Characteristics and outcomes of hospitalized and critically ill COVID-19 patients in the first phase of the pandemic in Canada: A National Cohort Study

For the SPRINT-SARI Canada Investigators and the Canadian Critical Care Trials Group

(submitted under a group authorship)

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Word Count: 1992 (excluding abstract, tables and figures)

Corresponding Author:

Srinivas Murthy, MD CM, MHSc

Srinivas.murthy@cw.bc.ca

604-875-2778

4500 Oak Street, Vancouver, BC, V6H 3V4

University of British Columbia

Corresponding author has no competing interests.

Abstract:

Background:

Clinical data on hospitalized patients with COVID-19 provide clinicians and public health officials with information to guide practice and policy.

Methods:

Through a network of hospitals, we report a national cohort study of hospitalized patients with a diagnosis of COVID-19. Descriptive analyses of characteristics, interventions, and outcomes were performed.

Results:

Between January and July 2020, among 811 hospitalized patients across 32 hospitals, the median age was 64 (IQR 52-75) years, 495 were male (61%), 46 (5%) were healthcare workers, 9 (1%) were pregnant, and 26 were under the age of 18 (3%) , with 9 under the age of 5 years (1%). The median time from symptom onset to hospital admission was 7 (IQR 3,10) days. The most common symptoms on admission were fever, shortness of breath, cough, and malaise. Diabetes, cardiac, kidney and respiratory disease were the most common co-morbidities. Among all patients, 328 received care in an ICU, admitted a median of 0 (IQR 0,1) days after hospital admission. Critically ill patients were treated with invasive mechanical ventilation (88%), renal replacement therapy (15%), and extra-corporeal membrane oxygenation (4%); 26% died. Among those receiving mechanical ventilation, 31% died. Age was an influential predictor of mortality (OR per additional year of life, 1.06, 95% CI 1.03-1.09).

Interpretation:

Patients admitted to hospital with COVID-19 commonly had fever, respiratory symptoms and comorbid conditions. Increasing age was associated with the development of critical illness and death; however, the majority of critically ill patients in Canada, including those requiring mechanical ventilation, survived and were discharged from hospital.

Word Count: 249

Introduction

A chief concern over the first months of the COVID-19 pandemic has been the capacity to provide care for acutely ill patients in hospitals and intensive care units (ICUs). The variability in outcomes of patients with COVID-19 internationally has been striking, with some reports describe intensive care unit mortality in ranges between 40 and 90%;[1-3] and systematic reviews including 10,000 patients worldwide reveal a combined ICU mortality of 42%.[4] Acute care features associated with mortality include healthcare resource utilization and availability, supportive care and specific treatment strategies.[5,6]

Canada has had over 10,000 hospitalizations due to COVID-19 and 110,000 confirmed cases as of July 15 2020.[7] These hospitalizations have resulted in health system strain – particularly so in acute care and long-term care homes; however, hospitals and intensive care units have not been overwhelmed to the extent experienced in many other countries,[1,8] perhaps due to public health strategies that have included physical distancing and border closures, effective hospital-based infection prevention and control practices and early cessation of non-emergent care, and luck.

Documenting the numbers and characteristics of COVID-19 patients requiring hospitalization or intensive care admission across Canadian hospitals is vital to facilitate comparison to other health jurisdictions and in preparation for future pandemic waves. We aim to describe a representative population of hospitalized and critically ill patients with COVID-19 and investigate predictors of outcome using a national pre-existing registry to characterize severe acute respiratory infection.[9]

Methods

Study Design

SPRINT-SARI is a global, multi-site observational cohort of patients admitted to hospital with severe acute respiratory infection. Data has been collected in Canada and across the world since 2016, establishing research infrastructure for pandemics to rapidly produce observational data.[10] In January 2020, the case report form was adapted for COVID-19, and has been used, in conjunction with the International Severe Acute Respiratory Consortium (ISARIC) and the World Health Organization (WHO), around the world to describe clinical disease due to COVID-19 across populations and inform policy globally. [11-13] SPRINT-SARI is administered in Canada from Sunnybrook Research Institute with a global data repository coordinated by the University of Oxford, which has over 100,000 patients as of July 2020. Participating Canadian sites were recruited through the Canadian Critical Care Trials Group, and through networks of the research team, and included both pediatric and adult hospitals across the country with both academic and community hospitals. These data from Canadian hospitals are included in global datasets available here.

Participants

The study population included all patients with a confirmed diagnosis of COVID-19 who received care in an intensive care unit (ICU) in study hospitals, and up to the first 60 patients receiving care in any location of the hospital. This sampling strategy was to more comprehensively sample critically ill patients. Data were collected on admission, daily, and upon hospital discharge. Data elements were standardized with global data collection efforts with ISARIC and the WHO to optimize international comparisons. ICUs were defined as per local practice, acknowledging that the capabilities and capacities of ICUs vary across hospitals. Co-morbidities were defined by the treating clinicians as documented in

patient charts. Patients were tested for SARS-CoV-2 according to local practice and treated according to local standards of care. This study was approved by local ethics boards, generally using a waiver of consent given the need to only collect routinely available clinical data, with no need for additional study-specific diagnostic testing.

Analyses

The primary outcome measure was in-hospital mortality censored as of July 7 2020. Secondary outcomes included in-hospital mortality for patients receiving any care in an ICU and for those receiving mechanical ventilation, and duration of ICU and hospital stay. Unadjusted odds ratios for mortality with baseline demographics including age and co-morbidities were calculated by univariate analysis, with no multivariate analysis performed given the size and heterogeneity of the included dataset. Descriptive statistics included frequency analysis (percentages) for categorical variables and means (standard deviation [SD]), or medians (interquartile range [IQR]) for continuous variables depending on data distribution. Data were submitted and checked for errors by manual inspection and electronic range limits. Symptoms were examined for pairwise comparisons. Patients still alive and in-hospital at time of censoring were not included in the outcome assessments. The Kaplan-Meier method was used to depict the probability of survival over the duration of follow-up and to generate survival curves. Estimates for distribution of time-based variables were obtained through a gamma distribution fitted onto the observed data, accounting for unobserved outcomes, with estimation by a maximum likelihood procedure and confidence intervals for the means and variances obtained by bootstrap. Confidence intervals and p values reported reflect a two-tailed α level of 0.05. Statistical analyses were performed in R (Vienna, Austria).[14] We used the STROBE statement to guide research reporting.[15]

Results

From January 24 until July 7 2020, 811 hospitalized patients across 32 hospitals (4 academic pediatric, 13 community, 15 adult academic) were included in the analysis, representing approximately 8% of all hospitalized patients in Canadian (total 10,728).[7] Of these, 328 patients required admission to an intensive care unit, representing approximately 14% of all ICU admissions (total 2,247).[7]

The median age of all patients was 64 (IQR 53-75) years, 495 were male (61%), 9 were pregnant (1.1%), 46 were healthcare workers (5.7%). Twenty-six were under the age of 18 (3.2%), with 9 under the age of 5 years (Table 1), with five children being admitted to ICUs in participating children's hospitals.

Presenting symptoms are described in Figure 1, most commonly fever on admission (74%), shortness of breath (67%), cough (49%), fatigue/malaise (43%), and diarrhea (26%). Mapping symptoms into clusters (Supplemental Figure 1) revealed no clear patterns of symptoms. The median time from symptom onset to hospital admission was 7 days (IQR 3,10). Table 1 shows the most common co-morbidities, including diabetes, hypertension, cardiac, kidney and respiratory disease. Among outpatient medications, 90 (11%) patients were on NSAIDS, 104 (13%) were on ACE-Inhibitors, and 122 (15%) were on angiotensin receptor blockers.

Of patients admitted to the ICU, 59% were on the first day of hospitalization and 76% of patients within the first two days of hospital admission. Supplemental Figure 5 shows the density function of time-to-outcome (death or recovery) in included patients.

The majority of patients received antibiotics (79%) or oxygen (74%). 22% of patients received an antiviral agent, with oseltamivir, lopinavir/ritonavir, hydroxychloroquine, and ribavirin being the four most commonly used; 19% of ward patients and 32% of ICU patients received systemic corticosteroids.

As of July 7th, 166 patients had died (20%). Of the 328 patients admitted to an ICU, 86 (26%) had died, with 20 patients (2.4%) still admitted to hospital as of July 7, 2020. Seven deaths occurred in individuals less than 50, with the youngest death at age 27 (Table 3). Each additional year of age being independently associated with death on univariate analysis (OR 1.06, 95% CI 1.03-1.09). 80 hospitalized patients died without having been admitted to an ICU (48% of all deaths).

Mortality among patients who received invasive mechanical ventilation was 31.2%, 69% among patients receiving ECMO and 46.9 % among those who received renal replacement therapy during their ICU course. Patients who died were also more likely to have comorbidities (Table 3), including hypertension (OR 2.52, 95% CI 1.7-3.78), chronic pulmonary disease (OR 3.11, 95% CI1.93 – 4.99), chronic renal disease (OR 2.31, 95% CI 1.43-3.69), diabetes (OR 2.28, 95% CI 1.5 – 3.45), or a malignant neoplasm (OR 2.31, 95% CI 1.18 – 4.42).

Discussion

We report a large cohort of hospitalized Canadian patients with COVID-19, describing demographics, interventions, and clinical outcomes of patients. The most common presenting symptoms are fever and cough, and the most common co-morbidities hypertension, diabetes, and chronic kidney disease. Patients hospitalized with COVID-19 who received intensive care had a mortality of 26%; substantially lower than in many reports from other regions of the world.[1,16,17]

Among patients admitted to ICU, or those requiring mechanical ventilation, mortality is lower than reported in many other countries in earlier phases of the pandemic.[1,4] The reasons for this difference are not clear, and might reflect differing demographics across studies, the impact of limited capacity for some elements of critical care during periods of greatest COVID-19-related health system stress, differences in admission decisions or treatments, or other factors. The association of worse outcomes with older age has been previously shown; and differences in the ages of published cohorts explaining a high degree of variation in country-based case-fatality rates.[18] We were unable to capture the presence of do-not-resuscitate or withdrawal of life-sustaining therapy orders and patient preferences, which may differ across the lifespan, and their impact on outcomes.

The patterns of comorbid conditions described in Canada are similar to those reported globally and in a regional report from British Columbia.[8 19] The proportion of patients with hypertension reflect Canada-wide population-based disease prevalence estimates (22.6%), while the proportion of patients with diabetes are higher than population-level prevalence (7%), not adjusted for age.[20,21] This could reflect specific associations of co-morbidities with COVID-19, be due to the purposeful oversampling of critically ill patients in this cohort, or, reflect other cohort specific features or sample size.

Fewer than 7% of patients presented without fever, shortness of breath, or fatigue or cough, similar to other cohorts.[17] Standard screening practices focused on respiratory symptoms in hospitals in Canada are likely to remain relevant.

There were few children or pregnant women in this cohort. The small numbers of children are in keeping with findings elsewhere, where severe pediatric disease is relatively rare. Given the small

numbers of both children and pregnant women, we cannot make strong inferences about typical clinical characteristics or outcomes in these populations.[19] Large-scale international collaboration is required for a better understanding of the health effects on these groups.

There has been uncertainty around optimal methods of oxygenation and ventilation support for critically ill patients with COVID-19, including the timing of intubation and mechanical ventilation, and the potential risk to health care workers in using non-invasive ventilation and high flow nasal oxygen, stemming from concern of aerosolization and nosocomial amplification of SARS-CoV-2,[22] which likely has influenced their infrequent use in this cohort. We have not examined the association of specific medication or ventilation treatments with clinical outcomes due to the inability to adequately adjust for confounding, immortal time, and treatment indication bias in observational studies such as this one.

The limitations of this study include the scope and granularity of data collected. Meant to be rapidly deployed, scalable, and operational at sites with varying research infrastructure, we have collected a minimal clinical dataset across Canadian hospitals. This has allowed the program to continue without pre-pandemic funding, minimizing the data collection burden at individual sites. We have not reported laboratory data in this report due to a large degree of missingness in the collected data, limiting analysis. There will be some uncertainty on long-term outcomes, better characterized through population-level studies as a number of patients have not had their final outcome declared or may have died after discharge to a long-term care facility. Symptom characterization was dependent on patient report or clinician charting – for example, the low rate of anosmia is likely in keeping with its lack of recognition early in the pandemic or in patients who were too sick to report it. More in-depth characterization of disease, and of specific sub-groups of patients, will subsequently be possible. The lack of pre-pandemic capacity for this work underscores the need for a national clinical characterization data infrastructure for hospitalized patients, that is rapidly accessible for Canadian clinicians, researchers, public health officials and policymakers to inform understanding of the baseline characteristics, risk factors for outcomes, hospital utilization, and benchmarking disease severity over waves of outbreaks and across different care systems.

In conclusion, we report clinical characteristics and outcomes of 811 hospitalized patients during the first wave of the COVID-19 pandemic in Canada. This data is crucial to maintain and expand during future pandemic waves to understand the impact of COVID-19 on our hospitals, to identify areas for improvements in clinical management, and to allow for ongoing international and temporal comparisons of outcomes for patients with COVID-19.

Acknowledgements:

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Figure Legends

Figure 1: Presenting symptoms seen at admission amongst hospitalized patients with COVID-19.

Figure 2: Presenting co-morbidities at admission amongst hospitalized patients with COVID-19.

Figure 3: Time-to-event analysis for mortality

Supplemental Figure 1: Heatmap for correlation between symptoms, with fill colour being the phi correlation coefficient between each pair of symptoms, calculated amongst patients with recorded presence or absence or both.

Supplemental Figure 2: Length of hospital stay by (A) sex and (B) location

Supplemental Figure 3: Length of hospital stay by age

Supplemental Figure 4: Distribution of combinations of four most common co-morbidities; filled and empty circles below the x-axis indicate the presence or absence of each comorbidity, with other

Supplemental Figure 5: Distribution of time from admission to outcome – either death or recovery. The blue curve is the gamma distribution fit to the data, and the black dashed line indicates the position of the expected mean. The expected mean differs from the observed mean in that it accounts for unobserved outcomes.

Table 1: Demographics of All Hospitalized or Critically Ill Patients with COVID-19

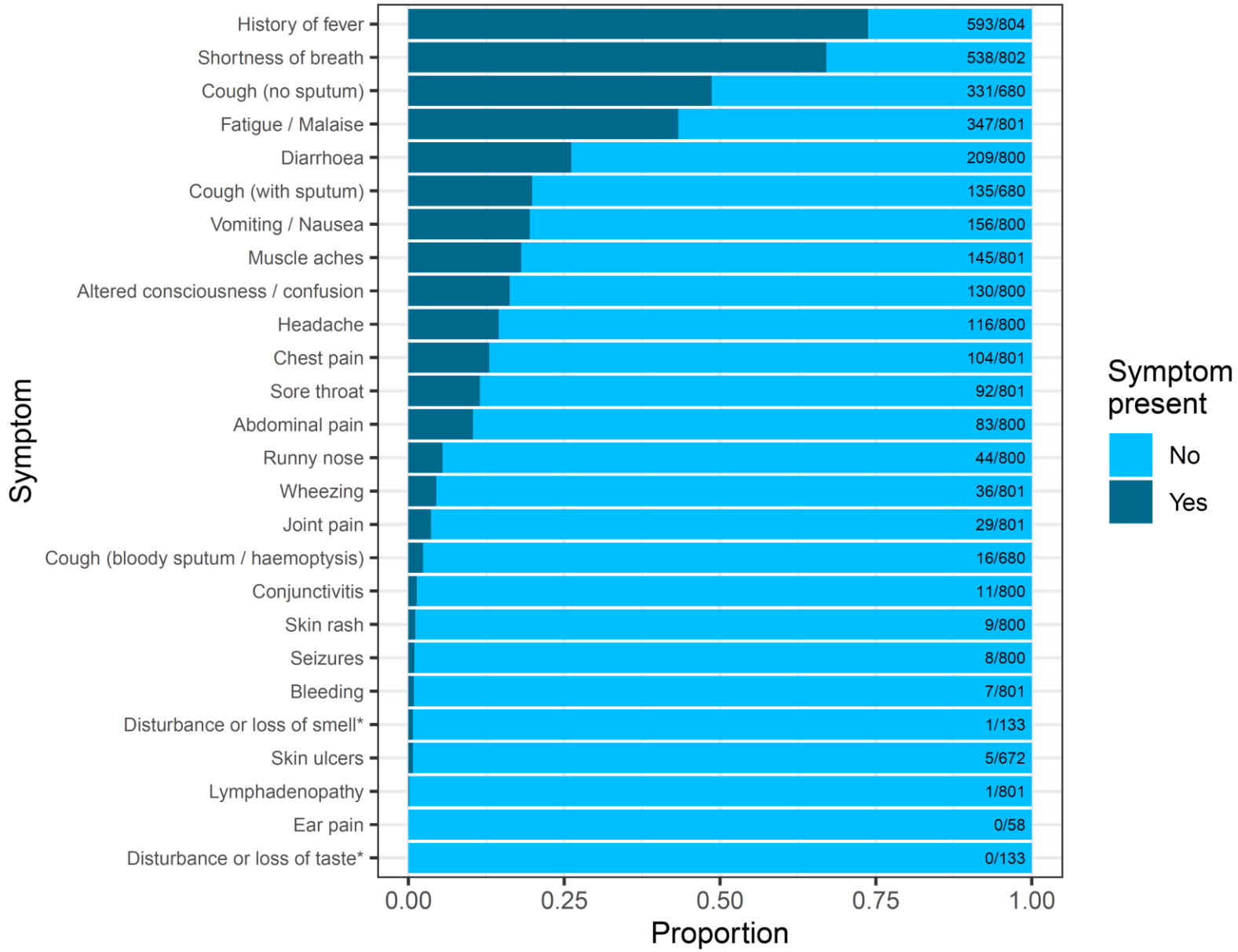
	All Hospitalized Patients N=811	**ICU Patients** N=328
Age, years, median, (IQR)	64 (53, 75)	65 (54, 72)
<19, n (%)	21 (2)	5 (1)
>70, n (%)	40 (8)	23 (7)
Female (n, %)	315 (39)	105 (32)
Co-morbidities (n, %)		
Diabetes	203 (25)	90 (27)
Cardiac disease	171 (21)	67 (20)
Chronic kidney disease	102 (13)	67 (20)
Liver disease	30 (4)	14 (4)
Asthma	90 (11)	38 (12)
Smoking	37 (5)	16 (5)
Obesity	23 (3)	15(5)
AIDS/HIV	8 (1)	3 (1)
Malignant neoplasm	28 (3)	13 (4)
Pregnancy	12 (1)	0
Time from symptom onset to hospital admission (mean, sd)	12.5 (8.8)	15 (9.3)
Overall mortality (n, %)	166 (20)	86 (26)

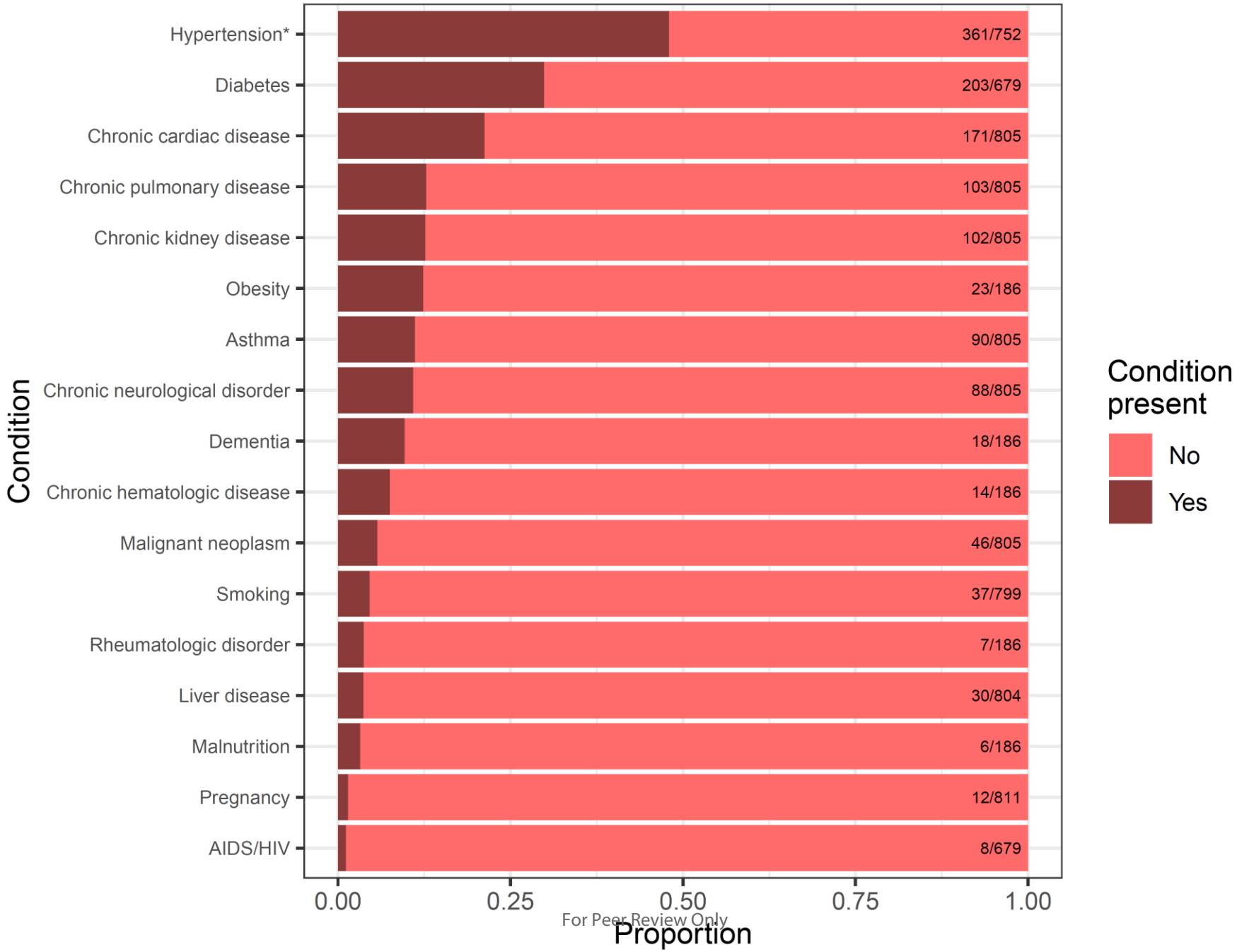
Table 2: Interventions received among All Hospitalized or Critically Ill Patients with COVID-19

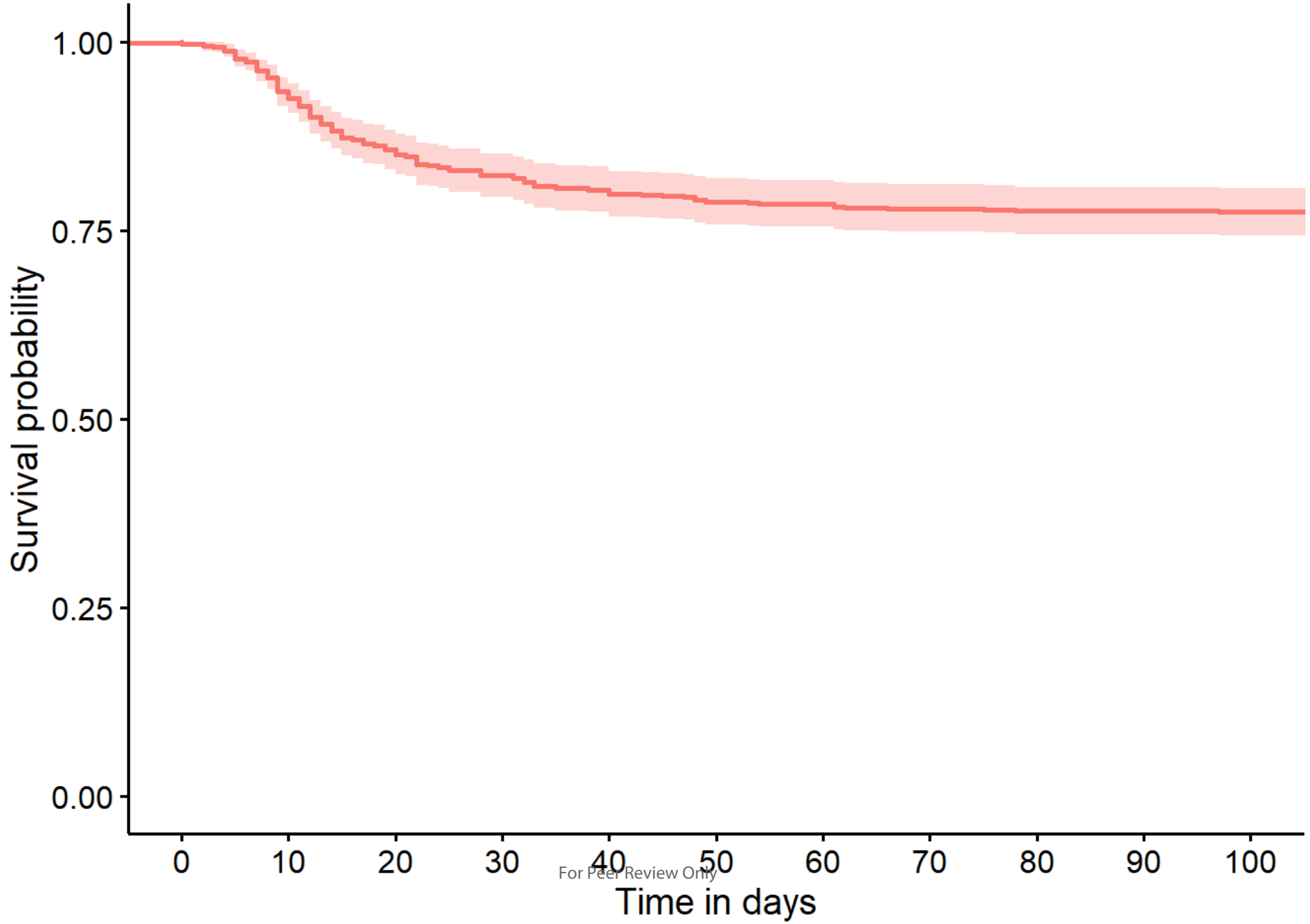
Treatments, n (%)	**All hospitalized Patients** N=811	**ICU Patients** N=328
Antibiotics	640 (79)	283 (86)
Antiviral agent	172 (22)	76 (23)
Systemic corticosteroids	185 (23)	95 (29)
Oxygen	602 (74)	328 (100)
High-flow nasal oxygen	105(13)	40 (12)
Non-invasive ventilation	54 (7)	35 (11)
Invasive ventilation	-	291 (88)
Prone ventilation	-	55 (17)
Inotropes/vasopressors	-	274 (83)
Renal replacement therapy	-	49 (15)
ECMO	-	13 (4)
Tracheostomy	-	10 (3)

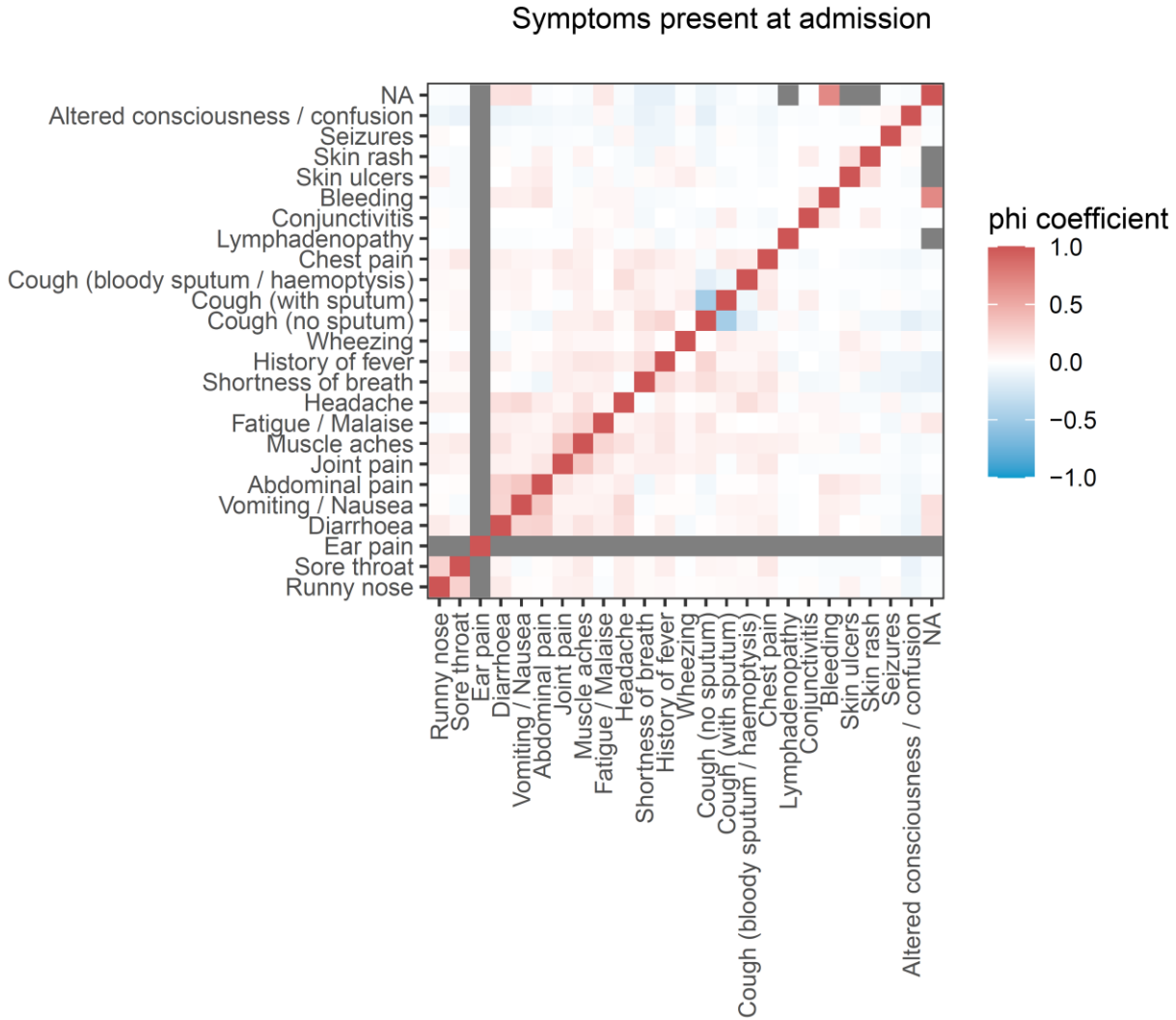
Table 3. Characteristics of Patients with COVID-19 who Died or Survived.

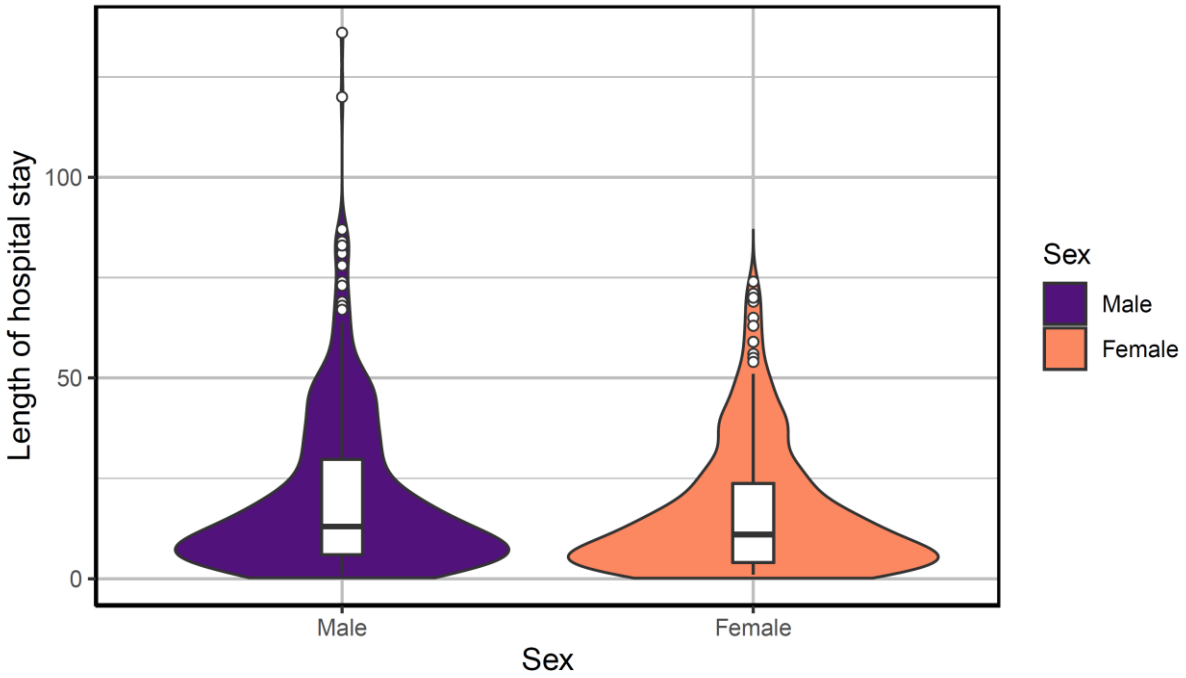
	Patients who Survived N=625	**Patients who Died N=166**	**P Value**
Age, Mean (SD)	50.4 (25.6)	71.7 (11.9)	<0.001
<18 years (N, %)	26 (100)	0	
19-39 years (N, %)	75 (96)	3 (4)	
40-59 years (N, %)	180 (88)	24 (12)	
60-79 years (N, %)	316 (82.5)	67 (17.5)	
≥ 80 years (N, %)	48 (40)	72 (60)	
Female (%)	37.5	43.9	0.171
Male (%)	62.5	56.1	
Co-morbidities (%)			
Hypertension	46	68	<0.001
Diabetes	24	42	<0.001
Chronic kidney disease	11	22	0.001
Asthma	11	16	0.155
Smoking	3	9	0.012
Pregnancy	100	0	
Time from symptom onset to hospital admission, days (Mean, SD)	6.9 (12.4)	3.9 (16.3)	0.035
Length of Stay in Hospital, days (Mean, SD)	15.9 (20.1)	16.4 (22.2)	0.77

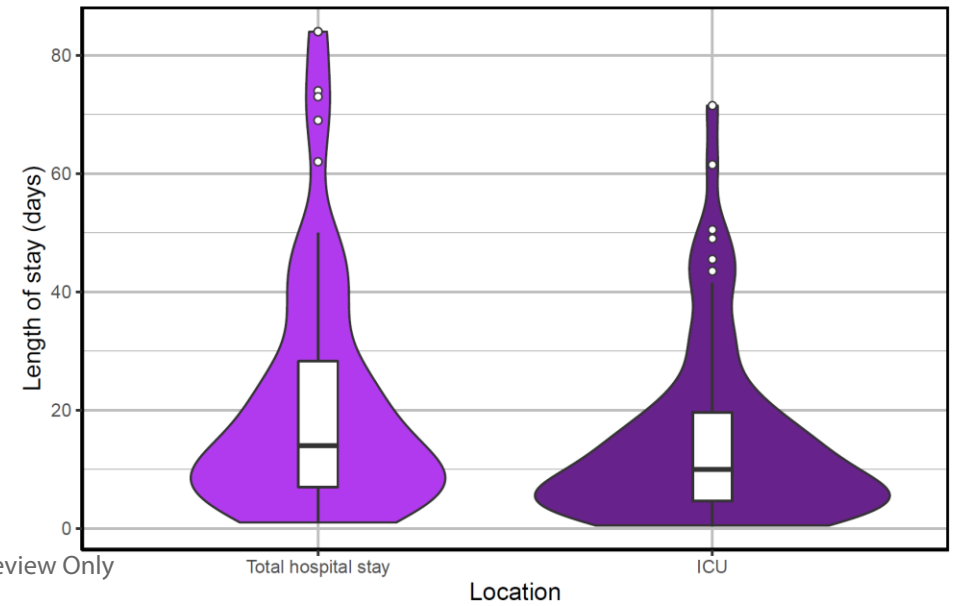


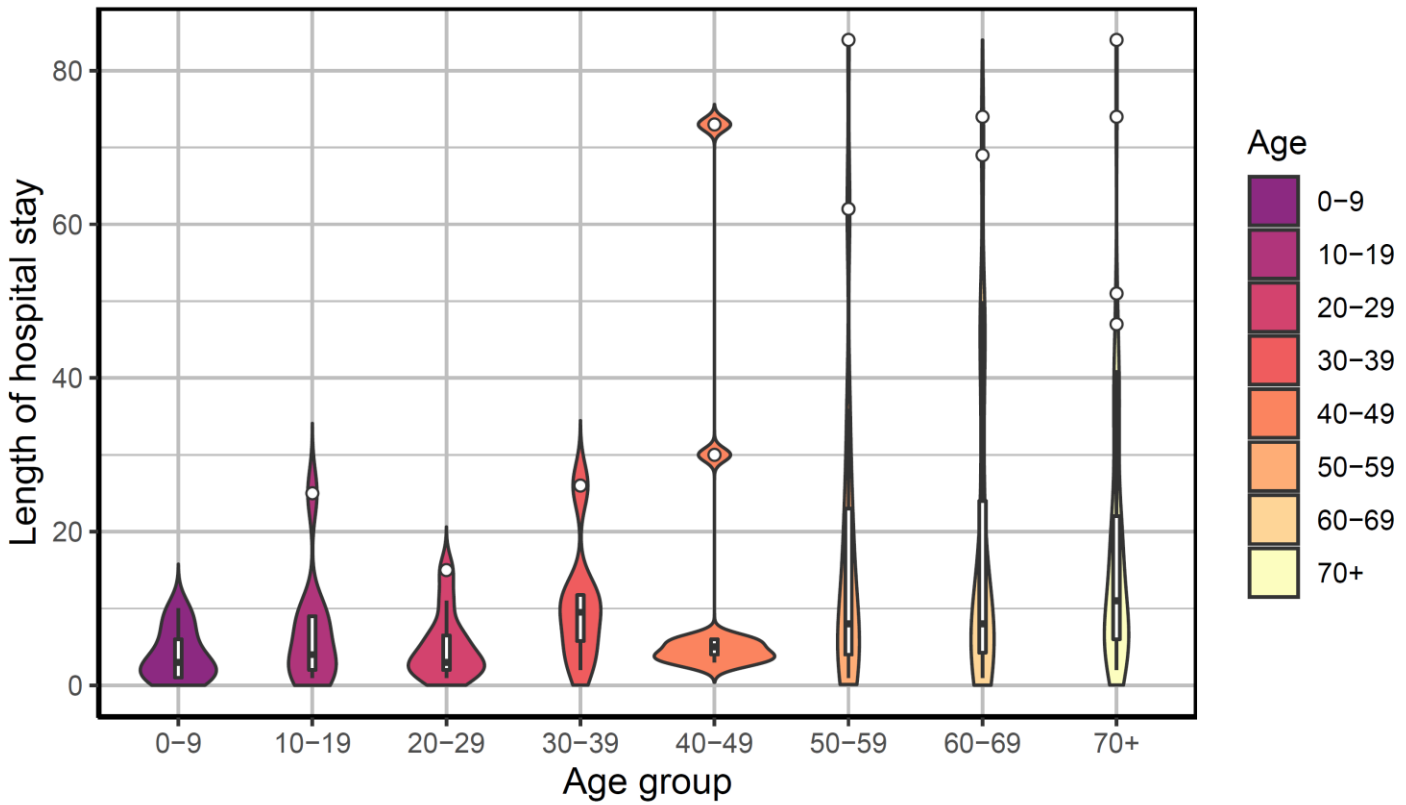











Length of hospital stay
0
20
40
60
80
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Age
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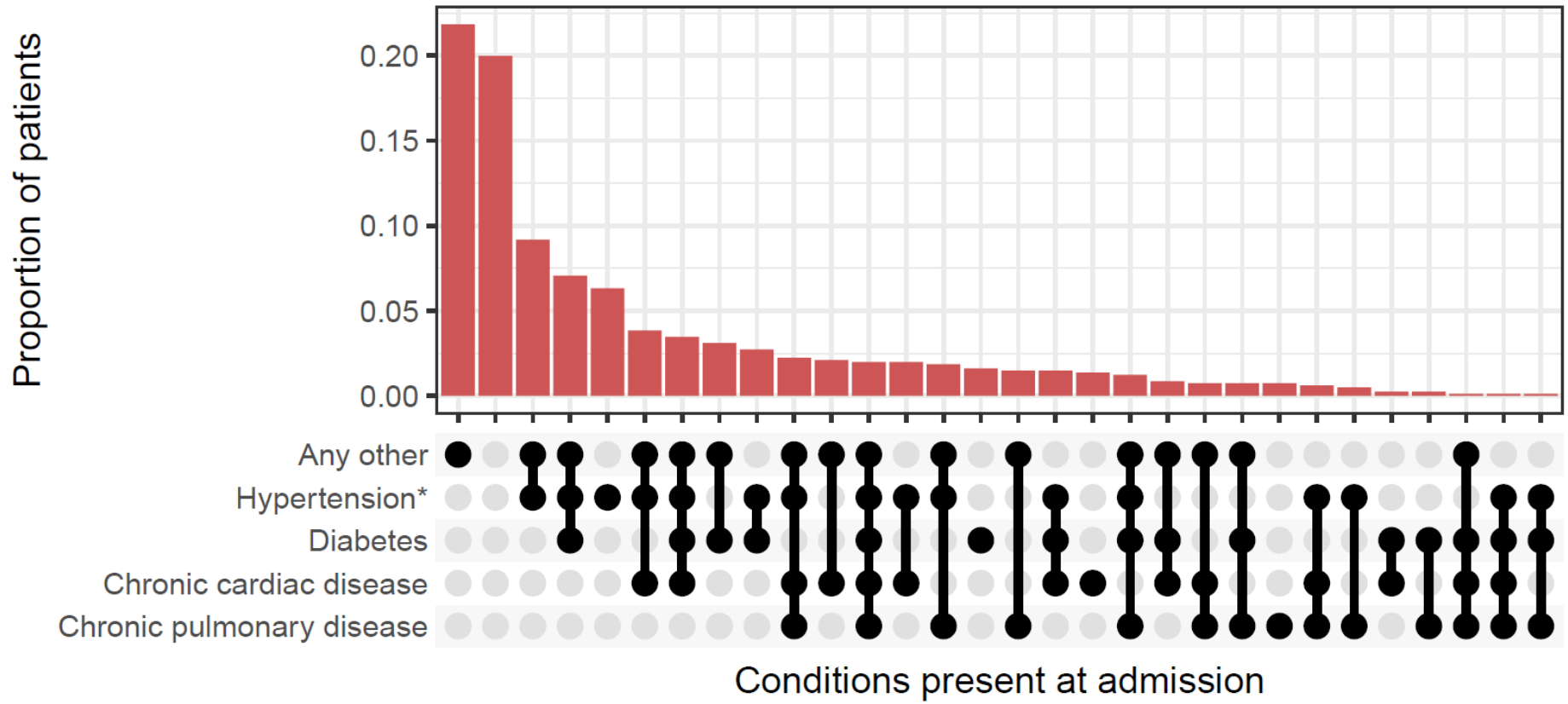
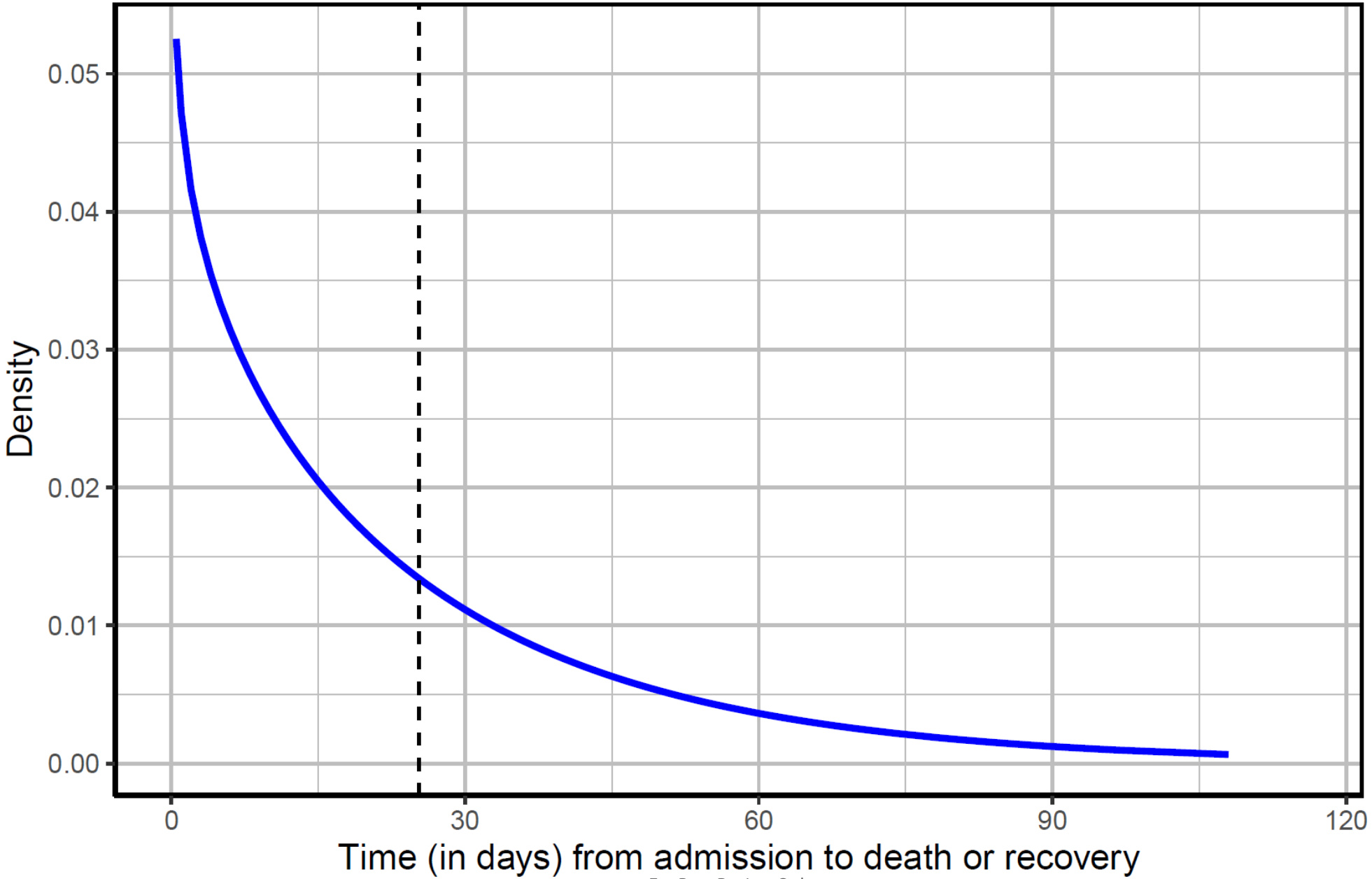
60–69
70+


Proportion of patients
0.20
0.15
0.10
0.05
0.00
Any other
Hypertension*
Diabetes
Chronic cardiac disease
Chronic pulmonary disease
Conditions present at admission



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			
Study design	4	Present key elements of study design early in the paper	1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Reported in results – add to methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	1
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	1-2
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	2
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	2
		(*d*) If applicable, explain how loss to follow-up was addressed	2
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	2
		(c) Summarise follow-up time (eg, average and total amount)	2
Outcome data	15*	Report numbers of outcome events or summary measures over time	2

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	2
		(*b*) Report category boundaries when continuous variables were categorized	2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	3
Discussion			
Key results	18	Summarise key results with reference to study objectives	3
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3-4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4
Generalisability	21	Discuss the generalisability (external validity) of the study results	4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Academic Adult Hospitals

Centre Hospital Universite de Montreal
Centre Hospital Universite de Sherbrooke
Hopital L'Enfant Jesus
Institut Universitaire de Cardiologie et de Pneumologie de Quebec
Kingston General Hospital
University of Manitoba
McGill University Health Centre
Mount Sinai Hospital
The Ottawa Hospital
Royal Alexandra Hospital
St. Michael's Hospital
Sunnybrook Hospital
St. Joseph's Hospital, Hamilton
University of Alberta Hospital
Vancouver General Hospital

Academic Pediatric Hospitals

The Hospital for Sick Children
Alberta Children's Hospital
St. Justine Hospital
Montreal Children's Hospital

Community Hospitals

William Osler Hospital
North York General Hospital
Toronto East General Hospital
Joseph Brant Hospital
Humber River Hospital
Victoria General Hospital
Lions Gate Hospital
Grand River Hospital
Grande Prairie Hospital
Red Deer Regional Hospital
Sturgeon Community Hospital
Grey Nuns Community Hospital
Brantford General Hospital