BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055832
Article Type:	Original research
Date Submitted by the Author:	27-Jul-2021
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Keywords:	COVID-19, ACCIDENT & EMERGENCY MEDICINE, EPIDEMIOLOGY

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Development and validation of a clinical risk score to predict SARS-CoV-2 infection in emergency department patients: The CCEDRRN COVID-19 Infection Score (CCIS)

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Abstract (283/300 words)

Objectives: To develop and validate a clinical risk score that can accurately quantify an emergency department patient's probability of SARS-CoV-2 infection without the need for laboratory testing

Design: Cohort study of participants in the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) registry. Regression models were fitted to predict a positive SARS-CoV-2 test result using clinical and demographic predictors, as well as an indicator of local SARS-CoV-2 incidence.

Setting: 32 emergency departments in eight Canadian provinces

Participants: 27,665 consecutively-enrolled patients who were tested for SARS-CoV-2 in participating emergency departments between March 1-October 30,2020

Main outcome measures: Positive SARS-CoV-2 nucleic acid test result within 14 days of an index emergency department encounter for suspected COVID-19 disease

Results: We derived a 10-item CCEDRRN COVID-19 Infection Score using data from 21,743 patients. This score included variables from history and physical examination, and an indicator of local disease incidence. The score had a c-statistic of 0.838 with excellent calibration. We externally validated the rule in 5,295 patients. The score maintained excellent discrimination and calibration, and had superior performance compared to another previously published risk score. Score cutoffs were identified that can rule-in or rule-out SARS-CoV-2 infection without the need for nucleic acid testing with 97.4 % sensitivity (95% CI 96.4–98.3) and 95.9% specificity (95% CI 95.5-96.0).

Conclusions The CCEDRRN COVID-19 Infection Score uses clinical characteristics and publicly available indicators of disease incidence to quantify a patient's probability of SARS-CoV-2 infection. The score can identify patients at sufficiently high risk of SARS-CoV-2 infection to warrant isolation and empiric therapy prior to test confirmation, while also identifying patients at sufficiently low risk of infection that they may not need testing.

Trial registration: CCEDRRN is registered at clinicaltrials.gov (NCT04702945).

Funding: The network is funded by the Canadian Institutes of Health Research (447679), BC Academic Health Science Network Society, BioTalent Canada, Genome BC (COV024; VAC007), Ontario Ministry of Colleges and Universities (C-655-2129), the Saskatchewan Health Research Foundation (5357) and the Fondation CHU de Québec (Octroi #4007). These organizations are not-for-profit, and had no role in study conduct, analysis, or manuscript preparation.

Summary Box

What is already known on this topic

- Most existing risk scores for identifying patients with high probability of SARS-CoV-2 infection include laboratory or diagnostic imaging results in addition to clinical variables and employ machine learning approaches that would require an advanced electronic medical record for implementation.
- The only risk prediction tool limited to clinical variables was derived in a population with a high proportion of SARS-CoV-2-positive patients, and is thus vulnerable to selection bias. This risk score also included three race or ethnicity variables, which may limit its generalizability is limited. outside of the population in which it was developed.

What this study adds

- We have derived and validated a user-friendly 10-item risk prediction tool that uses clinical variables available at the time of a patient's initial presentation. Our tool accurately excludes COVID-19 infection in one-third of patients and accurately rules in COVID-19 infection in high-risk patients.
- Patients classified as low-risk need not be tested, which is advantageous is low in settings where resources are limited. Patients classified as high-risk can be prioritized for rapid testing, isolation and/or early initiation of empiric therapy prior to the availability of COVID-19 test results.
- This risk score is generalizable across geographic settings and does not require diagnostic tests or advanced electronic decision support for implementation.

Strengths and Limitations

- Large cohort of consecutive eligible patients from a large, geographically distributed network of Canadian urban, regional, and rural emergency departments. Strict data quality protocols and data cleaning protocols ensured the reliability of collected data.
- In addition to clinical variables, we also included the average daily incidence of SARS-CoV-2 infections in a patient's health region, which is an essential predictor of the probability of a patient's risk of COVID infection.
- Some missing data required either multiple imputation or classification of missing categorical variables as being absent. The overall missingness of data in this registry is very low.
- Although the data collection for the CCEDRRN registry relies on abstraction from health records, this approach has been shown to be reliable in our study sites when compared to prospective data collection.
- This risk score was developed using data from patients enrolled in the first nine months of the pandemic when rates of influenza were low. As such, the score may need to be re-validated and refined in the future to reflect the influence of influenza, the emergence of variant strains of SARS-CoV-2, and widespread population immunization on patients' risk of infection.

MAIN DOCUMENT (3054 words)

Introduction

To date, the World Health Organization has reported 190 million diagnosed cases of coronavirus 2019 disease (COVID-19) with 4.2 million fatalities.[1] Despite the availability of vaccines to prevent COVID-19, incomplete population-level immunization and the emergence of variants means that hospitals around the world need to continue to identify and isolate patients with suspected COVID-19 from the time they arrive in the emergency department until their SARS-CoV-2 test results are available. In acutely ill patients, clinicians may need to initiate empiric therapy immediately. A quantitative risk score that can accurately predict the probability of a positive SARS-CoV-2 test result would guide initial isolation and empiric therapy prior to nucleic acid amplification test (NAAT) test result availability, while identifying patients with sufficiently low probability of COVID-19 who may not require testing or isolation.

Many risk prediction tools have been developed to predict the probability of SARS-CoV-2 infection.[2–14] A living systematic review of these models concluded that most were generated using poor methodological approaches and none were ready for widespread use.[2] Most published risk prediction tools included early laboratory or imaging findings, thus precluding their utility to guide immediate isolation and clinical decisions at the time of first clinical contact. Other risk prediction tools using machine learning included laboratory and imaging results and can only be implemented in hospitals using electronic health records with integrated decision support. None of these models accounted for the prevalence of COVID-19 disease in the local population, which is an important risk predictor, and most only included patients from the early stages of the pandemic.[2]

The objective of this study is to develop a clinical risk score to predict the probability of a positive SARS-CoV-2 nucleic acid test in a large, generalizable population of emergency department patients using only clinical characteristics and indicators of local SARS-CoV-2 incidence. This risk score is intended to guide SARS-CoV-2 testing, isolation, and empiric therapy decisions without relying on other laboratory testing or diagnostic imaging. This score could be invaluable in settings that may not have access to adequate resources for timely SARS-CoV-2 testing.

Methods

This analysis uses data from the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN, pronounced "SED-rin"). CCEDRRN is an ongoing multicenter, pan-Canadian registry that has been enrolling consecutive emergency department patients with suspected COVID-19 disease in hospitals in eight of ten Canadian provinces since March 1, 2020.[15] Information on the network, including detailed methods and participating sites, is available elsewhere.[15] This study follows the methodological and reporting recommendations outlined in the Transparency in reporting of a multivariable prediction model for individual diagnosis and prognosis (TRIPOD) criteria.[16] The CCEDRRN network protocol was approved by the research ethics boards of all participating institutions with a waiver of informed consent for data collection and linkage.

The CCEDRRN data collection form includes prespecified demographic and social variables, vital signs, symptoms, and comorbid conditions (derived from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) reporting form),[17,18] exposure risk variables, hospital laboratory and diagnostic imaging test results, SARS-CoV-2 NAAT results, and patient outcomes. Data were abstracted at each site using electronic medical record

extraction where available as well as manual review of either electronic or paper charts (depending on site-specific documentation practices) by trained research assistants who were blinded to the potential predictor variables at the time of data collection. Reliability of health record data abstraction was evaluated by comparison with prospective data collection in a sample of patients and found to be reliable.[15]

Each consecutive, eligible patient enrolled in the registry was assigned a CCEDRRN unique identifier. Trained research assistants entered anonymized participant data into a REDCap database (Version 10.9.4; Vanderbilt University, Nashville, Tennessee, USA). Regular data quality checks including verification of extreme or outlying values were performed by each participating site, coordinated by the CCEDRRN coordinating center.

Participants

We included data from consecutive patients presenting to 32 CCEDRRN sites that collected data on all patients tested for SARS-CoV-2 (Appendix Table 1). We included consecutive eligible patients aged 18 and older who had a biological sample (swab, endotracheal aspirate, bronchoalveolar lavage) specimen collected for NAAT on their index emergency department visit or, if admitted, within 24h of emergency department arrival. For patients with multiple emergency department encounters involving COVID-19 testing, we only used the first encounter in this analysis.

We excluded patients who had a positive SARS-CoV-2 NAAT within 14 days prior to their emergency department visit, patients with cardiac arrest prior to emergency department arrival, and those with missing outcome data.

Predictors

Candidate predictors were chosen based on clinical consensus and availability within the CCEDRRN registry. Predictors included known risk factors for SARS-CoV-2 infection, including work as a healthcare provider, institutional living (i.e., long term care, prison), close personal or household contacts with SARS-CoV-2 infection; symptoms including cough, anosmia or dysgeusia, fever, myalgias and vital signs on emergency department arrival. The full list of candidate variables, and their definitions are available in the supplementary appendix (Appendix Table 2).

In addition to these clinical variables, the seven-day average incident COVID-19 case count was calculated for the health region of each participating site using publicly available epidemiological data.[19] For each calendar day within each health region represented in the study, we calculated the average daily incident rate of new infections per 100,000 population over the preceding seven days. This seven-day average incidence was assigned to each patient based on the date of their index emergency department encounter and the health region of the forward sortation area of their postal code of residence. For patients with no fixed address, we allocated them to the health region of the hospital in which they were tested. As publicly available incident COVID-19 case data were not available for the early pandemic, we imputed values for the first five weeks of the pandemic by modeling the reported COVID-19 cases that had accumulated in every health region over time using linear interpolation (0.1% missing).

Outcome

The primary outcome of this analysis was the diagnosis of SARS-CoV-2 infection using a criterion standard of a positive NAAT at the time of index emergency department visit or within 14 days after the index encounter.

Sample size and precision

The 46 candidate predictors had 52 degrees of freedom and with an expected SARS-CoV-2 infection rate of 5%, a sample size of 1040 was sufficient for the derivation cohort based on an anticipated event rate of less than 20% and a requirement for 20 outcomes per degree of freedom.[20] Over 21,000 patients were available for the derivation cohort at the time of analysis, providing more than sufficient data for reliable prediction modeling.

Model development and validation

We randomly assigned study sites to the derivation and validation cohorts with the goal of assigning 75% of eligible patients and outcome events to the derivation cohort and 25% to the validation cohort. Thus, the derivation and validation cohorts are geographically distinct. Within the derivation cohort, candidate predictors were examined for co-linearity and missing or extreme values. In the presence of co-linearity, one predictor was dropped from the set of candidate predictors. Five multiple imputations were used for continuous variables with missing data. Patients with missing data for categorical variables were assumed to have the reference value for that categorical variable. The initial logistic regression model considered all candidate predictors, with continuous predictors fit with restricted cubic splines with three knots. The strengths of associations between predictors and outcome were assessed using an analysis of variance (ANOVA) plot to inform the degrees of freedom to allocate to each predictor. The model was fit again with these changes. A fast step-down procedure reduced the model to key predictors based on an Akaike's information criterion stopping rule with a threshold of 120 to enable a model with a relatively small number of predictors that would be clinically easy to use. Internal bootstrap validation with 1,000 bootstrap samples was conducted to provide an optimism-corrected C-statistic. Continuous predictors were categorized based on the relationship between the spline function and outcome.

We then developed the points-based CCEDRRN COVID-19 Infection Score (CCIS) using a nomogram to assign integer point values for each variable included in the derived model. Discrimination of the score was evaluated using the C-statistic. Calibration was evaluated using calibration curves and comparison of observed and expected outcomes. Diagnostic performance was evaluated using sensitivity and specificity, predictive values, and likelihood ratios at different point thresholds.

We then evaluated the discrimination, calibration, and performance characteristics of the CCIS in an external validation cohort of patients from geographically distinct study sites who were not part of the derivation cohort.

Validation of previously published models

We used our combined (derivation and validation) study cohort to externally validate the COvid Rule out Criteria (CORC) score developed by Kline et al (with race and ethnicity variables removed).[3] We compared measures of discrimination and calibration, along with sensitivity and specificity of risk score values for the CCIS and CORC (with race and ethnicity variables removed). We split each score into categories of low, moderate, and high-risk for SARS-CoV-2 infection. Low risk was defined as a score having a sensitivity for ruling-out infection of 95% or higher. High-risk was defined as a score having a specificity for ruling in infection of 95% or higher. We compared the performance of the two scores by calculating net reclassification improvement across low, moderate, and high-risk categories.[21,22]

All analyses were performed in R [23] using the rms package.[24]

Role of the funding sources

The funding organizations had no role in the study conduct, data analysis, manuscript preparation or submission.

Patient involvement

The CCEDRRN governance structure includes patient representatives on the Executive Committee, Scientific Steering Committee, Protocol Review and Publications Committee, Data Access and Monitoring Committee and Knowledge Translation Committee. The network also has a Patient Engagement Committee composed of patient partners from across Canada. Patient partners provided input into study design and selection of outcomes for all CCEDRRN analyses, and provide advice on knowledge sharing and translation strategies.

Results

This analysis is based on 27,665 consecutively enrolled patients from 32 participating emergency departments (Figure 1, Appendix Table 1). Sites and enrolment periods contributing patient data are shown in the supplementary appendix. Of the included patients, 1,677 (4.2%) had a positive SARS-CoV-2 NAAT result.

The study cohort was subdivided into a derivation cohort (21,743 patients from 16 sites, 940 (4.3%) SARS-CoV-2 positive) and a separate external validation cohort (5,922 patients from 16 different sites, 227 (3.8%) SARS-CoV-2 positive). Demographic and clinical characteristics of the derivation and validation cohorts are shown in Table 1. No continuous variable requiring multiple imputation had more than 3.4% missingness (Appendix Table 2).

In the derivation cohort, we derived a 10-variable model to predict the probability of a patient having a positive SARS-CoV-2 NAAT. The regression coefficients and odds ratios for each

variable in the model are shown in Table 2. The C-statistic for the derived model was 0.851 with excellent calibration.

We created a points-based CCEDRRN COVID-19 Infection Score (CCIS) using rounded regression coefficients with a range of negative two to nine points (Table 2). The C-statistic of the CCIS in the derivation cohort was 0.838 (0.824–0.852) with excellent calibration (Figure 2). A score of zero or less ruled out a positive SARS-CoV-2 test result in 5,996/21,743 patients (27.6%) with a sensitivity of 96.6% (95% CI 95.2–97.7). A score of four or more was observed in 1,338/21,743 patients (6.2%) and had a specificity of 95.6 (95% CI 95.3–95.8) for predicting a positive SARS-CoV-2 test result (Appendix Table 3).

We then quantified the performance of the CCIS in our external validation cohort. In this cohort, the C-statistic for the points-based risk score was 0.792 (Figure 2). A score of zero or less ruled out a positive SARS-CoV-2 test result in 1,863/5,925 patients (31.4%) with a sensitivity of 94.3% (95% CI 90.4–96.9). A score of four or more was observed in 174/5,925 patients (2.9%) and had a specificity of 97.8 (95% CI 97.4–98.1) for predicting a positive SARS-CoV-2 test result (Table 3).

In a combined cohort of patients (derivation and validation combined), we compared the discrimination and diagnostic performance of the CCIS to the CORC score. The CCIS had a C-statistic of 0.837 compared to 0.750 for the CORC score (with race/ethnicity variables removed) (Appendix Figure 1). A CCIS of zero or less ruled out SARS-CoV-2 infection in 28.4% of patients with a sensitivity of 96.1% (Appendix Table 4) whereas a CORC score of negative one or less ruled out SARS-CoV 2 infection in 9.9% of patients with 97.4% sensitivity (Appendix Table 5). Compared to the CORC score (with race/ethnicity variables removed), the CCIS showed substantial net reclassification improvement (NRI=0.310, Appendix Table 6).

Discussion

We have derived and validated a simple clinical risk score, the CCEDRRN COVID-19 Infection Score (CCIS), to predict an emergency department patient's probability of a positive SARS-CoV-2 NAAT. It utilizes only clinical variables available at the patient's bedside, along with a common publicly available measure of community COVID-19 incidence. In this study population, the score ruled out SARS-CoV-2 infection with 96.1% sensitivity in almost one-third of patients. It also identified patients at high risk of infection with over 95% specificity.

The CCIS has several important clinical applications. The ability to differentiate patients with high or low probability of COVID-19 disease could guide safe and effective patient isolation or cohorting from the time of hospital arrival, prior to the availability of SARS-CoV-2 test results. Identification of patients with extremely low risk of SARS-CoV-2 infection may even allow safe omission of testing, which will minimize testing resource utilization in settings with limited testing capacity. Identifying patients with a high probability of SARS-CoV-2 infection can help prioritize use of rapid antigen testing and initiation of effective empiric therapy in critically ill patients prior to availability of NAAT results. By presenting risk estimates and sensitivity for all risk score values, we allow end-users to choose cut-offs for ruling-in and ruling-out SARS-CoV-2 infection that make sense for their setting and application.

Several other risk prediction instruments have been developed to predict positive COVID-19 test results in undifferentiated patients. These tools were developed in studies with substantial methodological limitations and incorporate variables not immediately available at the time of a patient's hospital arrival, so are not useful to guide early isolation, testing and treatment decisions.[2] None of these risk prediction tools considered the prevalence of disease in the population. Prevalence can substantially change the approach to testing and cohorting, and this

will become increasingly important as prevalence rates drop and selective rather than liberal testing may be more appropriate.

United States-based investigators recently reported the development[3] and validation[25] of the CORC score using only clinical variables. The CORC score contains several similar variables to the CCIS. However, the CORC score was derived in a non-consecutive sample of patients which had a much higher incidence of disease than our study cohort and may be vulnerable to selection bias. The CORC score also included race and ethnicity as predictor variables. This inclusion of race and ethnicity variables limits the generalizability of the CORC score beyond the urban American population in which it was developed, as it does not reflect the international diversity of ethnic backgrounds. Moreover, it is unlikely race or ethnicity represents a biologic risk. The association between race and ethnicity and SARS-CoV-2 infection in the CORC score likely reflects other sociodemographic and geographic predictors of the risk of COVID-19 infection in the American population.[25] The CCIS was derived in consecutive patients with a suspected SARS-CoV-2 infection presenting to participating emergency departments, limiting potential for selection bias, and uses the seven-day average local incidence as an estimate of population risk. We believe this approach is more generalizable across populations and better reflects individual patients' pre-test probability of SARS-CoV-2 infection.[26]

Strengths and Limitations

The cohorts used to derive and validate the rule included comprehensive data on consecutive eligible patients from a large, geographically distributed network of Canadian urban, regional, and rural emergency departments. Strict data quality protocols and data cleaning protocols ensured the reliability of collected data.

In addition to clinical variables, we also included the average daily incidence of SARS-CoV-2 infections in a patient's health region, which is an essential predictor of the probability of a patient's risk of COVID infection. This information is publicly reported in many health jurisdictions and particularly in high- and low-prevalence regions. This information remains constant over long periods of time so it can easily be integrated into risk prediction for an individual patient. In practical application of this risk score, patients in areas with high disease burden will automatically score two points, meaning that few patients in these settings will be classified as low risk. Therefore, symptomatic patients would all warrant testing. This underscores the need for liberal isolation and testing practices in settings with high rates of community SARS-CoV-2 transmission.

This study has some limitations. Some missing data required either multiple imputation or classification of missing categorical variables as being absent. The overall missingness of data in this registry is very low. [15] Although the data collection for the CCEDRRN registry relies on abstraction from health records, this approach has been shown to be reliable in our study sites when compared to prospective data collection.[15]

The clinical variables in the model are not likely to be sensitive to changes in geographical changes in SARS-CoV-2 epidemiology. The variable of travel from a country with high incidence may become less informative as the pandemic has spread globally and "hot spots" change. However, high-prevalence areas may change over time, meaning that the risk factor of travel from a region with a high prevalence is likely to still be informative.

This risk score was developed using data from patients enrolled in the first nine months of the pandemic when rates of influenza were low. As such, the score may need to be re-validated and

refined in the future to reflect the influence of influenza, the emergence of variant strains of SARS-CoV-2, and widespread population immunization on patients' risk of infection.

Conclusion

We derived and successfully validated the CCEDRRN COVID-19 Infection Score to accurately predict the probability of SARS-CoV-2 nucleic acid test results in emergency department patients. The CCIS uses clinical variables, accounts for the incidence of SARS-CoV-2 in the community and is ready for immediate clinical use. This score has potential utility to guide early decisions around SARS-CoV-2 test utilization, patient isolation, and empiric therapy for patients solely based on clinical assessment.

Contributors

CMH, ADM, LJM, RJR, and JJP conceived the study, with input on the design and selection of variables from the other contributors. CMH, LJM, PA, SCB, PD obtained funding on behalf of the CCEDRRN investigators. CMH, ADM, PA, SCB, IC, PD, JH, BHR, RO, MW, and KY facilitated data collection along with other members of the CCEDRRN and can verify the underlying data. RJR and JJP developed the analytic plan. SV performed the analysis, with assistance from GG and RJR, including accessing and verification of underlying data. All contributors provided input on interpretation of findings. ADM, CMH, and RJR drafted the manuscript with additional input from all contributors.

Acknowledgment

We gratefully acknowledge the assistance of Ms. Amber Cragg in the preparation of this manuscript. We thank the UBC clinical coordinating centre staff, the UBC legal, ethics, privacy and contract staff and the research staff at each of the participating institutions in the network outlined in the attached Supplement. The network would not exist today without the dedication of these professionals.

Thank you to all our patient partners who shared their lived experiences and perspectives to ensure that the knowledge we co-create addresses the concerns of patients and the public. Creating the largest network of collaboration across Canadian Emergency Departments would not have been feasible without the tireless efforts of Emergency Department Chiefs, and research coordinators and research assistants at participating sites. Finally, our most humble and sincere gratitude to all our colleagues in medicine, nursing, and the allied health professions who have been on the front lines of this pandemic from day one staffing our ambulances, Emergency

Departments, ICUs, and hospitals bravely facing the risks of COVID-19 to look after our fellow citizens and after one another. We dedicate this network to you. (Supplementary Table)

Data Sharing

For investigators who wish to access Canadian COVID-19 Emergency Rapid Response Network data, proposals may be submitted to the network for review and approval by the network's peer-review publication committee, the data access and management committee and the executive committee, as per the network's governance. Information regarding submitting proposals and accessing data may be found at https://canadiancovid19ednetwork.org/.

Funding Acknowledgement

The network is funded by the Canadian Institutes of Health Research (447679), BC Academic Health Science Network Society, BioTalent Canada, Genome BC (COV024; VAC007), Ontario Ministry of Colleges and Universities (C-655-2129), the Saskatchewan Health Research Foundation (5357) and the Fondation CHU de Québec (Octroi #4007).

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Tables & Figures

Figure 1. Flow Diagram of Patients through the study. ED=emergency department; COVID=coronavirus disease

Figure 2. Distribution and performance of the CCEDRRN COVID Infection Score in the derivation cohort (left panel) and validation cohorts (right panel): A) distribution of the score, B) observed infection risk across the range of the score, C) predicted versus observed probability of infection risk, and D) receiver operating characteristic curve with area under the curve (AUC) and associated 95% confidence interval.

A)

B)

C)

D)

AUC 0.84 (0.82-0.85)

AUC 0.79 (0.76-0.82)

Table 1. Characteristics and selected outcomes of enrolled patients·

	Derivation (n=21743)	Validation (n=5922)
Age in years, median (IQR)	57 (38, 73)	56 (37, 73)
Female (%)	10992 (50·5)	3085 (52·1)
Arrival From, n (%)		
Home	19879 (91·4)	5429 (91·7)
Long-term care/Rehabilitation facility/Corrections facility	1000 (4·6)	262 (4·4)
No fixed address/ Shelter/ Single room occupancy	574 (2·6)	201 (3·4)
Inter-hospital transfer	290 (1·3)	30 (0·5)
Risk for Infection, n (%)		
Healthcare worker	505 (2·3)	567 (9·6)
Household/caregiver contact	566 (2·6)	161 (2·7)
Institutional exposure (e.g.,. LTC, prison)	1354 (6·2)	213 (3·6)
Microbiology lab	4 (0·0)	8 (0·1)
Travel	924 (4·2)	344 (5·8)
Other	1320 (6·1)	449 (7·6)
Unknown	5415 (24·9)	1856 (31·3)
No documented risk for infection	10028 (46·1)	1075 (18·1)
Arrival Vital Signs, median (IQR)		
Body temperature	36·7 (36·3, 37·1)	36·8 (36·5, 37·1)
Heart rate	91 (79, 107)	90 (78, 105)
Oxygen saturation	97 (95, 98)	97 (95, 99)
Respiratory rate	18 (18, 20)	18 (16, 20)
Systolic blood pressure	133 (118, 150)	136 (120, 149)
Common Comorbid Conditions, n (%)		
Active malignant neoplasm (cancer)	1678 (7·7)	333 (5·6)
Asthma	1699 (7·8)	468 (7·9)
Atrial fibrillation	1598 (7·3)	402 (6·8)
Chronic kidney disease	1214 (5·6)	321 (5·4)
Chronic lung disease (not asthma/pulmonary fibrosis)	1729 (8)	583 (9·8)
Chronic neurological disorder (not dementia; e.g., stroke/TIA, seizure disorder)	1310 (6)	400 (6·8)
Congestive heart failure	1450 (6·7)	368 (6·2)
Coronary artery disease	1591 (7·3)	449 (7·6)
Dementia	734 (3·4)	188 (3·2)
Diabetes	2583 (11·9)	916 (15·5)
Dialysis	198 (0·9)	28 (0·5)
Dyslipidemia	2375 (10·9)	543 (9·2)
Hypertension	6320 (29·1)	1697 (28·6)
Hypothyroidism	1344 (6·2)	397 (6·7)

Mild liver disease	280 (1·3)	90 (1·5)
Moderate/severe liver disease	245 (1·1)	88 (1·5)
Obesity (clinical impression)	284 (1·3)	108 (1·8)
Organ transplant	128 (0·6)	19 (0·3)
Rheumatologic disorder	1122 (5·2)	258 (4·4)
Other	10075 (46·3)	2174 (36·7)
Past malignant neoplasm (cancer)	936 (4·3)	256 (4·3)
Psychiatric condition/Mental health diagnosis	2967 (13·6)	831 (14)
Pulmonary fibrosis	80 (0·4)	26 (0·4)
Symptoms Reported, n(%)		
Abdominal pain	2725 (12·5)	540 (9·1)
Altered consciousness/confusion	1456 (6·7)	322 (5·4)
Bleeding (hemorrhage)	330 (1·5)	22 (0·4)
Chest pain (includes discomfort or tightness)	4242 (19·5)	974 (16·4)
Chills	2045 (9·4)	594 (10)
Conjunctivitis	49 (0·2)	26 (0·4)
Cough	7724 (35·5)	2663 (44·9)
Diarrhea	2140 (9·8)	526 (8·9)
Dizziness/Vertigo	1521 (7)	300 (5·1)
Dysgeusia/anosmia	140 (0·6)	33 (0·6)
Ear pain	144 (0·7)	30 (0·5)
Fatigue/malaise	3361 (15·5)	924 (15·6)
Fever	5055 (23·2)	1580 (26·7)
Headache	2144 (9·9)	624 (10·5)
Hemoptysis (bloody sputum)	298 (1·4)	66 (1·1)
Joint pain (arthralgia)	296 (1·4)	82 (1·4)
Lower chest wall indrawing	10 (0)	7 (0·1)
Lymphadenopathy	67 (0·3)	21 (0·4)
Muscle aches (myalgia)	1575 (7·2)	517 (8·7)
Nausea/vomiting	4219 (19·4)	935 (15·8)
No recorded symptoms	2113 (9·7)	431 (7·3)
Runny nose (rhinorrhea)	1061 (4·9)	501 (8·5)
Seizures	205 (0·9)	42 (0·7)
Shortness of breath (dyspnea)	8537 (39·3)	2383 (40·2)
Skin rash	241 (1·1)	38 (0·6)
Skin ulcers	27 (0·1)	<5
Sore throat	3024 (13·9)	985 (16·6)
Sputum production	1507 (6·9)	401 (6·8)
Wheezing	582 (2·7)	130 (2·2)
Tobacco Use, n (%)	1852 (8·5)	616 (10·4)
Illicit Substance Use, n (%)	1219 (5·6)	353 (6·0)

Oxygen Required in ED, n (%)	1919 (8·8)	627 (10·6)
Hospital Admission, n (%)	9913 (45·6)	2446 (41·3)
In-hospital Death, n (%)	753 (3·5)	213 (3·6)
7-day average incident COVID-19 cases, median (IQR)	1·3 (0·7, 3·2)	0·96 (0·5, 1·3)
SARS-CoV-2 Positive, n (%)	940 (4·3)	227 (3·8)

IQR=interquartile range; LTC=long-term care; TIA= transient ischemic attack; ED=emergency department

Table 2. Adjusted associations between model predictor variables and SARS-CoV-2 nucleic acid test results

Variable/Score Component	Regression Coefficient (SE)	Adjusted Odds Ratio (95% CI)	Score Value
7-day average incident COVID-19 cases			
0 – 2 daily cases per 100,000 population	-	-	0
2 to 7·99 daily cases per 100,000 population	1·22 (0·09)	3·38 (2·85– 4·00)	1
≥8 daily cases per 100,000 population	2·21 (0·10)	9·09 (7·53– 10·97)	2
Institutional exposure (e·g· LTC, prison) or Travel from country with known cases within 14 days	0·88 (0·09)	2·40 (2·01–2·87)	1
Healthcare worker/Microbiology lab	1·10 (0·16)	3·02 (2·22–4·10)	1
Household/caregiver contact	1·83 (0·12)	6·25 (4·92–7·93)	2
Temperature			
<36 and no self-reported fever	-0·75 (0·3)	0·47 (0·28–0·80)	-1
36 – 37·4 and no self-reported fever	-	-	0
≥37·5 or self-reported fever	1·21 (0·08)	3·36 (2·88–3·91)	1
Supplemental oxygen delivered in the ED	0·98 (0·1)	2·66 (2·18–3·24)	1
Cough	0·85 (0·08)	2·33 (2·01–2·71)	1
Dysgeusia/Anosmia	2·03 (0·24)	7·60 (4·76–12·15)	2
Muscle aches (Myalgia)	0·7 (0·11)	2·02 (1·64–2·48)	1
Current tobacco user	-1·13 (0·21)	0·32 (0·21–0·49)	-1

LTC: Long-term care; ED: Emergency Department

Table 3. Performance metrics for the CCEDRRN COVID-19 Infection Score for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the validation cohort

Score cutoff	n (%)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	LR+	LR-	PPV	NPV	COVID+ n (%)
Rule out:								
≤-2	17 (0·3)	100 (98·4–100)	0·3 (0·2–0·5)	1	NA	3·8	100	0 (0)
≤-1	310 (5·2)	99·6 (97·6–100)	5·4 (4·9–6·1)	1·1	0·1	4·0	99·7	1 (0·3)
≤0	1863 (31·5)	94·3 (90·4–96·9)	32·5 (31·3–33·7)	1·4	0·2	5·3	99·3	13 (0·7)
≤1	3806 (64·3)	78·9 (73.0–84.0)	66·0 (64·7–67·2)	2·3	0·3	8·5	98·7	48 (1·3)
≤2	5152 (87.0)	52·9 (46·2–60.0)	88·6 (87·7–89·4)	4·6	0·5	15·6	97·9	107 (2·1)
≤3	5748 (97·1)	20·7 (15·6–26·6)	97·8 (97·4–98·1)	9·3	0·8	27·0	96·9	180 (3·1)
Rule in:								
≥3	770 (13.0)	52·9 (46·2–59·5)	88·6 (87·7–89·4)	4·6	0·5	15·6	97·9	120 (15·6)
≥4	174 (2·9)	20·7 (15·6–26·6)	97·8 (97·4–98·1)	9·3	0·8	27·0	96·9	47 (27·0)
≥5	44 (0·7)	7·9 (4·8–12·2)	99·5 (99·3–99·7)	17·4	0·9	40·9	96·4	18 (40·9)
≥6	6 (0·1)	0·9 (0·1–3·2)	99·9 (99·8–100)	12·5	1	33·3	96·2	2 (33·3)
≥7	1 (<0.1)	0 (0–1·6)	100.0 (99·9–100)	NA	1	0	96·2	0 (0)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio

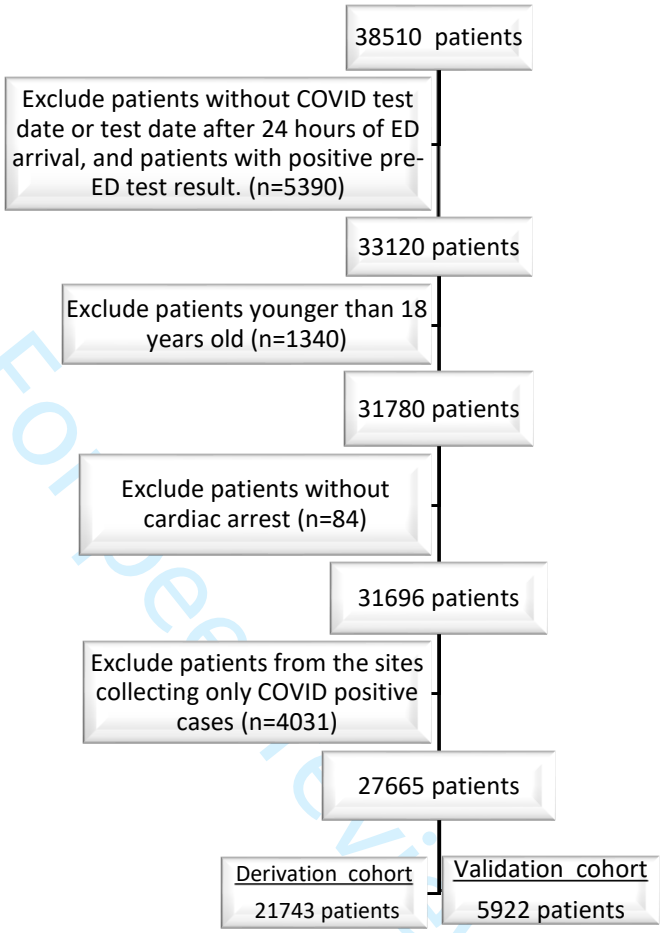
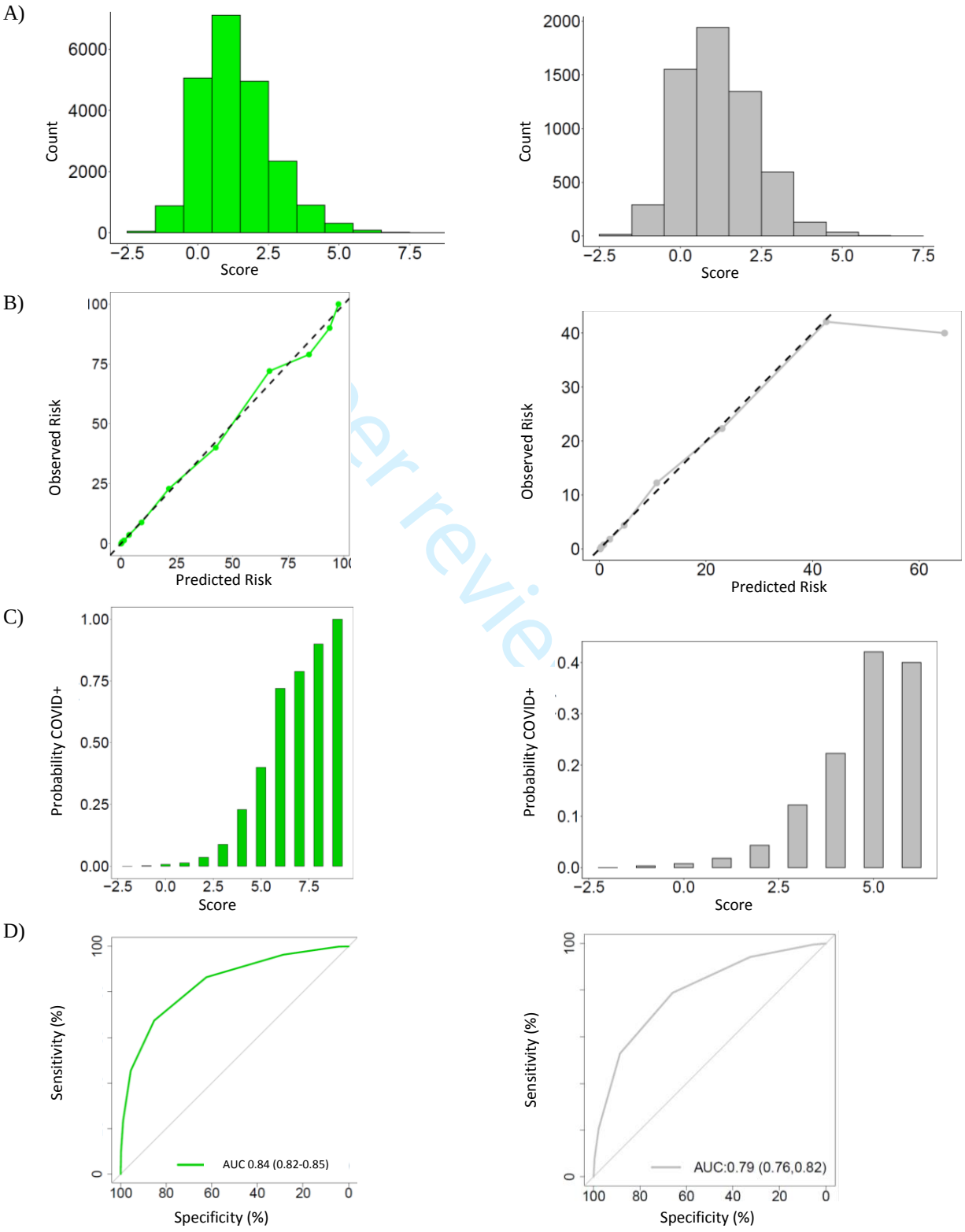


Figure 2. Distribution and performance of the CCEDRRN COVID Infection Score in the derivation cohort (left panel) and validation cohorts (right panel): A) distribution of the score, B) observed in-hospital mortality across the range of the score, C) predicted versus observed probability of in-hospital mortality, and D) receiver operating characteristic curve with area under the curve (AUC) and associated 95% confidence interval.



Appendices

Appendix Table 1. Patients enrolled by CCEDRRN site and time periods for data collection

Site (N patients contributed)	Mar 2020	Apr 2020	May 2020	Jun 2020	Jul 2020	Aug 2020	Sept 2020	Oct 2020	Total
Derivation Cohort	**3217**	**4797**	**5493**	**3096**	**2232**	**1276**	**1266**	**366**	**21743**
Abbotsford Regional Hospital		228	474	385	198				1285
Eagle Ridge Hospital	196	163							359
Foothills, Calgary	437	131							568
Halifax Infirmary/Dalhousie, Nova Scotia	17								17
Hants Community Hospital, Nova Scotia	1								1
Hôpital du Sacré-Coeur de Montreal	27	96	401						524
Hôtel-Dieu de Lévis	1	19	246						266
Jewish General Hospital	754	959	93						1806
Peter Lougheed Centre	321	1119	1169	605	638	552	616	215	5235
Royal Columbian Hospital	236	408	366						1010
Royal University, Saskatoon	132	275	357	296	340	265	193		1858
Saint John Regional Hospital, New Brunswick	98	102							200
South Campus, Calgary	367	598	612	526	586	459	457	151	3756
Sunnybrook Health Sciences Centre			473	593	470				1536
The Ottawa Hospital - Civic Campus	58	24	537						619
Vancouver General Hospital	572	675	765	691					2703
Validation Cohort	**2082**	**2012**	**695**	**381**	**330**		**422**		**5922**
Cobequid Community Health Centre	6								6
Dartmouth General College, Dartmouth Novia Scotia	7								7
Health Science North, Sudbury Ontario			295	381	330				1006

Hôpital de l'Enfant-Jésus, CHU de Québec-Université Laval	40	99	26						165
IUCPQ: Institut universitaire de cardiologie et de pneumologie de Québec	4	5	95						104
Lions Gate Hospital	294	220							514
Mount St Joseph's	236								236
Rockyview, Calgary	368	104							472
Saint Paul's Hospital	541								541
Saskatoon City Hospital, Saskatoon	33	53							86
Secondary Assessment Centers of Dartmouth General and Halifax Infirmary	3	70	66						139
St Paul's Hospital, Saskatoon	84	198							282
Surrey Memorial Hospital	404	927							1331
The Ottawa Hospital - General Campus	62	33	135						230
Toronto Western Hospital							422		422
University of Alberta Hospital		303	78						381

Appendix Table 2. Candidate variables for entry into regression model

Variable	Definition	N (%) Missing
Demographics		
Age	Age in years	0 (0)
Sex	Male, Female, Other	0 (0)
Arrival from	Home + other (not clearly documented)	0 (0)
	Single room + no fixed address + shelter	0 (0)
	Institutional living: long-term care/rehab + correctional	0 (0)
	Inter-hospital transfer	0 (0)
Infection risk		
Travel risk	Travel from country with known cases within 14 days	0 (0)
Institutional exposure	Possible exposure in institutional setting (e.· g.,· Long-term care, prison)	0 (0)
Healthcare worker	Healthcare worker/Microbiology lab employee	0 (0)
Household/caregiver contact	Household contact /caregiver of known positive case	0 (0)
No documented risk	Documented absence of risk factors	0 (0)
Emergency department variables		
ED arrival mode		2 (0)
Ambulance:	arrived by ambulance	
Self/police	self-transported or transported to ED by police	
Arrival heart rate	beats/minute	452 (2.1)
Arrival respiratory rate	breaths/minute	732 (3.4)
Arrival oxygen saturation	%	517 (2.4)
Lowest recorded oxygen saturation in ED	%	445 (2.0)
Fever		847 (3.9)
Temperature <36.0	Temperature <36.0C AND no self-reported fever	
Temperature 36.0-37.4	Temperature 36.0-37.4C AND no self-reported fever	
Temperature ≥37.5 or fever	Temperature ≥37.5 OR self-reported fever	
Respiratory distress	Increased work of breathing documented by treating clinician	1(0)
Supplemental oxygen delivered in the ED	Yes/No	0 (0)
COVID symptoms		
Abdominal pain	Patient-reported symptom as documented by treating clinician	0 (0)
Altered consciousness/confusion	Patient-reported symptom as documented by treating clinician	0 (0)
Bleeding (hemorrhage)	Patient-reported symptom as documented by treating clinician	0 (0)
Chest pain (includes discomfort or tightness)	Patient-reported symptom as documented by treating clinician	0 (0)
Chills	Patient-reported symptom as documented by treating clinician	0 (0)
Conjunctivitis	Patient-reported symptom as documented by treating clinician	0 (0)
Cough	Patient-reported symptom as documented by treating clinician	0 (0)

Diarrhea	Patient-reported symptom as documented by treating clinician	0 (0)
Dizziness/Vertigo	Patient-reported symptom as documented by treating clinician	0 (0)
Dysgeusia/anosmia	Patient-reported symptom as documented by treating clinician	0 (0)
Ear pain	Patient-reported symptom as documented by treating clinician	0 (0)
Fatigue/malaise	Patient-reported symptom as documented by treating clinician	0 (0)
Headache	Patient-reported symptom as documented by treating clinician	0 (0)
Hemoptysis (bloody sputum)	Patient-reported symptom as documented by treating clinician	0 (0)
Joint pain (arthralgia)	Patient-reported symptom as documented by treating clinician	0 (0)
Lymphadenopathy	Patient-reported symptom as documented by treating clinician	0 (0)
Muscle aches (myalgia)	Patient-reported symptom as documented by treating clinician	0 (0)
Nausea/vomiting	Patient-reported symptom as documented by treating clinician	0 (0)
No reported symptoms	Patient-reported symptom as documented by treating clinician	0 (0)
Runny nose (rhinorrhea)	Patient-reported symptom as documented by treating clinician	0 (0)
Seizures	Patient-reported symptom as documented by treating clinician	0 (0)
Shortness of breath (dyspnea)	Patient-reported symptom as documented by treating clinician	0 (0)
Skin rash	Patient-reported symptom as documented by treating clinician	0 (0)
Sore throat	Patient-reported symptom as documented by treating clinician	0 (0)
Sputum production	Patient-reported symptom as documented by treating clinician	0 (0)
Wheezing	Patient-reported symptom as documented by treating clinician	0 (0)
Current tobacco user	Documented current tobacco use	6 (0)
Current illicit user	Documented methamphetamine, opioid or other illicit drug use	6 (0)
7-day average incident COVID-19 cases	Daily reported incidence of new cases in health region, averaged over the seven days preceding hospital arrival. Reported in units of new cases/100,000 population	32 (0.1)

Appendix Table 3. Performance metrics for the CCEDRRN COVID-19 Infection Score for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the derivation cohort

Score	n (%)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	LR+	LR-	PPV	NPV	COVID+ n (%)
Rule out:								
≤-2	51 (0·2)	100 (99·6–100)	0·25 (0·2–0·3)	1.0	NA	4·3	100	0 (0)
≤-1	937 (4·3)	99·89 (99·4–100)	4·5 (4·2–4·8)	1·1	<0·1	4·5	99·9	1 (0·1)
≤0	5996 (27·6)	96·6 (95·2–97·7)	28·67 (28·1–29·3)	1·4	0·1	5·8	99·5	32 (0·5)
≤1	13114 (60·3)	86·6 (84·3–88·7)	62·43 (61·8–63·1)	2·3	0·2	9·4	99·0	126 (1·0)
≤2	18041 (83.0)	67·34 (64·2–70·3)	85·25 (84·8–85·7)	4·6	0·4	17·1	98·3	307 (1·7)
≤3	20405 (93·9)	45·11 (41·9–48·4)	95·61 (95·3–95·9)	10·3	0·6	31·7	97·5	516 (2·5)
Rule in:								
≥3	3702 (17·0)	67·34 (64·2–70·3)	85·25 (84·8–85·7)	4·6	0·4	17·1	98·3	633 (17·1)
≥4	1338 (6·2)	45·11 (41·9–48·4)	95·61 (95·3–95·9)	10·3	0·6	31·7	97·5	424 (31·7)
≥5	440 (2·0)	23·51 (20·8–26·4)	98·95 (98·8–99·1)	22·3	0·8	50·2	96·6	221 (50·2)
≥6	122 (0·6)	9·68 (7·9–11·8)	99·85 (99·8–99·9)	65.0	0·9	74·6	96·1	91 (74·6)
≥7	31 (0·1)	2·77 (1·8–4·0)	99·98 (99·9–100.0)	115·1	1.0	83·9	95·8	26 (83·9)
≥8	12 (0·1)	1·17 (0·6–2·1)	100 (100.0–100.0)	243·4	1.0	91·7	95·7	11 (91·7)
≥9	2 (<0·1)	0·21 (<0.1–0·8)	100 (100.0–100.0)	NA	1.0	100	95·7	2 (100)

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio

Appendix Table 4. Performance metrics for CCEDRRN COVID Infection Score for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the combined cohort

Score cutoff	n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	LR+	LR-	COVID+ n (%)
Rule out:								
≤-2	70 (0·3)	100 (99·7,100)	0·3 (0·2,0·3)	4·2	100	1	0	0 (0)
≤-1	1257 (4·5)	99·8 (99·4,100)	4·7 (4·5,5)	4·4	99·8	1·1	<0·1	2 (0·2)
≤0	7872 (28·5)	96·1 (94·8,97·1)	29·5 (29·0,30·1)	5·7	99·4	1·4	0·1	46 (0·6)
≤1	16962 (61·3)	85 (82·8,87·0)	63·4 (62·8,63·9)	9·3	99.0	2·3	0·2	175 (1·0)
≤2	23243 (84·0)	64·8 (62·0,67·5)	86·2 (85·7,86·6)	17·1	98·2	4·7	0·4	411 (1·8)
≤3	26169 (94·6)	40·3 (37·4,43·2)	96·1 (95·9,96·4)	31·4	97·3	10·4	0·6	697 (2·7)
Rule in:								
≥3	4422 (16.0)	64·8 (62·0,67·5)	86·2 (85·7,86·6)	17·1	98·2	4·7	0·4	756 (17·1)
≥4	1496 (5·4)	40·3 (37·4,43·2)	96·1 (95·9,96·4)	31·4	97·3	10·4	0·6	470 (31·4)
≥5	476 (1·7)	20·2 (18·0,22·6)	99·1 (99·0,99·2)	49·6	96·6	22·3	0·8	236 (49·6)
≥6	128 (0·5)	8 (6·5,9·7)	99·9 (99·8,99·9)	72·7	96·1	60·3	0·9	93 (72·7)
≥7	32 (0·1)	2·2 (1·5,3·2)	100 (100,100)	81·2	95·9	98·4	1.0	26 (81·3)
≥8	12 (<0·1)	0·9 (0·5,1·7)	100 (100,100)	91·7	95·8	249·8	1.0	11 (91·7)
≥9	2 (<0·1)	0·2 (0,0·6)	100 (100,100)	100	95·8	Inf	1.0	2 (100)

TP: True positives; FP: False positives; TN: True negatives; FN: False negatives; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio

Appendix Table 5. Performance metrics for the CORC score (race and ethnicity variables removed) for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the combined cohort

Score	n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	LR+	LR-	COVID+ n (%)
Rule out:								
≤-2	202 (0·7)	99·9 (99·5–100)	0·8 (0·7–0·9)	4·2	99·5	1·01	0·11	1 (0·5)
≤-1	2715 (9·8)	97·4 (96·4–98·3)	10·1 (9·8–10·5)	4·6	98·9	1·08	0·25	30 (1·1)
≤0	9089 (32·9)	90·1 (88·2–91·7)	33·9 (33·3–34·4)	5·7	98·7	1·36	0·29	116 (1·3)
≤1	17582 (63·9)	72·8 (70·2–75·4)	65·2 (64·6–65·7)	8·4	98·2	2·09	0·42	317 (1·8)
≤2	23421 (84·7)	51·2 (48·3–54·1)	86·2 (85·8–86·7)	14·1	97·6	3·72	0·57	569 (2·4)
≤3	26224 (94·8)	27·7 (25·1–30·3)	95·8 (95·5–96)	22·4	96·8	6·56	0·76	844 (3·2)
Rule in:								
≥3	4244 (15·3)	51·2 (48·3–54·1)	86·2 (85·8–86·7)	14·1	97·6	3·72	0·57	598 (14·1)
≥4	1441 (5·2)	27·7 (25·1–30·3)	95·8 (95·5–96)	22·4	96·8	6·56	0·76	323 (22·4)
≥5	358 (1·3)	11·1 (9·3–13)	99·1 (99–99·2)	36.0	96·2	12·79	0·9	129 (36·0)
≥6	54 (0·2)	3·1 (2·2–4·2)	99·9 (99·9–100)	66·7	95·9	45·41	0·97	36 (66·7)
≥7	7 (<0·1)	0·4 (0·1–1)	100 (100–100)	71·4	95·8	56·77	1	5 (71·4)

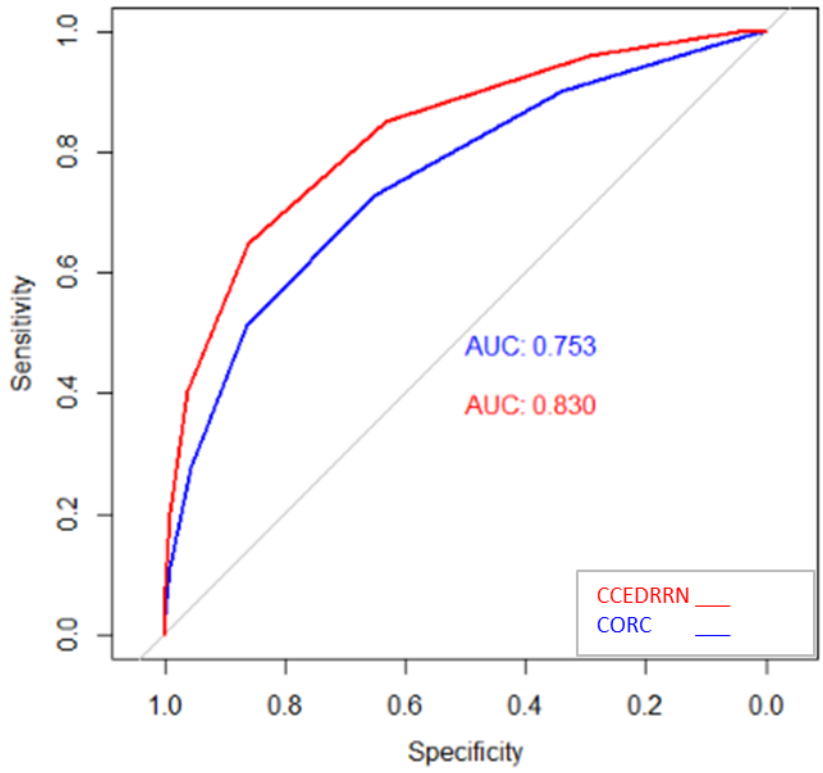
TP: True positives; FP: False positives; TN: True negatives; FN: False negatives; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio

Appendix Table 6. Net Reclassification Improvement of the CCEDRRN COVID-19 Infection Score compared to the CORC Score (race and ethnicity variables removed)

Primary Outcome : Covid Positive					
CORC risk category		**CCIS risk category**			**Total**
		Low	**Medium**	**High**	
	Low	12	18	0	30
	Medium	34	539	241	814
	High	0	94	229	323
	Total	46	651	470	1167
Primary Outcome: Covid Negative					
CORC risk category		**CCIS risk category**			
		Low	**Medium**	**High**	**Total**
	Low	1593	1092	0	2685
	Medium	6233	15756	706	22695
	High	0	798	320	1118
	Total	7826	17646	1026	26498

COVID Positive		**COVID Negative**	
Number of outcomes	1167	Number of outcomes	26498
Correct reclassification	259	Correct reclassification	7031
Incorrect reclassification	128	Incorrect reclassification	1798
Net reclassification	131	Net reclassification	5233
Net reclassification improvement (Event)	0.112	Net reclassification improvement (Non-event)	0.197
Total net reclassification improvement			0.310

Appendix Figure 1. Receiver operating characteristic curves for the CCEDRRN COVID Infection Score (CCIS) and the CORC score (race and ethnicity variables removed) in the combined study cohort



Canadian COVID-19 ED Network

Supplementary Table: Contributors to the Canadian COVID-19 Emergency Department Rapid Response Network

1. Purpose

This supplementary table provides details of the support staff at each of the participating institutions in the Canadian COVID-19 Emergency Department Rapid Response Network. This supplementary document should be attached to each peer-reviewed manuscript after the methods manuscript (M1). The purpose is to ensure research staffs and lead coordinators are appropriately recognized for their contributions to the network.

2. List of Support Staff

Table 1. Network coordinating centre staff at the University of British Columbia

Name	Roles	Contributions
Gelareh Ghaderi	Data analyst	Data processing and analysis for manuscripts.
Jeffrey Hau	Data manager	REDCap, data processing and analysis for manuscripts.
Vi Ho	National coordinator	Coordinate with provincial coordinators and training/onboarding of research assistants.
Joe Larkin	Project manager	Project management.
Fiona O'Sullivan	Data analyst	Data processing and analysis for manuscripts.
Serena Small	Research coordinator	Ethics & privacy reviews, data management plan, privacy impact assessment, and qualitative analyses
Amber Cragg	Research manager	Data and manuscript management
Wei Zhao	Data analyst	Data processing and analysis for manuscripts.
Vicky Wu	Data analyst	Data processing and analysis for manuscripts.
Elnaz Bodaghkhani	Research associate	Data and manuscript management

Table 2. Provincial Coordinators

Name	Province	Institutional affiliation	Contributions to CCEDRRN
Corinne DeMone	NS	Dalhousie University, Halifax, Nova Scotia	Research ethics board submission, manages research assistants, data cleaning and quality.
Jacqueline Fraser	NB	Dalhousie University, St. John New Brunswick	Site coordinator as well as research assistant.
Veronique Gélinas	QC	Centre intégré de santé et de services sociaux de Chaudière-Appalaches (Hôtel-Dieu de Lévis site), Lévis	Provincial research coordinator, translation of research material to French, ethics management.

Canadian COVID-19 ED Network

Connie Taylor	ON	Queen's University, Kingston	Coordination of research assistants in Ontario, maintenance of REB applications for the province
Kate Mackenzie	MB	Health Sciences Centre, Winnipeg	Lead RA for the province
Aimee Goss	SK	University of Saskatchewan, Saskatoon	Screens records in Saskatoon, data/extraction and entry, coordinates research assistants.
Hina Walia	AB	University of Calgary, Calgary	Provincial coordinator lead for Alberta, oversight of all Alberta sites.
Rajan Bola	BC	University of British Columbia, Vancouver	Provincial coordinator lead for BC, oversight of all BC sites.

Table 3. Institutional research assistant (RA) leads
Institutional RA leads are responsible for data extraction and integrity, communication with provincial leads.

Name	**Province**	**Institutional affiliation(s)**
Corinne DeMone	NS	Dartmouth General Hospital, Cobequid Community Health Centre, Hants Community Hospital Secondary Assessment Centers of the Dartmouth General Hospital, and Halifax Infirmary, Halifax
Jacqueline Fraser	NB	Saint John Regional Hospital, Saint John
Alexandra Nadeau	QC	CHU de Québec Université Laval, Quebec City
Audrey Nolet	QC	Centre intégré de santé et de services sociaux de Chaudière-Appalaches (Hôtel-Dieu de Lévis site), Lévis
Xiaoqing Xue	QC	Jewish General Hospital, Montréal
David Iannuzzi	QC	McGill University Health Center, Montréal
Chantal Lanthier	QC	Hôpital du Sacré-Cœur de Montréal, Montréal
Konika Nirmalanathan	ON	University Health Network, Toronto
Vlad Latiu	ON	Kingston General Hospital, Hotel Dieu Hospital, Kingston
Joanna Yeung	ON	Sunnybrook Health Sciences Center, Toronto
Natasha Clayton	ON	Hamilton General Hospital, Juravinski Hospital, Hamilton
Tom Chen	ON	London Health Sciences Centre, London
Jenna Nichols	ON	Health Sciences North, Sudbury
Kate Mackenzie	MB	Health Sciences Centre, Winnipeg
Aimee Goss	SK	St. Paul's Hospital, Royal University Hospital, Saskatoon City Hospital, Saskatoon
Stacy Ruddell	AB	Foothills Medical Centre, Peter Lougheed Centre, Rockyview General Hospital, South Health Campus, Calgary
Natalie Runham	AB	University of Alberta Hospital, Edmonton

Canadian COVID-19 ED Network

Name	Province	Institutional affiliation(s)
Karlin Su	AB	Royal Alexandra Hospital/Northeast Community Health Center, Edmonton
Josie Kanu	BC	St. Paul's Hospital, Mount Saint Joseph, Vancouver
Bernice Huynh	BC	Abbotsford Regional Hospital and Cancer Center, Abbotsford
Amanda Swirhun	BC	Royal Columbian Hospital, New Westminster
Tracy Taylor	BC	Eagle Ridge Hospital and Health Care Centre, Port Moody
Mai Hayashi	BC	Royal Inland Hospital, Kamloops
Mackenzie Cheyne	BC	Kelowna General Hospital, Kelowna
Sarim Asim	BC	Surrey Memorial Hospital, Surrey
Katherine Lam	BC	Vancouver General Hospital, Vancouver
Kelsey Compagna	BC	Lions Gate Hospital, Vancouver

Table 4. Contributing Study Sites and Investigators

Lead Investigator	Contributing Site / Code	Member Investigators
Maritime		
Patrick Fok		
Nova Scotia		
Hana Wiemer	Halifax Infirmary/ 902	Patrick Fok
	Dartmouth General Hospital/ 903	Hana Wiemer
	Hants Community Hospital/ 904	Samuel Campbell
	Cobequid Community Health Centre/ 905	Kory Arsenault
	Secondary Assessment Centers of Dartmouth General and Halifax Infirmary/ 908	Tara Dahn
New Brunswick		
Kavish Chandra	Saint John Regional Hospital/ 901	Kavish Chandra
Quebec		
Patrick Archambault	Hotel-Dieu de Lévis/ 701	Patrick Archambault
	Jewish General Hospital/ 702	Joel Turner
	Centre Hospitalier de l'Université Laval (CHU de Québec)/ 703	Éric Mercier
	L'hôpital Royal Victoria - Royal Victoria Hospital/ 705	Greg Clark
	Hôpital de l'Enfant-Jésus,CHU de Québec/ 706	Éric Mercier
	Hôpital du Saint-Sacrement, CHU de Québec/ 707	Éric Mercier
	Hôpital Saint-François d'Assise, CHU de Québec/ 708	Éric Mercier
	Hôtel-Dieu de Québec,CHU de Québec/ 709	Éric Mercier

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	IUCPQ: Institut universitaire de cardiologie et de pneumologie de Québec/ 710	Sébastien Robert
	Hôpital du Sacré-Coeur de Montreal/ 711	Raoul Daoust
Ontario		
Laurie Morrison & Steven Brooks	Sunnybrook/ 401	Ivy Cheng
	The Ottawa Hospital - Civic Campus/ 403	Krishan Yadav
	The Ottawa Hospital - General Campus/ 404	Krishan Yadav
	Kingston/Queens/ 406	Steven Brooks
	Hamilton General Hospital/ 407	Michelle Welsford
	Health Science North, Sudbury Ontario/ 408	Rob Ohle
	University Hospital – LHSC/ 409	Justin Yan
	North York General Hospital, Toronto/ 410	Rohit Mohindra
	Victoria Hospital – LHSC/ 412	Justin Yan
	Toronto Western Hospital/ 414	Megan Landes
Manitoba		
Tomislav Jelic	Health Sciences Centre/ 307	Tomislav Jelic
Saskatchewan		
Phil Davis	Pasqua Hospital, Regina/ 301	Ankit Kapur
	Regina General Hospital, Regina/ 302	Ankit Kapur
	St Paul's Hospital, Saskatoon/ 303	Phil Davis
	Royal University, Saskatoon/ 304	Phil Davis
	Saskatoon City Hospital, Saskatoon/ 305	Phil Davis
Alberta		
Andrew McRae	University of Alberta Hospital, Edmonton/ 201	Brian Rowe
	Foothills, Calgary/ 202	Katie Lin
	Rockyview, Calgary/ 203	Andrew McRae
	Peter Lougheed Centre/ 204	Andrew McRae
	South Campus, Calgary/ 205	Stephanie VandenBerg
	Northeast Community Health Centre, Edmonton/ 206	Jake Hayward, Jaspreet Khangura
	Royal Alexandra Hospital, Edmonton/ 306	Jake Hayward, Jaspreet Khangura
British Columbia		
Corinne Hohl	Vancouver General Hospital/ 101	Daniel Ting
	Lions Gate Hospital/ 102	Maja Stachura
	Saint Paul's Hospital/ 103	Frank Scheuermeyer

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Mount St Joseph's/ 104	Frank Scheuermeyer
Surrey Memorial Hospital/ 105	Balijeet Braar/ Craig Murray
Royal Columbian Hospital/ 106	John Taylor
Abbotsford Regional Hospital/ 107	Ian Martin
Eagle Ridge Hospital/ 108	Sean Wormsbecker
Victoria General Hospital/ 109	Matt Bouchard
Royal Jubilee Hospital/ 110	Matt Bouchard
Nanaimo General Hospital/ 111	Matt Bouchard
Royal Inland Hospital/ 112	Ian Martin
Kelowna General / Hospital/ 115	Lee Graham

It was not possible for us to recruit Members from Newfoundland and Labrador, Northwest Territories, Nunavut, Prince Edward Island and Yukon at the time of the inception of the registry.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Appendix table 2
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Appendix Table 2
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7-8
	10c	V	For validation, describe how the predictions were calculated.	9
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8,9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	10
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	8
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1, Appendix table 2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2
	15b	D	Explain how to the use the prediction model.	Table 2
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	10
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	12-13
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	16

TRIPOD Checklist: Prediction Model Development and Validation

Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

The CCEDRRN COVID-19 Infection Score (CCIS): development and validation in a Canadian cohort of a clinical risk score to predict SARS-CoV-2 infection in patients presenting to the emergency department with suspected COVID-19

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055832.R1
Article Type:	Original research
Date Submitted by the Author:	13-Oct-2021
Complete List of Authors:	McRae, Andrew; University of Calgary Cumming School of Medicine, Emergency Medicine Hohl, Corinne M.; The University of British Columbia Faculty of Medicine, Emergency Medicine Rosychuk, Rhonda; University of Alberta Faculty of Medicine & Dentistry, Paediatrics Vatanpour, Shabnam; University of Calgary Cumming School of Medicine, Emergency Medicine Ghaderi, Gelareh; The University of British Columbia Faculty of Medicine, Emergency Medicine Archambault, Patrick M.; Universite Laval Faculte de medecine, Emergency Medicine Brooks, Steven C.; Queen's University School of Medicine, Emergency Medicine Cheng, Ivy; Sunnybrook Health Sciences Centre, Emergency Medicine Davis, Philip; University of Saskatchewan College of Medicine, Emergency Medicine Hayward, Jake; University of Alberta Faculty of Medicine & Dentistry, Emergency Medicine Lang, Eddy; University of Calgary Cumming School of Medicine, Emergency Medicine Ohle, Robert; Northern Ontario School of Medicine, Emergency Medicine Rowe, Brian; University of Alberta Faculty of Medicine & Dentistry, Emergency Medicine Welsford, Michelle; McMaster University Faculty of Health Sciences, Emergency Medicine Yadav, Krishan; University of Ottawa Faculty of Medicine, Emergency Medicine Morrison, Laurie J.; St Michael's Hospital, Emergency Medicine Perry, Jeffrey; University of Ottawa Faculty of Medicine, Emergency Medicine
Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Epidemiology, Infectious diseases

Keywords:	COVID-19, ACCIDENT & EMERGENCY MEDICINE, EPIDEMIOLOGY

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The CCEDRRN COVID-19 Infection Score (CCIS): development and validation in a Canadian cohort of a clinical risk score to predict SARS-CoV-2 infection in patients presenting to the emergency department with suspected COVID-19

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Abstract (283/300 words)

Objectives: To develop and validate a clinical risk score that can accurately quantify the probability of SARS-CoV-2 infection in patients presenting to an emergency department without the need for laboratory testing

Design: Cohort study of participants in the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) registry. Regression models were fitted to predict a positive SARS-CoV-2 test result using clinical and demographic predictors, as well as an indicator of local SARS-CoV-2 incidence.

Setting: 32 emergency departments in eight Canadian provinces

Participants: 27,665 consecutively-enrolled patients who were tested for SARS-CoV-2 in participating emergency departments between March 1-October 30,2020

Main outcome measures: Positive SARS-CoV-2 nucleic acid test result within 14 days of an index emergency department encounter for suspected COVID-19 disease

Results: We derived a 10-item CCEDRRN COVID-19 Infection Score using data from 21,743 patients. This score included variables from history and physical examination, and an indicator of local disease incidence. The score had a c-statistic of 0.838 with excellent calibration. We externally validated the rule in 5,295 patients. The score maintained excellent discrimination and calibration, and had superior performance compared to another previously published risk score. Score cutoffs were identified that can rule-in or rule-out SARS-CoV-2 infection without the need for nucleic acid testing with 97.4 % sensitivity (95% CI 96.4–98.3) and 95.9% specificity (95% CI 95.5-96.0).

Conclusions The CCEDRRN COVID-19 Infection Score uses clinical characteristics and publicly available indicators of disease incidence to quantify a patient's probability of SARS-CoV-2 infection. The score can identify patients at sufficiently high risk of SARS-CoV-2 infection to warrant isolation and empiric therapy prior to test confirmation, while also identifying patients at sufficiently low risk of infection that they may not need testing.

Trial registration: CCEDRRN is registered at clinicaltrials.gov (NCT04702945).

Funding:

The Canadian Institutes of Health Research (447679), Ontario Ministry of Colleges and Universities (C-655-2129), Saskatchewan Health Research Foundation (5357), Genome BC (COV024 and VAC007) Fondation du CHU de Québec (Octroi No. 4007) Sero-Surveillance and Research (COVID-19 Immunity Task Force Initiative) provided peer-reviewed funding. The BC Academic Health Science Network and BioTalent Canada provided non-peer reviewed funding. These organizations are not-for-profit, and had no role in study conduct, analysis, or manuscript preparation.

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Strengths and Limitations of this Study

- Patients were enrolled in a large, geographically distributed network of Canadian urban, regional, and rural emergency departments, with strict data quality and cleaning protocols to ensure reliability of collected data.
- In addition to clinical variables, we also included the average daily incidence of SARS-CoV-2 infections in a patient's health region, which is an essential predictor of the probability of a patient's risk of COVID infection.
- Some missing data required either multiple imputation or classification of missing categorical variables as being absent, but the overall missingness of data in this registry is very low.
- Although the data collection for the CCEDRRN registry relies on abstraction from health records, this approach has been shown to be reliable in our study sites when compared to prospective data collection.
- This risk score was developed using data from patients enrolled in the first nine months of the pandemic when rates of influenza were low, so the score may need to be re-validated and refined in the future to reflect the influence of influenza, the emergence of variant strains of SARS-CoV-2, and widespread population immunization on patients' risk of infection.

MAIN DOCUMENT (3186 words)

Introduction

To date, the World Health Organization has reported 190 million diagnosed cases of coronavirus 2019 disease (COVID-19) with 4.2 million fatalities.[1] Despite the availability of vaccines to prevent COVID-19, incomplete population-level immunization and the emergence of variants of concern means that hospitals around the world need to continue to identify and isolate patients with suspected COVID-19 from the time they arrive in the emergency department until their SARS-CoV-2 test results are available. In acutely ill patients, clinicians may need to initiate empiric therapy immediately. A quantitative risk score that can accurately predict the probability of a positive SARS-CoV-2 test result would guide initial isolation and empiric therapy prior to nucleic acid amplification test (NAAT) test result availability, while identifying patients with sufficiently low probability of COVID-19 who may not require testing or isolation.

Many risk prediction tools have been developed to predict the probability of SARS-CoV-2 infection.[2–14] A living systematic review of these models concluded that most were generated using poor methodological approaches and none were ready for widespread use.[2] Most published risk prediction tools, including one identified as promising by the living systematic review, included early laboratory or imaging findings, thus precluding their utility to guide immediate isolation and clinical decisions at the time of first clinical contact. Other risk prediction tools using machine learning included laboratory and imaging results and can only be implemented in hospitals using electronic health records with integrated decision support. None of these models accounted for the prevalence of COVID-19 disease in the local population, which is an important risk predictor, and most only included patients from the early stages of the pandemic.[2]

The objective of this study is to develop a clinical risk score to predict the probability of a positive SARS-CoV-2 nucleic acid test in a large, generalizable population of patients presenting to emergency departments using only clinical characteristics and indicators of local SARS-CoV-2 incidence. This risk score is intended to guide SARS-CoV-2 testing, isolation, and empiric therapy decisions without relying on other laboratory testing or diagnostic imaging. This score could be invaluable in settings that may not have access to adequate resources for timely SARS-CoV-2 testing.

Methods

This analysis uses data from the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN, pronounced "SED-rin"). CCEDRRN is an ongoing multicenter, pan-Canadian registry that has been enrolling consecutive patients presenting to emergency departments with suspected COVID-19 disease in hospitals in eight of ten Canadian provinces since March 1, 2020.[15] Information on the network, including detailed methods and participating sites, is available elsewhere.[15] Sites and enrolment periods are shown in the supplementary appendix, Table 1. Additional information on network sites is available in the Network Appendix. This study follows the methodological and reporting recommendations outlined in the Transparency in reporting of a multivariable prediction model for individual diagnosis and prognosis (TRIPOD) criteria.[16] The CCEDRRN data collection form includes prespecified demographic and social variables, vital signs, symptoms, and comorbid conditions (derived from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) reporting form),[17,18] exposure risk variables, hospital laboratory and diagnostic imaging test results, SARS-CoV-2 NAAT results, and patient outcomes. Data were abstracted at each site using electronic medical record extraction where available as well as manual review of either

electronic or paper charts (depending on site-specific documentation practices) by trained research assistants who were blinded to the potential predictor variables at the time of data collection. Reliability of health record data abstraction was evaluated by comparison with prospective data collection in a sample of patients and found to be reliable.[15]

Each consecutive, eligible patient enrolled in the registry was assigned a CCEDRRN unique identifier. Trained research assistants entered anonymized participant data into a REDCap database (Version 10.9.4; Vanderbilt University, Nashville, Tennessee, USA). Regular data quality checks including verification of extreme or outlying values were performed by each participating site, coordinated by the CCEDRRN coordinating center.

Participants

We included data from consecutive patients tested for SARS-CoV-2 at 32 CCEDRRN sites. From each site's start date forward, we included consecutive eligible patients aged 18 and older who had a biological sample (swab, endotracheal aspirate, bronchoalveolar lavage) specimen collected for NAAT on their index emergency department visit or, if admitted, within 24h of emergency department arrival. For patients with multiple emergency department encounters involving COVID-19 testing, we only used the first encounter in this analysis.

We excluded patients who had a positive SARS-CoV-2 NAAT within 14 days prior to their emergency department visit, patients with cardiac arrest prior to emergency department arrival, and those with missing outcome data.

Predictors

Candidate predictors were chosen based on clinical consensus and availability within the CCEDRRN registry. Predictors included known risk factors for SARS-CoV-2 infection,

including work as a healthcare provider, institutional living (i.e., long term care, prison), close personal or household contacts with SARS-CoV-2 infection; symptoms including cough, anosmia or dysgeusia, fever, myalgias and vital signs on emergency department arrival. The full list of candidate variables, and their definitions are available in the supplementary appendix (Appendix Table 2).

In addition to these clinical variables, the seven-day average incident COVID-19 case count was calculated for the health region of each participating site using publicly available epidemiological data.[19] For each calendar day within each health region represented in the study, we calculated the average daily incident rate of new infections per 100,000 population over the preceding seven days. This seven-day average incidence was assigned to each patient based on the date of their index emergency department encounter and the health region of the forward sortation area of their postal code of residence. For patients with no fixed address, we allocated them to the health region of the hospital in which they were tested. As publicly available incident COVID-19 case data were not available for the early pandemic, we imputed values for the first five weeks of the pandemic by modeling the reported COVID-19 cases that had accumulated in every health region over time using linear interpolation (0.1% missing).

Outcome

The primary outcome of this analysis was the diagnosis of SARS-CoV-2 infection using a criterion standard of a positive NAAT at the time of index emergency department visit or within 14 days after the index encounter.

Sample size and precision

The 46 candidate predictors had 52 degrees of freedom and with an expected SARS-CoV-2 infection rate of 5%, a sample size of 1040 was sufficient for the derivation cohort based on an

anticipated event rate of less than 20% and a requirement for 20 outcomes per degree of freedom.[20] Over 21,000 patients were available for the derivation cohort at the time of analysis, providing more than sufficient data for reliable prediction modeling.

Model development and validation

We randomly assigned study sites to the derivation and validation cohorts with the goal of assigning 75% of eligible patients and outcome events to the derivation cohort and 25% to the validation cohort. Thus, the derivation and validation cohorts are geographically distinct. Within the derivation cohort, candidate predictors were examined for co-linearity and missing or extreme values. In the presence of co-linearity, one predictor was dropped from the set of candidate predictors. Five multiple imputations were used for continuous variables with missing data. Patients with values of "not recorded" for categorical variables (eg, smoking, need for supplemental oxygen) were assumed to have the reference value (ie. "no") for that categorical variable. The initial logistic regression model considered all candidate predictors, with continuous predictors fit with restricted cubic splines with three knots. The strengths of associations between predictors and outcome were assessed using an analysis of variance (ANOVA) plot to inform the degrees of freedom to allocate to each predictor. The model was fit again with these changes. A fast step-down procedure reduced the model to key predictors based on an Akaike's information criterion stopping rule with a threshold of 120 to enable a model with a relatively small number of predictors that would be clinically easy to use. Internal bootstrap validation with 1,000 bootstrap samples was conducted to provide an optimism-corrected C-statistic. Continuous predictors were categorized based on the relationship between the spline function and outcome.

We then developed the points-based CCEDRRN COVID-19 Infection Score (CCIS) using a nomogram to assign integer point values for each variable included in the derived model. Discrimination of the score was evaluated using the C-statistic. Calibration was evaluated using calibration curves and comparison of observed and expected outcomes. Diagnostic performance was evaluated using sensitivity and specificity, predictive values, and likelihood ratios at different point thresholds.

We then evaluated the discrimination, calibration, and performance characteristics of the CCIS in an external validation cohort of patients from geographically distinct study sites who were not part of the derivation cohort.

Validation of previously published models

We used our combined (derivation and validation) study cohort to externally validate the COvid Rule out Criteria (CORC) score developed by Kline et al (although we were not able to include race and ethnicity variables as these are not reliably recorded or reported in most Canadian hospitals).[3] We compared measures of discrimination and calibration, along with sensitivity and specificity of risk score values for the CCIS and CORC (with race and ethnicity variables removed). We split each score into categories of low, moderate, and high-risk for SARS-CoV-2 infection. Low risk was defined as a score having a sensitivity for ruling-out infection of 95% or higher. High-risk was defined as a score having a specificity for ruling in infection of 95% or higher. We compared the performance of the two scores by calculating net reclassification improvement across low, moderate, and high-risk categories.[21,22]

All analyses were performed in R [23] using the rms package.[24]

Role of the funding sources

The funding organizations had no role in the study conduct, data analysis, manuscript preparation or submission.

Patient and public involvement

The CCEDRRN governance structure includes patient representatives on the Executive Committee, Scientific Steering Committee, Protocol Review and Publications Committee, Data Access and Monitoring Committee and Knowledge Translation Committee. The network also has a Patient Engagement Committee composed of patient partners from across Canada. Patient partners provided input into study design and selection of outcomes for all CCEDRRN analyses, and provide advice on knowledge sharing and translation strategies.

Results

This analysis is based on 27,665 patients consecutively enrolled from 32 participating emergency departments between March and October, 2020 (Figure 1, Appendix Table 1). Sites and enrolment periods contributing patient data are shown in the supplementary appendix (Appendix Table 1). Of the included patients, 1,167 (4.2%) had a positive SARS-CoV-2 NAAT result, including 1133 who had a positive initial test and 34 who tested positive after a negative (27) or indeterminate (7) initial NAAT.

The study cohort was subdivided into a derivation cohort (21,743 patients from 16 sites, 940 (4.3%) SARS-CoV-2 positive) and a separate external validation cohort (5,922 patients from 16 different sites, 227 (3.8%) SARS-CoV-2 positive). Demographic and clinical characteristics of the derivation and validation cohorts are shown in Table 1. No continuous variable requiring multiple imputation had more than 3.4% missingness (Appendix Table 2).

In the derivation cohort, we derived a 10-variable model to predict the probability of a patient having a positive SARS-CoV-2 NAAT. The regression coefficients and odds ratios for each variable in the model are shown in Table 2. The C-statistic for the derived model was 0.851 with excellent calibration.

We created a points-based CCEDRRN COVID-19 Infection Score (CCIS) using rounded regression coefficients with a range of negative two to nine points (Table 2). The C-statistic of the CCIS in the derivation cohort was 0.838 (0.824–0.852) with excellent calibration (Figure 2). A score of zero or less ruled out a positive SARS-CoV-2 test result in 5,996/21,743 patients (27.6%) with a sensitivity of 96.6% (95% CI 95.2–97.7). A score of four or more was observed in 1,338/21,743 patients (6.2%) and had a specificity of 95.6 (95% CI 95.3–95.8) indicating a low frequency of false positives (Appendix Table 3).

We then quantified the performance of the CCIS in our external validation cohort. In this cohort, the C-statistic for the points-based risk score was 0.792 (Figure 2). A score of zero or less ruled out a positive SARS-CoV-2 test result in 1,863/5,925 patients (31.4%) with a sensitivity of 94.3% (95% CI 90.4–96.9). A score of four or more was observed in 174/5,925 patients (2.9%) and had a specificity of 97.8 (95% CI 97.4–98.1) indicating a low frequency of false positives (Table 3).

In a combined cohort of patients (derivation and validation combined), we compared the discrimination and diagnostic performance of the CCIS to the CORC score. The CCIS had a C-statistic of 0.837 compared to 0.750 for the CORC score (with race/ethnicity variables removed) (Appendix Figure 1). A CCIS of zero or less ruled out SARS-CoV-2 infection in 28.4% of patients with a sensitivity of 96.1% (Appendix Table 4) whereas a CORC score of negative one or less ruled out SARS-CoV 2 infection in 9.9% of patients with 97.4% (Appendix Table 5)

sensitivity. Compared to the CORC score (with race/ethnicity variables removed), the CCIS showed substantial net reclassification improvement (NRI=0.310, Appendix Table 6).

Discussion

We have derived and validated a simple clinical risk score, the CCEDRRN COVID-19 Infection Score (CCIS), to predict the probability of a positive SARS-CoV-2 NAAT in patients presenting to emergency departments. It utilizes only clinical variables available at the patient's bedside, along with a common publicly available measure of community COVID-19 incidence. In this study population, the score ruled out SARS-CoV-2 infection with 96.1% sensitivity in almost one-third of patients. It also identified patients at high risk of infection with over 95% specificity.

In addition to clinical variables, we also included the average daily incidence of SARS-CoV-2 infections in a patient's health region, which is an essential predictor of the probability of a patient's risk of COVID infection. Although access to timely incidence data may be challenging in under-resourced health systems, this information is publicly reported in many health jurisdictions. In practice, the local incidence would likely need to be shared within an emergency department on a daily basis. We developed data driven cutoffs for categorization of low, moderate and high incidence for calculation the CCIS. Thus, the clinician would only need to know whether local incidence is high, moderate or low to use this score, and the incidence category changes slowly over time. Patients who live and work in separate health regions could be assigned the higher incidence value at hospital presentation for a conservative risk estimate. Patients in areas with high disease burden will automatically score two points, meaning that few patients in these settings will be classified as low risk. Therefore, symptomatic patients would all warrant testing. This underscores the need for liberal isolation and testing practices in settings with high rates of community SARS-CoV-2 transmission.

The CCIS has several important clinical applications. The ability to differentiate patients with high or low probability of COVID-19 disease could guide safe and effective patient isolation or cohorting from the time of hospital arrival, prior to the availability of SARS-CoV-2 test results. Identification of patients with extremely low risk of SARS-CoV-2 infection may even allow safe omission of testing, which will minimize testing resource utilization in settings with limited testing capacity. Identifying patients with a high probability of SARS-CoV-2 infection can help prioritize use of rapid antigen testing and initiation of effective empiric therapy in critically ill patients prior to availability of NAAT results. By presenting risk estimates and sensitivity for all risk score values, we allow end-users to choose cut-offs for ruling-in and ruling-out SARS-CoV-2 infection that make sense for their setting and application.

Several other risk prediction instruments have been developed to predict positive COVID-19 test results in undifferentiated patients. These tools were developed in studies with substantial methodological limitations and incorporate variables not immediately available at the time of a patient's hospital arrival, so are not useful to guide early isolation, testing and treatment decisions.[2] None of these risk prediction tools considered the prevalence of disease in the population. Prevalence can substantially change the approach to testing and cohorting, and this will become increasingly important as prevalence rates drop and selective rather than liberal testing may be more appropriate.

United States-based investigators recently reported the development[3] and validation[25] of the CORC score using only clinical variables. The CORC score contains several similar variables to the CCIS. The CORC score included race and ethnicity as predictor variables, which may limit the generalizability of the CORC score beyond the urban American population in which it was developed, as it does not reflect the international diversity of ethnic backgrounds. Moreover, it is

unlikely race or ethnicity represents a biologic risk. The association between race and ethnicity and SARS-CoV-2 infection in the CORC score likely reflects other sociodemographic and geographic predictors of the risk of COVID-19 infection in the American population.[25] The CCIS uses the seven-day average local incidence as an estimate of population risk. We believe this approach is more generalizable across populations and better reflects individual patients' pre-test probability of SARS-CoV-2 infection.[26]

Strengths and Limitations

The cohorts used to derive and validate the rule included comprehensive data on consecutive eligible patients from a large, geographically distributed network of Canadian urban, regional, and rural emergency departments. Strict data quality protocols and data cleaning protocols ensured the reliability of collected data. This score may be employed at the time of a patient's arrival to hospital, does not require the use of additional laboratory testing or imaging, nor the use of electronic calculators or electronic medical records for implementation.

Some missing data required either multiple imputation or classification of missing categorical variables as being absent. The overall missingness of data in this registry is very low. [15] Although the data collection for the CCEDRRN registry relies on abstraction from health records, this approach has been shown to be reliable in our study sites when compared to prospective data collection.[15]

The clinical variables in the model are not likely to be sensitive to changes in geographical changes in SARS-CoV-2 epidemiology. The variable of travel from a country with high incidence may become less informative as the pandemic has spread globally and "hot spots"

change. However, high-prevalence areas may change over time, meaning that the risk factor of travel from a region with a high prevalence is likely to still be informative.

This risk score was developed using data from patients enrolled in the first nine months of the pandemic when rates of influenza were low. As such, the score may need to be re-validated and refined in the future to reflect the influence of influenza, the emergence of variant strains of SARS-CoV-2, and widespread population immunization on patients' risk of infection.

Conclusion

We derived and successfully validated the CCEDRRN COVID-19 Infection Score to accurately predict the probability of SARS-CoV-2 nucleic acid test results in patients presenting to emergency departments. The CCIS uses clinical variables, accounts for the incidence of SARS-CoV-2 in the community and is ready for immediate clinical use. This score has potential utility to guide early decisions around SARS-CoV-2 test utilization, patient isolation, and empiric therapy for patients solely based on clinical assessment.

Contributors

CMH, ADM, LJM, RJR, and JJP conceived the study, with input on the design and selection of variables from the other contributors. CMH, LJM, PA, SCB, PD and EL obtained funding on behalf of the CCEDRRN investigators. CMH, ADM, PA, SCB, IC, PD, JH, BHR, RO, MW, and KY facilitated data collection along with other members of the CCEDRRN and can verify the underlying data. RJR and JJP developed the analytic plan. SV performed the analysis, with assistance from GG and RJR, including accessing and verification of underlying data. All contributors provided input on interpretation of findings. ADM, CMH, and RJR drafted the manuscript with additional input from all contributors.

Acknowledgment

We gratefully acknowledge the assistance of Ms. Amber Cragg in the preparation of this manuscript. We thank the UBC clinical coordinating centre staff, the UBC legal, ethics, privacy and contract staff and the research staff at each of the participating institutions in the network outlined in the attached Supplement. The network would not exist today without the dedication of these professionals.

Thank you to all our patient partners who shared their lived experiences and perspectives to ensure that the knowledge we co-create addresses the concerns of patients and the public. Creating the largest network of collaboration across Canadian Emergency Departments would not have been feasible without the tireless efforts of Emergency Department Chiefs, and research coordinators and research assistants at participating sites. Finally, our most humble and sincere gratitude to all our colleagues in medicine, nursing, and the allied health professions who have been on the front lines of this pandemic from day one staffing our ambulances, Emergency

Departments, ICUs, and hospitals bravely facing the risks of COVID-19 to look after our fellow citizens and after one another. We dedicate this network to you. (Supplementary Table)

Data Availability Statement

For investigators who wish to access Canadian COVID-19 Emergency Rapid Response Network data, proposals may be submitted to the network for review and approval by the network's peer-review publication committee, the data access and management committee and the executive committee, as per the network's governance. Information regarding submitting proposals and accessing data may be found at https://canadiancovid19ednetwork.org/.

Funding Acknowledgement

The Canadian Institutes of Health Research (447679), Ontario Ministry of Colleges and Universities (C-655-2129), Saskatchewan Health Research Foundation (5357), Genome BC (COV024 and VAC007) Fondation du CHU de Québec (Octroi No. 4007). Sero-Surveillance and Research (COVID-19 Immunity Task Force Initiative) provided peer-reviewed funding. The BC Academic Health Science Network and BioTalent Canada provided non-peer reviewed funding. These organizations are not-for-profit, and had no role in study conduct, analysis, or manuscript preparation.

Competing interests

ADM, CMH, RR, PA, SCB, IC, PD, JH, EL, RO, BHR, MW, KY, LJM, JP are co-investigators on the funding sources listed above, and have no additional competing interests. GG and SV have no competing interests.

Ethics Approval

The CCEDRRN network protocol was approved with a waiver of informed consent by the University of British Columbia Research Ethics Board (UBC REB H20-01015), and subsequently by the research ethics boards of all participating institutions.

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Tables & Figures

Figure 1. Flow Diagram of Patients through the study (based on PRPC template)

ED=emergency department; COVID=coronavirus disease

Figure 2. Distribution and performance of the CCEDRRN COVID Infection Score in the derivation cohort (left panel) and validation cohorts (right panel): A) distribution of the score, B) observed in-hospital mortality across the range of the score, C) predicted versus observed probability of in-hospital mortality, and D) receiver operating characteristic curve with area under the curve (AUC) and associated 95% confidence interval.

A)

B)

C)

D)

AUC 0.84 (0.82-0.85)

AUC 0.79 (0.76-0.82)

Table 1. Characteristics and selected outcomes of enrolled patients·

	Derivation (n=21743)	Validation (n=5922)
Age in years, median (IQR)	57 (38, 73)	56 (37, 73)
Female (%)	10992 (50·5)	3085 (52·1)
Arrival From, n (%)		
Home	19879 (91·4)	5429 (91·7)
Long-term care/Rehabilitation facility/Corrections facility	1000 (4·6)	262 (4·4)
No fixed address/ Shelter/ Single room occupancy	574 (2·6)	201 (3·4)
Inter-hospital transfer	290 (1·3)	30 (0·5)
Risk for Infection, n (%)		
Healthcare worker	505 (2·3)	567 (9·6)
Household/caregiver contact	566 (2·6)	161 (2·7)
Institutional exposure (e.g.,. LTC, prison)	1354 (6·2)	213 (3·6)
Microbiology lab	4 (0·0)	8 (0·1)
Travel	924 (4·2)	344 (5·8)
Other	1320 (6·1)	449 (7·6)
Unknown	5415 (24·9)	1856 (31·3)
No documented risk for infection	10028 (46·1)	1075 (18·1)
Arrival Vital Signs, median (IQR)		
Body temperature	36·7 (36·3, 37·1)	36·8 (36·5, 37·1)
Heart rate	91 (79, 107)	90 (78, 105)
Oxygen saturation	97 (95, 98)	97 (95, 99)
Respiratory rate	18 (18, 20)	18 (16, 20)
Systolic blood pressure	133 (118, 150)	136 (120, 149)
Common Comorbid Conditions, n (%)		
Active malignant neoplasm (cancer)	1678 (7·7)	333 (5·6)
Asthma	1699 (7·8)	468 (7·9)
Atrial fibrillation	1598 (7·3)	402 (6·8)
Chronic kidney disease	1214 (5·6)	321 (5·4)
Chronic lung disease (not asthma/pulmonary fibrosis)	1729 (8)	583 (9·8)
Chronic neurological disorder (not dementia; e.g., stroke/TIA, seizure disorder)	1310 (6)	400 (6·8)
Congestive heart failure	1450 (6·7)	368 (6·2)
Coronary artery disease	1591 (7·3)	449 (7·6)
Dementia	734 (3·4)	188 (3·2)
Diabetes	2583 (11·9)	916 (15·5)
Dialysis	198 (0·9)	28 (0·5)
Dyslipidemia	2375 (10·9)	543 (9·2)
Hypertension	6320 (29·1)	1697 (28·6)
Hypothyroidism	1344 (6·2)	397 (6·7)

Mild liver disease	280 (1·3)	90 (1·5)
Moderate/severe liver disease	245 (1·1)	88 (1·5)
Obesity (clinical impression)	284 (1·3)	108 (1·8)
Organ transplant	128 (0·6)	19 (0·3)
Rheumatologic disorder	1122 (5·2)	258 (4·4)
Other	10075 (46·3)	2174 (36·7)
Past malignant neoplasm (cancer)	936 (4·3)	256 (4·3)
Psychiatric condition/Mental health diagnosis	2967 (13·6)	831 (14)
Pulmonary fibrosis	80 (0·4)	26 (0·4)
Symptoms Reported, n(%)		
Abdominal pain	2725 (12·5)	540 (9·1)
Altered consciousness/confusion	1456 (6·7)	322 (5·4)
Bleeding (hemorrhage)	330 (1·5)	22 (0·4)
Chest pain (includes discomfort or tightness)	4242 (19·5)	974 (16·4)
Chills	2045 (9·4)	594 (10)
Conjunctivitis	49 (0·2)	26 (0·4)
Cough	7724 (35·5)	2663 (44·9)
Diarrhea	2140 (9·8)	526 (8·9)
Dizziness/Vertigo	1521 (7)	300 (5·1)
Dysgeusia/anosmia	140 (0·6)	33 (0·6)
Ear pain	144 (0·7)	30 (0·5)
Fatigue/malaise	3361 (15·5)	924 (15·6)
Fever	5055 (23·2)	1580 (26·7)
Headache	2144 (9·9)	624 (10·5)
Hemoptysis (bloody sputum)	298 (1·4)	66 (1·1)
Joint pain (arthralgia)	296 (1·4)	82 (1·4)
Lower chest wall indrawing	10 (0)	7 (0·1)
Lymphadenopathy	67 (0·3)	21 (0·4)
Muscle aches (myalgia)	1575 (7·2)	517 (8·7)
Nausea/vomiting	4219 (19·4)	935 (15·8)
No recorded symptoms	2113 (9·7)	431 (7·3)
Runny nose (rhinorrhea)	1061 (4·9)	501 (8·5)
Seizures	205 (0·9)	42 (0·7)
Shortness of breath (dyspnea)	8537 (39·3)	2383 (40·2)
Skin rash	241 (1·1)	38 (0·6)
Skin ulcers	27 (0·1)	<5
Sore throat	3024 (13·9)	985 (16·6)
Sputum production	1507 (6·9)	401 (6·8)
Wheezing	582 (2·7)	130 (2·2)
Tobacco Use, n (%)	1852 (8·5)	616 (10·4)
Illicit Substance Use, n (%)	1219 (5·6)	353 (6·0)

Oxygen Required in ED, n (%)	1919 (8·8)	627 (10·6)
Hospital Admission, n (%)	9913 (45·6)	2446 (41·3)
In-hospital Death, n (%)	753 (3·5)	213 (3·6)
7-day average incident COVID-19 cases, median (IQR)	1·3 (0·7, 3·2)	0·96 (0·5, 1·3)
SARS-CoV-2 Positive, n (%)	940 (4·3)	227 (3·8)

IQR=interquartile range; LTC=long-term care; TIA= transient ischemic attack; ED=emergency department

Table 2. Adjusted associations between model predictor variables and SARS-CoV-2 nucleic acid test results

Variable/Score Component	Regression Coefficient (SE)	Adjusted Odds Ratio (95% CI)	Score Value
7-day average incident COVID-19 cases			
0 – 2 daily cases per 100,000 population	-	-	0
2 to 7·99 daily cases per 100,000 population	1·22 (0·09)	3·38 (2·85– 4·00)	1
≥8 daily cases per 100,000 population	2·21 (0·10)	9·09 (7·53– 10·97)	2
Institutional exposure (e·g· LTC, prison) or Travel from country with known cases within 14 days	0·88 (0·09)	2·40 (2·01–2·87)	1
Healthcare worker/Microbiology lab	1·10 (0·16)	3·02 (2·22–4·10)	1
Household/caregiver contact	1·83 (0·12)	6·25 (4·92–7·93)	2
Temperature			
<36 and no self-reported fever	-0·75 (0·3)	0·47 (0·28–0·80)	-1
36 – 37·4 and no self-reported fever	-	-	0
≥37·5 or self-reported fever	1·21 (0·08)	3·36 (2·88–3·91)	1
Supplemental oxygen delivered in the ED	0·98 (0·1)	2·66 (2·18–3·24)	1
Cough	0·85 (0·08)	2·33 (2·01–2·71)	1
Dysgeusia/Anosmia	2·03 (0·24)	7·60 (4·76–12·15)	2
Muscle aches (Myalgia)	0·7 (0·11)	2·02 (1·64–2·48)	1
Current tobacco user	-1·13 (0·21)	0·32 (0·21–0·49)	-1

LTC: Long-term care; ED: Emergency Department

Table 3. Performance metrics for the CCEDRRN COVID-19 Infection Score for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the validation cohort

Score cutoff	n (%)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	LR+	LR-	COVID+ n (%)
Rule out:						
≤-2	17 (0·3)	100 (98·4–100)	0·3 (0·2–0·5)	1	NA	0 (0)
≤-1	310 (5·2)	99·6 (97·6–100)	5·4 (4·9–6·1)	1·1	0·1	1 (0·3)
≤0	1863 (31·5)	94·3 (90·4–96·9)	32·5 (31·3–33·7)	1·4	0·2	13 (0·7)
≤1	3806 (64·3)	78·9 (73.0–84.0)	66·0 (64·7–67·2)	2·3	0·3	48 (1·3)
≤2	5152 (87.0)	52·9 (46·2–60.0)	88·6 (87·7–89·4)	4·6	0·5	107 (2·1)
≤3	5748 (97·1)	20·7 (15·6–26·6)	97·8 (97·4–98·1)	9·3	0·8	180 (3·1)
Rule in:						
≥3	770 (13.0)	52·9 (46·2–59·5)	88·6 (87·7–89·4)	4·6	0·5	120 (15·6)
≥4	174 (2·9)	20·7 (15·6–26·6)	97·8 (97·4–98·1)	9·3	0·8	47 (27·0)
≥5	44 (0·7)	7·9 (4·8–12·2)	99·5 (99·3–99·7)	17·4	0·9	18 (40·9)
≥6	6 (0·1)	0·9 (0·1–3·2)	99·9 (99·8–100)	12·5	1	2 (33·3)
≥7	1 (<0.1)	0 (0–1·6)	100.0 (99·9–100)	NA	1	0 (0)

LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio

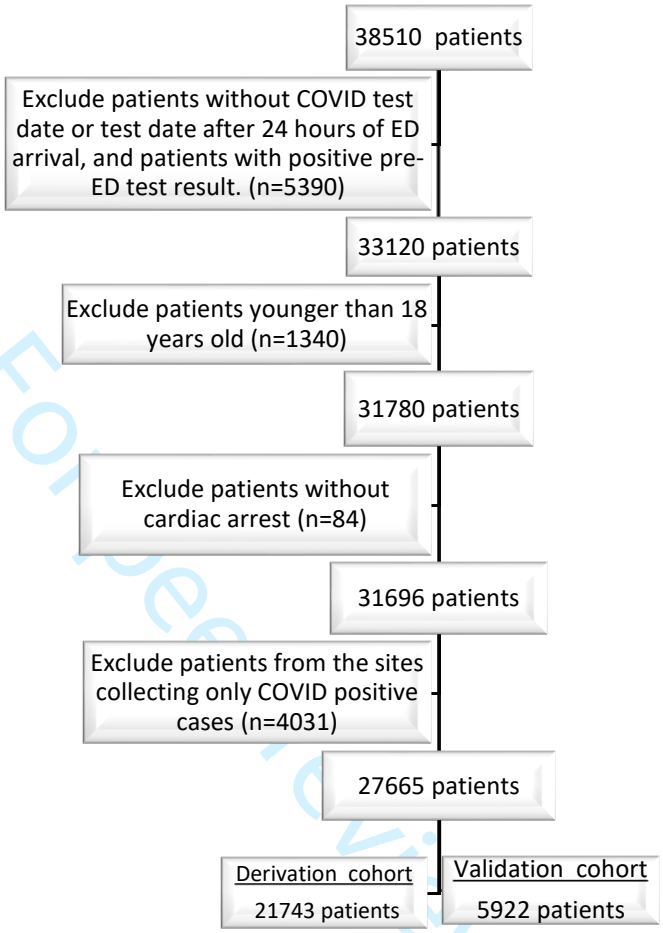
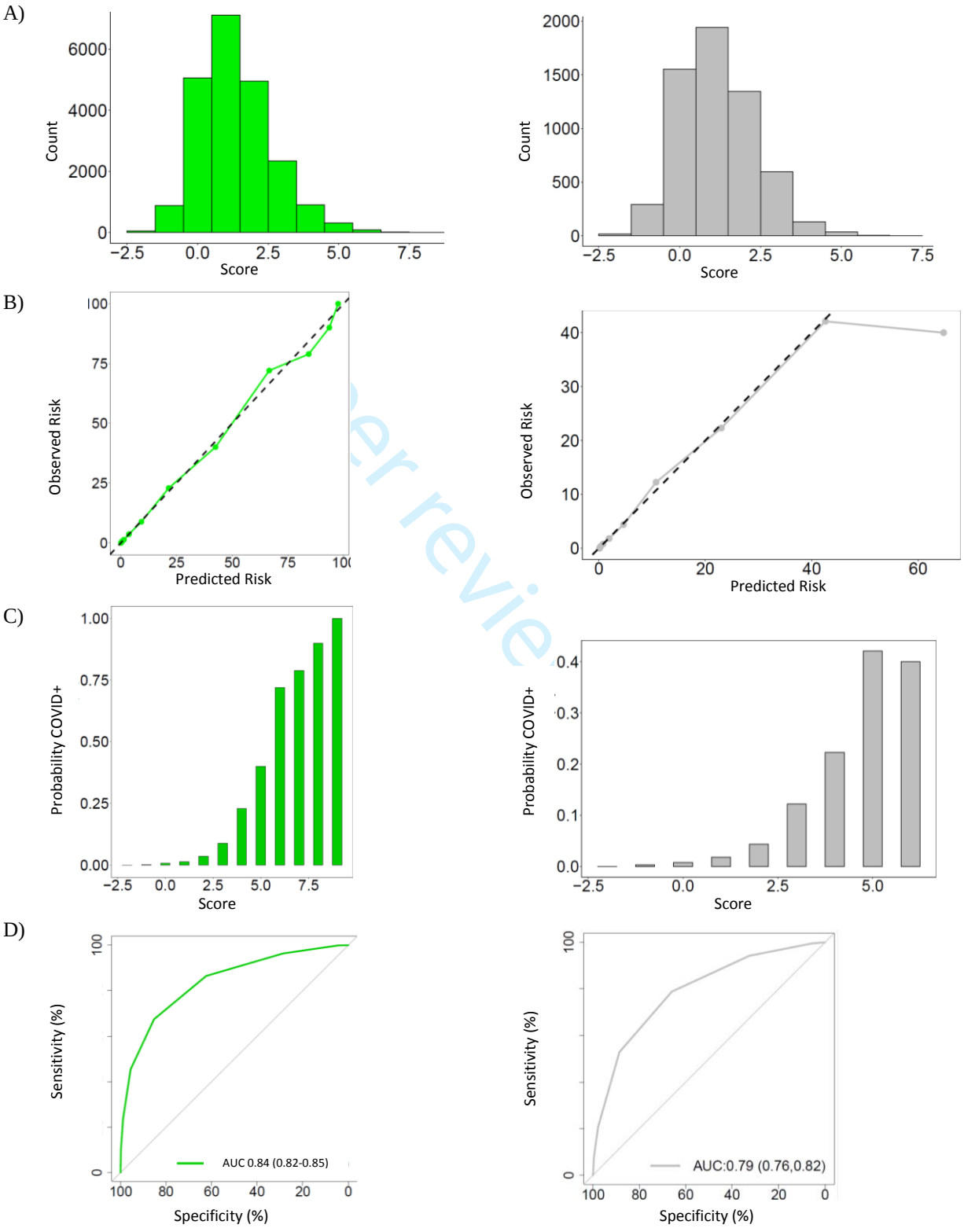


Figure 2. Distribution and performance of the CCEDRRN COVID Infection Score in the derivation cohort (left panel) and validation cohorts (right panel): A) distribution of the score, B) observed in-hospital mortality across the range of the score, C) predicted versus observed probability of in-hospital mortality, and D) receiver operating characteristic curve with area under the curve (AUC) and associated 95% confidence interval.



Appendices

Appendix Table 1. Patients enrolled by CCEDRRN site and time periods for data collection

Site (N patients contributed)	Mar 2020	Apr 2020	May 2020	Jun 2020	Jul 2020	Aug 2020	Sept 2020	Oct 2020	Total
Derivation Cohort	**3217**	**4797**	**5493**	**3096**	**2232**	**1276**	**1266**	**366**	**21743**
Abbotsford Regional Hospital		228	474	385	198				1285
Eagle Ridge Hospital	196	163							359
Foothills, Calgary	437	131							568
Halifax Infirmary/Dalhousie, Nova Scotia	17								17
Hants Community Hospital, Nova Scotia	1								1
Hôpital du Sacré-Coeur de Montreal	27	96	401						524
Hôtel-Dieu de Lévis	1	19	246						266
Jewish General Hospital	754	959	93						1806
Peter Lougheed Centre	321	1119	1169	605	638	552	616	215	5235
Royal Columbian Hospital	236	408	366						1010
Royal University, Saskatoon	132	275	357	296	340	265	193		1858
Saint John Regional Hospital, New Brunswick	98	102							200
South Campus, Calgary	367	598	612	526	586	459	457	151	3756
Sunnybrook Health Sciences Centre			473	593	470				1536
The Ottawa Hospital - Civic Campus	58	24	537						619
Vancouver General Hospital	572	675	765	691					2703
Validation Cohort	**2082**	**2012**	**695**	**381**	**330**		**422**		**5922**
Cobequid Community Health Centre	6								6
Dartmouth General College, Dartmouth Novia Scotia	7								7
Health Science North, Sudbury Ontario			295	381	330				1006

Hôpital de l'Enfant-Jésus, CHU de Québec-Université Laval	40	99	26						165
IUCPQ: Institut universitaire de cardiologie et de pneumologie de Québec	4	5	95						104
Lions Gate Hospital	294	220							514
Mount St Joseph's	236								236
Rockyview, Calgary	368	104							472
Saint Paul's Hospital	541								541
Saskatoon City Hospital, Saskatoon	33	53							86
Secondary Assessment Centers of Dartmouth General and Halifax Infirmary	3	70	66						139
St Paul's Hospital, Saskatoon	84	198							282
Surrey Memorial Hospital	404	927							1331
The Ottawa Hospital - General Campus	62	33	135						230
Toronto Western Hospital							422		422
University of Alberta Hospital		303	78						381

Appendix Table 2. Candidate variables for entry into regression model

Variable	Definition	N (%) Missing
Demographics		
Age	Age in years	0 (0)
Sex	Male, Female, Other	0 (0)
Arrival from	Home + other (not clearly documented)	0 (0)
	Single room + no fixed address + shelter	0 (0)
	Institutional living: long-term care/rehab + correctional	0 (0)
	Inter-hospital transfer	0 (0)
Infection risk		
Travel risk	Travel from country with known cases within 14 days	0 (0)
Institutional exposure	Possible exposure in institutional setting (e.· g.,· Long-term care, prison)	0 (0)
Healthcare worker	Healthcare worker/Microbiology lab employee	0 (0)
Household/caregiver contact	Household contact /caregiver of known positive case	0 (0)
No documented risk	Documented absence of risk factors	0 (0)
Emergency department variables		
ED arrival mode		2 (0)
Ambulance:	arrived by ambulance	
Self/police	self-transported or transported to ED by police	
Arrival heart rate	beats/minute	452 (2.1)
Arrival respiratory rate	breaths/minute	732 (3.4)
Arrival oxygen saturation	%	517 (2.4)
Lowest recorded oxygen saturation in ED	%	445 (2.0)
Fever		847 (3.9)
Temperature <36.0	Temperature <36.0C AND no self-reported fever	
Temperature 36.0-37.4	Temperature 36.0-37.4C AND no self-reported fever	
Temperature ≥37.5 or fever	Temperature ≥37.5 OR self-reported fever	
Respiratory distress	Increased work of breathing documented by treating clinician	1(0)
Supplemental oxygen delivered in the ED	Yes/No	0 (0)
COVID symptoms		
Abdominal pain	Patient-reported symptom as documented by treating clinician	0 (0)
Altered consciousness/confusion	Patient-reported symptom as documented by treating clinician	0 (0)
Bleeding (hemorrhage)	Patient-reported symptom as documented by treating clinician	0 (0)
Chest pain (includes discomfort or tightness)	Patient-reported symptom as documented by treating clinician	0 (0)
Chills	Patient-reported symptom as documented by treating clinician	0 (0)
Conjunctivitis	Patient-reported symptom as documented by treating clinician	0 (0)
Cough	Patient-reported symptom as documented by treating clinician	0 (0)

Diarrhea	Patient-reported symptom as documented by treating clinician	0 (0)
Dizziness/Vertigo	Patient-reported symptom as documented by treating clinician	0 (0)
Dysgeusia/anosmia	Patient-reported symptom as documented by treating clinician	0 (0)
Ear pain	Patient-reported symptom as documented by treating clinician	0 (0)
Fatigue/malaise	Patient-reported symptom as documented by treating clinician	0 (0)
Headache	Patient-reported symptom as documented by treating clinician	0 (0)
Hemoptysis (bloody sputum)	Patient-reported symptom as documented by treating clinician	0 (0)
Joint pain (arthralgia)	Patient-reported symptom as documented by treating clinician	0 (0)
Lymphadenopathy	Patient-reported symptom as documented by treating clinician	0 (0)
Muscle aches (myalgia)	Patient-reported symptom as documented by treating clinician	0 (0)
Nausea/vomiting	Patient-reported symptom as documented by treating clinician	0 (0)
No reported symptoms	Patient-reported symptom as documented by treating clinician	0 (0)
Runny nose (rhinorrhea)	Patient-reported symptom as documented by treating clinician	0 (0)
Seizures	Patient-reported symptom as documented by treating clinician	0 (0)
Shortness of breath (dyspnea)	Patient-reported symptom as documented by treating clinician	0 (0)
Skin rash	Patient-reported symptom as documented by treating clinician	0 (0)
Sore throat	Patient-reported symptom as documented by treating clinician	0 (0)
Sputum production	Patient-reported symptom as documented by treating clinician	0 (0)
Wheezing	Patient-reported symptom as documented by treating clinician	0 (0)
Current tobacco user	Documented current tobacco use	6 (0)
Current illicit user	Documented methamphetamine, opioid or other illicit drug use	6 (0)
7-day average incident COVID-19 cases	Daily reported incidence of new cases in health region, averaged over the seven days preceding hospital arrival. Reported in units of new cases/100,000 population	32 (0.1)

Appendix Table 3. Performance metrics for the CCEDRRN COVID-19 Infection Score for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the derivation cohort

Score	n (%)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	LR+	LR-	COVID+ n (%)
Rule out:						
≤-2	51 (0·2)	100 (99·6–100)	0·25 (0·2–0·3)	1.0	NA	0 (0)
≤-1	937 (4·3)	99·89 (99·4–100)	4·5 (4·2–4·8)	1·1	<0·1	1 (0·1)
≤0	5996 (27·6)	96·6 (95·2–97·7)	28·67 (28·1–29·3)	1·4	0·1	32 (0·5)
≤1	13114 (60·3)	86·6 (84·3–88·7)	62·43 (61·8–63·1)	2·3	0·2	126 (1·0)
≤2	18041 (83.0)	67·34 (64·2–70·3)	85·25 (84·8–85·7)	4·6	0·4	307 (1·7)
≤3	20405 (93·9)	45·11 (41·9–48·4)	95·61 (95·3–95·9)	10·3	0·6	516 (2·5)
Rule in:						
≥3	3702 (17·0)	67·34 (64·2–70·3)	85·25 (84·8–85·7)	4·6	0·4	633 (17·1)
≥4	1338 (6·2)	45·11 (41·9–48·4)	95·61 (95·3–95·9)	10·3	0·6	424 (31·7)
≥5	440 (2·0)	23·51 (20·8–26·4)	98·95 (98·8–99·1)	22·3	0·8	221 (50·2)
≥6	122 (0·6)	9·68 (7·9–11·8)	99·85 (99·8–99·9)	65.0	0·9	91 (74·6)
≥7	31 (0·1)	2·77 (1·8–4·0)	99·98 (99·9–100.0)	115·1	1.0	26 (83·9)
≥8	12 (0·1)	1·17 (0·6–2·1)	100 (100.0–100.0)	243·4	1.0	11 (91·7)
≥9	2 (<0·1)	0·21 (<0.1–0·8)	100 (100.0–100.0)	NA	1.0	2 (100)

LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio

Appendix Table 4. Performance metrics for CCEDRRN COVID Infection Score for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the combined cohort

Score cutoff	n (%)	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-	COVID+ n (%)
Rule out:						
≤-2	70 (0·3)	100 (99·7,100)	0·3 (0·2,0·3)	1	0	0 (0)
≤-1	1257 (4·5)	99·8 (99·4,100)	4·7 (4·5,5)	1·1	<0·1	2 (0·2)
≤0	7872 (28·5)	96·1 (94·8,97·1)	29·5 (29·0,30·1)	1·4	0·1	46 (0·6)
≤1	16962 (61·3)	85 (82·8,87·0)	63·4 (62·8,63·9)	2·3	0·2	175 (1·0)
≤2	23243 (84·0)	64·8 (62·0,67·5)	86·2 (85·7,86·6)	4·7	0·4	411 (1·8)
≤3	26169 (94·6)	40·3 (37·4,43·2)	96·1 (95·9,96·4)	10·4	0·6	697 (2·7)
Rule in:						
≥3	4422 (16.0)	64·8 (62·0,67·5)	86·2 (85·7,86·6)	4·7	0·4	756 (17·1)
≥4	1496 (5·4)	40·3 (37·4,43·2)	96·1 (95·9,96·4)	10·4	0·6	470 (31·4)
≥5	476 (1·7)	20·2 (18·0,22·6)	99·1 (99·0,99·2)	22·3	0·8	236 (49·6)
≥6	128 (0·5)	8 (6·5,9·7)	99·9 (99·8,99·9)	60·3	0·9	93 (72·7)
≥7	32 (0·1)	2·2 (1·5,3·2)	100 (100,100)	98·4	1.0	26 (81·3)
≥8	12 (<0·1)	0·9 (0·5,1·7)	100 (100,100)	249·8	1.0	11 (91·7)

LR+: Positive likelihood ratio; LR-: Negative likelihood ratio

Appendix Table 5. Performance metrics for the CORC score (race and ethnicity variables removed) for ruling in or ruling out SARS-CoV-2 infection at different score cut-off values in the combined cohort

Score	n (%)	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-	COVID+ n (%)
Rule out:						
≤-2	202 (0·7)	99·9 (99·5–100)	0·8 (0·7–0·9)	1·01	0·11	1 (0·5)
≤-1	2715 (9·8)	97·4 (96·4–98·3)	10·1 (9·8–10·5)	1·08	0·25	30 (1·1)
≤0	9089 (32·9)	90·1 (88·2–91·7)	33·9 (33·3–34·4)	1·36	0·29	116 (1·3)
≤1	17582 (63·9)	72·8 (70·2–75·4)	65·2 (64·6–65·7)	2·09	0·42	317 (1·8)
≤2	23421 (84·7)	51·2 (48·3–54·1)	86·2 (85·8–86·7)	3·72	0·57	569 (2·4)
≤3	26224 (94·8)	27·7 (25·1–30·3)	95·8 (95·5–96)	6·56	0·76	844 (3·2)
Rule in:						
≥3	4244 (15·3)	51·2 (48·3–54·1)	86·2 (85·8–86·7)	3·72	0·57	598 (14·1)
≥4	1441 (5·2)	27·7 (25·1–30·3)	95·8 (95·5–96)	6·56	0·76	323 (22·4)
≥5	358 (1·3)	11·1 (9·3–13)	99·1 (99–99·2)	12·79	0·9	129 (36·0)
≥6	54 (0·2)	3·1 (2·2–4·2)	99·9 (99·9–100)	45·41	0·97	36 (66·7)

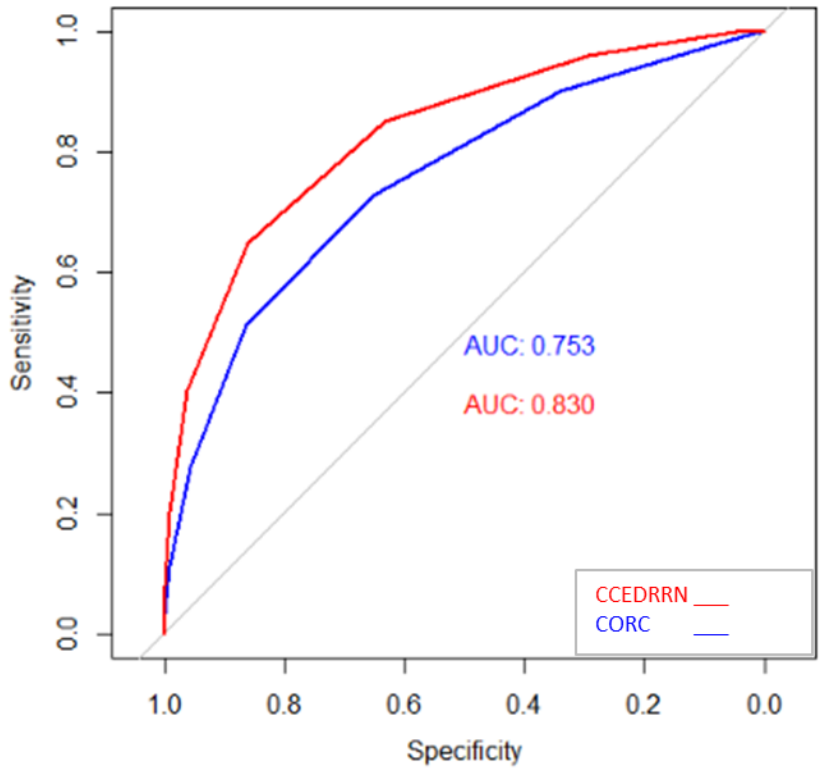
LR+: Positive likelihood ratio; LR-: Negative likelihood ratio

Appendix Table 6. Net Reclassification Improvement of the CCEDRRN COVID-19 Infection Score compared to the CORC Score (race and ethnicity variables removed)

Primary Outcome : Covid Positive					
CORC risk category		**CCIS risk category**			**Total**
		Low	**Medium**	**High**	
	Low	12	18	0	30
	Medium	34	539	241	814
	High	0	94	229	323
	Total	46	651	470	1167
Primary Outcome: Covid Negative					
CORC risk category		**CCIS risk category**			
		Low	**Medium**	**High**	**Total**
	Low	1593	1092	0	2685
	Medium	6233	15756	706	22695
	High	0	798	320	1118
	Total	7826	17646	1026	26498

COVID Positive		**COVID Negative**	
Number of outcomes	1167	Number of outcomes	26498
Correct reclassification	259	Correct reclassification	7031
Incorrect reclassification	128	Incorrect reclassification	1798
Net reclassification	131	Net reclassification	5233
Net reclassification improvement (Event)	0.112	Net reclassification improvement (Non-event)	0.197
Total net reclassification improvement			0.310

Appendix Figure 1. Receiver operating characteristic curves for the CCEDRRN COVID Infection Score (CCIS) and the CORC score (race and ethnicity variables removed) in the combined study cohort



Canadian COVID-19 ED Network

Supplementary Table: Contributors to the Canadian COVID-19 Emergency Department Rapid Response Network

1. Purpose

This supplementary table provides details of the support staff at each of the participating institutions in the Canadian COVID-19 Emergency Department Rapid Response Network. This supplementary document should be attached to each peer-reviewed manuscript after the methods manuscript (M1). The purpose is to ensure research staffs and lead coordinators are appropriately recognized for their contributions to the network.

2. List of Support Staff

Table 1. Network coordinating centre staff at the University of British Columbia

Name	Roles	Contributions
Gelareh Ghaderi	Data analyst	Data processing and analysis for manuscripts.
Jeffrey Hau	Data manager	REDCap, data processing and analysis for manuscripts.
Vi Ho	National coordinator	Coordinate with provincial coordinators and training/onboarding of research assistants.
Joe Larkin	Project manager	Project management.
Fiona O'Sullivan	Data analyst	Data processing and analysis for manuscripts.
Serena Small	Research coordinator	Ethics & privacy reviews, data management plan, privacy impact assessment, and qualitative analyses
Amber Cragg	Research manager	Data and manuscript management
Wei Zhao	Data analyst	Data processing and analysis for manuscripts.
Vicky Wu	Data analyst	Data processing and analysis for manuscripts.
Elnaz Bodaghkhani	Research associate	Data and manuscript management

Table 2. Provincial Coordinators

Name	Province	Institutional affiliation	Contributions to CCEDRRN
Corinne DeMone	NS	Dalhousie University, Halifax, Nova Scotia	Research ethics board submission, manages research assistants, data cleaning and quality.
Jacqueline Fraser	NB	Dalhousie University, St. John New Brunswick	Site coordinator as well as research assistant.
Veronique Gélinas	QC	Centre intégré de santé et de services sociaux de Chaudière-Appalaches (Hôtel-Dieu de Lévis site), Lévis	Provincial research coordinator, translation of research material to French, ethics management.

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Connie Taylor	ON	Queen's University, Kingston	Coordination of research assistants in Ontario, maintenance of REB applications for the province
Kate Mackenzie	MB	Health Sciences Centre, Winnipeg	Lead RA for the province
Aimee Goss	SK	University of Saskatchewan, Saskatoon	Screens records in Saskatoon, data/extraction and entry, coordinates research assistants.
Hina Walia	AB	University of Calgary, Calgary	Provincial coordinator lead for Alberta, oversight of all Alberta sites.
Rajan Bola	BC	University of British Columbia, Vancouver	Provincial coordinator lead for BC, oversight of all BC sites.

Table 3. Institutional research assistant (RA) leads
Institutional RA leads are responsible for data extraction and integrity, communication with provincial leads.

Name	**Province**	**Institutional affiliation(s)**
Corinne DeMone	NS	Dartmouth General Hospital, Cobequid Community Health Centre, Hants Community Hospital Secondary Assessment Centers of the Dartmouth General Hospital, and Halifax Infirmary, Halifax
Jacqueline Fraser	NB	Saint John Regional Hospital, Saint John
Alexandra Nadeau	QC	CHU de Québec Université Laval, Quebec City
Audrey Nolet	QC	Centre intégré de santé et de services sociaux de Chaudière-Appalaches (Hôtel-Dieu de Lévis site), Lévis
Xiaoqing Xue	QC	Jewish General Hospital, Montréal
David Iannuzzi	QC	McGill University Health Center, Montréal
Chantal Lanthier	QC	Hôpital du Sacré-Cœur de Montréal, Montréal
Konika Nirmalanathan	ON	University Health Network, Toronto
Vlad Latiu	ON	Kingston General Hospital, Hotel Dieu Hospital, Kingston
Joanna Yeung	ON	Sunnybrook Health Sciences Center, Toronto
Natasha Clayton	ON	Hamilton General Hospital, Juravinski Hospital, Hamilton
Tom Chen	ON	London Health Sciences Centre, London
Jenna Nichols	ON	Health Sciences North, Sudbury
Kate Mackenzie	MB	Health Sciences Centre, Winnipeg
Aimee Goss	SK	St. Paul's Hospital, Royal University Hospital, Saskatoon City Hospital, Saskatoon
Stacy Ruddell	AB	Foothills Medical Centre, Peter Lougheed Centre, Rockyview General Hospital, South Health Campus, Calgary
Natalie Runham	AB	University of Alberta Hospital, Edmonton

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Name	Province	Institutional affiliation(s)
Karlin Su	AB	Royal Alexandra Hospital/Northeast Community Health Center, Edmonton
Josie Kanu	BC	St. Paul's Hospital, Mount Saint Joseph, Vancouver
Bernice Huynh	BC	Abbotsford Regional Hospital and Cancer Center, Abbotsford
Amanda Swirhun	BC	Royal Columbian Hospital, New Westminster
Tracy Taylor	BC	Eagle Ridge Hospital and Health Care Centre, Port Moody
Mai Hayashi	BC	Royal Inland Hospital, Kamloops
Mackenzie Cheyne	BC	Kelowna General Hospital, Kelowna
Sarim Asim	BC	Surrey Memorial Hospital, Surrey
Katherine Lam	BC	Vancouver General Hospital, Vancouver
Kelsey Compagna	BC	Lions Gate Hospital, Vancouver

Table 4. Contributing Study Sites and Investigators

Lead Investigator	Contributing Site / Code	Member Investigators
Maritime		
Patrick Fok		
Nova Scotia		
Hana Wiemer	Halifax Infirmary/ 902	Patrick Fok
	Dartmouth General Hospital/ 903	Hana Wiemer
	Hants Community Hospital/ 904	Samuel Campbell
	Cobequid Community Health Centre/ 905	Kory Arsenault
	Secondary Assessment Centers of Dartmouth General and Halifax Infirmary/ 908	Tara Dahn
New Brunswick		
Kavish Chandra	Saint John Regional Hospital/ 901	Kavish Chandra
Quebec		
Patrick Archambault	Hotel-Dieu de Lévis/ 701	Patrick Archambault
	Jewish General Hospital/ 702	Joel Turner
	Centre Hospitalier de l'Université Laval (CHU de Québec)/ 703	Éric Mercier
	L'hôpital Royal Victoria - Royal Victoria Hospital/ 705	Greg Clark
	Hôpital de l'Enfant-Jésus,CHU de Québec/ 706	Éric Mercier
	Hôpital du Saint-Sacrement, CHU de Québec/ 707	Éric Mercier
	Hôpital Saint-François d'Assise, CHU de Québec/ 708	Éric Mercier
	Hôtel-Dieu de Québec,CHU de Québec/ 709	Éric Mercier

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	IUCPQ: Institut universitaire de cardiologie et de pneumologie de Québec/ 710	Sébastien Robert
	Hôpital du Sacré-Coeur de Montreal/ 711	Raoul Daoust
Ontario		
Laurie Morrison & Steven Brooks	Sunnybrook/ 401	Ivy Cheng
	The Ottawa Hospital - Civic Campus/ 403	Krishan Yadav
	The Ottawa Hospital - General Campus/ 404	Krishan Yadav
	Kingston/Queens/ 406	Steven Brooks
	Hamilton General Hospital/ 407	Michelle Welsford
	Health Science North, Sudbury Ontario/ 408	Rob Ohle
	University Hospital – LHSC/ 409	Justin Yan
	North York General Hospital, Toronto/ 410	Rohit Mohindra
	Victoria Hospital – LHSC/ 412	Justin Yan
	Toronto Western Hospital/ 414	Megan Landes
Manitoba		
Tomislav Jelic	Health Sciences Centre/ 307	Tomislav Jelic
Saskatchewan		
Phil Davis	Pasqua Hospital, Regina/ 301	Ankit Kapur
	Regina General Hospital, Regina/ 302	Ankit Kapur
	St Paul's Hospital, Saskatoon/ 303	Phil Davis
	Royal University, Saskatoon/ 304	Phil Davis
	Saskatoon City Hospital, Saskatoon/ 305	Phil Davis
Alberta		
Andrew McRae	University of Alberta Hospital, Edmonton/ 201	Brian Rowe
	Foothills, Calgary/ 202	Katie Lin
	Rockyview, Calgary/ 203	Andrew McRae
	Peter Lougheed Centre/ 204	Andrew McRae
	South Campus, Calgary/ 205	Stephanie VandenBerg
	Northeast Community Health Centre, Edmonton/ 206	Jake Hayward, Jaspreet Khangura
	Royal Alexandra Hospital, Edmonton/ 306	Jake Hayward, Jaspreet Khangura
British Columbia		
Corinne Hohl	Vancouver General Hospital/ 101	Daniel Ting
	Lions Gate Hospital/ 102	Maja Stachura
	Saint Paul's Hospital/ 103	Frank Scheuermeyer

Canadian COVID-19 ED Network

Mount St Joseph's/ 104	Frank Scheuermeyer
Surrey Memorial Hospital/ 105	Balijeet Braar/ Craig Murray
Royal Columbian Hospital/ 106	John Taylor
Abbotsford Regional Hospital/ 107	Ian Martin
Eagle Ridge Hospital/ 108	Sean Wormsbecker
Victoria General Hospital/ 109	Matt Bouchard
Royal Jubilee Hospital/ 110	Matt Bouchard
Nanaimo General Hospital/ 111	Matt Bouchard
Royal Inland Hospital/ 112	Ian Martin
Kelowna General / Hospital/ 115	Lee Graham

It was not possible for us to recruit Members from Newfoundland and Labrador, Northwest Territories, Nunavut, Prince Edward Island and Yukon at the time of the inception of the registry.

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Appendix table 2
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Appendix Table 2
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7-8
	10c	V	For validation, describe how the predictions were calculated.	9
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8,9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	10
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	8
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1, Appendix table 2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2
	15b	D	Explain how to the use the prediction model.	Table 2
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	10
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	12-13
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	16

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Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.