Comparison of baseline characteristics, treatment and clinical outcomes of critically ill COVID-19 patients admitted in the first and second waves in Australia

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In December 2019, several cases of atypical pneumonia caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in Wuhan, China.[1-3] This novel pathogen has now become responsible for a global pandemic of coronavirus disease 2019 (COVID-19), affecting over 190 million people worldwide and causing over 4.1 million deaths.[4]

Although research concerning COVID-19 has been produced at an extraordinary rate, longitudinal data comparing changes in clinical practice or the translation of new evidence into bedside care have traditionally lagged behind.[5,6] Indeed, there is currently limited evidence concerning what impact changes to public health measures (including travel bans, face masks, and social restrictions), the publication of several major trials (such as the RECOVERY[7] and ACTT-1[8] trials), and changes in clinical practice[9] have had on patient demographics, patient care, and outcomes.

Australia experienced a first wave of infections from February to June 2020.[10] In late June 2020, an outbreak likely originating from a quarantine facility in Melbourne resulted in a second wave of COVID-19 cases predominantly in the state of Victoria, resulting in the re-establishment of public health interventions to control the spread of SARS-CoV-2. The start of this second wave was also close to the publication of the two aforementioned large, multicentre, randomised controlled trials (RCTs) concerning specific COVID-19 therapies.

In this context, the aim of this study was to report the longitudinal differences in baseline characteristics, treatment and outcomes in patients with COVID-19 admitted to intensive care units (ICUs) between the first and second waves in Australia.

Methods

Study design

This was a multicentre, inception cohort study involving ICUs in Australia. Ethics approval was granted for each participating site via the Alfred Hospital (HREC/16/

ABSTRACT

Objective: To report longitudinal differences in baseline characteristics, treatment, and outcomes in patients with coronavirus disease 2019 (COVID-19) admitted to intensive care units (ICUs) between the first and second waves of COVID-19 in Australia.

Design, setting and participants: SPRINT-SARI Australia is a multicentre, inception cohort study enrolling adult patients with COVID-19 admitted to participating ICUs. The first wave of COVID-19 was from 27 February to 30 June 2020, and the second wave was from 1 July to 22 October 2020.

Results: A total of 461 patients were recruited in 53 ICUs across Australia; a higher number were admitted to the ICU during the second wave compared with the first: 255 (55.3%) versus 206 (44.7%). Patients admitted to the ICU in the second wave were younger (58.0 *v* 64.0 years; $P = 0.001$) and less commonly male (68.9% *v* 60.0%; $P = 0.045$), although Acute Physiology and Chronic Health Evaluation (APACHE) II scores were similar (14 *v* 14; $P = 0.998$). High flow oxygen use (75.2% *v* 43.4%; $P < 0.001$) and non-invasive ventilation (16.5% *v* 7.1%; $P = 0.002$) were more common in the second wave, as was steroid use (95.0% *v* 30.3%; $P < 0.001$). ICU length of stay was shorter (6.0 *v* 8.4 days; $P = 0.003$). In-hospital mortality was similar (12.2% *v* 14.6%; $P = 0.452$), but observed mortality decreased over time and patients were more likely to be discharged alive earlier in their ICU admission (hazard ratio, 1.43; 95% CI, 1.13–1.79; $P = 0.002$).

Conclusion: During the second wave of COVID-19 in Australia, ICU length of stay and observed mortality decreased over time. Multiple factors were associated with this, including changes in clinical management, the adoption of new evidence-based treatments, and changes in patient demographic characteristics but not illness severity.

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Alfred/59) or by separate applications to individual sites. The requirement for written informed consent from individual patients was waived.

Setting

Participating sites across Australia were identified following an expression of interest to the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) or through previous affiliation with the Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI) Australia project. Data were retrieved from 53 ICUs in Australia enrolling adult patients into SPRINT-SARI Australia. Originally, SPRINT-SARI was prepared to capture data in 78 ICUs over all Australia. However, due to the limited nature of the Australian outbreak, most of these ICUs did not receive patients with COVID-19.

Participants

All patients admitted to the ICU were included if they were older than 16 years and were polymerase chain reaction (PCR)-positive for COVID-19. Data of patients transferred between ICUs were aggregated and counted as a single ICU admission. This cohort captured more than 99% of all ICU admissions due to COVID-19 in Australia.[11] In addition, the data used for the COVID-19 period were also utilised by the Australian Government Department of Health to produce official fortnightly reports about patients with COVID-19 in the ICU. A description and road map of restrictions in Australia during COVID-19 are shown in the Online Appendix.

Data collection

The case report form used for data collection had extensive development by local and international clinical experts and included standardised data fields that aligned with SPRINT-SARI International.[12] Data in this report were entered by research coordinators at participating sites. The patient's relevant background and presenting symptoms were recorded on the day of study recruitment. Daily follow-up was then completed until discharge from ICU. A final form was completed with details of the hospital outcomes.

To support rapid data collection and reporting, SPRINT-SARI Australia hosts a data platform that includes an electronic data capture system, a secure repository and an analytic framework. Data were entered into a web-based REDCap data management system, securely stored, and used to inform regular reports. Further details about SPRINT-SARI Australia have been described elsewhere.[10]

Data definitions

Patients were categorised as part of the first wave if their ICU admission date was between 27 February and 30 June 2020 and as part of the second wave for ICU admissions between 1 July 2020 and 22 October 2020. Age was categorised as < 60, 60–69, 70–79 and ≥ 80 years. Patients transferred between ICUs were counted as a single ICU admission. No assumptions were made regarding missing data (Online Appendix, eTable4); all proportions were calculated as percentages of the patients with available data.

Clinical outcomes

In addition to an overall description of different characteristics during the two waves, the following patient-related outcomes were described in more detail:

- duration of ventilation in patients receiving invasive ventilation;
- ICU length of stay;
- hospital length of stay;
- ICU mortality; and
- in-hospital mortality.

The following outcomes reflecting process of care were assessed during any time in the patients' hospital admission:

- number of patients treated with mechanical ventilation;
- number of patients treated with high flow nasal cannula;
- number of patients treated with steroids;
- number of patients treated with remdesevir; and
- number of patients treated with prone positioning.

Statistical analysis

All data are reported according to the relevant time period (eg, first or second wave). Descriptive statistics for all variables were calculated. Continuous variables are reported as medians with interquartile ranges (IQRs) and categorical variables as percentages with 95% confidence intervals (CIs), where appropriate.

Univariable comparisons between periods (with the first wave as reference) were performed with generalised linear modelling with binomial distribution and identity link for categorical variables, and with quantile models considering a $T = 0.50$ and an asymmetric Laplace distribution, for continuous variables. Differences in categorical variables are presented as risk difference with 95% CI, and in continuous variables as median difference with 95% CI. Categorical variables with more than two categories were compared using Fisher exact tests and no effect estimate is presented.

Time until ICU and hospital discharge is presented in cumulative incidence plots, with death before discharge treated as a competing risk. The groups were compared and subdistribution hazard ratios were estimated with a Fine–Gray competing risk model. All models were reassessed in adjusted analysis considering Acute Physiology and Chronic Health Evaluation (APACHE) II score as a covariate and the centre as random effect.

Change in mortality over time against severity of illness was assessed by generating an exponentially weighted moving average (EWMA) plot. The EWMA was constructed considering a weight of 0.005, a target based on the initial predicted risk of death for each disease, and the boundaries of the predicted risk being three standard deviations. The predicted risk of death was derived from APACHE II considering admission due to respiratory infection. In the EWMA plot, we compared the observed in-hospital mortality with APACHE II-predicted mortality to monitor changes in this variable over time. The EWMA is an approach used to monitor variables that make use of the entire history of a given output. This is different from other control charts that tend to treat each data point individually. With this strategy, each output (previous sample mean) is given a weighting defined by the user, and the most recent samples are weighted the highest. In addition, the EWMA chart is more sensitive for detecting smaller and moderate shifts in the process, in this case, in in-hospital mortality.

All analyses were conducted in R v.4.0.2 (R Foundation)[12] and statistical significance was set at 0.05.

Results

Patients

From 27 February to 22 October 2020, 466 patients with SARS-CoV-2 infection confirmed by PCR were recruited in 53 sites across six states and two territories in Australia. From these, five patients younger than 16 years were excluded, leaving 461 patients with confirmed COVID-19 for the final analysis. This number represented over 99% of all COVID-19 ICU admissions across Australia.[11] Overall, 206 patients (44.7%) were included in the first wave and 255 (55.3%) in the second wave (Online Appendix, eFigure 1). The cumulative incidence of patients with COVID-19 and the number of ICU beds occupied per day by these patients are shown in Figure 1. The cumulative number of patients according to state is shown in the Online Appendix (eTable 1 and eFigure 2).

Baseline characteristics of the included patients are shown in Table 1 and Figure 2. Patients admitted in the second wave were younger, less often males, less often had chronic cardiac failure and were less frequently taking an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB). Fever, cough, and sore throat were less frequent at presentation during the second wave, shortness of breath was more frequent (Figure 2). At baseline, patients admitted during the second wave had a higher heart and respiratory rate and lower temperature and oxygen saturation measured by pulse oximetry (Spo_2). The only difference in laboratory findings at ICU admission was a lower lymphocyte count in the second wave (Online Appendix, eTable 2). Overall APACHE II illness severity scores were similar.

Interventions and complications

The interventions used and the development of complications in included patients are shown in Table 2 and Figure 2. While the use of remdesevir and steroids increased substantially in the second wave, the use of hydroxychloroquine decreased. The use of mechanical ventilation was similar between the periods, but in the second wave, the use of high flow nasal cannula, non-invasive ventilation and prone positioning was higher and the use of vasopressor, inotropic and neuromuscular blockage drugs was lower (Table 2 and Figure 2). During the second wave there was a lower incidence of viral pneumonitis.

Clinical outcomes

Hospital outcomes were available in all patients. Patients in the second wave had a shorter duration of ventilation and ICU and hospital length of stay compared with patients in the first wave (Table 3 and Figure 3). Crude ICU mortality in the second wave (10.6% *v* 14.6%; risk difference, –3.97; 95% CI, –10.26 to 2.07; $P = 0.203$) and hospital mortality (12.2 *v* 14.6%; risk difference, –2.41; 95% CI, –8.82 to 3.80; $P = 0.452$) were similar between the groups (Table 3). However, there was a greater likelihood of being discharged alive earlier at any time point during the second wave, even after adjustment for confounders (Figure 3). These findings were confirmed in analysis adjusted by APACHE II and considering the centre of inclusion as random effect (Online Appendix, eTable 3).

Over time, hospital mortality constantly decreased and at the end of the second wave, it was lower than the risk of death predicted by APACHE II (Figure 4).

Discussion

Key findings

In this large multicentre study comparing the first and second waves of the disease, the outcomes for critically ill patients with COVID-19 admitted to ICUs in Australia have significantly improved. Specifically, the length of stay steadily decreased and patients were more likely to be discharged alive earlier in their ICU admission. Moreover, mortality was increasingly lower than predicted by illness severity scores. Coupled with this was evidence of practice change, with patients in the second wave more commonly receiving less invasive forms of respiratory support (including high flow oxygen and non-

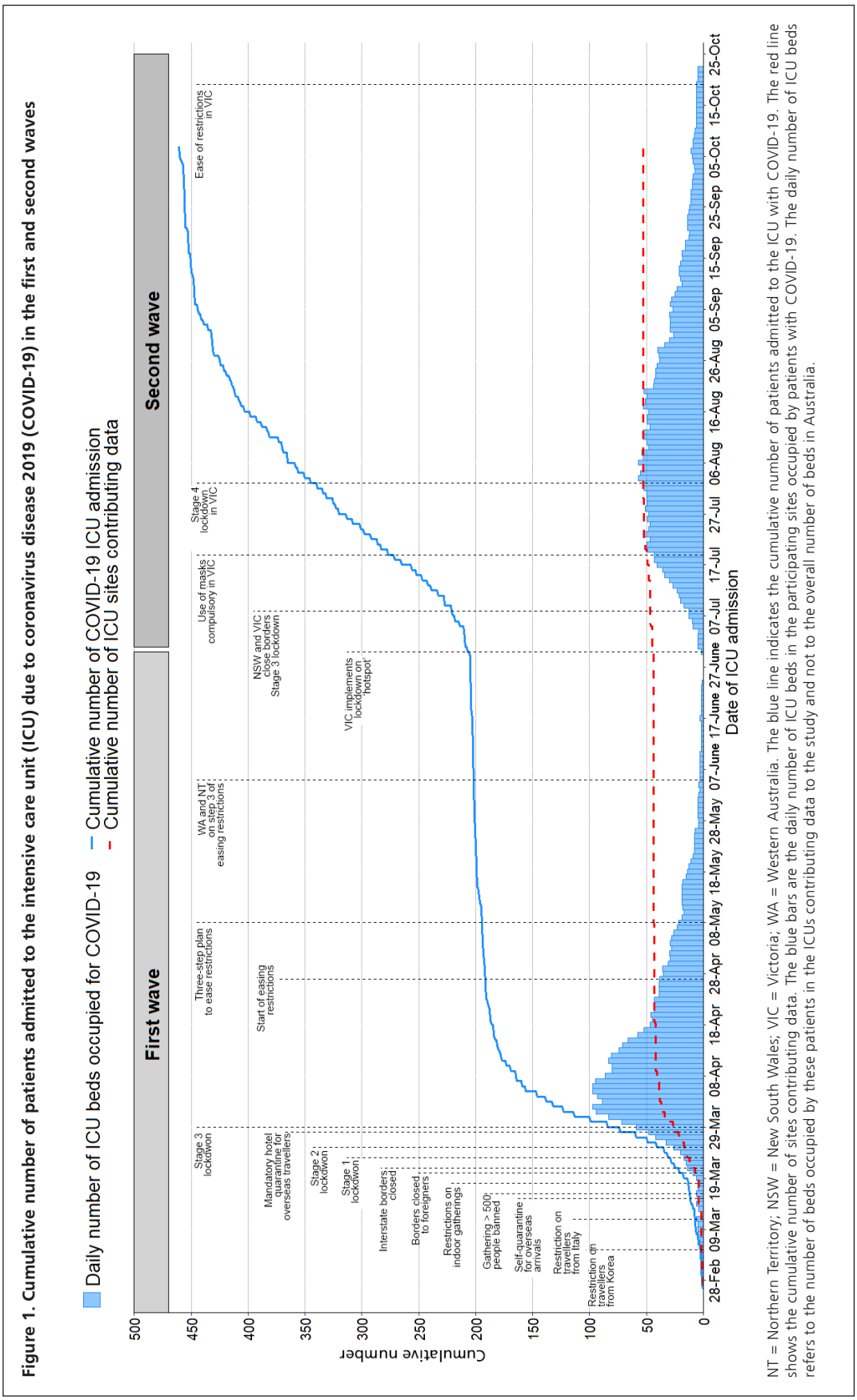


Figure 1. Cumulative number of patients admitted to the intensive care unit (ICU) due to coronavirus disease 2019 (COVID-19) in the first and second waves

NT = Northern Territory; NSW = New South Wales; VIC = Victoria; WA = Western Australia. The blue line indicates the cumulative number of patients admitted to the ICU with COVID-19. The red line shows the cumulative number of sites contributing data. The blue bars are the daily number of ICU beds in the participating sites occupied by patients with COVID-19. The daily number of ICU beds refers to the number of beds occupied by these patients in the ICUs contributing data to the study and not to the overall number of beds in Australia.

invasive ventilation), less vasopressor support, more proning and less neuromuscular blockade. There was a threefold increase in corticosteroid use and an almost 50% increase in the use of remdesevir in the second wave, while the use of hydroxychloroquine fell. Although there were slight changes in the demographic characteristics between the first and second wave, with patients in the second wave being younger, with a less male predominance and less likely to be taking an ACEI or ARB or have chronic heart failure, they were more likely to be admitted to the ICU with greater physiological derangement. In this respect, overall APACHE II scores did not differ significantly between the time periods.

Relationship to previous studies

Few studies have directly compared index and subsequent populations of critically ill patients with COVID-19. In an observational study of 2904 hospitalised patients with COVID-19 in Houston, Texas, there was a similar demographic shift towards younger patients with fewer comorbidities.[13] Utilisation of mechanical ventilation and hospital length of stay were also

Table 1. Baseline characteristics of the included patients at hospital admission

	First wave	Second wave	Absolute difference (95% CI)*	*P*
Total number of patients	206	255		
Age (years), median (IQR)	64.0 (54.0–72.0)	58.0 (49.5–68.0)	–5.18 (–8.14 to –2.23)	0.001
< 60	78 (37.9%)	137 (53.7%)		
60–69	56 (27.2%)	63 (24.7%)	na	0.002†
70–79	62 (30.1%)	43 (16.9%)		
≥ 80	10 (4.9%)	12 (4.7%)		
Sex, male	142 (68.9%)	153 (60.0%)	–8.93 (–17.57 to –0.14)	0.045
APACHE II score, median (IQR)	14.0 (10.0–18.0)	14.0 (10.0–18.0)	–0.00 (–1.36 to 1.36)	0.998
Days with symptoms, median (IQR)				
Hospital admission	6.0 (3.4–8.8)	7.0 (4.1–9.3)	0.97 (–0.12 to 2.06)	0.080
ICU admission	8.3 (5.2–11.2)	7.9 (5.4–10.4)	–0.25 (–1.33 to 0.84)	0.654
Median body mass index, kg/m^2 (IQR)	28.8 (24.5–32.3)	30.5 (26.8–35.7)	1.80 (–0.20 to 3.79)	0.078
Underweight	2/190 (1.1%)	0/209 (0.0%)		
Normal weight	54/190 (28.4%)	32/209 (15.3%)		
Overweight	52/190 (27.4%)	69/209 (33.0%)	na	0.011†
Obesity, class I	46/190 (24.2%)	51/209 (24.4%)		
Obesity, class II	22/190 (11.6%)	30/209 (14.4%)		
Obesity, class III	14/190 (7.4%)	27/209 (12.9%)		
Health care worker	17/196 (8.7%)	27/239 (11.3%)	2.62 (–3.13 to 8.27)	0.361
Number and type of co-existing disorders				
0	67 (32.5%)	79 (31.0%)		
1	43 (20.9%)	74 (29.0%)	na	0.236†
2	46 (22.3%)	50 (19.6%)		
> 2	50 (24.3%)	52 (20.4%)		
Diabetes	57 (27.7%)	79/236 (33.5%)	5.80 (–2.82 to 14.32)	0.185
Obesity	51 (24.8%)	68/235 (28.9%)	4.18 (–4.14 to 12.40)	0.322
Use of ACEI or ARB	51/205 (24.9%)	40/236 (16.9%)	–7.93 (–15.60 to –0.35)	0.041
Chronic cardiac failure	40 (19.4%)	26/236 (11.0%)	–8.40 (–15.24 to –1.74)	0.014
Smoker	27 (13.1%)	28/234 (12.0%)	–1.14 (–7.46 to 5.06)	0.719
Chronic pulmonary disease‡	16 (7.8%)	17/236 (7.2%)	–0.56 (–5.66 to 4.38)	0.822
Asthma	22 (10.7%)	38/236 (16.1%)	5.42 (–0.95 to 11.76)	0.092
Immunosuppression	13 (6.3%)	20/236 (8.5%)	2.16 (–2.81 to 7.11)	0.383
Chronic kidney disease	11 (5.3%)	17/236 (7.2%)	1.86 (–2.77 to 6.47)	0.418
Chronic haematological disease	9 (4.4%)	5/236 (2.1%)	–2.25 (–5.95 to 1.04)	0.187
Cancer	4 (1.9%)	12/236 (5.1%)	3.14 (–0.27 to 6.79)	0.068
Symptoms				
Fever	166/196 (84.7%)	172/236 (72.9%)	–11.81 (–19.36 to –4.14)	0.002
Cough	153/196 (78.1%)	155/236 (65.7%)	–12.38 (–20.68 to -3.91)	0.004
Shortness of breath	133/196 (67.9%)	185/236 (78.4%)	10.53 (2.17–18.94)	0.014
Fatigue	117/196 (59.7%)	126/236 (53.4%)	–6.30 (–15.60 to 3.09)	0.187
Myalgia	68/196 (34.7%)	70/235 (29.8%)	–4.91 (–13.78 to 3.93)	0.278
Diarrhoea	65/195 (33.3%)	59/235 (25.1%)	–8.23 (–16.87 to 0.38)	0.062
Sore throat	49/196 (25.0%)	37/236 (15.7%)	–9.32 (–17.03 to –1.74)	0.017
Anosmia	25/195 (12.8%)	25/235 (10.6%)	–2.18 (–8.47 to 3.90)	0.485
Runny nose	22/196 (11.2%)	25/236 (10.6%)	–0.63 (–6.70 to 5.26)	0.834
Signs at hospital admission, median (IQR)				
Heart rate, beats/min	95.0 (84.8–110.0)	103.0 (92.0–114.0)	7.74 (3.39–12.10)	0.001
Respiratory rate, breaths/min	28.0 (22.0–35.0)	32.0 (26.0–40.0)	4.02 (1.86–6.17)	< 0.001

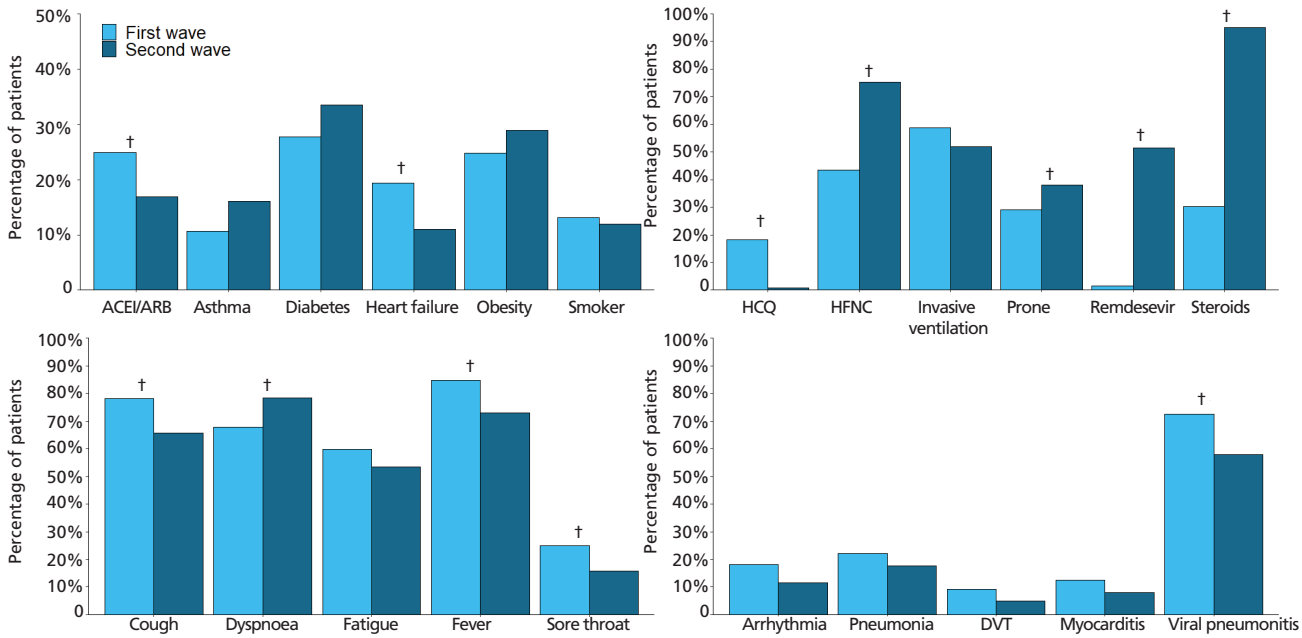
(Continues)

Table 1. Baseline characteristics of the included patients at hospital admission (*continued*)

	First wave	Second wave	Absolute difference (95% CI)*	*P*
Mean arterial pressure, mmHg	82.7 (72.0–96.0)	78.3 (69.0–93.3)	–4.30 (–8.91 to 0.32)	0.068
Temperature, °C	38.4 (37.8–39.0)	38.0 (37.2–38.8)	–0.40 (–0.66 to –0.14)	0.003
SpO_2, %	92.0% (89.0–95.0%)	91.0% (86.0–94.0%)	–1.93% (–3.46% to –0.41%)	0.013

APACHE = Acute Physiology and Chronic Health Evaluation; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ICU = intensive care unit; IQR = interquartile range; na = not applicable. Percentages may not total 100 because of rounding. * Absolute difference is risk difference for categorical variables and median difference for continuous variables. First wave was used as reference (negative values represent decrease in second wave). † *P* value estimated from Fisher exact test. ‡ Not considering asthma.

Figure 2. Coexisting disorders, symptoms, interventions and complications in patients admitted to the intensive care unit (ICU) due to coronavirus disease 2019 (COVID-19) in the first and second waves*



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; DVT = deep vein thrombosis; HCQ = hydroxychloroquine; HFNC = high flow nasal cannula. * Patients were categorised into "first wave" for ICU admissions occurring earlier than 1 July 2020 and into "second wave" for ICU admissions occurring from 1 July to 22 October 2020. † $P < 0.05$ (*P* value available in the tables).

reduced. In another observational study of 21 000 people admitted to critical care units in England between March and June 2020, mortality was demonstrated to decrease over time after adjusting for multiple factors.[14] Several other studies and a systematic review have also noted this trend.[15] Many of these studies were limited by a predominance of hospitalised and high dependency unit patients and lack of granular data about critical care interventions and treatments received. Furthermore, in comparison to countries with a much higher number of infections, the Australian health care system as a whole over this period was relatively well resourced and not under significant strain. However, given the second wave was more geographically isolated, with a much smaller number of hospitals managing these cases, it is likely resources, staff and equipment were affected locally.[16]

Data from this study illustrate that clinical management changed over the course of the COVID-19 pandemic. Several early guidelines suggested avoiding non-invasive ventilation and high flow oxygen due to concerns about aerosolisation of SARS-CoV-2, and instead recommended earlier intubation.[17] However,

Table 2. Interventions and development of complications in the included patients

	First wave	Second wave	Absolute difference (95% CI)*	*P*
Total number of patients	206	255		
Interventions				
Drugs				
▸ Antibiotics	178/195 (91.3%)	214/235 (91.1%)	–0.22 (–5.60 to 5.34)	0.937
▸ Steroids	59/195 (30.3%)	229/241 (95.0%)	64.76 (57.48–71.46)	< 0.001
▸ Hydroxychloroquine	35/193 (18.1%)	2/238 (0.8%)	–17.29 (–23.22 to –12.11)	< 0.001
▸ Oseltamivir	1/195 (0.5%)	0/238 (0.0%)	na	0.920†
▸ Lopinavir–ritonavir	9/195 (4.6%)	4/238 (1.7%)	–2.93 (–6.74 to 0.29)	0.088
▸ Remdesevir	3 (1.5%)	131 (51.4%)	49.92 (43.52–56.20)	< 0.001
Organ support‡				
▸ Mechanical ventilation	121 (58.7%)	125/241 (51.9%)	–6.87 (–16.02 to 2.38)	0.144
▸ Inotropic or vasopressor	113/196 (57.7%)	110/230 (47.8%)	–9.83 (–19.20 to –0.32)	0.042
▸ Neuromuscular blocking agent	88/196 (44.9%)	80/232 (34.5%)	–10.42 (–19.63 to –1.13)	0.028
▸ High flow nasal cannula	85/196 (43.4%)	176/234 (75.2%)	31.85 (22.83–40.54)	< 0.001
▸ Prone positioning	57/196 (29.1%)	88/231 (38.1%)	9.01 (0.03–17.85)	0.048
▸ Renal replacement therapy	25/196 (12.8%)	20/231 (8.7%)	–4.10 (–10.20 to 1.76)	0.174
▸ Non-invasive ventilation	14/197 (7.1%)	38/230 (16.5%)	9.42 (3.39–15.50)	0.002
▸ Other cardiac procedures	12/196 (6.1%)	10/232 (4.3%)	–1.81 (–6.34 to 2.42)	0.404
▸ Tracheostomy	13/196 (6.6%)	20/231 (8.7%)	2.03 (–3.14 to 7.12)	0.430
▸ Inhaled nitric oxide	13/196 (6.6%)	13/232 (5.6%)	–1.03 (–5.83 to 3.54)	0.659
▸ Extracorporeal membrane oxygenation	2/196 (1.0%)	10/232 (4.3%)	na	0.078†
Development of complications				
Viral pneumonitis	140/193 (72.5%)	129/223 (57.8%)	–14.69 (–23.62 to –5.57)	0.001
Bacterial pneumonia	42/190 (22.1%)	38/215 (17.7%)	–4.43 (–12.30 to 3.34)	0.265
Bacteraemia	29/190 (15.3%)	21/225 (9.3%)	–5.93 (–12.48 to 0.37)	0.068
Stroke	3/192 (1.6%)	0/226 (0.0%)	na	0.192†
Arrhythmia	35/193 (18.1%)	26/227 (11.5%)	–6.68 (–13.66 to 0.09)	0.055
Barotrauma§	12/193 (6.2%)	6/225 (2.7%)	–3.55 (–7.93 to 0.34)	0.082
Cardiac arrest	4/192 (2.1%)	4/226 (1.8%)	–0.31 (–3.33 to 2.46)	0.817
Pulmonary embolism	7/176 (4.0%)	11/224 (4.9%)	0.93 (–3.37 to 5.06)	0.651
Deep vein thrombosis	16/176 (9.1%)	11/226 (4.9%)	–4.22 (–9.65 to 0.73)	0.104
Myocarditis	22/176 (12.5%)	18/225 (8.0%)	–4.50 (–10.79 to 1.42)	0.144

ACEI = angiotensin-converting enzyme inhibitor; APACHE = Acute Physiology and Chronic Health Evaluation; ARB = angiotensin II receptor blocker; na = not applicable. Percentages may not total 100 because of rounding. * Absolute difference is risk difference. First wave was used as reference (negative values represent decrease in second wave). † *P* value estimated from Fisher exact test. ‡ Assessed daily until ICU discharge. § Defined as pneumothorax or pneumomediastinum or subcutaneous emphysema on chest x-ray or chest computed tomography scan.

as experience with COVID-19 in ICUs increased,[18] Australian practice returned towards more routine and evidence-based management of patients with severe respiratory failure, with an emphasis on less invasive respiratory supports, while proning (a labour-intensive procedure requiring multiple people to enter the patient's room) also increased over time. These changes were also reflected in evolving Australian national guidelines.[9]

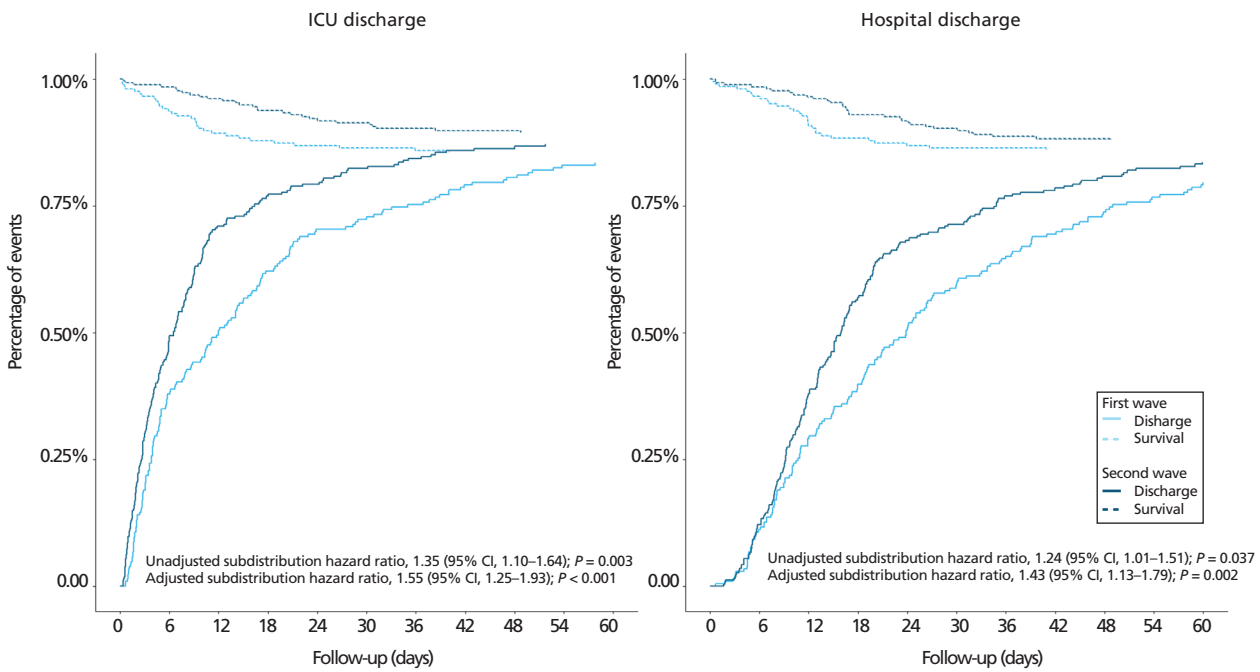
This study also illustrates the rapid translation of published trial data into Australian critical care practice between the first and second waves. Indeed, publication of the RECOVERY trial[7] resulted in a rapid and widespread threefold increase in corticosteroid use in Australian practice. Use of remdesivir, an antiviral drug, also significantly increased following the release of the ACTT II trial findings,[8] although the recently completed

Table 3. Clinical outcomes in the included patients

	First wave	Second wave	Absolute difference (95% CI)*	*P*
Total number of patients	206	255		
Duration of ventilation (days), median (IQR)	12.0 (7.0–14.0)	8.0 (4.0–17.0)	–3.05 (–5.22 to –0.89)	0.006
ICU length of stay (days), median (IQR)	8.1 (3.1–18.7)	5.9 (2.4–11.1)	1.35 (1.10–1.64)†	0.003
Truncated at extraction, days	8.4 (3.2–18.7)	6.0 (2.4–12.2)		
Hospital length of stay (days), median (IQR)	17.3 (8.9–30.5)	14.2 (8.6–21.1)	1.24 (1.01–1.51)†	0.037
Truncated at extraction, days	17.6 (9.0–32.4)	14.7 (8.9–23.0)		
ICU mortality	30 (14.6%)	27 (10.6%)	–3.97 (–10.26 to 2.07)	0.203
Hospital mortality	30 (14.6%)	31 (12.2%)	–2.41 (–8.82 to 3.80)	0.452

ICU = intensive care unit; IQR = interquartile range. Percentages may not total 100 because of rounding. * Absolute difference is risk difference for categorical variables and median difference for continuous variables. The first wave was used as reference (negative values represent decrease in second wave). † Subdistribution hazard ratio from a Fine–Gray competing risk model.

Figure 3. Cumulative incidence plot of intensive care unit (ICU) and hospital discharge according to the phase of the study*



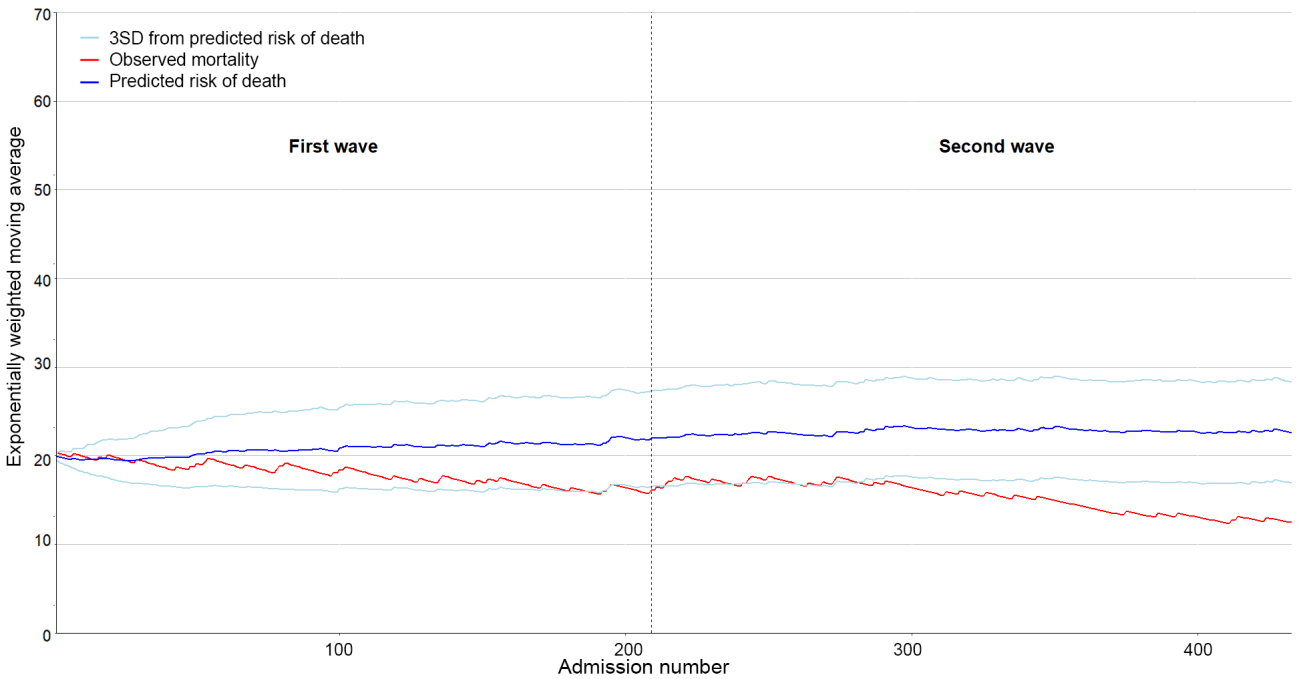
* Patients were categorised into "first wave" for ICU admissions occurring earlier than 1 July 2020 and into "second wave" for ICU admissions occurring from 1 July to 22 October 2020.

larger WHO SOLIDARITY trial has raised further questions about its effectiveness.[19] Finally, hydroxychloroquine, initially considered as a potential treatment for COVID-19, was not found to be effective and was potentially associated with increased death[20] and its use rapidly declined.

Study implications

This study implies that the outcomes of critically ill patients with COVID-19 admitted to ICUs across Australia have improved over two distinct waves of the disease. Multiple

Figure 4. Exponentially weighted moving average (EWMA)*



SD = standard deviation. * The EWMA was constructed considering a weight of 0.005, a target based on the initial predicted risk of death for each disease, and the boundaries of the predicted risk considered three standard deviations. The predicted risk of death was derived from Acute Physiology and Chronic Health Evaluation (APACHE) II score considering admission due to respiratory infection.

factors may be responsible, including changes in ICU practice that favoured less invasive forms of ventilation, the rapid uptake of new evidence-based treatments, the avoidance of non-evidence-based therapies, and possible changes in the demographic characteristics of patients that required ICU admission. Critically, this study has implications for other countries currently in the midst of or preparing for further COVID-19 outbreaks and reinforces the value of implementing and/or updating clinical practice guidelines with the latest evidence.

Strengths and limitations

This is the first study to provide detailed, national coverage of critically ill patients with COVID-19 over the course of both a complete first and second wave of cases. In both periods, over 99% of the critically ill patients with COVID-19 in intensive care across Australia were included, with complete follow-up, and the same case report forms and data definitions were used, making the two cohorts highly comparable.

This study has several limitations. Only patients admitted to the ICU were included, and as such, our findings do not extend to the larger population of patients with COVID-19 admitted to hospital. Moreover, we have not collected detailed data concerning ICU admission practices, triage decisions or ICU occupancy and, therefore, we cannot exclude changes in admission criteria or ICU strain as potential sources of bias, but we note that the admission APACHE II scores were consistent across both periods. In addition, we did not collect data on virus virulence or host response, which may have affected clinical outcomes. Data from the first wave included all states and territories in Australia, while the second wave was almost exclusively from a single state. The data were censored, so some of the data for the second wave patients may not have been complete. Finally, for some therapeutic variables, such as corticosteroids, we did not collect any further data concerning type, dose, duration or indication, such that we are unable to undertake any more granular analysis.

Conclusion

During the second wave of COVID-19 in Australia, ICU and hospital length of stay of patients with COVID-19 admitted to the ICU decreased, and observed in-hospital mortality declined over time and was significantly lower

than predicted by APACHE II scores. Multiple factors were associated with this, including changes in clinical management, the widespread and rapid adoption of evidenced-based practices, and changes in patient demographic characteristics but not illness severity.

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Competing interests

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