ORIGINAL ARTICLE

Clinical characteristics and outcomes of critically ill patients with one, two and three doses of vaccination against COVID-19 in Australia

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

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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: 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.

Methods: Data were extracted from the Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection Australia, in 57 ICU 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: There were 2970 patients admitted to ICU across participating sites from 26 June 2021 to 8 February 2022; 1134 (38.2%) patients were vaccine recipients, and 1836 (61.8%) patients were unvaccinated. Vaccine recipients were older, more comorbid and less likely to require organ support. Unadjusted inhospital mortality was greater in the vaccinated cohort. After adjusting for age, gender and comorbid status, no

Abbreviations: ANZIC-RC, Australian and New Zealand Intensive Care Research Centre; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory coronavirus 2; SPRINT-SARI, Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection.

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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.

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 coordinated 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 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 8 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 score21 was calculated within 24 h 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. Supporting Information Table S1 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 predefined 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 aged >65 years. A two-sided $P$-value <0.05 was considered as evidence of statistical significance. All analyses were performed using R software, version

![Figure 1](https://example.com/figure1.png)  
*Figure 1* Cumulative number of COVID-19 cases admitted to intensive care units (ICU) across Australia from the 26 June 2021 to 8 February 2022. (•), Total; (○), unvaccinated; (△), one dose; (▲), two doses; (●), booster.
4.0.3 (R Core Team). To address the potential residual confounding, E-values for the models are reported.

Results

From 26 June 2021 to 8 February 2022, a total of 2970 patients with COVID-19 was admitted to ICU 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

| Table 1 Baseline characteristics of the included patients |
|---------------------------------------------------------|
| Characteristic                                         | Vaccinated (n = 1134) | Unvaccinated (n = 1836) | P value | Number of vaccine doses | Vaccine type, no. (%) | 
| Age (years)                                           | 64.0 (51.0–73.0)      | 54.0 (42.0–65.0)        | <0.001  | 58.0 (46.0–68.0)        | 0.048                |

| >65 years, no. (%)                                     | 539 (47.5)            | 437 (23.8)              | <0.001  | 148 (34.4)              | 0.391                |

| Male gender, no. (%)                                   | 780 (68.8)            | 1080 (58.9)             | <0.001  | 290 (67.4)              | 0.383                |

| APACHE II                                             | 14.0 (11.0–19.0)      | 13.0 (9.0–16.0)         | <0.001  | 14.0 (10.0–17.0)        | 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)           | 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)          | 0.143                |

| Body mass index, kg/m²                                 | 30.3 (26.4–35.6)      | 31.9 (26.8–38.7)        | <0.001  | 30.6 (26.8–36.1)        | 0.098                |

| Healthcare worker, no. (%)                            | 3 (2.4)               | 7 (1.2)                 | 0.391   | 2 (1.9)                 | 0.424                |

| Pregnant, no. (%)                                      | 10 (3.3)              | 69 (10.1)               | <0.001  | 6 (4.7)                 | 0.494                |

| Number of doses, no. (%)                               | 430 (38.0)            | –                       | –       | –                       | –                    |

| One                                                    | 430 (38.0)            | –                       | –       | –                       | –                    |

| Two                                                    | 617 (54.5)            | –                       | –       | –                       | –                    |

| Three                                                  | 86 (7.6)              | –                       | –       | –                       | –                    |

| Time from the most recent dose                         | 84 (8.9)              | –                       | 64 (20.1) | 9 (1.6) | 11 (15.3) |

| Within 7 days                                          | 132 (14.0)            | –                       | 94 (29.6) | 20 (3.6) | 18 (25.0) |

| 7–14 days                                              | 724 (77.0)            | –                       | 160 (50.3) | 521 (94.7) | 43 (59.7) |

| >14 days                                               | –                     | –                       | –       | –                       | –                    |

| Vaccine type, no. (%)                                   | 445 (41.8)            | –                       | 234 (55.8) | 181 (31.6) | 30 (41.1) |

| Pfizer/BioNTech                                        | 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. (%)                         | 2 (1–3)               | 1 (0–2)                 | <0.001   | 1 (0–3)    | 2 (1–3)   | 2 (2–4)   | <0.001   |

| Number of co-existing disorders                        | 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) |

| 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 haematological 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    |

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. ACEi, angiotensin-converting enzyme inhibitor; APACHE, Acute Physiology and Chronic Health Evaluation; ARB, angiotensin II receptor blocker; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.
cases throughout the study period is demonstrated in Figure 1. There were 1860/2967 (62.7%) patients who were male, and 976 (32.9%) were aged ≥65 years at the time of ICU admission. A total of 1134 (38.2%) patients had received at least one dose of a SARS-CoV-2 vaccine, with 1836 (61.8%) patients classified as unvaccinated. Among vaccine recipients, 430/1133 (38%) had received their first dose, 617/1133 (54.5%) had received their second and 86/1133 (7.6%) had received a third or booster vaccine dose. There were 158/940 (16.8%) vaccine recipients who 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 (interquartile range (IQR) 51–73) vs 54 years (IQR 42–65), P < 0.001) and a greater proportion were male (780/1134 (68.8%) vs 1080/1834 (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 68–76), 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 Tables S2 and S3. When compared with the unvaccinated cohort, patients who had received at least one dose of vaccine 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 502/1503 (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 2331 (78.5%) patients, as a

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### Table 2. Clinical outcomes of COVID-19 patients

| Outcome                        | Vaccinated                     | Unvaccinated                  | 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   |                   |                     |                      |         |
| Treatment withdrawn, prognosis poor | 96/190 (50.5)                 | 98/251 (39.0)                 | 45/85 (52.9) | 47/95 (49.5) | 4/9 (44.4)  |                      | 0.871   |
| 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)           |                      |         |
| 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. ICU, intensive care unit.
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. Inhospital death occurred in 197/827 (23.8%) vaccine recipients and 260/1584 (16.4%) unvaccinated patients ($P < 0.001$). There was no statistically significant difference in ICU or inhospital death between those who had received one, two or three vaccine doses. The cumulative number of deaths throughout the study period is shown in Figure S1.

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 inhospital and ICU mortality. Following multiple imputation to account for missing data, there was no statistically significant association between vaccination and inhospital or ICU mortality (odds ratio (OR) 0.75 (0.54–1.05) $P = 0.095$; and OR 0.79 (0.55–1.13) $P = 0.194$ 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 (Tables S4, S5). Vaccine recipients maintained greater rates of diabetes, chronic cardiac failure, immunosuppression, chronic kidney disease and cancer. There was no statistically significant difference in inhospital or ICU mortality between groups aged >65 years.

**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 with 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 inhospital 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. A sensitivity analysis to exclude patients aged ≤65 years also demonstrated no difference in both inhospital 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, 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. 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.

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. Several case reports have described vaccine non-response, 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 aged >65 years. Reduced immunogenicity in patients with active malignancy and immunosuppression is also an important consideration 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 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 ICU 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, 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. 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 the 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.
Severe COVID-19 in vaccine recipients

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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References

1 Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021; 384: 403–16.
2 Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med 2021; 384: 1824–35.
3 Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021; 397: 99–111.
4 Agrawal U, Katiirkedi SV, McCowan C, Mulholland RH, Azcoaga-Lorenzo A, Amele S et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2.57 million people in Scotland (EAVE II): a prospective cohort study. Lancet Respir Med 2021; 9: 1439–49.
5 Lopez Bernal J, Andrews N, Gower C, Robertson C, Stone J, Tesser E et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021; 373: n1088.
6 Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 2021; 397: 1646–57.
7 Bahl A, Johnson S, Maine G, Garcia MH, Nimmagadda S, Qu L et al. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. Lancet Reg Health Am 2021; 4: 100065.
8 Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect 2021; 27: 1652–7.
9 Juthani PV, Gupta A, Borges KA, Price CC, Lee AI, Won CH et al. Hospitalisation among vaccine breakthrough COVID-19 infections. Lancet Infect Dis 2021; 21: 1485–6.
10 Rzynski P, Pagzan-Simon M, Simon K, Lapinski T, Zarebska-Michaluk D, Szczenpska B et al. Clinical characteristics of hospitalized COVID-19 patients who received at least one dose of COVID-19 vaccine. Vaccines 2021; 9: 781.
11 Mohapatra RK, Sarangi AK, Kandi V, Azam M, Tiwari R, Dhamla K. Omicron (B.1.1.529 variant of SARS-CoV-2); an emerging threat: current global scenario. J Med Virol 2021; 94: 1780–3.
12 Christensen PA, Olsen RJ, Long SW, Snelral R, Davis JJ, Saavedra MO et al. Signals of significantly increased vaccine breakthrough, decreased hospitalization rates, and less severe disease in patients with COVID-19 caused by the Omicron variant of SARS-CoV-2 in Houston, Texas. Am J Pathol 2022; 192: 320–31.
13 Danza P, Koo TH, Hadidz M, Fisher R, Traub E, OYong K et al. SARS-CoV-2 infection and hospitalization among adults aged ≥18 years, by vaccination status, before and during SARS-CoV-2 B.1.1.529 (Omicron) variant predominance – Los Angeles County, California, November 7, 2021–January 8, 2022. Morb Mortal Wkly Rep 2022; 71: 177–81.
14 Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gagliani M et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance – VISION network, 10 states, August 2021–January 2022. Morb Mortal Wkly Rep 2022; 71: 139–45.
15 Wrailt PR, Stern M, Priller A, Willmann A, Almanzar G, Vogel E et al. Three exposures to the spike protein of SARS-CoV-2 by either infection or vaccination elicit superior neutralizing immunity to all variants of concern. Nat Med 2022; 28: 496–503.
16 Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK et al. COVID-19 in critically ill patients in the Seattle Region – case series. N Engl J Med 2020; 382: 2012–22.
17 Burrell AJ, Pellegrini B, Salimi F, Begum H, Broadley T, Campbell LT et al. Outcomes for patients with COVID-19 admitted to Australian intensive care units during the first four months of the pandemic. Med J Aust 2021; 214: 23–30.
18 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020; 323: 1574–81.
19 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475–81.
20 Bosch W, Cowart JB, Bhakta S, Carter RE, Wadie HM, Shah SZ et al. COVID-19 vaccine-breakthrough infections requiring hospitalization in Mayo Clinic Florida through August 2021. Clin Infect Dis 2021: clab932. https://doi.org/10.1093/cid/clab932
Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Appendix S1 Supporting Information