Exploring Spatio-Temporal Heterogeneity and Correlation in COVID-19 Associated Emergency Department Visits and Follow-Up Events

by

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B.Sc., University of Winnipeg, 2022

Project Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Science

in the
Department of Statistics and Actuarial Science
Faculty of Science

SIMON FRASER UNIVERSITY
Summer 2024

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Abstract

The world has been transformed by the coronavirus disease 2019 (COVID-19) pandemic. Scientists, physicians and researchers have had to make decisions in evolving environments. Clinical decision rules aid in making these decisions, however standard approaches to derive these rules did not sufficiently address challenges arising for COVID-19 data analysis. Specifically, problems may arise from the use of multisite emergency department (ED) data, as sites may have different standards of practice and populations. This project investigates the heterogeneity of data collected across Canada during the pandemic by the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN). We use multilevel regression models to capture variations among EDs and provinces. These results are compared to a model employed by a previous study without addressing clustering effects presented in the data. Moreover, the regression analysis introduces three time-related covariates to explore potential evolution of time trends in COVID-19 associated ED visits and follow-up events.

Keywords: Correlation; Heterogeneity; Logistic Regression; Multilevel Regression Models; Random Effects

Acknowledgements

I would like to express my deepest gratitude to my co-supervisors, Joan Hu and Rhonda Rosychuk, as without them, this project would not have been possible. Joan, thank you for your constant support and guidance over the last couple of years. I truly appreciate all the time you spent sharing your wisdom and patiently answering any questions. Thank you Rhonda for your insights and recommendations, and for providing me with the opportunity to work on this project with CCEDRRN. This is precisely the area I had hoped to study upon beginning my graduate studies.

I would like to acknowledge the Canadian COVID-19 Emergency Department Rapid Response Network for sharing their data with me. I would also like to thank Dr. Corinne Hohl, for her expertise in the subject and assistance in gaining access to the data. Moreover, thank you Jeffrey Hau, for your guidance through the dataset and for taking the time to answer any questions that I had.

I am also grateful to each of my professors from my graduate studies for their engaging lectures and intriguing discussions: Ian Bercovitz, Joan Hu, Sonja Isberg, Richard Lockhart, Tom Loughin, Boxin Tang, and Liangliang Wang. Additionally, I would like to thank Shakhawat Hossain and Sohail Khan from the University of Winnipeg for their support throughout my undergraduate studies. Their dedication and excellence in teaching statistics inspired me to continue my studies after completion of my bachelor's degree. I would also like to thank my fellow graduate students for their friendship and interesting discussions over the past two years.

Finally, I am grateful to my family and friends. I would like to thank my parents, Kelly and Catherine, as well as my sisters, Regan and Connor, for their constant love and support throughout my studies. Thank you to my boyfriend, Lucas, for always being so positive and encouraging. I have genuinely valued the video calls and visits from all of my people in Winnipeg. I really appreciate the patience you all showed and interest you expressed listening to me discuss my courses and project at great length. I am also so grateful for my aunt Suzanne and family in Delta, who welcomed me with open arms and are my family away from home.

This project was supported by the Canadian Institutes of Health Research (CIHR).

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Chapter 1

Introduction

1.1 Background and Motivation

Over the last several years, the world has been transformed by the coronavirus disease 2019 (COVID-19) pandemic. The world has had to adapt and adjust, with scientists, physicians and researchers having to make decisions in a constantly changing environment. Clinical decision rules are tools which physicians use to ease decision making and increase the precision of patient assessments and diagnoses (McGinn et al., 2000): a number of these rules were developed to aid clinicians during the COVID-19 pandemic. However, many current statistical procedures used to derive clinical decision rules do not sufficiently address the challenges which arose for data analysis during this pandemic. One such challenge emerges from the use of multisite emergency department (ED) data, as ED sites may have different standards of practice and populations. Accounting for the magnitude of site heterogeneity in analysis may provide more appropriate conclusions than if it were to be ignored.

A number of clinical decision rules were developed to aid clinicians at the bedside during the COVID-19 pandemic. Many researchers developed clinical decision rules to risk-stratify patients for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (Schneider et al., 2021; Trubiano et al., 2020). There have also been numerous clinical decision rules developed with interest in a particular COVID-19 related adverse event in addition to death: admission to the intensive care unit (Azijli et al., 2021; Levine et al., 2021), invasive ventilation (Douillet et al., 2021), hypoxia (Levine et al., 2021), or respiratory decomposition (Sharp et al., 2021). Many different statistical approaches have been utilized to develop clinical decision rules throughout the course of the pandemic. For example, Schneider et al. (2021) used several different modelling and machine learning methods to obtain a metric to rule-in or rule-out SARS-CoV-2 infection using contact history and clinical symptoms. These methods included, but were not limited to, a conditional inference decision tree, a respective random forest, and a lasso model. Many of the previously developed clinical decision rules did not use a truly representative sample of patients (Brooks

et al., 2022) or, in the case of multisite studies, may not have appropriately captured the clustering which was present.

Brooks et al. (2022) developed the CCEDRRN COVID Discharge Score (CCDS) using a logistic regression model with seven predictors. These predictors consist of demographic variables as well as vital signs, each of which can be measured at the bedside and do not require laboratory or other tests that take time to obtain. The outcome of interest is admission to the hospital or in-hospital death within 72 hours of being discharged from the ED. This follow up period is shorter than what is used in previous clinical decision rules, however it is commonly used across healthcare as it can assess immediate risks which could be alleviated in the ED (Brooks et al., 2022). While this clinical decision rule is simpler to implement at the bedside and may be preferable over the others for a number of reasons, it only received moderate discrimination with an area under the curve (AUC) value of approximately 70%. This could be a result of not accounting for certain factors, whether they be patient, disease or contextual (Brooks et al., 2022). Properly accounting for these factors as well as the nested structure of patient visits within EDs across several provinces may improve this model.

The sudden emergence of the pandemic had researchers working quickly to make decisions based on analysis with many limitations. The proposed research will investigate the challenges associated with heterogeneity across sites and provinces, as well as their correlations. The inference derived from this study will aid in decision making during future pandemics.

1.2 CCEDRRN Registry

This project utilizes data collected by the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN). Established in 2020, CCEDRRN is a pan-Canadian registry which collected data on suspected or confirmed COVID-19 patients who presented to participating Canadian EDs throughout the pandemic. The goal of this registry is to provide population-based data over the course of the pandemic to aid in the derivation of clinical decision rules, and to study the efficacy for relevant therapies and vaccines (Hohl et al., 2021). The registry contains data from 55 participating EDs across 8 provinces and data collection occurred from March 1, 2020 to September 25, 2022.

Hohl et al. (2021) explain that the diverse sites from across the country allow for the inclusion of patients who may typically be excluded from clinical trials, such as First Nations people, study subjects who are pregnant, and prisoners. This resource aids in the understanding of the effects of the pandemic in these vulnerable populations and may provide information necessary to improve hospital care for these patients (Hohl et al., 2021). The data collected by the registry has been used in the implementation of at least two clinical decision rules in addition to the CCDS from Brooks et al. (2022). The CCEDRRN COVID-

19 Infection Score was developed by McRae et al. (2021) and Hohl et al. (2022) derived the CCEDRRN COVID-19 Mortality Score.

The CCEDRRN data includes a number of different variables from each ED visit. The CCDS (Brooks et al., 2022), which considers patient ED visits from March 1, 2020 to September 8, 2021, focuses on a subset of these variables as candidate predictors, chosen through literature review and consultation with clinicians. Each of these predictors are available at a patient's bedside and can be obtained without the need for further testing.

This data was collected over a period of three years and consists of ED visits from several provinces. Over time, the severity of COVID-19 evolved and provinces implemented different healthcare measures. This motivates analyses by ED, province, and pandemic wave. Further inquiry into the change in trends across Canada as well as over time will provide interesting insights into the behaviour of the disease.

1.3 Study Objectives

The analysis conducted in this project will utilize the data collected by CCEDRRN, considering the version of data as of September 2023. This includes ED visits from March 1, 2020 until September 25, 2022 and considers the same candidate predictors as those considered for the CCDS. This complete cohort includes additional ED visits from different pandemic waves, compared to the early cohort utilized by Brooks et al. (2022). We consider the same event as the CCDS: hospital admission or in-hospital death within 72 hours of being discharged from the ED. If patients are admitted to or die in the hospital within 72 hours of being discharged, this may be an indicator that the patient should not have been discharged initially. While we define the events using 72 hours, for computing purposes the variable was actually calculated using a timeline of 3 calendar days. As we are looking to compare the results from this study to the one performed by Brooks et al. (2022), we apply similar inclusion and exclusion criteria to the CCEDRRN data.

This study will examine the heterogeneity of data collected in Canadian EDs during the COVID-19 pandemic despite harmonizing data collection procedures. The hierarchical structure of EDs is of interest, as they are located in cities, which are within provinces (i.e., multilevel data). While practices and guidelines typically differ among provinces, they may also vary across hospitals within provinces, illustrating the importance of investigating the variation across these levels. Implementing a multilevel regression model through the inclusion of random effects for site and province may capture this variation more efficiently than the standard model.

This project is organized as follows. Our study criteria and a descriptive analysis of patient visits to the ED, with geographical stratification and consideration for time, will be summarized in Chapter 2. Chapter 3 will highlight insights obtained using a similar approach to the analysis of COVID-19 related events of interest. We also compare the

efficiency of several different regression models in this chapter. All analyses in Chapters 2 and 3 are performed using R Statistical Software (v4.0.5) on the secure computing environment CaraSpace, which is maintained by Popdata BC. This project concludes with a summary and discussion in Chapter 4, which will also include suggestions for future investigations.

Chapter 2

Analysis of COVID-19 Related Emergency Department Visits

Characteristics of patients who visited the ED throughout the pandemic may have varied depending on the ED or province, as well as over time. Thus, inquiry into the variation between the different levels of the data structure may provide further justification for the use of multilevel models. To investigate the effects of geography and time on patients who visited a participating ED throughout the pandemic, we conduct descriptive analyses in this chapter. We begin by summarizing the study criteria employed in this project, which is similar to the criteria utilized to derive the CCDS. We explore a number of patient characteristics and investigate any potential geographical or temporal effects.

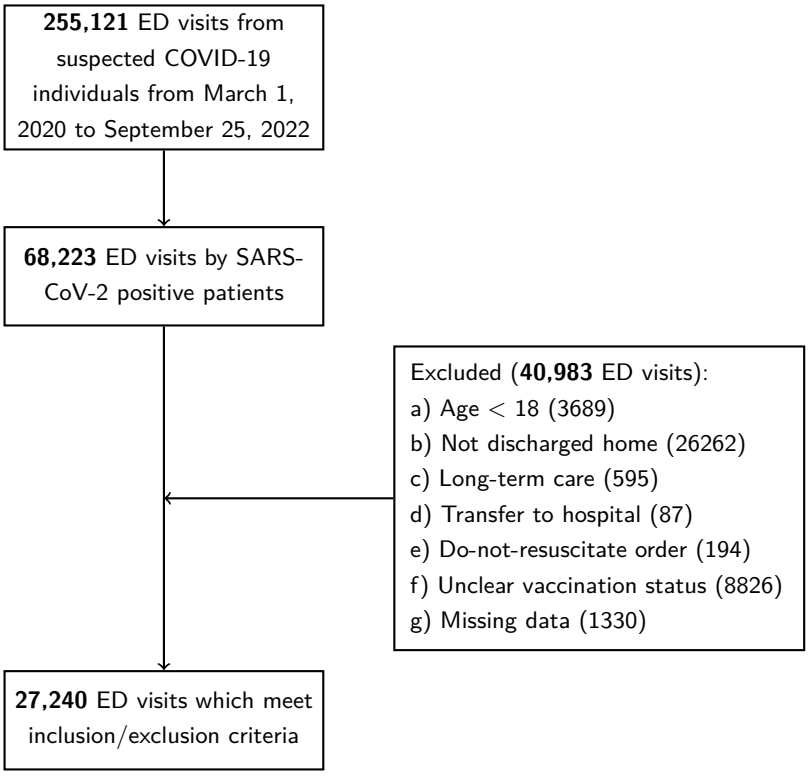
2.1 Study Criteria

Our project considers the same criteria as what was used to derive the CCDS. Specific interest lies in adults (aged 18 or older) confirmed to have COVID-19. A patient was considered COVID-19 positive if they received a positive test result either 14 days prior to the ED visit date or while in the ED, or had a discharge diagnosis of confirmed COVID-19.

We define vaccination status the same way as Brooks et al. (2022), which we summarize here. Any individuals who visited the ED in 2020 were considered unvaccinated, as vaccines were not approved by Health Canada until December 2020 (Brooks et al., 2022). The vaccination status of patients who presented to the ED in 2021 was coded based on medical records or telephone follow-up. If this information was not documented or unavailable, we implemented a rule developed by Brooks et al. (2022) to define vaccination status based on patient status as a healthcare worker, age, province of residence, and ED visit date. Since vaccine rollout was tightly controlled, this allowed researchers to easily assign patients as unvaccinated if they were not eligible at the time of the ED visit. Any patients who were eligible for the vaccine but had an unknown vaccination status were excluded from the study (Brooks et al., 2022).

Of the 255,121 visits to the ED in the CCEDRRN registry throughout our timeframe, 68,233 visits were made by COVID-19 positive patients. Aside from arrival respiratory rate (2.9% missing) and fever (2.8% missing), our data is complete. The visits which are missing these values are excluded from the study, as these instances only occurred in approximately 4.7% of visits. There were 27,240 visits which met the inclusion criteria, with the corresponding breakdown outlined in Figure 2.1. The data which met the inclusion criteria consists of patient information from ED visits to 55 sites across eight provinces. When considering trends by province, Manitoba is combined with Saskatchewan as there were less than five eligible visits reported in Manitoba. A list of the participating sites included in our study can be found in Table A.1. It should be noted that we consider ED visits as our unit of analysis, not individual patients. We refer to this final study cohort as the complete cohort, which is utilized for most of the analyses performed in this project.

Figure 2.1: Flow chart of inclusion and exclusion criteria



2.2 Descriptive Analysis

Upon arrival to a participating ED, patient information was recorded by clinicians and added into the patient's chart. This data included demographic information, comorbidities and vital signs. Clinicians collected COVID-19 specific information as well, such as exposure

risk, vaccination status and test results. Afterwards, research assistants went back to the chart to enter the data into the CCEDRRN database.

A selection of these characteristics and their corresponding spread or prevalence in the complete cohort across participating ED visits are listed in Table 2.1. The average age of patients who visited the ED was approximately 47 years old, with the majority of patients being female. The most commonly reported symptom was a cough, which occurred in about 62% of the study population. The vast majority of patients were unvaccinated (91.9%). This is expected, not only given the timeline of vaccination development and its corresponding rollout, but also since these individuals typically experienced more severe COVID-19 after testing positive for SARS-CoV-2 (Brooks et al., 2022), making these patients more likely to visit the ED. Of all the visits to the ED throughout this timeframe, there were 671 instances which resulted in one of our events of interest: 37 (0.1%) of which were in-hospital death.

Table 2.1: Summary of patient characteristics from ED visits in the complete cohort: visits between March 1, 2020 until September 25, 2022

		Complete Cohort (n = 27,240)
Age in years, mean (SD)		47 (17.3)
Female sex, n (%)		14,215 (52.2)
Pregnant, n (%)		590 (2.2)
Province, n (%)	**Sites**	
British Columbia	13	11,652 (42.8)
Québec	11	6,776 (24.9)
Alberta	7	3,535 (13.0)
Ontario	14	3,233 (11.9)
Nova Scotia	5	1,083 (4.0)
Saskatchewan	5	939 (3.4)
New Brunswick	1	22 (0.1)
Arrival from, n (%)		
Home/community		26,725 (98.1)
Institutional/no fixed address		515 (1.9)
Arrival mode, n (%)		
Self		26,725 (74.3)
Ambulance/police		7,003 (25.7)
Arrival heart rate, beats/min, mean (SD)		93.8 (17.7)
Arrival respiratory rate/min, mean (SD)		19.3 (4.2)
Arrival temperature, °C, mean (SD)		37 (0.8)
Presence of respiratory distress, n (%)		3,343 (12.3)
10 most common symptoms, n (%)		
Cough		16,941 (62.2)
Shortness of breath (dyspnea)		13,076 (48.0)
Fever		11,994 (44.0)

Table 2.1 continued

	Complete Cohort (n = 27,240)	
Chest pain (includes discomfort or tightness)	11,131	(40.9)
Fatigue/malaise	8,298	(30.5)
Headache	6,680	(24.5)
Chills	6,139	(22.5)
Nausea/vomiting	6,101	(22.4)
Sore throat	5,971	(21.9)
Myalgia (muscle ache)	5,955	(21.9)
10 most common comorbidities, n (%)		
Hypertension	5,142	(18.9)
Diabetes	3,121	(11.5)
Psychiatric condition/mental health diagnosis	2,547	(9.4)
Asthma	2,267	(8.3)
Coronary artery disease	969	(3.6)
Rheumatologic disorder	963	(3.5)
Chronic neuro disorder (not dementia)	869	(3.2)
Chronic lung disease (not asthma/IPF)	763	(2.8)
Active malignant neoplasm (cancer)	605	(2.2)
Atrial fibrillation	565	(2.1)
Smoking or vape use, n (%)		
Not documented	21,658	(79.5)
Never	3,875	(14.2)
Current or past user	1,707	(6.3)
Illicit substance use, n (%)		
Not documented	22,210	(81.5)
Never	4,026	(14.8)
Current or past user	1,004	(3.7)
Oxygen required in ED, n (%)	1,151	(4.2)
Medication administered in ED, n (%)		
Dexamethasone, hydrocortisone, or prednisone	2,011	(7.4)
COVID-19 vaccination status, n (%)		
Not vaccinated	25,041	(91.9)
Partially/fully vaccinated	2,199	(8.1)
Events, n (%)		
Admission within 72 hours	634	(2.3)
In-hospital death within 72 hours	37	(0.1)

Table 2.2: Distribution of gender in final study population: overall and compared to sex

	Overall	Sex	
Gender	**Study Population**	**Female**	**Male**
Female	17.97%	17.82%	0.15%
Male	15.80%	0.15%	15.65%
Two-spirit	0.02%	0.01%	0.01%
Something else	0.07%	0.05%	0.03%
Prefer not to answer	0.42%	0.17%	0.25%
Missing	65.72%	33.98%	31.74%

2.2.1 Sex and Gender Exploration

Following Brooks et al. (2022) work, primary interest in our investigations is in patient sex, however gender was also obtained in data collection. While there was a waiver of consent for collection of variables in patient charts, gender was collected as part of a telephone follow-up survey which required patient consent. Only 9448 ED visits had patients consent to the follow-up survey, which is approximately 35% of all participating visits to the ED. This lead to a considerable amount of missing and undocumented information in terms of patient gender. While there were 94 instances where a patient consented to participate in the follow-up but did not respond to this question, the remaining portion of missing responses is simply a result of the patient not participating in the follow-up. The missing responses by individuals who agreed to participate may actually be very informative, as the reason for the missing data may be related to the question itself. The exact reason for this missing data is unknown and further research is warranted to properly utilize this information. The distribution of responses for each gender under consideration is in Table 2.2. It should be noted that the terms used for gender in the follow-up study are consistent with what is used by the Government of Canada (Statistics Canada, 2022a), rather than gender terms such as man and woman (Eidinger, 2021).

McNemar's test was used to assess whether proportions of individuals whose gender is male or female differs from their recorded sex. To do so, we assume that the data is missing at random and exclude ED visits by individuals whose gender is missing from this analysis. This test obtains a p-value of 0.912, indicating that there is no statistically significant difference between the two groups. Thus, the number of individuals who are of male sex does not differ significantly from the number of individuals who identify as male. The same conclusion can be made for females.

2.3 Stratification by Province and Time Period

The data under study consists of patient visits to 55 EDs across seven provinces. The inclusion of different EDs across several provinces leads to data with variations in practice and

population diversities. Furthermore, as the pandemic evolved, subvariants of the disease were dominant across the country at different times, increasing heterogeneity. The following two sections will summarize investigations into any trends and associations observed in terms of variations across geography or over time. For the following exploratory analyses, we assume patient visits to the ED are independent and unless otherwise specified, a 5% significance level is considered: any test which results in a p-value less than 0.05 is considered statistically significant. The stats package (R Core Team, 2021) is utilized to conduct all tests used in this analysis to investigate any trends and differences with respect to geographical region or time. These tests include analysis of variance (ANOVA), chi-square, Fisher's, and Student's t-test.

2.3.1 Analysis by Province

The inclusion of EDs, which are nested within provinces, provides an opportunity for heterogeneity to arise. For example, provinces have different standards of practice for EDs within their geographical region. The patient characteristics explored previously are investigated further to check for any significant differences between provinces.

Testing Differences Across Provinces

Any differences in means of continuous variables for each province is compared using ANOVA tests. The chi-square test of homogeneity is used to assess the distribution of categorical variables by province. In the case of a province having a count less than five, Fisher's exact test is utilized. Each of these tests consider a significance level of 5%, and a summary of the results are displayed in Table 2.3. A statistically significant difference is found in at least one province for the majority of the variables considered: arrival heart rate, symptom of nausea/vomiting and patient admission within 72 hours of discharge are the only variables where a significant difference is not found among provinces.

Due to statistical significance in a number of the variables considered, we also evaluated practical significance using effect size. The effect size of province on each of the variables and the corresponding 95% confidence interval are also listed in Table 2.3. These were obtained using the effect size package (Ben-Shachar et al., 2020). For continuous variables, the effect size is defined using η^2, which measures the amount of variation in these variables that can be explained by province (Adams & Conway, 2014). Each of the variables considered here have very small effect sizes, illustrating they are not majorly affected by province. The association between two categorical variables is obtained using Cramer's V (Akoglu, 2018). These effect sizes are all fairly small, despite a number of the variables being statistically significantly different in at least one of the provinces. Province has the most noticeable effect on the presence of respiratory distress and the symptom of chills.

Table 2.3: Statistically significant differences between provinces

		Effect size	
	P-value	**Estimate**	**95% CI**
		η^2	
Age	<2e-16	0.01	(0.01, 0.01)
Arrival heart rate	0.119	<0.01	(0.00, 0.00)
Arrival respiratory rate	<2e-16	0.01	(0.01, 0.01)
Arrival temperature, °C	<2e-16	0.05	(0.04, 0.05)
		Cramer's V	
Sex	<0.001	0.05	(0.03, 0.06)
Pregnant	0.015	0.02	(0.00, 0.03)
Arrival from	<0.001	0.05	(0.04, 0.07)
Arrival mode	<0.001	0.03	(0.02, 0.04)
Presence of respiratory distress	<0.001	0.21	(0.20, 0.22)
10 most common symptoms			
Cough	<2e-16	0.12	(0.11, 0.13)
Shortness of breath (dyspnea)	<2e-16	0.09	(0.07, 0.10)
Fever	<2e-16	0.10	(0.08, 0.11)
Chest pain (includes discomfort or tightness)	<2e-16	0.07	(0.06, 0.08)
Fatigue / malaise	<2e-16	0.10	(0.09, 0.11)
Headache	<2e-16	0.06	(0.05, 0.08)
Nausea / vomiting	<0.001	0.08	(0.07, 0.09)
Chills	<0.001	0.22	(0.21, 0.23)
Myalgia (muscle ache)	<0.001	0.09	(0.08, 0.10)
Diarrhea	0.003	0.02	(0.00, 0.03)
10 most common comorbidities			
Hypertension	<0.001	0.07	(0.05, 0.08)
Diabetes	<0.001	0.06	(0.04, 0.07)
Psychiatric condition/mental health diagnosis	<0.001	0.07	(0.06, 0.08)
Asthma	<0.001	0.04	(0.02, 0.05)
Coronary artery disease	<0.001	0.05	(0.03, 0.06)
Rheumatologic disorder	<0.001	0.03	(0.00, 0.04)
Chronic neuro disorder (not dementia)	<0.001	0.04	(0.03, 0.05)
Chronic lung disease (not asthma/IPF)	0.001	0.02	(0.00, 0.03)
Active malignant neoplasm (cancer)	<0.001	0.05	(0.04, 0.06)
Past malignant neoplasm (cancer)	<0.001	0.06	(0.05, 0.07)
Smoking or vaping	<0.001	0.08	(0.07, 0.09)
Illicit substance use,	<0.001	0.07	(0.06, 0.08)
Oxygen required in ED	<0.001	0.06	(0.05, 0.07)
Medication administered in ED	0.001	0.03	(0.01, 0.04)
COVID-19 vaccination status	<0.001	0.16	(0.15, 0.18)
Events			
Composite event	0.017	0.02	(0.00, 0.03)

Table 2.3 continued

		Effect size	
	P-value	**Estimate**	**95% CI**
Admission within 72 hours	0.062	0.02	(0.00, 0.03)
In-hospital death within 72 hours	0.003	0.02	(0.00, 0.03)

2.3.2 Temporal Analysis

Our study utilizes the complete cohort of data collected by CCEDRRN. Upon comparison of Table 1 in Brooks et al. (2022) to Table 2.1 in this paper, there are a few interesting differences. Of the 15,305 patient visits considered in Brooks et al. (2022), 535 (3.5%) resulted in a patient being admitted to or dying in the hospital within 72 hours of being discharged. This is higher than what was seen in the data under study for this project, as only 2.4% of patient visits resulted in the event of interest. This motivates investigation into differences in these patient characteristics with respect to time.

Further analysis is performed after splitting the complete cohort into two subsets; the early cohort, which aligns with the timeframe considered by Brooks et al. (2022), and the late cohort, which includes the remaining data. The early cohort includes data from March 1, 2020 until September 8, 2021, with the intention to obtain a similar sample as the one used in Brooks et al. (2022). The late cohort consists of the remaining dataset and includes any ED visits at a participating hospital from September 9, 2021 until September 25, 2022.

Table 2.4 summarizes patient characteristics in these two cohorts. There are a number of similarities between the two cohorts, however there are some key differences. The proportion of patients of female sex increased slightly in the late cohort, compared to the early cohort. Furthermore, the late cohort also had a higher percentage of patients arrive at the ED themselves, rather than with the help of an ambulance or police. The presence of respiratory distress also dropped from 16% to 5.4% in ED visits from the early to the late cohort, respectively. While the exact reason for these changes in trend is unknown, they may indicate a decrease in the severity of these COVID-19 symptoms over time. This could be the result of a number of factors such as, but not limited to, disease variant, vaccination status, natural immunity, and implementation of public health measures. The proportion of ED visits which result in the event of interest is also higher in the earlier cohort, as this number drops from 3.4% to approximately 1% in the later cohort.

Table 2.4: Summary of patient characteristics from ED visits in the early and late cohorts

		Early Cohort (n = 17,668)			Late Cohort (n = 9,572)	
Age in years, mean (SD)		47.1	(16.4)		47.1	(18.7)
Female sex, n (%)		8,929	(50.5)		5,286	(55.2)
Pregnant, n (%)		306	(1.7)		284	(3.0)
Province, n (%)	**Sites**			**Sites**		
Alberta	7	3,535	(20.0)	0		—[a]
British Columbia	13	6,662	(37.7)	5	4,990	(52.1)
New Brunswick	1	5	(0.0)	1	17	(0.2)
Nova Scotia	5	219	(1.2)	4	864	(9.0)
Ontario	13	2,458	(13.9)	5	775	(8.1)
Québec	11	4,376	(24.8)	6	2,400	(25.1)
Saskatchewan	5	413	(2.3)	3	526	(5.5)
Arrival from, n (%)						
Home (community)		17,308	(98.0)		9,417	(98.4)
Institutional/No fixed address		360	(2.0)		155	(1.6)
Arrival mode, n (%)						
Ambulance/police		5,089	(28.8)		1,914	(20.0)
Self		12,579	(71.2)		7,658	(80.0)
Arrival heart rate, beats/min, mean (SD)		94	(17.2)		93.5	(18.6)
Arrival respiratory rate/min, mean (SD)		19.6	(4.3)		18.7	(3.8)
Arrival temperature, °C, mean (SD)		37	(0.8)		37	(0.8)
Presence of respiratory distress, n(%)		2,829	(16.0)		514	(5.4)
10 most common symptoms, n (%)						
Cough		10,755	(60.9)		6,186	(64.6)
Shortness of breath (dyspnea)		9,236	(52.3)		3,840	(40.1)
Fever		7,875	(44.6)		4,119	(43.0)
Chest pain (includes discomfort or tightness)		6,871	(38.9)		4,260	(44.5)
Fatigue / malaise		5,525	(31.3)		2,773	(29.0)
Headache		4,161	(23.6)		2,519	(26.3)
Nausea / vomiting		3,964	(22.4)		2,137	(22.3)
Chills		3,686	(20.9)		2,453	(25.6)
Myalgia (muscle ache)		3,651	(20.7)		2,304	(24.1)
Diarrhea		2,816	(15.9)		1,053	(11.0)
10 most common comorbidities, n (%)						
Hypertension		3,397	(19.2)		1,745	(18.2)
Diabetes		2,099	(11.9)		1,022	(10.7)
Psychiatric condition/mental health diagnosis		1,547	(8.8)		1,000	(10.4)
Asthma		1,394	(7.9)		873	(9.1)
Coronary artery disease		550	(3.1)		419	(4.4)
Rheumatologic disorder		524	(3.0)		439	(4.6)
Chronic neuro disorder (not dementia)		426	(2.4)		443	(4.6)

Table 2.4 continued

	Early Cohort (n = 17,668)		Late Cohort (n = 9,572)	
Chronic lung disease (not asthma/IPF)	413	(2.3)	350	(3.7)
Active malignant neoplasm (cancer)	291	(1.6)	314	(3.3)
Past malignant neoplasm (cancer)	283	(1.6)	229	(2.4)
Smoking or vape, n (%)				
Current or past	1,116	(6.3)	591	(6.2)
Never or not documented	16,598	(93.9)	9,010	(94.1)
Illicit substance use, n (%)				
Current or past	610	(3.5)	394	(4.1)
Never or not documented	17,058	(96.5)	9,178	(95.9)
Oxygen required in ED, n (%)	892	(5.0)	259	(2.7)
Medication administered in ED				
Dexamethasone, hydrocortisone, or prednisone	1,275	(7.2)	736	(7.7)
COVID-19 vaccination status, n (%)				
Not immunized	16,221	(91.8)	8,820	(92.1)
Partially/fully vaccinated	1,447	(8.2)	752	(7.9)
Events, n (%)				
Admission within 72 hours	539	(3.1)	95	(1.0)
In-hospital death within 72 hours	34	(0.2)	—	[b]

Early cohort: March 1, 2020 - September 8, 2021

Late cohort: September 9, 2020 - September 25, 2022

[a], no participating ED visits from Alberta in this cohort

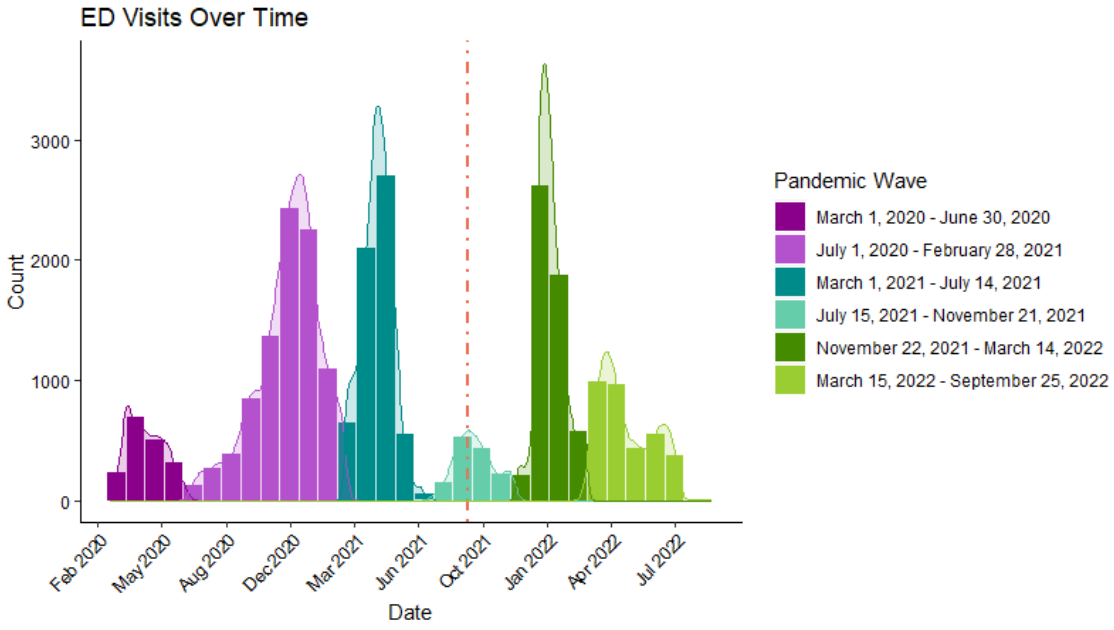
[b], count is less than 5 and is omitted

The histogram in Figure 2.2 visualizes the trend in the number of ED visits over time. Each colour indicates a different pandemic wave, defined using the same dates as what CCEDRRN has used previously: 1) March 1, 2020 - June 30, 2020; 2) July 1, 2020 - February 28, 2021; 3) March 1, 2021 - July 14, 2021; 40 July 16, 2021 - November 21, 2021; 5) November 22, 2021 - March 14, 2022; and 6) March 15, 2022 - July 31, 2022. Note that in our analysis, there were only 17 visits to the ED between August 1, 2022 - September 25, 2022, so we include these visits in the sixth wave. The red dot dash line is the cutoff between the early and late cohorts. The second and third wave appear to have had the highest number of ED visits.

Testing Differences by Time Period

The patient characteristics are studied in more detail to determine if there are any statistically significant differences between the early and late cohorts. Assuming equal variances, Student's t-test is used to assess whether the continuous variables in the two study cohorts have the same population mean. Similarly, the distribution of categorical variables in both

Figure 2.2: Histogram of ED visits across the study period with normal densities



cohorts are compared using the chi-square test of homogeneity. Both testing procedures consider a significance level of 5%, and the results from the analyses can be found in Table 2.5. These analyses indicate a statistically significant difference in the average patient arrival heart rate, respiratory rate, and temperature. In fact, the corresponding averages of these variables are higher in the early cohort. In other words, the average arrival heart rate, respiratory rate and temperature (degrees Celsius) decreased over time.

The distribution of a number of the categorical variables is statistically significantly different as well. Overall, only five of the variables considered obtained a p-value greater than 0.05: age, nausea/vomiting symptoms, smoking status, medication administered in the ED (dexamethasone, hydrocortisone, or prednisone), and COVID-19 vaccination status. The remaining variables are statistically significantly different between the two cohorts.

While the majority of variables obtained a statistically significant p-value, the corresponding effect sizes are actually fairly small. These effect sizes can also be found in Table 2.5. The effect size of study cohort on continuous variables is obtained using η^2 and Cramer's V is used to estimate the effect of study cohort on categorical variables. Despite many of these variables being significantly different between the two study cohorts, the effect of study cohort on these variables is minimal overall. The two variables which appear to be most affected by study cohort are province and respiratory distress.

Table 2.5: Statistically significant differences between the early and late cohorts

		Effect size	
	P-value	**Estimate**	**95% CI**
		η^2	
Age	0.974	<0.01	(0.00, 0.00)
Arrival heart rate	0.008	<0.01	(0.00, 0.00)
Arrival respiratory rate	<2e-16	0.01	(0.01, 0.01)
Arrival temperature, °C	<0.001	<0.01	(0.00, 0.00)
		Cramer's V	
Sex	<0.001	0.04	(0.03, 0.06)
Pregnant	<0.001	0.04	(0.03, 0.05)
Province	<2e-16	0.36	(0.35, 0.37)
Arrival from	0.018	0.01	(0.00, 0.03)
Arrival mode	<2e-16	0.10	(0.08, 0.11)
Presence of respiratory distress	<2e-16	0.22	(0.21, 0.23)
10 most common symptoms			
Cough	<0.001	0.04	(0.02, 0.05)
Shortness of breath (dyspnea)	<2e-16	0.12	(0.10, 0.13)
Fever	0.150	0.01	(0.00, 0.03)
Chest pain (includes discomfort or tightness)	<2e-16	0.05	(0.04, 0.07)
Fatigue / malaise	<0.001	0.02	(0.01, 0.04)
Headache	<0.001	0.03	(0.02, 0.04)
Nausea / vomiting	0.847	0.00	(0.00, 0.01)
Chills	<2e-16	0.05	(0.04, 0.07)
Myalgia (muscle ache)	<0.001	0.04	(0.03, 0.05)
Diarrhea	<2e-16	0.07	(0.06, 0.08)
10 most common comorbidities			
Hypertension	0.047	0.01	(0.00, 0.02)
Diabetes	0.003	0.02	(0.01, 0.03)
Psychiatric condition/mental health diagnosis	<0.001	0.03	(0.02, 0.04)
Asthma	<0.001	0.02	(0.01, 0.03)
Coronary artery disease	<0.001	0.03	(0.02, 0.04)
Rheumatologic disorder	<0.001	0.04	(0.03, 0.05)
Chronic neuro disorder (not dementia)	<2e-16	0.06	(0.05, 0.07)
Chronic lung disease (not asthma/IPF)	<0.001	0.04	(0.03, 0.05)
Active malignant neoplasm (cancer)	<2e-16	0.05	(0.04, 0.06)
Past malignant neoplasm (cancer)	<0.001	0.03	(0.02, 0.04)
Smoking or vaping	0.663	0.00	(0.00, 0.01)
Illicit substance use	0.006	0.02	(0.00, 0.03)
Oxygen required in ED	<2e-16	0.06	(0.04, 0.07)
Medication administered in the ED	0.162	<0.01	(0.00, 0.02)
COVID-19 vaccination status	0.346	0.00	(0.00, 0.02)
Events			

Table 2.5 continued

		Effect size	
	P-value	**Estimate**	**95% CI**
Composite event	<2e-16	0.07	(0.06, 0.08)
Admission within 72 hours	<2e-16	0.06	(0.05, 0.08)
In-hospital death within 72 hours	0.001	0.02	(0.01, 0.03)

Results in Table 2.5 indicate that age does not differ significantly between the two cohorts. Despite statistically significant differences present between cohorts in terms of arrival heart rate and arrival temperature, the η^2 for the effect of study cohort on age appears to be similar to the corresponding η^2 for these two variables. We investigate these results to further understand this situation. The histograms in Figure 2.3 illustrate what we saw earlier. There is no obvious change in trend of patient age across the two study cohorts. In fact, the similar effect sizes are due to the effect of rounding, as the effect size of study cohort on age is actually < 0.0001, while study cohort has an effect size of 0.0003 on arrival heart rate. Thus, while both of these effect sizes are small, study cohort has more of an effect on heart rate upon arrival to the ED than it does on patient age. Similar conclusions can be made in terms of patient temperature upon arrival to the ED: before rounding, the corresponding η^2 is 0.0005.

Vaccination Status

One interesting characteristic which is not significantly different across the two time periods is patient vaccination status. Despite the increase in vaccinations amongst the Canadian population over time, the proportion of patients included in the study who were vaccinated is not significantly different between the two time periods. Recall that CCEDRRN only collected data on patients who visited the ED, and as illustrated in this data, these individuals were mostly unvaccinated. This is consistent with our expectations as unvaccinated individuals who test positive for SARS-CoV-2 usually have more severe symptoms (Brooks et al., 2022). Thus, while the rate at which patients visited the ED may have decreased over time, the majority of these individuals continued to be unvaccinated, despite the rise in vaccinated individuals across the country.

2.4 Summary

In this chapter, we provided a thorough descriptive analysis of patients who visited the ED. We investigated certain patient characteristics which not only included demographic information and medical history, but also vital signs recorded at patient intake. Further analysis was performed to investigate any potential spatial or temporal effects in terms

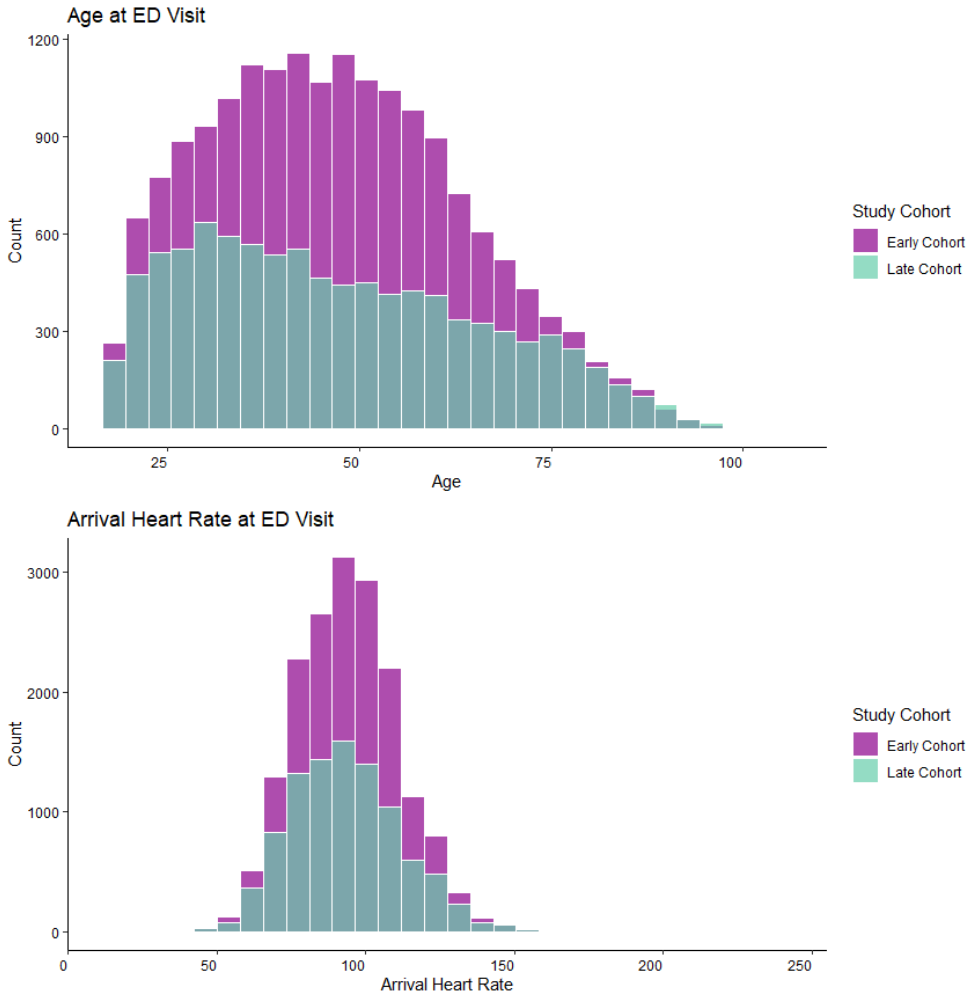


Figure 2.3: Histograms of age and arrival heart rate in each study cohort

of the patients who visited a participating ED. This revealed a significant difference in a number of patient characteristics across both geography and two time periods. These analyses indicate that there are likely geographical and temporal effects, and accounting for these in the model could result in more informative results.

Chapter 3

Analysis of COVID-19 Associated Follow-Up Events

3.1 Descriptive Analysis

Patient characteristics in the complete cohort were explored further in those who experienced the COVID-19 related event: hospital admission or in-hospital death within 72 hours of discharge. It is evident that the average age is higher in patients who experienced the event than the corresponding age in the overall study population, increasing from 47 to 56 years old. There were also noticeable differences with respect to patient sex, as the majority of patients who were either admitted to or died in the hospital within 72 hours of discharge were male (60.4%), where males made up less than half (47.8%) of the study population. Another interesting difference is in the number of patients who required oxygen upon arrival to the ED. Of all the patient visits included in this study, only 4% of visits involved supplemental oxygen, however this number rose to 49.9% in visits where the patient encountered an event. Several other intriguing characteristics are summarized in Table 3.1.

Table 3.1: Characteristics of patients who were admitted to or died in the hospital within 72 hours of ED discharge in the complete cohort

		Events (n = 671)
Age in years, mean (SD)		56.2 (16.3)
Female sex, n (%)		266 (39.6)
Pregnant, n (%)		12 (1.8)
Province, n (%)	**Sites**	
British Columbia	10	302 (45.0)
Québec	9	142 (21.2)
Alberta	7	110 (16.4)
Ontario	9	82 (12.2)
Nova Scotia	4	20 (3.0)
Saskatchewan	2	15 (2.2)

Table 3.1 continued

		Events (n = 671)	
New Brunswick	0	0	(0.0)
Arrival from, n (%)			
Home (community)		657	(97.9)
Institutional/No fixed address		14	(2.1)
Arrival mode, n (%)			
Ambulance/police		370	(55.1)
Self		301	(44.9)
Arrival heart rate, beats/min, mean (SD)		97.9	(18.4)
Arrival respiratory rate/min, mean (SD)		24.3	(7.0)
Arrival temperature, °C, mean (SD)		37.4	(1.1)
Presence of respiratory distress, n (%)		286	(42.6)
10 most common symptoms, n (%)			
Shortness of breath (dyspnea)		537	(80.0)
Cough		423	(63.0)
Fever		338	(50.4)
Fatigue/malaise		251	(37.4)
Chest pain (includes discomfort or tightness)		207	(30.8)
Nausea/vomiting		173	(25.8)
Diarrhea		158	(23.5)
Headache		115	(17.1)
Chills		111	(16.5)
Myalgia (muscle ache)		105	(15.6)
10 most common comorbidities, n (%)			
Hypertension		220	(32.8)
Diabetes		148	(22.1)
Psychiatric condition/mental health diagnosis		72	(10.7)
Rheumatologic disorder		64	(9.5)
Asthma		58	(8.6)
Coronary artery disease		53	(7.9)
Chronic lung disease (not asthma/IPF)		47	(7.0)
Obesity		40	(6.0)
Chronic kidney disease		39	(5.8)
Chronic neuro disorder (not dementia)		38	(5.7)
Smoking or vape use, n (%)			
Not documented		466	(69.5)
Never		127	(18.9)
Current or past user		78	(11.6)
Illicit substance use, n (%)			
Not documented		429	(63.9)
Never		214	(31.9)
Current or past user		28	(4.2)

Table 3.1 continued

	Events (n = 671)
Oxygen required in ED, n (%)	335 (49.9)
Medication administered in ED, n (%)	
Dexamethasone, hydrocortisone, or prednisone	304 (45.3)
COVID-19 vaccination status, n (%)	
Not vaccinated	604 (90.0)
Partially/fully vaccinated	67 (10.0)
Events, n (%)	
Admission within 72 hours	634 (94.5)
In-hospital death within 72 hours	37 (5.5)

3.2 Stratification by Province and Time Period

Our analysis in Section 2.3 revealed significant differences across geography as well as over time. These differences were found in a number of patient characteristics, including our defined COVID-19 related event: hospital admission or death within 72 hours of discharge. We now investigate these differences further to potentially provide insights into why this may be the case. The following tests consider a 5% level of significance and use the stats package (R Core Team, 2021).

3.2.1 Analysis by Province

Due to a small number of events in certain provinces, Fisher's exact test is utilized to investigate the association between patient event and province. This test obtained a p-value of 0.017, concluding that there is in fact a difference in terms of the number of events between provinces with a significance level of 5%. In other words, the proportion of events which occurred at participating EDs differs in at least one of the seven provinces considered. The corresponding percentages of events for each province can be found in Table 3.2. This table also lists the percentages of events across two time periods of interest, which were defined earlier. The first time period, the early cohort, considers the same timeframe as Brooks et al. (2022), and the late cohort includes the remaining data. The differences between these two time periods will be discussed further in the upcoming temporal analysis.

Post Hoc Tests

Post hoc tests are performed to determine which of the provinces differed from one another. Fisher's exact test is used on each of the $\binom{7}{2} = 21$ pairwise comparisons and the Bonferroni correction is applied to account for multiple comparisons. In this case, a p-value less than

Table 3.2: Percentage of ED visits resulting in hospital admission or in-hospital death within 72 hours of discharge by province in each study cohort

	Complete cohort	Early cohort	Late cohort
Alberta	3.1%	3.1%	—*
British Columbia	2.6%	3.8%	1.0%
New Brunswick	0.0%	0.0%	0.0%
Nova Scotia	1.8%	5.9%	0.8%
Ontario	2.5%	3.0%	1.2%
Québec	2.1%	2.7%	1.0%
Saskatchewan	1.6%	2.2%	1.1%

*, no participating ED visits during this time period

Complete cohort: ED visits from March 1, 2020 - September 25, 2022

Early cohort: ED visits from March 1, 2020 - September 8, 2021

Late cohort: ED visits from September 9, 2021 - September 25, 2022

Table 3.3: Time period of data collection in each province

	First ED visit	Last ED visit
Alberta	March 11, 2020	May 23, 2021
British Columbia	March 2, 2020	September 25, 2022
New Brunswick	May 4, 2020	April 11, 2022
Nova Scotia	March 14, 2020	May 16, 2022
Ontario	March 1, 2020	August 3, 2022
Québec	March 3, 2020	July 29, 2022
Saskatchewan	March 16, 2020	May 20, 2022

$0.05/21 = 0.0024$ is deemed significant. There is a significant difference in the number of events in Alberta compared to Québec, and the results from this analysis are in Table A.2. Since we are interested in a composite event, we use Fisher's exact test to investigate each component of the event of interest. This revealed a statistically significant difference between Alberta and Québec in terms of the number of in-hospital deaths within 72 hours of discharge (p-value = 0.001). However, there is no statistically significant difference between the number of hospital admissions within 72 hours of discharge in each of the provinces considered.

Upon further investigation, it was discovered that Alberta did not have any visits to a participating ED after May 23, 2021, while the other provinces had participating ED visits until 2022. The time period of data collection in each province can be found in Table 3.3. The differences in time periods for data collection is likely a factor contributing to the significant differences observed during this analysis.

3.2.2 Temporal Analysis

The percentage of ED visits which resulted in the event of interest for both time periods can be found broken down by each province in Table 3.2. As mentioned previously, Alberta did not have any participating ED visits in the late cohort. Excluding New Brunswick, which did not have any patient events over the entire study period, each of the remaining five provinces saw a lower percentage of events in the late cohort. In fact, this percentage decreases by at least 50% compared to the early cohort. These differences illustrate the evolution of the pandemic over time and how the inclusion of a covariate to account for this may be worth investigating further. The decreasing trend in the number of COVID-19 related events can be seen in Figure 3.1. The daily percentages of ED visits which had a patient experience the COVID-19 related event are plotted in Figure 3.2.

Figure 3.1: Histogram of COVID-19 related events across the study period with normal densities

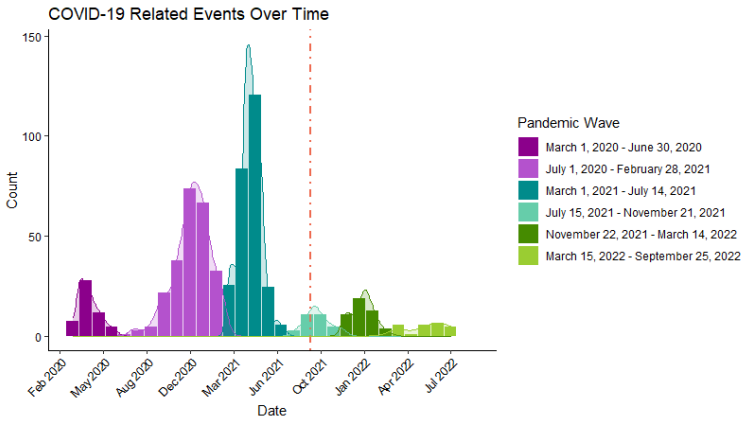
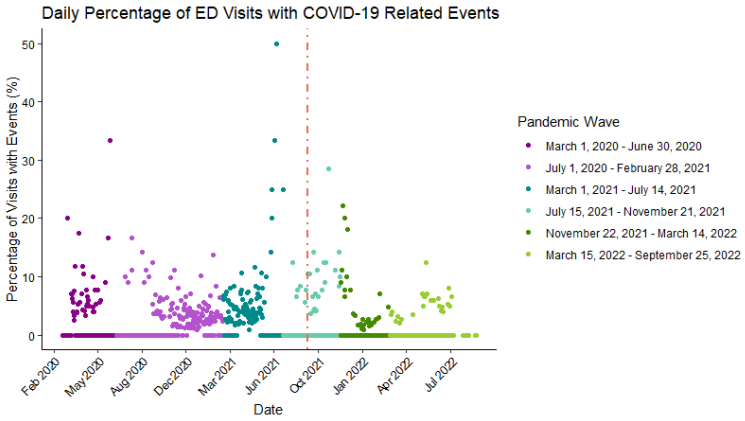


Figure 3.2: Plot of daily percentage of ED visits with COVID-19 related event



3.3 Regression Analysis

The CCDS was derived using a logistic regression model and the continuous predictors were fit using restricted cubic splines with 3 knots. Brooks et al. (2022) chose candidate predictors which include age, sex, pregnancy, type of residence, ED arrival mode, comorbidities, symptoms, respiratory rate, ED oxygen delivery, physician or nurse impression of respiratory distress, medication administered in ED, immunization status, and use of alcohol, tobacco, vapes, and illicit substances. Aside from arrival respiratory rate (4.2% missing) and fever (2.3% missing), the data used for their study was complete. The CCDS used multiple imputation to account for the missing data and the final model was obtained using a fast step-down procedure. This final model includes key predictors which consist of a subset of the candidate predictors: age, sex, temperature, arrival mode, pregnancy, respiratory distress, and arrival respiratory rate. The CCDS considers a composite outcome of hospital admission or in-hospital death within 72 hours of ED discharge. This modelling did not account for the multilevel structure of the CCEDRRN data.

The implementation of mulitilevel models, or mixed effects regression models, will allow for hierarchical data structures to be accounted for in modelling. The inclusion of random effects in these models incorporate the heterogeneity present across the different levels present in the data. This type of modelling is applicable to the CCEDRRN data, as the ED visits occurred at 55 different EDs within seven provinces: the EDs are nested within provinces. There is likely some sort of effect of ED sites as a result of distinct standards of practice at different hospitals. This ideology can further be applied to account for the heterogeneity present across provinces.

The following analyses will explore a binary response variable Y, which denotes whether or not the ED visit resulted in an event. The response variable will be either 0 or 1, where $Y = 1$ indicates the patient was admitted to or died in the hospital within 72 hours of ED discharge, and $Y = 0$ otherwise.

We initially consider a fixed-effects regression model with all candidate predictors, which are identical to those considered by Brooks et al. (2022). In our descriptive analyses, smoking/vape use and illicit substance use are broken down into three categories: not documented, never, and current or past user. We assume confirmation of past or present use is more likely to be reported in patient charts, while no previous use may be omitted. Therefore, we combine the not documented and never categories in our modelling. To investigate whether the inclusion of additional ED visits influences the predictors chosen for the final model compared to the previous work by Brooks et al. (2022), we repeat model selection using the same fast step-down procedure. Although the candidate variables considered in this project are the same as those considered for the CCDS, the variables included in the final model differ between the two projects. This may be a result of a combination of factors, such as the inclusion of additional visits in the dataset as well as differences in modelling pro-

Table 3.4: Final variables after model selection compared to the variables used in the CCDS.

Variables	Our model	CCDS
Age	•	•
Sex	•	•
Pregnant	•	•
Arrival mode	•	•
Respiratory distress	•	•
Chronic kidney disease or dialysis	•	
Arrival respiratory rate	•	•
Arrival temperature	•	•
Oxygen required in ED	•	
Medication administered in ED	•	

cedures; Brooks et al. (2022) modelled continuous predictors using restricted cubic splines, while we do not.

There are $p = 10$ final predictors in our model, which include age, sex, pregnancy, arrival mode, respiratory distress, chronic kidney disease or dialysis, arrival respiratory rate, temperature, oxygen required in ED, and ED medication. Table 3.4 lists the final variables after model selection in our project as well as in the CCDS. Each of the models considered in this section include these final variables. Seven of the variables in our model were also included in the CCDS. The additional three variables, which were not included in the derivation of the CCDS, are the presence of chronic kidney disease and/or need for dialysis, as well as the requirement of oxygen or medication while in the ED. One interesting thing to note is that the latter two of these additional variables are related to the medical intervention required, based on a patient's presentation to the ED. This may be an indicator of how patient care evolved as the pandemic progressed.

We investigate the fit of several models in this section. We use Akaike information criterion (AIC) and likelihood ratio tests to make comparisons and evaluate which of these models is best. The fixed effects logistic regression models are fitted using the stats (R Core Team, 2021) package, while the two- and three-level models, or mixed effects models, utilize the lme4 (Bates et al., 2015) package. The continuous variables are scaled to avoid large eigenvalues, ensuring we obtain an identifiable model.

3.3.1 Fixed Effects Logistic Regression Model

We begin by implementing a generalized linear model and perform a simple logistic regression analysis. This models the logit of the probability of an event Y_i, admission or death in the ED within 72 hours of discharge, occurring for ED visit i. A total of 27,240 ED visits met our inclusion criteria, so we consider $i = 1, \ldots, 27,240$. The model we consider in this case is written as

Table 3.5: Results for fixed effects regression model (3.1)

	Estimate	Std. Error	Pr(>|z|)	
Intercept	-4.699	0.255	< 2e-16	*
Age	0.286	0.046	< 0.000	*
Sex (vs. female)				
Male	0.227	0.091	0.012	*
Pregnant	0.788	0.323	0.015	*
Arrival mode (vs. ambulance/police)				
Self	-0.310	0.095	0.001	*
Respiratory distress	0.703	0.099	0.000	*
Chronic kidney disease or dialysis	0.590	0.204	0.004	*
Arrival respiratory rate	0.211	0.026	< 2e-16	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	-0.040	0.239	0.867	
$> 37.5°C$	0.367	0.244	0.132	
Oxygen required in ED	2.055	0.107	< 2e-16	*
Medication administered in ED	1.314	0.101	< 2e-16	*
AIC: 4545.2				

*, variable is significant at $\alpha = 0.05$

$$\text{logit}\{P(Y_i = 1|\mathbf{X}_i)\} = \mathbf{X}_i\boldsymbol{\beta}, \tag{3.1}$$

where $\boldsymbol{\beta}$ is a vector consisting of regression parameters including the intercept, and $\mathbf{X}$ is a $(p+1)$ vector of the intercept and covariates for the corresponding ED visit. A summary of the 11 parameter estimates obtained from the implementation of this regression model along with the corresponding standard errors and p-values are in Table 3.5.

Inclusion of Covariate for Study Cohort

Preliminary analyses in Section 2.3.2 indicate that time may play a crucial role in the modelling process. As a result of this, we add a covariate to model (3.1) which indicates the study cohort in which the ED visit occurred. This covariate is equal to 0 if the ED visit was part of the early cohort (March 1, 2020 - September 8, 2021), and 1 if was part of the late cohort (September 9, 2021 - September 25, 2022).

The results from this analysis are shown in Table 3.6. This model includes the same 10 variables we considered previously as well as the covariate for study cohort. The AIC value for this model is much smaller than the AIC for the model without it. The study cohort variable is also significant at a 5% level of significance. This illustrates that accounting for time in this way is beneficial. Furthermore, a likelihood ratio test comparing these two models confirms that including the study cohort variable improves the efficiency of the model with a p-value < 0.0001.

Table 3.6: Results for fixed effects regression model (3.1) with added covariate for study cohort

	Estimate	Std. Error	Pr(>|z|)	
Intercept	-4.516	0.255	< 2e-16	*
Age	0.324	0.047	< 0.000	*
Sex (vs. female)				
Male	0.212	0.091	0.020	*
Pregnant	0.901	0.323	0.005	*
Arrival mode (vs. ambulance/police)				
Self	-0.265	0.095	0.005	*
Respiratory distress	0.610	0.099	< 0.000	*
Chronic kidney disease or dialysis	0.684	0.206	0.001	*
Arrival respiratory rate	0.201	0.027	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.001	0.239	0.995	
$> 37.5°C$	0.375	0.244	0.124	
Oxygen required in ED	2.033	0.107	< 2e-16	*
Medication administered in ED	1.379	0.102	< 2e-16	*
Study cohort (vs. early cohort)				
Late cohort	-1.001	0.121	< 2e-16	*

AIC: 4466.9

*, variable is significant at $\alpha = 0.05$

Early cohort: ED visits from March 1, 2020 - September 8, 2021

Late cohort: ED visits from September 9, 2021 - September 25, 2022

Inclusion of Covariate for ED Visit Date

We consider an additional model which includes a covariate to denote the date of patient ED visit occurred. This fixed effects logistic regression model includes a continuous covariate for time in addition to the 10 variables defined previously. The results from this analysis are in Table A.3. The covariate for time in this model is significant with a level of significance of 5%. This model obtained a lower AIC (4468.6) than our initial model, which does not account for time. Furthermore, the AIC is very similar to our model which includes a covariate for study cohort (4466.9). In fact, there are no major differences between the two models: they both have similar standard errors, aside from the standard errors of the time covariate themselves. Study cohort obtained a standard error of 0.121, which is approximately double the corresponding value for the ED visit date covariate, 0.052. The two models deem the same 11 variables as significant at a level of 5%. Once again, a likelihood ratio test comparing this model to one which does not account for time confirms that including this variable improves model efficiency (p-value < 0.0001).

3.3.2 Two-Level Model: Random Effect for Site

We extend model (3.1) to investigate whether a random intercept for site should be included. A generalized linear mixed effects model with the logit link is used to implement this idea. This model is similar to (3.1) and is written as

$$\text{logit}\{P(Y_{ij} = 1|b_{0j}, \mathbf{X}_{ij})\} = \mathbf{X}_{ij}\boldsymbol{\beta} + b_{0j}, \tag{3.2}$$

where $\boldsymbol{\beta}$ and $\mathbf{X}$ are defined similarly to those in (3.1), and visit i occurs at ED site j, for $j = 1, \ldots, 55$. In other words, i denotes the level one unit (27,240 ED visits), and j denotes the level two unit (55 sites). This model also has a random intercept term for site, denoted by b_{0j}, which remains constant for all ED visits within a particular site. We assume that Y_{ij} are independent and follow a Bernoulli distribution, conditional on the site random effect b_{0j}, where $b_{0j} \sim N(0, \sigma_0^2)$.

The results from this analysis are shown in Table 3.7. As we expected, there is variability between EDs, which is estimated to be about 0.237, indicating the inclusion of random effects is likely advantageous. The random intercepts and corresponding standard errors for sites can be seen in the caterpillar plot in Figure 3.3. Upon comparison to the one-level (fixed effects) model, it is clear that the inclusion of a random intercept for site through a two-level model is beneficial, evident through comparison of AIC values and the likelihood ratio test. A smaller AIC value indicates a better model, and the corresponding value for our model with a random intercept for site is 4502.8, while the AIC for the one-level model is 4545.2. A likelihood ratio test also confirms these findings with a p-value < 0.0001.

Table 3.7: Results for multilevel regression model (3.2) with a random intercept for site

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.959	0.273	< 2e-16	*
Age	0.308	0.047	< 0.000	*
Sex (vs. female)				
Male	0.230	0.091	0.011	*
Pregnant	0.766	0.325	0.019	*
Arrival mode (vs. ambulance/police)				
Self	-0.305	0.096	0.001	*
Respiratory distress	0.618	0.106	< 0.000	*
Chronic kidney disease or dialysis	0.616	0.207	0.003	*
Arrival respiratory rate	0.203	0.026	< 0.000	*
Arrival temperature (vs. < 36°C)				
36°C – 37.5°C	0.074	0.240	0.758	
> 37.5°C	0.525	0.248	0.034	*
Oxygen required in ED	2.249	0.114	< 2e-16	*
Medication administered in ED	1.334	0.102	< 2e-16	*
Random Effects	**Var. Estimate**			
Site (Intercept)	0.237			
AIC: 4502.8				

*, variable is significant at $\alpha = 0.05$

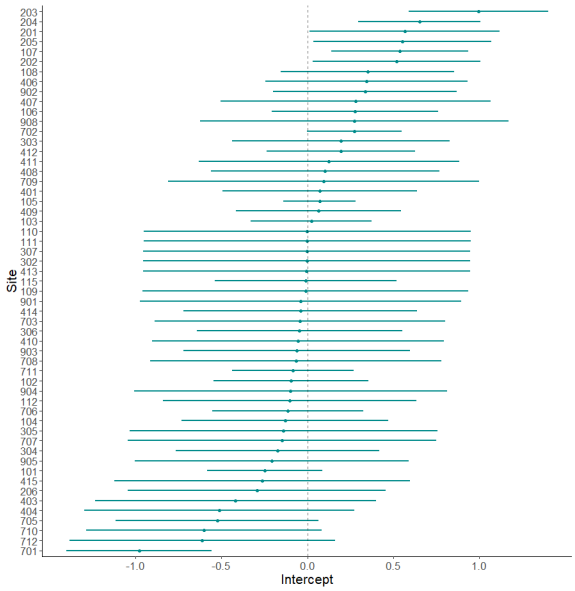


Figure 3.3: Caterpillar plot of site random intercepts and standard errors from model (3.2) using the complete cohort

Inclusion of Covariates for Time

Since including a covariate for time significantly improved model (3.1), we explore the effect of accounting for time in model (3.2) by considering two different scenarios. In the first model, we add the same indicator variable for study cohort as described in the previous section. The results from the analysis of this model with study cohort are in Table 3.8. Once again, this model obtained a smaller AIC (4447.2) than the corresponding two-level model without the covariate for study cohort (4502.8). Furthermore, accounting for study cohort in the model which includes a random intercept for site achieved a smaller AIC than the corresponding fixed effects model which includes study cohort (4466.9).

We also consider a model which includes a covariate for the date of patient ED visit. The results from this analysis are in Table A.4. As with the previous model, the inclusion of time in the model decreases the corresponding AIC value compared to the two-level mixed effects model without a time covariate.

Likelihood ratio tests are performed to examine the efficiency of these two models which include time. These results indicate that including the two variables for time improve efficiency over the two-level model without it.

Random Effect for Province

We have considered a number of two-level models which include a random intercept for ED sites. We now conduct similar analyses utilizing the two-level model defined in equation (3.1), however we include a random intercept for province rather than site. We also consider the scenarios which include a time related covariate for study cohort and for ED visit date. These results are summarized in Tables A.6 - A.8.

The results from these model indicate the two-level models with random effects for province are less efficient than the corresponding model which considers a random effect for site. The AIC values for the model with no time covariate (4520.0), the study cohort covariate (4455.7), and a variable for ED visit date (4452.9) are larger when province is considered than the corresponding models with a random effect for site.

3.3.3 Three-Level Model: Random Effects for Site and Province

The data considered in this analysis has three levels: ED visits are nested within different sites, and each ED is within a particular province. A generalized linear mixed effects model with the logit link is used to investigate whether random intercepts for site and province should be included. This model is written as

$$\text{logit}\left\{P\left(Y_{ijk}=1|b_{0jk}^{(2)},b_{0k}^{(3)},\mathbf{X}_{ijk}\right)\right\}=\mathbf{X}_{ijk}\boldsymbol{\beta}+b_{0jk}^{(2)}+b_{0k}^{(3)}, \tag{3.3}$$

where $\boldsymbol{\beta}$ and $\mathbf{X}$ are defined similarly to those in (3.1). In this case, visit i takes place at ED site j ($j=1,\ldots,55$) in province k ($k=1,\ldots,7$). Under this model, i, j and k denote the

Table 3.8: Results for multilevel regression model (3.2) with a random intercept for site and added covariate for study cohort

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.744	0.272	< 2e-16	*
Age	0.339	0.048	< 0.000	*
Sex (vs. female)				
Male	0.214	0.091	0.019	*
Pregnant	0.874	0.325	0.007	*
Arrival mode (vs. ambulance/police)				
Self	-0.258	0.096	0.007	*
Respiratory distress	0.559	0.105	< 0.000	*
Chronic kidney disease or dialysis	0.685	0.208	0.001	*
Arrival respiratory rate	0.197	0.027	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.077	0.241	0.751	
$> 37.5°C$	0.498	0.248	0.045	*
Oxygen required in ED	2.189	0.114	< 2e-16	*
Medication administered in ED	1.387	0.103	< 2e-16	*
Study cohort (vs. early cohort)				
Late cohort	-0.939	0.129	< 0.000	*

Random Effects	**Var. Estimate**
Site (Intercept)	0.179

AIC: 4447.2

*, variable is significant at $\alpha = 0.05$

Table 3.9: Results for multilevel regression model (3.3) with random intercepts for site and province

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.967	0.297	< 2e-16	*
Age	0.312	0.047	< 0.000	*
Sex (vs. female)				
Male	0.228	0.091	0.012	*
Pregnant	0.774	0.325	0.017	*
Arrival mode (vs. ambulance/police)				
Self	-0.305	0.096	0.001	*
Respiratory distress	0.596	0.106	< 0.000	*
Chronic kidney disease or dialysis	0.611	0.207	0.003	*
Arrival respiratory rate	0.204	0.026	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.109	0.240	0.649	
$> 37.5°C$	0.576	0.248	0.020	*
Oxygen required in ED	2.270	0.114	< 2e-16	*
Medication administered in ED	1.325	0.102	< 2e-16	*
Random Effects	**Var. Estimate**			
Site : Province (Intercept)	0.134			
Province (Intercept)	0.093			
AIC: 4499.3				

*, variable is significant at $\alpha = 0.05$

level one, two and three units. This model has a random intercept term for site as well as one for province, which are denoted by $b_{0jk}^{(2)}$ and $b_{0k}^{(3)}$, respectively. Once again, we assume Y_{ijk} are independent and follow a Bernoulli distribution, conditional on the random effects $b_{0jk}^{(2)}$ and $b_{0k}^{(3)}$. We also assume these random effects are independent from one another, and that $b_{0jk}^{(2)} \sim N(0, \sigma_{(2)}^2)$ and $b_{0k}^{(3)} \sim N(0, \sigma_{(3)}^2)$. The term $b_{0jk}^{(2)}$ remains constant for each visit at site j within province k, and $b_{0k}^{(3)}$ is constant across all visits within province k.

The variables chosen through model selection for the fixed effects logistic regression model are also considered the final variables for this model. Table 3.9 summarizes the results from this analysis. The inclusion of a random effect for province further reduced the AIC compared to our initial two-level model. Once again, accounting for the potential heterogeneity across provinces proves to be advantageous. As anticipated, there is some variability among both ED sites and provinces, estimated to be 0.134 and 0.093, respectively. The caterpillar plots in Figure 3.4, which display the random intercepts across sites and provinces, visualize the higher variability across sites over provinces.

The effects of a selection of predictors on the conditional probability of a patient experiencing the event from model (3.3) can be seen in Figure 3.5. These plots are obtained

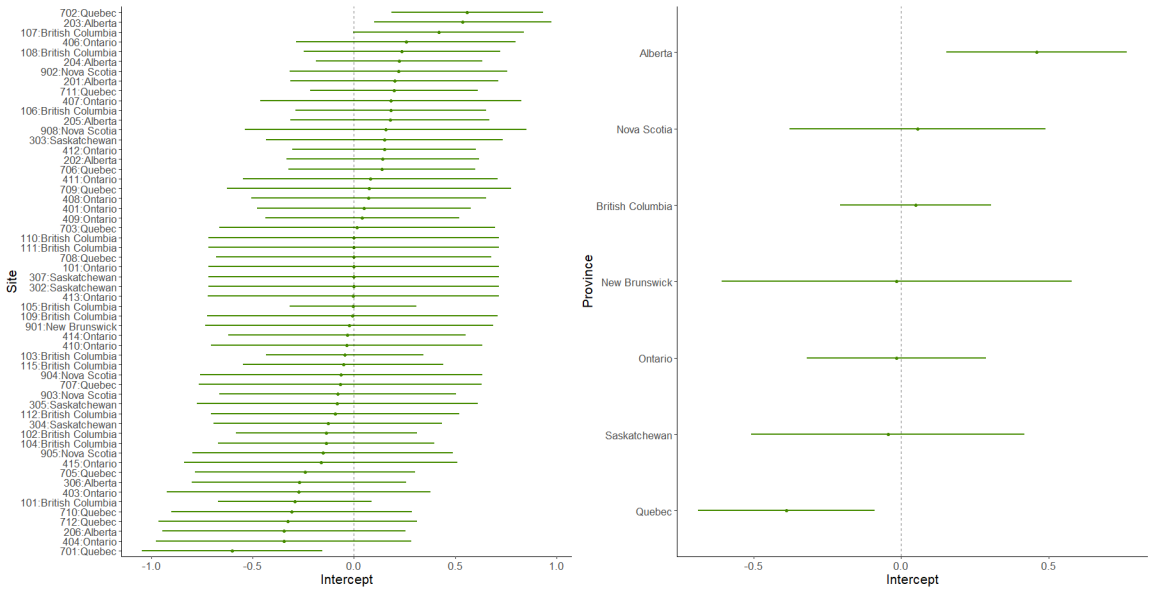


Figure 3.4: Caterpillar plots of random intercepts and standard errors for sites and provinces from model (3.3) using the complete cohort

using the effects package (Fox & Weisberg, 2019). Each plot includes 95% point-wise confidence intervals for the fitted effects, with bands for continuous predictors and error bars for categorical predictors (Fox & Weisberg, 2018). These plots confirm our findings from the descriptive analyses performed earlier. For example, the effect plot for patient age indicates older patients have a higher probability of experiencing the event of interest than younger patients.

Inclusion of Covariates for Time

We take this model one step further, and once again add a covariate which indicates the study cohort the ED visit occurred in. A summary of the results from this analysis are in Table 3.10. As expected, this model is a better fit to the data with an AIC of 4445.1, while the AIC for the three-level model without the time covariate is 4499.3.

We also conduct an analysis while including a covariate for ED visit date in model (3.3). As we saw with the one- and two- level models defined previously, the inclusion of this covariate increases model fit and the results are in Table A.5. In this case, the model obtained an AIC of 4441.4, which is once again very similar to the model which considered study cohort rather than Julian time.

These conclusions are confirmed by likelihood ratio tests. Both models which account for time have significant improvements over and are more efficient than the three-level model which ignores time.

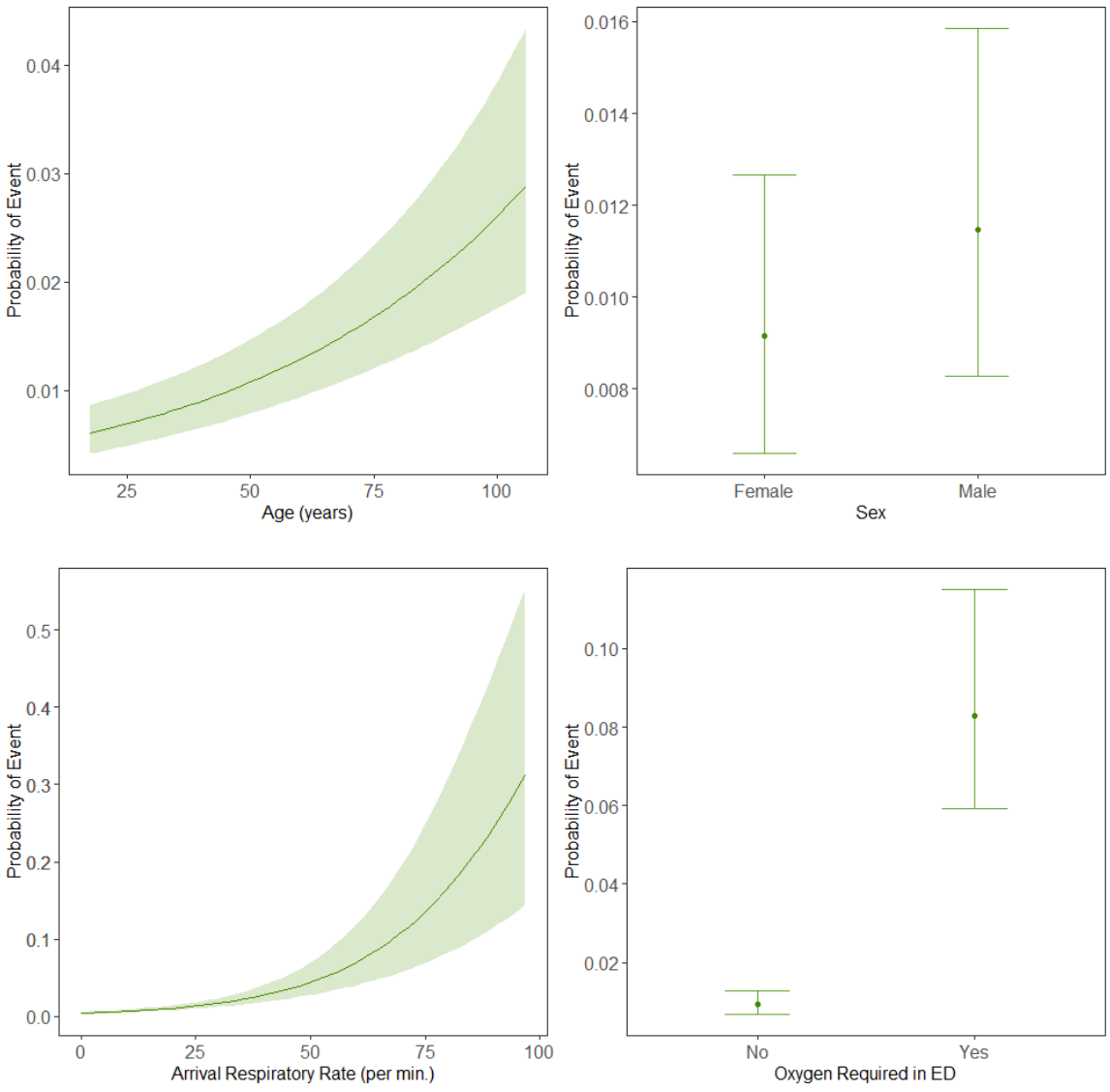


Figure 3.5: Effect plots for age, sex, arrival respiratory rate, and oxygen requirement in the ED using model (3.3) with the complete cohort

Table 3.10: Results for multilevel regression model (3.3) with random intercepts for site and province, and added covariate for study cohort

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.719	0.290	< 2e-16	*
Age	0.343	0.048	< 0.000	*
Sex (vs. female)				
Male	0.213	0.091	0.020	*
Pregnant	0.880	0.324	0.007	*
Arrival mode (vs. ambulance/police)				
Self	-0.260	0.096	0.007	*
Respiratory distress	0.542	0.105	< 0.000	*
Chronic kidney disease or dialysis	0.678	0.208	0.001	*
Arrival respiratory rate	0.197	0.027	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.103	0.241	0.668	
$> 37.5°C$	0.537	0.248	0.031	*
Oxygen required in ED	2.205	0.114	< 2e-16	*
Medication administered in ED	1.380	0.103	< 2e-16	*
Study cohort (vs. early cohort)				
Late cohort	-0.927	0.129	< 0.000	*

Random Effects	**Var. Estimate**
Site : Province (Intercept)	0.108
Province (Intercept)	0.068

AIC: 4445.1

*, variable is significant at $\alpha = 0.05$

Early cohort: ED visits from March 1, 2020 - September 8, 2021

Late cohort: ED visits from September 9, 2021 - September 25, 2022

3.3.4 Investigations into Pandemic Waves

The previous regression analyses indicate that accounting for time is beneficial in our models. We considered two different variables for time. The first was an indicator variable which denoted which study cohort the ED visit occurred in. The second variable considered time as a continuous predictor using the date of the ED visit. Both of these predictors proved to be advantageous over the model which did not take time into account at all.

Waves of infection were present as a result of many different factors, including the emerging of new variants as well as changes in human behaviour and attitudes towards the pandemic. We repeat our previous analyses, with the addition of a categorical predictor which denotes the pandemic wave each ED visit occurred in. The pandemic waves are defined the same way as previous CCEDRRN research, as explained previously. The results from this analysis are shown in Table 3.11. These results indicate that accounting for each level of the data and pandemic wave in the model further reduces the corresponding AIC value, illustrating an increase in model efficiency over the model which ignores pandemic wave.

Similar results are obtained using a two-level model with a random effect for province, which can be seen in Table A.9. However, once again, the model with a random effect for province is less efficient than the two-level model which includes a random effect for site. As the two-level model which accounts for heterogeneity across sites is preferred over the corresponding model for province, the remaining analyses in this thesis only consider this scenario. In other words, when referring to the two-level model in the following investigations, we consider the one which has a random effect for site.

3.3.5 Modelling with Interactions

It is reasonable to assume that these variables are interacting with one another to some extent. Based on our previous work, we explore different variable interactions with our three time covariates. To determine which variables to consider for interactions with our time variables, we utilize the effect sizes obtained in our descriptive analysis. We also examine models which include each pairwise interaction with the time variable of interest. We conduct analysis using each of the models discussed previously: fixed effects logistic regression model (one-level model), a multilevel model a random intercept for ED site (two-level model), and a multilevel model with random intercepts for ED site and province (three-level model).

Study Cohort

In the case of study cohort, we investigate its interaction with two variables: respiratory distress and the requirement of oxygen in the ED. These variables are the only two whose interaction with study cohort is statistically significant in the model. The results for each of

the three models with study cohort interactions is in Table 3.12. We reach similar conclusions in terms of model fit when comparing the one-, two-, and three-level models. There is only a small difference in AIC values between the two- and three-level models, and both are much lower than the one-level model. This may indicate that the two-level model is adequate to analyse this data, as the computation time required to model while considering EDs nested within provinces may outweigh the minor benefit in model fit. In fact, a likelihood ratio test comparing these two- and three-level models resulted in a p-value of 0.0580, indicating there is no significant difference between the two models.

ED Visit Date

Next, we study interactions with our continuous time variable. In this context, we consider the interaction of time with respiratory distress, as it is the only statistically significant pairwise interaction. The presence of respiratory distress also has the highest effect size of all variables, with a Cramer's V of 0.22. Thus, we only consider respiratory distress for our investigation into interactions with the continuous time. The results from these models can be found in Table 3.13. Once again, the two-level model appears to be sufficient in terms of modelling efficiency. In this case, the difference between the AIC values for the corresponding two- and three-level models is less than 3. A likelihood ratio test comparing these two models obtained a p-value equal to 0.0371. Considering a significance level of 5%, we conclude there is a significant difference between the two models, however this would not be the case if our significance level decreased to 1%.

Pandemic Wave

Similar to the case considering ED visit date, the only variable which has a significant interaction with pandemic wave is also the presence of respiratory distress. The results from these analyses are summarized in Table 3.14. The two- and three-level models obtained similar AIC values, indicating there may be no major difference in accounting for heterogeneity across provinces in this instance. As the case with the ED visit date interaction, a p-value of 0.0403 was obtained from a likelihood ratio test comparing the two- and three-level models which include an interaction time with pandemic wave. The conclusion made from this test depends on the significance level considered: at the 5% significance level, we conclude there is a significant difference between the two models, and the three-level model is more efficient.

Table 3.11: Results from each model with covariate for pandemic wave

	One-level model		Two-level model		Three-level model	
	Estimate (SE)	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**
Fixed Effects						
Intercept	-4.195 (0.294)	< 2e-16 *	-4.416 (0.311)	< 2e-16 *	-4.356 (0.329)	< 2e-16 *
Age	0.333 (0.049)	< 0.001 *	0.348 (0.049)	< 0.001 *	0.352 (0.049)	< 0.001 *
Sex (vs. female)						
Male	0.217 (0.091)	0.017 *	0.219 (0.091)	0.017 *	0.217 (0.091)	0.017 *
Pregnant	0.908 (0.325)	0.005 *	0.884 (0.327)	0.007 *	0.889 (0.326)	0.006 *
Arrival mode (vs. ambulance/police)						
Self	-0.268 (0.095)	0.005 *	-0.256 (0.096)	0.008 *	-0.259 (0.096)	0.007 *
Respiratory distress	0.585 (0.099)	< 0.001 *	0.531 (0.106)	< 0.001 *	0.514 (0.105)	< 0.001 *
Chronic kidney disease or dialysis	0.701 (0.206)	0.001 *	0.694 (0.209)	0.001 *	0.687 (0.209)	0.001 *
Arrival respiratory rate	0.201 (0.027)	< 0.001 *	0.197 (0.027)	< 0.001 *	0.197 (0.027)	< 0.001 *
Arrival temperature (vs. $< 36°C$)						
$36°C - 37.5°C$	0.012 (0.240)	0.962	0.090 (0.242)	0.709	0.115 (0.242)	0.635
$> 37.5°C$	0.372 (0.245)	0.128	0.502 (0.250)	0.044 *	0.537 (0.249)	0.031 *
Oxygen required in ED	2.011 (0.107)	< 2e-16 *	2.168 (0.115)	< 2e-16 *	2.180 (0.114)	< 2e-16 *
ED medication	1.425 (0.104)	< 2e-16 *	1.433 (0.105)	< 2e-16 *	1.428 (0.105)	< 2e-16 *
Pandemic wave (vs. wave 1)						
Wave 2	-0.387 (0.167)	0.020 *	-0.383 (0.172)	0.026 *	-0.416 (0.172)	0.016 *
Wave 3	-0.272 (0.170)	0.109	-0.311 (0.178)	0.082	-0.330 (0.178)	0.063
Wave 4	-0.964 (0.253)	< 0.001 *	-0.976 (0.261)	< 0.001 *	-0.976 (0.261)	< 0.001 *
Wave 5	-1.365 (0.219)	< 0.001 *	-1.311 (0.228)	< 0.001 *	-1.324 (0.228)	< 0.001 *
Wave 6	-1.694 (0.262)	< 0.001 *	-1.680 (0.271)	< 0.001 *	-1.685 (0.270)	< 0.001 *
Random Effects	**Var. Estimate**		**Var. Estimate**		**Var. Estimate**	
Site : Province (Intercept)	—[b]		0.182		0.100	
Province (Intercept)	—[b]		—[b]		0.072	
	AIC: 4450.3		**AIC: 4432.4**		**AIC: 4429.9**	

*, variable is significant at $\alpha = 0.05$

[b], not applicable for this model

Abbreviations: SE, standard error

Table 3.12: Interactions with study cohort

	One-level model		Two-level model		Three-level model	
	Estimate (SE)	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**
Fixed Effects						
Intercept	-4.522 (0.254)	< 2e-16 *	-4.707 (0.269)	< 2e-16 *	-4.689 (0.285)	< 2e-16 *
Age	0.321 (0.048)	< 0.001 *	0.334 (0.048)	< 0.001 *	0.337 (0.048)	< 0.001 *
Sex (vs. female)						
Male	0.212 (0.091)	0.020 *	0.214 (0.091)	0.019 *	0.212 (0.091)	0.020 *
Pregnant	0.884 (0.323)	0.006 *	0.861 (0.325)	0.008 *	0.869 (0.324)	0.007 *
Arrival mode (vs. ambulance/police)						
Self	-0.264 (0.095)	0.005 *	-0.257 (0.096)	0.007 *	-0.258 (0.096)	0.007 *
Respiratory distress	0.716 (0.104)	< 0.001 *	0.636 (0.111)	< 0.001 *	0.615 (0.110)	< 0.001 *
Chronic kidney disease or dialysis	0.658 (0.208)	0.002 *	0.663 (0.209)	0.002 *	0.657 (0.209)	0.002 *
Arrival respiratory rate	0.200 (0.027)	< 0.001 *	0.197 (0.027)	< 0.001 *	0.198 (0.027)	< 0.001 *
Arrival temperature (vs. < 36°C)						
36°C – 37.5°C	0.000 (0.238)	0.998	0.062 (0.240)	0.797	0.090 (0.240)	0.707
> 37.5°C	0.380 (0.243)	0.118	0.484 (0.247)	0.051 *	0.524 (0.248)	0.034 *
Oxygen required in ED	1.950 (0.113)	< 2e-16 *	2.091 (0.122)	< 2e-16 *	2.108 (0.122)	< 2e-16 *
ED medication	1.377 (0.102)	< 2e-16 *	1.384 (0.103)	< 2e-16 *	1.377 (0.103)	< 2e-16 *
Study cohort (vs. early cohort)						
Late cohort	-1.053 (0.164)	< 0.001 *	-1.034 (0.171)	< 0.001 *	-1.027 (0.171)	< 0.001 *
Interactions						
Respiratory distress : Late cohort	-1.077 (0.320)	0.001 *	-0.764 (0.332)	0.021 *	-0.730 (0.331)	0.027 *
Oxygen in ED : Late cohort	0.788 (0.268)	0.003 *	0.660 (0.271)	0.015 *	0.648 (0.271)	0.017 *
Random Effects	**Var. Estimate**		**Var. Estimate**		**Var. Estimate**	
Site : Province (Intercept)	—[b]		0.150		0.092	
Province (Intercept)	—[b]		—[b]		0.058	
	AIC: 4456.4		**AIC: 4443.2**		**AIC: 4441.4**	

*, variable is significant at $\alpha = 0.05$

[b], not applicable for this model

Abbreviations: SE, standard error

Table 3.13: Interactions with ED visit date

	One-level model			Two-level model			Three-level model		
	Estimate (SE)	**Pr(>|z|)**		**Estimate (SE)**	**Pr(>|z|)**		**Estimate (SE)**	**Pr(>|z|)**	
Fixed Effects									
Intercept	-4.850 (0.257)	< 2e-16	*	-5.066 (0.275)	< 2e-16	*	-5.039 (0.292)	< 2e-16	*
Age	0.296 (0.047)	< 0.001	*	0.312 (0.048)	< 0.001	*	0.315 (0.048)	< 0.001	*
Sex (vs. female)									
Male	0.234 (0.091)	0.010	*	0.233 (0.091)	0.011	*	0.230 (0.091)	0.012	*
Pregnant	0.884 (0.324)	0.006	*	0.860 (0.327)	0.008	*	0.868 (0.326)	0.008	*
Arrival mode (vs. ambulance/police)									
Self	-0.305 (0.095)	0.001	*	-0.290 (0.096)	0.002	*	-0.292 (0.096)	0.002	*
Respiratory Distress	0.500 (0.110)	< 0.001	*	0.462 (0.118)	< 0.001	*	0.453 (0.117)	< 0.001	*
Chronic kidney disease or dialysis	0.690 (0.207)	0.001	*	0.689 (0.209)	0.001	*	0.685 (0.209)	0.001	*
Arrival respiratory rate	0.201 (0.027)	< 0.001	*	0.198 (0.027)	< 0.001	*	0.198 (0.027)	< 0.001	*
Arrival temperature (vs. < 36°C)									
36°C – 37.5°C	0.007 (0.240)	0.975		0.068 (0.242)	0.779		0.093 (0.242)	0.702	
> 37.5°C	0.397 (0.245)	0.105		0.495 (0.249)	0.047	*	0.532 (0.250)	0.033	*
Oxygen required in ED	2.075 (0.107)	< 2e-16	*	2.218 (0.114)	< 2e-16	*	2.230 (0.114)	< 2e-16	*
ED medication	1.479 (0.104)	< 2e-16	*	1.484 (0.104)	< 2e-16	*	1.477 (0.104)	< 2e-16	*
ED visit date	-0.362 (0.059)	< 0.001	*	-0.376 (0.064)	< 0.001	*	-0.376 (0.064)	< 0.001	*
Interactions									
Respiratory distress : ED visit date	-0.333 (0.116)	0.004	*	-0.257 (0.123)	0.037	*	-0.248 (0.123)	0.044	*
Random Effects	**Var. Estimate**			**Var. Estimate**			**Var. Estimate**		
Site : Province (Intercept)	—[b]			0.192			0.112		
Province (Intercept)	—[b]			—[b]			0.068		
	AIC: 4462.3			**AIC: 4441.7**			**AIC: 4439.3**		

*, variable is significant at $\alpha = 0.05$

[b], not applicable for this model

Abbreviations: SE, standard error

Table 3.14: Interactions with pandemic wave

	One-level model		Two-level model		Three-level model	
	Estimate (SE)	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**
Fixed Effects						
Intercept	-4.394 (0.318)	< 2e-16 *	-4.596 (0.333)	< 2e-16 *	-4.538 (0.349)	< 2e-16 *
Age	0.334 (0.049)	0.000 *	0.347 (0.049)	<0.001 *	0.351 (0.049)	< 0.001 *
Sex (vs. female)						
Male	0.220 (0.091)	0.016 *	0.220 (0.092)	0.016 *	0.219 (0.092)	0.017 *
Pregnant	0.928 (0.323)	0.004 *	0.906 (0.325)	0.005 *	0.912 (0.324)	0.005 *
Arrival mode (vs. ambulance/police)						
Self	-0.276 (0.095)	0.004 *	-0.259 (0.096)	0.007 *	-0.262 (0.096)	0.006 *
Respiratory distress	1.130 (0.308)	0.000 *	1.057 (0.316)	0.001 *	1.031 (0.315)	0.001 *
Chronic kidney disease or dialysis	0.707 (0.207)	0.001 *	0.701 (0.209)	0.001 *	0.694 (0.209)	0.001 *
Arrival respiratory rate	0.199 (0.027)	0.000 *	0.197 (0.027)	<0.001 *	0.197 (0.027)	< 0.001 *
Arrival temperature (vs. < 36°C)						
36°C – 37.5°C	0.014 (0.240)	0.953	0.085 (0.243)	0.726	0.111 (0.243)	0.646
> 37.5°C	0.382 (0.245)	0.119	0.503 (0.250)	0.045 *	0.540 (0.250)	0.031 *
Oxygen required in ED	2.036 (0.108)	< 2e-16 *	2.177 (0.115)	< 2e-16 *	2.189 (0.115)	< 2e-16 *
ED medication	1.446 (0.105)	< 2e-16 *	1.452 (0.105)	< 2e-16 *	1.446 (0.105)	< 2e-16 *
Pandemic wave (vs. wave 1)						
Wave 2	-0.274 (0.213)	0.198	-0.262 (0.218)	0.230	-0.297 (0.218)	0.173
Wave 3	-0.024 (0.217)	0.912	-0.051 (0.224)	0.819	-0.075 (0.224)	0.739
Wave 4	-0.753 (0.309)	0.015 *	-0.787 (0.318)	0.013 *	-0.794 (0.318)	0.012 *
Wave 5	-0.994 (0.258)	0.000 *	-1.010 (0.267)	<0.001 *	-1.030 (0.267)	< 0.001 *
Wave 6	-1.459 (0.308)	0.000 *	-1.508 (0.317)	<0.001 *	-1.521 (0.315)	< 0.001 *
Interactions						
Respiratory distress : Wave 2	-0.342 (0.343)	0.319	-0.359 (0.348)	0.301	-0.355 (0.347)	0.306
Respiratory distress : Wave 3	-0.717 (0.343)	0.036 *	-0.730 (0.349)	0.037 *	-0.718 (0.348)	0.039 *
Respiratory distress : Wave 4	-0.677 (0.529)	0.201	-0.590 (0.539)	0.274	-0.571 (0.538)	0.289
Respiratory distress : Wave 5	-1.368 (0.502)	0.006 *	-1.139 (0.516)	0.027 *	-1.107 (0.516)	0.032 *
Respiratory distress : Wave 6	-0.804 (0.602)	0.181	-0.539 (0.617)	0.382	-0.502 (0.614)	0.414
Random Effects	**Var. Estimate**		**Var. Estimate**		**Var. Estimate**	
Site : Province (Intercept)	—[b]		0.167		0.092	
Province (Intercept)	—[b]		—[b]		0.066	
	AIC: 4449.1		**AIC: 4434.4**		**AIC: 4432.2**	

*, variable is significant at $\alpha = 0.05$

[b], not applicable for this model

Abbreviations: SE, standard error

3.3.6 Comparison to the CCEDRRN COVID Discharge Score

One of the motivating factors behind this project is to examine whether a modelling procedure which accounts for heterogeneity across levels outperforms the standard approach used by Brooks et al. (2022) to derive the CCDS. In order to investigate this further, we model the early cohort data using fixed effects logistic regression models as well as multilevel models and compare the results.

As mentioned previously, the CCDS was derived using data collected by CCEDRRN from March 1, 2020 - September 8, 2022. Therefore, the CCDS was derived in the midst of the pandemic and the inclusion of a covariate for time was unrealistic. While our analyses indicate that accounting for time greatly increases the adequacy of the model, in order to provide a more reasonable comparison between the modelling procedures in the two study periods we consider our model which excludes a covariate for time.

To complete the analysis, participating sites in the early cohort were split into derivation and validation sets. The sites were assigned randomly to a set, with approximately 75% of eligible patients and outcomes assigned to the derivation set, while the remaining 25% were assigned to the validation set. This closely follows the method used by Brooks et al. (2022). Using the derivation set, we include the 10 final predictors from our initial model and consider three different modelling procedures: a fixed effects logistic regression model, a two-level model (with a random intercept for site), and a three-level model (with random intercepts for site and province).

Our two- and three-level regression models, which account for clustering present within EDs or within EDs and provinces, respectively, both outperformed the fixed effects logistic regression model which ignores any clustering. These results are shown in Table 3.15. Just as we saw using the complete cohort, the two- and three-level models both outperform the one-level model, evident through smaller AIC values. Figures 3.6 and 3.7 illustrate the variation among the random intercepts from the two- and three-level regression models, respectively. The caterpillar plot in Figure 3.6 shows the range of random intercepts across sites, obtained from model (3.2). While the values of these intercepts are fairly small, they do differ between sites. A similar interpretation can be made upon review of Figure 3.7, which visualizes the random intercepts for site as well as province, estimated using model (3.3).

We also use likelihood ratio tests to assess if these models are statistically significantly different from one another. Once again, both multilevel models are significantly different than the single level model, as the two pairwise likelihood ratio tests obtained p-values <0.0001. Furthermore, the likelihood ratio test comparing the two multilevel models determined that these two models do not differ significantly, with a p-value of 0.3010. These likelihood ratio tests are summarized in Table 3.16.

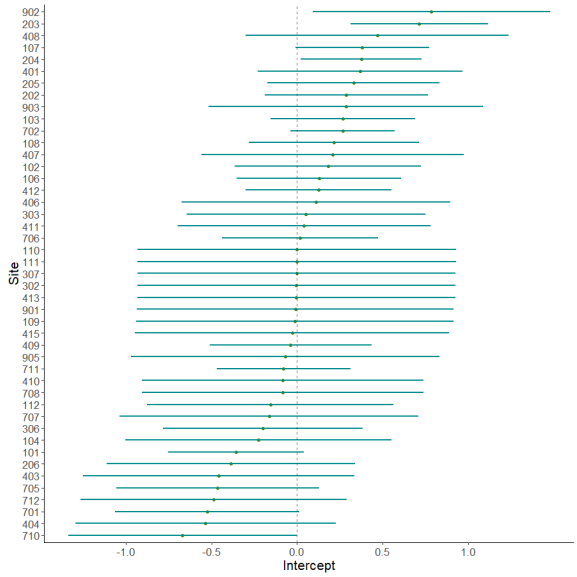


Figure 3.6: Caterpillar plot of site random intercepts and standard errors from model (3.2) using the derivation set from the early study cohort

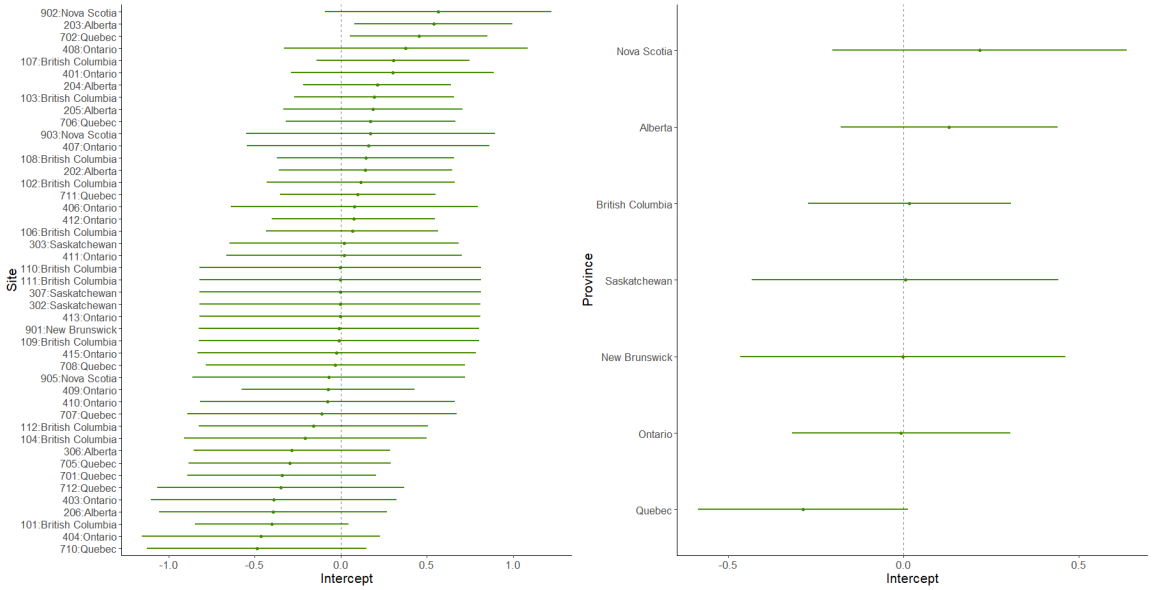


Figure 3.7: Caterpillar plots of random intercepts and standard errors for sites and provinces from model (3.3) using the derivation set from the early study cohort

Table 3.15: Regression analysis results using the derivation set from the early study cohort

	One-level model		Two-level model		Three-level model	
	Estimate (SE)	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**	**Estimate (SE)**	**Pr(>|z|)**
Fixed Effects						
Intercept	-4.638 (0.313)	< 2e-16 *	-4.875 (0.335)	< 2e-16 *	-4.830 (0.351)	< 2e-16 *
Age	0.281 (0.058)	< 0.001 *	0.296 (0.058)	< 0.001 *	0.299 (0.058)	< 0.001 *
Sex (vs. female)						
Male	0.144 (0.113)	0.202	0.151 (0.113)	0.182	0.149 (0.113)	0.186
Pregnant	0.868 (0.417)	0.037 *	0.830 (0.420)	0.048 *	0.832 (0.419)	0.047 *
Arrival mode (vs. ambulance/police)						
Self	-0.314 (0.118)	0.008 *	-0.292 (0.119)	0.014 *	-0.293 (0.119)	0.014 *
Respiratory distress	0.732 (0.119)	< 0.001 *	0.642 (0.130)	< 0.001 *	0.630 (0.129)	< 0.001 *
Chronic kidney disease or dialysis	0.913 (0.279)	0.001 *	0.933 (0.281)	0.001 *	0.930 (0.281)	0.001 *
Arrival respiratory rate	0.236 (0.035)	< 0.001 *	0.239 (0.036)	< 0.001 *	0.239 (0.036)	< 0.001 *
Arrival temperature (vs. $< 36°C$)						
$36°C - 37.5°C$	0.198 (0.294)	0.501	0.261 (0.296)	0.377	0.275 (0.295)	0.353
$> 37.5°C$	0.445 (0.302)	0.140	0.547 (0.306)	0.074	0.566 (0.307)	0.065
Oxygen required in ED	1.818 (0.131)	< 2e-16 *	2.000 (0.144)	< 2e-16 *	2.012 (0.144)	< 2e-16 *
ED medication	1.617 (0.124)	< 2e-16 *	1.624 (0.125)	< 2e-16 *	1.620 (0.125)	< 2e-16 *
Random Effects	**Var. Estimate**		**Var. Estimate**		**Var. Estimate**	
Site : province (Intercept)	—[b]		0.226		0.174	
Province (Intercept)	—[b]		—[b]		0.056	
	AIC: 2795.6		**AIC: 2782.2**		**AIC: 2783.1**	
	AUC: 0.8723		**AUC: 0.8738**		**AUC: 0.8757**	

*, variable is significant at $\alpha = 0.05$

[b], not applicable for this model

Abbreviations: SE, standard error; AUC, area under the receiver operating characteristic (ROC) curve

Table 3.16: P-values from likelihood ratio tests for model comparison using the derivation set from the early study cohort

	Corresponding Model	
	One-Level	Two-Level[a]
No Time Covariate (Early Cohort)		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.3010

[a], with site random effects

Using the validation set, we also obtain the area under the receiver operating characteristic curve (AUC) for these three models. Each of the models considered using the early cohort obtained an AUC of approximately 0.87, compared to the 0.70 AUC obtained in the derivation of the CCDS. This indicates that the models described here may be more efficient than the one utilized for the CCDS. The receiver operating characteristic (ROC) curve with the AUC for our three-level model with the early cohort is shown in Figure 3.8. The 95% confidence intervals for the specificity at different sensitivities are also included in this plot. These are obtained using marginal calculations, resulting in similar curves for the one- and two-level models. Thus, the one- and two-level model curves are omitted. The ROC curves, AUC values and confidence intervals are obtained using the pROC package (Robin et al., 2011) in R.

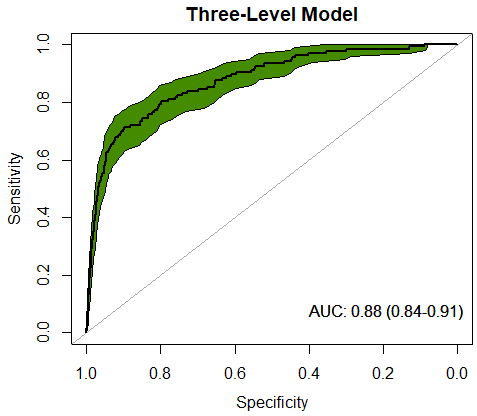


Figure 3.8: Receiver operating characteristic curve with area under the curve and corresponding 95% confidence intervals

There are two key differences between our models and the model used to derive the CCDS. While the two models include the same seven predictors, our models include three additional predictors. Our two- and three-level models also incorporate random effects to account for the clustering present across EDs and provinces. The analysis of the early cohort with multilevel data reveals that including these variables as well as accounting for the clustering of EDs nested within provinces improves the model efficiency. The early

Table 3.17: Summary of AIC values from each model using the complete cohort

	One-Level	Two-Level[a]	Three-Level
Time Covariate			
Excluded	4545.2	4502.8	4499.3
Study Cohort	4466.9	4447.2	4445.1
ED Visit Date	4468.6	4444.0	4441.4
Pandemic Wave	4450.3	4432.4	4429.9
Interactions			
Study Cohort[b]	4456.4	4443.2	4441.4
ED Visit Date[c]	4462.3	4441.7	4439.3
Pandemic Wave[d]	4449.1	4434.4	4432.2

[a], with site random effects

[b], study cohort interactions with respiratory distress and oxygen in ED

[c], ED visit date interactions with respiratory distress

[d], pandemic wave interactions with respiratory distress

cohort consists of ED visits within the same time period as Brooks et al. (2022) study, indicating that using a multilevel model in their study could have potentially improved the performance of the CCDS.

3.4 Summary

Overall, this analysis indicates that including a covariate which accounted for the timeframe the ED visit occurred in creates a more efficient model. The increase in model efficiency is clear when comparing AIC values for each model, and a summary of the AIC values for each model considered in this section is found in Table 3.17. In particular, the table compares results from models with and without the time covariate. Likelihood ratio tests were also utilized to evaluate model efficiency, and a summary of these results from the complete cohort are in Table 3.18.

The analysis also illustrates that including random intercepts for site is beneficial. The addition of a random intercept for province does not consistently increase the model efficiency as much as anticipated, as the AIC from this model is only slightly smaller than the AIC from the two-level model. Likelihood ratio tests confirm these findings depending on the significance level considered. Comparisons between the two- and three-level models in each scenario using the complete cohort obtained a p-value smaller than 0.05, but larger than 0.01. In other words, the inclusion of random intercepts for site may be sufficient in modelling this data; each of the three-level models indicate less heterogeneity across provinces than ED sites.

While the model with the lowest AIC overall is the one which incorporates all three levels of the data as well as a variable for pandemic wave, we compared the two study cohorts

using the model which excludes a time variable. The CCDS was derived to ease decision making during the pandemic, therefore accounting for time in the model was unfeasible. The results from this analysis reveal there was a higher amount of variability between both provinces and EDs in the early cohort compared to the late cohort. It is also evident that at the time of the early cohort, when the CCDS was being derived, it would have been beneficial to utilize multilevel modelling to account for heterogeneity present across the levels in the CCEDRRN data, evident through higher AUC values.

Table 3.18: P-values from likelihood ratio tests for model comparison from the complete cohort

	Corresponding Model	
	One-Level	**Two-Level**[a]
No Time Covariate		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0187
Time Covariate: Study Cohort		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0445
Time Covariate: ED Visit Date		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0313
Time Covariate: Pandemic Wave		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0331
Interaction with Study Cohort[b]		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0580
Interaction with ED Visit Date[c]		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0371
Interaction with Pandemic Wave[d]		
One-level	—	—
Two-level[a]	< 0.0001	—
Three-level	< 0.0001	0.0403

[a], with site random effects
[b], study cohort interactions with respiratory distress and oxygen in ED
[c], ED visit date interactions with respiratory distress
[d], pandemic wave interactions with respiratory distress

Chapter 4

Discussion

4.1 Project Summary

The COVID-19 pandemic brought to light a number of complexities encountered by scientists, physicians and researchers when making decisions in an environment which is rapidly changing. One of these complications occurs when faced with multilevel data, which is very common in many fields in addition to healthcare. One example is multisite data collected across Canada throughout the pandemic. This data includes information from different emergency departments, which are nested within provinces. Just as provinces likely have different standards of practice and populations, the same may be true for EDs within a province. Using methods which account for this heterogeneity may provide more reasonable conclusions than methods which do not consider the variation.

We explored the data collected by CCEDRRN to investigate whether accounting for heterogeneity across the levels present in the data is influential. This included thorough descriptive analyses of both patient visits to the ED as well as any patient visits which resulted in our event of interest: admission to the ED or in-hospital death within 72 hours of being discharged from the ED. We looked for any significant changes in trend in terms of ED and province, as well as any changes over time. We considered three different time variables: study cohort, the date of the ED visit, as well as the pandemic wave the visit occurred in. Our analysis found that there were differences in a number of patient characteristics across the country as well as over time. Rather than simply using descriptive statistics to evaluate any changes in trends across the country and over time, we investigated these features in more detail through the use of multilevel regression models.

We conducted a number of regression analyses using fixed effects and multilevel regression models. These multilevel models included a random intercept for ED to account for any major differences across sites. We also explored multilevel models which had random intercepts for EDs and for province. The inclusion of these random effects further account for any heterogeneity which may be present across EDs as well as across provinces. While accounting for this heterogeneity through the use of multilevel regression models resulted in

smaller AIC values, likelihood ratio tests confirmed our initial speculations that considering this heterogeneity is beneficial.

We also compared our results to those obtained by Brooks et al. (2022) for the derivation of the CCDS. The models considered the same initial candidate predictors, however after the pandemic progressed, an additional three variables are selected for the final model. We found that the use of our models may have improved model fit compared to the one utilized to derive the CCDS: the AUC confirmed these findings.

4.2 Final Remarks and Future Investigations

The thorough investigations in this project revealed a number of potential areas for future research. A non-exhaustive list of these topics is summarized below. This methodology and research could assist in modelling and evaluating clinical assessment and practice when faced with future pandemics.

4.2.1 Time

The temporal analysis summarized in Section 2.3.2 found that there were in fact statistically significant differences in a number of covariates as time progressed. Including a covariate which accounts for time may provide more meaningful conclusions. The inclusion of a covariate for time could help to describe the evolution of the disease over time, and also provide insights into the implementation of different public health measures as time progressed. Our analyses consider time as a linear predictor, however this may not be the most appropriate implementation of the variable. Further analysis could also be performed to investigate the inclusion of a non-linear time covariate.

We conducted analyses with covariates for the time period an ED visit occurred in, a continuous variable for ED visit date, as well as a variable which indicates the pandemic wave at the time of the ED visit, however time could also be defined a uniformly distributed variable. We recognize this may not be feasible in the derivation of clinical decision rules, which are being established in real time. In this case, the rule may be adjusted with the introduction of new variants as the pandemic evolved.

4.2.2 Additional Predictors

Our analysis uses the same candidate predictors as those considered by Brooks et al. (2022) for the CCDS. However, there are a number of other variables available in the CCEDRRN dataset, including patient race and ethnic group. The inclusion of the additional predictors collected by CCEDRRN may strengthen these models.

4.2.3 Data Entry Error

Upon final review of this project, we found that an error was made upon data entry. Specifically, the issue is with one ED visit which was recorded as occurring at site 101. This site is located in British Columbia, however the visit was documented as occurring in Ontario. Once this data entry error is resolved, likely through omission of this particular ED visit, the analyses run in this project could be performed again. While it may be reasonable to assume this one visit would not have a significant impact on the results discussed in this project, it would be relatively straightforward as we have everything required to run the analysis again.

4.2.4 Derivation of a Clinical Decision Rule

In the future, a clinical decision rule could be developed using one of the models defined in this paper. This could then be compared to the rule established using the standard approach by Brooks et al. (2022) to further evaluate the extent to which the two methods differ.

4.2.5 Correlated Random Effects

Our analysis assumes the site and province random effects are independent from one another. However, this assumption may be unrealistic. Exploring correlated random effects in these models may provide more practical results.

4.2.6 Geographical Location

Our spatial analysis in Section 2.3.1 obtained results which supported statistically significant differences among the seven provinces considered in this study. Provinces faced different severities of the disease at different times. They also implemented public health measures differently and investigating this further may be worthwhile. Furthermore, there may also be regions within a province which could be seen as more similar compared to the rest of the province, such as cities. Exploration into the trends within these regions may be worth considering as well. This analysis may involve the inclusion of weights for provinces based on population size, or even a simple covariate which accounts for geographical location.

4.2.7 Bias in Multilevel Models

The covariates explored in our models may be correlated with the random effects. If random effects are not independent from model covariates, resulting coefficient estimates may be biased. This potential bias is worthy of future investigation to determine the extent of any bias present in our models. In this case, the use of fixed effects models may be more suitable (Clark & Linzer, 2015; Kalbfleisch & Wolfe, 2013). Kalbfleisch and Wolfe (2013) discuss these issues and demonstrate the differences in modelling procedures using examples.

4.2.8 Machine Learning Techniques

This thesis explores the efficiency of multilevel regression models. While we utilized generalized linear mixed effects models, future work could adapt the models through the use of machine learning methods.

4.2.9 Simplified Estimation

The estimation procedures for models with binary outcomes are typically fairly complicated, however this is not the case when the response is normally distributed. Implementation of a model which has more straightforward modelling procedures for binary outcomes could greatly simplify the modelling process.

The results presented in this project do not include standard errors of the variance components for the random effects. Standard errors of these components could provide another measure to indicate how suitable our model estimates are.

4.2.10 Comparison of Sex and Gender

Further interest may lie in exploring any differences in outcomes in terms of patient gender compared to sex. The data used in this project did not contain complete information about patient gender. In fact, there was a considerable amount of missing or undocumented data for this question. The reason for the missing data may be of interest, as a patient may not have answered this question for a number of reasons. This may be due to several reactions to the question, for example did they feel the question was relevant to them, or were they hesitant about any potential repercussions regarding their responses.

4.2.11 Population-Adjusted Analysis

The CCEDRRN data consists of patient information from ED visits across the country, as long as the patient visited an ED which agreed to participate in the study. Unfortunately, this may not truly be a representative sample of our target population. For example, British Columbia had one fewer participating ED compared to Ontario, however, considering the population in 2022, Ontario had about 2.8 times the number of people than British Columbia (Statistics Canada, 2022b).

Approximately 42% of the patient visits in the complete cohort are from British Columbia, while only about 12% are from Ontario. These numbers are consistent with the percentage of patients who were admitted to or died in the hospital within 72 hours of being discharged from a participating ED: 45% visited an ED in British Columbia, and 12% in Ontario. In other words, the two provinces have similar numbers of EDs included in this study, despite the vast differences in population totals. Furthermore, Québec also had a higher population than British Columbia in 2022, although there were less EDs in the study from Québec than British Columbia. The Canadian population and number of participating EDs are broken

Table 4.1: Canadian population in 2022 by participating province

	Population in 2022	Participating EDs	Number of EDs*
Ontario	15,145,006	14	178
Québec	8,672,185	11	115
British Columbia	5,356,284	13	41
Alberta	4,510,891	7	109
Saskatchewan	1,178,422	5	64
Nova Scotia	1,025,445	5	17
New Brunswick	809,568	1	0

*, estimate of the number of EDs is based on information from the National Ambulatory Care Reporting System (NACRS) in 2021/2022 (Canadian Institute for Health Information, 2022)

down by province in Table 4.1. These issues are a limitation to our study, as the sample is non-representative of the population and the number of participating sites in a province is likely not proportional to the total number of sites in that province. This could potentially lead to biased inferences.

Typically, the ultimate goal of modelling is prediction and this could be problematic when it comes time to provide inferences to the Canadian population. In order to do so, future work could involve a population-adjusted analysis to account for these issues.

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Appendix A

Tables

Table A.1: Participating sites

Site	Hospital	Province	Number of visits, n
101	Vancouver General Hospital	BC	1621
102	Lions Gate Hospital	BC	873
103	Saint Paul's Hospital	BC	1680
104	Mount Saint Joseph's	BC	792
105	Surrey Memorial Hospital	BC	4618
106	Royal Columbian Hospital	BC	578
107	Abbotsford Regional Hospital	BC	623
108	Eagle Ridge	BC	360
109	Victoria General Hospital	BC	—*
110	Royal Jubilee Hospital	BC	—*
111	Nanaimo General Hospital	BC	—*
112	Royal Inland Hospital	BC	136
115	Kelowna General Hospital	BC	366
201	University of Alberta Hospital	AB	298
202	Foothills Medical Centre	AB	565
203	Rockyview General Hospital	AB	528
204	Peter Lougheed Centre	AB	1033
205	South Health Campus	AB	492
206	Northeast Community Health Centre	AB	310
302	Regina General Hospital	SK	—*
303	St Paul's Hospital	SK	273
304	Royal University	SK	613
305	Saskatoon City Hospital	SK	48
306	Royal Alexandra Hospital	AB	309
307	Health Sciences Centre and St. Boniface Hospital	MB	—*
401	Sunnybrook	ON	506
403	The Ottawa Hospital - Civic Campus	ON	170
404	The Ottawa Hospital - General Campus	ON	225
406	Kingston General Hospital	ON	341
407	Hamilton General Hospital	ON	80
408	Health Science North	ON	219
409	London Health Sciences Center	ON	498
410	North York General Hospital Toronto [Site Closed]	ON	138

Site	Hospital	Province	Number of visits, n
411	Juravinski Hospital	ON	103
412	Victoria Hospital-LHSC	ON	567
413	Toronto General Hospital	ON	—*
414	Toronto Western Hospital	ON	247
415	Hotel Dieu Hospital	ON	137
701	Hôtel-Dieu de Lévis	QC	937
702	Jewish General Hospital	QC	2448
703	Centre Hospitalier de l'Université Laval (CHU de Québec)	QC	77
705	Royal Victoria Hospital	QC	684
706	Hôpital de l'Enfant-Jésus (CHU de Québec)	QC	674
707	Hôpital du Saint-Sacrement (CHU de Québec)	QC	37
708	Hôpital Saint-François d'Assise (CHU de Québec)	QC	57
709	Hôtel-Dieu de Québec (CHU de Québec)	QC	17
710	IUCPQ	QC	187
711	Hôpital du Sacré-Coeur	QC	1436
712	Montréal General Hospital (MUHC)	QC	222
901	Saint John Regional Hospital	NB	22
902	Halifax Infirmary	NS	498
903	Dartmouth General Hospital	NS	298
904	Hants Community Hospital	NS	54
905	Cobequid Community Health Centre	NS	216
908	Secondary Assessment centers [Site Closed]	NS	17

*, count is less than 5 and is omitted

Abbreviations: AB, Alberta; BC, British Columbia; MB, Manitoba; NB, New Brunswick; NS, Nova Scotia; ON, Ontario; QC, Québec; SK, Saskatchewan; IUCPQ, Institut universitaire de cardiologie et de pneumologie de Québec

Table A.2: P-values from post-hoc analyses using Fisher's test to assess for differences in the number of events per province

	BC	AB	SK	ON	QC	NB	NS
BC	—	—	—	—	—	—	—
AB	0.0981	—	—	—	—	—	—
SK	0.0650	0.0103	—	—	—	—	—
ON	0.9003	0.1640	0.1091	—	—	—	—
QC	0.0363	0.0019*	0.3871	0.1699	—	—	—
NB	1.0000	1.0000	1.0000	1.0000	1.0000	—	—
NS	0.1558	0.0273	0.7341	0.2471	0.7293	1.0000	—

*, p-value < 0.0024

Abbreviations: AB, Alberta; BC, British Columbia; NB, New Brunswick; NS, Nova Scotia; ON, Ontario; QC, Québec; SK, Saskatchewan

Table A.3: Results for fixed effects regression model (3.1) with added covariate for ED visit date

	Estimate	Std. Error	Pr(>|z|)	
Intercept	-4.865	0.257	< 2e-16	*
Age	0.297	0.047	< 0.000	*
Sex (vs. female)				
Male	0.230	0.091	0.012	*
Pregnant	0.882	0.326	0.007	*
Arrival mode (vs. ambulance/police)				
Self	-0.295	0.095	0.002	*
Respiratory distress	0.632	0.099	< 0.000	*
Chronic kidney disease or dialysis	0.686	0.207	0.001	*
Arrival respiratory rate	0.202	0.027	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.008	0.240	0.972	
$> 37.5°C$	0.393	0.244	0.108	
Oxygen required in ED	2.049	0.107	< 2e-16	*
Medication administered in ED	1.459	0.103	< 2e-16	*
ED visit date	-0.448	0.052	< 2e-16	*

AIC: 4468.6

*, variable is significant at $\alpha = 0.05$

Table A.4: Results for multilevel regression model (3.2) with a random intercept for site and added covariate for ED visit date

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-5.092	0.275	< 2e-16	*
Age	0.315	0.048	< 0.000	*
Sex (vs. female)				
Male	0.230	0.091	0.012	*
Pregnant	0.859	0.328	0.009	*
Arrival mode (vs. ambulance/police)				
Self	-0.283	0.096	0.003	*
Respiratory distress	0.568	0.105	< 0.000	*
Chronic kidney disease or dialysis	0.687	0.209	0.001	*
Arrival respiratory rate	0.197	0.027	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.077	0.242	0.750	
$> 37.5°C$	0.501	0.249	0.044	*
Oxygen required in ED	2.208	0.114	< 2e-16	*
Medication administered in ED	1.469	0.104	< 2e-16	*
ED visit date	-0.438	0.057	< 0.000	*

Random Effects	**Var. Estimate**
Site (Intercept)	0.210

AIC: 4444.0

*, variable is significant at $\alpha = 0.05$

Table A.5: Results for multilevel regression model (3.3) with random intercepts for site and province, and added covariate for ED visit date

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-5.060	0.294	< 2e-16	*
Age	0.318	0.048	< 0.000	*
Sex (vs. female)				
Male	0.227	0.091	0.013	*
Pregnant	0.866	0.327	0.008	*
Arrival mode (vs. ambulance/police)				
Self	-0.286	0.096	0.003	*
Respiratory distress	0.555	0.105	< 0.000	*
Chronic kidney disease or dialysis	0.683	0.209	0.001	*
Arrival respiratory rate	0.198	0.027	< 0.000	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.101	0.242	0.677	
$> 37.5°C$	0.536	0.249	0.031	*
Oxygen required in ED	2.220	0.114	< 2e-16	*
Medication administered in ED	1.462	0.104	< 2e-16	*
ED visit date	-0.436	0.057	< 0.000	*

Random Effects	**Var. Estimate**
Site : Province (Intercept)	0.122
Province (Intercept)	0.076

AIC: 4441.4

*, variable is significant at $\alpha = 0.05$

Table A.6: Results for multilevel regression model (3.2) with a random intercept for province

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.874	0.288	< 2e-16	*
Age	0.307	0.046	< 0.001	*
Sex (vs. female)				
Male	0.228	0.091	0.012	*
Pregnant	0.827	0.322	0.010	*
Arrival mode (vs. ambulance/police)	-0.300	0.095	0.002	*
Self				
Respiratory distress	0.588	0.101	< 0.001	*
Chronic kidney disease or dialysis	0.571	0.206	0.005	*
Arrival respiratory rate	0.197	0.027	< 0.001	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.115	0.242	0.635	
$> 37.5°C$	0.537	0.249	0.031	*
Oxygen required in ED	2.180	0.114	< 2e-16	*
ED medication	1.428	0.105	< 2e-16	*
Random Effects	**Var. Estimate**			
Province (Intercept)	0.091			
AIC: 4520.0				

*, variable is significant at $\alpha = 0.05$

Table A.7: Results for multilevel regression model (3.2) with a random intercept for province and added covariate for study cohort

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.596	0.279	< 2e-16	*
Age	0.339	0.048	< 0.001	*
Sex (vs. female)				
Male	0.211	0.091	0.021	*
Pregnant	0.920	0.323	0.004	*
Arrival mode (vs. ambulance/police)				
Self	-0.260	0.095	0.006	*
Respiratory distress	0.536	0.101	< 0.001	*
Chronic kidney disease or dialysis	0.657	0.207	0.002	*
Arrival respiratory rate	0.200	0.027	< 0.001	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.105	0.240	0.662	
$> 37.5°C$	0.523	0.248	0.035	*
Oxygen required in ED	2.140	0.112	< 2e-16	*
ED medication	1.361	0.102	< 2e-16	*
Study cohort (vs. early cohort)				
Late cohort	-0.953	0.124	< 0.001	*
Random Effects	**Var. Estimate**			
Province (Intercept)	0.059			
AIC: 4455.7				

*, variable is significant at $\alpha = 0.05$

Table A.8: Results for multilevel regression model (3.2) with a random intercept for province and added covariate for ED visit date

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.942	0.280	< 2e-16	*
Age	0.314	0.047	< 0.001	*
Sex (vs. female)				
Male	0.225	0.091	0.013	*
Pregnant	0.909	0.325	0.005	*
Arrival mode (vs. ambulance/police)				
Self	-0.288	0.095	0.002	*
Respiratory distress	0.557	0.101	< 0.001	*
Chronic kidney disease or dialysis	0.662	0.208	0.001	*
Arrival respiratory rate	0.200	0.027	< 0.001	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.108	0.241	0.654	
$> 37.5°C$	0.536	0.248	0.031	*
Oxygen required in ED	2.155	0.111	< 2e-16	*
ED medication	1.441	0.104	< 2e-16	*
ED visit date	-0.446	0.055	< 0.001	*

Random Effects	**Var. Estimate**
Province (Intercept)	0.063

AIC: 4452.9

*, variable is significant at $\alpha = 0.05$

Table A.9: Results for multilevel regression model (3.2) with a random intercept for province and added covariate for pandemic wave

	Estimate	Std. Error	Pr(>|z|)	
Fixed Effects				
Intercept	-4.194	0.316	< 2e-16	*
Age	0.351	0.049	< 0.001	*
Sex (vs. female)				
Male	0.216	0.091	0.018	*
Pregnant	0.923	0.325	0.004	*
Arrival mode (vs. ambulance/police)				
Self	-0.264	0.095	0.006	*
Respiratory distress	0.507	0.102	< 0.001	*
Chronic kidney disease or dialysis	0.671	0.208	0.001	*
Arrival respiratory rate	0.199	0.027	< 0.001	*
Arrival temperature (vs. $< 36°C$)				
$36°C - 37.5°C$	0.112	0.241	0.642	
$> 37.5°C$	0.518	0.248	0.037	*
Oxygen required in ED	2.118	0.112	< 2e-16	*
ED medication	1.412	0.105	< 2e-16	*
Pandemic wave (vs. wave 1)				
Wave 2	-0.482	0.169	0.004	*
Wave 3	-0.355	0.174	0.042	*
Wave 4	-0.999	0.257	< 0.001	*
Wave 5	-1.396	0.222	< 0.001	*
Wave 6	-1.732	0.265	< 0.001	*

Random Effects	**Var. Estimate**
Province (Intercept)	0.064

AIC: 4437.6

*, variable is significant at $\alpha = 0.05$