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Admission hyperglycemiaas a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: Data from the Spanish SEMI-COVID-19 Registry

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**A complete list of the SEMI-COVID-19 Network members is provided in the Appendix

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Abstract

Background: Hyperglycemia has emerged as an important risk factor for death in coronavirus disease 2019 (COVID-19)**.** The aim of this study was to evaluate the association between blood glucose (BG) levels and in-hospital mortality in non-critically patients hospitalized with COVID-19.

Methods: This is a retrospective multi-center study involving patients hospitalized in Spain. Patients were categorized into three groups according to admission BG levels: <140 mg/dl, 140-180 mg/dl, and >180 mg/dl. The primary endpoint wasall-cause in-hospital mortality.

Results: Of the 11,312 patients, only 2,128 (18.9%) had diabetes, and2,289 (20.4%) diedduring hospitalization. The in-hospital mortality rates were 15.7% (<140 mg/dl), 33.7% (140-180 mg), and 41.1% (>180 mg/dl), p<0.001. The cumulative probability of mortality was significantly higher in patients with hyperglycemia compared to patients with normoglycemia(log rank, p<0.001), independently of pre-existingdiabetes.Hyperglycemia (after adjusting for age, diabetes, hypertension, and other confounding factors) was an independent risk factor of mortality (BG >180 mg/dl: HR 1.50; 95%CI: 1.31-1.73) (BG 140-180 mg/dl: HR 1.48; 95%CI: 1.29-1.70).Hyperglycemia was also associated with requirementformechanical ventilation, ICU admission,and mortality.

Conclusion: Admission hyperglycemiais a strong predictor of all-cause mortality in non-critically hospitalized COVID-19 patients regardless ofprior history of diabetes.

Key words: SARS-CoV-2, COVID-19, hyperglycemia, mortality, diabetes.

Key Messages:

- Admission Hyperglycemia is a stronger and independent risk factor for mortality in COVID-19.
- Screening for hyperglycemia, in patients without diabetes, and early treatment of hyperglycemia shouldbe mandatory in the management of patients hospitalized with COVID-19.
- Admission hyperglycemia should not be overlooked in all patients regardless prior history of diabetes.

Introduction

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic emerged in China, more than 300,000 confirmed cases and approximately 28,500 COVID-19related deaths have been reported in Spain as of the date of writing of this article[1].

Acutehyperglycemiahas been associated with in-hospital complications in non-critically ill patients with and without diabetes mellitus (DM)[2]. In regard to COVID-19, elevated blood glucose(BG) levelsis also associated with in-hospital complications, including mechanicalventilation requirement, intensive care unit (ICU) admission, and death[3–7].Thus, hyperglycemia, particularly upon admission, could be a marker of poor prognosisregardless of diabetes status. This suggests that elevated BG may play a decisiverole in the severityof the disease at an early stage [8–10].

There are at least twoplausible reasons why hyperglycemia, particularly acute hyperglycemia, could be harmful in patients with COVID-19[11]. First, SARS-CoV-2 could infect endocrine pancreas cells through their expression of angiotensin-converting enzyme 2 (ACE2) receptors, resulting in an impairment in ß-cell insulin secretion[12]. Second, inflammation during COVID-19 could also generate insulin resistance. Both mechanisms combined could induce hyperglycemiain early stages of the disease.Oncea patient presents with hyperglycemia, it could play a direct role in worsening the infection. Hyperglycemia upregulates ACE2 expression and induces glycosylation ofACE2, facilitating the invasion of cells by SARS-CoV-2[13].

Although several studies and meta-analyses have shown that patients with diabetes have a significantly higher risk of severe COVID-19 and increased mortality rates[14–16], the impact of hyperglycemia itself, rather than the presence of DM, has not been sufficiently described in non-critically patients hospitalized with COVID-19.

Therefore, our study sought to evaluate whether acute hyperglycemia at admission, independently of diabetes status,was associated with all-cause in-hospital mortality in a large cohort of patients with SARS-CoV-2 infection in Spain. Additionally, we explored the relationship between high BG and length of stay (LOS), ICU admission, and/or mechanical ventilation.

Methods

Study design and population

The SEMI-COVID-19Registry is an ongoing nationwide, multicenter, observational,retrospective cohort registryinvolving 109 hospitals in Spain. It includes consecutivepatients≥18 yearsof age hospitalized from March 1 to May 31, 2020, who wereadmittedwith COVID-19confirmed microbiologically by reverse transcription polymerase chain reaction (RT-PCR) testing of a nasopharyngeal sample, sputum or bronchoalveolar lavage samples. Exclusion criteria were subsequent admissions of the same patientand denialor withdrawal ofinformed consent.Patients were treated at their attending physician's discretion, according to local protocols and theirclinical judgement.

Registry information and data collection

Information on the registry is available in a previous published study, which includes all necessary details about procedures and describes the baseline characteristics of all patients included. Data are collected retrospectively and include approximately 300 variables grouped under variousheadings, such as epidemiological data, medical history and use of medications, symptoms and physical examination findings atadmission, laboratory anddiagnostic imaging tests,pharmacological treatment, and so on[17]. Patients were classified as diabetic when diabetes was present in the history profile or they took antidiabetic drugs before admission. The management of hyperglycemia during hospitalization was using insulin in basal bolus regimen according to local protocols.

The Spanish Agency of Medicines and Medical Devices (AEMPS, for its initials in Spanish) has ruled that due to the nature of the registry, the study only required the approval of Ethics Committees. The SEMI-COVID-19 Registry was approved by the Provincial Research Ethics Committee of Málaga (Spain).Informed consent was obtained from all patients. When it was not possible to obtain informed consent in writing due to biosafety concerns or if the patient had already been discharged, informed consent was requested verbally and noted on the medical record.The STROBE statement guidelines were followed in the conduct and reporting of the study.

Study outcomes

The primary endpoint was all-cause mortality during hospitalizationaccording to BG levels at admission. The secondary outcomes were LOS and the composite of theinvasive or non-invasivemechanical ventilation, ICU admission or death. The follow-up period was from admission to discharge or death.

Statistical Analysis

BG levels obtained from a sample taken at admission were categorized into three groups according to standard glycemic targets in hospitalized patients: <140 mg/dl, 140-180 mg/dl, and >180 mg/dl

. Hypoglycemia was defined as a BG level below 70 mg/dl. Baseline characteristics were described according to these groups. Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test.

Results are shown as means (standard deviation, SD) or medians (25th to 75th percentile) for continuous variables and numbers (%) for categorical variables.

To compare baseline demographic data and clinical characteristics among the BG level groups, we used analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables. Differences in proportions were analyzed using thechi-square test. Correlations between admission serum glucose levels and the main quantitative variableswere calculated using Spearman's rank correlation coefficient test. In addition, the association between BG levels and death was analyzed using Kaplan-Meier survivalcurves; the log-rank test wasused to compare survival curvesaccording tothe BG level groups. A multivariate Cox proportional hazard regression model with BG levels as the predictor variable for all-cause mortality was used to estimate hazard ratios (HR) with a 95% confidence interval (CI). Multivariate model was developed by using a forward stepwise method, including all variables with $p < 0.1$ on the univariate analysis. We also used a logistic regression to evaluate the relationship between BG levels and the composed secondary endpoint. All statistical analyses wereperformed using SPSSsoftware (version 26.0, Chicago, IL, USA). A two-sided p value < 0.05 was considered statistically significant.

Results

Baseline characteristics and correlation with blood glucose

Clinical characteristics were collected from a total of 11,312 participants out of the 12,826 confirmed cases of COVID-19included in the registry as of May 29, 2020. A flow chart illustrating patient inclusion is shown in figure 1.Baseline clinicalfeatures and the most relevant laboratory variables grouped according to admission BG levels are listed in table 1. Overall, the mean age was 67.06 years (SD 16.4) and 57.1% of patients were male. The prevalence of diabetes was 18.9%.

Patients with higher admission BG levels were older, predominantlymale, and more frequently had a prior history of diabetes, hypertension, and othercomorbidities. In addition, lymphocytes <800/mm^3, LDH >400 U/L, D-dimer >1000 ng/mL, and elevated serum creatinine and C-reactive protein (CRP)levels were more frequent in patients with elevated admission BG.No differences were found in serum ferritin or interleukin-6 levels according to admission BG levels, table 1.

Admission BG levels showed weak correlations with age (ρ=0.252, p<0.001), LDH (ρ=0.156, p<0.001), lymphocytes (ρ=-0.166, p<0.001), D-dimer (ρ=0.196, p<0.001), serum creatinine (ρ = 0.213, p<0.001), and CRP (ρ = 0.196, p<0.001).

Association between blood glucose and outcomes

In total, 2,289 (20.2%) patients died during hospitalization. Main outcomes according to BG levels are showed in table 2. All-cause mortality was higher in patients with admission BG levels >180 mg/dl (41.1%) compared to patients with levels of 140-180 mg/dl (33.0%) or <140 mg/dl (15.7%) (figure 2a). Indeed, there was a gradual increase in all-cause mortality as admission BG levels increased, and there were no differences in mortality rates within each category of BG levels between patients with or without a previous history of diabetes (figure 2a).

Kaplan-Meier survival curves according to admission BG levels are shownin figure 2b (log-rank p<0.001). Similarly, survival curves after classifying the cohort according to diabetes status did not show any changes (log-rank p<0.001), figure 2c and 2d.

After performing a multivariate stepwise Cox regression model adjusted for age, gender, hypertension, diabetes, COPD, dependency, lymphopenia, anemia (hemoglobin<10 g/dl), serum creatinine, CRP>60 mg/L, LDH>400 U/L, and D-dimer>1000 ng/ml, elevated admission BG levels remained a significant predictor of death compared to BG <140 mg/dl, with the following findings: BG >180 mg/dl (HR 1.50, 95%CI: 1.31-1.73; p<0.001) and BG 140-180 mg/dl (HR 1.48, 95%CI: 1.29-1.70; p< 0.001). In this model, age, male gender, hypertension, COPD, dependency/frailty, creatinine levels, CRP>60 U/L, and LDH>400 U/L were also independently associated with all-cause mortality (table 3).

LOS was slightly longer in patients with BG >180 mg/dl (12 days versus 11.5 days for BG 140-180 mg/dl and 11.1 days for BG <140 mg/dl; p< 0.011). Invasive or non-invasiveventilation and ICU admission were also associated with higher admission BG levels (table 2). Finally, admission BG levels were independently related to the composite outcome (ICU admission, mechanicalventilation, and/or death):BG >180 mg/dl (OR 2.02, 95%CI: 1.67-2.44; p<0.001) and BG 140-180 mg/dl (OR 1.70, 95%CI: 1.43-2.02; p<0.001) compared to BG <140 mg/dl (table 4).

Discussion

After analyzing the data from 11,312 consecutive non-critically patients with confirmed COVID-19admitted to Spanish hospitals, we found that the admission BG level was an independent predictor of all-cause mortality during hospitalization.

A small number of observational studies have analyzed the relationship betweenglycemic control and clinical outcomes in patients hospitalized due to COVID-19 with and without diabetes. All of them provide clinical evidence of a correlation between uncontrolled hyperglycemia with poor prognosis and a particularly high mortality rate[3–7]. To date, our study has included by far the greatest number of valid patients. Furthermore, our study was conducted according to defined admission BG levelgroups, thus preventing the inclusion of patients withhyperglycemia secondary to hospital management that may occur because of, for example, treatment with steroids. The above results were also confirmed in COVID-19 patients without a history of diabetes.

In a large retrospective study conducted by Zhu et al.[3] that included 7,337 patients with COVID-19 hospitalized among 19 hospital in Hubei province, China, patients with diabetes had a significantly higher mortality rate (7.8% versus 2.7%; HR 1.49, 95%CI: 1.13-1.96; $p=0.005$) than patients without diabetes.They also compared 528 patients with a history of poorly-controlled diabetes (defined as BG >180 mg/dl) to 282 well-controlled patients (BG 70-180 mg/dl),finding that well-controlled patients had markedly lower all-cause mortality during hospitalization compared to poorly-controlled patients (HR: 0.13, CI95%: 0.04-0.44, $p<0.001$).Similarly, our study also showed 1.63-fold increase inmortality in patients with diabetes on the univariate analysis. However, Zhu et al. did not include patients without diabetes in their study, so the effect of hyperglycemia in the non-diabetic population with COVID-19 cannot be analyzed.

A retrospective observational study (n=1,122) by Bode et al.[5] from 88 hospitals in the USAstudied the clinical outcomes of 451patients with diabetes (HbA1c≥6.5%) and/or uncontrolled hyperglycemia (defined as ≥2 BG values>180 mg/dl in a 24-hour period with HbA1c ≤6.5% or no A1c available)using data abstracted from Glytec's data warehouse.Among the 570 patients who died or were discharged, the mortality rate was 28.8% in the group with diabetes and/or uncontrolled hyperglycemia (n=184)compared to 6.2% inthe control group (n=386) ($p<0.001$). The mortality rate was particularly high amongpatients with uncontrolled hyperglycemiawithout diabetes (41.7%) compared topatients with diabetes(14.8%) ($p<0.001$). This finding is consistent with our results (a mortality rate of 43.3% in non-diabetic patients with admission BG >180 mg/dl). Overall, these findings suggest that stress hyperglycemia could play a crucial role in the prognosis of patients hospitalized with COVID-19.

Twoobservational studies conducted in Wuhan, China compared the relationship between hyperglycemia and outcomes in patients hospitalized with confirmed COVID-19.Zhang et al. [6]evaluated the relationship between hyperglycemia and outcomes in patients (n=166) hospitalized with confirmed COVID-19 with diabetes and secondary hyperglycemiaclassified into three groups: control (group 1: nohistory of diabetes and basal BG <126 mg/dl), secondary hyperglycemia (group 2: no history of diabetes andbasal BG ≥126 mg/dl and HbA1c <6.5%), and diabetes (group 3: basal BG ≥126 mg/dl and history of diabetes or HbA1c ≥6.5%). The mortality rates in groups 2 and 3 were significantly higher compared to group 1 (21.3%, 14.3%, and 9.5%, respectively; p<0.05 for both). The composite outcome of ICU admission, use of either invasive or non-invasive mechanical ventilation, or death occurred in 38.1% of patients in group 2 and in 27.9% of patients of group 3. After adjusted for confounding variables, the OR for composite outcomes were 5.47 (95%IC 1.56-19.82) and 2.61 (IC95% 0.86-7.88) in groups 2 and 3 compared to group 1.These results suggest that stress hyperglycemia is also related to poor prognosis and mortality in patients infected by SARS-CoV-2.

Wu et al.[7]collected data on 2,041 patients admitted to two medical centers. They compared non-critical patients at admission (n=1,690) to critical patients at the time of admission or at the time of transition from the non-critical group (n=697). Elevated admission BG levels (defined as admission BG ≥110 mg/dl) were an independent risk factor for progression to critical status (ICU admission, mechanical ventilation, compromised hemodynamic) or death among non-critical patients (OR 1.30; 95%CI 1.03-1.63, p=0.026). Higher median BG levels after a non-critical patient becomes criticalwere also independently associated with higher in-hospital mortality(OR 2.39; 95%CI 1.41-4.07, p=0.001). Similar to our results, hyperglycemia but not diabetes was associated to worse outcomes and death on the multivariate analysis.

Sardu et al.[4]studied 59 patientswith COVID-19 hospitalized in twoItalianhospitals. Patients were divided into ahyperglycemicgroup (n=25), defined as patients withadmission BG >140 mg/dl, and a normoglycemic group (n=34). In the hyperglycemic group, 18 (72%) patients had prior history of diabetes and 15 (60%) were treated with an insulin infusion until they reached a BG level <140 mg/dl. At baseline, interlukin-6 and D-dimer levels were also significantly higher in the hyperglycemic group than in the normoglycemic group ($p<0.001$). After adjusting the model for confounding variables, patients with hyperglycemia treated with an insulin infusion had a lower risk of complications than patients who did not receive an insulin infusion. Additionally, interleukin-6 and D-dimer levels were reduced after treating thehyperglycemia. The authors concluded that optimal glycemic control during hospitalization could be associated with reduced risk of severe disease and death.

Another recent study showed that COVID-19 patients with recently-diagnosed diabetes had the highest risk of all-cause mortality compared tothose who had diabetes for a longer time (HbA1c ≥6.5%), hyperglycemia, or normoglycemia[18]. Wang et al.[10] showed, in a relatively small sample (n=695),that fasting BG >126 mg/dl at admission was an independent predictor for 28-day mortality in patients without a previous diagnosis of diabetes.

Our study, which analyses the largest number of patientsof any study to date, isconsistent with all these results and reinforces the strong association foundbetween hyperglycemia and in-hospital mortalityin non-critically patients hospitalized with COVID-19, independently of prior history of diabetes.Acute hyperglycemia occurs in about 22% ofpatients hospitalized for COVID-19, while 18.9% of patients had diabetes, but 10% of them had admission BG < 140 mg/dl. Other data registry shows that acute hyperglycemia occurs in about 50%, while the prevalence of diabetes is about 7%[19].

One question that remains to be answered is whether hyperglycemia plays any role in the physiopathology of the disease or if it is just an inflammatory bystander. Apart from the glycosylation of ACE2 receptors that facilitates virus binding and the inflammatory process that increases insulin resistance, the hypoxia that is normally present in patients with COVID-19 is frequently accompanied by disordered cellular glucose metabolism.

Under anaerobic conditions, glucose ferments into lactate, which producesa limited amount of adenosine triphosphate (ATP). Hypoxia and ATP depletion cause an elevation of blood lactate and LDH levels. In our study, elevation of the LDH level was also associated with mortality according to BG levels, a finding that is consistent with the mechanism described above. This finding suggests that an early imbalance in glucose metabolism could be involved in a crucial manner in the physiopathology of the viral respiratory infection. Only one very small study suggests that supplemental oxygen at the earliest stages of COVID-19 could be useful in correcting ananaerobic glucose metabolism imbalance[20].Adequate oxygen delivery and blood glucose monitoring should be carried out for patients who are asked to remain at home in the early stages of the infection in order to prevent clinical deterioration.Early correction of hyperglycemia in the course of COVID-19 could result in a decrease in the release of inflammatory cytokines and a reduction in the virus' ACE binding capacity, consequently resulting in better outcomes[11].

Both strategies—screening forhyperglycemia in patients without diabetes and early treatment of hyperglycemia—should be mandatory in the managementofpatients hospitalized with COVID-19[21]. Unfortunately, insufficient evidence is available onthe benefits of strict glycemic control in patients hospitalized with COVID-19 due to the fact that glycemic management was underestimated during outbreak and the difficulties of multiple daily insulin injections and frequentpoint-of-care glucose testing in areas with high burden of COVID-19 patients[22,23].Thus, to date, early glycemiccontrol may be a suitable therapeutic option to reduce the pooroutcomes in hospitalized hyperglycemic COVID-19 patientswith or without a previous diabetes diagnosis[24].

This study has several limitations. First, it is anobservational retrospective cohort study conducted during an outbreak, so there may be residual or unmeasured confounding factors. Second, most patients did not have a HbA1c measurement and as such,some patients classified as non-diabetic could have unknown diabetes. Third, the registry is missing data on some relevantinflammatory variables such as interleukin-6, D-dimer, and serum ferritin. Finally, time from hospital admission to ICU admission was not available.

On the other hand, as a strengthen, our registry isthe largest available cohorts of non-critically ill hospitalized patients with confirmed COVID-19 in contrast to other studies focuses on critically patients and it includes data from over 11,000 patients on admission BG levels before starting any treatment.

In conclusion, our study foundthat admission hyperglycemia was an independent predictor ofprogression to critical condition and all-cause mortality in non-critically patients hospitalized with COVID-19. Moreover, this finding is independent of a prior history of diabetes. These results provided a simple and practical way to stratify risk of death in hospitalized patients with COVID-19. Hence, admission hyperglycemia should not be overlooked, but rather detected and appropriatelytreatedto improve the outcomes of COVID-19 patients with and without diabetes.

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Contribution statement: The research initiative and study concept were taken and designed by FJCS and AHJ. FJCS, FJMM, AHJ and RGH designed the present analysis. FJCS performed statistical analysis. FJCS, FJMM and RGH interpreted the data and drafted the manuscript.All authors interpreted the results, edited and revised the manuscript and read and approved the final version of the manuscript.

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Data availability: The steering committee of the Spanish SEMI-COVID-19 Registrywill consider reasonable requests for the sharing of data. Requests should be made to the corresponding author.

Conflict of interest: The authors hereby declare that they have no conflict of interest related to this article.

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Table 1: Baseline characteristics of SEMI-COVID-19 Registry participants, according to admission blood glucose levels.

Variables	**Patients with available data**	**Total N=11312**	**Admission BG <140 mg/dl N=8870 (78.41%)**	**Admission BG 140-180 mg/dl N=1340 (11.84%)**	**Admission BG >180 mg /dl N=1102 (9.74%)**	**p value**
Demographics						
Mean age in years (SD)	11312	67.06 (16.24)	65.2 (16.4)	73.34 (13.4)	74.31 (13.29)	<0.001
Gender, male	11312	6445 (57.1%)	5000 (56.4%)	752 (56.2%)	693 (62.9%)	<0.001
Medical History, n (%)						
Diabetes	11274	2125 (18.9%)	887 (10.0%)	512 (38.4%)	726 (66.0%)	<0.001
Hypertension	11291	5668 (50.2%)	3992 (45.1%)	879 (65.7%)	797 (72.5%)	<0.001
Dyslipidemia	11292	4466 (39.6%)	3125 (35.3%)	713 (53.3%)	628 (57.1%)	<0.001
Obesity	10285	2191 (21.3%)	1606 (19.9%)	314 (25.7%)	271 (27.3%)	<0.001
Dementia	11281	1128 (10.0%)	747 (8.4%)	183 (13.7%)	198 (18.0%)	<0.001
PAD	11280	540 (4.8%)	353 (4.0%)	90 (6.7%)	97 (8.8%)	<0.001
COPD	11287	793 (7.0%)	568 (6.4%)	130 (9.7%)	95 (8.6%)	<0.001
Atrial fibrillation	11280	1257 (11.1%)	878 (9.9%)	193 (14.5%)	186 (16.9%)	<0.001
CAD	11206	490 (4.4%)	293 (3.3%)	105 (7.9%)	92 (8.4%)	<0.001
Heart failure	11285	830 (7.4%)	543 (6.1%)	145 (10.8%)	142 (12.9%)	<0.001
CKD	11279	689 (6.1%)	431 (4.9%)	121 (9.1%)	137 (12.5%)	<0.001
Stroke	11228	815 (7.2%)	552 (6.2%)	111 (8.3%)	152 (13.8%)	<0.001
Dependent/frail patients	11162	1829 (16.4%)	1214 (13.9%)	303 (23%)	312 (28.8%)	<0.001
Previous Diabetes Treatment, n (%)						
Metformin	2124	1270 (59.8%)	531 (59.8%)	317 (62,2%)	422 (58.1%)	0.360
iDPP4	2082	649 (31.2%)	207 (23.9%)	161 (32.2%)	281 (39.2%)	<0.001
iSGLT2	2115	61 (2.9%)	28 (3.2%)	17 (3.3%)	16 (2.2%)	0.424
arGLP1	2087	108 (5.2%)	45 (5.2%)	28 (5.6%)	35 (4.9%)	0.872
Insulin	2112	121 (5.7%)	43 (4.9%)	38 (7.5%)	40 (5.6%)	0.132
Charlson Index	10971	3 (1-5)	3 (1-5)	4 (3-6)	5 (4-7)	<0.001
Blood Count						
Lymphocyte count (10^6(L)	11272	940(700-1300)	990 (700-1300)	865 (600-1200)	810 (540-1200)	<0.001
< 800, n (%)		*4417 (39.0%)*	*3244 (36.7%)*	*631 (47.2%)*	*542 (49.5%)*	<0.001
800-1200, n (%)		*3611 (31.9%)*	*2929 (33.1%)*	*400 (29.9%)*	*282 (25.7%)*	
>1200, n (%)		*3244 (28.7%)*	*2667 (30.2%)*	*305 (22.8%)*	*272 (24.8%)*	
Hemoglobin (g/dL)	11297	13.7 (1.89)	13.80 (1.83)	13.49 (2.01)	13.34 (2.1)	<0.001
Biochemistry						
Glucose (mg/dl),	11312	127.04 (57.8)	106.08 (16.09)	156.84 (11.68)	259.57 (99.49)	<0.001
Creatinine (mg/dl)	11285	0.90(0.74-1.16)	0.81 (0.67-1.0)	0.88 (0.7.1.18)	0.94 (0.7-1.38)	<0.001
Urea (mg/dl),	9082	37 (27-55)	35 (26-49)	44 (31-67)	55 (37.89)	<0.001
Sodium (meq/L),	11267	137.5 (4.68)	137.6 (4.2)	137.2 (5.2)	137.1 (6.8)	<0.001
Potassium (meq/L)	11046	4.12 (0,56)	4.1 (0.53)	4.1 (0.14)	4.3 (0.68)	<0.001
LDH (U/L)	9817	313 (243-417)	308 (239-406)	336 (256-454)	333 (255-465)	<0.001
<250, n (%)		*2756 (24.4%)*	*2276 (29.3%)*	*270 (23.6%)*	*210 (23%)*	<0.001
250-400, n (%)		*4331 (38.3%)*	*3471 (44.7%)*	*471 (41.2%)*	*389 (42.6%)*	
>400, n (%)		*2730 (24,1%)*	*2013 (25.9%)*	*403 (35.2%)*	*314 (34.4%)*	
C-reactive protein (mg/L)	10853	58.4 (18-126)	54 (17-116)	83 (24-160)	80 (26-161)	<0.001
D-dimer (ng/mL)	8726	630 (359-1176)	588 (338-1063)	830 (454-1530)	945(511-2108)	<0.001
<500, n (%)		*3452 (30.5%)*	*2966 (43%)*	*290 (28.6%)*	*196 (24.1%)*	<0.001
500-1000, n (%)		*2615 (23.1%)*	*2076 (31.1%)*	*306 (30.1%)*	*233 (28.7%)*	
>1000, n (%)		*2659 (23.5%)*	*1856 (26.9%)*	*419 (41.3%)*	*384 (47.2%)*	
Serum ferritin (mcg/L)	4400	611 (291-1214)	598 (286-1200)	692 (317-1344)	639(305-1253)	**0.070**
Interleukin-6 (pg/mL)	1621	29.8 (11.0-64.4)	29.8 (11.7-63.9)	33.6 (6.9-73.4)	25.4 (10.4-57.8)	**0.815**
Treatment, n (%)						
Hydroxychloroquine	11241	9680 (86.1%)	7729 (87.6%)	1089 (82%)	862 (78.8%)	<0.001
Lopinavir/Ritonavir	11226	6986 (62.2%)	5633 (64.0%)	748 (56.3%)	605 (55.5%)	<0.001
Tocilizumab	11198	1000 (8.9%)	757 (8.6%)	130 (9.9%)	113 (10.4%)	0.074
Systemic Steroids	11312	3950 (35.3%)	2875 (32.7%)	698 (45.9%)	467 (42.8%)	<0.001

Quantitative variables are shown as mean (standard deviation) or median (25th percentile-75th percentile). PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CKD, chronic kidney disease; LDH: lactate dehydrogenase.

Table 2: Outcomes according to admission blood glucose levels.

Variables	Patients with available data	Total N=11312	Admission BG <140 mg/dl N=8870	Admission BG 140-180 mg/dl N=1340	Admission BG >180 mg /dl N=1102	p value
Outcomes, n (%)						
Death	11312	2289 (20.2%)	1394 (15.7%)	442 (33.0%)	453 (41.1%)	<0.001
Mechanical ventilation	11217	1156 (10.2%)	790 (9%)	190 (14.3%)	176 (16.1%)	<0.001
ICU Admission	11299	935 (8.3%)	668 (7.5%)	142 (10.6%)	125 (11.4%)	<0.001
Composited Endpoint	11240	2978 (26.3%)	1911 (21.7%)	534 (40%)	533 (48.6%)	<0.001
Length of Stay, days	11312	11.29 (9.39)	11.1 (9.1)	11.5 (9.8)	12.01 (10.6)	0.011

ICU: intensive care unit; composited endpoint: death, mechanical ventilation, and/or ICU admission.

Table 3:
Association with all-cause in-hospital mortality. Adjusted multivariate Cox regression Model.

	Univariate Analysis		**Multivariate Analysis**	
Variables	**HR (CI95%)**	**p value**	**HR (CI95%)**	**p value**
Age	1.067 (1.063-1.071)	< 0.001	1.055 (1.049-1.061)	< 0.001
Admission blood glucose				
<140 mg/dl	1		1	
140-180/dl	1.96 (1.75-2.19)	< 0.001	1.48 (1.29-1.70)	< 0.001
>180 mg/dl	2.30 (2.03-2.60)	< 0.001	1.50 (1.31-1.73)	< 0.001
Male	1.14 (1.05-1.24)	0.002	1.15 (1.03-1.30)	0.013
Hypertension	2.20 (2.01-2.41)	<0.001	1.14 (1.01-1.29)	0.029
Diabetes	1.63 (1.49-1.79)	<0.001		0.377
COPD	1.82 (1.61-2.05)	<0.001	1.27 (1.08-1.49)	<0.003
Dependency/frailty	3.21 (2.95-3.50)	<0.001	1.58 (1.39-1.80)	<0.001
Lymphopenia <800 (10^6/L)	1.76 (1.58-1.96)	<0.001		0.868
Hemoglobin <10 g/dl	1.77 (1.52-2.07)	<0.001		0.630
Creatinine mg/dl	1.25 (1.22-1.28)	<0.001	1.33 (1.30-1.37)	<0.001
CRP >60 mg/L	2.13 (1.94-2.33)	<0.001	1.65 (1.47-1.85)	<0.001
LDH >400 U/L	2.73 (2.38-3.14)	<0.001	2.53 (2.51-2.97)	<0.001
D-dimer >1000 ng/ml	2.60 (2.29-2.95)	<0.001		0.149

OR, odds ratio; COPD, chronic obstructive pulmonary disease; CRP, protein-C reactive; LDH, lactate dehydrogenase. The model included all variables of medical history and laboratory findings

Table 4: Association with composite outcome (death, mechanical ventilation, and/or ICU admission). Adjusted multivariate logistic regression model.

	Univariate Analysis		**Multivariate Analysis**	
Variables	**OR (CI95%)**	**p value**	**OR (CI95%)**	**p value**
Age	1.050 (1.046-1.053)	<0.001	1.024 (1.019-1.029)	<0.001
Admission blood glucose				
<140 mg/dl	1		1	
140-180 mg/dl	2.40 (2.13-2.71)	<0.001	1.70 (1.43-2.02)	<0.001
>180 mg/dl	3.41 (2.99-3.88)	<0.001	2.02 (1.67-2.44)	<0.001
Male	1.37 (1.25-1.49)	<0.001	1.13 (0.99-1.28)	0.066
Hypertension	2.08 (1.91-2.27)	<0.001	NS	0.226
Diabetes	1.86 (1.69-2.067)	<0.001	NS	0.618
COPD	2.34 (2.02-2.71)	<0.001	1.59 (1.28-1.99)	<0.001
Dependency/frailty	2.28 (2.96-3.64)	< 0.001	1.97 (1.66-2.32)	< 0.001
Lymphopenia <800	2.69 (2.41-3.01)	<0.001	1.85 (1.57-2.17)	<0.001
Hemoglobin <10 g/dl	2.46 (2.03-2.99)	<0.001	NS	0.212
Creatinine mg/dl	1.76 (1.66-1.88)	<0.001	1.33 (1.24-1.42)	<0.001
CRP >60 mg/L	2.61-2.38-2.85)	<0.001	1.69 (1.63-2.35)	<0.001
LDH >400 U/L	5.17 (4.51-5.92)	<0.001	4.78 (3.97-5.75)	<0.001
D-dimer >1000 ng/ml	3.04 (2.69-3.43)	<0.001	1.23 (1.05-1.43)	0.008

OR, odds ratio; COPD, chronic obstructive pulmonary disease; CRP, protein-C reactive; LDH, lactate dehydrogenase. The model included all variables of medical history and laboratory findings.

Legends for figures

Figure 1: Patient Inclusion Flow-Chart

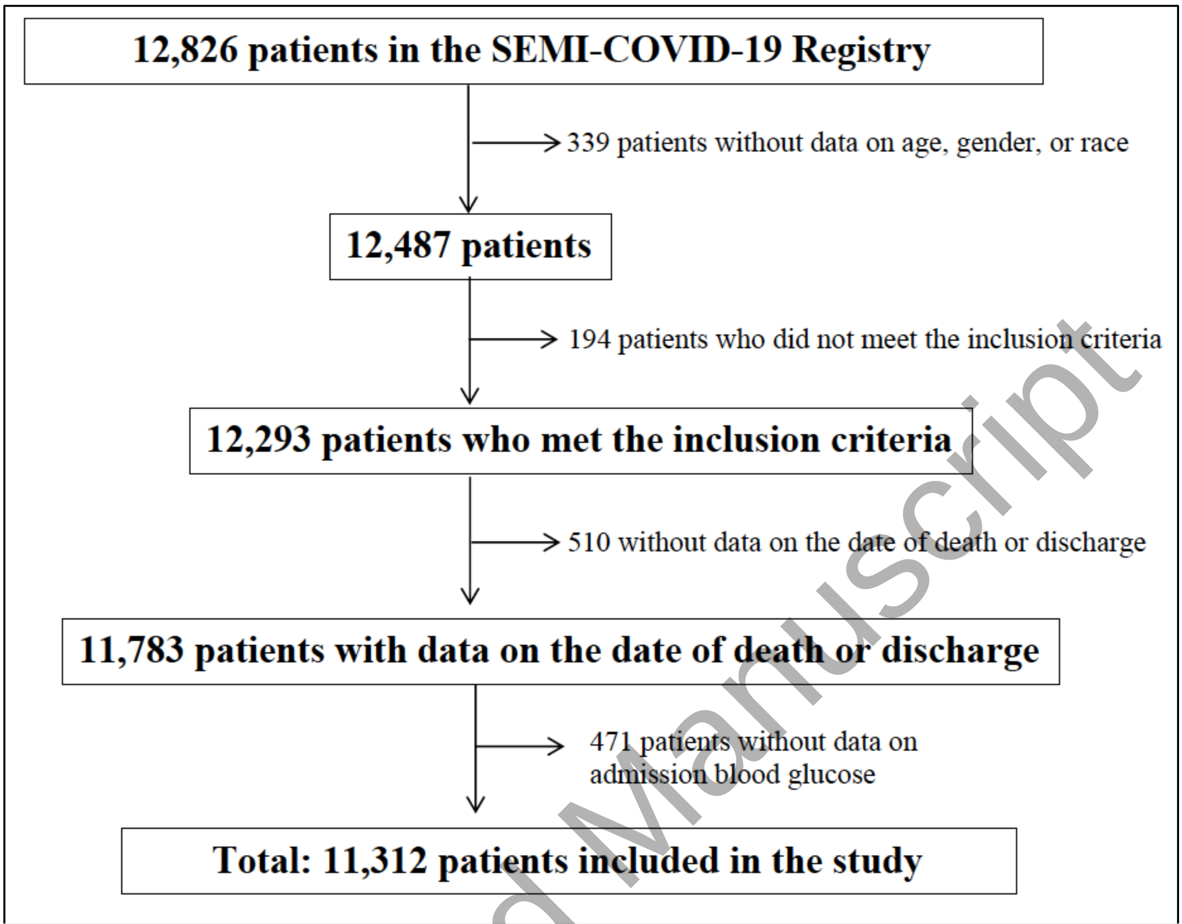

Figure 2: All-cause mortality (%) during hospitalization according to admission BG groups in all patients and based on the diabetes status, p value <0.0001 (a). Kaplan-Meier curves according to admission BG levels in all patients (b) and in patients with diabetes (c) and without diabetes (c). BG <140 mg/dl (upper line), BG 140-180 mg/dl (middle line), BG >180 mg/dl (lower line). Log rank p<0.0001 for all curves.