Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Clinical Virology Plus 1 (2021) 100054

Contents lists available at ScienceDirect

Journal of Clinical Virology Plus

journal homepage: www.elsevier.com/locate/jcvp

Nosocomial infections amongst critically ill COVID-19 patients in Australia

Mahesh Ramanan[a,f,g,*], Aidan Burrell[b,e], Eldho Paul[c], Tony Trapani[b,e], Tessa Broadley[b,e], Steve McGloughlin[b,e], Craig French[d], Andrew Udy[c]

[a] Caboolture Hospital, 120 McKean Street, Caboolture, Queensland, Australia
[b] Department of Epidemiology and Preventative Medicine, School of Public Health, Monash University, Melbourne, Australia
[c] Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, 553St Kilda Road, Melbourne, Victoria, Australia
[d] Western Health, Furlong Road, St Albans, Victoria, Australia
[e] Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, 553St Kilda Road, Melbourne, Victoria, Australia
[f] Critical Care Division, The George Institute for Global Health, University of New South Wales, 1 King Street, Newtown, New South Wales, 2042, Australia
[g] School of Medicine, University of Queensland, St. Lucia, Queensland, 4072, Australia

ARTICLE INFO

Keywords:
COVID-19
Critical care
Bloodstream infections
Nosocomial infections
Healthcare-associated pneumonia

ABSTRACT

Purpose: To determine the frequency of nosocomial infections including hospital-acquired pneumonia (HAP) and bloodstream infection (BSI), amongst critically ill patients with COVID-19 infection in Australian ICUs and to evaluate associations with mortality and length of stay (LOS).

Methods: The effect of nosocomial infections on hospital mortality was evaluated using hierarchical logistic regression models to adjust for illness severity and mechanical ventilation.

Results: There were 490 patients admitted to 55 ICUs during the study period. Adjusted odds ratio (OR) for hospital mortality was 1.61 (95% confidence interval (CI) 0.61–4.27, $p = 0.3$) when considering BSI, and 1.76 (95% CI 0.73–4.21, $p = 0.2$) for HAP. The average adjusted ICU LOS was significantly longer for patients with BSI (geometric mean 9.0 days vs 6.3 days, $p = 0.04$) and HAP (geometric mean 13.9 days vs 6.0 days $p<0.001$).

Conclusion: Nosocomial infection rates amongst patients with COVID-19 were low and their development was associated with a significantly longer ICU LOS.

1.0. Background

The coronavirus disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has resulted in >183 million confirmed cases and >3.9 million deaths globally since first being detected in December 2019 in Wuhan, China [1]. Like other respiratory viral infections, such as influenza, COVID-19 has been associated with secondary bacterial and fungal infections [2–5].

Secondary infections in patients with influenza viral pneumonitis, including during the2009 H1N1 pandemic [6], have been well characterised and are known to be associated with higher illness severity, usage of healthcare resources, morbidity and mortality [7–11]. These infections, most commonly *Streptococcus pneumoniae* and *Staphylococcus aureus*, occurred in 23% of patients with H1N1 [8]. Viral co-infections have been reported in 10–60% of these patients [7].

However, there is paucity of such data for COVID-19[12]. A single-centre study demonstrated that mechanically ventilated COVID-19 patients were twice as likely to develop a ventilator-associated pneumonia (VAP) than patients without COVID-19, but both groups had similar pulmonary microbiomes [13]. Another single-centre study conducted in a repurposed COVID-19 ICU reported that 67% of COVID-19 patients in their cohort had bloodstream infections (BSI) [4]. A large cohort study of mostly non-critically ill hospitalized COVID-19 patients reported that nosocomial infections, mostly respiratory and bloodstream, were rare in a cohort where most patients (82.3%) did not have microbiological investigations [14].

Further studies evaluating the characteristics and outcomes of COVID-19 patients with nosocomial infections are required to enable clinicians to risk stratify patients and guide therapy.

The *Short Period Incidence Study of Severe Acute Respiratory Infections* (SPRINT-SARI Australia) study[15] has been prospectively collecting comprehensive data on critically ill patients with COVID-19 admitted to Australian intensive care units (ICU) from February 2020.

We used the SPRINT-SARI Australia database to determine clinical characteristics and outcomes, including mortality and lengths of stay, of COVID-19 patients admitted to Australian ICUs who developed noso-

* Corresponding author at: Intensive Care Unit, Level 2, Caboolture Hospital, 120 McKean Street, Caboolture, Queensland, 4035, Australia.
E-mail address: Mahesh.ramanan@health.qld.gov.au (M. Ramanan).

https://doi.org/10.1016/j.jcvp.2021.100054
Received 11 July 2021; Received in revised form 2 November 2021; Accepted 8 November 2021

comial infections compared to patients who did not develop such infections. Our primary hypothesis was that clinical outcomes would be inferior in those patients who developed a nosocomial infection, independent of admission illness severity.

2.0. Methods

This multicentre cohort study was performed following the recommendations of the STROBE Statement[16]. Ethics approval with full consent waiver was granted under the National Mutual Acceptance scheme by the Alfred Health Human Research Ethics Committee (HREC/16/Alfred/59) or by specific applications at individual sites.

2.1. Study design

The methodology for SPRINT-SARI Australia has been described in detail elsewhere [15]. In brief, the SPRINT-SARI Australia case report form, developed together with partners from the International Severe Acute Respiratory and Emerging Infection Consortium [17], prospectively collected data on all COVID-19 admissions to participating ICUs. Patients had to have a positive polymerase chain reaction (PCR) test for COVID-19 and require ICU admission for COVID-19 related indications.

There were 79 participating ICUs across Australia. Decisions to admit and discharge patients were made by treating clinicians, mostly specialist intensive care physicians, based on local protocols at individual sites.

2.2. Data

Data pertaining to baseline demographics, clinical characteristics, treatments, microbiology and clinical outcomes were extracted from the SPRINT-SARI Australia database for patients admitted from inception until 30 September 2020. Data for patients without a complete outcome (i.e., they were still alive in ICU or hospital) were collected for descriptive purposes, but not used for analysing mortality.

Hospital-acquired pneumonia (HAP) was defined as an acute infectious process of the lungs with clinical and, if available, radiological evidence of focal or diffuse lung infiltrates that the treating clinician believed to be due to pneumonia occurring after 48 h of hospital admission [18]. When this occurred within 48 h of hospital admission, we termed this co-infection. We considered HAP with a microbiological diagnosis (i.e., evidence of an infectious organism from bronchoalveolar lavage, endotracheal aspirates or sputum samples) and/or BSI as constituting a nosocomial infection. Patients who had evidence of an infectious organism from bronchoalveolar lavage, endotracheal aspirates or sputum samples without meeting criteria for HAP were defined as having a colonising organism.

BSI was defined as presence of bacteria in blood detected on blood cultures. BSIs with organisms known to cause contamination such as coagulase negative Staphylococci were considered to be contaminants and not included in the BSI group unless specified in the database as a true BSI. Nosocomial infection was defined as the presence of either BSI and/or HAP.

2.3. Statistical analyses

Continuous variables were assessed for normality and summarised using mean and standard deviation or median and interquartile range (IQR) according to data type and distribution. Categorical variables were summarised using counts and proportions.

The primary outcome measure was hospital mortality. The primary exposure variables were the development of BSI or HAP during ICU admission. Univariable analysis was performed using logistic regression to determine the association between BSI, HAP and hospital mortality. Multivariable analysis was performed using hierarchical logistic regression adjusting for Acute Physiology And Chronic Health Evaluation 2 (APACHE-2) score and receipt of mechanical ventilation with patients nested within sites and sites treated as random effects. Sensitivity analyses were performed by excluding patients who did not receive mechanical ventilation throughout their ICU admission. A further sensitivity analysis was conducted by using nosocomial infection as a composite exposure variable that included both BSI and HAP. The secondary outcomes, ICU and hospital lengths of stay were analysed using generalised linear mixed modelling adjusting for APACHE-2 and mechanical ventilation with patients nested within sites and sites treated as random effects. The lengths of stay were analysed as log-transformed continuous variables due to positively skewed distributions. Multivariable competing-risks regression was used to identify predictors and quantify cumulative incidence of nosocomial infection with death as a competing risk. Patients with missing data for the outcomes being analysed or the covariates were excluded from the respective analyses. We did not perform any imputation for missing data.

Results are reported as odds ratios (OR) for hospital mortality, geometric means for lengths of stay and hazard ratios (HR) for nosocomial infection with corresponding 95% confidence intervals (95% CI). A two-sided p value of 0.05 was chosen to indicate statistical significance in all analyses.

Microbiological characteristics were summarised using descriptive statistics.

All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 15 (StataCorp, Texas, USA).

2.5. Funding

SPRINT-SARI Australia is supported by funding from the Australian Department of Health (Standing Deed SON60002733). This post-hoc analysis did not receive any specific funding.

3.0. Results

3.1. Patient characteristics

There were 490 patients with confirmed COVID-19 admitted to 55 Australian ICUs during the study period. Of these, 36%(176/490) were female and the overall median age was 61 years(IQR 50–70). Other characteristics of the cohort are presented in Table 1.

3.2. Nosocomial infections

There were 30 out of 490 patients (6%) who developed BSI and 36(6%) who developed HAP during their ICU stay. There were 6 patients (1%) who developed both BSI and HAP leaving 430 patients (88%) who did not develop a nosocomial infection.

In the univariable competing risks models, we found that temperature (highest in first 24 h), body-mass index (BMI) and mechanical ventilation were all significantly associated with development of nosocomial infection. Mechanical ventilation was strongly and independently associated with development of nosocomial infection after adjustment for age, sex, APACHE-2 score, temperature and BMI in a competing-risks regression model (HR 6.62, 95% CI 2.29–19.10, $p = 0.0005$). BMI was also independently associated with nosocomial infection in this model with a HR of 1.04 per 1 unit of BMI (95% CI 1.02–1.06, $p = 0.001$). The other variables in the model were not statistically significant.

The cumulative incidence function for development of nosocomial infection is displayed in Fig. 1. The incidence of nosocomial infection increased over time from Day 0 to approximately Day 60 of hospitalization.

3.3. Outcomes

Hospital mortality for patients with BSI and HAP were 27%(8/30) and 23%(8/35) compared to 11%(46/422) for patients without nosocomial infection. Lengths of stay and readmission rates as presented in Table 3.

Table 1
Patient characteristics.

N	BSI $n = 30$	HAP $n = 36$	Neither BSI nor HAP $n = 430$	Total $n = 490$
Age, years, median (interquartile range)	68(63–72), $n = 30$	62.5(56–73), $n = 36$	60(49–70), $n = 430$	61(50–70), $n = 490$
Female sex	8/30 (27%)	9/36 (25%)	160/430 (37%)	176/490 (36%)
Cruise ship traveller	6/30 (20%)	7/36 (19%)	45/430 (10%)	55/490 (11%)
International traveller	11/30 (37%)	16/36 (44%)	100/430 (23%)	123/490 (25%)
Baseline observations				
Temperature degrees celsius, median (interquartile range)	38(37.3–38.9), $n = 29$	38.6(37.7–39), $n = 35$	38.2(37–39), $n = 388$	38.2(37.4–38.9), $n = 446$
Heart rate beats per minute, median (interquartile range)	105(99–113), $n = 29$	102(95–111), $n = 35$	99(86–111), $n = 389$	100(86–111), $n = 447$
Respiratory rate, breaths per minute, median (interquartile range)	31(24–38), $n = 27$	28(23–34), $n = 33$	30(24–38), $n = 382$	30(24–38), $n = 436$
Systolic blood pressure, mm Hg, median (interquartile range)	117(95–155), $n = 29$	112(100–135), $n = 36$	113(98–137), $n = 390$	113(98–138), $n = 449$
Comorbidities				
Diabetes	9/30 (30%)	10/36 (28%)	103/409 (25%)	120/469 (26%)
Chronic cardiac disease[†]	7/30 (23%)	4/36 (11%)	60/409 (15%)	70/469 (15%)
Chronic pulmonary disease[‡]	5/30 (17%)	4/36 (11%)	28/408 (7%)	35/468 (7%)
Obesity[§]	7/30 (23%)	15/36 (42%)	108/408 (26%)	128/468 (27%)
Malignancy	1/30 (3%)	2/36 (6%)	14/409 (3%)	17/469 (4%)
Baseline investigations[^]				
P:F ratio, median (interquartile range)	104(69–182.5), $n = 27$	123(82–166), $n = 30$	138(100–194), $n = 325$	135.5556(96.31461–191.9643), $n = 376$
pCO2, mm Hg, median (interquartile range)	37(30–47), $n = 19$	40(35–47), $n = 25$	37(33–44), $n = 242$	37(33–44), $n = 280$
pH, median (interquartile range)	7.39(7.36–7.44), $n = 19$	7.37(7.32–7.45), $n = 25$	7.42(7.37–7.47), $n = 241$	7.42(7.36–7.47), $n = 279$
Lactate, mmol/L, median (interquartile range)	1.8(0.9–2.7), $n = 27$	1.5(0.9–2.2), $n = 29$	1.4(1.1–1.9), $n = 318$	1.4(1.1–1.95), $n = 368$
Creatinine, micromole/L, median (interquartile range)	102(67–154), $n = 17$	80(65–111), $n = 22$	75(60–100), $n = 228$	76(61–104), $n = 262$
White cell count, X 10^9/mm^3, median (interquartile range)	6.3(5–13.14), $n = 16$	7.75(3.5–16.0), $n = 16$	8.4(6.2–11.2), $n = 180$	8.1(6–11.3), $n = 207$
APACHE-2 score, median (interquartile range)	18(12–21), $n = 30$	17.5(13–20), $n = 36$	14(10–17), $n = 396$	14(10–18), $n = 456$
ICU Interventions				
Mechanical ventilation	25/30 (83%)	33/36 (92%)	217/430 (50%)	269/490 (55%)
Non-invasive ventilation	5/30 (17%)	4/36 (11%)	47/430 (11%)	54/490 (11%)
Renal replacement therapy	10/30 (33%)	10/36 (28%)	30/430 (7%)	48/490 (10%)
Prone positioning	10/30 (33%)	20/36 (56%)	123/430 (29%)	151/490 (31%)
Extracorporeal life support	3/30 (10%)	1/36 (3%)	13/430 (3%)	17/490 (3%)

BSI = bloodstream infection; HAP = hospital acquired pneumonia; P:*F* = PaO2:FiO2; APACHE-2 = Acute physiology and chronic health evaluation-2 score; ICU = intensive care unit

#Worst observations within first 24 h of hospital admission.

[†] Includes history of coronary artery disease, congenital heart disease, cardiomyopathy, congestive heart failure, rheumatic heart disease.

[‡] Includes history of chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, interstitial lung disease, requirement for domiciliary oxygen therapy.

[§] body-mass index ≥ 30.0.

[^] worst laboratory investigation values within first 24 h of hospital admission.

After adjustment for APACHE-2 score and mechanical ventilation in the multivariable hierarchical logistic regression model, the adjusted OR for hospital mortality was 1.61(95% CI 0.61–4.27, $p = 0.3$) with BSI. With HAP, the adjusted OR was 1.76(95% CI 0.73–4.21, $p = 0.2$). Sensitivity analyses for both these models were conducted by removing patients who did not receive mechanical ventilation. The respective ORs for the BSI and HAP models changed minimally to 1.43(95% CI 0.51–4.04, $p = 0.5$) and 1.40(95% CI 0.57–3.44, $p = 0.5$). There were similarly minimal changes to the results when use of antibiotics was added as a fixed effect to both models. When nosocomial infection was the exposure variable, the adjusted OR for hospital mortality was 2.30(95% CI 1.12–4.73, $p = 0.02$).

The average ICU length of stay, after adjustment for APACHE-2 score and mechanical ventilation, was significantly longer for patients with BSI compared to those without BSI (geometric mean 9.0 days, 95% CI 6.4–12.7, vs 6.3 days, 95% CI 5.5–7.3, $p = 0.04$) and HAP (geometric mean 13.9, 95% CI 10.3–18.8 vs 6.0, 95% CI 5.2–6.8. $p<0.001$). The average hospital length of stay, after adjustment for the same covariates, was not significantly longer for patients with BSI (geometric mean 19.7 days, 95% CI 14.4–26.9 vs 14.8 days, 95% CI 13.1–16.6, $p = 0.07$) but was longer for patients with HAP (geometric mean 29.0 days, 95% CI 22.0–38.2 vs 14.0 days, 95% CI 12.6–15.7, $p<0.001$).

3.4. Microbiological findings

3.4.1. Nosocomial infection

Six out of 30 patients (20%) with BSI had gram positive cocci isolated from their blood. One of these was a methicillin-resistant *Staphylococcus aureus* (MRSA), two were *Enterococcus faecalis* and three were *Enterococcus faecium*. There were 12 patients (40%) with gram negative organisms including 3 with *Enterobacter cloacae*, 2 each with *Pseudomonas aeruginosa* and *Escherichia coli*, 1 each with *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia*, and a further 3 patients with multiple organisms on blood culture. There were a further 12 patients (40%) with missing data concerning the BSI organism.

Twelve out of 36 patients (33%) had HAP with gram positive cocci isolated from cultures of respiratory samples including 1 patient with MRSA and 11 with other *Staphylococcal* species. There were 21 patients

Table 2
Microbiological findings in patients with nosocomial infections.

BSI $n = 30$			HAP $n = 36$		
	Species	n (%)		Species	n (%)
Gram positive cocci	Total	6(20%)	Gram positive cocci	Total	12 (30%)
	Enterococcus faecalis	2(7%)		*Staphylococcus aureus* (methicillin resistant)	1(3%)
	Enterococcus faecium	3(10%)		Other *Staphylococcal spp.*	11(28%)
	Staphylococcus aureus (methicillin resistant)	1(3%)	Gram negative bacilli	Total	15(38%)
Gram negative bacilli	Total	12(40%)		*Enterobacter* spp.	1(3%)
	Enterobacter cloacae	3(10%)		*E. coli*	1(3%)
	E. coli	2(7%)		*Klebsiella pneumoniae*	3(8%)
	Klebsiella pneumoniae	1(3%)		*Pseudomonas aeruginosa*	4(10%)
	Pseudomonas aeruginosa	2(7%)		*Stenotrophomonas maltophilia*	1(3%)
	Stenotrophomonas maltophilia	1(3%)		Unspeciated	3(8%)
Mixed*		3(10%)	Mixed^		8(20%)
Not available		12(40%)	Fungi	Total	1(3%)
				Aspergillus fumigatus	1(3%)
			Viral	Total	2(5%)
				Herpes simplex virus	1(3%)
				Ebstein-Barr virus	1(3%)

BSI = bloodstream infection; HAP = hospital acquired pneumonia.

* The 3 patients with mixed BSI had the following combinations of organisms: Enterobacter cloacae and Pseudomonas aeruginosa; Klebsiella pneumoniae and Stenotrophomonas maltophilia; Klebsiella aerogenes and Proteus mirabilis.

^ The 8 patients with mixed nosocomial pneumonia had the following combinations of organisms: *Staphylococcus aureus* and unspeciated yeast; *Staphylococcus aureus* and *Ralstonia* spp.; *Enterobacter cloacae* and *Pseudomonas aeruginosa; Klebsiella aerogenes* and *Proteus mirabilis; Klebsiella oxytoca* and *Raoultella* spp.; *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* and 2 patients had unspeciated mixed organisms.

Table 3
Outcomes.

Outcome	BSI $n = 30$	HAP $n = 40$	Neither BSI nor HAP $n = 430$	Total $n = 490$
Hospital mortality	8/30 (27%)	9/39 (23%)	46/422 (11%)	63/485 (13%)
ICU length of stay	16.1(4.5–35.1), $n = 30$	21.7(16–36.4), $n = 40$	5.7(2.6–12), $n = 425$	6.7(2.8–15.1), $n = 489$
Hospital length of stay	24.8(12.9–47.8), $n = 30$	33.7(23–50.7), $n = 39$	13.2(7.8–22.3), $n = 423$	14.6(8.1–25.2), $n = 486$
ICU readmission	1/29 (3%)	3/37 (8%)	25/381 (7%)	29/441 (7%)

BSI = bloodstream infection; HAP = hospital acquired pneumonia; ICU = intensive care unit.

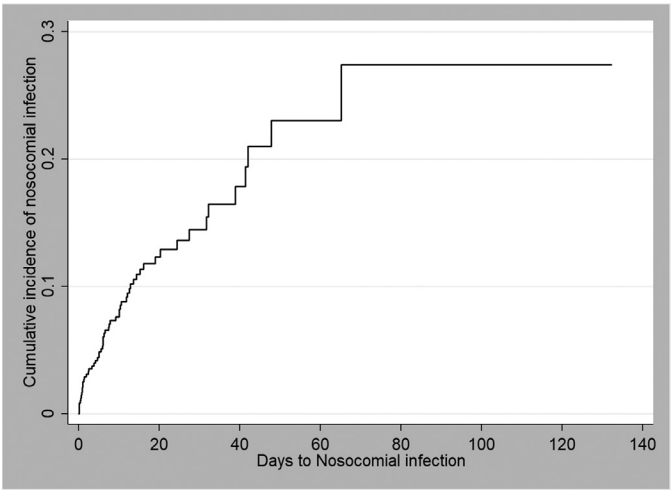

Fig. 1. Cumulative incidence of nosocomial infections. This figure shows the cumulative incidence of nosocomial infection in critically ill COVID-19 patients upto Day 140 of hospitalisation.

(58%) with gram negative bacilli of which 8 were mixed growths and 4 were *Pseudomonas aeruginosa*. One patient had a fungal pathogen (*Aspergillus spp*) identified as the source of their HAP, and 2 had viruses isolated. Details of HAP and BSI organisms are presented in Table 2.

3.4.2. Co-infections (within 48 h of admission to ICU)

The overall rate of co-infection was 6% (27/490). There were 3 patients (12%) with viral co-infections, 9 (33%) with gram positive cocci, 12 (44%) with gram negative bacilli and 2 (7%) with fungal co-infections (details in Table 4). Of patients with co-infection, 11 (41%) went on to develop HAP.

Table 4
Colonising organisms ($n = 28$).

Gram positive cocci	Species	n (%)
	Staphylococcus aureus	5(18%)
	Enterococcus species	3(11%)
	Other Staphylococcal species	2(7%)
Gram negative bacilli		
	Pseudomonas aeruginosa	3(11%)
	Klebsiella species	2(7%)
	Enterobacter species	2(7%)
	E. coli	1(4%)
	Serratia marcescens	1(4%)
	Haemophilus influenzae	1(4%)
	Acinetobacter species	1(4%)
Fungi		
	Candida species	4(14%)
	Aspergillus species	2(7%)
	Unspeciated	1(4%)

3.4.3. Colonising organisms

In addition to the patients who developed HAP, there were 28 patients (6%) who had positive microbiological findings on respiratory specimen culture but did not meet criteria for diagnosis of HAP. Amongst these patients with colonising organisms in their respiratory system, there were ten gram-positive cocci including 5 *Staphylococcus aureus* (of which 2 were MRSA). There were eleven gram-negative

bacilli, 4 *Candida* species and 2 *Aspergillus* species. Details are presented in Table 4.

3.5. Nurse:patient ratios

Nurse:patient ratios in Australian ICUs are strictly mandated at 1.0 for mechanically ventilated patients, though the ratio can be 0.5 for certain selected non-ventilated patients. Over 90% of our cohort received a nurse:patient ratio of at least 1.0, with a further 8% of patients receiving a ratio of 0.5 and only 1% receiving a ratio lower than 0.5. All the patients with nosocomial infections had a ratio of 1.0 or 2.0.

4.0. Discussion

4.1. Key findings

Nosocomial infections, BSI and HAP, occurred in 6% and 7% of patients with COVID-19 admitted to Australian ICUs respectively. The development of either BSI or HAP, was not independently associated with an increase in the risk of hospital mortality, after adjustment for illness severity and requirement for mechanical ventilation. However, both BSI and HAP were associated with significantly longer ICU lengths of stay.

4.2. Comparisons to literature

In the pre-COVID-19 ICU literature, it has been reported that 5–7% of ICU patients develop BSI, with up to 40% of patients in septic shock trials developing BSI[19]. Amongst ICU patients, BSI is known to be associated with increased risk of mortality[20] and both HAP and nosocomial infections with increased mortality and length of stay in ICU and hospital[21,22].

An Italian cohort study[4] found that 67% of patients with COVID-19 admitted to an ICU during the “first wave” of COVID-19 infections in Italy (February 2020 to April 2020) developed BSI, with most isolated organisms (80%) being gram positive cocci. The proportion of mechanically ventilated was high (93%) and the overall mortality rate was 49%. Another Italian study[5] during the “first wave” reported 40% of patients developed BSI also with a preponderance of gram positive cocci and ICU mortality was reported as 26%.

There are notable differences between our study and this prior work, which may account for the observed differences in BSI rates and other outcomes. We reported on cases from a longer recruitment period which incorporated both the first and second waves of COVID-19 in Australia. Our database provided near-complete coverage of Australian ICUs which admitted COVID-19 patients compared to these single or two centre studies from Italy. Australia has had less community transmission of COVID-19 and has thus far experienced fewer cases than Italy (121 versus 7075 cases per 100,000 population)[1]. Thus, Australian ICUs were not required to operate beyond their usual capacity[15]. At the height of the first wave in the repurposed Italian ICU[4], the authors reported that nurse:patient ratios were as low as 0.2. Comparatively, such measures were never required in Australia with maintenance of usual nurse:patient ratios.

Reports of secondary infections from Wuhan, China, early in the pandemic suggested low rates (1–10%) but it is notable that follow-up periods were short and incomplete in these studies[23,24]. A study from New York, USA, reported that 6% of their cohort developed BSI[*25*]. For similar reasons discussed above, these results may not be directly comparable to our study.

A single-centre UK study reported that 48% of patients with COVID-19 admitted to their ICU developed microbiologically confirmed VAP[*13*] with ICU mortality rate of 38%. They have reported maintenance of usual nurse:patient ratios, though the nurses were not always critical care trained. Despite differences in patient characteristics, rates of VAP and outcomes, there were similarities with our study in the organisms isolated from respiratory samples with a preponderance of gram-negative bacilli. This is in contrast to nosocomial infections seen in influenza, where high proportions of gram-positive HAP are found.

4.3. Implications of findings

Several important implications arise from our findings. The rates of nosocomial infections in critically ill patients with COVID-19 in Australia, such as BSI and HAP, were low. This is surprising, given the prolonged lengths of stays in ICU and hospital. One explanation could be that patients who developed nosocomial infections on hospital wards, prior to or after ICU admission, were not identified in this study. We have demonstrated that risk of nosocomial infection in this cohort does increase as a function of hospital length of stay. The other implication of this low rate of nosocomial infection (HAP particularly), in combination with the gram-negative predominance, is that COVID-19 may not be a significant driver of nosocomial infection. Rather, the observed rate of nosocomial infection may be related to ICU stay in general, as would apply to any patient requiring ICU admission.

This study also highlights the role of resourcing issues on the outcomes of patients with COVID-19. Australian ICUs, faced with relatively low numbers of COVID-19 patients, were not required to repurpose non-ICU areas for ICU-level care, were able to maintain usual nurse:patient ratios and were able to operate within usual capacity[*15*].

Nonetheless, nosocomial infections in our cohort were associated with significantly longer ICU and hospital lengths of stay, and by extension, resource utilization. Therefore, vigilant monitoring for nosocomial infection, and attention to preventative strategies (infection control practices such as hand washing, evidence-based use of personal protective equipment and environmental controls such as negative pressure rooms) remain important.

4.4. Strengths and limitations

This study was performed using data from a database with near-national coverage of ICUs that admitted critically ill patients with COVID-19. Data collection was performed by experienced research staff using standardized case report forms. The follow-up rate was high, with near-complete data for the primary outcome. Competing-risks analyses were performed to account for death as a competing risk for development of nosocomial infection.

There were, however, important limitations to consider. This was an observational study with confounding from numerous sources that may affect the rate of nosocomial infections and mortality. There was no routine screening for HAP or BSI. We only reported on patients who developed clinically apparent nosocomial infections. Only patients who were admitted to an ICU were included, and ICU admission criteria were at the discretion of clinicians at individual sites. Additional microbiological data, such as antimicrobial sensitivity and minimum inhibitory concentrations, were unavailable. Genome sequencing data to identify COVID-19 variants of concern were unavailable. There were missing data for some patients with positive blood cultures. The generalizability of our findings to other countries with different healthcare systems and higher rates of COVID-19 transmission is also uncertain. The sample size and event rates were low and hence this study was under-powered to detect small effect sizes. The point estimates suggested that nosocomial infections were associated with increased mortality, but the confidence intervals were wide and included the possibility of both harm and benefit.

5.0. Conclusion

In a healthcare system operating within capacity, the proportions of COVID-19 patients admitted to ICU who developed serious nosocomial infections, were low. In these patients, significant increases in both ICU and hospital length of stay were observed. The microbiology of noso-

comial infections in this population was different to that observed in countries with higher rates of COVID-19 and those with influenza.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Mahesh Ramanan: Conceptualization, Data curation, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Aidan Burrell:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Eldho Paul:** Methodology, Validation, Formal analysis, Writing – review & editing. **Tony Trapani:** Data curation, Resources, Writing – review & editing. **Tessa Broadley:** Data curation, Resources, Writing – review & editing. **Steve McGloughlin:** Methodology, Writing – review & editing. **Craig French:** Supervision, Writing – review & editing. **Andrew Udy:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

Acknowledgments

The SPRINT-SARI Australia Management Committee are Aidan Burrell, Allen Cheng, Andrew Udy, Annamaria Palermo, Benjamin Reddi, Claire Reynolds, Craig French, D James Cooper, Edward Litton, Husna Begum, Lewis Campbell, Mahesh Ramanan, Mark Plummer, Richard McAllister, Simon Erickson, Tessa Broadley, Tony Trapani and Winston Cheung.

The SPRINT-SARI Australia Investigators are Adam Visser, Adrian Mattke, Adrian Regli, Alan Rashid, Alexis Tabah, Alison Walker, Allen Cheng, Amanda Corley, Andrew Udy, Anil Ramnani, (Isabel) Anne Leditschke, Anthony Eidan, Bart DeKeulenaer, Baumik Mevavala, Ben Mulholland, Benjamin Reddi, Brent Richards, Cameron Knott, Cara Moore, Carmel Delzoppo, Catherine Boschert, Catherine Tacon, Claire Corrigan, Craig French, Danielle Austin, David Brewster, David Cooper, David Crosbie, David Hawkins, Edda Jessen, Eduardo Martinez, Edward Fysh, Edward Litton, Felix Oberender, Forbes McGain, Gavin Salt, Glenn Eastwood, Gopal Taori, Hannah Thompson, Hayden White, Hergen Buscher, Ian Seppelt, Ifrah Khan, Janelle Young, Jayshree Lavana, Jeremy Cohen, Jessica Lugsdin, Jill Garlick, Jim Buttery, John Botha, John Santamaria, Jonathan Barrett, Kasha Singh, Kevin Laupland, Khaled El-Khawas, Kristine Estensen, Kush Deshpande, Kyle White, Leigh Fitzpatrick, Lewis Campbell, Mahesh Ramanan, Manoj Saxena, Marie Draper, Marion Kainer, Mark Kol, Mark Page, Mark Plummer, Martin Sterba, Matthew Anstey, Matthew Brain, Matthew Maiden, Myrene Kilminster, Naomi Hammond, Neeraj Bhadange, Nicole Humphreys, Paras Jain, Paul Azzi, Paul Secombe, Paula Lister, Peter Chan, Peter McCanny, Phillip Britton, Pierre Janin, Rashmi Runiyar, Ravi Krishnamurthy, Ravikiran Sonawane, Ravindranath Tiruvoipati, Rebecca Jessup, Richard Totaro, Rinaldo Bellomo, Ritesh Sanghavi, Samantha Bates, Sandra Peake, Shailesh Bihari, Shane George, Sharon Waterson, Simon Erickson, Steve Webb, Subhash Arora, Subodh Ganu, Thomas Rozen, Toni McKenna, Umesh Kadam, Vineet Nayyar, Wei Han Choy and Wisam Albassam.

The SPRINT-SARI Australia participating sites are Albury Wodonga Health, Alice Springs Hospital, Angliss Hospital, Austin Hospital, Ballarat Base Hospital, Bankstown-Lidcombe Hospital, Barwon Health, Bendigo Hospital, Box Hill Hospital, Bunbury Hospital, Bundaberg Hospital, Caboolture Hospital, Cabrini Hospital Malvern, Cairns Hospital, Calvary Mater Newcastle, Campbelltown Hospital, Canberra Hospital, Casey Hospital, Concord Hospital, Dandenong Hospital, Epworth Richmond, Fiona Stanley Hospital, Flinders Medical Centre, Frankston Hospital, Gold Coast University Hospital, Hervey Bay Hospital, Ipswich Hospital, John Hunter Hospital, Joondalup Health Campus, Launceston General Hospital, Lismore Base Hospital, Liverpool Hospital, Logan Hospital, Lyell McEwan Hospital, Maroondah Hospital, Mater Hospital Brisbane, Mildura Base Hospital, Monash Children's Hospital, Monash Medical Centre, Nepean Hospital, Northeast Health Wangaratta, Northern Hospital, Perth Children's Hospital, Port Macquarie Base Hospital, Prince of Wales Hospital, Princess Alexandra Hospital, Queensland Children's Hospital, Redcliffe Hospital, Rockingham Hospital, Royal Adelaide Hospital, Royal Brisbane and Women's Hospital, Royal Children's Hospital, Royal Darwin Hospital, Royal Hobart Hospital, Royal Melbourne Hospital, Royal North Shore Hospital, Royal Perth Hospital, Royal Prince Alfred Hospital, Sir Charles Gairdner Hospital, St George Hospital, St John of God Hospital Midland, St John of God Hospital Murdoch, St Vincent's Hospital Melbourne, St. Vincent's Hospital Sydney, Sunshine Coast University Hospital, Sydney Children's Hospital Randwick, The Alfred Hospital, The Children's Hospital at Westmead, The Prince Charles Hospital, The Queen Elizabeth Hospital, Toowoomba Hospital, Warrnambool Base Hospital, Werribee Mercy Hospital, Western Health (Footscray), Western Health (Sunshine), Westmead Hospital, Wollongong Hospital and Women's and Children's Hospital Adelaide.

References

[1] World Health Organization. COVID-19 Weekly Epidemiological Update 47, World Heal Organ (2021) 1–23.
[2] B.J. Langford, M. So, S. Raybardhan, V. Leung, D. Westwood, D.R. Macfadden, et al., Bacterial co-infection and secondary infection in patients with COVID- 19 : a living rapid review and meta-analysis, Clin. Microbiol. Infect. 26 (2020) 1622–1629, doi:10.1016/j.cmi.2020.07.016.
[3] T.M. Rawson, Moore Lu, N. Zhu, N. Ranganathan, K. Skolimowska, M. Gilchrist, et al., Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing Timothy, Clin. Infect. Dis. 71 (2020) 2459–2468, doi:10.1093/cid/ciaa530.
[4] C. Bonazzetti, V. Morena, A. Giacomelli, L. Oreni, G. Casalini, L.R. Galimberti, et al., Unexpectedly High Frequency of Enterococcal Bloodstream Infections in Coronavirus Disease 2019 Patients Admitted to an Italian ICU: an Observational Study, Crit. Care Med. (2020) E31–E40, doi:10.1097/CCM.0000000000004748.
[5] D.R. Giacobbe, D. Battaglini, L. Ball, I. Brunetti, B. Bruzzone, G. Codda, et al., Bloodstream infections in critically ill patients with COVID-19, Eur. J. Clin. Invest. 50 (2020) 1–8, doi:10.1111/eci.13319.
[6] Macintyre C.R., Chughtai A.A., Barnes M., Ridda I., Seale H., Toms R., et al. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a (H1N1) pdm09 2018:1–20.
[7] F.P. Esper, T. Spahlinger, L. Zhou, Rate and influence of respiratory virus co-infection on pandemic (H1N1) influenza disease *, J. Infect. 63 (2011) 260–266, doi:10.1016/j.jinf.2011.04.004.
[8] E.Y. Klein, B. Monteforte, A. Gupta, W. Jiang, L. May, Y. Hsieh, The frequency of influenza and bacterial coinfection : a systematic review and meta-analysis, Influenza Other Respi. Viruses 10 (2016) 394–403, doi:10.1111/irv.12398.
[9] T.W. Rice, L. Rubinson, T.M. Uyeki, F.L. Vaughn, B.B. John, R.R.M. Iii, et al., Critical Illness from 2009 Pandemic Influenza A (H1N1) Virus and Bacterial Co-Infection in the United States, Crit. Care Med. 40 (2012) 1487–1498, doi:10.1097/CCM.0b013e3182416f23.Critical.
[10] N.S. Shah, J.A. Greenberg, M.C. Mcnulty, K.S. Gregg, J. Riddell, J.E. Mangino, et al., Bacterial and viral co-infections complicating severe influenza : incidence and impact among 507U . S . patients, 2013 –14, J. Clin. Virol. 80 (2016) 12–19, doi:10.1016/j.jcv.2016.04.008.
[11] Ignacio I. Martín-Loeches, Ana A. Sanchez-Corral, Emili E. Diaz, Rosa R.María M. Granada, Rafael R. Zaragoza, Christian C. Villavicencio, Antonio A. Albaya, Enrique E. Cerdá, Rosa R.María M. Catalán, Pilar P. Luque, Amparo A. Paredes, Ines I. Navarrete, Jorid J. Rello, Alejandro A. Rodrgiuez, Community-Acquired Respiratory Coinfection in Critically Ill Patients With Pandemic 2009 Infl uenza, Chest 139 (2011) 555–562, doi:10.1378/chest.10-1396.
[12] M.J. Cox, N. Loman, D. Bogaert, J.O. Grady, Co-infections: potentially lethal and unexplored in COVID-19, Lancet Microbe 1 (2020) e11, doi:10.1016/S2666-5247(20)30009-4.
[13] M. Maes, E. Higginson, J. Pereira-Dias, M.D. Curran, S. Parmar, F. Khokhar, et al., Ventilator-associated pneumonia in critically ill patients with COVID-19, Crit. Care 25 (2021) 1–11, doi:10.1186/s13054-021-03460-5.
[14] C.D. Russell, C.J. Fairfield, T.M. Drake, L. Turtle, R.A. Seaton, D.G. Wootton, et al., Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study, Lancet Microbe 5247 (2021) 1–12, doi:10.1016/s2666-5247(21)00090-2.
[15] A.J. Burrell, B. Pellegrini, F. Salimi, H. Begum, T. Broadley, L.T. Campbell, A.C. Cheng, W. Cheung, D.J. Cooper, A. Earnest, S.J. Erickson, C.J. French, J.M. Kaldor, E. Litton, S. Murthy, R.E. McAllister, A.D. Nichol, A. Palermo, M.P. Plummer, M. Ramanan, B.A. Reddi, C. Reynolds, U.A. Trapan, Outcomes for patients with COVID-19 admitted to Australian intensive care units during the first four months of the pandemic, Med. J. Aust. 214 (2021) 23–30, doi:10.5694/mja2.50883.
[16] Elm E von, Altman DG, Egger M., Pocock S.J., Gøtzsche P.C., Vandenbroucke J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Play Healthc

Using Play to Promot Child Dev Wellbeing 2007;85:867–72. https://doi.org/10.4324/9781315883595-19.
[17] International Severe Acute Respiratory and emerging Infection Consortium. Glob Heal Netw 2021. https://isaric.tghn.org/ (accessed March 12, 2021).
[18] America ATSIDS of, Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia, Am. J. Respir. Crit. Care Med. 171 (2005) 388–416, doi:10.1164/rccm.200405-644ST.
[19] J.F. Timsit, E. Ruppé, F. Barbier, A. Tabah, M. Bassetti, Bloodstream infections in critically ill patients: an expert statement, Intensive Care Med. 46 (2020) 266–284, doi:10.1007/s00134-020-05950-6.
[20] C. Adrie, M. Garrouste-Orgeas, W. Ibn Essaied, C. Schwebel, M. Darmon, B. Mourvillier, Attributable mortality of ICU-acquired bloodstream infections: impact of the source, causative micro-organism, resistance profile and antimicrobial therapy, J. Infect. 74 (2017) 131–141, doi:10.1016/j.jinf.2016.11.001.
[21] R. Ohannessian, M.P. Gustin, T. Bénet, S. Gerbier-Colomban, R. Girard, L. Argaud, et al., Estimation of extra length of stay attributable to hospital-acquired infections in adult ICUs using a time-dependent multistate model, Crit. Care Med. 46 (2018) 1093–1098, doi:10.1097/CCM.0000000000003131.
[22] M. Ferrer, A. Torres, Epidemiology of ICU-acquired pneumonia, Curr. Opin. Crit. Care 24 (2018) 325–331, doi:10.1097/MCC.0000000000000536.
[23] Nanshan N. Chen, Min M. Zhou, Xuan X. Dong, Jieming J. Qu, Fengyun F. Gong, Yang Y. Han, Yang Y. Qiu, Jingli J. Wang, Ying Y. Liu, Yuan Wei, Jia'an J. Xia, Ting T. Yu, L.Z. Xinxin Zhang, Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: a DescriptNanshan Chen 1, Min Zhou 2, Xuan Dong 1, Jieming Qu 2, Fengyun Gong 3, Yang Han 4, Yang Qiu 5, Jingli Wang 3, Ying Liu 6, Yuan, Lancet 395 (2020) 507–513.
[24] Chaolin C. Huang, Yeming Y. Wang, Xingwang X. Li, Lili Ren, Jianping J. Zhao, Yi Y. Hu, Li L. Zhang, Guohui G. Fan, Jiuyang J. Xu, Xiaoying X. Gu, Zhenshun Z. Cheng, Ting T. Yu, Jiaan J. Xia, Yuan Y. Wei, Wenjuan W. Wu, Xuelei X. Xie, Wen W. Yin, Hui H. Li, Min M. Liu, Yan Y. Xiao, Hong H. Gao, Li L. Guo, B.C. Jungang Xie, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.
[25] P. Goyal, J.J. Choi, L.C. Pinheiro, E.J. Schenck, R. Chen, A. Jabri, et al., Clinical Characteristics of Covid-19 in New York City, N. Engl. J. Med. 382 (2020) 2372–2374, doi:10.1056/NEJMc2010419.