Association of Early-Phase In-Hospital Glycemic Fluctuation With Mortality in Adult Patients With Coronavirus Disease 2019

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OBJECTIVE

To investigate the association of in-hospital early-phase glycemic control with adverse outcomes among inpatients with coronavirus disease 2019 (COVID-19) in Wuhan, China.

RESEARCH DESIGN AND METHODS

The study is a large case series, and data were obtained regarding consecutive patients hospitalized with COVID-19 in the Central Hospital of Wuhan between 2 January and 15 February 2020. All patients with definite outcomes (death or discharge) were included. Demographic, clinical, treatment, and laboratory information were extracted from electronic medical records. We collected daily fasting glucose data from standard morning fasting blood biochemistry to determine glycemic status and fluctuation (calculated as the square root of the variance of daily fasting glucose levels) during the 1st week of hospitalization.

RESULTS

A total of 548 patients were included in the study (median age 57 years; 298 [54%] were women, and $n = 99$ had diabetes [18%]), 215 suffered acute respiratory distress syndrome (ARDS), 489 survived, and 59 died. Patients who had higher mean levels of glucose during their 1st week of hospitalization were older and more likely to have a comorbidity and abnormal laboratory markers, prolonged hospital stays, increased expenses, and greater risks of severe pneumonia, ARDS, and death. Compared with patients with the lowest quartile of glycemic fluctuation, those who had the highest quartile of fluctuation magnitude had an increased risk of ARDS (risk ratio 1.97 [95% CI 1.01, 4.04]) and mortality (hazard ratio 2.73 [95% CI 1.06, 7.73]).

CONCLUSIONS

These results may have implications for optimizing glycemic control strategies in COVID-19 patients during the early phase of hospitalization.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has ravaged more than 200 countries and areas since it was first discovered in December 2019. The outbreak and worldwide spread of SARS-CoV-2 have resulted in a global pandemic of coronavirus disease 2019 (COVID-19) with over tens of millions infections and nearly 1 million deaths as of September 2020 (1).

Previous studies have demonstrated that the presence of underlying diseases is common and may predispose a patient to poorer or fatal conditions after COVID-19

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infection (2–6). Diabetes, one of the most common comorbidities of COVID-19, is present in 7–20% of patients according to these reports. Similarly, diabetes and hyperglycemia are common in patients infected with severe acute respiratory syndrome coronavirus and exhibit independent predictive value for mortality (7). Besides confirmed diabetes, in-hospital hyperglycemia is probably due to undiagnosed diabetes, prior poor glucose control, glucocorticoid therapy, and stress hyperglycemia. Strengthening glucose control is critical for inpatients with and without diabetes to reduce the risk of in-hospital adverse events (8).

To the best of our knowledge, no previous study has yet evaluated the association of early-phase glucose management and glycemic fluctuations with adverse outcomes in hospitalized patients with COVID-19. In this work, we aim to describe the 1st-week glycemic status of COVID-19 patients admitted to the Central Hospital of Wuhan during the epidemic and further investigate the association of early-phase glycemic control with hospital expenses, length of hospital stay, acute respiratory distress syndrome (ARDS) incidence, and subsequent mortality.

RESEARCH DESIGN AND METHODS

Patients

This large case series was performed at the Central Hospital of Wuhan, one of the designated hospitals for treating patients with COVID-19 in Wuhan, China. A total of 709 patients with confirmed COVID-19 were hospitalized between January 2 and 15 February 2020. The throat-swab specimens of all patients had been repeatedly tested for SARS-CoV-2 by RT-PCR on admission and hospitalization according to a previously described protocol (4). The case definitions of confirmed human infection with SARS-CoV-2 were in accordance with the interim guidance from the World Health Organization (9). Patients with definite clinical outcomes (i.e., discharged or death) were followed up until 23 March 2020, and 27 patients without clinical end points were excluded. We also excluded 3 patients who died within 7 days of admission, 2 pregnant women, 37 patients with COVID-19 who transferred to other hospitals, and 92 patients with missing information on fasting glucose. A detailed flow diagram of our sample is presented in Supplementary Fig. 1. Finally, 548 patients were included in the analyses. A comparison of baseline characteristics between these 548 patients and 161 patients who were excluded is presented in Supplementary Table 1. The requirement for informed consent was waived due to the urgent need to collect data on the newly emerged pathogen. This study was approved by the Ethics Committees of the Central Hospital of Wuhan.

Data Collection

The clinical electronic medical records of all patients with SARS-CoV-2 infection were reviewed by three first-line clinical physicians (W.S., Y.Li., and L.Z.) and double-checked by a fourth researcher (L.C.). Demographic, clinical, laboratory, treatment, and outcome data were extracted with use of a standardized data collection form modified according to the World Health Organization/International Severe Acute Respiratory and Emerging Infection Consortium case record forms.

We collected data on age, sex, symptoms from onset to admission, underlying comorbidities (i.e., chronic pulmonary disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic kidney disease), laboratory findings on admission and during hospitalization (i.e., white blood cell count, lymphocyte count, C-reactive protein, procalcitonin, creatinine, ALT, D-dimer, lactate dehydrogenase, and creatine kinase–MB), treatment (i.e., oxygen therapy, antiviral agents, antibacterial agents, corticosteroids, immunoglobulin, and hypoglycemic therapy), arterial blood gas analysis (i.e., the ratio of partial pressure of oxygen to fraction of inspired oxygen [PaO_2:FiO_2], and lactate concentration), and living status. We also collected information on the hospital expenses of all patients.

Fasting Blood Glucose Parameters

Fasting glucose was recorded from standard morning fasting blood biochemistry. The median length of hospital stay for nonsurvivors in our cohort was 17 days (interquartile range [IQR] 14–22), and patients often suffered sepsis and multiple organ injury during the 2nd week after admission according to our observations and a recent report (5). These conditions resulted in dramatic increases in glucose. To evaluate the predictive value of glucose fluctuation for subsequent adverse outcomes, we only focused on the 1st-week glycemic status and excluded patients with missing data of fasting glucose on admission or during the 1st week of admission. Admission glucose was denoted as G_0 (admission fasting glucose or the first-time fasting glucose), the peak value of the 1st-week glucose was denoted as G_{peak}, and the mean value of the 1st-week glucose level was denoted as G_{mean}. The SD of the 1st-week glucose (G_{SD}) was calculated as the square root of the variance of daily fasting glucose levels to represent glycemic fluctuations. According to the latest *Standards of Medical Care in Diabetes* from the American Diabetes Association (8), glycemic targets for our patients were classified as $\leq$6.1 mmol/L, 6.1–7.8 mmol/L, 7.8–10 mmol/L, and $>$10 mmol/L. Glycosylated hemoglobin (HbA_{1c}) is not a routine examination and was only performed on some patients with diabetes at admission.

Definitions and Outcomes

The illness severity of COVID-19 was defined according to the Chinese management guideline for COVID-19 (version 7.0) (10). We scored the severity of each patient by using CURB-65, a simple 6-point score (0–5) based on confusion, urea ($>$7 mmol/L), respiratory rate ($>$30/min), blood pressure (systolic $<$90 mmHg or diastolic $<$60 mmHg), and age ($\geq$65 years) (11). ARDS was determined by the consensus of two trained physician reviewers (D.L. and Y.W.) using the Berlin Definition, i.e., the development of acute, bilateral pulmonary infiltrates and hypoxemia (PaO_2:FiO_2 $\leq$300 mmHg) not primarily due to heart failure or volume overload (12). The discharge criteria were as follows: *1*) normal temperature for 3 days, *2*) symptom relief, *3*) negative throat-swab specimens repeated twice with at least a 1-day interval, and *4*) significant improvement in exudative lesions in lung imaging (10). The primary outcome was all-cause mortality during hospitalization, and we recorded the duration from admission to death or discharge. The secondary outcome was incidence of SARS-CoV-2–related ARDS. Hospital expenses and length of hospital stay were also noted.

Statistical Analysis

Differences in clinical characteristics and laboratory findings between groups were compared by use of the Kruskal-Wallis

test (continuous variables) and the χ^2 test or Fisher exact test (categorical variables). Kaplan-Meier methods were used for survival curve plotting. The associations of glycemic parameters with length of hospital stay and hospitalization expenses were fitted and presented as smoothing splines by use of generalized additive models. Previous reports of temporal changes in laboratory markers showed a decreasing trend of lymphocyte count and increasing trend of C-reactive protein, D-dimer, and lactate dehydrogenase (5). We also plotted smoothing splines to present the association of 1st-week glycemic status with subsequent changes in these laboratory markers.

We performed Cox proportional hazards regression to estimate the association between glycemic parameters and all-cause mortality adjusting for age, sex, comorbidities (including chronic pulmonary disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic kidney disease), glucocorticoids use, and baseline CURB-65 score. To tightly control the confounding factors from the baseline disease severity, we further adjusted for baseline oxygen saturation, lymphocyte count, and C-reactive protein (all continuous). The time to events was denoted as the days from the first-time fasting glucose to death or hospital discharge. The time from admission to ARDS could not be precisely identified in some cases. Therefore, we estimated the association of glycemic parameters with ARDS using the Delta method to compute the risk ratio (RR), and 95% CIs were estimated with 1,000 bootstrap replicates. Stratified analyses were performed for examination of the association of glycemic parameters with ARDS and mortality in the strata of age, sex, glucocorticoid therapy, diabetes, and hypertension. We used the joint test to obtain a *P* value for interaction for examining statistical significance of the difference between subgroups. All analyses were performed with R software (https://www.r-project.org) (version 3.6.1; The R Foundation) and EmpowerStats (http://www.empowerstats.com) (X&Y Solutions, Inc., Boston, MA). A two-sided significance level of 0.05 was used for evaluation of statistical significance.

RESULTS

A total of 548 adult inpatients infected with SARS-CoV-2 (median age 57 years [IQR 39–68]; $n = 298$ [54%] women) were included in these analyses. Among them, 197 (36%) had hypertension, 99 (18%) had diabetes, 32 (6%) had chronic kidney disease, 53 (10%) had cardiovascular disease, 37 (7%) had cerebrovascular disease, 37 (7%) had chronic pulmonary disease, 489 (89%) survived and were discharged, and 59 (11%) died. The data on clinical characteristics, laboratory markers, treatment, and outcomes according to patients' 1st-week mean glucose, i.e., ≤6.1 mmol/L (normal glucose), 6.1–7.8 mmol/L, 7.8–10 mmol/L, and >10 mmol/L (poor control), are presented in Table 1. Patients who had poor glycemic control during early phase were older, mostly male, and more likely to have underlying comorbidities, including hypertension, diabetes, chronic kidney disease, cardiovascular disease, and cerebrovascular disease. In the group of patients with mean glucose >10 mmol/L, the use rate of hypoglycemic medications (including insulin, $n = 29$ [66%]) was 75% (33 of 44), and 25% (11 of 44) of them did not receive any hypoglycemic treatment. According to the recorded glucose (<3.9 mmol/L) and nurses' records, 7% (41 of 548) of patients suffered hypoglycemia during hospitalization. Additionally, compared with those with normal glucose, patients with poor glycemic control had higher blood lactate levels, higher CURB-65 scores, and lower PaO_2:FiO_2. We observed that levels of several admission laboratory markers tended to be abnormal with deteriorating glycemic status. Patients with poor glycemic control were more likely to develop ARDS and have higher mortality, prolonged length of hospital stay, and higher hospital expenses.

A total of 99 (18%) patients reported diabetes; the use rate of hypoglycemic medications (including insulin, $n = 64$ of 99 [65%]) was 88% (87 of 99), and 12% (12 of 99) did not receive hypoglycemic treatment, 6% (6 of 99) suffered hypoglycemia, 55% (54 of 99) developed ARDS, and 17% (17 of 99) died. The clinical characteristics and laboratory findings of 99 COVID-19 patients with diabetes are presented in Supplementary Table 2. Compared with patients without diabetes, patients with preexisting diabetes had a higher risk of all-cause mortality, with age- and sex-adjusted hazard ratio (HR) 1.83 (95% CI 1.04, 3.21), $P = 0.03$ (Supplementary Fig. 2*A*). However, we did not observe any significant association between diabetes and mortality (adjusted HR 1.28 [95% CI 0.72, 2.25]) in the mutual adjustment model (including age, sex, hypertension, diabetes, chronic kidney disease, cardiovascular disease, and chronic obstructive pulmonary disease).

The Kaplan-Meier survival curve in Supplementary Fig. 2*B* and *C* shows the highest mortality in patients with the highest glucose level and the greatest magnitude of glycemic fluctuation. Similar trends were observed among 449 COVID-19 patients without preexisting diabetes (Supplementary Fig. 3). We further investigated the association of glycemic parameters (i.e., G_0, G_{peak}, G_{mean}, and G_{SD}) with risk of mortality and ARDS (Table 2). Patients with higher levels of G_{peak} or G_{mean} and a larger magnitude of glucose fluctuation (G_{SD}) presented higher risk of mortality and ARDS incidence, and these associations seemed to occur in a dose-dependent manner. However, the association between admission fasting glucose (G_0) and adverse outcomes became nonsignificant after adjustment for baseline disease severity (model 2 and model 3 in Table 2). The associations of G_{peak}, G_{mean}, and G_{SD} with mortality were attenuated but still significant after adjustment for glucocorticoids use and baseline CURB-65 score (model 2). Further controlling the confounders of disease severity and baseline inflammation slightly decreased the HRs for G_{peak} (2.20 [95% CI 1.70, 2.86; model 2] and 1.85 [95% CI 1.37, 2.49; model 3]) and G_{mean} (2.73 [95% CI 2.02, 3.70; model 2] and 2.43 [95% CI 1.78, 3.33; model 3]) but not for G_{SD} (1.74 [95% CI 1.15, 2.62; model 2] and 1.83 [95% CI 1.19, 2.82; model 3]). The multivariable-adjusted RRs for ARDS per SD increment of natural log (ln)-transformed glycemic parameters were 1.17 (95% CI 0.91, 1.59), 1.46 (95% CI 1.14, 2.00), 1.46 (95% CI 1.14, 2.00), and 1.25 (95% CI 1.01, 1.66) for G_0, G_{peak}, G_{mean}, and G_{SD}, respectively. In sensitivity analyses, the associations remained similar when we excluded 99 patients with diabetes (Supplementary Table 3). We performed stratified analyses to examine the association of glucose levels (G_{mean}) and glycemic fluctuations (G_{SD}) with mortality and ARDS in the strata of age, sex, glucocorticoid therapy, diabetes, and hypertension

Table 1—Clinical features and laboratory findings according to mean levels of the 1st-week glucose

	Mean glucose levels, mmol/L				
	≤6.1 (n = 356)	6.1–7.8 (n = 97)	7.8–10 (n = 51)	>10 (n = 44)	P
Age, years	50 (35–64)	64 (55–71)	65 (54–72)	65 (55–73)	<0.001
Male	144 (40)	52 (54)	30 (59)	24 (55)	0.01
Symptom onset					
Fever	281 (79)	80 (82)	38 (75)	33 (75)	0.63
Cough	237 (67)	64 (66)	36 (71)	34 (77)	0.50
Dyspnea	133 (37)	45 (46)	20 (39)	21 (48)	0.29
Fatigue	123 (35)	41 (42)	18 (35)	19 (43)	0.42
Muscle ache	89 (25)	25 (26)	9 (18)	9 (20)	0.62
Diarrhea	38 (11)	7 (7)	4 (8)	2 (5)	0.46
Headache	20 (6)	8 (8)	3 (6)	4 (9)	0.69
Pharyngalgia	15 (4)	2 (2)	2 (4)	3 (7)	0.59
Comorbidities					
Hypertension	93 (26)	48 (49)	28 (55)	28 (64)	<0.001
Diabetes	19 (5)	22 (23)	23 (45)	35 (80)	<0.001
Chronic kidney disease	8 (2)	12 (12)	5 (10)	8 (18)	<0.001
Cardiovascular disease	25 (7)	15 (15)	4 (8)	9 (20)	0.005
Cerebrovascular disease	16 (4)	10 (10)	6 (12)	5 (11)	0.04
Chronic pulmonary disease	23 (6)	7 (7)	2 (4)	0 (0)	0.30
In-hospital treatment					
Quinolones	240 (67)	63 (65)	31 (61)	30 (68)	0.79
Cephalosporins	151 (42)	55 (57)	35 (69)	24 (55)	<0.001
Ribavirin	324 (91)	84 (87)	42 (82)	37 (84)	0.15
Oseltamivir	92 (26)	28 (29)	14 (27)	10 (23)	0.88
Arbidol	100 (28)	21 (22)	8 (16)	9 (20)	0.16
Glucocorticoids	195 (55)	72 (74)	39 (76)	27 (61)	<0.001
Intravenous immunoglobulin	175 (49)	59 (61)	25 (49)	26 (59)	0.16
Noninvasive ventilation	27 (8)	22 (23)	21 (41)	18 (41)	<0.001
Hypoglycemic agents	13 (4)	23 (24)	23 (45)	33 (75)	<0.001
Biguanides	7 (2)	5 (5)	7 (14)	11 (25)	<0.001
α-Glucosidase inhibitors	4 (1)	16 (16)	12 (24)	16 (36)	<0.001
Glinides	4 (1)	7 (7)	3 (6)	5 (11)	<0.001
Thiazolidinediones	1 (0)	1 (1)	2 (4)	2 (5)	0.01
DPP-4 inhibitors	4 (1)	4 (4)	4 (8)	6 (14)	<0.001
Insulin therapy	4 (1)	17 (18)	18 (35)	29 (66)	<0.001
Without any hypoglycemic treatment	343 (96)	74 (76)	28 (55)	11 (25)	<0.001
Hypoglycemia	33 (9)	6 (6)	1 (2)	1 (2)	0.12
Blood gas analysis and severity					
Lactate, mmol/L	1.2 (0.8–1.8)	1.3 (0.9–2.3)	1.7 (1.2–2.5)	1.5 (1.2–2.4)	<0.001
PaO_2:FiO_2, mmHg	420 (286–522)	286 (207–430)	253 (141–331)	230 (149–326)	<0.001
Baseline CURB-65	0 (0–1)	1 (0–1)	1 (0–2)	1 (1–2)	<0.001
Disease severity					<0.001
Mild	244 (69)	41 (42)	15 (29)	12 (27)	
Severe or critical	112 (31)	56 (58)	36 (71)	32 (73)	
Laboratory findings on admission to hospital					
White blood cell count, $\times 10^9$/L	4.7 (3.6–6.0)	5.4 (4.0–7.5)	5.5 (3.9–7.9)	5.0 (3.7–7.8)	<0.001
Lymphocyte count, $\times 10^9$/L	1.1 (0.7–1.4)	0.8 (0.6–1.2)	0.6 (0.5–1.2)	0.8 (0.5–1.1)	<0.001
C-reactive protein, mg/dL	1.1 (0.3–3.5)	3.6 (1.5–6.2)	2.9 (1.3–4.8)	4.7 (2.3–9.1)	<0.001
Procalcitonin, ng/mL	0.05 (0.04–0.08)	0.08 (0.06–0.13)	0.08 (0.06–0.18)	0.11 (0.05–0.28)	<0.001
Creatinine, μmol/L	62 (51–76)	69 (54–91)	71 (57–98)	73 (53–83)	0.002
ALT, units/L	18 (12–30)	26 (16–37)	25 (15–33)	21 (15–32)	0.001
Fibrinogen, g/L	2.8 (2.4–3.3)	3.3 (2.8–3.8)	3.2 (2.8–3.6)	3.4 (2.9–4.0)	<0.001
D-dimer, μg/L	0.5 (0.2–1.0)	0.7 (0.4–1.8)	0.9 (0.4–1.6)	1.1 (0.5–3.4)	<0.001
Lactate dehydrogenase, units/L	180 (144–231)	224 (180–321)	232 (180–287)	227 (191–369)	<0.001
Creatine kinase–MB, units/L	7 (5–10)	9 (7–13)	9 (8–12)	9 (6–13)	<0.001
Outcomes					
ARDS	100 (28)	52 (54)	34 (67)	29 (66)	<0.001
Death	9 (3)	18 (19)	16 (31)	16 (36)	<0.001
Length of hospital stay, days*	23 (16–32)	26 (21–37)	28 (20–36)	30 (23–38)	<0.001
Hospitalization expenses, ×1,000 RMB	22 (13–34)	31 (20–47)	30 (19–48)	30 (19–52)	<0.001

Data are presented as number (percentage) for categorical data and median (IQR) for continuous data. DPP-4, dipeptidyl peptidase 4. *Only showing these data for survivors.

Table 2—Associations of glycemic parameters with ARDS and all-cause mortality in COVID-19 patients

		HR (95% CI) for mortality			
	Death/total, *n*	Crude model	Model 1	Model 2	Model 3
G_0, mmol//L					
≤6.1	17/315	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
6.1–7.8	20/115	2.80 (1.46, 5.34)	2.08 (1.04, 4.12)	1.91 (0.96, 3.82)	1.53 (0.76, 3.10)
7.8–10	10/63	2.39 (1.09, 5.22)	2.03 (0.83, 4.92)	1.81 (0.74, 4.41)	1.11 (0.43, 2.84)
>10	12/55	3.35 (1.60, 7.02)	2.01 (0.84, 4.79)	1.92 (0.79, 4.66)	1.28 (0.51, 3.22)
Per SD increment of ln(G_0)		1.43 (1.18, 1.74)	1.42 (1.11, 1.82)	1.25 (0.96, 1.63)	1.15 (0.87, 1.53)
G_{peak}, mmol//L					
≤6.1	2/224	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
6.1–7.8	12/127	8.68 (1.94, 38.82)	6.03 (1.33, 27.26)	5.83 (1.28, 26.47)	7.77 (1.64, 36.88)
7.8–10	9/83	8.96 (1.93, 41.51)	6.75 (1.44, 31.62)	6.48 (1.37, 30.62)	6.18 (1.28, 29.88)
>10	36/114	29.26 (7.04, 121.60)	20.61 (4.79, 88.68)	18.68 (4.29, 81.35)	12.75 (2.86, 56.90)
Per SD increment of ln(G_{peak})		2.12 (1.73, 2.59)	2.27 (1.77, 2.92)	2.20 (1.70, 2.86)	1.85 (1.37, 2.49)
G_{mean}, mmol//L					
≤6.1	9/356	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
6.1–7.8	18/97	6.58 (2.96, 14.66)	4.35 (1.90, 9.97)	4.05 (1.75, 9.39)	2.75 (1.12, 6.74)
7.8–10	16/51	10.98 (4.85, 24.87)	10.29 (4.40, 24.05)	9.18 (3.84, 21.94)	6.03 (2.39, 15.25)
>10	16/44	15.02 (6.64, 34.00)	28.64 (11.00, 74.52)	23.23 (8.37, 64.53)	12.23 (4.22, 35.46)
Per SD increment of ln(G_{mean})		2.22 (1.83, 2.68)	3.10 (2.36, 4.09)	2.73 (2.02, 3.70)	2.43 (1.78, 3.33)
G_{SD}, mmol//L*					
≤0.4	5/140	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
0.4–0.9	7/135	1.16 (0.37, 3.65)	0.89 (0.28, 2.82)	0.99 (0.31, 3.20)	0.95 (0.30, 3.02)
0.9–1.8	17/138	2.67 (0.98, 7.24)	1.86 (0.67, 5.14)	1.76 (0.63, 4.89)	1.92 (0.68, 5.42)
>1.8	30/135	4.71 (1.83, 12.17)	2.85 (1.07, 7.64)	2.64 (1.02, 7.15)	2.73 (1.06, 7.73)
Per SD increment of ln(G_{SD})		2.27 (1.66, 3.11)	2.14 (1.46, 3.16)	1.74 (1.15, 2.62)	1.83 (1.19, 2.82)
		RR (95% CI) for ARDS			
	ARDS/total, *n*	Crude model	Model 1	Model 2	Model 3
G_0, mmol//L					
≤6.1	92/315	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
6.1–7.8	54/115	2.15 (1.36, 3.38)	1.82 (1.07, 3.03)	1.72 (1.00, 2.93)	1.40 (0.76, 2.51)
7.8–10	36/63	3.23 (1.88, 5.88)	2.63 (1.36, 5.44)	2.53 (1.30, 5.26)	2.01 (0.98, 4.22)
>10	33/55	3.64 (2.10, 6.83)	2.71 (1.29, 6.23)	2.42 (1.16, 5.61)	1.73 (0.75, 4.33)
Per SD increment of ln(G_0)		1.67 (1.38, 2.12)	1.53 (1.22, 2.01)	1.44 (1.17, 1.87)	1.17 (0.91, 1.59)
G_{peak}, mmol//L					
≤6.1	51/224	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
6.1–7.8	49/127	2.13 (1.35, 3.49)	1.73 (1.04, 2.94)	1.44 (0.83, 2.67)	1.41 (0.79, 2.66)
7.8–10	44/83	3.83 (2.28, 6.42)	2.89 (1.63, 5.32)	2.31 (1.27, 4.47)	2.19 (1.18, 4.16)
>10	71/114	5.60 (3.48, 9.67)	3.80 (2.11, 7.56)	2.65 (1.39, 5.42)	2.23 (1.14, 4.94)
Per SD increment of ln(G_{peak})		2.12 (1.74, 2.62)	1.92 (1.53, 2.54)	1.67 (1.32, 2.25)	1.46 (1.14, 2.00)
G_{mean}, mmol//L					
≤6.1	100/356	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
6.1–7.8	52/97	2.96 (1.92, 4.75)	2.16 (1.31, 3.86)	1.83 (1.07, 3.22)	1.50 (0.85, 2.68)
7.8–10	34/51	5.12 (2.85, 10.20)	3.84 (2.04, 8.64)	2.93 (1.50, 6.59)	2.09 (0.94, 5.61)
>10	29/44	4.95 (2.76, 11.11)	4.26 (2.13, 11.10)	3.25 (1.61, 8.68)	3.05 (1.45, 7.28)
Per SD increment of ln(G_{mean})		2.04 (1.68, 2.60)	1.88 (1.48, 2.49)	1.66 (1.32, 2.24)	1.48 (1.14, 2.07)
G_{SD}, mmol//L*					
≤0.4	31/140	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
0.4–0.9	47/135	1.88 (1.07, 3.35)	1.50 (0.82, 2.80)	1.39 (0.75, 2.63)	1.29 (0.70, 2.42)
0.9–1.8	59/138	2.63 (1.55, 4.51)	1.96 (1.12, 3.65)	1.78 (0.99, 3.34)	1.54 (0.85, 2.97)
>1.8	78/135	4.81 (2.80, 8.20)	3.01 (1.63, 5.99)	2.25 (1.10, 4.69)	1.97 (1.01, 4.04)
Per SD increment of ln(G_{SD})		1.94 (1.59, 2.42)	1.64 (1.33, 2.18)	1.36 (1.04, 1.84)	1.25 (1.01, 1.66)

Model 1: adjustments for age (continuous), sex, baseline comorbidities (including chronic obstructive pulmonary disease, hypertension, diabetes, chronic kidney disease, cardiovascular disease, and cerebrovascular disease). Model 2: model 1 adjustments plus glucocorticoids use (yes/no) and baseline CURB-65 score. Model 3: model 2 adjustments plus baseline oxygen saturation, lymphocyte count, and C-reactive protein (all continuous). ref., reference. *Additional adjustment for baseline glucose level in model 2 and model 3.

(Fig. 1). We found that G_{mean} and G_{SD} were positively associated with mortality risk in all subgroups. The association of G_{mean} and G_{SD} with ARDS seemed stronger in patients receiving glucocorticoid than in those without glucocorticoid therapy (all P interaction <0.05).

Levels of G_{peak}, G_{mean}, and G_{SD} were associated with changes in several laboratory markers (Supplementary Fig. 4). These three glycemic parameters were negatively associated with 14-day lymphocyte count and positively associated with 14-day C-reactive protein, 14-day lactate dehydrogenase, and 14-day D-dimer. However,

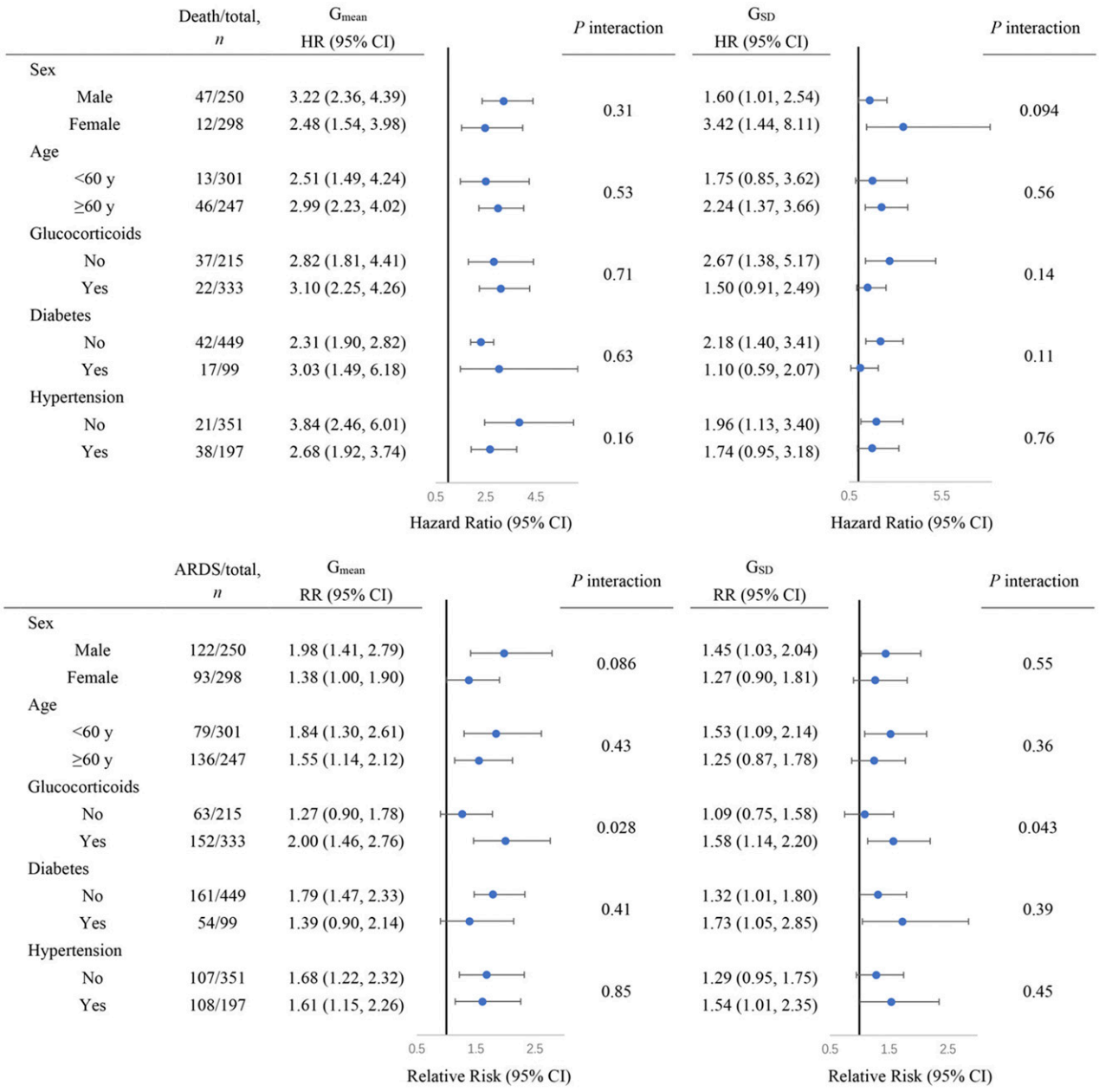

Figure 1—Association of mean glucose levels and glycemic fluctuations with ARDS and all-cause mortality in stratified analyses. G_{mean} and G_{SD} were ln transformed and modeled as per SD increase. The multivariate model was adjusted for age (continuous), sex, comorbidities (including chronic pulmonary disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic kidney disease), glucocorticoids use (yes/no), and baseline CURB-65 score. Associations of G_{SD} with mortality and ARDS were further adjusted for baseline glucose level. y, years.

these associations seemed weak for G_0. In addition, we observed positive associations of G_0, G_{peak}, G_{mean}, and G_{SD} with length of hospital stay and hospital expenses after adjustment for potential confounders (Fig. 2). High levels of early-phase glucose and large magnitude of glycemic fluctuations were associated with prolonged hospital stays and increased expenses.

CONCLUSIONS

In this large case series, we described the clinical manifestations, treatment, and laboratory markers of 548 hospitalized COVID-19 patients according to their blood glucose control. Compared with admission fasting glucose, the parameters of mean glucose, peak glucose, and the magnitude of glycemic fluctuations during the early-phase hospitalization were more relevant to adverse outcomes. These glycemic parameters were associated with increased hospital expenses, prolonged length of stay, and augmented risk of ARDS and all-cause mortality. We observed that more than one-half (55%) of the patients with a mean glucose of 7.8–10 mmol/L, one-quarter of patients with a mean glucose of >10 mmol/L, and 12% of patients with diabetes did not receive any hypoglycemic treatment during hospitalization. The low proportion of hypoglycemic therapy use among patients with COVID-19 with hyperglycemia or diabetes during the early phase of the SARS-CoV-2 outbreak may be largely explained by the shortage of medical resources, including staff, beds, and norms and standards of clinical practice.

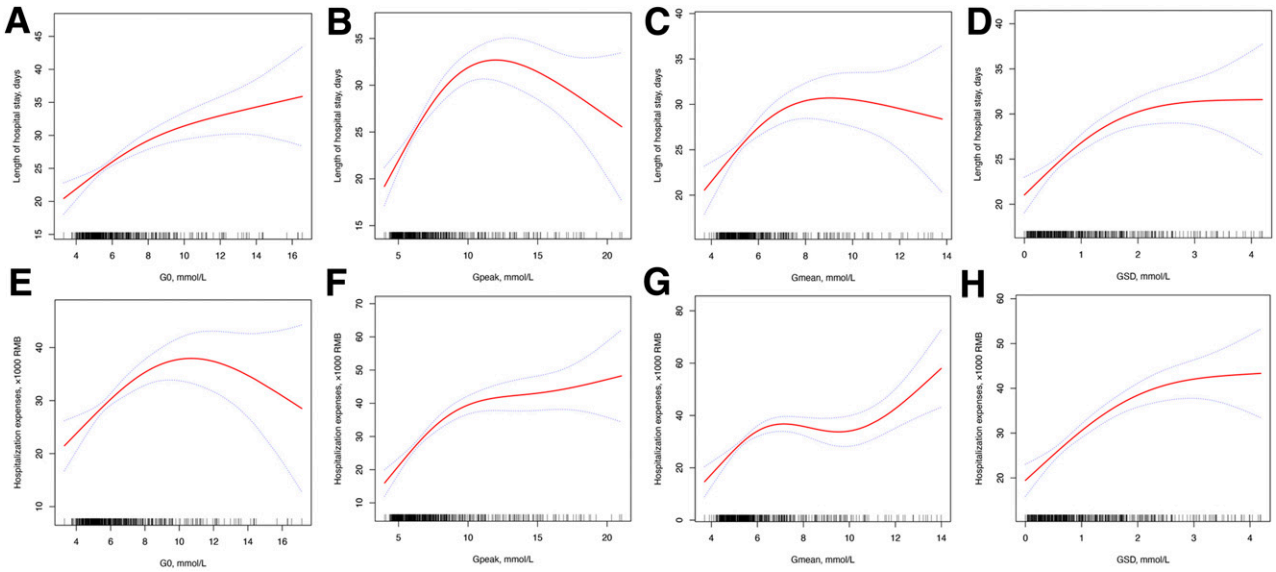

Figure 2—Association of glycemic parameters with length of hospital stay (*A–D*) and hospitalization expenses (*E–H*). Smoothing splines were generated by generalized additive models and adjusted for age (continuous), sex, comorbidities (including chronic pulmonary disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic kidney disease), glucocorticoids use (yes/no), and baseline CURB-65 score. Red line, estimated length of hospital stay or hospitalization expenses; blue dotted line, 95% CIs.

Optimal in-hospital glycemic control is associated with better prognosis for COVID-19 patients with diabetes (13). Recent evidence indicated that diabetes status and admission fasting glucose were associated with poor prognosis of COVID-19 patients (14–18). We observed a significant association between diabetes and mortality after adjusting for age and sex. However, this association became null when we performed mutual adjustment with other comorbidities. These comorbidities (e.g., hypertension and cardiovascular disease) are largely overlapped with diabetes. More evidence is warranted to determine the effect size of preexisting diabetes on poor prognosis of COVID-19 independent of other comorbidities. In the regression model with adjustment for age, sex, and comorbidities, we observed significant associations for all glycemic parameters and adverse outcomes. With further adjustment for glucocorticoids use, disease severity, and inflammation, the null finding was observed between fasting glucose at admission and poor prognosis. Inflammation triggers hyperglycemia and vice versa, and a severe condition of COVID-19 will predispose a patient to acute hyperglycemia (19,20). Some studies did not adjust for comorbidities (18) or baseline disease severity and inflammation level (14–16), which might overestimate the association between admission fasting glucose and adverse outcomes. The associations of G_{peak}, G_{mean}, and G_{SD} with mortality and ARDS were much attenuated but still significant and presented a dose-dependent relationship in the fully adjusted model, indicating that elevated peak and mean value of fasting glucose and glycemic fluctuations during the early-phase hospitalization were independently associated with ARDS and subsequent mortality in COVID-19 patients with and without diabetes. To the best of our knowledge, we report for the first time the association between glucose variability and adverse COVID-19 outcomes, which might add to the knowledge of glycemic control strategies for COVID-19 and provide insights for further research. Hyperglycemia acutely increased the peripheral cytokine levels through an oxidative mechanism (19). In a recent mechanism study, Codo et al. (21) found that elevated glucose levels and glycolysis promote SARS-CoV-2 replication and proinflammatory cytokine production in monocytes, which drives in T cell dysfunction and lung epithelial death. Therefore, glycemic monitoring and control are important for all COVID-19 patients, regardless of whether they have diabetes.

An interesting finding in the current study involves the relationship between glycemic control and length of hospital stay and expenses. The length of hospital stay is associated with disease recovery and viral clearance (10), and increased expenses signify higher medical economic burdens in the context of the COVID-19 pandemic. From a public health perspective, reductions in length of stay and expenses help relieve individual, social, medical, and economic burdens. However, we cannot conclude that aggressive glucose control early in the course of disease would reduce length of stay, decrease economic burden, and curb risk of ARDS or death because of the potential reverse causation bias. Although maintaining glucose homeostasis has direct and immediate benefits for inpatients with hyperglycemia or diabetes (8), it is important to evaluate the potential clinical benefits of early effective glucose control for patients infected with SARS-CoV-2. Measurements of admission HbA_{1c}, in-hospital random blood glucose, or postprandial blood glucose may assist blood glucose management and the hypoglycemia strategy. Optimizing medication regimens to attenuate glucose swings is equally important.

Recently published clinical trial evidence supports the benefits of glucocorticoids in the treatment of severe COVID-19 (22,23). Although glucocorticoids contribute to hyperglycemia, our stratified analyses revealed a positive association

of glycemic level and fluctuation with mortality in the glucocorticoid use group and the nonuse group. The magnitude of the association of glycemic level and fluctuation with ARDS risk was more pronounced in patients receiving glucocorticoids than in those not receiving such treatment. However, these results should be interpreted cautiously because patients with ARDS were more likely to receive glucocorticoid treatment and reverse causality may thus be present. Further trials are warranted to confirm the clinical benefits of strengthened glycemic control in COVID-19 patients receiving glucocorticoid therapy. Unknown diabetes may be attributed to hyperglycemia during hospitalization (24). The prevalence of reported diabetes in our cohort was 18% (99 of 548), which is comparable with that in recent reports from Wuhan (5,25). However, we cannot rule out the possibility of unreported diabetes, and we did not measure HbA_{1c} for all patients. Therefore, we adjusted for reported diabetes in our regression models and performed sensitivity analyses in the strata of diabetes. Our results on the association of glycemic level and fluctuation with ARDS and mortality are robust in the multivariable regression models and in stratified analyses.

The current study has several limitations. First, real-time continuous glucose monitoring provides more accurate glycemic fluctuation parameters than daily fasting blood biochemistry (26). However, continuous glucose monitoring may be unavailable in emergency circumstances during an epidemic outbreak. Additionally, HbA_{1c} was not routinely measured in the cohort, which precluded conclusions on how long-standing poor glycemic control contributes to adverse outcomes among inpatients infected with SARS-CoV-2. Second, this study was conducted at a single-center hospital, and we could not rule out differences in patients' disease severity, hardware or facility standards, and doctors' professional experience among designated COVID-19 hospitals (4,5). These differences may affect in-hospital glucose management and the corresponding outcomes. Meanwhile, the single-center design might limit the sample size and contribute to the imprecision of many of the estimates; thus, further investigation through a multicenter design or nationwide data are warranted. Third, while we performed multivariable analyses and sensitivity analyses, we cannot exclude the presence of residual confounders (e.g., the degree of specific organ damage or the differences in the treatment regimens used) and potential biases. Fourth, given the observational nature, direct causal inference could not be drawn. Finally, due to the rapid increase in related publications and preprints since the outbreak of COVID-19, researchers should pay attention to other publications that use data from the Central Hospital of Wuhan to avoid inclusion of overlapping patients in future reviews or meta-analyses (27).

In summary, early-phase in-hospital fasting glucose level and glycemic fluctuation were independently associated with poor prognosis in adult patients hospitalized for COVID-19. Our findings may have implications for optimizing glycemic control strategies in patients with COVID-19 during the early course of hospitalization.

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