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RESEARCH ARTICLE

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Diabetes predicts severity of COVID-19 infection in a retrospective cohort: A mediatory role of the inflammatory biomarker C-reactive protein

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Abstract

Diabetes is a risk factor for developing severe COVID-19, but the pathogenesis remains unclear. We investigated if the association of diabetes and COVID-19 severity may be mediated by inflammation. We also hypothesized that this increased risk may extend to prediabetes. Hospitalized patients in Singapore with COVID-19 were subdivided into three groups in a retrospective cohort: normoglycemia (HbA1c: ≤5.6%), prediabetes (HbA1c: 5.7%–6.4%) and diabetes (HbA1c: ≥6.5%). The primary outcome of severe COVID-19 was defined by respiratory rate ≥30, SpO2 ≤93% or intensive care unit admission. The association between clinical factors on severe COVID-19 outcome was analyzed by cox regression. Adjusted mediation analysis of C-reactive protein (CRP) on the relationship between diabetes and severe COVID-19 was performed. Of 1042 hospitalized patients, mean age 39 ± 11 years, 13% had diabetes, 9% prediabetes and 78% normoglycemia. Severe COVID-19 occurred in 4.9% of subjects. Compared to normoglycemia, diabetes was significantly associated with severe COVID-19 on both univariate (hazard ratio [HR]: 9.94; 95% confidence interval [CI]: 5.54–17.84; $p < .001$) and multivariate analysis (HR: 3.99; 95% CI: 1.92–8.31; $p < .001$), while prediabetes was not a risk factor (HR: 0.94; 95% CI: 0.22–4.03; $p = .929$). CRP, a biomarker of inflammation, mediated 32.7% of the total association between diabetes and severe COVID-19 outcome. In conclusion, CRP is a partial mediator of the association between diabetes and severe COVID-19 infection, confirming that inflammation is important in the pathogenesis of severe COVID-19 in diabetes.

KEYWORDS
diabetes, inflammation, mediation, prediabetes, severe COVID-19

1 | INTRODUCTION

Early in the COVID-19 outbreak, Singapore's index case was reported in January 2020.[1] Since then, COVID-19 has become a global pandemic, claiming the lives of over a million people worldwide.[2] Diabetes has emerged as a significant risk factor for adverse COVID-19 outcome in various populations,[3–5] in addition to age and other comorbidities such as obesity, hypertension, chronic heart, and lung disease.[4,6] While several studies have demonstrated a two to threefold risk of poor clinical outcomes including severe COVID-19 infection, intensive care

unit (ICU) admission and mortality in COVID-19 patients with diabetes,[4,7] the pathogenesis remains unclear.

Diabetes has been described as a chronic inflammatory state evident by raised inflammatory markers such as C-reactive protein (CRP).[8] Hyperglycemia upregulates the expression of proinflammatory cytokines, setting up the stage for a hyper-inflammatory response in acute infection,[9,10] which has been proposed to result in multiorgan failure and death in COVID-19.[10,11] Interestingly, long-term glycemic control was not consistently associated with COVID-19 severity and mortality.[12,13] Emerging evidence have shown the importance of inpatient hyperglycemia as a significant predictor of adverse outcomes, in patients with and without diabetes.[14,15] Although studies have demonstrated the association between hyperglycemia and an impaired innate and adaptive immune system, increasing the risk of sepsis,[16,17] it is uncertain at what threshold of hyperglycemia this occurs.

The impact of prediabetes on COVID-19 outcomes is lacking in the literature. Fasting glucose exceeding 5.6 mmol/L was associated with increased nonvascular, noncancer deaths and all-cause mortality.[18] Similarly, a large meta-analysis demonstrated prediabetes to be a risk factor for all-cause mortality.[19] However, few studies have investigated the significance of prediabetes in sepsis and acute illness. Impaired fasting glucose was found to predict an adverse prognosis among hospitalized patients with COVID-19.[20] There was, however, no available glycated hemoglobin (HbA1c) data to establish longer-term glycemic control to distinguish inpatient stress-induced hyperglycemia from prediabetes. Given that the population prevalence of prediabetes is estimated at 13.5%–58% depending on the definition used,[21] an excess risk identified could have substantial impact on morbidity and mortality in this COVID-19 pandemic.

The association between diabetes and severity of COVID-19 infection has previously been demonstrated, but the mechanisms for this are unclear. In this study, we sought to confirm if the presence of diabetes was associated with poorer COVID-19 outcomes, and if so, whether they were mediated by a proinflammatory state. Using CRP as a biomarker of inflammation, we hypothesize that diabetes was associated with an increased risk of severe COVID-19 via a heightened inflammatory burden. As identifying modifiable risk factors could be helpful in devising new therapeutic strategies in our longer-term fight against COVID-19, a secondary aim was to identify factors associated with adverse outcomes in patients hospitalized with COVID-19 infection, particularly inpatient hyperglycemia, as well as longer-term glycemic control as measured by HbA1c. Last, we also explored prediabetes as a possible adverse prognostic factor which would emphasize the need for preventive strategies.

2 | METHODS

2.1 | Study setting

Singapore has one of the world's lowest mortality rate for COVID-19,[2] postulated to be due to several factors including early detection, extensive contact tracing, younger demographics, preemptive hospitalization even if well, and mandatory mask-wearing which have been shown to reduce not just infection rates but severity of illness in those infected.[22] Hence, the setting of this cohort in Singapore implies the vast majority are clinically well due to the Ministry of Health's adopted strategy to admit all patients diagnosed with COVID-19 to hospitals or community facilities for monitoring and isolation.[1]

2.2 | Study design

This is a retrospective cohort study of patients admitted to Khoo Teck Puat Hospital in Singapore from February 1 to May 31, 2020, who were diagnosed with COVID-19 infection via reverse transcription polymerase chain reaction (RT-PCR) on throat and nasopharyngeal swab. This study was approved by the Institutional Review Board (DSRB 2020/00750).

Data was obtained from electronic health records. We collected information on patient demographics, co-morbidities, clinical characteristics, medications, HbA1c in the current admission, as well as COVID-19-related biochemistry. Random glucose was measured within the first 48 h of admission, whereas subsequently glucose measurements were performed premeals. Average glucose was computed if ≥2 readings were available throughout admission. Baseline CRP level was obtained within the first 48 h of admission. All patients admitted for COVID-19 had a predefined set of laboratory investigations to be performed and HbA1c or glucose was not part of this routine set.

Exclusion criteria included pregnancy and those with missing data on the primary outcome of oxygen saturation, respiratory rate or admission to ICU.

2.3 | Definitions of diabetes, prediabetes, and normoglycemia

Diabetes mellitus (DM) was defined as HbA1c ≥6.5%[23] or self-reported history of diabetes or use of glucose-lowering medications. Prediabetes (pre-DM) and normoglycemia were defined as HbA1c 5.7–6.4 or HbA1c ≤5.6%, respectively, without a self-reported history of diabetes or use of glucose-lowering medications.

2.4 | Outcomes

The primary outcome was defined as the development of severe COVID-19, defined by SpO2 ≤93% on room air, respiratory rate ≥30[24] or need for ICU care. In addition, we compared length of stay, dyspnea (defined by respiratory rate ≥30 or SpO2 ≤93%), need for ICU and mortality.

2.5 | Statistical analysis

Statistics were performed using STATA version 14 (Stata). Continuous variables were presented as mean ± *SD* or median (interquartile range [IQ]), and categorical data were shown as *n* (%). The Student *t* test and Mann–Whitney *U* test were used to compare differences of continuous variables between two independent groups; and χ^2 test was used to compare categorical variables. Nonnormally distributed continuous variables were natural log-transformed before regression analysis. Cox proportional hazards regression was used to analyze the association between baseline factors and events of severe COVID-19, dyspnea or ICU admission, while linear regression was used to analyze the outcome of inpatient length of stay. Considering that the number of adverse events was small, only four variables (age, sex, body mass index [BMI], and having ≥2 comorbidities), selected a priori,[25] were included as covariates in the regression models to avoid overfitting issues. Adjusted mediation analysis was performed to examine the mediatory effect of CRP, LDH, and hypoglycemia on the relationship between DM and the inpatient outcomes using the STATA "binary_mediation" (for binary outcome) and "sgmediation" (for continuous outcome) commands with bootstrapping. The Baron and Kenny three-step model[26] was used to assess (1) Association between diabetes status and development of severe COVID-19, (2) Association between diabetes status and CRP level, LDH level and hypoglycaemia events, and (3) weakening of association between diabetes status and development of severe COVID-19 when CRP, LDH, or hypoglycaemia was added to the model. The $p < .05$ indicated statistical significance.

3 | RESULTS

3.1 | Population characteristics and outcome

A total of 1042 subjects were hospitalized with COVID-19 infection (Table 1). The predominantly male cohort (95%) of relatively young age (mean: 39 ± 11 years) was due to Singapore's outbreak of COVID-19 among foreign worker dormitories and a low community transmission rate.[27] Subjects were classified as DM, pre-DM and normoglycemia in 13%, 9% and 78%, respectively. The mean BMI was 24.2 kg/m^2, as defined by the World Health Organization criteria of BMI in Asians,[28] with 62% being overweight or obese. The difference in BMI was significant between DM status groups (p-trend <0.001) with highest mean BMI 25.5 kg/m^2 in the DM group. Overall, 7% of subjects had ≥2 comorbidities of hypertension, hyperlipidemia, cardiovascular disease (CVD), chronic kidney disease (CKD), chronic respiratory disease excluding the presence of diabetes. A significantly higher proportion of subjects with DM (33%) had ≥2 comorbidities as compared to the pre-DM (12%) and normoglycemia (1%) groups (p-trend <0.001; Table S1).

Admission glucose levels were significantly different between DM status groups: 12.1 mmol/L in DM, 7.4 mmol/L in pre-DM, and 6.2 mmol/L in normoglycemia patients (p-trend <0.001) (Table 1). The mean HbA1c was 8.5%, 5.9% and 5.4% in the DM, pre-DM and normoglycemia groups, respectively (p-trend <0.001). The admission glucose and average glucose during hospitalization were also significantly higher in the DM group compared to other groups. Of the subjects with DM, 89% were on glucose-lowering agents and 15% were on insulin. Median CRP at admission was low at 3.7 (1.2–9.5) mg/L, reflective of Singapore's strategy of preemptive hospitalization of all COVID-19 patients even if well. Subjects with DM had the highest CRP of 10.1 mg/L (p-trend <0.001). The need for systemic treatment for COVID-19 infection such as hydroxychloroquine, glucocorticoids, interleukin (IL)-6 inhibitors and antibiotics were also greater in the DM group. The use of other pertinent medications is detailed in Table S1.

The primary outcome of severe COVID-19 infection occurred in 51 patients (4.9%) of the overall cohort (Table 1). A total of 27 (2.6%) patients were admitted to ICU, 46 (4.4%) developed dyspnea, and 5 (0.5%) demised. The median length of stay was 8 (IQ: 5–12) days.

3.2 | Diabetes as a risk factor for severe disease

A significantly greater proportion of subjects with DM developed the primary outcome of severe COVID-19 (22%) as compared to pre-DM (2%) and normoglycemia (2%) subjects, respectively (Table 1). This was verified on Cox regression, where diabetes was significantly associated with the occurrence of severe COVID-19 on both univariate (Table 2 Model 1; hazard ratio [HR]: 9.94; 95% confidence interval [CI]: 5.54–17.84; $p < .001$) and multivariate analysis (Table 2 Model 2; HR: 3.99; 95% CI: 1.92–8.31; $p < .001$) compared to normoglycemia.

3.3 | Diabetes is associated with ICU admission, development of dyspnea, increased length of stay, and need for systemic treatment

This trend towards more severe illness in subjects with DM was also consistent in the secondary outcomes of developing dyspnea and requiring ICU admission, as compared to pre-DM and normoglycemia groups (Table 1). After adjusting for significant confounders, the presence of DM was associated with an increased HR of 4.05 (95% CI: 1.94–8.43) $p < .001$ for developing dyspnea, and HR of 10.93 (95% CI: 3.54–33.77) $p < .001$ for requiring ICU admission compared to normoglycemic patients (Table 3). Length of stay was significantly longer in DM subjects compared to other groups (Table 1). This was consistently observed in the univariate and multivariate analyses (Table 3). Mortality was higher in DM subjects, however, it did not reach statistical significance due to very low mortality in the cohort (0.5%).

3.4 | Prediabetes is not an adverse prognostic factor

In contrast, prediabetes was not associated with the occurrence of severe COVID-19 disease compared to the normoglycemia group on

TABLE 1 Clinical characteristics and inpatient events stratified by DM status

Variable	Total (*n* = 1042)	Normoglycaemia (*n* = 809)	Pre-DM (*n* = 93)	DM (*n* = 140)	*p* Value
Demographics					
Age (years)	39 ± 11	36 ± 10	44 ± 9	48 ± 13	<.001
Male, *n* (%)	994 (95.4)	772 (95.4)	93 (100.0)	129 (92.1)	.020
Ethnic, *n* (%)					<.001
Chinese	141 (13.5)	89 (11.0)	22 (23.7)	30 (21.4)	
Malay	32 (3.1)	22 (2.7)	1 (1.1)	9 (6.4)	
Indian	325 (31.2)	265 (32.8)	16 (17.2)	44 (31.4)	
Others	544 (52.2)	433 (53.5)	54 (58.1)	57 (40.7)	
BMI (kg/m^2)	24.2 ± 3.4	23.9 ± 3.4	24.4 ± 2.6	25.5 ± 3.6	<.001
	[*n* = 1038]	[*n* = 805]			
Laboratory tests					
Admission glucose (mmol/L)	7.5 ± 3.6	6.2 ± 1.2	7.4 ± 1.8	12.1 ± 5.8	<.001
	[*n* = 695]	[*n* = 467]	[*n* = 91]	[*n* = 137]	
Average glucose during admission (mmol/L)	7.3 ± 2.0	6.2 ± 1.0	7.0 ± 1.3	9.3 ± 2.2	<.001
	[*n* = 458]	[*n* = 240]	[*n* = 80]	[*n* = 138]	
HbA1c (%)	6.9 ± 1.9	5.4 ± 0.2	5.9 ± 0.2	8.5 ± 2.0	<.001
	[*n* = 255]	[*n* = 53]		[*n* = 109]	
TC (mmol/L)	4.2 ± 1.0	4.2 ± 0.8	4.4 ± 1.2	4.2 ± 1.0	.771
	[*n* = 128]	[*n* = 31]	[*n* = 33]	[*n* = 64]	
HDL-C (mmol/L)	0.9 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.8 ± 0.2	.152
	[*n* = 128]	[*n* = 31]	[*n* = 33]	[*n* = 64]	
LDL-C (mmol/L)	2.8 ± 0.8	2.7 ± 0.8	2.7 ± 0.9	2.8 ± 0.9	.889
	[*n* = 131]	[*n* = 31]	[*n* = 35]	[*n* = 65]	
TG (mmol/L)	1.9 (1.3–2.6)	1.8 (1.2–2.3)	1.9 (1.4–2.8)	1.9 (1.4–2.7)	.170
	[*n* = 128]	[*n* = 31]	[*n* = 33]	[*n* = 64]	
LDH (U/L)	190 (168–219)	189 (168–213)	192.5 (167–235)	194 (166–248)	.181
	[*n* = 951]	[*n* = 744]	[*n* = 86]	[*n* = 121]	
ALT (U/L)	32 (22–49)	32 (21–49)	31 (25–44)	34 (22–52)	.598
	[*n* = 1012]	[*n* = 783]	[*n* = 92]	[*n* = 137]	
AST (U/L)	26 (20–36)	26 (20–35)	25 (21–34)	28 (20–41)	.430
	[*n* = 1010]	[*n* = 782]	[*n* = 91]	[*n* = 137]	
Creatinine (μmol/L)	78 (69–87)	78 (69–86)	78 (72–87)	76 (66–90)	.637
	[*n* = 1028]	[*n* = 796]		[*n* = 139]	
WBC ($x10^9/L$)	6.4 (5.2–7.9)	6.3 (5.2–7.7)	6.9 (5.7–8.7)	6.8 (5.2–8.9)	.003
	[*n* = 1032]	[*n* = 800]		[*n* = 139]	
Lymphocytes ($x10^9/L$)	1.6 (1.2–2.2)	1.6 (1.2–2.1)	1.8 (1.3–2.4)	1.6 (1.1–2.1)	.099
	[*n* = 1032]	[*n* = 800]		[*n* = 139]	
CRP (mg/L)	3.7 (1.2–9.5)	3.3 (1.1–7.7)	2.7 (0.9–9.8)	10.1 (2.5–34.2)	<.001
	[*n* = 1026]	[*n* = 795]		[*n* = 138]	

TABLE 1 (Continued)

Variable	Total (n = 1042)	Normoglycaemia (n = 809)	Pre-DM (n = 93)	DM (n = 140)	p Value
Clinical events					
Hypoglycaemic event, n (%)	11 (1.6)	1 (0.2)	0 (0)	10 (7.4)	<.001
	[n = 694]	[n = 467]	[n = 91]	[n = 136]	
Severe covid, n (%)	51 (4.9)	18 (2.2)	2 (2.2)	31 (22.1)	<.001
Dyspnoea, n (%)	46 (4.4)	17 (2.1)	1 (1.1)	28 (20.0)	<.001
ICU, n (%)	27 (2.6)	5 (0.6)	1 (1.1)	21 (15.0)	<.001
Death, n (%)	5 (0.5)	1 (0.1)	0 (0.0)	4 (2.9)	.287
LOS, days	8 (5–12)	8 (4–11)	9 (6–13)	11 (7–20)	<.001

Note: If there was missing data, the number of available data is indicated in square brackets. Cells without square brackets have no missing data.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CRP, C-reactive protein; DM, diabetes mellitus; HDL-C, high density lipoprotein-cholesterol; ICU, intensive care unit; LDH, lactic acid dehydrogenase; LDL-C, low density lipoprotein-cholesterol; LOS, length of stay; TC, total cholesterol; TG, triglycerides; WBC, white blood cells.

TABLE 2 Baseline factors associated with COVID-19 severity (Cox regression)

Variables	Model 1 (univariable) HR (95% CI), p value	Model 2 (multivariable) HR (95% CI), p value	Model 3 (multivariable) HR (95% CI), p value
Age	1.08 (1.06–1.10), <.001	1.04 (1.01–1.07), .004	1.03 (1.00–1.06), .026
Men	0.25 (0.12–0.53), <.001	0.79 (0.34–1.81), .571	0.76 (0.32–1.77), .520
DM status			
Normal	1	1	1
Pre-DM	0.94 (0.22–4.03), .929	0.68 (0.10–2.99), .611	0.49 (0.11–2.24), .356
DM	9.94 (5.54–17.84), <.001	3.99 (1.92–8.31), <.001	2.30 (1.06–5.01), .036
HTN	7.17 (4.12–12.50), <.001	–	–
HLD	2.83 (0.88–9.10), .081	–	–
CVD	17.67 (9.61–32.47), <.001	–	–
CRD	5.63 (1.75–18.07), .004	–	–
CKD	4.04 (2.21–7.40), <.001	–	–
≥2 Comorbidities	11.07 (6.32–19.40), <.001	1.99 (0.88–4.48), .097	1.93 (0.87–4.29), .106
BMI	1.17 (1.10–1.24), <.001	1.09 (1.02–1.16), .014	1.06 (0.99–1.14), .092
LDH*	12.36 (6.59–23.18), <.001	–	–
AST*	2.08 1.28–3.37), .003	–	–
Creatinine*	3.39 (1.65–6.94), .001	–	–
WBC*	2.11 (0.94–4.75), .072	–	–
Lymphocytes*	0.34 (0.20–0.59), .002	–	–
CRP*	2.32 (1.92–2.82), <.001	–	2.10 (1.50–2.93), <.001

Note: Model 1: Unadjusted; Model 2: Adjusted for baseline age, sex, DM, BMI, ≥2 comorbidities (including HTN, HLD, CVD, CRD, and CKD); Model 3: Model 2 adjusted for baseline CRP (natural log-transformed). *Natural log-transformation.

Abbreviations: AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CRD, chronic respiratory disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HLD, hyperlipidaemia; HR, hazards ratio; HTN, hypertension; LDH, lactic acid dehydrogenase, WBC, white blood cells.

TABLE 3 Association of DM (vs. non-DM) with COVID-19 severity (Cox regression), dyspnea (Cox regression), ICU admission (Cox regression), or inpatient length of stay (linear regression)

Variables	Model 1 (univariable) HR (95% CI), *p* value	Model 2 (multivariable) HR (95% CI), *p* value	Model 3 (multivariable) HR (95% CI), *p* value
Outcome: COVID-19 severity			
DM	10.01 (5.68–17.63), <.001	4.24 (12.11–8.55), <.001	2.71 (1.34–5.47), .005
CRP	2.32 (1.92–2.82), <.001	–	1.74 (1.41–2.14), <.001
Outcome: dyspnea			
DM	10.05 (5.53–18.25), <.001	4.05 (1.94–8.43), <.001	2.34 (1.13–4.88), .023
CRP	2.58 (2.10–3.17), <.001	–	1.94 (1.54–2.43), <.001
Outcome: ICU admission			
DM	23.29 (9.40–57.72), <.001	10.93 (3.54–33.77), <.001	6.15 (1.99–19.05), .002
CRP	2.88 (2.18–3.81), <.001	–	2.00 (1.45–2.76), <.001
	B (95% CI), *p* value	B (95% CI), *p* value	B (95% CI), *p* value
Outcome: LOS			
DM	5.83 (4.69–6.98), <.001	2.16 (0.99–3.33), <.001	1.70 (0.51–2.88), .005
CRP	0.94 (0.67–1.22), <.001	–	0.44 (0.18–0.70), .001

Note: Model 1: Unadjusted; Model 2: Adjusted for baseline age, sex, DM, BMI, ≥2 comorbidities (including HTN, HLD, CVD, CRD and CKD); Model 3: Model 2 adjusted for baseline CRP (natural log-transformed).

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CRD, chronic respiratory disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HLD, hyperlipidaemia; HR: hazards ratio; HTN, hypertension; ICU, intensive care unit; LOS, length of stay.

cox regression (Table 2). In addition, patients with pre-DM and normoglycemia had similar secondary outcomes with respect to development of dyspnea ($p = .503$), need for ICU care ($p = .607$) and length of stay ($p = .055$).

3.5 | Long-term glycemic control and admission hyperglycemia

Using HbA1c as a measure of long-term glycemic control, there was no difference in primary outcome of developing severe COVID-19 infection when 109 DM subjects with available HbA1c measurements were stratified according to HbA1c thresholds of less than or greater than 9%, 8%, and 7% (Table S2).

In the overall cohort, admission hyperglycemia was associated with a 6% increased risk of COVID-19 severity, however, significance was lost on adjusted analysis (Table S2). In the DM group, admission hyperglycemia was not associated with COVID-19 severity on unadjusted and adjusted analysis. Average glucose throughout admission was not correlated with COVID-19 severity in either the overall cohort or DM group.

3.6 | Other adverse prognostic markers for severe COVID-19 infection

Besides diabetes, other factors including age, female gender, and comorbidities such as hypertension, CVD, chronic respiratory disease, CKD, BMI, and the presence of ≥2 comorbidities were associated with the development of severe COVID-19 on univariate analysis (Table 2). Laboratory markers of severe COVID-19 infection include raised LDH, CRP, AST, creatinine, and lymphopenia. On multivariate analysis, age, diabetes, and higher BMI remained significantly associated with severe COVID-19 infection (Table 2). As expected, female gender was no longer an adverse prognostic factor after correction for significant confounders such as age and comorbidities. This reflects the young healthy male-predominant foreign worker population of COVID-19 infections in Singapore.

3.7 | CRP is a partial mediator of the association between DM and severe COVID-19

As shown in Table 3 Model 3, addition of CRP into the Cox model diminished the association between DM and severe COVID-19. Similar observations were made for the secondary outcomes (Table 3, Model 3), suggesting a mediatory effect of CRP. Mediation analysis revealed that CRP mediated 32.7% of the total association of DM and severe COVID-19 outcome in the covariate-adjusted model (Table 4). In addition, CRP explained 40.4%, 27.2%, and 18.2% of the association between DM and dyspnea, need for ICU and length of stay, respectively.

Incidence of hypoglycemia, as well as LDH levels, were also investigated as possible mediators of the association between DM and severe COVID-19 outcome. Although the incidence of hypoglycemia appeared to mediate 24.2% of the total association of DM and severe

TABLE 4 Mediation effects of C-reactive protein on the relationship between DM (vs. non-DM) and inpatient events

Mediated pathway	Total effect Coefficient (95% CI)	Direct effect Coefficient (95% CI)	Indirect effect Coefficient (95% CI)	Proportion mediation (%)
DM → CRP→COVID-19 severity	0.26 (0.16–0.37)	0.18 (0.07–0.28)	0.09 (0.04–0.13)	32.7
DM → CRP → Dyspnea	0.25 (0.13–0.36)	0.15 (0.03–0.26)	0.10 (0.06–0.14)	40.4
DM → CRP → ICU admission	0.38 (0.21–0.54)	0.27 (0.10–0.44)	0.10 (0.04–0.16)	27.1
DM → CRP → LOS	2.08 (0.43–3.72)	1.70 (0.08–3.72)	0.38 (0.11–0.65)	18.2

Note: All models were adjusted for baseline covariates including age, sex, BMI, ≥2 comorbidities (including HTN, HLD, CVD, CRD, and CKD).
Abbreviations: BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; CRD, chronic respiratory disease; CRP, C-reactive protein (natural log-transformed); CVD, cardiovascular disease; HLD, hyperlipidaemia; HTN, hypertension; ICU, intensive care unit; LOS, length of stay.

COVID-19 outcome, this indirect effect was nonsignificant (Table S3). LDH levels were not associated with DM status, and was not a significant mediator of the effect of DM on severe COVID-19 outcome.

4 | DISCUSSION

Our findings that DM is associated with poorer COVID-19 prognosis, including longer inpatient stay and severe pneumonia requiring admission to ICU, are consistent with findings from other centers worldwide.[5,6] Other comorbidities such as hypertension, CVD, chronic respiratory disease, and CKD identified to be adverse prognostic factors in our study have also been confirmed in other cohorts.[5,29]

In patients with DM, an exaggerated immune response to COVID-19 infection, coupled with a preexisting heightened inflammatory state, may explain in part, the more severe COVID-19 disease outcome observed in this group. A hyper-inflammatory response has been described to account for the morbidity and mortality in severe COVID-19 infection.[11] The pathogenic link between diabetes and COVID-19 severity can be described by the following mechanisms: (i) immune dysfunction; (ii) reduced viral clearance; and (iii) heightened inflammatory state.[9,17] Diabetes is associated with higher CRP levels,[9] similar to our findings. Chronic hyperglycemia is known to incite a proinflammatory, prooxidative state which is linked to adverse outcome in the critical care setting.[10,30] Our finding of CRP as a significant mediator of the association between preexisting diabetes and severe COVID-19 infection outcome is in keeping with this. The RECOVERY trial found improved mortality with the use of dexamethasone, a potent anti-inflammatory, in severely ill COVID-19 patients.[31] Further analysis of the DM subgroup may be considered to evaluate if this group could potentially derive the most benefits from dexamethasone.

Apart from indicating a preexisting proinflammatory state, elevated CRP levels observed in patients with diabetes may also be due to superimposed hospital-acquired infections complicating the course of COVID-19 illness, as evidenced in our study by a greater need for antibiotics in the DM group. There is an increased susceptibility to bacterial infections due to impaired innate and cell-mediated immune responses in diabetes.[16] However, it is also important to note that the effect of inflammation as measured by CRP on COVID-19 severity is not solely modulated by DM status. Other factors apart from DM that modulate vascular inflammation, such as the presence of CVD, malignancy or smoking status, may also influence COVID-19 outcomes, however, it was not possible to explore these associations in the scope of this study.

As CRP only mediated a portion of the association between diabetes and severe COVID-19 outcomes, other factors may play an important role. Inpatient hypoglycemia has also been known to be correlated with mortality in hospitalized patients, possibly related to cardiovascular and neurological complications.[32] Although there was a greater number of hypoglycemic events in patients with DM compared to non-DM subjects in our cohort, hypoglycemia was not a significant mediator on the severity of COVID-19 disease in DM patients. Furthermore, although LDH level was strongly associated with severe COVID-19 disease, which was similar to other reports,[33] LDH did not mediate the association between DM and severe COVID-19 outcome. LDH is an intracellular enzyme which catalyzes the interconversion of pyruvate and lactate found in cells throughout all organ systems. While CRP is an acute phase reactant, LDH is a biomarker that indicates the degree of tissue damage.[33] This may suggest a differential role of the inflammatory biomarkers CRP and LDH in predicting poorer outcomes in COVID-19 patients with and without DM respectively. As CRP was only a partial mediator of DM on COVID-19 severity, the authors propose that other potential mediators of adverse COVID-19 outcomes in DM, such as D-dimer or other prothrombotic markers,[34] could be further investigated, as diabetes has been described to be a hypercoagulable state in addition to a chronic inflammatory state.[35] Hence, inflammation alone as determined by the biomarker CRP could not entirely mediate the association of adverse outcomes observed in patients with diabetes.

Our study is among the first to investigate the association between pre-diabetes and COVID-19 outcomes. Normoglycemia, prediabetes and DM exist in the continuum. Therefore, we expected a higher baseline CRP level (representative of the proinflammatory state) and a higher incidence of severe COVID-19 in the prediabetes group as compared to the normoglycemia group. However, our study suggested that prediabetes was not associated with a higher baseline CRP level or increased incidence of severe COVID-19 disease.

This supports the findings from a recent study.[36] Even though primary outcome event numbers were small in this group to draw a definitive conclusion, there was no trend towards poorer outcomes, even with baseline CRP level. A graded increase in some biomarkers of inflammation such as white cell count and fibrinogen was reported from normoglycemia to prediabetes to diabetes, while other markers such as neopterin, albumin, and hematocrit showed no such changes in prediabetes.[37] If the subclinical effects of immune dysregulation were small in prediabetes, the low incidence of severe outcomes in our cohort may have precluded the ability of our study to elucidate such effects. To date, in individuals with dysglycemia, the duration and degree of exposure to hyperglycemia required to incite chronic inflammation and immune dysfunction is unknown. The impact of prediabetes on the morbidity and mortality of COVID-19 infection needs to be addressed in future studies.

In our study, both admission and inpatient hyperglycemia among DM patients were not associated with an adverse outcome. However, in the overall cohort, there was a trend to a poorer outcome with admission hyperglycemia. As less than two-thirds of the cohort of subjects without diabetes had an admission glucose measured, it was not possible to draw conclusions from this group. Interestingly, studies consistently found a stronger association between hyperglycemia and adverse outcomes in COVID-19 patients without diabetes than in patients with preexisting diabetes,[13,15,16,38] likely reflecting the severity of critical illness resulting in stress-induced hyperglycemia and severe insulin resistance in nondiabetic patients.[39] Adaptation to chronic hyperglycemia in preexisting diabetes may account for these differences, as evidenced by a lack of benefit for intensive glucose control in critically-ill patients with diabetes compared to nondiabetes in a landmark trial, which was not explained by more hypoglycemic events.[40]

There have been variable observations on the effect of poor long-term glycemic control, as measured by HbA1c, on the development of severe COVID-19 disease and risk of mortality. Two large population-based studies in the United Kingdom (UK) reported increased mortality with poorer long-term diabetes control.[4,41] However, in the absence of other clinical measures of severity, population-based data on COVID-19 mortality in the UK may be interpreted cautiously due to concerns which led to the change of definition in August 2020.[42] Furthermore, the surge in non-COVID-related deaths compared to previous years corresponding to the COVID-19 pandemic suggests a number of misclassified COVID-19 deaths in the UK.[43] On the other hand, in other hospitalized cohorts with COVID-19, HbA1c in patients with diabetes did not predict severe disease or mortality,[44,45] in agreement with our study. These findings were verified by larger studies by Cariou and Agarwal which found that long-term glycemic control was not associated with COVID-19 severity and mortality, in both adjusted and unadjusted analyses.[13,14] The reasons for this discrepancy are unclear, given the mechanistic links between hyperglycemia and a dysregulated immune response.[10]

An inherent difficulty in interpreting HbA1c as a representation of the severity of diabetes is due to the heterogeneity of diabetes, in which other factors such as duration of diabetes, degree of insulin resistance versus beta-cell dysfunction, presence of macrovascular complications, glycemic variability and hypoglycemic events may contribute to the overall prognosis. We cannot exclude differences in our population characteristics as a possible reason for the differences in outcome seen compared to other studies which showed worse outcomes at higher HbA1c levels[4,41]; these differences include younger age, male predominance, Asian ethnicity, lower prevalence of comorbidities and lower BMI in our cohort. Further studies that analyze the duration and variability of exposure to chronic hyperglycemia, among other factors mentioned above, are required to ascertain the relationship between diabetes and COVID-19 severity.

4.1 | Limitations and strengths

The low mortality rate (0.5%) and low occurrence of severe COVID-19 (4.9%) in our cohort reflects the national statistic of 29 fatalities out of 58,629 confirmed COVID-19 cases to date.[2] The differences in our cohort also explain the lower baseline CRP levels seen and may have limited the ability of our study to detect small differences in outcome with prediabetes and long-term glycemic control. Second, a male predominance and relatively low severity of COVID-19 illness in our study may limit generalizability to other hospitalized cohorts abroad. However, these findings could still be relevant to clinically well COVID-19 patients monitored in the community or primary care setting. Third, patients with Types 1 and 2 DM were not differentiated in our study, as both types of diabetes were reported to have an increased risk of adverse COVID-19 outcome,[46,47] and separating them would have further reduced the statistical power of our analysis. Fourth, testing of IL-6 or tumor necrosis factor-α as inflammatory markers were not available for routine use in Singapore as they are not cost-effective compared to CRP. Last, data on the duration of diabetes and diabetes complications were not available.

Strengths of the study should be acknowledged. All patients were diagnosed with COVID-19 via validated RT-PCR methods in the current admission rather than using a clinical diagnosis. The use of HbA1c data in addition to a self-reported history of diabetes increased the detection of newly diagnosed diabetes. As opposed to the use of fasting plasma glucose, HbA1c data allowed a clearer distinction between stress-induced hyperglycemia with and without diabetes. Given the impossibility in proving causality in the COVID-19 pandemic with observational studies, the use of mediation analysis in this study strengthens the causal association between diabetes, inflammation and development of severe outcomes.

5 | CONCLUSION

This study consistently demonstrates diabetes to be associated with all measures of adverse COVID-19 outcomes, including severity, need for ICU admission, development of dyspnea and length of stay

in both unadjusted and adjusted models. CRP was a partial mediator of the association between diabetes and these adverse outcomes, confirming that inflammation is an important process in the pathogenesis of severe COVID-19 in diabetes. More studies are required to elucidate other mechanisms which contribute to the severe COVID-19 outcomes observed in diabetes. In this population of patients with diabetes, inpatient hyperglycemia and longer term glycemic control as measured by HbA1c were not associated with severe COVID-19 infection. Prediabetes has not been identified so far to be an adverse prognostic marker in COVID-19, although larger studies are required to clarify this. Nonetheless, those with prediabetes remains an important group to target with population-based prevention strategies before they progress to diabetes which is unequivocally linked to poorer outcomes.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Huilin Koh, Angela Mei Chung Moh, Ester Yeoh, and Caroline Wei Shan Hoong designed the study. Yi Lin collected the data. Angela Mei Chung Moh and Serena Kiat Mun Low analysed the data. Huilin Koh and Caroline Wei Shan Hoong wrote the manuscript with input from Ester Yeoh, Say Tat Ooi, Seng Kiong Tan, and Jaime Hui Xian Lin.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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