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ORIGINAL ARTICLE

Nosocomial COVID-19 infection in the era of vaccination and antiviral therapy

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Abstract

Background and Aims: Coronavirus disease 2019 (COVID-19) vaccination and antiviral therapies have altered the course of the COVID-19 pandemic through mitigating severe illness and death. However, immunocompromised, elderly and multimorbid patients remain at risk of poor outcomes and are overrepresented in hospital populations. The aim of this study was to describe the characteristics and outcomes of patients with nosocomial COVID-19 infection.

Methods: This was a retrospective, observational study of patients who acquired COVID-19 after 7 days of hospital admission within the Southern Adelaide Local Health Network (SALHN) in South Australia between 1 June 2022 and 30 November 2022. Data were ascertained from the electronic medical record and the South Australian registry of births, deaths and marriages.

Results: Of 1084 COVID-19 inpatient cases managed in SALHN, 295 (27%) were nosocomial, with 215 included in the study. The median age of patients was 80 years (interquartile range [IQR], 68–88 years), the median Charlson Comorbidity Index score was 5 (IQR, 4–7) and 6% were immunocompromised. Most nosocomial COVID-19 infections were of mild severity (81%). The 30-day all-cause mortality rate following COVID-19 infection was 6%, and, in most cases, a cause of death other than COVID-19 was recorded on the death certificate.

Conclusion: The majority of cases of nosocomial COVID-19 infection were mild, with a lower mortality rate than in earlier studies. This finding is likely attributable to immunity through vaccination and prior infection, early antiviral therapy and attenuated severity of the Omicron variant. The high proportion of nosocomial infections supports ongoing infection control measures.

Introduction

Sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), was first identified in December 2019 in China. The ensuing COVID-19 pandemic has had an enormous impact on human health, with almost 7 million deaths reported.[1] COVID-19 vaccination and antiviral therapeutics have radically altered the course of the pandemic by mitigating severe disease and death. However, there are members of the population, such as the elderly, chronically ill and immunocompromised, who remain at risk of poor outcomes from COVID-19. Such people concentrate in hospitals where they are at risk of acquiring the infection.

Previous studies investigating nosocomial COVID-19 were largely performed before the availability of COVID-19 vaccination and effective antiviral therapies.[2–5] Reported rates of nosocomial COVID-19 cases vary between 5% and

Abbreviations: ATAGI, Australian Technical Advisory Group on Immunisation; COPE-Nosocomial Study, COVID in Older People; COVID-19, coronavirus disease 2019; DMARD, disease-modifying antirheumatic drug; GLM, generalised linear model; IQR, interquartile range; NAAT, nucleic acid amplification testing; SALHN, Southern Adelaide Local Health Network; SARS-CoV-2, sudden acute respiratory syndrome coronavirus 2

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17%.[4,5] The mortality rate of nosocomial COVID-19 in these studies ranged from 27% to 41%. In the COPE-Nosocomial Study (COVID in Older People), conducted in early 2020, nosocomial COVID-19 infection was associated with a similar mortality rate compared with community-acquired infections,[2] whereas, in others, patients with nosocomial COVID-19 did worse.[3–5]

Since this time, the availability of antiviral therapy, preexisting immunity through both vaccination and prior infection and the emergence of the Omicron variant and sublineages associated with milder disease have made these findings difficult to generalise to current hospitalised patients.[6,7] In this context, new data regarding the outcome of nosocomial COVID-19 are warranted. The aim of this study was to describe the characteristics and outcomes of patients who acquired COVID-19 infection during hospitalisation at our institution in the era of COVID-19 vaccination and antiviral therapy.

Methods

We conducted a retrospective observational study of patients diagnosed with nosocomial COVID-19 at hospitals within the Southern Adelaide Local Health Network (SALHN) in South Australia: Flinders Medical Centre, Noarlunga Hospital and Repatriation General Hospital. These hospitals provide care to a population of approximately 350 000 people in the southern metropolitan area of Adelaide as well as the southeastern region of the state. Nosocomial COVID-19 infection was defined in accordance with the South Australian Health Department criteria as the diagnosis of COVID-19 after 7 days of inpatient admission or within 2 to 7 days of inpatient admission with a hospitalbased epidemiological link. These cases were identified electronically through the SALHN Infection Control and Prevention Unit database, which draws cases from the SA Pathology Laboratory. Cases were then verified by reviewing medical records.

Patients included in this study were aged 18 years or older and had a diagnosis of COVID-19 by nucleic acid amplification testing (NAAT) performed on nasopharyngeal, sputum or bronchoalveolar lavage specimens collected between 1 June 2022 and 30 November 2022, while they were admitted to an acute medical or surgical unit. During the study period, daily COVID-19 rapid antigen testing was performed in all admitted patients to identify asymptomatic and presymptomatic patients, with positive cases then confirmed by NAAT.

The study period was selected because COVID-19 management had become relatively standardised with expert consensus guidelines for antiviral prescribing and reliable access to antiviral therapies in South Australia: remdesivir in late 2021 and nirmatrelvir/ritonavir and molnupiravir in early 2022. Furthermore, COVID-19 vaccination, which began in February 2021 in South Australia, had reached high coverage rates, with 93.5% of the population having received two vaccine doses.[8]

Patients admitted to long-stay rehabilitation or mental health units were excluded as were patients who were not candidates for active treatment at the time of their COVID-19 diagnosis. Staff and visitors who acquired COVID-19 in the hospital were not included in the analysis.

Definitions of data points were agreed upon by the study investigators and then extracted by manual review of the electronic medical records. The following sources of information were used: Sunrise electronic medical record (Allscripts), Open Architecture Clinical Information System (OACIS) and Enterprise pathology laboratory information system.

The data included demographic characteristics, comorbidities, immunocompromised status, COVID-19 vaccination status, severity of COVID-19 infection, treatment received, ventilatory support, length of hospital stay, readmission within 30 days of discharge and all-cause mortality at 30 days from the date of COVID-19 diagnosis. The cause of death was obtained from the death certificate in either the medical record or from the South Australian registry of births, deaths and marriages.

Charlson Comorbidity Index (CCI) was calculated for each patient based on the medical conditions documented prior to their COVID-19 diagnosis.[9] Immunocompromised status was adapted from the Australian Technical Advisory Group on Immunisation (ATAGI) recommendations for COVID-19 booster vaccination and defined as: active haematological malignancy, B-cell depleting therapy within the past 12 months, haematological stem cell transplant within 24 months, solid organ transplant, active chemotherapy within 6 months, primary immunodeficiencies, HIV with CD4 count <250 cells/μL, high-dose corticosteroid therapy, selected disease-modifying antirheumatic drugs (DMARDs) and biological therapies.[10] COVID-19 vaccination status was determined by review of electronic medical records.

Asymptomatic COVID-19 was defined as a lack of change in symptoms or vital observations at 48 h before and 10 days after COVID-19 NAAT positivity. The severity of COVID-19 infection was defined by South Australian guidelines, broadly categorised as mild: no oxygen requirement; moderate: oxygen requirement; severe: high flow oxygen or noninvasive ventilation; and critical: mechanical ventilation; which are similar to Australian COVID-19 Living Guidelines criteria.[11] COVID-19 antiviral, corticosteroid and immunomodulatory therapy and ventilation support were recorded. The length of hospital admission and readmission within 30 days of discharge for any reason were recorded.

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The primary outcome was all-cause mortality, defined as the binary variable indicating whether a patient was deceased within 30 days from the date of COVID-19 diagnosis. Patients were categorised as either 'survived' (coded as 0) or 'deceased' (coded as 1) based on their vital status at the end of the 30-day follow-up period.

Data analysis was performed in STATA version 18.0 (StataCorp LLC). Descriptive summaries for continuous variables were based on the appropriate measures of central tendency and dispersion: either mean and standard deviation or median and interquartile range (IQR). Counts and percentages were used for categorical variables.

Chi-square and/or Fisher exact test were used to compare patient's baseline demographic and clinical characteristics. The association between the exposure variables, including sex, age, vaccination status, antiviral medication, COVID-19 severity and immunocompromise with mortality at 30 days were assessed. A generalised linear model (GLM) with a binomial distribution and logit link function was used to model the probability of 30-day mortality. The model was adjusted for explanatory variables with a P value ≤0.2 in the preliminary univariate analysis. The final model was selected based on the Akaike information criterion to balance goodness of fit and model complexity. The GLM is appropriate for binary outcome variables and allows for the estimation of adjusted odds ratios and 95% confidence intervals for the explanatory variables. The model is specified as follows:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k$$

where

$$p = p\text{robability of } 30-\text{day mortality},$$

$$\beta_o = \text{intercept, and}$$

$\beta_1, \beta_2, \ldots \beta_k$ = coefficients associated with explanatory variables $x_1, x_2, \ldots x_k$.

Overall, inference was based on a 5% level of significance.

This study was approved as a quality improvement project by the SALHN Office for Research on 20 March 2023 (reference number 4470).

Results

Between 1 June 2022 and 30 November 2022, 1084 cases of COVID-19 were managed within SALHN hospital inpatients. Of these cases, 291 (27%) were nosocomial and were considered for inclusion in this study. Seventy-six cases were excluded based on admission to a subacute unit (rehabilitation 38 cases and mental health 30 cases), the patient being palliated at the time of COVID-19 diagnosis (seven cases) and SARS-CoV-2 NAAT results indicative of prior infection (one case). After exclusion, 215 patients remained in the study for analysis (Fig. 1).

The median age was 80 years (IQR, 68–88 years) and there were 111 women and 104 men. The majority of patients lived independently in the community (117 of 215; 54%), while 41% (88 of 215) required support at home and 5% (10 of 215) lived in residential care. The median CCI was 5 (IQR, 4–7), with the most prevalent comorbidities being dementia (66; 31%), diabetes (62; 29%), cardiac failure (39; 18%), ischaemic heart disease (36; 17%), malignancy (30; 14%) and cerebrovascular disease (30; 14%). Thirteen (6%) patients were immunocompromised (Table 1).

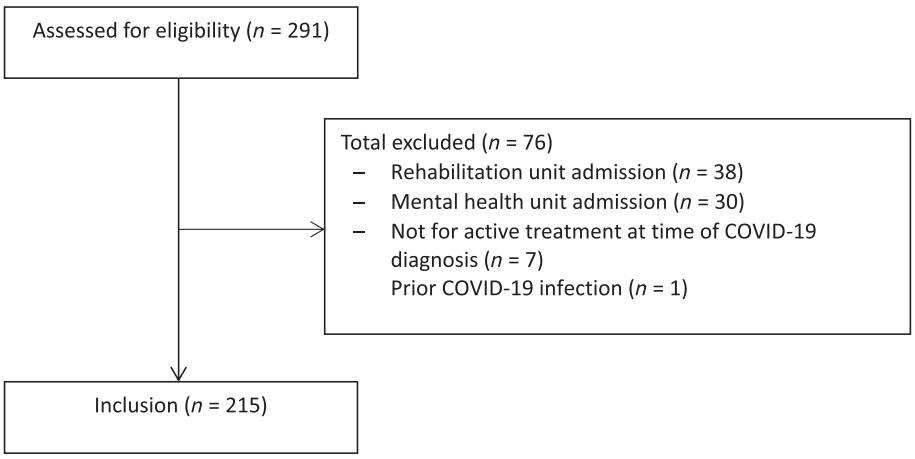

Figure 1 Flowchart of patients included in the study. COVID-19, coronavirus disease 2019.

Table 1 Demographic characteristics and comorbidities of the study population

	Alive, (%) or mean (SD)	Dead, (%) or mean (SD)	Total or mean (SD)	*P* value
	N = 203	*N* = 12	*N* = 215	
Age group (≥66 years)	163 (80.3)	11 (91.7)	174 (80.9)	0.470†
Sex (male)	97 (47.8)	7 (58.3)	104 (48.4)	0.477
Charlson Comorbidity Index	5.1 (2.3)	6.9 (2.4)	5.3 (2.4)	**0.012**‡
Previous myocardial infarction	31 (15.3)	5 (41.7)	36 (16.7)	**0.017**
Previous TIA/CVA	29 (14.3)	1 (8.3)	30 (14.0)	1.000†
Peripheral vascular disease	13 (6.4)	4 (33.3)	17 (7.9)	**0.009**†
Dementia	62 (30.5)	4 (33.3)	66 (30.7)	1.000†
Congestive cardiac failure	35 (17.2)	4 (33.3)	39 (18.1)	0.237†
Chronic kidney disease	10 (4.9)	0 (0)	10 (4.7)	1.000†
COPD	25 (12.3)	4 (33.3)	29 (13.5)	0.061†
Diabetes	60 (29.6)	2 (16.7)	62 (28.8)	0.516†
Chronic liver disease	10 (4.9)	1 (8.3)	11 (5.1)	0.477†
Immunocompromise	13 (6.4)	0 (0)	13 (6.1)	1.000†
COVID-19 severity: moderate–severe	34 (16.8)	6 (50.0)	40 (18.6)	**0.004**
Dexamethasone	33 (16.3)	4 (33.3)	37 (17.2)	0.131†
Supported living	94 (46.3)	4 (33.3)	98 (45.6)	0.553†
Antiviral therapy	153 (75.4)	11 (91.7)	164 (76.3)	0.302†
COVID-19 vaccination	164 (90.1)	8 (88.9)	172 (90.1)	1.000†

†Fisher exact test.
‡Student *t* test.
Chi-squared test, column percentages presented.
Note: The bold values indicate p 0.05.
COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVA: cerebrovascular accident; TIA, transient ischaemic attack.

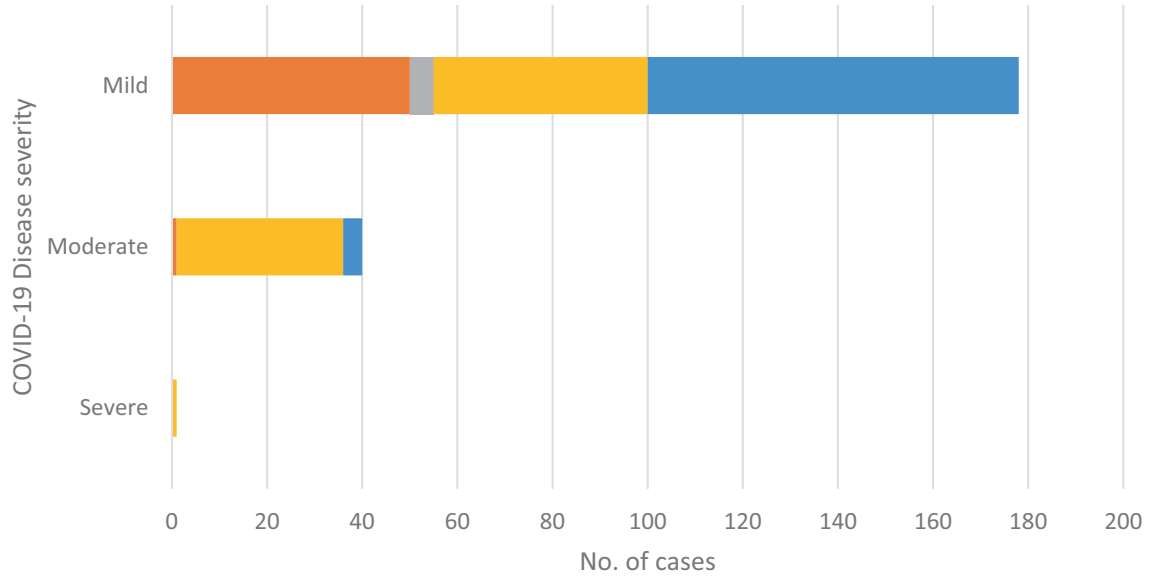

Figure 2 Coronavirus disease 2019 (COVID-19) severity and antiviral treatment. (■) No antiviral; (■) molnupiravir; (■) remdesivir; (■) nirmatrelvir/ritonavir.

COVID-19 vaccination status was documented for 89% (191 of 215) of the patients, among whom 90% (172 of 191) had at least one COVID-19 vaccination dose and 84% (145 of 172) of the vaccinated patients had three or more doses.

Symptomatic COVID-19 illness occurred in 84% (171 of 203) of patients for whom data were available. The majority of cases were categorised as mild disease (175 of 215; 81%), with smaller numbers of moderate (39 of 215; 18%) and severe (one of 215; 0.005%) illness

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(Fig. 2). There were no cases of critical COVID-19 in the study. Three patients required intensive care unit admission at the time of COVID-19 infection: one patient required ventilatory support in the form of noninvasive ventilation, and the other two patients were admitted for reasons unrelated to COVID-19.

Antiviral medication was given to 164 patients (76%), with nirmatrelvir/ritonavir being the most frequently used agent (80; 37%), followed by remdesivir (77; 36%). Two patients were administered nirmatrelvir/ritonavir before being changed to remdesivir. Molnupiravir was administered to five patients (2%). Fifty-one of 215 (24%) patients did not receive antiviral medication; in 37 cases, this was because the patient did not meet criteria for risk of progression to severe disease. In the remaining 14 of 51 cases, patients did meet criteria for antiviral treatment: nine patients were not offered treatment, four patients declined treatment and one patient was palliated within 24 h of COVID-19 diagnosis and therefore not offered treatment.

Dexamethasone was prescribed to 17% of the patients (37 of 215), most of whom had moderate or severe COVID-19. Baricitinib and tocilizumab were not administered to any patients in this study. Most patients with moderate or severe COVID-19 had transient hypoxemia of less than 48 h duration (17 of 40), coexistent causes of hypoxemia (12 of 40) or a documented contraindication to immunomodulator therapy (two of 40). The remainder had persistent hypoxemia without an alternative explanation (nine of 40).

The mortality rate within 30 days of COVID-19 diagnosis was 6% (12 of 215). In one case, COVID-19 was recorded as the primary cause of death; in two cases, it was listed as a contributing condition and in the remaining nine cases it was not documented in the death certificate (Table 2). Factors associated with death were higher CCI, history of myocardial infarction or peripheral vascular disease and moderate or severe COVID-19 (Table 1). Risk factors for mortality within 30 days by multivariable analysis were higher CCI and moderate to severe COVID-19 with a history of diabetes being protective (Table 3).

Hospital readmissions were common, with 42 of 204 (21%) patients being readmitted within 30 days of

Table 2 Death certificate details of patients who died within 30 days of COVID-19 diagnosis

Age (years)	Sex	Time from COVID-19 diagnosis (days)	Severity of COVID-19	Documented primary cause of death	Other factors listed as contributing to death
87	Female	21	Mild	Dementia	-
92	Female	10	Mild	COVID-19	-
92	Female	11	Moderate	Acute ischaemic limb	-
53	Male	14	Mild	Haemorrhagic CVA	Liver cirrhosis
81	Female	25	Moderate	*Staphylococcus aureus* infective endocarditis	COVID-19
72	Male	30	Mild	Ischaemic heart disease	COPD
83	Male	3	Moderate	Malignancy unclear primary	-
88	Male	15	Moderate	Decompensated cardiac failure Hospital-acquired pneumonia	COVID-19
85	Male	7	Moderate	Upper gastrointestinal haemorrhage	-
72	Male	22	Mild	Metastatic prostate cancer	-
91	Male	25	Moderate	Pneumonia	-
78	Female	25	Mild	Metastatic lung cancer	-

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVA, cerebrovascular accident.

Table 3 Multivariable analysis of determinants for mortality within 30 days of COVID-19 diagnosis

Risk factor	Adjusted OR	Robust standard error	*P* value	95% CI
Charlson Comorbidity Index	1.68	0.37	**0.019**	1.09–2.58
Male	1.48	1.14	0.611	0.33–6.68
Age (≥66 years)	0.51	0.67	0.609	0.04–6.75
Antiviral therapy	2.85	3.30	0.366	0.29–27.65
Supported living	0.18	0.17	0.070	0.03–1.15
COVID-19 severity: moderate–severe	7.01	6.03	**0.024**	1.30–37.80
Diabetes	0.10	0.09	**0.019**	0.02–0.69
COVID-19 vaccinated	0.68	1.17	0.822	0.02–19.85

CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.
Note: The bold values indicate p 0.05.

discharge, with conditions not directly related to COVID-19 infection.

Discussion

The 30-day all-cause mortality following nosocomial COVID-19 infection in this study (6%) was lower than previously reported. In addition, the majority of patients (81%) had mild disease with very low rates of severe or critical illness. There are likely several key reasons for this.

Unlike earlier studies, nosocomial COVID-19 occurred in a population with a higher level of preexisting immunity through either vaccination or prior infection. COVID-19 vaccination has demonstrated a protective effect against severe disease and death, an effect that is strongest for the messenger RNA vaccines.[12–15] Vaccination status was available for 89% of the patients included in this study and 90% had been administered at least one dose of COVID-19 vaccine, with the majority of the vaccinated (84%) patients receiving three or more doses. This high vaccination rate likely contributes to the low mortality rate seen in this vulnerable cohort of patients.

COVID-19 became endemic in South Australia in late 2021 following intensive public health measures. Therefore, some patients in the study population may have developed preexisting immunity through previous COVID-19 infection. It was not possible to accurately collect these data for this study.

During waves of COVID-19 infection, we undertook routine daily COVID-19 rapid antigen surveillance testing on all admitted patients to identify asymptomatic and presymptomatic patients.[16] This practice resulted in the identification of asymptomatic, minimally symptomatic and mild severity COVID-19 at a very early stage of infection (typically within 24–48 h), which allowed rapid initiation of antiviral therapies in patients at risk of progression to severe disease. Large, randomised trials have demonstrated the benefit of nirmatrelvir/ritonavir given within 5 days of symptom onset and remdesivir given within 7 days of symptom onset in unvaccinated patients.[17,18] While the degree of benefit is less certain in vaccinated patients, most patients in our study received antiviral treatment within 48 h of diagnosis and this is likely to have contributed to the relatively positive outcomes observed.[19,20]

Medical staff have had to absorb rapid developments in COVID-19 management over the past 3 years. This study shows relatively high rates of guideline-concordant use of antiviral medications and dexamethasone. Baricitinib and tocilizumab have shown benefit in patients with hypoxemia and systemic inflammation from COVID-19.[21–23] The lack of use of these agents in moderate COVID-19 in this cohort appears to be explained by many having transient hypoxemia or multifactorial respiratory pathology leading clinicians to a 'watch-and-wait' strategy. However, in a minority of patients with persistent hypoxemia from COVID-19, these medications could have been used.

Omicron variants of COVID-19 are associated with milder illness compared with earlier variants: whether this is primarily because of immunity gained through vaccination or previous infection or a decrease in the intrinsic virulence of the virus is contentious.[6,7] Whole-genome sequencing data are not available for the patients in this study. The common variants circulating in South Australia during the study period were all Omicron sublineages (BA.4, BA.5, BQ.1 and BA.275), so it is reasonable to infer that these variants accounted for most of the infections in the study population (unpublished data, SA Pathology).

The study population was elderly with high rates of medical comorbidity, and a large proportion required living arrangements with supported care. Over 30% of patients had cognitive impairment. These findings are partly explained by several large outbreaks that occurred in geriatric wards in the hospital. Outbreaks on these wards were driven by communal activities and the difficulty of this patient group adhering to infection control measures such as mask-wearing, personal hygiene and isolation. The high numbers of nosocomial COVID-19 in this group reflect pragmatic considerations and the balance that must be struck between limiting the spread of an airborne virus and the negative psychosocial effects of infection control practices and their impact on the quality of nursing care.

While many patients in the study were relatively immunocompromised through age and comorbidity, the proportion with significant immunocompromise was lower than anticipated at 6%. This may reflect greater efforts that were taken to protect haematology, oncology and solid organ transplant populations from COVID-19 in our hospitals and may have contributed to the low COVID-19 mortality rate.

The incidence of nosocomial COVID-19 infection (27%) was higher than in other studies worldwide: 5% in a multicentre Spanish study,[5] 12% in the COPE-Nosocomial Study[2] and 17% in a large Welsh study.[4] It is difficult to draw comparisons given the myriad of factors involved, including different hospital populations and testing algorithms, earlier and possibly less transmissible COVID-19 variants, changing infection control practices and the lack of a uniform definition of nosocomial COVID-19 infection. In our hospitals, challenges such as ageing infrastructure, a lack of single patient rooms and bathrooms, a lack of negative pressure ventilated rooms,

'thoroughfare wards' and staff fatigue likely account for the large numbers of nosocomial infections.

The attribution of death to COVID-19 is the subject of ongoing debate: whether some patients die from indirect effects of the virus or rather the infection affects a group vulnerable to death from other causes. Autopsies are rarely performed during routine care in Australia and the certification of death is, in most cases, limited to the judgement of the medical practitioner at the time.[24] In this study, COVID-19 was mentioned on the death certificate in 3 of 12 cases. While many of the deceased patients had other significant conditions, such as infective endocarditis, metastatic malignancy or advanced dementia, some did not, raising the question of whether COVID-19 was underappreciated as a contributor to death. This notion is supported by our finding that moderate to severe COVID-19 was identified as an independent risk factor for death. Diabetes was associated with a reduced risk of death, which is an unexpected finding and differs from the results of earlier, large studies.[25,26] It is possibly skewed by the small number of patients who died.

Limitations of this study pertain to the retrospective method of collecting data from medical records, which relies on accurate and relevant documentation. In addition, there have been different definitions of nosocomial COVID-19 infection applied in earlier studies ranging from 5 to 14 days hospital admission.[2–5] We chose the nosocomial COVID-19 definition used in South Australia of acquisition after 7 days of hospital admission. There is evidence that the median incubation period of Omicron variants is shorter at 3.42 days than earlier COVID-19 variants[27]; therefore, while it is likely that most cases in our study are true nosocomial infections, it is possible that a small number were community-acquired cases with an incubation period longer than 7 days. It is also possible that some nosocomial cases that occurred earlier than 7 days were missed by this definition.

Conclusion

This study provides contemporary data about nosocomial COVID-19 infection in a vulnerable hospital population with high vaccination coverage and readily available antiviral therapy. In comparison with earlier studies, the all-cause mortality from nosocomial COVID-19 was lower likely as a consequence of vaccination, immunity through prior infection, antiviral therapy and potentially attenuation in the virulence of Omicron variants. While these developments have transformed the nature of the COVID-19 pandemic, the burden of infection in hospitalised patients justifies ongoing infection control measures as well as future efforts at improving hospital infrastructure to protect patients from airborne infection.

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