care clinic visits, many potential cancer cases did not receive timely screening or diagnostic evaluation. General trends indicated decreased volumes of imaging studies worldwide.^{14–17} These decreases in imaging volumes are speculated to have deleterious effects on disease prevalence and severity. This was true for acute abdominal pathologies at one center in Toronto, Canada, where increases in proportion, severity, and requirement for surgical intervention were observed.¹⁸ Similar findings were also expected for cancer diagnoses. One study predicted that due to decreased screening, approximately 1400 cancerous and precancerous lesions were missed during the primary pandemic period (three months in March to June of 2020) at one American hospital.¹⁹

Head and neck cancers are defined as malignant tumours arising in the oral cavity, oropharynx, hypopharynx, nasopharynx, lip, larynx, paranasal sinus, and salivary glands,

and are the 7th most frequently occurring cancer worldwide.²⁰ Risk factors for these cancers include exposure to tobacco, alcohol use, and viruses, including human papillomavirus and Epstein-Barr virus, and they have a high mortality rate due to the lack of treatment options and the natural history of disease progression.^{20,21} Thyroid cancer is a cancer of the endocrine system that occurs most commonly in young women aged 20 to 55 years in the form of papillary or follicular cancer and is the 10th most common cancer in Canada.²² Risk factors for thyroid cancers include non-cancerous conditions of the thyroid (such as hyperthyroidism), inherited cancers, exposure to ionizing radiation, and obesity, and have a net 5-year survival rate of 97% in Canada.²³

The Canadian Association of Head and Neck Surgical Oncology (CAHNSO) issued recommendations for managing head and neck cancers during the COVID-19 pandemic; these were helpful for current diagnoses, yet the pandemic appeared to affect undiagnosed cancers disproportionately.²⁴ Fewer cancer diagnoses were reported during the COVID-19 pandemic in Slovenia, England, the Netherlands, the United States, and Brazil at the beginning of the pandemic.^{25–29} Unfortunately, timely diagnosis of cancer is one of the most significant factors contributing to prognosis and treatment options available to patients.³⁰ Due to the high mortality rates, lack of treatment options available for head and neck cancers, the increased incidence of these cancers nationwide, and the global effects of the COVID-19 pandemic, this study aims to provide further insight into the impacts of the pandemic on these cancers in NL.

This study hypothesized that head, neck, and thyroid cancer incidence would reflect global patterns of delayed detection and increased rates of advanced-stage cancers at diagnosis during and after the COVID-19 pandemic. Thus, this study aimed to explore changes in diagnostic patterns and cancer staging at presentation of these cancers, associated with healthcare disruptions and service access during the COVID-19 pandemic in NL, Canada.

METHODS

This retrospective review included all patients diagnosed with a primary head and neck or thyroid cancer in NL from April 2019 to March 2022. Thyroid cancers were also included to increase the comprehensiveness of analyses of cancers diagnosed in this body region; these were analyzed with head and neck cancers for all analyses besides total yearly case counts.

Data were obtained from the NL Cancer Care Registry following ethical and regulatory approval from the registry, the local Health Research Ethics Board (HREB), and the local Research Proposals Approval Committee (RPAC). The cancer registry used in this study is a legislated, population-based database authorized under provincial privacy

legislation to collect, use, and share health data; it receives comprehensive data from across the province, including screening results, diagnoses, and treatment information from multiple healthcare settings. Data access and collection were performed using the NL Centre for Health Information (NLCHI) Provincial Data Lab repository within a secure virtual environment to collect the relevant data variables, including age, gender, positively identified cases of head and neck cancer, date of cancer diagnosis, head and neck cancer subtype (thyroid; non-thyroid), and cancer stage.

Analyses were conducted across three time periods: pre-COVID (April 2019 to March 2020), peak COVID (April 2020 to March 2021), and post-COVID (April 2021 to March 2022).

Cancer severity was classified using the TNM Classification of Malignant Tumours staging system.³¹ Early-stage cancers were defined as primary tumour stage T2 or less ($\leq T2$) without nodal or metastatic involvement, while advanced-stage cancers were defined as T3 or greater ($\geq T3$), any nodal involvement ($\geq N1$), or the presence of metastatic disease ($\geq M1$).³¹ Proportions of advanced-stage diagnoses were calculated for April to December 2019 and 2020; staging data for 2021 and 2022 were not available within the local registry at the time of data collection and thus could not be included in this analysis.

Statistical analyses were performed using R version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). Patient demographics and outcomes were summarized across the three defined periods. Descriptive statistics were calculated for age and biological sex. Chi-square tests of independence, the Kruskal-Wallis test, and Poisson regression analyses were used to evaluate differences in incidence and stage at diagnosis between periods, with post-hoc testing and corrections applied where appropriate. Statistical significance was set at $p < 0.05$.

RESULTS

Between April 2019 and March 2022, 592 patients diagnosed with head and neck cancers, including thyroid cancers, in NL were included in the final data analysis. The sample had a mean patient age of 61.4 ± 13.2 years, with the majority of patients aged 60–79 years, and a nearly even sex distribution (299 males and 293 females). Patient demographics are summarized in Table 1.

From April 2019 to March 2020 (pre-COVID), 215 cancers were diagnosed, the majority comprising thyroid cancers (58.1%), and non-thyroid cancers comprising 41.9%. During the COVID-19 peak (April 2020 to March 2021), 184 cancers were diagnosed, with 95 (51.6%) non-thyroid and 89 (48.4%) thyroid cancers. In the post-COVID period (April 2021 to March 2022), 193 cancers were diagnosed: 104 (53.9%)

non-thyroid and 89 (46.1%) thyroid (see Table 2).

Table 1. Patient demographics for head/neck and thyroid cancer diagnoses.

Demographic Variable	n (%)
Total Patients	592
Sex	
Male	299 (50.5%)
Female	293 (49.5%)
Mean Age $\pm$ SD (Years)	61.4 $\pm$ 13.2
Age Group	
<20 Years	3 (0.5%)
20–39 Years	29 (4.9%)
40–59 Years	213 (36.0%)
60–79 Years	311 (52.5%)
80+ Years	36 (6.1%)

A Chi-square test of independence revealed a statistically significant decrease in thyroid cancer diagnoses across the three time periods ($\chi^2(2) = 8.55$, $p = 0.0140$), with proportions declining from 58.1% in 2019-20 ($n = 125$; 95% confidence interval (CI), 51.5%-64.7%) to 46.1% in 2021-22 ($n = 89$; 95% CI, 39.1%-53.1%). Post-hoc pairwise comparisons using Chi-square tests with Bonferroni correction (adjusted $\alpha = 0.0167$) showed that no individual year-to-year comparison reached statistical significance. However, the largest observed difference was between 2019-20 and 2021-22 ($p = 0.0199$), suggesting a potential downward trend. In contrast, the incidence of non-thyroid head and neck cancers remained stable across the time periods ($\chi^2(2) = 1.05$, $p = 0.593$), comprising 41.9% in 2019-20 ($n = 90$; 95% CI, 35.3%-48.5%) and 53.9% in 2021-22 ($n = 104$; 95% CI, 46.9%-60.9%) (see Table 2).

Table 2. Number and proportion of head/neck versus thyroid cancer diagnoses by year.

Year (April–March)	Head/Neck Cancers, n (%) (95% CI)	Thyroid Cancers, n (%) (95% CI)	Total Cases, n
2019–2020	90 (41.9) (35.3–48.5)	125 (58.1) (51.5–64.7)	215
2020–2021	95 (51.6) (44.4–58.9)	89 (48.4) (41.1–55.6)	184
2021–2022	104 (53.9) (46.9–60.9)	89 (46.1) (39.1–53.1)	193

Monthly observed head/neck and thyroid cancer case counts from April 2019 to March 2022 were compared across three time periods: 2019-2020, 2020-2021, and 2021-2022 (see Figure 1). Kruskal-Wallis testing revealed no significant

difference in monthly case distributions across the three years ($\chi^2(2) = 1.72$, $p = 0.423$), indicating that overall case counts of all three cancers remained stable over the study period.

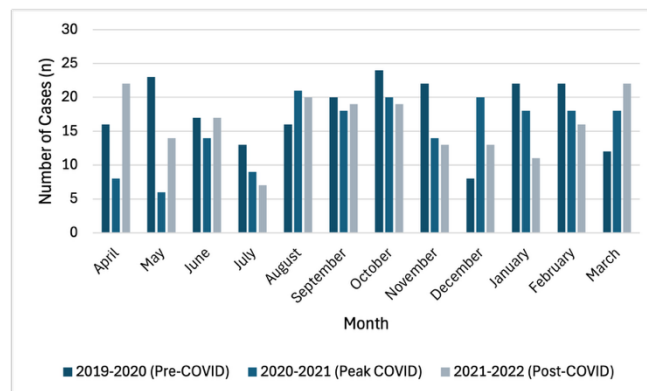


Figure 1. Monthly head/neck and thyroid cancer cases before, during, and after the COVID-19 peak.

Finally, to evaluate changes in cancer severity, the monthly proportion of advanced-stage head/neck and thyroid cancers from April to December 2019 was compared with the same months in 2020 (see Figure 2). A Chi-square test of independence confirmed a significant increase in the proportion of advanced cases during the pandemic ($\chi^2(1) = 6.54$, $p = 0.011$). Proportions fluctuated monthly but were consistently higher in 2020; for example, April 2019 had 19% advanced cases (SE = 9.6%; 95% CI, 0.2%-38.2%) versus 38% in April 2020 (SE = 17.2%; 95% CI, 4.4%-71.6%). Similarly, June 2019 had 29% advanced cases (SE = 10.9%; 95% CI, 7.7%-50.3%) compared to 50% in June 2020 (SE = 13.4%; 95% CI, 23.8%-76.2%).

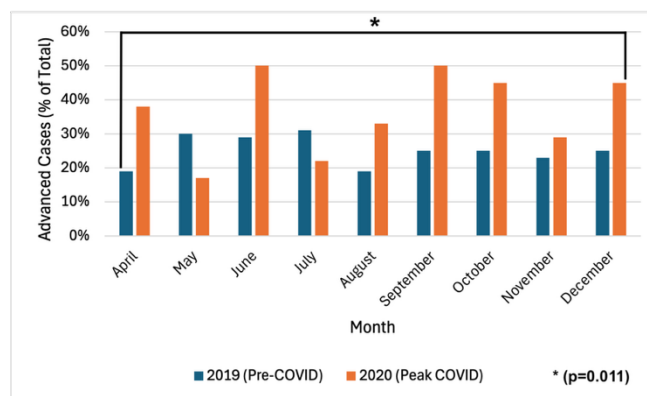


Figure 2. Monthly proportions of advanced head/neck and thyroid cancers before and during the COVID-19 peak.

While the monthly proportions of advanced-stage cancers among diagnosed cases increased significantly during the pandemic, this analysis does not account for changes in the underlying population or in total case detection rates.

Therefore, population-standardized incidence rates of advanced cancers were subsequently calculated; due to the unavailability of advanced cancer staging data beyond March 2021 at the time of analysis, only the pre-COVID and peak-COVID periods were included. Poisson regression modelling, adjusted for month and population size, showed a non-significant increase in the rate of advanced cancer diagnoses in 2020-21 compared to 2019-20 (incidence rate ratio (IRR) = 1.28, 95% CI 0.84 - 1.93, $p = 0.245$), suggesting stability in population-adjusted advanced cancer incidence despite observed changes in relative proportions.

DISCUSSION

This population-based study evaluated patterns of head, neck, and thyroid cancer diagnosis in NL across three distinct periods: pre-COVID (2019-20), peak COVID (2020-21), and post-COVID (2021-22). Overall, the total number of diagnosed cases of head and neck cancer remained stable over the three years. In addition, although the proportion of advanced-stage presentations increased during the pandemic, the population-adjusted incidence of advanced cancers did not change significantly.

The observed decrease in the proportion of thyroid cancers – from 58.1% in 2019-20 to 46.1% in 2021-22 – was statistically significant when analyzed across all three time periods. However, post-hoc pairwise comparisons with Bonferroni correction did not identify significant year-to-year differences, likely due to reduced statistical power after adjustment. Still, the largest decline occurred between 2019-20 and 2021-22, suggesting a possible downward trend in thyroid cancer detection. These findings are consistent with international reports documenting reduced diagnoses of low-risk or subclinical thyroid cancers during the COVID-19 pandemic, likely reflecting the deferral of non-urgent investigations such as neck ultrasound and fine-needle aspiration, reduced provision of public healthcare, and reduced healthcare-seeking behaviour during periods of heightened public health restrictions.^{11,27,32–38} In contrast, non-thyroid head and neck cancer diagnoses remained stable across the three years. These cancers tend to present with more acute or disruptive symptoms, such as hoarseness, dysphagia, or visible lesions, which may prompt more urgent investigation and referral even amid healthcare system disruptions.³⁹ The consistency in head and neck cancer diagnoses suggests that patients with symptomatic disease were still able to access diagnostic services during the pandemic.

A significant increase in the proportion of advanced-stage cancers among diagnosed cases was observed during the pandemic peak (April-December 2020) compared to the same months in 2019. Monthly data showed higher proportions of advanced disease in nearly every month of the 2020 period, supporting concerns about delayed presentations. However,

when adjusted for population size and month using Poisson regression, the incidence rate of advanced cancers in 2020-21 was not significantly different from 2019-20. This suggests that while the proportion of advanced cases increased among those diagnosed, the overall population-level burden of advanced disease remained relatively stable. These findings suggest that the observed rise in advanced-stage proportions may be due to a decrease in the detection of early-stage cancers, rather than a true increase in advanced disease incidence. This indicates that during a time of considerable strain on the healthcare system and resource scarcity, more advanced cancers were likely still appropriately triaged and prioritized for investigation above less advanced cancers.

The demographic distribution of our cohort reflects the predominance of head and neck cancer diagnoses among older adults, consistent with prior epidemiological studies.^{40,41} While monthly case counts remained statistically stable, visual inspection of the data revealed a decrease in diagnoses during April and May 2020, aligning with the onset of public health restrictions. These patterns may reflect temporary interruptions in routine care and changes in healthcare-seeking behaviour related to fear of COVID-19 exposure and reprioritization of diagnostic services. Similar disruptions in cancer diagnostic pathways and delays in presentation have been reported globally, reinforcing the need for resilient cancer care systems during public health crises.^{27,32–38}

These results underscore the importance of maintaining access to diagnostic services during times of healthcare disruption, particularly for cancers like thyroid cancer that often depend on elective imaging and asymptomatic detection. The rise in the proportion of advanced-stage presentations among diagnosed patients emphasizes the potential downstream consequences of diagnostic delays, even when total case volumes appear unchanged.

Several limitations should be noted surrounding this study. First, advanced staging data were only available through March 2021, limiting assessment of post-pandemic trends. Further, survival and long-term outcomes were not evaluated, which limits the interpretation of the clinical significance of delayed presentations. Additionally, as a retrospective observational study, the results may inherently be influenced by documentation or coding inconsistencies. As well, analyses were limited by the grouping of head and neck cancers with thyroid cancers based on the data available within the registry for use. Ideally, given the differences between these types of cancers, future studies would analyze these entities separately.

In terms of strengths, this population-based study contains a comprehensive analysis and presentation of data by leveraging the use of the provincial cancer registry, showcasing real-time data during a global pandemic and

healthcare crisis. Similarly, the study offers a comparison of trends over multiple time periods (pre-, peak-, and post-), thoroughly investigating both mid-pandemic as well as the periods immediately preceding and following it. Finally, given the relatively small population of NL, very little data exists for patients in the areas under study. This allows novel insights into healthcare trends in a location with limited representation in the literature.

CONCLUSION

This study demonstrated that during the COVID-19 pandemic, population-level diagnoses of head, neck, and thyroid cancers in NL remained stable, reflecting a healthcare system that prioritized the detection of cancers with greater morbidity and mortality risk. The decreased detection of primarily low-risk thyroid cancers likely represents appropriate triaging during a period of constrained resources. However, the increased proportion of advanced-stage cancers underscores the potential risks associated with delayed early detection and the need for vigilant follow-up. Maintaining access to timely diagnostic care and public education during healthcare disruptions is critical to mitigating indirect harms from pandemics. Future research should focus on long-term outcomes, including survival and recurrence, as well as exploring patient and provider perspectives to identify and address barriers to care. These efforts are essential to ensure resilient cancer care systems capable of balancing urgent clinical needs with the prevention of delayed diagnoses during times of crisis.

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DISCLOSURES

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