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Electrocardiogram abnormalities and higher body mass index as clinically applicable factors for predicting poor outcome in patients with coronavirus disease 2019

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Abstract

Background: Patients with coronavirus disease 2019 (COVID-19) have high resource utilization. Identifying the causes of severe COVID-19 is helpful for early intervention to reduce the consumption of medical resources. **Methods:** We included 103 patients with COVID-19 in this single-center observational study. To evaluate the incidence, predictors, and effects of COVID-19, we analyzed demographic information, laboratory results, comorbidities, and vital signs as factors for association with severe COVID-19. **Results:** The incidence of severe COVID-19 was 16.5% and the percent poor outcome (including mortality, entering in ICU or transferred to a superior hospital) was 6.8%. The majority of severe COVID-19 patients had abnormal electrocardiogram (ECG) (82.35%), hypertension (76.47%) and other cardiac diseases (58.82%). Multivariate logistic regression was used to determine the predictors of severe illness. Abnormal body mass index (BMI) and ECG ($P < 0.05$) were independent predictors of severe COVID-19. ECG abnormality was associated with increased odds of poor outcome (area under the receiver operating characteristic curves [AUC], 0.793; $P = 0.010$) and severe COVID-19 (AUC, 0.807; $P < 0.0001$). Overweight was also associated with increased odds of poor outcome (AUC, 0.728; $P = 0.045$) and severe illness COVID-19 (AUC, 0.816; $P < 0.0001$). **Conclusion:** Overweight and electrophysiological disorders on admission are important predictors of prognosis of patients with COVID-19.

Keywords

electrocardiogram abnormalities, overweight, coronavirus disease 2019

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1 Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in December 2019 as a respiratory infection with epidemic potentials[1]. The clinical spectrum of COVID-19 is wide, ranging from mild to life threatening. To date over 127.3 million confirmed cases of COVID-19 have been reported to World Health Organization (WHO), including 2.78 million deaths[2].

The typical presentation of COVID-19 involves fever and cough, but some cases of COVID-19 may progress to acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock[3-4]. Early reports showed COVID-19 is more common in the elderly, men (*vs.* women), and patients with diabetes mellitus, hypertension, cardiovascular diseases, and malignancy[5]. A large cohort study of over 433 000 COVID-19 patients found that obesity was associated with hospitalization[6]. Another cohort study of COVID-19 patients showed those with diabetes had an increased risk of hospital admission and critical illness[7]. Increased leukocytes, neutrophils and neutrophil-to-lymphocyte ratio (NLR), N terminal pro B type natriuretic peptide (NT-proBNP), D-dimer and other laboratory biomarkers have been identified to be risk factors for worse outcomes[8-10]. Many studies have reported various contributing factors to the disease severity. Early identification of risk factors for COVID-19 severity is helpful for clinicians in identifying patients who require appropriate supportive care to prevent disease progression and adverse outcome.

We report here our analyses of 103 patients admitted for COVID-19 in an infectious diseases specialized hospital in Harbin, China, on the association of major risk factors with clinical characteristics and outcomes of COVID-19 patients.

2 Methods

2.1 Study population

Patients with COVID-19 were admitted to Harbin Infectious Disease Hospital, which was assigned for the treatment of confirmed COVID-19 infection in Harbin, China. All participants were enrolled once they had been confirmed with COVID-19 according to the new coronavirus pneumonia diagnosis and treatment plan (trial version 4) developed by the National Health Committee of the People's Republic of China (http://www.nhc.gov.cn/) from January 15, 2020 to March 22, 2020, and their outcomes were evaluated till April 7, 2020. Only patients aged ≥ 18 years with no missing data were included for the evaluation of predictors of outcomes. Epidemiological and clinical features, laboratory tests, and outcomes (to be specified below) were obtained from medical records. Items of data referred to WHO case record form with modifications. Ethical approval for the study was granted by the Ethics Commission of Harbin Infectious Disease Hospital (2020 No.20). Written informed consent for the study was obtained from all participants.

2.2 Patient Status

Patients were stratified according to the severity of the disease. The clinical classifications were as follows: (1) non-severe ill patients: mild, with fever, respiratory tract symptoms, and imaging shows pneumonia, (2) severe ill patients: meeting any of the following: a) respiratory distress, respiratory rate ≥ 30 beats/min, b) in the resting state, mean oxygen saturation ≤ 93%, c) arterial blood oxygen partial pressure/oxygen concentration ≤ 39.997 kPa, d) respiratory failure occurs and requires mechanical ventilation, e) shock occurs. The data on age, sex, body-mass index, comorbidities, and laboratory test results of patients on admission were extracted. The total number of comorbidities were evaluated including hypertension, diabetes mellitus, cardiovascular diseases, respiratory diseases and others (nervous system diseases, arthrolithiasis, hepatitis B, renal failure, and rheumatoid). Electrocardiogram (ECG) abnormalities included sinus tachycardia, ST elevation or depression, premature atrial contraction, T-wave inversion, and P pulmonale.

2.3 Outcomes

Outcomes included poor outcome and medical costs. The poor outcome included mortality and admission to ICU or transferred to a superior hospital. Medical costs were evaluated both as a continuous variable and as a categorical variable, evaluating the proportion of patients with a medical cost higher than the median among the total study population.

2.4 Statistical analysis

All statistical analyses were performed using SPSS version 13.0 (IBM Inc., Chicago, USA). Continuous variables of baseline patient and hospital characteristics, treatment variables, and complications were compared using Student's *t* test and discrete variables by the Fisher Exact Test. Predictors of severe COVID-19 were determined by performing univariate logistic regression on each demographic variable using survey statistics; those with a *P* value of < 0.01 in univariate analyses were included in the multiple variable logistic regression model using forward prediction. Area under the receiver operating characteristic curves (AUC) was used to assess the discriminatory capacity of each logistic regression model. Thereafter, hierarchical multivariate logistic regression models were constructed with all defined predictor variables to evaluate outcomes. A *P* value of < 0.05 was considered statistically significant.

3 Results

3.1 Demographics of study population

A total of 103 patients with confirmed COVID-19 were included in the study population. The demographics of patients and clinical characteristics were compared by severity of COVID-19 as detailed in Table 1. The average age of study patients was 50.4 ± 15.87 years with 50 (48.5%) males and 53 (51.5%) females. Many parameters were altered by COVID-19, including patients' age, weight, BMI and laboratory test results on admission. The average body mass index (BMI) of the study patients was 24.6 ± 3.68, including 5 patients with BMI > 30. In all cases, 45.6% (47/103) of the cohort patients had other comorbidities, including hypertension (33.0%), cardiovascular diseases (21.4%), diabetes mellitus (11.7%), respiratory diseases (1.9%), nervous system diseases (1.9%), and others (8.7%). On admission, several laboratory investigations were performed. Creatine kinase and Creatine kinase MB form were 151.15 U/L and 15.59 U/L, respectively. Moreover, the incidence of severe COVID-19 was 16.5%. The percentage of poor outcome was 6.8% (the mortality was 2.9%, and the percent ICU admission or transfer to a superior hospital was 6.8%).

3.2 Increased cardiac damage in severe patients

The factors related to cardiovascular conditions were compared between non-severe and severe COVID-19 patients (Table 2). The majority of severe COVID-19 patients had abnormal ECG (82.35%) or hypertension (76.47%), and other cardiac diseases (58.82%). The mean BMI of the severe patients was higher than that of non-severe patients (28.36 *vs.* 23.86, *P* < 0.0001). The average levels of aspartate

Table 1 The demographics and clinical characteristics of 103 patients with COVID-19

Demography and clinical characteristic	Value
Age, years	50.40 ± 15.87
Sex, *n* (%)	
Male	50 (48.5)
Female	53 (51.5)
Body mass index, kg/m^2	24.6 ± 3.68
Comorbidities[a] (*n* = 47), *n* (%)	
Hypertension	34 (33.0)
Diabetes mellitus	12 (11.7)
Cardiovascular diseases	22 (21.4)
Nervous system diseases	2 (1.9)
Respiratory diseases	2 (1.9)
Others	9 (8.7)
ECG abnormalities, *n* (%)	32 (31.1)
Symptoms on admission, *n* (%)	
Fever	81 (77.88)
Cough	63 (60.58)
Myalgias	42 (40.38)
Diarrhea	17 (16.34)
Upper airway congestion	44 (42.31)
Presentation values	
White blood cell count, ×10^9/L	5.38 ± 2.90
Lymphocyte count, ×10^9/L	1.29 ± 0.57
Lymphocyte percentage, %	25.76 ± 10.91
Alanine aminotransferase, U/L	35.74 ± 87.88
Aspartate aminotransferase, U/L	39.57 ± 124.10
Blood urea nitrogen, mmol/L	4.13 ± 3.71
Creatinine, μmol/L	69.42 ± 128.75
Cystatin C, mg/L	1.03 ± 0.97
Creatine Kinase, U/L	151.15 ± 435.97
Creatine Kinase MB Form, U/L	15.59 ± 21.65
C-reactive protein, mg/L	16.99 ± 19.75
Treatment, *n* (%)	
Single antiviral agent	58 (56.3)
Combined antiviral agents	23 (22.3)
Developing Severe COVID-19, *n* (%)	17 (16.5)
Poor outcome, *n* (%)[b]	7 (6.8)
Total medical costs, Chinese yuan	14671.88

[a], More than one comorbidity was reported for some patients; [b], Mortality, ICU admission or transfer to a superior hospital; ECG, electrocardiogram; COVID-19, coronavirus disease 2019.

Table 2 Comparisons of risk factors of cardiovascular disease in patients with severe and non-severe COVID-19

Item	Non-severe (*n* = 89)	Severe (*n* = 14)	*P* value
Median body mass index, kg/m^{2*}	23.86 ± 2.96	28.36 ± 4.68	< 0.0001
Comorbidities, *n* (%)			
Hypertension	21 (24.42)	13 (76.47)	< 0.0001
Diabetes mellitus	7 (8.14)	5 (29.41)	0.013
Cardiovascular diseases	12 (13.95)	10 (58.82)	< 0.0001
ECG, *n* (%)			< 0.0001
Normal	68 (79.07)	3 (17.65)	
Abnormal	18 (20.93)	14 (82.35)	
Myocardial enzymes[*]			
Aspartate aminotransferase, U/L	26.47 ± 9.51	105.94 ± 303.48	0.296
Creatine Kinase, U/L	95.44 ± 72.31	432.94 ± 1040.61	0.200
Creatine Kinase MB Form, U/L	12.47 ± 4.90	31.41 ± 50.41	0.141

[*], values are mean ± SD; COVID-19, coronavirus disease 2019; ECG, electrocardiogram.

aminotransferase (105.94 U/L) and creatine kinase (432.94 U/L) in severe patients were higher than in non-severe patients.

3.3 Association of obesity and ECG abnormalities with severe patients

To identify the risk factors for severe COVID-19, univariate logistic regression was used to analyze the impact of age, sex, BMI, comorbidities, and abnormal ECG at admission on the mortality of severe COVID-19 (Table 3). Variables that were significant in univariate models were then included in the multiple variable logistic regression analysis of severe COVID-19 (Table 4). The AUC of severe COVID-19 patients was 0.85. The mean BMI with an odds ratio (OR) of 2.972 and a 95% confidence interval (CI) of 1.037-8.519 (*P* = 0.043) and ECG abnormalities (*OR*, 52.695; 95% *CI*, 1.709-1624.474; *P* = 0.023) were associated with COVID-19.

3.4 Association of obesity and ECG abnormalities with poor outcomes

The outcomes were compared based on BMI and ECG results (Fig. 1). Abnormal ECG was associated with increased odds of poor outcome (AUC, 0.793; *P* = 0.010) and severe COVID-19 (AUC, 0.807; *P* < 0.0001). Overweight was also associated with increased odds of poor outcome (AUC, 0.728; *P* = 0.045) and severe COVID-19 (AUC, 0.816; *P* < 0.0001). Both BMI and ECG results were not found to be associated with medical costs more than 14 671.88 Chinese yuan. Survival curve (Fig. 2) showed that 2 of the 3 deaths recordedin our study cohort occurred in patients whose BMI was over 24.6 kg/m^2. All 3 deaths had abnormal ECG at

Table 3 Univariate logistic regression evaluating potential predictors of severe COVID-19

Variable	*OR*	95% *CI*	*P* Value
Age, years	1.050	1.012-1.090	0.009
Sex			
Male	Ref.	—	—
Female	0.931	0.328-2.640	0.893
Median body mass index, kg/m^2	1.445	1.178-1.772	0.0004
Comorbidities			
Hypertension	10.060	2.958-34.206	0.0002
Diabetes mellitus	4.702	1.284-17.227	0.019
Cardiovascular diseases	8.810	2.811-27.610	0.0002
Nervous system diseases	—	—	—
Respiratory diseases	—	—	—
Others	1.505	0.285-7.958	0.631
ECG abnormalities	17.630	4.566-68.062	<0.0001
Laboratory test results on admission			
White blood cell count, ×10^9/L	1.353	1.055-1.734	0.017
Lymphocyte count, ×10^9/L	0.084	0.018-0.399	0.002
Lymphocyte percentage, %	0.882	0.823-0.945	0.0004
Alanine aminotransferase, U/L	1.005	0.996-1.013	0.264
Aspartate aminotransferase, U/L	1.033	0.994-1.073	0.096
Blood urea nitrogen, mmol/L	1.492	1.043-2.136	0.029
Creatinine, μmol/L	1.018	0.995-1.043	0.129
Creatine kinase, U/L	1.005	1.000-1.010	0.073
Creatine kinase MB Form, U/L	1.114	1.005-1.236	0.041
C-reactive protein, mg/L	1.060	1.027-1.094	0.0003
Treatment			
Single antiviral agent	Ref.	—	—
Combined antiviral agents	2.423	0.512-11.477	0.265

ECG, electrocardiogram; OR, odds ratio; CI, confidence interval.

admission. The median time of death was 8 (range 1-14) days.

4 Discussion

Some reports showed older age, overweight and co-morbid conditions including hypertension, obesity and diabetes were associated with incidence and severity of COVID-19[11-13]. Therefore, identifying risk factors of severe COVID-19 is imperative. The present study uncovered that 16.5% developed severe COVID-19 and the percentage of poor outcome was 6.8% (2.9% mortality rate of and 6.8% ICU admission or transfer to a superior hospital). ECG abnormalities and overweight were identified as predictors of severe COVID-19. Multivariate analysis revealed that the presence of abnormal ECG on admission and overweight/obesity are the two significant predicting factors of outcome. The percent poor outcomes increased with abnormal ECG. These findings have important implications in making clinical decisions on COVID-19 patients and in better understanding of the pathophysiology of this disease as well.

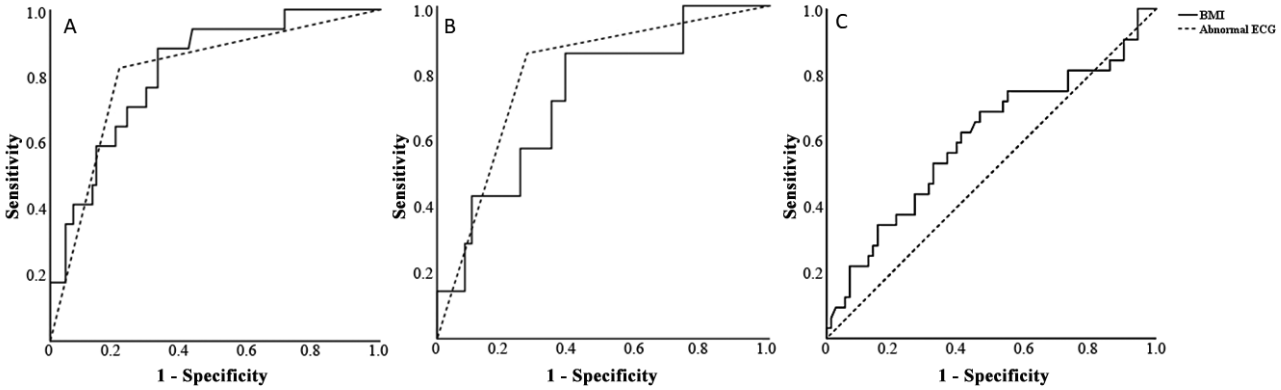
Table 4 Multivariate logistic regression evaluating potential predictors of developing severe COVID-19

Variable	*OR*	95% *CI*	*P* Value
Age, years	1.110	0.969-1.273	0.133
Median body mass index, kg/m^2	2.972	1.037-8.519	0.043
Comorbidities			
Hypertension	5.137	0.119-222.528	0.395
Cardiovascular disease	1.347	0.009-211.636	0.908
ECG abnormalities	52.695	1.709-1624.474	0.023
Laboratory test results on admission			
Lymphocyte count, ×10^9/L	3.685	0.032-418.741	0.589
Lymphocyte percentage, %	0.674	0.435-1.046	0.079
C-reactive protein, mg/L	1.040	0.957-1.131	0.358

ECG, electrocardiogram; OR, odds ratio; CI, confidence interval.

Early identification of those "at risk" of poor outcome is an essential part of the clinical assessment of human diseases. Li et al found that hypertension was an independent risk factor for severe COVID-19[14]. In our study, the baseline characteristics of patients with non-severe and severe COVID-19 were comparatively analyzed in 103 patients. The independent risk factors of severe illness were determined by univariate and multivariate logistic regressions. Hypertension was found being associated with severe COVID-19 by univariate logistic regression in our study, but it was not included in the multivariate logistic regression. ECG abnormalities and overweight were identified as important risk factors for severe COVID-19, which is in line with a recent report by Gao and colleagues[15]. Impaired chest-wall elastance and reduced respiratory system compliance leading to damaged lung function contribute to increased risk of severe COVID-19 in obese patients.

An early study showed myocardial injury is significantly associated with fatal outcome of COVID-19; in addition, it is associated with cardiac dysfunction and arrhythmias[16]. A study concluded that the level of cardiac troponin I was significantly higher in COVID-19 patients admitted to ICU, suggesting that myocardial injury is associated with COVID-19 severity and mortality[17]. In our study, neither creatine kinase nor creatine kinase MB form was associated with developing severe illness in COVID-19 patients. However, ECG abnormalities was associated with the outcome. This is similar to the observation in patients with sepsis, whose heart rate variability in ECG was considered the best indicator for septic shock[18] or mortality[19].



	95% *CI*	*P* Value	AUC
BMI	0.716-0.917	<0.0001*	0.816
ECG	0.691-0.924	<0.0001*	0.807

	95% *CI*	*P* Value	AUC
BMI	0.547-0.909	0.045*	0.728
ECG	0.010-0.631	0.010*	0.793

	95% *CI*	*P* Value	AUC
BMI	0.479-0.727	0.095	0.603
ECG	0.380-0.622	0.983	0.501

Fig. 1 AUCs for severe ill COVID-19 (A), poor outcome (B) and medical costs > 14 671.88 Chinese yuan (C) for ECG abnormalities and body-mass index
AUC, area under the receiver operating characteristic curves; BMI, body mass index; COVID-19, coronavirus disease 2019; ECG, electrocardiogram.

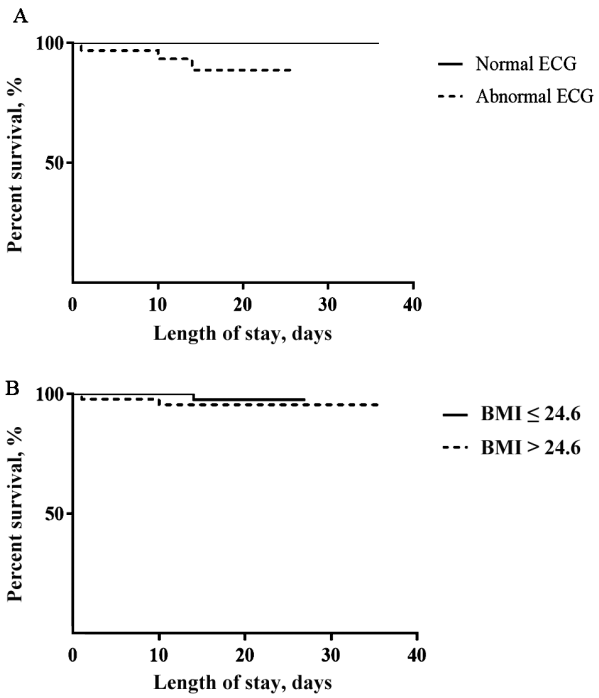


Fig. 2 Survival curves of ECG abnormalities (A) and body-mass index (B)
BMI, body-mass index; ECG, electrocardiogram.

Another research showed NLR is an independent risk factor for mortality in hospitalized patients with COVID-19[20], among multiple predictors such as age, sex, symptoms, and blood laboratory findings. BMI was excluded as a risk factor in in this study and ECG was not included in the analysis. However, other published studies identified BMI as a predictor of microbiological persistence in patients with mycobacterium avium complex lung disease[21]. The virus persistence in respiratory might imply a lymphoid hypertrophy and a stimulatory effect for inflammation[22]. Virus persistence may have a pathogenetic potential for development of lymphoid hypertrophy and a chronic stimulatory effect for inflammation.

In this study, we quantified the total direct economic burden of COVID-19 related hospitalizations. Because of the highly spreading nature of the disease, all COVID-19 patents were hospitalized. The mean cost per patient was 14 671.88 Chinese yuan and higher in severe patients. By comparison, the medical costs per COVID-19 patient in Harbin is lower than in the Netherlands (mean cost per patient of 6 100-8 300 euro)[23].

There are limitations in our study. We collected data from only one single center and the sample size is small. In addition, the laboratory test of cardiac function, including troponin I and brain natriuretic peptide, were not available in the medical records. Third, the medical cost data were obtained from only one city, which may not be applicable to other cities or to the whole country.

5 Conclusion

Overweight and electrophysiological disturbances on admission are important predictors of critical COVID-19. COVID-19 patients with electrophysiological disturbances and overweight/obesity have higher mortality rate and are more likely to be admitted to ICU or to be transferred to a superior hospital. These findings might be of important clinical value in the management of COVID-19 patients to mitigate the development of COVID-19 cases into critical stage.

Authors' contributions

Cai B and Li J generated the idea for and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Sun Z and Hou Y contributed to writing of the report and the statistical analysis. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Ethical approval and consent to participate

This clinical study was approved by the Ethics Commission of Harbin Infectious Disease Hospital (2020 No.20). Written informed consent for the study was obtained from all participants.

Conflicts of interests

All authors declare no competing interests.

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