Received: 5 May 2020 | Accepted: 13 June 2020

DOI: 10.1002/jmv.26183

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Impact of comorbidities on patients with COVID-19: A large retrospective study in Zhejiang, China

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Funding information
National Major Science and Technology Research Projects for the Control and Prevention of Major Infectious Diseases in China, Grant/Award Number: 2017ZX10202202

Abstract

Coronavirus disease 2019 (COVID-19) has become a serious public health problem worldwide. Here, we stratified COVID-19 patients based on their comorbidities to assess their risk of serious adverse outcomes. We collected 856 hospitalized cases diagnosed with COVID-19 from 17 January to 7 February 2020, in Zhejiang Province, and analyzed their comorbidities and composite endpoint (including admission to intensive care unit owing to disease progression, shock, invasive ventilation, and death) to determine the relationship between comorbidities and adverse outcomes. The median age of patients was 46 (36-56) years; 439 (51.3%) were men, 242 (28.3%) had comorbidities, and 152 (17.8%) had two or more comorbidities. The most common comorbidity was hypertension (142 [16.6%]), followed by diabetes (64 [7.5%]). Of the 856 patients, there are 154 (18.0%) severe cases. Thirty-two (3.7%) reached composite endpoints, of which 22 (9.1%) were from the comorbidity group and 10 (1.6%) from the non-comorbidity group ($P < .001$). After adjusting for age and gender status, the risk of reaching the composite endpoint was higher in the group with comorbidity than in that without comorbidity (hazard ratio [HR] 3.04, 95% confidence interval [CI]: 1.40-6.60). HR values for patients with one, two, and three or more comorbidities were 1.61 (95% CI: 0.44-5.91), 3.44 (95% CI: 1.31-9.08), and 6.90 (95% CI: 2.69-17.69), respectively. COVID-19 patients with comorbidities had worse clinical outcomes as compared with those without any comorbidity. The higher the number of comorbidities, the greater was the risk of serious adverse outcomes.

KEYWORDS

adverse outcome, comorbidity, COVID-19

1 | INTRODUCTION

Since the first report of the new coronavirus pneumonia in Wuhan, Hubei, in December 2019,[1] the cumulative number of confirmed cases has exceeded two million worldwide. The cumulative death toll exceeded 100 000 by 16 April 2020, raising a serious global concern.

According to previous reports, coronavirus disease 2019 (COVID-19) is clinically manifested as, but not limited to, fever, cough, sputum, headache, fatigue, and diarrhea. Most patients with COVID-19 have comorbidities such as hypertension, diabetes, cardiovascular disease, and chronic liver disease.[1-3] The presence of comorbidities was shown to be related to high mortality among hospitalized patients with the Middle East respiratory syndrome

coronavirus (MERS-CoV) infection.[4-7] In patients with H7N9, comorbidities were considered as important factors for poor prognosis.[8,9] Similar conclusions have been reported in several clinical reports on patients with influenza[10,11] or severe acute respiratory syndrome coronavirus (SARS-CoV)[12] infections. The new coronavirus-19 is extremely contagious with an estimated basic reproduction number between two and three,[13,14] which is comparable to that of the SARS-CoV.[15] meanwhile, elderly people are more likely to be infected, and a considerable part of them carry up with chronic diseases,[16] While their own resistance to the disease is low, they are prone to develop into serious cases and have adverse outcomes.[17,18] A large number of epidemiological studies have analyzed the proportion of comorbidities between the mild and severe groups, the proportion of comorbidities in the severe case group is higher than that in the mild.[19-21] However, clinical and epidemiological characteristics of patients with and without comorbidities have not been studied. Further, the relationship between comorbidities and serious adverse outcomes of COVID-19 remains unclear. In the present study, we analyzed different manifestations in patients with COVID-19 based on the presence, type, and number of comorbidities, and assessed their relationship with the risk of serious adverse outcomes.

2 | METHODS

2.1 | Data sources and ethics

In this large retrospective study, we collected the data of 856 patients diagnosed with COVID-19 from 17 January to 7 February 2020, based on the Chinese version of the COVID-19 Diagnosis and Treatment Program (6th Edition).[22] Data on their clinical and epidemiological characteristics were collected by the Health Commission of Zhejiang province, China. All patients were assigned to designated hospitals in the Zhejiang Province for diagnosis and treatment. The results of our analyses have been reported to the People's Government of Zhejiang Province and will be shared with the World Health Organization. This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (NO. IIT20200005C).

2.2 | Procedures

Epidemiology data, laboratory tests, clinical features, imaging data, treatment methods, and clinical outcomes of the patients were reported to the Zhejiang Health Committee of China by the designated hospital. Comorbidities were determined according to the patient's readme at the time of admission. The data were recorded in an electronic database by an independent researcher and verified by another experienced clinician. All patients underwent corresponding imaging examinations (chest radiograph/computed tomography) and conventional respiratory virus screening (including parainfluenza virus, avian influenza, adenovirus, SARS, and MERS) on admission. The clinical outcomes were followed up to 7 February 2020.

2.3 | Related definitions

Comorbidity: the presence and the number of comorbidities were mainly depend on patients' self-report on admission, including hypertension, heart diseases, diabetes, chronic obstructive pulmonary disease (COPD), asthma, chronic liver disease, chronic kidney disease, malignant tumor, human immunodeficiency virus infection, hematologic disease, and other comorbidities that may have influence on the illness, including the use of immunosuppressants, tuberculosis,hyperthyroidism, hypothyroidism, and cerebrovascular diseases.

We divided COVID-19 cases into severe and common groups. Severe cases included severe and critically ill patients, while the common group included common types and patients with no pneumonia upon imaging on admission but confirmed by laboratory tests. The classification was based on the Chinese version of the diagnosis and treatment of COVID-19 (6th edition).

The endpoint outcome comprised a composite endpoint, including admission to the intensive care unit owing to disease progression or failure of other organs and mechanical ventilation caused by respiratory failure, shock, and death.

2.4 | Statistical analysis

Statistical analyses were performed using the SPSS software version 25.0. The normally distributed continuous measurement data are expressed as mean ± standard deviation, while non-normally distributed measurement data are expressed as median and quartile (Q1-Q3). Categorical variables are expressed as number (%); the t test and the χ^2 test were used for comparisons between groups, while a non-parametric test was used as appropriate. Statistical significance was defined by a two-sided α value of less than .05.

To calculate survival time, the first time to reach the composite endpoint prevailed. The Cox proportional hazard regression model was used to determine potential risk factors for reaching the composite endpoint. The results are expressed as hazard ratio (HR) and 95% confidence interval (CI). Age and sex status were adjusted using the Cox regression model.

3 | RESULTS

3.1 | Demographic and epidemiologic characteristics

As of 7 February 2020, a total of 856 patients with COVID-19 in the Zhejiang Province were included in this study. These patients comprised 417 (48.7%) female and 439 (51.3%) male; their median age was 46 (36-56) years. A total of 417 (48.7%) patients had a history of

contact with the epidemic area, 366 (42.8%) had been in close contact with COVID-19 patients, and 216 (25.2%) were family cluster cases. In total, 7.0% of the patients were current smokers. The most common symptoms on admission were fever (81.5%), cough (64.6%), and expectoration (33.9%). Rare symptoms included fatigue (18%), sore throat (14.3%), muscle pain (11.2%), and headache (9.3%). The median time from disease onset to confirm the diagnosis was 4 (2-7) days. Nearly 90% of the patients had changes in imaging on admission. Severe cases accounted for 18% of the total patients, and 32 (3.7%) patients reached the composite endpoint during this study (Table 1).

3.2 | Clinical features and outcomes of patients with comorbidities

Of the 856 patients, 242 (28.3%) had comorbidities, including hypertension (142 [16.6%]), diabetes (64 [7.5%]), heart disease (13 [1.5%]), chronic hepatitis B (27 [3.1%]), malignant tumors (8 [0.9%]), chronic kidney disease (7 [0.8%]), and COPD (5 [0.6%]). Patients with comorbidities were older than those without (55 ± 13.3 vs 42.6 ± 14.6 years, $P < .001$). Clinical manifestations, including hemoptysis (4.5% vs 0.5%, $P < .001$), diarrhea (9.9% vs. 6.7%, $P = .03$), and shortness of breath (11.2% vs 2.3%, $P < .001$), and imaging abnormalities (93.4% vs 87.8%, $P = .017$) were more severe in the comorbidity group than those in the non-comorbidity group. 82 (33.9%) cases are severe cases in the group of comorbidity while only 72 (11.7%) in the group of non-comorbidity, the differences were statistically significant. The rate of reaching the composite endpoint was significantly different between the comorbidity and non-comorbidity groups (9.1% vs 1.6%, $P < .001$) (Table 1).

3.3 | Clinical features and outcomes of patients stratified by comorbidities

Of the 242 patients with comorbidities, 90 had only one type of comorbidity, 97 had two comorbidities, and 55 had three or more comorbidities. The higher the number of comorbidities, the older were the patients (62.0 ± 13.1 vs 55.8 ± 10.4 vs 48.6 ± 14.5 years for ≥3, 2, and 1 comorbidity, respectively, $P < .001$). The number of severe cases increased with the number of comorbidities (21.1% vs 37.1% vs 49.1%, $P = .016$),as well as the the number of patients reaching the composite endpoint (3.3%, 8.2%, and 20.0%, respectively). No significant difference was observed in the patients that reached the composite endpoints between the groups with one and two comorbidities ($P = .154$), while the number of patients with three or more comorbidities reaching the composite endpoints was significantly different from that reported in other two groups (Table 2). We listed the clinical and epidemiological characteristics of some common comorbidities, including hypertension, diabetes, chronic hepatitis B, malignant tumors, heart disease, and chronic kidney disease. The incidence of severe disease was higher among patients with these comorbidities than in those without.

Severe COVID-19 was detected in 59 (41.5%) and 95 (13.3%) patients with and without hypertension, 22 (34.4%) and 132 (16.7%) patients with and without diabetes, 7 (25.9%) and 147 (17.7%) with and without chronic hepatitis B, 5 (62.5%) and 149 (17.6%) with and without malignant tumor, 5 (38.5%) and 149 (17.7%) with and without heart disease, and 2 (28.6%) and 152 (17.9%) with and without chronic kidney disease (Table 3).

3.4 | Prognostic analysis

During this study, 32 patients reached the composite endpoint, and all of them were admitted to the intensive care unit, 29 received invasive ventilation, nine received extracorporeal membrane oxygenation, two received continuous renal replacement therapy, four experienced shock, and only one died. In comparison with the patients without comorbidities, those with comorbidities had a significantly higher risk of reaching the composite endpoint. As the number of comorbidities increased, the risk of reaching the composite endpoint also increased (Figure 1). After adjusting for age and gender status, we divided patients based on the type and number of comorbidities and performed a Cox proportional hazard regression analysis (Figure 2). The results of the multivariate regression analysis showed that hypertension was the risk factor for the composite endpoint (HR: 4.74; 95% CI: 2.22-10.09). We also divided the patients with hypertension into angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and non-ACEI/ARB groups based on their medication and compared the epidemiology data, clinical characteristics, and prognosis. No significant difference was observed between the epidemiology data and clinical characteristics of these two groups (Online Supplement Table E1). We used the Cox regression analysis to explore the risk of reaching the composite endpoint in these two groups after adjusting for age and sex status, but no significant difference was found (Online Supplement Table E2). In comparison with the patients without comorbidities, those with two or more comorbidities had a higher risk of reaching the composite endpoint (HR: 3.44; 95% CI: 1.31-9.08 for two comorbidities and HR: 6.90; 95% CI: 2.69-17.69 for three or more comorbidities).

4 | DISCUSSION

This is a large multicenter retrospective study conducted on SARS-CoV-2 infection cases in Zhejiang, well representing the epidemiological situation of COVID-19 in central China. Comorbidity has always been a risk factor for many diseases, including the pandemic SARS,[12] MERS,[7] H7N9,[9] or even common influenza[11] and community-acquired pneumonia.[23] Patients with underlying diseases, in general, show worse outcomes than the otherwise healthy patients, and their resistance to most diseases is low. This situation promotes the progression of disease condition. In patients with COVID-19, comorbidities are common.

TABLE 1 Demographic and epidemiological characteristics of patients with COVID-19 with and without comorbidities.

Variable	Total (n = 856)	Comorbidity		P value
		Yes (n = 242)	No (n = 614)	
Age, y	46 (35-56)	55 ± 13.3	42.6 ± 14.6	<.001
Sex				
Male	439 (51.3%)	137 (56.6%)	302 (49.2%)	.05
Female	417 (48.7%)	105 (43.4%)	312 (50.8%)	
Current smoker	60 (7.0%)	17 (7.0%)	43 (7.0%)	.991
Exposure history				
From Wuhan	417 (48.7%)	110 (45.5%)	307 (50.0%)	.231
Contact with patients	366 (42.8%)	93 (38.4%)	273 (44.5%)	.108
Family cluster	216 (25.2%)	50 (20.7%)	166 (27.0%)	.053
Symptoms				
Fever	698 (81.5%)	206 (85.1%)	492 (80.1%)	.09
Cough	553 (64.6%)	167 (69.0%)	386 (62.9%)	.09
Sputum production	290 (33.9%)	99 (40.9%)	191 (31.1%)	.006
Hemoptysis	14 (1.6%)	11 (4.5%)	3 (0.5%)	<.001
Sore throat	122 (14.3%)	35 (14.5%)	87 (14.2%)	.912
Nasal obstruction	50 (5.8%)	7 (2.9%)	43 (7.0%)	.021
Muscle ache	96 (11.2%)	38 (15.7%)	58 (9.4%)	.009
Fatigue	154 (18.0%)	53 (21.9%)	101 (16.4%)	.062
Diarrhea	65 (7.6%)	24 (9.9%)	41 (6.7%)	.03
Nausea/vomiting	28 (3.3%)	11 (4.5%)	17 (2.8%)	.188
Headache	80 (9.3%)	19 (7.9%)	61 (9.9%)	.346
Shortness of breath	41 (4.8%)	27 (11.2%)	14 (2.3%)	<.001
Time from onset of illness to consultation	2 (1-4)	2 (1-5)	2 (1-4)	.232
Time from onset of illness to confirm the diagnosis	4 (2-7)	4 (2-8)	4 (2-7)	.077
Time from onset of illness to hospitalization	3 (1-6)	4 (1-7)	3 (1-6)	.03
Chest x-ray/CT findings				
Abnormal lung imaging on admission	765 (89.4%)	226 (93.4%)	539 (87.8%)	.017
Unilateral pneumonia	182 (21.3%)	41 (16.9%)	141 (23.0%)	.052
Bilateral pneumonia	313 (36.6%)	88 (36.4%)	225 (36.6%)	.939
Multiple mottling and ground-glass opacity	270 (31.5%)	97 (40.1%)	173 (28.2%)	.001
Clinical type				
Mild/ordinary type	702 (82.0%)	160 (66.1%)	542 (88.3%)	
Severe/critical type	154 (18.0%)	82 (33.9%)	72 (11.7%)	<.001
Composite endpoint	32 (3.7%)	22 (9.1%)	10 (1.6%)	<.001
Mechanical ventilation	29 (3.4%)	21 (8.7%)	8 (1.3%)	<.001
Admission to intensive care unit	32 (3.7%)	22 (9.1%)	10 (1.6%)	<.001
CRRT	2 (0.2%)	2 (0.8%)	0	.08
ECOM	9 (1.1%)	5 (2.1%)	4 (0.7%)	.148
Shock	4 (0.5%)	4 (1.7%)	0	.006
Death	1 (0.1%)	1 (0.4%)	0	.283

Note: Data is expressed as mean ± standard deviation, median with quartile (Q1-Q3), and number (%).
Abbreviations: COVID-19, coronavirus disease; CRRT, continuous renal replacement therapy; CT, computed tomography; ECOM, extracorporeal membrane oxygenation.

Approximately 30% to 50% of the patients were reported to have one or more comorbidities, the most common being hypertension (30%-50%), diabetes (8%-20%), cardiovascular disease (5%-20%), chronic liver disease (1%-5%), and chronic kidney disease (1%-4%).[3,19,24,25] Patients with comorbidities have compromised immune status, decreased disease resistance, and are more likely to suffer from severe infection than those without comorbidities. Our study describes the relationship between comorbidities and clinical outcomes of COVID-19 that plays an important role in the clinical diagnosis, treatment, and prevention of COVID-19. Our results show that severe COVID-19 is more common among patients with comorbidities than in those without any comorbidity,

TABLE 2 Demographic and epidemiological characteristics of patients with COVID-19 with different numbers of comorbidities

Variable	1 Comorbidity (group 1) (n = 90)	2 Comorbidities (group 2) (n = 97)	≧3 Comorbidities (group 3) (n = 55)	*P* value (global test)	*P* value (group 1 vs group 2)	*P* value (group 1 vs group 3)	*P* value (group 2 vs group 3)
Age, y	48.6 ± 14.5	55.8 ± 10.4	62.0 ± 13.1	<.001	.002	<.001	.015
Sex							
Male	47 (52.2%)	56 (57.7%)	34 (61.8%)	.506			
Female	43 (47.8%)	41 (42.3%)	21 (38.2%)				
Current smoker	6 (6.7%)	7 (7.2%)	4 (7.3%)	.986			
Exposure history							
From Wuhan	42 (46.7%)	46 (47.4%)	22 (40.0%)	.649			
Contact with patients	39 (43.3%)	36 (37.1%)	18 (32.7%)	.419			
Family cluster	22 (24.4%)	22 (22.7%)	6 (10.9%)	.121			
Symptoms							
Fever	75 (83.3%)	84 (86.6%)	47 (85.5%)	.819			
Cough	64 (71.1%)	60 (61.9%)	43 (78.2%)	.097			
Sputum production	40 (44.4%)	34 (35.1%)	25 (45.5%)	.315			
Hemoptysis	4 (4.4%)	4 (4.1%)	3 (5.5%)	.929			
Sore throat	14 (15.6%)	14 (14.4%)	7 (12.7%)	.895			
Nasal obstruction	4 (4.4%)	2 (2.1%)	1 (1.8%)	.539			
Muscle ache	12 (13.3%)	17 (17.5%)	9 (16.4%)	.725			
Fatigue	21 (23.3%)	21 (21.6%)	11 (20.0%)	.892			
Diarrhea	12 (13.3%)	9 (9.3%)	3 (5.5%)	.294			
Nausea/vomiting	3 (3.3%)	6 (6.2%)	2 (3.6%)	.603			
Headache	10 (11.1%)	7 (7.2%)	2 (3.6%)	.256			
Shortness of breath	5 (5.6%)	15 (15.5%)	7 (12.7%)	.091			
Time from onset of illness to consultation	2 (1-4.3)	2 (1-5)	2 (0-5)	.781			
Time from onset of illness to confirm the diagnosis	4 (2-7.3)	5 (3-8)	5 (2-8)	.665			
Time from onset of illness to hospitalization	3.5 (1-5.3)	4 (1.5-7)	3 (1-7)	.50			
Chest x-ray/CT findings							
Abnormal lung imaging on admission	80 (88.9%)	92 (94.8%)	54 (98.2%)	.07			
Unilateral pneumonia	21 (23.3%)	13 (13.4%)	7 (12.7%)	.124			
Bilateral pneumonia	35 (38.9%)	37 (38.1%)	16 (29.1%)	.531			
Multiple mottling and ground-glass opacity	24 (26.7%)	42 (43.3%)	31 (56.4%)	.001	.017	<.001	.121
Clinical type							
Mild/ordinary type	71 (78.9%)	61 (62.9%)	28 (50.9%)				
Severe/critical type	19 (21.1%)	36 (37.1%)	27 (49.1%)	.002	.016	<.001	.15
Composite endpoint	3 (3.3%)	8 (8.2%)	11 (20.0%)	.003	.154	<.001	.035
Mechanical ventilation	3 (3.3%)	8 (8.2%)	10 (18.2%)	.008	.154	.006	.069
Admission to intensive care unit	3 (3.3%)	8 (8.2%)	11 (20.0%)	.003	.154	<.001	.035
CRRT	1 (1.1%)	0	1 (1.8%)	.459			
ECOM	1 (1.1%)	1 (1.0%)	3 (5.5%)	.133			
Shock	2 (2.2%)	0	2 (3.6%)	.208			
Death	0	0	1 (1.8%)	.181			

Note: Data is expressed as mean ± standard deviation, median with quartile (Q1-Q3), and number (%).

Abbreviations: COVOD-19, coronavirus disease 19; CRRT, continuous renal replacement therapy; CT, computed tomography; ECOM, extracorporeal membrane oxygenation.

TABLE 3 Demographics and clinical characteristics of patients with COVID-19 stratified by different comorbidities

	Hypertension		Diabetes		Chronic hepatitis B	
Variable	**yes (n = 142)**	**no (n = 714)**	**yes (n = 64)**	**no (n = 792)**	**yes (n = 27)**	**no (n = 829)**
Age, y	57 (49-66)	40 (31-52.2)	58.1 ± 11.2	43.4 ± 15.3	45.3 ± 10.2	44.8 ± 16.5
Sex						
Male	84 (59.2%)	355 (49.7%)	36 (56.3%)	403 (50.9%)	18 (66.7%)	421 (50.8%)
Female	58 (40.8%)	359 (50.3%)	28 (43.8%)	389 (49.1%)	9 (33.3%)	408 (49.2%)
Current smoker	11 (7.7%)	49 (6.9%)	5 (7.8%)	55 (6.9%)	1 (3.7%)	59 (7.1%)
Exposure history						
From Wuhan	67 (47.2%)	350 (49.0%)	26 (40.6%)	391 (49.4%)	14 (51.9%)	403 (48.6%)
Contact with patients	48 (33.8%)	318 (44.5%)	21 (32.8%)	345 (43.6%)	13 (48.1%)	353 (42.6%)
Family cluster	26 (18.3%)	190 (26.6%)	10 (15.6%)	206 (26.0%)	7 (25.9%)	209 (25.2%)
Symptoms						
Fever	123 (86.6%)	575 (80.5%)	57 (89.1%)	641 (80.9%)	22 (81.5%)	676 (81.5%)
Cough	96 (67.6%)	457 (64.0%)	46 (71.9%)	507 (64.0%)	22 (81.5%)	531 (64.1%)
Sputum production	54 (38.0%)	236 (33.1%)	25 (39.1%)	265 (33.5%)	15 (55.6%)	275 (33.2%)
Hemoptysis	7 (4.9%)	7 (1.0%)	1 (1.6%)	13 (1.6%)	2 (7.4%)	12 (1.4%)
Sore throat	20 (14.1%)	102 (14.3%)	9 (14.1%)	113 (14.3%)	3 (11.1%)	119 (14.4%)
Nasal obstruction	3 (2.1%)	47 (6.6%)	1 (1.6%)	49 (6.2%)	2 (7.4%)	48 (5.8%)
Muscle ache	22 (15.5%)	74 (10.4%)	12 (18.8%)	84 (10.6%)	3 (11.1%)	93 (11.2%)
Fatigue	30 (21.1%)	124 (17.4%)	16 (25.0%)	138 (17.4%)	6 (22.2%)	148 (17.9%)
Diarrhea	12 (8.5%)	53 (7.4%)	6 (9.4%)	59 (7.4%)	6 (22.2%)	59 (7.1%)
Nausea/vomiting	7 (4.9%)	21 (2.9%)	2 (3.1%)	26 (3.3%)	1 (3.7%)	27 (3.3%)
Headache	7 (4.9%)	73 (10.2%)	4 (6.3%)	76 (9.6%)	2 (7.4%)	78 (9.4%)
Shortness of breath	21 (14.8%)	20 (2.8%)	5 (7.8%)	36 (4.5%)	0	41 (4.9%)
Time from onset of illness to consultation	2 (0-5)	2 (1-4)	2 (0.3-5)	2 (1-4)	3 (1-6)	2 (1-4)
Time from onset of illness to confirm the diagnosis	5 (2-8)	4 (2-7)	4 (2-8)	4 (2-7)	4 (3-8)	4 (2-7)
Time from onset of illness to hospitalization	4 (1-7)	3 (1-6)	3 (1-7)	3 (1-6)	4 (2-8)	3 (1-6)
Chest x-ray/CT findings						
Abnormal lung imaging on admission	136 (95.8%)	629 (88.1%)	60 (93.8%)	705 (89.0%)	25 (92.6%)	740 (89.3%)
Unilateral pneumonia	19 (13.4%)	163 (22.8%)	10 (15.6%)	172 (21.7%)	7 (25.9%)	175 (21.1%)
Bilateral pneumonia	48 (33.8%)	265 (37.1%)	22 (34.4%)	291 (36.7%)	12 (44.4%)	301 (36.3%)
Multiple mottling and ground-glass opacity	69 (48.6%)	201 (28.2%)	28 (43.8%)	242 (30.6%)	6 (22.2%)	264 (31.8%)
Clinical type						
Mild/ordinary type	83 (58.5%)	619 (86.7%)	42 (65.6%)	660 (83.3%)	20 (74.1%)	682 (82.3%)
Severe/critical ype	59 (41.5%)	95 (13.3%)	22 (34.4%)	132 (16.7%)	7 (25.9%)	147 (17.7%)
Composite endpoint	19 (13.4%)	13 (1.8%)	7 (10.9%)	25 (3.2%)	2 (7.4%)	30 (3.6%)
Mechanical ventilation	18 (12.7%)	11 (1.5%)	7 (10.9%)	22 (2.8%)	2 (7.4%)	27 (3.3%)
Admission to intensive care unit	19 (13.4%)	13 (1.8%)	7 (10.9%)	25 (3.2%)	2 (7.4%)	30 (3.6%)
CRRT	1 (0.7%)	1 (0.1%)	0	2 (0.3%)	1 (3.7%)	1 (0.1%)
ECOM	4 (2.8%)	5 (0.7%)	1 (1.6%)	8 (1.0%)	1 (3.7%)	8 (1.0%)
Shock	2 (1.4%)	2 (0.3%)	2 (3.1%)	2 (0.3%)	1 (3.7%)	3 (0.4%)
Death	1 (0.7%)	0	1 (1.6%)	0	0	1 (0.1%)
	Malignancy		**Heart disease**		**Chronic kidney disease**	
Variable	**yes (n = 8)**	**no (n = 848)**	**yes (n = 13)**	**no (n = 843)**	**yes (n = 7)**	**no (n = 849)**
Age, y	59 (55-67)	42.5 (30-63)	64.4 ± 16.2	42.5 ± 14.3	48.3 ± 16.4	47.0 ± 16.5
Sex						
Male	3 (37.5%)	436 (51.4%)	7 (53.8%)	432 (51.2%)	6 (85.7%)	433 (51.0%)
Female	5 (62.5%)	412 (48.6%)	6 (46.2%)	411 (48.8%)	1 (14.3%)	416 (49.0%)
Current smoker	1 (12.5%)	59 (7.0%)	0	60 (7.1%)	1 (14.3%)	59 (6.9%)

TABLE 3 (Continued)

Variable	Malignancy		Heart disease		Chronic kidney disease	
	yes (n = 8)	no (n = 848)	yes (n = 13)	no (n = 843)	yes (n = 7)	no (n = 849)
Exposure history						
from Wuhan	5 (62.5%)	412 (48.6%)	3 (23.1%)	414 (49.1%)	3 (42.9%)	414 (48.8%)
Contact with patients	3 (37.5%)	363 (42.8%)	5 (38.5%)	361 (42.8%)	3 (42.9%)	363 (42.8%)
Family cluster	3 (37.5%)	213 (25.1%)	3 (23.1%)	213 (25.3%)	0	216 (25.4%)
Symptoms						
Fever	8 (100.0%)	690 (81.4%)	11 (84.6%)	687 (81.5%)	6 (85.7%)	692 (81.5%)
Cough	7 (87.5%)	546 (64.4%)	11 (84.6%)	542 (64.3%)	6 (85.7%)	547 (64.4%)
Sputum production	3 (37.5%)	287 (33.8%)	7 (53.8%)	283 (33.6%)	3 (42.9%)	287 (33.8%)
Hemoptysis	1 (12.5%)	13 (1.5%)	1 (7.7%)	13 (1.5%)	1 (14.3%)	13 (1.5%)
Sore throat	2 (25.0%)	120 (14.2%)	1 (7.7%)	121 (14.4%)	2 (28.6%)	120 (14.1%)
Nasal obstruction	0	50 (5.9%)	0	50 (5.9%)	0	50 (5.9%)
Muscle ache	0	96 (11.3%)	4 (30.8%)	92 (10.9%)	1 (14.3%)	95 (11.2%)
Fatigue	1 (12.5%)	153 (18.0%)	3 (23.1%)	151 (17.9%)	1 (14.3%)	153 (18.0%)
Diarrhea	0	65 (7.7%)	1 (7.7%)	64 (7.6%)	0	65 (7.7%)
Nausea/vomiting	0	28 (3.3%)	1 (7.7%)	27 (3.2%)	0	28 (3.3%)
Headache	0	80 (9.4%)	2 (15.4%)	78 (9.3%)	1 (14.3%)	79 (9.3%)
Shortness of breath	2 (25.0%)	39 (4.6%)	1 (7.7%)	40 (4.7%)	0	41 (4.8%)
Time from onset of illness to consultation	1.5 (0-3.8)	2 (1-4)	2 (1-6.5)	2 (1-4)	1 (0-4)	2 (1-4)
Time from onset of illness to confirm the diagnosis	4.5 (2.2-10)	4 (2-7)	6 (4.5-9)	4 (2-7)	3 (2-8)	4 (2-7)
Time from onset of illness to hospitalization	3.5 (0.8-7)	3 (1-6)	5 (2-7)	3 (1-6)	3 (1-8)	3 (1-6)
Chest x-ray/CT findings						
Abnormal lung imaging on admission	8 (100.0%)	757 (89.3%)	13 (100.0%)	752 (89.2%)	7 (100.0%)	758 (89.3%)
Unilateral pneumonia	0	182 (21.5%)	1 (7.7%)	181 (21.5%)	2 (28.6%)	180 (21.2%)
Bilateral pneumonia	4 (50.0%)	309 (36.4%)	4 (30.8%)	309 (36.7%)	2 (28.6%)	311 (36.6%)
Multiple mottling and ground-glass opacity	4 (50.0%)	266 (31.4%)	8 (61.5%)	262 (31.1%)	3 (42.9%)	267 (31.4%)
Clinical type						
Mild/ordinary type	3 (37.5%)	699 (82.4%)	8 (61.5%)	694 (82.3%)	5 (71.4%)	697 (82.1%)
Severe/critical type	5 (62.5%)	149 (17.6%)	5 (38.5%)	149 (17.7%)	2 (28.6%)	152 (17.9%)
Composite endpoint	1 (12.5%)	31 (3.7%)	0	32 (3.8%)	0	32 (3.8%)
Mechanical ventilation	1 (12.5%)	28 (3.3%)	0	29 (3.4%)	0	29 (3.4%)
Admission to intensive care unit	1 (12.5%)	31 (3.7%)	0	32 (3.8%)	0	32 (3.8%)
CRRT	0	2 (0.2%)	0	2 (0.2%)	0	2 (0.2%)
ECOM	0	9 (1.1%)	0	9 (1.1%)	0	9 (1.1%)
Shock	0	4 (0.5%)	0	4 (0.5%)	0	4 (0.5%)
Death	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)

Note: Data is expressed as mean ± standard deviation, median with quartile (Q1-Q3), and number (%).
Abbreviations: COVID-19, coronavirus disease 19; CRRT, continuous renal replacement therapy; CT, computed tomography; ECOM, extracorporeal membrane oxygenation.

consistent with clinical manifestations, imaging findings and number of reaching the composite endpoint. Differences were all statistically significant, corroborating the previous finding that comorbidity is a risk factor for patients with COVID-19. Further, Many reports[16] have shown that advanced age is closely related to the severely poor prognosis of COVID-19. those with comorbidities were generally older than patients without comorbidities ($P < .001$). This may be one of the factors contributing to the exacerbation of condition in patients with comorbidities.

Among the comorbidities evaluated in the present study, hypertension and diabetes were the most common and probably related to the high incidence of the disease in the entire population. We evaluated the relationship between different comorbidities and COVID-19 outcomes using the Cox regression analysis after adjusting for age and gender status. The results show that only hypertension (HR: 4.74; 95% CI: 2.22-10.09), but not other comorbidities, was associated with COVID-19 outcomes ($P > .05$). SARS-COV-2 binds to the angiotensin-converting enzyme 2. more and more scholars pay

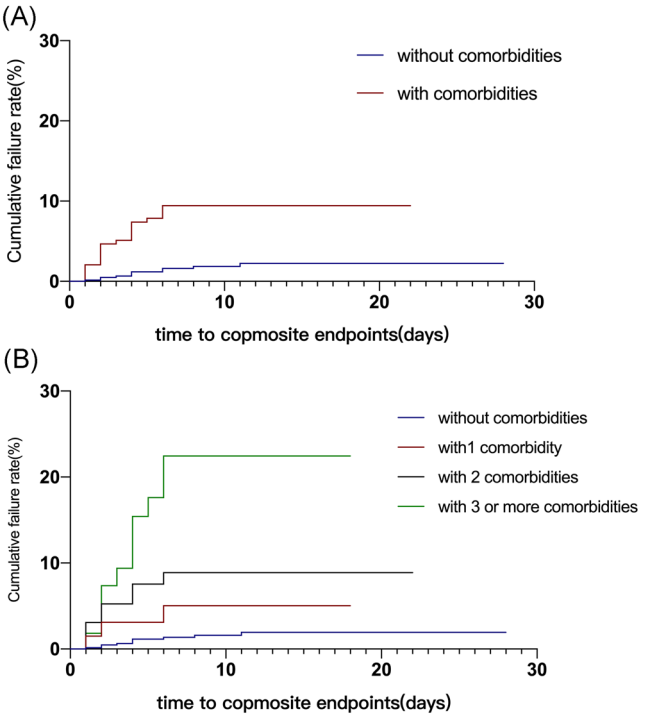

FIGURE 1 Comparison of the time-dependent risk of reaching to the composite endpoints. A, Comparison of time-dependent risk of reaching the composite endpoints in patients with comorbidities (red curve) and without comorbidities (blue curve). B, Comparison of time-dependent risk of reaching the composite endpoints among patients without comorbidity (blue curve), with 1comorbidity (red curve), two comorbidities (black curve) and with three or more comorbidities (green curve)

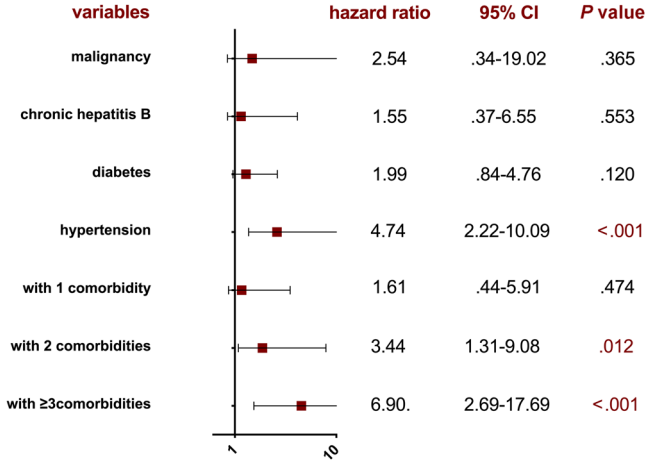

FIGURE 2 Variables and hazard ratios in cox proportional hazard models. The figure shows the hazard ratio and 95% confidence interval of some variables in the proportional risk model. *P* value less than .05 is considered to be statistically significant and regards as a risk factor for the occurrence of composite endpoints (admission to intensive care unit [ICU], shock, invasive mechanical ventilation, death). The scale bar in the middle is the hazard ratio. The cox proportional hazard regression model was used to determine the potential risk factors related to the endpoints with the risk ratio and 95% confidence interval (CI) reported. Age and sex status have been adjusted in the model

close attention to the effect in medications that act on the renin-angiotensin aldosterone system to COVID-19.We divided hypertension patients into ACEI/ARB and non-ACEI/ARB groups, and analyzed their epidemiology data, clinical characteristics, and prognosis. However, no significant difference was observed, consistent with the results of a previous report.[26] The impact of ACEI/ARB drugs on COVID-19 remains controversial.[27,28] Given the relatively few cases except hypertension, the error may be related to the small sample size. Further studies are warranted to determine the relationship between other comorbidities and serious adverse outcomes.

We observed that the number of comorbidities was related to adverse outcomes of patients. The higher the number of comorbidities, the greater was the risk of adverse events (Figure 1). The HR was 3.44 (95% CI: 1.31-9.08) for patients with two comorbidities and 6.90 (95% CI: 2.69-17.69) for those with three or more comorbidities; the *P* value was less than .05. Therefore, upon admission to a hospital, patients should be carefully interrogated about their existing comorbidities and then classified depending on the number of comorbidities. Patients with many comorbidities had poor physical conditions and were at a high risk of adverse outcomes. Therefore, more attention should be paid to the changes in the condition of COVID-19 patients with underlying diseases. In particular, elderly patients with comorbidities should be more carefully monitored to prevent occurrence of serious adverse events.

In summary, our report systematically describes the impact of the presence, type, and number of comorbidities on the clinical outcomes of patients with COVID-19. The relationship between comorbidities and adverse outcomes was further clarified, which would be helpful for the prevention and treatment of the epidemic. This is the first comprehensive investigation on the comorbidities of patients with COVID-19 in the Zhejiang province and may represent the global scenario. Our research has a few limitations, the most important being collection of information on comorbidities. Considering the severity of the epidemic and the shortage of medical resources, some admitted patients (especially patients with mild infection) did not receive systemic imaging examination. The diagnosis rate of basic disease varied; hence, we mainly focused on the self-report of patients at the time of admission. However, some of the comorbidities were under-reported for various reasons such as economic conditions and lack of awareness on health. This may lower the significance of our statistics of comorbidities but not much from the actual situation because the proportion of comorbidities in our report is generally consistent with the existing literature in the country.[3,25] Additionally, our study was a retrospective analysis. Since the error in data collection may slightly reduce some credibility, we need to consider prospective cohort studies to provide more reliable data in future. Some patients continued to be hospitalized during this study completion and their outcomes were not available, which may warrant further research.

ACKNOWLEDGMENTS

We thank the Health Commission of Zhejiang Province, China for coordinating data collection; Thanks to all front-line medical staff in Zhejiang Province for their contribution to the control of COVID-19.

AUTHOR CONTRIBUTIONS

CY designed the study and drafted the manuscript. YY and JS designed the study and supervised the whole study process. SZ, XZ, and HC performed data analysis. JL, JG, YL, HJ, JH, CJ, GY, and YZ participated in the collection of data. YY reviewed the manuscript before submission. All authors scrutinized the manuscript and approved the final version for publication.

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SUPPORTING INFORMATION

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

How to cite this article: Ye C, Zhang S, Zhang X, et al. Impact of comorbidities on patients with COVID-19: A large retrospective study in Zhejiang, China. *J Med Virol*. 2020;92:2821–2829. https://doi.org/10.1002/jmv.26183