Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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ORIGINAL RESEARCH

Newly-Diagnosed Diabetes and Sustained Hyperglycemia are Associated with Poorer Outcomes in COVID-19 Inpatients Without Pre-Existing Diabetes

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Purpose: To analyze the impact of hyperglycemia on the clinical outcome of COVID-19 in patients with newly diagnosed diabetes (NDD).

Patients and Methods: We performed a retrospective study of 3114 cases of COVID-19 without pre-existing diabetes, 351 of which had NDD, in Hubei Province, China. The Cox regression model was used to calculate the risk of adverse clinical outcomes comparing the NDD vs non-NDD group before and after propensity score-matched (PSM) analysis. Patients with NDD were further divided into a sustained hyperglycemia group, a fluctuating group, and a remitted group based on their blood glucose levels during hospitalization as well as into hypoglycemic agent users and nonusers.

Results: Compared to the non-NDD individuals, individuals with NDD had a significantly increased risk of all-cause mortality (adjusted HR after PSM, 2.65; 95% CI, 1.49–4.72; $P = 0.001$) and secondary outcomes involving organ damage during the 28-day follow-up period. Subgroup analyses indicated that among individuals with NDD, the individuals with remitted hyperglycemia had the lowest 28-day mortality, whereas those with sustained hyperglycemia had the highest (IRR 24.27; 95% CI, 3.21–183.36; $P < 0.001$). Moreover, individuals treated with hypoglycemic agents had significantly lower all-cause mortality than those not treated with hypoglycemic agents (IRR 0.08; 95% CI, 0.01–0.56; $P < 0.001$).

Conclusion: Our study reinforces the clinical message that NDD is strongly associated with poor outcomes in COVID-19 patients. Furthermore, resolved hyperglycemia in the later phase of the disease and the use of hypoglycemic agents were associated with improved prognosis in patients with NDD.

Keywords: COVID-19, newly diagnosed diabetes, hyperglycemia, prognosis, blood glucose

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) continues to escalate with particular intensity around the world. As of 10 September 2021, there have been more than 223 million confirmed cases of COVID-19 globally, including 4,602,882 deaths. Diabetes mellitus (DM) is one of the most common comorbidities in patients with COVID-19.[1,2] A large number of studies almost unanimously showed that COVID-19 patients with DM are more likely to develop severe illness and have a higher risk of mortality than non-DM patients.[3,4] Intriguingly, several recent studies suggest a bidirectional relationship between DM and COVID-19.[4,5]

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Indeed, new-onset hyperglycemia is observed in COVID-19 patients without pre-existing diabetes.[6,7] More importantly, currently available evidence hints that COVID-19 patients with newly diagnosed diabetes (NDD) have poorer outcomes than those with normoglycemia and those with pre-existing diabetes.[8,9]

Despite the significance of these findings, most of the current evidence implicating NDD in worse COVID-19 prognosis has come from relatively limited sample cohorts.[9–11] In addition, most of these studies used baseline blood glucose for diagnosis rather than repeated measurements obtained during hospitalization.[9,11–13] Another unsettled issue is that an independent association is difficult to determine due to the existence of substantial confounding factors. For instance, concerns have been raised that in-hospital use of glucocorticoids may mediate the detrimental effects of NDD on COVID-19 severity.[14] Additionally, it is unclear whether the alteration of glucose metabolism that occurs with a sudden onset in severe COVID-19 persists or remits during the later phase of the disease. Moreover, our previous study demonstrated that well-controlled blood glucose is associated with a significant reduction in mortality in COVID-19 patients with pre-existing diabetes.[15] This indicates that glycemic management can be crucial in improving COVID-19 outcomes in diabetic patients. However, whether unsatisfactory glucose control mediates the impact of NDD on COVID-19 outcome has yet to be investigated.

Materials and Methods

Study Design and Participants

This retrospective, multicenter study involved 7871 original participants diagnosed with COVID-19; each of the participants had at least two fasting plasma glucose (FPG) records and was admitted to one of 17 hospitals in Hubei Province, China between December 30th, 2019 and April 12th, 2020 (Figure 1). COVID-19 was diagnosed based on chest computed tomography (CT) and/or reverse transcription-polymerase chain reaction (RT-PCR) following WHO interim guidance[16] and the criteria of the New Coronavirus Pneumonia Prevention and Control Program (5th edition) published by the National Health Commission of China.[17] This study was performed in compliance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the central ethics committee of Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University. The study design was also individually approved by each collaborating hospital or by the hospital's institutional ethics board. The requirement to obtain informed consent from the study participants was waived by the ethics committees of the individual hospitals due to the urgency of the COVID-19 pandemic. Personal identification information (eg, name and ID) of the study subjects were anonymized and replaced with a coding system before data extraction. Among the initially included participants, those for whom complete electronic medical records were not available (eg, transfer to any other hospital), individuals <18 or >75 years of age, pregnant women, and individuals with acute lethal organ injury (ie, acute coronary syndrome, acute stroke, and severe acute pancreatitis) were excluded. Subjects with a previous history of diabetes or with a previous history of using glucose-lowering medication and those who received glucocorticoid treatment during hospitalization were also excluded from our final analysis (Figure 1).

Data Collection

The medical records of the patients were analyzed by an integrated research group that included physicians, data scientists, and statisticians. Basic information, clinical characteristics, laboratory findings, radiographic manifestations from CT, therapeutic intervention, and outcomes during hospitalization were extracted from electronic medical records. Major clinical symptoms (ie, fever, cough, fatigue, dyspnea, diarrhea, and comorbidities) were collected. Laboratory findings, including a routine blood test, FPG, 2-h postprandial blood glucose (2hPG) and random blood glucose, C-reactive protein (CRP), procalcitonin, D-dimer, and serum biochemical markers of liver injury, kidney injury and cardiac dysfunction, were also recorded during hospitalization. In-hospital medication and life support intervention included the types of drugs administered, oxygen inhalation treatment and use of mechanical ventilation. The primary and secondary outcomes were evaluated by physicians. To guarantee accuracy and consistency, the participants' medical records were reviewed, confirmed, and double-checked by experienced physicians.

Definitions and Outcomes

The diagnosis of NDD was confirmed by at least two FPG readings ≥7 mmol/L according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017 edition) and the American Diabetes Association (ADA) guidelines criteria.[18,19] Among patients with NDD and ≥3 FPG records during hospitalization, we conducted

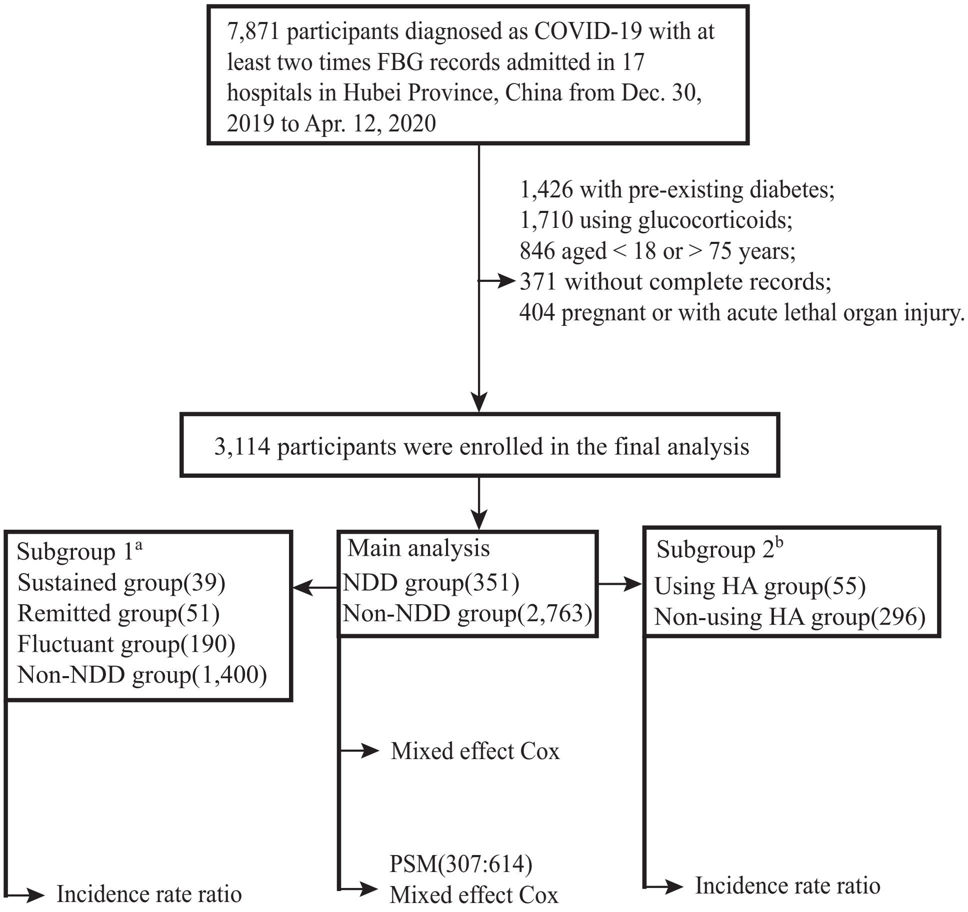

Figure 1 The flow chart of patient inclusion and analysis procedures in the study. [a]The participants with at least three times fasting blood glucose records. [b]The particients with newly-diagnosed diabetes.
Abbreviations: FBG, fasting blood glucose; NDD, newly-diagnosed diabetes; HA, hypoglycemic agents.

subgroup analyses in which we divided these patients into a sustained hyperglycemia group (FPG ≥7 mmol/L in all records), a remitted group (FPG ≥7 mmol/L at the first two records but <7 mmol/L at later tests), and a fluctuating group (the remaining participants). We also analyzed NDD patients in subgroups based on whether or not they received hypoglycemic agents (HA, either insulin or oral hypoglycemic agents).

The primary endpoint was 28-day all-cause death. The secondary endpoints were the occurrence of acute respiratory distress syndrome (ARDS), acute liver injury, acute kidney injury, acute cardiac injury, or heart failure. ARDS was defined according to the WHO interim guideline "Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected". Acute kidney injury was diagnosed by an elevation in serum creatinine level ≥26.5 μmol/L within 48 hours.[20] Acute cardiac injury was defined as a serum level of cardiac troponin I/T (cTnI/T) above the upper limit of normal (ULN).[21] Acute liver injury was determined based on serum alanine transaminase (ALT) or alkaline phosphatase levels more than 3-fold the ULN.[22]

Propensity Score-Matched Analysis

We used propensity score-matched analysis (PSM) to match the patients with and without NDD.[23] Baseline matching variables with a standardized difference (SD) greater than 0.10 were selected; they are as follows: age, sex, oxygen saturation, respiratory rate, pre-existing comorbidities (coronary heart disease, hypertension, chronic kidney disease, and chronic liver disease), and biomarkers indicative of disease severity and organ injury (ie, neutrophil count increase, CRP increase, lymphocyte count decrease, alanine aminotransferase (ALT) increase, creatinine increase, high-sensitivity C-reactive protein (hs-CRP) increase, procalcitonin increase, HDL-C decrease, triglyceride (TG) increase, and bilateral lesions on chest CT).

Mixed-Effects Cox Model

The Cox proportional hazards model was used to calculate the risk of primary and secondary endpoints and the corresponding hazard ratio (HR) comparing the NDD group with the non-NDD group before and after PSM. Baseline covariates that changed the HRs by at least 10% when added to the Cox model and that had an SD greater than 0.10 between the groups were adjusted.[24,25] In the mixed-effects Cox model, we modeled the site as a random effect and used correlation testing based on the Schoenfeld residuals to verify proportional hazard assumptions.[25] In the Cox analysis, discharged patients were treated as having no competing risk, but their data were not censored. The reasons for this are as follows: one, individuals with COVID-19 would not be discharged unless continuous viral PCR was negative twice in succession and their symptoms were relieved; two, because it was necessary to quarantine individuals for two weeks after their discharge from the hospital, any deaths that occurred among these patients would be documented. Discharged individuals were less likely to die from COVID-19 than patients who remained hospitalized, and information on their survival after discharge was still available.[25]

Missing Data and Imputation

A complete set of variables for each patient was used for matching in PSM analysis and for adjustment in Cox analysis. We used nonparametric missing value imputation based on the missForest procedure in R to impute the missing data on the noninvasive test.[26] A random forest model based on the remaining variables in the dataset was constructed and used to predict the missing values with an estimation of the internally cross-validated errors.[23]

Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR), and categorical variables are presented as frequency and percentage (%). For continuous variables, Student's t-tests (for normally distributed data) and Mann–Whitney *U*-tests (for nonnormally distributed data) were used to analyze comparisons between groups. For categorical variables, Fisher's exact test and the chi-square test were used to analyze comparisons. Dynamic changes in the levels of laboratory indicators in different groups were presented using locally weighted scatterplot smoothing (LOESS). The risk for endpoint outcomes and corresponding HR were analyzed using the mixed-effects Cox model. E-value analysis was performed to address potential underlying confounding effects and to assess the robustness of the association between NDD and all-cause mortality in the Cox model.[27] Person-time data (incidence) of two groups with different exposures (ie, the sustained hyperglycemia group or the fluctuating group vs the remitted group, or NDD patients with HA vs those without) are expressed as the difference between incidence rates (IRs) or as incidence rates ratios (IRRs). The IRRs of endpoint outcomes were calculated to estimate the difference in absolute change in the incidences of two comparison groups.[25] The cumulative rates of death were compared by applying the Kaplan–Meier method.[28] A difference with a two-sided α less than 0.05 was considered statistically significant. All statistical analyses were performed using R-3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical Characteristics of COVID-19 Patients with and without NDD Upon Admission

A total of 3114 of 7871 patients with COVID-19 admitted to 17 hospitals in Hubei Province, China were included in our final analyses; among them, 351 (11.27%) were classified as NDD cases (192 males, 54.70%), and 2763 (88.73%) were designated as non-NDD cases (1198 males, 43.36%) (Figure 1). Patients with NDD were older (61 years vs 56 years, $P < 0.001$), more likely to be male (54.70% vs 43.36%, $P < 0.001$) and had more symptoms of dyspnea (30.48% vs 18.02%, $P < 0.001$) than non-NDD patients. In addition. NDD patients had a higher burden of pre-existing comorbidities, including hypertension (37.89% vs 25.73%, $P < 0.001$), chronic renal disease (5.70% vs 1.63%, $P < 0.001$), chronic liver disease (3.13% vs 1.70%, $P = 0.097$), coronary heart disease (7.69% vs 5.57%, $P = 0.140$), and cerebrovascular disease (3.70% vs 1.95%, $P = 0.053$) than non-NDD patients. The median interval from symptom onset to admission in patients with or without NDD was 11 (IQR, 7–17) and 13 (IQR, 7–21) days, respectively (Table 1).

Compared to patients without NDD, higher proportions of patients with NDD had lymphopenia (55.04% vs 27.80%), increased leukocyte counts (19.60% vs 4.34%), or increased neutrophil counts (27.38% vs 7.22%). Blood glucose levels in NDD cases were higher than those in the

Table 1 Characteristics of COVID-19 Patients in the Newly-Diagnosed Diabetes (NDD) and Non-NDD Groups Before and After Propensity Score Matching

Parameters	**Unmatched**				**Matched (1:2)**			
	NDD (n = 351)	**Non-NDD (n = 2763)**	***P*-value**	**SD**	**NDD (n = 307)**	**Non-NDD (n = 614)**	***P*-value**	**SD**
Clinical characteristics on admission								
Days from symptom to hospital, median(IQR)	11(7–17)	13(7–21)	0.002	−0.157	10(7–17)	11(7–18)	0.067	−0.063
Age, median (IQR)	61(51–68)	56(42–65)	<0.001	0.427	59(51–66)	61(50–68)	0.224	−0.031
Male gender, n (%)	192(54.70%)	1198(43.36%)	<0.001	0.228	159(51.79%)	299(48.70%)	0.415	0.062
Heart rate, median (IQR), bpm	85(78–98)	83(78–94)	0.069	0.126	84(78–97)	84(78–96)	0.597	0.044
Respiratory rate, median (IQR), bpm	20(19–22)	20(19–20)	<0.001	0.319	20(19–21)	20(19–21)	0.873	0.038
DBP, median (IQR), mmH	79(71–88)	79(71–87)	0.841	0.025	79(71–87)	79(71–87)	0.839	0.019
SBP, median (IQR), mmHg	128.5(119–140)	127(119–138)	0.214	0.096	128(118–140)	128(118–140)	0.944	0.046
Fever, n (%)	277(78.92%)	2041(73.87%)	0.048	0.119	239(77.85%)	480(78.18%)	0.978	−0.008
Cough, n (%)	231(65.81%)	1764(63.84%)	0.506	0.041	197(64.17%)	410(66.78%)	0.476	−0.055
Fatigue, n (%)	102(29.06%)	809(29.28%)	0.982	−0.005	91(29.64%)	184(29.97%)	0.980	−0.007
Dyspnea, n (%)	107(30.48%)	498(18.02%)	<0.001	0.294	80(26.06%)	125(20.36%)	0.061	0.135
Comorbidities on admission								
COPD, n (%)	5(1.42%)	26(0.94%)	0.387	0.045	3(0.98%)	3(0.49%)	0.406	0.057
Cerebrovascular diseases, n (%)	13(3.70%)	54(1.95%)	0.053	0.106	8(2.61%)	12(1.95%)	0.689	0.044
Chronic liver disease, n (%)	11(3.13%)	47(1.70%)	0.097	0.093	9(2.93%)	16(2.61%)	0.943	0.020
Hypertension, n (%)	133(37.89%)	711(25.73%)	<0.001	0.263	113(36.81%)	235(38.27%)	0.719	−0.030
Coronary heart disease, n (%)	27(7.69%)	154(5.57%)	0.140	0.085	24(7.82%)	54(8.79%)	0.706	−0.035
Chronic renal diseases, n (%)	20(5.70%)	45(1.63%)	<0.001	0.218	8(2.61%)	21(3.42%)	0.641	−0.048
Chest CT on admission								
Unilateral lesion, n (%)	29(8.26%)	316(11.44%)	0.090	−0.107	23(7.49%)	59(9.61%)	0.347	−0.076
Bilateral lesions, n (%)	283(80.63%)	2189(79.23%)	0.588	0.035	250(81.43%)	509(82.90%)	0.646	−0.038
Laboratory examination on admission								
Leukocyte count > 9.5, 10^9/L, n/N (%)	68/347(19.60%)	118/2716(4.34%)	<0.001	0.483	40/303 (13.20%)	59/611(9.66%)	0.131	0.112
Neutrophil count > 6.3, 10^9/L, n/N (%)	95/347(27.38%)	196/2716(7.22%)	<0.001	0.553	58/303 (19.14%)	115/611(18.82%)	0.979	0.008
C-reactive protein > ULN, n/N (%)	90/151(59.60%)	471/1433(32.87%)	<0.001	0.557	86/147 (58.50%)	130/266(48.87%)	0.076	0.194
ALT > 40 U/L, n/N (%)	81/317(25.55%)	531/2589(20.51%)	0.045	0.120	66/275 (24.00%)	142/568(25.00%)	0.818	−0.023
AST > 40 U/L, n/N (%)	90/317(28.39%)	410/2590(15.83%)	<0.001	0.306	68/275 (24.73%)	120/568(21.13%)	0.276	0.086

(*Continued*)

Table 1 (Continued).

Parameters	Unmatched				Matched (1:2)			
	NDD (n = 351)	Non-NDD (n = 2763)	*P*-value	SD	NDD (n = 307)	Non-NDD (n = 614)	*P*-value	SD
Urea > ULN, n/N (%)	42/345(12.17%)	69/2710(2.55%)	<0.001	0.375	25/301(8.31%)	34/606(5.61%)	0.159	0.106
Creatinine > ULN, n/N (%)	36/346(10.40%)	108/2701(4.00%)	<0.001	0.250	22/302(7.28%)	43/602(7.14%)	1.000	0.005
Blood glucose, mmol/L, median (IQR)	7.60(6.50–9.49)	5.18(4.70–5.83)	<0.001	1.237	7.51(6.4–9.25)	5.45(4.91–6.22)	<0.001	1.042
LDL-c > ULN, n/N (%)	33/274(12.04%)	293/2192(13.37%)	0.607	−0.040	30/236 (12.71%)	61/473(12.90%)	1.000	−0.006
TC > ULN, n/N (%)	27/291(9.28%)	316/2379(13.28%)	0.067	−0.127	24/249(9.64%)	56/534(10.49%)	0.812	−0.028
hs-CRP > ULN, n/N (%)	249/291 (85.57%)	1180/2045(57.7%)	<0.001	0.650	206/248 (83.06%)	389/484(80.37%)	0.433	0.070
Procalcitonin > ULN, n/N(%)	149/292 (51.03%)	628/2241(28.02%)	<0.001	0.484	111/250 (44.4%)	218/490(44.49%)	1.000	−0.002
D-dimer > ULN, n/N (%)	198/334 (59.28%)	983/2524(38.95%)	<0.001	0.415	158/294 (53.74%)	310/574(54.01%)	0.998	−0.005
Lymphocyte count < 1.1, 10^9/L, n/N (%)	191/347 (55.04%)	755/2716(27.80%)	<0.001	0.576	149/303 (49.17%)	286/611(46.81%)	0.546	0.047
SpO2 ≤ 93%, n/N (%)	79/274(28.83%)	195/2176(8.96%)	<0.001	0.525	51/238 (21.43%)	101/504(20.04%)	0.734	0.034
Management during hospitalization								
Oxygen inhalation, n (%)	309(88.03%)	2076(75.14%)	<0.001	0.337	265(86.32%)	505(82.25%)	0.139	0.112
Immunoglobin, n (%)	77(21.94%)	358(12.96%)	<0.001	0.238	70(22.80%)	108(17.59%)	0.072	0.130
Invasive ventilation, n (%)	69(19.66%)	14(0.51%)	<0.001	0.671	39(12.70%)	6(0.98%)	<0.001	0.478
Noninvasive ventilation, n (%)	85(24.22%)	100(3.62%)	<0.001	0.623	54(17.59%)	40(6.51%)	<0.001	0.345
Renal replacement therapy, n (%)	16(4.56%)	4(0.14%)	<0.001	0.294	7(2.28%)	1(0.16%)	0.002	0.194
ICU treatment, n (%)	80(22.79%)	119(4.31%)	<0.001	0.561	57(18.57%)	50(8.14%)	<0.001	0.310
Antiviral drug, n (%)	168(47.86%)	2027(73.36%)	<0.001	−0.541	165(53.75%)	452(73.62%)	<0.001	−0.422
Antibiotics drug, n (%)	145(41.31%)	1422(51.47%)	<0.001	−0.205	142(46.25%)	345(56.19%)	0.005	−0.200
Traditional Chinese medicine (%)	183(52.14%)	2110(76.37%)	<0.001	−0.523	180(58.63%)	455(74.1%)	<0.001	−0.332
Anti-hypertensive drug, n (%)	88(25.07%)	745(26.96%)	0.490	−0.043	85(27.69%)	211(34.36%)	0.049	−0.145
Lipid-lowering drug, n (%)	26(7.41%)	233(8.43%)	0.580	−0.038	26(8.47%)	69(11.24%)	0.235	−0.093
Hypoglycemic drugs, n (%)	55(15.67%)	68(2.46%)	<0.001	0.473	53(17.26%)	24(3.91%)	<0.001	0.445
Vasoactive drug, n (%)	13(3.70%)	8(0.29%)	<0.001	0.246	12(3.91%)	3(0.49%)	<0.001	0.235

Note: $P < 0.05$ was considered significant.

Abbreviations: NDD, newly-diagnosed diabetes; IQR, interquartile range; SD, standardized difference; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ULN, upper limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; hs-CRP, high-sensitivity C-reactive protein; ICU, intensive care unit.

non-NDD group (7.60 [6.50–9.49] mmol/L vs 5.18 [4.70–5.83] mmol/L). Elevated serum markers indicating inflammation (CRP [59.60% vs 32.87%] and procalcitonin [51.03% vs 28.02%]), liver injury (AST [28.39% vs 15.83%]), abnormal kidney function (creatinine [10.40% vs 4.00%] and urea nitrogen [12.17% vs 2.55%]), and

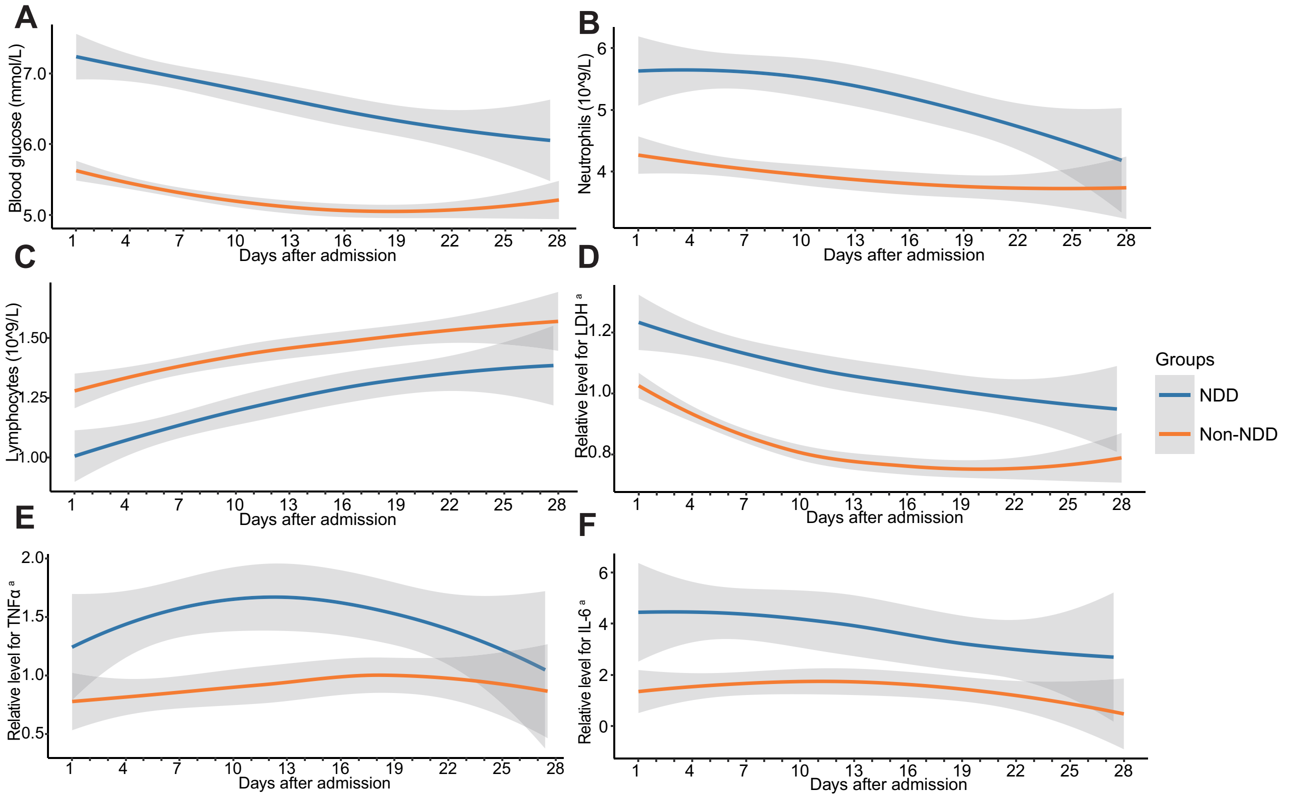

Figure 2 Dynamic profiles of BG (**A**), neutrophils (**B**), lymphocytes (**C**), LDH (**D**), TNFα (**E**), and IL-6 (**F**) in NDD and Non-NDD groups during hospitalization. [a]The relative levels of LDH, TNFα and IL-6 were applied and normalized according to their upper limits of the normal range in each hospital.
Abbreviations: BG, blood glucose; NDD, newly-diagnosed diabetes; LHD, lactate dehydrogenase; TNFα, tumor necrosis factor-α; IL-6, Inter Leukin 6.

coagulation disorder (D-dimer [59.28% vs 38.95%]) were found more frequently in the NDD group than in the non-NDD group. Additionally, SpO2 ≤ 93% occurred more frequently in patients with NDD than in those without NDD (28.83% vs 8.96%) (Table 1).

Dynamic Changes in Inflammatory Markers During Hospitalization

To determine the changes in parameters that are indicative of inflammation in the patients, multiple measurements of inflammation indicators were performed during hospitalization, and the results were recorded. LOESS models were used to illustrate the dynamic changes in FPG, lymphocytes, neutrophil count, lactate dehydrogenase (LDH), TNFα, and IL-6 in the NDD and non-NDD groups during hospitalization (Figure 2). All these parameters except lymphocyte counts were elevated more significantly upon admission and maintained at a higher level during the later phase of the disease in patients with NDD than in patients without NDD.

COVID-19 Patients with NDD Required More Intensive in-Hospital Treatment

As shown in Table 1, participants with NDD received more intensive interventions than did the non-NDD cases; this was manifested by the higher proportions of NDD patients who required treatment with vasoactive drugs (3.70% vs 0.29%), immunoglobin (21.94% vs 12.96%), oxygen inhalation (88.03% vs 75.14%), invasive mechanical ventilation (IMV) (19.66% vs 0.51%), noninvasive ventilation (24.22% vs 3.62%), renal replacement therapy (4.56% vs 0.14%), and intensive care unit (ICU) treatment (22.79% vs 4.31%) (Table 1).

NDD Was Strongly Associated with All-Cause Mortality and Multiorgan Damage in Patients with COVID-19

We observed that in-hospital death was significantly higher (18.52% vs 1.16%) among patients with NDD than among non-NDD individuals during the 28-day follow-up period (Table S1). In the mixed-effects Cox model using the hospital site as a random effect, the crude HR for all-cause mortality

Table 2 Hazard Ratios for Outcomes in NDD and Non-NDD Groups Under Cox Adjusted Model and Propensity Score Matching Model

NDD vs Non-NDD	Unmatched						Matched	
	Crude		Model 1[a]		Model 2[b]		Adjusted[c]	
	HR (95% CI)	*P*-value[d]	HR (95% CI)	*P*-value[d]	HR (95% CI)	*P*-value[d]	HR (95% CI)	*P*-value[d]
All-cause mortality	15.17(9.89,23.29)	<0.001	10.86(7.01,16.83)	<0.001	3.63(2.24,5.88)	<0.001	2.65(1.49,4.72)	0.001
ARDS	5.52(4.40,6.92)	<0.001	4.68(3.72,5.90)	<0.001	2.53(1.96,3.26)	<0.001	2.36(1.73,3.23)	<0.001
Acute kidney injury	53.48(24.04,118.97)	<0.001	41.68(18.44,94.23)	<0.001	15.70(6.67,36.98)	<0.001	14.65(4.27,50.27)	<0.001
Acute liver injury	3.23(2.35,4.43)	<0.001	3.43(2.47,4.75)	<0.001	2.17(1.51,3.13)	<0.001	2.21(1.43,3.40)	<0.001
Acute heart injury	9.44(6.85,13.01)	<0.001	6.89(4.97,9.57)	<0.001	3.72(2.61,5.29)	<0.001	2.80(1.82,4.31)	<0.001
Heart failure	4.11(3.28,5.15)	<0.001	3.42(2.72,4.31)	<0.001	1.93(1.50,2.49)	<0.001	1.67(1.24,2.25)	0.001

Notes: [a]In mixed-effect Cox model, adjusted variables included age and gender. [b]In mixed-effect Cox model, adjusted variables included age, gender, indicators of the severity of COVID-19, and comorbidities (hypertension, coronary heart disease, and chronic renal diseases). [c]Mixed-effect Cox model using the hospital site as a random effect and adjusting imbalanced TBIL and dyspnea. [d]*P* values were calculated based on Cox proportional hazard model. $P < 0.05$ was considered significant.
Abbreviations: NDD, newly-diagnosed diabetes; CI, confidence interval; ARDS, acute respiratory distress syndrome.

between the two groups was 15.17 (95% CI, 9.89–23.29; $P < 0.001$) (Table 2). After adjustment for confounding factors, including age, sex, comorbidities, and indicators of COVID-19 severity, the aHR for all-cause mortality between the two groups was 3.63 (95% CI, 2.24–5.88; $P < 0.001$) (Table 2). Considering the effects of unmeasured potential confounders, we conducted E-value analysis and found that the E-value (6.72 with CI 3.91 in the fully adjusted model) was substantially greater than the accepted risk factors for COVID-19 mortality. The Kaplan–Meier survival curves also illustrated that the NDD group had a significantly higher mortality than the non-NDD group (Figure S1). In addition, compared with the non-NDD subjects, patients with NDD had higher occurrence of multiorgan damage, including ARDS (35.90% vs 7.42%), acute kidney injury (13.11% vs 0.25%), acute liver injury (15.10% vs 5.68%), acute heart injury (23.93% vs 2.57%), and heart failure (33.05% vs 8.54%) (Table S1). After applying a mixed-effects Cox model and adjusting for age, sex, comorbidities, and severity of COVID-19, the respective HRs for ARDS, acute kidney injury, acute liver injury, acute heart injury, and heart failure were 2.53 (95% CI, 1.96–3.26; $P < 0.001$), 15.70 (95% CI, 6.67–36.98; $P < 0.001$), 2.17 (95% CI, 1.51–3.13; $P < 0.001$), 3.72 (95% CI, 2.61–5.29; $P < 0.001$), and 1.93 (95% CI, 1.50–2.49; $P < 0.001$), respectively, between the two groups (Table 2).

To determine the robustness and reliability of the association between NDD and clinical outcomes, we further conducted a PSM analysis in which 307 individuals with NDD and 614 non-NDD cases were matched at a ratio of 1:2 (Figure 1). Using a mixed-effects Cox model to further adjust imbalanced variables after matching (ie, total bilirubin and dyspnea), the association between patients with NDD and poor outcomes remained consistent and statistically significant, indicating a higher risk of all-cause mortality for patients with NDD than for non-NDD subjects (aHR, 2.65; 95% CI, 1.49–4.72; $P = 0.001$) (Tables 2 and S2). The Kaplan–Meier survival curves also showed that the NDD group had a significantly higher mortality after PSM (Figure 3). Moreover, after PSM, NDD was associated with a significantly increased risk of secondary endpoints, including ARDS, acute kidney injury, acute liver injury, acute heart injury, and heart failure, compared with non-NDD, with adjusted HRs of 2.36 (95% CI, 1.73–3.23; $P < 0.001$), 14.65 (95% CI, 4.27–50.27; $P < 0.001$), 2.21 (95% CI, 1.43–3.40; $P < 0.001$), 2.80 (95% CI, 1.82–4.31; $P < 0.001$), and 1.67 (95% CI, 1.24–2.25; $P = 0.001$), respectively (Tables 2 and S2).

Sustained Hyperglycemia Was Intensively Associated with Poor Outcomes in COVID-19 Patients with NDD

Subgroup analyses indicated that among patients with NDD who had ≥ 3 FPG records, 13.93(39/280) had sustained hyperglycemia throughout hospitalization; hyperglycemia was resolved in 18.21%(51/280) of patients, and the remaining 67.86%(190/280) showed a fluctuating pattern (Table S3). The dynamic trajectory of the patients' blood glucose levels is depicted in Figure S2. The IR of death during the 28-day follow-up was 1.79 cases per 100 person-days in the subgroup with sustained hyperglycemia, 0.76 cases per 100 person-days in the fluctuating group, and 0.07 cases per 100 person-days in the remitted group (Table 3). Compared to the individuals with remitted hyperglycemia, those with sustained hyperglycemia

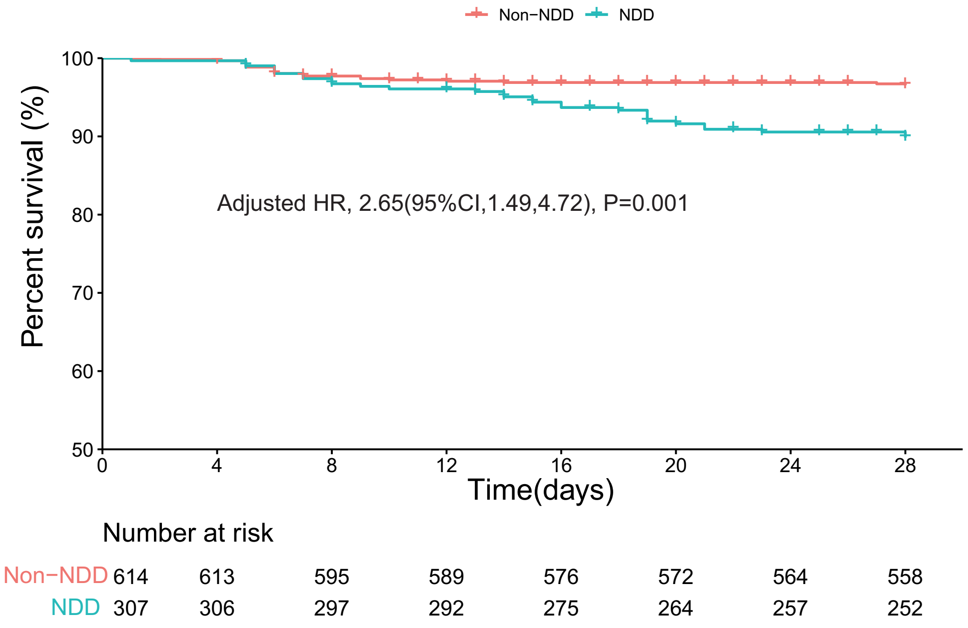

Figure 3 Kaplan-Meier curves for cumulative probability of COVID-19 mortality during hospitalization in NDD and Non-NDD groups in the propensity score-matched model.
Abbreviation: NDD, newly-diagnosed diabetes.

had the highest 28-day mortality (IRR 24.27; 95% CI, 3.21–183.36; $P < 0.001$), followed by the fluctuating group (IRR 10.31; 95% CI, 1.41–75.13; $P = 0.004$) (Table 3). The Kaplan–Meier survival curves also illustrated that patients with sustained hyperglycemia had the highest mortality risk, followed by patients with a fluctuating pattern, while patients with resolved hyperglycemia had the lowest risk (Figure 4).

Table 3 Association of Dynamic Blood Glucose Patterns with 28-Day Poor Outcomes in Patients with NDD

Outcomes	Incidence Rate (%)	Incidence Rate Ratio (95% CI)	P-value
Sustained vs Remitted group			
All-cause mortality	1.79 vs 0.07	24.27(3.21,183.36)	<0.001
ARDS	3.15 vs 1.17	2.69(1.34,5.40)	0.004
Acute liver injury	1.18 vs 0.95	1.23(0.51,2.96)	0.637
Acute heart injury	2.04 vs 0.31	6.65(2.21,19.96)	<0.001
Heart failure	2.50 vs 0.90	2.78(1.28,6.04)	0.007
Fluctuant vs Remitted group			
All-cause mortality	0.76 vs 0.07	10.31(1.41,75.13)	0.004
ARDS	2.62 vs 1.17	2.24(1.25,3.99)	0.005
Acute liver injury	0.60 vs 0.95	0.63(0.31,1.27)	0.196
Acute heart injury	1.41 vs 0.31	4.58(1.66,12.61)	0.001
Heart failure	2.33 vs 0.90	2.60(1.35,5.00)	0.003

Note: $P < 0.05$ was considered significant.
Abbreviations: NDD, newly-diagnosed diabetes; CI, confidence interval; ARDS, acute respiratory distress syndrome.

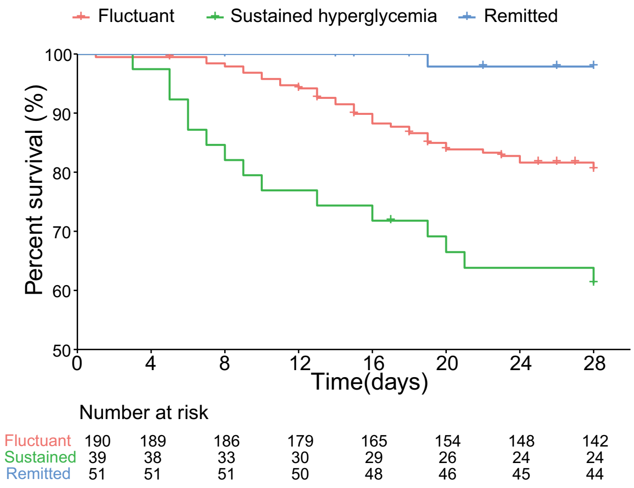

Figure 4 Survival curves of newly-diagnosed diabetes patients with sustained, fluctuant, and remitted blood glucose levels.

Similar trends in secondary outcomes were observed, as shown in Table 3.

Using HA Was Correlated with a Reduced Risk of Adverse Outcomes in COVID-19 Patients with NDD

To further explore whether using HA was correlated with a reduced risk of primary and secondary outcomes in patients with NDD, we conducted another subgroup analysis

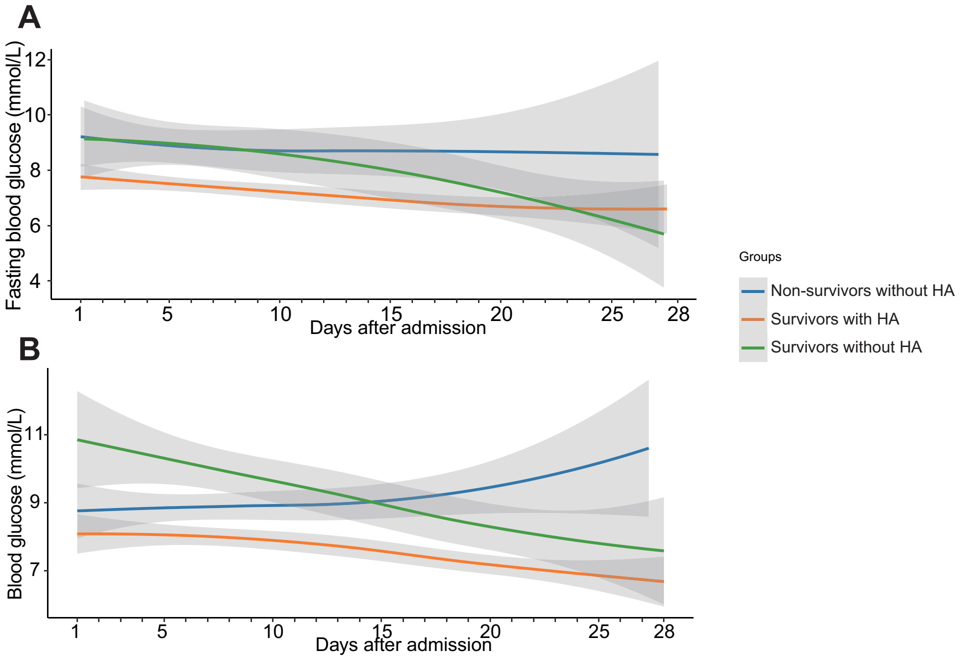

Figure 5 Dynamic profiles of fasting blood glucose (**A**) and blood glucose (**B**) in survivors with HA, survivors without HA, and non-survivors without HA from patients with newly-diagnosed diabetes during hospitalization.
Abbreviation: HA, hypoglycemic agents.

of NDD patients in which we compared patients using HA with nonusers. The baseline characteristics of the two groups are shown in Table S4. Among the 55 patients using HA, 16 (29.09%) used insulin, 21 (38.18%) used oral hypoglycemic agents (including metformin, glycosidase inhibitors, dpp4 inhibitors, nateglinide, and sulfonylureas) and 18 (32.73%) used both insulin and oral hypoglycemic agents (Tables S5 and S6). Only one of the 55 patients who used insulin treatment died (Table S7). As shown in Figure 5, the dynamic trajectory of FPG in nonsurvivors who did not use HA was distinct from that in survivors with/without HA. The FPG levels in nonsurvivors without HA were maintained at higher levels during hospitalization, whereas those in survivors gradually decreased. Similar trends were observed in the levels measured in all blood glucose tests (including FPG, 2 h-PG, and random blood glucose). The in-hospital death rate was markedly lower in NDD individuals taking HA than in nonusers (n = 1, 1.82% vs n = 64, 21.62%; $P = 0.001$). The IR of all-cause mortality was 0.07 cases per 100 person-days in HA users and 0.90 cases per 100 person-days in nonusers. Compared to nonusers, patients using HA had lower all-cause mortality (IRR 0.08; 95% CI, 0.01–0.56; $P < 0.001$). Those using HA also had a lower occurrence of secondary outcomes, including ARDS (IRR 0.32; 95% CI, 0.16–0.63; $P < 0.001$), acute kidney injury (IRR 0.35; 95% CI, 0.11–1.14; $P = 0.069$), acute liver injury (IRR 0.78; 95% CI 0.35–1.72; $P = 0.533$), acute heart injury (IRR 0.22; 95% CI 0.08–0.61; $P = 0.001$), and heart failure (IRR 0.60; 95% CI 0.34–1.07; $P = 0.078$), than nonusers (Table 4).

Discussion

In our analysis of 3114 COVID-19 patients without pre-existing diabetes who did not receive corticosteroid treatment during hospitalization, NDD was associated with a significantly higher risk of in-hospital death and of secondary endpoints such as ARDS and acute organ

Table 4 Association of Hypoglycemic Agents (HA) Use with 28-Day Poor Outcomes in Patients with NDD

HA Users vs Non-Users	Incidence Rate (%)	Incidence Rate Ratio (95% CI)	*P*-value
All-cause mortality	0.07 vs 0.90	0.08(0.01,0.56)	<0.001
ARDS	0.72 vs 2.24	0.32(0.16,0.63)	<0.001
Acute kidney injury	0.22 vs 0.61	0.35(0.11,1.14)	0.069
Acute liver injury	0.53 vs 0.68	0.78(0.35,1.72)	0.533
Acute heart injury	0.29 vs 1.29	0.22(0.08,0.61)	0.001
Heart failure	1.11 vs 1.85	0.60(0.34,1.07)	0.078

Note: $P < 0.05$ was considered significant.
Abbreviations: HA, hypoglycemic agents, NDD, newly-diagnosed diabetes; CI, confidence interval; ARDS, acute respiratory distress syndrome.

injuries. Furthermore, among patients with NDD, those who displayed sustained hyperglycemia throughout the hospitalization period were at the highest risk of poor outcomes. Patients taking HA had a significantly lower occurrence of adverse outcomes than nonusers. Our study is the largest to date to investigate the relationship between NDD and COVID-19 outcomes and the first to indicate that sustained hyperglycemia is associated with poorer outcomes in COVID-19 patients with NDD.

Several previous studies have shown a link between NDD and COVID-19 outcomes, as summarized in recent reviews and meta-analyses.[6,29–31] It is important to note that these studies used very different criteria to define NDD. In a single-center retrospective analysis of 453 Chinese COVID-19 patients, Li et al found NDD (defined as admission FBG ≥ 7 mmol/L and/or HbA1c ≥ 6.5%) in 21% of the cases (94/453) and reported a significant increase in all-cause mortality (HR 9.42; 95% CI, 2.18–40.7) in those patients compared to patients with normoglycemia (FBG < 5.6 mmol/L and HbA1c < 5.7%).[9] In addition, patients with NDD had a higher percentage of admissions to the ICU (11.7%), and more of them required invasive mechanical ventilation (11.7%) than did patients with normal glucose levels (1.5% and 2.3%, respectively). Similarly, Wang et al conducted a retrospective study of COVID-19 patients at two hospitals in China and reported that 29% (176/605) of such patients had NDD (defined by admission FBG ≥ 7 mmol/L). Patients with NDD had a higher risk of in-hospital complications (HR 3.99; 95% CI, 2.71–5.88) and all-cause death (HR 2.30; 95% CI, 1.49–3.55) than individuals with baseline FBG <6.1 mmol/l.[11] Moreover, in a retrospective study of 413 COVID-19 patients in an Italian hospital, Fadini et al reported NDD (defined as HbA1c ≥ 6.5% or a random glucose level ≥ 11.1 mmol/L) in 5% of the cases (21/413) and found a significantly higher risk of severe COVID-19 (ICU admission or death; RR 3.06; 95% CI, 2.04–4.57) in those patients compared to patients with normoglycemia.[10] The prevalence of NDD in our cohort was 11.27%, lower than that reported in the studies by Li et al[9] and Wang et al[11] but higher than that reported in the study by Fadini et al.[10] A recent meta-analysis of 3711 COVID-19 cases in eight studies showed a pooled proportion of patients with NDD of 14.4% (13.4% in China).[6] The differences in NDD prevalence among studies result in part from differences in the diagnostic criteria used. In the present study, NDD was defined as at least two FPG measurements ≥ 7 mmol/L, in accordance with the ADA criteria.[19] However, due to the urgency of the circumstances during the COVID-19 outbreak, HbA1c and symptoms of hyperglycemia were not measured or recorded in our study. Despite differences in the criteria used to define NDD, the present study and earlier studies have consistently indicated that NDD is significantly associated with adverse outcomes in COVID-19 patients.[9–11,30]

The existence of confounding factors may bias the association between NDD and COVID-19 outcomes to a large extent.[32] For instance, in-hospital use of glucocorticoids may represent an important confounder that was not properly adjusted for or matched in the aforementioned studies, in which a greater proportion of individuals with NDD received glucocorticoid treatment compared to individuals with known diabetes and those with normal blood glucose.[10,14,33] To avoid this confounding effect, we excluded participants who received in-hospital glucocorticoid therapy. In addition, inflammatory activation may mediate the association between NDD and COVID-19 severity.[9,32,34] In our study and prior studies,[9–11] inflammatory markers such as neutrophil count, CRP, hs-CRP, and procalcitonin levels were significantly higher in patients with NDD than in those without NDD at admission and in the later phase of hospitalization. As has been well studied in patients with severe pneumonia, overactivated inflammatory responses could drive stress hyperglycemia and a severe disease course.[35,36] Thus, there is a possibility that a high blood glucose level might simply represent a biomarker of more severe disease. Nevertheless, in our analyses, the aHRs for the outcomes remained consistent and statistically significant after rigorous adjustment and matching, indicating that the association was independent of baseline confounders, including markers of inflammation. It is also noteworthy that prior studies consistently found that COVID-19 patients with NDD had poorer prognoses than did patients with pre-existing diabetes.[9–11,30] This could be partially explained by the fact that diabetes is often associated with manifest organ impairment that can be accounted for clinically and statistically,[10,37] In contrast, individuals who are unaware of their diabetes status may have occult organ impairment that is likely to be ignored by their treating physicians, and this impairment may not be accounted for in the statistical adjustment.[10] Nonetheless, the association between NDD and COVID-19 outcomes is unlikely to be due only to possible occult multiorgan damage, given the relatively large adjusted effect sizes in our study and previous studies.[10]

Previous studies have reported that hyperglycemia is usually transient in patients hospitalized with severe acute respiratory syndrome (SARS).[38] However, whether the alterations in glucose metabolism that occur with sudden onset of COVID-19 persist or remit during the later phase of the disease and what the impact of these changes are on the prognosis are unclear.[39] Montefusco et al applied continuous glucose monitoring in a cohort of patients hospitalized for COVID-19 in Italy and reported glycemic alterations not only in the acute phase of COVID-19 but also long after remission of the disease. Indeed, glycemic abnormalities could be detected for at least 2 months in patients who recovered from COVID-19.[40] Consistent with that study, our subgroup analyses showed that only 18.21% of patients with NDD displayed a remitted blood glucose pattern and that 13.93% had sustained hyperglycemia during the 28-day hospitalization. Moreover, among patients with NDD, those with sustained hyperglycemia were at the highest risk of poor outcomes, while the remitted group had the lowest risk, further suggesting that hyperglycemia may influence disease progression. The possible mechanisms by which NDD might contribute to poor COVID-19 outcomes include metabolic inflammation, an impaired innate immune response, possibly an altered level of angiotensin-converting enzyme 2 (ACE2), vascular dysfunction and the existence of a prothrombotic state due to hyperglycemia.[1,2] Nevertheless, the pathophysiology of COVID-19-related diabetes is complex and remains unclear.[7] The possible role of hyperglycemia as a driving force in COVID-19 progression needs to be confirmed in future studies.

A number of studies have provided clinical evidence linking improved blood glucose control to better outcomes in COVID-19 patients with pre-existing diabetes.[15,41–44] For example, the study by Zhu et al, which included 7337 individuals with COVID-19, indicated that patients with well-controlled blood glucose (glycemic variability within the range 3.9 to 10.0 mmol/L) experienced significantly lower mortality than patients with poorly controlled blood glucose (upper limit of glycemic variability exceeding 10.0 mmol/L) during hospitalization (adjusted HR, 0.14).[15] However, whether unsatisfactory glucose control mediates the impact of NDD on COVID-19 outcome has not yet been investigated. Our subgroup analyses demonstrated that patients with NDD whose hyperglycemia later resolved had the best prognosis among the three subgroups studied. In addition, NDD patients using HA had significantly lower in-hospital death and fewer secondary outcomes than nonusers. These results provide further evidence linking blood glucose control and COVID-19 prognosis in patients with NDD. However, the effects of specific types of HA on COVID-19 prognosis remains largely unknown. Evidence from Yu et al showed that insulin treatment was associated with enhanced systemic inflammation and aggravated injuries of vital organs,[45] whereas metformin has shown benefits against COVID-19 through mechanisms besides lowering blood glucose such as attenuating inflammation and heart injury.[46] Thus, the independent effect of HA on clinical outcomes warrants to be further studied.

Limitations

Our study has notable strengths, including large sample size, rigorous control of confounders, and the utilization of repeated measured blood glucose data. Nonetheless, it has several limitations. First, due to the retrospective nature of the study, a causal relationship between NDD and COVID-19 outcomes cannot be established. Second, some clinical variables were unavailable for all patients due to the urgent circumstances caused by the COVID-19 outbreak. For example, HbA1c was not measured in most patients, and this might have biased the detection of pre-existing diabetes. Third, blood glucose level determinations were conducted at different time intervals for each patient. Bias might occur due to more frequent testing of patients with severe illness. Fourth, a sample of 3114 subjects may allow for reasonable power in the study, but the subgroup analysis may be underpowered due to the small sample size. Moreover, due to the limited number of events, we were unable to further analyze the independent relationship between the use of specific HA and clinical outcomes or to investigate whether the beneficial effects of HA on clinical outcome are independent of glycemic conditions. Fifth, all data were obtained from hospitalized patients in 17 hospitals in Hubei Province, China. Thus, the results from our study cannot be extrapolated to the outpatient setting or to ethnically or geographically diverse populations without careful validation.

Conclusion

In conclusion, our study reinforces the clinical message that NDD is strongly associated with poor outcomes in COVID-19 patients without pre-existing diabetes. Furthermore, our study provides preliminary evidence linking unsatisfactory blood glucose control to poor COVID-19 outcomes in NDD patients. Therefore, it seems reasonable that COVID-19 patients with NDD should be under intensive blood glucose surveillance and should be managed carefully to achieve tight glucose control, similar to patients with known diabetes, although further evidence from clinical trials is urgently needed.

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Disclosure

The authors report no conflicts of interest in this work.

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