Association Between Vaccination Status and Outcomes in Patients Admitted to the ICU With COVID-19*

Sean van Diepen, MD, MSc[1,2,3]
Finlay A. McAlister, MD, MSc[2,4,5]
Luan Manh Chu, PhD[4,6]
Erik Youngson, MMath[4,6]
Padma Kaul, PhD[2,4]
Sameer S. Kadri, MD, MSc[7]

OBJECTIVES: Although COVID-19 vaccines can reduce the need for intensive care unit admission in COVID-19, their effect on outcomes in critical illness remains unclear. We evaluated outcomes in vaccinated patients admitted to the ICU with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and the association between vaccination and booster status on clinical outcomes.

DESIGN: Retrospective cohort.

SETTING AND PATIENTS: All patients were admitted to an ICU between January 2021 (after vaccination was available) and July 2022 with a diagnosis of COVID-19 based on a SARS-CoV-2 polymerase chain reaction test in Alberta, Canada.

INTERVENTIONS: None.

MEASUREMENT: The propensity-matched primary outcome of all-cause in-hospital mortality was compared between vaccinated and unvaccinated patients, and vaccinated patients were stratified by booster dosing. Secondary outcomes were mechanical ventilation (MV) duration ICU length of stay (LOS).

MAIN RESULTS: The study included 3,293 patients: 743 (22.6%) were fully vaccinated (54.6% with booster), 166 (5.0%) were partially vaccinated, and 2,384 (72.4%) were unvaccinated. Unvaccinated patients were more likely to require invasive MV (78.4% vs 68.2%), vasopressor use (71.1% vs 66.6%), and extracorporeal membrane oxygenation (2.1% vs 0.5%). In a propensity-matched analysis, in-hospital mortality was similar (31.8% vs 34.0%, adjusted odds ratio [OR], 1.25; 95% CI, 0.97–1.61), but median duration MV (7.6 vs 4.7 d; $p < 0.001$) and ICU LOS (6.6 vs 5.2 d; $p < 0.001$) were longer in unvaccinated compared to fully vaccinated patients. Among vaccinated patients, greater than or equal to 1 booster had lower in-hospital mortality (25.5% vs 40.9%; adjusted OR, 0.50; 95% CI, 0.0.36–0.68) and duration of MV (3.8 vs 5.6 d; $p = 0.025$).

CONCLUSIONS: Nearly one in four patients admitted to the ICU with COVID-19 after widespread COVID-19 vaccine availability represented a vaccine-breakthrough case. Mortality risk remains substantial in vaccinated patients and similar between vaccinated and unvaccinated patients after the onset of critical illness. However, COVID-19 vaccination is associated with reduced ICU resource utilization and booster dosing may increase survivability from COVID-19-related critical illness.

KEY WORDS: COVID-19; intensive care units; mechanical ventilation; mortality; vaccination

The World Health Organization declared COVID-19, due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, a pandemic on March 11, 2020 (1). Infections remain an important global public health problem and severe SARS-CoV-2 infections resulting in hospitalizations and/or ICU admission strained healthcare systems during the

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KEY POINTS

Question: What is the association between COVID-19 vaccination and booster status on outcomes in patients already admitted to the ICU with serious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections?

Findings: In 3,292 critically ill patients, we observed that unvaccinated patients were more likely to require invasive mechanical ventilation (MV), vasopressor use, and extracorporeal membrane oxygenation. In a propensity matched analysis, in-hospital mortality was similar, but median duration of MV and ICU length of stay were longer in unvaccinated patients (by 3 and 1.5 d, respectively). Among vaccinated patients, in-hospital mortality and duration of MV were lower among vaccinated patients with greater than or equal to 1 booster dose.

Meaning: In critically ill patients with COVID-19, mortality risk remains substantial in vaccinated patients and similar between vaccinated and unvaccinated patients. However, COVID-19 vaccination substantially reduces ICU resource utilization and booster dosing appears to further reduce duration of MV and increase survivability from COVID-19-related critical illness.

pandemic (2–5). Vaccination against SARS-CoV-2 has been shown to effectively reduce infections, reduce transmissions, with excellent protection against severe outcomes such as death and ICU admission (6–10). However, SARS-CoV-2 mutations have resulted in an increase in vaccine-breakthrough infections including severe infections (11, 12). Although vaccinations have been associated with a reduced risk of death or mechanical ventilation (MV) among hospitalized patients with breakthrough infections (13), little is known about how effective vaccination is among those admitted to the ICU with breakthrough COVID-19 infections. Thus far, only two modest-sized cohorts limited to 26 and 100 fully vaccinated admitted to an ICU have described a potential protective association with mortality (14, 15). Accordingly, using data on all ICU admissions in an entire Canadian province, we examined the frequency of vaccination among patients admitted to the ICU with COVID-19 and compared differences in patient characteristics and outcomes between vaccinated and unvaccinated patients with COVID-19.

MATERIALS AND METHODS

Study Design and Data Sources

We linked population-based administrative provincial databases to create a cohort of patients admitted to ICUs with a diagnosis of COVID-19 after the widespread free availability of COVID-19 vaccines in Alberta, Canada (therefore excluding patients admitted during the first 10 mo of the pandemic). Using previously described methodology (16), the dataset was created by linking individual patient information using anonymized unique identifiers from six datasets: 1) Electronic Medical Records (eCritical Alberta) that contained patient admission Sequential Organ Failure Assessment (SOFA) scores, admission Acute Physiology, Age, Chronic Health Evaluation (APACHE) III, laboratory information, the provision and duration of end organ support therapies (including MV, intermittent and continuous renal replacement therapies, vasopressor support), MV settings, arterial blood gas and laboratory values, ICU admission and discharge information, and ICU survival; 2) the Discharge Abstract Database, which captures all acute care hospitalizations, the primary diagnosis, up to 24 secondary diagnoses, up to 20 procedures, ICU admission and discharge status, including mortality; 3) the Immunization and Adverse Reaction to Immunization which includes dates and types of COVID-19 vaccination administered anywhere in Alberta, whether given at pharmacies, clinics, public health units, or in hospital; 4) the Provincial Laboratory database (which includes all positive reverse transcriptase-quantitative polymerase chain reaction (RT-PCR) tests for SARS-CoV-2, with genomic confirmation of all variants of concern (VOC) screen-positive tests after February 7, 2021); and 5) the Alberta Health Care Insurance Registry, which provides demographic and vital status data of all Albertans.

The University of Alberta Research Ethics Board approved this study (Pro00101096; Study title: Improving Canadian Outcomes Research On the Novel SARS-CoV-2 using Analytics: the CORONA Consortium; Amendment approval March 30, 2022) and waived the need for individual patient consent given the use of

de-identified patient data. Study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Patient Population

We created an inception cohort of ill patients greater than or equal to 18 years who were admitted to an ICU with a new primary or secondary diagnosis of COVID-19 between January 1, 2021, and July 31, 2022. These dates were chosen as COVID-19 vaccination became available in December, 2020 in Alberta. Patients with COVID-19 were identified using International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code U07.1, which has sensitivity of 94%–98% and a positive predictive value of 94.5%, and confirmed with Provincial Laboratory database test results (17, 18). Given the COVID-19 surge necessitated an expansion beyond the pre-COVID-19 ICU bed base, the study included patients admitted to any special care unit (i.e., medical, cardiovascular, pediatric, neurologic, etc). If a patient had multiple ICU admissions, only the first (index) was included in the analysis. Patient comorbidities were identified using previously validated ICD-10 code-based case definitions from all healthcare encounters in the 2 years before and including the index admission (19).

Vaccination status was classified using Provincial Governmental standards and Health Canada Approved vaccines (20). Fully vaccinated status was defined as having at least two doses of BNT162b2 (Pfizer, New York, NY), mRNA-1273 (Moderna, Cambridge, MA), and/or ChAdOx1 nCoV-19 (Astrazeneca, Cambridge, United Kingdom), NVX-CoV2373 (Novavax, Gaithersburg, MD), or one dose of Ad26.COV2.S (Janssen, Beerse, Belgium), with at least 14 days between the last dose and admission to hospital. Booster status was defined as at least one additional vaccine dose following a primary vaccination series. Unvaccinated status was defined as having no vaccinations. All other patients were classified as partially vaccinated.

Outcomes

The primary analysis compared outcomes of vaccinated versus unvaccinated patients with COVID-19 admitted to ICUs. The primary outcome was all-cause in-hospital mortality. Secondary outcomes of interest included provision and duration of invasive or noninvasive MV, provision and duration of extracorporeal membrane oxygenation (ECMO), ICU length of stay (LOS), hospital LOS, and 30-day all-cause mortality. We prespecified three subgroup analyses. First, we limited the population to those who required the provision of invasive MV. Second, we explored outcomes across COVID-19 variants. And third, outcomes between vaccinated patients with and without a booster dose were analyzed.

Statistical Methods

Bivariate analyses were stratified by vaccination status (partially vaccinated, fully vaccinated, and no vaccinations) using means ± SDs and medians with interquartile ranges for continuous variables and frequencies with percentages for categorical variables. The Kruskal-Wallis (exact) test was used for continuous variables and the Chi-square or Fisher exact test for categorical variables were used to compare differences between the three vaccination categories.

To mitigate the bias of baseline patient characteristics on exposure of vaccination status, we used propensity-score methods to reduce the effect of confounding. The individual propensities for vaccination status were estimated from a multivariable binomial logistic regression (LR) model. A propensity score-matched cohort in which LR was used to estimate the probability of exposed group based on baseline variables (age at admission, sex, SOFA score, past medical history of hypertension, diabetes, and coronary artery disease, COVID-19 waves), and exposed group (fully vaccinated) was matched with unexposed (no vaccinations) using 1:1 nearest-neighbor matching and on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score. The standard differences between variables after matching are presented in **Supplemental Table 1** and **Supplemental Figure 1** (http://links.lww.com/CCM/H348). Notably, COVID-19 wave was included as a covariate to mitigate the potential confounders of variants and pharmacotherapy using previously published dates (21). We then conducted multivariable LR adjusting for any hospitalization in the previous year, Charlson score, COVID-19 status before hospitalization, and presented odds ratio (OR) and 95% CI for in-hospital mortality.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was set at a p value of 0.05 and all statistical tests were two-sided.

RESULTS

The study identified 3,598 patients admitted to an ICU with COVID-19 between January 1, 2021, and July 31, 2022. We excluded 142 patients who did not have active health coverage at the time of hospitalization and 163 patients who had missing record identifiers. The final study population included 3,293 patients admitted to 30 ICUs with COVID-19, among whom 743 (22.6%) were fully vaccinated, 166 (5.0%) were partially vaccinated, and 2,384 (72.4%) were unvaccinated. Baseline characteristics stratified by vaccination status are presented in **Supplemental Table 2** (http://links.lww.com/CCM/H348). Unvaccinated patients were younger, had fewer pre-ICU comorbidities (including chronic lung disease, heart failure, cerebrovascular disease, chronic kidney disease, autoimmune disease, and solid organ transplantation), were more likely to have tested positive for COVID-19 before hospitalization, and were less likely to have been hospitalized in the previous year. Unvaccinated patients in the ICU were most frequently infected with the Delta variant and vaccinated patients most often had the Omicron variant. In the overall cohort, 12 patients (0.36%) were hospitalized and in an ICU before the index hospitalization, among whom 9 patients had a positive COVID-19 test.

Differences between the vaccinated population with (n = 406) and without (n = 337) a booster vaccination are presented in **Supplemental Table 3** (http://links.lww.com/CCM/H348). Patients with at least one booster vaccination were more frequently older, lived in an urban area, had a past history of hypertension or chronic kidney disease, and were hospitalized with the Omicron variant.

Critical Care Acuity and Therapies

The proportion of patients who received invasive and noninvasive MV was 75.7% and 12.9%, respectively. A total of 7.3% of patients received both. Unvaccinated patients who were admitted to the ICU had lower APACHE II and III risk scores and creatinine levels, and were more likely to receive invasive MV, vasopressor use, and ECMO (**Table 1**). Among patients who received MV, unvaccinated patients more frequently exhibited higher positive end airway, mean airway, and plateau pressures.

Outcomes

The overall in-hospital mortality was 27.2%, including 31.2.1% in the invasive MV cohort and 6.9% in those who did not receive invasive MV. Unadjusted all-cause in-hospital mortality was 25.3%, 30.1%, and 32.6% in the unvaccinated, partially vaccinated, and fully vaccinated cohorts, respectively (**Table 2**). The median duration of MV (7.2 vs 6.2 vs 4.5 d; $p < 0.001$) and ICU LOS (7.9 vs 6.3 vs 5.0 d; $p < 0.001$) were the longest in the unvaccinated cohort. In the subgroup of vaccinated patients admitted to the ICU, patients with a booster dose had a lower duration of MV (3.8 vs 5.6 d; $p = 0.025$), but no difference in ICU LOS was observed (4.8 vs 5.3 d; $p = 0.210$).

In the propensity-matched analysis comparing 658 unvaccinated patients with 658 fully vaccinated patients (Supplemental Table 3, http://links.lww.com/CCM/H348), there was no difference in in-hospital mortality (31.8% vs 34.0%, adjusted OR, 1.25; 95% CI, 0.97–1.61). Median MV duration (7.6 vs 4.7 d; $p < 0.001$), ICU LOS (8.3 vs 5.2 d; $p < 0.001$), and hospital LOS (18.8 vs 15.1 d; $p < 0.001$) remained longer in unvaccinated patients (**Fig. 1**; **Supplemental Table 4**, http://links.lww.com/CCM/H348).

In a prespecified sensitivity analysis that explored mortality across COVID-19 variants, no differences were observed in mortality between vaccinated and unvaccinated patients admitted with wild-type, Alpha, Delta, or Omicron variants. The percentage of ICU patients who were fully vaccinated at the midpoint of wave 2 (from January 1 to February 14, 2021), wave 3 (from February 15, 2021, to July 14, 2021), wave 4 (from July 15 to November 27, 2021), wave 5 (November 28, 2021, onwards), who were fully vaccinated was 0.0%, 0.2%, 4.6%, and 17.8%, respectively. In the subgroup of patients that required invasive MV (n = 2,494), there was no significant difference in in-hospital mortality between unvaccinated and fully vaccinated patients (adjusted OR, 1.29; 95% CI, 0.98–1.69). In the subgroup of vaccinated patients, at least one booster dose was associated with lower in-hospital mortality (25.5% vs 40.9%; adjusted OR, 0.50; 95% CI, 0.36–0.68). We observed no difference in mortality between boosted versus fully vaccinated

TABLE 1.
Critical Care Variables by Vaccination Status

Characteristic	Vaccination status			p
	Unvaccinated (*n* = 2,384)	Partially vaccinated (*n* = 166)	Fully vaccinated (*n* = 743)	
Time in hospital before ICU admission, median (Q1–Q3), hr	7.0 (0.0–48.0)	13.0 (0.0–59.0)	4.0 (0.0–43.0)	0.057
APACHE II score, median (Q1–Q3) (*n* = 3,114)	19.0 (14.0–27.0)	21.0 (17.0–29.0)	23.0 (17.0–31.0)	< 0.001
APACHE III score median (Q1–Q3) (*n* = 3,165)	60.0 (44.0–85.0)	67.0 (51.0–94.0)	74.0 (52.0–102.0)	< 0.001
Sequential organ failure assessment score median (Q1–Q3) (*n* = 3,228)	7.0 (4.0–9.0)	7.0 (4.0–10.0)	7.0 (4.0–10.0)	0.006
Mechanical ventilation, *n* (%)				
Invasive	1,870 (78.4)	117 (70.5)	507 (68.2)	< 0.001
Noninvasive	314 (13.6)	23 (13.9)	77 (10.4)	0.027
Renal replacement therapy, *n* (%)				
Continuous	132 (5.5)	7 (4.2)	52 (7.0)	0.177
Intermittent	72 (3.0)	7 (4.2)	32 (4.3)	0.08
Vasopressor use, *n* (%)	1,695 (71.1)	113 (68.1)	495 (66.6)	0.018
Duration of vasopressors use, median (Q1–Q3), d	2.7 (1.1–6.4)	2.3 (1.1–5.6)	3.8 (1.4–7.9)	0.129
Extracorporeal membrane oxygenation, *n* (%)	49 (2.1)	2 (1.2)	4 (0.5)	0.043
Ventilator settings				
Maximum FIO_2, median (Q1–Q3), % (*n* = 1,824)	100.0 (100.0–100.0)	100.0 (95.0–100.0)	100.0 (70–100.0)	< 0.001
Highest positive end-expiratory pressure, median (Q1–Q3), cmH_2O (*n* = 1,723)	16.0 (13.0–18.0)	15.2 (10.0–18.0)	12.0 (10.0–16.0)	< 0.001
Highest mean airway pressure, median (Q1–Q3), cmH_2O (*n* = 1,754)	23.0 (19.0–26.0)	21.0 (17.0–26.0)	19.0 (15.0–24.0)	< 0.001
Highest plateau pressure, median (Q1–Q3), cmH_2O (*n* = 1,500)	29.0 (26.0–33.0)	29.0 (25.0–32.0)	27.0 (22.0–31.0)	< 0.001
Highest tidal volume, median (Q1–Q3), cmH_2O (*n* = 1,551)	480.0 (420.0–550.0)	500.0 (410.0–550.0)	500.0 (440.0–580.0)	< 0.001
Lowest tidal volume, median (Q1–Q3), cmH_2O (*n* = 1,551)	400.0 (340.0–450.0)	390.0 (320.0–450.0)	420.0 (350.0–490.0)	< 0.001
Laboratory values				
Lowest PaO_2, median (Q1–Q3), mm Hg	60.0 (54.0–66.1)	61.0 (54.0–68.0)	63.0 (57.0–72.0)	< 0.001
Admission creatinine, median (Q1–Q3), µmol/L (*n* = 2,096)	76.0 (68.0–98.0)	83.0 (68.0–124.0)	99.0 (72.0–157.0)	< 0.001
Peak creatinine, median (Q1–Q3), µmol/L (*n* = 2,189)	84.0 (68.0–98.0)	88.0 (72.0–98.0)	96.0 (79.0–173.0)	< 0.001

APACHE = Acute Physiology and Chronic Health Evaluation.

TABLE 2.
Unadjusted Outcomes Variables by Vaccination Status

Characteristic	Vaccination status			p
	Unvaccinated (*n* = 2,384)	Partially vaccinated (*n* = 166)	Fully vaccinated (*n* = 743)	
In-hospital mortality, *n* (%)	604 (25.3)	50 (30.1)	242 (32.5)	< 0.001
Duration of invasive MV, median (Q1–Q3), d	7.2 (3.1–13.8)	6.2 (2.8–11.7)	4.5 (1.6–10.2)	< 0.001
Duration of noninvasive MV, median (Q1–Q3), d	1.1 (0.4–2.5)	2.0 (0.4–3.7)	0.8 (0.2–1.6)	0.024
ICU LOS, median (Q1–Q3), d	7.8 (3.4–14.3)	6.3 (2.5–12.0)	5.0 (2.2–10.7)	< 0.001
Hospital LOS, median (Q1–Q3), d	17.0 (10.4–31.1)	18.3 (9.3–34.8)	14.6 (6.4–29.8)	< 0.001

LOS = length of stay, MV = mechanical ventilation.

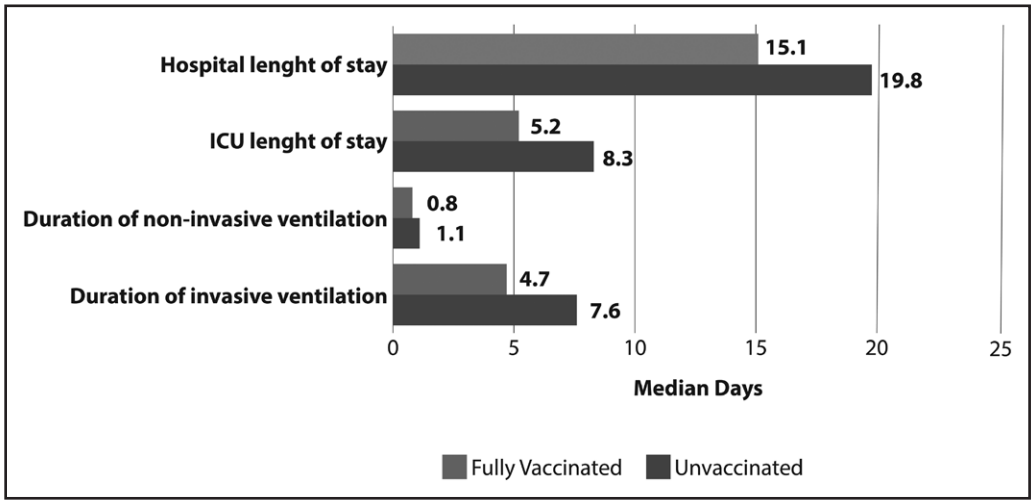

Figure 1. Resource utilization outcomes among patients admitted to the ICU with COVID-19 by vaccination status in propensity-matched cohort.

patients stratified by variant (**Supplemental Table 5**, http://links.lww.com/CCM/H348).

DISCUSSION

In a pan-provincial analysis of all patients admitted to an ICU with COVID-19 after widespread availability of COVID-19 vaccines, we found that nearly one in every four (23%) patients were fully vaccinated breakthrough cases (but nearly half had not had a booster dose). Second, critically ill unvaccinated patients were younger, had fewer comorbidities, and had lower ICU admission acuity scores. COVID-19 mortality remained substantial regardless of vaccination status, and there was no statistically significant difference in adjusted all-cause mortality risk between propensity-matched unvaccinated and vaccinated patients, but unvaccinated patients had higher use of invasive MV and ECMO, and longer MV duration and hospital LOS. Among fully vaccinated patients, we observed a significant protective association between booster vaccination dosing and in-hospital mortality and duration of MV.

Vaccination is effective to reduce severe cases of SARS-CoV-2 infections requiring ICU admission or MV (13, 22, 23). A recent retrospective population-based cohort study of 1,053 patients admitted to the ICU showed that the cumulative frequency of ICU admissions for unvaccinated, partially vaccinated, and fully vaccinated patients was 230.6, 30.8, and 5.5/100,000 population, with potential for 1,028 avoidable ICU admissions and total avoidable costs of $61.3 million CAD in one Canadian province (24). However, our study focuses on the unfortunate subset that developed critical illness from COVID-19, and who are often neglected in population-based studies in which ICU admission is often an outcome rather than a study population. Our study suggests that while vaccine-induced immunity might still help keep many with COVID-19 of the ICU, once critical illness and/

or organ failure needing ICU support occur, immunity induced by primary vaccination series may be a less important factor on the pathway from critical illness to death versus recovery. However, we did find a lower burden of critical care interventions (vasopressor use, frequency and duration of invasive MV, and ECMO cannulation) and an overall shorter ICU and hospital LOS among vaccinated patients admitted to an ICU with a breakthrough COVID-19 infection compared with unvaccinated patients. This was observed although unvaccinated ICU patients were younger with less comorbid illness and lower baseline scores of acute illness severity. These findings are consistent with a study of 100 vaccinated ICU patients with COVID-19 from 15 centers in France, which reported a lower unadjusted provision of MV (23% vs 60%) compared with unvaccinated patients (15). Collectively, this may indicate a morbidity benefit and healthcare resource savings experienced by vaccinated patients with COVID-19 needing ICU admission.

The lack of a protective association with mortality but lower resource needs among vaccinated patients admitted to the ICU with a diagnosis of COVID-19 and a positive RT-PCR test for SARS-CoV-2 compared with unvaccinated patients, along with the protective association with a booster dose among vaccinated patients, are three potentially important and novel contributions to the literature. A recent three-center study from Greece reported that fully vaccinated patients with acute respiratory distress syndrome (ARDS) were generally older and had more comorbidities compared with unvaccinated patients, but full vaccination was also associated with lower mortality (61.5% vs 68.2%) (14). Similarly, the aforementioned French study reported no difference in ICU mortality (31% vs 29%) between vaccinated and unvaccinated patients with COVID-19 (15). Finally, an analysis of 553 patients (139 vaccinated) admitted to an ICU in Italy reported that vaccinated patients were typically older with more comorbidities (25, 26). Notwithstanding, unadjusted ICU and hospital mortality rates (32.4% vs 29.9%) were similar between vaccinated and unvaccinated patients. The lack of an observed difference in this study, including among patients who received invasive MV, could be potentially explained by the much larger ICU patient population in this analysis (n = 3,297 vs n = 265), which allows for a more robust analysis matched on local waves of COVID-19 and multivariable adjustment to account for differences in baseline risk. It should be noted that the present analysis provides a more comprehensive view of ICU resource utilization for all COVID-19 admissions, whereas the aforementioned analysis was limited to those with ARDS. Notwithstanding, while the much lower median mortality rate observed in this analysis (27.2% vs 67.5%) could be dismissed by differences in ICU versus ARDS inclusion criteria and age differences between the studies, the median SOFA score in the present cohort (7.0 vs 5.0) was higher. Moreover, the lower mortality observed among vaccinated patients with at least one booster vaccine dose may be potentially reflective of improved immunologic response in this population, and is consistent with prior observational studies reporting improved vaccine efficacy with booster dosing against the Omicron variant (27, 28). Thus, differences in clinical practice or unmeasured confounders cannot be excluded.

Our study findings could be used to help support continued public health efforts informing patients that vaccinations (and booster doses in those already vaccinated twice) are effective in preventing critical illness, including the need for ICU admission, or the need for MV or ECMO when in ICU (28). From a public health perspective, vaccination remains an important tool in reducing ICU resource utilization, given that vaccinated patients have shorter durations of MV and ICU LOS; a finding particularly germane to overcrowded and strained healthcare systems. Future directions for research could be focused on evaluating the interaction between prior infection (29), vaccination status, and outcomes in this high-risk population. Similarly, although the associations between the types of vaccinations (13) and VOCs (30) on the risk of severe infections have been described, the lack of a clear association between vaccination status and outcomes by VOC described herein were likely underpowered and merit further study.

Limitations

This analysis has limitations that merit consideration. First, the study was not randomized with unvaccinated patients accounting for nearly three-quarters of the ICU and unmeasured confounders including differences in goals-of-care, other health-related behaviors, postadmission ICU complications, or prior recovery from

COVID-19 could remain unbalanced between vaccination cohorts. However, we believe that a randomized trial will not be possible to address this important public health question and that a robust propensity-matched analysis is the optimal statistical approach under the circumstances. Second, traditional ICU admission risk scores have suboptimal discrimination and our dataset does contain the validated 4C score (31), but the study cohorts were propensity matched and adjusted for clinically relevant unbalanced variables. Finally, the study did not contain information on in-hospital COVID-19-specific therapies such as dexamethasone (32), tocilizumab (33), baricitinib (34), antibody therapies, or remdesivir (35), which evolved over time; however, the study did match unvaccinated and vaccinated patients within waves in an effort to minimize discrepancies in available therapies.

CONCLUSIONS

Over three quarters of 3,293 patients admitted to ICUs with serious SARS-CoV-2 infections, during the 18 months postwidespread COVID-19 vaccination availability in an entire Canadian province, were unvaccinated. Unvaccinated ICU patients with COVID-19, despite being younger with fewer comorbidities, had a higher rate of MV, ECMO cannulation, MV duration, and hospital LOS compared with vaccinated patients. The risk of mortality among vaccinated patients remained very high and no statistically significant differences were observed in adjusted in-hospital mortality between unvaccinated and vaccinated patients, although those with a booster dose after their initial vaccination series did exhibit the lowest mortality rates. These findings suggest that, in addition to COVID-19 vaccinations preventing the development of serious infections, even if patients have a breakthrough infection requiring ICU admission, prior vaccination reduces health resource utilization substantially and booster dosing may reduce mortality.

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1 *Department of Critical Care Medicine, University of Alberta, Edmonton, AB, Canada.*

2 *The Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada.*

3 *Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB, Canada.*

4 *The Alberta Strategy for Patient Oriented Research Support Unit, AB, Canada.*

5 *Division of General Internal Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada.*

6 *Provincial Research Data Services, Alberta Health Services, Edmonton, AB, Canada.*

7 *Critical Care Medicine Department, NIH Clinical Center, Bethesda, MD.*

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For information regarding this article, E-mail: sv9@ualberta.ca

To comply with Alberta's Health Information Act and the legal data-sharing agreements between the investigators and Alberta Health Services/Alberta Health, the dataset used for this study cannot be made publicly available.

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