

Clinical Research Article

No Evidence of Long-Term Disruption of Glycometabolic Control After SARS-CoV-2 Infection

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Abbreviations: ACE2, angiotensin converting enzyme-2; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DFG, fasting glucose in the diabetes range; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HR, hazard ratio; IFG, impaired fasting glucose; LDH, lactate dehydrogenase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; rTPCR, reverse-transcriptase polymerase chain reaction; TMPRSS2, transmembrane serine protease 2.

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Abstract

Purpose: To assess whether dysglycemia diagnosed during severe acute respiratory syndrome coronavirus 2 pneumonia may become a potential public health problem after resolution of the infection. In an adult cohort with suspected coronavirus disease 2019 (COVID-19) pneumonia, we integrated glucose data upon hospital admission with fasting blood glucose (FBG) in the year prior to COVID-19 and during postdischarge follow-up.

Methods: From February 25 to May 15, 2020, 660 adults with suspected COVID-19 pneumonia were admitted to the San Raffaele Hospital (Milan, Italy). Through structured interviews/ medical record reviews, we collected demographics, clinical features, and laboratory tests upon admission and additional data during hospitalization or after discharge and in the previous year. Upon admission, we classified participants according to American Diabetes Association criteria as having (1) preexisting diabetes, (2) newly diagnosed diabetes, (3) hyperglycemia not in the diabetes range, or (4) normoglycemia.

FBG prior to admission and during follow-up were classified as normal or impaired fasting glucose and fasting glucose in the diabetes range.

Results: In patients with confirmed COVID (n = 589), the proportion with preexisting or newly diagnosed diabetes, hyperglycemia not in the diabetes range and normoglycemia was 19.6%, 6.7%, 43.7%, and 30.0%, respectively. Patients with dysglycemia associated to COVID-19 had increased markers of inflammation and organs' injury and poorer clinical outcome compared to those with normoglycemia. After the infection resolved, the prevalence of dysglycemia reverted to preadmission frequency.

Conclusions: COVID-19-associated dysglycemia is unlikely to become a lasting public health problem. Alarmist claims on the diabetes risk after COVID-19 pneumonia should be interpreted with caution.

Key Words: COVID-19, diabetes, humans

Individuals with either type 1 or type 2 diabetes are more likely to develop severe coronavirus disease 2019 (COVID-19) and to die from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than people who do not have diabetes (1-7). Moreover, acute metabolic decompensation of preexisting diabetes is a well-recognized complication of SARS-CoV-2 infection (8,9). Furthermore, isolated cases of new-onset diabetes have been reported during COVID-19 (10-16), suggesting the possibility that SARS-CoV-2 might exert direct cytotoxicity against beta cells with a diabetogenic effect (17,18). Intriguingly, in vitro studies reported that the putative receptor angiotensin converting enzyme-2 (ACE2) and the effector protease transmembrane serine protease 2 (TMPRSS2), 2 factors associated with SARS-CoV-2 infection (19), are expressed in isolated human islets and in pancreatic endocrine cells derived from human pluripotent stem cells (20,21). This would be consistent with the observation that, using both pseudoviral particles and live SARS-CoV-2, pancreatic alpha and beta cells appear permissive to SARS-CoV-2 infection (21,22). Finally, the existence of a SARS-CoV-2-induced beta-cell transdifferentiation was recently suggested (23). However, other studies have disproved a significant expression of ACE2 and TMPRSS2 in native human pancreatic islet beta cells from normal donors, suggesting that a direct diabetogenic effect of SARS-CoV-2 via ACE2 and TMPRSS2 is unlikely (24,25). Despite these discrepancies, all studies agreed that SARS-CoV-2 can be detected in the pancreas where it may cause inflammation and indirectly affect beta cells. Consistently, pancreatic enlargement, abnormal amylase or lipase levels, and pancreatitis were described in critically ill COVID-19 patients (26-28). However, the evidence that different pancreatic tissues are susceptible to SARS-CoV-2 infection does not automatically imply that SARS-CoV-2 infection will have a permanent effect on glucose homeostasis after infection resolution or will trigger a permanent diabetes.

Recently, Montefusco et al (29) reported that among patients with new-onset hyperglycemia at hospital admission for COVID-19, persistent hyperglycemia continued to be observed in the 6 months after resolution of SARS-CoV-2 infection in 20 out of 57 of patients (35.1%), and overt diabetes was diagnosed in 1 out of 57 of patients (1.6%), suggesting the persistence of aberrant glycometabolic control long after recovery from COVID-19. Using a classification of dysglycemia associated with SARS-CoV-2 infection that differs from that of Montefusco et al (29), we previously reported in a cohort of patients with confirmed COVID-19 that only a small percentage of patients without preexisting diabetes maintained or achieved aberrant glycometabolic control during follow-up, possibly unrelated to the SARS-CoV-2 infection (30). To address the discrepancy between these 2 studies, we analyzed glucose data at the time of admission in a cohort of 660 adult cases with suspected COVID-19. We classified their dysglycemia according to the criteria used by Montefusco et al (29) and assessed whether this persists throughout follow-up or reverts when the viral infection resolves.

Materials and Methods

Study Population and Data Sources

The study population consisted of 660 adults (aged ≥ 18 years) with suspected COVID-19 pneumonia admitted between February 25 and May 15, 2020, to the emergency or clinical departments of the IRCCS San Raffaele Hospital (Milan, Italy) and for whom a serum sample was stored in our institutional biobank (31). This series of patients is part of an institutional clinical-biological cohort (COVID-BioB; ClinicalTrials.gov Identifier: NCT04318366) of patients with COVID-19 (32). The Institutional Review Board (protocol number 34/int/2020) approved the study. Informed consent was obtained by all participants according to Institutional Review Board guidelines.

A confirmed COVID-19 case was defined as previously described (33). Briefly, a patient with SARS-CoV-2 positive reverse-transcriptase polymerase chain reaction (rtPCR) from a nasal/throat swab and signs, symptoms, and radiological findings suggestive of COVID-19 pneumonia was classified as positive ($n = 558$). In case of multiple (at least 2) SARS-CoV-2 negative rtPCR in the presence of radiological findings suggestive of COVID-19 pneumonia, subjects were classified as having a confirmed infection if they were positive for immunoglobulin M/immunoglobulin G against SARS-CoV-2 spike protein (34) ($n = 28$). SARS-CoV-2 infection was excluded in subjects with multiple (at least 2) SARS-CoV-2 negative rtPCR and negative for immunoglobulin M/immunoglobulin G against SARS-CoV-2 spike protein ($n = 74$). Demographic information, clinical features, and laboratory tests were obtained within 72 h from admission. Data were collected as previously described (33) during hospitalization or after discharge from both structured baseline patient interviews and hospital paper or electronic medical records. We also reviewed the electronic medical records in the year prior to the hospital admission for COVID-19.

Laboratory Variables

Routine blood tests encompassed serum biochemistry [including renal function and lactate dehydrogenase (LDH)], complete blood counts with differential, inflammation markers [C-reactive protein (CRP), ferritin, interleukin-6 (IL-6)], and D-dimer.

Definition of Glycemic Alteration

Fasting blood glucose (FBG) were measured in each patient at different time points after admission to the emergency room and during hospitalization. A mean of 4 ± 1.6 (SE) time points per patients were available. In the year prior to hospital admission, we retrieved FBG for 234 out of the 660 patients in our cohort. Glycated hemoglobin (HbA1c) levels during in hospital stay or in the year prior to hospital admission were also abstracted, where available. We also recorded FBG, body mass index (BMI), and HbA1c during the postdischarge follow-up (ie, at the 1-, 3-, 6-, and 12-month outpatient visits), where available. Regarding glucose treatment modalities applied during the hospitalization period, as no specific guidelines were available during the first wave, patients were treated as suggested by American Diabetes Association (ADA) Standards of Medical Care in Diabetes—2020 (35): insulin therapy was initiated for treatment of persistent hyperglycemia starting at a threshold ≥ 180 mg/dL (10.0 mmol/L). Once insulin therapy was started, a target glucose range of 140 to 180 mg/dL (7.8–10.0 mmol/L) was recommended.

We stratified glucose abnormalities at the time of hospitalization using the criteria recently reported by Montefusco et al (29). Briefly, study participants were defined as having (1) preexisting diabetes if prior to hospital admission for COVID-19 they had a documented diagnosis of diabetes or were prescribed diabetes medications; (2) newly diagnosed diabetes if they had a negative history of diabetes, no prescription of diabetes medications, and a FBG during hospitalization, in the absence of infusions of dextrose, of 7.0 mmol/L or higher (ADA criteria); (3) hyperglycemia not in the diabetes range if they had random blood glucose levels between 100 and 199 mg/dL or 2 FBG >100 mg/dL and <126 mg/dL; or (4) normoglycemia if they had no history of diabetes and had normal glucose levels according to the ADA criteria. FBG recorded before admission and during the follow-up were classified as normal fasting glucose, impaired fasting glucose (IFG), or fasting glucose in the diabetes range (DFG) according to ADA criteria.

Statistical Analysis

Categorical variables are reported as frequency or percentage, continuous variables as median with interquartile range, or mean with SD. Categorical variables were compared using Chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using paired/unpaired *t*-test, analysis of variance (Bonferroni post hoc test), Mann-Whitney test, Kruskal-Wallis test (Dunn's post hoc test), and Wilcoxon, as appropriate. Spearman correlation was performed to assess the association between glycemia and biochemistry variables. The time to event was estimated according to Kaplan-Meier, from the date of symptom onset to the date of the event or of last follow-up visit, whichever occurred first. We used univariate and multivariate Cox proportional hazards models to study the association between patient characteristics with time to adverse outcome (a composite endpoint of admission to intensive care unit or death, whichever occurred first). The effect estimates were reported as hazard ratios (HRs) with the corresponding 95% CI estimated according to the Wald approximation. Two-tailed *P*-values are reported, with *P*-value < 0.05 indicating statistical significance. All CIs are 2-sided and not adjusted for multiple testing unless otherwise specified. Statistical analyses were performed with SPSS 24 (SPSS Inc./IBM) and GraphPad Prism version 5.04.

Results

Glucose Categories at the Time of Admission for Suspected COVID-19 Pneumonia

From February 25 to May 15, 2020, 660 adults with suspected COVID-19 pneumonia were enrolled in our institutional clinical-biological cohort (COVID-BioB).

A diagnosis of COVID-19 was confirmed in 586 out of 660 cases (88.8%, COVID cohort), while the SARS-CoV-2 infection was excluded in the remaining 74 cases (5.1%, No-COVID cohort). In the COVID cohort, 154 out of 586 patients (26.3%) presented with increased blood glucose levels (Fig. 1A). One hundred and fifteen out of 154 (19.6%) had preexisting diabetes, while a new diagnosis of diabetes was made in the remaining 39 patients (6.7%) during their in hospital stay. Hyperglycemia not in the diabetes range was observed during hospitalization in 256 out of 586 subjects (43.7%), without preexisting or newly diagnosed diabetes, while the remaining 176 patients (30%) had normal blood glucose levels throughout their hospital stay. Among the 74 patients in whom COVID-19 was not confirmed, 17 (23.0%) had diabetes, either preexisting diabetes ($n = 10$, 13.5%) or newly diagnosed diabetes ($n = 7$, 9.5%); 15 (20.2%) had hyperglycemia not in the diabetes range; and 42 (56.8%) were normoglycemics throughout their hospital stay (Fig. 1A). Demographic and clinical characteristics of our study population are reported in Table 1, where we combined patients with preexisting diabetes and newly diagnosed diabetes. As expected, mean HbA1c levels were significantly higher in patients with diabetes compared to patients with hyperglycemia not in the diabetes range or normoglycemia but not different between patients with hyperglycemia and normoglycemia (Fig. 1B). On the other hand, mean FGB and peak blood glucose levels during hospital stay were different between groups, with the highest levels in patients with diabetes (Fig. 1C). Upon admission patients with diabetes exhibited significantly higher white blood cell count [7.9 (5.8-11.7) vs 6.4 (4.7-9) $\times 10^9/L$, $P < 0.0001$], neutrophil-to-lymphocyte ratio [3.32 (0.72-6) vs 2.33 (0.64-3.87), $P < 0.0001$], serum creatinine [1.1 (0.86-1.5) vs 0.92 (0.77-1.14) mg/dL, $P < 0.0001$], LDH [380 (301-524) vs 277 (229-380) U/L, $P < 0.0001$], CRP [84.3 (27.1-168) vs 48.7 (14-123.3) mg/L, $P < 0.001$], ferritin [1058 (546-1662) vs 929 (385-929) mcg/L, $P < 0.001$], and D-dimer [1.79 (0.94-3.81) vs 0.88 (0.4-1.81) mcg/L, $P < 0.0001$] levels compared to patients with normoglycemia (Fig. 2). Generally, patients with hyperglycemia not in the diabetes range showed intermediate levels between patients with diabetes and patients with normoglycemia (Fig. 2). IL-6 levels were not different between groups. In the overall population, Spearman's correlation showed negligible or weak correlation, although statistically significant, between mean FGB or peak glycemia values during hospitalization and the biochemistry variables analyzed [Supplementary Figure 1 (36)]. Glucose abnormalities were strongly associated with an increased risk of adverse clinical outcome, as defined by composite endpoint of admission to intensive care unit or death, whichever occurred first (Fig. 1D-1E, Table 1). Sex- and age-adjusted

Cox proportional hazards model showed an increased risk for the adverse clinical outcome in patients with diabetes compared to those with normoglycemia [HR 3.28 (95% CI 2.04-5.3); $P < 0.001$] or hyperglycemia not in the diabetes range [HR 1.59, (95% CI 1.14-2.2); $P = 0.006$]. Moreover, an increased risk of adverse clinical outcome was evident also for patients with hyperglycemia not in the diabetes range compared to normoglycemics ones [HR 2.16 (95% CI 1.35-3.4); $P = 0.001$]. A multivariate analysis, including BMI, creatinine hypertension, cardiovascular disease, and known markers of diseases severity at admission (LDH, CRP, white blood cell), confirmed diabetes as an independent predictor of adverse clinical outcome (Fig. 1E). Finally, patients with diabetes and hyperglycemia not in the diabetes range had a longer hospital stay compared to patients with normoglycemia (Fig. 1F).

FBG Prior to COVID-19 and After Hospital Discharge, by the Glucose Categories at the Time of Hospitalization for COVID-19

The median follow-up time after symptoms onset was 215 (95% CI 208-222) and 198 (95% CI 110-285) days for the COVID and No-COVID cohorts, respectively. Among discharged patients, 355 out of 475 in the COVID cohort [74.7%, median time after discharge 6 (3-6) months] and 23 out of 65 in the No-COVID cohort [35.4%, median time after discharge 6 (3-12) months] had at least 1 FBG during postdischarge follow-up. Moreover, our retrospective abstraction from electronic medical records provided FBG values in the year prior to hospital admission for COVID-19 for 199 out of 586 (34%) and 35 out of 74 (47.3%) patients in the COVID and No-COVID cohorts, respectively. In the COVID cohort, we analyzed FBG prior to COVID-19 hospitalization and after hospital discharge in the different glucose categories at the time of hospitalization for COVID-19 (Fig. 3). Among 115 patients with preexisting diabetes, in the year prior to admission FBG was available for 50 subjects (43.5%) and during follow-up for 63 out of 76 surviving patients (82.1%). As expected, most patients showed DFG both before and after SARS-CoV-2 infection, without significant changes during the time. During the follow-up, no diabetic patients required drug treatment escalation. A marginal trend in increasing FBG was evident during hospitalization [from 137 (116-172) mg/dL to 150 (115-230) mg/dL, $P = 0.11$], followed by return to preinfection levels during follow-up [134 (108-169) mg/dL, $P = 0.84$]. Among 295 patients with newly diagnosed diabetes or hyperglycemia not in the diabetes range, FBG prior to COVID-19 was available for 84 patients (28.5%) and FBG during follow-up for 178 out of the 238 surviving patients (74.8%). Of note, in this group in 33.3% of patients

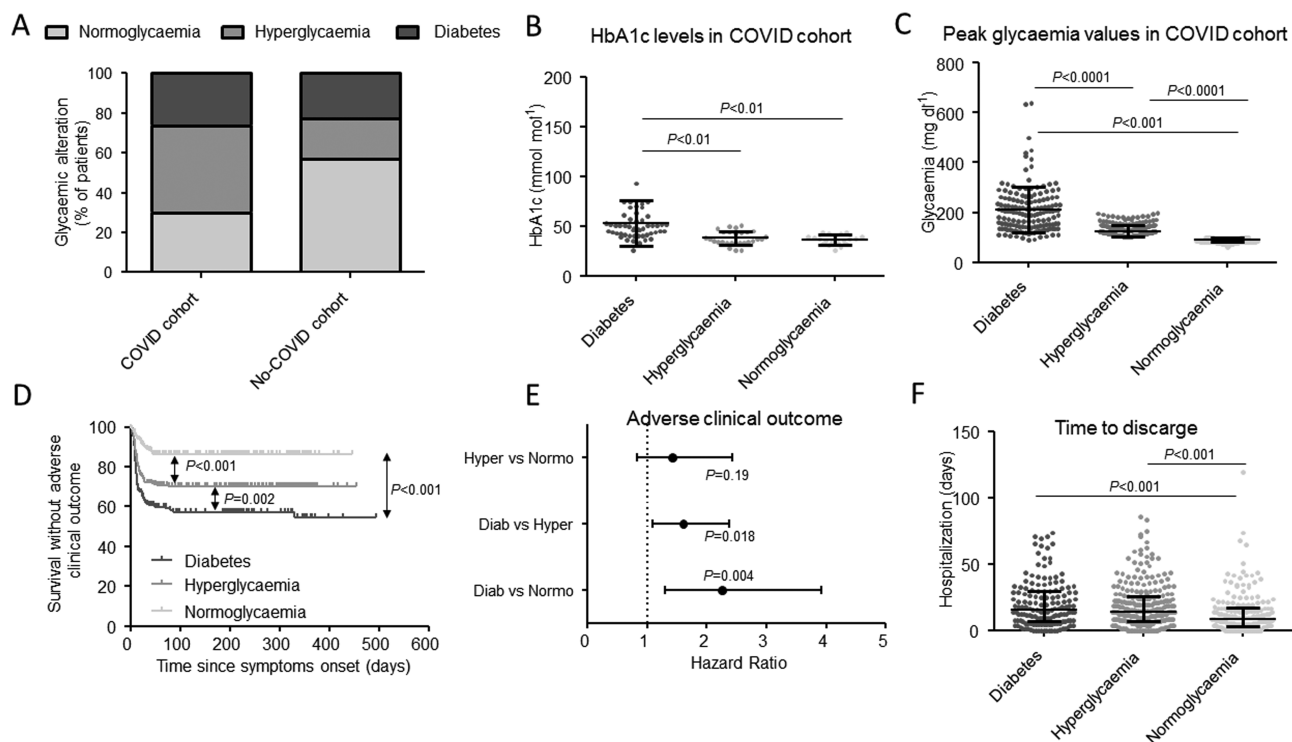


Figure 1. Dysglycemia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We analyzed a series of 586 cases with confirmed coronavirus disease 2019 (COVID-19; COVID cohort) and 74 cases in which SARS-CoV-2 infection was excluded (No-COVID cohort). (A) Glucose abnormalities at hospital admission. Bar plots represent the proportion of individuals with diabetes (either preexisting or newly diagnosed), hyperglycemia not in the diabetes range and normoglycemia in the COVID-19 cohort and No-COVID cohort. (B and C) Mean glycated hemoglobin levels and mean peak blood glucose levels were summarized for patients with diabetes (either preexisting or newly diagnosed), hyperglycemia not in the diabetes range, and normoglycemia. Scatterplots show the mean \pm SD; the error bars represent the SD, and each dot represents an individual patient. (D) Kaplan-Meier time-to-event analysis for survival without adverse clinical outcome in the three patient groups. Log-rank (Mantel-Cox) test. (E) Forest plot of the hazard ratio for diseases severity (composite endpoint of admission to the intensive care unit or death, whichever occurred first) in the 3 patient groups. Sex-and age-adjusted multivariate Cox proportional hazards model including body mass index, creatinine, hypertension, cardiovascular disease, lactate dehydrogenase, C-reactive protein, and white blood cells. (F) Time to hospital discharge in the 3 patient groups. Scatterplots show the mean \pm SD; the error bars represent the SD, with each dot representing an individual patient. (B, C, and E) One-way analysis of variance with Bonferroni correction.

IFG/DFG was already present prior to SARS-CoV-2 infection. A significant increase of FBG was evident during hospitalization [from 95 (85-107) to 102 mg/dL (93-115), $P = 0.003$] followed by return to preinfection levels during follow-up [97.5 (90-107) mg/dL; $P = 0.24$ vs preinfection levels, $P = 0.004$ vs hospitalization]. Among the 176 patients with normoglycemia during hospitalization, FBG prior to COVID-19 was available for 65 subjects (36.9%) and glucose measurements during follow-up for 112 out of the 161 surviving patients (69.6%). In this group a significant decrease of FBG was evident during hospitalization [from 91 (86-96.5) to 85 (78-89) mg/dL, $P < 0.001$] followed by a return to preinfection levels during follow-up [94 (88-100) mg/dL; $P = 0.72$ vs preinfection levels, $P < 0.001$ vs hospitalization]. A reduction in BMI from baseline was reported at the last observation in patients with newly diagnosed diabetes or hyperglycemia not in the diabetes range during hospitalization (Fig. 4). On the contrary, a modest increase in BMI during follow-up was evident in patients

with normoglycemia during hospitalization. HbA1c did not change significantly during the observation period in all 3 groups (Fig. 4). The same analysis was performed also in the No-COVID cohort with similar results, even if the low number of patients in this cohort does not allow to draw definite conclusions [Supplementary Figure 2 (36)].

Discussion

Whether dysglycemia associated with SARS-CoV-2 infection should be considered a specific clinical entity, and whether it persists or reverts when the viral infection resolves is still a matter of discussion. To address this issue, we studied a cohort of 621 adults patients with suspected COVID-19 pneumonia, assessing dysglycemia not only at the time of hospitalization but also in the year prior to COVID-19 hospitalization and during postdischarge follow-up, when FBG were available. Our study generated several interesting findings.

Table 1. Demographics and clinical characteristics of the study population, stratified by glucose categories at the time of admission for suspected COVID-19 pneumonia

	COVID cohort					No-COVID cohort	
	All	Diabetes	Hyperglycemia	Normoglycemia	Missing	P	P vs COVID
N	586	154	256	176	0	0.001	74
M/F	391/195	97/78	183/71	98/78	0	0.001	41/33
Age, years	64 ± 14.5	68.3 ± 12.4 ^{a,b}	63.6 ± 14	61.1 ± 16	0	<0.001	62 ± 18
BMI, kg/m ²	28 ± 5.32	29.7 ± 6 ^{a,b}	27.6 ± 4.3	27.2 ± 5.8	72	<0.001	24.7 ± 3.9
Europeans	496 (84.6)	136(88.3)	212 (82.8)	148 (84.1)	0	0.4	63 (85.1)
Hypertension, n (%)	288 (49.2)	107 (69)	119 (47)	62 (35)	1	<0.001	25 (33.8)
CAD, n (%)	85 (14.5)	38 (25)	28 (11)	19 (11)	1	<0.001	13 (17.6)
ACE/ARB, n (%)	164 (28.3)	61 (40)	68 (27)	35 (20)	7	<0.001	18 (25)
Steroid therapy during hospitalization	112 (19.1)	31(20.1)	55 (21.5)	26 (14.8)	0	0.64	—
Swab negativization, days	40 (38.2-41.7)	41 (38-44)	40 (37-43)	37 (33-41)	1	0.49	—
Death, n (%)	111 (18.9)	50 (32.5)	46 (18)	15 (8.5)	0	<0.001	9 (12.2)
Intensive care unit, n (%)	93 (15.9)	35 (23)	48 (19)	10 (5.7)	0	<0.001	0 (0)
Mean fasting glycemia, mg/dL	113.6 ± 43.5	162.5 ± 57 ^{a,b}	104 ± 15 ^c	84.5 ± 9	0	<0.001	102 ± 32
Max fasting glycemia, mg/dL	137.2 ± 68	211.3 ± 92 ^{a,b}	125.1 ± 22 ^c	89.8 ± 8	0	<0.001	113 ± 66
HbA1c, mmol/mol	45.7 ± 19	53 ± 23 ^{a,b}	38 ± 7	36 ± 5	484	<0.001	41 ± 8
White blood count, ×10 ⁹ /L	7 (5.1-9.8)	7.6 (5.8-11.7) ^{a,b}	6.9 (5.1-9.6)	6.4 (4.7-9)	0	<0.001	9.1 (6.9-11.4)
Red blood count, million/mm ³	4.45 (4.01-4.9)	4.4 (3.9-5)	4.5 (4.1-4.9)	4.6 (4.2-5.0)	0	0.24	4.5 (4.1-4.8)
Hemoglobin, g/dL	13 (11.5-14.4)	12.8 (11.3-14.4)	13.3 (12-14.3)	13 (11.5-14.4)	0	0.15	13.4 (12.1-14.5)
Hematocrit, %	38.95 (35-42.3)	39.1 (34.8-43.5)	39.2 (35.7-42.2)	38.9 (34.5-42.7)	0	0.56	39.45 (35.9-43.1)
Platelet count, ×10 ⁹ /L	232 (170-309.5)	236 (175-314)	232 (171-314)	228 (169-301)	0	0.65	239.5 (172.7-305)
Neutrophils, ×10 ⁹ /L	5.2 (3.5-7.9)	5.8 (4.1-8.8) ^a	5.2 (3.6-7.7)	4.7 (3-6.2)	9	<0.001	6.35 (4.6-9.3)
Lymphocytes, ×10 ⁹ /L	1 (0.7-1.4)	1 (0.7-1.4)	0.9 (0.7-1.2) ^c	1.2 (0.7-1.5)	16	0.003	1.4 (0.9-2)
Monocytes, ×10 ⁹ /L	0.5 (0.3-0.7)	0.5 (0.3-0.8)	0.4 (0.3-0.6)	0.5 (0.4-0.7)	16	0.079	0.7 (0.5-0.8)
Patients with a FBG available in the year prior to admission, n (%)	199 (34)	56 (36.4)	78 (30.5)	65 (37)	—	—	35 (47.3)
Patients discharged alive with at least 1 FBG at follow-up, n (%)	355 (74.3)	83 (79.8)	160 (76.2)	112 (69.6)	—	—	23 (35.4)

Abbreviations: ACE/ARB, angiotensin converting enzyme/angiotensin-receptor blockers; BMI, body mass index; CAD, coronary artery disease; FBG, fasting blood glucose; COVID-19, coronavirus disease 2019; M/F, male/female.

^aPost hoc analysis: $P < 0.05$ diabetes vs normoglycemia.

^bPost hoc analysis: $P < 0.05$ diabetes vs hyperglycemia.

^cPost hoc analysis: $P > 0.05$ hyperglycemic vs normoglycemia.

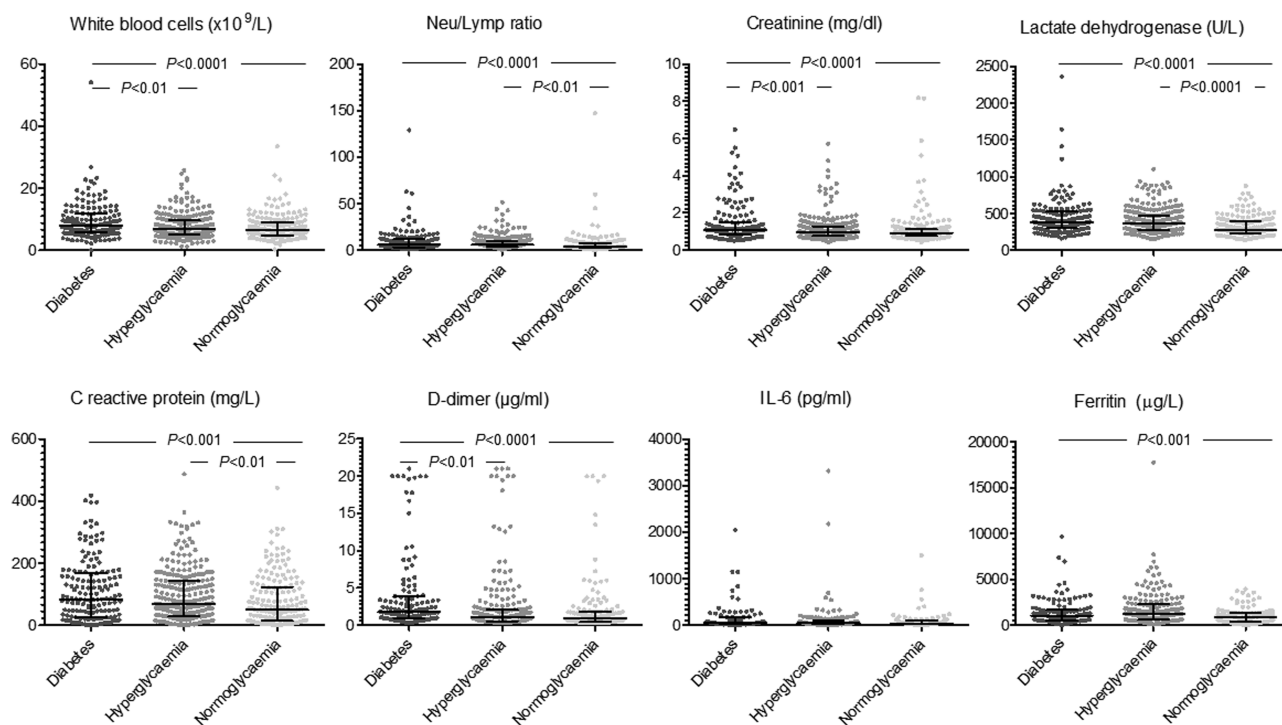


Figure 2. Biochemistry at admission according to glucose abnormalities. Routine blood tests encompassed serum biochemistry [including serum creatinine and lactate dehydrogenase (LDH)], complete blood count with differential, inflammation markers [C-reactive protein (CRP), ferritin, interleukin-6 (IL-6)], and D-dimer. Scatterplots show the median; the error bars represent the interquartile range, and each dot represents an individual patient. Kruskal-Wallis with Dunn's correction was used for comparison between groups.

First, the dysglycemia associated with COVID-19 (ie, newly diagnosed diabetes or hyperglycemia not in the diabetes range) resolved in the majority of patients after the SARS-CoV-2 infection resolved. A similar behavior was also evident in the No-COVID cohort, and it is, therefore, reasonable to speculate that reversible transient factors, such as inflammation-induced insulin resistance, may be causing dysglycemia in patients with pneumonia from SARS-CoV-2 or other pathogens (37). This hypothesis is supported by the association between biochemical markers of inflammation during hospitalization and the degree of dysglycemia. Therefore, this finding does not support the persistence of a long-term disruption of glycometabolic control after SARS-CoV-2 infection, as claimed by other authors (29). One possible explanation for this discrepancy is a potential assessment bias (ie, how patients with dysglycemia are identified and classified) in observational studies conducted under emergency conditions. Obviously, a biased stratification of the groups leads to biased conclusions, independently by the quality of data and the statistical analysis performed. A negative history of diabetes or prediabetes cannot rule out the presence of undiagnosed diabetes. Thanks to the access, although retrospective, to FBG values in the year prior to hospitalization for COVID-19, in our cohort we could document that DFG or IFG were often preexistent in patients that at hospital admission for

suspected COVID-19 were classified as normoglycemics or with newly diagnosed diabetes or with hyperglycemia not in the diabetes range. Moreover, the prevalence of IFG, DFG, and FBG, as well as median HbA1c and BMI before and 6 months after SARS-CoV-2 infection (ie, outside an acute illness) were similar in the 3 groups.

Second, the prevalence of preexisting diabetes was similar in patients of the COVID and No-COVID cohorts, while the prevalence of newly diagnosed diabetes and hyperglycemia not in the diabetes range was higher in the COVID-19 cohort. This suggests that diabetes per se, as risk factor, is not unique to COVID-19. On the other hand, the well-known high level of inflammatory stress associated with the acute phase of COVID-19 pneumonia may account for the excess difference in newly diagnosed diabetes and hyperglycemia not in the diabetes range between the COVID and No-COVID cohort. Third, the prevalence of the dysglycemia associated with SARS-CoV-2 infection may vary significantly according to the criteria used to define glucose abnormalities. In this study, overt hyperglycemia was present in 43.7% of patients during hospitalization. This prevalence is comparable to that reported by Montefusco et al (29) (not unexpectedly, having used the same classification criteria) but certainly higher than that previously reported by us (38) or by other groups (39) using other classification. This underlines the need for

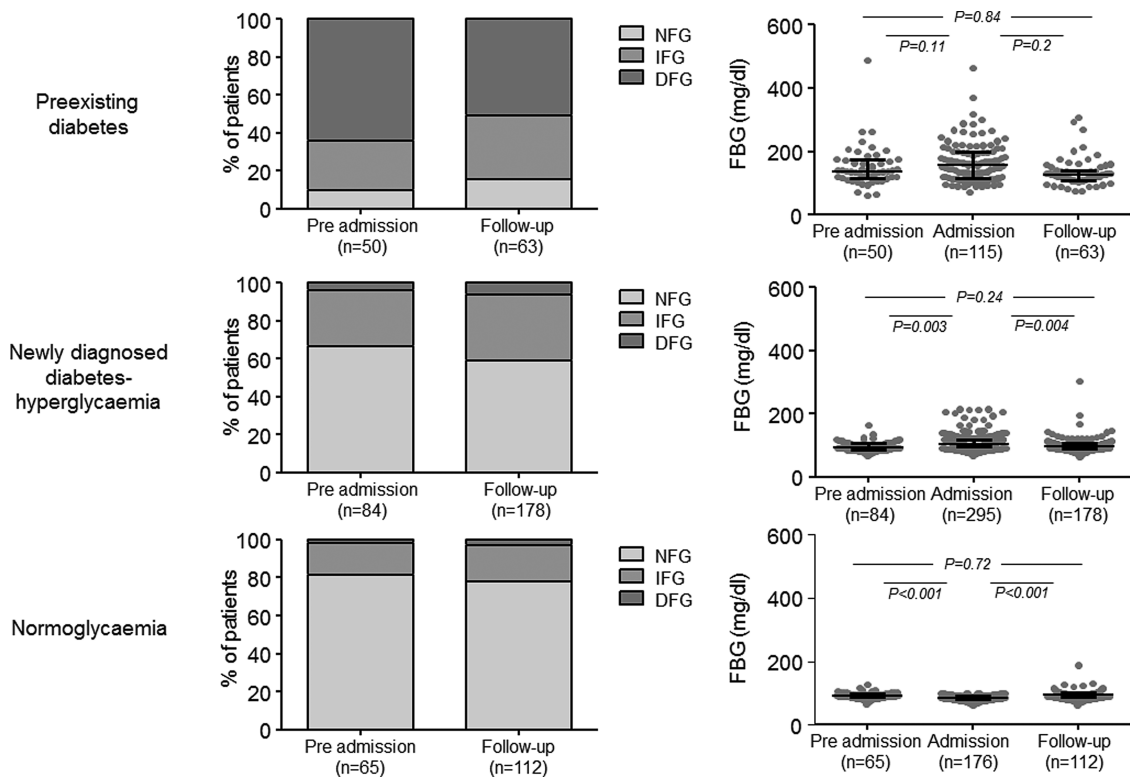


Figure 3. Glucose abnormalities and fasting blood glucose before admission and after discharge stratified by dysglycemia at the time of coronavirus disease 2019 (COVID-19) hospitalization in the COVID cohort. Left panels: For each glucose abnormality at the time of hospital admission for COVID-19 we show glucose abnormalities before admission and at last follow-up for the COVID cohort. Bar plots represents the proportion of individuals with normal fasting glucose (NFG), impaired fasting glucose (IFG) and fasting glucose in the diabetes range (DFG), defined according to American Diabetes Association criteria. Right panels: fasting blood glucose (FBG) before admission, during hospitalization (admission), and at last follow-up. In the scatterplots each dots represents an individual patient, the horizontal line is the mean, the error bars represent the SD. Paired t-test was used to compare time points.

standardizing the criteria to define the different categories of glucose abnormalities to allow comparison of the results from different studies.

Fourth, regardless of its reversibility, our study documented that dysglycemia was associated with an adverse clinical outcome of SARS-CoV-2 infection and that this association was independent from the major risk factors for disease severity. As good glycemic control was indeed shown to reduce disease severity and mortality in COVID-19 patients with hyperglycemia (40), early recognition and treatment of COVID-associated hyperglycemia may greatly benefit these patients. Therefore, our findings do strongly support the need to screen all patients with COVID-19 pneumonia for hyperglycemia (ie, with either fasting blood glucose and/or HbA1c) at the time of hospital admission, despite a mute personal or family history of diabetes.

Whether COVID-associated dysglycemia is a new clinical entity is still a matter of discussion. In terms of pathophysiology, dysglycemia may include (1) stress-induced hyperglycemia; (2) previously unrecognized (pre)diabetes (either type 2 or, less likely, type 1 diabetes); (3) a form of diabetes due to the direct effect of the SARS-CoV-2 on

the pancreas; or (4) a form of diabetes secondary to the treatment of COVID-19 (eg, with glucocorticoids or other medications possibly inducing secondary hyperglycemia/diabetes) (37, 41-47). In our cohort, enrolled during the first wave of the pandemic, the use of glucocorticoids was very limited and, therefore, unlikely to have played a role in the pathogenesis of hyperglycemia. Since FBG reverted to preadmission values in most patients when the infection resolved, it is reasonable to hypothesize that reversible transient factors, such as inflammation-induced insulin resistance, may have played a major role in causing dysglycemia (37). In any case, we cannot exclude that more than 1 cause may have contributed to the dysglycemia associated with SARS-CoV-2. Definitively addressing the specific role of SARS-CoV-2 in COVID-associated dysglycemia would require the systematic availability of pancreatic tissue and advanced studies on insulin secretion and resistance before, during, and after the infection, studies that would be extremely difficult or unrealistic to perform. Recently, in contrast to our data, some retrospective cohort studies have reported excess risk and relative hazards for developing incident diabetes after the acute phase of

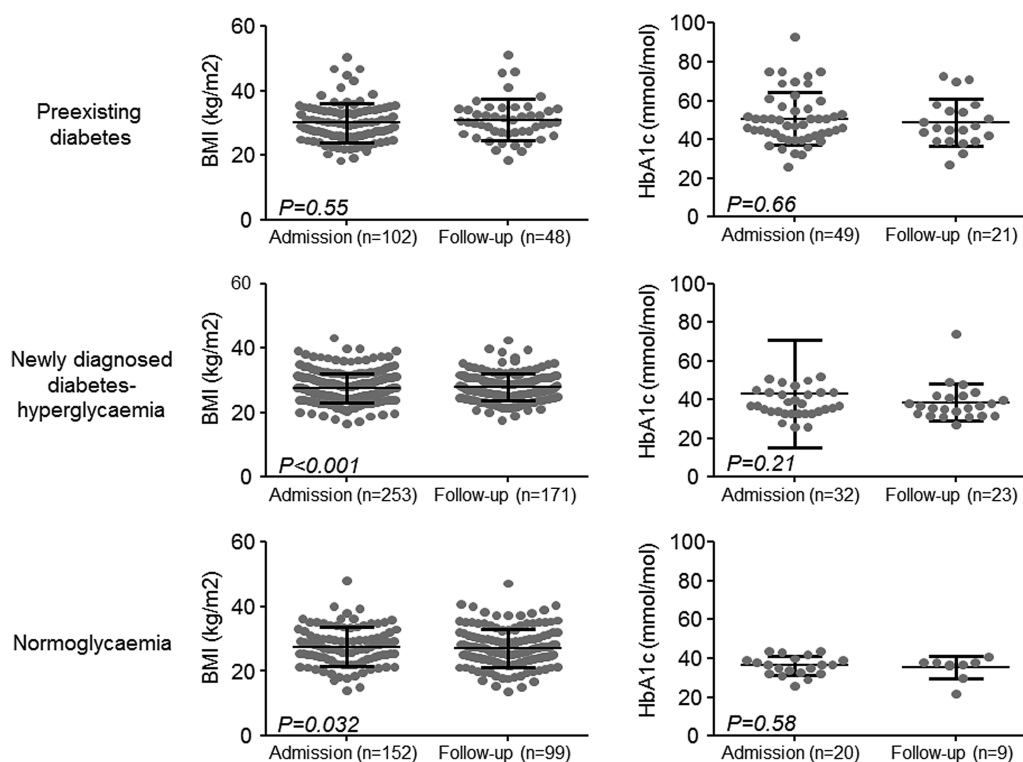


Figure 4. Body mass index (BMI) and glycated hemoglobin at admission and after discharge stratified by dysglycemia at the time of coronavirus disease 2019 (COVID-19) hospitalization in the COVID cohort. BMI and glycated hemoglobin at hospital admission and at last follow-up. In the scatterplots each dots represents an individual patient, the horizontal line is the mean; the error bars represent the SD. Paired *t*-test was used to compare time points.

SARS-CoV-2 infection in adults (48,49). Significant risk differences for type 2 diabetes after SARS-CoV-2 infection ranged from 0.47 to 0.82 per 100 people, and HRs ranged from 1.39 to 1.83. The major limitation of these studies is that the incident new cases in the postacute phase may be just the identification of a preexisting condition that was simply undiagnosed before. In fact, epidemiological evidence in many countries suggests that for any 2 patients with diagnosed diabetes there might be 1 with undiagnosed diabetes. Moreover, those studies identified an excess risk for diabetes that was not unique to SARS-CoV-2, since it was also observed with other serious viral infections. For example, compared to individuals who were hospitalized with seasonal influenza, patients who were hospitalized for COVID-19 did not have a significantly higher burden of type 2 diabetes, while they had a significant trend to a lower burden of type 1 diabetes (48,49).

Our study has some limitations. First, our cohort consists of hospitalized patients with COVID-19, excluding asymptomatic or paucisymptomatic patients who were treated at home. Second, preadmission and postdischarge FBG were not available for all patients, and we cannot exclude a selection bias. Third, death might be an important competing risk (in the sense that prevent us from appreciating diabetes cases in patients who are deceased), and we

did not perform a competing risk analysis. Fourth, we only systematically assessed FBG, and we acknowledge that more specific markers of beta cell function, such as serum insulin and or C-peptide levels, would have provided relevant information. Fifth, this has been a single-center study, covering mainly Europeans. Consequently, the conclusion should be limited to Europeans, and we cannot exclude that in other ethnic groups the COVID-19 encounter may led to a different clinical outcome in view of different beta cell functional capacity (ie, Asians as compared to Europeans). Finally, a 6-month follow-up may be too short to unveil a direct diabetogenic effects of the SARS-CoV-2 virus. In fact, there may be a delay between immunologic factors or infection damages and the onset of diabetes. It will be, therefore, crucial to conduct long-term follow-up studies in these patients.

Conclusions

COVID-associated dysglycemia is a complication of SARS-CoV-2 infection, and this clinical entity still needs to be adequately characterized in relationship with preexisting (pre) diabetes or glucose intolerance. It is clear from our study that patients with COVID-associated dysglycemia had increased levels of inflammatory markers and indicators of

organ injuries and showed a poorer clinical outcome. This strongly support the need to screen all patients COVID-19 pneumonia for hyperglycemia at the time of admission, despite a mute personal or family history of diabetes, and treat their hyperglycemia promptly to achieve and maintain a good glycemic control during hospitalization. On the other hand, our data do not support the persistence of a long-term disruption of glycometabolic control after SARS-CoV-2 infection. Large epidemiological studies in the next years will be required to clarify whether COVID-19 induce permanent diabetes. However, at this time, any alarmist claim on an increased risk of diabetes after SARS-CoV-2 infection should be interpreted with caution.

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