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Association of hyperglycaemia at-admission & diabetes mellitus with 28 day mortality in patients admitted with moderate-severe SARS-CoV-2 infection: A retrospective study

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***Background & objectives*: The association between hyperglycaemia at admission, diabetes mellitus (DM) status and mortality in hospitalized SARS-CoV-2 infected patients is not clear. The purpose of this study was to determine the relationship between DM, at-admission hyperglycaemia and 28 day mortality in patients admitted with moderate-severe SARS-CoV-2 infection requiring intensive care.**

***Methods*: All consecutive moderate-to-severe patients with SARS-CoV-2 infection admitted to the intensive care units (ICUs) over six months were enrolled in this single-centre, retrospective study. The predicators for 28 day mortality were analysed from the independent variables including DM status and hyperglycaemia at-admission.**

***Results*: Four hundred and fifty two patients with SARS-CoV-2 were admitted to the ICU, with a mean age of 58.5±13.4 yr, 78.5 per cent being male, HbA_{1c} of 7.2 per cent (6.3-8.8) and 63.7 per cent having DM. Overall, 28 day mortality was 48.9 per cent. In univariate analysis, mortality in diabetes patients was comparable with non-diabetes (47.9 *vs*. 50.6%, *P*=0.58), while it was significantly higher in hyperglycaemic group (60.4 *vs*. 35.8%, *P*<0.001). In multivariate Cox regression analysis, after adjusting for age, sex and comorbidities, hyperglycaemia at-admission was an independent risk factor of mortality [hazard ratio (HR) 1.45, 95% confidence interval (CI) (1.06-1.99), *P*<0.05].**

***Interpretation & conclusions*: This study showed that the presence of hyperglycaemia at-admission in critically ill SARS-CoV-2 patients was an independent predictor of 28 day mortality. However, the findings may be susceptible to unmeasured confounding, and more research from prospective studies is required.**

Key words Critical illness - COVID-19 - diabetes mellitus - hyperglycaemia - intensive care units - mortality - SARS-CoV-2

SARS-CoV-2 or COVID-19 virus was declared as a global pandemic by the WHO on March 11, 2020[1]. The severity of symptomatic infection ranged from mild to critical; however, most infections were not severe.

However, in India, 43.2 million cases were reported as of the last week of June 2022, with a mortality rate of 1.2 per cent[2].

Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) were the two main cofactors required by the SARS-CoV-2 to enter into the human cells, replicate and start an inflammatory condition that can progress to cytokine storms and death[3]. Because of the disease's severity, which includes severe pneumonia, acute respiratory distress syndrome (ARDS) and multiorgan failure, hospitalization can be prolonged, resulting in poor overall outcomes[3]. Severe infections and poor outcomes have been associated with advanced age and comorbid conditions such as hypertension, diabetes and chronic lung and renal disease[4].

In a meta-epidemiological review it was found that 2-3 fold increased relative risk of infection-related mortality and pneumonia-specific mortality in patients with diabetes[5]. Diabetes patients may have had a worse SARS-CoV-2 outcome because of multiple organ damage caused by micro- and macro-vascular disease[6]. In diabetes patients with SARS-CoV-2 infection, the upregulation of ACE2 expression in cardiomyocytes, combined with non-enzymatic glycation, resulted in a poor clinical outcome[7].

Hyperglycaemia can occur in patients with and without diabetes hospitalized for SARS-CoV-2 and was common amongst critically ill patients[8]. Several studies found that at admission hyperglycaemia, regardless of diabetes status, was associated with an increase in poor outcomes and mortality in hospitalized SARS-CoV-2 patients[9,10]. Thus, there were conflicting studies related to the association between diabetes, at-admission hyperglycaemia and mortality. However, it is important to understand because optimal glycaemic control is critical for improving SARS-CoV-2 outcomes[11].

There are only a few studies available in patients with moderate-to-severe SARS-CoV-2 infection admitted to the intensive care unit (ICU) which evaluated the relationship between diabetes mellitus (DM) status, at-admission hyperglycaemia and mortality rate[8,10]. However, in these studies, patients were not matched for age, sex, diabetes status and pre-existing comorbidities. Therefore, the aim of the present study was to evaluate the association of DM and hyperglycaemia at-admission with 28 day mortality, among SARS-CoV-2–infected patients requiring intensive care.

Material & Methods

This retrospective, single-centre study was conducted at the 250-bed dedicated facility for SARS-CoV-2/COVID-19 patients at Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), a tertiary care university hospital in Lucknow, Uttar Pradesh, India. All consecutive adult patients (age ≥18 yr) with laboratory-confirmed SARS-CoV-2 infection who required ICU admission between May 1, and November 1, 2020 were enrolled. Patients admitted to the ICU with mild SARS-CoV-2 infection and comorbidities were excluded.

All patients with SARS-CoV-2 received standard treatment, including antiviral therapy, steroid therapy, respiratory support, symptomatic and supportive treatment and antimicrobial therapy as per the guidelines of Ministry of Health and Family Welfare, Directorate General of Health Services, Government of India[12]. The Institutional Ethics Committee of SGPGIMS approved the study (2020-300-DM-EXP-33).

Data collection: Hospital information system (HIS), admission registers and patient records files were used to identify all SARS-CoV-2 patients admitted to the ICU. Data about age, sex and detailed medical history were collected. A history of renal replacement therapy (RRT) and end-stage kidney disease was noted. Symptoms of SARS-CoV-2 at the time of hospital admission were entered. The vital signs at ICU admission were also recorded using a standardized proforma from the HIS and admission notes. On admission, the fraction of inspired oxygen, the partial pressure of oxygen, oxygen saturation and coexistent infection were also recorded. During the ICU stay of the patient, detailed treatment history was also recorded in the case report form.

The duration of ICU stays, incidence of complications such as acute kidney injury, disseminated intravascular coagulation (DIC), shock, duration of ventilation and number of patients who had died and had been discharged from the ICU, were recorded. Various laboratory parameters such as haemoglobin, total leucocyte counts (TLC), neutrophil–lymphocyte ratio (NL ratio), platelet count, blood sugar, glycosylated haemoglobin (HbA_{1c}), creatinine, liver function test, C-reactive protein (CRP), serum ferritin, procalcitonin, electrolytes and coagulation parameters were also noted.

DM was defined as either having a pre-existing type 2 DM or the presence of HbA_{1c} ≥6.5 per cent

(48 mmol/mol), at any time before ICU admission[13]. As per the current international guidelines on the management of patient with sepsis and septic shock suggested hyperglycaemia ≥180 mg/dl in ICU population[14]. Standard definitions were used for different variables [ICU severity scoring, acute kidney injury, DIC, ARDS, atherosclerotic cardiovascular disease (ASCVD)][15-20].

Statistical anlaysis: The study population was divided into subgroups based on survivor or non-survivor, DM or non-DM and the presence or absence of hyperglycaemia at-admission. Descriptive statistics were presented by continuous variables in mean±standard deviation or median [interquartile range (IQR)] and categorical variables in frequency and percentage. Independent sample t test was used to compare means between survivor or non-survivor, DM or non-DM and hyperglycaemia or non-hyperglycaemia patients, whereas Mann-Whitney U test was used to compare the medians. Chi-square test was used to compare the proportions between different groups of patients. Cox proportional hazard model (time-to-event analysis) was performed to estimate the association of patient mortality with demographic and clinical variables in univariate model. All the significant variables found in univariate analysis were included in multivariate analysis and results are presented in terms of hazard ratio (HR) and its 95 per cent confidence interval (CI).

The analyses were also carried out as HR for 28 day mortality after adjustment for age and sex (Model 1) and then further adjusted for age, sex, presence of comorbidities, TLC, NL ratio, albumin, procalcitonin, CRP and ferritin (Model 2). Propensity score matching (PSM) was used to match the age, sex, presence of any comorbidities and diabetes status between at-admission hyperglycaemia and normoglycaemia patients. The Kaplan–Meier method (log-rank test) was used to estimate the survival time and survival probability at different time points within four subgroups based on the presence or absence of DM and at-admission hyperglycaemia. Statistical Package for the Social Sciences, version-23 (IBM Corp., Chicago, USA) was used for data analysis.

Results

A total of 1667 confirmed SARS-CoV-2 infected patients were admitted during the study period. Of these, 572 patients were admitted to the ICU. One hundred and one patients were excluded as they did not match the inclusion criteria. Blood sugar data was missing in 11 non-diabetes patients and eight diabetes patients. Finally, 452 of the patients were included in the study. The baseline characteristics for all patients (n=452) are shown in Table I. The mean age of the study population was 58.5±13.4 yr and 355 (78.5%) were males.

There were 288 (67.3%) patients with diabetes. Newly diagnosed diabetes was present in 52 (18.2%) patients. Seven (2.4%) patients were admitted with diabetes ketoacidosis. There was no difference in proportion of diabetes patients in survivor versus non-survivor groups [150 (64.9) *vs*. 138 (62.4), *P*=0.58]. Two hundred and forty patients (53.1%) were hyperglycaemic at-admission. At-admission blood sugar was significantly higher in non-survivor group [220 (154-312) *vs.* 170 (126-275), *P*<0.001], but no difference was observed in HbA_{1c} in survivor *vs.* non-survivor group (Table I).

After admission in ICU, 240 (53.1%) patients required insulin for control of hyperglycaemia. Number of patients with DM was significantly higher in hyperglycaemic group [198 (82.5%) *vs.* 90 (42.5%), *P*<0.001]. The median blood glucose level was much lower in the normoglycaemic group than the hyperglycaemic group [134.5 mg/dl (109-156) *vs.* 288 mg/dl (230-356), *P*<0.001]. Similarly, HbA_{1c} was 6.5 per cent (5.9-7.7) in normoglycaemic and 7.9 per cent (6.7-9.4) in hyperglycaemic group (*P*<0.001) (Table II).

Among the total admitted patients in the ICU, more than half were hypertensive, 91 (20.1%) had ASCVD, and 83 (18.4%) had chronic kidney disease. More than half of the patients had at least one comorbidity other than diabetes (Table II). Compared with survivors, non-survivors were older (60.7±13.7 *vs.* 56.4±12.8, *P*<0.001) and were more likely to have comorbidities of ASCVD [54 (24.4%) *vs.* 37 (16%), *P*<0.05], chronic liver disease [17 (7.7%) *vs.* 3 (1.3%), *P*<0.05] and presence of malignancies [20 (9.0%) *vs.* 8 (3.5%), *P*<0.05]. There were no significant differences in various symptoms of SARS-CoV-2 in patients with non-survivor as compared to survivor (Table I).

Sequential Organ Failure Assessment (SOFA) score was significantly higher in non-survivors [12 (10-14) *vs.* 5 (3-7), *P*<0.001]. However, no difference was found in SOFA score between diabetes and non-diabetes. TLC, NL ratio, creatinine, CRP,

Table I. Baseline demographic, clinical parameters, biochemical, treatment, complications and intensive care unit outcomes parameters of survivor and non-survivor patients with SARS-CoV-2 infection

Variable	Total (n=452)	Survivor (n=231)	Non-survivor (n=221)
Age (yr)	58.5±13.4	56.4±12.8	60.7±13.7***
Sex (male)	355 (78.5)	180 (77.9)	175 (79.2)
Symptoms			
Fever	437 (97.1)	225 (97.4)	212 (96.8)
Cough	420 (93.3)	217 (93.9)	203 (92.7)
Dyspnoea	414 (92.0)	208 (90.0)	206 (94.1)
Pectoralgia	78 (17.3)	35 (15.2)	43 (19.6)
Duration of symptoms (days)	7 (5-10)	7 (5-10)	7 (5-14)
Comorbidities			
T2DM	288 (63.7)	150 (64.9)	138 (62.4)
Hypertension	270 (59.7)	133 (57.6)	137 (62.0)
ASCVD	91 (20.1)	37 (16.0)	54 (24.4)*
Chronic kidney disease	83 (18.4)	36 (15.6)	47 (21.3)
Chronic pulmonary diseases	40 (8.8)	22 (9.5)	18 (8.1)
Presence of any malignancy	28 (6.2)	8 (3.5)	20 (9.0)*
Chronic liver disease	20 (4.4)	3 (1.3)	17 (7.7)**
SOFA score	8 (5-12)	5 (3-7)	12 (10-14)***
Haematological parameters			
Haemoglobin (g/dl)	9.6±2.4	10.0±2.3	9.1±2.3***
TLC ($\times 10^9$/l)	17.6 (12.7-24.9)	14.6 (11.3-18.9)	23.0 (16.1-32.3)***
NL ratio	30.0 (12.9-47.5)	18.5 (10.8-32.0)	46.5 (22.5-48.3)***
Biochemical parameters			
Albumin (g/dl)	3.03±0.6	3.2±0.5	2.8±0.6***
Creatinine (mg/dl)	1.5 (1.1-2.8)	1.2 (1.0-1.8)	2.3 (1.3-.4.4)***
RBS (mg/dl)	191 (139-296.8)	170 (126-275)	220 (154-312)***
HbA_{1c} (%)	7.2 (6.3-8.8)	7.4 (6.4-8.9)	7.0 (6.2-8.6)
Inflammatory markers			
ESR (mm/h)	77.2±32.6	74.4±32.1	80.5±33.0
CRP (mg/dl)	129.5 (65-205)	98.5 (46.0-165.5)	164.0 (93.8-248.6)***
Ferritin (ng/ml)	1292 (580-2000)	989 (410-19.4)	2000 (960-2000)***
Procalcitonin (ng/ml)	0.51 (0.11-2.62)	0.16 (0.08-0.57)	1.57 (0.46-6.69)***
Coagulation parameters			
Plasma fibrinogen (mg/dl)	602.8±196.7	603.5±178.8	602.0±215.5
D-dimer positivity	407 (91.9)	202 (87.8)	205 (96.2)**
Treatment			
Antivirals	440 (97.3)	227 (98.3)	213 (96.4)
Steroids	436 (96.5)	226 (97.8)	210 (95.0)
Tocilizumab	64 (14.2)	31 (13.4)	33 (14.9)
Plasma therapy	71 (15.7)	26 (11.3)	45 (20.4)**
Anticoagulants	443 (98.0)	228 (98.7)	215 (97.3)
Need for RRT	84 (18.6)	20 (8.7)	64 (29.0)***

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Variable	Total (n=452)	Survivor (n=231)	Non-survivor (n=221)
Need for vasopressors	231 (51.1)	16 (6.9)	215 (97.3)***
Complications			
ARDS	443 (93.6)	203 (87.9)	220 (99.5)***
Acute kidney injury	186 (41.2)	47 (20.3)	139 (62.9)***
Shock	230 (50.9)	15 (6.5)	215 (97.3)***
DIC	424 (93.8)	204 (88.3)	220 (99.5)***
Clinical outcome			
Duration of ICU stay (days)	14 (8-19.8)	17 (12-23)	9 (6-15.5)***
Mechanical ventilation	228 (50.4)	20 (8.7)	208 (94.1)***
Duration of ventilation (days)	5 (2-8)	7 (5-8)	3 (1-8)***

*P**<0.05, **<0.01 ***<0.001 compared to survivors. Data presented in mean±SD/median (IQR)/n (%) compared by independent samples t test/Mann-Whitney U test/Chi-square test, respectively. SD, standard deviation; IQR, interquartile range; ASCVD, atherosclerotic cardiovascular disease; SOFA score, Sequential Organ Failure Assessment Score; TLC, total leucocyte count; NL ratio, neutrophil-lymphocyte ratio; RBS, random blood sugar (on admission); HbA_{1c}, glycosylated haemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RRT, renal replacement therapy; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; ICU, intensive care unit; T2DM, type 2 diabetes mellitus

fibrinogen and procalcitonin were significantly higher in non-survivor patients but no difference was observed between diabetes and non-diabetes (Tables I and II).

Treatments, complications and clinical outcomes: Details of the treatment received are shown in Tables I and II. In our study, 425 (94%) had severe SARS-CoV-2 infection, and the remainder [27 (6%)] had a moderate disease. A significantly higher proportion of non-survivor patients required RRT [64 (29.0%) *vs.* 20 (8.7%), *P*<0.001] and vasopressors [215 (97.3%) *vs.* 16 (6.9%), *P*<0.001]. There was no significant difference in the proportion of patients in different groups who received steroids, antivirals, antibiotics, anticoagulants and tocilizumab. The median length of ICU stay was 14 (IQR 8-19.8) days. Overall, 228 (50.4%) - patients required mechanical ventilation. Compared with survivors, significantly higher number of non-survivors developed ARDS [220 (99.5%) *vs.* 203 (87.9%), *P*<0.001] and required mechanical ventilation [208 (94.1%) *vs.* 20 (8.7%), *P*<0.001] and 208 (91.2%) patients requiring mechanical ventilation had died by 28 days (Table I).

Diabetes mellitus, at-admission hyperglycaemia and 28 day mortality: The prevalence of 28 day mortality in the study population was 48.9 per cent (95% CI 44.3-53.5). There was no difference in 28 day mortality in patients with DM as compared to non-diabetes patients [138 (47.9%) *vs.* 83 (50.6%), *P*=0.58]. Patients with hyperglycaemic at-admission had significantly high 28 day mortality [145 (60.4%) *vs.* 76 (35.8), *P*<0.001] (Table II).

In multivariable Cox regression analysis, age [HR 1.02, 95% CI (1.004-1.030), *P*<0.05], at-admission hyperglycaemia [HR 1.43, 95% CI (1.05-1.96), *P*<0.05], chronic liver disease [HR 2.02, 95% CI (1.17-3.49), *P*<0.05], TLC [HR 1.011, 95% CI (1.004-1.017), *P*<0.01], N/L ratio [HR 1.005, 95% CI (1.000-1.010), *P*<0.05], ferritin [HR 1.033, 95% CI (1.008-1.058), *P*<0.05] and procalcitonin [HR 1.62, 95% CI (1.19-2.22), *P*<0.01] were the independent risk factors of mortality in patients with SARS-CoV-2. DM diagnosis and gender, on the other hand, were not predictive of increased ICU mortality (Table III).

In Model 1, hyperglycaemia [HR 1.80, 95% CI (1.36-2.38), *P*<0.001] remained an independent predictor of mortality, with age [HR 1.02, 95% CI (1.01-1.03), *P*<0.01] playing an independent role. In Model 2, after adjusting for clinical confounders, the HRs for mortality in the hyperglycaemic group remained significant [HR 1.45, 95% CI (1.06-1.99), *P*<0.05] (Table IV).

A PSM analysis was done to eliminate confounding variables that might have interfered with the association between hyperglycaemia and mortality. In the PSM analysis, it was possible to match a ratio of 1:1 between the normoglycaemic and the hyperglycaemic groups. As shown in Table IV, the outcomes of the PSM patients revealed that compared to the normoglycaemia group, the patients with at-admission hyperglycaemia had HR of 1.72 for mortality [95% CI, (1.02-2.91); *P*<0.05].

Table II. Demographic, clinical characteristics, biochemical parameters, treatment, complications and intensive care unit outcomes of all patients with SARS-CoV- 2 infection according to diabetes mellitus and at-admission plasma glucose level

Variables	Diabetes (n=288)	Non-diabetes (n=164)	Normoglycaemia (n=212)	Hyperglycaemia (n=240)
Age (yr)	60.9±11.0***	54.2±16.0	56.3±14.7	60.4±11.8††
Sex (male)	221 (76.7)	134 (81.7)	164 (77.4)	191 (79.6)
Symptoms				
Fever	277 (96.5)	160 (98.2)	204 (96.7)	233 (97.5)
Cough	267 (93.0)	153 (93.9)	197 (93.4)	223 (93.3)
Dyspnoea	266 (92.7)	148 (90.8)	190 (90.0)	224 (93.7)
Pectoralgia	53 (18.5)	25 (15.3)	33 (15.6)	45 (18.8)
Duration of symptoms (day)	7 (5-10)	7 (5-10)	7 (5-10)	7 (5-11)
Comorbidities				
T2DM	288 (63.7)***	164 (36.3)	90 (42.5)	198 (82.5)†††
Hypertension	206 (71.5)***	64 (39.0)	105 (49.5)	165 (69.8)†††
ASCVD	79 (27.4)***	12 (7.3)	35 (16.5)	56 (23.3)
Chronic kidney disease	54 (18.2)	29 (17.7)	34 (16.0)	49 (20.4)
Chronic pulmonary diseases	18 (6.2)*	22 (13.4)	26 (12.3)	14 (5.8)†
Presence of any malignancy	11 (3.8)**	17 (10.4)	18 (8.5)	10 (4.2)
Chronic liver disease	10 (3.4)	10 (6.1)	8 (3.8)	12 (5.0)
SOFA score	8 (4.3-13)	9 (5-12)	7 (4-11)	10 (5-13)†††
Haematological parameters				
Haemoglobin (g/dl)	9.7±2.3	9.4±2.4	9.6±2.4	9.5±2.3
TLC ($\times 10^9$/l)	17.7 (12.8-24.9)	17.6 (12.3-25.9)	16.5 (12.1-22.7)	19.2 (13.2-27.3)†
NL ratio	30.7 (15.0-47.5)	23.0 (12.5-47.5)	22.5 (11.0-46.5)	31.3 (17.6-48.0)†††
Biochemical parameters				
Albumin (g/dl)	3.0±0.6	3.1±0.5	3.1±0.6	3.0±0.6††
Creatinine (mg/dl)	1.5 (1.1-3.0)	1.4 (1-2.6)	1.3 (1.0-2.4)	1.8 (1.2-3.6)†††
RBS (mg/dl)	240 (170-340.1)***	136 (109-181.8)	134.5 (109-156)	288 (230-356)†††
HbA_{1c} (%)	7.8 (6.7-9.4)***	5.8 (5.5-6.1)	6.5 (5.9-7.7)	7.9 (6.7-9.4)†††
Inflammatory markers				
ESR (mm/h)	77.2±31.6	77.3±34.6	72.9±34.8	81.0±30.1††
CRP (mg/dl)	131.0 (64.8-206.5)	122.0 (63.5-203.5)	110 (59-195.5)	139.8 (68.8-216.3)†
Ferritin (ng/ml)	1211 (492-2000)	1440 (783-2000)	1180 (542-2000)	1526 (601-2000)
Procalcitonin (ng/ml)	0.43 (0.12-2.6)	0.57 (0.10-2.7)	0.31 (0.10-1.96)	0.75 (0.14-4.5)††
Coagulation parameters				
Plasma fibrinogen (mg/dl)	607.6±193.5	594.5±202.5	579.3±192.6	624.5±198.3†
D-dimer positivity	263 (92.3)	144 (91.1)	287 (90.8)	220 (92.8)
Treatment				
Antivirals (remdesivir)	280 (97.2)	160 (97.6)	208 (98.1)	232 (96.7)
Steroids	281 (97.6)	155 (94.5)	206 (97.2)	230 (95.8)
Tocilizumab	46 (16.0)	18 (11.0)	28 (13.2)	36 (15.0)
Plasma therapy	55 (19.1)**	16 (9.8)	31 (14.6)	40 (16.7)
Anticoagulants	284 (98.6)	159 (97.0)	207 (97.6)	236 (98.3)

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Variables	Diabetes (n=288)	Non-diabetes (n=164)	Normoglycaemia (n=212)	Hyperglycaemia (n=240)
Need for RRT	56 (19.4)	28 (17.1)	24 (11.3)	60 (25.0)†††
Need for vasopressors	147 (51.0)	84 (51.2)	82 (38.7)	149 (62.1)†††
Complications				
ARDS	270 (93.8)	153 (93.3)	197 (92.9)	226 (94.2)
Acute kidney injury	124 (43.1)	62 (37.8)	66 (31.1)	120 (50.0)†††
Shock	146 (50.7)	84 (51.2)	81 (38.2)	149 (62.1)†††
DIC	275 (95.5)*	149 (90.9)	195 (92.0)	229 (95.4)
Clinical outcome				
Duration of ICU stay (days)	14 (8.3-20)	13 (8-19)	15 (9-20)	13 (7-19)†
Mechanical ventilation	146 (50.7)	82 (50.0)	80 (37.7)	148 (61.7)†††
Duration of ventilation (days)	5 (2-8)	5 (2-8)	6 (3-8)	5 (1-7.8)†
28 day ICU mortality	138 (47.9)	83 (50.6)	76 (35.8)	145 (60.4)†††

P^{*}<0.05, **<0.01, ***<0.001 compared to non-diabetes subgroup. P †<0.05, ††<0.01, †††<0.001 compared to normoglycaemia group. Data presented in mean±SD/median (IQR)/n (%) compared by independent samples t test/Mann-Whitney U test/Chi-square test, respectively. SD, standard deviation; IQR, interquartile range; ASCVD, atherosclerotic cardiovascular disease; SOFA score, Sequential Organ Failure Assessment score; TLC, total leucocyte count; NL ratio, neutrophil-lymphocyte ratio; RBS, random blood sugar (at admission); HbA_{1c}, glycosylated haemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RRT, renal replacement therapy; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; ICU, intensive care unit; T2DM, type 2 diabetes mellitus

On Kaplan-Meier analysis, when patients were stratified into four groups based on whether they had diabetes or not, and hyperglycaemia or not at the time of admission, the probability of 28 day ICU mortality was higher in the non-diabetes with at-admission hyperglycaemia and diabetes with at-admission hyperglycaemia groups (P<0.001, Figure).

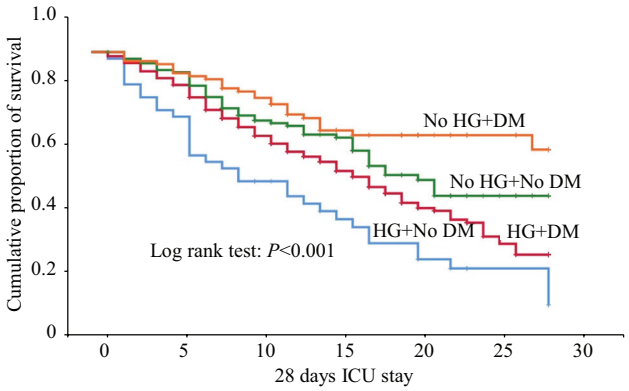

Figure. Kaplan-Meier analysis showing survival from severe disease (SARS-CoV-2) infection through 28 days in ICU for patients with hyperglycaemia (HG) and no diabetes mellitus (HG+No DM), HG and diabetes (HG+DM), no HG but with diabetes (No HG+DM), and no HG and no diabetes (No HG+No DM), log rank (Mantel-Cox) Chi-Square 33.7, P<0.001.

Discussion

In our study, 59.7 per cent of critically ill patients with SARS-CoV-2 had diabetes, and 53.1 per cent had hyperglycaemia. Patient mortality was comparable between diabetic and non-diabetic patients. Multivariate Cox regression analysis as well as PSM revealed that hyperglycaemia at-admission was an independent factor of 28 day mortality.

DM has been identified as a risk factor for SARS-CoV-2 patient's poor prognosis and mortality[6,21,22]. A study of 7337 SARS-CoV-2 patients reported that patients with diabetes had significantly higher mortality (7.8% *vs.* 2.7%, HR 1.49) and higher medical intervention rates than those without diabetes[22]. On the other hand, the study done by Mazori *et al*[8] in critically ill patients with SARS-CoV-2 found that diabetes was not significantly associated with higher in-hospital mortality (HR 1.16; 95% CI, 0.25-5.42), as found in our study. However, other studies found that hyperglycaemia was associated with increased morbidity and mortality in critically ill SARS-CoV-2 patients, regardless of pre-existing diabetes[9,23,24]. A study by Apicella *et al*[21], which included known diabetes patients, concluded that at-admission hyperglycaemia was a poor prognostic parameter (HR 1.80, 95% CI 1.03-3.15). Another retrospective study from Italy reported that hyperglycaemia at-admission was a predictor of severe SARS-CoV-2

Table III. Risk factors associated with 28 day mortality in patients with SARS-CoV-2 infection using cox proportional regression analysis

Variables	Univariable cox regression			Multivariable cox regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.02	1.01-1.03	<0.01	1.02	1.004-1.030	<0.05
Sex	0.92	0.67-1.27	0.62	1.08	0.75-1.55	0.69
Hyperglycaemia (>180 mg/dl)	1.89	1.43-2.50	<0.001	1.43	1.05-1.96	<0.05
Hypertension	1.07	0.82-1.41	0.61			
History of DM	0.90	0.68-1.18	0.43			
ASCVD	1.39	1.02-1.89	<0.05	1.36	0.97-1.90	0.08
Chronic renal failure	1.14	0.82-1.57	0.44			
Chronic pulmonary disease	0.88	0.55-1.43	0.61			
Chronic liver disease	1.95	1.19-3.20	<0.01	2.02	1.17-3.49	<0.05
Presence of any malignancies	1.91	1.20-3.02	<0.01	1.30	0.71-2.38	0.39
ARDS	13.46	1.9-95.2	<0.05	6.40	0.89-46.02	0.08
TLC	1.013	1.008-1.018	<0.001	1.011	1.004-1.017	<0.01
N/L ratio	1.009	1.004-1.013	<0.001	1.005	1.000-1.010	<0.05
Creatinine	1.09	1.05-1.14	<0.001	1.21	0.86-1.71	0.28
CRP	1.03	1.02-1.04	<0.001	1.009	0.994-1.025	0.24
Ferritin	1.05	1.03-1.07	<0.001	1.033	1.008-1.058	<0.05
Procalcitonin	2.19	1.67-2.88	<0.001	1.62	1.19-2.22	<0.01
Albumin	0.59	0.46-0.75	<0.001	1.03	0.74-1.42	0.88

For purpose of analysis, TLC was in units of 1000×10^9/l, CRP in units of 10 mg/dl, ferritin in units of 100 ng/ml. HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease. ARDS, acute respiratory distress syndrome; TLC, total leucocyte count; N/L ratio, neutrophil-lymphocyte ratio; CRP, C-reactive protein; DM, diabetes mellitus

in patients without a history of diabetes than those with a history of diabetes[24]. The cumulative mortality risk in patients with hyperglycaemia was significantly higher compared to patients with normoglycaemia (log-rank, $P<0.001$), irrespective of pre-existing diabetes, as reported in 11,312 patients from the Spanish SEMI-COVID-19 Registry[9].

These findings corroborated our findings, which revealed that SARS-CoV-2 patients with hyperglycaemic regardless of diabetes status had a poorer laboratory profile and a significantly higher mortality rate compared to in normoglycaemic patients. It was also found that more patients with hyperglycaemia had shock, acute kidney injury and the need for mechanical ventilation. Overall, these findings suggest that hyperglycaemia could play an essential role in the prognosis of patients with SARS-CoV-2 admitted to the ICU.

Many possible mechanisms could contribute to infection with SARS-CoV-2 and poor prognosis with at-admission hyperglycaemia. SARS-CoV-2 binds ACE2 receptors and TMPRSS2 with pancreatic beta-cells, making it a viral attack target and causing insulin secretion to decrease[25]. Hyperglycaemia was also caused by an increase in insulin resistance because of the massive production of cytokines by SARS-CoV-2 infection[26]. In SARS-CoV-2 infection, the pathogen could proliferate unhindered within the host due to the disturbed immunity in hyperglycaemic patients[27]. Hyperglycaemia inhibits neutrophil chemotaxis, reduces neutrophil, macrophage, and monocyte phagocytosis and impairs innate cell-mediated immunity, resulting in a hyperinflammatory response[28].

The proportion of TLC, NL ratio, ferritin, procalcitonin and CRP levels in patients with hyperglycaemia was consistently increased in the present study. Furthermore, the inflammatory response seen in our patients was supported by a meta-analysis by Hariyanto *et al*[29] that elevated inflammatory biomarkers were associated with an increased risk of mortality. Thus, evidence suggested that patients with severe SARS-CoV-2 had an increased incidence

Table IV. Hazard ratio for 28 day mortality in SARS-CoV- 2 infection stratified by hyperglycaemia

Variables	Normoglycaemia	Hyperglycaemia	*P*
HR as per Model 1 and 2			
Number of patients	212	240	
Number of deaths	76	145	
Unadjusted HR (95% CI)	1.00	1.89 (1.43-2.50)	<0.001
Adjusted HR (95% CI)			
Model 1	1.00	1.80 (1.36-2.38)	<0.001
Model 2	1.00	1.45 (1.06-1.99)	<0.05
HR after propensity score-matched			
Number of patients	73	73	
Number of deaths	23	37	
Propensity score-matched HR (95% CI)	1.00	1.72 (1.02-2.91)	<0.05

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, presence of comorbidities (hypertension, DM, ASCVD, chronic kidney disease, chronic pulmonary disease, chronic liver disease, presence of malignancies), TLC, NL ratio, creatinine, albumin, procalcitonin, CRP and ferritin; Propensity score-matched, for age, sex, DM, and pre-existing comorbidities. HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; TLC, total leucocyte count; NL ratio, neutrophil-lymphocyte ratio; CRP, C-reactive protein; DM, diabetes mellitus

of cytokine storm syndrome[30]. Furthermore, patients with hyperglycaemia have been more susceptible to cytokine storms because of an increased inflammatory response[31].

Endothelial activation and dysfunction caused by SARS-CoV-2 infection and various cytokines were predicted to cause vascular inflammation, permeability, activation of the clotting cascade, thrombosis formation and alveolar oedema, all of which contributed to ARDS and increased mortality[32]. This explained why hyperglycaemic patients with a high SOFA score had a poor prognosis in our study patients, and it also supported the direct relationship between glucose level and disease progression. It was found that the proportion of patients admitted to the ICU who were hyperglycaemic at the time of admission were older and had a higher mortality rate. This was observed in other study also and could be because of immune senescence[5]. In our study, ASCVD, chronic liver disease, presence of any malignancies and presence of ARDS were associated with increased risk of mortality. A similar association of comorbidities, mortality and hyperglycaemia with or without diabetes was reported in other studies[10,31].

Regardless of the underlying mechanisms, our findings supported the need for early detection of at-admission hyperglycaemia, which was associated with a poor prognosis. It was hypothesized that treating hyperglycaemia early in SARS-CoV-2 patients would result in better outcomes[23]. A more extensive prospective cohort study of moderate-to-severe SARS-CoV-2 patients would help define further clinical parameters, risk factors and the effect of glycaemic control on outcomes.

Our study had certain limitations. It was a retrospective study done in a single-centre level-3 facility hospital for severe SARS-CoV-2 pneumonia. There might be undiscovered confounders (such as unavailable detailed medication history due to strain healthcare system) and selection bias (tertiary care facility) which could have influenced our findings.

A matched control study from a non-COVID-19 ICU is required to determine the burden and association of stress-induced hyperglycaemia with survival outcomes in COVID-19 patients. Due to retrospective nature of the study, we were unable to determine whether active management of blood glucose levels to a more normal range could improve the severity or adverse outcome. Pre-existing diabetes would be another independent predictor of mortality if all SARS-CoV-2 patients were studied (regardless of whether they were admitted to the general ward, high-dependency unit or ICU).

All electronic hospital records were manually reviewed to investigate the relationship between hyperglycaemia, diabetes and ICU outcomes. A confounders-adjusted and PSM analysis of 28 day ICU

mortality helped us better understand the effects of diabetes and hyperglycaemia.

In conclusion, our findings showed that DM status *per se* did not associate with mortality among critically ill SARS-CoV-2 patients. However, the presence of hyperglycaemia at the time of admission was an independent predictor of mortality and remained a significant risk factor for mortality even after adjusting for age, diabetes and comorbidities. The findings may be susceptible to unmeasured confounding, and more research from prospective studies is required.

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