STROKE RISK ASSESSMENT IN THE EMERGENCY DEPARTMENT: PROGNOSTIC MODELS, TEST MODALITIES AND VARIATION OF PRACTICE

Kasim Abdulaziz

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School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

Thesis Supervisors and Advisory Committee Members

Thesis Supervisor:	Dr. Jeffrey J Perry
Thesis Co-supervisor:	Dr. Monica Taljaard
Thesis Advisory Committee Members:	Dr. Dar Dowlatshahi
	Dr. Ian G Stiell
	Dr. George A Wells

ABSTRACT

Introduction: Stroke is a common and serious disorder and a leading cause of death and disability. Most strokes are ischemic with a significant portion preceded by transient ischemic attack (TIA). Early TIA diagnosis and stroke prevention are critical to prevent subsequent poor outcomes. There may be deficiencies and opportunities for improvements in current TIA patient management.

Objectives: The main objectives of this thesis were threefold: to 1) examine reporting quality of derivation and validation studies for prognosis of stroke in patients with TIA, 2) examine practice variation in Canadian stroke prevention clinics, and 3) derive and validate a clinical prediction score for clinically significant symptomatic carotid artery disease (i.e., stenosis ≥ 50%) in patients with TIA.

Methods: To achieve these objectives we conducted a systematic review of prediction model studies for TIA patients, conducted an electronic survey of stroke prevention clinic leads, and derived and internally validated a clinical prediction tool.

Results: For the systematic review, 7,026 articles were screened; 60 were retained consisting of 100 derivation and validation studies. Among the 100 derivation and validation studies, few reported whether assessment of outcome (24%) and predictors (12%) was blinded; sample size justifications (49%), description of method for handling missing data (16%), and calibration method (5%) were seldom reported. Thirty-eight clinicians at 76 eligible clinics responded to the survey (response rate 50%). The majority of clinics (66%) were open at least five days a week. Most high-risk patients were not seen by the clinics within 48 hours. COVID-19 had a negative impact on routine patient care including longer wait times. The clinical prediction model for clinically significant symptomatic carotid artery disease included 13 predictors with an

optimism-corrected C-statistic of 0.781 (95% CI: 0.769-0.798) and good calibration. We simplified the model into a score (Symcard Score), with suggested cut-points for high (15+ points), medium (12-14), and low-risk (≤11) stratification. A substantial portion (38%) of TIA patients were classified as low-risk [sensitivity 92.9% (95% CI: 91.0%-94.5%), specificity 41.1% (95% CI: 40.1%-42.1%), and diagnostic yield 1.7% (95% CI: 1.3%-2.1%)].

Conclusions: Many studies deriving or validating clinical prediction models for the prognosis of stroke in patients with TIA do not report essential items adequately, precluding effective critical appraisal of such tools for potential use in clinical settings. There is wide variation in management of TIA patients among stroke prevention clinics and potentially suboptimal patient care. Only a portion of TIA patients require vascular imaging — yet, no tool was previously available to identify such patients, leading to unnecessary imaging and delayed care. We derived and internally validated a prediction score for the diagnosis of clinically significant carotid artery disease that has good discrimination and calibration. After external validation, the Symcard Score can potentially support clinicians and avoid or delay a significant percentage of vascular imaging for patients with TIA, especially in crowded emergency departments.

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LIST OF ABBREVIATIONS

CHARMS	CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
CIHR	Canadian Institutes of Health Research
CSBPR	Canada, the Canadian Stroke Best Practice Recommendations
CT	Computed tomography
CTA	Computed tomography angiography
ECG	Electrocardiogram
ED	Emergency department
EVP	Events per variable
IQR	Interquartile range
MeSH	Medical Subject Headings
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PROBAST	Prediction model Risk Of Bias ASsessment Tool
PROSPERO	The International Prospective Register of Systematic Reviews
SPC	Stroke prevention clinic
TIA	Transient ischemic attack
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

1. INTRODUCTION

1.1. Background

Stroke is a common and serious disorder and a leading cause of mortality and morbidity worldwide.[1] Annually, an estimated 15 million people worldwide suffer a stroke of which 5 million die and another 5 million are left permanently disabled.[2] Strokes are of two types, ischemic (obstruction of blood flow to the brain) and hemorrhagic (bleeding in the brain). Although most epidemiological data combine ischemic and hemorrhagic (including intracerebral hemorrhages and subarachnoid hemorrhages) strokes under the common term stroke, the vast majority of strokes (87%) are ischemic in nature.[3] With urgent patient management, many of the ischemic strokes can be prevented. Transient ischemic attack (TIA)/minor stroke (i.e., non-disabling stroke) provides an ideal opportunity for ischemic stroke prevention as a large proportion of ischemic strokes are preceded by a TIA/minor stroke. However, there is a wide variation in the management of patients with TIA/minor stroke. The goal of this thesis is to study strategies followed by healthcare professionals in managing TIA/minor stroke patients, to identify and appraise existing clinical prediction models to identify high-risk TIA/minor stroke patients, and to derive a clinical prediction model to help triage patients for vascular imaging for clinically significant carotid artery disease which will improve TIA/minor stroke patient management strategies.

1.1.1 Transient Ischemic Attack

According to the traditional time-based definition, TIA/minor stroke is a sudden, focal neurological deficit of presumed vascular origin and confined to an area of the brain or eye

perfused by a specific cerebral artery and of a duration less than 24 hours.[10] TIA/minor stroke often precedes subsequent ischemic stroke with risk estimates of up to 25% within 3 months with about half of the events occurring within the first 48 hours.[4–8] An estimated crude TIA/minor stroke incidence of 1.19 per 1,000 person-years has been recently reported.[9] However, precise estimates of the incidence and prevalence of TIA/minor stroke are difficult to determine due to under- and over-diagnosis and the varying criteria or TIA definitions used for identifying patients. Several studies have demonstrated that this arbitrary time threshold of 24 hours was too broad because one third of classically-defined TIA/minor stroke patients show brain injury on diffusion-weighted magnetic resonance imaging.[11–13] Hence, a tissue-based (i.e., evidence of infarction) definition was proposed but it is dependent on having access to early magnetic resonance imaging which is not readily available in most health facilities around the world.[14] Several other tissue-based definitions have been proposed since, attempting to clarify the original tissue-based definition.[15] Many clinicians question the usefulness of the tissue-based definition and oppose its use since it impedes research and clinical status is what matters most to patients.[15] In addition, there has also been variations in distinguishing TIA and minor strokes. More recently, it has been suggested that TIAs and minor strokes are essentially the same and to consider them as such.[16] In this thesis, we use the clinical, time-based, definition for TIA and consider minor stroke as a TIA.

Regardless of the criteria and definitions used to identify cases, TIA/minor stroke carries a serious risk of subsequent stroke or death shortly after diagnosis, and thus represents an ideal opportunity for stroke prevention.[6] With urgent and optimized treatment, risk of stroke after TIA/minor stroke could be reduced to about 1%.[17,18] One possible strategy to reduce risk of

strokes in patients with TIA/minor stroke would be to assess all the TIA/minor stroke patients equally on a first come, first serve basis without triaging and admit all patients to the hospital. Such a strategy would not make good use of resources that are limited and already constrained in emergency departments. In other words, TIA/minor stroke is a common condition requiring a significant amount of resource-intensive investigations to determine the etiology to prevent subsequent stroke. In addition, an estimated 50% of all clinically diagnosed TIA/minor stroke patients are stroke mimics who are not at risk of subsequent stroke and do not require such thorough investigations.[19–21] Additionally, as resources are limited in many parts of the world, it is not feasible to investigate all TIA/minor stroke patients immediately. Hence, unless high-risk patients are identified and managed immediately, many will have a subsequent stroke prior to having their management optimized. Numerous studies have identified risk factors and derived clinical prediction models, with varying presentation formats such as risk scores, to identify stroke risk level in TIA/minor stroke patients for rapid treatment of the risk factors to prevent subsequent stroke.

1.1.2 Clinical prediction models

Clinical prediction models are mathematical equations that relate one or more predictors to the probability or risk of having an outcome such as a condition or disease (diagnostic) or the probability or risk of developing the outcome in the future (prognostic). Clinical prediction models are commonly developed with regression analysis techniques with logistic regression analysis being the most commonly used for prediction of binary events and Cox regression analysis being the most commonly used for time-to-event analysis.[22] Clinical prediction models are multivariable since reliable estimates of diagnostic or prognostic probabilities or risks cannot

be obtained from a single predictor.[23] Predictors are also referred to as covariates, risk indicators, risk factors, prognostic factors, factors, determinants, features, test results, explanatory variables, exposure variable, or independent variables. The predictors are often specified from demographic characteristics (e.g., age and sex), past medical history (e.g., diabetes and hypertension), history of symptoms at onset (e.g., unilateral weakness of an arm and duration of symptoms), physical exam (e.g., visual field deficit and speech difficulty), vitals measurements (e.g., systolic blood pressure and heart rate), and test results (e.g., blood work and imaging). Depending on the presentation format and author preference, a clinical prediction model could also be referred to as a prognostic model, diagnostic model, clinical prediction score, clinical prediction index, clinical decision rule, risk score, and nomogram, among other names.

Development of a clinical prediction model often involves several steps (Figure 1.1). To begin with, development of a new clinical prediction model needs a clinical justification (i.e., a clinical need). Previous literature has identified three categories of justifications for developing a clinical prediction model for patient care by clinicians including a common clinical condition which implies that many patients can potentially benefit from the model, undesirable practice variation, and need for improved practice efficiency.[24,25] Although most clinical prediction models are derived without a formal justification, a formal needs assessment is recommended. Two examples of formal needs assessments are the Ottawa Ankle Rule[26] and the Canadian TIA Score[27] studies. Once the need for a clinical prediction model has been adequately justified, development of the prediction model can proceed. Development of a clinical prediction model for use in various settings requires at least two consecutive phases to maximize the accuracy and clinical utility: 1) derivation, including internal validation, and 2) external validation (evaluation

to check accuracy in an independent population and setting).[24,28–31] A clinical prediction model should potentially also undergo a clinical impact evaluation to demonstrate whether using the model improves decision-making and patient outcomes.[32,33] Rigorous development and validation of clinical prediction models is important because unreliable predictions could cause more harm than benefit in guiding clinical decisions. Numerous methodological standards and guides have been developed for clinical prediction modelling.[22,24,34–38] Despite the substantial body of methodological literature and guides on performing prediction modelling research, most clinical prediction modelling studies suffer from methodological shortcomings or at least poor reporting, as indicated by several systematic reviews of existing prediction modelling studies.[38–40]

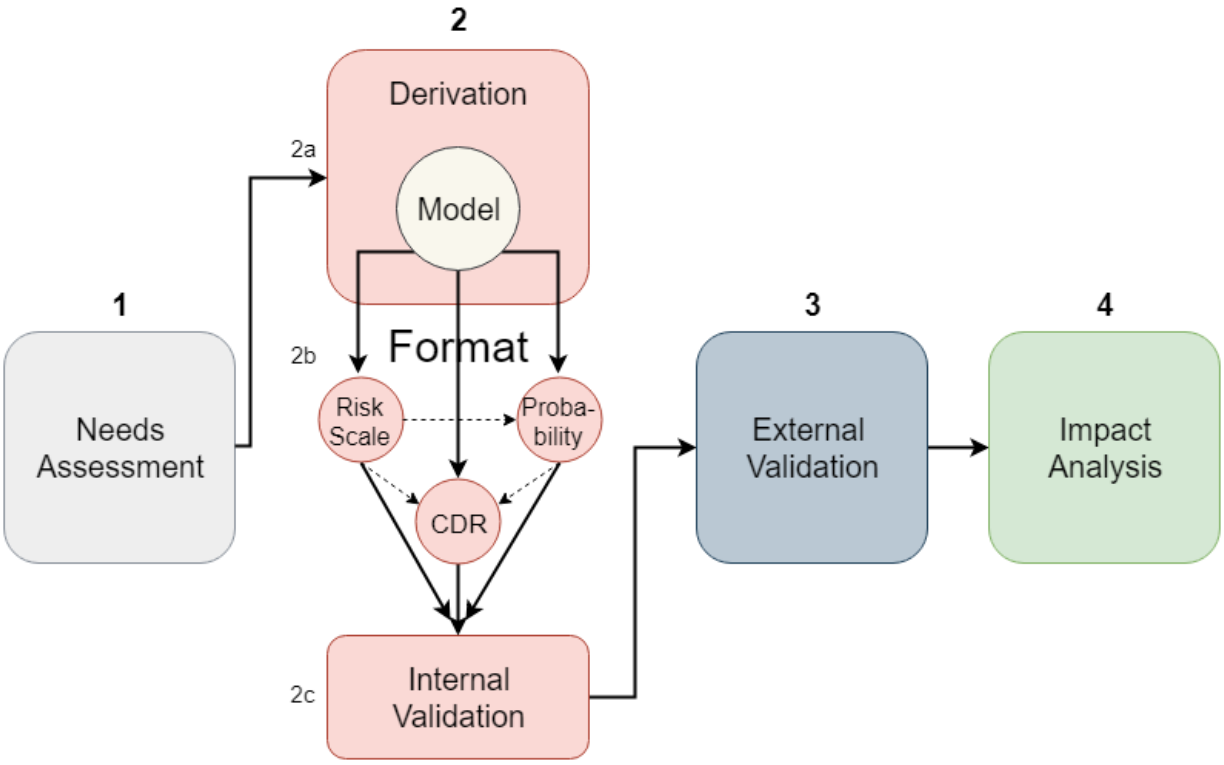

Figure 1.1. Steps for clinical prediction model development and use. CDR, clinical decision rule; Probability, probability tables or regression formula; Risk Scale, risk table or nomogram.

In addition to methodological standards for the development and validation of clinical prediction models, reporting and appraisal guidelines have been developed to guide authors in reporting and appraising prediction models. Reporting guidelines help authors report essential items when publishing a study while appraisal guidelines help authors extract and appraise existing studies. Appraisal guidelines such as the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[41] and the Prediction model Risk Of Bias ASsessment Tool (PROBAST)[42], have been developed for data extraction and critical appraisal and assessment of risk of bias in modelling studies. However, to use such appraisal guides to their full extent, essential items need to be reported in the paper deriving or validating a prediction model. Reporting guidelines such as the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) have been developed for studies developing, validating, or updating a prediction model.[43]

Artificial intelligence, including clinical prediction models, are becoming increasingly abundant and important in recent years in the current era of personalized medicine.[22] Several clinical prediction models have been derived and validated for the prognosis of stroke in patients with TIA/minor stroke.[44,45] An example of such a clinical prediction model is the Canadian TIA Score, that has been developed and validated for identifying low, medium, and high risk patients with the majority of emergency physicians and neurologists showing interest in using it.[46,47] Several other clinical prediction rules have been developed and validated for identifying low and

high-risk patients including the ABCD^2 and ABCD^{2}i scores.[4,48,49] After risk stratifying with a risk tool (i.e., a clinical prediction model), the TIA/minor stroke patients can be more efficiently managed. In other words, the urgency and level of care will depend on predicted stroke risk.[44,45] Some TIA/minor stroke patients would be treated while others would be referred to an outpatient ambulatory care stroke prevention clinic, if available.

To make recommendations about uptake in clinical practice, understanding the methodological quality of the prediction model studies is essential. To our knowledge, there have been no reviews published of the methodological or reporting quality of these models. Thus, we aimed to identify existing clinical prediction models and assess the reporting quality of the derivation and validation of these models using the recommendations in the TRIPOD guideline.

1.1.3 Stroke prevention clinics

Traditionally, and still in some parts of the world, TIA/minor stroke patients are admitted to hospital (inpatient-based model) for rapid investigation and comprehensive management.[50] In an effort to optimize health resource utilization with improved patient outcomes, outpatient-based models have been introduced.[50–53] A stroke prevention clinic (SPC), also known as rapid access TIA clinic, is a specialized outpatient clinic that provides rapid access to experts, diagnostic tests, and treatments. Referrals to SPCs are initiated from emergency departments (ED), family physicians, and specialists. The role of an SPC is to provide an integrated, comprehensive, and interdisciplinary approach to stroke prevention in a timely manner to ensure that TIA/minor stroke patients receive evidence-based care with best practices. The clinics are often managed by

stroke neurologists, internists, stroke prevention nurse specialists, nurse practitioners, and administrative assistants.

Currently, no standardized strategies exist for referrals and care and there may be variation in how patients with suspected TIA/minor stroke are identified and managed.[54,55] Based on key-informant (i.e., information gathering) interviews with several neurologists at The Ottawa Hospital, we found that there was suspected variation among SPCs in how TIA/minor stroke patients are managed. For example, some SPCs may be (a) open limited hours a week, (b) triage patients without assessing and considering risk levels, (c) have protocols in place to have patients complete some tests prior to their clinic appointment, (d) have long wait times for some tests which varies depending on referring source, and (e) lack urgent communication protocols between SPCs and radiology departments. However, the true extent of variation in practice among all stroke prevention clinics in Canada was unknown. Understanding the extent of variation in practice can help develop strategies to standardize practices across SPCs which may ultimately reduce the incidence of subsequent stroke.

1.1.4 Symptomatic carotid artery disease risk and vascular imaging

As discussed in section 1.1, close to 90% of all strokes are ischemic in origin.[3] An ischemic stroke occurs due to significant stenosis or narrowing of a blood vessel to the brain, causing obstruction of blood flow to the brain. Stenosis can be caused by either atherosclerosis (i.e., plaque buildup), blood clots or dissection or a combination of these. Blood clots, or plaque debris, can be formed in the blood vessels, called thrombi, or developed elsewhere in the body

and travels to the blood vessel, called emboli. A dissection is a tear in the artery wall that allows blood to flow between the wall layers resulting in stenosis. Stenosis can occur in any blood vessel including the two large blood vessels in the neck, called carotid arteries, that carry blood to the brain. Stenosis of the carotid arteries is one of five etiological subtypes of ischemic stroke. The five different etiological subtypes of ischemic stroke are large-artery atherosclerosis, cardioembolism (e.g., atrial fibrillation), small vessel occlusion (lacunar stroke), stroke of other determined etiology (e.g., vasculitis), and stroke of undetermined etiology (cryptogenic stroke).[56] Among these etiological subtypes of ischemic stroke, patients with extracranial large-artery atherosclerosis, which includes the internal carotid artery, have the highest risk for early recurrent stroke.[56,57] An estimated 20-25% of ischemic strokes are caused by large-artery atherosclerosis, while an estimated 10-20% of ischemic strokes are specifically attributed to extracranial internal carotid artery stenosis or disease.[58,59] With urgent diagnosis and intervention, risk of stroke can be reduced substantially in these patients.

Urgent and accurate diagnosis and degree of stenosis or occlusion of carotid artery disease is essential for determining appropriate medical interventions for stroke prevention. Previous research, including two major randomized control trials, has shown that patients with clinically significant symptomatic extracranial carotid artery atherosclerosis benefit from urgent revascularization in addition to medical management.[60,61] Revascularization techniques for extracranial carotid artery atherosclerosis include carotid endarterectomy or carotid angioplasty and stenting. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Symptomatic Carotid Surgery Trial (ESCT), have shown that carotid endarterectomy for patients with severe (70-99%) carotid artery stenosis reduces stroke risk

significantly.[60,61] The Canadian Stroke Best Practice Recommendations suggest that patients with symptomatic ipsilateral 50-99% carotid artery stenosis be urgently evaluated for potential carotid revascularization (i.e., carotid stent or endarterectomy).[62] More specifically, urgent carotid endarterectomy is recommended in men with 50-99% and women with 70-99% symptomatic carotid artery stenosis.[62] Recent guidelines by the American Heart Association/American Stroke Association recommend carotid revascularization for patients with symptomatic internal carotid artery stenosis of 50-99%, depending on patient characteristics and time of TIA/minor stroke onset.[63] Similar recommendations are made by the Society for Vascular Surgery.[64] Hence, diagnosis of clinically significant symptomatic carotid artery disease (i.e., carotid artery stenosis of 50% or more) and accurate degree of stenosis is urgently required.

Diagnosis of carotid artery disease requires vascular imaging. Several imaging modalities exist for the diagnosis of carotid artery disease including conventional digital subtraction cerebral angiography, magnetic resonance angiography (MRA), computed tomography angiography (CTA, when dye is used with x-ray slices to show blood vessels), and duplex ultrasonography (i.e., Doppler ultrasound), each of which has its own benefits and drawbacks.[65] MRA use magnets to create imaging which is reformatted to show the blood vessels (time of flight or TOF) or contrast enhanced (CE). The conventional intra-arterial angiography, most commonly performed using digital subtraction angiography, is considered the "gold standard" technique for evaluating the presence and extent of carotid stenosis. However, intra-arterial angiography is invasive, expensive, and has risks that include iodinated contrast and radiation exposure, an estimated 4% risk of transient ischemic attack and a 1% risk of disabling stroke or death.[65,66] Given the invasiveness of testing, the risks, costs, and the presence of non-invasive alternatives,

routine usage of intra-arterial angiography for carotid artery disease has been curtailed.[65] Therefore, most carotid imaging are now performed non-invasively with MRA, CTA, or Doppler ultrasound. MRA can provide detailed assessment of stenosis with high resolution images of soft tissue without exposure to iodinated contrast dye or radiation.[67] However, widespread application of MRA modality is difficult due to its inaccessibility in most centers, low signal-to-noise ratios, and costs.[67] CTA is routinely used for characterization of stenosis and can demonstrate detailed images of the carotid arteries. However, CTA requires iodinated contrast and exposes the patient to radiation in addition to calcification artifacts or mimics leading to inaccurate assessment of stenosis.[65] Generally, CTA has a similar performance as MRA and at times better performance than MRA, depending on the situation. Finally, carotid ultrasound is affordable and more readily available than CTA or MRA but does not perform as well and the accuracy is highly operator-dependent.[68] Given the limitations and controversy regarding the best modality for the diagnosis of carotid artery disease, it is not uncommon that more than one non-invasive modality is used for confirmatory testing. In fact, carotid ultrasound is often complemented with CTA or MRA for accurate diagnosis of carotid artery disease when available. In addition to limitations with each modality, access to vascular imaging for patients with transient ischemic attack varies between hospitals which may incur delays to diagnosis and intervention.[69]

The vast majority of transient ischemic attack patients do not have significant carotid stenosis requiring surgery and hence do not need vascular imaging. In other words, only a limited number (up to 20%) of ischemic strokes are caused by extracranial internal carotid artery disease with the remaining caused by other etiological subtypes. In addition, most of the 20% of TIA patients

with extracranial internal carotid artery disease etiology will not benefit from surgery due to stenosis being less than 50% or not being appropriate candidates for surgical procedures (i.e., surgery will likely lead to death). Furthermore, misdiagnosis of TIA/minor stroke is common: an estimated 50% of all patients diagnosed with TIA/minor stroke are in fact stroke mimics.[19–21] Hence, imaging all of TIA/minor stroke patients may lead to unnecessary exposure to iodinated contrast dye or radiation and use of resources that are stretched and at capacity in the emergency departments. In addition, vascular imaging is not readily available at all centers. Therefore, a clinical prediction model to identify true TIA/minor stroke patients with clinically significant symptomatic carotid artery disease could potentially help avoid unnecessary vascular imaging or, at minimum, prioritize patients based on risk level so that high-risk patients are managed more quickly while not causing harm to those having to wait longer. Several prediction models have been derived for *asymptomatic* carotid artery disease.[70–75] To our knowledge, none have been developed to determine urgency of vascular imaging or the diagnosis of clinically significant symptomatic ipsilateral extracranial carotid artery disease.

1.2. Thesis objectives and format

The goal of this thesis was to identify areas for improvement in TIA/minor stroke patient management and support clinical decision-making for the prevention of stroke in patients with TIA/minor stroke through three main objectives:

1) Examine reporting quality of existing clinical prediction model studies for patients with TIA/minor stroke;
2) Examine variation of practice among Canadian stroke prevention clinics in managing TIA/minor stroke patients; and

3) Derive and validate a clinical prediction risk model for the diagnosis of clinically significant symptomatic carotid artery disease.

The presentation of this thesis follows a manuscript-based format. Each objective is achieved and presented by a manuscript presented below.

The first objective of this thesis, presented in chapter 2 (manuscript 1 - published), was to examine the reporting quality of existing clinical prediction model studies. This objective was achieved through a systematic review.

The second objective of this thesis, presented in chapter 3 (manuscript 2 – published), was to examine variation of practice among Canadian stroke prevention clinics. To understand the extent of variation we conducted a survey of all Canadian stroke prevention clinics. The aims of this study were twofold: (1) to describe variation in management practices for TIA/minor stroke patients and (2) to characterize the impact of the COVID-19 pandemic on the management of TIA/minor stroke patients including the use of virtual care by the stroke prevention clinics.

The third and final objective of this thesis, presented in chapter 4 (manuscript 3 – prepared for submission), was to derive and internally validate a clinical prediction model for the diagnosis of clinically significant symptomatic carotid artery disease (i.e., carotid stenosis of 50% or more).

2. SYSTEMATIC REVIEW OF EXISTING CLINICAL PREDICTION MODELS

Manuscript 1: Quality and Transparency of Reporting Derivation and Validation Prognostic Studies of Recurrent Stroke in Patients with TIA and Minor Stroke: A Systematic Review

2.1. Preface to manuscript 1

This chapter presents the manuscript of the first objective of the thesis which is the systematic review of the reporting quality of derivation and validation studies of clinical prediction model for stroke in patients with TIA/minor stroke that was published in Diagnostic and Prognostic Research in 2022 as:

> Abdulaziz KE, Perry JJ, Yadav K, Dowlatshahi D, Stiell IG, Wells GA, Taljaard M. Quality and transparency of reporting derivation and validation prognostic studies of recurrent stroke in patients with TIA and minor stroke: a systematic review. Diagn Progn Res. 2022 May 19;6(1):9. doi: 10.1186/s41512-022-00123-z. PMID: 35585563; PMCID: PMC9118704.

KEA was responsible for the concept and study design with contributions from all authors. Article selection was performed by KEA and KY. Data were extracted by KEA. Data analyses were conducted by KEA. KEA interpreted the data with assistance from JJP and MT. KEA wrote the first draft of the manuscript with critical review by all authors. All authors approved the final version of the manuscript.

Supporting information on this manuscript are provided in Appendix 7.1. Research Ethics Board approval was not required for this study.

2.2. Abstract

Background: Clinical prediction models/scores help clinicians make optimal evidence-based decisions when caring for their patients. To critically appraise such prediction models for use in a clinical setting, essential information on the derivation and validation of the models needs to be transparently reported. In this systematic review, we assessed the quality of reporting of derivation and validation studies of prediction models for the prognosis of recurrent stroke in patients with transient ischemic attack or minor stroke.

Methods: MEDLINE and EMBASE databases were searched up to February 04, 2020. Studies reporting development or validation of multivariable prognostic models predicting recurrent stroke within 90 days in patients with TIA or minor stroke were included. Included studies were appraised for reporting quality and conduct using a select list of items from the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement.

Results: After screening 7026 articles, 60 eligible articles were retained, consisting of 100 derivation and validation studies of 27 unique prediction models. Four models were newly derived while 23 were developed by validating and updating existing models. Of the 60 articles, 15 (25%) reported an informative title. Among the 100 derivation and validation studies, few reported whether assessment of the outcome (24%) and predictors (12%) was blinded. Similarly, sample size justifications (49%), description of methods for handling missing data (16.1%), and model calibration (5%) were seldom reported. Among the 96 validation studies, 17 (17.7%) clearly reported on similarity (in terms of setting, eligibility criteria, predictors, and outcomes) between the validation and the derivation datasets. Items with the highest prevalence of

adherence were the source of data (99%), eligibility criteria (93%), measures of discrimination (81%) and study setting (65%).

Conclusions: The majority of derivation and validation studies for the prognosis of recurrent stroke in TIA and minor stroke patients suffer from poor reporting quality. We recommend that all prediction model derivation and validation studies follow the TRIPOD statement to improve transparency and promote uptake of more reliable prediction models in practice.

Trial registration: The protocol for this review was registered with PROSPERO (Registration number CRD42020201130).

Keywords: Prediction models, Prediction rules, Clinical decision rules, Risk scores, Recurrent stroke, Transient ischemic attack, Cerebral ischemia, TRIPOD, CHARMS, Reporting quality

2.3. Background

Clinical prediction models (also called clinical prediction rules, clinical prediction scores, clinical decision rules, or prognostic models) aid clinicians in making diagnostic and therapeutic decisions at the bedside and reduce inefficient provision of resources when presented and applied appropriately [1–3]. Such tools are commonly used by clinicians, and especially in the emergency department, to identify patients at high risk of stroke as it is not practical to treat everyone due to limited resources. Transient ischemic attack (TIA, i.e. a cerebral ischemia without lasting symptoms) and minor stroke carry a serious risk of subsequent stroke or death shortly after diagnosis, and thus represent an opportunity for stroke prevention [4].

To maximize the accuracy and clinical utility of clinical prediction models, they need to go through at least two consecutive phases: derivation including internal validation and external validation (evaluation to check accuracy in an independent population and setting) [2, 5–9]. Numerous methodological standards and guides have been developed for clinical prediction modelling [3, 6, 10–14]. Unfortunately, several systematic reviews have indicated shortcomings in methodological quality of many existing prediction studies [14, 15]. In addition to methodological standards for the development and validation of clinical prediction models, appraisal guidelines such as the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) [16] and the Prediction model Risk Of Bias ASsessment Tool (PROBAST) [17] have been developed for data extraction and critical appraisal and assessment of risk of bias in modelling studies. To use such appraisal guides to their full extent, essential items need to be reported in the paper deriving or validating a prediction model. The strengths and weaknesses of a prediction model study can only be

revealed with full and transparent reporting to enable its interpretation and usefulness and enhance the uptake and implementation of validated models for use in clinical settings [18]. Complete and transparent reporting also support future prediction model studies by allowing researchers to validate and compare existing prediction models [18]. For this reason, reporting guidelines such as the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) have been developed for studies developing, validating, or updating a prediction model [19].

Several clinical prediction models exist for the prognosis of stroke in patients with TIA and minor stroke. To critically appraise their methodological quality and make recommendations about future updates and/or adoption in clinical practice, better reporting quality of prediction models is essential. Although several systematic reviews have been conducted of the quality of reporting of prediction model studies in various other clinical domains [15, 20–28], to our knowledge, there have been no reviews of the reporting quality of prognostic models for stroke. Thus, we aimed to identify existing clinical prediction models and assess their reporting quality using the recommendations in the TRIPOD statement.

The overall goal of this study is to critically appraise existing derivation and validation studies of prediction models, in terms of reporting quality, for the prognosis of recurrent stroke within 90 days in patients with TIA or minor stroke. The specific objectives are:

1. To identify and characterize derivation and validation studies of existing multivariable clinical prediction models in the literature for the prognosis of recurrent stroke within 90 days in patients with TIA or minor stroke;
2. To characterize the quality of reporting of a select list of essential items for both the derivations and validations.

2.4. Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (See Fig. 1 and Additional file 1) [29]. To help us guide the framing of the review aim, search strategy, and study inclusion and exclusion criteria, we used key items from the TRIPOD and the CHARMS Checklist, presented in additional files (See Supplementary Table 1, Additional file 2).

2.4.1 Search strategy

We conducted comprehensive electronic searches to identify all published studies of clinical prediction models for the prognosis of recurrent stroke within 90 days in patients with TIA or minor stroke.

We searched the Ovid interface, as well as Medline and Embase databases using a strategy that included the National Library of Medicine's Medical Subject Headings (MeSH) and non-MeSH keywords up to February 04, 2020. The search strategy used TIA and stroke search syntax and used established search filters for prediction models [30–33]. Due to the low quality of reporting

of prediction modelling studies, we further modified the search filter by including additional and more specific search terms to be more comprehensive in identifying relevant studies. We developed the search strategy with the help of an experienced medical librarian. It was later validated by a second medical librarian in accordance with the Peer Review of Electronic Search Strategies (PRESS) guidelines [34]. A copy of the search strategy can be found in additional files (See Additional file 3). We also used Google Scholar to search and find any additional articles by searching for relevant keywords in the Google Scholar search engine. In addition, we searched the citations from the included studies for additional eligible studies of clinical prediction models.

2.4.2 Inclusion and exclusion criteria

This systematic review focused on studies of any design that developed or validated multivariable prediction models or scoring rules for the prognosis of recurrent stroke within 90 days for patients diagnosed with TIA or minor stroke.

We considered a clinical prediction model to be any tool that combined at least two predictors to estimate a probability or score for the outcome of stroke within 90 days. We excluded studies that investigated a single predictor, test, or marker. We also excluded studies that investigated only causality between one or more variables and an outcome, and predictor finding studies, i.e. studies which aim to explore which predictors, out of a number of candidate predictors, are independently associated with a diagnostic or prognostic outcome rather than deriving or

validating a prediction model [14]. We excluded five studies in languages other than English. We did not apply publication date restrictions.

2.4.3 Screening

After retrieving the potentially relevant articles from the search, we imported the records into Covidence (https://www.covidence.org). We removed duplicates and two reviewers (KEA and KY) independently screened the title, abstract, and keywords. Prior to embarking on screening, the two reviewers screened a sample of records as part of a training and calibration exercise, and the screening criteria were clarified where necessary.

We retrieved the full text of the articles that were considered potentially relevant by at least one of the reviewers in the title or abstract screen. One of the reviewers then reviewed the full text of each of the articles to determine eligibility. We excluded articles for which we could not obtain full text.

2.4.4 Data extraction

One reviewer (KEA) extracted data from each included study using an extraction form that was specifically designed and pilot tested for the review. We extracted data separately for each derivation or validation cohort (hereafter called cohort) in a publication.

The data extraction form was based on selected items from the TRIPOD and CHARMS checklists for reporting and critical appraisal of prognostic model studies. We focused on items that are essential for the appraisal of derivation and validation studies. Although we initially set out to assess both reporting quality and quality of methodological conduct, we ultimately decided to focus on quality of reporting as our appraisal of methodological conduct was hampered by a lack of clarity in the reporting. For feasibility reasons and to keep the project manageable, we did not assess adherence to all the TRIPOD items. We extracted information pertaining to items 1, 3 through 9, 13, 14, 16, and 22 of the TRIPOD statement, covering the title, background and rationale, methods, and results along with information about funding that was thought to be particularly relevant to the field; we did not extract information about items 2, 10, 11, 15, 17 through 21 covering the abstract, specifics of statistical analysis methods, model specification, discussion, and other information (supplemental information) sections. Some TRIPOD items are applicable to both derivation and validation studies, while others are applicable to validation studies only. We distinguished between validation studies without updating and validation studies with updating (i.e. studies developing an updated model based on an existing model). For validation studies with updating, we also extracted whether the update was performed in accordance with suggested methodology by Su and colleagues [35]. In particular, we extracted whether the order of performing the update was as follows: (a) recalibrating the intercept only, (b) recalibrating the intercept and adjusting the other regression coefficients by a common factor, (c) category b plus extra adjustment of a subset of the existing coefficients to a different strength, (d) category c plus adding new predictors, (e) re-estimating all of the original regression coefficients, and (f) category e plus adding new additional predictors [35]. This order of performing the update was recommended so that authors consider less extensive update methods

prior to considering more extensive revisions. For example, it might suffice to recalibrate the intercept only to improve the performance of the model in the setting it is being validated in.

A list of extracted items can be found in additional files (See Supplementary Table 2, Additional file 2).

As this was a study on quality of reporting, we did not perform risk of bias assessment on individual studies. We have registered the protocol for this study with PROSPERO (Registration number CRD42020201130) prior to extracting the data.

2.4.5 Analysis

We summarized and presented the results of this systematic review using descriptive statistics (numbers and percentages). We classified each item as adherent, not adherent, or unclear or not reported. We combined a few studies classified as non-adherent with unclear or not reported to create a combined category of "Non-adherence, unclear, or not reported". In other words, we consider not reporting or unclear reporting as a form of non-adherence.

2.5. Results

2.5.1 Search results

Our database search identified 9036 articles. After removal of duplicates, 7026 titles and abstracts were screened for eligibility. After title and abstract screening, 6696 records were excluded leaving 330 full-text articles for eligibility assessment. Two additional articles were later identified by hand searching the reference lists. A total of 60 articles ultimately met our inclusion criteria (Fig. 1). Reasons for exclusion are outlined in Fig. 1.

2.5.2 Study characteristics

A total of 100 derivation and validation studies were performed on 27 prediction models within 60 published articles. Among the 100 derivation and validation studies, 27 were classified as prediction model development (either anew or by model updating) while the remaining 73 were classified as validation. Of the 27 prediction models, four were newly developed (i.e. not based on existing models) while 23 were developed based on existing models (i.e. validation with model updating). All 60 articles were published between 2000 and 2020. The studies were conducted in 18 different countries, mostly the UK (8 or 13.3%) and China (8 or 13.3%) followed by the USA (7 or 11.7%). Countries with three or fewer studies were grouped together under the other category and included the following countries: Austria, Bulgaria, Canada, Germany, Greece, Italy, Japan, Norway, Singapore, Spain, Sweden, Switzerland, and Turkey. The country of the study was not reported for 4 (6.7%) of the studies.

A list of the included studies can be found in the additional files (See Additional file 4). Distribution of included studies by year of publication is presented in Fig. 2.

2.5.3 Reporting of items applicable at the article level

Results of reporting of items applicable at the article level are presented in Table 1. According to the TRIPOD statement, an informative study title entails identifying the study as derivation or validation of a multivariable prediction model, the target population, and the outcome to be predicted (TRIPOD item 1). Fifteen out of 60 studies (25.0%) adhered to the title recommendations. The source and role of funders (TRIPOD item 22) was provided by 14 (23.3%) of the 60 published articles.

2.5.4 Reporting of essential items common to both derivation and validation studies

Results of reporting of essential items common to derivation and external validation studies are presented in Table 2.

Introduction (TRIPOD item 3)

Background information includes the medical context and rationale for deriving or validating the model. Background information was provided in 66 (66%) derivation and validation studies.

Methods (TRIPOD items 4–12)

Study design or source of data was reported in 99 (99%) of the 100 derivation and validation studies while key study dates (i.e. start and end dates of cohort data collection) were reported in 95 (95%) and study setting (i.e. tertiary, community, or both) was reported in 65 (65%). Fifty-six (56%) recruited participants from multiple sites with 41 (41%) recruiting from one site. Fifty-one (51%) provided information on their recruitment methods of which 50 (50%) recruited consecutive participants. Eligibility criteria for participants was clearly reported in 93 (93%) of the derivation and validation studies.

A clear outcome definition (clinical vs tissue-based) was reported in 80 (80%) of the derivation and validation studies. Forty-four (44%) conveyed that the same outcome definition and method of measurement were used in all patients. The majority, 73 (73%), used a 90-day outcome of stroke followed by a 7-day outcome in 66 (66%) followed by other combinations of outcome

time periods. Assessment of the outcome without knowledge of the candidate predictors was reported in 24 (24%). In terms of predictor definitions and measurement, a total of 63 (63%) of the derivation and validation studies reported information on how to measure all measurement predictors while 47 (47%) reported information on when to measure all measurement predictors. Assessment of predictors without knowledge of the outcome or other predictors was reported in 12 (12%).

Sample size justification was reported in 49 (49%) of the derivation and validation studies. Information on missing data and methods of handling the missing data were reported in 15 (16.1%) out of 93 applicable derivations and validations with possible missing data. One (1.1%) study reported that a multiple imputation method was used. Information on risk group creation was provided in 25 (25%).

Results (TRIPOD items 13–17)

The flow of participants was reported in 21 (21%) of the derivations and validation studies. Thirty-four (34%) reported information about the prevalence of participants with any missing values, 28 (28%) reported the number of participants with missing data for each predictor, while 7 (7%) reported that there were no missing data.

Measures of discrimination were reported in 81 (81%) of the derivation and validation studies with c-statistic being the most commonly used measure (79%); measures of calibration were reported in 5 (5%), all of which used the Hosmer-Lemeshow test. Sensitivity and specificity

were both reported in 28 (28%) while net reclassification improvement and predictive values were reported in 13 (13%) and 11 (11%) respectively.

2.5.5 Reporting of essential items relevant to all validations

Results of reporting of essential items relevant to validation studies only are presented in Table 3.

Methods (TRIPOD items 4–12 relevant to validations only)

Among the 96 validation studies, 17 (17.7%) mentioned either similarities or differences in definitions of all four of setting, eligibility criteria, predictors, and outcomes between the validation and derivation of the model. Similarly, the distribution of important variables of at least age and sex was presented along with the development study counterparts for 21 (21.9%) of the validations.

As for model evaluation, the type of external validation (e.g. temporal, geographical, or methodological) was provided for 94 (97.9%) of the validation studies. The majority or 64 (66.7%) of the external validations were geographical. Of the 96 external validations, 23 were external model validations with model updating.

2.5.6 Reporting of essential items applicable to validations with updating only

Table 4 presents the results of reporting of essential items that are applicable to validation studies with updating only. A rationale for updating the model was provided by all 23 studies. Two (8.7%) studies reported that they have attempted to update the model with less extensive

revisions prior to considering more extensive revisions. One study reported applying a method of shrinkage of predictor weights or regression coefficients. When it comes to reporting the results of the updated models, 13 (56.5%) of the studies reported such results (e.g. model specification, model performance, recalibration).

2.6. Discussion

2.6.1 Summary of main findings

We assessed the quality of reporting of derivation and validation studies of prediction models for the prognosis of recurrent stroke in patients with TIA and minor stroke. We found inadequate reporting against selected items in TRIPOD. Items that were especially poorly reported included an informative title, blind assessment of outcome and predictors, sample size justification, use of shrinkage methods, reporting and handling of missing data, reporting of all performance measurements, and comparability between the validation and derivation dataset. Source of data, eligibility criteria, and study setting had better quality of reporting.

Incomplete reporting of blinding is detrimental to assessment of risks of bias and appraisals of the quality of prognostic models. Inadequate sample sizes, a common problem with prediction models, could lead to overfitting and the performance of a prognostic model being overestimated [36, 37]. Sample size justifications for derivation and validation studies are often based on the concept of events per variable (EPV) [10]. However, there is disagreement as to what the EPV should be [10, 38]. More recently, sample size calculation methods have been developed based on the total number of participants, the number of events relative to the number of potential

candidate predictor parameters, the outcome proportion (incidence) in the study population, and the expected predictive performance of the model [36]. Missing data can present several problems including reduction in statistical power, bias in the estimation of parameters due to data loss, reduction in representativeness of the samples, and complications in the analysis of the study leading to invalid conclusions such as distorted performance of the prediction model [39]. Failure to adequately report on measures of discrimination and calibration prevents users from making informed decisions about the likely accuracy of the model when used in practice. When validating a model externally, similarities or differences in setting, eligibility criteria, predictors, and outcomes between the validation and derivation dataset need to be reported to understand the extent of reproducibility and generalizability of the model.

As in other systematic reviews, we found that some items are less well reported than others. Although it would be ideal to have all items completely reported, they are not equally important for the appraisal of a prediction model's performance. However, they are all still important for the likelihood of future validation and uptake in clinical practice. For example, if information on handling of missing data is not reported, we cannot be certain of the true performance of the prediction model; on the other hand, if the title is not adequately reported as recommended in the TRIPOD statement, it does not mean that the quality of the prediction model is compromised, although retrieval of studies for possible updating would be compromised.

2.6.2 Comparison with other reviews

Our findings are comparable to those in several other systematic reviews of prediction models, published prior to and after the publication of the TRIPOD statement. A systematic review by Heus et al. assessed reporting quality of prediction model studies within 37 clinical domains [20]. Their review excluded studies published prior to the publication of the TRIPOD statement in 2015. Reporting of background information, missing data, and calibration were better than in our review which may be explained by the fact that their review focused on high-impact journals only. Jiang et al. [21] studied the quality of reporting of derivation and validation of melanoma prediction model studies with no restriction on the date of publication. Their findings aligned with our findings although they found better reporting of blinding of predictors and comparability of validation and derivation datasets. A recent systematic review by Najafabadi et al. examined pre- and post- TRIPOD publications in seven high-impact medical journals and found that although there have been some improvements in the methodological conduct, such as better reporting of missing data, use of multiple imputations, reporting the full prediction model and reporting information on performance measures, the overall quality of reporting has not improved [25].

2.6.3 Strengths and limitations

To our knowledge, this is the first systematic review specifically evaluating the reporting quality of derivation and validation studies of prediction models for the prognosis of stroke in patients with TIA. Our results add to the growing number of studies finding poor reporting quality of prediction models.

Our study has some limitations. Although we did not extract information on all TRIPOD items, we extracted and reported most items with an emphasis on reporting rather than methodological conduct. An item that we missed extracting was the reporting of a full model equation. Although we have attempted to extract information on each item in accordance with the TRIPOD statement, we may have been overly conservative in our assessment of some items: for example, we considered blinding of outcome and predictors as reported if and only if they were explicitly mentioned by the authors.

Although we have searched through two of the major medical databases (Medline and Embase) with the help of two experienced medical librarians and with a sensitive search strategy, we may have missed some eligible articles due to inadequate reporting of information by some authors. In addition, we excluded five studies published in non-English languages due to language barriers. Furthermore, our search covered publications up to February 04, 2020, after which there may be additional publications. However, given that this is a review of the quality of reporting and the comparability of our findings to existing systematic reviews, it is unlikely that any possible missed articles would change the conclusion of this systematic review. A final limitation is that the fulltext screening and data extractions were conducted by a single reviewer. However, given the objective nature of many items, it is unlikely that there would have been substantial misclassification.

2.6.4 Conclusion

Current reporting of multivariable prediction models for the prognosis of stroke in patients with TIA do not meet TRIPOD requirements for reporting. Essential items in need of improvement are providing an informative title, providing a justification for the sample size, providing information on missing data and handling of missing data, blinding of outcome and predictors, applying and reporting a shrinkage method, and clear reporting around comparability between the validation and derivation cohorts when validating. An example prediction model for the prognosis of stroke with a high number of items reported is the validation of the Canadian TIA score study [40]. In addition to adhering to the TRIPOD statement, more comprehensive guidance with breakdown of items by study types and examples with templates would be helpful. In other words, to provide details of what is expected of authors for each item with examples and to provide templates for the authors working on prediction model development studies without external validation, prediction model development studies with external validation, and external model validation studies with or without model updating. In addition, transparent and complete reporting can be facilitated by journals and peer reviewers requiring that authors follow the TRIPOD guidelines when submitting a derivation or validation study. Finally, we found a large number of studies validating and updating existing models, in accordance with recommendations that a prediction model be updated rather than a new one created [35]. However, additional guidance is required with respect to validating and updating a prediction model.

2.7. Abbreviations

CHARMS: CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies;

EVP: Events per variable;

MeSH: Medical Subject Headings;

PRESS: Peer Review of Electronic Search Strategies;

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis;

PROBAST: Prediction model Risk Of Bias ASsessment Tool;

PROSPERO: The International Prospective Register of Systematic Reviews;

TIA: Transient ischemic attack;

TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

2.8. Acknowledgements

We are grateful to Lindsey Sikora and Amanda Hodgson, Health Sciences Research Liaison Librarians at the University of Ottawa, for their help in guiding us with the development of the search strategy.

2.9. Authors' Contributions

All authors contributed to the concept and design of the study. Article selection was performed by KEA and KY. Data were extracted by KEA. Data analyses were conducted by KEA. KEA, JJP, and MT assisted in interpreting the data. KEA wrote the first draft of the manuscript, which was revised by all authors. All authors approved the final version of the manuscript.

2.10. Funding

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2.11. Availability of data and materials

Not applicable

2.12. Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

2.13. Author details

[1]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. [2]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada. [3]Department of Emergency Medicine, University of Ottawa, Ottawa, Ontario, Canada. [4]Department of Medicine (Neurology), University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. [5]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

2.14. Tables

Table 2.1 Reporting of items applicable at article level

Characteristic	**Number (%) N=60**
Clear reporting in the title of the study as derivation or validation of a multivariable prediction model, the target population, and the outcome to be predicted	
Yes	15 (25.0)
Country of study	
UK	8 (13.3)
China	8 (13.3)
USA	7 (11.7)
Iran	5 (8.3)
Australia	4 (6.7)
Others	24 (40.0)
Unclear or not reported	4 (6.7)
Source and role of funders provided	
Yes	14 (23.3)

Table 2.2 Reporting of essential items applicable to both derivation and validation studies.

Characteristic	**Number (%) N=100**
GENERAL INFORMATION	
Rationale provided for the derivation or validation of the model	
Yes	66 (66.0)
Source of data	
Prospective cohort	60 (60.0)
Retrospective cohort - registry data	17 (17.0)
Retrospective cohort - data from past studies	12 (12.0)
Retrospective cohort - chart review	10 (10.0)
Unclear or not reported	1 (1.0)
Inclusion criteria (definition used for selection)	
TIA - Classical time-based definition	92 (92.0)
TIA - Tissue-based definition	5 (5.0)
Minor Stroke - Classical time-based definition	8 (8.0)
Minor Stroke - Tissue-based definition	1 (1.0)
Unclear or not reported	7 (7.0)
Time-based versus tissue-based inclusion criteria	
Time-based TIA/minor stroke	88 (88.0)
Tissue-based TIA/minor stroke	5 (5.0)
Unclear or not reported	7 (7.0)
TIA versus minor stroke inclusion criteria	
TIA only	85 (85.0)
Both TIA and minor stroke	8 (8.0)
Unclear or not reported	7 (7.0)
Definition used for outcome of stroke	
Clinical definition	73 (73.0)
Tissue-based definition	7 (7.0)
Unclear or not reported	20 (20.0)
Time of outcome prediction	
2-day	28 (28.0)
3-day	2 (2.0)
7-day	66 (66.0)
14-day	2 (2.0)
28-day	4 (4.0)
30-day	16 (16.0)

90-day	73 (73.0)
Additional outcome periods considered in study	8 (8.0)
1-year	2 (2.0)
3-year	4 (4.0)
14-year	2 (2.0)
Recruitment method	
Consecutive participants	50 (50.0)
Nonconsecutive sample	1 (1.0)
Unclear or not reported	49 (49.0)
Number of sites	
1	41 (41.0)
2	2 (2.0)
3	3 (3.0)
4	0 (0.0)
5-9	13 (13.0)
10+	38 (38.0)
Unclear or not reported	3 (3.0)
Setting	
Tertiary	48 (48.0)
Community	10 (10.0)
Tertiary and community	7 (7.0)
Unclear or not reported	35 (35.0)
Location	
Urban	50 (50.0)
Rural	0 (0.0)
Urban and rural	8 (8.0)
Unclear or not reported	42 (42.0)
Study dates were provided	
Yes	95 (95.0)
OUTCOME TO BE PREDICTED	
Same outcome definition (and method of measurement) used in all patients	
Yes	44 (44.0)
Explicitly stated that outcome was assessed without knowledge of the candidate predictors (i.e., blinded)	
Yes	24 (24.0)
CANDIDATE PREDICTORS	

All measurement predictors defined with information on how to measure	
Yes	63 (63.0)
All measurement predictors defined in terms of when to measure (e.g. pre hospital, blood pressure measurement time, etc)	
Yes	47 (47.0)
Explicitly stated that predictors were assessed blinded for outcome, and for each other	
Yes	12 (12.0)
SAMPLE SIZE	
Sample size justification provided (practical justification such as using existing study cohort or an RCT data is considered justified)	
Yes	49 (49.0)
Flow of participants provided through a flow diagram	
Yes	21 (21.0)
MISSING DATA	
Number of participants with any missing value (on any of predictors and outcomes) reported	
Yes	34 (34.0)
Number of participants with missing data for each predictor reported	
Yes	28 (28.0)
Number of participants lost to follow-up reported*	
Yes	17 (27.9)
No, unclear or not reported	44 (72.1)
Not applicable (retrospective cohort)	39 (39.0)
Handling of missing data*	
Complete case analysis	14 (15.1)
Predictor with missing values omitted	0 (0.0)
Single imputation	0 (0.0)
Multiple imputation	1 (1.1)
Not handled, unclear or not reported	78 (83.9)
Not applicable (there were no missing data)	7 (7.0)
MODEL PERFORMANCE	
Method used for calibration	
Calibration plot	0 (0.0)
Calibration slope	0 (0.0)

Hosmer-Lemeshow test	5 (5.0)
Unclear or not reported	95 (95.0)
Method used for discrimination	
C-statistic/AUC-ROC	79 (79.0)
D-statistic	0 (0.0)
Log-rank	2 (2.0)
Unclear or not reported	19 (19.0)
Classification measures reported	
Sensitivity	28 (28.0)
Specificity	28 (28.0)
Predictive values	11 (11.0)
Net reclassification improvement	13 (13.0)
Unclear or not reported	60 (60.0)
A priori cut points used for the classification measures	
Yes	25 (25.0)
Confidence intervals (CIs) provided for the performance measures	
Yes	65 (65.0)

* Denominator is the applicable cases

Table 2.3 Reporting of essential items applicable to validation studies only.

Characteristic	Number (%) N=96
COMPARISON WITH DERIVATION COHORT	
Mention of differences (or no difference) in definitions between the validation and the derivation cohort for each of the following	
Setting	17 (17.7)
Eligibility criteria	21 (21.9)
Predictors	21 (21.9)
Outcome	21 (21.9)
Unclear or not reported	71 (74.0)
Mention of differences (or no difference) in definitions between the validation and the derivation cohort	
Mentioned all four (setting, eligibility, predictors, outcome)	17 (17.7)
Some are mentioned	8 (8.3)
Unclear or not reported	71 (74.0)
Distribution of important variables (demographics [at least age and sex], predictors and outcome) presented along with the development study	
Yes	21 (21.9)
MODEL EVALUATION	
Type of external validation	
Temporal	4 (4.2)
Geographical	64 (66.7)
Methodological/Setting (different setting such as ED vs clinic)	26 (27.1)
Unclear or not reported	2 (2.1)
Model adjusted or updated	
Yes	23 (24.0)

Table 2.4 Reporting of essential items relevant to validation studies with updating only.

Characteristic	**Number (%) N=23**
Rationale provided for updating the model	
Yes	23 (100.0)
Authors showed that less extensive update methods were inadequate prior to considering more extensive revisions[a]	
Yes	2 (8.7)
If the model is derived or updated by methods (c) to (f), was any method of shrinkage of predictor weights or regression coefficients applied[b]	
Uniform shrinkage	0 (0.0)
Penalized estimation	0 (0.0)
Other (method by van Houwelingen)	1 (3.7)
Unclear or not reported	26 (96.3)
Results from model updating (i.e., model specification, model performance, recalibration) presented (i.e. updated intercept, regression coefficients, discrimination with CI or SE, calibration)	
Yes	13 (56.5)

[a] *Less extensive updates*: a) Recalibrating the intercept only, b) Recalibrating the intercept and adjust the other regression coefficients by a common factor, c) Category b plus extra adjustment of a subset of the existing coefficients to a different strength, and d) Category c plus adding new predictors. *Extensive revisions*: e) Re-estimating all of the original regression coefficients, and f) category e plus adding new additional predictors

[b] The denominator is 27 (N=4 derivations and N=23 external validation with updating)

2.15. Figures

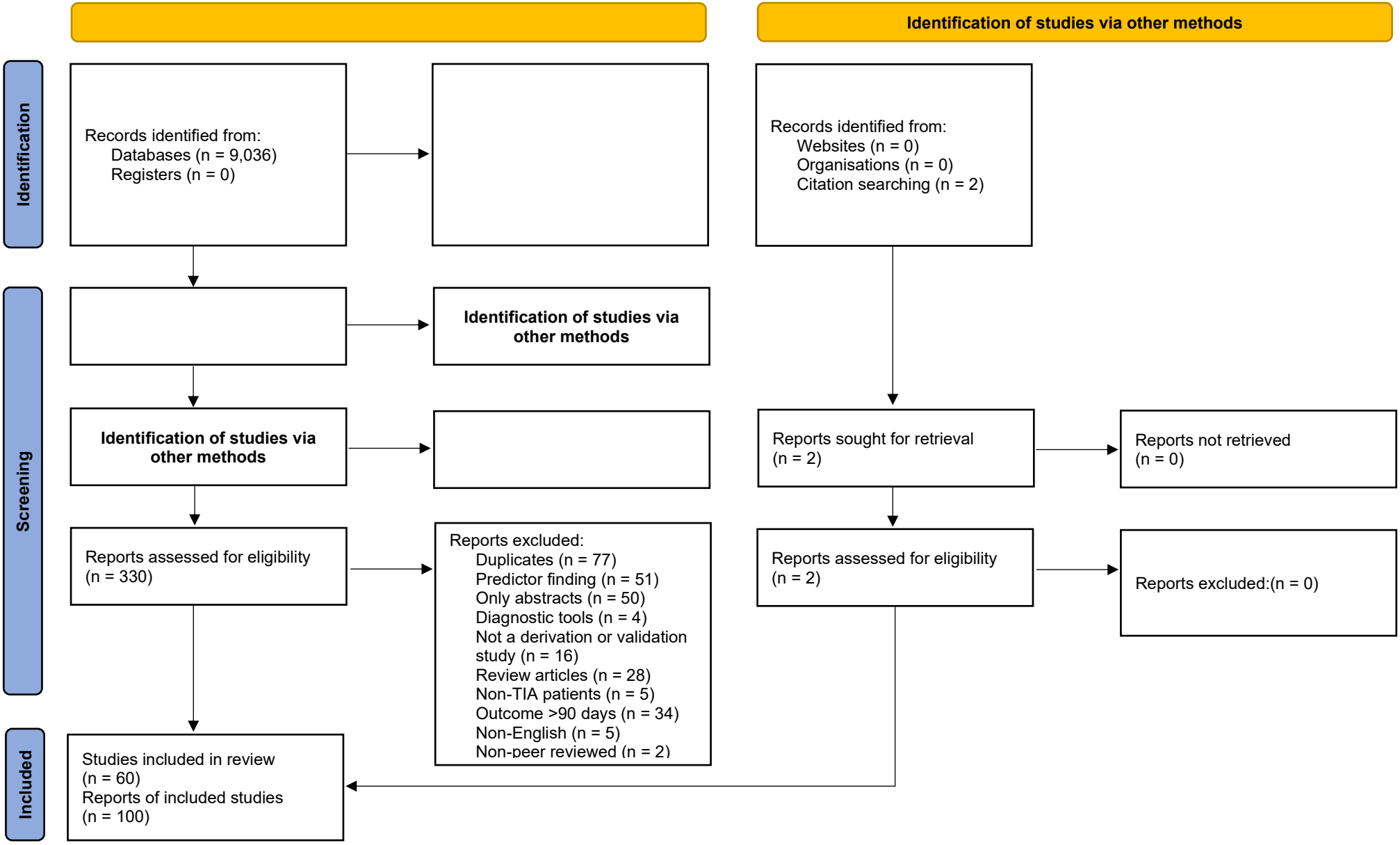

Identification of studies via other methods
Identification
Records identified from:
Databases (n = 9,036)
Registers (n = 0)
Records identified from:
Websites (n = 0)
Organisations (n = 0)
Citation searching (n = 2)
Screening
Identification of studies via other methods
Identification of studies via other methods
Reports sought for retrieval (n = 2)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 330)
Reports excluded:
Duplicates (n = 77)
Predictor finding (n = 51)
Only abstracts (n = 50)
Diagnostic tools (n = 4)
Not a derivation or validation study (n = 16)
Review articles (n = 28)
Non-TIA patients (n = 5)
Outcome >90 days (n = 34)
Non-English (n = 5)
Non-peer reviewed (n = 2)
Reports assessed for eligibility (n = 2)
Reports excluded:(n = 0)
Included
Studies included in review (n = 60)
Reports of included studies (n = 100)

Figure 2.1 Study selection adapted from PRISMA (30)

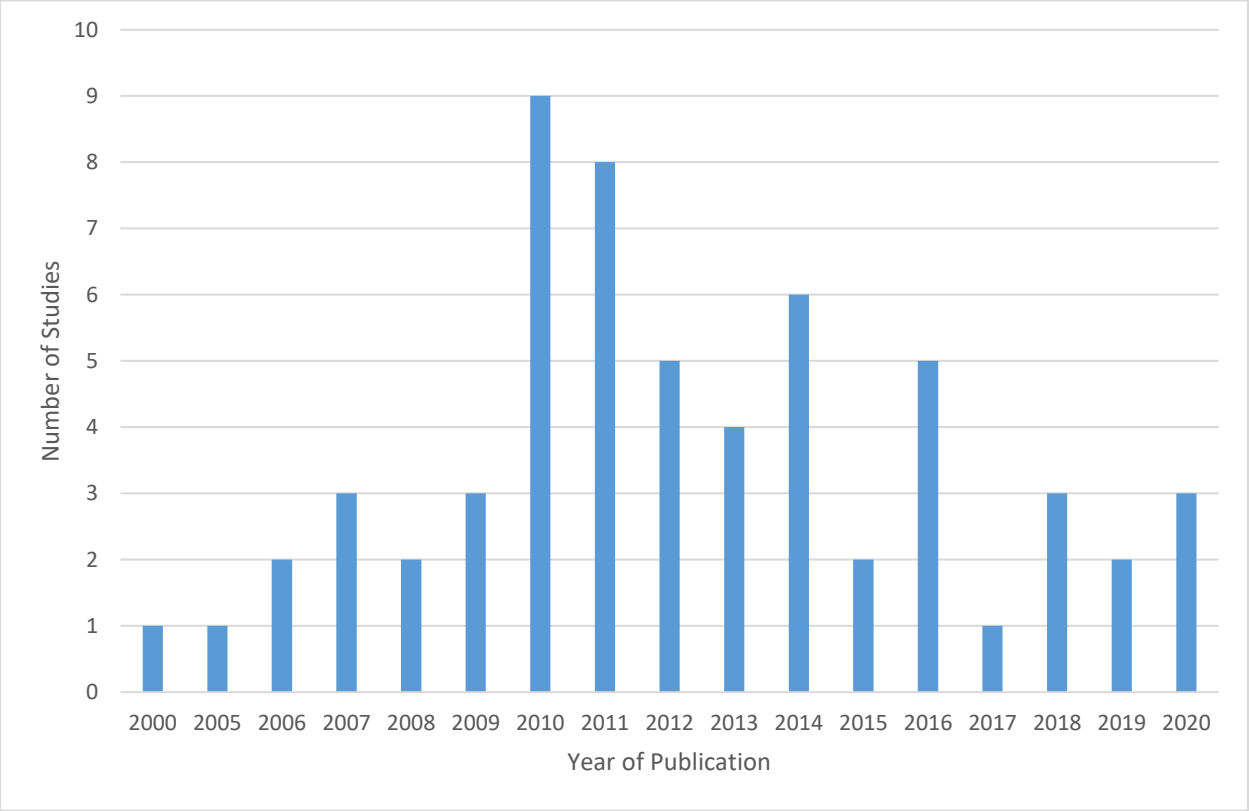
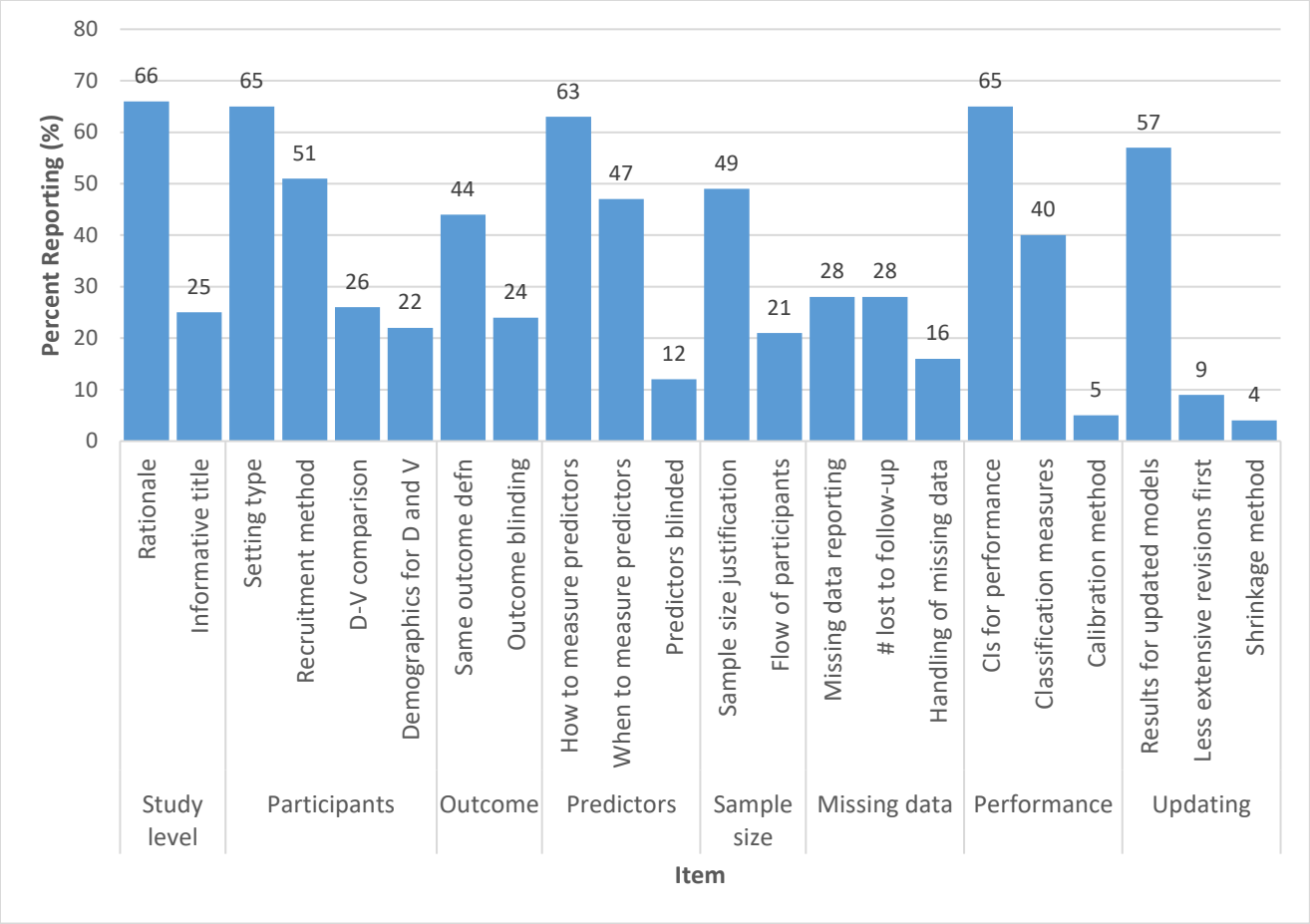


Figure 2.2 Distribution of included studies by year of publication



D, derivation; V, validation; CIs, confidence intervals

Figure 2.3 Summary of reporting quality: percentage of studies adhering to each reporting item

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2.17. Supplementary Information

2.17.1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			Page #
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6-7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Additional file 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8-9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Additional file 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Additional file 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	N/A
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
methods		intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	12
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Additional file 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
biases			
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	22-25
	23b	Discuss any limitations of the evidence included in the review.	25-26
	23c	Discuss any limitations of the review processes used.	25
	23d	Discuss implications of the results for practice, policy, and future research.	26
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	11
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	11
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	28
Competing interests	26	Declare any competing interests of review authors.	28
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	28

2.17.2 Table S1. Key items used to guide the framing of the review aim, search strategy, and study inclusion and exclusion criteria

Item	This Review
Prognostic versus diagnostic prediction model	Prognostic prediction models
Intended scope of the review	Models to inform physician's therapeutic decision making
Type of prediction modelling studies	Prediction model development without external validation Prediction model development with external validation External model validation with and without model updating
Target population to whom the prediction model applies	Patients diagnosed with TIA/Minor Stroke
Outcome to be predicted	Subsequent Stroke (whether primary or secondary outcome)
Time span of prediction	Subsequent Stroke within 90 days
Intended moment of using the model	Models to be used at the moment of diagnosis of TIA/Minor Stroke

2.17.3 Table S2. List of extracted items

Study Characteristics	
Title	• Reporting in the title of the study as derivation or validation of a multivariable prediction model (or synonyms), the target population, and the outcome to be predicted is reported in the title (Y/N). All the items need to be reported to score a yes.
Country of study	
Source and role of funders	• The source of funding is reported or there is explicit mention that there was no external funding involved AND the role of funders is reported when there was funding (Y/N).
Items applicable to both derivation and validation studies*	
Rationale	• Rationale for developing or validating the multivariable prediction model (Y/N). Any sort of rationale is considered.
Participants	• Study setting (tertiary, community, or both) • Location (urban, rural, or both) • Recruitment method (consecutive, nonconsecutive participants) • Number of centres • Definition (multi-select) used for inclusion of participants (Time-based TIA, tissue-based TIA, time-based minor stroke, tissue-based minor stroke)
Source of data	• Source of data (prospective, retrospective registry, retrospective chart review, retrospective data from previous studies)
Study dates	• Study start date and end dates are both provided (Y/N)
Outcome	• Definition used for outcome (clinical, tissue-based) • Timing of outcome (2-day, 7-day, 30-day, 90-day, others) • Same outcome definition and method of measurement used in all patients (Y/N). Authors should indicate that an attempt was made to ensure the same definition was used for all patients. For example, for retrospective cohorts it is possible that stroke was defined differently for some of the patients based on medical imaging. It has to be clear that the same definition is used otherwise we flag as unclear (that we have grouped together into a No). • Outcome assessed without knowledge of the candidate predictors (Y/N). For retrospective studies it is possible that the outcome was assessed after information about predictors was reviewed in a chart. Authors need to clearly state that.
Candidate predictors	• All measurement predictors defined with information (enough to be able to replicate) on how to measure (Y/N). If no measurement predictors are present we select a yes. If multiple measurement predictors are available, information on all need to be provided in order to score a yes.

	• All measurement predictors defined with information on when to measure (Y/N). As with above, we score a yes if no measurement predictors were available. • Clear description whether predictor assessments were blinded for outcome and for each other (Y/N)
Sample size	• Sample size justification is provided (Y/N). It is explained how the study sample size was arrived at such as statistical grounds or practical/logistical grounds (e.g. an existing study cohort or data set of a RCT)
Missing data	• Number of participants with any missing value for the outcome or predictors reported (Y/N) • Number of participants with missing data for each predictor reported (Y/N) • Number of participants lost to follow-up reported in case of prospective cohorts (Y/N) • How missing data was handled (complete case analysis, predictor with missing values omitted, single imputation, multiple imputation, Not handled/unclear or not reported, or not applicable if there were no missing data). If there is no missing data, there should be an explicit mention that there is no missing data for all predictors and outcome, otherwise it will be considered unclear or not reported.
Model performance	• Method was used for calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) • Method used for discrimination (C-statistic/AUC, D-statistic, log-rank) • Which classification measures are reported (sensitivity, specificity, predictive values, net reclassification improvement) • Explicitly mentioned that a priori cut-points were used for the classification measures or not (Y/N) • Is the confidence interval (or standard error) for at least the discrimination measure presented? (Y/N)
Items applicable to validation studies only	
Comparisons with development study	• Differences or similarities in definitions with the development study are described. Mentioning of similarities or differences in each of the four (setting, eligibility criteria, predictors and outcome) as a multi-select • Distribution of important demographic variables (at least age and sex), are presented along with the development study (Y/N)
External validation type	• The type of external validation (temporal, geographical, methodological/setting (different setting such as ED versus clinic))
Model update	• Was the model updated? (Y/N)

Items applicable to model updating studies only	
Rationale for update	• Is a clear rationale provided for updating the model (Y/N)? Any rationale for trying to come up with a 'better' prediction model is accepted
Priority of update	• Have the authors shown that less extensive updating methods were inadequate prior to considering more extensive revisions? (Y/N). *Less extensive updates include*: a) Recalibrating the intercept only, b) Recalibrating the intercept and adjust the other regression coefficients by a common factor, c) Category b plus extra adjustment of a subset of the existing coefficients to a different strength, and d) Category c plus adding new predictors}. *Extensive revisions include*: e) Re-estimating all of the original regression coefficients, and f) category e plus adding new additional predictors
Shrinkage method	• If the model is derived or updated by methods (c) to (f) above, method of shrinkage of predictor weights or regression coefficients applied (No shrinkage, uniform shrinkage, penalized estimation, other)
Results of update	• If the model is updated, are the results from model updating (i.e., model specification, model performance, and recalibration) presented? (i.e. updated intercept, regression coefficients, discrimination with CI or SE, calibration) (Y/N). A minimum of discrimination is required to answer Yes.

2.17.4 Literature Search Strategy

Medline:

1 exp Stroke/
2 stroke.tw.
3 (cerebrovascular adj1 accident*).tw.
4 (cerebral adj1 vascular adj1 accident*).tw.
5 (cva or cvas).tw.
6 (cerebral adj1 accident*).tw.
7 (brain adj1 isch?emia).tw.
8 (cerebral adj1 isch?emia).tw.
9 (cerebrovascular adj1 isch?emia).tw.
10 (cerebral adj1 vascular adj1 isch?emia).tw.
11 (cerebral adj1 infarction).tw.
12 (brain adj1 infarction).tw.
13 (brain adj1 stem adj1 infarction).tw.
14 (cerebrovascular adj1 apoplex*).tw.
15 (brain adj1 vascular adj1 accident*).tw.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 Ischemic Attack, Transient/
18 (tia or tias).tw.
19 (transient adj1 isch?emic adj1 attack*).tw.
20 (transient adj1 brain adj1 attack*).tw.
21 (transient adj1 cerebral adj1 attack*).tw.
22 (transient adj1 cerebral adj1 isch?em*).tw.
23 (transient adj1 brain adj1 stem adj1 isch?em*).tw.
24 (transient adj1 brainstem adj1 isch?em*).tw.
25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 decision support techniques/
27 Prognosis/mt [Methods]
28 Nomograms/
29 nomogram*.tw.
30 (predict* adj2 model*).tw.
31 (predict* adj2 rule*).tw.
32 (predict* adj2 score*).tw.
33 (decision adj2 model*).tw.
34 (decision adj2 rule*).tw.
35 (decision adj2 score*).tw.
36 (risk adj2 model*).tw.
37 (risk adj2 rule*).tw.
38 (risk adj2 score*).tw.
39 (decision adj2 aid).tw.

40 validation.tw.
41 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42 16 and 25 and 41

Embase:

1 exp cerebrovascular accident/

2 stroke*.tw.

3 (cerebrovascular adj1 accident*).tw.

4 (cerebral adj1 vascular adj1 accident*).tw.

5 (cva or cvas).tw.

6 (cerebral adj1 accident*).tw.

7 (brain adj1 isch?em*).tw.

8 (cerebral adj1 isch?em*).tw.

9 (cerebrovascular adj1 isch?em*).tw.

10 (cerebral adj1 vascular adj1 isch?em*).tw.

11 (cerebral adj1 infarction*).tw.

12 (brain adj1 infarction*).tw.

13 (brain adj1 stem adj1 infarction*).tw.

14 (cerebrovascular adj1 apoplex*).tw.

15 (brain adj1 vascular adj1 accident*).tw.

16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17 transient ischemic attack/

18 (tia or tias).tw.

19 (transient adj1 isch?emic adj1 attack*).tw.

20 (transient adj1 brain adj1 attack*).tw.

21 (transient adj1 cerebral adj1 attack*).tw.

22 (transient adj1 cerebral adj1 isch?em*).tw.

23 (transient adj1 brain adj1 stem adj1 isch?em*).tw.

24 (transient adj1 brainstem adj1 isch?em*).tw.

25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26 decision support system/

27 prognosis/

28 nomogram/

29 nomogram*.tw.

30 ((predicti* or decision? or prognos* or risk? or derivation? or derive? or develop* or validation? or validate? or refinement? or refine? or computer or web-based) adj5 (model? or rule? or scori* or score? or tool? or index or indexes or indices or scale? or algorithm? or nomogram? or aid? or aided or support or system? or criteria or stratif* or identification or calculator? or instrument?)).tw.

31 ((scori* or score?) adj5 (model? or rule? or tool? or index or indexes or indices or scale? or algorithm? or nomogram? or aid? or aided or support or system? or criteria or stratif* or identification or calculator? or instrument?)).tw.

32 validation.tw.

33 algorithm.tw.

34 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 16 and 25 and 34

2.17.5 List of included studies.

1. Johnston SC, Hamilton-Bruce MA, Price C, et al. Short-term Prognosis After Emergency Department Diagnosis of TIA. *JAMA*. 2000;284(22):2901. doi:10.1001/jama.284.22.2901

2. Rothwell P, Giles M, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366(9479):29-36. doi:10.1016/S0140-6736(05)66702-5

3. Cucchiara BL, Messe SR, Taylor RA, et al. Is the ABCD score useful for risk stratification of patients with acute transient ischemic attack? *Stroke*. 2006;37(7):1710-1714. doi:10.1161/01.STR.0000227195.46336.93

4. Tsivgoulis G, Spengos K, Manta P, et al. Validation of the ABCD score in identifying individuals at high early risk of stroke after a transient ischemic attack: A hospital-based case series study. *Stroke*. 2006;37(12):2892-2897. doi:10.1161/01.STR.0000249007.12256.4a

5. Koton S, Rothwell PM. Performance of the ABCD and ABCD2 scores in TIA patients with carotid stenosis and atrial fibrillation. *Cerebrovasc Dis*. 2007;24(2-3):231-235. doi:10.1159/000104483

6. Bray JE, Coughlan K, Bladin C. Can the ABCD Score be dichotomised to identify high-risk patients with transient ischaemic attack in the emergency department? *Emerg Med J*. 2007;24(2):92-95. doi:10.1136/emj.2006.041624

7. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*.

2007;369(9558):283-292. doi:10.1016/S0140-6736(07)60150-0

8. Selvarajah JR, Smith CJ, Hulme S, et al. Prognosis in patients with transient ischaemic attack (TIA) and minor stroke attending TIA services in the North West of England: The NORTHSTAR Study. *J Neurol Neurosurg Psychiatry*. 2008;79(1):38-43. doi:10.1136/jnnp.2007.129163

9. Sciolla R, Melis F. Rapid identification of high-risk transient ischemic attacks: Prospective validation of the ABCD score. *Stroke*. 2008;39(2):297-302. doi:10.1161/STROKEAHA.107.496612

10. Fothergill A, Christianson TJH, Brown RD, Rabinstein AA. Validation and refinement of the ABCD2 score: A population-based analysis. *Stroke*. 2009;40(8):2669-2673. doi:10.1161/STROKEAHA.109.553446

11. Ay H, Arsava EM, Johnston SC, et al. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: The CIP model. *Stroke*. 2009;40(1):181-186. doi:10.1161/STROKEAHA.108.521476

12. Cucchiara BL, Messe SR, Sansing L, et al. D-dimer, Magnetic Resonance Imaging Diffusion-weighted Imaging, and ABCD2 Score for Transient Ischemic Attack Risk Stratification. *J Stroke Cerebrovasc Dis*. 2009;18(5):367-373. doi:10.1016/j.jstrokecerebrovasdis.2009.01.006

13. Tsivgoulis G, Stamboulis E, Sharma VK, et al. Multicenter external validation of the ABCD2 score in triaging TIA patients. *Neurology*. 2010;74(17):1351-1357. doi:10.1212/WNL.0b013e3181dad63e

14. Sheehan OC, Kyne L, Kelly LA, et al. Population-based study of ABCD2 score, carotid stenosis, and atrial fibrillation for early stroke prediction after transient ischemic attack: The North Dublin TIA study. *Stroke*. 2010;41(5):844-850. doi:10.1161/STROKEAHA.109.571844

15. Ong MEH, Chan YH, Lin WP, Chung WL. Validating the ABCD2 Score for predicting stroke risk after transient ischemic attack in the ED. *Am J Emerg Med*. 2010;28(1):44-48. doi:10.1016/j.ajem.2008.09.027

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3. STROKE PREVENTION CLINICS

Manuscript 2: Practice Variation among Canadian Stroke Prevention Clinics: Pre, During and Post-COVID-19

3.1. Preface to manuscript 2

This chapter presents the manuscript of the second objective of the thesis which is a survey of stroke prevention clinics across Canada to study the variation of practiced in TIA/minor stroke patient management which is published in The Canadian Journal of Neurological Sciences in 2022 as:

> Abdulaziz, K., Taljaard, M., Dowlatshahi, D., Stiell, I., Wells, G., & Perry, J. (2022). Practice Variation among Canadian Stroke Prevention Clinics: Pre, During and Post-COVID-19. Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 1-28. doi:10.1017/cjn.2022.260

KEA was responsible for the study design with contributions from all authors. KEA conducted interviews, executed the surveys, conducted analyses, and wrote the draft manuscript. All authors contributed to the final manuscript review.

Supporting information on this manuscript are provided in appendix 7.2. This study has received Ottawa Health Science Network Research Ethics Board approval.

3.2. Abstract

Background: Stroke is a common and serious disorder. With optimal care, 90-day recurrent stroke risk can be reduced from 10% to about 1%. Stroke prevention clinics (SPCs) can improve patient outcomes and resource allocation but lack standardization in patient management. The extent of variation in patient management among SPCs is unknown. Our aims were to assess baseline practice variation between Canadian SPCs and the impact of COVID-19 on SPC patient care.

Methods: We conducted an electronic survey of 80 SPCs across Canada from May to November 2021. SPC leads were contacted by email with up to five reminders.

Results: Of 80 SPCs contacted, 76 were eligible from which 38 (50.0%) responded. The majority (65.8%) of SPCs are open 5 or more days a week. Tests are more likely to be completed before the SPC visit if referrals were from clinic's own emergency department compared to other referring sources. COVID-19 had a negative impact on routine patient care including longer wait times (increased for 36.4% clinics) and higher number of patients without completed bloodwork prior to arriving for appointments (increased for 27.3% clinics). During COVID-19 pandemic, 87.9% of SPCs provided virtual care while 72.7% plan to continue with virtual care post-COVID-19 pandemic.

Conclusion: Despite the time-sensitive nature of transient ischemic attack patient management, some SPCs in Canada are not able to see patients quickly. SPCs should endeavor to implement strategies so that they can see high-risk patients within the highest risk timeline and implement strategies to complete some tests while waiting for SPC appointment.

3.3. Introduction

Stroke is a common disorder, and a leading cause of death and disability worldwide.[1] Transient ischemic attack (TIA) or minor stroke patients (here onwards just called TIA) are at elevated risk of a subsequent stroke in the days to weeks following their initial event.[2,3] Up to 10% of patients with TIA will have a subsequent stroke within 90 days without urgent care, but with optimized treatment this risk can be reduced to about 1%.[4,5] The urgency and level of care provided for TIA patients often depends on the perceived risk of subsequent major stroke.[6,7] Traditionally, and still in some parts of the world, TIA patients were admitted to hospital for rapid investigation and comprehensive management.[8] In an effort to optimize health resource utilization with improved patient outcomes, outpatient-based models have been introduced.[8–11] A stroke prevention clinic (SPC) is a specialized outpatient clinic that provides rapid access to experts, diagnostic tests, and treatments. Such clinics are meant to provide an integrated, comprehensive, and interdisciplinary approach to stroke prevention in a timely manner.

In Canada, the Canadian Stroke Best Practice Recommendations (CSBPR) provide guidelines for the prevention and management of stroke.[12] However, we suspect that they are not always followed, for varying reasons, leading to variation in how patients with suspected TIA are identified and managed.[13,14] For example, although CSBPR suggests managing high-risk patients within 48 hours of symptom onset, we suspect that not all organizations meet this recommendation. From information-gathering interviews with local neurologists (key informants), we found that some SPCs might (a) be open limited hours a week, (b) triage patients without assessing and considering risk levels, (c) have protocols in place to have patients complete some tests prior to their clinic appointment, (d) have long wait times for some tests

which varies depending on referring source, and (e) lack urgent communication protocols between SPCs and radiology departments. The extent of variation in practice is unknown. Understanding the extent of variation in practice can help develop or modify strategies and guidelines to standardize practices across SPCs which may ultimately reduce the incidence of subsequent stroke.

To understand the extent of variation we conducted a survey of all Canadian SPCs. Prior to implementing the survey, the COVID-19 pandemic started and so we modified our questionnaire to include additional items to understand the impact of the COVID-19 pandemic on TIA patient management.

The aims of this study were twofold: (1) to describe variation in management practices for TIA patients and (2) to characterize the impact of the COVID-19 pandemic on the management of TIA patients including the use of virtual care by the SPCs.

3.4. Methods

3.4.1 Study design and participants

We conducted a self-administered electronic survey of SPCs in Canada. To be eligible, the respondents must have been physician leads, managers, or coordinators at any of the SPCs in Canada. A list of SPCs was provided by the Heart and Stroke Foundation of Canada from which we identified 80 unique SPCs as of May 5, 2021. We obtained the contact information of the

person running each SPC using web searches and by calling the clinics. The study was conducted from May 2021 through November 2021. We designed the survey following Dillman's techniques.[15] This study has received Ottawa Health Science Network Research Ethics Board approval.

3.4.2 Questionnaire development

We developed the questionnaire in three stages. First, we conducted telephone interviews with key informants to gather information to prepare a draft survey questionnaire. Second, we conducted cognitive interviews (assessing participants' understanding of the questionnaire as they complete each question) to evaluate the clarity, comprehensibility, and face validity of each question in the draft survey. Third, we pilot tested the draft survey questionnaire using a smaller subsample of the SPCs to assess the whole questionnaire and the survey process.[15]

The final questionnaire included 36 questions. Questionnaires consisted of an eligibility question, information about clinic hours of operation and scheduling (14 items), medical imaging (13 items), bloodwork and medications (three items), impact of the COVID-19 pandemic (five items), and additional information (one item). To improve response rate, most items (including questions on wait times) were designed as closed-ended questions where respondents' answers were limited to a fixed set of responses. The questionnaire was developed with attention to clarity regarding question applicability to the pre-pandemic period. The questionnaire, landing page, recruitment, and reminder emails were translated into French by a medical translator.

3.4.3 Survey administration

The survey invitation was personalized for each SPC so that the lead's name was inserted on all emails along with a unique link for each clinic. Every email and the landing page of the survey included names of the lead principal investigators, contact information, and affiliations, as an indication of a legitimate source.

We pilot tested the survey on 15 SPCs across the provinces and territories. After revising the survey questionnaire for clarity and verifying the feasibility of the process (i.e., our survey questions were answered as intended), invitations were distributed to the remaining 65 SPCs.

The survey was initiated with a recruitment email containing both official languages (English and French) and links to the survey powered by SurveyMonkey (www.surveymonkey.com). A reminder email along with links to the survey questionnaire was emailed every week to non-responders for up to 4 weeks. A final reminder was initiated 2 weeks after the last email reminder by calling the clinic. Several attempts were made to reach clinics by telephone over a period of 3 weeks.

3.4.4 Data analysis

We calculated descriptive statistics to characterize the SPC responses. Continuous variables were expressed as mean and standard deviation or median with interquartile ranges (IQR), while

categorical data were expressed as frequencies and percentages. We used boxplots to help visualize the distribution of some of the continuous variables. Chi-squared tests were conducted to compare the geographic region (Western Canada, Ontario, and Eastern Canada) of respondents and non-respondents to examine the possibility of non-response bias. We used Fisher's exact test to study the association between seeing high-risk patients within 48 hours and number of days clinics are open. Two-sided significance tests were set at an alpha level of 0.05.

We grouped data based on referring source and other characteristics to organize the results. To reduce the number of items in the tables, we combined categories with sparse numbers. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

3.5. Results

3.5.1 General results

Of 80 SPCs invited, four indicated they were ineligible (by answering "no" to the question: "are you the physician lead or coordinator/manager of the SPC or answering on his/her behalf?"). Of the remaining 76 SPCs, 38 (50.0%) completed the electronic survey (including eight from the pilot survey and four from final phone reminders). Five respondents provided partial responses.

Table 1 describes the structure of the SPCs. The clinics were open from half a day per week (2.6%) up to 7 days per week (2.6%) with about a quarter (26.3%) being open 2 days or fewer

per week. Two thirds (63.2%) of the clinics were open 5 days a week. Clinic hours varied from less than 4 hours to more than 12 hours per day. Table 2 shows that there is a significant difference in being able to see most high-risk TIA patients within 48 hours and how many days the clinics are open during the week. A small portion (10.5%) of the clinics do not accommodate urgent patients. Patient referrals to the clinics are mostly from their own emergency departments (EDs) (median percentage of patients referred (IQR): 50 (40-70)) followed by family physicians (median (IQR): 20 (15-30)). The initial diagnosis of TIA was confirmed less often when the referral was from family physicians (median (IQR): 30 (20-50)) compared to the organization's own ED, other EDs, or other specialists. Except for one clinic (2.6%), all the clinics use an appointment system that considers patient risk level. The clinic that does not consider risk levels normally sees all patients within a week. For clinics that do consider patient risk levels, the wait times for low-risk patients are within 30 days for 64.8% of SPCs. Wait times for high-risk patients are within 24 hours for 8.1% of SPCs and between 1 to 2 days for 29.7% of SPCs. We found that 29.0% of the clinics do not a have a protocol in place to consult neurology while the patient is in the ED while 32.3% consult neurology for high-risk patients only. We found 60.0% of the organizations admit patients for revascularization directly from the ED. Two clinics are not able to bypass normal wait times for vascular imaging for urgent cases.

To test for the possibility of non-response bias, we compared the geographic region (Western Canada, Ontario, and Eastern Canada) of respondents and non-respondents. Chi-squared analysis showed no indication of a significant difference (p value: 0.17) in responses when we compared the regions (Table 3). We did not have other characteristics to test for non-response bias.

Figure 1 provides the proportion of patients with completed tests at the SPC assessment. When referrals were from the organization's own ED, most tests were already completed. There was more variation for family physician and other specialist referrals. MRI, 24-hour heart rate monitoring, and echocardiogram were the least likely to be completed at the time of SPC assessments.

Duration of waiting times for test results is as follows: for CT, 77.8% within 24 hours and 11.1% between 1 and 7 days; for MRI, 43.8% within 24 hours and 31.3% between 1 and 7 days; for Doppler ultrasound 51.6% within 24 hours and 25.8% between 1 and 7 days; for echocardiogram 15.2% within 24 hours while 36.4% between 1 and 7 days; for Holter 30.3% between 1 and 7 days and 33.3% between 8 and 14 days; for bloodwork 45.5% within 24 hours and 45.5% between 1 and 7 days (Figure 2).

3.5.2 Virtual Care and Impact of COVID-19 Pandemic on TIA Stroke Patient Management

Prior to the COVID-19 pandemic, 13 (39.4%) of the 33 SPCs were providing virtual care on a limited basis. During the pandemic, all but 4 (12.1%) SPCs were providing virtual care, with 60.6% providing virtual care for more than half of their patients; 15.2% of the clinics operated only virtual clinics. Among the 29 clinics that provided virtual care to patients during the pandemic, 20.7% of the clinics provided virtual care to all patients, 41.4% provided virtual care for low to medium-risk patients, and 31.0% provided virtual care for follow-ups and new consultations (Table 4). A large percentage (72.7%) of the 33 clinics plan to provide virtual care post-COVID-19 pandemic (Figure 3).

Figure 4 shows the impact of the COVID-19 pandemic on SPCs patient management. Compared to pre-COVID period, the most impacted services by the COVID-19 were the number of referrals from family physicians (declined for 36.4% clinics), wait times once a patient was referred to the clinic (increased for 36.4% clinics), number of patients having already completed bloodwork prior to arriving for their appointment (declined for 27.3% clinics), number of referrals from the clinic's own ED (increased for 24.2% clinics), and proportion of true TIA patients versus mimics (increased for 24.2% clinics).

3.6. Discussion

3.6.1 Summary of main findings

We found substantial variation among SPCs in management practices such as hours of operation, duration of wait times to see high-risk patients, capacity for add-on urgent patients, tests completed prior to SPC appointment, time for results, and referrals of patients with incorrect diagnosis of TIA. Although time is essential for TIA patient management, most high-risk patients are not seen by the clinics within 2 days, the highest risk period. To compensate for this, most are not seen routinely in the ED by neurology either. Thus, many of the high-risk patients are not being seen quickly enough within 48 hours to meet existing recommendations. SPCs also reported that on average about half of the patients are incorrectly diagnosed and referred to the clinics; thus, impacting wait times for true TIA patients. Wait times for testing are often short

except for echocardiogram and Holter. There is a significant variation in the duration of Holter monitoring.

We found a substantial impact of COVID-19 on clinic routines. There was a substantial decline in referrals to SPCs, especially from family physicians, increase in wait times for appointments and test results, and a decline in TIA mimic referrals. While a small portion of SPCs were making use of virtual care prior to COVID-19, a significant portion of the clinics are planning to use virtual care post-COVID-19.

3.6.2 Interpretations

TIA is a medical emergency that requires urgent management to prevent subsequent stroke. The risk of stroke is greatest in the first few days after a TIA with stroke rates as high as 8% within the first 2 days of TIA.[2] Hence, there is need for urgent intervention depending on stroke risk level. Admission of all patients is an inefficient use of health resources.[16] Our data show that a significant percentage of SPCs are open 3 days or fewer per week with a quarter only open 2 days or less per week. We suspect that the clinics opening three or fewer days per week are situated in low-populated areas, such as remote or rural areas. Our results show clinics open three or fewer days a week are unable to see most of their high-risk patients within 48 hours. A possible explanation for this is that there might be a high volume of referrals to the clinics but not enough resources to open the clinics more often. About half of the clinics open 4 or more days per week are also unable to see most of their high-risk patients within 48 hours.

Referrals to SPCs are initiated from EDs, family physicians, or specialists. Referrals should be triaged based on patient's risk of subsequent stroke. Advanced clinical prediction rules, such as the Canadian TIA Score, have been developed and validated for identifying low, medium, and high-risk patients.[17,18] Other clinical prediction rules have been developed and validated for identifying low-risk and high-risk patients including the $ABCD^2$ and $ABCD^2i$ Scores.[19–21] However, there are some limitations with clinical prediction rules such as accuracy and non-availability of all the factors during the referral.

In Canada, national guideline recommendations have been developed by Heart and Stroke Foundation of Canada for the management and treatment of TIA patients.[12] All patients suspected with TIA should complete neurologic and cardiac examination including imaging, bloodwork, electrocardiogram, echocardiogram for select patients and, if no etiology found extended cardiac monitoring.[22–24] TIA patients require optimization of antithrombotic agents (anticoagulants or antiplatelets) and prompt carotid revascularization for symptomatic carotid artery stenosis if present.[22] The Canadian Stroke Best Practice Recommendations are not always followed, for varying and possibly valid reasons, leading to variations of practice. Not adhering to the guidelines might be out of the control of SPC personnel such as competing priorities.

Having tests completed prior to the SPC appointment could expedite diagnosis and treatment. Our data show investigations were often done prior to SPC assessment for referrals from the organization's own ED. There was less variation among the organization's own EDs while there was a wide variation among family physicians and specialists. This shows that there are likely

better protocols in place for the organization's own ED while there is less coordination for inter-organizational referrals. Standardization of community referrals may help decrease variability. However, we acknowledge that it would be challenging to reach and impose standardized referrals in some jurisdictions. In addition, unless a solution is found and implemented to reduce TIA mimics, diagnostic imaging departments could be swamped with test requests if all tests were to be completed for all patients prior to SPC appointments. At the clinics, there is also variation on when tests are ordered based on the structure of the clinic. In some clinics, patients are first seen by a doctor who risk stratifies the patients prior to ordering tests with priority given to high-risk patients while in some clinics tests are ordered first, irrespective of patient risk level, prior to seeing a medical doctor. Hence, the variation in test wait times shown by our results could be due to the structure of the clinics.

Misdiagnosis of TIA is common with an estimated 50% of all TIA patients being stroke mimics.[25–27] With such high misdiagnosis rates, there is potential for delay in care for patients at high risk of stroke. However, TIA is a complex medical emergency with multiple risk factors making it challenging to diagnose, especially in resource- and time-limited settings. In addition, reliability of reporting the events experienced by the patients may vary, leading to subjective diagnosis, even among stroke neurologists.[28–30] Furthermore, TIA patients with mimics still require timely diagnosis and management. Derivation and guidelines on use of clinical prediction rules to identify stroke mimics could potentially allow for faster assessments for higher risk patients. Several prediction rules for the diagnosis of TIA/stroke mimics (e.g., DOT score, Dawson score) have been derived but not adequately validated.[31–33]

A significant percentage of the SPCs turned to virtual care during the COVID-19 pandemic. Although most clinics did not use virtual care prior to the pandemic, most clinics are planning to continue using virtual care post-COVID-19. It is likely that the virtual care has helped reduce a load on the SPCs and opened capacity for high-risk patients.

3.6.3 Comparison with previous literature

Given the urgency and risk of TIA patients, SPCs need to be accessible. Similarly, all clinics should have a triaging system. Two studies, by Wasserman *et al* and Martinez-Martinez *et al*, have shown stroke risk reduction with risk stratification and referrals to SPCs.[10,34] The study by Martinez-Martinez and colleagues reported a median wait time of 1.5 days to SPCs which is shorter in duration than shown by our study. Although the study by Wasserman and colleagues reported that most patients were seen within 48 hours in the ED, they did not report the time it takes from ED to SPC appointment. Wasserman and colleagues showed that neurology was consulted in the ED for only 5% of patients compared to more than 32% reported by our study.

Our results show that the COVID-19 pandemic had a significant impact on TIA patient management. During the pandemic, the proportion of referrals from family physicians declined while the referrals increased from EDs. This was likely due to family physician clinics being closed. It could have also been due to patients not seeking medical help unless they deemed it an emergency. Other studies have found similar findings in reduction of patients during the pandemic period with similar conclusions.[35–41] Also in agreement with our study, a study by Dowlatshahi and colleagues showed a drop in presentation rates to a comprehensive stroke

centre in Ottawa, Canada at the beginning of the pandemic.[42] Similarly, a study by D'Anna showed a decline of referrals to North West London, UK SPC clinics during the COVID-19 pandemic.[43] Our study found the proportion of true TIA patients versus mimics increased during the pandemic. Patients with milder stroke symptoms may have intentionally avoided seeking medical care during the COVID-19 pandemic while the patients with more severe cases, such as symptoms due to large vessel occlusion, sought medical help as these more severe symptoms are less likely to be ignored by patients or family members.[38,43] Another study by D'Anna also observed this marked decrease in mimic diagnoses during the pandemic.[40]

3.6.4 Study limitations

Despite our efforts to obtain high-quality data, the quality of responses may have been affected by the COVID-19 pandemic. Given that this was a self-reported questionnaire, respondents may have not answered all the questions accurately. Another limitation is that we had a limited set of characteristics to test for nonresponse bias.

3.6.5 Clinical implications

Despite the need for urgent assessment and management, there is delay in seeing some high-risk TIA patients within 48 hours. About a quarter of SPCs are open 2 or fewer days a week, leaving the possibility of some high-risk patients having to wait more than the 48-hour critical time for TIA patients depending on referral volumes. A significant percentage of patients referred to SPCs are stroke mimics taking resources from true TIA patients. Using a clinical diagnostic tool, such as the DOT score, after its external validation, could help minimize misdiagnosis of TIA.

Stroke prediction tools, such as the Canadian TIA Score, are also important to prioritize high-risk patients.

3.6.6 Research Implications

Our study has shown several gaps in knowledge of SPCs and how they function and interact with other stakeholders. We have also shown the impact of the COVID-19 pandemic on patient management. We have found that referrals from an SPC's own ED are better managed than from other EDs, family physicians, or specialists. Understanding the reasons behind these discrepancies could help improve referral systems. We have also shown that several clinics are open 3 or fewer days a week with a quarter being open 2 days or fewer each week and not being able to see most high-risk patients within 48 hours. Half of the clinics that do open 4 or more days are also struggling with seeing most of their high-risk patients. The reasons behind this deficiency and the outcomes of patients seeking medical help at these clinics need to be investigated and compared to other clinics. We suspect there would be more stroke outcomes for high-risk patients at these clinics having to wait longer than 48 hours due to limited clinic days. Clinic structure regarding testing first prior to assessment versus assessment first followed by testing on patient outcomes also needs to be investigated.

3.6.7 Conclusion

TIA is a serious condition that requires urgent care, depending on the risk level. Outpatient SPCs have been setup to provide more efficient and effective care. Although there are guidelines on the management of TIA patients, they are not fully implemented leading to variations of practice.

We suggest that SPCs investigate delays and attempt to see high-risk patients within 48 hours. We also suggest that better systems are put in place between SPCs and referring sources, especially family physicians, so that patients are risk classified and some test are completed prior to their appointments, as appropriate without causing further delays.

3.7. Acknowledgements

The authors thank Dr Dylan Blacquiere, Dr Grant Stotts, Dr Michel Shamy, and Dr Vivien Parker (Neurologists) at The Ottawa Hospital who allowed us to interview them and for their feedback, Dr Christophe Fehlmann who helped with the initial translations of the letters and survey questionnaire into the French language, Angela Marcantonio for her assistance throughout the project, and those individuals who completed our questionnaire.

3.8. Funding

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3.9. Conflict of interest

Dr Jeffrey Perry holds a peer-reviewed mid-career salary support award from the Heart and Stroke Foundation of Ontario. None of the other authors have any conflict of interest or information to disclose in relation to this study.

3.10. Statement of authorship

KEA, JJP, and MT designed the study. KEA conducted interviews, executed the surveys, conducted analyses, and wrote the draft manuscript. DD, IGS, and GAW provided input into the study design. All authors contributed to the final manuscript review.

3.11. Tables

Table 3.1 Characteristics of stroke prevention clinics

Information	**Number (%) (N=38)**
Professionals involved in care at clinic	
Neurologists	17 (44.7)
Nurse practitioner/specialists	17 (44.7)
Internists	16 (42.1)
Stroke neurologists	15 (39.5)
Registered nurses	11 (29.0)
Vascular surgeons	4 (10.5)
Others	4 (10.5)
Family physicians	1 (2.6)
Geriatricians	0 (0.0)
Days per week clinic is open	
½	1 (2.6)
1	5 (13.2)
2	4 (10.5)
3	1 (2.6)
4	2 (5.3)
5	24 (63.2)
6	0 (0.0)
7	1 (2.6)
Hours per day clinic is open	
<4	5 (13.2)
4-8	30 (79.0)
9-12	2 (5.3)
>12	1 (2.6)
Number of patients seen each day clinic is open, median (IQR)	7 (5-15)
Distribution of patient referrals, median (IQR)	
Own ED	50 (40-70)
Other ED	15 (7-20)
Family physicians	20 (15-30)
Other specialists	5 (5-15)
Initial diagnosis confirmed as a TIA by referral, median (IQR)	
Own ED	50 (30-70)
Other ED	50 (20-60)
Family physicians	30 (20-50)
Other specialists	50 (20-60)
No capacity for add-on urgent patients	6 (15.8)
Triaging system	
No appointments, first-come first-served basis	0 (0.0)
Appointment system without considering risk levels	1 (2.6)

Appointment system that considers risk level	37 (97.4)
Wait times for appointment system that considers risk level	
Low-risk:	
< 24 hours	0 (0.0)
< 7 days	4 (10.8)
< 14 days	8 (21.6)
< 30 days	12 (32.4)
< 3 months	10 (27.0)
> 3 months	2 (5.4)
High-risk:	
< 24 hours	3 (8.1)
< 2 days	11 (29.7)
< 3 days	8 (21.6)
< 4 days	1 (2.7)
< 5 days	3 (8.1)
< 6 days	0 (0.0)
< 7 days	4 (10.8)
< 14 days	6 (16.2)
> 14 days	0 (0.0)
ED has a protocol to consult neurology	
Yes, routinely	11 (35.5)
Yes, only high-risk patients	10 (32.3)
Not routinely	9 (29.0)
Missing	1 (3.2)
Admit patients for revascularization directly from the ED	18 (60.0)
Modalities most often used for vascular imaging	
Computed tomography angiography (CTA)	30 (79.0)
Doppler	14 (36.8)
Magnetic resonance angiography (MRA)	0 (0.0)
Clinic is notified immediately by Radiology with important results, such as >50% stenosis	14 (36.8)
For urgent cases, clinic cannot bypass normal wait times	2 (5.3)
Holter monitor duration normally requested	
24 hours	7 (18.4)
48 hours	8 (21.1)
72 hours	2 (5.3)
7 days	3 (7.9)
14 days	9 (23.7)
> 14 days	4 (10.5)
Missing	5 (13.2)

ED, Emergency Department; IQR, Interquartile range; TIA, Transient Ischemic Attack;

Table 3.2 Association between seeing high-risk patients within 48 hours and number of days clinics are open

	Most high-risk patients seen within 48 hours	**Most high-risk patients not seen within 48 hours**	**p value***
Days open / week			0.025
≥ 4 days	13 (92.9)	12 (54.6)	
≤ 3 days	1 (7.1)	10 (45.5)	

Data are reported as number (%) of stroke prevention clinics

* p value obtained using Fisher's Exact Test

Table 3.3 Chi-squared tests of non-response bias

Characteristic	Respondents, n (%)	Non-respondents n (%)	p value
Region			0.172
Western Canada[a]	9 (23.7)	14 (36.8)	
Ontario	20 (52.6)	12 (31.6)	
Eastern Canada[b]	9 (23.7)	12 (31.6)	

[a] British Columbia, Alberta, Saskatchewan, Manitoba

[b] Quebec, New Brunswick, Nova Scotia, Newfoundland, Prince Edward Island

Table 3.4 Extent of virtual care

	Number (%) (N=33)
During COVID-19 Pandemic virtual care provided to (if applicable)	
All patients	6 (20.7)
Most low-risk patients only	5 (17.2)
Most low to medium-risk patients only	7 (24.1)
Follow-ups	7 (24.1)
New consults and follow-ups	2 (6.9)
At patient request	2 (6.9)
Plans for virtual care post COVID-19 pandemic	
For most patients	3 (9.1)
For most low-risk patients only	9 (27.3)
Follow-ups	4 (12.1)
New consults and follow-ups	2 (6.1)
At patient request	5 (15.2)
Physician preference	1 (3.0)
No	9 (27.3)

Five clinics did not answer questions related to COVID-19 and were excluded from the denominator

3.12. Figures

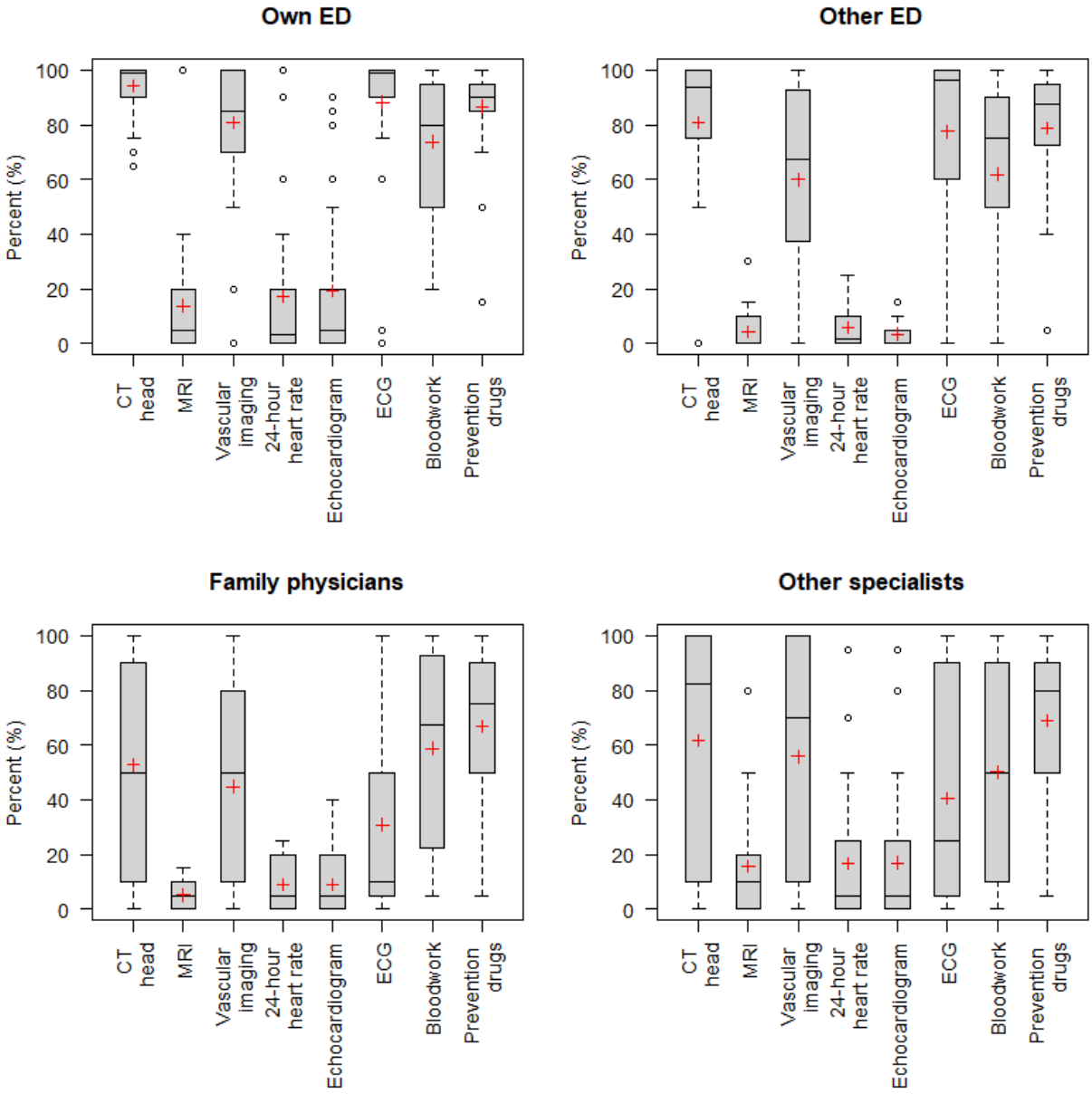

Figure 3.1 Percentage of patients having already completed a test by the time they arrive at the stroke prevention clinic, by referring source

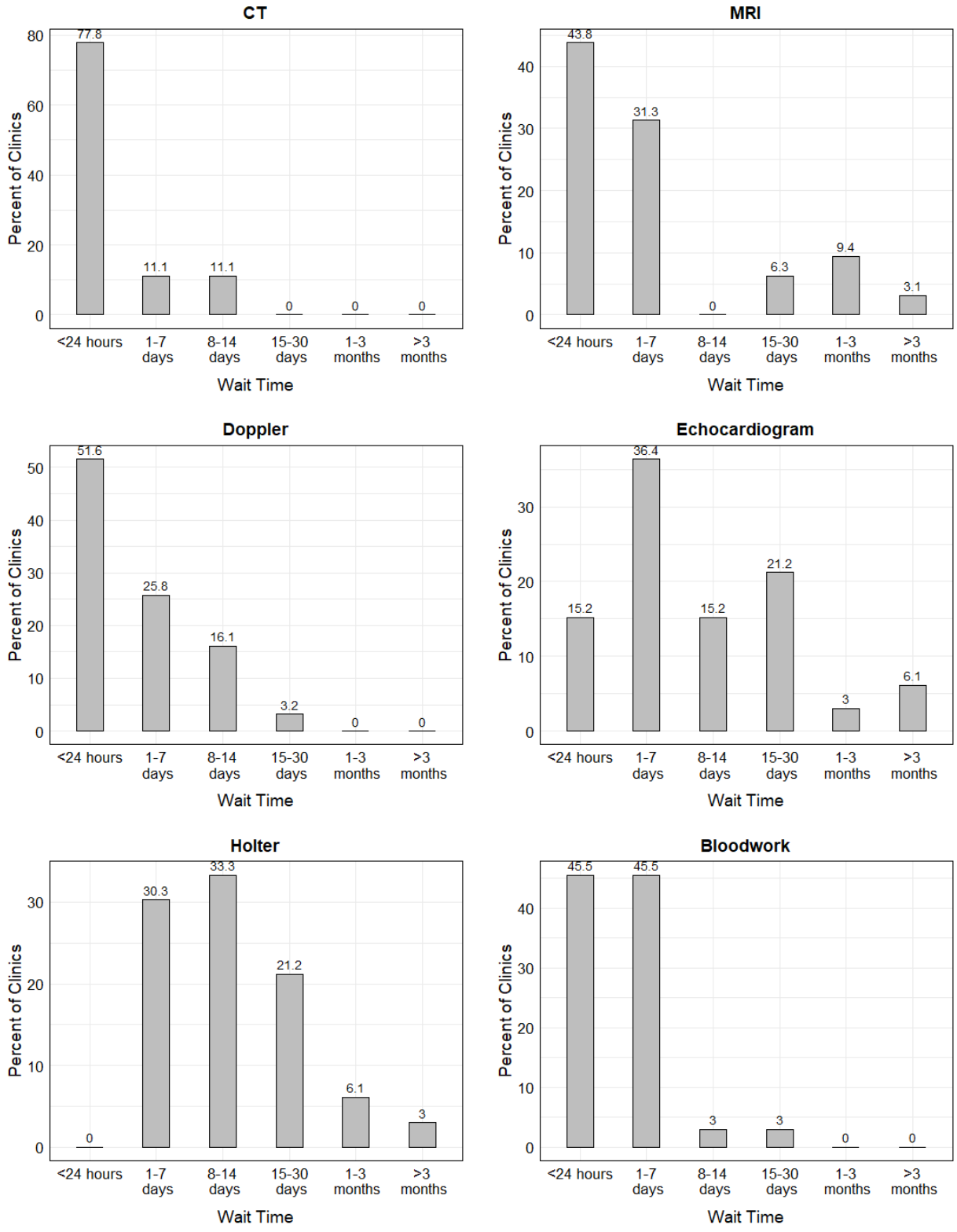

Figure 3.2 Time required for results to become available

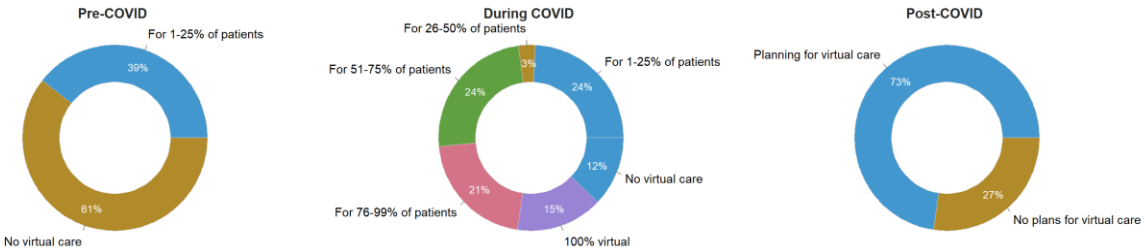

Figure 3.3 Percent of clinics using virtual care

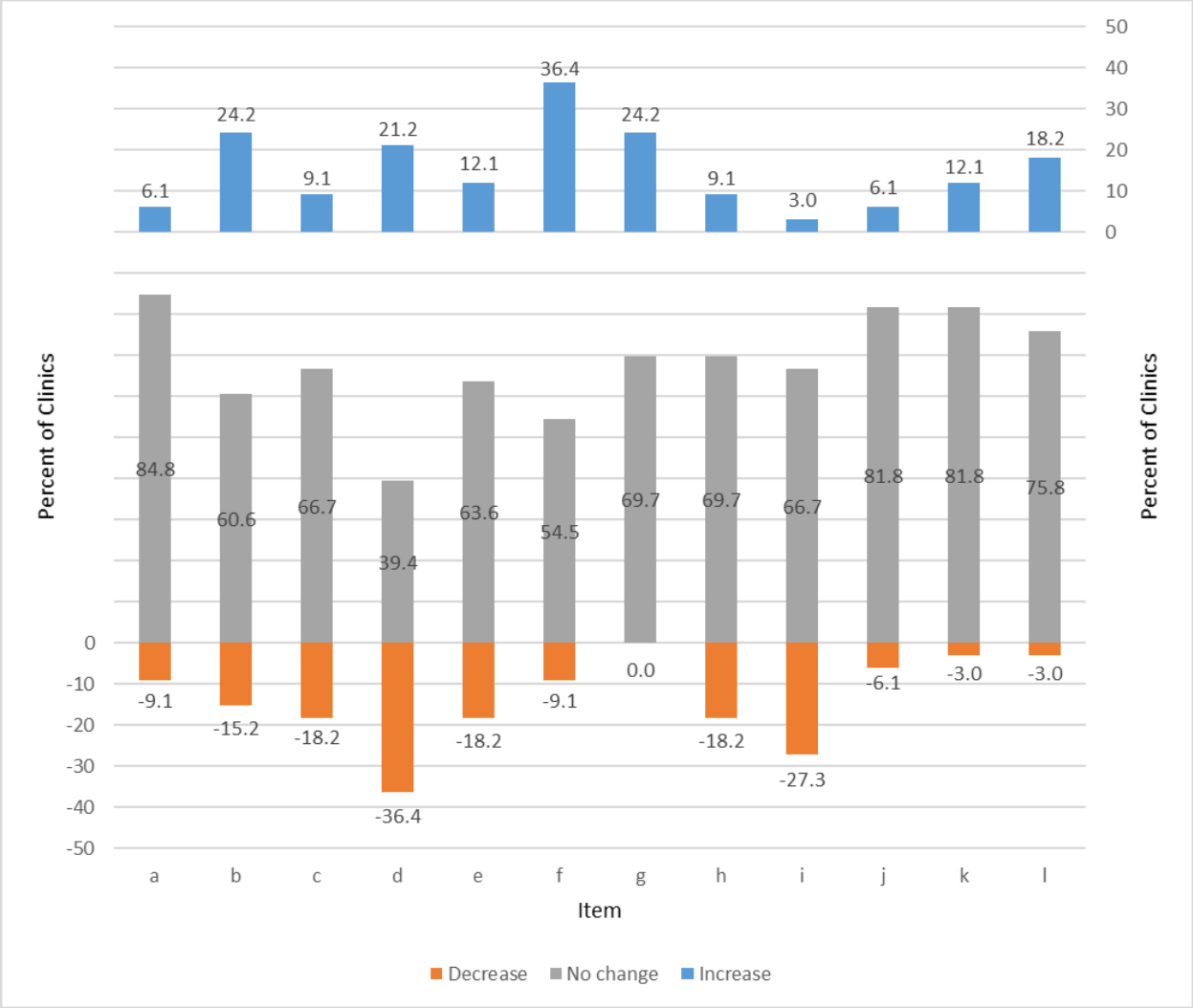

Figure 3.4 Impact of COVID-19 pandemic on clinic services.

(from pre-COVID to COVID period). a. Hours the clinic is physically open / week. b. Referrals from own emergency department. c. Referrals from other emergency departments. d. Referrals from family physicians. e. Referrals from other specialists. f. Wait times for an appointment once a patient is referred to clinic. g. Proportion of true TIA patients versus mimics. h. Patients having completed imaging prior to appointment. i. Patients having completed bloodwork prior to appointment. j. Patients already taking prevention drugs (e.g. anticoagulants and antiplatelet) prior to appointment. k. If patients need medical imaging done, time it takes to have the results. l. If patients need bloodwork done after arriving, time it takes to have the results. *One clinic did not answer items d, h, i, k, l; two clinics did not answer items c, e, g, j

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4. DERIVATION OF A CLINICAL PREDICTION MODEL

Manuscript 3: Derivation of a Clinical Prediction Score for the Diagnosis of Clinically Significant Symptomatic Carotid Artery Disease

4.1. Preface to manuscript 3

This chapter of the manuscript presents the third objective of the thesis which is the development and internal validation of the clinical prediction risk score for patients with clinically significant symptomatic carotid artery disease. The manuscript has been prepared and is being submitted for publication as follows:

> Kasim E. Abdulaziz, MSc; Monica Taljaard, PhD; Dar Dowlatshahi, MD; Ian G. Stiell, MD; George A. Wells, PhD; Marco L.A. Sivilotti, MD; Marcel Émond, MD; Mukul Sharma, MD; Grant Stotts, MD; Jacques Lee, MD; Andrew Worster, MD; Judy Morris, MD; Ka Wai Cheung, MD; Albert Y. Jin, MD; Wieslaw J. Oczkowski, MD; Demetrios J. Sahlas, MD; Heather E. Murray, MD; Ariane MacKey, MD; Steve Verreault, MD; Marie-Christine Camden, MD; Samuel Yip, MD; Philip Teal, MD; David J Gladstone, MD; Mark I Boulos, MD; Nicolas Chagnon, MD; Elizabeth Shouldice, MD; Clare Atzema, MD; Tarik Slaoui, MD; Jeanne Teitlebaum, MD; Jeffrey J. Perry, MD. Derivation and Validation of a Clinical Prediction Score for the Diagnosis of Clinically Significant Symptomatic Carotid Artery Disease

KEA was responsible for the study design with contributions from all authors. KEA reviewed study charts and prepared the data for analyses. KEA analysed the data and derived and validated the models. KEA wrote the draft manuscript. All authors contributed to the final manuscript review.

Supporting information and additional analyses on this manuscript are provided in appendix 7.3.

This study has received Ottawa Health Science Network Research Ethics Board approval.

4.2. Key Points

Question: Following acute transient ischemic attack (TIA), can a risk prediction model using readily available clinical factors accurately identify the presence of clinically significant carotid artery disease?

Findings: In this cohort study of 9,882 patients, a 13-predictor risk score was derived: optimism-corrected C-statistic 0.781, with good calibration. At the suggested low-risk cut-point of 11, one-third of TIA patients could potentially avoid immediate vascular imaging in emergency departments.

Meaning: This tool can be used to delay, and possibly forgo, imaging of the neck in many TIA patients, reducing the burden on emergency departments.

4.3. Abstract

Importance: Among patients suffering a Transient Ischemic Attack (TIA), the subset with moderate to severe carotid artery disease contralateral to their symptoms benefit from urgent vascular intervention to prevent stroke. Thus, the identification of carotid atherosclerosis is a priority in the emergency evaluation of TIA. However, the majority of patients evaluated for suspected TIA do not need revascularization, especially given that approximately half are TIA mimics. Hence, imaging all patients with suspected TIA is inefficient and increases wait times, particularly in crowded emergency departments.

Objective: To derive and internally validate a clinical prediction score to identify symptomatic carotid artery stenosis ≥ 50% in patients with suspected TIA.

Design: Secondary analysis of a prospective cohort study.

Setting: 14 Canadian tertiary and community emergency departments over 12 years.

Participants: Among 11,555 consecutive adult patients attending the emergency department with TIA/minor stroke symptoms, 9,882 were included in the analysis (48 patients lost to follow-up and 1,625 without formal carotid imaging were excluded).

Main Outcome: Symptomatic carotid artery disease with stenosis ≥ 50%.

Results: Of 9,882 patients, 5,048 (51.1%) were women, the mean age was 68.1 (SD: 14.4) years, and 888 (9.0%) had symptomatic carotid artery stenosis. Logistic regression was used to derive a full prespecified model with 29 predictor variables that was approximated with a 13-variable reduced model. The optimism-corrected C-statistic for the reduced model was 0.781 (95% CI: 0.769-0.798), and it had a calibration slope of 1. We simplified the model into a score (Symcard

Score), with suggested cut-points for high (15+ points out of 30), medium (12-14), and low-risk (≤11) stratification. A substantial portion (38.0%) of TIA patients met the definition of low-risk, 33.8% were classified as medium risk, and 28.2% as high risk. At the low risk cut-point, sensitivity was 92.9% (95% CI: 91.0%-94.5%), specificity 41.1% (95% CI: 40.1%-42.1%), and diagnostic yield 1.7% (95% CI: 1.3%-2.1%)].

Conclusions and Relevance: This arithmetically simple carotid artery disease score, based on readily available information at the time of emergency department presentation, predicts the presence of clinically significant symptomatic ipsilateral carotid artery disease in patients with TIA symptoms with a good discrimination and calibration. Low-risk patients are possible candidates for either forgoing vascular imaging of the neck or delayed imaging as outpatients; medium-risk patients too may be possible candidates for delayed imaging of the neck, depending on resource availability. After external validation, this clinical score could potentially reduce the need for immediate vascular imaging in a substantial proportion of patients being evaluated for TIA or minor stroke in the emergency department.

4.4. Introduction

Ninety percent of strokes are ischemic in origin,[1] and 10-20% of these strokes are attributed to extracranial internal carotid artery disease (i.e., carotid artery stenosis).[2,3] Up to 10% of transient ischemic attack (TIA)/minor stroke patients exhibit extracranial internal carotid artery disease,[4] which poses the highest risk for recurrent stroke in the days following transient ischemic attack (TIA)/minor stroke.[5–8] Guidelines recommend carotid revascularization for patients diagnosed with symptomatic carotid artery stenosis of 50-99%.[9–11] Vascular intervention in this group can prevent stroke, making the identification of carotid artery stenosis a priority in the emergency evaluation of TIA/minor stroke patients.

Diagnosis of carotid artery disease is often confirmed by vascular imaging. Duplex ultrasound of the carotids is often available on an outpatient basis for patients discharged from the emergency department, but has increasingly been replaced by emergency (i.e. same-day) computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the neck, generally performed at the same time as the CTA (or MRA) of the head.[12] CTA is more readily available than MRA, but requires radiation exposure and contrast; both CTA and MRA involve a variable delay to formal interpretation by a radiologist, time when the emergency department bed could be used by another patient.[13] The convenience of formally imaging the neck vessels at the same time as the cranium has led to almost every patient deemed to possibly have experienced a TIA/minor stroke undergoing imaging of both the head and neck. Such practice is likely inefficient, increasing wait times for other patients in the queue for imaging, contributing to incidental findings of no significance, and requiring prolonged stays or interfacility transport when vascular imaging is not readily available. Further, it has been estimated that half of all

these possible TIA/minor stroke patients are ultimately diagnosed as TIA mimics.[14–16] Hence, there is a need for more efficient care pathway for identifying clinically significant carotid artery disease in emergency department patients being assessed for TIA/minor stroke.

While several prediction models have been derived for *asymptomatic* carotid artery disease,[17–22] none were developed to determine urgency of vascular imaging, nor in the setting of symptomatic disease. The goal of this study was to derive a clinical prediction model for the identification of clinically significant carotid artery disease in emergency department patients deemed to have experienced a TIA/minor stroke. Our specific objectives were to: (a) derive a clinical prediction model, (b) internally validate the model, and (c) present the prediction model using a scoring system we term the **Sym**ptomatic **c**arotid **ar**tery **d**isease (Symcard) Score.

4.5. Methods

4.5.1 Patient population

Data for this secondary analysis are taken from two large, prospective multicenter cohort studies of TIA/minor stroke patients seen at 14 Canadian emergency departments (11 university-affiliated tertiary care hospitals and three urban community hospitals) from 2006 to 2017.[23,24] Consecutive patients aged 18 years or older attending the emergency department with a clinical diagnosis of TIA or minor stroke (i.e., suspected of TIA) at the time of discharge or neurologist consultation were eligible for enrollment 24/7/365 during the study period. Patients were excluded if they were diagnosed with a disabling stroke, were treated with tissue plasminogen

activator (tPA) or embolectomy for an acute stroke, had a decline in level of consciousness from baseline, or presented to the emergency department more than seven days after onset of symptoms. To identify carotid artery disease, we retained only those patients from the original study cohorts who had the diagnosis of the outcome confirmed by vascular imaging of the neck within 90 days of the index visit.

Each of the local Research Ethics Boards (REBs) approved the study.

4.5.2 Outcome measure

Our outcome of interest was clinically significant carotid artery disease, defined to be extracranial internal carotid stenosis ≥ 50% [including complete occlusion], dissection, or any thrombus in the internal carotid artery, combined with symptoms that were contralateral to carotid artery disease. When multiple vascular imaging modalities were available, we selected the most accurate, based on decreasing order: (1) catheter angiography, (2) CTA, (3) contrast enhanced MRA, (4) time of flight (TOF) MRA, (5) carotid Doppler. The local radiologist interpretation of stenosis, as recorded in the medical record, was used to determine the outcome. The physician (typically emergency medicine, but also neurology or internal medicine) primarily responsible for the patient's assessment and care determined study eligibility (especially that TIA/minor stroke was most likely diagnosis) and completed the study forms, which included pre-specified and pre-defined neurological symptoms and findings, onset, duration and other symptoms. Carotid artery abnormality was deemed to be symptomatic when the study form or medical record identified contralateral symptoms of altered sensation or weakness, or motor

weakness on physical exam, or language disturbance (aphasia or dysarthria on history or exam for the left carotid, or only dysarthria for the right; no further attempt was made to impute hand or language dominance).

4.5.3 Data analysis strategy

Our analyses were guided by recommended methods for derivation of clinical prediction models,[25–27] including pre-specification of 29 predictors (see eTable 4.1), based on literature review and clinical expertise, and multiple imputation of missing data. We combined systolic and diastolic blood pressure measurements into a single variable, termed isolated systolic hypertension, based on its known strong association with carotid artery diseases.[17,28–30] Based on the first recorded blood pressure obtained at triage, we further stratified isolated systolic hypertension as severe (systolic blood pressure, SBP ≥ 150 mmHg and diastolic blood pressure, DBP < 75 mmHg), less severe (SBP ≥ 130 mmHg and DBP < 80 mmHg), and other. Our sample size was considered adequate based on having at least double the recommended 15 events per predictor parameter.[26]

We conducted the analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and the Hmisc and rms packages in R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

4.5.4 Coding of predictors, handling of missing data, and multicollinearity

Prior to modelling, age and platelet count were categorized based on known clinical cut-points and knot locations suggested by restricted cubic splines of the two predictor variables.

Multicollinearity among the 29 predictor variables was examined using a variable clustering algorithm and variance inflation factors (VIFs).[31]

Prior to multiple imputation, we made several attempts to recover missing information by reviewing study and patient charts. For patients who did not have laboratory testing on the index visit, we used single imputation to set missing values for platelets and glucose to the arithmetic average of the normal range (i.e., platelets 300 x 10^9/L; glucose 7.5 mmol/L) because the absence of laboratory tests typically indicate a high likelihood that values were within the normal range. We also inspected the data for outliers prior to multiple imputations. In addition to the 29 predictors and outcome, another 10 auxiliary variables were identified as useful for generating multiple imputation values (eTable 4.2). We imputed missing values for all predictors by generating 10 multiple imputations with the aregImpute function of the Hmisc R package using the method of predictive mean matching. The aregImpute takes all aspects of uncertainty in the imputations into account by using the bootstrap to approximate the process of drawing predicted values from a full Bayesian predictive distribution. The results were combined across the 10 multiple imputation datasets using Rubin's rules.[32]

4.5.5 Model fitting and reduction

A full prespecified model with 29 predictors was fitted to the 10 multiple imputation datasets using logistic regression modeling. Associations were expressed using Odds Ratio (OR) with 95% confidence interval (CI). We used a stepdown approach to simplify the full model with stopping rule based on Akaike information criterion (AIC).[26] We assessed the model discrimination and calibration using the concordance index (i.e., C-statistic) and calibration plots and slopes. We internally validated our model using 1000 bootstrap samples[26,27] and calculated the optimism-corrected C-statistic.

4.5.6 Presentation of the model using a scoring system

To aid implementation in a clinical setting, we used a nomogram to present the prediction model as a scoring system. Each predictor was assigned points based on the strength and direction of the association with the outcome. We then calculated the total number of points for each patient and assessed the sensitivity and specificity for each cut-point. To verify that there was minimal change in performance, we estimated a model with the score as the only predictor and compared the C-statistic from this model to the C-statistic from the full model. We defined three risk categories, using risk thresholds for symptomatic carotid artery disease of <5% as low-risk, 5% to 10% as medium-risk, and >10% as high-risk.

4.6. Results

A flow diagram of patient enrollment is presented in eFigure 4.1. From a total of 11,555 subjects in the original cohort studies, 48 were excluded due to lost to follow-up and 1,625 had no vascular imaging of the neck performed, leaving a total of 9,882 (85.5%) retained for this study. No problems with multicollinearity (i.e., VIFs above 4) were identified (see Appendix 7.3.1).

The characteristics of the patients with and without the main outcome are presented in Table 4.1. Most subjects never had a prior TIA (73.5%) and had symptoms last 10 or more minutes (85.0%). A significant proportion had hypertension (62.8%). A total of 888 (9.0%) subjects had the main outcome of clinically significant symptomatic carotid artery disease identified on formal imaging within 90 days of the index visit. The characteristics of the patients with and without vascular imaging of the neck, along with standardized differences, are shown in eTable 4.3.

A total of 13.3% patients had a missing value for at least one of the 29 predictors with syncope or near syncope having the most missing values (5.2%) followed by abnormal finger-nose test on physical exam (5.1%).

The full prespecified model is presented in eTable 4.4; it had a naïve C-statistic of 0.789 and calibration slope of 1 (eFigure 4.2). The reduced model from the stepdown procedure had 13 predictors (Table 4.2). This reduced model had a calibration slope of 1 (Figure 4.1), a naïve C-statistic of 0.785 and optimism corrected C-statistic of 0.781 (95% CI: 0.769-0.798). Notably,

vertigo and duration of symptoms were associated with reduced odds of the outcome whereas all remaining predictors were associated with increased odds.

The final scoring system based on the reduced model is shown in Table 4.3, with a score ranging from -4 to 30. The C-statistic for the model with the total score as the only predictor was 0.782 (95% CI: 0.768-797), and its calibration plot is presented in eFigure 4.3. The formula for calculating the risk of clinically significant symptomatic carotid artery disease is as follows:

$$\text{Estimated probability of outcome} = \frac{\exp(\beta_0+\beta_1\times score)}{1+\exp(\beta_0+\beta_1\times score)} = \frac{\exp(-6.8334+0.3228\times score)}{1+\exp(-7.7593+0.3850\times score)}$$

Score cut-points, risk stratification, and classification performance of the score-only model are presented in Table 4.4. The probability of clinically significant symptomatic carotid artery disease ranged from 0.1% to 86.8%. Those with a Symcard Score of 11 or less (38.0% of the cohort; diagnostic yield of vascular imaging 1.7%) were classified low-risk, between 12 and 14 medium-risk (33.8% of cohort; diagnostic yield 7.2%), and 15 or more high-risk (28.2% of cohort; diagnostic yield 21.0%). A single cut-off of 12 points yielded a sensitivity of 92.9% (95% CI: 91.0%-94.5%) and a specificity of 41.1% (95% CI: 40.1%-42.1%).

4.7. Discussion

4.7.1 General discussion

In this study we derived and internally validated a clinical prediction model for the diagnosis of clinically significant symptomatic carotid artery disease using prospectively collected,

multicenter cohort data. The approximation of the full model contained 13 predictors that are readily available in the emergency department at the time of initial assessment, and it had a very good discrimination and calibration. To facilitate clinical use, we converted the approximation into a simple scoring system. Our tool has the potential to reduce or delay non-urgent vascular imaging.

The Symcard score aims to standardize and optimize patient management in the emergency department; our score provides a more objective measure of risk than any currently available. In the past we have shown that there is a variation of practice in managing TIA/minor stroke patients.[33] One of the variations of practice was the modality, timing, and consistency of obtaining formal vascular imaging of the neck prior to stroke prevention clinic follow up. There has also been a secular shift over the last decade in emergency medicine towards much more frequent, same-day use of CTA to image the neck vessels following possible TIA/minor stroke. With an overall diagnostic yield below 10% for identifying patients that benefit from emergency vascular intervention, and the substantial number of TIA mimics being investigated, there is an important opportunity for artificial intelligence tools which allow more selective use of imaging. While each healthcare system or facility may adjust the exact threshold, we suggest that Symcard low-risk patients be discharged from the emergency department and outpatient Doppler studies performed within 30 days; medium-risk patients being discharged from the emergency department might have outpatient Doppler studies performed in the short-term follow up. The risk estimate can also be used to inform patient-centred discussions, which ideally would include the likely risks and benefits of urgent vascular intervention—arguably the ultimate reason for obtaining the imaging test.

Comparisons of studies on carotid artery disease are challenging due to lack of consistency in outcome definitions, widely varying patient characteristics, and study populations used for studying carotid artery disease. Prior studies have involved populations with a higher prevalence of carotid stenosis (from 12.5% to 28%), with different and varying selection criteria such as disabling stroke, elderly age, and more severe cases of stenosis.[34–37] Prediction models exist for the prediction of *asymptomatic* carotid artery stenosis in broad population groups,[17–22] rather than patients being assessed for TIA/minor stroke. We included the predictor variables, or variations thereof, for the derivation of our model, with the exception of height, which was not recorded in our dataset. In addition, we considered other variables that had plausible biological association, including duration of symptoms of 10 minutes. We were surprised to note the negative association with carotid artery disease, especially given the known strong positive association between symptom duration and subsequent stroke in both the Canadian TIA Score and variations of the ABCD scoring system. This apparent contradiction reflects the different outcomes being measured. Another possible explanation is that approximately 50% of our population could be patients with TIA mimics, leading to such association.

4.7.2 Strengths and limitations

A strength of our study is the use of a very large dataset, rigorously collected as part of a prospective multicenter cohort study, allowing many events per candidate predictor in the target population of interest. One limitation is that we excluded patients without vascular imaging. This was necessary for the confirmation of the outcome. Another limitation is that our definition of

"clinically significant" carotid artery disease relied on an assessment of lateralization of neurological symptoms, especially language disturbance, which can be imperfect. Finally, our model with 13 predictors and a total of 30 points may require visual or electronic aids for implementation in practice. While some predictors could be automatically retrieved by a modern electronic medical record platform and are well defined, several predictors including the neurological signs and symptoms will still require expert ascertainment, with the potential for interobserver variability.

4.7.3 Clinical implications

After future external validation, the Symcard Score can potentially help identify patients who might benefit from urgent vascular neck imaging. Although we have suggested a cut-off of less than 5% as low risk for outcome, clinicians can use other cut-off points for managing their patients, depending on the desired sensitivity at the cut-off. This tool can be used in conjunction with the Canadian TIA Score and other similar risk scores upon validation, which identify TIA/minor stroke patients at risk of stroke, irrespective of the etiology.

4.7.4 Research implications

Although the Symcard Score has a good discrimination and very good calibration, and offers high sensitivity and narrow 95% CI, external validation is recommended. Future research could examine integration of the Symcard Score into other risk tools such as the Canadian TIA Score.[38] Future research can also measure the cost effectiveness of using this tool, and the impact on patient-informed decisions.

4.7.5 Conclusion

The Symptomatic carotid artery disease (Symcard) Score uses 13 readily available predictors at the time of initial assessment for TIA/minor stroke to predict whether carotid artery pathology will be identified on formal vascular imaging of the neck. Incorporating this clinical score into TIA management plans could standardize the diagnostic approach and priorities, allowing more selective imaging of the neck vessels based on the expected diagnostic yield.

4.8. Acknowledgements

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4.9. Funding

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4.10. Conflict of Interest

Dr. Jeffrey Perry and Dr. Clare Atzema hold a peer-reviewed mid-career salary support award from the Heart and Stroke Foundation of Ontario. None of the other authors have any conflict of interest or information to disclose in relation to this study.

4.11. Tables

Table 4.1 Characteristics of Patients with and without Outcome at Time of Index Emergency Department Visit

Characteristic	**Patients with Outcome (N=888)**	**Patients without Outcome (N=8,994)**	**Overall (N=9,882)**
Demographics			
Age			
<40	1 (0.1)	290 (3.2)	291 (2.9)
40-49	14 (1.6)	786 (8.7)	800 (8.1)
50-64	151 (17.0)	2,596 (28.9)	2,747 (27.8)
65+	722 (81.3)	5,322 (59.2)	6,044 (61.2)
Female sex	363 (40.9)	4,685 (52.1)	5,048 (51.1)
Clinical features			
Initial TIA (Never had TIA in past)	549 (61.8)	6,714 (74.7)	7,263 (73.5)
Duration of symptoms ≥ 10 minutes	718 (80.9)	7,681 (85.4)	8,399 (85.0)
History of altered sensation	360 (40.5)	4,069 (45.2)	4,429 (44.8)
History of unilateral weakness	457 (51.5)	3,292 (36.6)	3,749 (37.9)
Dysarthria or aphasia (history or exam)	546 (61.5)	3,437 (38.2)	3,983 (40.3)
History of gait disturbance	181 (20.4)	1,948 (21.7)	2,129 (21.5)
Visual loss (history or exam)	92 (10.4)	1,385 (15.4)	1,477 (15)
Lightheaded	128 (14.4)	1,724 (19.2)	1,852 (18.7)
Vertigo	36 (4.1)	971 (10.8)	1,007 (10.2)
Confusion	123 (13.9)	1,201 (13.4)	1,324 (13.4)
Syncope or near syncope	42 (4.7)	455 (5.1)	497 (5)
Abnormal finger-nose test on physical exam	58 (6.5)	418 (4.7)	476 (4.8)
Past medical history: hypertension or already on antihypertensive medications	712 (80.2)	5,491 (61.1)	6,203 (62.8)
Past medical history: diabetes or lab glucose > 11 mmol/L	238 (26.8)	1,704 (19.0)	1,942 (19.7)
Past medical history: current smoker	140 (15.8)	1,029 (11.4)	1,169 (11.8)
Past medical history: congestive heart failure	37 (4.2)	217 (2.4)	254 (2.6)
Past medical history: coronary artery disease	282 (31.8)	1,411 (15.7)	1,693 (17.1)
Past medical history: peripheral vascular disease	86 (9.7)	279 (3.1)	365 (3.7)
Past medical history: known prior stroke	170 (19.1)	1,006 (11.2)	1,176 (11.9)
Past medical history: carotid stenosis	147 (16.6)	189 (2.1)	336 (3.4)
Past medical history: high cholesterol or already on statin medication	519 (58.5)	3,851 (42.8)	4,370 (44.2)
Past medical history: valvular heart disease	42 (4.7)	286 (3.2)	328 (3.3)
Vital signs			
Systolic blood pressure, mean (SD)	156.9 (27.7)	152.9 (25.7)	153.3 (25.9)

Diastolic blood pressure, mean (SD)	79.5 (15.7)	83.0 (13.5)	82.7 (13.7)
Laboratory findings			
Glucose value, mean (SD)	7.0 (2.9)	6.5 (2.3)	6.6 (2.4)
Platelet value ≥ 400 x 109/L	35 (3.9)	216 (2.4)	251 (2.5)
Image findings			
Atrial fibrillation on ECG	62 (7)	453 (5)	515 (5.2)
Infarction (new or old) on CT	401 (45.2)	2,313 (25.7)	2,714 (27.5)
Number of imaging completed per patient			
1	568 (64.0)	7,633 (84.9)	8,201 (83.0)
2+	320 (36.0)	1,361 (15.1)	1,681 (17.0)
Imaging modality used for final diagnosis			
Doppler ultrasound	322 (36.3)	5,223 (58.1)	5,545 (56.1)
Computed tomography angiography (CTA)	477 (53.7)	3,129 (34.8)	3,606 (36.5)
Magnetic resonance angiography (MRA)	63 (7.1)	625 (7.0)	688 (7.0)
Catheter angiography	26 (2.9)	17 (0.2)	43 (0.4)
Outcome composition			
Moderate (50-69%)	487 (54.8)	N/A	N/A
Severe (>= 70-98%)	254 (28.6)	N/A	N/A
Pre-occlusion, or 99%, or "severely stenosed"	21 (2.4)	N/A	N/A
Complete occlusion or 100%	85 (9.6)	N/A	N/A
Any thrombus in carotid	48 (5.4)	N/A	N/A
Dissection	38 (4.3)	N/A	N/A

SD, standard deviation; TIA, transient ischemic attack; ECG, electrocardiogram; CT, computed tomography. N/A, not applicable. Data are reported as number (%) unless otherwise stated

Table 4.2 Summary of Reduced Model

Predictor	**Odds Ratio (95% Confidence Interval)**
Age	
<40	0.2 (0.0, 1.7)
40-49 - Reference	Reference
50-64	2.7 (1.5, 4.8)
65+	4.9 (2.7, 8.7)
Male sex	1.5 (1.3, 1.7)
Duration of symptoms ≥ 10 minutes	0.7 (0.6, 0.8)
Isolated Systolic Hypertension	
SBP >= 150 mmHg and DBP < 75 mmHg (severe)	2.1 (1.7, 2.6)
SBP > 130 mmHg and DBP < 80 mmHg (less severe)	1.3 (1.1, 1.6)
History of altered sensation	1.3 (1.1, 1.5)
History of unilateral weakness	1.7 (1.5, 2)
Aphasia or dysarthria (history or exam)	2.5 (2.1, 2.9)
Vertigo	0.4 (0.3, 0.6)
History of hypertension	1.5 (1.2, 1.8)
Past medical history: current smoker	1.9 (1.5, 2.4)
Past medical history: CAD	1.4 (1.2, 1.7)
Past medical history: carotid stenosis	6.8 (5.3, 8.8)
Infarct (new or old) on CT	1.6 (1.3, 1.8)

SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; CT, computed tomography

Table 4.3 Symptomatic Carotid Artery Disease Scoring System

Predictor	**Points**
Age	
40-49	5
50-64	8
65+	10
Male sex	1
Duration of symptoms ≥ 10 minutes	-1
Isolated systolic hypertension	
SBP ≥ 150 mmHg and DBP < 75 mmHg (severe)	2
SBP > 130 mmHg and DBP < 80 mmHg (less severe)	1
History of altered sensation	1
History of unilateral weakness	2
Dysarthria or aphasia (history or exam)	3
Vertigo	-3
History of hypertension	1
Past medical history: current smoker	2
Past medical history: CAD	1
Past medical history: carotid stenosis	6
Infarction (new or old) on CT	1
Total (-4 to 30)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; CT, computed tomography

Table 4.4 Classification Performance of the Symcard Score by Score Cut-off and Risk Category

Score	No. (%) of patients (N = 9,882)	Observed no. (%) of patients with outcome	Estimated no. (%) of patients with outcome			Risk Category	Proportion of patients (%)	No. (%) of patients with outcome	Sensitivity (95% CI) at score cut-off	Specificity (95% CI) at score cut-off
			Estimate	Lower 95% CI	Upper 95% CI					
-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Low	38.0	63 (1.7)	100 (99.6, 100)	0 (0, 0)
-3	2 (0)	0 (0)	0 (0)	0 (0)	0 (0.1)				100 (99.6, 100)	0 (0, 0)
-2	2 (0)	0 (0)	0 (0.1)	0 (0)	0 (0.1)				100 (99.6, 100)	0 (0, 0.1)
-1	11 (0.1)	0 (0)	0 (0.1)	0 (0.1)	0 (0.1)				100 (99.6, 100)	0 (0, 0.1)
0	42 (0.4)	0 (0)	0 (0.1)	0 (0.1)	0 (0.2)				100 (99.6, 100)	0.2 (0.1, 0.3)
1	40 (0.4)	0 (0)	0 (0.1)	0 (0.1)	0 (0.2)				100 (99.6, 100)	0.6 (0.5, 0.8)
2	63 (0.6)	0 (0)	0 (0.2)	0 (0.1)	0 (0.3)				100 (99.6, 100)	1.1 (0.9, 1.3)
3	58 (0.6)	1 (1.7)	0 (0.3)	0 (0.2)	0 (0.4)				100 (99.6, 100)	1.8 (1.5, 2.1)
4	62 (0.6)	0 (0)	0 (0.4)	0 (0.3)	0 (0.5)				99.9 (99.4, 100)	2.4 (2.1, 2.8)
5	185 (1.9)	0 (0)	1 (0.5)	1 (0.4)	1 (0.7)				99.9 (99.4, 100)	3.1 (2.8, 3.5)
6	192 (1.9)	2 (1)	1 (0.7)	1 (0.6)	2 (0.9)				99.9 (99.4, 100)	5.2 (4.7, 5.6)
7	288 (2.9)	1 (0.3)	3 (1)	2 (0.8)	4 (1.3)				99.7 (99, 99.9)	7.3 (6.7, 7.8)
8	525 (5.3)	8 (1.5)	7 (1.4)	6 (1.2)	9 (1.7)				99.6 (98.9, 99.9)	10.5 (9.8, 11.1)
9	587 (5.9)	8 (1.4)	11 (1.9)	10 (1.6)	13 (2.3)				98.7 (97.7, 99.3)	16.2 (15.5, 17)
10	796 (8.1)	20 (2.5)	21 (2.6)	18 (2.3)	24 (3)				97.8 (96.5, 98.6)	22.7 (21.8, 23.5)
11	905 (9.2)	23 (2.5)	33 (3.6)	29 (3.2)	37 (4.1)				95.5 (93.9, 96.8)	31.3 (30.3, 32.3)
12	1023 (10.4)	54 (5.3)	50 (4.9)	46 (4.5)	56 (5.4)	Medium	33.8	241 (7.2)	92.9 (91, 94.5)	41.1 (40.1, 42.1)
13	1134 (11.5)	76 (6.7)	76 (6.7)	70 (6.1)	82 (7.3)				86.8 (84.4, 89)	51.9 (50.8, 52.9)
14	1180 (11.9)	111 (9.4)	106 (9)	99 (8.4)	114 (9.7)				78.3 (75.4, 80.9)	63.6 (62.6, 64.6)
15	936 (9.5)	139 (14.9)	112 (12)	105 (11.2)	120 (12.8)	High	28.2	584 (21.0)	65.8 (62.5, 68.9)	75.5 (74.6, 76.4)
16	706 (7.1)	115 (16.3)	112 (15.9)	105 (14.9)	119 (16.9)				50.1 (46.8, 53.5)	84.4 (83.6, 85.1)
17	475 (4.8)	93 (19.6)	98 (20.6)	92 (19.3)	105 (22.1)				37.2 (34, 40.4)	90.9 (90.3, 91.5)
18	275 (2.8)	56 (20.4)	73 (26.4)	68 (24.6)	78 (28.4)				26.7 (23.8, 29.7)	95.2 (94.7, 95.6)
19	141 (1.4)	39 (27.7)	47 (33.2)	43 (30.7)	50 (35.8)				20.4 (17.8, 23.2)	97.6 (97.3, 97.9)
20	93 (0.9)	44 (47.3)	38 (40.7)	35 (37.5)	41 (43.9)				16 (13.6, 18.6)	98.8 (98.5, 99)
21	46 (0.5)	23 (50)	22 (48.6)	21 (44.8)	24 (52.5)				11 (9.1, 13.3)	99.3 (99.1, 99.5)
22	38 (0.4)	21 (55.3)	22 (56.7)	20 (52.3)	23 (60.9)				8.5 (6.7, 10.5)	99.6 (99.4, 99.7)
23	41 (0.4)	31 (75.6)	26 (64.3)	24 (59.7)	28 (68.7)				6.1 (4.6, 7.9)	99.7 (99.6, 99.8)
24	18 (0.2)	9 (50)	13 (71.4)	12 (66.7)	14 (75.6)				2.6 (1.7, 3.9)	99.9 (99.8, 99.9)
25	10 (0.1)	8 (80)	8 (77.5)	7 (73)	8 (81.4)				1.6 (0.9, 2.6)	100 (99.9, 100)
26	6 (0.1)	4 (66.7)	5 (82.6)	5 (78.5)	5 (86.1)				0.7 (0.3, 1.5)	100 (99.9, 100)
27	2 (0)	2 (100)	2 (86.8)	2 (83.2)	2 (89.7)				0.2 (0, 0.8)	100 (100, 100)
28	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				0 (0, 0)	100 (100, 100)

29	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				0 (0, 0)	100 (100, 100)
30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				0 (0, 0)	100 (100, 100)

CI, confidence interval

4.12. Figures

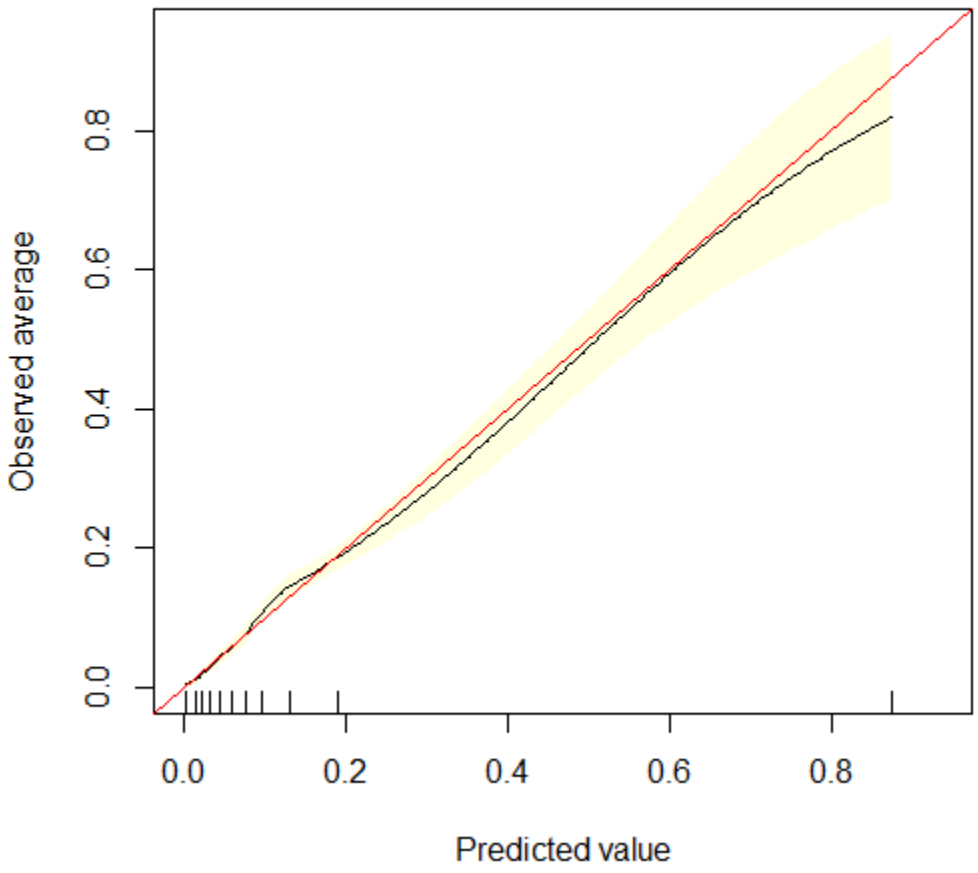

Figure 4.1 Calibration Plot of Reduced Model

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4.14. eTables

eTable 4.1 Pre-specified List of Predictors

Predictor	Description
agecatv2	Age category
sex	Sex
init_tia	Initial TIA (Never had TIA in past)
dursymptoms10	Duration of symptoms ≥ 10 minutes
isolatedSysHyper	Isolated systolic hypertension category
lab_platelet400	Platelet value ≥ 400 x 109/L
altered_sensation_his	History of altered sensation
unilateral_weakness_his	History of unilateral weakness
langdisturb_hisphys	Dysarthria or aphasia (history or exam)
gaitdistub_his	History of gait disturbance
visualloss_hisphys	Visual loss (history or exam)
lightheaded	Lightheaded
vertigo	Vertigo
confusion	Confusion
syncope	Syncope or near syncope
abnfingernosetest	Abnormal finger-nose test on physical exam
hist_hypertension	Past medical history: hypertension or already on antihypertensive medications
diabetes_glucose	Past medical history: diabetes or lab glucose > 11 mmol/L
Pmedhis_smoker	Past medical history: current smoker
Pmedhis_chf	Past medical history: congestive heart failure
pmedhis_cad	Past medical history: coronary artery disease
pmedhis_pvd	Past medical history: peripheral vascular disease
pmedhis_kps	Past medical history: known prior stroke
pmedhis_cs	Past medical history: carotid stenosis
hist_hchol	Past medical history: high cholesterol or already on statin medication
pmedhis_vhd	Past medical history: valvular heart disease
onAntipltherapy	Already on antiplatelet medications
afib_ecg	Atrial fibrillation on ECG
infarct_ct	Infarction (new or old) on CT

TIA, Transient Ischemic Attack; ECG, electrocardiogram; CT, computed tomography

eTable 4.2 Auxiliary Variables used in Multiple Imputation

Variable	**Description**
Site	Study site
Phase	Phase 1 or Phase 2 of study
Adm_status	Admission status
Sbp	Systolic blood pressure
Dbp	Diastolic blood pressure
Hr_rate	Heart rate
Symptoms	Symptoms on arrival
Pdrift	Pronator drift
Glucosevalue	Laboratory glucose value
Pmedhis_diab	Past medical history of diabetes

eTable 4.3 Characteristics of Patients with and without Vascular Imaging at Time of Index Emergency Department Visit

Characteristic	Patients with Vascular Imaging (N=9,882)	Patients without Vascular Imaging (N=1,625)	Standardized Difference
Demographics			
Age, mean (SD)	68.1 (14.4)	69.4 (15.8)	0.08
Female sex	5,048 (51.1)	907 (55.8)	0.09
Clinical features			
Initial TIA (Never had TIA in past)	7,259 (73.5)	1,056 (65.0)	0.18
Duration of symptoms ≥ 10 minutes	8,400 (85.0)	1,406 (86.5)	0.04
History of altered sensation	4,427 (44.8)	701 (43.1)	0.03
History of unilateral weakness	3,747 (37.9)	504 (31.0)	0.15
Dysarthria or aphasia (history or exam)	3,983 (40.3)	618 (38.0)	0.05
History of gait disturbance	2,135 (21.6)	380 (23.4)	0.04
Visual loss (history or exam)	1,476 (14.9)	211 (13.0)	0.06
Lightheaded	1,845 (18.7)	367 (22.6)	0.10
Vertigo	1,006 (10.2)	218 (13.4)	0.10
Confusion	1,328 (13.4)	249 (15.3)	0.05
Syncope or near syncope	488 (4.9)	121 (7.5)	0.10
Abnormal finger-nose test on physical exam	464 (4.7)	80 (4.9)	0.01
Past medical history: hypertension or already on antihypertensive medications	6,203 (62.8)	1,075 (66.2)	0.07
Past medical history: diabetes or lab glucose > 11 mmol/L	1,942 (19.7)	316 (19.5)	0.01
Past medical history: current smoker	1,168 (11.8)	180 (11.1)	0.02
Past medical history: congestive heart failure	253 (2.6)	56 (3.5)	0.05
Past medical history: coronary artery disease	1,693 (17.1)	320 (19.7)	0.07
Past medical history: peripheral vascular disease	365 (3.7)	59 (3.6)	0.00
Past medical history: known prior stroke	1,174 (11.9)	312 (19.2)	0.20
Past medical history: carotid stenosis	336 (3.4)	69 (4.3)	0.04
Past medical history: high cholesterol or already on statin medication	4,370 (44.2)	748 (46.0)	0.04
Past medical history: valvular heart disease	327 (3.3)	70 (4.3)	0.05
Vital signs			
Systolic blood pressure, mean (SD)	153.2 (25.9)	149.6 (26.5)	0.14
Diastolic blood pressure, mean (SD)	82.7 (13.7)	81.3 (14.2)	0.10
Laboratory findings			
Glucose value, mean (SD)	6.6 (2.4)	6.6 (2.2)	0.01
Platelet value, mean (SD)	241.0 (75.4)	241.1 (81.2)	0.00
Image findings			
Atrial fibrillation on ECG	515 (5.2)	105 (6.5)	0.05
Infarction (new or old) on CT	2,714 (27.5)	468 (28.8)	0.03
Outcome			
Symptomatic carotid artery disease	888 (9.0)	N/A	N/A

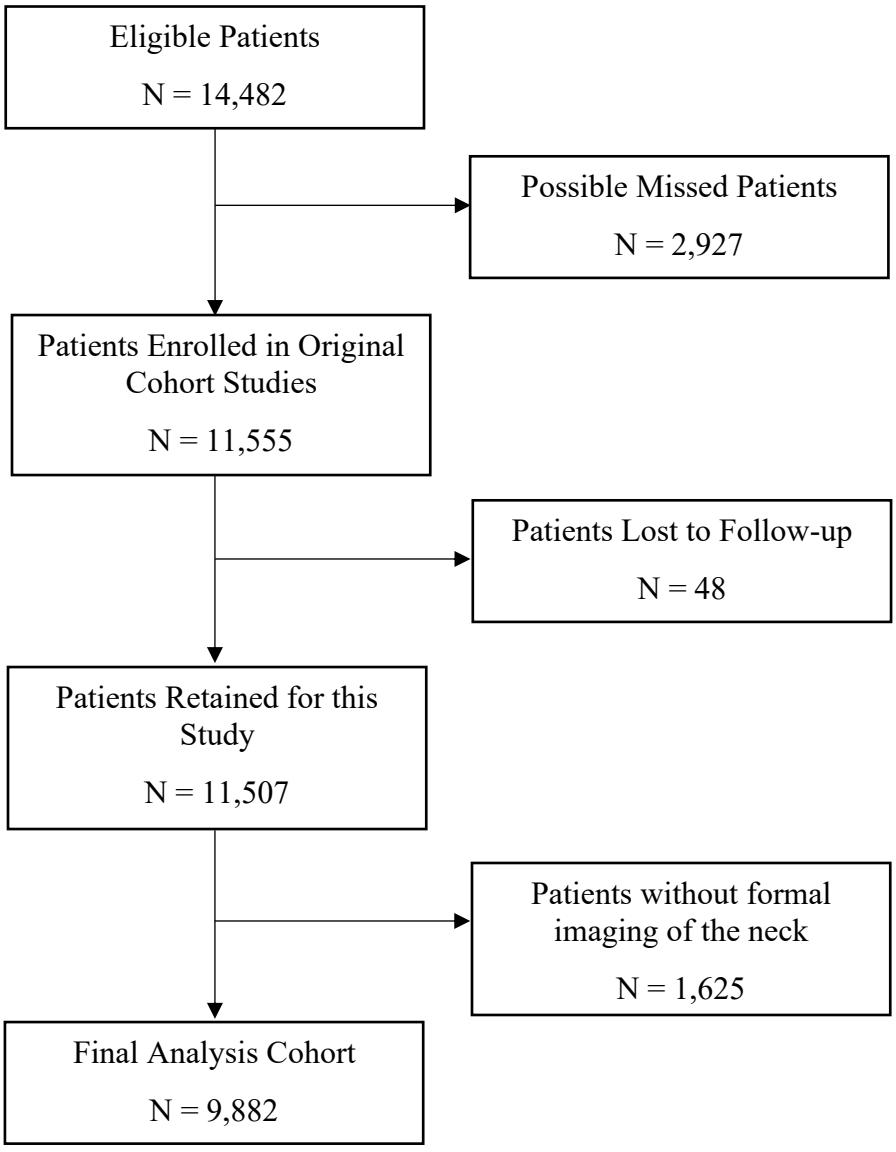
SD, standard deviation; TIA, transient ischemic attack; ECG, electrocardiogram; CT, computed tomography. N/A, not applicable. Data are reported as number (%) unless otherwise stated

eTable 4.4 Summary of the Full Prediction Model

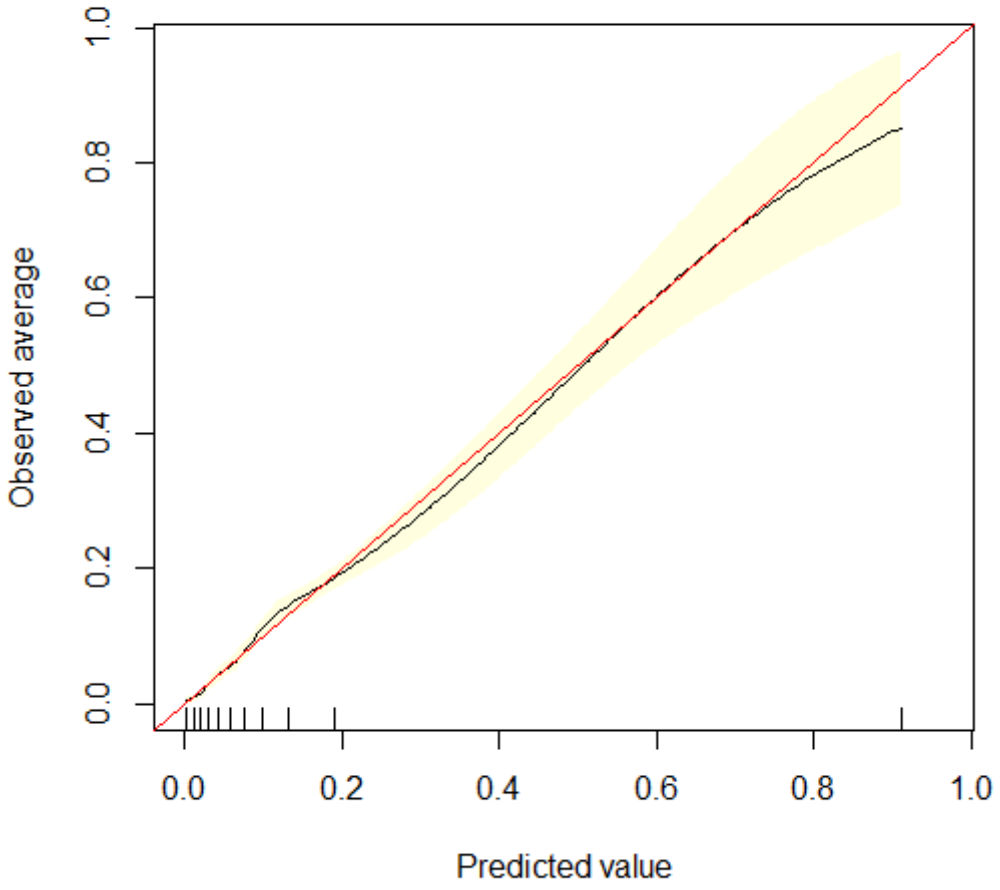
Predictor	**Odds Ratio (95% Confidence Interval)**
Age	
<40	0.3 (0.0, 2.0)
40-49	Reference
50-64	2.7 (1.5, 5.1)
65+	5.0 (2.7, 9.3)
Platelet value ≥ 400 x 10^9/L	1.7 (1.1, 2.6)
Male sex	1.5 (1.3, 1.7)
Initial TIA (Never had TIA in past)	0.8 (0.7, 1)
Duration of symptoms ≥ 10 minutes	0.7 (0.6, 0.9)
Isolated systolic hypertension, SBP >= 150 and DBP < 75	2 (1.6, 2.5)
Isolated systolic hypertension, SBP > 130 and DBP < 80	1.3 (1, 1.6)
History of altered sensation	1.3 (1.1, 1.5)
History of unilateral weakness	1.7 (1.4, 2)
Dysarthria or aphasia (history or exam)	2.5 (2.1, 3)
History of gait disturbance	0.9 (0.7, 1.1)
Visual loss (history or exam)	0.9 (0.7, 1.2)
Lightheaded	0.8 (0.6, 1)
Vertigo	0.5 (0.3, 0.7)
Confusion	0.8 (0.7, 1.1)
Syncope or near syncope	1 (0.7, 1.5)
Abnormal finger-nose test on physical exam	1.2 (0.8, 1.7)
Past medical history: hypertension or already on antihypertensive medications	1.4 (1.1, 1.7)
Past medical history: diabetes or lab glucose > 11 mmol/L	1.1 (0.9, 1.3)
Past medical history: current smoker	1.9 (1.5, 2.5)
Past medical history: congestive heart failure	0.9 (0.6, 1.4)
Past medical history: coronary artery disease	1.2 (1, 1.5)
Past medical history: peripheral vascular disease	1.5 (1.1, 2)
Past medical history: known prior stroke	0.8 (0.7, 1.1)
Past medical history: carotid stenosis	6.5 (4.9, 8.5)
Past medical history: high cholesterol or already on statin medication	1 (0.9, 1.2)
Past medical history: valvular heart disease	1 (0.7, 1.5)
Already on antiplatelet medications	1.2 (1, 1.4)
Atrial fibrillation on ECG	1.1 (0.8, 1.5)
Infarction (new or old) on CT	1.5 (1.3, 1.8)

4.15. eFigures

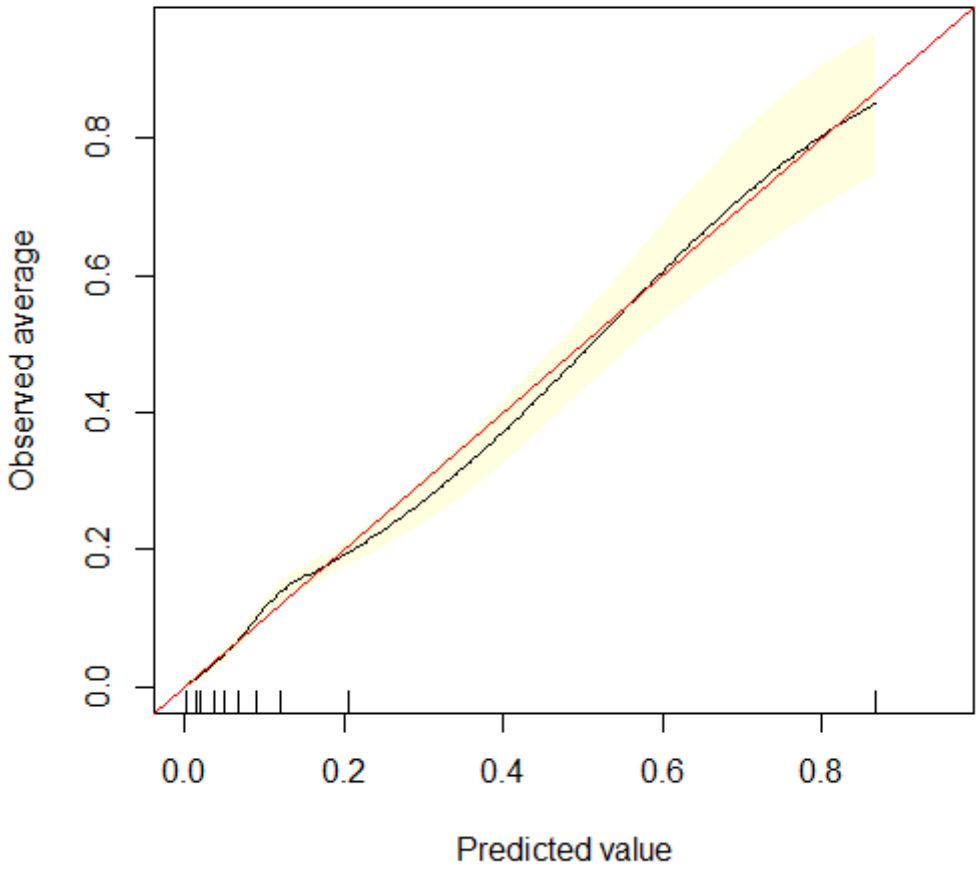
eFigure 4.1 Patient Enrollment



eFigure 4.2 Calibration Plot of the Full Pre-specified Model



eFigure 4.3 Calibration Plot of the Model with the Score as the Only Predictor



5. DISCUSSION

Stroke is a common and serious disorder with a significant portion preceded by TIA/minor stroke. With urgent TIA/minor stroke patient management, a significant portion of ischemic strokes can be prevented. Although there have been advancements in stroke care in the past few decades (90-day stroke risk reduced from 10% to 4%; and down to 1% with optimized care), there is room for improvement. The aim of this thesis was to identify deficiencies in patient management (i.e., clinical areas for improvement), research and reporting and support clinical decision making for management of TIA/minor stroke. Three main areas of TIA/minor stroke patient management were examined, and recommendations and a clinical decision tool provided. The first area of focus was reporting quality of prognostic studies for stroke in patients with TIA/minor stroke. The second was practice variation among Canadian stroke prevention clinics. The third was clinical management of symptomatic carotid artery disease in patients with TIA/minor stroke. in which we derived and internally validated a clinical prediction risk score. Our recommendations and the novel clinical prediction risk score can potentially help improve TIA/minor stroke patient management in the future.

5.1. Summary of research findings

In the first part of the thesis, we conducted a systematic review using comprehensive electronic searches to identify all published studies of clinical prediction models for the prognosis of recurrent stroke within 90 days in patients with TIA/minor stroke. Over 7,000 articles were screened from which 60 articles on the derivation and validation of 27 unique prediction models were retained. The quality of reporting of derivation and validation studies of prediction models for the prognosis of recurrent stroke in patients with TIA and minor stroke was assessed using

the TRIPOD guideline. We found current reporting of multivariable prediction models for the prognosis of stroke in patients with TIA/minor stroke do not meet the TRIPOD guideline for transparent reporting. The most common items to improve upon to meet the reporting of TRIPOD items include providing an informative title, providing a justification for the sample size, providing information on missing data and handling of the missing data, and comparing the validation cohort to derivation cohort when validating. We suggest that authors deriving or validating prediction models adhere to the TRIPOD guideline, more comprehensive guidelines be developed with better instructions for authors, and guidelines be established by journal publishers to enforce transparent reporting.

For the second component of the thesis, we conducted a national electronic survey of Canadian stroke prevention clinics to examine practice variations in TIA/minor stroke management. We found substantial variation among stroke prevention clinics in management practices such as hours of operation, duration of wait times to see high-risk patients, capacity for add-on urgent patients, tests completed prior to appointment, time for results, and referrals of patients with incorrect diagnosis of TIA/minor stroke. Although time is essential for TIA/minor stroke patient management, most high-risk patients are not seen by the clinics within 48 hours, and thus, existing recommendations are not met. Stroke prevention clinics also reported that on average about half of the patients are incorrectly diagnosed and referred to the clinics; thus, impacting wait times for true TIA/minor stroke patients. Wait times for testing are often short except for echocardiogram and Holter. There is a significant variation in the duration of Holter monitoring. We also found a substantial impact of COVID-19 on clinic routines including decline in referrals to stroke prevention clinics, increase in wait times for appointments and test results, and a

decline in TIA/minor stroke mimic referrals. A significant portion of the stroke prevention clinics have started using virtual care during the COVID-19 pandemic and plan to continue with virtual care post-COVID for low to medium risk patients. We suggest that stroke prevention clinics evaluate their management practices and improve patient care by using triaging tools to risk-stratify patients for appointments, increase hours of operation, if needed, to ensure high-risk patients are seen within 48 hours, and increase use of virtual care for low-risk patients to free-up resources for high-risk patients.

In the third component of the thesis, we derived and internally validated a clinical prediction model for the diagnosis of clinically significant symptomatic carotid artery disease from data on 9,882 patients that were prospectively collected for a multicenter TIA/minor stroke study from 2006 to 2017. The derivation and internal validation were guided by robust regression modelling strategies including pre-specification of predictors based on literature review and clinical expertise, use of restricted cubic splines for continuous predictors, and handling of missing data using multiple imputations. From a pre-specified list of 29 predictors, a 13-predictor model was derived. The model has an optimism-corrected C-statistic of 0.781 with a very good calibration. To aid implementation in a clinical setting, we presented the clinical prediction model in an easy-to-use format (i.e., a scoring system) and named it Symcard Score. The total score ranges from -4 to 30 points. The C-statistic for model with the total score as the only predictor was 0.782. The probability of clinically significant symptomatic carotid artery disease was as high as 86.8%. Patients with a predicted probability of <5% (i.e., Symcard Score of 11 or less) were classified as low-risk for clinically significant symptomatic carotid artery disease; patients with a predicted probability of 5% to <10% (i.e., Symcard Score of 12 to 14) were classified as medium-risk; and

patients with higher predicted probabilities (i.e., Symcard Score of 15 or more) were considered high-risk. A clinically sensible score cut-off of 12 points (38.0% of patients) yielded a sensitivity of 92.9%, specificity of 41.1%, and a diagnostic yield of 1.7%. Our scoring system showed that the majority (71.8%) of the TIA patients were at low to medium risk for clinically significant symptomatic carotid artery disease and at least 38.0% of vascular imaging can be delayed or avoided.

5.2. Overall strength and limitations of this thesis

An overall strength of this thesis is that we studied a broad spectrum of areas of TIA/minor stroke patient management for improvement including (a) quality of prognostic models by studying the quality of reporting of derivation and validation tools for TIA/minor stroke patients, (b) flow and management of TIA/minor stroke patients between emergency departments, family physicians, other specialties and stroke prevention clinics, pre, during, and post-COVID-19, and (c) derivation and internal validation of a novel clinical prediction model for the diagnosis and risk-stratification of patients with clinically significant symptomatic carotid artery disease.

To our knowledge, this thesis was the first to study the reporting quality of studies for the prognosis of stroke in patients with TIA/minor stroke. Although we were not able to critically appraise each prediction model due to lack of reporting quality of the studies deriving or validating the clinical prediction models, we were able to study the quality of reporting in such studies. Quality of reporting could be an indication of the quality of the prediction model, in general. The quality of reporting was assessed using a standardized guideline, TRIPOD, so that

the results could be evaluated and compared with other similar reviews studying the quality of reporting of prediction model derivation and validation studies, even if they are for different domains. For example, the quality of reporting of the studies for the derivation and validation of prediction models for stroke in patients with TIA/minor stroke could be compared to the quality of reporting of derivation and validation of studies for the prediction of cancer survival. A limitation of this thesis is that we were unable to assess methodological quality of prediction models due to low reporting quality.

Our survey of Canadian stroke prevention clinics was unique in that it described various areas of variation from referral system to vascular imaging types used to timing of various tests. Another strength of the study was investigating the impact of the COVID-19 pandemic on TIA/minor stroke patient management. This thesis also studied how virtual care was used prior to the COVID period, how it benefited stroke prevention clinics and how it is being planned to be used post-COVID pandemic. However, there were some limitations with the survey. The response rate was lower than expected although it is in line with other electronic surveys and especially surveys of health professionals such as physician leads.[76] Another limitation of this thesis was that we could not link the data from the survey with existing TIA/minor stroke patient data which would have allowed us to assess associations of various practice variations with stroke outcomes.

Another contribution of this thesis was identifying that the majority of TIA/minor stroke patients are at low to medium risk of having clinically significant symptomatic carotid artery disease and hence do not need urgent vascular imaging. This was achieved through derivation and internal

validation of a robust and novel clinical prediction model using prospectively collected data on TIA/minor stroke patients. This thesis in general, and the clinical prediction model more specifically, used data from both tertiary and community hospitals across 14 different sites making the results more generalizable to other communities and settings. The clinical prediction model was formatted into a risk score (Symcard Score) that can be used as is or by electronic means using mobile or web applications. The Symcard Score can be applied independently to TIA/minor stroke patients or be integrated into the Canadian TIA Score and other stroke risk prediction models. It was not possible to externally validate the Symcard Score within the scope of this thesis but a future external validation is being planned. Another limitation of this thesis is that all three components of the thesis were based on a time-based or clinical definition of TIA/minor stroke and so the findings may not validate well in settings using tissue-based definition of TIA/minor stroke. However, it is the clinical definition that is being used in the emergency departments when managing TIA/minor stroke patients. Such a clinical definition is also mostly used for research in the emergency departments.

5.3. Implications for practice and future research

Results from this thesis have several implications for practice and future research on TIA/minor stroke patients. Prior to using any clinical prediction model on patients, its methodological quality needs to be assessed in addition to external validation. Our findings demonstrate that there is inadequate reporting of essential items for critical appraisal of prediction models for the prognosis of recurrent stroke in patients with TIA/minor stroke and hence a possibility of suboptimal methodological quality of such prediction models. Hence, the prediction models should be used with caution until they are appraised and externally validated. Our results add to

the growing number of studies finding poor reporting quality of prediction models and hence the need for further investigation into reasons behind inadequate reporting of such studies and the development of better strategies.

In our survey of stroke prevention clinics, we found that there is delay in seeing some high-risk patients within 48 hours recommended by stroke guidelines. We found that there was an association between not being able to see high-risk patients within 48 hours and number of days the stroke prevention clinics were open during the week. Hence, some stroke prevention clinics either need to increase the number of days they are open or increase the resources, depending on the reasons for such delays at their clinic. We also found that a significant percentage of patients referred to stroke prevention clinics were stroke mimics leading to use of resources and delays for high-risk patients. More effort needs to be put into identifying stroke mimics such as using clinical prediction models to guide some decision making. In this thesis, we also found that the triaging and referral system was better managed when referrals were from a stroke prevention clinic's own emergency department than from other emergency departments. Future research could investigate reasons behind such variation and suggest improvements. Future research could also investigate the association between the number of days a clinic is open and association with stroke outcomes and suggest better strategies for improvement.

As mentioned earlier, a significant percentage of TIA/minor stroke patients are at low risk for clinically significant symptomatic carotid artery disease and therefore do not need urgent vascular imaging. The Symcard Score can potentially help identify these patients with good

discrimination and calibration. Depending on resources and patient volumes, clinicians could use various cut-points from the Symcard Score for triaging and decision making. The Symcard Score could be used independently on TIA/minor stroke patients or be integrated into an existing clinical prediction model for TIA/patients. Given the Symcard Score's performance, there is interest in integrating the Symcard Score into the Canadian TIA Score for risk-stratification. Although the Symcard Score was derived and internally validated on 14 Canadian hospitals, it can be used in other settings after its external validation. Hence, future research will need to externally validate the Symcard Score in various settings prior to use in their hospitals. Future research can also establish the cost effectiveness of using the Symcard Score given that many vascular imaging will be delayed or avoided.

5.4. Conclusions

Stroke is a common and serious disorder worldwide. Urgent TIA/minor stroke diagnosis and treatment is key to prevention of stroke and requires an accurate and coordinated response from all areas of care involved. This thesis identified several areas of TIA/minor stroke patient care requiring improvement and provided support for clinical decision making. We found most derivation and validation studies for the prognosis of stroke in TIA/minor stroke patients have inadequate reporting of essential items for critical appraisal and hence, such prediction models need to be used cautiously. We discovered there is wide variation among stroke prevention clinics in TIA/minor stroke patient management and need for more efficient and urgent care. To support TIA/minor stroke patient care, we derived and internally validated a clinical prediction risk score (Symcard Score) for the diagnosis of clinically significant symptomatic carotid artery disease with a good discrimination and calibration. The Symcard Score will help risk-stratify

patients into low and high-risk for clinically significant symptomatic carotid artery disease and delay or minimize the need for urgent vascular imaging for a significant portion of TIA/minor stroke patients.

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7. GENERAL APPENDICES

7.1. Chapter 2 General Appendices

7.1.1 Published manuscript

Abdulaziz et al. Diagnostic and Prognostic Research (2022) 6:9
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Diagnostic and Prognostic Research

REVIEW

Quality and transparency of reporting derivation and validation prognostic studies of recurrent stroke in patients with TIA and minor stroke: a systematic review

Kasim E. Abdulaziz[1,2*], Jeffrey J. Perry[1,2,3], Krishan Yadav[1,3], Dar Dowlatshahi[2,3,4], Ian G. Stiell[1,2,3], George A. Wells[1,2,5] and Monica Taljaard[1,2]

Abstract

Background: Clinical prediction models/scores help clinicians make optimal evidence-based decisions when caring for their patients. To critically appraise such prediction models for use in a clinical setting, essential information on the derivation and validation of the models needs to be transparently reported. In this systematic review, we assessed the quality of reporting of derivation and validation studies of prediction models for the prognosis of recurrent stroke in patients with transient ischemic attack or minor stroke.

Methods: MEDLINE and EMBASE databases were searched up to February 04, 2020. Studies reporting development or validation of multivariable prognostic models predicting recurrent stroke within 90 days in patients with TIA or minor stroke were included. Included studies were appraised for reporting quality and conduct using a select list of items from the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement.

Results: After screening 7026 articles, 60 eligible articles were retained, consisting of 100 derivation and validation studies of 27 unique prediction models. Four models were newly derived while 23 were developed by validating and updating existing models. Of the 60 articles, 15 (25%) reported an informative title. Among the 100 derivation and validation studies, few reported whether assessment of the outcome (24%) and predictors (12%) was blinded. Similarly, sample size justifications (49%), description of methods for handling missing data (16.1%), and model calibration (5%) were seldom reported. Among the 96 validation studies, 17 (17.7%) clearly reported on similarity (in terms of setting, eligibility criteria, predictors, and outcomes) between the validation and the derivation datasets. Items with the highest prevalence of adherence were the source of data (99%), eligibility criteria (93%), measures of discrimination (81%) and study setting (65%).

* Correspondence:
[1]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[2]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
Full list of author information is available at the end of the article

Conclusions: The majority of derivation and validation studies for the prognosis of recurrent stroke in TIA and minor stroke patients suffer from poor reporting quality. We recommend that all prediction model derivation and validation studies follow the TRIPOD statement to improve transparency and promote uptake of more reliable prediction models in practice.

Trial registration: The protocol for this review was registered with PROSPERO (Registration number CRD42020201130).

Keywords: Prediction models, Prediction rules, Clinical decision rules, Risk scores, Recurrent stroke, Transient ischemic attack, Cerebral ischemia, TRIPOD, CHARMS, Reporting quality

Background

Clinical prediction models (also called clinical prediction rules, clinical prediction scores, clinical decision rules, or prognostic models) aid clinicians in making diagnostic and therapeutic decisions at the bedside and reduce inefficient provision of resources when presented and applied appropriately [1–3]. Such tools are commonly used by clinicians, and especially in the emergency department, to identify patients at high risk of stroke as it is not practical to treat everyone due to limited resources. Transient ischemic attack (TIA, i.e. a cerebral ischemia without lasting symptoms) and minor stroke carry a serious risk of subsequent stroke or death shortly after diagnosis, and thus represent an opportunity for stroke prevention [4].

To maximize the accuracy and clinical utility of clinical prediction models, they need to go through at least two consecutive phases: derivation including internal validation and external validation (evaluation to check accuracy in an independent population and setting) [2, 5–9]. Numerous methodological standards and guides have been developed for clinical prediction modelling [3, 6, 10–14]. Unfortunately, several systematic reviews have indicated shortcomings in methodological quality of many existing prediction studies [14, 15]. In addition to methodological standards for the development and validation of clinical prediction models, appraisal guidelines such as the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) [16] and the Prediction model Risk Of Bias ASsessment Tool (PROBAST) [17] have been developed for data extraction and critical appraisal and assessment of risk of bias in modelling studies. To use such appraisal guides to their full extent, essential items need to be reported in the paper deriving or validating a prediction model. The strengths and weaknesses of a prediction model study can only be revealed with full and transparent reporting to enable its interpretation and usefulness and enhance the uptake and implementation of validated models for use in clinical settings [18]. Complete and transparent reporting also support future prediction model studies by allowing researchers to validate and compare existing prediction models [18]. For this reason, reporting guidelines such as the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) have been developed for studies developing, validating, or updating a prediction model [19].

Several clinical prediction models exist for the prognosis of stroke in patients with TIA and minor stroke. To critically appraise their methodological quality and make recommendations about future updates and/or adoption in clinical practice, better reporting quality of prediction models is essential. Although several systematic reviews have been conducted of the quality of reporting of prediction model studies in various other clinical domains [15, 20–28], to our knowledge, there have been no reviews of the reporting quality of prognostic models for stroke. Thus, we aimed to identify existing clinical prediction models and assess their reporting quality using the recommendations in the TRIPOD statement.

The overall goal of this study is to critically appraise existing derivation and validation studies of prediction models, in terms of reporting quality, for the prognosis of recurrent stroke within 90 days in patients with TIA or minor stroke. The specific objectives are:

1. To identify and characterize derivation and validation studies of existing multivariable clinical prediction models in the literature for the prognosis of recurrent stroke within 90 days in patients with TIA or minor stroke;
2. To characterize the quality of reporting of a select list of essential items for both the derivations and validations.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (See Fig. 1 and Additional file 1) [29]. To help us guide the framing of the review aim, search strategy, and study inclusion and exclusion criteria, we used key items from the TRIPOD and the CHARMS Checklist,

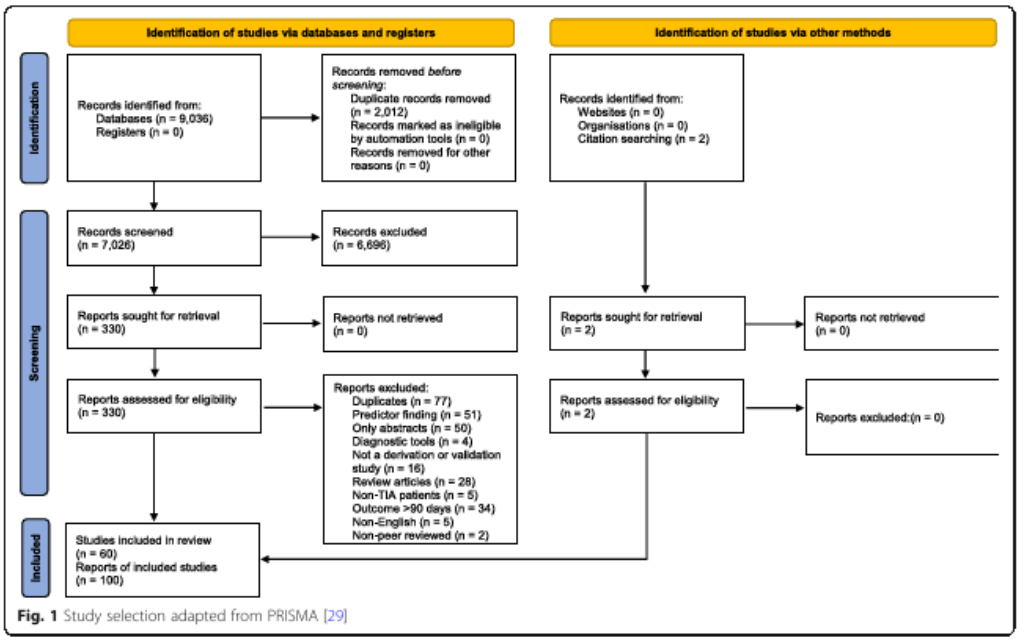

Fig. 1 Study selection adapted from PRISMA [29]

presented in additional files (See Supplementary Table 1, Additional file 2).

Search strategy

We conducted comprehensive electronic searches to identify all published studies of clinical prediction models for the prognosis of recurrent stroke within 90 days in patients with TIA or minor stroke.

We searched the Ovid interface, as well as Medline and Embase databases using a strategy that included the National Library of Medicine's Medical Subject Headings (MeSH) and non-MeSH keywords up to February 04, 2020. The search strategy used TIA and stroke search syntax and used established search filters for prediction models [30–33]. Due to the low quality of reporting of prediction modelling studies, we further modified the search filter by including additional and more specific search terms to be more comprehensive in identifying relevant studies. We developed the search strategy with the help of an experienced medical librarian. It was later validated by a second medical librarian in accordance with the Peer Review of Electronic Search Strategies (PRESS) guidelines [34]. A copy of the search strategy can be found in additional files (See Additional file 3). We also used Google Scholar to search and find any additional articles by searching for relevant keywords in the Google Scholar search engine. In addition, we searched the citations from the included studies for additional eligible studies of clinical prediction models.

Inclusion and exclusion criteria

This systematic review focused on studies of any design that developed or validated multivariable prediction models or scoring rules for the prognosis of recurrent stroke within 90 days for patients diagnosed with TIA or minor stroke.

We considered a clinical prediction model to be any tool that combined at least two predictors to estimate a probability or score for the outcome of stroke within 90 days. We excluded studies that investigated a single predictor, test, or marker. We also excluded studies that investigated only causality between one or more variables and an outcome, and predictor finding studies, i.e. studies which aim to explore which predictors, out of a number of candidate predictors, are independently associated with a diagnostic or prognostic outcome rather than deriving or validating a prediction model [14]. We excluded five studies in languages other than English. We did not apply publication date restrictions.

Screening

After retrieving the potentially relevant articles from the search, we imported the records into Covidence (https://www.covidence.org). We removed duplicates and two

reviewers (KEA and KY) independently screened the title, abstract, and keywords. Prior to embarking on screening, the two reviewers screened a sample of records as part of a training and calibration exercise, and the screening criteria were clarified where necessary.

We retrieved the full text of the articles that were considered potentially relevant by at least one of the reviewers in the title or abstract screen. One of the reviewers then reviewed the full text of each of the articles to determine eligibility. We excluded articles for which we could not obtain full text.

Data extraction

One reviewer (KEA) extracted data from each included study using an extraction form that was specifically designed and pilot tested for the review. We extracted data separately for each derivation or validation cohort (hereafter called cohort) in a publication.

The data extraction form was based on selected items from the TRIPOD and CHARMS checklists for reporting and critical appraisal of prognostic model studies. We focused on items that are essential for the appraisal of derivation and validation studies. Although we initially set out to assess both reporting quality and quality of methodological conduct, we ultimately decided to focus on quality of reporting as our appraisal of methodological conduct was hampered by a lack of clarity in the reporting. For feasibility reasons and to keep the project manageable, we did not assess adherence to all the TRIPOD items. We extracted information pertaining to items 1, 3 through 9, 13, 14, 16, and 22 of the TRIPOD statement, covering the title, background and rationale, methods, and results along with information about funding that was thought to be particularly relevant to the field; we did not extract information about items 2, 10, 11, 15, 17 through 21 covering the abstract, specifics of statistical analysis methods, model specification, discussion, and other information (supplemental information) sections. Some TRIPOD items are applicable to both derivation and validation studies, while others are applicable to validation studies only. We distinguished between validation studies without updating and validation studies with updating (i.e. studies developing an updated model based on an existing model). For validation studies with updating, we also extracted whether the update was performed in accordance with suggested methodology by Su and colleagues [35]. In particular, we extracted whether the order of performing the update was as follows: (a) recalibrating the intercept only, (b) recalibrating the intercept and adjusting the other regression coefficients by a common factor, (c) category b plus extra adjustment of a subset of the existing coefficients to a different strength, (d) category c plus adding new predictors, (e) re-estimating all of the original regression coefficients, and (f) category e plus adding new additional predictors [35]. This order of performing the update was recommended so that authors consider less extensive update methods prior to considering more extensive revisions. For example, it might suffice to recalibrate the intercept only to improve the performance of the model in the setting it is being validated in.

A list of extracted items can be found in additional files (See Supplementary Table 2, Additional file 2).

As this was a study on quality of reporting, we did not perform risk of bias assessment on individual studies. We have registered the protocol for this study with PROSPERO (Registration number CRD42020201130) prior to extracting the data.

Analysis

We summarized and presented the results of this systematic review using descriptive statistics (numbers and percentages). We classified each item as adherent, not adherent, or unclear or not reported. We combined a few studies classified as non-adherent with unclear or not reported to create a combined category of "Non-adherence, unclear, or not reported". In other words, we consider not reporting or unclear reporting as a form of non-adherence.

Results

Search results

Our database search identified 9036 articles. After removal of duplicates, 7026 titles and abstracts were screened for eligibility. After title and abstract screening, 6696 records were excluded leaving 330 full-text articles for eligibility assessment. Two additional articles were later identified by hand searching the reference lists. A total of 60 articles ultimately met our inclusion criteria (Fig. 1). Reasons for exclusion are outlined in Fig. 1.

Study characteristics

A total of 100 derivation and validation studies were performed on 27 prediction models within 60 published articles. Among the 100 derivation and validation studies, 27 were classified as prediction model development (either anew or by model updating) while the remaining 73 were classified as validation. Of the 27 prediction models, four were newly developed (i.e. not based on existing models) while 23 were developed based on existing models (i.e. validation with model updating). All 60 articles were published between 2000 and 2020. The studies were conducted in 18 different countries, mostly the UK (8 or 13.3%) and China (8 or 13.3%) followed by the USA (7 or 11.7%). Countries with three or fewer studies were grouped together under the other category and included the following countries: Austria, Bulgaria,

Canada, Germany, Greece, Italy, Japan, Norway, Singapore, Spain, Sweden, Switzerland, and Turkey. The country of the study was not reported for 4 (6.7%) of the studies.

A list of the included studies can be found in the additional files (See Additional file 4). Distribution of included studies by year of publication is presented in Fig. 2.

Reporting of items applicable at the article level

Results of reporting of items applicable at the article level are presented in Table 1. According to the TRIPOD statement, an informative study title entails identifying the study as derivation or validation of a multivariable prediction model, the target population, and the outcome to be predicted (TRIPOD item 1). Fifteen out of 60 studies (25.0%) adhered to the title recommendations. The source and role of funders (TRIPOD item 22) was provided by 14 (23.3%) of the 60 published articles.

Reporting of essential items common to both derivation and validation studies

Results of reporting of essential items common to derivation and external validation studies are presented in Table 2.

Introduction (TRIPOD item 3)

Background information includes the medical context and rationale for deriving or validating the model. Background information was provided in 66 (66%) derivation and validation studies.

Table 1 Reporting of items applicable at the article level

Characteristic	Number (%) *N* = 60
Clear reporting in the title of the study as derivation or validation of a multivariable prediction model, the target population, and the outcome to be predicted	
Yes	15 (25.0)
Country of study	
UK	8 (13.3)
China	8 (13.3)
USA	7 (11.7)
Iran	5 (8.3)
Australia	4 (6.7)
Others	24 (40.0)
Unclear or not reported	4 (6.7)
Source and role of funders provided	
Yes	14 (23.3)

Methods (TRIPOD items 4–12)

Study design or source of data was reported in 99 (99%) of the 100 derivation and validation studies while key study dates (i.e. start and end dates of cohort data collection) were reported in 95 (95%) and study setting (i.e. tertiary, community, or both) was reported in 65 (65%). Fifty-six (56%) recruited participants from multiple sites with 41 (41%) recruiting from one site. Fifty-one (51%) provided information on their recruitment methods of which 50 (50%) recruited consecutive participants. Eligibility criteria for participants was clearly reported in 93 (93%) of the derivation and validation studies.

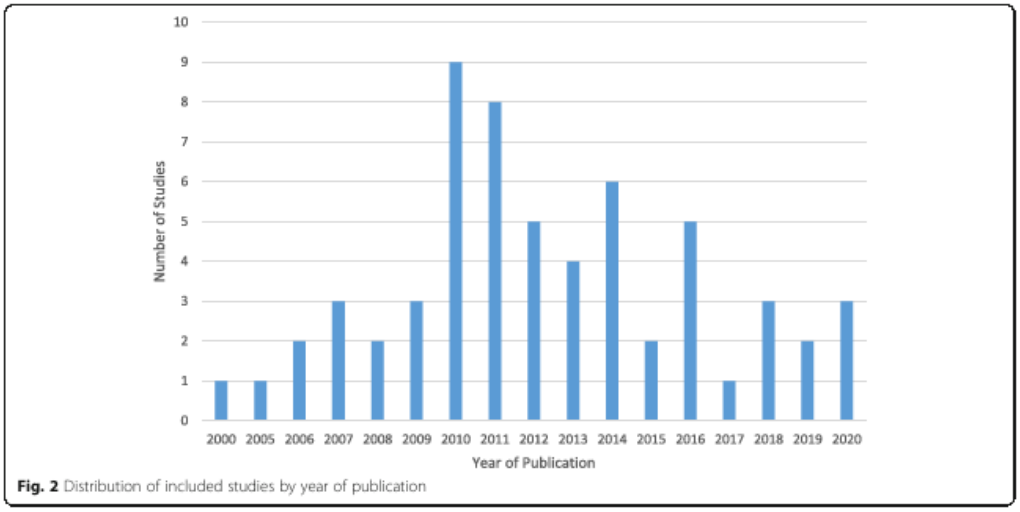

Fig. 2 Distribution of included studies by year of publication

Table 2 Reporting of essential items applicable to both derivation and validation studies

Characteristic	Number (%) *N* = 100
General information	
Rationale provided for the derivation or validation of the model	
Yes	66 (66.0)
Source of data	
Prospective cohort	60 (60.0)
Retrospective cohort—registry data	17 (17.0)
Retrospective cohort—data from past studies	12 (12.0)
Retrospective cohort—chart review	10 (10.0)
Unclear or not reported	1 (1.0)
Inclusion criteria (definition used for selection)	
TIA—Classical time-based definition	92 (92.0)
TIA—Tissue-based definition	5 (5.0)
Minor Stroke—Classical time-based definition	8 (8.0)
Minor Stroke—Tissue-based definition	1 (1.0)
Unclear or not reported	7 (7.0)
Time-based versus tissue-based inclusion criteria	
Time-based TIA/minor stroke	88 (88.0)
Tissue-based TIA/minor stroke	5 (5.0)
Unclear or not reported	7 (7.0)
TIA versus minor stroke inclusion criteria	
TIA only	85 (85.0)
Both TIA and minor stroke	8 (8.0)
Unclear or not reported	7 (7.0)
Definition used for outcome of stroke	
Clinical definition	73 (73.0)
Tissue-based definition	7 (7.0)
Unclear or not reported	20 (20.0)
Time of outcome prediction	
2-day	28 (28.0)
3-day	2 (2.0)
7-day	66 (66.0)
14-day	2 (2.0)
28-day	4 (4.0)
30-day	16 (16.0)
90-day	73 (73.0)
Additional outcome periods considered in study	8 (8.0)
1-year	2 (2.0)
3-year	4 (4.0)
14-year	2 (2.0)
Recruitment method	
Consecutive participants	50 (50.0)
Nonconsecutive sample	1 (1.0)
Unclear or not reported	49 (49.0)

Table 2 Reporting of essential items applicable to both derivation and validation studies *(Continued)*

Characteristic	Number (%) $N = 100$
Number of sites	
1	41 (41.0)
2	2 (2.0)
3	3 (3.0)
4	0 (0.0)
5–9	13 (13.0)
10+	38 (38.0)
Unclear or not reported	3 (3.0)
Setting	
Tertiary	48 (48.0)
Community	10 (10.0)
Tertiary and community	7 (7.0)
Unclear or not reported	35 (35.0)
Location	
Urban	50 (50.0)
Rural	0 (0.0)
Urban and rural	8 (8.0)
Unclear or not reported	42 (42.0)
Study dates were provided	
Yes	95 (95.0)
Outcome to be predicted	
Same outcome definition (and method of measurement) used in all patients	
Yes	44 (44.0)
Explicitly stated that outcome was assessed without knowledge of the candidate predictors (i.e. blinded)	
Yes	24 (24.0)
Candidate predictors	
All measurement predictors defined with information on how to measure	
Yes	63 (63.0)
All measurement predictors defined in terms of when to measure (e.g. pre-hospital, blood pressure measurement time, etc)	
Yes	47 (47.0)
Explicitly stated that predictors were assessed blinded for outcome, and for each other	
Yes	12 (12.0)
Sample size	
Sample size justification provided (practical justification such as using existing study cohort or an RCT data is considered justified)	
Yes	49 (49.0)
Flow of participants provided through a flow diagram	
Yes	21 (21.0)
Missing data	
Number of participants with any missing value (on any of predictors and outcomes) reported	
Yes	34 (34.0)
Number of participants with missing data for each predictor reported	
Yes	28 (28.0)
Number of participants lost to follow-up reported*	

Table 2 Reporting of essential items applicable to both derivation and validation studies *(Continued)*

Characteristic	Number (%) $N = 100$
Yes	17 (27.9)
No, unclear or not reported	44 (72.1)
Not applicable (retrospective cohort)	39 (39.0)
Handling of missing data*	
Complete case analysis	14 (15.1)
Predictor with missing values omitted	0 (0.0)
Single imputation	0 (0.0)
Multiple imputation	1 (1.1)
Not handled, unclear, or not reported	78 (83.9)
Not applicable (there were no missing data)	7 (7.0)
Model performance	
Method used for calibration	
Calibration plot	0 (0.0)
Calibration slope	0 (0.0)
Hosmer-Lemeshow test	5 (5.0)
Unclear or not reported	95 (95.0)
Method used for discrimination	
C-statistic/AUC-ROC	79 (79.0)
D-statistic	0 (0.0)
Log-rank	2 (2.0)
Unclear or not reported	19 (19.0)
Classification measures reported	
Sensitivity	28 (28.0)
Specificity	28 (28.0)
Predictive values	11 (11.0)
Net reclassification improvement	13 (13.0)
Unclear or not reported	60 (60.0)
A priori cut points used for the classification measures	
Yes	25 (25.0)
Confidence intervals (CIs) provided for the performance measures	
Yes	65 (65.0)

*Denominator is the applicable cases

A clear outcome definition (clinical vs tissue-based) was reported in 80 (80%) of the derivation and validation studies. Forty-four (44%) conveyed that the same outcome definition and method of measurement were used in all patients. The majority, 73 (73%), used a 90-day outcome of stroke followed by a 7-day outcome in 66 (66%) followed by other combinations of outcome time periods. Assessment of the outcome without knowledge of the candidate predictors was reported in 24 (24%). In terms of predictor definitions and measurement, a total of 63 (63%) of the derivation and validation studies reported information on how to measure all measurement predictors while 47 (47%) reported information on when to measure all measurement predictors. Assessment of predictors without knowledge of the outcome or other predictors was reported in 12 (12%).

Sample size justification was reported in 49 (49%) of the derivation and validation studies. Information on missing data and methods of handling the missing data were reported in 15 (16.1%) out of 93 applicable derivations and validations with possible missing data. One (1.1%) study reported that a multiple imputation method was used. Information on risk group creation was provided in 25 (25%).

Results (TRIPOD items 13–17)

The flow of participants was reported in 21 (21%) of the derivations and validation studies. Thirty-four (34%) reported information about the prevalence of participants with any missing values, 28 (28%) reported the number of participants with missing data for each predictor, while 7 (7%) reported that there were no missing data.

Measures of discrimination were reported in 81 (81%) of the derivation and validation studies with c-statistic being the most commonly used measure (79%); measures of calibration were reported in 5 (5%), all of which used the Hosmer-Lemeshow test. Sensitivity and specificity were both reported in 28 (28%) while net reclassification improvement and predictive values were reported in 13 (13%) and 11 (11%) respectively.

Reporting of essential items relevant to all validations

Results of reporting of essential items relevant to validation studies only are presented in Table 3.

Methods (TRIPOD items 4–12 relevant to validations only)

Among the 96 validation studies, 17 (17.7%) mentioned either similarities or differences in definitions of all four of setting, eligibility criteria, predictors, and outcomes between the validation and derivation of the model. Similarly, the distribution of important variables of at least age and sex was presented along with the development study counterparts for 21 (21.9%) of the validations.

As for model evaluation, the type of external validation (e.g. temporal, geographical, or methodological) was provided for 94 (97.9%) of the validation studies. The majority or 64 (66.7%) of the external validations were geographical. Of the 96 external validations, 23 were external model validations with model updating.

Reporting of essential items applicable to validations with updating only

Table 4 presents the results of reporting of essential items that are applicable to validation studies with updating only. A rationale for updating the model was provided by all 23 studies. Two (8.7%) studies reported that they have attempted to update the model with less extensive revisions prior to considering more extensive revisions. One study reported applying a method of shrinkage of predictor weights or regression coefficients. When it comes to reporting the results of the updated models, 13 (56.5%) of the studies reported such results (e.g. model specification, model performance, recalibration).

Table 3 Reporting of essential items applicable to validation studies only

Characteristic	Number (%) *N* = 96
Comparison with derivation cohort	
Mention of differences (or no difference) in definitions between the validation and the derivation cohort for each of the following	
Setting	17 (17.7)
Eligibility criteria	21 (21.9)
Predictors	21 (21.9)
Outcome	21 (21.9)
Unclear or not reported	71 (74.0)
Mention of differences (or no difference) in definitions between the validation and the derivation cohort	
Mentioned all four (setting, eligibility, predictors, outcome)	17 (17.7)
Some are mentioned	8 (8.3)
Unclear or not reported	71 (74.0)
Distribution of important variables (demographics [at least age and sex], predictors, and outcome) presented along with the development study	
Yes	21 (21.9)
Model evaluation	
Type of external validation	
Temporal	4 (4.2)
Geographical	64 (66.7)
Methodological/setting (different setting such as ED vs clinic)	26 (27.1)
Unclear or not reported	2 (2.1)
Model adjusted or updated	
Yes	23 (24.0)

Table 4 Reporting of essential items relevant to validation studies with updating only

Characteristic	Number (%) $N = 23$
Rationale provided for updating the model	
Yes	23 (100.0)
Authors showed that less extensive update methods were inadequate prior to considering more extensive revisions[a]	
Yes	2 (8.7)
If the model is derived or updated by methods (c) to (f), was any method of shrinkage of predictor weights or regression coefficients applied[b]	
Uniform shrinkage	0 (0.0)
Penalized estimation	0 (0.0)
Other (method by van Houwelingen)	1 (3.7)
Unclear or not reported	26 (96.3)
Results from model updating (i.e. model specification, model performance, recalibration) presented (i.e. updated intercept, regression coefficients, discrimination with CI or SE, calibration)	
Yes	13 (56.5)

[a]*Less extensive updates*: (a) Recalibrating the intercept only, (b) Recalibrating the intercept and adjust the other regression coefficients by a common factor, (c) Category b plus extra adjustment of a subset of the existing coefficients to a different strength, and (d) Category c plus adding new predictors. *Extensive revisions*: (e) Re-estimating all of the original regression coefficients and (f) category e plus adding new additional predictors
[b]The denominator is 27 ($N = 4$ derivations and $N = 23$ external validation with updating)

A summary of the quality of reporting can be found in Fig. 3.

Discussion

Summary of main findings

We assessed the quality of reporting of derivation and validation studies of prediction models for the prognosis of recurrent stroke in patients with TIA and minor stroke. We found inadequate reporting against selected items in TRIPOD. Items that were especially poorly reported included an informative title, blind assessment of outcome and predictors, sample size justification, use of shrinkage methods, reporting and handling of missing data, reporting of all performance measurements, and comparability between the validation and derivation dataset. Source of data, eligibility criteria, and study setting had better quality of reporting.

Incomplete reporting of blinding is detrimental to assessment of risks of bias and appraisals of the quality of prognostic models. Inadequate sample sizes, a common problem with prediction models, could lead to overfitting and the performance of a prognostic model being overestimated [36, 37]. Sample size justifications for derivation and validation studies are often based on the concept of events per variable (EPV) [10]. However, there is disagreement as to what the EPV should be [10, 38]. More recently, sample size calculation methods have been developed based on the total number of participants, the number of events relative to the number of potential candidate predictor parameters, the outcome proportion (incidence) in the study population, and the

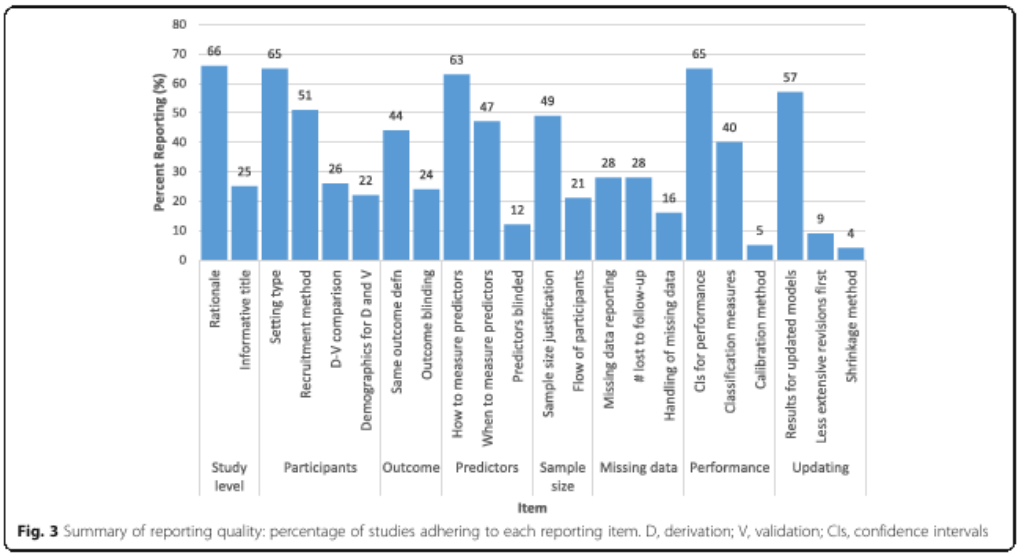

Fig. 3 Summary of reporting quality: percentage of studies adhering to each reporting item. D, derivation; V, validation; CIs, confidence intervals

expected predictive performance of the model [36]. Missing data can present several problems including reduction in statistical power, bias in the estimation of parameters due to data loss, reduction in representativeness of the samples, and complications in the analysis of the study leading to invalid conclusions such as distorted performance of the prediction model [39]. Failure to adequately report on measures of discrimination and calibration prevents users from making informed decisions about the likely accuracy of the model when used in practice. When validating a model externally, similarities or differences in setting, eligibility criteria, predictors, and outcomes between the validation and derivation dataset need to be reported to understand the extent of reproducibility and generalizability of the model.

As in other systematic reviews, we found that some items are less well reported than others. Although it would be ideal to have all items completely reported, they are not equally important for the appraisal of a prediction model's performance. However, they are all still important for the likelihood of future validation and uptake in clinical practice. For example, if information on handling of missing data is not reported, we cannot be certain of the true performance of the prediction model; on the other hand, if the title is not adequately reported as recommended in the TRIPOD statement, it does not mean that the quality of the prediction model is compromised, although retrieval of studies for possible updating would be compromised.

Comparison with other reviews

Our findings are comparable to those in several other systematic reviews of prediction models, published prior to and after the publication of the TRIPOD statement. A systematic review by Heus et al. assessed reporting quality of prediction model studies within 37 clinical domains [20]. Their review excluded studies published prior to the publication of the TRIPOD statement in 2015. Reporting of background information, missing data, and calibration were better than in our review which may be explained by the fact that their review focused on high-impact journals only. Jiang et al. [21] studied the quality of reporting of derivation and validation of melanoma prediction model studies with no restriction on the date of publication. Their findings aligned with our findings although they found better reporting of blinding of predictors and comparability of validation and derivation datasets. A recent systematic review by Najafabadi et al. examined pre- and post-TRIPOD publications in seven high-impact medical journals and found that although there have been some improvements in the methodological conduct, such as better reporting of missing data, use of multiple imputations, reporting the full prediction model and reporting information on performance measures, the overall quality of reporting has not improved [25].

Strengths and limitations

To our knowledge, this is the first systematic review specifically evaluating the reporting quality of derivation and validation studies of prediction models for the prognosis of stroke in patients with TIA. Our results add to the growing number of studies finding poor reporting quality of prediction models.

Our study has some limitations. Although we did not extract information on all TRIPOD items, we extracted and reported most items with an emphasis on reporting rather than methodological conduct. An item that we missed extracting was the reporting of a full model equation. Although we have attempted to extract information on each item in accordance with the TRIPOD statement, we may have been overly conservative in our assessment of some items: for example, we considered blinding of outcome and predictors as reported if and only if they were explicitly mentioned by the authors.

Although we have searched through two of the major medical databases (Medline and Embase) with the help of two experienced medical librarians and with a sensitive search strategy, we may have missed some eligible articles due to inadequate reporting of information by some authors. In addition, we excluded five studies published in non-English languages due to language barriers. Furthermore, our search covered publications up to February 04, 2020, after which there may be additional publications. However, given that this is a review of the quality of reporting and the comparability of our findings to existing systematic reviews, it is unlikely that any possible missed articles would change the conclusion of this systematic review. A final limitation is that the full-text screening and data extractions were conducted by a single reviewer. However, given the objective nature of many items, it is unlikely that there would have been substantial misclassification.

Conclusion

Current reporting of multivariable prediction models for the prognosis of stroke in patients with TIA do not meet TRIPOD requirements for reporting. Essential items in need of improvement are providing an informative title, providing a justification for the sample size, providing information on missing data and handling of missing data, blinding of outcome and predictors, applying and reporting a shrinkage method, and clear reporting around comparability between the validation and derivation cohorts when validating. An example prediction model for the prognosis of stroke with a high number of items reported is the validation of the Canadian TIA

score study [40]. In addition to adhering to the TRIPOD statement, more comprehensive guidance with breakdown of items by study types and examples with templates would be helpful. In other words, to provide details of what is expected of authors for each item with examples and to provide templates for the authors working on prediction model development studies without external validation, prediction model development studies with external validation, and external model validation studies with or without model updating. In addition, transparent and complete reporting can be facilitated by journals and peer reviewers requiring that authors follow the TRIPOD guidelines when submitting a derivation or validation study. Finally, we found a large number of studies validating and updating existing models, in accordance with recommendations that a prediction model be updated rather than a new one created [35]. However, additional guidance is required with respect to validating and updating a prediction model.

Abbreviations

CHARMS: CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies; EVP: Events per variable; MeSH: Medical Subject Headings; PRESS: Peer Review of Electronic Search Strategies; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; PROBAST: Prediction model Risk Of Bias ASsessment Tool; PROSPERO: The International Prospective Register of Systematic Reviews; TIA: Transient ischemic attack; TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41512-022-00123-z.

Additional file 1. PRISMA checklist.

Additional file 2 : Table S1. Key items used to guide the framing of the review aim, search strategy, and study inclusion and exclusion criteria - and - **Table S2.** List of extracted items. This file contains adapted TRIPOD data elements used to design and extract the data.

Additional file 3. Literature Search Strategy.

Additional file 4. List of included studies.

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Authors' contributions

All authors contributed to the concept and design of the study. Article selection was performed by KEA and KY. Data were extracted by KEA. Data analyses were conducted by KEA. KEA, JJP, and MT assisted in interpreting the data. KEA wrote the first draft of the manuscript, which was revised by all authors. All authors approved the final version of the manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

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Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. [2]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada. [3]Department of Emergency Medicine, University of Ottawa, Ottawa, Ontario, Canada. [4]Department of Medicine (Neurology), University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. [5]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

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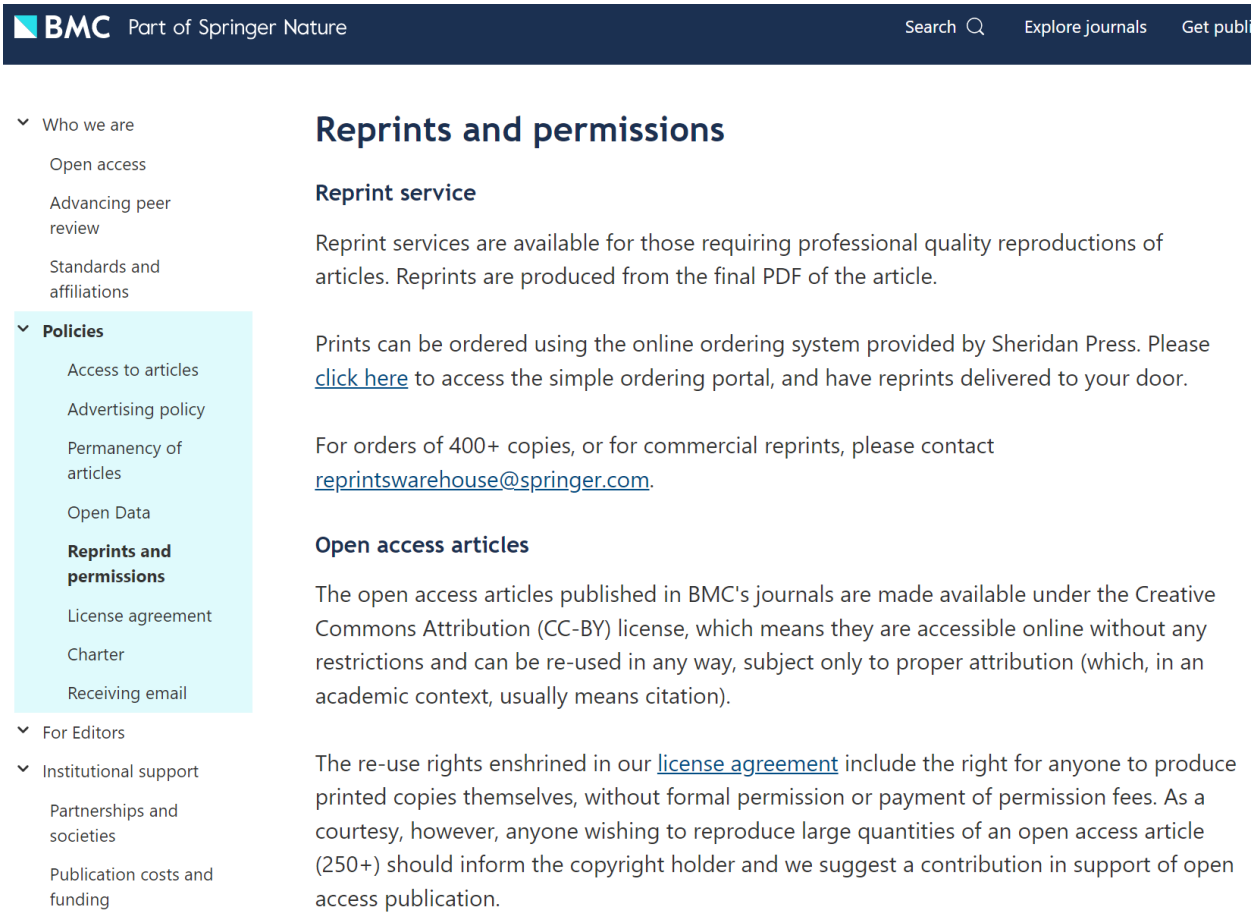

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7.2. Chapter 3 General Appendices

7.2.1 Survey questionnaire – English

Survey of Stroke Prevention Clinics in Canada

A. Eligibility

1. Are you the physician lead or coordinator of the stroke prevention clinic or answering on his/her behalf?
○ Yes
○ No

If No, please let us know by providing us with the lead's contact information on the next page or by sending an email to ######@ohri.ca

If Yes, please complete and submit the questionnaire

B. General Information

*The following questions refer to your **pre-COVID** period.*

2. Could you please tell us who is involved in patient care at your stroke prevention clinic? Select all that apply
☐ Neurologists
☐ Internists
☐ Vascular surgeons
☐ Stroke neurologists
☐ Geriatricians
☐ Family physicians
☐ Nurse practitioner/specialists
☐ Others (please specify): _____

3. Normally, how often is your clinic open?
○ 1 day/week
○ 2 days/week
○ 3 days/week
○ 4 days/week

○ 5 days/week
○ 6 days/week
○ 7 days/week
○ Other (please specify): _____

4. Normally, how many hours is your clinic open during the days it is operating?
○ <4 hours
○ 4-8 hours
○ 9-12 hours
○ >12 hours

5. On average, how many patients, in total, attend the clinic each day the clinic is open? (best estimate)

_____

6. Does your clinic have a way of seeing add-on patients who are not scheduled? (e.g. keep open appointments, extend the clinic hours or increase staffing)
○ Yes
○ No

7. Please indicate the approximate proportion (distribution) of stroke prevention clinic referrals from each of the following sources: (sum should add-up to 100%; if unknown use best estimate)
* Our own organization's emergency department(s): |___|___|___| **%**
* Other local emergency departments: |___|___|___| **%**
* Family physicians: |___|___|___| **%**
* Other specialists: |___|___|___| **%**

8. What kind of appointment/triaging system does your clinic use for patients being referred to your clinic?
○ No appointments, first come first serve basis (e.g. all patients arrive at a clinic at a certain time)
○ Appointment system that considers patient risk level (prioritizes seeing high-risk and moderate-risk patients first)
○ Appointment system but without considering risk levels (e.g. based on date/time of referral)

9. How does your clinic accommodate extra urgent patients on a given day? Select all that apply *{This question is only asked if Q6 is answered with a Yes}*
☐ Clinic hours are extended
☐ Increase staffing
☐ Spots are reserved for urgent cases
☐ Double booking
☐ Rescheduling lower-priority patients when possible
☐ Other (please specify): _____

10. Normally, how long do most high-risk patients wait for an appointment once they have been referred to your clinic? *{Question asked if first item of Q8 is answered, i.e. with risk levels}*

○ Under 24 hours
○ Under 2 days
○ Under 3 days
○ Under 4 days
○ Under 5 days
○ Under 6 days
○ Under 7 days
○ Under 8 days
○ Under 9 days
○ Under 10 days
○ Under 11 days
○ Under 12 days
○ Under 13 days
○ Under 14 days
○ More than 14 days

11. Normally, how long do most low-risk patients wait for an appointment once they have been referred to your clinic? *{Question asked if first item of Q8 is answered, i.e. appointments made considering risk levels}*

○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ Under 30 days
○ Under 3 months
○ More than 3 months

12. Normally, how long do most patients wait for an appointment once they have been referred to your clinic? *{Question asked if 2nd item of Q8 is answered, i.e. appointments made but without risk levels}*

○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ Under 30 days
○ Under 3 months
○ More than 3 months

13. Approximately what proportion of the patients attending your clinic eventually have the initial diagnosis confirmed as a TIA or minor stroke from each of the following sources? (i.e. not thought to have had a stroke mimic) (best estimate)

* Our own organization's emergency department(s): |___|___|___| **%**
* Other organizations' emergency departments: |___|___|___| **%**

* Family physicians: |___|___|___| **%**
* Other specialists: |___|___|___| **%**

14. Does your organization's emergency department have a protocol in place to routinely consult neurology to see patients while they are in the emergency department?
○ Yes, routinely (i.e. see most TIA patients)
○ Yes, only high-risk patients
○ Not routinely
○ Not applicable

15. Does your organization admit patients for revascularization directly from the emergency department (either under neurology or a surgical service)?
○ Yes
○ No
○ Not applicable

C. Medical Imaging

*The following questions refer to your **pre-COVID** period.*

16. On <u>average</u>, what <u>percentage</u> (%) of patients referred from your OWN EMERGENCY DEPARTMENT(S), have each of the following imaging <u>completed</u> by the time they arrive for the appointment at your clinic? (based on data or best estimate) *{Question asked if "Own emergency department" of question 7 is filled with a value other than 0}*
* Brain CT scan: |___|___|___| **%**
* MRI imaging: |___|___|___| **%**
* Vascular imaging (Doppler, CTA, or MRA): |___|___|___| **%**
* 24-hour heart rate monitoring: |___|___|___| **%**
* Echocardiogram: |___|___|___| **%**
* Electrocardiogram (ECG): |___|___|___| **%**

17. On <u>average</u>, what <u>percentage</u> (%) of patients referred from OTHER EMERGENCY DEPARTMENT(S), have each of the following imaging <u>completed</u> by the time they arrive for the appointment at your clinic? (based on data or best estimate) *{Question asked if "Other local emergency department(s)" of question 7 is filled with a value other than 0}*
* Brain CT scan: |___|___|___| **%**
* MRI imaging: |___|___|___| **%**
* Vascular imaging (Doppler, CTA, or MRA): |___|___|___| **%**
* 24-hour heart rate monitoring: |___|___|___| **%**
* Echocardiogram: |___|___|___| **%**
* Electrocardiogram (ECG): |___|___|___| **%**

18. On average, what percentage (%) of patients referred from FAMILY PHYSICIANS, have each of the following imaging completed by the time they arrive for the appointment at your clinic? (based on data or best estimate) *{Question asked if "Family physicians" of question 7 is filled with a value other than 0}*

* Brain CT scan: |___|___|___| **%**
* MRI imaging: |___|___|___| **%**
* Vascular imaging (Doppler, CTA, or MRA): |___|___|___| **%**
* 24-hour heart rate monitoring: |___|___|___| **%**
* Echocardiogram: |___|___|___| **%**
* Electrocardiogram (ECG): |___|___|___| **%**

19. On average, what percentage (%) of patients referred from OTHER SPECIALISTS, have each of the following imaging completed by the time they arrive for the appointment at your clinic? (based on data or best estimate) *{Question asked if "Other" of question 7 is filled with a value other than 0}*

* Brain CT scan: |___|___|___| **%**
* MRI imaging: |___|___|___| **%**
* Vascular imaging (Doppler, CTA, or MRA): |___|___|___| **%**
* 24-hour heart rate monitoring: |___|___|___| **%**
* Echocardiogram: |___|___|___| **%**
* Electrocardiogram (ECG): |___|___|___| **%**

20. For vascular imaging, which modality do you most often use to assess TIA/minor stroke patients? Select all that apply

☐ Doppler
☐ CTA
☐ MRA
☐ Others (please specify): _____

21. For clinic patients that need to have a CT head scan, how long does it normally take for the results to be available?

○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ More than 14 days
○ Not applicable (all of our patients already have a CT head scan completed prior to their appointment)

22. For clinic patients that need to have MR imaging, how long does it normally take for the results to be available?

○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ Under 30 days
○ Under 3 months

○ More than 3 months
○ Not applicable (all of our patients already have an MR imaging completed prior to their appointment)

23. For clinic patients that need to have Doppler ultrasound, how long does it normally take for the results to be available?
○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ More than 14 days
○ Not applicable (all of our patients already have a Doppler ultrasound completed prior to their appointment)

24. Does radiology contact you with important results, such as >50% stenosis, immediately?
○ Yes
○ No

25. For clinic patients that need an echocardiogram, how long does it normally take for the results to be available?
○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ Under 30 days
○ Under 3 months
○ More than 3 months
○ Not applicable (all of our patients already have an echocardiogram completed prior to their appointment)

26. For clinic patients that need Holter monitoring, what duration do you normally request?
○ 24 hours
○ 48 hours
○ 72 hours
○ 7 days
○ 14 days
○ >14 days
○ Not applicable (all of our patients already have a Holter completed prior to their appointment)

27. For clinic patients that need Holter monitoring, how long does it normally take for the results to be available?
○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ Under 30 days
○ Under 3 months
○ More than 3 months

○ Not applicable (all of our patients already have a Holter completed prior to their appointment)

28. When there is a need for urgent investigations, to which of the following can you get quick access (i.e. bypass normal wait times through formal or informal interaction with cardiology or radiology)?
Select all that apply
☐ CT head scan
☐ MRI
☐ Doppler ultrasound
☐ CTA
☐ MRA
☐ Echocardiogram
☐ Holter
☐ None

D. Bloodwork and Medications

*The following questions refer to **pre-COVID** period.*

29. On average, what proportion of patients referred to your clinic from the following sources already have (before arriving for their appointment) completed bloodwork that is normally needed by your clinic? (based on data or best estimate)
* Our own organization's emergency department(s): |___|___|___| **%**
* Other organizations' emergency departments: |___|___|___| **%**
* Family physicians: |___|___|___| **%**
* Other specialists: |___|___|___| **%**

30. For patients needing bloodwork after the clinic assessment, how long does it normally take for the results to be available?
○ Under 24 hours
○ Under 7 days
○ Under 14 days
○ More than 14 days

31. On average, what proportion of patients referred to your clinic from the following sources are already taking prevention drugs (e.g. anticoagulants and antiplatelet) before they arrive at your clinic? (based on data or best estimate)
* Our own organization's emergency department(s): |___|___|___| **%**
* Other organizations' emergency departments: |___|___|___| **%**
* Family physicians: |___|___|___| **%**
* Other specialists: |___|___|___| **%**

E. Impact of the COVID-19 Pandemic

32. Since the onset of the COVID-19 pandemic, to what extent have the following changed compared to your pre-COVID period? (considering an equivalent time period)

	Decreased	No Change	Increased
a. Number of hours the clinic is physically open / week	○	○	○
b. Number of referrals from your own emergency department	○	○	○
c. Number of referrals from other emergency departments	○	○	○
d. Number of referrals from family physicians	○	○	○
e. Number of referrals from other specialists	○	○	○
f. Wait times for an appointment once a patient is referred to your clinic	○	○	○
g. Proportion of true TIA patients vs mimics	○	○	○
h. Number of patients having completed imaging (e.g. CT, MRI, vascular imaging) prior to arriving for their appointment	○	○	○
i. Number of patients having completed bloodwork prior to arriving for their appointment	○	○	○
j. Number of patients already taking prevention drugs (e.g. anticoagulants and antiplatelet) prior to arriving for their appointment	○	○	○
k. If patients need medical imaging done, time it takes to have the results of the imaging (CT, MRI, Doppler, etc) to be available	○	○	○
l. If patients need bloodwork done after arriving, time it takes to have the results of bloodwork to be available	○	○	○

33. Prior to the COVID-19 pandemic, what percentage of your practice consisted of virtual care (e.g. telephone or video-conferencing)?

○ 0%
○ 1-25%
○ 26-50%
○ 51-75%
○ 76-99%
○ 100%

34. Since the onset of the COVID-19 pandemic, what percentage of your practice consists of virtual care?

○ 0%
○ 1-25%
○ 26-50%
○ 51-75%
○ 76-99%

○ 100%

35. Since the onset of the COVID-19 pandemic, which patients do you most often see using virtual care?
○ All patients
○ Most low-risk patients only
○ Most low to medium-risk patients only
○ Not applicable (we don't do virtual care)
○ Other (please specify): _____

36. Do you foresee virtual care being implemented at your site post COVID-19 pandemic and to what extent?
○ Yes, for most patients
○ Yes, for most low-risk patients only
○ No
○ Other (please specify): _____

F. Additional Information

37. Do you have any additional comments regarding this survey?

_____

G. Lead Physician's Contact Information

38. Kindly provide us with the contact information of the lead for your stroke prevention clinic *{this question is asked if the participant answers No on the first question and is redirected to this question)*

Name: _____
Email Address: _____
Phone Number: _____

Thank you for taking the time to complete this questionnaire. Your input is appreciated.

7.2.2 Survey questionnaire – French

Enquête sur les cliniques de prévention des AVC au Canada

A. Admissibilité

1. Êtes-vous le médecin responsable ou le coordinateur de la clinique de prévention des accidents vasculaires cérébraux ou répondez-vous en son nom?
○ Oui
○ Non

Si «Non», veuillez nous le faire savoir en nous fournissant les coordonnées du responsable à la page suivante ou en envoyant un courriel à ######@ohri.ca

Si oui, veuillez remplir et soumettre le questionnaire

B. Informations générales

*Les questions suivantes se rapportent à votre période **avant la COVID**.*

2. Pourriez-vous nous dire qui s'occupe des soins aux patients dans votre clinique de prévention des accidents vasculaires cérébraux? Sélectionnez tous ceux qui s'appliquent
☐ Neurologues
☐ Internistes
☐ Chirurgiens vasculaires
☐ Neurologues spécialistes des AVC
☐ Gériatres
☐ Médecins de famille
☐ Infirmiers praticiens/spécialistes
☐ Autres (veuillez préciser) : _____

3. A quelle fréquence votre clinique est-elle ouverte en temps <u>normal</u>?
○ 1 jour/semaine
○ 2 jours/semaine
○ 3 jours/semaine
○ 4 jours/semaine
○ 5 jours/semaine

○ 6 jours/semaine
○ 7 jours/semaine
○ Autres (veuillez préciser) : _____

4. <u>Normalement</u>, combien d'heures votre clinique est-elle ouverte pendant les jours où elle fonctionne?
○ <4 heures
○ 4 à 8 heures
○ 9 à 12 heures
○ >12 heures

5. <u>En moyenne</u>, combien de patients, au total, fréquentent la clinique chaque jour où elle est ouverte? (meilleure estimation)

_____

6. Votre clinique a-t-elle un moyen de recevoir des patients supplémentaires qui ne sont pas prévus? (par exemple, maintenir des rendez-vous ouverts, prolonger les heures d'ouverture de la clinique ou augmenter le personnel)
○ Oui
○ Non

7. Veuillez indiquer la <u>proportion approximative</u> (répartition) des orientations vers les cliniques de prévention des accidents vasculaires cérébraux provenant de chacune des sources suivantes : (la somme doit être égale à 100 %; si elle est inconnue, utilisez la meilleure estimation)
* Le(s) service(s) d'urgence de notre propre organisation : |___|___|___| **%**
* Autres services d'urgence locaux : |___|___|___| **%**
* Les médecins de famille : |___|___|___| **%**
* Autres spécialistes : |___|___|___| **%**

8. Quel type de système de rendez-vous/triage votre clinique utilise-t-elle pour les patients qui vous sont aiguillés?
○ Pas de rendez-vous, selon le principe du premier arrivé, premier servi (par exemple, tous les patients arrivent dans une clinique à une certaine heure)
○ Système de rendez-vous qui tient compte du niveau de risque du patient (donne la priorité aux patients à risque élevé et à risque modéré)
○ Système de rendez-vous, mais sans tenir compte des niveaux de risque (par exemple, en fonction de la date/heure de l'orientation)

9. Comment votre clinique accueille-t-elle le surplus des patients très urgents? Sélectionnez tout ce qui s'applique *{Cette question n'est posée que si le participant répond «Oui» à la Q6}*
☐ Les heures d'ouverture des cliniques sont prolongées
☐ Augmenter les effectifs

☐ Des places sont réservées aux cas urgents
☐ Double réservation
☐ Changer le rendez-vous des cas moins urgents si possible
☐ Autres (veuillez préciser) : _____

10. <u>En temps normal</u>, combien de temps la plupart des patients à risque élevé attendent-ils pour un rendez-vous une fois qu'ils ont été orientés vers votre clinique? *{Cette question n'est posée que si le participant répond à la première partie de la Q8, c.-à-d., avec risques élevés}*
○ Moins de 24 heures
○ Moins de 2 jours
○ Moins de 3 jours
○ Moins de 4 jours
○ Moins de 5 jours
○ Moins de 6 jours
○ Moins de 7 jours
○ Moins de 8 jours
○ Moins de 9 jours
○ Moins de 10 jours
○ Moins de 11 jours
○ Moins de 12 jours
○ Moins de 13 jours
○ Moins de 14 jours
○ Plus de 14 jours

11. <u>En temps normal</u>, combien de temps la plupart des patients à faible risque attendent-ils pour un rendez-vous une fois qu'ils ont été orientés vers votre clinique? *{Cette question n'est posée que si le participant répond à la première partie de la Q8, c.-à-d., rendez-vous obtenu en raison de risques élevés}*
○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Moins de 30 jours
○ Moins de 3 mois
○ Plus de 3 mois

12. <u>En temps normal</u>, combien de temps la plupart des patients attendent-ils pour un rendez-vous une fois qu'ils ont été orientés vers votre clinique? *{Cette question n'est posée que si le participant répond à la première partie de la Q8, c.-à-d., rendez-vous obtenu mais à faible risque}*
○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Moins de 30 jours
○ Moins de 3 mois
○ Plus de 3 mois

13. Environ quelle proportion des patients qui fréquentent votre clinique voit finalement le diagnostic initial confirmé comme étant un AIT ou un accident vasculaire cérébral mineur par chacune des sources suivantes? (c'est-à-dire qu'on ne pense pas qu'ils aient subi un événement ressemblant à un accident vasculaire cérébral («stroke mimic**»)** (meilleure estimation)
* Le(s) service(s) d'urgence de notre propre organisation : |___|___|___| **%**
* Autres services d'urgence locaux : |___|___|___| **%**
* Les médecins de famille : |___|___|___| **%**
* Autres spécialistes : |___|___|___| **%**

14. Le service d'urgence de votre organisation dispose-t-il d'un protocole permettant de consulter régulièrement le service de neurologie pour voir les patients qui sont admis à **l'urgence?**
○ Oui, de façon régulière (c'est-à-dire voir la plupart des patients ayant subi un AIT)
○ Oui, seulement les patients à risque élevé
○ Pas systématiquement
○ Sans objet

15. Votre organisation admet-elle des patients pour une revascularisation directement à partir du service d'urgence (soit sous la direction d'un service de neurologie ou d'un service chirurgical)**?**
○ Oui
○ Non
○ Sans objet

C. Imagerie médicale

*Les questions suivantes se rapportent à votre période **avant la COVID**.*

16. En moyenne, quel pourcentage (%) des patients aiguillés par votre (vos) PROPRE(S) SERVICE(S) D'URGENCE ont subi chacun des examens d'imagerie suivants avant d'arriver à leurs rendez-vous dans votre clinique? (sur la base de données ou de la meilleure estimation) *{Cette question n'est posée que si le champ «Le(s) service(s) d'urgence de notre propre organisation» de la Q7 a été rempli avec une valeur autre que «0»}*
* TDM de la tête : |___|___|___| **%**
* Imagerie par RM : |___|___|___| **%**
* Imagerie vasculaire (Doppler, ATDM ou ARM) : |___|___|___| **%**
* Surveillance du rythme cardiaque sur 24 heures : |___|___|___| **%**
* Échocardiogramme : |___|___|___| **%**
* Électrocardiogramme (ECG) : |___|___|___| **%**

17. En moyenne, quel est le pourcentage (%) de patients aiguillés par un ou plusieurs AUTRES SERVICES D'URGENCE qui ont subi chacun des examens d'imagerie suivants avant d'arriver à leurs rendez-vous dans votre clinique? (sur la base de données ou de la meilleure estimation) *{Cette question n'est posée que si le champ «Autres services d'urgence locales» de la Q7 a été rempli avec une valeur autre que «0»}*
* TDM de la tête : |___|___|___| **%**

* Imagerie par RM : |___|___|___| **%**
* Imagerie vasculaire (Doppler, ATDM ou ARM) : |___|___|___| **%**
* Surveillance du rythme cardiaque sur 24 heures : |___|___|___| **%**
* Échocardiogramme : |___|___|___| **%**
* Électrocardiogramme (ECG) : |___|___|___| **%**

18. En moyenne, quel est le pourcentage (%) de patients aiguillés par des MÉDECINS DE FAMILLE qui ont subi chacun des examens d'imagerie suivants avant d'arriver à leurs rendez-vous dans votre clinique? (sur la base de données ou de la meilleure estimation) *{Cette question n'est posée que si le champ «Les médecins de famille» de la Q7 a été rempli avec une valeur autre que «0»}*
* TDM de la tête : |___|___|___| **%**
* Imagerie par RM : |___|___|___| **%**
* Imagerie vasculaire (Doppler, ATDM ou ARM) : |___|___|___| **%**
* Surveillance du rythme cardiaque sur 24 heures : |___|___|___| **%**
* Échocardiogramme : |___|___|___| **%**
* Électrocardiogramme (ECG) : |___|___|___| **%**

19. En moyenne, quel est le pourcentage (%) de patients aiguillés par d'AUTRES SPÉCIALISTES qui ont subi chacun des examens d'imagerie suivants avant d'arriver à leurs rendez-vous dans votre clinique? (sur la base de données ou de la meilleure estimation) *{Cette question n'est posée que si le champ «Autres spécialistes» de la Q7 a été rempli avec une valeur autre que «0»}*
* TDM de la tête : |___|___|___| **%**
* Imagerie par RM : |___|___|___| **%**
* Imagerie vasculaire (Doppler, ATDM ou ARM) : |___|___|___| **%**
* Surveillance du rythme cardiaque sur 24 heures : |___|___|___| **%**
* Échocardiogramme : |___|___|___| **%**
* Électrocardiogramme (ECG) : |___|___|___| **%**

20. Pour l'examen d'imagerie vasculaire, quelle modalité utilisez-vous le plus souvent pour évaluer les patients atteints d'AIT ou d'AVC mineur? Sélectionnez tout ce qui s'applique

☐ Doppler
☐ ATDM
☐ ARM
☐ Autres (veuillez préciser) : _____

21. Pour les patients des cliniques qui doivent subir une TDM de la tête, combien de temps faut-il normalement pour que les résultats soient disponibles?

○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Plus de 14 jours
○ Sans objet (tous nos patients ont déjà passé une TDM de la tête avant leur rendez-vous)

22. Pour les patients des cliniques qui ont besoin d'un examen d'imagerie par RM, combien de temps faut-il normalement pour que les résultats soient disponibles?

○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Moins de 30 jours
○ Moins de 3 mois
○ Plus de 3 mois
○ Sans objet (tous nos patients ont déjà subi un examen d'imagerie par RM avant leur rendez-vous)

23. Pour les patients de la clinique qui doivent subir une échographie Doppler, combien de temps faut-il normalement pour que les résultats soient disponibles?

○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Plus de 14 jours
○ Sans objet (tous nos patients ont déjà passé une échographie Doppler avant leur rendez-vous)

24. La radiologie vous contacte-t-elle immédiatement avec des résultats importants, tels qu'une sténose >50 %?

○ Oui
○ Non

25. Pour les patients des cliniques qui ont besoin d'un échocardiogramme, combien de temps faut-il normalement pour que les résultats soient disponibles?

○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Moins de 30 jours
○ Moins de 3 mois
○ Plus de 3 mois
○ Sans objet (tous nos patients ont déjà passé un échocardiogramme avant leur rendez-vous)

26. Pour les patients des cliniques qui ont besoin d'une surveillance par Holter, quelle durée demandez-vous normalement?

○ 24 heures
○ 48 heures
○ 72 heures
○ 7 jours
○ 14 jours
○ >14 jours
○ Sans objet (tous nos patients ont déjà un Holter complété avant leur rendez-vous)

27. Pour les patients des cliniques qui ont besoin d'une surveillance par Holter, combien de temps faut-il normalement pour que les résultats soient disponibles?
○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Moins de 30 jours
○ Moins de 3 mois
○ Plus de 3 mois
○ Sans objet (tous nos patients ont déjà un Holter complété avant leur rendez-vous)

28. Lorsqu'il est nécessaire de procéder à des investigations urgentes, auxquelles pouvez-vous accéder rapidement (c'est-à-dire contourner les délais d'attente normaux grâce à une interaction formelle ou informelle avec la cardiologie ou la radiologie)? Sélectionnez tout ce qui s'applique
☐ TDM de la tête
☐ IRM
☐ Échographie Doppler
☐ ATDM
☐ ARM
☐ Échocardiogramme
☐ Holter
☐ Aucun

D. Analyses sanguines et médicaments

*Les questions suivantes se rapportent à votre période **avant la COVID**.*

29. En moyenne, quelle proportion des patients référés à votre clinique par les sources suivantes ont déjà (avant de se présenter à leur rendez-vous) effectué les analyses sanguines dont votre clinique a normalement besoin? (sur la base de données ou de la meilleure estimation)
* Le(s) service(s) d'urgence de notre propre organisation : |___|___|___| **%**
* Autres services d'urgence locaux : |___|___|___| **%**
* Les médecins de famille : |___|___|___| **%**
* Autres spécialistes : |___|___|___| **%**

30. Pour les patients qui ont besoin d'une analyse sanguine après l'évaluation de la clinique, combien de temps faut-il normalement pour que les résultats soient disponibles?
○ Moins de 24 heures
○ Moins de 7 jours
○ Moins de 14 jours
○ Plus de 14 jours

31. En moyenne, quelle proportion des patients référés à votre clinique par les sources suivantes prennent déjà des médicaments de prévention (par exemple, des anticoagulants et des

antiplaquettaires) avant d'arriver dans votre clinique? (sur la base de données ou de la meilleure estimation)

* Le(s) service(s) d'urgence de notre propre organisation : |___|___|___| **%**
* Autres services d'urgence locaux : |___|___|___| **%**
* Les médecins de famille : |___|___|___| **%**
* Autres spécialistes : |___|___|___| **%**

E. Impact de la pandémie de COVID-19

32. Depuis le début de la pandémie de COVID-19, dans quelle mesure les éléments suivants ont-ils changé par rapport à la période précédant la COVID? (en considérant une période équivalente)

	Diminution	**Pas de changement**	**Augmentation**
a. Nombre d'heures d'ouverture de la clinique/semaine	o	o	o
b. Nombre de patients référés par votre propre service d'urgence	o	o	o
c. Nombre de patients référés par d'autres services d'urgence	o	o	o
d. Nombre de patients référés par les médecins de famille	o	o	o
e. Nombre de patients référés par d'autres spécialistes	o	o	o
f. Délais d'attente pour un rendez-vous une fois qu'un patient est aiguillé vers votre clinique	o	o	o
g. Proportion de patients ayant subi un vrai AIT par rapport aux imités	o	o	o
h. Nombre de patients ayant effectué un examen d'imagerie (par exemple, TDM, IRM, imagerie vasculaire) avant de se présenter à leur rendez-vous	o	o	o
i. Nombre de patients ayant effectué des analyses sanguines avant de se présenter à leur rendez-vous	o	o	o
j. Nombre de patients prenant déjà des médicaments de prévention (par exemple, anticoagulants et antiplaquettaires) avant de se présenter à leur rendez-vous	o	o	o

k. Si les patients ont besoin d'un examen d'imagerie médicale, combien de temps faut-il pour que le résultat (TDM, IRM, Doppler, etc.) soit disponible	○	○	○
l. Si les patients doivent effectuer des analyses sanguines après leur arrivée, combien de temps faut-il pour que les résultats de ces analyses soient disponibles	○	○	○

33. Avant la pandémie de COVID-19, quel pourcentage de votre pratique consistait en des soins virtuels (par exemple, par téléphone ou vidéoconférence)?

○ 0 %
○ 1 à 25 %
○ 26 à 50 %
○ 51 à 75 %
○ 76 à 99 %
○ 100 %

34. Depuis le début de la pandémie de COVID-19, quel pourcentage de votre pratique consiste en des soins virtuels?

○ 0 %
○ 1 à 25 %
○ 26 à 50 %
○ 51 à 75 %
○ 76 à 99 %
○ 100 %

35. Depuis le début de la pandémie de COVID-19, quels sont les patients que vous voyez le plus souvent en utilisant les soins virtuels?

○ Tous les patients
○ La plupart des patients à faible risque seulement
○ La plupart des patients à risque faible ou moyen seulement
○ Sans objet (nous ne faisons pas de soins virtuels)
○ Autres (veuillez préciser) : _____

36. Prévoyez-vous la mise en place de soins virtuels sur votre site à la suite de la pandémie de COVID-19 et dans quelle mesure?

○ Oui, pour la plupart des patients
○ Oui, pour la plupart des patients à faible risque seulement
○ Non
○ Autres (veuillez préciser): _____

F. Informations complémentaires

37. Avez-vous d'autres commentaires concernant ce sondage?

_____

G. Coordonnées du médecin responsable

38. Veuillez nous fournir les coordonnées du responsable de votre clinique de prévention des AVC
{cette question est posée si le participant répond «Non» à la première question et est redirigé vers cette question}

Nom : _____
Adresse électronique : _____
Numéro de téléphone : _____

Merci d'avoir pris le temps de remplir ce questionnaire. Votre contribution est appréciée.

7.2.3 Certificate of translation

The Ottawa Hospital | L'Hôpital d'Ottawa

Note to File

Date: April 14, 2021

RE: 20200705-01H – Stroke Risk Assessment in Emergency Department

Subject: Certification of Translation

Please be advised that the translation from English to French is a true and accurate translation of the following:

Questionnaire of SPC, dated 2020-12-06	First Reminder Email Script, dated 2021-02-02
Final Reminder Phone Script, dated 2021-01-14	Second Reminder Email Script, dated 2021-02-02
Recruitment Email Script, dated 2021-02-02	Third Reminder Email Script, dated 2021-02-02
Landing Page Survey, dated 2021-01-14	Fourth Reminder Email Script, dated 2021-02-02

Éric Lépine
Name of Translator

Signature of Translator

April 14, 2021
Date

***Please ensure you provide this *Certificate of Translation* with your submission to REB.**

Inspired by research. Inspiré par la recherche.
Driven by compassion. Guidé par la compassion.

7.2.4 Research Ethics Board Approvals

The Ottawa Hospital | L'Hôpital d'Ottawa

RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

February 08, 2021

Dr. Jeffrey Perry

Ottawa Hospital - Civic Campus
Department of Emergency Medicine
F6, Room 647
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Re: OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

Protocol ID#: 20200705-01H;

Stroke Risk Assessment in the Emergency Department: Prognostic Models, Test Modalities and Variation of Practice

Dear Dr. Jeffrey Perry,

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact REBadministration@ohri.ca or 613-798-5555 extension 16719.

Nancy Camack, BScN RN MBA CCRP
Director, Clinical Research Administration
Ottawa Hospital Research Institute | Institut de recherche de l'Hôpital d'Ottawa

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9
613-798-5555 extension 16719 Fax : 613-761-4311 http://www.ohri.ca/ohsn-reb

The Ottawa Hospital | L'Hôpital d'Ottawa

uOttawa

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Date:	April 29, 2021
Principal Investigator:	Dr. Jeffrey Perry, TOH/OHRI
Protocol ID:	20200705-01H
Study Title:	Stroke Risk Assessment in the Emergency Department: Prognostic Models, Test Modalities and Variation of Practice
Post Approval Submission Type:	French Translated Documents
Review Type:	Delegated
Translated Documents Approval Date:	April 29, 2021
Approval Expiry Date:	February 5, 2022

Dear Dr. Perry,

The Ottawa Health Science Network Research Ethics Board has reviewed the French translated document(s) and translation certificate(s) and granted approval as of the date noted above.

Documents Approved:

Document Name	Document Version Date
French Final Reminder Phone Script	January 14, 2021
French 1st Reminder Email Script	February 2, 2021
French 2nd Reminder Email Script	February 2, 2021
French 3rd Reminder Email Script	February 2, 2021
French 4th Reminder Email Script	February 2, 2021
French Landing Page of Survey	January 14, 2021
French Questionnaire of SPCs	December 6, 2020
French Recruitment Email Script	February 2, 2021

REB members involved in the research project do not participate in the review, discussion or decision.

If the study is to continue beyond the expiry date noted above, a Continuing Review Form must be received by the OHSN-REB on or prior to the full board submission deadline date of the meeting scheduled to occur a minimum of 30 days prior to the study expiry date. If the study has been completed by the expiry noted above, a Study Closure Report must be received by the OHSN-REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the Clinical Trials Ontario REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

/ac

7.2.5 Published manuscript

The Canadian Journal of Neurological Sciences (2022), 1–10
doi:10.1017/cjn.2022.260

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Practice Variation among Canadian Stroke Prevention Clinics: Pre, During, and Post-COVID-19

Kasim E. Abdulaziz[1,2], Monica Taljaard[1,2], Dar Dowlatshahi[2,3,4], Ian G. Stiell[1,2,3], George A. Wells[1,2,5] and Jeffrey J. Perry[1,2,3]

[1]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, [2]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, [3]Department of Emergency Medicine, University of Ottawa, Ottawa, Ontario, Canada, [4]Department of Medicine (Neurology), University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada and [5]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

ABSTRACT: ***Background:*** Stroke is a common and serious disorder. With optimal care, 90-day recurrent stroke risk can be reduced from 10% to about 1%. Stroke prevention clinics (SPCs) can improve patient outcomes and resource allocation but lack standardization in patient management. The extent of variation in patient management among SPCs is unknown. Our aims were to assess baseline practice variation between Canadian SPCs and the impact of COVID-19 on SPC patient care. ***Methods:*** We conducted an electronic survey of 80 SPCs across Canada from May to November 2021. SPC leads were contacted by email with up to five reminders. ***Results:*** Of 80 SPCs contacted, 76 were eligible from which 38 (50.0%) responded. The majority (65.8%) of SPCs are open 5 or more days a week. Tests are more likely to be completed before the SPC visit if referrals were from clinic's own emergency department compared to other referring sources. COVID-19 had a negative impact on routine patient care including longer wait times (increased for 36.4% clinics) and higher number of patients without completed bloodwork prior to arriving for appointments (increased for 27.3% clinics). During COVID-19 pandemic, 87.9% of SPCs provided virtual care while 72.7% plan to continue with virtual care post-COVID-19 pandemic. ***Conclusion:*** Despite the time-sensitive nature of transient ischemic attack patient management, some SPCs in Canada are not able to see patients quickly. SPCs should endeavor to implement strategies so that they can see high-risk patients within the highest risk timeline and implement strategies to complete some tests while waiting for SPC appointment.

RÉSUMÉ : ***Variation des pratiques dans les cliniques canadiennes de prévention des AVC : avant, pendant et après la pandémie de COVID-19. Contexte :*** Les AVC sont des affections courantes et graves. Avec des soins optimaux, le risque de récidive d'un AVC pendant une période de 90 jours peut être réduit de 10 à environ 1 %. Les cliniques de prévention des AVC (CPAVC) peuvent améliorer l'évolution de l'état de santé des patients et l'allocation des ressources, mais elles manquent de pratiques standardisées en matière de prise en charge des patients. L'étendue de la variation de ces pratiques parmi les CPAVC demeure inconnue. Notre objectif a donc consisté ici à évaluer la variation de ces pratiques au sein des CPAVC canadiennes et à mesurer l'impact de la pandémie de COVID-19 sur les soins prodigués aux patients. ***Méthodes :*** Pour ce faire, nous avons mené de mai à novembre 2021 un sondage électronique auprès de 80 CPAVC situées partout au Canada. À noter que les responsables de ces cliniques ont été contactés par courriel avec jusqu'à cinq rappels. ***Résultats :*** Sur 80 CPAVC contactées, 76 étaient admissibles ; 38 d'entre elles (50,0 %) ont répondu. La majorité (65,8 %) des CPAVC sont ouvertes cinq jours ou plus par semaine. Des tests de dépistage d'une infection à la COVID-19 sont apparus plus susceptibles d'être effectués avant de visiter ces établissements si les patients avaient été orientés par le service des urgences de la clinique plutôt que par d'autres sources. La pandémie de COVID-19 a également eu un impact négatif sur les soins de routine prodigués aux patients, notamment des temps d'attente plus longs (36,4 % des CPAVC) et un nombre plus élevé de patients n'ayant pas effectué d'analyses sanguines avant leur rendez-vous (27,3 % des CPAVC). Pendant la pandémie de COVID-19, il est à noter que 87,9 % des CPAVC ont fourni des soins virtuels et que 72,7 % d'entre elles prévoient de continuer à le faire après la pandémie de COVID-19. ***Conclusion :*** Bien qu'une prise en charge rapide de ces patients soit importante, certaines CPAVC au Canada ne sont pas en mesure de les voir rapidement. Elles devraient ainsi s'efforcer de mettre en œuvre des stratégies leur permettant de voir les patients à haut risque dans des délais plus courts et d'adopter des stratégies pour effectuer certains tests de dépistage en attendant un rendez-vous.

Keywords: Transient ischemic attack; Rapid access clinics; Neck imaging; Timing of tests; TIA patient management; COVID-19 impact; Virtual care; Telemedicine; Telehealth

(Received 30 April 2022; date of acceptance 27 May 2022)

Correspondence to: Kasim E. Abdulaziz. E-mail:
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Introduction

Stroke is a common disorder and a leading cause of death and disability worldwide.[1] Transient ischemic attack (TIA) or minor stroke patients (here onwards just called TIA) are at elevated risk of a subsequent stroke in the days to weeks following their initial event.[2,3] Up to 10% of patients with TIA will have a subsequent stroke within 90 days without urgent care, but with optimized treatment this risk can be reduced to about 1%.[4,5] The urgency and level of care provided for TIA patients often depends on the perceived risk of subsequent major stroke.[6,7] Traditionally, and still in some parts of the world, TIA patients were admitted to hospital for rapid investigation and comprehensive management.[8] In an effort to optimize health resource utilization with improved patient outcomes, outpatient-based models have been introduced.[8–11] A stroke prevention clinic (SPC) is a specialized outpatient clinic that provides rapid access to experts, diagnostic tests, and treatments. Such clinics are meant to provide an integrated, comprehensive, and interdisciplinary approach to stroke prevention in a timely manner.

In Canada, the Canadian Stroke Best Practice Recommendations (CSBPR) provide guidelines for the prevention and management of stroke.[12] However, we suspect that they are not always followed, for varying reasons, leading to variation in how patients with suspected TIA are identified and managed.[13,14] For example, although CSBPR suggests managing high-risk patients within 48 hours of symptom onset, we suspect that not all organizations meet this recommendation. From information-gathering interviews with local neurologists (key informants), we found that some SPCs might (a) be open limited hours a week, (b) triage patients without assessing and considering risk levels, (c) have protocols in place to have patients complete some tests prior to their clinic appointment, (d) have long wait times for some tests which varies depending on referring source, and (e) lack urgent communication protocols between SPCs and radiology departments. The extent of variation in practice is unknown. Understanding the extent of variation in practice can help develop or modify strategies and guidelines to standardize practices across SPCs which may ultimately reduce the incidence of subsequent stroke.

To understand the extent of variation we conducted a survey of all Canadian SPCs. Prior to implementing the survey, the COVID-19 pandemic started and so we modified our questionnaire to include additional items to understand the impact of the COVID-19 pandemic on TIA patient management.

The aims of this study were twofold: (1) to describe variation in management practices for TIA patients and (2) to characterize the impact of the COVID-19 pandemic on the management of TIA patients including the use of virtual care by the SPCs.

Methods

Study Design and Participants

We conducted a self-administered electronic survey of SPCs in Canada. To be eligible, the respondents must have been physician leads, managers, or coordinators at any of the SPCs in Canada. A list of SPCs was provided by the Heart and Stroke Foundation of Canada from which we identified 80 unique SPCs as of May 5, 2021. We obtained the contact information of the person running each SPC using web searches and by calling the clinics. The study was conducted from May 2021 through November 2021. We designed the survey following Dillman's techniques.[15] This study has received Ottawa Health Science Network Research Ethics Board approval.

Questionnaire Development

We developed the questionnaire in three stages. First, we conducted telephone interviews with key informants to gather information to prepare a draft survey questionnaire. Second, we conducted cognitive interviews (assessing participants' understanding of the questionnaire as they complete each question) to evaluate the clarity, comprehensibility, and face validity of each question in the draft survey. Third, we pilot tested the draft survey questionnaire using a smaller subsample of the SPCs to assess the whole questionnaire and the survey process.[15]

The final questionnaire included 36 questions. Questionnaires consisted of an eligibility question, information about clinic hours of operation and scheduling (14 items), medical imaging (13 items), bloodwork and medications (three items), impact of the COVID-19 pandemic (five items), and additional information (one item). To improve response rate, most items (including questions on wait times) were designed as closed-ended questions where respondents' answers were limited to a fixed set of responses. The questionnaire was developed with attention to clarity regarding question applicability to the pre-pandemic period. The questionnaire, landing page, recruitment, and reminder emails were translated into French by a medical translator.

Survey Administration

The survey invitation was personalized for each SPC so that the lead's name was inserted on all emails along with a unique link for each clinic. Every email and the landing page of the survey included names of the lead principal investigators, contact information, and affiliations, as an indication of a legitimate source.

We pilot tested the survey on 15 SPCs across the provinces and territories. After revising the survey questionnaire for clarity and verifying the feasibility of the process (i.e., our survey questions were answered as intended), invitations were distributed to the remaining 65 SPCs.

The survey was initiated with a recruitment email containing both official languages (English and French) and links to the survey powered by SurveyMonkey (www.surveymonkey.com). A reminder email along with links to the survey questionnaire was emailed every week to non-responders for up to 4 weeks. A final reminder was initiated 2 weeks after the last email reminder by calling the clinic. Several attempts were made to reach clinics by telephone over a period of 3 weeks.

Data Analysis

We calculated descriptive statistics to characterize the SPC responses. Continuous variables were expressed as mean and standard deviation or median with interquartile ranges (IQR), while categorical data were expressed as frequencies and percentages. We used boxplots to help visualize the distribution of some of the continuous variables. Chi-squared tests were conducted to compare the geographic region (Western Canada, Ontario, and Eastern Canada) of respondents and non-respondents to examine the possibility of non-response bias. We used Fisher's exact test to study the association between seeing high-risk patients within 48 hours and number of days clinics are open. Two-sided significance tests were set at an alpha level of 0.05.

We grouped data based on referring source and other characteristics to organize the results. To reduce the number of items in the tables, we combined categories with sparse numbers. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 80 SPCs invited, four indicated they were ineligible (by answering "no" to the question: "are you the physician lead or coordinator/manager of the SPC or answering on his/her behalf?"). Of the remaining 76 SPCs, 38 (50.0%) completed the electronic survey (including eight from the pilot survey and four from final phone reminders). Five respondents provided partial responses.

Table 1 describes the structure of the SPCs. The clinics were open from half a day per week (2.6%) up to 7 days per week (2.6%) with about a quarter (26.3%) being open 2 days or fewer per week. Two-thirds (63.2%) of the clinics were open 5 days a week. Clinic hours varied from less than 4 hours to more than 12 hours per day. Table 2 shows that there is a significant difference in being able to see most high-risk TIA patients within 48 hours and how many days the clinics are open during the week. A small portion (10.5%) of the clinics do not accommodate urgent patients. Patient referrals to the clinics are mostly from their own emergency departments (EDs) (median percentage of patients referred (IQR): 50 (40–70)) followed by family physicians (median (IQR): 20 (15–30)). The initial diagnosis of TIA was confirmed less often when the referral was from family physicians (median (IQR): 30 (20–50)) compared to the organization's own ED, other EDs, or other specialists. Except for one clinic (2.6%), all the clinics use an appointment system that considers patient risk level. The clinic that does not consider risk levels normally sees all patients within a week. For clinics that do consider patient risk levels, the wait times for low-risk patients are within 30 days for 64.8% of SPCs. Wait times for high-risk patients are within 24 hours for 8.1% of SPCs and between 1 and 2 days for 29.7% of SPCs. We found that 29.0% of the clinics do not a have a protocol in place to consult neurology while the patient is in the ED while 32.3% consult neurology for high-risk patients only. We found 60.0% of the organizations admit patients for revascularization directly from the ED. Two clinics are not able to bypass normal wait times for vascular imaging for urgent cases.

To test for the possibility of non-response bias, we compared the geographic region (Western Canada, Ontario, and Eastern Canada) of respondents and non-respondents. Chi-squared analysis showed no indication of a significant difference (p value: 0.17) in responses when we compared the regions (Table 3). We did not have other characteristics to test for non-response bias.

Figure 1 provides the proportion of patients with completed tests at the SPC assessment. When referrals were from the organization's own ED, most tests were already completed. There was more variation for family physician and other specialist referrals. MRI, 24-hour heart rate monitoring, and echocardiogram were the least likely to be completed at the time of SPC assessments.

Duration of waiting times for test results is as follows: for CT, 77.8% within 24 hours and 11.1% between 1 and 7 days; for MRI, 43.8% within 24 hours and 31.3% between 1 and 7 days; for Doppler ultrasound 51.6% within 24 hours and 25.8% between 1 and 7 days; for echocardiogram 15.2% within 24 hours while 36.4% between 1 and 7 days; for Holter 30.3% between 1 and 7 days

Table 1: Characteristics of stroke prevention clinics

Information	Number (%) ($N = 38$)
Professionals involved in care at clinic	
Neurologists	17 (44.7)
Nurse practitioner/specialists	17 (44.7)
Internists	16 (42.1)
Stroke neurologists	15 (39.5)
Registered nurses	11 (29.0)
Vascular surgeons	4 (10.5)
Others	4 (10.5)
Family physicians	1 (2.6)
Geriatricians	0 (0.0)
Days per week clinic is open	
½	1 (2.6)
1	5 (13.2)
2	4 (10.5)
3	1 (2.6)
4	2 (5.3)
5	24 (63.2)
6	0 (0.0)
7	1 (2.6)
Hours per day clinic is open	
<4	5 (13.2)
4–8	30 (79.0)
9–12	2 (5.3)
>12	1 (2.6)
Number of patients seen each day clinic is open, median (IQR)	7 (5–15)
Distribution of patient referrals, median (IQR)	
Own ED	50 (40–70)
Other ED	15 (7–20)
Family physicians	20 (15–30)
Other specialists	5 (5–15)
Initial diagnosis confirmed as a TIA by referral, median (IQR)	
Own ED	50 (30–70)
Other ED	50 (20–60)
Family physicians	30 (20–50)
Other specialists	50 (20–60)
No capacity for add-on urgent patients	6 (15.8)
Triaging system	
No appointments, first-come first-served basis	0 (0.0)
Appointment system without considering risk levels	1 (2.6)
Appointment system that considers risk level	37 (97.4)
Wait times for appointment system that considers risk level	
Low risk:	
<24 hours	0 (0.0)
<7 days	4 (10.8)

(*Continued*)

Table 1: (*Continued*)

Information	Number (%) ($N = 38$)
<14 days	8 (21.6)
<30 days	12 (32.4)
<3 months	10 (27.0)
>3 months	2 (5.4)
High risk:	
<24 hours	3 (8.1)
<2 days	11 (29.7)
<3 days	8 (21.6)
<4 days	1 (2.7)
<5 days	3 (8.1)
<6 days	0 (0.0)
<7 days	4 (10.8)
<14 days	6 (16.2)
>14 days	0 (0.0)
ED has a protocol to consult neurology	
Yes, routinely	11 (35.5)
Yes, only high-risk patients	10 (32.3)
Not routinely	9 (29.0)
Missing	1 (3.2)
Admit patients for revascularization directly from the ED	18 (60.0)
Modalities most often used for vascular imaging	
Computed tomography angiography (CTA)	30 (79.0)
Doppler	14 (36.8)
Magnetic resonance angiography (MRA)	0 (0.0)
Clinic is notified immediately by radiology with important results, such as >50% stenosis	14 (36.8)
For urgent cases, clinic cannot bypass normal wait times	2 (5.3)
Holter monitor duration normally requested	
24 hours	7 (18.4)
48 hours	8 (21.1)
72 hours	2 (5.3)
7 days	3 (7.9)
14 days	9 (23.7)
>14 days	4 (10.5)
Missing	5 (13.2)

ED, Emergency Department; IQR, interquartile range; TIA, transient ischemic attack.

and 33.3% between 8 and 14 days; for bloodwork 45.5% within 24 hours and 45.5% between 1 and 7 days (Figure 2).

Virtual Care and Impact of COVID-19 Pandemic on TIA Stroke Patient Management

Prior to the COVID-19 pandemic, 13 (39.4%) of the 33 SPCs were providing virtual care on a limited basis. During the pandemic, all but 4 (12.1%) SPCs were providing virtual care, with 60.6% providing virtual care for more than half of their patients; 15.2% of the clinics operated only virtual clinics. Among the 29 clinics that provided virtual care to patients during the pandemic, 20.7% of the clinics provided virtual care to all patients, 41.4% provided virtual care for low to medium-risk patients, and 31.0% provided virtual care for follow-ups and new consultations (Table 4). A large percentage (72.7%) of the 33 clinics plan to provide virtual care post-COVID-19 pandemic (Figure 3).

Table 2: Association between seeing high-risk patients within 48 hours and number of days clinics are open

	Most high-risk patients seen within 48 hours	Most high-risk patients not seen within 48 hours	*p* value*
Days open/week			
≥4 days	13 (92.9)	12 (54.6)	0.025
≤3 days	1 (7.1)	10 (45.5)	

Data are reported as number (%) of stroke prevention clinics.
*p value obtained using Fisher's exact test.

Figure 4 shows the impact of the COVID-19 pandemic on SPCs patient management. Compared to pre-COVID period, the most impacted services by the COVID-19 were the number of referrals from family physicians (declined for 36.4% clinics), wait times once a patient was referred to the clinic (increased for 36.4% clinics), number of patients having already completed bloodwork prior to arriving for their appointment (declined for 27.3% clinics), number of referrals from the clinic's own ED (increased for 24.2% clinics), and proportion of true TIA patients versus mimics (increased for 24.2% clinics).

Discussion

Summary of Main Findings

We found substantial variation among SPCs in management practices such as hours of operation, duration of wait times to see high-risk patients, capacity for add-on urgent patients, tests completed prior to SPC appointment, time for results, and referrals of patients with incorrect diagnosis of TIA. Although time is essential for TIA patient management, most high-risk patients are not seen by the clinics within 2 days, the highest risk period. To compensate for this, most are not seen routinely in the ED by neurology either. Thus, many of the high-risk patients are not being seen quickly enough within 48 hours to meet existing recommendations. SPCs also reported that on average about half of the patients are incorrectly diagnosed and referred to the clinics; thus, impacting wait times for true TIA patients. Wait times for testing are often short except for echocardiogram and Holter. There is a significant variation in the duration of Holter monitoring.

We found a substantial impact of COVID-19 on clinic routines. There was a substantial decline in referrals to SPCs, especially from family physicians, increase in wait times for appointments and test results, and a decline in TIA mimic referrals. While a small portion of SPCs were making use of virtual care prior to COVID-19, a significant portion of the clinics are planning to use virtual care post-COVID-19.

Interpretations

TIA is a medical emergency that requires urgent management to prevent subsequent stroke. The risk of stroke is greatest in the first

Table 3: Chi-squared tests of non-response bias

Characteristic	Respondents, *n* (%)	Non-respondents, *n* (%)	*p* value
Region			
Western Canada[a]	9 (23.7)	14 (36.8)	0.172
Ontario	20 (52.6)	12 (31.6)	
Eastern Canada[b]	9 (23.7)	12 (31.6)	

[a]British Columbia, Alberta, Saskatchewan, Manitoba.
[b]Quebec, New Brunswick, Nova Scotia, Newfoundland, Prince Edward Island.

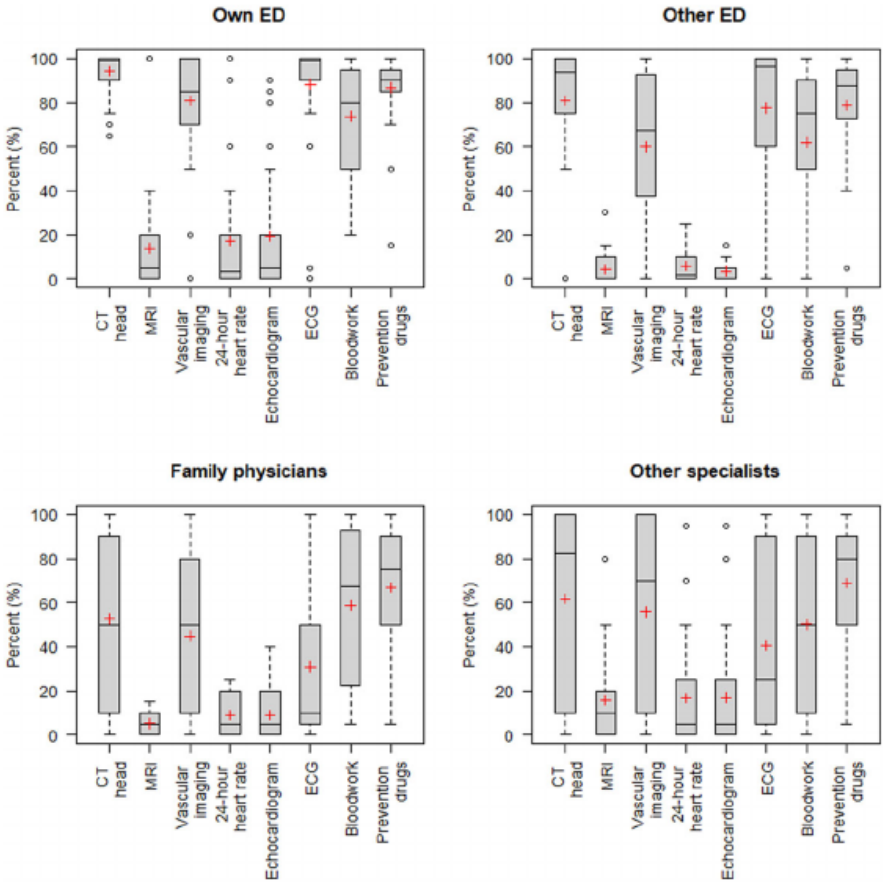

Figure 1: Percentage of patients having already completed a test by the time they arrive at the stroke prevention clinic, by referring source.

few days after a TIA with stroke rates as high as 8% within the first 2 days of TIA.[2] Hence, there is need for urgent intervention depending on stroke risk level. Admission of all patients is an inefficient use of health resources.[16] Our data show that a significant percentage of SPCs are open 3 days or fewer per week with a quarter only open 2 days or less per week. We suspect that the clinics opening three or fewer days per week are situated in low-populated areas, such as remote or rural areas. Our results show clinics open 3 or fewer days a week are unable to see most of their high-risk patients within 48 hours. A possible explanation for this is that there might be a high volume of referrals to the clinics but not enough resources to open the clinics more often. About half of the clinics open 4 or more days per week are also unable to see most of their high-risk patients within 48 hours.

Referrals to SPCs are initiated from EDs, family physicians, or specialists. Referrals should be triaged based on patient's risk of

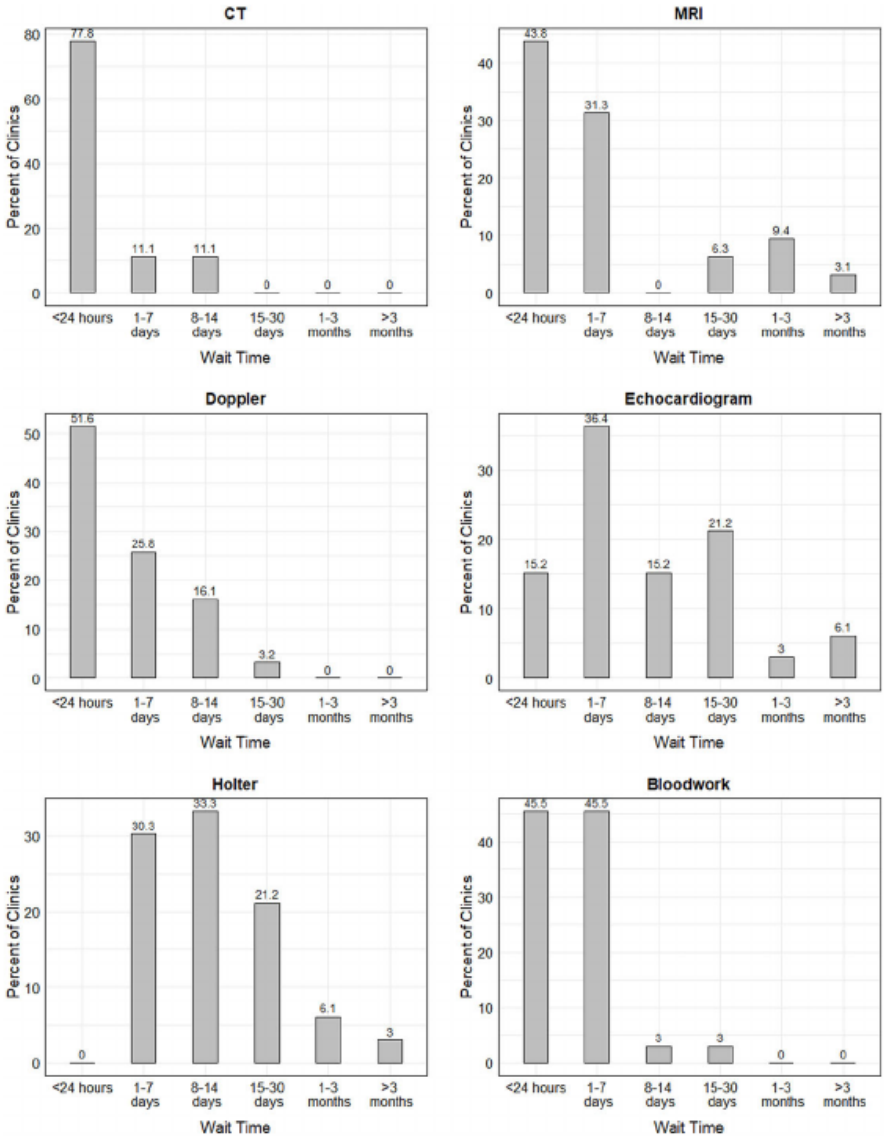

Figure 2: Time required for results to become available.

subsequent stroke. Advanced clinical prediction rules, such as the Canadian TIA Score, have been developed and validated for identifying low, medium, and high-risk patients.[17,18] Other clinical prediction rules have been developed and validated for identifying low-risk and high-risk patients including the ABCD^2 and ABCD^{2}i Scores.[19–21] However, there are some limitations with clinical prediction rules such as accuracy and non-availability of all the factors during the referral.

In Canada, national guideline recommendations have been developed by Heart and Stroke Foundation of Canada for the management and treatment of TIA patients.[12] All patients suspected with TIA should complete neurologic and cardiac examination including imaging, bloodwork, electrocardiogram, echocardiogram for select patients and, if no etiology found extended cardiac monitoring.[22–24] TIA patients require optimization of antithrombotic agents (anticoagulants or antiplatelets) and prompt carotid revascularization for symptomatic carotid artery stenosis if present.[22] The Canadian Stroke Best Practice Recommendations are not always followed, for varying and possibly valid reasons, leading to variations of practice. Not adhering

Table 4: Extent of virtual care

	Number (%) ($N = 33$)
During COVID-19 Pandemic virtual care provided to (if applicable)	
All patients	6 (20.7)
Most low-risk patients only	5 (17.2)
Most low to medium-risk patients only	7 (24.1)
Follow-ups	7 (24.1)
New consults and follow-ups	2 (6.9)
At patient request	2 (6.9)
Plans for virtual care post-COVID-19 pandemic	
For most patients	3 (9.1)
For most low-risk patients only	9 (27.3)
Follow-ups	4 (12.1)
New consults and follow-ups	2 (6.1)
At patient request	5 (15.2)
Physician preference	1 (3.0)
No	9 (27.3)

Five clinics did not answer questions related to COVID-19 and were excluded from the denominator.

to the guidelines might be out of the control of SPC personnel such as competing priorities.

Having tests completed prior to the SPC appointment could expedite diagnosis and treatment. Our data show investigations were often done prior to SPC assessment for referrals from the organization's own ED. There was less variation among the organization's own EDs while there was a wide variation among family physicians and specialists. This shows that there are likely better protocols in place for the organization's own ED while there is less coordination for inter-organizational referrals. Standardization of community referrals may help decrease variability. However, we acknowledge that it would be challenging to reach and impose standardized referrals in some jurisdictions. In addition, unless a solution is found and implemented to reduce TIA mimics, diagnostic imaging departments could be swamped with test requests if all tests were to be completed for all patients prior to SPC appointments. At the clinics, there is also variation on when tests are ordered based on the structure of the clinic. In some clinics, patients are first seen by a doctor who risk stratifies the patients prior to ordering tests with priority given to high-risk patients while in some clinics tests are ordered first, irrespective of patient risk level, prior to seeing a medical doctor. Hence, the variation in test wait times shown by our results could be due to the structure of the clinics.

Misdiagnosis of TIA is common with an estimated 50% of all TIA patients being stroke mimics.[25–27] With such high misdiagnosis rates, there is potential for delay in care for patients at high risk of stroke. However, TIA is a complex medical emergency with multiple risk factors making it challenging to diagnose, especially in resource- and time-limited settings. In addition, reliability of reporting the events experienced by the patients may vary, leading to subjective diagnosis, even among stroke neurologists.[28–30] Furthermore, TIA patients with mimics still require timely diagnosis and management. Derivation and guidelines on use of clinical prediction rules to identify stroke mimics could potentially allow for faster assessments for higher risk patients. Several prediction rules for the diagnosis of TIA/stroke mimics (e.g., DOT score, Dawson score) have been derived but not adequately validated.[31–33]

A significant percentage of the SPCs turned to virtual care during the COVID-19 pandemic. Although most clinics did not use virtual care prior to the pandemic, most clinics are planning to continue using virtual care post-COVID-19. It is likely that the virtual care has helped reduce a load on the SPCs and opened capacity for high-risk patients.

Comparison with Previous Literature

Given the urgency and risk of TIA patients, SPCs need to be accessible. Similarly, all clinics should have a triaging system. Two studies, by Wasserman *et al* and Martinez-Martinez *et al*, have shown stroke risk reduction with risk stratification and referrals to SPCs.[10,34] The study by Martinez-Martinez and colleagues reported a median wait time of 1.5 days to SPCs which is shorter in duration than shown by our study. Although the study by Wasserman and colleagues reported that most patients were seen within 48 hours in the ED, they did not report the time it takes from ED to SPC appointment. Wasserman and colleagues showed that neurology was consulted in the ED for only 5% of patients compared to more than 32% reported by our study.

Our results show that the COVID-19 pandemic had a significant impact on TIA patient management. During the pandemic, the proportion of referrals from family physicians declined while the referrals increased from EDs. This was likely due to family physician clinics being closed. It could have also been due to patients not seeking medical help unless they deemed it an emergency. Other studies have found similar findings in reduction of patients during the pandemic period with similar conclusions.[35–41] Also in agreement with our study, a study by Dowlatshahi and colleagues showed a drop in presentation rates to a comprehensive stroke centre in Ottawa, Canada at the beginning of the pandemic.[42] Similarly, a study by D'Anna showed a decline of referrals to North West London, UK SPC clinics during the COVID-19 pandemic.[43] Our study found the proportion of true TIA patients versus mimics increased during the pandemic. Patients with milder stroke symptoms may have intentionally avoided seeking medical care during the COVID-19 pandemic while the patients with more severe cases, such as symptoms due to large vessel occlusion, sought medical help as these more severe symptoms are less likely to be ignored by patients or family members.[38,43] Another study by D'Anna also observed this marked decrease in mimic diagnoses during the pandemic.[40]

Study Limitations

Despite our efforts to obtain high-quality data, the quality of responses may have been affected by the COVID-19 pandemic. Given that this was a self-reported questionnaire, respondents may have not answered all the questions accurately. Another limitation is that we had a limited set of characteristics to test for non-response bias.

Clinical Implications

Despite the need for urgent assessment and management, there is delay in seeing some high-risk TIA patients within 48 hours. About a quarter of SPCs are open 2 or fewer days a week, leaving the possibility of some high-risk patients having to wait more than the 48-hour critical time for TIA patients depending on referral volumes.

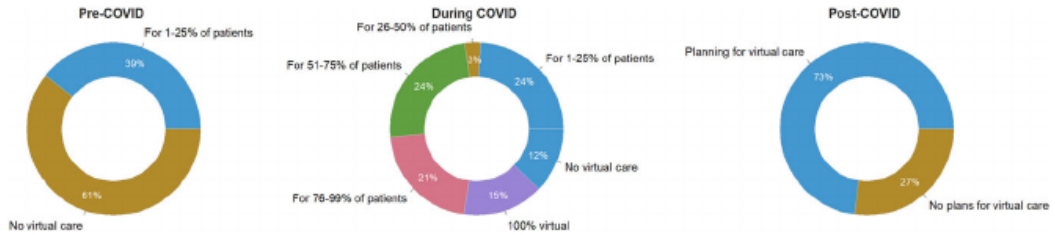

Figure 3: Percent of clinics using virtual care.

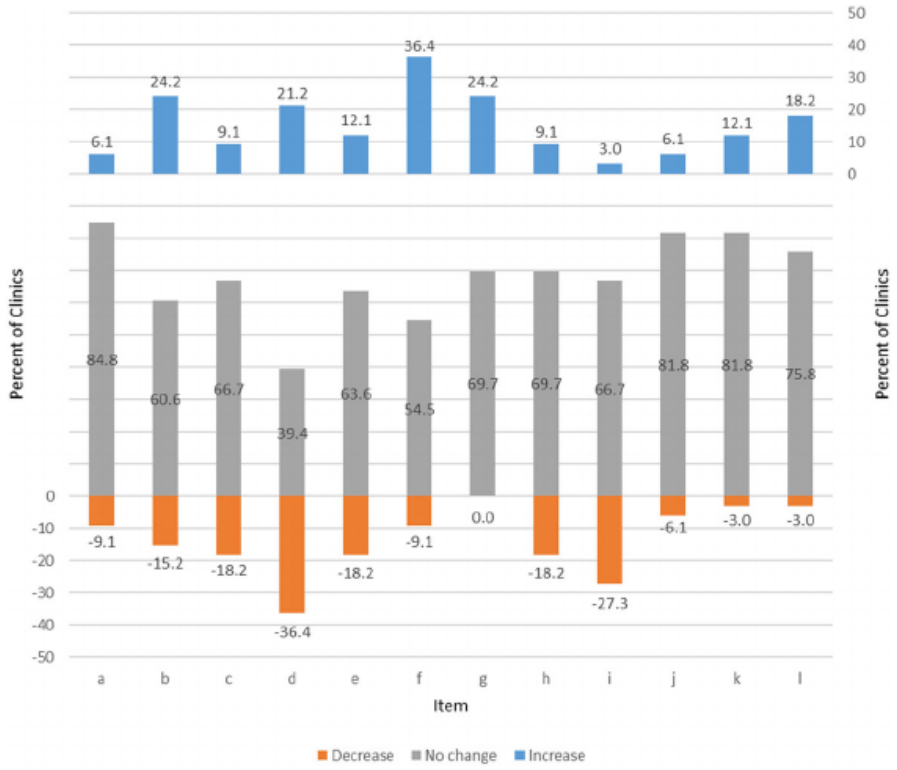

Figure 4: Impact of COVID-19 pandemic on clinic services (from pre-COVID to COVID period). a. Hours the clinic is physically open/week. b. Referrals from own emergency department. c. Referrals from other emergency departments. d. Referrals from family physicians. e. Referrals from other specialists. f. Wait times for an appointment once a patient is referred to clinic. g. Proportion of true TIA patients versus mimics. h. Patients having completed imaging prior to appointment. i. Patients having completed bloodwork prior to appointment. j. Patients already taking prevention drugs (e.g. anticoagulants and antiplatelet) prior to appointment. k. If patients need medical imaging done, time it takes to have the results. l. If patients need bloodwork done after arriving, time it takes to have the results. *One clinic did not answer items d, h, i, k, l; two clinics did not answer items c, e, g, j.

A significant percentage of patients referred to SPCs are stroke mimics taking resources from true TIA patients. Using a clinical diagnostic tool, such as the DOT score, after its external validation, could help minimize misdiagnosis of TIA. Stroke prediction tools, such as the Canadian TIA Score, are also important to prioritize high-risk patients.

Research Implications

Our study has shown several gaps in knowledge of SPCs and how they function and interact with other stakeholders. We have also shown the impact of the COVID-19 pandemic on patient management. We have found that referrals from an SPC's own ED are

better managed than from other EDs, family physicians, or specialists. Understanding the reasons behind these discrepancies could help improve referral systems. We have also shown that several clinics are open 3 or fewer days a week with a quarter being open 2 days or fewer each week and not being able to see most high-risk patients within 48 hours. Half of the clinics that do open 4 or more days are also struggling with seeing most of their high-risk patients. The reasons behind this deficiency and the outcomes of patients seeking medical help at these clinics need to be investigated and compared to other clinics. We suspect there would be more stroke outcomes for high-risk patients at these clinics having to wait longer than 48 hours due to limited clinic days. Clinic structure regarding testing first prior to assessment versus assessment first followed by testing on patient outcomes also needs to be investigated.

Conclusion

TIA is a serious condition that requires urgent care, depending on the risk level. Outpatient SPCs have been setup to provide more efficient and effective care. Although there are guidelines on the management of TIA patients, they are not fully implemented leading to variations of practice. We suggest that SPCs investigate delays and attempt to see high-risk patients within 48 hours. We also suggest that better systems are put in place between SPCs and referring sources, especially family physicians, so that patients are risk classified and some test are completed prior to their appointments, as appropriate without causing further delays.

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Conflict of Interest. Dr Jeffrey Perry holds a peer-reviewed mid-career salary support award from the Heart and Stroke Foundation of Ontario. None of the other authors have any conflict of interest or information to disclose in relation to this study.

Statement of Authorship. KEA, JJP, and MT designed the study. KEA conducted interviews, executed the surveys, conducted analyses, and wrote the draft manuscript. DD, IGS, and GAW provided input into the study design. All authors contributed to the final manuscript review.

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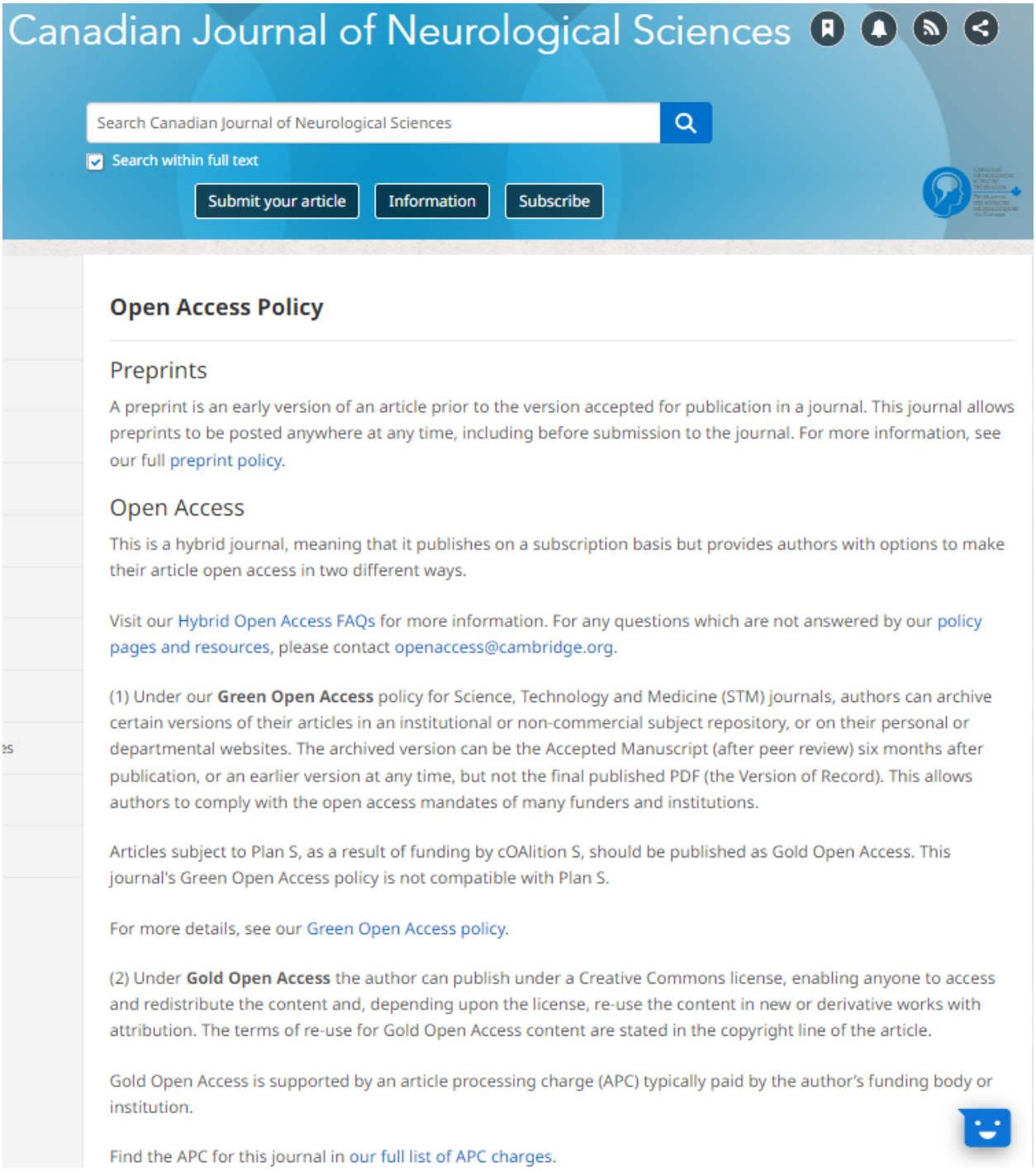
7.2.6 Permission to use in thesis

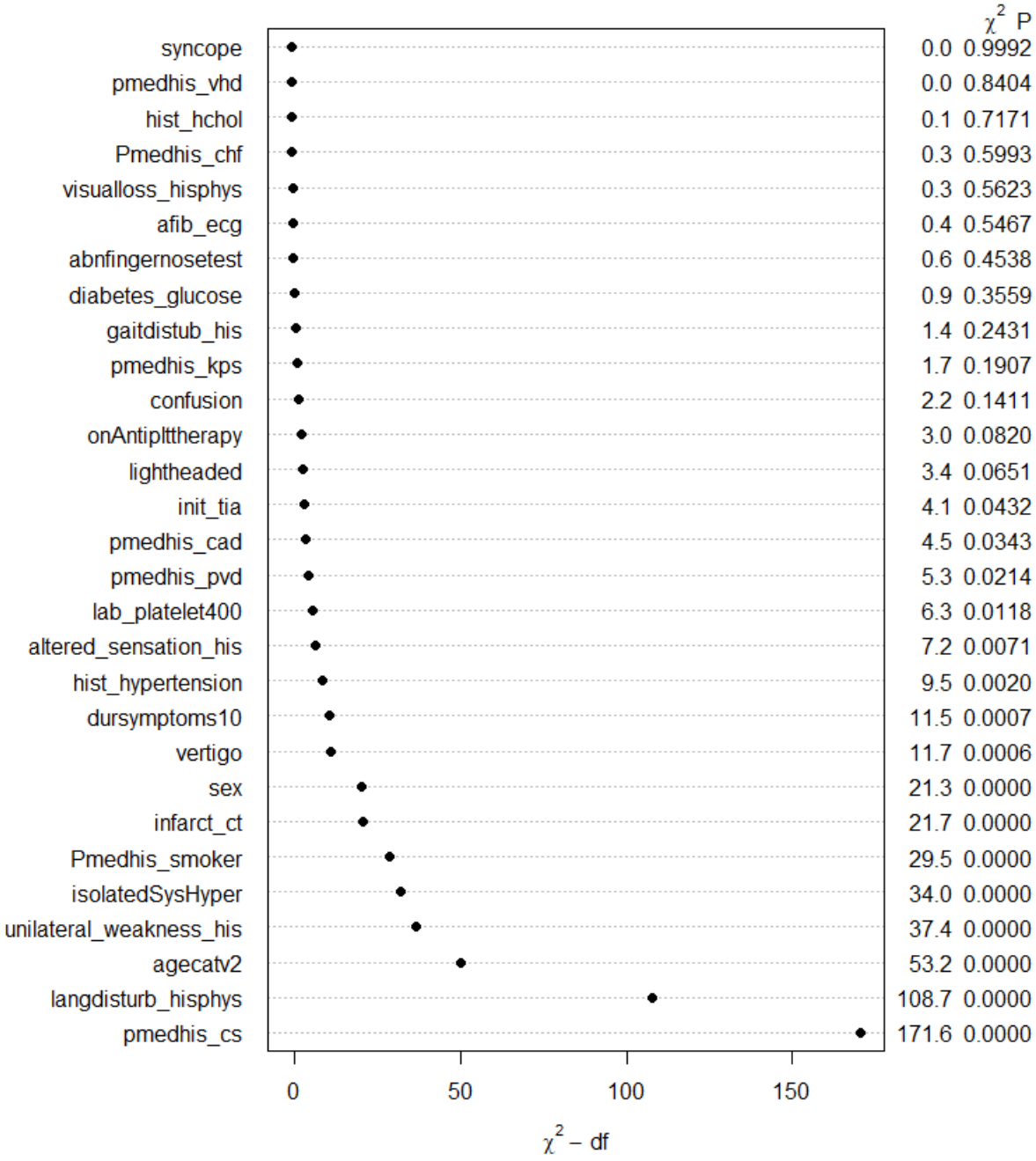


7.3. Chapter 4 General Appendices

7.3.1 Results of Multicollinearity check

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Variance Inflation
Intercept	1	-0.11024	0.02774	-3.97	<.0001	0
agecatv2	1	0.02777	0.00477	5.82	<.0001	1.39584
sex	1	-0.02385	0.00644	-3.70	0.0002	1.04543
init_tia	1	-0.02025	0.00923	-2.19	0.0283	1.58677
dursymptoms10	1	-0.05458	0.01095	-4.98	<.0001	1.10519
isolatedSysHyper	1	0.01125	0.00410	2.74	0.0061	1.04905
altered_sensation_his	1	0.01973	0.00717	2.75	0.0060	1.29271
unilateral_weakness_his	1	0.03422	0.00684	5.00	<.0001	1.10970
langdisturb_hisphys	1	0.06334	0.00704	9.00	<.0001	1.19935
gaitdistub_his	1	-0.01511	0.00851	-1.77	0.0760	1.16111
visualloss_hisphys	1	0.00327	0.00940	0.35	0.7279	1.10782
lightheaded	1	-0.00642	0.00878	-0.73	0.4643	1.12044
vertigo	1	-0.04858	0.01519	-3.20	0.0014	1.15554
confusion	1	-0.02053	0.00967	-2.12	0.0338	1.10161
syncope	1	0.00326	0.01602	0.20	0.8388	1.06824
abnfingernosetest	1	0.03136	0.01489	2.11	0.0352	1.03561
hist_hypertension	1	0.01705	0.00747	2.28	0.0226	1.33369
diabetes_glucose	1	0.01506	0.00852	1.77	0.0771	1.11367
Pmedhis_smoker	1	0.04582	0.01008	4.54	<.0001	1.06789
Pmedhis_chf	1	0.00478	0.02154	0.22	0.8242	1.06992
pmedhis_cad	1	0.03252	0.00965	3.37	0.0008	1.26575
pmedhis_pvd	1	0.05394	0.01836	2.94	0.0033	1.09188
pmedhis_kps	1	0.00007286	0.01107	0.01	0.9947	1.28788
pmedhis_cs	1	0.24061	0.02071	11.62	<.0001	1.08255
hist_hchol	1	0.00296	0.00741	0.40	0.6895	1.36237
pmedhis_vhd	1	-0.01111	0.01887	-0.59	0.5559	1.03413
onAntipltherapy	1	0.00245	0.00842	0.29	0.7712	1.69992
afib_ecg	1	-0.00277	0.01603	-0.17	0.8627	1.09383
infarct_ct	1	0.03100	0.00782	3.96	<.0001	1.18954
lab_platelet400	1	0.06260	0.02096	2.99	0.0028	1.02550

7.3.2 ANOVA plot



7.3.3 Number of times predictors are selected by the stepdown procedure

Variable	Label	Times selected
agecatv2	**Age category**	**1000**
sex	**Sex**	**982**
init_tia	Initial TIA (Never had TIA in past)	322
dursymptoms10	**Duration of symptoms ≥ 10 minutes**	**777**
lab_platelet400	Platelet value ≥ 400 x 109/L	495
isolatedSysHyper	**Isolated systolic hypertension category**	**998**
altered_sensation_his	**History of altered sensation**	**682**
unilateral_weakness_his	**History of unilateral weakness**	**1000**
langdisturb_hisphys	**Dysarthria or aphasia (history or exam)**	**1000**
gaitdistub_his	Gait disturbance (history or exam)	154
visualloss_hisphys	Visual loss (history or exam)	40
lightheaded	Lightheaded	400
vertigo	**Vertigo**	**895**
confusion	Confusion	186
syncope	Syncope or near syncope	11
abnfingernosetest	Abnormal finger-nose test on physical exam	31
hist_hypertension	**Past medical history: hypertension**	**842**
diabetes_glucose	Past medical history of diabetes or lab glucose > 15 mmol/L	85
Pmedhis_smoker	**Past Medical History: Current Smoker**	**993**
Pmedhis_chf	Past Medical History: CHF	24
pmedhis_cad	**Past Medical History: Coronary Artery Disease**	**511**
pmedhis_pvd	Past Medical History: Peripheral Vascular Disease	478
pmedhis_kps	Past Medical History: Known Prior Stroke	88

pmedhis_cs	**Past Medical History: carotid stenosis**	**1000**
hist_hchol	Past medical history of high cholesterol or already on antiplatelet medication	55
pmedhis_vhd	Past Medical History: Valvular Heart Disease	34
onAntiplttherapy	Already on antiplatelet medications	367
afib_ecg	Atrial fibrillation on ECG	37
infarct_ct	**Infarction (new or old) on CT**	**977**

Predictors kept in our final model are highlighted in bold

7.3.4 Supplementary Analyses

Chapter 4 of the thesis presented derivation and internal validation of our prediction model on patients at all-risk levels for subsequent stroke so that the prediction model can flexibly be applied to different settings. In other words, it can be applied to all TIA patients irrespective of their risk for stroke level and hence independent of other risk scores such as the Canadian TIA Score.[77] We assume the prediction model can also be applied in combination with other risk scores. More specifically, we anticipate that our prediction model would more likely be applied to patients at medium risk of stroke given that high-risk patients should be imaged anyway and no need to image low-risk patients. Hence, additional analyses were conducted to apply the prediction model to patients at medium risk of stroke using the Canadian TIA Score.

Our model performed in a similar matter on the medium-risk patients as with all-risk patients. Results of the model's performance on medium-risk patients are presented in Appendix 7.3.5.

7.3.5 Classification performance on medium-risk patients

Classification performance, sensitivity, and specificity by score cut-off and risk category of the Symcard Score for symptomatic carotid artery disease in TIA patients at medium risk of stroke classified by the Canadian TIA Score

Score	No. (%) of patients (N = 7,053)	Observed no. (%) of patients with outcome	Estimated no. (%) of patients with outcome			Risk Category	Proportion of patients (%)	No. (%) of patients with outcome	Sensitivity (95% CI) at score cut-off	Specificity (95% CI) at score cut-off
			Estimate	Lower 95% CI	Upper 95% CI					
-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				100 (99.4, 100)	0 (0, 0)
-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				100 (99.4, 100)	0 (0, 0)
-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				100 (99.4, 100)	0 (0, 0)
-1	6 (0.1)	0 (0.0)	0 (0.1)	0 (0.1)	0 (0.1)				100 (99.4, 100)	0 (0, 0)
0	35 (0.5)	0 (0.0)	0 (0.1)	0 (0.1)	0 (0.2)				100 (99.4, 100)	0.1 (0, 0.2)
1	26 (0.4)	0 (0.0)	0 (0.1)	0 (0.1)	0 (0.2)				100 (99.4, 100)	0.6 (0.5, 0.9)
2	42 (0.6)	0 (0.0)	0 (0.2)	0 (0.1)	0 (0.3)				100 (99.4, 100)	1 (0.8, 1.3)
3	43 (0.6)	1 (2.3)	0 (0.3)	0 (0.2)	0 (0.4)				100 (99.4, 100)	1.7 (1.4, 2)
4	33 (0.5)	0 (0.0)	0 (0.4)	0 (0.3)	0 (0.5)	**Low**	37.3	41 (1.6)	99.8 (99.1, 100)	2.3 (2, 2.7)
5	127 (1.8)	0 (0.0)	1 (0.5)	1 (0.4)	1 (0.7)				99.8 (99.1, 100)	2.9 (2.5, 3.3)
6	108 (1.5)	1 (0.9)	1 (0.7)	1 (0.6)	1 (0.9)				99.8 (99.1, 100)	4.8 (4.3, 5.4)
7	172 (2.4)	0 (0.0)	2 (1)	1 (0.8)	2 (1.3)				99.7 (98.8, 100)	6.5 (5.9, 7.1)
8	345 (4.9)	6 (1.7)	5 (1.4)	4 (1.2)	6 (1.7)				99.7 (98.8, 100)	9.1 (8.4, 9.9)
9	409 (5.8)	6 (1.5)	8 (1.9)	7 (1.6)	9 (2.3)				98.6 (97.3, 99.4)	14.4 (13.5, 15.2)
10	601 (8.5)	11 (1.8)	16 (2.6)	14 (2.3)	18 (3)				97.6 (96, 98.7)	20.6 (19.6, 21.6)
11	684 (9.7)	16 (2.3)	25 (3.6)	22 (3.2)	28 (4.1)				95.7 (93.8, 97.2)	29.7 (28.6, 30.9)
12	776 (11)	41 (5.3)	38 (4.9)	35 (4.5)	42 (5.4)				93.0 (90.6, 94.9)	40.1 (38.9, 41.3)
13	886 (12.6)	59 (6.7)	59 (6.7)	54 (6.1)	64 (7.3)	**Medium**	36.1	182 (7.2)	86.0 (82.9, 88.7)	51.4 (50.2, 52.6)
14	881 (12.5)	82 (9.3)	79 (9)	74 (8.4)	85 (9.7)				75.9 (72.3, 79.4)	64.2 (63, 65.4)
15	695 (9.9)	105 (15.1)	83 (12)	78 (11.2)	89 (12.8)				62.0 (57.9, 65.9)	76.6 (75.5, 77.6)
16	500 (7.1)	80 (16)	79 (15.9)	74 (14.9)	84 (16.9)				44.0 (40, 48.2)	85.7 (84.8, 86.5)
17	303 (4.3)	57 (18.8)	63 (20.6)	58 (19.3)	67 (22.1)				30.4 (26.7, 34.3)	92.2 (91.5, 92.8)
18	173 (2.5)	34 (19.7)	46 (26.4)	42 (24.6)	49 (28.4)				20.7 (17.4, 24.2)	96 (95.5, 96.5)
19	87 (1.2)	25 (28.7)	29 (33.2)	27 (30.7)	31 (35.8)	**High**	26.6	363 (19.3)	14.9 (12.1, 18)	98.1 (97.8, 98.5)
20	55 (0.8)	25 (45.5)	22 (40.7)	21 (37.5)	24 (43.9)				10.6 (8.2, 13.4)	99.1 (98.8, 99.3)
21	23 (0.3)	11 (47.8)	11 (48.6)	10 (44.8)	12 (52.5)				6.3 (4.5, 8.6)	99.6 (99.4, 99.7)
22	17 (0.2)	9 (52.9)	10 (56.7)	9 (52.3)	10 (60.9)				4.4 (2.9, 6.4)	99.7 (99.6, 99.9)
23	15 (0.2)	10 (66.7)	10 (64.3)	9 (59.7)	10 (68.7)				2.9 (1.7, 4.6)	99.9 (99.7, 99.9)

24	5 (0.1)	4 (80)	4 (71.4)	3 (66.7)	4 (75.6)				1.2 (0.5, 2.5)	99.9 (99.8, 100)
25	4 (0.1)	2 (50)	3 (77.5)	3 (73)	3 (81.4)				0.5 (0.1, 1.5)	100 (99.9, 100)
26	1 (0)	0 (0)	1 (82.6)	1 (78.5)	1 (86.1)				0.2 (0, 1)	100 (99.9, 100)
27	1 (0)	1 (100)	1 (86.8)	1 (83.2)	1 (89.7)				0.2 (0, 1)	100 (99.9, 100)
28	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				0 (0, 0)	100 (100, 100)
29	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				0 (0, 0)	100 (100, 100)
30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				0 (0, 0)	100 (100, 100)

7.3.6 Research Ethics Board Approval

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9 613-798-5555 extension 16719 Fax: 613-761-4311

http://www.ohri.ca/ohsn-reb

Tuesday, July 6, 2021

Dr. Jeffrey Perry
Ottawa Hospital - Civic Campus
Department of Emergency Medicine
F6, Room 647
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Dear Dr. Perry:

RE: Protocol #2007300-01H - Phase 1: Clinical Decision Rule for High Risk TIA patients in the ED
Renewal Expiry Date - Wednesday, July 6, 2022

I am pleased to inform you that your Continuing Review Form was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol or the consent form without the OHSN-REB's review and approval.

Date of approval: July 6, 2021

Renewal is valid for a period of one year. If the study is to continue beyond the expiry date, a Continuing Review Form should be submitted to the REB, in hardcopy. All Continuing Review Forms, regardless of review type (i.e., full board or delegated), must now be submitted according to the full board meeting submission deadlines AND at least 30 days prior to the expiry date of the study to prevent a lapse in approval. If the study is completed by this date, a Study Closure Form should be submitted.

Projected end date of study completion has been extended to December 2022.

Protocol February 25, 2021 is currently approved by the REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations; or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19; and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Yours sincerely,

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

/dw

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9 613-798-5555 extension 16719 Fax: 613-761-4311

http://www.ohri.ca/ohsn-reb

Tuesday, July 27, 2021

Dr. Jeffrey Perry
Ottawa Hospital - Civic Campus
Department of Emergency Medicine
F6, Room 647
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Dear Dr. Perry:

RE: Protocol #20120596-01H - Phase II: Clinical Decision Rule for High Risk TIA Patients in the ED
Renewal Expiry Date - Wednesday, July 27, 2022

I am pleased to inform you that your Continuing Review Form was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol or the consent form without the OHSN-REB's review and approval.

Date of approval: July 27, 2021

Renewal is valid for a period of one year. If the study is to continue beyond the expiry date, a Continuing Review Form should be submitted to the REB, in hardcopy. All Continuing Review Forms, regardless of review type (i.e., full board or delegated), must now be submitted according to the full board meeting submission deadlines AND at least 30 days prior to the expiry date of the study to prevent a lapse in approval. If the study is completed by this date, a Study Closure Form should be submitted.

Protocol dated February 25, 2021 is currently approved by the REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations; or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19; and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Yours sincerely,

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

/dw