Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control?

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OBJECTIVE

An important prognostic factor in any form of infection seems to be glucose control in patients with type 2 diabetes. There is no information about the effects of tight glycemic control on coronavirus disease 2019 (COVID-19) outcomes in patients with hyperglycemia. Therefore, we examined the effects of optimal glycemic control in patients with hyperglycemia affected by COVID-19.

RESEARCH DESIGN AND METHODS

Fifty-nine patients with COVID-19 hospitalized with moderate disease were evaluated. On the basis of admission glycemia >7.77 mmol/L, patients were divided into hyperglycemic and normoglycemic groups. Interleukin 6 (IL-6) and D-dimer levels were evaluated at admission and weekly during hospitalization. The composite end point was severe disease, admission to an intensive care unit, use of mechanical ventilation, or death.

RESULTS

Thirty-four (57.6%) patients were normoglycemic and 25 (42.4%) were hyperglycemic. In the hyperglycemic group, 7 (28%) and 18 (72%) patients were diagnosed with diabetes already before admission, and 10 (40%) and 15 (60%) were treated without and with insulin infusion, respectively. The mean of glycemia during hospitalization was 10.65 ± 0.84 mmol/L in the no insulin infusion group and 7.69 ± 1.85 mmol/L in the insulin infusion group. At baseline, IL-6 and D-dimer levels were significantly higher in the hyperglycemic group than in the normoglycemic group (*P* < 0.001). Even though all patients were on standard treatment for COVID-19 infection, IL-6 and D-dimer levels persisted higher in patients with hyperglycemia during hospitalization. In a risk-adjusted Cox regression analysis, both patients with hyperglycemia and patients with diabetes had a higher risk of severe disease than those without diabetes and with normoglycemia. Cox regression analysis evidenced that patients with hyperglycemia treated with insulin infusion had a lower risk of severe disease than patients without insulin infusion.

CONCLUSIONS

Insulin infusion may be an effective method for achieving glycemic targets and improving outcomes in patients with COVID-19.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) pandemic, which has affected >150,000 individuals and is the cause of ~24,000 deaths in Italy as of this writing, representing almost 10% of infected patients. Furthermore, 5–10% of patients with COVID-19 require intensive care unit (ICU) admission and mechanical ventilation (https://www.epicentro.iss.it). Hyperglycemia (defined as a blood glucose level >7.77 mmol/L) can occur in both patients with and patients without diabetes hospitalized for COVID-19 and is common among acute hospital admissions and critically ill patients, encompassing those with no previous history of hyperglycemia (1,2). However, precise numbers on the prevalence and incidence of this stress hyperglycemia during infection are limited. In one study, patients with infectious diseases without underlying diabetes had average plasma glucose values of 10.77 ± 3.66 mmol/L in the absence of nutritional support, and >50% of all patients developed stress-induced hyperglycemia (3). Moreover, several studies demonstrated that admission hyperglycemia was associated with an increase of poor outcomes and mortality in hospitalized patients presenting with an infectious disease (4). Possible mechanisms for this increased mortality include hyperglycemia-induced changes in coagulation, worsening of endothelial function, and inflammatory cytokine overproduction. Indeed, our group demonstrated that healthy subjects and patients with impaired glucose tolerance have inflammatory cytokines interleukin (IL) 6, tumor necrosis factor-α (5), and D-dimer (6) overproduction following the appearance of hyperglycemia. Interestingly enough, COVID-19 infection is associated with severe pneumonia disease, disseminated intravascular coagulation, and septic shock with strong increases in plasma IL-6 (7) and D-dimer (8) levels. Thus, elevated blood glucose may worsen the prognosis of patients with COVID-19, raising the risk for mechanical ventilation, shock, and multiple organ failure necessitating ICU treatment. Thus, the absolute burden of infection attributable to poor glycemic control in this population would be substantial. In this context, a central question is should patients with hyperglycemia be treated with more attention to glycemic control during the COVID-19

infection? The Standards of Medical Care in Diabetes recently developed by the American Diabetes Association (ADA) recommend the range of 7.77–9.99 mmol/L as a target level of blood glucose for the majority of critically ill patients (9). In addition, the recommendation from the Surviving Sepsis Campaign showed that ≤9.99 mmol/L should be targeted in the management of blood glucose (10). Finally, the recommendations suggest that it is reasonable to consider intensive glucose control, with insulin infusion, in patients with significant hyperglycemia (plasma glucose >9.99 mmol/L), regardless of prior diabetes history. To date, it is unclear whether tight glycemic control (blood glucose range 7.77–9.99 mmol/L) is effective and warranted in patients with COVID-19 with moderate disease. Therefore, our study evaluated whether hyperglycemia is associated with a further increase in plasma inflammatory cytokine (IL-6) levels and coagulation activation (as monitored by plasma D-dimer levels) in hospitalized patients with COVID-19. Moreover, we evaluated whether poor glycemic control was associated with poor outcomes and whether early optimal glycemic control along with hospitalization reduces plasma IL-6 and D-dimer levels, thus improving outcomes for hospitalized patients with COVID-19.

RESEARCH DESIGN AND METHODS

Patients
We analyzed 187 patients positive for COVID-19 admitted to the Infection Disease Departments of Vanvitelli University and San Sebastiano Caserta Hospital since 20 February 2020. Among them, we selected 59 patients with moderate pneumonia disease (Fig. 1). COVID-19 infection was categorized as follows (11): mild (patients with fever and no evidence of pneumonia on imaging), moderate (patients with fever, respiratory tract symptoms, and pneumonia on imaging without the need for invasive ventilation), and critical (occurrence of respiratory failure requiring mechanical ventilation, presence of shock, other organ failure that requires monitoring, and treatment in the ICU). Patients with previous inflammatory disorders, malignancy, renal diseases, or infections as well as patients with critical COVID-19 infection at admission were not eligible for the study. All patients were treated with standard protocol, including noninvasive oxygen

therapy, hydroxychloroquine 200 mg (1 × 2/day), and lopinavir/ritonavir cps 200/50 mg. Patients were categorized as normoglycemic and hyperglycemic as well as with or without diabetes on the basis of a diagnosis preceding the current illness (9). Hyperglycemia was defined as an admission plasma glucose level of >7.7 mmol/L (9). Although intravenous infusion insulin is currently the most effective method for controlling glucose among hospitalized patients, there is insufficient evidence for recommending or discouraging its early infusion (level of evidence C). Therefore, after describing the possible risks and benefits of insulin infusion therapy, patients voluntarily decided whether to receive insulin infusion therapy. Continuous insulin infusion of 50 IU Actrapid HM (Novo Nordisk) in 50 mL NaCl (0.9% using a Perfusor fm pump) was started when blood glucose levels were >9.9 mmol/L and adjusted to keep blood glucose between 7.77 and 9.99 mmol/L. When blood glucose fell to <7.7 mmol/L, insulin infusion was tapered and eventually stopped. After the start of the insulin infusion protocol, a glycemic control was provided every hour to obtain three consecutive values that were within the goal range. The infusion lasted until stable glycemic goal and at least for 24 h. Thereafter, subcutaneous insulin was initiated at the cessation of the infusion in the infusion group and at admission into the no insulin infusion group. Short-acting insulin was given before meals, and intermediate long-acting insulin was given in the evening. Patients with previous diabetes stopped at admission oral antidiabetic drugs, such as metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, sodium–glucose cotransporter 2 inhibitors, and glucagon-like peptide 1 agonists. The investigation conformed with the principles outlined in the Declaration of Helsinki for use of human tissue or subjects. The study protocol was approved by the institutional ethics committees. Written informed consent was obtained from all patients.

Laboratory and Imaging Evaluations
Real-Time RT-PCR Assay for SARS-CoV-2
Respiratory specimens were collected by the local center for disease control and then shipped to designated authoritative laboratories to detect SARS-CoV-2. The presence of SARS-CoV-2 in respiratory specimens was detected by real-time RT-PCR methods.
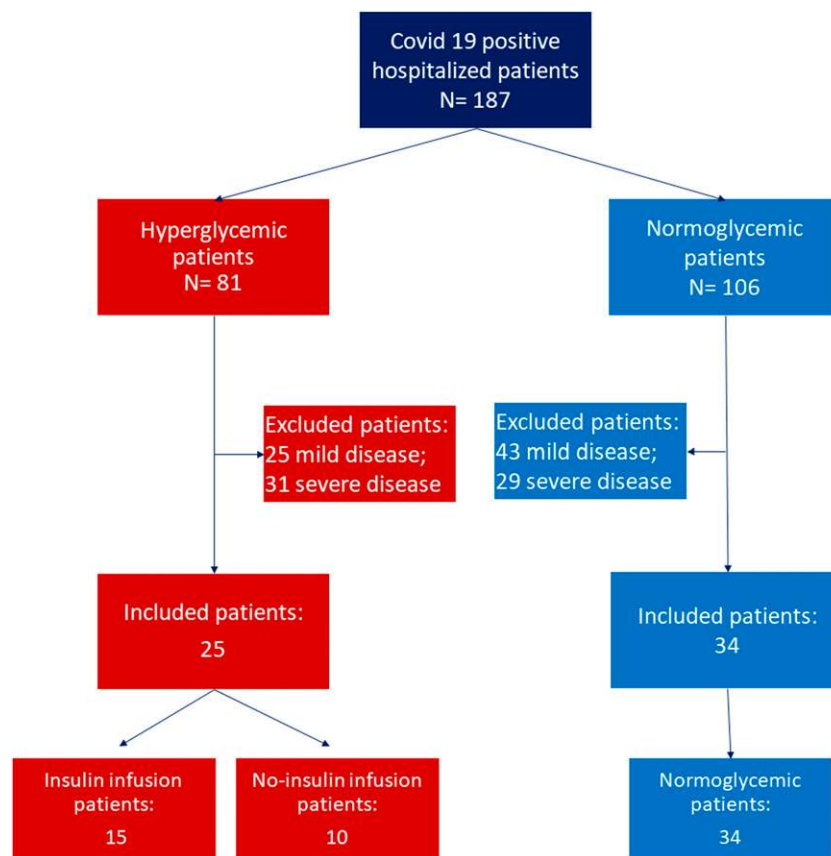
Figure 1—Flowchart of study population.

Laboratory analyses were obtained on admission before starting COVID-19 medical therapy and during hospitalization.

Clinical Laboratory Measurements

Respiratory specimens, including nasal and pharyngeal swabs or sputum, were tested to exclude evidence of other viral infections, including influenza, respiratory syncytial virus, avian influenza, parainfluenza, and adenovirus. Routine bacterial and fungal examinations were also performed. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, and measures of electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, and creatine kinase. Venous blood for IL-6 (Human Quantikine ELISA Kit; R&D Systems) and D-dimer (Human ELISA Kit; Invitrogen) levels were collected in EDTA-coated tubes immediately after patients arrived at the department and weekly during hospitalization. Radiologic assessments included chest radiography or computed tomography (CT) at admission and weekly during hospitalization, and all laboratory testing was

performed according to the clinical care needs of the patient. We determined the presence of a radiologic abnormality on the basis of the documentation or description in medical charts; if imaging scans were available, they were reviewed by attending physicians in respiratory medicine who extracted the data. Major disagreement between two reviewers was resolved by consultation with a third reviewer.

Study Outcomes

The composite end point was admission to an ICU, the use of mechanical ventilation, or death. These outcomes were used in a previous study to assess the severity of COVID-19 infectious disease (12).

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs) or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. Because the cohort of patients in our study was not derived from random selection, all statistics are deemed to be descriptive only. Risk-adjusted Cox regression analysis curves show survival from severe disease through

days of hospitalization. Cox models were adjusted for age, sex, BMI, blood pressure, heart rate, cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels, heart disease, hypertension, dyslipidemia, current smoking, β-blockers, ACE inhibitors, calcium inhibitors, thiazide diuretics, and aspirin. Kaplan-Meier survival analysis was performed in patients divided into the following groups: normoglycemia without diabetes, normoglycemia with diabetes, hyperglycemia without diabetes, and hyperglycemia with diabetes. $P < 0.05$ was considered statistically significant. All calculations were performed using SPSS version 23 statistical software.

RESULTS

Baseline Characteristics of Patients on Admission and Outcome

All patients had moderate COVID-19 disease (fever, respiratory tract symptoms, pneumonia on imaging) without the need for invasive ventilation. All were treated with the standard COVID-19 protocol, including oxygen therapy, hydroxychloroquine, and antiviral treatment (Table 1). Of the 59 study patients, 34 (57.6%) were normoglycemic and 25 (42.4%) were hyperglycemic (glucose >7.7 mmol/L). At admission, glycemia was 6.3 ± 0.66 mmol/L in patients with normoglycemia and 11.04 ± 1.22 mmol/L in those with hyperglycemia. Eight (23.5%) patients with normoglycemia and 18 (72%) with hyperglycemia had a diagnosis of diabetes before hospitalization. There were no differences in the mean age, sex, BMI, sex distribution, smoking habits, levels of plasma cholesterol, and triglycerides among the groups. The use of diuretics, ACE inhibitors, statins, and calcium channel blocker therapy was similar in all study groups (Table 1). β-Blocker use was almost twice as frequent in patients with hyperglycemia compared with those with normoglycemia, and the use of angiotensin receptor blockers tended to be greater in those with an elevated glucose (Table 1). Among patients with a diagnosis of diabetes before hospitalization, there were no differences in antidiabetic drugs being taken (eg, insulin, oral drugs) when they were categorized as hyperglycemic and normoglycemic (Table 1). The median time from illness onset (before admission) to discharge or death was 18 days (IQR 14–20) in patients with hyperglycemia and 16 days (IQR 14–19) in patients with normoglycemia. At admission, IL-6 and

Table 1—Baseline clinical characteristics of patients with COVID-19

	Patients with normoglycemia	Patients with hyperglycemia	P value	Hyperglycemia without insulin infusion	Hyperglycemia with insulin infusion	P value
Patients	34 (57.6)	25 (42.4)		10 (40)	15 (60)	
Age (years)	66.6 ± 11.5	68.5 ± 5.8	0.468	68.9 ± 6.0	68.2 ± 5.9	0.776
Sex (M/F), n	28/6	20/5		8/2	12/3	
BMI (kg/m^2)	27.9 ± 1.6	27.5 ± 1.3	0.251	27.3 ± 1.4	27.6 ± 1.3	0.599
Systolic BP (mmHg)	122.4 ± 8.5	116.2 ± 5.4	0.002	115.9 ± 5.8	116.3 ± 5.3	0.849
Diastolic BP (mmHg)	79.3 ± 6.6	79.9 ± 7.1	0.769	81.7 ± 5.6	78.7 ± 7.8	0.301
Heart rate (bpm)	86.4 ± 6.0	88.4 ± 11.6	0.413	93.1 ± 11.6	85.2 ± 10.9	0.097
Risk factors						
Diabetes	8 (23.5)	18 (72)	0.001	7 (70)	11 (73.3)	0.601
Heart disease	7 (20.6)	5 (20)	0.129	2 (20)	3 (20)	0.488
Hypertension	26 (76.5)	18 (72)	0.462	8 (80)	10 (66.7)	0.399
Hyperlipemia	9 (26.5)	6 (24.4)	0.538	2 (20)	4 (26.7)	0.545
Cigarette smoking	6 (17.6)	5 (20)	0.539	2 (20)	3 (20)	0.687
Active treatments						
β-Blockers	12 (35.3)	17 (68)	0.013	6 (60)	11 (73.3)	0.393
ACE inhibitors	13 (38.2)	10 (40)	0.551	6 (60)	4 (26.7)	0.106
ARBs	13 (38.2)	15 (60)	0.082	6 (60)	9 (60)	0.663
Calcium inhibitors	6 (17.6)	6 (24)	0.390	3 (30)	3 (20)	0.455
Statins	19 (55.9)	9 (36)	0.106	6 (60)	3 (20)	0.053
Thiazide diuretics	7 (20.6)	5 (20)	0.610	1 (10)	4 (26.7)	0.313
Insulin	4 (11.8)	3 (12)	0.287	1 (10)	2 (20)	0.468
Oral antidiabetic drugs	7 (20.6)	17 (68)	0.052	7 (70)	10 (66.7)	0.118
Aspirin	29 (85.3)	23 (92)	0.359	9 (90)	14 (93.3)	0.650
Low-molecular-weight heparin	6 (17.6)	6 (24)	0.390	2 (20)	4 (26.7)	0.545
Laboratory analyses						
Plasma glucose (mmol/L)	6.3 ± 0.99	11.04 ± 2.06	<0.001	11.06 ± 1.98	12.32 ± 1.48	0.792
Cholesterol (mg/dL)	209.2 ± 16.9	203.2 ± 22.1	0.244	200.6 ± 15.6	205.0 ± 25.9	0.637
LDL-C (mg/dL)	136.1 ± 16.7	129.5 ± 20.9	0.185	126.5 ± 15.1	131.5 ± 24.4	0.562
HDL-C (mg/dL)	36.1 ± 2.9	37.1 ± 4.1	0.257	39.6 ± 4.4	37.1 ± 4.0	0.892
Triglycerides (mg/dL)	187.1 ± 23.9	190.9 ± 28.1	0.577	186.2 ± 21.1	194.1 ± 32.2	0.501
Creatinine (mg/dL)	1.0 ± 0.18	0.9 ± 0.15	0.083	0.9 ± 0.14	0.9 ± 0.15	0.555
COVID-19 treatments						
Antiviral drugs	33 (97.1)	24 (96)	0.436	10 (100)	14 (93.3)	0.880
Hydroxychloroquine	34 (100)	25 (100)	—	10 (100)	15 (100)	—
Antibiotics	33 (97.1)	25 (100)	0.985	10 (100)	15 (100)	—
Oxygen therapy	8 (23.5)	6 (24)	0.744	2 (20)	3 (20)	0.455

Data are mean ± SD or n (%) unless otherwise specified. ARB, angiotensin receptor blocker; BP, blood pressure; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

D-dimer levels were higher in patients with hyperglycemia than in those with normoglycemia ($P < 0.001$) (Fig. 2). Moreover, both IL-6 and D-dimer levels were correlated with admission blood glucose levels (Fig. 2). All patients had interstitial lung abnormalities on chest CT scans once admitted. In all patients, the typical findings of chest CT images of COVID-19 on admission showed bilateral ground glass opacity without subsegmental areas of consolidation or mass shadows. Subsequent chest CT images (7 days later) revealed that pneumonia disease progressed with subsegmental areas of consolidation and with mass shadows of high density in both lungs in 10 (40%) patients with hyperglycemia and

3 (8.8%) with normoglycemia ($P < 0.01$). The composite end point occurred in 13 (52%) patients with hyperglycemia and 5 (14.7%) with normoglycemia ($P < 0.01$). Further details regarding the individual components are provided in Supplementary Table 1. In a risk-adjusted Cox regression analysis, both patients with diabetes and patients with hyperglycemia had a higher risk of severe disease than patients without diabetes and normoglycemia (Fig. 3). Moreover, in Kaplan-Meier survival analysis, small numbers of patients with hyperglycemia with or without previous diabetes were free from severe disease compared with patients with normoglycemia without previous diabetes ($P < 0.02$) (Fig. 3).

Glucose-Lowering Treatment and Outcome

Among the 25 (42.4%) patients with glycemic levels >7.7 mmol/L, 15 were treated with insulin infusion. Eleven (44%) patients with diabetes who were hyperglycemic and 4 (11.8%) patients without diabetes who were hyperglycemic were treated with insulin infusion. There were no statistically significant differences in clinical and laboratory data among patients treated with or without insulin infusion (Table 1). At admission, blood glucose levels were 12.32 ± 1.48 mmol/L in insulin infusion–treated patients and 11.06 ± 1.98 mmol/L in no insulin infusion–treated patients. In the insulin infusion group, the mean time
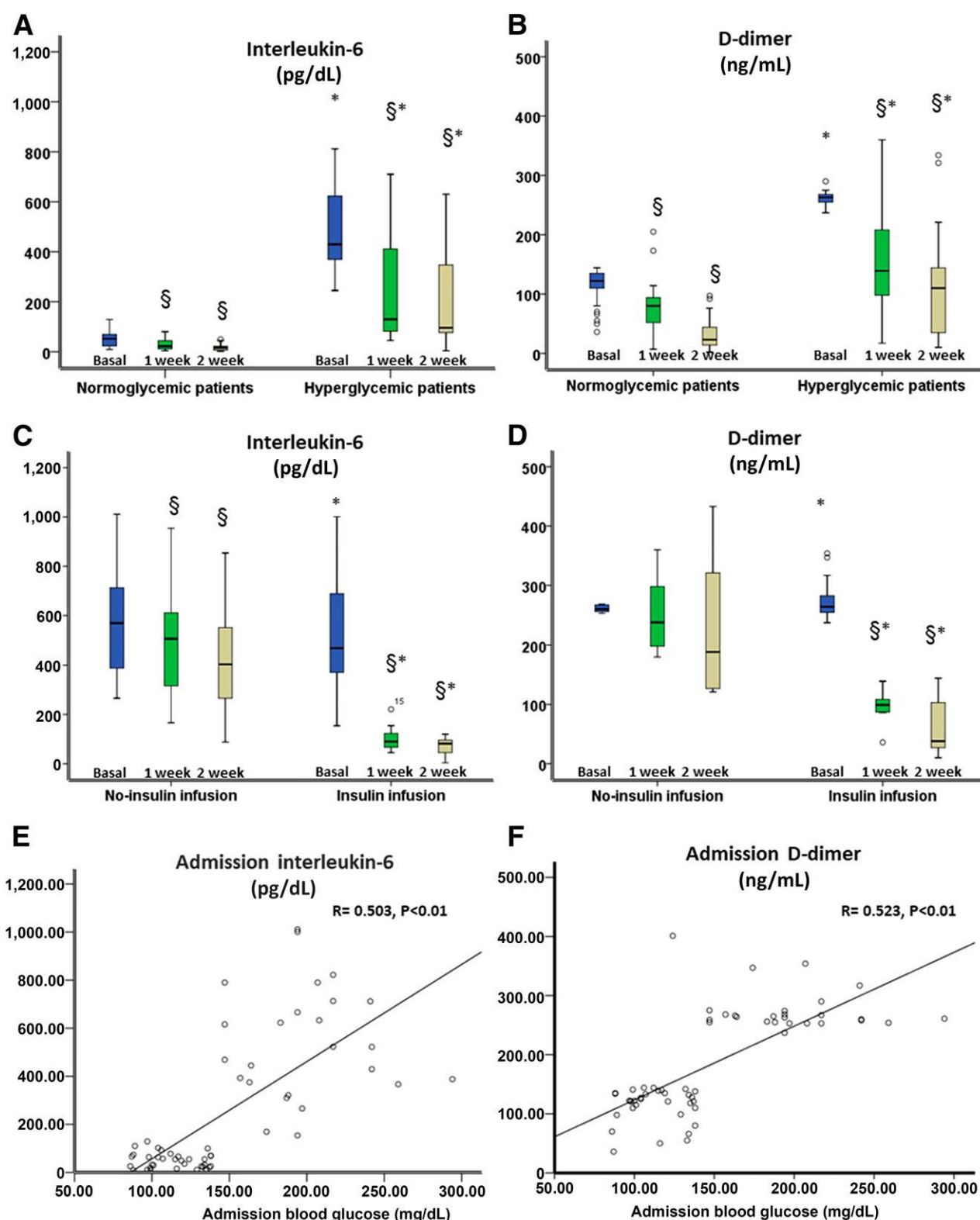
Figure 2—*A*: IL-6 levels at admission, 1 week, and 2 weeks and after hospitalization in patients with hyperglycemia and normoglycemia. *B*: D-dimer levels at admission, 1 week, and 2 weeks and after hospitalization in patients with hyperglycemia and normoglycemia. *C*: IL-6 levels at admission, 1 week, and 2 weeks and after hospitalization in patients with hyperglycemia treated with insulin infusion and those not treated with insulin infusion. *D*: D-dimer levels at admission, 1 week, and 2 weeks and after hospitalization in patients with hyperglycemia treated with insulin infusion and those not treated with insulin infusion. For panels *A*–*D*, box plots display the median, 25th and 75th percentiles, and range. *E*: Regression analysis between admission blood glucose levels and admission IL-6 levels. *F*: Regression analysis between admission blood glucose levels and admission D-dimer levels. *$P < 0.05$ vs. normoglycemia and vs. baseline values. §$P < 0.05$ vs. baseline.
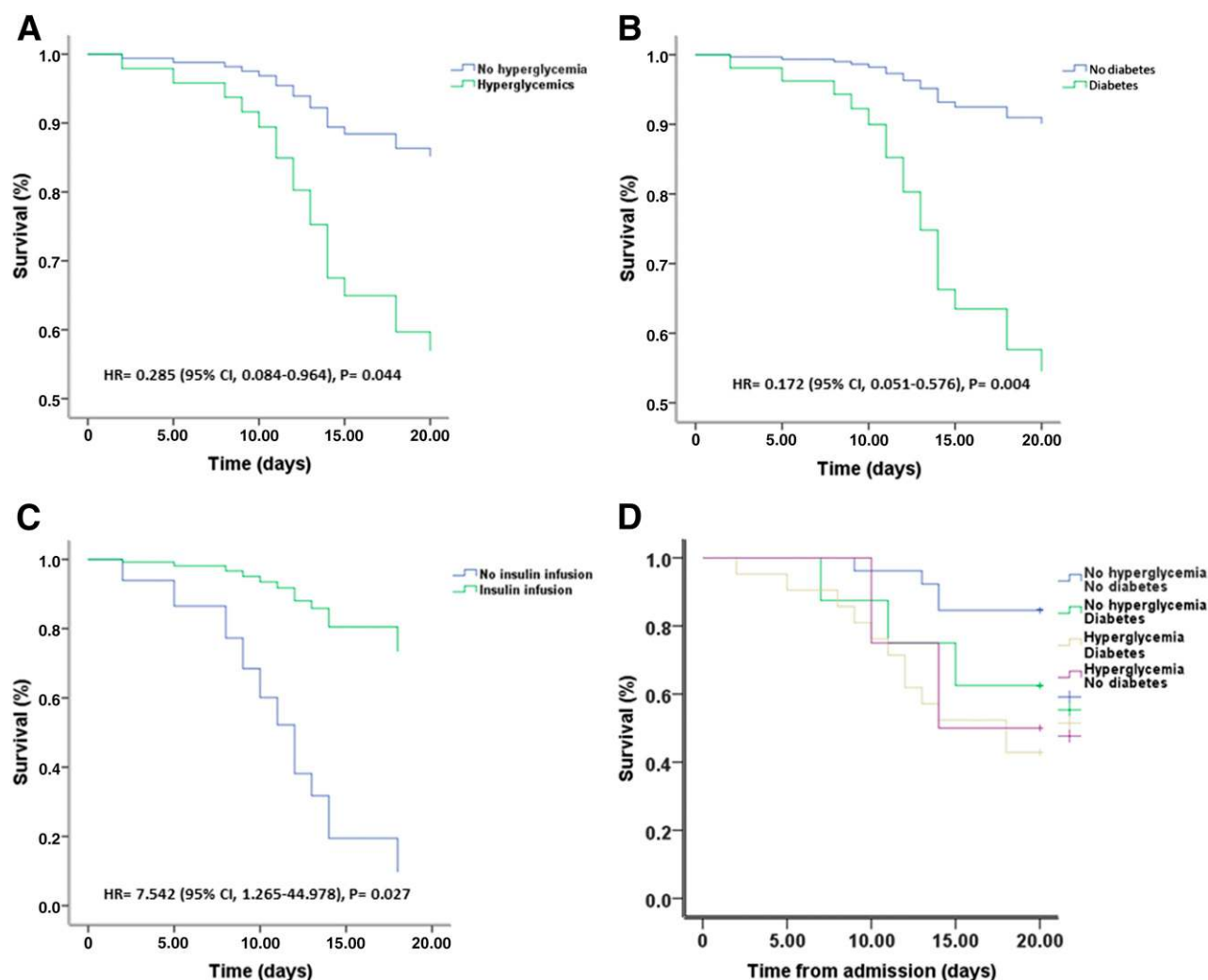
A

HR= 0.285 (95% CI, 0.084-0.964), P= 0.044

B

HR= 0.172 (95% CI, 0.051-0.576), P= 0.004

C

HR= 7.542 (95% CI, 1.265-44.978), P= 0.027

D

Figure 3—*A*: Risk-adjusted Cox regression analysis curves showing survival from severe disease through 18 days for patients with COVID-19 stratified by hyperglycemia vs. normoglycemia. *B*: Risk-adjusted Cox regression analysis curves showing survival from severe disease through 18 days for patients with COVID-19 stratified by with diabetes vs. no diabetes. *C*: Risk-adjusted Cox regression analysis curves showing survival from severe disease through 18 days for patients with hyperglycemia and COVID-19 stratified by insulin infusion vs. no insulin infusion treatment. *D*: Kaplan-Meier analysis showing survival from severe disease through 18 days for patients with hyperglycemia and no diabetes, hyperglycemia and diabetes, no hyperglycemia but with diabetes, and no hyperglycemia and no diabetes. HR, hazard ratio.

required to achieve the blood glucose target was 8.7 ± 2.7 h, and the subsequent mean duration of the insulin infusion was 32.7 ± 4.9 h. After insulin infusion, multidose insulin (three or more daily doses) was used in all patients of both groups. The mean glycemia during hospitalization was 10.65 ± 0.84 mmol/L in the no insulin infusion group and 7.69 ± 1.85 mmol/L in the insulin infusion group ($P < 0.001$). After the treatment period, plasma glucose reduction was greater in the insulin infusion group than in the no insulin infusion group (4.57 ± 1.09 vs. 1.96 ± 1.06 mmol/L; $P < 0.001$). During hospitalization, IL-6 and D-dimer levels were higher in the no insulin infusion group compared with insulin infusion

patients ($P < 0.001$) (Fig. 2). In patients with hyperglycemia, chest CT images during hospitalization revealed that pneumonia disease progressed with subsegmental areas of consolidation and with mass shadows of high density in both lungs in 7 (70%) of 10 patients with hyperglycemia without insulin infusion and 3 (20%) patients with hyperglycemia with insulin infusion ($P < 0.01$). The composite end point occurred in five (33%) patients in the insulin infusion group and in eight (80%) patients in the no insulin infusion group ($P < 0.01$). In a risk-adjusted Cox regression analysis, patients with hyperglycemia treated without insulin infusion had a higher risk of severe disease than those treated with

insulin infusion (Fig. 3), which includes increased mortality (Supplementary Tables 1).

CONCLUSIONS

Our key message is that optimal glycemic control during hospitalization has been associated with reduction risk of severe disease and death in patients with COVID-19. Moreover, among patients screened for the study, more patients in the hyperglycemic group were excluded from this analysis because of severe disease (38% vs. 27%). Still, hyperglycemia remained a strong prognostic predictor of outcome in hospitalized patients with COVID-19. Furthermore, patients with COVID-19 who were hyperglycemic versus normoglycemic displayed a higher

cumulative incidence of severe disease. Moreover, insulin infusion–mediated optimal blood glucose control improves prognosis for hospitalized patients with COVID-19 and hyperglycemia. Previous studies evidenced that hyperglycemia has been linked to poor outcomes in acutely ill hospitalized patients (13). Possible mechanisms for this increased mortality include hyperglycemia-induced changes in the immune system and increases in inflammatory cytokines. It is relatively clear from preclinical and clinical studies that several features associated with diabetes influence host response to infection. Hyperglycemia affects different components of the host response, including the function of immune cells and regulation of cytokines (14). Serum concentrations of both proinflammatory cytokines and anti-inflammatory cytokines, including IL-2R, IL-6, tumor necrosis factor-α, and IL-10, increased in the majority of patients with severe disease and were markedly higher than those with moderate disease, suggesting that cytokine storms might be associated with disease severity (15). Similarly, SARS was also characterized by exuberant inflammatory responses and lung damage. A previous study using a mouse model of SARS demonstrated that rapid kinetics of SARS-CoV replication and delay in IFN-I signaling promoted inflammatory monocyte-macrophage accumulation, resulting in elevated lung cytokine/chemokine levels, vascular leakage, and suboptimal T-cell responses (16). Interestingly, we observed that patients with hyperglycemia presented higher IL-6 levels compared with those with normoglycemia. Moreover, higher plasma blood glucose levels on admission were associated with higher plasma IL-6 levels. Despite full therapy for COVID-19 infection, patients with hyperglycemia presented with higher levels of IL-6 compared with those with normoglycemia during hospitalization. Thus, elevated blood glucose may itself cause an inflammatory response, leading to severe COVID-19 disease and death. On the other hand, patients with COVID-19–associated pneumonia exhibit a number of abnormal coagulation parameters (17), and coagulation abnormalities have been associated with a higher mortality rate (18,19). Patterns of disseminated intravascular coagulation were reported in deaths, and within this group, the D-dimer levels were higher (18,19).

Interestingly, we observed that patients with hyperglycemia who progressed to severe disease presented higher D-dimer levels compared with those with normoglycemia. Moreover, higher blood glucose levels on admission were associated with higher D-dimer at admission. Despite full therapy for COVID-19 infection, patients with hyperglycemia presented with higher levels of D-dimer compared with patients with normoglycemia during hospitalization. Thus, elevated blood glucose may itself cause an inflammatory response and an abnormal coagulation system, leading to severe COVID-19 disease and death.

The present findings mainly show a protective effect of tight glycemic control on outcomes of patients with hyperglycemia with COVID-19 infection. Indeed, our observations evidence that a more substantial drop in glucose levels, obtained by insulin infusion, is associated with better outcomes in patients with COVID-19. As background for this association, we observed that insulin-treated patients with hyperglycemia reached optimal glucose levels and low levels of both IL-6 and D-dimer, and thus, they had a low risk of severe disease and death along with the hospitalization. Previous studies evidenced that cytokine levels returned to normal after insulin infusion and resolution of the hyperglycemic crisis, reducing the risk of death (20,21). After adjustment for baseline glucose and other clinical predictors, we found that for every 0.56 mmol/L drop in glucose level between admission and 18 days, there was an 11% relative decrease in severe disease risk in patients with hyperglycemia. However, this relation was not evidenced in patients with baseline glucose <7.7 mmol/L. Against these data, previous studies and a meta-analysis of randomized trials of intensive insulin therapy in critically ill patients failed to find any benefit of tight glycemic control for all-cause mortality; moreover, tight versus mild glycemic control increased the frequency of mild and/or severe hypoglycemia by about fivefold. All stratified analyses of mortality (by ICU type [medical, surgical, or mixed], time period [ICU stay, hospital stay, 28 days, 3 months, or 6 months], or the presence of diabetes) did not identify any significant differences among the glycemic control groups (22). However, although the investigators did not observe a significant reduction in

overall mortality in patients receiving the insulin infusion, they suggested that the clustered ranking plot suggests that mild glycemic control (140 to <180 mg/dL) achieves the best outcome in relation to all-cause mortality and hypoglycemia, which is consistent with the ADA (9) and the American Association of Clinical Endocrinologists/ADA target glucose levels (23).

Our real-life study needs to extend our observations to a larger cohort of randomized patients. Because there was no randomization of insulin infusion treatment, comparison of the patients receiving and not receiving insulin infusion cannot be assumed to be causal but can be considered highly suggestive. In the small numbers available, lack of significance between the differences does not mean lack of important differences. However, to the best of our knowledge, this is the largest observational study among patients with hyperglycemia with COVID-19 who have experienced a definite outcome. Our data evidenced that optimal glucose control in the immediate postadmission period for almost 18 days was associated with a significant reduction of inflammatory cytokines and procoagulative status. Because inflammatory cytokines and procoagulative status have been shown to induce poor outcome in patients with COVID-19, we speculate that optimal glycemic control, by reducing IL-6 and D-dimer levels, may reduce the risk of progression of the infectious disease. Thus, in the critical care setting, insulin infusion may be an effective method for achieving glycemic targets and reducing mortality in patients with COVID-19.

as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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