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Original Article

Association of Overlapped and Un-overlapped Comorbidities with COVID-19 Severity and Treatment Outcomes: A Retrospective Cohort Study from Nine Provinces in China*

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Abstract

Objective Several COVID-19 patients have overlapping comorbidities. The independent role of each component contributing to the risk of COVID-19 is unknown, and how some non-cardiometabolic comorbidities affect the risk of COVID-19 remains unclear.

Methods A retrospective follow-up design was adopted. A total of 1,160 laboratory-confirmed patients were enrolled from nine provinces in China. Data on comorbidities were obtained from the patients' medical records. Multivariable logistic regression models were used to estimate the odds ratio (*OR*) and 95% confidence interval (95% *CI*) of the associations between comorbidities (cardiometabolic or non-cardiometabolic diseases), clinical severity, and treatment outcomes of COVID-19.

Results Overall, 158 (13.6%) patients were diagnosed with severe illness and 32 (2.7%) had unfavorable outcomes. Hypertension (2.87, 1.30–6.32), type 2 diabetes (T2DM) (3.57, 2.32–5.49), cardiovascular disease (CVD) (3.78, 1.81–7.89), fatty liver disease (7.53, 1.96–28.96), hyperlipidemia (2.15, 1.26–3.67), other lung diseases (6.00, 3.01–11.96), and electrolyte imbalance (10.40, 3.00–26.10) were independently linked to increased odds of being severely ill. T2DM (6.07, 2.89–12.75), CVD (8.47, 6.03–11.89), and electrolyte imbalance (19.44, 11.47–32.96) were also strong predictors of unfavorable outcomes. Women with comorbidities were more likely to have severe disease on admission (5.46, 3.25–9.19), while men with comorbidities were more likely to have unfavorable treatment outcomes (6.58, 1.46–29.64) within two weeks.

Conclusion Besides hypertension, diabetes, and CVD, fatty liver disease, hyperlipidemia, other lung diseases, and electrolyte imbalance were independent risk factors for COVID-19 severity and poor treatment outcome. Women with comorbidities were more likely to have severe disease, while men with comorbidities were more likely to have unfavorable treatment outcomes.

Key words: Comorbidities; COVID-19; Severity; Gender; Age; Treatment outcome

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INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) has resulted in a pandemic that has led to a worldwide health crisis. Studies have reported that patients admitted to the intensive care unit (ICU) had a higher number of comorbidities (72.2%) than those not admitted to the ICU (37.3%)[1]. Hence, the presence of a comorbidity has been considered to be a risk factor for mortality due to COVID-19.

One systematic review reported that hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases (CVDs) were related to the severity of COVID-19, while no association between liver disease, renal disease, or non-cardiometabolic diseases and clinical severity of COVID-19 was observed[2]. In addition, limited by only a few studies comparing the comorbidities of patients with severe and non-severe COVID-19, subgroup analyses could not be analyzed by gender and age groups. Two recent studies have found that patients with comorbidities had unfavorable outcomes (defined as admission to an ICU, invasive ventilation, or death) compared to those without any comorbidities[3,4]. However, one study did not separate specific components of comorbidity, and the other only included patients with overlapping hypertension, diabetes, and COPD. For one thing, how non-cardiometabolic disease comorbidities affect the risk of COVID-19 remains unclear. In addition, the independent role of these components contributes to the risk of COVID-19 (e.g., which component has the strongest power of prediction of severity and treatment outcomes), due to the substantial overlap between them[5].

Based on a retrospective cohort study that enrolled patients from nine provinces of China, we examined the association between specific components of comorbidities (overlapped and un-overlapped, including cardiometabolic diseases and non-cardiometabolic diseases), number of comorbidities, and clinical severities, as well as treatment outcomes of COVID-19. Subgroup analyses by gender and age were also performed.

METHODS

Study Population and Area

A retrospective follow-up design was adopted in this study. Laboratory-confirmed hospitalized patients aged 18–87 years were enrolled from 53 hospitals in nine provinces of China (Anhui, Fujian, Guangxi, Hebei, Heilongjiang, Shaanxi, Sichuan, Shanxi, and Chongqing) between January 13 and April 13, 2020. Each patient was followed up for a fixed period of two weeks to observe treatment outcomes. Information on demographics, medical histories, first-onset symptoms of COVID-19, diagnosis of clinical severity on admission, treatment regimen, and progression of disease during the two-week follow up were collected from the patients' medical records.

Comorbidities

Patients' comorbidities were self-reported (such as a history of stroke) or diagnosed (such as hypertension) on admission. In this study, comorbidities were divided into cardiometabolic and non-cardiometabolic diseases. Cardiometabolic comorbidities (present or not) included hypertension, type 2 diabetes (T2DM), heart disease, stroke, CVD (either heart disease or stroke), fatty liver disease, hyperlipidemia, and hyperuricemia. Non-cardiometabolic comorbidities included other lung diseases (pulmonary emphysema, bronchitis, and COPD), allergic diseases, hepatitis B, pulmonary tuberculosis (active or obsolete), electrolyte imbalance (e.g., hyponatremia and/or hypokalemia), abnormal liver or kidney function, and depression. The number of comorbidities was categorized as follows: none, one, two, and three or more comorbidities.

Clinical Severity and Treatment Outcome

COVID-19 severity was determined according to the *Diagnosis and Treatment Protocol for COVID-19* (*seventh edition*)[6].

Briefly, three types of severity were defined by the protocol:

1) Mild cases, mild clinical symptoms and no signs of pneumonia observed on CT image.

2) Moderate cases, only have fever and respiratory symptoms with radiological findings of pneumonia on CT image.

3) Severe cases, having any of the following: (a) respiratory distress and needs invasive ventilation, (b) pulse oxygen saturation ≤ 93% , or (c) arterial partial pressure of oxygen (PaO_2)/oxygen concentration ≤ 300 mmHg.

In the present study, mild and moderate cases were classified as non-severe cases, and COVID-19 patients were categorized as non-severe and severe cases.

The treatment outcomes of all patients were assessed at the end of the two-week follow-up and were categorized as either favorable or unfavorable outcomes. Patients with favorable outcomes were defined as having recovered or having improved condition at the end of the two-week follow-up window. Patients with unfavorable outcomes were defined as having died of COVID-19 or aggravated condition (e.g., disease progressed from moderate illness to severe illness) at the end of the two-week follow-up window.

Covariates

The following factors were used as covariates in the analyses: age, sex, Body Mass Index (BMI), ever visited Wuhan city, first-onset symptoms of COVID-19, and unfavorable outcome. Age was categorized as < 60 and ≥ 60 years. Sex was categorized as male or female. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2)[7]. Ever went to Wuhan City was defined as ever going to Wuhan from December 2019 and thereafter. The first-onset symptoms of COVID-19 (present or not) included fever, fatigue, cough, congestion or runny nose, anorexia, sore throat, diarrhea, shortness of breath, and chills. Unfavorable outcome was defined as having any of the following: 1) patients deteriorated such as patients with advanced symptom, or were transferred to the ICU or superior hospitals to receive further treatment; 2) death.

Statistical Analysis

Patients' characteristics on admission are presented as means and standard deviation or median (interquartile: Q1, Q3) for continuous variables and percentages (%) for categorical variables. We used multivariable logistic regression models to estimate the odds ratio (*OR*) and 95% confidence interval (95% *CI*) for the associations between comorbidities (present or not and number of comorbidities) and clinical severity as well as treatment outcome of COVID-19. Patients with no comorbidities were used as the reference group for comparison with patients with any comorbidities. Non-severe patients were used as the reference group for clinical severity, and patients with favorable outcomes were used as the reference group for treatment outcome. Province-level variability was included in the model as a random effect.

We first analyzed the associations of overlapping components of comorbidities with clinical severity and treatment outcome. We then analyzed the un-overlapped associations between them to assess the independent role of each comorbidity component. We also separated the analyses by sex (male and female) and age (< 60 and ≥ 60 years). All statistical models were adjusted for age, sex, BMI, and first-onset symptoms of COVID-19. When analyzing the association between comorbidities and treatment outcomes, treatment regimens during follow-up were further adjusted.

The SURVEYLOGISTIC procedure was performed with the logit link that estimates sampling errors based on the clustered sample survey from multiple provinces and incorporates that in the estimates. All

statistical tests were two-sided, and the level of significance was 5%. Statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

Participant Characteristics

In total, 1,160 patients were included, and 52.2% were male, with age [median (Q1, Q3)] of 46.0 (33.0, 57.0) years. There were 341 (29.4%) patients with more than one comorbidity. Among the 1,160 patients, 158 (13.6%) were diagnosed with severe illness and 32 (2.7%) had unfavorable outcomes at the end of the two-week follow-up window. Patients with severe COVID-19 were older than those with non-severe COVID-19 (median: 57.0 *vs.* 44.0 years), and patients who had unfavorable outcomes were older than those with favorable outcomes (median: 60.0 *vs.* 46.0 years). Patients who were > 60 years of age had a higher percentage of severe illness, comorbidity, and unfavorable outcomes. Cough (49.8%) and fever (44.7%) were the two most common onset symptoms. Overall, patients with symptoms (except sore throat) had a higher percentage of severe illness and unfavorable outcomes (Table 1).

Hypertension (16.2%), T2DM (7.7%), and CVD (6.3%) were the three most common comorbidities. Other lung diseases (2.3%) and hepatitis B (2.1%) were common comorbidities of non-cardiometabolic disease. Around one-third of patients had one or more comorbidities (Table 2). The distribution of clinical severity and treatment outcome in the un-overlapped component of comorbidities are listed in Supplementary Table S1 (available in www.besjournal.com).

In addition, 1,109 (95.6%) patients received treatment with combination of Chinese and Western medicine during hospitalization, 1,012 (91.3%) patients received Qingfei Paidu decoction of Chinese medicine, and 25 (2.4%) had unfavorable outcomes. However, 2.7% of unfavorable outcomes among all patients.

Types of Comorbidity and Clinical Severity and Treatment Outcome

Compared with patients with no comorbidities, patients with any comorbidity had > 3-fold higher odds of being severely ill (*OR*, 3.55; 95% *CI*, 1.94–6.50) and having unfavorable outcomes (3.65, 2.23–5.98). Patients with hypertension, T2DM, and CVD (either heart diseases or stroke) had higher odds of being severely ill, with *OR* (95% *CI*) of 3.40 (1.70, 6.80), 3.36 (1.95, 5.77), and 3.65 (2.21, 6.03), respectively. They were also more likely to have unfavorable treatment outcomes, with *OR* (95% *CI*) of 2.34 (1.44, 3.80), 4.12 (2.20, 7.72), and 4.45 (2.14, 9.26), respectively. Patients with fatty liver disease and hyperlipidemia also had an increased odd of being severely ill, although their 95% *CI* spanned one (Table 3).

In terms of non-cardiometabolic disease, other lung diseases (4.96, 2.51–9.80), tuberculosis (2.89, 1.85–4.54), electrolyte imbalance (15.33, 3.54–66.40), and abnormal liver/kidney function (6.83, 1.44–32.48) were linked to elevated odds of having severe illness. The latter two also had higher odds of having unfavorable treatment outcomes, with *OR* (95% *CI*) of 12.49 (5.52, 28.28) and 7.69 (2.01, 29.41), respectively (Table 3). The *OR* s (95% *CI*) between allergic diseases, hepatitis B, tuberculosis, depression, and treatment outcome were not reported due to due to the small number of patients with these morbidities.

After the associations of un-overlapped components with severity and treatment outcomes were analyzed, hypertension (2.87, 1.30–6.32), T2DM (3.57, 2.32–5.49), CVD (3.78, 1.81–7.89), fatty liver disease (7.53, 1.96–28.96), hyperlipidemia (2.15, 1.26–3.67), other lung diseases (6.00, 3.01–11.96), and electrolyte imbalance (10.40, 3.00–26.10) were independently linked to increased odds of severe illness. T2DM (6.07, 2.89–12.75), CVD (8.47, 6.03–11.89), and electrolyte imbalance (19.44, 11.47–32.96) were also strong predictors of unfavorable outcomes (Table 4).

Number of Comorbidities and Clinical Severity and Treatment Outcome

Compared with patients with no comorbidities, patients with one, two, three, or more comorbidities had increased odds of being severely ill, with *OR* (95% *CI*) of 3.43 (2.06, 5.72), 3.64 (1.07, 11.23), and 5.32 (2.16, 13.10), respectively. They also had elevated odds of having an unfavorable outcome, with *OR* (95% *CI*) of 3.00 (1.53, 5.87), 3.81 (1.60, 9.06), and 5.44 (2.48, 11.91), respectively. A dose-response trend was found between the number of comorbidities and the likelihood of being severely ill or having an unfavorable outcome ($P < 0.001$). Similar results were found when analyses were performed for comorbidities of cardiometabolic diseases or non-cardiometabolic diseases (Table 5).

Table 1. Characteristics of patients by clinical severity, treatment outcome and having comorbidity or not

Variables	*n* (%)	Clinical severity		Treatment outcome		Comorbidity or not	
		Non-severe cases (%) (*n* = 1,002)	Severe cases (%) (*n* = 158)	Favorable outcome (%) (*n* = 1,128)	Unfavorable outcome (%) (*n* = 32)	No (%) (*n* = 819)	Yes (%) (*n* = 341)
Sex							
Male	606 (52.2)	519 (85.6)	87 (14.4)	594 (98.0)	12 (2.0)	412 (68.0)	194 (32.0)
Female	554 (47.8)	483 (87.2)	71 (12.8)	534 (96.4)	20 (3.6)	407 (73.5)	147 (26.5)
Age, median (Q1, Q3)	46.0 (33.0, 57.0)	44.0 (32.0, 55.0)	57.0 (45.0, 67.0)	46.0 (32.0, 56.0)	60.0 (46.0, 71.0)	40.0 (30.0, 51.0)	56.0 (48.0, 65.0)
Age (categorized)							
< 60	917 (79.1)	828 (90.3)	89 (9.7)	901 (98.3)	16 (1.7)	717 (78.2)	200 (21.8)
≥ 60	243 (20.9)	174 (71.6)	69 (28.4)	227 (93.4)	16 (6.6)	102 (42.0)	141 (58.0)
BMI, Mean (SD)	23.8 (3.4)	23.6 (3.3)	24.9 (3.7)	23.8 (3.4)	24.0 (3.2)	23.5 (3.3)	24.6 (3.4)
Onset symptoms							
Fever							
No	641 (55.3)	575 (89.7)	66 (10.3)	631 (98.4)	10 (1.6)	462 (72.1)	179 (27.9)
Yes	519 (44.7)	427 (82.3)	92 (17.7)	497 (95.8)	22 (4.2)	357 (68.8)	162 (31.2)
Fatigue							
No	841 (72.5)	752 (89.4)	89 (10.6)	822 (97.7)	19 (2.3)	609 (72.4)	232 (27.6)
Yes	319 (27.5)	250 (78.4)	69 (21.6)	306 (95.9)	13 (4.1)	210 (65.8)	109 (34.2)
Cough							
No	582 (50.2)	533 (91.6)	49 (8.4)	573 (98.5)	9 (1.6)	424 (72.9)	158 (27.2)
Yes	578 (49.8)	469 (81.1)	109 (18.9)	555 (96.0)	23 (4)	395 (68.3)	183 (31.7)
Congestion or runny nose							
No	1126 (97.1)	973 (86.4)	153 (13.6)	1,096 (97.3)	30 (2.7)	780 (70.1)	332 (29.9)
Yes	34 (2.9)	29 (85.3)	5 (14.7)	32 (94.1)	2 (5.9)	39 (81.3)	9 (18.8)
Anorexia							
No	1,032 (89.0)	909 (88.1)	123 (11.9)	1,010 (97.9)	22 (2.1)	737 (71.4)	295 (28.6)
Yes	128 (11.0)	93 (72.7)	35 (27.3)	118 (92.2)	10 (7.8)	82 (64.1)	46 (35.9)
Sore throat							
No	1,046 (90.2)	895 (85.6)	151 (14.4)	1,014 (96.9)	32 (3.1)	734 (70.2)	312 (29.8)
Yes	114 (9.8)	107 (93.9)	7 (6.1)	114 (100)	0 (0.0)	85 (74.6)	29 (25.4)
Diarrhea							
No	1,113 (95.9)	963 (86.5)	150 (13.5)	1,084 (97.4)	29 (2.6)	787 (70.7)	326 (29.3)
Yes	47 (4.1)	39 (83)	8 (17.0)	44 (93.6)	3 (6.4)	32 (68.1)	15 (31.9)
Shortness of breath							
No	1,027 (88.5)	917 (89.3)	110 (10.7)	1,004 (97.8)	23 (2.2)	735 (71.6)	292 (28.4)
Yes	133 (11.5)	85 (63.9)	48 (36.1)	124 (93.2)	9 (6.8)	84 (63.2)	49 (36.8)
Chills							
No	1,095 (94.4)	951 (86.9)	144 (13.2)	1,065 (97.3)	30 (2.7)	780 (71.2)	315 (28.8)
Yes	65 (5.6)	51 (78.5)	14 (21.5)	63 (96.9)	2 (3.1)	39 (60.0)	26 (40.0)
Ever went to Wuhan city							
No	658 (56.7)	572 (86.9)	86 (13.1)	636 (96.7)	22 (3.3)	450 (68.4)	208 (31.6)
Yes	322 (27.8)	287 (89.1)	35 (10.9)	315 (97.8)	7 (2.2)	235 (73.0)	87 (27.0)

Note. Q1, the first quartile; Q3, the third quartile; SD, standard deviation.

Comorbidity and Clinical Severity and Treatment Outcome in Subgroups

Women with comorbidities (*OR*, 5.46; 95% *CI*, 3.25–9.19) had higher odds of being severely ill than men with comorbidities did (2.46, 1.15–5.28), while men (6.58, 1.46–29.64) with comorbidities had a higher likelihood of having an unfavorable outcome than women did (2.38, 1.78–3.19). In patients aged > 60 years, CVD was highly associated with an unfavorable outcome (5.39, 1.74–16.68), and in patients aged < 60 years, T2DM was strongly correlated with unfavorable outcomes (8.03, 2.26–28.55) (Table 6).

DISCUSSION

Our findings indicate that COVID-19 patients with

Table 2. Distribution of clinical severity and treatment outcome of COVID-19 by component and number of comorbidities

Variables	*n* (%)	Clinical severity			Treatment outcome		
		Non-severe cases (%)	Severe cases (%)	*P* value*	Favorable outcome (%)	Unfavorable outcome (%)	*P* value*
No comorbidity at all	819 (70.6)	758 (92.6)	61 (7.4)		808 (98.7)	11 (1.3)	
Had any comorbidity	341 (29.4)	244 (71.6)	97 (28.4)	< 0.0001	320 (93.8)	21 (6.2)	< 0.0001
Comorbidity of cardiometabolic diseases							
Hypertension	188 (16.2)	136 (72.3)	52 (27.7)	< 0.0001	179 (95.2)	9 (4.8)	0.0023
T2DM	89 (7.7)	65 (73.0)	24 (27.0)	< 0.0001	83 (93.3)	6 (6.7)	0.0004
Heart disease	53 (4.6)	32 (60.4)	21 (39.6)	< 0.0001	44 (83.0)	9 (17.0)	< 0.0001
Stroke	24 (2.1)	18 (75.0)	6 (25.0)	0.0017	22 (91.7)	2 (8.3)	0.0501
CVD (either heart disease or stroke)	73 (6.3)	47 (64.4)	26 (35.6)	< 0.0001	63 (86.3)	10 (13.7)	< 0.0001
Fatty liver	8 (0.7)	6 (75.0)	2 (25.0)	0.0626	8 (100.0)	–	–
Hyperlipidemia	9 (0.8)	7 (77.8)	2 (22.2)	0.0964	9 (100.0)	–	–
Hyperuricemia	7 (0.6)	6 (85.7)	1 (14.3)	0.4220	6 (85.7)	1 (14.3)	0.0977
Had hypertension and T2DM together	38 (3.3)	27 (71.1)	11 (28.9)	< 0.0001	36 (94.7)	2 (5.3)	0.1098
Had hypertension and CVD together	37 (3.2)	23 (62.2)	14 (37.8)	< 0.0001	32 (86.5)	5 (13.5)	< 0.0001
Had CVD and T2DM together	17 (1.5)	12 (70.6)	5 (29.4)	0.0009	17 (100.0)	–	–
Had hypertension, CVD and T2DM together	12 (1.0)	8 (66.7)	4 (33.3)	0.0009	12 (100.0)	–	–
Comorbidity of non-cardiometabolic disease							
Other lung diseases	27 (2.3)	15 (55.6)	12 (44.4)	< 0.0001	26 (96.3)	1 (3.7)	0.3242
Allergic diseases	7 (0.6)	1 (14.3)	6 (85.7)	< 0.0001	7 (100.0)	–	–
Hepatitis B	24 (2.1)	22 (91.7)	2 (8.3)	0.8709	24 (100.0)	–	–
Pulmonary tuberculosis	9 (0.8)	7 (77.8)	2 (22.2)	0.0964	9 (100.0)	–	–
Electrolyte disturbance	16 (1.4)	7 (43.8)	9 (56.3)	< 0.0001	12 (75.0)	4 (25.0)	0.0001
Abnormal liver or kidney function	17 (1.5)	9 (52.9)	8 (47.1)	< 0.0001	15 (88.2)	2 (11.8)	0.0266
Depression	6 (0.5)	5 (83.3)	1 (16.7)	0.3751	6 (100)	–	–
Number of any comorbidity							
0	819 (70.6)	758 (92.6)	61 (7.5)		808 (98.7)	11 (1.3)	
1	230 (19.8)	168 (73.0)	62 (27.0)	< 0.0001	218 (94.8)	12 (5.2)	< 0.0001
2	83 (7.2)	59 (71.1)	24 (28.9)		77 (92.8)	6 (7.2)	
3	28 (2.4)	17 (60.7)	11 (39.3)		25 (89.3)	3 (10.7)	

Note. T2DM, type 2 diabetes; CVD, cardiovascular disease. **P* values were calculated by comparing the distribution of severity and treatment outcome in patients with no comorbidity at all group.

hypertension, T2DM, CVD, fatty liver disease, and hyperlipidemia were more likely to have severe illness on admission, and the first three diseases were also predicted to have unfavorable treatment outcomes. Besides, other lung diseases and electrolyte imbalance were strong independent risk factors for COVID-19 severity and unfavorable outcomes. There was a dose-response trend between the number of comorbidities and severity or unfavorable treatment outcome. Women with comorbidities were more likely to be severe on admission, while men with comorbidities were more likely to have unfavorable treatment outcomes within two weeks.

Two systematic reviews have reported that the most prevalent comorbidities were hypertension (16.4%–21.1%), diabetes (7.9%–9.7%), CVD (8.4%–12.1%), and respiratory system disease (1.5%)[8,9]. However, no other comorbidities were reported. In addition to observing a similar prevalence of cardiometabolic diseases, we also reported the prevalence of hepatitis B (2.1%) and tuberculosis (0.8%) because some studies have reported a coinfection of hepatitis B, tuberculosis, and COVID-19[10,11]. In addition, previous studies have reported various electrolyte abnormalities on admission in

Table 3. The odds ratio and 95% confidence interval (*OR*, 95% *CI*) between comorbidities and clinical severity and treatment outcome of COVID-19: components were overlapped

Variables	Severe illness*		Unfavorable outcome†	
	Unadjusted *OR*	Adjusted *OR*	Unadjusted *OR*	Adjusted *OR*
No comorbidity at all	Ref	Ref	Ref	Ref
Had any comorbidity	4.94 (2.91, 8.39)	3.55 (1.94, 6.50)	4.82 (2.77, 8.40)	3.65 (2.23, 5.98)
Comorbidity of cardiometabolic disease				
Hypertension	4.75 (2.61, 8.66)	3.40 (1.70, 6.80)	3.69 (2.18, 6.26)	2.34 (1.44, 3.80)
T2DM	4.59 (2.72, 7.74)	3.36 (1.95, 5.77)	5.31 (2.90, 9.72)	4.12 (2.20, 7.72)
Heart disease	8.16 (4.86, 13.71)	4.24 (2.36, 7.62)	15.03 (9.85, 22.92)	6.31 (3.63, 10.98)
Stroke	4.14 (1.60, 10.70)	3.44 (1.22, 9.66)	6.68 (2.00, 22.34)	1.84 (0.33, 10.23)
CVD (either heart disease or stroke)	6.87 (4.28, 11.05)	3.65 (2.21, 6.03)	11.66 (8.17, 16.64)	4.45 (2.14, 9.26)
Fatty liver	4.14 (0.95, 18.15)	3.41 (0.91, 12.75)	–	–
Hyperlipidemia	3.55 (1.67, 7.56)	1.76 (0.97, 3.20)	–	–
Hyperuricemia	2.07 (0.17, 25.61)	1.31 (0.1, 17.63)	–	–
Had hypertension and T2DM together	5.06 (2.61, 9.84)	3.01 (1.19, 7.62)	4.08 (1.13, 14.76)	2.51 (0.71, 8.86)
Had hypertension and CVD together	7.56 (3.76, 15.23)	4.52 (2.59, 7.87)	11.48 (4.90, 26.87)	3.96 (0.98, 16.02)
Had CVD and T2DM together	5.18 (1.07, 25.00)	3.93 (0.97, 15.94)	–	–
Had hypertension, CVD and T2DM together	6.21 (1.38, 27.90)	4.0 (1.22, 13.16)	–	–
Comorbidity of non-Cardiometabolic disease				
Other lung diseases	9.94 (6.61, 14.96)	4.96 (2.51, 9.80)	2.83 (0.57, 14.13)	2.11 (0.46, 9.80)
Allergic diseases	–	–	–	–
Hepatitis B	1.13 (0.63, 2.03)	0.83 (0.51, 1.37)	–	–
Pulmonary tuberculosis	3.55 (2.19, 5.76)	2.89 (1.85, 4.54)	–	–
Electrolyte disturbance	15.98 (4.41, 57.95)	15.33 (3.54, 66.40)	15.59 (4.80, 50.66)	12.49 (5.52, 28.28)
Abnormal liver/kidney function	11.05 (3.68, 33.18)	6.83 (1.44, 32.48)	9.79 (2.29, 41.89)	7.69 (2.01, 29.41)
Depression	–	–	–	–

Note. * Patients who were diagnosed as non-severe were used as reference group. † Patients who had favorable outcome at end of follow-up window were used as reference group. T2DM, type 2 diabetes; CVD, cardiovascular disease. A short dash '–' was used when there was no statistical power to estimate the association.

patients whose condition progresses to the severe COVID-19, including sodium, potassium, chloride, and calcium level abnormalities[12,13]. In addition, abnormal organ function damage (liver and kidney injuries) was more prevalent in severely ill patients than in mild patients[14-16]. We also reported the prevalence of electrolyte imbalance (1.4%) and abnormal liver or kidney function (1.5%).

One meta-analysis of hypertension reported that patients with high blood pressure had 2-fold higher odds of developing severe COVID-19 (using the same definition in the present study), than patients without hypertension did (*OR*, 2.27; 95% *CI*, 1.80–2.86)[17]. A recent study also found that patients with hypertension had a higher risk of unfavorable treatment outcomes (defined as admission to ICU or death) (*HR*, 1.58; 95% *CI*, 1.07–2.32)[3]. The rates of severe illness of COVID-19 are significantly higher in patients with diabetes than in those without diabetes[18]. Two recent meta-analyses reported that preexisting diabetes was associated with an approximate 2-fold higher likelihood of having severe/critical COVID-19 illness and about 3-fold increased risk of in-hospital mortality[19,20]. A large-scale study in the United States found that patients with concomitant coronary artery disease had a higher relative risk (*RR*) of mechanical ventilation (*RR*, 1.88; 95% *CI*, 1.52–2.35) and mortality (2.24, 1.98–2.55)[21]. In addition, heart disease is independently associated with adverse outcomes irrespective of baseline comorbidities[22]. Studies also found that people with nonalcoholic fatty liver disease were over six times more likely to develop severe COVID-19 than were

Table 4. The odds ratio and 95% confidence interval (*OR*, 95% *CI*) of comorbidities with clinical severity and treatment outcome of COVID-19: components were un-overlapped

Variables	Severe illness*		Unfavorable outcome†	
	Unadjusted *OR*	Adjusted *OR*	Unadjusted *OR*	Adjusted *OR*
No comorbidity at all	Ref	Ref	Ref	Ref
Comorbidity of cardiometabolic disease				
Hypertension	4.10 (2.04, 8.23)	2.87 (1.30, 6.32)	1.19 (0.36, 4.00)	0.93 (0.27, 3.22)
T2DM	4.39 (2.79, 6.90)	3.57 (2.32, 5.49)	7.00 (3.58, 13.69)	6.07 (2.89, 12.75)
CVD (either heart disease or stroke)	6.83 (3.31, 14.12)	3.78 (1.81, 7.89)	14.13 (6.72, 29.70)	8.47 (6.03, 11.89)
Fatty liver	8.28 (2.02, 33.97)	7.53 (1.96, 28.96)	–	–
Hyperlipidemia	3.11 (1.60, 6.02)	2.15 (1.26, 3.67)	–	–
Hyperuricemia	–	–	–	–
Had hypertension and T2DM together	4.58 (1.88, 11.13)	3.04 (0.91, 10.20)	6.12 (1.42, 26.45)	4.73 (0.88, 25.37)
Had hypertension and CVD together	8.28 (3.31, 20.74)	4.65 (2.00, 10.81)	18.36 (7.01, 48.11)	9.90 (3.24, 30.25)
Had CVD and T2DM together	3.11 (0.42, 23.02)	1.96 (0.35, 11.13)	–	–
Had hypertension, CVD and T2DM together	6.21 (1.38, 28.06)	3.69 (0.86, 15.79)	–	–
Comorbidity of non-Cardiometabolic disease				
Other lung diseases	8.28 (4.88, 14.07)	6.00 (3.01, 11.96)	5.25 (1.1, 25.02)	3.89 (0.67, 22.61)
Allergic diseases				
Hepatitis B	0.80 (0.30, 2.00)	0.80 (0.30, 2.35)	–	–
Pulmonary tuberculosis	2.50 (0.60, 9.90)	1.90 (0.68, 5.08)	–	–
Electrolyte disturbance	12.80 (5.07, 32.23)	10.40 (3.00, 26.10)	16.30 (6.60, 40.20)	19.44 (11.47, 32.96)
Abnormal liver/kidney function	12.40 (0.70, 131.90)	10.50 (0.59, 87.34)	–	–
Depression	–	–	–	–

Note. * Patients who were diagnosed as non-severe were used as reference group. † Patients who had favorable outcome at end of follow-up window were used as reference group. T2DM, type 2 diabetes; CVD, cardiovascular disease. A short dash '–' was used when there was no statistical power to estimate the association.

Table 5. The odds ratio and 95% confidence interval (*OR*, 95% *CI*) between number of comorbidities and clinical severity and treatment outcome

Number of comorbidities	Severe case*		Unfavorable outcome†	
	Unadjusted *OR*	Adjusted *OR*	Unadjusted *OR*	Adjusted *OR*
Number of any comorbidity				
0	Ref	Ref	Ref	Ref
1	4.59 (2.80, 7.50)	3.43 (2.06, 5.72)	4.04 (2.08, 7.87)	3.00 (1.53, 5.87)
2	5.06 (2.00, 12.83)	3.64 (1.07, 11.23)	5.72 (2.04, 16.04)	3.81 (1.60, 9.06)
3 or more	8.04 (2.69, 24.07)	5.32 (2.16, 13.10)	8.82 (2.44, 31.89)	5.44 (2.48, 11.91)
P-value for trend		< 0.0001		< 0.0001
Number of cardiometabolic disease				
0	Ref	Ref	Ref	Ref
1	4.33 (2.72, 6.90)	3.10 (1.86, 5.16)	3.91 (2.02, 7.57)	2.81 (1.39, 5.68)
2	5.06 (2.02, 12.67)	3.31 (1.17, 9.41)	6.30 (2.35, 16.85)	4.24 (1.82, 9.91)
3 or more	8.04 (2.69, 24.07)	4.54 (1.57, 13.16)	8.82 (2.44, 31.90)	5.01 (2.61, 9.64)
P-value for trend		< 0.0001		< 0.0001
Number of non-cardiometabolic disease				
0	Ref	Ref	Ref	Ref
1	5.48 (2.36, 12.76)	5.00 (2.16, 11.59)	4.79 (1.57, 14.66)	3.85 (1.39, 10.66)
2 or more	8.75 (3.86, 18.84)	4.94 (2.02, 12.05)	5.13 (2.67, 9.86)	2.93 (1.41, 6.09)

Note. * Patients who were diagnosed as non-severe were used as reference group. † Patients who had favorable outcome at end of follow-up window were used as reference group.

Table 6. The odds ratio and 95% confidence interval (*OR*, 95% *CI*) between types of comorbidities and clinical severity and treatment outcome by gender and age

Variables	Gender		Age	
	Male	Female	<60	≥ 60
Being diagnosed as severe illness*				
No comorbidity at all	Ref	Ref	Ref	Ref
Any comorbidity	2.46 (1.15, 5.28)	5.46 (3.25, 9.19)	3.54 (1.76, 7.13)	3.26 (1.56, 6.78)
Hypertension	2.12 (0.84, 5.31)	5.40 (2.98, 9.80)	3.31 (1.32, 8.32)	3.05 (1.33, 7.00)
T2DM	1.92 (0.87, 4.23)	5.86 (3.53, 9.75)	2.47 (1.69, 3.61)	3.95 (1.43, 10.89)
CVD	1.94 (0.82, 4.58)	4.75 (2.49, 9.05)	1.57 (0.74, 3.37)	4.25 (2.26, 8.00)
Having unfavorable outcome†				
No comorbidity at all	Ref	Ref	Ref	Ref
Any comorbidity	6.58 (1.46, 29.64)	2.38 (1.78, 3.19)	4.63 (1.40, 15.27)	2.79 (1.25, 6.21)
Hypertension	3.28 (0.58, 18.53)	2.11 (1.25, 3.56)	3.31 (0.76, 14.47)	2.35 (0.85, 6.54)
T2DM	10.38 (2.62, 41.17)	2.72 (1.38, 5.35)	8.03 (2.26, 28.55)	1.85 (0.49, 6.92)
CVD	3.75 (1.54, 9.12)	4.97 (1.89, 13.06)	3.21 (1.19, 8.65)	5.39 (1.74, 16.68)

Note. * Patients who were diagnosed as non-severe were used as reference group. † Patients who had favorable outcome at end of follow-up window were used as reference group. T2DM, type 2 diabetes; CVD, cardiovascular disease.

those without nonalcoholic fatty liver disease[23,24].

Cardiometabolic diseases usually have shared pathologies. A person having one cardiometabolic disease may also have some others simultaneously, especially those with hypertension, T2DM, and CVD. We found consistent results with the previous findings listed above. However, prior studies did not separate cardiometabolic comorbidities that overlapped with each other; thus, the independent role of each specific disease in the severity of COVID-19 could not be analyzed. We found that after considering the overlap among them, fatty liver disease, T2DM, and CVD were stronger risk factors than hypertension was for COVID-19 severity. One possible mechanism between fatty liver disease and COVID-19 severity is that the impaired hepatic innate immune status plays a critical role in COVID-19 outcome[23]. Consistent with previous studies[3,4], a dose-response trend was observed between the number of comorbidities and severity of COVID-19.

Evidence has shown that patients with severe COVID-19 tend to have a higher proportion of electrolyte imbalances, such as hypokalemia and hyponatremia, at baseline compared with those with a mild from of the disease[12,25]. However, no study has examined the association between electrolyte imbalance and severity of COVID-19. Our findings showed that patients with electrolyte imbalance had much higher odds of developing severe COVID-19. A recent systematic review found that COVID-19 patients with COPD had a 2.62-fold higher risk of severe COVID-19 and a 50% higher risk of death than that of COVID-19 patients without comorbidities[26]. However, not all respiratory diseases progress to COPD. Besides COPD, we also included chronic bronchitis, bronchial asthma, or pneumonia in the present study. Consistent with previous studies[2,8], we found that preexisting respiratory diseases increased nearly five times the odds of having severe illness and twice the odds of an unfavorable outcome. Studies have reported the coinfection of COVID-19 and tuberculosis[27,28], which both attack primarily the lungs. People who experienced tuberculosis who now have COVID-19 may have poorer treatment outcomes. Our findings showed that patients who had tuberculosis coinfection and COVID-19 had nearly 3-fold higher odds of having severe COVID-19.

Although we included abnormal liver/kidney function in this study and found a much higher association with COVID-19 severity and unfavorable outcome, it should be noted that liver/kidney disturbance might be a potential organ injury caused by the COVID-19 infection rather than a comorbidity. Studies have indicated that some patients with COVID-19 show varying levels of liver disease[29,30] and acute renal injury[15,31]. Moreover, patients with acute kidney or renal injury have a higher mortality rate compared to other patients[31].

In the subgroup analyses, we found that men with comorbidities were more likely to have unfavorable outcomes, consistent with the fact that male sex is an independent risk of mortality in COVID-19[32]. Intriguingly, we also found that women with comorbidities had higher odds of being diagnosed with severe illness on admission than men did (*OR*: 5.46 *vs.* 2.38). It seems that although women are more vulnerable to comorbidities than men are, and they are less likely to experience unfavorable outcomes such as death.

Study Strengths and Limitations

The main notable strengths of our study are that we demonstrated the association of un-overlapped comorbidities with the severity and treatment outcome of COVID-19. This information helps to identify the independent role of each comorbidity in COVID-19 prognosis and outcome. In addition, performed subgroup analyses by sex and age group, which were not performed many of the previous studies.

Our study has several limitations. As we collected information from patients' medical records in the hospital, some variables were missing (such as smoking status and educational level), which would cause some residual bias. Second, some comorbidities included in the present study might have been caused by the COVID-19 rather than a preexisting condition before acquiring COVID-19, such as electrolyte imbalance and abnormal liver/kidney function. From this point of view, they might be complications instead of comorbidities. Third, limited by the sample number of patients with unfavorable outcomes, we did not have sufficient statistical power to analyze the association of allergic diseases, hepatitis B, tuberculosis, and depression with treatment outcomes. In addition, we did not have sufficient statistical power to analyze association with mortality in subgroups. Further studies are necessary to analyze the role of comorbidities on severity and mortality with regard to education and ethnicity. Finally, as the prevalence of comorbidities may differ across countries, caution should be exercised when extrapolating our findings to other countries.

Conclusions

In conclusion, the presence of a comorbidity was associated with an increased likelihood of developing severe COVID-19 and having unfavorable treatment outcomes. Hypertension, T2DM, CVD, fatty liver disease, and hyperlipidemia were linked to COVID-19 severity. Other lung diseases and electrolyte imbalance were strong independent risk factors for COVID-19 severity and unfavorable outcomes. Women with comorbidities were more likely to be severe on admission, while men with comorbidities were more likely to have unfavorable treatment outcomes. Identifying patients with different types and numbers of comorbidities may help clinicians to assess the clinical severity on admission and predict the potential treatment outcome in advance, thereby implementing targeted treatment and management of these patients. These patients may also need close monitoring in clinical practice.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

Experiments were conceived and designed by MA Yan, ZHU Dong Shan, SHI Nan Nan, ZHANG Hua Min, WANG Yan Ping, and WANG Yong Yan. Data were inputted by CHEN Ren Bo, LIU Si Hong, and FAN Yi Pin. Patients were enrolled by WU Gui Hui, YANG Pu Ye, BAI Jiang Feng, CHEN Hong, CHEN Li Ying, FENG Qiao, GUO Tuan Mao, HOU Yong, HU Gui Fen, HU Xiao Mei, HU Yun Hong, HUANG Jin, HUANG Qiu Hua, HUANG Shao Zhen, JI Liang, JIN Hai Hao, LEI Xiao, LI Chun Yan, LI Min Qing, LI Qun Tang, LI Xian Yong, LIU Hong De, LIU Jin Ping, LIU Zhang, MA Yu Ting, MAO Ya, MO Liu Fen, NA Hui, WANG Jing Wei, SONG Fang Li, SUN Sheng, WANG Dong Ting, WANG Ming Xuan, WANG Xiao Yan, WANG Yin Zhen, WANG Yu Dong, WU Wei, WU Lan Ping, XIAO Yan Hua, XIE Hai Jun, XU Hong Ming, XU Shou Fang, XUE Rui Xia, YANG Chun, YANG Kai Jun, YUAN Sheng Li, ZHANG Gong Qi, ZHANG Jin Bo, ZHANG Lin Song, ZHAO Shu Sen, ZHAO Wan Ying, ZHENG Kai, ZHOU Ying chun, ZHU Jun Teng, ZHU Tian Qing. Data analysis was carried out by MA Yan and ZHU Dong Shan. The paper was written by MA Yan, ZHU Dong shan, CHEN Ren Bo, SHI Nan Nan, and LIU Si Hong.

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