Clinical Characteristics and Outcomes of Critically Ill Patients with 1, 2 and 3 doses of Vaccination against COVID-19 in Australia

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Abstract

Background

Vaccination has been shown to be highly effective in preventing death and severe disease from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Currently few studies have directly compared vaccinated and unvaccinated patients with severe COVID-19 in the intensive care unit (ICU).

Aims

Our aim was to compare the clinical characteristics and outcomes of vaccine recipients and unvaccinated patients with SARS-CoV-2 infection admitted to the ICU in a nationwide setting.

Materials and Methods

Data were extracted from the Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection Australia, in 57 ICUs during Delta and Omicron predominant periods of the COVID-19 pandemic. The primary outcome was in-hospital mortality. Secondary outcomes included duration of mechanical ventilation, ICU length of stay, hospital length of stay, and ICU mortality.

Results

2,970 patients were admitted to ICU across participating sites from 26 June 2021 to 8 February 2022. 1,134 (38.2%) patients were vaccine recipients, and 1,836 (61.8%) patients were unvaccinated. Vaccine recipients were older, more comorbid, and less likely to require organ support. Unadjusted in-hospital mortality was greater in the vaccinated cohort. After adjusting for age, gender and comorbid status, no statistically significant association between in-hospital or ICU mortality, and vaccination status, was apparent.

Conclusion

We found COVID-19 infection can cause severe disease and death in vaccine recipients, though comorbid status and older age were significant contributors to mortality. Organ support requirements and the number of deaths were highest in the unvaccinated cohort.

Key words
COVID-19; SARS-CoV-2; SARS-CoV-2 vaccine; breakthrough infection; intensive care

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Introduction

The rapid introduction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines has been a landmark response to the COVID-19 pandemic. Phase 3 clinical trials and emerging real-world data have demonstrated substantial efficacy of multiple SARS-CoV-2 vaccines against symptomatic disease [1-6]. However, there are reports of both breakthrough infection, defined as patients with a positive PCR for SARS-CoV-2 >14 days after receiving the final dose of their primary vaccine series, and vaccine non-response, with a sub-population of these infections causing severe disease requiring admission to the intensive care unit (ICU) [7-10].

With SARS-CoV-2 B.1.1.529 (Omicron) gaining predominance globally [11], less is known about vaccine effectiveness for this variant of concern. Emerging evidence suggests that although breakthrough infections are more common with Omicron, hospitalisation is less likely when compared with the Alpha or Delta variants [12]. Real world data support that vaccination reduces the risk of hospitalisation in these patients, with the most marked reduction in those who have received a third dose [13-15].

While previous studies have described the clinical characteristics of patients with COVID-19 admitted to ICU [16-19], there are currently limited data comparing the ICU course of vaccine recipients with unvaccinated patients in a national setting [7, 9, 10, 20]. The Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI) Australia has collected observational data on patients with COVID-19 admitted to ICUs nationally during the pandemic, encompassing both Delta and Omicron variant predominant periods. The aim of this study was to compare the clinical characteristics and outcomes of unvaccinated patients with those who had received one, two and three doses of a SARS-CoV-2 vaccine during the COVID-19 pandemic in Australia.

Materials and Methods

Study setting and population

SPRINT-SARI Australia is a multicentre, prospective, observational cohort study of patients with COVID-19 admitted to ICU. SPRINT-SARI Australia is supported by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group and is co-ordinated by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) at Monash University. Consecutive patients ≥16 years of age with polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection, and admitted to a participating ICU, are eligible to be included. Recruitment commenced in February 2020, and is ongoing. All ICU admissions are screened for patients with COVID-19 by dedicated research staff.

For the purposes of this analysis, patients admitted to ICU between 26 June 2021 and 8 February 2022 were included. PCR-negative patients were excluded, along with any patients whose test results were not available by the end of the study period. Patients were further stratified according to their vaccination status at the time of admission for the purposes of comparison.

Data collection

Data reported to SPRINT-SARI Australia were extracted on the 8th of February 2022. A total of 57 participating sites contributed data during the study period. Data collected from both electronic and paper medical records were entered into a database (REDCap) and de-identified. The ANZIC-RC maintained the database and performed all analyses. Data quality assessment and protocol standardisation was employed to minimise bias and has been previously described [17].

Baseline demographics and clinical characteristics were collected. The Acute Physiology and Chronic Health Evaluation (APACHE) II score [21] was calculated within 24 hours of ICU

admission. Data on investigations, ICU treatments, and interventions were collected daily until day 28 of the ICU admission. The primary outcome was in-hospital mortality.

Approval for data collection was granted under the National Mutual Acceptance scheme, by the Human Research Ethics Committees of Alfred Health (reference: HREC/16/Alfred/59), or by separate application to individual sites. The requirement for written informed consent from individual patients was waived. Research governance approval was granted by the Chief Health Officers of South Australia and Victoria and supported by the Chief Health Officer of Queensland. Individual site research governance approvals were granted at all sites where it was required.

Vaccination status

Patients were classified as 'vaccinated' or 'unvaccinated' at the time of ICU admission. Those in the 'vaccinated' cohort were defined as patients with a positive PCR for SARS-CoV-2 after receiving at least one dose of mRNA (Pfizer-BioNTech, Moderna) or viral vector (Oxford/AstraZeneca) vaccine. 'Vaccinated' individuals were further stratified into those who had received one, two or three doses of their respective vaccine. Recipients of three doses were both those who received a third dose in their primary series or received a booster dose in addition to their primary vaccination series.

Outcome measures

The primary outcome was in-hospital mortality. Secondary outcomes included duration of mechanical ventilation, ICU length of stay, hospital length of stay, and ICU mortality.

Statistical analysis

In the main analyses, no assumptions were made for missing data and complete cases were included only. *Supplementary Table 1* demonstrates the rate of missing data across all

variables, and denominators vary due to the presence of missing data. The cumulative number of patients during the study period is reported in cumulative plots.

To assess the association between vaccination status and ICU and in-hospital mortality, a mixed-effect multivariable logistic regression model was used, considering vaccination status, use of mechanical ventilation on day 1, time from symptoms until ICU admission, APACHE II and each patient's risk of being vaccinated as fixed effect, and the hospital and week of admission as random effect. The risk of being vaccinated at ICU admission was determined using a covariate-balancing propensity score and considered: age, gender, number of comorbidities, diabetes, chronic cardiac failure, chronic pulmonary disease, immunosuppression, chronic kidney disease, cancer and body mass index. The list of predictors was pre-defined and selected according to clinical relevance, based on clinical data and previous studies. Due to the amount of missing data, a multiple imputation strategy was used to confirm the findings.

As a sensitivity analysis, we re-assessed the analyses in a cohort of patients older than 65 years old. A two–sided p value < 0.05 was considered as evidence of statistical significance. All analyses were performed using R software, version 4.0.3 (R Core Team). To address the potential residual confounding, E-values for the models are reported.

Results

From the 26th of June 2021 to the 8th of February 2022, a total of 2,970 patients with COVID-19 were admitted to ICUs across 57 participating sites in the SPRINT-SARI Australia database. Throughout this time, both Delta and Omicron variants predominated SARS-CoV-2 infections across Australia, with the first case of the Delta variant identified in May 2021 and the first cases of the Omicron variant in December 2021 [22, 23]. There were no patients excluded from the analysis. The cumulative number of cases throughout the study period are demonstrated in *Figure 1*. 1,860/2,967 (62.7%) patients were male, and 976 (32.9%) were

>65 years at time of ICU admission. A total of 1,134 (38.2%) patients had received at least one dose of a SARS-CoV-2 vaccine, with 1,836 (61.8%%) patients classified as unvaccinated. Among vaccine recipients, 430/1,133 (38%) had received their first dose, 617/1,133 (54.5%) had received their second, and 86/1,133 (7.6%) had received a third or booster vaccine dose. 158/940 (16.8%) vaccine recipients were admitted to ICU ≤14 days after their first dose.

Demographic characteristics

Baseline demographic characteristics are demonstrated in *Table 1*. Vaccine recipients were older [64 years (IQR 51-73) vs 54 years (IQR 42-65), *p<0.*001] and a greater proportion were male [780/1,134 (68.8%) vs 1,080/1,834 (58.9%), *p<0.001*]. Patients who had received one dose of a SARS-CoV-2 vaccine were younger when compared with those who had received two or three doses [58 years (IQR 46-68) vs 67 (IQR 55-75) vs 70 (IQR 57-76), *p <0.001*].

Vaccine recipients were more comorbid, with ≥3 co-existing conditions reported in 393 (34.7%) patients, compared with 296 (16.1%) patients in the unvaccinated group (*p<0.001*). Patients who had received three doses of vaccine had the greatest proportion of individuals with ≥3 co-existing conditions when compared with one- or two-dose recipients alone. Diabetes, chronic cardiac failure, chronic pulmonary disease, immunosuppression, chronic kidney disease, chronic haematological disease and cancer were more prevalent conditions in vaccine recipients.

Clinical characteristics

The clinical characteristics comparing vaccination status are demonstrated in *Supplementary Tables 2 and 3*. When compared to the unvaccinated cohort, patients who had received at least once vaccine dose were less likely to require invasive ventilation, inotropic or vasopressor support, prone positioning, tracheostomy and extracorporeal membrane oxygenation. Patients who had received three doses of vaccine were less likely to require invasive ventilation, and tracheostomy when compared with one- and two-dose recipients.

The most common complication was bacterial pneumonia across both cohorts [265/807 (32.8%) vs 502/1,503 (33.4%) respectively]. Vaccine recipients had decreased rates of bacteraemia and barotrauma, albeit experienced cardiac arrest more often, when compared with the unvaccinated cohort.

Primary outcome

Clinical outcomes are demonstrated in *Table 2*. Hospital outcomes were available for 2,331 (78.5%) patients, as a proportion of patients remained in hospital at the time of data extraction. Vaccine recipients had a shorter duration of ventilation, length of ICU stay, and length of hospital stay when compared with the unvaccinated cohort. Patients who had received one dose of vaccine had a longer duration of ventilation, ICU length of stay and hospital length of stay when compared with two- and three-dose recipients. In-hospital death occurred in 197/827 (23.8%) vaccine recipients and 260/1,584 (16.4%) unvaccinated patients (*p<0.001)*. There was no statistically significant difference in ICU or in-hospital death between those who had received one, two or three vaccine doses. The cumulative number of deaths throughout the study period are shown in *Supplementary Figure 1. Figure 2* demonstrates the vaccination status of patients who died stratified by age group. When comparing individual vaccine groups, 2.2% of deaths occurred in patients who had received three doses of vaccine, 21.9% in two-dose recipients, 18.8% in one-dose recipients, and 56.9% in unvaccinated individuals.

A multivariate analysis was utilised to examine the interaction between vaccination status and in-hospital and ICU mortality. Following multiple imputation to account for missing data, there was no statistically significant association between vaccination and in-hospital or ICU mortality [OR 0.75 (0.54 to 1.05) *p=0.095*; and OR 0.79 (0.55 to 1.13) *p=0.194* respectively]. Raw E-values were 1.09 and 1.34 for hospital and ICU mortality respectively, and 1.53 and 1.61 following multiple imputation.

Impact on older patients

We performed a sensitivity analysis comparing patients >65 years old in the vaccinated and unvaccinated cohorts (*Supplementary Tables 4 and 5*). Vaccine recipients maintained greater rates of diabetes, chronic cardiac failure, immunosuppression, chronic kidney disease, and cancer. There was no statistically significant difference in in-hospital or ICU mortality between groups >65 years of age.

Discussion

This nationwide, observational study compared demographic, clinical characteristics and outcomes of unvaccinated patients with those who had received one, two and three doses of a SARS-CoV-2 vaccine, admitted to ICU with severe COVID-19 across all states and territories in Australia. We found that the proportion of vaccine recipients admitted to ICU increased throughout the study period, in keeping with increasing community vaccination in Australia. We also found that despite the known effectiveness of vaccines, SARS-CoV-2 infection in vaccine recipients can result in severe disease, which was associated with increased crude mortality compared to unvaccinated patients.

However, vaccine recipients were older, and more comorbid when compared with unvaccinated patients with COVID-19 and after adjustment for confounding factors, there was no statistically significant association between vaccination and in-hospital or ICU mortality. This finding is important. In Australia, the early emphasis on vaccinating the elderly population resulted in a higher proportion of vaccinated patients being older with significant comorbidities. The higher unadjusted mortality therefore emphasises the influence of both comorbid status and older age on mortality in vaccine recipients with severe COVID-19. These findings are in accordance with previously published studies [4, 7, 8, 20]. A sensitivity analysis to exclude patients aged ≤65 years also demonstrated no difference in both in-hospital and ICU mortality between vaccinated and unvaccinated cohorts, and no difference when comparing patients who had received one, two or three vaccine doses.

SARS-CoV-2 infection in patients who had received three vaccine doses accounted for 7.6% of our vaccinated group. While infections in this cohort have been described across specific settings [24, 25], several studies demonstrate that a third vaccine dose is more effective than two doses in preventing symptomatic infection and hospitalisations across both Delta and Omicron variant infections [13, 14, 25, 26]. In response to the emergence of new variants of concern and waning immunity over time, there is ongoing discussion surrounding redefining a primary vaccination series for SARS-CoV-2, with evidence suggesting that a three-vaccination course produces superior neutralising immunity [15].

We hypothesise that vaccine non-response may have also contributed to the mortality findings in our vaccinated cohort, with the inability to generate antibodies to the vaccine portending a poor clinical course if infected with SARS-CoV-2. Although an immune correlate of protection has not been definitively established for COVID-19 and assays are poorly standardised, it has been suggested that neutralisation antibody titres may be an important predictor of vaccine efficacy [27, 28]. Several case reports have described vaccine non-response [29, 30], however data in this area are still emerging.

Anti-SARS-CoV-2 spike protein IgG antibodies were not routinely measured in our study and therefore the proportion of vaccine non-responders in the vaccinated cohort is not known. The influence of immunosenescence on vaccine response should be considered given the greater proportion of vaccinated patients >65 years of age [31-33]. Reduced immunogenicity in patients with active malignancy and immunosuppression is also an important consideration [34-36], as these comorbidities were more frequent in our vaccinated cohort. These data support the possibility of measuring serology and considering the early use of neutralising antibodies in seronegative patients, reflected in the RECOVERY trial and current Australian Taskforce recommendations [37, 38], alongside the consideration of additional doses of vaccine in this vulnerable cohort.

Strengths and limitations

This is one of the first nationwide studies to compare the clinical characteristics and outcomes of vaccine recipients compared with unvaccinated patients with COVID-19 in the ICU. The majority of major ICUs in Australia were included, generating nationally representative data for a healthcare system operating within its capacity. Experienced data collectors retrieved the data via a standardised case report form.

It should be acknowledged that 38% of our vaccinated cohort had only received one dose of their primary vaccination series. Single dose mRNA vaccine effectiveness for prevention of severe disease and mortality has been reported as 62% and 72% respectively [39], suggesting that partial vaccination does not exclude the risk of severe COVID-19 disease or mortality. Furthermore, 16.8% of our vaccinated cohort had received their first dose within 14 days of ICU admission, and the amount of protection provided during this initial period is unclear [5]. Given there is a difference in protection mounted from one, two and three doses of vaccine, these data may not provide a true reflection of the correlation between vaccination status and severe COVID-19.

As an ICU based surveillance system, these findings only reflect those admitted to ICU; a specific and vulnerable cohort of patients with severe or critical disease. This represents a strong selection bias, isolating characteristics that predispose to critical illness, and residual confounding may have contributed to some of the observed effects. The choice to vaccinate is strongly associated with patient factors including those which increase risk for severe illness, such as comorbidities and age. It should also be noted that not all patients with severe disease were admitted to ICU, and these findings therefore do not wholly encompass the interaction between vaccination and the development of critical illness. This may limit the generalisability of these findings to older people where there is concern about waning protection from vaccination.

The study is also limited by its observational design. Given the number of patients remaining in hospital at the time of data extraction, there was a proportion of missing outcome data and the focus was on short-term mortality. Anti-SARS-CoV-2 serology was not routinely collected, and the number of vaccine non-responders is therefore unknown.

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Conclusion

This study found that vaccine recipients admitted to ICU with SARS-CoV-2 infection across Australia were older and had a greater number of comorbidities when compared with their unvaccinated counterparts. Vaccine recipients were less likely to require organ support in the ICU. Crude mortality was higher in critically ill vaccine recipients with COVID-19, although this did not persist after adjusting for comorbid status and age. Moreover, the absolute burden of mortality was highest in the unvaccinated cohort.

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Figure legends

Figure 1. Cumulative Number of COVID-19 Cases Admitted to Intensive Care Units Across Australia from the 26th of June 2021 to the 8th of February 2022.

Abbreviations: ICU; intensive care unit.

Figure 2. Percentage of Patients with COVID-19 Admitted to the Intensive Care Unit Who Died, According to Age and Vaccination Status.

Table 1 - Baseline Characteristics of the Included Patients

	Vaccination Status			Number of Vaccine Doses			
	Vaccinated (*n* = 1134)	**Unvaccinated (*n* = 1836)**	***p* value**	**One Dose (*n* = 430)**	**Two Doses (*n* = 617)**	**Three Doses (*n* = 86)**	***p* value**
Age, years	64.0 (51.0 - 73.0)	54.0 (42.0 - 65.0)	< 0.001	58.0 (46.0 - 68.0)	67.0 (55.0 - 75.0)	70.0 (57.0 - 76.0)	< 0.001
> 65 years - no. (%)	539 (47.5)	437 (23.8)	< 0.001	148 (34.4)	336 (54.5)	54 (62.8)	< 0.001
Male gender - no. (%)	780 (68.8)	1080 (58.9)	< 0.001	290 (67.4)	432 (70.0)	57 (66.3)	0.576
APACHE II	14.0 (11.0 - 19.0)	13.0 (9.0 - 16.0)	< 0.001	14.0 (10.0 - 17.0)	15.0 (11.0 - 20.0)	16.0 (11.0 - 20.8)	0.009
Days from symptoms to hospital admission	5.9 (3.0 - 8.2)	6.8 (4.2 - 9.1)	< 0.001	6.2 (3.4 - 8.1)	5.8 (2.9 - 8.4)	4.5 (2.1 - 7.9)	0.115
Days from symptoms to ICU admission	7.4 (4.3 - 10.4)	8.3 (6.0 - 10.7)	< 0.001	7.7 (5.5 - 10.3)	7.3 (3.7 - 10.5)	7.1 (3.4 - 10.4)	0.143
Body mass index, kg/m^2	30.3 (26.4 - 35.6)	31.9 (26.8 - 38.7)	< 0.001	30.6 (26.8 - 36.1)	29.7 (26.0 - 35.2)	30.6 (25.7 - 33.3)	0.098
Healthcare worker - no. (%)	3 (2.4)	7 (1.2)	0.391	2 (1.9)	1 (4.8)	0 (0.0)	0.424
Pregnant - no. (%)	10 (3.3)	69 (10.1)	< 0.001	6 (4.7)	4 (2.5)	0 (0.0)	0.494
Number of doses - no. (%)			---				---
One	430 (38.0)	---		---	---	---	
Two	617 (54.5)	---		---	---	---	
Three	86 (7.6)	---		---	---	---	
Time from the most recent dose			---				< 0.001

Table 1 - Baseline Characteristics of the Included Patients

	Vaccination Status			Number of Vaccine Doses			
	Vaccinated (*n* = 1134)	**Unvaccinated (*n* = 1836)**	***p* value**	**One Dose (*n* = 430)**	**Two Doses (*n* = 617)**	**Three Doses (*n* = 86)**	***p* value**
Within 7 days	84 (8.9)	---		64 (20.1)	9 (1.6)	11 (15.3)	
7 - 14 days	132 (14.0)	---		94 (29.6)	20 (3.6)	18 (25.0)	
More than 14 days	724 (77.0)	---		160 (50.3)	521 (94.7)	43 (59.7)	
Vaccine type - no. (%)			---				< 0.001
Pfizer/BioNTech	445 (41.8)	---		234 (55.8)	181 (31.6)	30 (41.1)	
Oxford/AstraZeneca	571 (53.6)	---		168 (40.1)	366 (63.9)	37 (50.7)	
Moderna	23 (2.2)	---		10 (2.4)	12 (2.1)	1 (1.4)	
Other	26 (2.4)	---		7 (1.7)	14 (2.4)	5 (6.8)	
Co-existing disorders - no. (%)							
Number of co-existing disorders	2 (1 - 3)	1 (0 - 2)	< 0.001	1 (0 - 3)	2 (1 - 3)	2 (2 - 4)	< 0.001
0	248 (21.9)	612 (33.3)	< 0.001	118 (27.4)	123 (19.9)	7 (8.1)	< 0.001
1	264 (23.3)	563 (30.7)		122 (28.4)	127 (20.6)	14 (16.3)	
2	229 (20.2)	365 (19.9)		68 (15.8)	138 (22.4)	23 (26.7)	
≥ 3	393 (34.7)	296 (16.1)		122 (28.4)	229 (37.1)	42 (48.8)	

Table 1 - Baseline Characteristics of the Included Patients

	Vaccination Status			Number of Vaccine Doses			
	Vaccinated (*n* = 1134)	**Unvaccinated (*n* = 1836)**	***p* value**	**One Dose (*n* = 430)**	**Two Doses (*n* = 617)**	**Three Doses (*n* = 86)**	***p* value**
Diabetes	429 (40.1)	457 (26.4)	< 0.001	139 (34.2)	247 (42.7)	43 (51.2)	0.003
Obesity	315 (30.1)	597 (35.0)	0.009	135 (33.9)	161 (28.4)	19 (23.5)	0.077
Use of ACEi or ARB	285 (26.9)	295 (17.1)	< 0.001	101 (25.0)	159 (27.8)	25 (29.8)	0.498
Chronic cardiac failure	243 (22.8)	184 (10.6)	< 0.001	67 (16.5)	146 (25.4)	30 (35.7)	< 0.001
Smoker	186 (18.0)	256 (15.1)	0.048	78 (19.7)	92 (16.5)	16 (20.3)	0.383
Chronic pulmonary disease	137 (12.9)	94 (5.4)	< 0.001	41 (10.1)	82 (14.3)	14 (16.9)	0.073
Asthma	110 (10.4)	201 (11.6)	0.322	37 (9.1)	61 (10.7)	12 (14.5)	0.298
Immunosuppression	156 (14.8)	51 (3.0)	< 0.001	32 (7.9)	97 (17.2)	27 (32.5)	< 0.001
Chronic kidney disease	153 (14.4)	72 (4.2)	< 0.001	31 (7.6)	100 (17.5)	21 (25.0)	< 0.001
Chronic hematological disease	51 (4.8)	28 (1.6)	< 0.001	7 (1.7)	40 (6.9)	4 (4.8)	< 0.001
Cancer	50 (4.7)	21 (1.2)	< 0.001	13 (3.2)	28 (4.9)	9 (10.7)	0.018

Table 1 - Baseline Characteristics of the Included Patients

	Vaccination Status			Number of Vaccine Doses			
	Vaccinated (***n*** **= 1134)**	**Unvaccinated** (***n*** **= 1836)**	***p*** **value**	**One Dose** (***n*** **= 430)**	**Two Doses** (***n*** **= 617)**	**Three Doses** (***n*** **= 86)**	***p*** **value**

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.

Independent categorical variables were compared with Fisher exact test and continuous variables with Wilcoxon rank-sum test.

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation.

Table 2 - Clinical Outcomes of COVID-19 Patients

	Vaccination Status			Number of Vaccine Doses			
	Vaccinated (*n* = 1134)	**Unvaccinated (*n* = 1836)**	***p* value**	**One Dose (*n* = 430)**	**Two Doses (*n* = 617)**	**Three Doses (*n* = 86)**	***p* value**
Duration of ventilation, days	8.0 (4.0 - 13.0)	10.0 (5.0 - 17.0)	< 0.001	9.0 (5.0 - 14.0)	8.0 (3.0 - 12.2)	3.0 (2.0 - 8.0)	< 0.001
ICU length of stay, days	4.5 (2.1 - 9.9)	6.2 (2.9 - 12.7)	< 0.001	5.7 (2.5 - 11.8)	3.9 (1.7 - 9.4)	2.3 (1.2 - 6.0)	< 0.001
Hospital length of stay, days	11.6 (7.1 - 19.3)	13.4 (8.5 - 22.7)	< 0.001	13.6 (8.4 - 21.5)	10.6 (6.8 - 17.5)	6.6 (3.2 - 12.2)	< 0.001
ICU mortality - no. (%)	169 / 921 (18.3)	232 / 1652 (14.0)	0.005	72 / 402 (17.9)	87 / 471 (18.5)	10 / 47 (21.3)	0.807
Hospital mortality - no. (%)	197 / 827 (23.8)	260 / 1584 (16.4)	< 0.001	86 / 393 (21.9)	100 / 396 (25.3)	10 / 37 (27.0)	0.464
Cause of death - no. (%)			0.066				0.871
Treatment withdrawn, prognosis poor	96 / 190 (50.5)	98 / 251 (39.0)		45 / 85 (52.9)	47 / 95 (49.5)	4 / 9 (44.4)	
Brain injury	3 / 190 (1.6)	6 / 251 (2.4)		2 / 85 (2.4)	1 / 95 (1.1)	0 / 9 (0.0)	
Brain death	0 / 190 (0.0)	4 / 251 (1.6)		0 / 85 (0.0)	0 / 95 (0.0)	0 / 9 (0.0)	
Arrhythmia	2 / 190 (1.1)	0 / 251 (0.0)		1 / 85 (1.2)	1 / 95 (1.1)	0 / 9 (0.0)	
Cardiogenic shock	5 / 190 (2.6)	7 / 251 (2.8)		1 / 85 (1.2)	3 / 95 (3.2)	1 / 9 (11.1)	
Distributive (septic) shock	9 / 190 (4.7)	25 / 251 (10.0)		3 / 85 (3.5)	5 / 95 (5.3)	1 / 9 (11.1)	
Hypovolemic shock	1 / 190 (0.5)	0 / 251 (0.0)		0 / 85 (0.0)	1 / 95 (1.1)	0 / 9 (0.0)	

Table 2 - Clinical Outcomes of COVID-19 Patients

	Vaccination Status			Number of Vaccine Doses			
	Vaccinated (*n* = 1134)	**Unvaccinated (*n* = 1836)**	***p* value**	**One Dose (*n* = 430)**	**Two Doses (*n* = 617)**	**Three Doses (*n* = 86)**	***p* value**
Hypoxic respiratory failure	51 / 190 (26.8)	75 / 251 (29.9)		24 / 85 (28.2)	25 / 95 (26.3)	2 / 9 (22.2)	
Metabolic	1 / 190 (0.5)	2 / 251 (0.8)		0 / 85 (0.0)	1 / 95 (1.1)	0 / 9 (0.0)	
Other	22 / 190 (11.6)	34 / 251 (13.5)		9 / 85 (10.6)	11 / 95 (11.6)	1 / 9 (11.1)	

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.

Independent categorical variables were compared with Fisher exact test and continuous variables with Wilcoxon rank-sum test.

Abbreviations: ICU: intensive care unit.

Abbreviations

SARS-CoV-2; severe acute respiratory coronavirus 2

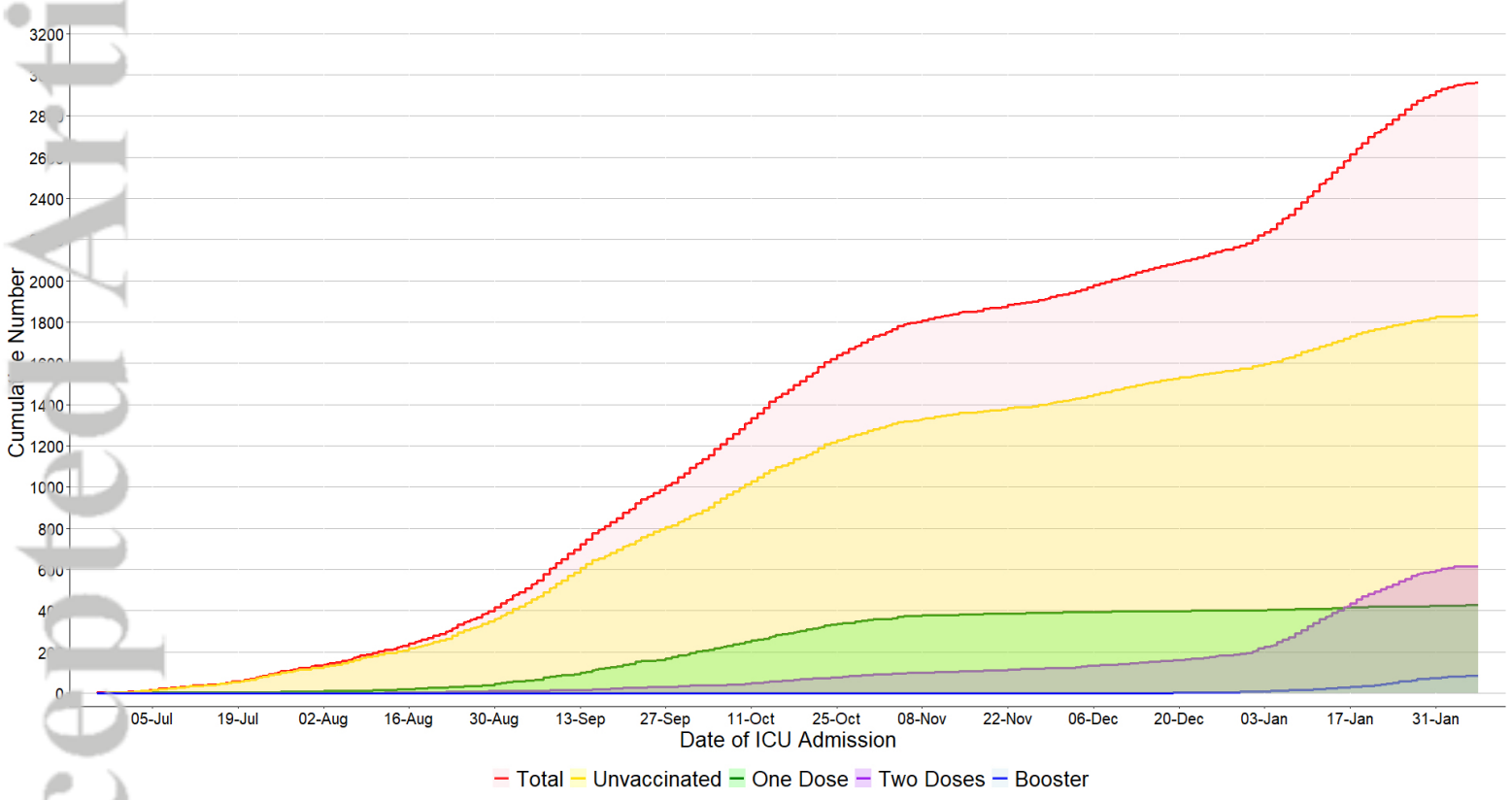
ICU; intensive care unit

SPRINT-SARI; Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection

ANZIC-RC; Australian and New Zealand Intensive Care Research Centre

PCR; polymerase chain reaction

APACHE; Acute Physiology and Chronic Health Evaluation



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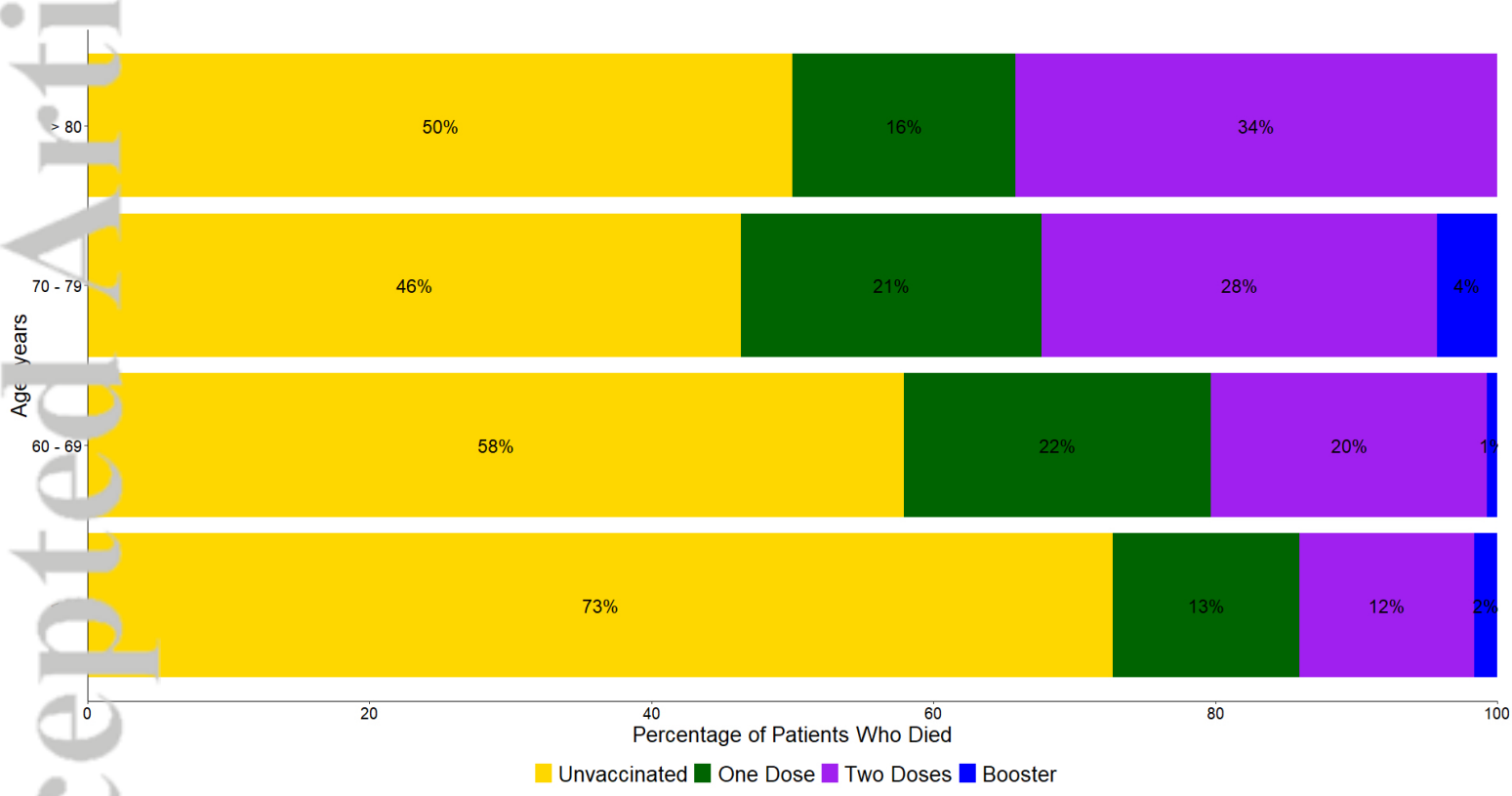

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