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Diabetes & Metabolism 47 (2020) 101254

Available online at ScienceDirect www.sciencedirect.com

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Original article

Association of hyperglycaemia with hospital mortality in nondiabetic COVID-19 patients: A cohort study

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ARTICLE INFO

Article history:
Received 18 November 2020
Received in revised form 26 February 2021
Accepted 16 March 2021
Available online 26 March 2021

Keywords:
COVID-19
Diabetes
Hospital mortality
Hyperglycaemia

ABSTRACT

Objective. – Diabetes is a known risk factor for mortality in Coronavirus disease 2019 (COVID-19) patients. Our objective was to identify prevalence of hyperglycaemia in COVID-19 patients with and without prior diabetes and quantify its association with COVID-19 disease course.
Research design and methods. – This observational cohort study included all consecutive COVID-19 patients admitted to John H Stroger Jr. Hospital, Chicago, IL from March 15, 2020 to May 3, 2020 and followed till May 15, 2020. The primary outcome was hospital mortality, and the studied predictor was hyperglycaemia [any blood glucose ≥7.78 mmol/L (140 mg/dL) during hospitalization].
Results. – Of the 403 COVID-19 patients studied, 51 (12.7%) died; 335 (83.1%) were discharged while 17 (4%) were still in hospital. Hyperglycaemia occurred in 228 (56.6%) patients; 83 of these hyperglycaemic patients (36.4%) had no prior history of diabetes. Compared to the reference group no-diabetes/no-hyperglycaemia patients the no-diabetes/hyperglycaemia patients showed higher mortality [1.8% versus 20.5%, adjusted odds ratio 21.94 (95% confidence interval 4.04–119.0), $P < 0.001$]; improved prediction of death ($P = 0.01$) and faster progression to death ($P < 0.01$). Hyperglycaemia within the first 24 and 48 h was also significantly associated with mortality (odds ratio 2.15 and 3.31, respectively).
Conclusions. – Hyperglycaemia without prior diabetes was common (20.6% of hospitalized COVID-19 patients) and was associated with an increased risk of and faster progression to death. Development of hyperglycaemia in COVID-19 patients who do not have diabetes is an early indicator of progressive disease.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in over 98 million cases and 2.1 million deaths globally [1]. Diabetes is associated with a higher mortality, need for intensive care, acute respiratory distress syndrome in COVID-19 disease [2]. Diabetes ($HbA1_C \geq 6.5\%$) and/or uncontrolled hyperglycaemia (≥2 glucose measurements >10.0 mmol/L (>180 mg/dL)) are associated with poor outcomes in COVID-19 patients [3]. However, stress hyperglycaemia (defined as blood glucose values exceeding 7.78 mmol/L (140 mg/dL)) in the absence of diabetes is seen in severe acute illness [4–6]. Previous studies have shown that in critically ill patients, stress hyperglycaemia is associated with poor clinical outcomes during hospitalization [7]. Stress hyperglycaemia can prolong the length of hospital stay [8] – a parameter that is closely linked with poor outcomes in COVID-19 patients [9]. An excess of circulating proinflammatory cytokines (common in COVID-19 patients) is associated with the consequences of hyperglycaemia [10]. Sardu et al. [11] showed that hyperglycaemia during hospitalization correlated with interleukin-6 and D-dimer concentrations in COVID-19 patients. However, the mechanistic basis and replicability of associations of hyperglycaemia in absence of diabetes with COVID-19 disease course remains understudied.

In this investigation, we focused on the potential of hyperglycaemia detected early during hospitalization of COVID-19 as an

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https://doi.org/10.1016/j.diabet.2021.101254
1262-3636/

indicator of mortality. We hypothesized that hyperglycaemia even in the absence of diabetes may be associated with adverse outcomes in COVID-19 patients. Here, we report the independent association of hyperglycaemia with clinical course in COVID-19 patients using a single-centre data of hospitalized COVID-19 patients from the United States of America.

Methods

Study participants

This retrospective, hospital record-based study was conducted at John H. Stroger, Jr Hospital of Cook County, Chicago, IL. All COVID-19 patients admitted between March 15, 2020 and May 3, 2020 and followed till the censoring date of May 15, 2020 were included. Thus, follow-up of the cohort was done from the date of admission to the hospital to one of the following endpoints: in-hospital death; hospital discharge or censoring on the day the study ended (May 15, 2020). On the censoring day, 17 (4%) patients were still in hospital. COVID-19 was confirmed using the polymerase chain reaction for the RdRp and N genes. Clinical data of these patients was collected by chart reviews. The study was approved by the Institutional Review Board of the Cook County Health, Chicago, IL with waiver of informed consent.

Outcomes and predictors

The primary outcomes were hospital mortality and time to progress to mortality. Outcome ascertainment was censored on May 15, 2020. Patients still in hospital who did develop an outcome under consideration were censored for computation of length of stay and time-to-event analyses. Main predictor of interest was hyperglycaemia defined as at least one BG value $\geq$7.78 mmol/L (140 mg/dL) – a cut-off recommended as a treatment target in critically ill patients [12] and a definition of hyperglycaemia in non-critically ill hospitalized patients [13]. To examine the use of hyperglycaemia as an early predictor of adverse outcomes, we also considered occurrence of hyperglycaemia within the first 24 h (HG_{24}) and 48 h (HG_{48}) of admission. BG values were retrospectively derived from the database and represented a mixture of fasting and non-fasting measurements and venous and capillary sources. Detailed information collected on socio-demographics, presenting symptoms, comorbidities, laboratory investigations, history of medications and substance use from the electronic health records. Severity of illness at admission was quantified using the qSOFA score that combines information from respiratory rate, systolic blood pressure and mental status into a single metric [14].

Statistical analyses

Descriptive statistics included mean $\pm$ standard deviation for continuous variables and number (%) for categorical variables. The time trends of BG values during hospitalization were examined using generalized estimating equations (GEE). The GEE models used Gaussian family function, identity link function and equal correlation structure. BG time trends were smoothed using cubic splines with a knot every day for the first 14 days of admission. The association of diabetes and hyperglycaemia with outcomes was tested for significance using the Pearson's chi-square test and the Kruskal-Wallis test as appropriate. The association with risk of mortality was quantified as odds ratios (OR) using multivariable stepwise logistic regression analyses with forward addition strategy and a retention criterion of 0.05. The forward addition strategy was used since it is robust to the number of predictors for a moderate size dataset and accounts for the potential collinearity among covariates without overfitting the data. We did not input missing data and the stepwise models described below have been run on participants without missing data. The first step of the forward addition strategy – included a total of 59 covariates – 4 sociodemographic variables (age, gender, ethnicity and black race), 12 symptoms (cough, cough with sputum, nasal congestion, headache, fever, fever with chills, shortness of breath, nausea/vomiting, diarrhoea, myalgia, altered mental status and fatigue), 14 comorbidities (hypertension, diabetes, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, asthma, other lung disease, chronic kidney disease, end-stage renal disease, chronic liver disease, cancer, ever smoker, alcohol consumption and qSOFA score), 11 laboratory investigations (total white cell count, neutrophil count, lymphocyte count, platelet count, haemoglobin concentration, serum sodium, serum bicarbonates, serum creatinine, serum globulin, proteinuria, haematuria) 15 medications (insulin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, beta-blockers, other anti-hypertensive, statins, non-steroidal anti-inflammatory drugs, aspirin, vitamin D, hydroxychloroquine, azithromycin, rivaroxaban, chemotherapy and steroids) and 3 substance use variables (marijuana, cocaine and heroin). In the second step of this analysis, we added hyperglycaemia to the full model (total number of covariates 60). Lastly, to understand the association of hyperglycaemia with and without diabetes, we replaced the covariate hyperglycaemia with indicators for diabetes and hyperglycaemia groups and used the DM-/HG- patients as the reference group. Improvement in the prediction of the mortality using hyperglycaemia was also assessed by estimating the area under a receiver-operating characteristic curve (AUROC) from the fitted logistic regression models. Statistical significance for difference between two AUROCs was tested using the DeLong and DeLong test. To ensure robustness of the analyses conducted, we embarked upon some additional analyses. First, since some patients initially not identified as having diabetes could have been misclassified, we conducted sensitivity analyses by restricting the analyses to patients on whom HbA1C data was available; in this subset we reclassified patients with HbA1C $\geq$ 6.5% as diabetes. To arrive at robust estimates of standard errors and 95% confidence intervals, we conducted bootstrapping using the number of participants on whom HbA1C data was available and with 1000 replicates. Second. We tested the hypothesis that the number of glucose measurements ordered till detection of hyperglycaemia is not a simple proxy measure of hyperglycaemia. Third, to ensure that the estimates of AUROC were unaffected by sample characteristics, we conducted 10-fold cross validation. For this, the folds were obtained a priori by shuffling the entire dataset and diving randomly into 10 equal parts. Ten-fold cross-validation proceeded by using each fold as the validation set and the remaining folds as the derivation set.

To test whether a continuous variable was associated with mortality in a linear fashion, we compared the likelihood ratio χ^2 statistic and the pseudo-R^2 of the untransformed covariate with a quadratic polynomial, cubic polynomial, log-transformed and square-root transformed variable as predictor. Further, we examined the strength of association of the quartiles of the untransformed variable with mortality and estimated the significance value of a linear trend using the Cochran-Armitage trend test. The association of early detection of hyperglycaemia with mortality was assessed by replacing the variable hyperglycaemia with hyperglycaemia during the first 24 h (HG_{24}) or 48 h (HG_{48}) in the multivariable stepwise logistic regression analyses described above.

To test the association of the study groups with the time to in-hospital mortality, we used Kaplan–Meier plots, logrank test and Cox proportional hazards regression to estimate the hazard ratios (HR). To test the independence of association from potential confounders, we used a forward addition, stepwise Cox regression

Table 1
Baseline characteristics of study participants (total n = 403).

Characteristic[c]	Mean/N[a]	SD/%	N available[b]
Socio-demographic characteristics			
Age (y)	54.96	13.55	403
Males	273	67.7	403
Hispanic/Latino ethnicity	221	54.8	403
Race			
Black/African American	153	38.0	403
White	137	34.0	403
Other	79	19.6	403
American Indian	25	6	403
Asian	7	1	403
Multiple	2	<1	403
Presenting symptoms			
Cough	101	25.1	403
Fever	75	18.6	403
Shortness of breath	61	15.1	403
Myalgia/arthralgia	47	11.7	403
Fatigue	35	9	403
Fever with chills	28	7	403
Cough with sputum	23	6	403
Diarrhoea	21	5	403
Sore throat	10	3	403
Nausea/vomiting	10	2	403
Nasal congestion	8	2	403
Headache	7	2	403
Altered mental status	7	2	403
Haemoptysis	2	<1	403
Comorbidities			
Hypertension	196	48.6	403
Obesity (BMI $\geq$ 30 kg/m^2)	185	45.9	403
Diabetes	155	38.5	403
Coronary artery disease	31	8	403
Chronic kidney disease	31	8	403
Asthma	27	7	403
Other lung disease	25	6	403
Chronic liver disease	25	6	403
Cancer	25	6	403
Chronic heart failure	21	5	403
COPD	17	4	403
ESRD	15	3	403
HIV/AIDS	10	2	403
Atrial fibrillation	9	2	403
Smoking status			
Non-smoker	276	68.8	401
Former smoker	51	12.7	401
Current smoker	39	10	401
Unknown	35	9	401
qSOFA score			
qSOFA 0	110	27.3	403
qSOFA 1	205	50.9	403
qSOFA 2	86	21.3	403
qSOFA 3	2	<1	403
Other early features			
Highest temperature in 24 h (°C)	38.19	0.89	402
Lowest systolic BP in 24 h (mmHg)	108.90	15.88	403
Highest heart rate in 24 h (bpm)	105.08	16.53	403
Highest respiratory rate in 24 h (/min)	26.96	13.12	403
Initial laboratory investigations			
White cell count ($\times 10^9$ cells/L)	7.56	3.97	402
Platelet count ($\times 10^9$ cells/L)	224.15	112.90	402
Haemoglobin (g/L)	1.34	0.22	402
Differential white cell count			
Neutrophils (%)	74.12	11.66	373
Lymphocytes (%)	16.58	9.29	373
Eosinophils (%)	0.43	0.99	373
Basophils (%)	0.45	0.30	375
Monocytes (%)	8.42	3.68	373
Serum ferritin (μg/L)	784.88	1063.95	263
Serum sodium (mEq/L)	135.39	5.00	403
Serum potassium (mEq/L)	4.15	0.59	371
Serum bicarbonates (mEq/L)	24.10	4.17	403
First blood glucose level (mmol/L)	8.04	4.24	403
First blood glucose level (mg/dL)	144.72	76.32	403
Serum creatinine (μmol/L)	145.01	221.93	403
Serum albumin (g/L)	0.35	0.05	375
Serum globulin (g/L)	0.30	0.10	403
Serum AST (U/L)	55.24	78.39	357
Serum ALT (IU/L)	44.74	55.53	375
Serum LDH (U/L)	375.84	475.00	313
Serum D-dimer (mg/L)	2.18	3.30	221
Lowest plasminogen (mg/L)	540.36	190.66	152
Serum Troponin (μg/L)	0.26	1.86	116
Serum creatine kinase (U/L)	2682.92	16006.10	53
Serum C-reactive protein (mg/L)	12.72	8.88	279
Proteinuria	8	2	403
Haematuria	52	12.9	403
HbA1c (%)	7.22	2.29	279
Medication history			
Insulin	69	17.1	403
ACE inhibitors	85	21.1	403
Angiotensin receptor blockers	28	7	403
Mineralocorticoid receptor antagonist	10	3	403
Beta-blocker	62	15.4	403
Other antihypertensive	103	25.6	403
Statin	137	34.0	403
NSAID	28	7	403
Aspirin	77	19.1	403
Vitamin C supplementation	1	<1	403
Vitamin D supplementation	6	1	403
Hydroxychloroquine	2	<1	403
Azithromycin	4	1	403
Warfarin	10	2	403
Apixiban	4	1	403
Riveroxaban	7	2	403
Steroids	3	1	403
Chemotherapy	16	4	403
Calcineurin inhibitor	3	1	403
Mycophenolate mofetil	2	<1	403
Azathioprine	1	<1	403
Substance use			
Marijuana	16	4	403
Cocaine	19	5	403
Heroin	22	5	403
Amphetamine	2	<1	403
Outcomes			
ICU admission	97	24.1	403
ARDS	61	15.1	403
Mechanical ventilation	56	13.9	403
Death	51	12.7	403

Abbreviations: °C — degrees in centigrade, mmHg — millimetres of mercury, bpm — beats per minute, /min-per minute, L — Litre, g/L — grams per Litre, % — percentage, μg/L — microgram per Litre, mEq/L — milliequivalent per Litre, mmol/L — millimole per Litre, mg/dL — milligram per decilitre, μmol/L — micromole per Litre, g/L — grams per Litre, U/L — units per Litre, IU/L — international units per Litre, mg/L — milligram per Litre, mg/L — milligram per Litre.

[a] Columns indicate mean and standard deviation (SD) for continuous variables and number (N) and percentage for categorical variables.

[b] Total number of study participants on whom data was available.

[c] Parentheses show units.

variable selection strategy similar to the one used in logistic regression analyses explained above. Even though the study enrolled the patients from the time of admission, for the survival analyses, participants were considered to enter the cohort on the date and time of the first detection of hyperglycaemia; if hyperglycaemia was never detected then date and time of hospital admission was considered as the entry point. Exit from the cohort was as defined earlier.

All statistical analyses were conducted using Stata 12.0 software package (Stata Corp., College Station, TX). The statistical significance was assessed at a type I error rate of 0.05.

Results

Study participants

We included a total of 403 (out of 406 eligible, 99.3%) COVID-19 patients who were admitted to the study centre and had non-missing

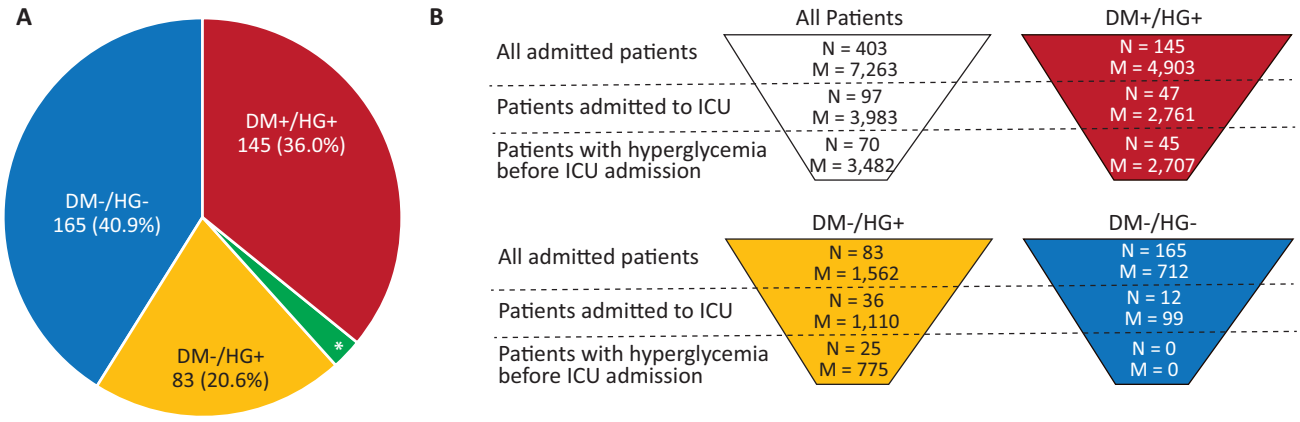

Fig. 1. Distribution of study groups and blood glucose measurements in hospitalized COVID-19 patients. (A) The pie chart shows number (%) of patients in the color-coded study groups. These color-codes are consistently used throughout the rest of the paper. DM+/HG+, patients with diabetes and hyperglycaemia; DM+/HG-, patients with diabetes but no hyperglycaemia; DM-/HG+, patients with hyperglycaemia who did not have diabetes; DM-/HG-, patients who had neither diabetes nor hyperglycaemia **(B)** Funnel plots showing the distribution of patient subsets when considered in all study participants (funnel with white background); in the DM-/HG+ group (yellow background); in the DM+/HG+ group (red background); and in the DM-/HG- group (blue background). N, number of patients; M, number of blood glucose measurements; *, DM+/HG- group (N = 10 (2.5%)).

data for diabetes and other comorbidities. Clinical characteristics of the study participants are detailed in Table 1. Majority of the patients were male (67.7%), of Hispanic/Latino ethnicity (54.8%) and Black/African American race (38.0%). Of the study participants, 97 (24.1%) patients needed ICU admission; 56 (13.9%) patients needed mechanical ventilation; and 51 (12.7%) patients died.

Prevalence of hyperglycaemia and diabetes

Hyperglycaemia was observed in 228 (56.6%) patients (Fig. 1A, yellow and red slices of the pie combined). The presence of hyperglycaemia and diabetes identified four subsets of patients: those with diabetes and hyperglycaemia (DM+/HG+, n = 145, 36.0%), patients with diabetes but no hyperglycaemia (DM+/HG−, n = 10, 2%), patients with hyperglycaemia who did not have diabetes (DM−/HG+, n = 83, 20.6%) and patients who had neither diabetes nor hyperglycaemia (DM−/HG−, n = 165, 40.9%) (Fig. 1A).

HbA1c values within the past year were available for 279 patients (69.2%, Table 1). The median (interquartile range) HbA1c values for the four groups were as follows: DM+/HG+ group (available n = 141) – 8.0% (3.3%); DM+/HG− group (available n = 8) – 6.8% (0.75%); DM−/HG+ group (available n = 51) – 5.7% (0.8%) and DM−/HG− group (available n = 79) – 5.6% (0.6%). Three (2%) patients belonging to the DM−/HG− group and 10 (19.6%) patients belonging to the DM−/HG+ group had one HbA1c value $\geq$ 6.5%.

As shown in Fig. 1B (White funnel), for the 403 patients included in this study, we had a total of 7263 (average 2.91 measurements per patient per day) BG measurements over the entire period of hospitalization. Of these, 3983 BG measurements were on 97 patients who were admitted to ICU during hospital stay and 70/97 (72.2%) patients had their first hyperglycaemia finding before ICU admission. Of the 83 patients in the DM-/HG+ group (Fig. 1B, yellow funnel), 36 were admitted to ICU and 25/36 (69.4%) patients had their first hyperglycaemia finding before ICU hospitalization. The average time (95% CI) from first hyperglycaemia finding to ICU admission was 6.83 days (5.32–8.36 days) in all patients (n = 70) and 7.32 days (4.45–10.2 days) in the DM−/HG+ group (n = 25).

Glycaemia during hospitalization

Fig. 2A shows the cubic spline smoothed, non-linear trends of glycemia in the study participants over the period of hospitalization according to the study groups. DM−/HG− patients (blue curve) had well-maintained BG levels that stayed around 5.56 mmol/L (100 mg/dL) throughout the first two-weeks of hospitalization with very little fluctuation. The DM+/HG-patients (green curve) also mimicked the blue curve albeit with wider confidence bands and smaller number of data points. DM+/HG + patients (red curve) demonstrated consistently high BG values with substantially larger fluctuations.

BG levels of the DM−/HG+ patients (yellow curve) showed an interesting pattern. For the first week, these patients had low average values that appeared to increase in the second week. Indeed, during the second week the DM+/HG+ and DM−/HG+ patients (red and yellow curve, respectively) showed overlapping confidence bands indicating no statistical difference in average BG levels. Consistent with these observations, the average coefficient of variation of BG values in the DM+/HG+ (red curve), DM+/HG− (green curve), DM−/HG+ (yellow curve) and DM−/HG− (blue curve) patients was 28.3%, 9.8% (likely influenced by a shorter duration of follow-up, Fig. 2A), 24.9% and 7.3%, respectively.

Association of hyperglycaemia and diabetes with mortality

In the first step of the forward addition, stepwise logistic regression analyses, higher neutrophil percentage, older age, insulin therapy (as outpatient), haematuria, high serum globulin at admission, low platelet count and nasal congestion significantly associated covariates retained in this final model (Table 2, Step 1). Interestingly, as shown in Table S1 (see supplementary materials associated with this article on line) and Figure S1 (see supplementary materials associated with this article on line), the association of neutrophilia with mortality was linear. In the second step of this analysis, we added hyperglycaemia to the full model (total number of covariates 60) and found that hyperglycaemia was retained in the final model with an OR of 14.0. In this model, two new covariates (fever with chills and marijuana use) got added to the final model at the expense of the symptom of nasal congestion. The AUROC for models in step1 and step 2 was 0.86 (95% CI 0.81–0.91) and 0.90 (95% CI 0.86–0.94), implying a statistically significant improvement in prediction (increase in AUROC 0.04, DeLong and DeLong $P = 0.01$). Lastly, to understand the association of hyperglycaemia with and without diabetes, we replaced the covariate hyperglycaemia with indicators for diabetes and hyperglycaemia groups and used the DM-/HG- patients as the reference group. The results (Table 2, step 3) showed that occurrence of

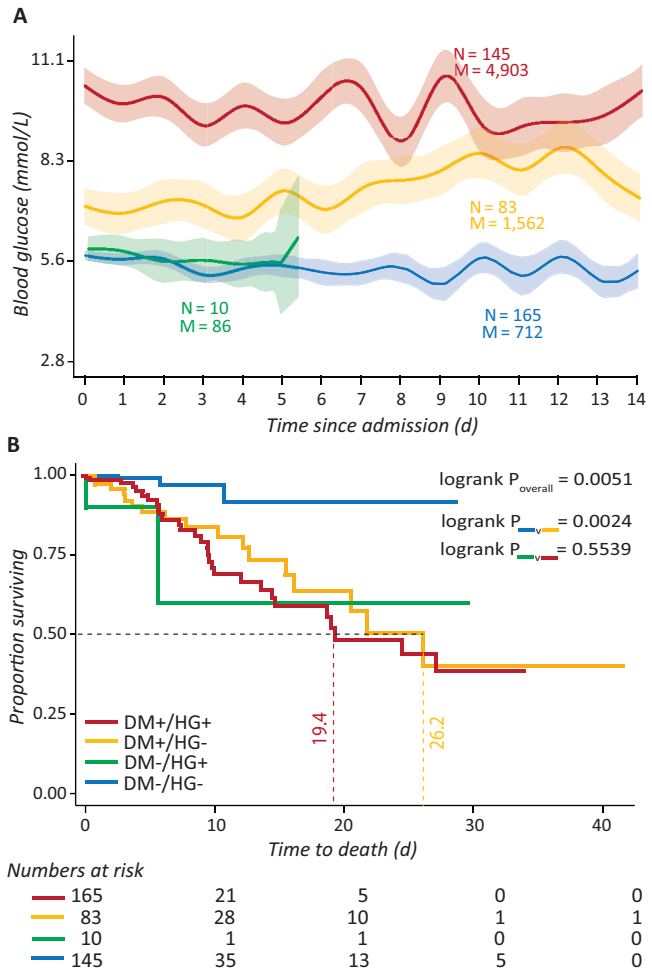

Fig. 2. Glycemia trends and association of hyperglycaemia with time to death in hospitalized COVID-19 patients. (A) Trends in glycemia over two-weeks following hospital admission for the diabetes- and hyperglycaemia-based, color-coded study groups. N and M indicate number of patients and number of BG measurements, respectively. Shown in the plot for each study group are cubic spline-smoothed, non-linear glycemia trends obtained using generalized estimating equations. Thick lines show point estimates and light-coloured areas show 95% confidence bands. **(B)** Kaplan-Meier plot for time to death in the color-coded study groups left-censored at the time of first detection of hyperglycaemia. Median time to death is indicated using color-coded numbers and dashed vertical lines. Statistical significance for difference in survival curves was tested using the overall as well as comparison-specific logrank test (indicated at the top-right corner).

Table 2
Association of hyperglycaemia and diabetes with the risk of death using stepwise logistic regression (n = 373). Results shown are from final model for each scenario.

Covariates	OR	95% CI
Step 1: using 59 covariates[a]		
Differential neutrophil count[b] **(%)**	1.10	1.06–1.15
Age **(y)**	1.05	1.02–1.08
On insulin	2.65	1.17–5.97
Haematuria	4.27	1.78–10.3
Initial Serum globulin **(g/L)**	2.99	1.50–5.95
Initial Platelet count (×**10^9 cells/L)**	0.99	0.99–1.00
Nasal congestion	9.06	1.33–61.9
Step 2: Step 1 covariates + hyperglycaemia		
Differential neutrophil count[b] **(%)**	1.09	1.04–1.14
Hyperglycaemia	14.0	3.47–56.3
Age **(y)**	1.05	1.02–1.09
Haematuria	3.28	1.78–10.3
Initial Serum globulin **(g/L)**	2.99	1.50–5.96
Fever with chills	5.69	1.51–21.5
Marijuana use	20.9	2.51–174.8
Initial Platelet count **(x10^9 cells/L)**	0.99	0.99–1.00
Step 3: Step 1 covariates + combination of diabetes and hyperglycaemia		
Differential neutrophil count[b] **(%)**	1.09	1.04–1.14
Glycaemic status		
No-diabetes/no-hyperglycaemia	Ref	
No-diabetes/hyperglycaemia	21.94	4.04–119.0
Diabetes/no-hyperglycaemia	5.97	0.32–111.8
Diabetes/hyperglycaemia	17.06	3.46–84.1
Age **(y)**	1.06	1.02–1.09
Haematuria	3.39	1.39–8.34
Initial Serum globulin **(g/L)**	2.88	1.46–5.70
Fever with chills	6.10	1.62–23.0
Marijuana use	17.78	1.97–160.5
Initial Platelet count **(x10^9 cells/L)**	0.99	0.99–1.00

OR, odds ratio; CI, confidence interval; Ref, reference category.
Abbreviations: % — percentage, y — years, g/L — grams per Litre, L — Litre.
[a] Results are from the final model retained after stepwise forward addition strategy. The full list of included variables in given in the Methods section. Variables in the final model are shown in the order of entry into the model.
[b] used as a continuous variable and expressed as percentage.

hyperglycaemia in patients with or without diabetes was significantly associated with hospital mortality. All other covariates retained in the final model in this step 3 were the same as those retained in step 2. This analytic strategy demonstrated that hyperglycaemia with or without diabetes was an independent predictor of hospital mortality.

We assessed the robustness of this finding in several ways. First, sensitivity analyses on patients with HbA1c data reaffirmed these results with a comparably high OR (13.0 Table S2; see supplementary materials associated with this article on line) and bootstrap CIs mostly above unity. Second, the first detection of hyperglycaemia was not influenced by the number of BG measurements ordered till that time point (adjusted OR 0.94, 95% CI 0.87–1.03). Third, we conducted a 10-fold cross-validation of the final model (Table 2, step 2); the results of which (Table S3; see supplementary materials associated with this article on line) showed a consistent prediction across folds (average 10-fold accuracy 0.75) implying that the model did not overfit the data. Together, these results indicated that our observation of the association between hyperglycaemia and mortality risk in hospitalized COVID-19 patients was robust to potential misclassification and indication biases.

Hyperglycaemia as an early indicator of mortality

To examine the clinical use of hyperglycaemia as a predictor of mortality, we investigated whether detection of hyperglycaemia early after admission can still provide a prognostic value. Average time from hospital admission to the first detection of hyperglycaemia was 0.11 days (95% CI 0–0.27 days) in diabetes patients and 2.15 days (95% CI 1.46–2.83 days) in non-diabetes patients. Of the 228 patients with hyperglycaemia, 177 (77.6%) were detected by the end of 24 h and an additional 17 (total of 194, 85.1%) by the end of 48 h. For this, we repeated the analyses shown in Table 2, step 2 by replacing the variable hyperglycaemia with hyperglycaemia detected during the first 24 h (HG_{24}) or 48 h (HG_{48}). We found (Table S4; see supplementary materials associated with this article on line) that both HG_{24} and HG_{48} were significant and independent predictor of mortality (HG 24 - OR 2.15, 95% CI 1.00–4.59, HG 48 OR - 3.31, 95% CI 1.44–7.62). Sensitivity analyses (Table S1; see supplementary materials associated with this article on line) in patients with HbA1c data suggested that while HG_{24} was marginally non-significant, HG_{48} was an independent predictor of mortality. Together, these results indicated that hyperglycaemia was an early predictor of the risk of mortality in the study cohort.

Table 3
Association of hyperglycaemia and diabetes with the time to death using stepwise Cox regression (n = 373).

Covariates	HR	95% CI
Step 1: using 59 covariates[a]		
Fatigue	3.33	1.53–7.23
Dialysis	2.95	1.21–7.22
Differential neutrophil count[b]	1.05	1.01–1.08
Initial Serum globulin (g/L)	2.25	1.32–3.84
Initial Platelet count (x10^9 cells/L)	0.99	0.99–1.00
Steroids	12.21	1.49–100.0
Step 2: Step 1 covariates + hyperglycaemia		
Hyperglycaemia	5.56	1.62–19.0
Fatigue	3.24	1.46–7.16
Age **(y)**	1.03	1.01–1.06
Steroids	13.88	1.64–117.65
Initial Serum globulin **(g/L)**	2.15	1.31–3.50
Initial platelet count **(x10^9 cells/L)**	0.99	0.99–1.00
Differential neutrophil count[b] **(%)**	1.04	1.00–1.08
Marijuana use	6.07	1.24–29.6
Rivaroxaban	8.37	1.04–66.8
Step 3: Step 1 covariates + combination of diabetes and hyperglycaemia		
Glycaemic status		
No-diabetes/no-hyperglycaemia	Ref	
No-diabetes/hyperglycaemia	8.86	1.90–41.4
Diabetes/no-hyperglycaemia	10.6	0.85–131.8
Diabetes/hyperglycaemia	7.58	1.73–33.1
Fatigue	3.41	1.49–7.80
Age **(y)**	1.04	1.01–1.06
Steroids	16.0	1.83–139.8
Initial Serum globulin **(g/L)**	2.26	1.41–3.60
Initial Platelet count **(x10^9 cells/L)**	0.99	0.99–1.00
Differential neutrophil count[b] **(%)**	1.04	1.01–1.07
Marijuana use	5.19	0.99–160.5
Rivaroxaban	9.63	1.19–78.3

HR, hazards ratio; CI, confidence interval; Ref, reference category.
Abbreviations: % — percentage, y — years, g/L — grams per Litre, L — Litre.
[a] Results are from the final model retained after stepwise forward addition strategy. The full list of included variables in given in the Methods section. Variables in the final model are shown in the order of entry into the model.
[b] used as a continuous variable and expressed as percentage.

Association of hyperglycaemia and diabetes with time to death

The Kaplan–Meier plot (Fig. 2B) showed 90% survival in the DM−/HG− group (blue curve) while the DM+/HG+ patient group (red curve) rapidly progressed to death with a median survival time of 19.4 days. Interestingly, the DM−/HG+ group (yellow curve) substantially overlapped the survival curve for the DM+/HG+ group with a median survival time of 26.2 days. Survival curves for the DM+/HG+ (red curve) and DM−/HG+ (yellow curve) patients crossed each other towards the end of follow-up indicating comparable survival. These results showed that the hyperglycaemia and diabetes-based patient groups were significantly associated (logrank $P < 0.01$) with survival in hospitalized COVID-19 patients. Further, as shown in Fig. 2B, within the group of COVID-19 patients without diabetes those with hyperglycaemia rapidly progressed to death significantly faster as compared to those without hyperglycaemia (logrank $P < 0.01$) but such a significant difference was not observed in patients with diabetes.

Analogous to the logistic regression analyses for association with risk of death, we next conducted stepwise Cox regression analyses to test the association with time to death. These results showed (Table 3) that the variables retained in Step 1 mostly matched those in Step 1 of Table 2 with the exception of fatigue, dialysis and steroid use. In Step 2, hyperglycaemia was retained as the most significant predictor (HR 5.56, 95% CI 1.62–19.0). Also, age, marijuana use and rivaroxaban medication were retained in the final model and dialysis was not retained. In Step 3, we observed that as compared to the reference group of DM−/HG−, hyperglycaemia (with or without diabetes) progressed to death significantly rapidly (HR 7.58 95 % CI 1.73–33.1 and 8.86 95% CI 1.90–41.4, respectively). Further, when we investigated the association of early hyperglycaemia with time to mortality using Cox proportional hazards regression, we found that the direction of association was consistent with the results of corresponding logistic regression analyses but statistical significance for the association of HG_{24} and HG_{48} with time to death was not observed (Table S5; see Supplementary materials associated with this article on line).

Discussion

The prevalence of hyperglycaemia in our study of hospitalized COVID-19 patients was 56.6% which is higher than the 38–40% prevalence reported in non-COVID-19 patients [15]. Our analyses have uncovered hospitalized nondiabetic COVID-19 patients with hyperglycaemia as a subgroup (20.6%) that is associated with a high risk of death and progress rapidly to death. Diabetes patients are a known high-risk group in COVID-19 disease [2,16]. While our results support this view, they also imply that it may be more informative to focus on the glycaemic status as an indicator of the clinical course of COVID-19 patients. Focusing on hyperglycaemia, as shown by results in Table 2, Table 3 and Fig. 2, can potentially inform a clinician early and accurately about the anticipated disease course. Our results also point toward the possibility of using hyperglycaemia within the first 48 h of admission as an independent predictor of COVID-19 prognosis. It is noteworthy that our definition of hyperglycaemia is inherently biased towards picking up hyperglycaemia early during disease.

We and others have previously demonstrated that the degree of hyperglycaemia in critically ill patients without diabetes plays a significant prognostic role in predicting hospital mortality [8,17,18]. Indeed, Max Harry Weil, father of critical care medicine, knew by 1973 that in critically ill patients, "Elevation of blood sugar reflects secretion of increased amounts of catecholamines from the adrenal medulla" [19]. Epinephrine-induced phosphorylation of the insulin receptor reduces its tyrosine kinase activity [20] and causes prompt and prolonged inhibition of pancreatic insulin secretion [21]. Thus, early appearance of hyperglycaemia in nondiabetic COVID-19 patients likely signals increased systemic stress.

We conjecture that hyperglycaemia may contribute to development of cytokine storm [11,22,23] and severe lung pathology in critically ill COVID-19 patients by promoting proinflammatory glycosylation of the Fc portion of IgG. A key characteristic that determines IgG pathogenicity is Fc glycosylation [24]. As discussed by Bermingham et al. [25], hyperglycaemia can drive production of diphosphate-*N*-acetylglucosamine, a substrate for glycosylation of IgG-Fc. Elevated HbA1c is associated with pro-inflammatory glycosylation of IgG-Fc in both Type 1 and Type 2 diabetics [26,27] and predicts a more difficult course of COVID-19 [28]. Hoepel et al. [29] found increased Fc glycosylation in anti-Spike IgG from severely ill COVID-19 patients and went on to show that macrophages responded to these patients' Spike-IgG immune complexes by producing inflammatory cytokines. In an in vitro model with human macrophages, pulmonary artery endothelial cells, and platelets, these Spike-IgG immune complexes induced long-lasting endothelial disruption and platelet activation. Spike-IgG immune complexes without enhanced Fc glycosylation did not induce these pathophysiological responses, and specific blockade of the macrophage Fcγ2 receptor blocked the inflammatory response to enhanced Fc-glycosylated IgG-Spike immune complexes [29]. Similarly, Zlamal et al. [30] have demonstrated platelets' Fcγ2-receptor is responsible for platelet activation by IgG immune complexes from patients with severe COVID-19.

Platelet activation induced by enhanced Fc glycosylated immune complexes is consistent with platelet hyperactivity in severe COVID-19 patients [31] and autopsy histopathology identifying platelet-fibrin microthrombi in the lungs [32]. Excessive macrophage stimulation by enhanced Fc-glycosylated immune complexes is consistent with the macrophage activation syndrome (MAS) often manifest in the laboratory values seen in severe COVID-19 [33]. The result is hypercoagulability with compromised micro perfusion, pulmonary endothelial fluid leakage, and severe respiratory distress syndrome that can result in death.

However, this prognostic role of hyperglycaemia varies by the primary cause of critical care such that primary diagnoses like trauma, coma and neurological diseases are especially prone to high likelihood of adverse outcomes associated with hyperglycaemia [8]. Our results need to be viewed in the light of the emerging literature on association of hyperglycaemia with COVID-19 prognosis. Studies have shown that pre-existing diabetes [2], newly detected diabetes [34], prediabetes [35], uncontrolled hyperglycaemia ($\geq$2 BG values of $\geq$10 mmol/L(180 mg/dl) [3]) or fasting BG $\geq$ 7 mmol/L ($\geq$126 mg/dL) [36] are significant determinants of COVID-19 prognosis. Our study adds to these findings the observation that hyperglycaemia detected early after hospitalization in patients without a history of diabetes can also independently predict the disease course in COVID-19 patients. Notably, as posited by Sathish et al. [37], SARS-CoV-2 may directly injure the pancreatic β-cells, may impede insulin signalling pathways or activate the renin-angiotensin system and via a combination of these mechanisms may contribute to new onset diabetes. We do not have post-discharge follow-up data on the study subjects to evaluate whether the hyperglycaemia detected during current hospitalization persisted after discharge, however, there remains a distinct possibility that the nondiabetic hyperglycaemia observed during a COVID-19 hospitalization may be a harbinger of new or unmasked diabetes.

Three other incidental findings in this study merit a mention. First, haematuria was found to be significantly associated with the risk of mortality in the logistic regression model. There is burgeoning evidence to support the association of haematuria, proteinuria and acute kidney injury (AKI) during COVID-19 disease and these parameters are considered to be early indicators of the renal involvement in COVID-19 [38]. The observed independent association of haematuria with mortality in this study, thus raises the possibility of kidney involvement. Whether this association is further accentuated by the presence of diabetes and/or hyperglycaemia needs to be investigated in future studies. Second, we found that differential neutrophil count remained a significantly associated covariate across all models. Several other studies have demonstrated the prognostic utility of relative or absolute neutrophilia in COVID-19 [39]. Third, our study found that high initial platelet count was associated with a reduced risk of mortality – a finding that concurs with other observations [40]. Thus, our results concur with most of the other haematological associations with in-hospital mortaliHG24ty in COVID-19 patients, but additionally reports the association of diabetic as well as nondiabetic hyperglycaemia even after accounting for known haematological associations. Notably, the prevalence of other factors retained in final models shown in Tables 2 and 3 was low and thus resulted in wide confidence intervals that need to be evaluated in larger samples in future studies.

Our study has some limitations. First, this is a retrospective, observational study of hospitalized COVID-19 patients and is thus prone to all the limitations of observational studies. For instance, causative association cannot be established from our results. While our analyses attempted to ensure that hyperglycaemia preceded the outcomes of interest, the possibility of a temporal bias cannot be refuted. Second, our study does not include any practice changes based on hyperglycaemia detection. However, our results suggest that a closer clinical scrutiny of COVID-19 patients based on glycaemic status may provide additional insights into their clinical course. Studies in future need to specifically address these hypotheses. Third, although we have provided a coherent model of the pathophysiology, whether hyperglycaemia in COVID-19 patients is consequential or coincidental to disease biology is currently unknown and cannot be surmised from our results. Studies are needed to specifically understand the biology of hyperglycaemia in COVID-19 patients. Fourth, since the BG data were retrospectively derived from the source of blood sample, its relation to fasting status remains unknown in this study. This heterogeneity of BG sampling could have biased our OR estimates. Despite this potential measured and unmeasured confounding, our results from sensitivity analyses indicate that our interpretations are likely to have been minimally influenced by confounding due to BG sampling. Fifth, the likelihood of undiagnosed diabetes at admission was 4% and 10% in the no-diabetes/no-hyperglycaemia and no-diabetes/hyperglycaemia groups, respectively. We evaluated, through sensitivity analyses, the influence of this misclassification on our interpretations. While the sensitivity analyses demonstrated the robustness of our inferences, larger multicentric studies are needed before the findings can be generalized. Sixth, information on neither the duration of diabetes nor the duration and dose of antidiabetic medication was available. In the same vein, it should be noted that glucose lowering agents such as metformin have been shown to influence outcomes in COVID-19 patients [41,42]. However, none of the admitted COVID-19 patients received any glucose lowering drug other than insulin which was accounted for in our analyses. Our study represents the clinical practice during very early stages of the pandemic when clear protocols for dysglycaemic COVID-19 patients were not in place. Whether development and implementation of such protocols can improve COVID-19 outcomes cannot be directly answered by our study and should be evaluated in future studies. Seventh, arguably drugs such as dexamethasone that are used in the management of respiratory distress can directly inflate blood glucose levels and may masquerade as hyperglycaemia. During the very early stages of the pandemic that our study data captures, corticosteroids were not commonly used. Indeed, in our dataset only three patients had received steroids during index hospitalization. Therefore, we believe that the potential influence of glucose-altering drugs on our inferences would be minimal.

Nevertheless, we have observed the appearance of hyperglycaemia in nondiabetic COVID-19 patients who are much more likely to progress to severe disease. We suggest this is an early marker of a stress response that results in amplification of the pathophysiology outlined above. Close and perhaps continuous monitoring of blood glucose in hospitalized COVID-19 patients could provide clinicians with early recognition of this risk. Hyperglycaemia as defined in this study is mostly inclusive of and incremental to known diabetes status both in terms of prevalence and its association with mortality. Thus, presence of hyperglycaemia can enable early identification of patients at risk for poor outcomes and improve risk stratification of COVID-19 patients.

Funding

None.

Conflict of interest

None of the authors have a conflict of interest to disclose.

Acknowledgments

H.K., A.M.A. and M.M. conceptualized the study. H.K. and M.M. conducted statistical analyses and wrote the first draft of the manuscript. A.M.A., M.A., J.V., A.R.A., J.P.R., A.J.J., M.I., S.Z., R.P.M. and P.H. contributed to data collection and critical revision of the manuscript. B.C.W. provided the pathophysiological foil to the inference and wrote the related parts. All authors read and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.diabet.2021.101254.

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