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ORIGINAL ARTICLE

Diabetes and hyperglycaemia among hospitalised patients with COVID-19 in Western Sydney: a retrospective cohort study

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Key words
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Abstract

Background: Diabetes has been recognised as a major risk factor for COVID-19 mortality and hospital complications in earlier studies.
Aims: To examine the characteristics of hospitalised COVID-19 patients with diabetes and the impact of diabetes and hyperglycaemia on hospital outcomes.
Methods: This was a retrospective cohort study. Admission glucose levels, HbA1c, diabetes status and hospital outcomes were determined for subjects admitted from June to November 2021 by matching a pathology data set, a clinical data set and the hospital administrative database. The outcomes of interest were death, intensive care unit (ICU) admission and length of stay (LOS).
Results: There were 1515 individuals admitted with COVID-19 with 49 deaths (3.2%) and 205 (13.5%) ICU admissions. The median length of hospital stay was 3.7 days. Three hundred and ten patients (20%) had diabetes, with 46 (15%) newly diagnosed. Patients with diabetes had a higher mortality than patients who did not have diabetes (8% vs 2%, $P < 0.001$), were more likely to be admitted to ICU (20% vs 12%, $P = 0.001$) and have longer median LOS stay (6.6 (interquartile range (IQR) 2.9–12.5) vs 2.9 (IQR 0.5–7.1) days, $P < 0.001$). In multivariate models, neither diabetes nor admission glucose predicted death. Admission glucose level but not diabetes was an independent predictor of ICU admission and LOS.
Conclusions: There is a high prevalence of diabetes among patients hospitalised with COVID-19, with worse outcomes. In contrast to previous studies, the association of diabetes with mortality was not significant when adjusted for other variables. This is possibly related to the benefits of vaccination and current medical and ICU interventions.

Introduction

In mid-2021, New South Wales (NSW) faced a major outbreak of the Delta variant of COVID-19. Between 23 June and 11 November 2021, there were 72 178 COVID-19 cases reported in NSW, with 18 518 (26%) from Western Sydney. Although NSW had already experienced the first wave of COVID-19 in 2020, and therefore had a level of preparedness, the rapid increase in cases created an unprecedented level of stress on hospital services. Hospitals had to rapidly develop systems for evaluating, isolating and managing large numbers of patients with COVID-19. Elective surgery was cancelled, and many outpatient services were closed or transitioned to telehealth. Dedicated COVID wards were established and medical, nursing, allied health and administrative staff were redeployed to focus on patients with COVID-19.

Risk factors associated with severe disease or death arising from COVID-19 include obesity, older age, male gender, social deprivation, diabetes, chronic kidney disease, neurocognitive disorders, respiratory disease, hypertension and cardiovascular disease.[1–5] In Australia, the commonest comorbidity among patients admitted to the intensive care unit (ICU) since the start of the pandemic is diabetes.[6]

Conflict of interest: None.

In general, the risk of death or severe disease among people with diabetes is two to three times that of people without diabetes.[5] Hyperglycaemia, either on admission or during the course of the hospital stay, has been associated with increased mortality.[5,7,8] Epidemiological studies indicate higher COVID-19 mortality among people with diabetes who have a high HbA1c.[4,9] However, clinical studies have not shown a clear relationship between HbA1c and mortality or the need for mechanical ventilation.[10–12]

Associated factors which may account for the increased risk for severe disease among people with diabetes include older age and comorbidities such as obesity and hypertension.[13] Both diabetes and hyperglycaemia *per se* are also pro-inflammatory, pro-apoptotic, pro-thrombotic states and impair neutrophil and immune function.[5]

We examined the large number of cases of COVID-19 admitted to Westmead Hospital during this period in 2021 to better understand the relationship between diabetes, admission glucose and hospital outcomes.

Methods

This was a retrospective cohort study examining patients admitted to Westmead Hospital between 23 June and 11 November 2021 with a primary diagnosis of COVID-19. Approval was obtained from the Western Sydney Local Health District (WSLHD) Human Research Ethics Committee. The primary aims of the study were to determine the characteristics and outcomes of hospitalised COVID-19 patients with diabetes compared to those who did not have diabetes and evaluate the impact of diabetes and hyperglycaemia on hospital outcomes.

A local COVID-19 protocol, which included the measurement of venous glucose and HbA1c, was implemented. A diabetes dashboard linked to the electronic medical record (eMR) provided a data source for glucose and HbA1c test results.[14] The diabetes team also maintained a database of all patients with COVID-19 who were reviewed, which included identification of established diabetes or newly diagnosed diabetes. Third, a data set of all patients with COVID-19 was extracted from the hospital administrative database. This data set included patient demographics, International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, and the key outcomes of death, admission to ICU and hospital length of stay (LOS). The ICD-10 codes enabled extraction of coded comorbidities, categorised into the following groups: smoking, diabetes, hypertension, coronary artery disease, chronic lung disease, chronic kidney disease (CKD, stage 3 or higher), major mental health disorder, dementia, cerebrovascular disease and cancer. ICD-10 codes were also used to determine whether the patient was likely to have had COVID pneumonitis (codes 'viral pneumonia', 'respiratory infection' and 'respiratory failure') or be admitted for COVID symptoms (codes 'Pleurisy', 'Dyspnoea', 'Cough', 'Fever', 'Malaise', 'Nausea and Vomiting', 'Acute pharyngitis', 'Nasopharyngitis', 'Myalgia' as well as the previously listed codes for COVID pneumonitis).

The Socio-Economic Index For Areas (SEIFA) Score was determined from the postcode of residence, using the Index of Relative Socio-economic Disadvantage. The three data sets (diabetes dashboard, diabetes team clinical data set and COVID-19 administrative data set) were linked for the time period of interest. Where data were discrepant or unclear, and for cases of diabetic ketoacidosis, the patient eMR was reviewed.

The first venous glucose level taken on the day of admission was accepted as the admission random glucose level. HbA1c results were included if they had been performed during the admission or in the 3 months prior. Patients were classified as newly diagnosed diabetes if they had an HbA1c ≥ 6.5 mmol/L, and the diagnosis was made for the first time during the admission, even if a clinical diagnosis had not been made. We did not include patients who became hyperglycaemic following high-dose glucocorticoid therapy who had normal glucose or HbA1c levels on admission in the category of newly diagnosed diabetes.

In accordance with our treatment protocol, patients were treated with dexamethasone, remdesivir, baricitinib or tocilizumab when appropriate. Admission to ICU was usually because of the need for increased respiratory or circulatory support. Patients in ICU mostly required invasive or non-invasive mechanical ventilation and in some cases extracorporeal membrane oxygenation.

Comparison between groups was undertaken by independent sample *t*-tests for continuous variables and chi-squared tests for categorical variables. LOS was highly skewed so comparisons were performed with the Mann–Whitney *U* test. Multivariate analysis was undertaken using binary logistic regression for categorical outcomes and linear regression for continuous outcomes. LOS was log-transformed for multivariate analysis. *P* values <0.05 were considered significant. Data analysis was performed using SPSS (IBM Corp, version 27).

Results

There were 1704 admissions for 1515 individuals. For patients with multiple admissions, the admission with the longest LOS was utilised for analysis. For the cohort, the age was 46.7 ± 18.2 years, with 47% male (Table 1). The population was relatively disadvantaged, with a SEIFA score of 940 ± 74 and 35% speaking a language other than English at home. There were 673 (56%) patients who had

Table 1 Subject characteristics and outcomes, by diabetes status

	Overall, $N = 1515$	Diabetes, $N = 310$	Not diabetic, $N = 1205$	P value
Age (years)	46.7 ± 18.2	60.5 ± 15.0	43.1 ± 17.2	<0.001
Male	713 (47%)	171 (55%)	542 (45%)	0.001
Speaks English at home	975 (65%)	159 (52%)	816 (69%)	<0.001
SEIFA score	940 ± 74	932 ± 72	942 ± 74	0.03
ATSI	35 (2%)	10 (3%)	25 (2%)	0.29
Smoker	270 (18%)	47 (15%)	223 (19%)	0.18
Comorbidities				
Hypertension	266 (18%)	103 (33%)	163 (14%)	<0.001
Cardiovascular disease	61 (4%)	26 (8%)	35 (3%)	<0.001
Cerebrovascular disease	6 (0.4%)	2 (0.6%)	4 (0.3%)	0.36
Major mental health disorder	65 (4%)	17 (6%)	48 (4%)	0.27
Chronic lung disorder	154 (10%)	42 (14%)	112 (9%)	0.04
Dementia	15 (1%)	4 (1%)	11 (1%)	0.52
Chronic kidney disease	49 (3%)	30 (10%)	19 (2%)	<0.001
Cancer	8 (0.5%)	4 (1.3%)	4 (0.3%)	0.06
Admitted for COVID-19 symptoms	1365 (90%)	291 (94%)	1074 (89%)	0.01
COVID-19 pneumonitis	920 (61%)	247 (80%)	673 (56%)	<0.001
HbA1c (%)	6.3 ± 1.6	7.9 ± 2.1	5.6 ± 0.4	<0.001
HbA1c (mmol/mol)	45 ± 18	63 ± 24	38 ± 4	<0.001
Glucose on admission (mmol/L)	7.3 ± 3.9	10.7 ± 5.9	6.0 ± 1.2	<0.001
Length of hospital stay (days)	3.7 (0.7–8.0)	6.6 (2.9–12.5)	2.9 (0.5–7.1)	<0.001
Admitted to ICU	205 (13.5%)	60 (19%)	145 (12%)	0.001
Death	49 (3.2%)	25 (8%)	24 (2%)	<0.001

Data presented as mean ± SD, median (IQR) or N (% total). P value relates to difference between people with and without diabetes.
ATSI, Aboriginal or Torres Strait Islander; ICU, intensive care unit; IQR, interquartile range; SEIFA, Socio-Economic Index for Areas.

coding suggestive of COVID pneumonitis and 1074 (89%) with COVID symptoms, indicating that this was the main reason for admission. The remaining patients were largely admitted for other medical issues, pregnancy or social reasons and/or had incidental COVID-19 infection. There were 49 deaths (3.2%), 205 (13.5%) ICU admissions and a median LOS of 3.2 (interquartile range (IQR) 0.8–8.0) days. Fifty-five women were pregnant.

There were 264 subjects with known diabetes and 46 newly diagnosed with diabetes, giving a total of 310 (20%) subjects with diabetes. Three of these patients had known type 1 diabetes. There were 946 subjects who had an HbA1c performed, and 1068 had a formal venous glucose taken at the time of admission. Subjects without a formal glucose measurement on admission were mostly admitted for brief observation only (median LOS 0.6 days (IQR 0.3–4.2)). These were younger, more likely to speak English at home, less likely to be male or have diabetes and less likely to be admitted to ICU or die (Table S1).

Patients with and without diabetes

Subjects with diabetes had higher HbA1c and admission glucose than those who did not have diabetes (Table 1). They were more likely to be male or older and less likely to speak English at home and had a lower SEIFA score. They were more likely to have background hypertension, cardiovascular disease, chronic lung disease, CKD or cancer. Subjects with diabetes were more likely to have COVID symptoms (94% vs 89%) or pneumonitis (80% vs 56%) compared to non-diabetic patients. They had greater mortality than patients who did not have diabetes (8% vs 2%, $P < 0.001$), were more likely to be admitted to ICU (20% vs 12%, $P = 0.001$) and were more likely have longer median LOS (6.6 (IQR 2.9–12.5) vs 2.9 (IQR 0.5–7.1) days, $P < 0.001$).

Relationship between glucose and HbA1c with ICU admission, mortality and length of hospital stay for entire cohort

The relationship between glucose and HbA1c categories, irrespective of diabetes status, with ICU admission, mortality and hospital LOS, is depicted in Figure 1. Compared to subjects with an admission glucose level < 6 mmol/L, all groups in the higher glucose categories had a higher rate of admission to ICU, mortality and LOS.

For HbA1c, compared to the reference group of <6% (48 mmol/L), all higher HbA1c groups had increased mortality, ICU admission and LOS. The exception was that there was no significant difference in ICU admission between those in the reference group and HbA1c ≥8.0% (64 mmol/mol).

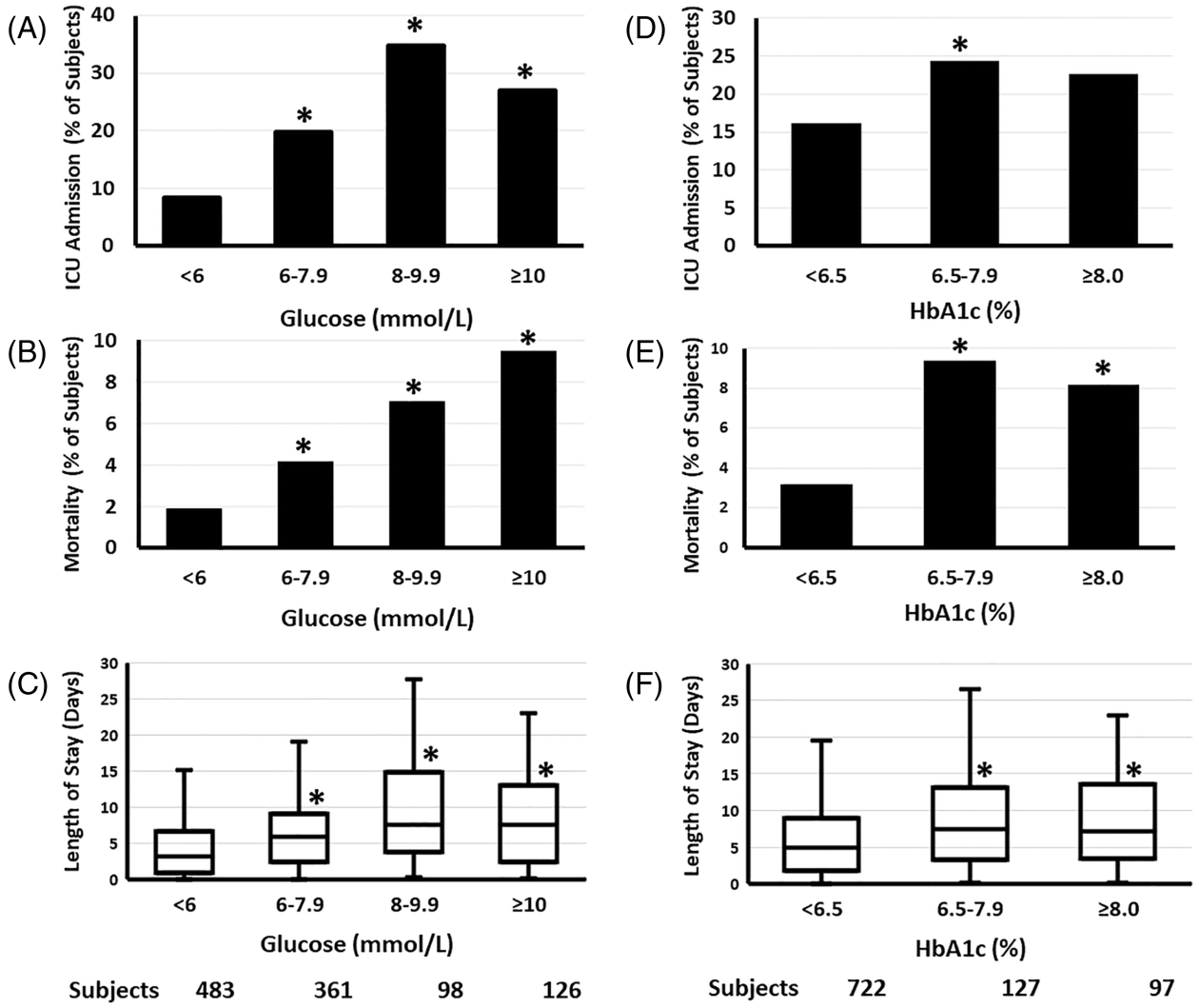

Figure 1 Rates of ICU admission (panels A and D) and mortality (panels B and E) and hospital length of stay (panels C and F) by glucose and HbA1c category for whole cohort. Length of stay shown as median, interquartile range and 95th percentile. *$P < 0.05$ compared to reference group (<6 mmol/L for glucose, <6.5% for HbA1c). ICU, intensive care unit.

Independent predictors of ICU admission, mortality and hospital length of stay

Multivariate analysis was performed to assess the independent predictors of death, ICU admission and LOS. As the data for LOS were heavily skewed, the data were log-transformed prior to multiple regression. In all three multivariate models, the only independent predictor of death was age (Table 2). Neither diabetes nor admission glucose levels predicted death. Age, however, was not a consistent independent predictor of admission to ICU. Instead, either diabetes or glucose level was a predictor of ICU admission in each of the models. Both age and either diabetes or glucose were consistent predictors of hospital LOS.

Known diabetes and newly diagnosed diabetes

Compared to patients with known diabetes, those with newly diagnosed diabetes were more likely to be male and have CKD, but otherwise there were no differences in characteristics (Table 3). Patients with newly diagnosed diabetes were more likely to be admitted to ICU and have longer LOSs, but there were no differences in mortality.

Two patients not known to have diabetes had a glucose level in the diabetic range on admission (12.3 and 11.1 mmol/L) and an HbA1c in the prediabetic but not diabetic range (6.1% and 6% respectively). These two subjects were not considered to have diabetes in the analyses.

Table 2 Significant independent predictors of death, ICU admission and length of hospital stay on multivariate analysis

		Death			ICU admission			Length of stay		
	Variable	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	*B* coefficient	95% CI	*P* value
Model 1	Age	1.10	1.08–1.13	<0.01	1.01	1.00–1.02	<0.01	0.01	0.01–0.01	<0.01
	Male	1.65	0.86–3.16	0.13	1.68	1.24–2.29	<0.01	0.07	0.01–0.13	0.04
	Diabetes	1.61	0.86–3.04	0.14	1.47	1.02–2.12	0.04	0.18	0.10–0.27	<0.01
Model 2	Age	1.11	1.08–1.14	<0.01	1.00	0.99–1.01	0.48	0.01	0.01–0.01	<0.01
	English at home	1.06	0.51–2.19	0.88	1.48	1.00–2.19	0.05	0.08	0.01–0.16	0.04
	Male	1.64	0.79–3.41	0.19	1.47	1.02–2.11	0.04	0.09	0.02–0.16	0.02
	Glucose (mmol/L)	1.07	0.97–1.19	0. 18	1.10	1.03–1.18	<0.01	0.02	0.01–0.04	<0.01
Model 3	Age	1.11	1.08–1.13	<0.01	1.01	0.99–1.02	0.37	0.01	0.01–0.01	<0.01
	English at home	1.06	0.51–2.20	0.87	1.46	0.98–2.17	0.06	0.09	0.01–0.17	0.02
	Male	1.57	0.77–3.35	0.21	1.47	1.02–2.11	0.04	0.01	0.01–0.16	0.02
	Glucose (mmol/L)	1.07	0.97–1.19	0.17	1.11	1.04–1.18	<0.01	0.02	0.01–0.04	<0.01

Model 1 included age, male gender, SEIFA score, speaking English at home, diabetes. Model 2 included age, male gender, SEIFA score, speaking English at home, HbA1c and admission glucose. Model 3 included age, male gender, SEIFA score, speaking English at home, HbA1c, admission glucose and diabetes.

CI, confidence interval; ICU, intensive care unit; SEIFA, Socio-Economic Index for Areas.

Diabetic ketoacidosis

There were nine cases of diabetic ketoacidosis on admission. Seven had known type 2 diabetes, of whom five were taking SGLT-2 inhibitors and one had diabetes due to past pancreatic disease. The ninth case was a 32-year-old male for whom this was the initial presentation of diabetes. His initial venous glucose was 24.6 mmol/L, pH 7.24, bicarbonate 10, base excess −16, ketones 4.6 mmol/L. His HbA1c was 13%. C-peptide was undetectable, but this was taken after commencement of an insulin glucose infusion. Glutamic acid decarboxylase, islet cell and zinc transporter-8 antibody levels were not raised. Six months after admission, he remained on insulin therapy.

Table 3 Comparison of patients with known diabetes and newly diagnosed diabetes

	Known diabetes, *N* = 264	Newly diagnosed diabetes, *N* = 47	*P* value
Age (years)	60.9 ± 14.8	57.9 ± 16.3	0.21
Male	138 (52%)	33 (72%)	0.02
Speaks English at home	134 (51%)	25 (54%)	0.75
SEIFA score	932 ± 73	934 ± 68	0.86
ATSI	6 (2%)	4 (9%)	0.045
HbA1c (%)	7.9 ± 2.2	8.1 ± 2.1	0.61
HbA1c (mmol/mol)	63 ± 23	65 ± 24	0.71
Glucose on admission (mmol/L)	10.7 ± 6.1	10.9 ± 5.2	0.80
Smoker	38 (14%)	9 (20%)	0.38
Comorbidities			
Hypertension	93 (35%)	10 (22%)	0.09
Coronary artery disease	21 (8%)	5 (11%)	0.56
Cerebrovascular disease	1 (0.4%)	1 (2%)	0.28
Major mental health disorder	13 (5%)	4 (9%)	0.29
Chronic lung disorder	33 (13%)	9 (20%)	0.24
Dementia	4 (2%)	0 (0%)	1.0
Chronic kidney disease	30 (11%)	0 (0%)	0.01
Cancer	4 (2%)	0 (0%)	1.0
ICU admission	42 (16%)	18 (39%)	<0.01
Death	21 (8%)	4 (9%)	0.77
Length of stay (days)	6.2 (2.1–12.2)	9.9 (6.3–14.1)	<0.01

Data presented as mean ± SD, median (IQR) or *N* (% total).

ATSI, Aboriginal or Torres Strait Islander; ICU, intensive care unit; IQR, interquartile range; SEIFA, Socio-Economic Index for Areas.

Discussion

In this first Australian study describing an entire cohort of hospitalised patients with COVID-19, 20% of subjects had diabetes. This is considerably higher than the self-reported community prevalence of diabetes of 5.4%, but similar to the point prevalence of diabetes in Australian hospitals.[15–17] Overall mortality was relatively low at 3.2%, but diabetes was associated with a fourfold increase in mortality, almost a doubling in risk of admission to ICU and longer length of hospital stay compared to subjects without diabetes. Subjects with diabetes were older, less likely to speak English at home and were even more socioeconomically disadvantaged compared to those who did not have diabetes. They were more likely to have medical comorbidities. Diabetes patients who were hospitalised with COVID-19 were more likely to have COVID symptoms or pneumonitis.

The crude relative risk of death (fourfold) among subjects with diabetes is similar to that observed in other studies,[5] though our absolute death rate was lower (8%). One study, with 952 subjects with diabetes in a cohort of 7337 subjects, found that with adjustment for age, gender and hospital site, there was an attenuation of the effect of diabetes on mortality, with a hazard ratio of 1.70.[18] Another study with 63 subjects with diabetes out of a cohort of 258, which adjusted for age and comorbidities found a hazard ratio of 3.64.[19] In contrast to these previous studies, we found that diabetes was not independently associated with an increase in mortality. Most earlier studies examining the impact of diabetes on COVID-19 mortality were performed in 2020, prior to the introduction of current therapies and vaccination. It is likely that with adequate preparedness, early recognition and intervention, sufficient state-of-the-art ICU facilities and newer combination treatments proven to be effective in attenuating severe COVID-19 disease the risk of death posed by diabetes will be minimised. However, since diabetes or glucose levels predicted admission to ICU and longer LOS, diabetes remains an independent predictor for severe disease.

Although several studies have shown that there is an association between admission fasting blood glucose and adverse hospital outcomes, surprisingly few have examined the relationship based on admission random glucose levels. A recent meta-analysis found only five such studies with a total of 1150 subjects looking at mortality and two studies with 514 patients examining ICU admission.[20] One individual study found higher mortality among patients with an admission glucose level ≥ 7.78 mmol/L.[21] Our study also found a graded relationship between admission glucose levels and mortality, ICU admission and LOS. The risk increased above 6 mmol/L, a very modest level of hyperglycaemia. This is generally consistent with earlier findings regarding the relationship between admission glucose and hospital mortality prior to the advent of COVID-19.[22] In multivariate models, we found that admission glucose did not independently predict death, but it is a stronger predictor of ICU admission and LOS than diabetes status. Again, it is likely that access to effective treatment for COVID-19 attenuates the effect of hyperglycaemia on the risk of death. Hyperglycaemia might also be a marker of illness severity, that is, stress hyperglycaemia, rather than a primary contributor to the acute illness.

There are intriguing reports that COVID-19 infection may result in the new development of diabetes. ACE-2 receptors, the receptor for COVID-19 entry into cells, are expressed in both the endocrine and exocrine pancreas, and it has been postulated that SARS CoV-2 may impair β-cell function or cause sufficient damage to induce diabetes.[23,24] Some studies have reported a high rate of newly diagnosed diabetes among COVID patients requiring hospitalisation, this being present in 14.4% of all subjects in one meta-analysis.[25]

However, only 3.1% of our cohort had a new diagnosis of diabetes. A recent American study found a similar 4% of their cohort had newly diagnosed diabetes.[26] Our cases of newly diagnosed diabetes almost certainly had unrecognised pre-existing diabetes, given their elevated HbA1c. Therefore, COVID-19 did not cause new-onset diabetes, but rather facilitated its diagnosis. Although subjects of Aboriginal or Torres Strait Islander background who had COVID-19 were not more likely to have diabetes, they were more likely to have newly diagnosed diabetes. This may reflect greater barriers to care in general for this population.

Altough their mortality rate was not greater than for patients with established diabetes, the patients with newly diagnosed diabetes were more likely to be admitted to ICU and have longer LOSs. Our data did not provide clear insights into the reasons for this, apart from a higher rate of CKD, and notably they did not have higher glucose levels on admission. It is possible that the patients with newly diagnosed diabetes had other undiagnosed and untreated comorbidities and were therefore more susceptible to severe illness.

There are reports of an increase in ketoacidosis with new-onset diabetes among children, possibly related to COVID-19 infection.[27] Although it has been suggested that COVID-19 may cause β-cell damage and insulin deficiency because of the presence of the ACE-2 receptor in the pancreatic islets resulting in acute type 1 diabetes, the clinical evidence for this remains paltry. The only case of diabetic ketoacidosis with a new diagnosis of diabetes we observed probably had diabetes prior to COVID-19 infection, given the HbA1c of 13%. Therefore, both in terms of the cases of new diabetes and

diabetic ketoacidosis, there was little evidence in our cohort that COVID-19 infection caused diabetes.

There are some limitations to our study. In the challenging nursing environment that was faced by the hospital, many patients were not weighed, and therefore we did not include weight in our data set. We did not have details of glucose readings during the entire course of the hospital admission and therefore were unable to examine the relationship between this and outcomes. In particular, dexamethasone therapy, which is routine for hospitalised patients with COVID-19 suffering hypoxia, commonly causes or exacerbates hyperglycaemia.[28] We are unable to comment on whether improved glucose levels might result in better outcomes.

We also found that, despite the protocol for measuring glucose and HbA1c on admission, substantial numbers of patients had a fingerstick glucose instead, or it was missed completely. The study substantially relied on ICD-10 coding to establish comorbidities and complications, and it is possible that not all of these were accurate. We were unable to determine vaccination status through data set matching, so we did not have data on how this influences the relationship between COVID-19 and diabetes or glucose levels. Our study was conducted over the period when Delta was the dominant SARS CoV-2 variant causing COVID-19. Therefore, we did not yet have data as to whether diabetes and hyperglycaemia affected hospital outcomes for patients with the Omicron variant of SARS CoV-2. Finally, this was a single-centre study, which may limit the generalisability of our findings.

Conclusion

There is an over-representation of diabetes among the ethnically diverse and relatively socioeconomically disadvantaged patients with COVID-19 requiring hospital admission in Western Sydney, though the prevalence of diabetes in this group was not markedly different from hospitalised patients in general. Patients with diabetes have worse outcomes, though its effect on mortality was not significant when adjusted for other variables. Our data did not suggest that COVID-19 was directly responsible for the development of diabetes in any of the new cases diagnosed.

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Supporting Information

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

Table S1. Differences between COVID subjects who had or did not have an admission venous glucose level.