Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) outbreak is evolving rapidly worldwide.

Objective: To evaluate the risk of serious adverse outcomes in patients with COVID-19 by stratifying the comorbidity status.

Methods: We analysed data from 1590 laboratory confirmed hospitalised patients from 575 hospitals in 31 provinces/autonomous regions/provincial municipalities across mainland China between 11 December 2019 and 31 January 2020. We analysed the composite end-points, which consisted of admission to an intensive care unit, invasive ventilation or death. The risk of reaching the composite end-points was compared according to the presence and number of comorbidities.

Results: The mean age was 48.9 years and 686 (42.7%) patients were female. Severe cases accounted for 16.0% of the study population. 131 (8.2%) patients reached the composite end-points. 399 (25.1%) reported having at least one comorbidity. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). 130 (8.2%) patients reported having two or more comorbidities. After adjusting for age and smoking status, COPD (HR (95% CI) 2.681 (1.424–5.048)), diabetes (1.59 (1.03–2.45)), hypertension (1.58 (1.07–2.32)) and malignancy (3.50 (1.60–7.64)) were risk factors of reaching the composite end-points. The hazard ratio (95% CI) was 1.79 (1.16–2.77) among patients with at least one comorbidity and 2.59 (1.61–4.17) among patients with two or more comorbidities.

Conclusion: Among laboratory confirmed cases of COVID-19, patients with any comorbidity yielded poorer clinical outcomes than those without. A greater number of comorbidities also correlated with poorer clinical outcomes.

Introduction

Since November 2019, the rapid outbreak of coronavirus disease 2019 (COVID-19), which arose from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has recently become a public health emergency of international concern [1]. COVID-19 has contributed to an enormous adverse impact globally. As of 10 March 2020 there have been 113 702 laboratory confirmed cases and 4012 deaths globally [2].

According to the latest reports, the clinical manifestations of COVID-19 are heterogeneous [3–12]. On admission, 20–51% of patients were reported as having at least one comorbidity, with diabetes (10–20%), hypertension (10–15%) and other cardiovascular and cerebrovascular diseases (7–40%) being most common [3, 4, 6]. Previous studies have demonstrated that the presence of any comorbidity has been associated with a 3.4-fold increased risk of developing acute respiratory distress syndrome in patients with H7N9 infection [13]. As with influenza [14–18], SARS-CoV [19] and Middle East Respiratory Syndrome coronavirus (MERS-CoV) [20–28], COVID-19 is more readily predisposed to respiratory failure and death in susceptible patients [4, 5]. Nonetheless, previous studies have had certain limitations in study design including the relatively small sample sizes and single centre observations. Studies that address these limitations are needed to explore the factors underlying the adverse impact of COVID-19.

Our objective was to evaluate the risk of serious adverse outcomes in patients with COVID-19 by stratification according to the number and type of comorbidities, thus unravelling the sub-populations with poorer prognosis.

Methods

Data sources and data extraction

This was a retrospective case study that collected data from patients with COVID-19 throughout China, under the coordination of the National Health Commission which mandated the reporting of clinical information from individual designated hospitals that admitted patients with COVID-19. This study is approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University. After careful review of medical charts, we compiled the clinical data of laboratory confirmed hospitalised cases from 575 hospitals (representing 31.7% of the certified hospitals admitting patients with COVID-19) between 11 December 2019 and 31 January 2020. The diagnosis of COVID-19 was made based on the World Health Organization interim guidance [29]. Because of the urgency of data extraction, complete random sampling could not be applied in our settings. All clinical profiles outside the Hubei province were centrally provided by the National Health Commission. Three respiratory experts from Guangzhou were dispatched to Wuhan for raw data extraction from Wuhan JinYinTan Hospital where most cases in Wuhan were located. Our cohort included 132 patients from Wuhan JinYinTan Hospital, and one each

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from 338 hospitals. Our cohort represented the overall situation as of 31 January 2020, taking into account the proportion of hospitals (~25%) and patient number (1590 (13.5%) out of 11 791 cases), as well as the broad coverage (covering all major provinces/cities/autonomous regions). Confirmed cases denoted the patients whose high throughput sequencing or real-time, reverse-transcription PCR assay findings for nasal and pharyngeal swab specimens were positive [3]. For further details refer to the supplementary material. The interval between the potential earliest date of transmission source contacts (wildlife, suspected or confirmed cases) and the potential earliest date of symptom onset (i.e. cough, fever, fatigue and myalgia) was used to calculate the incubation period. Because the latest date was recorded in some patients who had continuous exposure to contamination sources, the incubation period of <1 day was not included in our analysis. The incubation periods were summarised based on the patients who had delineated the specific date of exposure.

The clinical data (including recent exposure history, clinical symptoms and signs, comorbidities, and laboratory findings upon admission) were reviewed and extracted by experienced respiratory clinicians, who subsequently entered the data into a computerised database for further double checking of all cases. Manifestations on chest radiograph or computed tomography (CT) was summarised by integrating the documentation or description in medical charts and, if available, a further review by our medical staff. Major disagreement of the radiologic manifestations between the two reviewers was resolved by consultation with another independent reviewer. Because the disease severity reportedly predicted poorer clinical outcomes of avian influenza [13], patients were classified as having severe or non-severe COVID-19 based on the 2007 American Thoracic Society Infectious Disease Society of America guidelines [30], taking into account its global acceptance for severity stratification of community-acquired pneumonia although no validation was conducted in patients with viral pneumonia. The predictive ability of the need for intensive care unit (ICU) admission and mortality has been validated previously [31, 32]. Briefly, severe cases denoted at least one major criterion (septic shock requiring vasoactive medications, or respiratory failure requiring mechanical ventilation), or at least three minor criteria (respiratory rate $\geqslant$30 breaths·min^{-1}, oxygen index $\leqslant$250, multiple lobe infiltration, delirium or loss of consciousness, blood urea nitrogen $\geqslant$20 mg·dL^{-1}, blood leukocyte count $\leqslant$4000 cells·dL^{-1}, blood platelet count $\leqslant$100 000 cells·dL^{-1}, body temperature <36°C, and hypotension necessitating vasoactive drugs for maintaining blood pressure).

Comorbidities were determined based on patient's self-report on admission. Comorbidities were initially treated as a categorical variable (yes versus no) and subsequently classified based on the number (single versus multiple). Furthermore, comorbidities were sorted according to the organ systems (i.e. respiratory, cardiovascular, endocrine). Comorbidities that were classified into the same organ system (i.e. coronary heart disease, hypertension) would be merged into a single category.

The primary end-point of our study was a composite measure which consisted of the admission to ICU, invasive ventilation or death. This composite measure was adopted because all individual components were serious outcomes of H7N9 infections [13]. The secondary end-point was the mortality rate.

Statistical analysis

Statistical analyses were conducted with SPSS software (version 23.0; SPSS, Chicago, IL, USA). No formal sample size estimation was made because there has not been any published nationwide data on COVID-19. Nonetheless, our sample size was deemed sufficient to power the statistical analysis given its representativeness of the national patient population. Continuous variables were presented as mean±SD or median (interquartile ranges (IQR)) as appropriate, and the categorical variables were presented as counts and percentages. Since no random sampling was conducted, all statistical analyses were descriptive and no p-values were presented for the statistical comparisons except for the Cox proportional hazards regression model. Cox proportional hazards regression models were applied to determine the potential risk factors associated with the composite end-points, with the hazard ratio and 95% confidence interval being reported. Our findings indicated that the statistical assumption of proportional hazards analysis was not violated. Moreover, a Cox regression model was considered more appropriate than a logistic regression model because it took into account the potential impact of the various durations of follow-up from individual patients. Age and smoking status were adjusted for in the proportional hazards regression model because they had been recognised as the risk factors of comorbidities even in the general population. Smoking status was stratified as current smoker, ex-smoker and never-smoker in the regression models.

Results

Demographic and clinical characteristics

The National Health Commission diagnosed 11 791 patients in China with laboratory confirmed COVID-19 as of 31 January 2020. At this time-point, for data cut-off, our database included 1590 cases from 575 hospitals in 31 province/autonomous regions/provincial municipalities (refer to supplementary

material). Of these 1590 cases, mean age was 48.9 years. 686 (42.7%) patients were female. 647 (40.7%) patients were managed inside the Hubei province, and 1334 (83.9%) patients had contact history with Wuhan city. The most common symptom was fever on or after hospitalisation (88.0%), followed by dry cough (70.2%). Fatigue (42.8%) and productive cough (36.0%) were less common. At least one abnormal chest CT manifestation (including ground-glass opacities, pulmonary infiltrates and interstitial disorders) was identified in >70% of patients. Severe cases accounted for 16.0% of the study population. 131 (8.2%) patients reached the composite end-points during the study (table 1). Overall, the median (IQR) follow-up duration was 10 (8–14) days.

Presence of comorbidities and clinical characteristics and outcomes of COVID-19

Of the 1590 cases, 399 (25.1%) reported having at least one comorbidity. The prevalence of specific comorbidities was: hypertension (n=269, 16.9%), other cardiovascular diseases (n=59, 3.7%) cerebrovascular diseases (n=30, 1.9%), diabetes (n=30, 8.2%), hepatitis B infections (n=28, 1.8%), COPD (n=24, 1.5%), chronic kidney diseases (n=21, 1.3%), malignancy (n=18, 1.1%) and immunodeficiency (n=3, 0.2%). None of the cases had doctor-diagnosed asthma. At least one comorbidity was seen more commonly in severe cases than in non-severe cases (32.8% versus 10.3%). Patients with at least one comorbidity were older (mean age 60.8 versus 44.8 years), were more likely to have shortness of breath (41.4% versus 17.8%), nausea or vomiting (10.4% versus 4.3%), and tended to have abnormal chest radiograph manifestations (29.2% versus 15.1%) (table 1).

Clinical characteristics and outcomes of COVID-19 stratified by the number of comorbidities

We have further identified 130 (8.2%) patients who reported having two or more comorbidities. Two or more comorbidities were more commonly seen in severe cases than in non-severe cases (40.0% versus 29.4%). Patients with two or more comorbidities were older (mean age 66.2 versus 58.2 years), were more likely to have shortness of breath (55.4% versus 34.1%), nausea or vomiting (11.8% versus 9.7%), unconsciousness (5.1% versus 1.3%) and have less abnormal chest radiographs (20.8% versus 23.4%) compared with patients who had one comorbidity (table 2).

Clinical characteristics and outcomes of COVID-19 stratified by organ systems of comorbidities

A total of 269 (16.9%) patients reported hypertension, 59 (3.7%) reported cardiovascular diseases, 30 (1.9%) reported cerebrovascular diseases, 30 (8.2%) reported diabetes, 28 (1.8%) reported hepatitis B infections, 24 (1.5%) reported COPD, 21 (1.3%) reported chronic kidney diseases, 18 (1.1%) reported malignancy and three (0.2%) reported immunodeficiency. Severe cases were more likely to have hypertension (32.7% versus 12.6%), cardiovascular diseases (33.9% versus 15.3%), cerebrovascular diseases (50.0% versus 15.3%), diabetes (34.6% versus 14.3%), hepatitis B infections (32.1% versus 15.7%), COPD (62.5% versus 15.3%), chronic kidney diseases (38.1% versus 15.7%) and malignancy (50.0% versus 15.6%) compared with non-severe cases. Furthermore, comorbidities were more common in patients treated in the Hubei province compared with those managed outside the Hubei province as well as patients with a Wuhan exposure history compared with those without (table 3).

Prognostic analyses

Overall, 131 (8.3%) patients reached the composite end-points during the study. 50 (3.1%) patients died, 99 (6.2%) were admitted to the ICU and 50 (3.1%) received invasive ventilation. The composite end-point was documented in 77 (19.3%) patients who had at least one comorbidity as opposed to 54 (4.5%) patients without comorbidities. 37 (28.5%) patients had two or more comorbidities. Significantly more patients with hypertension (19.7% versus 5.9%), cardiovascular diseases (22.0% versus 7.7%), cerebrovascular diseases (33.3% versus 7.8%), diabetes (23.8% versus 6.8%), COPD (50.0% versus 7.6%), chronic kidney diseases (28.6% versus 8.0%) and malignancy (38.9% versus 7.9%) reached the composite end-points compared with those without (table 3).

Patients with two or more comorbidities had significantly escalated risks of reaching to the composite end-point compared with those who had a single comorbidity, and even more so compared with those with no comorbidities (all p<0.05) (figure 1). After adjusting for age and smoking status, patients with COPD (HR (95% CI) 2.68 (1.42–5.05)), diabetes (1.59 (1.03–2.45)), hypertension (1.58 (1.07–2.32)) and malignancy (3.50 (1.60–7.64)) were more likely to reach the composite end-points than those without (figure 2). Results of unadjusted analysis are presented in table E1 and E2. Overall, findings of unadjusted and adjusted analysis were not materially altered. As compared with patients without comorbidity, the HR (95% CI) was 1.79 (1.16–2.77) among patients with at least one comorbidity and 2.59 (1.61–4.17) among patients with two or more comorbidities (figure 2). Subgroup analysis by stratifying patients according to their age (<65 years versus ⩾65 years) did not reveal substantial difference in the strength of associations between the number of comorbidities and mortality of COVID-19 (table E3).

TABLE 1 Demographics and clinical characteristics of patients with or without any comorbidities

Variables	Any comorbidity		
	Total	No	Yes
Subjects n	1590	1191	399
Age years	48.9±16.3	44.8±15.2	60.8±13.4
Incubation period day	3.6±4.2	3.7±4.3	3.5±3.9
Temperature on admission °C	37.4±0.9	37.4±0.9	37.3±0.9
Respiratory rate on admission breath·min^{-1}	21.2±12.0	21.2±13.7	21.3±4.7
Heart rate on admission beat·min^{-1}	88.7±14.6	88.5±14.7	89.2±14.4
Systolic pressure on admission mmHg	126.1±16.4	123.5±15.2	133.2±17.5
Diastolic pressure on admission mmHg	79.5±25.6	79±28.9	80.9±12.6
Highest temperature °C	38.3±1.6	38.3±1.1	38.2±2.6
Sex			
Male	904/1578 (57.3)	667/1182 (56.4)	237/396 (59.8)
Female	674/1578 (42.7)	515/1182 (43.6)	159/396 (40.2)
Smoking status			
Never/unknown	1479/1590 (93)	1127/1191 (94.6)	352/399 (88.2)
Former/current	111/1590 (7)	64/1191 (5.4)	47/399 (11.8)
Symptoms			
Fever	1351/1536 (88)	1002/1148 (87.3)	349/388 (89.9)
Conjunctival congestion	10/1345 (0.7)	7/1014 (0.7)	3/331 (0.9)
Nasal congestion	73/1299 (5.6)	59/979 (6)	14/320 (4.4)
Headache	205/1328 (15.4)	151/1002 (15.1)	54/326 (16.6)
Dry cough	1052/1498 (70.2)	775/1116 (69.4)	277/382 (72.5)
Pharyngodynia	194/1317 (14.7)	148/999 (14.8)	46/318 (14.5)
Productive cough	513/1424 (36)	363/1064 (34.1)	150/360 (41.7)
Fatigue	584/1365 (42.8)	435/1031 (42.2)	149/334 (44.6)
Haemoptysis	16/1315 (1.2)	9/991 (0.9)	7/324 (2.2)
Shortness of breath	331/1394 (23.7)	185/1041 (17.8)	146/353 (41.4)
Nausea/vomiting	80/1371 (5.8)	44/1025 (4.3)	36/346 (10.4)
Diarrhoea	57/1359 (4.2)	39/1023 (3.8)	18/336 (5.4)
Myalgia/arthralgia	234/1338 (17.5)	174/1007 (17.3)	60/331 (18.1)
Chill	163/1333 (12.2)	129/1006 (12.8)	34/327 (10.4)
Signs			
Throat congestion	21/1286 (1.6)	16/973 (1.6)	5/313 (1.6)
Tonsil swelling	31/1376 (2.3)	22/1024 (2.1)	9/352 (2.6)
Enlargement of lymph nodes	2/1375 (0.1)	1/1027 (0.1)	1/348 (0.3)
Rash	3/1378 (0.2)	2/1032 (0.2)	1/346 (0.3)
Unconsciousness	20/1421 (1.4)	11/1063 (1)	9/358 (2.5)
Abnormal chest image			
Radiograph	243/1590 (15.3)	236/1566 (15.1)	44036 (29.2)
Computed tomography	1130/1590 (71.1)	1113/1566 (71.1)	17/24 (70.8)
Hubei			
Yes	647/1590 (40.7)	434/1191 (36.4)	213/399 (53.4)
No	943/1590 (59.3)	757/1191 (63.6)	186/399 (46.6)
Wuhan contacted			
Yes	1334/1590 (83.9)	983/1191 (82.5)	351/399 (88)
No	256/1590 (16.1)	208/1191 (17.5)	48/399 (12)
Severity	254/1590 (16)	123/1191 (10.3)	131/399 (32.8)
Composite end-point	131/1590 (8.2)	54/1191 (4.5)	77/399 (19.3)
Death	50/1590 (3.1)	15/1191 (1.3)	35/399 (8.8)
Admission to ICU	99/1590 (6.2)	45/1191 (3.8)	54/399 (13.5)
Invasive ventilation	50/1590 (3.1)	19/1191 (1.6)	31/399 (1.6)

Data are presented as mean±sd or n/N (%), where N is the total number of patients with available data. ICU: intensive care unit.

Discussion

Our study is the first nationwide investigation that systematically evaluates the impact of comorbidities on the clinical characteristics and prognosis in patients with COVID-19 in China. Circulatory and endocrine comorbidities were common among patients with COVID-19. Patients with at least one comorbidity, or

TABLE 2 Demographics and clinical characteristics of patients with 1 or ⩾2 comorbidities

Variables	1 comorbidity	⩾2 comorbidities
Subjects n	269	130
Age years	58.2±13.1	66.2±12.2
Incubation period days	3.2±3.1	4.0±5.2
Temperature on admission °C	37.4±0.9	37.1±0.9
Respiratory rate on admission breath·min^{-1}	21.4±4.6	21.2±5
Heart rate beat·min^{-1}	90.2±14.6	87.2±13.7
Systolic pressure on admission mmHg	132.2±16.5	135.3±19.4
Diastolic pressure on admission mmHg	81.7±12.5	79.5±12.9
Highest temperature °C	38.2±3.0	38.4±0.8
Sex		
Male	158/268 (59.0)	79/128 (61.7)
Female	110/268 (41.0)	49/128 (38.3)
Smoking status		
Never/unknown	234/269 (87.0)	118/130 (90.8)
Former/current	35/269 (13.0)	12/130 (9.2)
Symptoms		
Fever	241/263 (91.6)	108/125 (86.4)
Conjunctival congestion	3/222 (1.4)	0/109 (0)
Nasal congestion	5/213 (2.3)	9/107 (8.4)
Headache	34/220 (15.5)	20/106 (18.9)
Dry cough	195/258 (75.6)	82/124 (66.1)
Pharyngodynia	33/218 (15.1)	13/100 (13.0)
Productive cough	101/241 (41.9)	49/119 (41.2)
Fatigue	97/227 (42.7)	52/107 (48.6)
Haemoptysis	4/219 (1.8)	3/105 (2.9)
Shortness of breath	79/232 (34.1)	67/121 (55.4)
Nausea/vomiting	23/236 (9.7)	13/110 (11.8)
Diarrhoea	11/229 (4.8)	7/107 (6.5)
Myalgia/arthralgia	45/227 (19.8)	15/104 (14.4)
Chill	25/222 (11.3)	9/105 (8.6)
Signs		
Throat congestion	4/216 (1.9)	1/97 (1)
Tonsil swelling	5/234 (2.1)	4/118 (3.4)
Enlargement of lymph nodes	1/232 (0.4)	0/116 (0)
Rash	0/231 (0)	1/115 (0.9)
Unconsciousness	3/240 (1.3)	6/118 (5.1)
Abnormal chest image		
Radiograph	63/269 (23.4)	27/130 (20.8)
Computed tomography	200/269 (74.3)	96/130 (73.8)
Hubei		
Yes	120/269 (44.6)	93/130 (71.5)
No	149/269 (55.4)	37/130 (28.5)
Wuhan contacted		
Yes	229/269 (85.1)	122/130 (93.8)
No	40/269 (14.9)	8/130 (6.2)
Severity	79/269 (29.4)	52/130 (40.0)
Composite end-point	40/269 (14.9)	37/130 (28.5)
Deaths	15/269 (5.6)	20/130 (15.4)
Admission to ICU	31/269 (11.5)	23/130 (17.7)
Invasive ventilation	17/269 (6.3)	14/130 (10.8)

Data are mean±SD, n/N (%), where N is the total number of patients with available data. ICU: intensive care unit.

even more so, were associated with poor clinical outcomes. These findings have provided further objective evidence, with a large sample size and extensive coverage of the geographic regions across China, to take into account baseline comorbid diseases in the comprehensive risk assessment of prognosis among patients with COVID-19 on hospital admission.

Overall, our findings have echoed the recently published studies in terms of the commonness of comorbidities in patients with COVID-19 [3–7]. Despite considerable variations in the proportion in

TABLE 3 Demographics and clinical characteristics of patients stratified by different comorbidities

	COPD		Diabetes		Hypertension		Cardiovascular disease		Cerebrovascular disease	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Subjects n	1566	24	1460	130	1321	269	1531	59	1560	30
Age years	48.5±16.0	74.7±6.8	47.8±16.1	61.2±13.4	46.2±15.6	62.1±12.5	48.2±15.9	66.3±15.1	48.5±16.1	70.4±8.9
Incubation period day	3.6±4.2	4.5±3.2	3.6±4.1	3.8±5.0	3.6±4.2	3.6±4.1	3.7±4.2	3.3±3.7	3.6±4.2	3.8±3.4
Temperature on admission °C	37.4±0.9	37.3±0.9	37.4±0.9	37.2±1.0	37.4±0.9	37.2±0.9	37.4±0.9	37.3±1	37.4±0.9	36.9±0.8
Respiratory rate on admission breath·min^{-1}	21.2±12.1	21.8±5.2	21.2±12.4	21.4±5.4	21.2±13.1	21.3±4.5	21.2±12.2	21.4±6.2	21.3±12.1	19.9±3.3
Heart rate beat·min^{-1}	88.6±14.6	90.2±12.8	88.6±14.6	89.1±14.3	88.6±14.7	89±14.3	88.8±14.6	86.4±14.9	88.8±14.6	84.5±11.4
Systolic pressure on admission mmHg	126±16.4	131±17.5	125.3±15.9	134.4±19.1	123.9±15.2	135.4±18.2	125.8±16.3	132.3±18.8	125.9±16.4	132.9±16
Diastolic pressure on admission mmHg	79.6±25.7	77±11.9	79.4±26.4	80.9±13.2	79.2±27.7	81±12.5	79.6±25.9	78.4±13.6	79.6±25.8	77.4±9.6
Highest temperature °C	38.3±1.6	38.5±0.6	38.3±1.7	38.4±0.8	38.3±1.3	38.2±2.7	38.3±1.7	38.5±0.8	38.3±1.6	38.2±1
Sex										
Male	884/1554 (56.9)	20/24 (83.3)	828/1449 (57.1)	76/129 (58.9)	748/1312 (57)	156/266 (58.6)	868/1520 (57.1)	36/58 (62.1)	881/1548 (56.9)	23/30 (76.7)
Female	670/1554 (43.1)	4/24 (16.7)	621/1449 (42.9)	53/129 (41.1)	564/1312 (43)	110/266 (41.4)	652/1520 (42.9)	22/58 (37.9)	667/1548 (43.1)	7/30 (23.3)
Smoking status										
Never/unknown	1458/1566 (93.1)	21/24 (87.5)	1368/1460 (93.7)	111/130 (85.4)	1232/1321 (93.3)	247/269 (91.8)	1426/1531 (93.1)	53/59 (89.8)	1453/1560 (93.1)	26/30 (86.7)
Former/current	108/1566 (6.9)	3/24 (12.5)	92/1460 (6.3)	19/130 (14.6)	89/1321 (6.7)	22/269 (8.2)	105/1531 (6.9)	6/59 (10.2)	107/1560 (6.9)	4/30 (13.3)
Symptoms										
Fever	1331/1513 (88)	20/23 (87.0)	1239/1412 (87.7)	112/124 (90.3)	1113/1273 (87.4)	238/263 (90.5)	1308/1482 (88.3)	43/54 (79.6)	1328/1507 (88.1)	23/29 (79.3)
Conjunctival congestion	10/1325 (0.8)	0/20 (0)	9/1237 (0.7)	1/108 (0.9)	9/1120 (0.8)	1/225 (0.4)	10/1299 (0.8)	0/46 (0)	10/1320 (0.8)	0/25 (0)
Nasal congestion	72/1281 (5.6)	1/18 (5.6)	66/1195 (5.5)	7/104 (6.7)	62/1079 (5.7)	11/220 (5)	67/1253 (5.3)	6/46 (13.0)	73/1275 (5.7)	0/24 (0)
Headache	202/1309 (15.4)	3/19 (15.8)	187/1225 (15.3)	18/103 (17.5)	166/1106 (15)	39/222 (17.6)	197/1283 (15.4)	8/45 (17.8)	197/1303 (15.1)	8/25 (32.0)
Dry cough	1038/1474 (70.4)	14/24 (58.3)	972/1378 (70.5)	80/120 (66.7)	854/1238 (69)	198/260 (76.2)	1018/1442 (70.6)	34/56 (60.7)	1035/1469 (70.5)	17/29 (58.6)
Pharyngodynia	189/1300 (14.5)	5/17 (29.4)	182/1219 (14.9)	12/98 (12.2)	165/1102 (15)	29/215 (13.5)	185/1272 (14.5)	9/45 (20)	192/1296 (14.8)	2/21 (9.5)
Productive cough	502/1400 (35.9)	11/24 (45.8)	462/1309 (35.3)	51/115 (44.3)	403/1178 (34.2)	110/246 (44.7)	499/1373 (36.3)	14/51 (27.5)	504/1397 (36.1)	9/27 (33.3)
Fatigue	573/1347 (42.5)	11/18 (61.1)	529/1257 (42.1)	55/108 (50.9)	488/1143 (42.7)	96/222 (43.2)	564/1318 (42.8)	20/47 (42.6)	574/1344 (42.7)	10/21 (47.6)
Haemoptysis	15/1296 (1.2)	1/19 (5.3)	12/1214 (1.0)	4/101 (4.0)	12/1096 (1.1)	4/219 (1.8)	15/1268 (1.2)	1/47 (2.1)	16/1292 (1.2)	0/23 (0)
Shortness of breath	316/1371 (23)	15/23 (65.2)	277/1279 (21.7)	54/115 (47.0)	223/1154 (19.3)	108/240 (45)	310/1342 (23.1)	21/52 (40.4)	319/1366 (23.4)	12/28 (42.9)
Nausea/vomiting	77/1350 (5.7)	3/21 (14.3)	69/1264 (5.5)	11/107 (10.3)	55/1134 (4.9)	25/237 (10.5)	73/1321 (5.5)	7/50 (14.0)	79/1348 (5.9)	1/23 (4.3)

Continued

TABLE 3 Continued

	COPD		Diabetes		Hypertension		Cardiovascular disease		Cerebrovascular disease	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Diarrhoea	57/1338 (4.3)	0/21 (0)	48/1255 (3.8)	9/104 (8.7)	46/1129 (4.1)	11/230 (4.8)	53/1313 (4.0)	4/46 (8.7)	57/1336 (4.3)	0/23 (0)
Myalgia/ arthralgia	231/1320 (17.5)	3/18 (16.7)	218/1234 (17.7)	16/104 (15.4)	188/1112 (16.9)	46/226 (20.4)	227/1294 (17.5)	7/44 (15.9)	233/1317 (17.7)	1/21 (4.8)
Chill	159/1313 (12.1)	4/20 (20.0)	151/1230 (12.3)	12/103 (11.7)	140/1111 (12.6)	23/222 (10.4)	161/1290 (12.5)	2/43 (4.7)	162/1310 (12.4)	1/23 (4.3)
Signs										
Throat congestion	21/1269 (1.7)	0/17 (0)	20/1189 (1.7)	1/97 (1)	18/1075 (1.7)	3/211 (1.4)	21/1245 (1.7)	0/41 (0)	21/1266 (1.7)	0/20 (0)
Tonsil swelling	31/1355 (2.3)	0/21 (0)	28/1265 (2.2)	3/111 (2.7)	25/1133 (2.2)	6/243 (2.5)	29/1326 (2.2)	2/50 (4.0)	31/1348 (2.3)	0/28 (0)
Enlargement of lymph nodes	2/1355 (0.1)	0/20 (0)	2/1267 (0.2)	0/108 (0)	2/1135 (0.2)	0/240 (0)	1/1325 (0.1)	1/50 (2.0)	2/1347 (0.1)	0/28 (0)
Rash	3/1357 (0.2)	0/21 (0)	2/1270 (0.2)	1/108 (0.9)	2/1141 (0.2)	1/237 (0.4)	3/1327 (0.2)	0/51 (0)	3/1351 (0.2)	0/27 (0)
Unconsciousness	18/1400 (1.3)	2/21 (9.5)	18/1309 (1.4)	2/112 (1.8)	12/1175 (1.0)	8/246 (3.3)	17/1371 (1.2)	3/50 (6)	19/1392 (1.4)	1/29 (3.4)
Abnormal chest image										
Radiograph	236/1566 (15.1)	7/24 (29.2)	218/1460 (14.9)	25/130 (19.2)	178/1321 (13.5)	65/269 (24.2)	231/1531 (15.1)	12/59 (20.3)	231/1560 (14.8)	12/30 (40)
Computed tomography	1113/1566 (71.1)	17/24 (70.8)	1034/1460 (70.8)	96/130 (73.8)	926/1321 (70.1)	204/269 (75.8)	1090/1531 (71.2)	40/59 (67.8)	1111/1560 (71.2)	19/30 (63.3)
Hubei										
Yes	633/1566 (40.4)	14/24 (58.3)	568/1460 (38.9)	79/130 (60.8)	491/1321 (37.2)	156/269 (58)	609/1531 (39.8)	38/59 (64.4)	623/1560 (39.9)	24/30 (80.0)
No	933/1566 (59.6)	10/24 (41.7)	892/1460 (61.1)	51/130 (39.2)	830/1321 (62.8)	113/269 (42)	922/1531 (60.2)	21/59 (35.6)	937/1560 (60.1)	6/30 (20.0)
Wuhan contacted										
Yes	1312/1566 (83.8)	22/24 (91.7)	1216/1460 (83.3)	118/130 (90.8)	1092/1321 (82.7)	242/269 (90)	1282/1531 (83.7)	52/59 (88.1)	1306/1560 (83.7)	28/30 (93.3)
No	254/1566 (16.2)	2/24 (8.3)	244/1460 (16.7)	12/130 (9.2)	229/1321 (17.3)	27/269 (10)	249/1531 (16.3)	7/59 (11.9)	254/1560 (16.3)	2/30 (6.7)
Severity	239/1566 (15.3)	15/24 (62.5)	209/1460 (14.3)	45/130 (34.6)	166/1321 (12.6)	88/269 (32.7)	234/1531 (15.3)	20/59 (33.9)	239/1560 (15.3)	15/30 (50)
Composite end-point	119/1566 (7.6)	12/24 (50.0)	100/1460 (6.8)	31/130 (23.8)	78/1321 (5.9)	53/269 (19.7)	118/1531 (7.7)	13/59 (22.0)	121/1560 (7.8)	10/30 (33.3)
Deaths	44/1566 (2.8)	6/24 (25.0)	37/1460 (2.5)	13/130 (10.0)	22/1321 (1.7)	28/269 (10.4)	42/1531 (2.7)	8/59 (13.6)	44/1560 (2.8)	6/30 (20)
Admission to ICU	92/1566 (5.9)	7/24 (29.2)	80/1460 (5.5)	19/130 (14.6)	61/1321 (4.6)	38/269 (14.1)	91/1531 (5.9)	8/59 (13.6)	92/1560 (5.9)	7/30 (23.3)
Invasive ventilation	45/1566 (2.9)	5/24 (20.8)	39/1460 (2.7)	11/130 (8.5)	28/1321 (2.1)	22/269 (8.2)	44/1531 (2.9)	6/59 (10.2)	46/1560 (2.9)	4/30 (13.3)

TABLE 3 Continued

	Hepatitis B infection		Malignancy		Chronic kidney disease		Immunodeficiency	
	No	Yes	No	Yes	No	Yes	No	Yes
Subjects n	1562	28	1572	18	1569	21	1587	3
Age years	48.9±16.3	50.8±14.8	48.7±16.2	63.1±12.1	48.8±16.2	63.7±14	48.9±16.3	51±21.7
Incubation period day	3.7±4.2	3±2.8	3.7±4.2	3.1±3.1	3.6±4.1	3.3±7.5	3.6±4.1	12.7±16.3
Temperature on admission °C	37.4±0.9	37.3±0.8	37.4±0.9	37.3±0.9	37.4±0.9	37.2±1	37.4±0.9	36.6±0.2
Respiratory rate on admission breath·min⁻¹	21.2±12.1	21.2±3	21.3±12.1	20.2±1.6	21.3±12.1	19±2.8	21.3±12	19±1
Heart rate beat·min⁻¹	88.7±14.6	86.3±13.2	88.7±14.6	89.4±13.1	88.7±14.6	89.1±12.5	88.7±14.6	91±18.5
Systolic pressure on admission mmHg	126.1±16.4	124.8±14.7	126±16.4	128.3±14.5	125.9±16.3	135.4±20.5	126.1±16.4	127.3±7.4
Diastolic pressure on admission mmHg	79.6±25.7	78.3±13	79.5±25.7	81.2±8.8	79.5±25.7	79.8±14	79.5±25.6	84.7±15
Highest temperature °C	38.3±1.5	37.6±4.4	38.3±1.6	38.5±0.9	38.3±1.6	38.5±0.5	38.3±1.6	38±0.5
Sex								
Male	885/1550 (57.1)	19/28 (67.9)	893/1560 (57.2)	11/18 (61.1)	891/1559 (57.2)	13/19 (68.4)	904/1575 (57.4)	0/3 (0)
Female	665/1550 (42.9)	9/28 (32.1)	667/1560 (42.8)	7/18 (38.9)	668/1559 (42.8)	6/19 (31.6)	671/1575 (42.6)	3/3 (100)
Smoking status								
Never/unknown	1454/1562 (93.1)	25/28 (89.3)	1465/1572 (93.2)	14/18 (77.8)	1459/1569 (93)	20/21 (95.2)	1477/1587 (93.1)	2/3 (66.7)
Former/current	108/1562 (6.9)	3/28 (10.7)	107/1572 (6.8)	4/18 (22.2)	110/1569 (7)	1/21 (4.8)	110/1587 (6.9)	1/3 (33.3)
Symptoms								
Fever	1326/1508 (87.9)	25/28 (89.3)	1335/1519 (87.9)	16/17 (94.1)	1334/1516 (88)	17/20 (85)	1348/1533 (87.9)	3/3 (100)
Conjunctival congestion	9/1323 (0.7)	1/22 (4.5)	10/1330 (0.8)	0/15 (0)	10/1328 (0.8)	0/17 (0)	10/1343 (0.7)	0/2 (0)
Nasal congestion	73/1277 (5.7)	0/22 (0)	71/1285 (5.5)	2/14 (14.3)	73/1282 (5.7)	0/17 (0)	73/1297 (5.6)	0/2 (0)
Headache	202/1306 (15.5)	3/22 (13.6)	203/1314 (15.4)	2/14 (14.3)	203/1311 (15.5)	2/17 (11.8)	205/1326 (15.5)	0/2 (0)
Dry cough	1037/1472 (70.4)	15/26 (57.7)	1039/1481 (70.2)	13/17 (76.5)	1037/1479 (70.1)	15/19 (78.9)	1050/1495 (70.2)	2/3 (66.7)
Pharyngodynia	188/1294 (14.5)	6/23 (26.1)	193/1303 (14.8)	1/14 (7.1)	191/1300 (14.7)	3/17 (17.6)	193/1315 (14.7)	1/2 (50)
Productive cough	508/1401 (36.3)	5/23 (21.7)	504/1408 (35.8)	9/16 (56.3)	505/1407 (35.9)	8/17 (47.1)	512/1421 (36)	1/3 (33.3)
Fatigue	570/1340 (42.5)	14/25 (56)	577/1349 (42.8)	7/16 (43.8)	581/1350 (43)	3/15 (20)	583/1363 (42.8)	1/2 (50)
Haemoptysis	16/1293 (1.2)	0/22 (0)	15/1299 (1.2)	1/16 (6.3)	16/1300 (1.2)	0/15 (0)	16/1313 (1.2)	0/2 (0)
Shortness of breath	321/1370 (23.4)	10/24 (41.7)	323/1377 (23.5)	8/17 (47.1)	321/1375 (23.3)	10/19 (52.6)	330/1392 (23.7)	1/2 (50)
Nausea/vomiting	78/1349 (5.8)	2/22 (9.1)	78/1355 (5.8)	2/16 (12.5)	79/1351 (5.8)	1/20 (5)	80/1369 (5.8)	0/2 (0)
Diarrhoea	55/1337 (4.1)	2/22 (9.1)	57/1343 (4.2)	0/16 (0)	56/1339 (4.2)	1/20 (5)	56/1356 (4.1)	1/3 (33.3)
Myalgia/arthralgia	232/1316 (17.6)	2/22 (9.1)	231/1322 (17.5)	3/16 (18.8)	233/1323 (17.6)	1/15 (6.7)	233/1336 (17.4)	1/2 (50)
Chill	161/1310 (12.3)	2/23 (8.7)	162/1318 (12.3)	1/15 (6.7)	161/1317 (12.2)	2/16 (12.5)	163/1331 (12.2)	0/2 (0)
Signs								
Throat congestion	21/1264 (1.7)	0/22 (0)	20/1271 (1.6)	1/15 (6.7)	21/1271 (1.7)	0/15 (0)	20/1284 (1.6)	1/2 (50)
Tonsil swelling	30/1353 (2.2)	1/23 (4.3)	30/1359 (2.2)	1/17 (5.9)	30/1356 (2.2)	1/20 (5)	31/1373 (2.3)	0/3 (0)
Enlargement of lymph nodes	2/1352 (0.1)	0/23 (0)	2/1359 (0.1)	0/16 (0)	2/1355 (0.1)	0/20 (0)	2/1372 (0.1)	0/3 (0)
Rash	3/1355 (0.2)	0/23 (0)	3/1361 (0.2)	0/17 (0)	3/1360 (0.2)	0/18 (0)	3/1376 (0.2)	0/2 (0)
Unconsciousness	19/1397 (1.4)	1/24 (4.2)	20/1404 (1.4)	0/17 (0)	20/1401 (1.4)	0/20 (0)	20/1418 (1.4)	0/3 (0)
Abnormal chest image								
Radiograph	240/1562 (15.4)	3/28 (10.7)	239/1572 (15.2)	4/18 (22.2)	240/1569 (15.3)	3/21 (14.3)	243/1587 (15.3)	0/3 (0)
Computed tomography	1111/1562 (71.1)	19/28 (67.9)	1113/1572 (70.8)	17/18 (94.4)	1116/1569 (71.1)	14/21 (66.7)	1127/1587 (71)	3/3 (100)

TABLE 3 Continued

	Hepatitis B infection		Malignancy		Chronic kidney disease		Immunodeficiency	
	No	Yes	No	Yes	No	Yes	No	Yes
Hubei								
Yes	638/1562 (40.8)	9/28 (32.1)	635/1572 (40.4)	12/18 (66.7)	631/1569 (40.2)	16/21 (76.2)	645/1587 (40.6)	2/3 (66.7)
No	924/1562 (59.2)	19/28 (67.9)	937/1572 (59.6)	6/18 (33.3)	938/1569 (59.8)	5/21 (23.8)	942/1587 (59.4)	1/3 (33.3)
Wuhan contacted								
Yes	1312/1562 (84)	22/28 (78.6)	1316/1572 (83.7)	18/18 (100)	1316/1569 (83.9)	18/21 (85.7)	1331/1587 (83.9)	3/3 (100)
No	250/1562 (16)	6/28 (21.4)	256/1572 (16.3)	0/18 (0)	253/1569 (16.1)	3/21 (14.3)	256/1587 (16.1)	0/3 (0)
Severity	245/1562 (15.7)	9/28 (32.1)	245/1572 (15.6)	9/18 (50)	246/1569 (15.7)	8/21 (38.1)	253/1587 (15.9)	1/3 (33.3)
Composite end-point	128/1562 (8.2)	3/28 (10.7)	124/1572 (7.9)	7/18 (38.9)	125/1569 (8)	6/21 (28.6)	130/1587 (8.2)	1/3 (33.3)
Deaths	49/1562 (3.1)	1/28 (3.6)	47/1572 (3.0)	3/18 (16.7)	45/1569 (2.9)	5/21 (23.8)	50/1587 (3.2)	0/3 (0)
Admission to ICU	98/1562 (6.3)	1/28 (3.6)	94/1572 (6.0)	5/18 (27.8)	98/1569 (6.2)	1/21 (4.8)	98/1587 (6.2)	1/3 (33.3)
Invasive ventilation	48/1562 (3.1)	2/28 (7.1)	48/1562 (3.1)	2/18 (11.1)	49/1569 (3.1)	1/21 (4.8)	50/1587 (3.2)	0/3 (0)

Data are mean±SD, n/N (%), where N is the total number of patients with available data. ICU: intensive care unit.
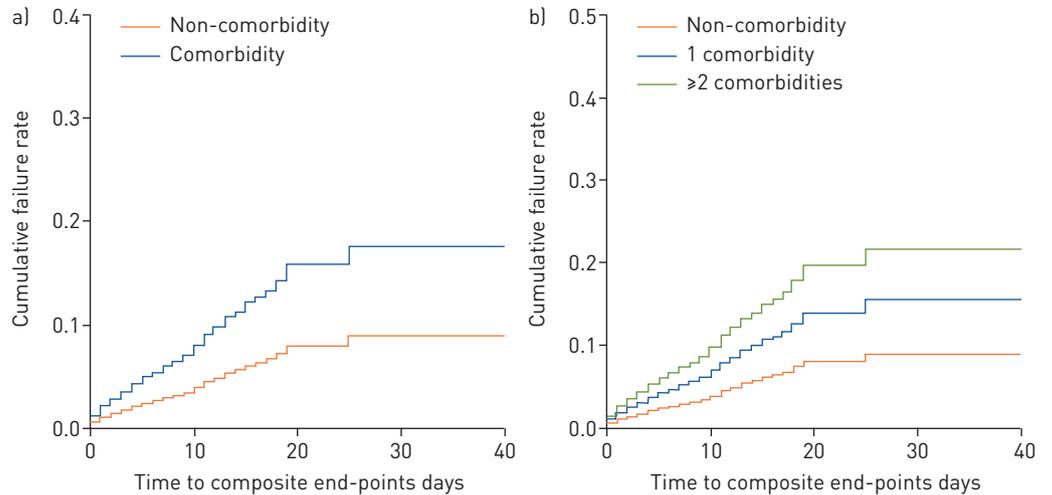
FIGURE 1 a) The time-dependent risk of reaching the composite end-points between patients with or without any comorbidity. b) The time-dependent risk of reaching the composite end-points between patients without any comorbidity, patients with a single comorbidity and patients with two or more comorbidities. Cox proportional hazard regression models were applied to determine the potential risk factors associated with the composite end-points, with the hazard ratio and 95% confidence interval being reported.

individual studies due to the limited sample size and the region where patients were managed, circulatory diseases (including hypertension and coronary heart diseases) remained the most common category of comorbidity [3–7]. Apart from circulatory diseases, endocrine diseases such as diabetes were also common in patients with COVID-19. Notwithstanding the commonness of circulatory and endocrine comorbidities, patients with COVID-19 rarely reported having comorbid respiratory diseases (particularly COPD). The reasons underlying this observation have been scant, but could have arisen from the lack of awareness and the lack of spirometric testing in community settings that collectively contributed to the under-diagnosis of respiratory diseases [33]. It should be stressed that the observed frequency of comorbidity may also reflect the transmission dynamics within particular age groups, case detection or testing practices or hospital admission policies during the early phases of the epidemic. Consistent with recent reports [3–7], the percentage of patients with comorbid renal disease and malignancy was relatively low. Our findings have therefore added to the existing literature on the spectrum of comorbidities in patients with COVID-19 based on the larger sample sizes and representativeness of the whole patient population in China.

A number of existing literature reports have documented the escalated risks of poorer clinical outcomes in patients with avian influenza [14–18], SARS-CoV [19] and MERS-CoV infections [20–28]. The most common comorbidities associated with poorer prognosis included diabetes [25, 29], hypertension [28],

Features		HR (95% CI)	p-value
Type of comorbidities			
COPD		2.681 (1.424–5.058)	0.002
Diabetes		1.586 (1.028–2.449)	0.037
Hypertension		1.575 (1.069–2.322)	0.022
Malignant tumour		3.501 (1.604–7.643)	0.002
Comorbidities n			
1		1.789 (1.155–2.772)	0.009
≥2		2.592 (1.611–4.171)	<0.001

FIGURE 2 Predictors of the composite end-points in the proportional hazards model. Hazard ratio (95% confidence interval) are shown for the risk factors associated with the composite end-points (admission to intensive care unit, invasive ventilation or death). The comorbidities were classified according to the organ systems as well as the number. The scale bar indicates the hazard ratio. Cox proportional hazard regression models were applied to determine the potential risk factors associated with the composite end-points, with the hazard ratio (95% confidence interval) being reported. The model has been adjusted with age and smoking status.

respiratory diseases [19, 28], cardiac diseases [19, 28], pregnancy [16], renal diseases [28] and malignancy [19]. Our findings suggested that, similar with other severe acute respiratory outbreaks, comorbidities such as COPD, diabetes, hypertension and malignancy predisposed to adverse clinical outcomes in patients with COVID-19. The strength of association between different comorbidities and the prognosis, however, was less consistent when compared with the literature reports [16, 19, 25, 28]. For instance, the risk between cardiac diseases and poor clinical outcomes of influenza, SARS-CoV or MERS-CoV infections was inconclusive [16, 19, 25, 28]. Except for diabetes, no other comorbidities were identified to be the predictors of poor clinical outcomes in patients with MERS-CoV infections [25]. Few studies, however, have explored the mechanisms underlying these associations. KULSCAR et al. [27] showed that MERS-CoV infections resulted in prolonged airway inflammation, immune cell dysfunction and an altered expression profile of inflammatory mediators in diabetic mice models. A network-based analysis indicated that SARS-CoV infections led to immune dysregulation that could help explain the escalated risk of cardiac diseases, bone diseases and malignancy [34]. Therefore, immune dysregulation and prolonged inflammation might be the key drivers of the poor clinical outcomes in patients with COVID-19 but await verification in more mechanistic studies.

It has been well accepted that some comorbidities frequently coexist. For instance, diabetes [35] and COPD [36] frequently coexist with hypertension or coronary heart diseases. Therefore, patients with coexisting comorbidities are more likely to have poorer baseline well-being. Importantly, we have verified the significantly escalated risk of poor prognosis in patients with two or more comorbidities compared with those who had no or only a single comorbidity. Our findings implied that both the category and number of comorbidities should be taken into account when predicting the prognosis in patients with COVID-19.

Our findings suggested that patients with comorbidities had greater disease severity compared with those without. Furthermore, a greater number of comorbidities correlated with greater disease severity of COVID-19. The proper triage of patients should be implemented by carefully inquiring about the medical history because this will help identify patients who would be more likely to develop serious adverse outcomes of COVID-19. Moreover, better protection should be given to the patients with COIVD-19 who had comorbidities upon confirmation of the diagnosis.

A main limitation was the self-reporting of comorbidities on admission. Under-reporting of comorbidities, which could have stemmed from the lack of awareness and/or the lack of diagnostic testing, might contribute to the underestimation of the true strength of association with the clinical prognosis. Under-reporting of comorbidities could also lead to over-estimation of strength of association with adverse outcome. However, significant under-reporting was unlikely because the spectrum of our report was largely consistent with existing literature [3–7] and all patients were subject to a thorough history taking after hospital admission. The relatively low age might help explain the low prevalence of COPD in our cohort. Moreover, the duration of follow-up was relatively short and some patients remained in hospital at the time of writing. More studies that explore the associations in a sufficiently long time-frame are warranted. Caution should be exercised when extrapolating our findings to other countries where there are outbreaks of COVID-19 since the prevalence of comorbidities may differ among different countries. Therefore, future studies that include an external validation of the results would be desirable. Although the temperature and systolic blood pressure differed between some subgroups, they were unlikely to be clinically relevant. Finally, because of the rapid evolving outbreak globally, ongoing studies with the inclusion of more patients would be needed to increase the statistical power and lend support to subgroup analyses stratified by the specific comorbidities (*i.e.* COPD) and their association with the risk of death.

Conclusions

Among laboratory confirmed cases of COVID-19, patients with any comorbidity yielded poorer clinical outcomes than those without. A greater number of comorbidities also correlated with poorer clinical outcomes. A thorough assessment of comorbidities may help establish risk stratification of patients with COVID-19 upon hospital admission.

The version of this article originally published in early view format contained some transcription errors in the total subject numbers presented in table 3. This was an issue that arose in compiling the table and the underlying results and conclusions are not affected by the correction.

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