Accepted Manuscript online: 2023-04-04 Article published online: 2023-05-22

Association Between Prehospital Blood Glucose Levels and Outcomes in Patients With COVID-19 Infection: A Retrospective Cohort Study

OPEN ACCESS

Authors
Christophe A. Fehlmann[1, 2], Laurent Suppan[1], Christophe Gaudet-Blavignac[3, 4], Nadia Elia[1], Karim Gariani[5]

Affiliations
1 Division of Emergency Medicine, Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland
2 School of Epidemiology and Public Health, University of Ottawa, K1G 5Z3 Ottawa, Ontario, Canada.
3 Division of Medical Information Sciences, Geneva University Hospitals, Geneva, Switzerland
4 Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland
5 Service of Endocrinology, Diabetes, Nutrition, and Therapeutic Education, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland.

Key words
prehospital care, emergency medical services, medical mobile units, covid-19, blood glucose, diabetes, patient disposition

received 17.01.2023
revised 16.02.2023
accepted 17.02.2023
accepted manuscript online 04.04.2023
published online 22.05.2023

Bibliography
Exp Clin Endocrinol Diabetes 2023; 131: 338–344
DOI 10.1055/a-2068-6821
ISSN 0947-7349

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr Karim Gariani
Service of Endocrinology, Diabetes, Nutrition, and Therapeutic Education
Faculty of Medicine, Geneva University Hospitals
1205 Geneva
Rue Gabrielle-Perret-Gentil 4
CH-1211 Geneva 14
Switzerland
karim.gariani@hcuge.ch

Supplementary Material is available under https://doi.org/10.1055/a-2017-5338

ABSTRACT

Background Hyperglycaemia is associated with worse outcomes in many settings. However, the association between dysglycaemia and adverse outcomes remains debated in COVID-19 patients. This study determined the association of prehospital blood glucose levels with acute medical unit (intensive care unit or high dependency unit) admission and mortality among COVID-19-infected patients.

Methods This was a single-centre, retrospective cohort study based on patients cared for by the prehospital medical mobile unit from a Swiss university hospital between March 2020 and April 2021. All adult patients with confirmed or suspected COVID-19 infection during the study period were included. Data were obtained from the prehospital medical files. The main exposure was prehospital blood glucose level. A 7.8 mmol/L cut-off was used to define high blood glucose level. Restricted cubic splines were also used to analyse the exposure as a continuous variable. The primary endpoint was acute medical unit admission; secondary endpoints were 7-day and 30-day mortality. Multivariable logistic regressions were performed to compute odds ratios.

Results A total of 276 patients were included. The mean prehospital blood glucose level was 8.8 mmol/l, and 123 patients presented high blood glucose levels. The overall acute medical unit admission rate was 31.2 %, with no statistically significant difference according to prehospital blood glucose levels. The mortality rate was 13.8 % at 7 days and 25 % at 30 days. The 30-day mortality rate was higher in patients with high prehospital blood glucose levels, with an adjusted odds ratio of 2.5 (1.3–4.8).

Conclusions In patients with acute COVID-19 infection, prehospital blood glucose levels do not seem to be associated with acute medical unit admission. However, there was an increased risk of 30-day mortality in COVID-19 patients who presented high prehospital blood glucose levels.

Introduction

The successive waves of the coronavirus disease 2019 (COVID-19) pandemic had variable effects in different parts of the world. While lockdowns were usually associated with a decrease in emergency department (ED) visits, acute overcrowding was also reported in many centres [1]. To limit overcrowding, emergency physicians should be able to rapidly identify patients at risk of developing severe forms of COVID-19. Some risk factors are already known and include age, male gender and several chronic comorbidities such as obesity, hypertension, chronic kidney disease, malignancy, cardiovascular disease, and diabetes [2–6]. Other clinical and biological parameters could also prove relevant and should therefore be studied. Among them, blood glucose levels deserve particular attention. Indeed, hyperglycaemia appears to be a marker of severity in infections and other stress states such as myocardial infarction or stroke [7, 8]. There is, however, contradicting evidence regarding the association between high blood glucose levels and severe forms of COVID-19, and the significance of hyperglycaemia remains debated in this context [9, 10].

The hypothesis underlying the present study was that high prehospital blood glucose (PBG) levels may serve as a prognostic marker for poor outcomes, including acute medical unit admission and mortality among COVID-19-infected patients. Thus, the main objective of this study was to determine the presence of an association between PBG levels and patient disposition and mortality in this population.

Methods

Study design and setting

This monocentric retrospective cohort study was designed and reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement guidelines [11]. Its protocol was approved by the regional research ethics committee (CCER – Commission Cantonale d'Ethique de la Recherche sur l'être humain, Geneva, Switzerland – Project ID 2021–01463). The study, whose structure has already been described, was carried out in the prehospital unit of the Geneva University Hospitals (HUG, Geneva, Switzerland) [12]. Briefly, medical mobile units called SMUR (Service mobile d'urgence et de réanimation, in French) are dispatched whenever life-threatening emergencies are identified by dispatchers or when paramedics request medical backup. These units are not designed to transport patients and are always sent out alongside an ambulance staffed by two paramedics. After each prehospital intervention, two independent mission reports are generated. The first is a handwritten report, which is filled by paramedics according to a standardized format. The second is a computerized, semi-structured electronic report. It is completed by the prehospital emergency physician and includes structured fields for all vital parameters, including blood glucose. These latter reports are systematically reviewed by supervisors on a daily basis for teaching and quality control purposes.

Participants

All patients in whom a COVID-19 infection was suspected (solely based on the prehospital physician's clinical assessment) or confirmed (biological evidence of acute infection, such as a polymerase chain reaction [PCR] test) and who had been taken care of by a SMUR unit between March 2020 and April 2021 were included. Recording COVID-19 status in the SMUR prehospital file has been mandatory since the first COVID-19 pandemic wave. Patients in whom a COVID-19 diagnosis was subsequently not confirmed were excluded. These patients were identified by merging the prehospital database with the COVID-19 institutional database, which included only confirmed cases, defined as a positive reverse transcription–PCR (RT-PCR) testing on a nasopharyngeal swab or lower respiratory tract sample or clinically confirmed COVID-19 diagnosis. Patients transferred from other healthcare facilities were also excluded, as any glycaemic imbalance would have been treated before the arrival of a SMUR unit. Patients who were not transported to the HUG, the only public hospital in this region, were also excluded since their follow-up data was not recorded in the institutional database. Finally, patients for whom no PBG value was available were also excluded.

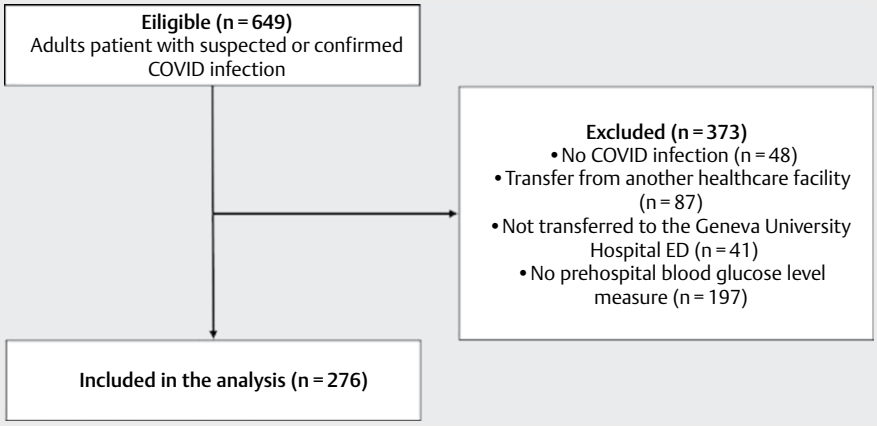
Variables, data sources and measurement

The main exposure was the PBG level. This value is routinely collected by paramedics using handheld glucometers, the brand of which varies from one emergency medical service (EMS) to another. Prehospital blood glucose values were automatically extracted from the SMUR prehospital files. If no PBG value could be retrieved through this automatic extraction, the handwritten EMS mission reports were manually searched by one author (KG). Prehospital blood glucose levels were handled as both a categorical and a continuous value. Categorization was carried out by defining two groups (high versus non-high) using a 7.8 mmol/L (140 mg/dL) cut-off [13]. The primary outcome was acute medical unit admission within 48 hours. Intensive care units and high-dependency units were considered acute medical units. Secondary outcomes were 7-day and 30-day mortality. Other variables of interest included patient age and sex, previous medical history, prehospital vital signs (first values obtained in the field), respiratory management on site, ED temperature, ED blood results and ED length of stay.

Apart from the manual search for completing missing PBG values, all data were electronically extracted from the SMUR database or from the institutional COVID-19 database [14]. Medical history diagnoses were based on the International Classification of Diseases-10 diagnoses coded in the discharge letters related to the index episode and the three previous hospitalisations.

Statistical methods and sample size

Baseline characteristics were described using frequency and percentage for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Comparisons of all variables between the two groups (high versus non-high PBG levels) were performed using the Chi-square test, Student t-test, or Wilcoxon Mann-Whitney test, as appropriate. Outcomes were tabulated and compared using the same tests. Multivariable logistic regression models were used to compute odds ratios adjusted for age (continuous, using restricted cubic splines), diabetes and hypertension. The crude association between PBG levels and acute medical unit admission was graphically represented using restricted cubic splines with five knots and statistical



▶ **Fig. 1** Flowchart of patient inclusion.

significance was assessed through the Wald test, testing the null hypothesis that all coefficients were equal to zero. Assuming an average acute medical unit admission rate of 30 %, and about 50 % of patients with hyperglycaemia, 256 patients were required to have an 80 % chance of detecting, at the 5 % significance level, a 1.8 higher risk (22 % versus 38 %) in the high-level group. Statistical analyses were performed under Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC), including the package *mkspline.* For all tests, a two-sided p-value below 0.05 was considered significant.

Results

Participants

Between March 2020 and April 2021, 649 patients met the inclusion criteria, and 276 were finally included (▶ **Fig. 1**). A total of 241 PBG values were retrieved through electronic extraction. All other files were systematically searched and allowed the inclusion of 35 more values that had not been recorded in the medical prehospital file.

Descriptive data

Patient characteristics are reported in ▶ **Table 1**. The mean age was 73 (SD = 16) and 156 (56.5 %) patients were male. The mean PBG level was 8.8 mmol/l (SD = 4.6), with a median of 7.5 mmol/l (6.2: 9.7). Patients excluded for missing PBG values were slightly younger than those included and were less likely to have hypertension and diabetes. Their outcomes were, however, similar (▶ **Table S1**).

Based on the pre-specified 7.8 mmol/L cut-off, 123 (44.6 %, 123/276) patients had high PBG levels and 153 (55.4 %) had non-high levels. Compared to patients with high PBG levels, patients with non-high PBG levels were younger and had less hypertension and diabetes (▶ **Table 1**). There was no evidence of a difference in vital signs, except for respiratory rate and oxygen saturation, which were higher and lower, respectively, in patients with high PBG levels. There was no clinically relevant difference regarding blood values.

Outcome data

Eighty-six (31.2 %) patients were admitted to an acute medical unit. Overall, there was no statistically significant difference between the high and non-high PBG level groups (▶ **Table 2**), with a crude odds ratio (OR) of 1.3 (0.8–2.1) and an adjusted OR of 1.5 (0.8–2.7). Patients with high PBG levels were, however, more frequently admitted to intensive care units. ▶ **Fig. 2** presents the association between PBG level and acute medical unit admission and displays a non-statistically significant trend, with an increase in acute medical unit admissions as PBG levels rise.

The mortality rate was 13.8 % at 7 days and 25.0 % at 30 days. While there was no difference at 7 days according to PBG levels, patients with high PBG levels were more likely to die at 30 days than patients with non-high levels, with a crude OR of 2.6 (1.5–4.6). After adjustment for age, diabetes, and hypertension, the OR was 2.5 (1.3–4.8). The relationship between PBG levels and 30-day mortality seemed to follow a U-shaped curve, with increased mortality rates for hypoglycaemic and hyperglycaemic patients. For the latter, a plateau phase seems to be reached after 12 mmol/L (▶ **Fig. 3**).

Discussion

This study shows an important variation in PBG levels among patients with COVID-19. While no association was found between acute medical unit admission and blood glucose levels, 30-day mortality was significantly higher when glycaemia was too high. Too low levels of glycaemia seem to impact 30-day mortality as well.

When the pre-specified, literature-based threshold of 7.8 mmol/L was used [13], the prevalence of high blood glucose levels was high among patients with COVID-19. This high prevalence is similar to that reported in other studies, even though the cut-off used to define high blood glucose levels was not uniform [15–17]. In addition, the mean prehospital blood glucose level in our study was 8.8 mmol/L, a value consistent with that reported in prior studies [15–17]. Patients with high PBG levels were more likely to be admitted to the ICU, but there was no statistically significant difference when all acute medical units were considered jointly.

▶ **Table 1** Patient characteristics.

	All patients (N = 276)	Patients with non-high prehospital blood glucose value (N = 153)	Patients with high prehospital blood glucose value (N = 123)	p-value
Prehospital blood glucose level (mmol/L) – median [IQR]	7.5 [6.2–9.7]	6.3 [5.5–7.0]	10.0 [8.9–12.6]	NA
Age – mean ± SD	73 ± 16	71 ± 17	77 ± 13	0.002
Sex (male) – n (%)	156 (56.5)	80 (52.3)	76 (61.8)	0.11
Patient history – n (%)				
Hypertension	130 (47.1)	60 (39.2)	70 (56.9)	0.003
COPD	36 (13.0)	21 (13.7)	15 (12.2)	0.71
Ischemic heart disease	39 (14.1)	16 (10.5)	23 (18.7)	0.051
Diabetes	76 (27.5)	21 (13.7)	55 (44.7)	< 0.001
High cholesterol levels	47 (17.0)	20 (13.1)	27 (22.0)	0.051
Stroke	11 (4.0)	6 (3.9)	5 (4.1)	0.95
Prehospital vital signs				
Heart rate (/min) – mean ± SD	101 ± 25	101 ± 23	102 ± 28	0.80
SBP (mmHg) – mean ± SD	137 ± 31	139 ± 28	135 ± 34	0.35
Respiratory rate (/min) – mean ± SD	30 ± 10	27 ± 10	33 ± 10	< 0.001
Oxygen saturation (%) – median [IQR]	93 [85–96]	94 [85–97]	91 [85–95]	0.034
Prehospital NIV – n (%)	27 (9.8)	12 (7.8)	15 (12.2)	0.23
Prehospital intubation – n (%)	10 (3.6)	5 (3.3)	5 (4.1)	0.72
ED temperature (°C) – mean (SD)	37.1 ± 0.8	37.1 ± 0.7	37.2 ± 0.8	0.24
ED blood analysis				
Haemoglobin (g/l) – median [IQR]	133 [117–146]	136 [119–147]	130 [115–142]	0.044
Leucocytes (G/l) – median [IQR]	9 [7–14]	9 [7–13]	9 [7–14]	0.84
C-reactive protein (mg/L) – median [IQR]	51 [12–125]	36 [9–104]	66 [17–134]	0.15

IQR: interquartile range; SD: standard deviation; COPD: chronic obstructive pulmonary disease; ED: emergency department; NIV: non invasive ventilation; SBP: systolic blood pressure.

This suggests that PBG levels could be particularly useful in discriminating the more severe cases.

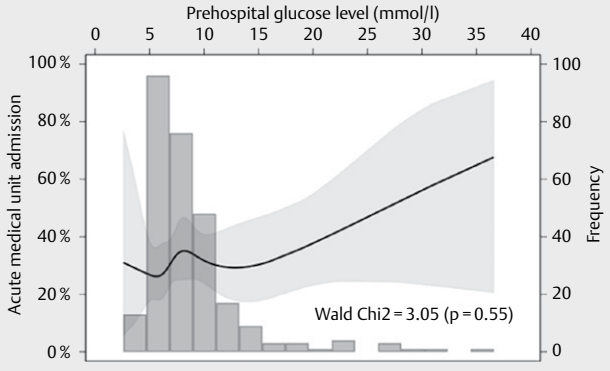
Several mechanisms could explain the increased severity and mortality in COVID-19 patients who presented high PBG levels. Among such mechanisms, innate immunity impairment and decreased polymorphonuclear neutrophil cell performance could play a major role [18, 19]. Adaptive immunity dysfunction has also been observed in relation to hyperglycaemia with delayed T-cell function [20]. Overproduction of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha, endothelial dysfunction, elevated oxidative stress and coagulation abnormalities inducing a procoagulant state have all also been reported in association with hyperglycaemia. In fact, these biological alterations have been shown to be induced by hyperglycaemia in in-vitro models. In clinical situations, they are associated with more severe outcomes in septic patients, particularly in those with COVID-19 infection [15, 21]. Furthermore, hyperglycaemic states increase oxidative stress, leading to the amplification of the generation of reactive oxygen species and/or reduction of antioxidant defence mechanisms that may promote viral replication [22]. In addition, the production of reactive oxygen species and viral activation of the renin-angiotensin-aldosterone system through the increased expression of angiotensin II-induced insulin resistance and vascular endothelial alteration. This, in turn, generates a vicious circle which entertains hyperglycaemia and promotes disseminated intravascular coagulation, thromboembolism and cardiovascular events, ultimately increasing mortality [23]. Finally, hyperglycaemia may aggravate lung damage in acute lung injury, thus promoting the development of acute respiratory distress syndrome [24].

Consistent with the results of this study, several reports have revealed that, in septic patients, the association between dysglycaemia and adverse outcomes follows a U-shaped curve. In other words, patients with either too low and/or too high blood glucose levels have worse outcomes than individuals whose blood glucose is in the normal/moderate range [4, 25]. However, it remains to be elucidated whether the association of dysglycaemia and mortality in stress-related conditions such as sepsis or myocardial infarction is solely caused by the toxic effects of hyperglycaemia or if hypo- and hyperglycaemia are simply a marker of stress and severity of the disease. While early insulin administration is strongly recommended in case of stress-induced hyperglycaemia, treatment modalities and glycaemic control monitoring remain debated [26].

Few prehospital studies have evaluated the impact of blood glucose levels on patient outcomes. Recently, Kreutziger et al. report-

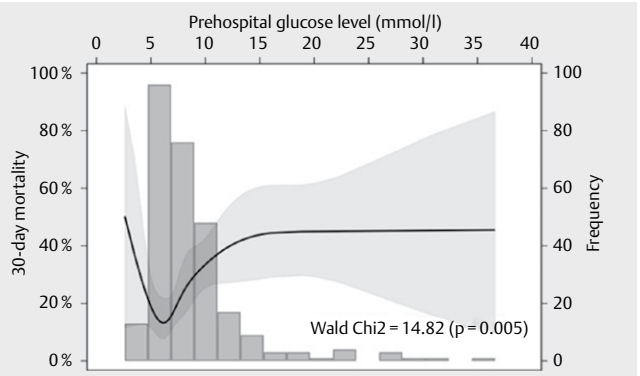
▶ **Table 2** Patient outcomes.

	All patients (N = 276)	Patients with non-high prehospital blood glucose value (N = 153)	Patients with high prehospital blood glucose value (N = 123)	p-value
Primary outcome admission				
Acute medical unit – n (%)	86 (31.2)	44 (28.8)	42 (34.1)	0.34
Intensive care unit	*41 (14.9)*	*16 (10.5)*	*25 (20.3)*	*0.022*
High-dependency unit only	*45 (16.3)*	*28 (18.3)*	*17 (13.8)*	*0.32*
Secondary outcomes				
7-day mortality – n (%)	38 (13.8)	16 (10.5)	22 (17.9)	0.075
30-day mortality – n (%)	69 (25.0)	26 (17.0)	43 (35.0)	<0.001



▶ **Fig. 2** Association between prehospital blood glucose level and acute medical unit admission.

ed that both low and high blood glucose levels are common in traumatic shock [27]. However, the predictive capacity of dysglycaemia in this setting is still unknown. More recently still, Abramson et al. reported that prehospital hyperglycaemia is associated with worse outcomes after out-of-hospital cardiac arrests [28]. The impact of prehospital dysglycaemia could, however, extend beyond the range of specific pathologies. Indeed, a large retrospective observational study showed the association of the inclusion of blood glucose assessment in the National Early Warning Score (NEWS) with improved identification of patients at risk of death [29]. In the specific context of COVID-19, dysglycaemia may represent a potentially useful prehospital indicator in addition to classic parameters such as respiratory (SpO2, respiratory rate) or hemodynamic



▶ **Fig. 3** Association between prehospital blood glucose level and 30-day mortality.

parameters [30, 31]. This could help reduce ED length of stay by enabling more efficient patient disposition.

Antidiabetic drugs are also a parameter that can play a role in the prognosis of diabetic patients hospitalized with COVID-19. Several studies have been interested in this question and a meta-analysis has shown that in diabetic patients hospitalized with COVID, serum glucose transport protein-2 inhibitors taken before the hospitalization are associated with a lower risk of a bad outcome compared to insulin, dipeptidyl peptidase-4 inhibitors or sulfonylurea. In addition, taking glucagon-like peptide-1 or metformin also seems to be associated with a better outcome [32].

Limitations

This study has several limitations which should be considered when interpreting its results. The limited sample size prevented the inclusion of additional covariates in our multivariable model and the risk of residual confounding cannot be excluded. Among such confounders, the effect of in-hospital treatment on mortality would have been interesting to study. However, the aforementioned limitation and the fact that this information could not be retrieved prevented this analysis from being performed. In addition, reliable information regarding oral hypoglycaemic medication was lacking. As such drugs are known to be associated with a lower risk of adverse effects than insulin [32], residual confounding cannot be excluded. Another risk of bias is linked to the important proportion of missing blood glucose values, which led to the exclusion of many patients. As these patients were clinically different from those included in the analysis according to their demographic characteristics, their PBG levels could have been lower, thereby impacting the association. In addition, the time elapsed between symptom onset and prehospital intervention could not be retrieved, and baseline glucose levels could not be obtained. Blood glucose values may vary during the course of a COVID-19 infection, especially due to the impact of inflammatory cytokines, which may result in cytokine storms. In addition, other factors, such as psychological stress, may also alter blood glucose levels [33]. Therefore, the PBG values reported in this study do not necessarily reflect baseline glycaemic control and some patients with insufficient glycaemic control may be part of this cohort. While this is an incontrovertible limitation,

the patients evaluated by a SMUR unit were all considered critically ill either by emergency medical communication centres dispatchers or by paramedics who requested an on-site reinforcement. Such patients are often unable to provide information regarding their baseline glycaemic control and this study, therefore, reflects actual prehospital conditions. Furthermore, even though the time elapsed since symptom onset could not be reported, it has been shown that aggravation was predictably happening after 7 days in most patients [34]. Therefore, it is likely that most patients reported in the current study were taken care of approximately 7 days after the onset of symptoms. Finally, the generalisation to other systems could be limited. Indeed, many hospitals adapted their acute medical unit admission criteria during the COVID-19 pandemic waves, and these criteria differed from one hospital to another. As with many others, the prehospital system from which data was obtained is also specific, and this could add to the generalisation issue. Nevertheless, some strengths should also be acknowledged. The main strength resides in the use of restricted cubic splines, which helped avoid the loss of information that could have arisen from the binarization of continuous variables. This allowed the observation of a non-linear association which might help future researchers in this field.

Prospective studies should now be conducted to confirm whether PBG levels can be used as a self-standing prognostic marker among individuals with COVID-19 infection. In addition, while a target glucose level of 7.8–10.0 mmol/L is recommended in critical patients, there is no recommendation currently available for the specific prehospital setting [35]. Future studies assessing different targets of glycaemia with insulin management could be useful to evaluate the potential benefit of prehospital insulin administration, in particular among COVID-19-infected patients.

Conclusion

In patients with acute COVID-19 infection, PBG levels do not seem to be associated with acute medical unit admission. However, an increased risk of 30-day mortality was found in COVID-19 patients who presented high PBG levels.

Ethics Approval and Consent to Participate

This study was approved on 27.07.2021 by the institutional ethics committee of Geneva (CCER – Commission Cantonale d'Ethique de la Recherche sur l'être humain), Switzerland (Project ID 2021–01463). Patient consent was waived by this committee. All procedures were performed in accordance with relevant guidelines.

Availability of Data and Materials

The data that support the findings of this study (dataset, Stata code) are freely available on the Open Science Framework (https://doi.org/10.17605/OSF.IO/XMW4U).

Authors' Contributions (Based on CrediT Taxonomy)

Conceptualisation: K Gariani, L Suppan, N Elia and CA Fehlmann. Data curation: L Suppan and C Gaudet-Blavignac. Formal analysis: L Suppan and CA Fehlmann. Acquisition of funds: L Suppan. Investigation: CA Fehlmann. Methodology: L Suppan and CA Fehlmann. Project administration: L Suppan and CA Fehlmann. Supervision: CA Fehlmann. Validation: L Suppan and CA Fehlmann. Visualisation: K Gariani, L Suppan and CA Fehlmann. Writing – original draft: K Gariani, L Suppan and CA Fehlmann. Writing –review and editing: K Gariani, L Suppan, C Gaudet-Blavignac, N Elia and CA Fehlmann.

Acknowledgments

The Authors would like to thank the Medical Information Sciences Division (SIMED) from Geneva University Hospital for their involvement in the creation and management of the COVID database.

Conflict of Interest

The authors declare that they have no competing interests.

One sentence summary In patients with COVID-19 infection, prehospital blood glucose levels do not seem to be associated with acute medical unit admission. An increased risk of 30-day mortality was however found in patients with high prehospital blood glucose levels

References

[1] Bouillon-Minois JB, Raconnat J, Clinchamps M et al. Emergency department and overcrowding during COVID-19 outbreak; a letter to editor. Arch Acad Emerg Med 2021; 9: e28. DOI: 10.22037/aaem.v9i1.1167

[2] Zhou Y, Yang Q, Chi J et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. Int J Infect Dis 2020; 99: 47–56. DOI: 10.1016/j.ijid.2020.07.029

[3] Biswas M, Rahaman S, Biswas TK et al. Association of sex, age, and comorbidities with mortality in COVID-19 patients: A systematic review and meta-analysis. Intervirology 2020; 1–12. DOI: 10.1159/000512592

[4] Petrakis V, Panagopoulos P, Trypsianis G et al. Fasting plasma glucose increase and neutrophil to lymphocyte ratio (NLR) as risk predictors of clinical outcome of COVID-19 pneumonia in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 2023. DOI: 10.1055/a-2009-6937

[5] Petrakis V, Panagopoulos P, Papazoglou D et al. Diabetes mellitus and hypertension as major risk factors of mortality from Covid-19 pneumonia. Exp Clin Endocrinol Diabetes 2022; 130: 205–206. DOI: 10.1055/a-1325-0381

[6] Petrakis V, Panagopoulos P, Trypsianis G et al. Glucose on admission: Unfavourable effects on hospitalisation and outcomes in type 2 diabetes mellitus patients with COVID-19 pneumonia. Exp Clin Endocrinol Diabetes 2022; 130: 561–562. DOI: 10.1055/a-1686-8738

[7] Marik PE, Bellomo R Stress hyperglycemia: An essential survival response!. Crit Care 2013; 17: 305. DOI: 10.1186/cc12514

[8] Ishihara M Acute hyperglycemia in patients with acute myocardial infarction. Circ J 2012; 76: 563–571. DOI: 10.1253/circj.cj-11-1376

[9] Cariou B, Hadjadj S, Wargny M et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: The CORONADO study. Diabetologia 2020; 63: 1500–1515. DOI: 10.1007/s00125-020-05180-x

[10] Mirani M, Favacchio G, Carrone F et al. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: A case series from an Academic Hospital in Lombardy, Italy. Diabetes Care 2020; 43: 3042–3049. DOI: 10.2337/dc20-1340

[11] von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 2008; 61: 344–349. DOI: 10.1016/j.jclinepi.2007.11.008

[12] Chan M, Fehlmann CA, Pasquier M et al. Endotracheal intubation success rate in an urban, supervised, resident-staffed emergency mobile system: An 11-year retrospective cohort study. J Clin Med 2020; 9:. DOI: 10.3390/jcm9010238

[13] American Diabetes Association Professional Practice C 16. Diabetes care in the hospital: Standards of medical care in diabetes-2022. Diabetes Care 2022; 45: S244–S253. DOI: 10.2337/dc22-S016

[14] Gaudet-Blavignac C, Ehrsam J, Turbe H et al. Deep SNOMED CT enabled large clinical database about COVID-19. Stud Health Technol Inform 2022; 294: 317–321. DOI: 10.3233/SHTI220466

[15] Sardu C, D'Onofrio N, Balestrieri ML et al. Outcomes in patients with hyperglycemia affected by COVID-19: Can we do more on glycemic control? Diabetes Care 2020; 43: 1408–1415. DOI: 10.2337/dc20-0723

[16] Martinez-Murillo C, Ramos Penafiel C, Basurto L et al. COVID-19 in a country with a very high prevalence of diabetes: The impact of admission hyperglycaemia on mortality. Endocrinol Diabetes Metab 2021; 4: e00279. DOI: 10.1002/edm2.279

[17] Bode B, Garrett V, Messler J et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020; 14: 813–821. DOI: 10.1177/1932296820924469

[18] Delamaire M, Maugendre D, Moreno M et al. Impaired leucocyte functions in diabetic patients. Diabet Med 1997; 14: 29–34. DOI: 10.1002/(SICI)1096-9136(199701)14:1<29::AID-DIA300>3.0.CO;2-V

[19] Jafar N, Edriss H, Nugent K The effect of short-term hyperglycemia on the innate immune system. Am J Med Sci 2016; 351: 201–211. DOI: 10.1016/j.amjms.2015.11.011

[20] Martinez N, Vallerskog T, West K et al. Chromatin decondensation and T cell hyperresponsiveness in diabetes-associated hyperglycemia. J Immunol 2014; 193: 4457–4468. DOI: 10.4049/jimmunol.1401125

[21] Schuetz P, Castro P, Shapiro NI Diabetes and sepsis: Preclinical findings and clinical relevance. Diabetes Care 2011; 34: 771–778. DOI: 10.2337/dc10-1185

[22] Delgado-Roche L, Mesta F Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. Arch Med Res 2020; 51: 384–387. DOI: 10.1016/j.arcmed.2020.04.019

[23] Lim S, Bae JH, Kwon HS et al. COVID-19 and diabetes mellitus: From pathophysiology to clinical management. Nat Rev Endocrinol 2021; 17: 11–30. DOI: 10.1038/s41574-020-00435-4

[24] Lapar DJ, Hajzus VA, Zhao Y et al. Acute hyperglycemic exacerbation of lung ischemia-reperfusion injury is mediated by receptor for advanced glycation end-products signaling. Am J Respir Cell Mol Biol 2012; 46: 299–305. DOI: 10.1165/rcmb.2011-0247OC

[25] Capes SE, Hunt D, Malmberg K et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet 2000; 355: 773–778. DOI: 10.1016/S0140-6736(99)08415-9

[26] Stoudt K, Chawla S Don't sugar coat it: Glycemic control in the intensive care unit. J Intensive Care Med 2019; 34: 889–896. DOI: 10.1177/0885066618801748

[27] Kreutziger J, Lederer W, Schmid S et al. Blood glucose concentrations in prehospital trauma patients with traumatic shock: A retrospective analysis. Eur J Anaesthesiol 2018; 35: 33–42. DOI: 10.1097/EJA.0000000000000733

[28] Abramson TM, Bosson N, Whitfield D et al. Elevated prehospital point-of-care glucose is associated with worse neurologic outcome after out-of-hospital cardiac arrest. Resusc Plus 2022; 9: 100204. DOI: 10.1016/j.resplu.2022.100204

[29] Vihonen H, Laaperi M, Kuisma M et al. Glucose as an additional parameter to National Early Warning Score (NEWS) in prehospital setting enhances identification of patients at risk of death: An observational cohort study. Emerg Med J 2020; 37: 286–292. DOI: 10.1136/emermed-2018-208309

[30] Midez R, Fehlmann CA, Marti C et al. Association between prehospital hypoxemia and admission to intensive care unit during the COVID-19 pandemic: A retrospective cohort study. Medicina (Kaunas) 2021; 57:. DOI: 10.3390/medicina57121362

[31] Jouffroy R, Lemoine S, Derkenne C et al. Prehospital management of acute respiratory distress in suspected COVID-19 patients. Am J Emerg Med 2021; 45: 410–414. DOI: 10.1016/j.ajem.2020.09.022

[32] Zhu Z, Zeng Q, Liu Q et al. Association of glucose-lowering drugs with outcomes in patients with diabetes before hospitalization for COVID-19: A systematic review and network meta-analysis. JAMA Netw Open 2022; 5: e2244652. DOI: 10.1001/jamanetworkopen.2022.44652

[33] Tay MZ, Poh CM, Renia L et al. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol 2020; 20: 363–374. DOI: 10.1038/s41577-020-0311-8

[34] Yamasaki Y, Ooka S, Matsuoka S et al. Predicting the aggravation of coronavirus disease-19 pneumonia using chest computed tomography scans. PLoS One 2022; 17: e0276738. DOI: 10.1371/journal.pone.0276738

[35] Costantini E, Carlin M, Porta M et al. Type 2 diabetes mellitus and sepsis: State of the art, certainties and missing evidence. Acta Diabetol 2021; 58: 1139–1151. DOI: 10.1007/s00592-021-01728-4