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RESEARCH ARTICLE

Clinical Characteristics, Associated Factors, and Predicting COVID-19 Mortality Risk: A Retrospective Study in Wuhan, China

Caizheng Yu, MPH,[1] Qing Lei, PhD,[2] Wenkai Li, PhD,[3] Xiong Wang, PhD,[4] Wei Liu, MPH,[1] Xionglin Fan, PhD,[2] Wengang Li, MPH[1]

Introduction: COVID-19 has become a serious global pandemic. This study investigates the clinical characteristics and the risk factors for COVID-19 mortality and establishes a novel scoring system to predict mortality risk in patients with COVID-19.

Methods: A cohort of 1,663 hospitalized patients with COVID-19 in Wuhan, China, of whom 212 died and 1,252 recovered, were included in this study. Demographic, clinical, and laboratory data on admission were collected from electronic medical records between January 14, 2020 and February 28, 2020. Clinical outcomes were collected until March 26, 2020. Multivariable logistic regression was used to explore the association between potential risk factors and COVID-19 mortality. The receiver operating characteristic curve was used to predict COVID-19 mortality risk. All analyses were conducted in April 2020.

Results: Multivariable regression showed that increased odds of COVID-19 mortality was associated with older age (OR=2.15, 95% CI=1.35, 3.43), male sex (OR=1.97, 95% CI=1.29, 2.99), history of diabetes (OR=2.34, 95% CI=1.45, 3.76), lymphopenia (OR=1.59, 95% CI=1.03, 2.46), and increased procalcitonin (OR=3.91, 95% CI=2.22, 6.91, per SD increase) on admission. Spline regression analysis indicated that the correlation between procalcitonin levels and COVID-19 mortality was nonlinear (p=0.0004 for nonlinearity). The area under the receiver operating curve of the COVID-19 mortality risk was 0.765 (95% CI=0.725, 0.805).

Conclusions: The independent risk factors for COVID-19 mortality included older age, male sex, history of diabetes, lymphopenia, and increased procalcitonin, which could help clinicians to identify patients with poor prognosis at an earlier stage. The COVID-19 mortality risk score model may assist clinicians in reducing COVID-19–related mortality by implementing better strategies for more effective use of limited medical resources.

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INTRODUCTION

In December 2019, several pneumonia cases of unknown origin were identified in Wuhan, Hubei, China.[1,2] The pathogen has been identified as a novel coronavirus (CoV) belonging to the β-CoV genus and has been renamed severe acute respiratory syndrome (SARS) CoV-2 (SARS-CoV-2, previously named 2019 novel CoV).[3] This novel virus shared 87.99% sequence identity to bat SARS–like CoV and 79.5% of its

From the [1]Department of Public Health, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]Department of Pathogen Biology, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Department of Orthopedics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; and [4]Department of Laboratory Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Address correspondence to: Wengang Li, MPH, Department of Public Health, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, China. E-mail: 228907211@qq.com.

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sequence with SARS-CoV.[4,5] SARS-CoV-2 has a strong affinity for angiotensin-converting enzyme 2 receptors, which was an early indicator of its potential for becoming a pandemic threat.[6] By May 8, 2020, a total of 3.76 million cases have been confirmed globally, including 84,415 cases in China. Of these, 259,474 patients have died of this viral infection worldwide, including 4,643 in China.[7] According to WHO, the crude mortality rate of CoV disease 2019 (COVID-19) was about 6.9%.[7] However, the origins and possible intermediate host of SARS-CoV-2 remain unclear.

The clinical characteristics of COVID-19 have been well described,[1,8−11] but there are few published analyses focused specifically on COVID-19 mortality.[12] In addition, there have been limited studies exploring the potential risk factors for COVID-19 mortality. Therefore, this study examines potential risk factors for COVID-19 mortality and aims to establish a COVID-19 mortality risk prediction model at a single-center hospital.

METHODS

Study Sample

The authors obtained the medical records of 1,663 hospitalized patients with a laboratory-confirmed diagnosis of COVID-19 from Tongji Hospital, Wuhan, China, between January 14, 2020 and February 28, 2020. As of March 26, 2020, the clinical outcomes of the total hospitalized patient population were collected. After the exclusion of patients who were still hospitalized (n=196) or transferred to other hospitals (n=3), a total of 1,464 eligible patients were included in the final analysis. Patients missing procalcitonin (PCT; n=324) and lymphocyte count (LY; n=117) data were further excluded, leaving 1,140 and 1,347 patients included in the analyses of PCT and LY with COVID-19 mortality, respectively. The study population selection is shown in Appendix Figure 1 (available online).

A laboratory-confirmed case of COVID-19 was defined as a positive real-time reverse transcriptase−polymerase chain reaction (RT-PCR) test result assay obtained through oral pharyngeal swab specimens. Investigators collected demographic information, exposure history, medical history, comorbidities, signs and symptoms, chest computed tomography, laboratory findings on admission, and clinical outcomes from electronic medical records. Laboratory results (blood count, chemical analysis, and coagulation testing) were included in laboratory testing. The date of disease onset, SARS-CoV-2 laboratory confirmation, hospital admission, discharge, and death were also recorded. The study was approved by the Tongji Hospital Ethics Committee.

Measures

Oral pharyngeal swab samples (stored in 5-milliliter (mL) virus preservation solution) were collected for SARS-CoV-2 viral nucleic acid detection. Virus RNA was extracted within 24 hours by Tianlong PANA9600 automatic nucleic acid extraction system (Tianlong, China). Two target genes (*ORF1ab* and *N* genes) were simultaneously amplified and tested with RT-PCR. RT-PCR assays were conducted on a Tianlong Gentier 96E real-time polymerase chain reaction system with the following conditions: incubation at 50°C for 15 minutes, predenaturation at 95°C for 15 minutes, 45 cycles of denaturation at 94°C for 15 seconds, and extension at 55°C for 45 seconds (collecting fluorescence signal). A cycle threshold value (Ct-value) <40 for both genes was defined as a positive test, a Ct-value ≥40 was defined as a negative test, and a single Ct-value <40 required confirmation by retesting.

Statistical Analysis

Wilcoxon rank sums test was performed to test differences between recovered patients and patients who died of COVID-19, and chi-square test or Fisher's exact test, when appropriate, was conducted for categorical variables. Multivariate logistic regression was performed to investigate the associations (OR, 95% CI) of potential risk factors with COVID-19 mortality. Referring to previous studies,[12−16] age (<65 years, ≥65 years), sex (female, male), history of hypertension (*yes*/*no*) and diabetes (*yes*/*no*), lymphopenia (<1.1 × 10^9/liter (L), ≥1.1 × 10^9/L), increased alanine aminotransferase (ALT) (<40 U/L, ≥41 U/L), increased lactate dehydrogenase (LDH) (<214 U/L, ≥214 U/L), increased D-dimer (<0.5 mg/L, ≥0.5 mg/L), and increased PCT (<0.05 ng/mL, ≥0.05 ng/mL) were included in multivariable logistic regression model. In the analysis of PCT and LY with COVID-19 mortality, PCT and LY were categorized into 3 groups according to the tertile (T) of distribution. The p-value for trend was calculated from group medians. The association of PCT concentration with the risk of COVID-19 mortality was also evaluated using restricted cubic splines, with 3 knots defined at the 5^{th}, 50^{th}, and 90^{th} percentiles of the PCT concentrations; the reference value (OR=1) was 0.05 ng/mL for PCT concentrations and data from the <5^{th} and >95^{th} percentiles were deleted. Variables that were at a statistically significant level (p<0.05) in the multivariable logistic regression were included in the prediction model. The receiver operating characteristic curve was used for prediction of COVID-19 mortality, and the Youden index was used to identify the optimal cut off point.[17] The novel scoring model was established, and the mortality risk scores were determined by multivariate logistic regression to reflect their weights of impact on the COVID-19 mortality. The mortality risk score was calculated according to the ORs and rounded to the nearest integer.[18] The total risk score was the sum of the scores of each variable (age, sex, history of diabetes, lymphopenia, and increased PCT). SPSS, version 13.0, and SAS, version 9.4, were used to conduct all statistical analyses. All analyses were conducted in April 2020. The 2-sided statistical tests were considered significant at p<0.05.

RESULTS

Baseline characteristics of the recovered patients (n=1,252) and patients who died of COVID-19 (n=212) are shown in Table 1. A total of 1,464 hospitalized patients infected with COVID-19 (728 female and 736 male) were included in this study. The median age of the patients was 64.0 years (IQR=51.0−71.0), and 48.3% were aged >65 years. The median interval from the onset of symptoms to COVID-19 laboratory confirmation was 9.0 days (IQR=5.0−14.0), from the onset of symptoms

Table 1. Baseline Characteristics of Patients Infected With COVID-19

Characteristics	All patients	Recovery and discharge	Death	*p*-value
n	1,464	1,252	212	
Age, years				
Median (IQR)	64.0 (51.0–71.0)	62.5 (49.0–70.0)	69.0 (62.5–77.0)	**<0.0001**
Age groups, *n* (%)				**<0.0001**
<65	757 (51.7)	692 (55.3)	65 (30.7)	
≥65	707 (48.3)	560 (44.7)	147 (69.3)	
Female, *n* (%)	728 (49.7)	666 (53.2)	62 (29.3)	**<0.0001**
Family infection, *n* (%)	112 (7.7)	105 (8.4)	7 (3.3)	0.01
Time from onset to diagnosis, days, median (IQR)	9.0 (5.0–14.0)	9.0 (4.0–14.0)	9.0 (6.0–14.0)	0.24
Time from onset to admission, days, median (IQR)	10.0 (6.0–14.0)	10.0 (6.0–14.0)	9.0 (6.0–14.0)	0.73
Length of hospital stay, days, median (IQR)	22.0 (14.0–30.0)	23.0 (17.0–31.5)	9.0 (4.0–15.0)	**<0.0001**
Time from onset to outcome, days, median (IQR)	33.0 (25.0–42.0)	34.5 (27.0–43.0)	19.5 (13.5–27.0)	**<0.0001**
Time from diagnosis to outcome, days, median (IQR)	23.0 (15.0–31.0)	24.0 (17.0–32.0)	9.0 (4.0–15.0)	**<0.0001**
Comorbidity, *n* (%)				
Hypertension	306 (20.9)	231 (18.5)	75 (35.4)	**<0.0001**
Diabetes	211 (14.4)	142 (11.3)	69 (32.6)	**<0.0001**
CHD	117 (8.0)	93 (7.4)	24 (11.3)	0.053
Chronic obstructive pulmonary disease	50 (3.4)	39 (3.1)	11 (5.2)	0.12
Cerebrovascular disease	47 (3.2)	39 (3.1)	8 (3.8)	0.61
Chronic liver disease	36 (2.5)	32 (2.6)	4 (1.9)	0.56
Chronic renal disease	27 (1.8)	24 (1.9)	3 (1.4)	0.79
Cancer	17 (1.2)	11 (0.9)	6 (2.8)	0.03
Signs and symptoms, *n* (%)				
Fever	1,259 (86.0)	1,065 (85.1)	194 (91.5)	**0.01**
Fatigue	346 (23.6)	222 (17.7)	124 (58.5)	**<0.0001**
Cough	520 (35.5)	483 (38.6)	37 (17.5)	**<0.0001**
Loss of appetite	63 (4.3)	50 (4.0)	13 (6.1)	0.16
Myalgia	54 (3.7)	48 (3.8)	6 (2.8)	0.47
Dyspnea	69 (4.7)	58 (4.6)	11 (5.2)	0.72
Pharyngalgia	23 (1.6)	21 (1.7)	2 (0.9)	0.43
Diarrhea	74 (5.1)	68 (5.4)	6 (2.8)	0.11
Nausea	17 (1.2)	16 (1.3)	1 (0.5)	0.49
Dizziness/headache	29 (2.0)	26 (2.1)	3 (1.4)	0.79
Vomiting	17 (1.2)	17 (1.4)	0 (0.0)	0.16
Chest tightness	174 (11.9)	151 (12.1)	23 (10.9)	0.61
Runny nose	4 (0.3)	4 (0.3)	0 (0.0)	1.00
Laboratory results, *n* (%)				
Lymphopenia	680 (50.5)	576 (48.9)	104 (61.5)	**0.002**
Mononucleosis	353 (26.2)	303 (25.7)	50 (29.6)	0.29
Neutrophilia	205 (15.2)	158 (13.4)	47 (27.8)	**<0.0001**
Thrombocytopenia	109 (8.1)	85 (7.3)	24 (14.2)	**0.002**
Leukocytosis	120 (8.9)	93 (7.9)	27 (16.0)	**0.0006**
Increased ALT	259 (20.3)	227 (20.3)	32 (20.1)	0.95
Increased AST	254 (19.9)	208 (18.6)	46 (28.9)	**0.002**
Increased creatinine	102 (8.0)	78 (7.0)	24 (15.2)	**0.0004**
Increased LDH	965 (75.8)	833 (74.7)	132 (83.5)	**0.02**
Increased C-reactive protein	1,023 (79.9)	892 (79.9)	131 (79.9)	0.99
Increased D-dimer	822 (62.9)	703 (61.7)	119 (71.7)	**0.01**
Prolonged thrombin time	79 (6.5)	62 (5.9)	17 (10.9)	**0.02**
Increased PCT	558 (49.0)	444 (44.6)	114 (78.6)	**<0.0001**

Note: Boldface indicates statistical significance ($p<0.05$).
Data are medians (IQR) for skewed parameters or number (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase; PCT, procalcitonin.

Table 2. Logistic Regression Model for COVID-19 Mortality With Its Potential Risk Factors

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age, years				
<65	1.00 (ref)		1.00 (ref)	
≥65	2.80 (2.05, 3.82)	<0.0001	2.15 (1.35, 3.43)	**0.001**
Sex (male)	2.75 (2.01, 3.77)	<0.0001	1.97 (1.29, 2.99)	**0.002**
History of hypertension	2.42 (1.77, 3.32)	<0.0001	1.08 (0.68, 1.72)	0.74
History of diabetes	3.77 (2.70, 5.28)	<0.0001	2.34 (1.45, 3.76)	**0.0005**
Lymphopenia[a]	1.67 (1.20, 2.33)	0.002	1.59 (1.03, 2.46)	**0.04**
Increased ALT[b]	0.99 (0.65, 1.49)	0.95	0.81 (0.49, 1.34)	0.42
Increased LDH[c]	1.72 (1.11, 2.67)	0.02	1.19 (0.66, 2.16)	0.56
Increased D-dimer[d]	1.57 (1.10, 2.25)	0.01	0.78 (0.48, 1.27)	0.31
Increased PCT[e]	4.56 (3.01, 6.92)	<0.0001	3.62 (2.24, 5.84)	**<0.0001**

Note: Boldface indicates statistical significance ($p<0.05$).
[a]Lymphopenia (<1.1, ≥1.1, × 10^9/L).
[b]Increased ALT (<40, ≥41, U/L).
[c]Increased LDH (<214, ≥214, U/L).
[d]Increased D-dimer (<0.5, ≥0.5, mg/L).
[e]Increased PCT (<0.05, ≥0.05, ng/mL).
ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; L, liter; LDH, lactate dehydrogenase; mL, milliliter; PCT, procalcitonin.

to hospital admission was 10.0 days (IQR=6.0–14.0), from the onset of symptoms to recovery was 34.5 days (IQR=27.0–43.0), and from the onset of symptoms to death was 19.5 days (IQR=13.5–27.0). The median length of patients' hospital stay was 22.0 days (IQR=14.0–30.0). Among the total 1,464 hospitalized patients, 38.8% had at least 1 comorbidity; hypertension (20.9%), diabetes (14.4%), and coronary heart disease (CHD) (8.0%) were the most common pre-existing diseases. In addition, the main clinical symptoms in hospitalized cases were fever (86.0%), cough (35.%), fatigue (23.6%), and chest tightness (11.9%). Compared with recovered patients, those who died of COVID-19 were more likely to be male and older and tended to have a shorter time from the onset of symptoms to death and shorter time of hospital stay (all $p<0.01$). In addition, patients who died of COVID-19 had a higher proportion of comorbidities, including hypertension, diabetes, and CHD (all $p<0.01$) and the presence of clinical symptoms such as fever, cough, and fatigue (all $p<0.01$).

More than 50% of patients had decreased LY (50.5%), increased levels of LDH (75.8%), increased C-reactive protein (79.9%), and increased D-dimer (62.9%). Increased PCT (49%), mononucleosis (26.2%), increased ALT (20.3%), and increased aspartate aminotransferase (AST) (19.9%) were observed. In addition, lymphopenia, neutrophilia, thrombocytopenia, leukocytosis, increased AST, increased creatinine, increased LDH, increased D-dimer, prolonged thrombin time, and increased PCT were significantly different between recovered patients and those who died of COVID-19 (all $p<0.05$).

As shown in Table 2, compared with the patients aged <65 years, patients aged ≥65 years had higher odds of COVID-19 mortality (OR=2.15, 95% CI=1.35, 3.43). Male patients had higher odds of COVID-19 mortality than female patients (OR=1.97, 95% CI=1.29, 2.99). Patients with history of diabetes (OR=2.34, 95% CI=1.45, 3.76), lymphopenia (OR=1.59, 95% CI=1.03, 2.46), and increased PCT (OR=3.62, 95% CI=2.24, 5.84) also had higher odds of COVID-19 mortality.

Owing to the 324 missing PCT results and 117 missing LY results on admission, 1,140 and 1,347 patients were included in the analyses of PCT and LY with COVID-19 mortality, respectively. The association of PCT levels with the risk of COVID-19 mortality is shown in Appendix Table 1 (available online). Compared with individuals in the lowest T, the ORs of COVID-19 mortality were 2.27 (95% CI=1.11, 4.66) and 6.90 (95% CI=3.49, 13.65) for T2 and T3 of PCT concentrations after adjustment for age and sex ($p<0.0001$ for trend). Additional adjustment for history of hypertension and diabetes obtained similar results (T2 vs T1: OR=2.31, 95% CI=1.12, 4.77; T3 vs T1: OR=6.30, 95% CI=3.16, 12.56; $p<0.001$ for trend) (Appendix Table 1, available online). Further adjustment for lymphopenia, increased ALT, increased LDH, and increased D-dimer did not substantially change the association. A 1-SD (SD=0.6 ng/mL) increase in PCT concentration was associated with a 3.91-fold increased risk of COVID-19 mortality after adjustment for potential confounders (OR=3.91, 95% CI=2.22, 6.91). Furthermore, spline regression analysis indicated that the association

between PCT concentrations and COVID-19 mortality was nonlinear (p=0.0004 for nonlinearity) (Appendix Figure 2, available online).

The association of LY levels with the risk of COVID-19 mortality is presented in Appendix Table 1 (available online). Compared with individuals in the highest T, the ORs of COVID-19 mortality were 1.75 (95% CI=1.15, 2.67) and 1.35 (95% CI=0.87, 2.10) for T1 and T2 of LY concentrations, respectively, after adjustment for age and sex (p=0.009 for trend). Additional adjustment for history of hypertension and diabetes obtained similar results (T1 vs T3: OR=1.65, 95% CI=1.08, 2.53; T2 vs T3: OR=1.29, 95% CI=0.83, 2.02; p=0.02 for trend) (Appendix Table 1, available online). After further adjustment for increased AST, increased creatinine, increased D-dimer, and increased PCT, LY T1 had a marginally higher risk of COVID-19 mortality than T3 (OR=1.64, 95% CI=0.95, 2.84; p=0.08 for trend) (Appendix Table 1, available online). A 1-SD (SD=0.52 × 10^9/L) decrease in LY concentration was associated with a 31% increased risk of COVID-19 mortality after adjustment for potential confounders (OR=1.31, 95% CI=1.03, 1.67) (Appendix Table 1, available online).

The categorical variable model for COVID-19 mortality prediction is shown in Table 3. Age (<65 years, ≥65 years), sex (female, male), history of diabetes (*yes*/*no*), and increased PCT (<0.05 ng/mL, ≥0.05 ng/mL) were significantly associated with COVID-19 mortality, and lymphopenia (<1.1 × 10^9/L, ≥1.1 × 10^9/L) had a marginal association with COVID-19 mortality. To more fully inform clinical utilization, the authors developed a novel scoring system for COVID-19 mortality risk (Table 4). The optimal cut off point for COVID-19 mortality risk was 3, and the area under the receiver operating curve of the COVID-19 mortality risk score was 0.765 (95% CI=0.725, 0.805) (Appendix Figure 3, available online).

Table 3. Multivariate Prediction of COVID-19 Mortality According to Categorical Variables

Variable	OR (95% CI)	*p*-value	COVID-19 mortality risk score
Age, years			
<65	ref	—	0
≥65	2.11 (1.39, 3.21)	**0.0004**	2
Sex			
Female	ref	—	0
Male	2.02 (1.37, 2.99)	**0.0004**	2
History of diabetes			
Without	ref	—	0
With	2.52 (1.62, 3.94)	**<0.0001**	3
Lymphopenia, × 10^9/L			
≥1.1	ref	—	0
<1.1	1.45 (0.98, 2.15)	0.06	1
Increased PCT, ng/mL			
<0.05	ref	—	0
≥0.05	3.13 (2.02, 4.84)	**<0.0001**	3

Note: Boldface indicates statistical significance (p<0.05).
COVID-19, coronavirus disease 2019; L, liter; mL, milliliter; PCT, procalcitonin.

Table 4. Developed COVID-19 Mortality Risk Scores for Prediction

Total risk score	Sensitivity, %	Specificity, %	COVID-19 mortality risk
0	98.1	13.6	16.1
1	97.2	21.5	17.3
2	86.8	39.5	19.5
3	82.1	53.0	22.8
4	64.2	61.4	22.0
5	48.6	74.3	24.3
6	37.7	85.9	31.2
7	31.1	90.0	34.5
8	18.4	95.7	42.0
9	13.7	97.3	46.2
10	10.4	98.3	50.9
11	0.0	100.0	—

Note: The total risk score was the sum of the scores of each variable (age, sex, history of diabetes, lymphopenia, and increased PCT). Cut off value=3.
COVID-19, coronavirus disease 2019; PCT, procalcitonin.

DISCUSSION

In this study of hospitalized patients with COVID-19 in Wuhan, China, conducted between mid-January to late March 2020, the authors found that patients who were male, were elderly (>65 years), and had a history of diabetes, lymphopenia, and increased PCT tended to have higher odds of mortality. After further adjustment for potential confounders, significant independent associations were observed between older age, male sex, history of diabetes, lymphopenia, and increased PCT and a higher risk of COVID-19 mortality.

The age (median=64.0 years, IQR=51.0–71.0 years) of the overall population in this study was higher than that of individuals in other studies, which might be related to the fact that more serious patients were admitted to Tongji Hospital. Consistent with a previous study,[13] this study found that increased age was positively correlated with the risk of COVID-19 mortality. Previous studies reported that older age was an independent predictor of mortality in SARS and Middle East respiratory syndrome.[19,20] A macaque model found that older

macaques tended to have stronger host innate responses to SARS-CoV infection than younger macaque.[21] In addition, with increased age, T-cell and B-cell functions become potentially more defective with the overproduction of type 2 cytokines, which might be implicated in the poor clinical prognosis with COVID-19 infection.[13,22] These findings might help explain the relationship between older age and COVID-19 mortality, as was observed in this and other studies.

Compared with female patients, male patients had higher odds of COVID-19 mortality after adjustment for potential risk factors, which was inconsistent with the findings from another study based on 191 patients from 2 different hospitals.[13] This might be due to, in part, the difference in the size of the study sample and the different sociodemographic composition of the study populations. However, other studies have also found that male patients tended to have a higher risk of COVID-19 mortality,[12,23] consistent with this study. Moreover, previous studies have reported that more men than women were affected by SARS and Middle East respiratory syndrome infection.[19,24] Compared with men, women may tend to have healthier lifestyles and behaviors combined with sex differences in immune response, which might explain the potential mechanism behind this observed sex difference.[25]

The findings from this study indicated that patients with a history of diabetes had higher odds of COVID-19 mortality after adjustment for potential risk factors. Previous studies found that the presence of diabetes increased morbidity and mortality in patients with COVID-19, which was consistent with these findings.[12,26] In addition, a previous study found that plasma glucose levels and diabetes were independent predictors for mortality and morbidity in patients with SARS.[27] Patients with diabetes tended to have a higher affinity for cellular binding and efficient virus entry, decreased viral clearance, diminished T-cell function, and increased susceptibility to hyperinflammation and cytokine storm syndrome, which could all be contributing factors to greater susceptibility to COVID-19 among patients with diabetes and their generally poorer prognosis.[28]

No studies have yet investigated whether PCT is an independent risk factor for COVID-19 mortality. This study showed that PCT concentrations were positively correlated with COVID-19 mortality after adjustment for potential risk factors. Although the inflammatory mediator PCT is an established marker of bacterial infection and antibiotic stewardship,[29,30] PCT has been reported to be associated with clinical prognosis in myocardial infarction, cancer, sepsis, and ventilator-associated pneumonia.[15,16,31] In addition, previous studies have found that a high PCT concentration was an independent prognostic biomarker of mortality risk in both healthy populations and patients who were critically ill.[15,16,32] In sepsis, PCT promotes inflammation and immunosuppression and can play a dual role as a biomarker of diagnosis and prognosis as well as a disease mediator.[33] In vitro, Liappis et al.[34] also observed that clinically relevant doses of PCT induced the secretion of the proinflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8. Patients with COVID-19, especially severe cases, have significantly increased serum levels of inflammatory cytokines (such as IL-6, IL-1β, IL-2, IL-8, IL-17, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, IP10, MCP1, MIP1α, and TNF-α), which could lead to disease progression and death.[35] Therefore, PCT-increased COVID-19 mortality might be implicated in the induction of proinflammatory cytokines, although the exact mechanism behind this requires further investigation.

Previous studies have shown that deceased patients with COVID-19 tended to have lower LY, which is consistent with the findings of this study.[12,13] However, Zhou et al.[13] did not find a significant association between lymphopenia and COVID-19 mortality after adjustment for potential risk factors. The different sample size of the study population and their sociodemographic composition again might explain some of these observed differences. This study revealed that patients with lymphopenia had a higher risk of COVID-19 mortality, whereas a previous study found that the percentage of lymphocytes in the blood was negatively correlated with the severity and prognosis of COVID-19.[36] SARS-CoV-2 might contribute to the destruction of lymphatic organs, cause lymphocytic dysfunction, induce apoptosis or necrosis of lymphocytes, and suppress lymphocytes through disordered metabolic molecules, which might work collectively to result in lymphopenia.[36] Further studies are needed to clarify the underlying mechanism.

The strengths of this study include the relatively large sample size and the ability to investigate the associations between potential risk factors and COVID-19 mortality with moderate statistical power. This study is the first that the authors are aware to report that male sex, increased PCT levels, and lymphopenia are independent risk factors for COVID-19 mortality. In addition, a novel scoring system was established to predict mortality risk in patients with COVID-19 in this study.

Limitations

Nonetheless, some limitations should be considered. First, this study was performed in a single medical center; thus, the findings may not be representative of the

general population. Second, the authors have not yet collected information on treatments in this study. The mechanism between risk factors and COVID-19 mortality still requires further study.

CONCLUSIONS

This study of hospitalized patients with COVID-19 in Wuhan, China, found that many patients had at least 1 comorbidity, with hypertension, diabetes, and CHD as the most common pre-existing conditions. Older age, male sex, history of diabetes, lymphopenia, and increased PCT on admission had significant associations with COVID-19 mortality. These independent risk factors can assist clinicians in identifying patients who are likely to have a poorer prognosis at an early stage in the clinical course of the disease. In addition, the COVID-19 mortality risk score model developed in this study is intended to help clinicians reduce the COVID-19–related mortality by implementing better strategies for more effective use of limited medical resources.

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CY and QL contributed equally to this work. CY, XF, and WL were co-corresponding authors. CY, QL, XF, and WL designed the study, interpreted data, and wrote the first draft of the paper. CY, QL, WL, and XW took responsibility for the accuracy of the data analysis. CY, QL, WL, and WL performed data collection and designed the study's analytic strategy. All authors have read and approved the final manuscript.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2020.05.002.

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