

Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: A retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital

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Abstract

It is widely recognized that hypertension is one of the major risk factor for disease severity and mortality in patients with coronavirus disease 2019 (COVID-19). However, type 2 diabetes mellitus (T2DM) and hypertension are frequent comorbid conditions, complicating the assessment of hypertension's individual contribution to the risk. The aims of this study were to evaluate the contributions of hypertension alone, T2DM alone, or their combination to the risk of death, acute respiratory distress syndrome (ARDS)/respiratory failure, and severe COVID-19 infection. Additionally, we assessed risks associated with elevated blood pressure and fasting blood glucose on the same three clinical outcomes. Multivariate logistic models were used for these analyses. Among the 3400 patients, 3327(97.9%) survived and 73(2.1%) died. Compared to patients having neither hypertension nor T2DM ($n = 1392$), the risk of mortality was significantly higher in patients with T2DM alone ($n = 226$, OR 5.26 [95% CI: 2.39–11.58]) or with T2DM in combination with hypertension ($n = 507$, OR 3.02, [95% CI: 1.48–6.15]). Similarly, T2DM was a risk factor for development of ARDS/respiratory failure and severe infection. Hypertension alone ($n = 1275$) only conferred additional risk for the development of severe infection (OR 1.22 [95% CI: 1.00–1.51]). In conclusion, neither hypertension nor elevated blood pressure was independent risk factors for death or ARDS/respiratory failure but hypertension marginally increased the risk of severe COVID-19 infection. The risk associated with hypertension is accentuated through its confounding effect on T2DM.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in December 2019 and has subsequently spread worldwide, causing a pandemic of coronavirus disease 2019

(COVID-19). Recent studies have suggested that hypertension and type 2 diabetes mellitus (T2DM) were the most frequent comorbidities in infected patients and are also considered independent risk factors for disease severity and mortality.^{1–4} However, hypertension and T2DM are commonly encountered together. Epidemiological

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studies have indicated that ~40% of patients with T2DM also have hypertension.^{5,6} Conversely, hypertension is reported to occur in over two-thirds of patients with T2DM.⁷ Yet, no study has thus far addressed the individual effects of hypertension alone, T2DM alone, or their combination on the risk of mortality and morbidity in patients with COVID-19.

Furthermore, several hypotheses regarding independent mechanistic roles of hypertension and T2DM in worsening outcomes have been advanced. Among those, viral tropism for pancreatic β -cells and pulmonary vascular endothelial cells and how those are potentially modified in patients with preexisting conditions, and treatments for those conditions, have been discussed. For example, similar to prior infection disease epidemics, it has been hypothesized that hyperglycemia at the time of hospital admission, even in the absence of a history of T2DM, was associated with worse clinical outcomes.⁸⁻¹⁰ Whether comparable associations exist for admission blood pressure, history of hypertension, and outcomes has not been explored.

Accordingly, the primary purpose of this study was to determine the impact of hypertension alone, T2DM alone, or their combination, on mortality and disease severity in patients hospitalized with COVID-19. Secondly, we more specifically evaluated the impact of elevated blood pressure and elevated fasting blood glucose, individually and in combination, on clinical outcomes.

2 | METHODS

2.1 | Study population

This study included patients who were hospitalized with COVID-19 infection at either the Huoshen Mountain Hospital or the Guanggu Fangcang Shelter Hospital, Wuhan, China between January and April 2020. All original clinical data, including epidemiological, demographic, clinical, laboratory, radiology, treatment, and outcome data from these patients were entered and housed in the Chinese PLA General Hospital electronic medical records system from where data were extracted.

For inclusion in these study it was required that: (1) the patient was hospitalized and had laboratory-confirmed COVID-19 infection defined as a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay or high-throughput sequencing of nasal and pharyngeal swab specimens for SARS-CoV-2 virus; and (2) the patient be ≥ 18 years. The exclusion criteria were as follows: (1) lack of data concerning blood pressure; (2) lack of fasting blood glucose results; and (3) subjects was diagnosed with type 1 diabetes mellitus.

2.2 | Patient subgroups

For the main analysis, to specifically address the risks associated with hypertension and T2DM, patients were grouped by comorbid condition as follows: (1) neither hypertension nor T2DM; (2) hypertension alone; (3) T2DM alone; and (4) both hypertension and T2DM. To further isolate the effects of hypertension and T2DM, we also

identified a subgroup of patients who did not have any known comorbid conditions other than hypertension or T2DM.

Patients were designated as having hypertension if he/she was prescribed antihypertensive treatments or if mean systolic blood pressure was ≥ 140 mmHg or mean diastolic blood pressure was ≥ 90 mmHg based on at least two measurements within the first 2 days of admission; patients meeting these criteria without known history of hypertension were considered to have new-onset hypertension. Subjects with a history of T2DM and taking oral antidiabetic agents or insulin starting at age ≥ 40 years were considered to have T2DM. Additionally, patients were designated as having T2DM if fasting blood glucose concentration was ≥ 7 mmol/L on the first available test within the first 2 days of admission; patients with elevated fasting blood glucose without prior history of T2DM were considered to have new-onset diabetes.¹¹

To specifically assess the effects of blood pressure and fasting blood glucose, we also grouped patients as follows: (1) blood pressure $< 140/90$ mmHg and fasting blood glucose < 7 mmol/L; (2) blood pressure $\geq 140/90$ mmHg and fasting blood glucose < 7 mmol/L; (3) blood pressure $< 140/90$ mmHg and fasting blood glucose ≥ 7 mmol/L; and (4) blood pressure $\geq 140/90$ mmHg and fasting blood glucose ≥ 7 mmol/L. Values for blood pressure and fasting blood glucose were the same as those defined above. Patients' history of prior hypertension or T2DM did not factor into this grouping.

2.3 | Study outcomes and definitions

The primary outcome measures were death or hospital discharge. Importantly, the following standardized criteria were used for hospital discharge: (1) absence of fever for at least 3 days; (2) substantial improvement of chest x-ray appearance of both lungs; (3) remission of respiratory symptoms; and (4) two negative SARS-CoV-2 RT-PCR obtained at least 24 h apart.¹²

The secondary outcome measures were severe COVID-19 infection and ARDS/respiratory failure. COVID-19 illness severity (non-severe vs. severe) was assessed at the time of hospital admission using the American Thoracic Society guidelines for community-acquired pneumonia and Chinese management guidelines for COVID-19.^{12,13} Patients were designated as having non-severe COVID-19 if he/she with mild upper respiratory tract symptoms and/or mild chest x-ray changes.¹² Subjects with any of the following conditions: (1) respiration rate ≥ 30 times/min; (2) resting blood oxygen saturation $\leq 93\%$; (3) partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) ≤ 300 mmHg; (4) with respiratory or other organ failure that requires intensive care; or (5) shock were considered to have severe COVID-19.¹²

Acute respiratory distress syndrome was defined according to the guidance of World Health Organization for COVID-19 and respiratory failure was defined as impairment of respiratory function requiring intubation or mechanical ventilation, with severity graded according to the maximum respiratory support received at any time point during hospitalization.¹⁴

2.4 | Data completeness and review

All patients had a definite clinical outcome (discharge or death), since Huoshen Mountain Hospital (built new) and Guanggu Fangcang Shelter Hospital (completely transformed) were designated as emergency specialty field hospitals that were established in January 2020 in Wuhan in response to the COVID-19 pandemic and were fully closed on April 14, 2020. All clinical data were reviewed by two senior physicians (XZ Guan and LJ Jia) and two senior radiologists (N Xing and LQ Cheng) and were finally reviewed by the primary author (YH Sun) to confirm the final disposition.

2.5 | Statistical analysis

Patients characteristics are summarized with descriptive statistics (median [IQR] for continuous variables and N [%] for categorical variables). Comparisons of proportions between study groups were made using the chi-square tests or Fisher's exact tests for categorical variables and Kruskal-Wallis test for continuous variables. Bonferroni corrections were performed for Kruskal-Wallis analyses with multiple comparisons.

Multivariate logistic models were used to estimate the effect of hypertension, T2DM and their combination on the odds of developing: (1) death (primary outcome); (2) ARDS/respiratory failure; and (3) severe COVID-19 infection. Similarly, multivariate logistic models were also used to estimate the effect of elevated blood pressure alone, elevated fasting blood glucose alone or in combination on the same three clinical outcomes. Other factors associated with clinical outcomes of COVID-19 were evaluated using multivariate logistic model as covariables. The following variables were considered: age, sex, other comorbid conditions (cardiovascular disease, cerebrovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, endocrine/Immune system disease, or tumor), and ACEIs/ARBs treatments. The unadjusted risk values for all variables included in the multivariate logistic models were evaluated with binary logistic regression.

For all analyses, aside from hypertension, other types of cardiovascular diseases (eg, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, and abdominal aortic aneurysm) were grouped together into one category.

All p values reported are two-sided, with the significance level set to .05. Statistical analyses were performed using SAS (version 9.4; SAS Institute) and R (version 3.6.1; R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Study population and primary outcome

Between February 4, 2020 and April 14, 2020, 4961 patients were admitted to the Huoshen Mountain Hospital or Guanggu Fangcang Shelter Hospital for suspected COVID-19 infection. As detailed in

Figure S1A in Appendix S1, from among these 4961 patients, 3400 were ≥ 18 years old without type 1 diabetes mellitus and with required core test information were confirmed to have COVID-19; definitive outcomes were available for all patients.

Overall patient characteristics are summarized in Table 1, along with a comparison of characteristics of survivors versus non-survivors. A total of 3400 patients were included in this study. The median age was 61 years (IQR, 50–68 years), and 1751 (51.5%) were female. 2361 (69.4%) patients had comorbidities, including hypertension ($n = 1782$ [52.4%]), T2DM ($n = 733$ [21.6%]), cardiovascular disease ($n = 343$ [10.1%]), cerebrovascular disease ($n = 161$ [4.7%]), chronic kidney disease ($n = 75$ [2.2%]), chronic liver disease ($n = 132$ [3.9%]), chronic lung disease ($n = 111$ [3.3%]), endocrine/Immune system disease not including diabetes ($n = 148$ [4.4%]), and tumors ($n = 99$ [2.9%]). 3327 (97.9%) patients survived to discharge and 73 (2.1%) patients died. Patients who died were significantly older, more likely male, had greater prevalence of T2DM, cardiovascular disease, cerebrovascular disease, chronic kidney disease, and tumors. Fasting blood glucose levels at the beginning of hospitalization were also higher in patients who died. Additionally, the prevalence of ACEI and ARB use not differs between survivors and non-survivors. However, the prevalence of beta-blockers, diuretics, and insulin use was higher in patients who died.

When patients were grouped into four subgroups: (1) neither hypertension nor T2DM; (2) hypertension alone, (3) T2DM alone; and (4) both hypertension and T2DM (Table 2), there were significant differences noted among these subgroups in age, sex, blood pressure at hospital admission, fasting blood glucose at hospital admission, cardiovascular disease, cerebrovascular disease, chronic kidney disease, and tumors. Multivariable analysis showed that compared to patients without hypertension or T2DM, the risk of mortality was significantly higher in patients with T2DM alone (OR 5.26 [95% CI: 2.39–11.58]) or with T2DM in combination with hypertension (OR 3.02 [95% CI: 1.48–6.15]) (details in Table 3a). Hypertension alone did not confer additional risk (OR 0.73 [95% CI: 0.33–1.61]). As further summarized in Table 3a, older age, male sex, and a history of cardiovascular disease, chronic kidney disease, or tumor (benign or malignant) also inferred independent risk of mortality. However, ACEI and/or ARB use did not increase the risk of death. Additional analysis comparing the odds ratio of death between hypertension alone vs T2DM alone, hypertension alone vs hypertension plus T2DM, and T2DM alone vs hypertension plus T2DM confirmed that hypertension did not increase the risk of mortality (Table S1A in Appendix S1).

Specific COVID-19 mortality attributable to hypertension or diabetes is probably underscored because of the confounding effects for cardiovascular disease, cerebrovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, endocrine/Immune system disease, or tumor (benign or malignant). To exclude possible confounding effects of comorbid conditions listed above, we assessed the risk of mortality among the 2604 patients who did not have any other identified comorbidities other than hypertension or

TABLE 1 Demographic characteristics of all patients, and a comparison broken down by survivors and non-survivors

Characteristic	All patients (N = 3400)	Survivors n = 3327 (97.9%)	Non-survivors n = 73 (2.1%)	p value
Age, years, median [IQR]	61 (50, 68)	60 (50, 68)	75 (67, 82)	<.001
Age group, No. (%)				
18–65	2103 (61.9%)	2089 (62.8%)	14 (19.2%)	<.001
≥65	1297 (38.2%)	1238 (37.2%)	59 (80.8%)	
Sex, No. (%)				
Female	1751 (51.5%)	1729 (52.0%)	22 (30.1%)	<.001
Male	1649 (48.5%)	1598 (48.0%)	51 (69.9%)	
Hypertension (total), No. (%)				
Hypertension (total), No. (%)	1782 (52.4%)	1737 (52.2%)	45 (61.6%)	.110
Systolic blood pressure, median [IQR]	130 (120, 140)	130 (120, 140)	130 (120, 146)	.111
Diastolic blood pressure, median [IQR]	80 (74, 89)	80 (74, 89)	79 (68, 85)	<.001
Type 2 diabetes mellitus (total), No. (%)				
Type 2 diabetes mellitus (total), No. (%)	733 (21.6%)	687 (20.6%)	46 (63.0%)	<.001
Fasting plasma glucose, median [IQR]	4.9 (4.5, 5.8)	4.9 (4.5, 5.7)	7.5 (5.7, 9.7)	<.001
Other comorbid conditions, No. (%)				
Cardiovascular disease	343 (10.1%)	314 (9.4%)	29 (39.7%)	<.001
Cerebrovascular disease	161 (4.7%)	148 (4.5%)	13 (17.8%)	<.001
Chronic kidney disease	75 (2.2%)	67 (2.0%)	8 (11.0%)	<.001
Chronic liver disease	132 (3.9%)	131 (3.9%)	1 (1.4%)	.261
Chronic lung disease	111 (3.3%)	106 (3.2%)	5 (6.9%)	.082
Endocrine/Immune system disease	148 (4.4%)	143 (4.3%)	5 (6.9%)	.291
Tumor	99 (2.9%)	92 (2.8%)	7 (9.6%)	<.001
Antihypertensive treatment, No. (%)				
ACE inhibitors	43 (1.3%)	42 (1.3%)	1 (1.3%)	.935
ARBs	264 (7.8%)	257 (7.7%)	7 (9.6%)	.556
Calcium-channel blockers	1054 (31.0%)	1025 (30.8%)	29 (39.7%)	.103
Beta-blockers	525 (15.4%)	507 (15.2%)	18 (24.7%)	.028
Diuretics	260 (7.7%)	207 (6.2%)	53 (72.6%)	<.001
Antidiabetic treatment, No. (%)				
Insulin	327 (9.6%)	274 (8.2%)	53 (72.6%)	<.001
Other hypoglycemic agents	447 (13.2%)	443 (13.3%)	4 (5.5%)	.05

T2DM. This analysis (detailed in Table S1B in Appendix S1) confirmed the above results that T2DM, but not hypertension, increased the risk of death.

Similarly, analyses restricted to patients with a prior history of hypertension alone to those with neither hypertension nor T2DM also confirmed a lack of increased risk associated

with hypertension, independent of whether other comorbidities were or were not included in the analysis (Tables S1C and S1D in Appendix S1).

As detailed in Figure S1B in Appendix S1, patients were also grouped according to actual blood pressures (Systolic blood pressure <140 vs. ≥140 mmHg or Diastolic blood pressure <90 vs.

TABLE 2 Demographic characteristics with patients grouped according to whether they have hypertension (HTN) alone, type 2 diabetes mellitus (T2DM) alone, or in combination

Characteristic	All patients (N = 3400)	Neither HTN nor T2DM n = 1392 (40.9%)	HTN alone n = 1275 (37.5%)	T2DM alone n = 226 (6.7%)	HTN + T2DM n = 226 (6.7%)	p value	Multiple comparisons
Age, years, median [IQR]	61 (50, 68)	55 (43, 65)	63 (54, 70)	61.5 (55, 68)	66 (58, 72)	<.001	[*] , [†] , [‡] , [§] , [¶]
Age group, No. (%)							
18–65	2103 (61.9%)	1025 (73.6%)	713 (55.9%)	146 (64.6%)	219 (43.2%)	<.001	[*] , [†] , [‡] , [§] , [¶]
≥65	1297 (38.2%)	367 (26.4%)	562 (44.1%)	80 (35.4%)	288 (56.8%)		
Sex, No. (%)							
Female	1751 (51.5%)	782 (56.2%)	614 (48.2%)	103 (45.6%)	252 (49.7%)	<.001	[*] , [†] , [‡]
Male	1649 (48.5%)	610 (43.8%)	661 (51.8%)	123 (54.4%)	255 (50.3%)		
Systolic blood pressure, median [IQR]	130 (120, 140)	122 (115, 130)	140 (129, 148)	121 (114, 130)	140 (129, 151)	<.001	[*] , [†] , [‡] , [§] , [¶]
Diastolic blood pressure, median [IQR]	80 (74, 89)	77 (70, 81)	89 (80, 95)	76 (70, 80)	85 (78, 93)	<.001	[*] , [†] , [‡] , [§] , [¶]
Fasting plasma glucose, median [IQR]	4.9 (4.5, 5.8)	4.6 (4.3, 5.1)	4.8 (4.4, 5.3)	7.9 (6.8, 10.3)	7.7 (6.0, 9.7)	<.001	[*] , [†] , [‡] , [§] , [¶]
Other comorbid conditions, No. (%)							
Cardiovascular disease	343 (10.1%)	69 (5.0%)	147 (11.5%)	23 (10.2%)	104 (20.5%)	<.001	[*] , [†] , [‡] , [§] , [¶]
Cerebrovascular disease	161 (4.7%)	22 (1.6%)	73 (5.7%)	9 (4.0%)	57 (11.2%)	<.001	[*] , [†] , [‡] , [§] , [¶]
Chronic kidney disease	75 (2.2%)	16 (1.2%)	30 (2.4%)	5 (2.2%)	24 (4.7%)	<.001	[*] , [‡] , [§]
Chronic liver disease	132 (3.9%)	53 (3.8%)	60 (4.7%)	7 (3.1%)	12 (2.4%)	.120	[§]
Chronic lung disease	111 (3.3%)	51 (3.7%)	38 (3.0%)	10 (4.4%)	12 (2.4%)	.350	
Endocrine/Immune system disease	148 (4.4%)	46 (3.3%)	67 (5.3%)	8 (3.5%)	27 (5.3%)	.053	[*] , [‡]
Tumor	99 (2.9%)	31 (2.2%)	36 (2.8%)	13 (5.8%)	19 (3.8%)	.018	[†] , ^{**}
Antihypertensive treatment, No. (%)							
ACE inhibitors	43 (1.3%)	2 (0.1%)	23 (1.8%)	0	18 (3.6%)	<.001	[*] , [‡] , ^{**} , [§] , [¶]
ARBs	264 (7.8%)	10 (0.7%)	172 (13.5%)	3 (1.3%)	79 (15.6%)	<.001	[*] , [‡] , ^{**} , [¶]
Calcium-channel blockers	1054 (31.0%)	66 (4.7%)	650 (51.0%)	21 (9.3%)	317 (62.5%)	<.001	[*] , [†] , [‡] , ^{**} , [§] , [¶]
Beta-blockers	525 (15.4%)	128 (9.2%)	249 (19.5%)	30 (13.3%)	118 (23.3%)	<.001	[*] , [‡] , ^{**} , [¶]
Diuretics	260 (7.7%)	45 (3.2%)	107 (8.4%)	25 (11.1%)	83 (13.4%)	<.001	[*] , [†] , [‡] , [§]
Antidiabetic treatment, No. (%)							
Insulin	327 (9.6%)	34 (2.4%)	38 (3.0%)	76 (33.6%)	179 (35.3%)	<.001	[†] , [‡] , ^{**} , [§]
Other hypoglycemic agents	447 (13.2%)	4 (0.3%)	14 (1.1%)	113 (50%)	316 (62.3%)	<.001	[*] , [†] , [‡] , ^{**} , [§] , [¶]

Note: Significantly ($p < .05$):

*None vs HTN;

[†]None vs DM;

[‡]None vs DM + HTN;

[§]HTN vs DM + HTN;

[¶]DM vs DM + HTN;

**HTN vs DM.

TABLE 3A Risk factors associated with death in patients with confirmed COVID-19 infection (primary outcome)

Covariate	Survivors, %	Non-survivors, %	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Comorbid conditions *						
Neither hypertension nor T2DM	1379 (41.5%)	13 (17.8%)	1 [Reference]	<.001	1 [Reference]	<.001
Hypertension alone	1261 (37.9%)	14 (19.2%)	1.18 (0.55, 2.52)		0.73 (0.33, 1.61)	
T2DM alone	211 (6.3%)	15 (20.6%)	7.54 (3.54, 16.08)		5.26 (2.39, 11.58)	
Hypertension and T2DM	476 (14.3%)	31 (42.5%)	6.91 (3.59, 13.31)		3.02 (1.48, 6.15)	
Age group						
18–65	2089 (62.8%)	14 (19.2%)	1 [Reference]	<.001	1 [Reference]	<.001
≥65	1238 (37.2%)	59 (80.8%)	7.11 (3.95, 12.79)		4.76 (2.56, 8.87)	
Sex						
Female	1729 (52.0%)	22 (30.1%)	1 [Reference]	<.001	1 [Reference]	.003
Male	1598 (48.0%)	51 (69.9%)	2.51 (1.51, 4.15)		2.20 (1.30, 3.73)	
Cardiovascular disease						
No	3013 (90.6%)	44 (60.3%)	1 [Reference]	<.001	1 [Reference]	<.001
Yes	314 (9.4%)	29 (39.7%)	6.32 (3.90, 10.25)		2.85 (1.65, 4.94)	
Cerebrovascular disease						
No	3179 (95.5%)	60 (82.2%)	1 [Reference]	<.001	1 [Reference]	.127
Yes	148 (4.5%)	13 (17.8%)	4.65 (2.50, 8.67)		1.72 (0.86, 3.44)	
Chronic kidney disease						
No	3260 (98.0%)	65 (89.0%)	1 [Reference]	<.001	1 [Reference]	.030
Yes	67 (2.0%)	8 (11.0%)	5.99 (2.76, 12.98)		2.71 (1.10, 6.68)	
Chronic liver disease						
No	3196 (96.1%)	72 (98.6%)	1 [Reference]	.284	1 [Reference]	.276
Yes	131 (3.9%)	1 (1.4%)	0.34 (0.05, 2.46)		0.33 (0.04, 2.45)	
Chronic lung disease						
No	3221 (96.8%)	68 (93.2%)	1 [Reference]	.090	1 [Reference]	.976
Yes	106 (3.2%)	5 (6.8%)	2.23 (0.88, 5.66)		0.99 (0.36, 2.71)	
Endocrine/Immune system disease						
No	3184 (95.7%)	68 (93.2%)	1 [Reference]	.295	1 [Reference]	.924
Yes	143 (4.3%)	5 (6.8%)	1.64 (0.65, 4.12)		1.05 (0.37, 2.98)	
Tumor						
No	3235 (97.2%)	66 (90.4%)	1 [Reference]	.001	1 [Reference]	.041
Yes	92 (2.8%)	7 (9.6%)	3.73 (1.67, 8.35)		2.55 (1.04, 6.25)	
ACEIs/ARBs treatment						
No	3033 (91.2%)	65 (89.0%)	1 [Reference]	.529	1 [Reference]	.425
Yes	294 (8.8%)	8 (11.0%)	1.27 (0.60, 2.67)		0.72 (0.32, 1.63)	

*Patients grouped according to the diagnosis of hypertension and type 2 diabetes mellitus (T2DM).

≥90 mmHg) and fasting blood glucose levels (<7.0 vs. ≥7.0 mmol/L). Paralleling the primary analysis, fasting blood glucose ≥7.0 mmol/L was associated with markedly increased risk of mortality, independent of blood pressure and independent of whether other comorbidities were or were not included in the analysis (Table 3b, Tables S1E and S1F in Appendix S1). Blood pressure was not a risk factor for mortality.

3.2 | Secondary outcome: ARDS and respiratory failure

Among 3400 patients infected and hospitalized with COVID-19, 144 were diagnosed with ARDS/respiratory failure either at the time of hospital admission or at some point during hospitalization. As detailed in Table 4a, and similar to mortality, the results of multivariable analysis

TABLE 3B Risk factors associated with death in patients with confirmed COVID-19 infection (primary outcome)

Covariate	Survivors, %	Non-survivors, %	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Comorbid conditions *						
BP < 140/90 mmHg and FBG < 7 mmol/L	1846 (55.5%)	26 (35.6%)	1 [Reference]	<.001	1 [Reference]	<.001
BP ≥ 140/90 mmHg and FBG < 7 mmol/L	1022 (30.7%)	7 (9.6%)	0.49 (0.21, 1.12)		0.44 (0.19, 1.03)	
BP < 140/90 mmHg and FBG ≥ 7 mmol/L	255 (7.7%)	23 (31.5%)	6.40 (3.60, 11.39)		4.61 (2.50, 8.48)	
BP ≥ 140/90 mmHg and FBG ≥ 7 mmol/L	204 (6.1%)	17 (23.3%)	5.92 (3.16, 11.09)		4.22 (2.17, 8.18)	
Age group						
18–65	2089 (62.8%)	14 (19.2%)	1 [Reference]	<.001	1 [Reference]	<.001
≥65	1238 (37.2%)	59 (80.8%)	7.11 (3.95, 12.79)		4.57 (2.47, 8.47)	
Sex						
Female	1729 (52.0%)	22 (30.1%)	1 [Reference]	<.001	1 [Reference]	.001
Male	1598 (48.0%)	51 (69.9%)	2.51 (1.51, 4.15)		2.42 (1.42, 4.13)	
Cardiovascular disease						
No	3013 (90.6%)	44 (60.3%)	1 [Reference]	<.001	1 [Reference]	<.001
Yes	314 (9.4%)	29 (39.7%)	6.32 (3.90, 10.25)		2.92 (1.68, 5.07)	
Cerebrovascular disease						
No	3179 (95.5%)	60 (82.2%)	1 [Reference]	<.001	1 [Reference]	.152
Yes	148 (4.5%)	13 (17.8%)	4.65 (2.50, 8.67)		1.66 (0.83, 3.34)	
Chronic kidney disease						
No	3260 (98.0%)	65 (89.0%)	1 [Reference]	<.001	1 [Reference]	.008
Yes	67 (2.0%)	8 (11.0%)	5.99 (2.76, 12.98)		3.41 (1.38, 8.45)	
Chronic liver disease						
No	3196 (96.1%)	72 (98.6%)	1 [Reference]	.284	1 [Reference]	.326
Yes	131 (3.9%)	1 (1.4%)	0.34 (0.05, 2.46)		0.36 (0.05, 2.74)	
Chronic lung disease						
No	3221 (96.8%)	68 (93.2%)	1 [Reference]	.090	1 [Reference]	.718
Yes	106 (3.2%)	5 (6.9%)	2.23 (0.88, 5.66)		0.83 (0.30, 2.30)	
Endocrine/Immune system disease						
No	3184 (95.7%)	68 (93.2%)	1 [Reference]	.295	1 [Reference]	.811
Yes	143 (4.3%)	5 (6.8%)	1.64 (0.65, 4.12)		1.14 (0.39, 3.29)	
Tumor						
No	3235 (97.2%)	66 (90.4%)	1 [Reference]	.001	1 [Reference]	.067
Yes	92 (2.8%)	7 (9.6%)	3.73 (1.67, 8.35)		2.37 (0.94, 5.94)	
ACEIs/ARBs treatment						
No	3033 (91.2%)	65 (89.0%)	1 [Reference]	.529	1 [Reference]	.260
Yes	294 (8.8%)	8 (11.0%)	1.27 (0.60, 2.67)		0.63 (0.28, 1.42)	

*Patients grouped according to blood pressure (BP) and fasting blood glucose (FBG) levels.

showed the T2DM alone (OR 4.38 [95% CI: 2.41–7.95]) or in combination with hypertension (OR 3.39 [95% CI: 2.04–5.64]) increased the risk of these outcomes. Older age, male sex, cardiovascular disease, and chronic kidney disease also remained significant in this model. ACEI/ARB use did not impact the odds of developing ARDS/respiratory failure. Additional analysis comparing the odds ratio of ARDS/respiratory

failure between hypertension alone versus T2DM alone, hypertension alone vs hypertension plus T2DM, and T2DM alone vs hypertension plus T2DM confirmed that hypertension did not increase the risk of developing ARDS/respiratory failure (Table S2A in Appendix S1).

Similar to the primary outcome analysis, to exclude possible confounding effects of comorbid conditions, a sensitivity analysis that

included only the 2604 patients who did not have any comorbidities (cardiovascular disease, cerebrovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, endocrine/Immune system disease, or tumor) other than hypertension or T2DM confirmed the above results for this outcome (Table S2B in Appendix S1).

Comparing patients with prior hypertension alone vs those having neither hypertension nor T2DM also confirmed that hypertension did not increase the risk of developing ARDS/respiratory failure, independent of whether other comorbidities were or were not included in the analysis (Tables S2C and S2D in Appendix S1).

Grouping patients by blood pressures and fasting blood glucose levels yielded similar results: patients with increased fasting blood glucose levels were at increased risk of ARDS/respiratory failure independent of blood pressure, and independent of whether patients with or without other comorbidities were included in the analysis (Table 4b, Tables S2E and S2F in Appendix S1). Elevated blood pressure did not increase the risk of ARDS/respiratory failure.

Of the 144 patients diagnosed with ARDS/respiratory failure, 69 (47.9%) died in hospital. Multivariable analysis odds ratios for death were 0.47 [95% CI: 0.17–1.35], 1.80 [95% CI: 0.54–5.95], and 1.66 [95% CI: 0.61–4.53], respectively, among patients with hypertension alone, T2DM alone, and combined hypertension and T2DM compared with patients having neither hypertension nor T2DM; older age and male sex also remained significant in this analysis. A sensitivity analysis that included 75 of the ARDS/respiratory failure patients without any comorbidities other than hypertension or T2DM confirmed the above results (detailed further in Table S2G in Appendix S1). Thus, the presence of hypertension or T2DM did not increase the risk of death in patients once they experienced ARDS/respiratory failure.

3.3 | Secondary outcome: severe COVID-19 infection

As detailed in Table 5a, and similar to mortality, the results of multivariable analysis showed the T2DM alone (OR 2.21 [95% CI: 1.60–3.06]) or in combination with hypertension (OR 1.95 [95% CI: 1.51–2.50]) increased the risk of severe infection; however, in this case, hypertension alone also conferred a mild increase of risk (OR 1.22 [95% CI: 1.00–1.50]), though less so than T2DM. Older age, male sex, cardiovascular disease, and chronic lung disease were also associated with additional risk. However, ACEI/ARB use did not impact the odds of developing severe COVID-19 infection. Additional odds ratios for developing severe COVID-19 infection based on hypertension and T2DM profiles are further summarized in Table S3A in Appendix S1.

To exclude possible confounding effects of comorbid conditions, a sensitivity analysis that included only the 2604 patients who did not have any other comorbidities (cardiovascular disease, cerebrovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, endocrine/Immune system disease, or tumor)

confirmed that hypertension alone, T2DM alone, and hypertension plus T2DM were each associated with an increased risk of developing severe COVID-19 infection (Table S3B in Appendix S1).

However, when patients were grouped according to blood pressure and fasting blood glucose, elevated fasting blood glucose but not elevated blood pressure was a risk factor for developing severe infection and this was independent of whether patients did or did not have other comorbid conditions (Table 5b, Tables S3C and S3D in Appendix S1).

4 | DISCUSSION

Prior studies have shown that there is a high prevalence of hypertension and T2DM in patients infected with COVID-19, which have both been associated with increased risk of death, ARDS/respiratory failure and severe COVID-19 infection. However, because hypertension and T2DM commonly occur together, their independent contributions have not been clearly defined.

An outstanding clinical research that included 2877 confirmed COVID-19 patients,¹⁵ Gao and colleagues demonstrated that after adjusted for confounders and compared with non-hypertensive patients, the hypertensive patients indicated a significant increase in the risk of mortality from COVID-19. However, this study did not address the contributions of diabetes. Even in the latest review, hypertension is considered an independent major factor for worse clinical outcomes.⁴ In our large patient cohort with well-defined characteristics and outcomes, we have demonstrated that T2DM is a major independent risk factor for adverse outcomes associated with COVID-19; hypertension itself contributed only to a relatively small degree to the development of severe infection, but not to death nor development of ARDS/respiratory failure. These findings were robust in that they survived adjustment for other comorbid conditions and that they survived multiple sensitivity analyses. It should be noted that the risk associated with hypertension is accentuated through its confounding effect on T2DM. Also, once ARDS/respiratory failure was established, neither hypertension nor T2DM increased the risk of death. Very significantly, elevated fasting blood glucose more so than a history of T2DM was the major driver of increased risk of all adverse outcomes, whereas elevated blood pressure was noncontributory. Regarding other comorbidities, we also identified advanced age, male sex, history of other cardiovascular diseases, chronic kidney disease and tumors as risk factors for adverse outcomes. Chronic lung disease emerged only as a risk factor for development of severe infection, but not mortality, ARDS or respiratory failure. Finally, our results further confirmed prior findings that under all circumstances investigated, ACEI/ARB use did not contribute to disease severity or final clinical outcome.^{16,17}

A recent meta-analysis¹⁸ that included outcomes from 3994 COVID-19 positive patients derived from 16 publications, all from China and published between December 2019 and February

TABLE 4A Risk factors associated with development of acute respiratory distress syndrome (ARDS) and/or respiratory failure (RF) in patients with confirmed COVID-19 infection (secondary outcome)

Covariate	Non-ARDS/ RF, %	ARDS/RF, %	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Comorbid conditions *						
Neither hypertension nor T2DM	1364 (41.9%)	28 (19.4%)	1 [Reference]	<.001	1 [Reference]	<.001
Hypertension alone	1234 (37.9%)	41 (28.5%)	1.62 (0.995, 2.63)		1.19 (0.72, 1.98)	
T2DM alone	204 (6.3%)	22 (15.3%)	5.25 (2.95, 9.36)		4.38 (2.41, 7.95)	
Hypertension and T2DM	454 (13.9%)	53 (36.8%)	5.69 (3.55, 9.10)		3.39 (2.04, 5.64)	
Age group						
18–65	2062 (63.3%)	41 (28.5%)	1 [Reference]	<.001	1 [Reference]	<.001
≥65	1194 (36.7%)	103 (71.5%)	4.34 (3.00, 6.27)		3.14 (2.12, 4.65)	
Sex						
Female	1695 (52.1%)	56 (38.9%)	1 [Reference]	.002	1 [Reference]	.042
Male	1561 (41.9%)	88 (61.1%)	1.71 (1.21, 2.40)		1.45 (1.01, 2.08)	
Cardiovascular disease						
No	2952 (90.7%)	105 (72.9%)	1 [Reference]	<.001	1 [Reference]	.026
Yes	304 (9.3%)	39 (27.1%)	3.61 (2.45, 5.31)		1.64 (1.06, 2.53)	
Cerebrovascular disease						
No	3115 (95.7%)	124 (86.1%)	1 [Reference]	<.001	1 [Reference]	.132
Yes	141 (4.3%)	20 (13.9%)	3.56 (2.16, 5.88)		1.52 (0.88, 2.62)	
Chronic kidney disease						
No	3196 (98.2%)	129 (89.6%)	1 [Reference]	<.001	1 [Reference]	<.001
Yes	60 (1.8%)	15 (10.4%)	6.19 (3.43, 11.20)		3.53 (1.80, 6.91)	
Chronic liver disease						
No	3132 (96.2%)	136 (94.4%)	1 [Reference]	.291	1 [Reference]	.316
Yes	124 (3.8%)	8 (5.6%)	1.49 (0.71, 3.10)		1.48 (0.69, 3.21)	
Chronic lung disease						
No	3157 (97.0%)	132 (91.7%)	1 [Reference]	<.001	1 [Reference]	.088
Yes	99 (3.0%)	12 (8.3%)	2.90 (1.55, 5.41)		1.81 (0.92, 3.59)	
Endocrine/Immune system disease						
No	3117 (95.7%)	135 (93.8%)	1 [Reference]	.257	1 [Reference]	.820
Yes	139 (4.3%)	9 (6.3%)	1.50 (0.75, 3.00)		0.91 (0.42, 1.98)	
Tumor						
No	3167 (97.3%)	134 (93.1%)	1 [Reference]	.005	1 [Reference]	.134
Yes	89 (2.7%)	10 (6.9%)	2.66 (1.35, 5.22)		1.75 (0.84, 3.62)	
ACEIs/ARBs treatment						
No	2973 (91.3%)	125 (86.8%)	1 [Reference]	.065	1 [Reference]	.996
Yes	283 (8.7%)	19 (13.2%)	1.60 (0.97, 2.63)		1.00 (0.58, 1.73)	

*Patients grouped according to the diagnosis of hypertension and type 2 diabetes mellitus (T2DM).

2020,^{1,3,19–32} identified hypertension, T2DM, a history of cardiovascular diseases, chronic obstructive pulmonary disease and chronic kidney disease as having significant associations with the development of serious events (including ICU admission, ARDS, and mechanical ventilation).¹⁸ However, only the presence of T2DM had a significant impact on death. Since this was not a patient-level meta-analysis, the study was not able to identify the independent contributions of hypertension and T2DM.

A more recent study and meta-analysis¹¹ that included some of the same references and additional small reports (several non-peer-reviewed) specifically identified T2DM as a risk factor for death, based on univariate analysis. Additionally, that study did not address the contributions of hypertension. Accordingly, our study presents the first, largest, and most comprehensive analysis providing direct evidence of the primary importance of T2DM and lack of impact of hypertension in determining outcomes after

TABLE 4B Risk factors associated with development of acute respiratory distress syndrome (ARDS) and/or respiratory failure (RF) in patients with confirmed COVID-19 infection (secondary outcome)

Covariate	Non-ARDS/ RF, %	ARDS/RF, %	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Comorbid conditions *						
BP < 140/90 mmHg and FBG < 7 mmol/L	1819 55.9%	53 36.8%	1 [Reference]	<.001	1 [Reference]	<.001
BP ≥ 140/90 mmHg and FBG < 7 mmol/L	1004 30.8%	25 17.4%	0.86 (0.53, 1.38)		0.79 (0.48, 1.29)	
BP < 140/90 mmHg and FBG ≥ 7 mmol/L	242 7.4%	36 25.0%	5.11 (3.28, 7.96)		4.19 (2.63, 6.68)	
BP ≥ 140/90 mmHg and FBG ≥ 7 mmol/L	191 5.9%	30 20.8%	5.39 (3.36, 8.64)		4.38 (2.66, 7.20)	
Age group						
18–65	2062 63.3%	41 28.5%	1 [Reference]	<.001	1 [Reference]	<.001
≥65	1194 36.7%	103 71.5%	4.34 (3.00, 6.27)		3.12 (2.11, 4.62)	
Sex						
Female	1695 52.1%	56 38.9%	1 [Reference]	.002	1 [Reference]	.016
Male	1561 41.9%	88 61.1%	1.71 (1.21, 2.40)		1.56 (1.09, 2.25)	
Cardiovascular disease						
No	2952 90.7%	105 72.9%	1 [Reference]	<.001	1 [Reference]	.019
Yes	304 9.3%	39 27.1%	3.61 (2.45, 5.31)		1.69 (1.09, 2.25)	
Cerebrovascular disease						
No	3115 (95.7%)	124 (86.1%)	1 [Reference]	<.001	1 [Reference]	.132
Yes	141 (4.3%)	20 (13.9%)	3.56 (2.16, 5.88)		1.53 (0.88, 2.64)	
Chronic kidney disease						
No	3196 (98.2%)	129 (89.6%)	1 [Reference]	<.001	1 [Reference]	<.001
Yes	60 (1.8%)	15 (10.4%)	6.19 (3.43, 11.20)		4.24 (2.14, 8.41)	
Chronic liver disease						
No	3132 (96.2%)	136 (94.4%)	1 [Reference]	.291	1 [Reference]	.237
Yes	124 (3.8%)	8 (5.6%)	1.49 (0.71, 3.10)		1.60 (0.73, 3.50)	
Chronic lung disease						
No	3157 (97.0%)	132 (91.7%)	1 [Reference]	<.001	1 [Reference]	.205
Yes	99 (3.0%)	12 (8.3%)	2.90 (1.55, 5.41)		1.57 (0.78, 3.13)	
Endocrine/Immune system disease						
No	3117 (95.7%)	135 (93.8%)	1 [Reference]	.257	1 [Reference]	.931
Yes	139 (4.3%)	9 (6.3%)	1.50 (0.75, 3.00)		0.97 (0.44, 2.12)	
Tumor						
No	3167 (97.3%)	134 (93.1%)	1 [Reference]	.005	1 [Reference]	.190
Yes	89 (2.7%)	10 (6.9%)	2.66 (1.35, 5.22)		1.65 (0.78, 3.46)	
ACEIs/ARBs treatment						
No	2973 (91.3%)	125 (86.8%)	1 [Reference]	.065	1 [Reference]	.960
Yes	283 (8.7%)	19 (13.2%)	1.60 (0.97, 2.63)		0.99 (0.57, 1.70)	

*Patients grouped according to blood pressure (BP) and fasting blood glucose (FBG) levels.

accounting for other comorbid conditions. It is also noteworthy that consistent with the prior study²⁸ that a history of tumors increased the risk of mortality, though not specifically of severe infection, ARDS, or respiratory failure.

As reviewed in detail by Apicella and colleagues,⁴ a few recent studies have specifically identified the increased risks associated with hyperglycemia upon hospital admission independent of a prior history of T2DM.^{8–10} Whether admission hyperglycemia

TABLE 5A Risk factors associated with development of severe infection in patients with confirmed COVID-19 infection (secondary outcome)

Covariate	Non-severe COVID-19 infection, %	Severe COVID-19 infection, %	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Comorbid conditions *						
Neither hypertension nor T2DM	1168 (44.1%)	224 (29.8%)	1 [Reference]	<.001	1 [Reference]	<.001
Hypertension alone	990 (37.4%)	285 (37.9%)	1.50 (1.24, 1.82)		1.22 (1.00, 1.51)	
T2DM alone	154 (5.8%)	72 (9.6%)	2.44 (1.78, 3.34)		2.21 (1.60, 3.06)	
Hypertension and T2DM	336 (12.7%)	171 (22.7%)	2.65 (2.10, 3.35)		1.95 (1.51, 2.50)	
Age group						
18–65	1760 (66.5%)	334 (45.6%)	1 [Reference]	<.001	1 [Reference]	<.001
≥65	888 (33.5%)	409 (54.4%)	2.36 (2.01, 2.79)		1.94 (1.62, 2.31)	
Sex						
Female	1416 (53.5%)	335 (44.6%)	1 [Reference]	<.001	1 [Reference]	.002
Male	1232 (46.5%)	417 (55.4%)	1.43 (1.22, 1.68)		1.30 (1.10, 1.54)	
Cardiovascular disease						
No	2437 (92.0%)	620 (82.5%)	1 [Reference]	<.001	1 [Reference]	.002
Yes	211 (8.0%)	132 (17.5%)	2.46 (1.95, 3.11)		1.50 (1.16, 1.93)	
Cerebrovascular disease						
No	2547 (96.2%)	692 (92.0%)	1 [Reference]	<.001	1 [Reference]	.247
Yes	101 (3.8%)	60 (8.0%)	2.19 (1.57, 3.04)		1.23 (0.87, 1.75)	
Chronic kidney disease						
No	2603 (98.3%)	722 (96.0%)	1 [Reference]	<.001	1 [Reference]	.184
Yes	45 (1.7%)	30 (4.0%)	2.40 (1.50, 3.84)		1.41 (0.85, 2.34)	
Chronic liver disease						
No	2552 (96.4%)	716 (95.2%)	1 [Reference]	.147	1 [Reference]	.300
Yes	96 (3.6%)	36 (4.8%)	1.34 (0.90, 1.98)		1.24 (0.82, 1.88)	
Chronic lung disease						
No	2585 (97.6%)	704 (93.6%)	1 [Reference]	<.001	1 [Reference]	<.001
Yes	63 (2.4%)	48 (6.4%)	2.80 (1.90, 4.11)		2.09 (1.39, 3.15)	
Endocrine/Immune system disease						
No	2546 (96.2%)	706 (93.9%)	1 [Reference]	.008	1 [Reference]	.118
Yes	102 (3.9%)	46 (6.1%)	1.63 (1.14, 2.33)		1.36 (0.93, 2.00)	
Tumor						
No	2577 (97.3%)	724 (96.3%)	1 [Reference]	.135	1 [Reference]	.647
Yes	71 (2.7%)	28 (3.7%)	1.40 (0.90, 2.19)		1.12 (0.70, 1.78)	
ACEIs/ARBs treatment						
No	2437 (92.0%)	661 (87.9%)	1 [Reference]	<.001	1 [Reference]	.221
Yes	211 (8.0%)	91 (12.1%)	1.59 (1.23, 2.06)		1.19 (0.90, 1.58)	

*Patients grouped according to the diagnosis of hypertension and type 2 diabetes mellitus (T2DM).

identifies a population of undiagnosed T2DM patients, reflects direct effects on pancreatic β -cell function by the SARS-CoV-2, or a more general reaction to the proinflammatory state is not yet identified. Also unknown is if tighter glycemic control following admission results in better outcomes³³ and, if so, which drugs provide better or worse outcomes.⁴ Careful prospective studies will be required before specific treatment guidelines can be provided.

4.1 | Limitations

The main limitation of the study is that it is based on a retrospective analysis. However, because of the unique nature of the two primary hospitals from which data were derived, there were defined start and end dates for hospital admissions and every patient was accounted for with regard to primary and secondary outcomes and

TABLE 5B Risk factors associated with development of severe infection in patients with confirmed COVID-19 infection (secondary outcome)

Covariate	Non-severe COVID-19 infection, %	Severe COVID-19 infection, %	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Comorbid conditions *						
BP < 140/90 mmHg and FBG < 7 mmol/L	1504 56.8%	368 48.9%	1 [Reference]	<.001	1 [Reference]	<.001
BP ≥ 140/90 mmHg and FBG < 7 mmol/L	819 30.9%	210 27.9%	1.05 (0.87, 1.27)		0.98 (0.80, 1.19)	
BP < 140/90 mmHg and FBG ≥ 7 mmol/L	180 6.8%	98 13.0%	2.23 (1.70, 2.92)		1.92 (1.45, 2.54)	
BP ≥ 140/90 mmHg and FBG ≥ 7 mmol/L	145 5.5%	76 10.1%	2.14 (1.59, 2.89)		1.82 (1.33, 2.48)	
Age group						
18–65	1760 (66.5%)	334 (45.6%)	1 [Reference]	<.001	1 [Reference]	<.001
≥65	888 (33.5%)	409 (54.4%)	2.36 (2.01, 2.79)		1.98 (1.67, 2.36)	
Sex						
Female	1416 (53.5%)	335 (44.6%)	1 [Reference]	<.001	1 [Reference]	<.001
Male	1232 (46.5%)	417 (55.4%)	1.43 (1.22, 1.68)		1.34 (1.13, 1.58)	
Cardiovascular disease						
No	2437 (92.0%)	620 (82.5%)	1 [Reference]	<.001	1 [Reference]	<.001
Yes	211 (8.0%)	132 (17.5%)	2.46 (1.95, 3.11)		1.56 (1.21, 2.01)	
Cerebrovascular disease						
No	2547 (96.2%)	692 (92.0%)	1 [Reference]	<.001	1 [Reference]	.196
Yes	101 (3.8%)	60 (8.0%)	2.19 (1.57, 3.04)		1.26 (0.89, 1.79)	
Chronic kidney disease						
No	2603 (98.3%)	722 (96.0%)	1 [Reference]	<.001	1 [Reference]	.111
Yes	45 (1.7%)	30 (4.0%)	2.40 (1.50, 3.84)		1.51 (0.91, 2.51)	
Chronic liver disease						
No	2552 (96.4%)	716 (95.2%)	1 [Reference]	.147	1 [Reference]	.267
Yes	96 (3.6%)	36 (4.8%)	1.34 (0.90, 1.98)		1.26 (0.84, 1.91)	
Chronic lung disease						
No	2585 (97.6%)	704 (93.6%)	1 [Reference]	<.001	1 [Reference]	.001
Yes	63 (2.4%)	48 (6.4%)	2.80 (1.90, 4.11)		1.96 (1.30, 2.94)	
Endocrine/Immune system disease						
No	2546 (96.2%)	706 (93.9%)	1 [Reference]	.008	1 [Reference]	.094
Yes	102 (3.9%)	46 (6.1%)	1.63 (1.14, 2.33)		1.39 (0.95, 2.04)	
Tumor						
No	2577 (97.3%)	724 (96.3%)	1 [Reference]	.135	1 [Reference]	.663
Yes	71 (2.7%)	28 (3.7%)	1.40 (0.90, 2.19)		1.11 (0.70, 1.77)	
ACEIs/ARBs treatment						
No	2437 (92.0%)	661 (87.9%)	1 [Reference]	<.001	1 [Reference]	.104
Yes	211 (8.0%)	91 (12.1%)	1.59 (1.23, 2.06)		1.26 (0.95, 1.66)	

*Patients grouped according to blood pressure (BP) and fasting blood glucose (FBG) levels.

clinical characteristics including admission blood pressures and fasting blood glucose levels. Concerns about the retrospective nature of the analysis were further minimized by the fact that this was an observational study of patients receiving standard of care treatment and no intervention was being evaluated.

Our study also has limitations in classifying new-onset hypertensive or new-onset diabetic cases. Although patients with elevated blood pressure on admission without a history of hypertension showed symptoms and other indices similar to those of patients with a history of hypertension, we cannot rule out the

possible existence of truly non-hypertensive patients with elevated blood pressure at admission among the new-onset hypertension. It is for this reason that the analysis of risk associated with elevated blood pressure independent of hypertensive history is so important and informative. Similarly, patients with hyperglycemia on admission showed symptoms and biochemical indices similar to those of patients with history of diabetes, as in other prior studies, we cannot rule out the possible existence of truly non-diabetic patients with hyperglycemia at admission among those considered to have new-onset diabetes.

5 | CONCLUSION

In this large retrospective study, we show that neither hypertension nor elevated blood pressure were independent risk factors for death or ARDS/respiratory failure but hypertension did confer a slightly increased risk of developing severe COVID-19 infection. In contrast, T2DM was an independent and strong risk factor for death, ARDS/respiratory failure, and severe COVID-19 infection. Hyperglycemia on admission, regardless of diabetic history, was similarly a strong risk factor for adverse outcome. Once ARDS/respiratory failure occurred, neither hypertension nor T2DM increased the risk of death; however, advanced age and male sex were risk factors for death in the setting of ARDS/respiratory failure. ACEI and/or ARB use did not impact the odds of death, developing ARDS/respiratory failure, or severe COVID-19 infection. Nor did ACEI and/or ARB use increase the risk of death once ARDS/respiratory failure had developed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

YH Sun performed study design, statistical analysis, data interpretation, and manuscript writing. XZ Guan, LJ Jia, N Xing, LQ Cheng, B Liu, and SB Zhang performed data collection and manuscript revision. KL He administrated and supervised the study. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional ethics committee of the Chinese PLA General Hospital, and a waiver of the requirement for patient consent was obtained. All patients included in this study did not receive financial compensation.

PERMISSIONS

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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