Original Article
Gender, age and comorbidities as the main prognostic factors in patients with COVID-19 pneumonia

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic has spread to almost all countries. The currently reported epidemiological statistics show that age, gender, and type of comorbidities may be high-risk factors for critically ill patients with COVID-19. However, there is no comprehensive analysis of these risk factors. In the present study, we systematically explored the prognostic value of the clinical factors (gender, age and comorbidities) in 189 COVID-19 patients from Wuhan, China. We discovered that the gender, age and comorbidities were tightly associated with the survival of COVID-19 patients via performing Kaplan-Meier curve analysis. Compared with the female patients, male patients have a lower survival rate. Similarly, the older patients and those with more comorbidities also tended to have an unfavorable survival outcome. In addition, further stratified analysis of COVID-19 patients according to the three risk factors indicated that some laboratory indicators including CRP, IL-6 and lymphocytes showed significant trends in gender, age and comorbidities groups. Together, these result which may provide a certain reference value for the prevention and treatment of COVID-19.

Keywords: COVID-19, risk factors, gender, age, comorbidities

Introduction

At the end of 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan, China [1]. The receptor-binding domain structure of SARS-CoV-2 has been confirmed to be highly similar to that of the severe acute respiratory syndrome Coronavirus (SARS-CoV) [2, 3]. Covid-19 is more transmissible than SARS occurred in 2002-03 [4, 5]. At present, the COVID-19 has become a pandemic in the world. Since the outbreak, it has caused a large number of casualties and economic losses in a short time. Globally, there have been over 8.06 million confirmed cases of COVID-19, and 440 thousand deaths, reported by WHO on 17 June 2020 [6].

In confirmed cases in China, although the infection rate among men and women is similar, the death rate among men is 4.7% compared with 2.8% for women. Similarly,In Italy, the reported death rate in men (16.6%) is significantly higher than that in women 9.1% [7]. Among the death population of COVID-19 cases, the elderly accounts for a large proportion [8]. Patients with diabetes mellitus, obesity and/or hypertension and COVID-19 have increased mortality and morbidity rate. However, the association of diabetes mellitus hypertension and cardiovascular diseases for COVID-19 is still unknown [9]. Coronary heart disease and other comorbidities are also closely related to the death rate of COVID-19 [10-14]. Although some studies have revealed the correlation between gender and the prevalence, severity and mortality of COVID-19 pneumonia [15, 16], there is no detailed analysis on the underlying mechanism. Considering that many patients with COVID-19 are complicated with multiple comorbidities [17-19], classifying comorbidities and paying attention to the impact of different comorbidities on the relevant clinical indicators and prognosis of patients with COVID-19 is of great significance for clinical guidance.

Herein, we grouped 189 COVID-19 inpatients in Tongji Hospital Affiliated to Tongji medical col-

lege HUST according to gender, age, and comorbidity types, and analyzed the changes in experimental indicators of patients with COVID-19 under these three factors to find their impact on the severity of the disease. Among them, the patients were divided into those with no comorbidity, one comorbidity, equal or greater than two comorbidities.

Materials and methods

Patients

A total of 189 patient with COVID-19 who were admitted from February 10 to March 28, 2020 in Tongji Hospital Affiliated to Tongji medical college HUST were enrolled. Among all the patients (n=189) tested for SARS-Cov-2, 145 (76.7%) were positive and 44 (23.3%) were clinically diagnosed; They were clinically diagnosed based on the clinical symptoms: 1). fever or respiratory symptoms; 2). early onset of the total number of white blood cells normal or decreased, or decreased lymphocyte count; 3). with typical changes in chest radiology or with a positive result on real-time reverse transcription polymerase chain reaction assay of nasal and pharyngeal swab specimens.

Type of disease

According to the seventh version of the guidelines on the Diagnosis and Treatment of COVID-19 issued by the National Health Commission, COVID-19 severity was classified into below types: 1. Mild type: The clinical symptoms were mild with no abnormal radiological findings. 2. Moderate type: Fever, cough and other symptoms were presented as well as pneumonia on chest computed tomography. 3. Severe type: The disease was classified as severe if one of the following conditions was met: (1) Respiratory distress, respiratory rate ≥30 per min; (2) Oxygen saturation on room air at rest ≤93%; (3) Partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤300 mmHg. 4. Critical type: The disease was classified as critical if one of the following conditions was met: (1) Respiratory failure occurred and mechanical ventilation was required; (2) Shock; (3) T monitoring treatment.

Statistics analysis

We categorized clinical information into continuous data and categorical data. For the continuous data, we used the One-Way ANOVA test with unpaired parameter. The Chi-square test or Fisher exact test was applied to analyze categorical data as appropriate. P value ≤0.05 was considered as statistically significant. The relationship between clinical characteristics and overall survival of COVID-19 was estimated using the univariate cox regression analysis in the survival R package. Moreover, Kaplan-Meier curve and log-rank test analysis was used to identify survival difference of categorical variables in COVID-19 patients. All analyses were performed with the R package. For all statistical analysis, the P value less than 0.05 was considered as statistically significant.

Results

Landscape of clinical feature

A total of 189 patients (Alive: 164, Dead: 25) were enrolled in our study. According to the clinical types, patients were further classified into common (N=93), severe (N=60) and critical severe types (N=36). The median age in the common, severe and critical severe types were 57 years, 64.5 years and 69.5 years, respectively, suggesting that elderly patients are prone to have critical type of COVID-19 ($P<0.001$). Additionally, the prevalence of patients with COVID-19 was higher in males (N=102) compared with females (n=87), and the proportion of male cases in the critical severe cases was significantly higher ($P=0.042$). Most COVID-19 patients presented with at least one symptom in the initial of infection, of which fever was the most common symptoms, accounting for 75.13% of the cases. The expectoration ranked second among the symptoms which accounted for 55.1% of the cases, and dyspnea presented in 33.33% of the cases, following the fever and expectoration ($P<0.001$). In addition, we also found that hypertension, diabetes and coronary heart disease were the most common comorbidities, which represent 65 (34.39%), 29 (15.34%) and 14 (7.41%) cases, respectively. Moreover, critical severe types had more hypertension cases ($P<0.001$). We further compared the index level in the three types. As shown in **Table 1**, the levels of leukocyte, albumin, C-reactive protein (CRP), interleukin 6 (IL-6) and D-dimer presented a clear increasing trend (all $P<0.05$), while lymphocyte, oxygen saturation and albumin showed a decreasing trend (all $P<0.001$).

Table 1. The statistics clinical information of 189 COVID-19 patients

Items	Sub-items	Case distribution	Common (93)	Severe (60)	Critical severe (36)	df	P
Age (years)	Median	63 (51-71)	57 (42.5-67.5)	64.5 (52.5-71.75)	69.5 (62.25-78.5)		<0.0001
	≥60	58.20%	42 (45.2%)	37 (61.7%)	31 (86.1%)	18.324	<0.0001
	≥70	29.70%	19 (20.4%)	19 (31.7%)	18 (50.0%)	11.059	0.0040
Gender	Male	102 (53.97%)	48 (51.61%)	28 (46.67%)	26 (72.22%)	6.324	0.0423
	Female	87 (46.03%)	45 (48.39%)	32 (53.33%)	10 (27.78%)		
Symptoms	Fever	142 (75.13%)	62 (66.67%)	47 (78.33%)	28 (77.78%)	0.939	0.6253
	Cough	55 (29.10%)	27 (29.03%)	21 (35.00%)	7 (19.44%)	2.639	0.2672
	expectoration	108 (57.14%)	44 (47.31%)	40 (66.67%)	24 (66.67%)	7.226	0.0270
	Fatigue	43 (22.75%)	19 (20.43%)	10 (16.67%)	14 (38.89%)	6.883	0.0320
	pharyngalgia	20 (10.58%)	15 (25.00%)	5 (8.33%)	0 (0.00%)	7.605	0.0223
	myalgia	28 (14.81%)	16 (17.20%)	7 (11.67%)	5 (13.89%)	0.916	0.6324
	Diarrhea	37 (19.58%)	23 (24.73%)	7 (1.67%)	7 (19.44%)	3.954	0.1384
	Dyspnea	63 (33.33%)	24 (25.80%)	16 (26.67%)	23 (63.89%)	18.696	<0.0001
Vital signs	Highest temperature (°C)	38.60±0.68	38.55±0.74	38.73±0.60	38.47±0.67	1.480	0.2313
	Respiratory rate (breaths per min)	22.60±5.30	20.13±3.59	25.70±5.80	23.51±5.03	25.988	<0.0001
	Oxygen saturation (%)	94.41±5.08	97.04±1.63	93.02±4.52	90.29±7.33	33.034	<0.0001
comorbidity		93 (49.21%)	29 (31.2%)	33 (55.00%)	31 (86.10%)	32.510	<0.0001
	High blood pressure	65 (34.39%)	18 (19.35%)	21 (35.00%)	26 (72.22%)	32.163	<0.0001
	Diabetes mellitus	29 (15.34%)	9 (9.68%)	12 (20.00%)	8 (22.22%)	4.611	0.0997
	Chronic obstructive pulmonary disease	10 (5.29%)	3 (3.23%)	4 (6.67%)	3 (8.33%)	1.683	0.4310
	Coronary heart disease	14 (7.41%)	3 (3.23%)	6 (10.00%)	5 (13.89%)	5.164	0.0756
	Cerebrovascular diseases	6 (2.65%)	2 (2.15%)	1 (1.67%)	3 (8.33%)	3.878	0.1439
	Tumor	5 (5.38%)	2 (2.15%)	2 (3.33%)	1 (2.78%)	0.563	0.853
Days of onset (days)	Time from onset to visit	4.31±5.42	4.22±5.00	5.22±6.54	3.03±4.10	1.879	0.1556
Primary leukocyte count (×10⁹/L)		6.84±3.47	5.84±1.97	6.51±2.30	10.06±5.72	24.117	<0.0001
Primary lymphocyte count (×10⁹/L)		1.37±0.78	1.55±0.789	1.31±0.69	0.96±0.81	7.600	0.0007
Primary albumin (g/L)		35.45±5.21	37.07±3.98	35.78±4.89	30.63±5.78	24.498	<0.0001
Primary C-reactive protein (mg/L)		36.26±52.01	14.05±25.62	29.05±34.65	108.89±65.23	76.854	<0.0001
Primary IL-6 (pg/ml)		96.68±499.67	8.78±27.04	11.01±14.15	346.67±949.60	5.639	0.0046
Primary D-dimer(ug/mL)		3.01±5.85	0.98±1.66	1.90±2.88	10.07±9.94	42.770	<0.0001

Table 2. The clinical information for the survival of COVID-19 patients which group by age, gender and comorbidity

Characteristic		Alive (N=164)	Dead (N=25)	P value
Age	<60	77	2	0.0005
	≥60	87	23	
Gender	Female	83	6	0.0233
	Male	81	19	
Comorbidities	0	91	5	0.0012
	1	48	10	
	≥2	25	10	

Analysis of risk factors (age, gender and comorbidities) for the COVID-19 patients

Abundant studies have been reported that gender, age and comorbidities were the risk factors for the COVID-19 patients. In our analysis, we found that males showed more death cases than females (*P*=0.0233). Also, older patients had more death cases (*P*=0.0005). Moreover, patients with one or more than two comorbidities were at greater risk of death (*P*=0.0012) (**Table 2**).

In order to further evaluate the association between overall survival and clinical characteristics, we conducted a univariate cox regression analysis. As shown in **Figure 1**, we identified 21 risk factors associated with survival of COVID-19 patients. Interestingly, we found that seven factors including oxygen saturation, leukocyte, albumin, CRP index, IL-6 index, troponin and lymphocyte were associated with survival of COVID-19 patients. We further compared the level of the clinical indicators among gender, different age and comorbidities. As showed in the **Figure 2**, the levels of IL-6 index and CRP index were significantly higher in males compared to females (**Figure 2A** and **2B**), while the level of lymphocyte in males was lower than females (**Figure 2F**). Kaplan-Meier curve and log-rank test analysis result showed that female patients had prolonged survival time compare to male patients (*P*<0.05).

Moreover, we evaluated the level of clinical indicators among different age groups (<60 and ≥60). As shown in **Figure 3A-G**, the level of IL-6, CRP, tuberculosis and leukocyte presented significantly increasing trend from <60 group to ≥60 group. However, the level of albu-

min, lymphocyte and oxygen saturation exhibited a declining trend from <60 group to ≥60 group. The Kaplan-Meier curve and log-rank test analysis result indicated that patients in the younger age group (<60) had a better survival outcome than patients in the older age group (≥60) (**Figure 3H**).

In addition, considering some cases had multiple comorbidities, we further classified the patients into group without comorbidity (0), group with one comorbidity (1) and group with equal to or more than two comorbidities (≥2). As shown in **Figure 4**, six of seven indexes including IL-6, CRP, tuberculosis, albumin, lymphocyte and oxygen saturation presented a significant difference between 0 comorbidity group and ≥2 comorbidity group. We also observed a significant survival difference among comorbidity groups (*P*<0.0001). These results indicate that patients in the female group, younger group and no comorbidity group respond better to COVID-19 infection and have a better immune response.

Discussion

In the present study, a total of 189 hospitalized patients were recruited from a teaching affiliated hospital in Wuhan, China. Among them, about 91 patients (48.15%) developed at least one comorbidity, and 80% death cases were with comorbidity. By performing univariate cox regression analysis, we identified 21 risk factors that associated with overall survival of COVID-19 patients. The age, gender and comorbidity were also identified as risk factors in our study, consistent with most previous studies [14, 20, 21]. Kaplan-Meier curve analysis results revealed that the elderly patients had a worse survival outcome compared to younger patients. The reason maybe that the nutritional status and immune function of elderly patients are relatively poor, which may lead to the immune defense function damage and develop into severe pneumonia, thereby increasing the risk of death. Moreover, we showed that the risk factors including leukocyte, CRP, IL-6 and tuberculosis were significantly higher in elderly group compared to younger group, while the protective factors albumin and lymphocyte presented opposite trend in younger group and elderly group. Taking into account the immune function is
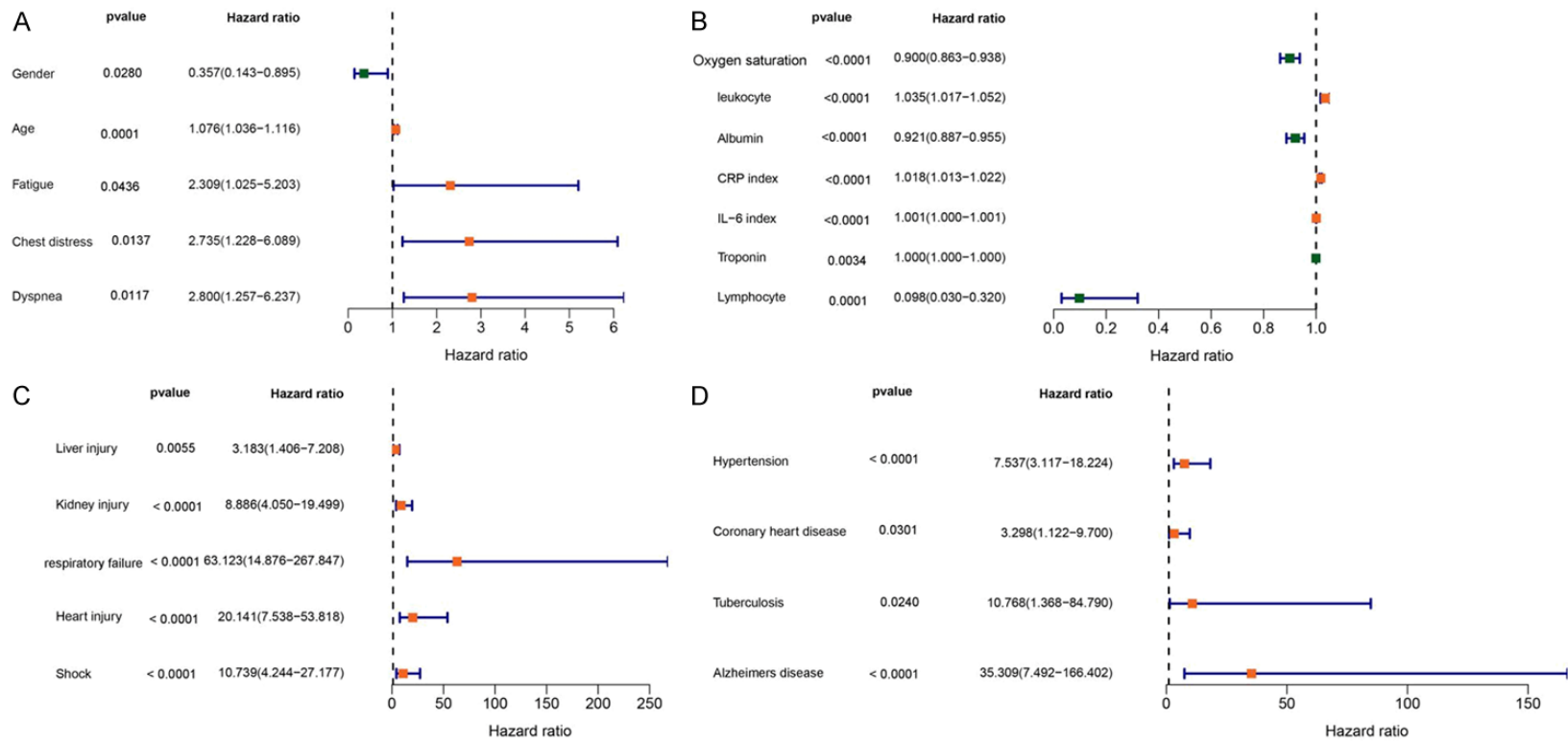
Figure 1. Exploring the relationship between COVID-19 patients survival and clinical trait including clinical signs (A), clinical indicators (B), complications (C) and comorbidity (D) by using the cox regression analysis, the red boxplot represent the protective factors, while the green boxplot represent the risky factors.
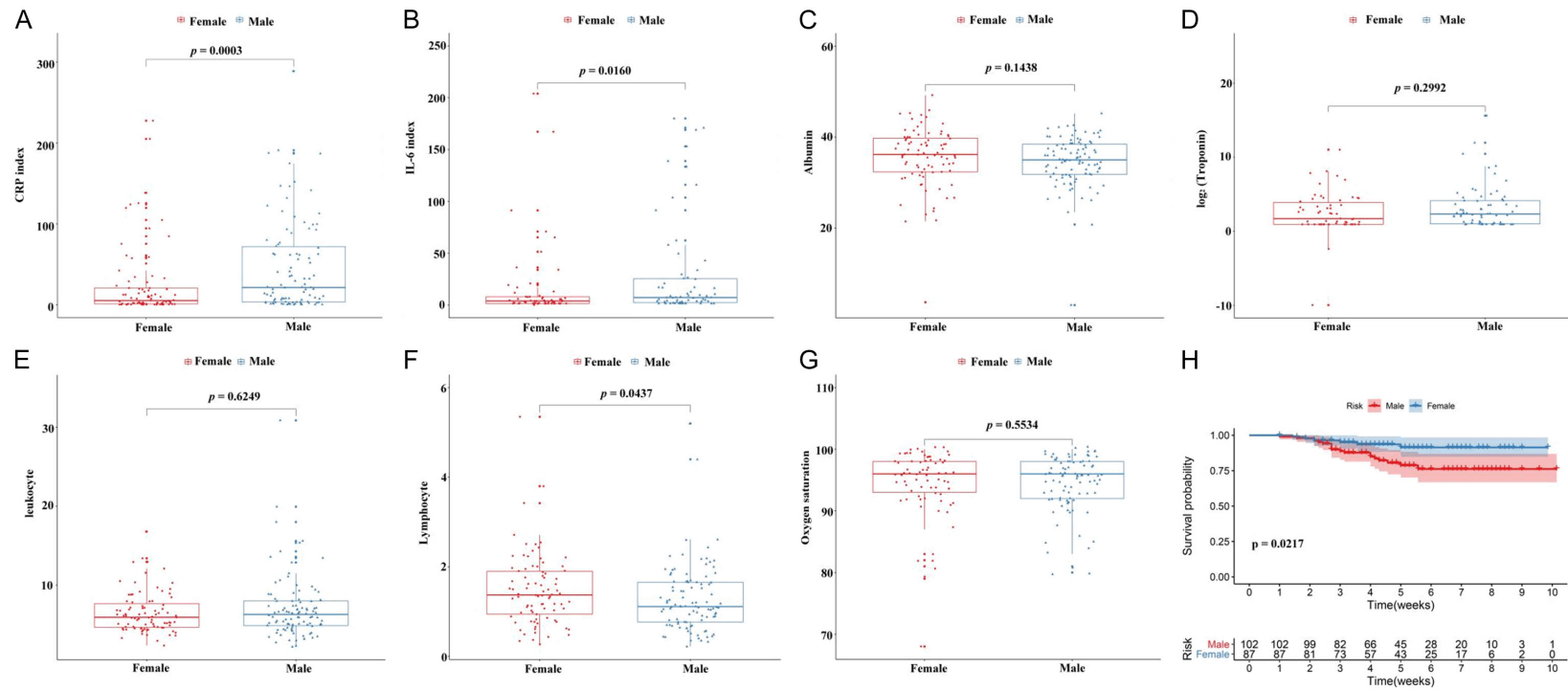
Figure 2. The relationship between laboratory indicators and gender were shown in (A-G), and K-M curve analysis for the survival of COVID-19 patients in gender group (Male VS Female) (H).
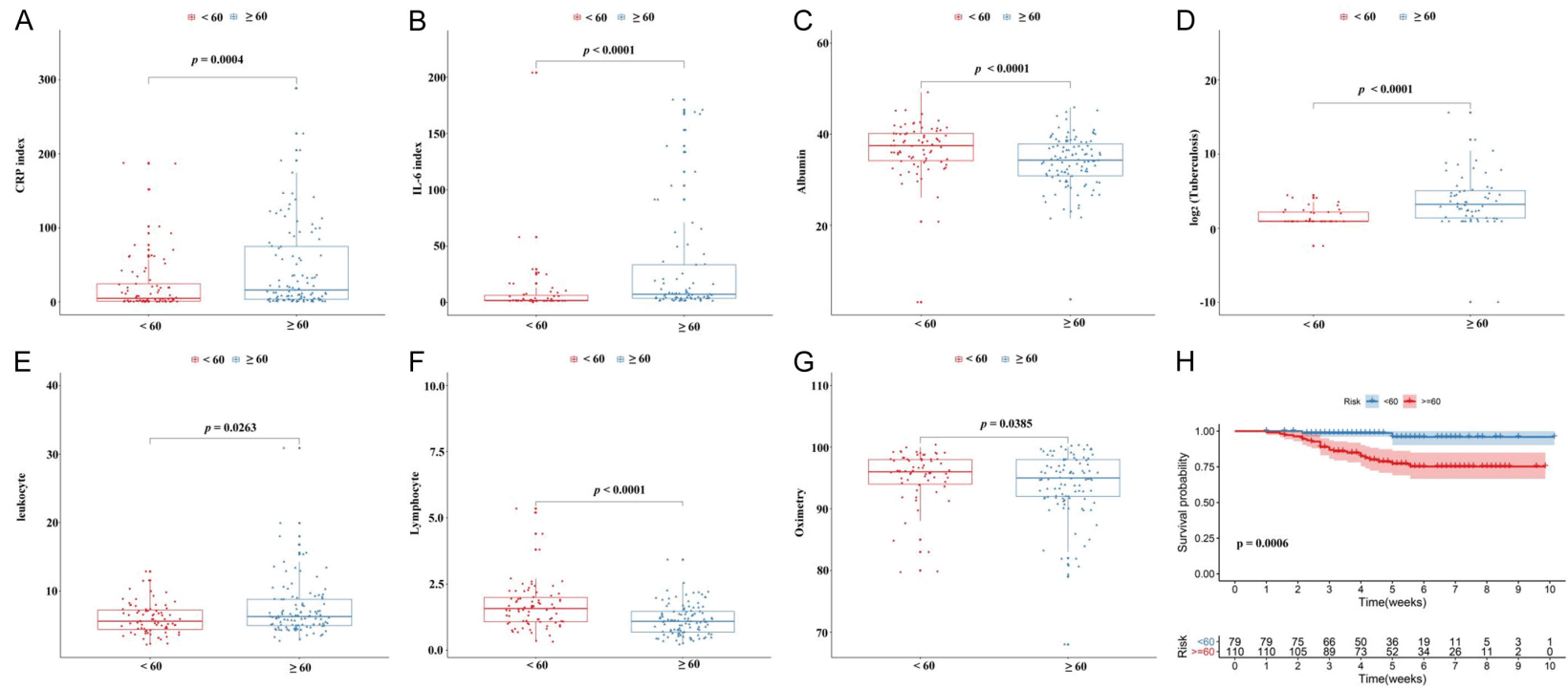
Figure 3. The relationship between laboratory indicators and gender were shown in the (A-G), and K-M curve analysis for the survival of COVID-19 patients in age group (≤60 VS >60) (H).
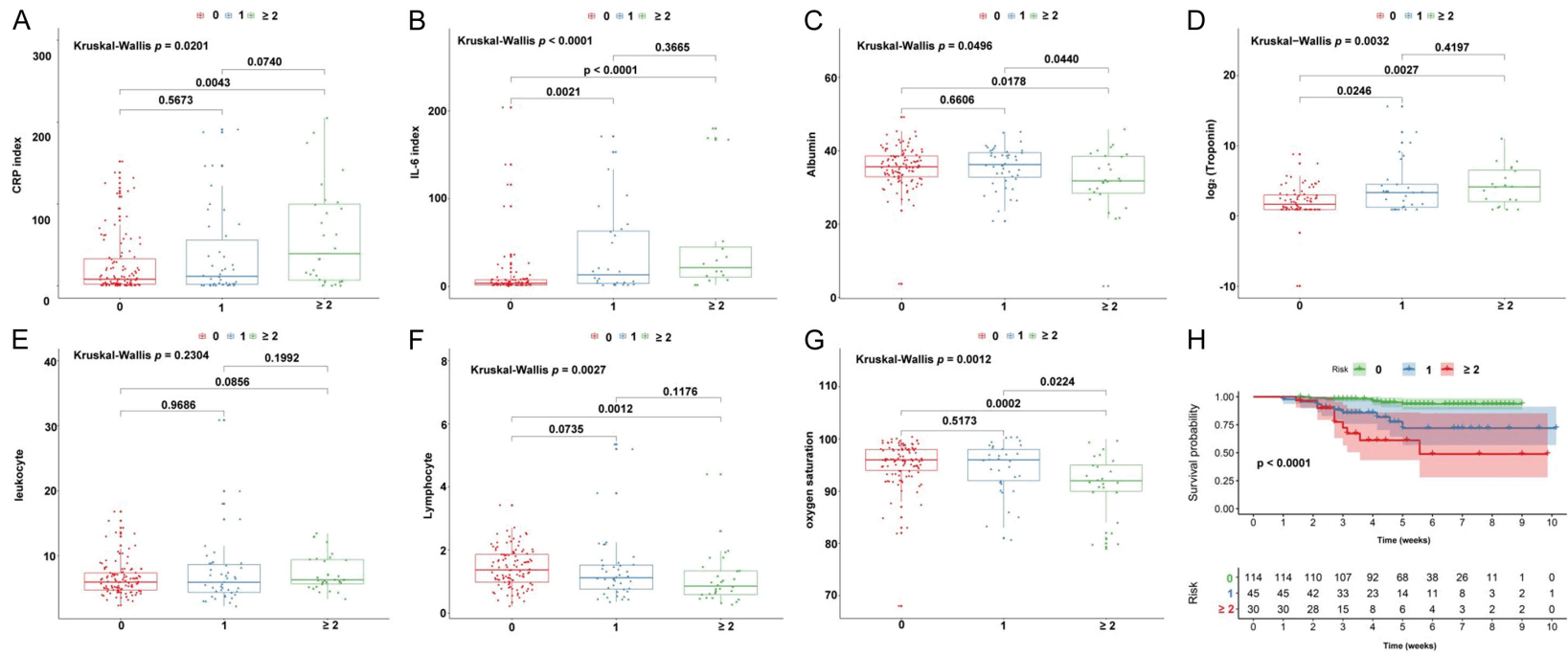
Figure 4. The relationship between laboratory indicators and gender were shown in (A-G), and K-M curve analysis for the survival of COVID-19 patients in comorbidities group (0 VS 1 VS ≥2) (H).

positively correlated with albumin and lymphocyte, it is not surprised that the younger patients have a better survival outcome [22, 23].

Although males and females have similar susceptiblility to SARS-CoV-2, males are more likely to have higher severity and mortality, which is similar to the feature of SARS 2003 and Middle East Respiratory Syndrome (MERS) [24-27]. Our study showed that gender was an independent risk factor for COVID-19 deaths. In further COX risk analysis, CRP and IL-6 were significantly higher in ≥60 years patient group than in <60 years patient group, and the survival curve suggested that female was a protective factor for COVID-19 deaths.

So far, the mechanisms underlying the observed gender differences are not entirely clear. Based on the current understanding of gender differences in respiratory virus diseases, some assumptions can be put forward. Some lifestyles, such as smoking, are most likely associated with the negative progression and adverse outcomes of COVID-19 in males [28]. In addition, it is known that, in general, innate and immune responses are more intense and stronger in females than in males. Pro-inflammatory cytokines and chemokines express stronger in males. In particular, the core cytokine storm, IL-6 receptor, is highly expressed in lung epithelial cells in males, suggesting that males are more susceptible to cytokine storm that can lead to the deterioration of COVID-19 [26, 29, 30], which is consistent with our result. Angiotensin I converting enzyme 2 (ACE2) is crucial for SARS CoV-2 entry into host cells which is similar to SARS-CoV. ACE2 is the main receptor mediating viral attachment to target cells [31]. Cell type-specific expression of the ACE2 receptor in type II alveolar epithelial cells is higher in males than in females [32, 33]. Therefore, male respiratory system is more vulnerable. ACE2 provide a key link between infectious agents, immunity, inflammation, and cardiovascular disease, which will be mention in the following discussion.

Comorbidity has also been reported as an important risk factor for mortality in COVID-19 patients. Patients with at least one comorbidity, were associated with poor clinical outcomes. IL-6, CRP, Troponin, lymphocyte count and blood oxygen saturation showed differenc-

es among groups of on comorbidity, one comorbidity, and ≥2 comorbidities. Meanwhile, the survival curve indicates that the number of comorbidities is an important risk factor for the prognosis of patients. These findings have provided further evidence for taking into account baseline comorbid diseases in the comprehensive risk assessment of prognosis among patients with COVID-19 [34].

The level of ACE2 receptor is associated with blood pressure level. The patient with hypertension may decrease the level of ACE2 receptors compared with no hypertension patients. SARS-CoV-2 infects cells through ACE2 receptor. ACE2 is highly expressed in the lung, and Imai et al. confirmed the protective effect of ACE2 in acute lung injury. Once SARS-CoV-2 infects the lungs, the amount and function of ACE2 protein in the lungs are reduced, which leads to acute lung failure. Once they are infected with SARS-CoV-2, ACE2 receptor expression will be less. The early manifestations of hypertension patients with COVID-19 are hypertension. In the later stage, COVID-19 patients may present shock and hypotension after respiratory failure and multiple organ failure, thereby entering the severe and critical stage. Diabetic patients are with hyperglycemia, various metabolic disorders. They are susceptible populations to infections of viruses, bacteria and other pathogenic microorganisms. Once diabetic patients are infected, it will not only aggravate basic diseases, but also easily lead to multiple organ failure. Moreover, type 2 diabetes is associated with reduced ACE2 activity [30]. Similarly, myocardial damage is also common in patients with COVID-19. Different reports have used different definitions for acute myocardial injury, including increase in cardiac enzymes (different biomarkers and cut-offs) and/or electrocardiographic abnormalities [17].

Coronary heart disease mainly manifests as acute myocardial injury, accompanied by an increase of leukocyte count, CRP, and troponin. Similar results were obtained in our study. Plasma IL-6 concentrations are elevated in COVID-19 patients with cardiac injury, and abnormalities in a variety of cytokines are prominent in patients with severe COVID-19 disease. Therefore, those patients with underlying conditions (such as hypertension, diabe-

tes, and/or cardiovascular disease, etc.) are at higher risk of a rapid progression to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction, arrhythmia, kidney damage, heart failure, liver dysfunction, and/or secondary infection, and death [35].

However, several limitations need to elaborated. Firstly, the sample size was small. Secondly, some cases lacked of complete date of the exposure history and laboratory tests. Moreover, some patients are still under treatment in the hospital and their survival outcome is unclear at the time of data collection.

In conclusion, we identified three risk factors including age, gender and comorbidities that associated with the survival of COVID-19 patients. These risk factors may contribute to understanding the underlying mechanism of COVID-19 and provide reference for clinician to personalize management and treatment of patients.

Disclosure of conflict of interest

None.

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