Host susceptibility to severe COVID-19: a retrospective analysis of 487 case outside Wuhan

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Research

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Abstract

Background: The recent outbreak of SARS-CoV-2 infection results in a considerable morbidity and mortality, mainly in China. The study is to investigate the intrinstic features of infected patients that associated with severe type of this disease.

Method: A total of 487 laboratory-confirmed COVID-19 patients were included in analysis. The demographic and epidemiological of patients representing as mild and severe at admission were compared. A step-wise multivariate logistic regression analysis were performed to identify significant risk factors associated with severe COVID-19 . A score systemc incorporating risk factors was established for risk stratification and validated in a small cohort during in-hospital follow-up.

Results: Of all patients, 49 (10.1%) cases are severe at admission. Severe cases are elder [56(17) vs. 45(19), P<0.001), with more male (73.5% vs. 50.9%, P=0.003). They have a higher incidence of hypertension (53.1% vs. 16.7%, P<0.001), diabetes (14.3% vs. 5.0%, P=0.009), cardiovascular diseases (8.2% vs. 1.6%, P=0.003) and malignancy (4.1% vs. 0.7%, P=0.025), and less exposure to epidemic area (49.0% vs. 65.1%, P=0.027), but more infected familiy members(P=0.031). On multivariate analysis, elder age, male and presence of hypertension are independently associated with severe disease at admission. A host risk score, incorporating age, sex and hypertension history, clearly stratifies risk of developing severe type of COVID-19 both in patients at admission and during in-hospital follow-up.

Conclusions: Elder age, male and presence of hypertension are associated with host susceptibility to developing severe COVID-19. The host risk score may be a useful tool to identify high risk indiviuals but requires validation.

Introduction

Coronaviruses are positive- sense RNA viruses that typically affect the respiratory tract, but also the gut of mammals and humans[1]. Coronavirus infections in humans generally result in mild symptoms[1], except two zoonotic coronavirus, severe acute respiratory syndrome coronavirus [SARS-CoV][2, 3] and Middle East respiratory syndrome coronavirus [MERS-CoV])[4] that crossed species to infect human populations and cause a high mortality in the past two decades. On Dec, 2019, another zoonotic coronavirus, formally named SARS-CoV-2, has been identified in Wuhan, China, in individuals exposed to the Huanan (Southern China) Seafood Wholesale Market and has been demonstrated to be responsible for the recent outbreak of pneumonia originating from Wuhan[5]. This virus, of probable bat origin[6, 7], may be transmitted to humans via intermediate hosts, as SARS-CoV and MERS-CoV do[8], and spread rapidly among human populations by person-to-person transmission[9–11] with an estimated reproductive number of more than 2[9, 12]. Up to Feb 11, 2020, it is reported that over 70,000 persons has been infected with SARS-CoV-2 in China[13]. Notably, some cases were clinical diagnosed without evidence of nucluei acid test.

Patients with coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 infection represents a specturm of clinical presentations[14–17]. Some patients are asympomatic, or only manifest as upper

respiratory tract or gastrointestinal symptoms without pulmonary involvement. However, like outbreaks caused by SARS-CoV and MERS-CoV, SARS-CoV-2 causes pneumonia that can be severe and characterized by fever, cough, dyspnea, bilateral pulmonary infiltrates and acute respiratory injury. It is estimated that approximately 20% of patients developing severe respiratory illness, with the overall mortality around 2.3%[13].

Given the substantial rate of severe cases, it is critical to identify individuals who confer intrinstic susceptibility to become severe or even critically illed upon infected, especially when there is no definite drug directly targeting at SARS-CoV-2 that has been proven to be clinically effective. These patients should be paid particular attention to prevent infection, or under close monitoring when infection is suspected. Also, this population may benefit most from early anti-viral treatment if an effective drug is established. Currently, there is scarce literature on this topic. In the study, we explored potential host risk factors associated with severe cases at admission in a retrospective cohort of 487 patients with community-acquired COVID-19 and attempt to establish a score systemc to identify high risk individuals.

Patients And Methods

Patients

487 cases with COVID-19, who were referred from January 16, 2020 to Feb 17, 2020 in the designated hospitals in Zhejiang Province, were retrospectively included in the study. All the patients were laboratory-confirmed by nuclei acid test of SARS-CoV-2. The study was conducted according to the principles of the Declaration of Helsinki. The ethics committee of First Affiliated Hospital of Zhejiang University reviewed and approved this study. Written consent was obtained from each patient or his/her authorized representatives following a full explanation of the study.

Diagnostic procedures

The sputum, nasopharyngeal or oropharyngeal swab specimen were collected from suspected patients in the designated hospitals and tested for SARS-CoV-2 by a real-time RT-PCR appraoch as previously defined[5] in hospital laboratories or local centres for disease control and prevention. Other common respiratory viruses including influenza virus, respiratory syncytial virus, parainfluenza virus and adenovirus were also tested for differential diagnosis. SARS-CoV and MERS-CoV were not detected because infection cases of the two virus had never been reported in Zhejiang Province. In addition, a pulmonary CT scan, as well as whole blood count and biochemical test, were generally performed as an initial evaluation, which would not be delayed awaiting for the result of nucleu acid test. Meanwhile, a pursue for epidemiological history, including recent exposure to epidemic area and suspected/confirmed patients, was also performed.

Data collection and follow-up

Two researchers independently reviewed medical records, laboratory findings, and pulmonary CT scan of each patient with COVID-19, provided by the local health authority. Demographic (age, sex, occupation and smoking history), epidemiological (recent exposure and family cluster) and clinical data (comorbidities, symptoms, laboratory and CT findings, and management) were inputed into a pre-specified, electronic data collection form. All data were checked by another two researcher ().Clinical outcomes were followed up to Feb 17, 2020. Occurrence of death and severe cases are primary endpoint events.

Definition

Severe COVID-19 is diagnosed when one of the following criteria was met: (1) respiratory rate>30 times/min; (2) transcutaneous oxygen saturation<93%; or (3) hypoxaemia defined as arterial oxygen tension (PaO_2) over inspiratory oxygen fraction (FIO_2) of less than 300 mm Hg. Acute respiratory distress syndrome (ARDS).

Statistical analysis

Continuous variables were represented as the mean ± standard deviation (SD) or the median (interquartile range) and compared via the Mann-Whitney u test. Nominal variables were expressed as a number (percent) and compared by a Chi-square test. Host risk factors associated with severe COVID-19 were explored by a multivariate logistic regression using a backward-forward approach. The entry and removal probability for stepwise was set as 0.5 and 0.10 respectively. A host risk score was calculated by the sum of point of each risk factor that was dichotomized. An optimal cut-off point for dichotomizing continuous variables was determined by the Youden index that indicates a best perfomance of discriminating severe patients from those mild. A linear-by-linear association test was performed to evaluate the step-wise incidence changes of severe cases when patients were categorized based on the host risk score. Statistical differences were considered significant if a two-sided P-value was less than 0.05. All the Statistical analysis was performed with SPSS 20.0 (SPSS Inc; Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc; San Diego, CA, USA).

Results

Comparisons of demographic and epidemiological data of severe and non-severe COVID-19 patients

A total of 487 COVID-19 patients were included for analysis, with 49 (10.1%) cases were severe at admission. As shown in Table 1, severe cases were elder [56(17) vs. 45(19), P<0.001) and of higher male proportion (73.5% vs. 50.9%, P=0.003). 36.7% of severe patients were agricultural workers, followed by self-employed (32.7%) and retired persons (24.5%), a different constitution from mild cases. No significant difference in smoking history was found between the two groups. As to comorbidities, severe cases have a higher incidence of hypertension (53.1% vs. 16.7%, P<0.001), diabetes (14.3% vs. 5.0%, P=0.009), cardiovascular diseases (8.2% vs. 1.6%, P=0.003) and malignancy (4.1% vs. 0.7%, P=0.025). Regarding to epidemiological history, severe patients had less exposure to epidemic area (49.0% vs.

65.1%, P=0.027) and likely confirmed cases (26.5% vs. 39.5%, P=0.077), but more high-dense familiy clusters (P=0.031).

Risk factors associated with severe COVID-19 at admission

Next, we explored among demographic and epidemiological factors to identify risk factors associated with severe COVID-19 presenting at admission to hospital, by a multivariate logistic regression. Given that the time from onset of symptoms to admission is a notable confounder, an analysis adjusting this variable was performed as well. As shown in Table.2, on multivariate analysis, host factors including elder age, male and presence of hypertension, were statistically significant risk factors of development of severe diseases, irrespective of adjustment of time to admission. A n exposure history to patients, was found to be significant, if the model is unadjusted by time to admission.

The correlation between host risk score and incidence of severe COVID-19

Finally, as shown in Table.3, we defined a host risk score on the basis of the three risk factors, to assess the intrinstic host susceptibility to develop severe cases of COVID-19. Age was dichotomized by the cut-off point of 50 which is determined by Youden index of AuROC. As shown in Figure.1A, a step-wise increase in the incidence of severe COVID-19 at admission was observed with the increment of the host risk score (P<0.001). The performance of the score was also validated in 66 patients who presented mild at admission and were under follow-up during hospital stay. 15 patients progressed to severe COVID-19 within a median follow-up time of 15 days. No death was reported by the end ot follow-up . A similar trend to the above was confirmed when analyzing the correlationg between host risk score and occurrence of severe COVID-19 (P=0.014) (see Figure.1B).

Discussion

For the first time, we found that hypertension as a host risk factor, along with other two known factors elder age and male sex, are associated with severe COVID-19. And we constructed a host risk score to reflect the intrinstic susceptiblity to develop severe type of this disease, which may provide guidance on tailor of preventive and therapeutic measures .

A major finding that hypertension as a host risk factor for severe COVID-19 may underscore the involvement of renin-angiotensin system (RAS) in the pathogenesis of this disease. The RAS is important in maintaining lood pressure homeostasis, as well as fluid and salt balance[18]. To activate the renin-angiotensin system, ACE cleaves angiotensin I to generate angiotensin II, which acts on Ang II type 1 and type 2 receptors (AT1R and AT2R) and resuls in a variety of biological effects including vasoconstriction, salt and water reabsorption, oxidative stress and inflammation, whereas ACE2 conferts Ang I into Ang 1–9 and Ang II into Ang 1–7, which serves as a physiological mechanism counteracting RAS activation[18]. It has been speculated that, angiotensin-converting enzyme 2 (ACE2), previously known as the receptor

for SARS-Cov [19, 20] and NL63[21], is also the receptor for SARS-CoV-2 infection in human beings[22, 23]. And ACE2, as well as other components of RAS, have also been implicated in the development of severe acute lung injury. Mice studies have shown that ACE, angiotensin II and AT1a, induce lung edemas and thereby promote disease progression[24]. In contrast, ACE2 has been shown to prevent from severe acute lung injury[24]. It thereby implies that an unbalance between ACE and ACE2 expression in lung may predispose the host to severe acute lung injury. Given that such disburtance of RAS may be present in patients with hypertension, it may explain their increased susceptibility to develop severe type of COVID-19. Actually, it has been reported that ACE2 expression at both mRNA and protein level were significantly reduced in hypertensive rat strains[25]. ACE2 or other RAS components therefore may represent potential therapeutic targets in control of COVID-19 severity, although further investigations using human samples are apparently required.

To assess host susceptiblity to disease severity is of important clinical relevance. First, individuals with high risk should be identified to take appropriate prevention measures and a priority of pre-exposure vaccination and/or post-exposure antiviral prophylaxis should be given to these persons if an effective vaccine or antiviral drug is developed. Second, individuals with high risk should be informed to seek for medical institutions if any suspected symptom. Third, close monitoring is required to detect early progression, for high risk population with confirmed COVID-19. Finally, as it has been shown that influenza patients of high risk for complication benefit from early antiviral treatment[26], it would be prudent to enroll sufficient COVID-19 patients at high risk of progression in clinical trials evaluating the efficacy of antiviral therapies, not only for the scientific purposes but also as a compassionate treatment[27]. In this regard, our study provides a useful tool to assess host risk to develop severe disease, although it needs be validated.

The present study suffers from several limitations. First, there is no information on the specific time point at which patients develop severe cases before admission and thereby a logistic regression analysis was performed. Nevertheless, it may be alternative to use the time to admission instead and the risk factors remained to be significant when adjusted by the time variable. In addition, considering that patients un-severe at admission may progress during hospitalization, the host risk score was also validated in 66 patients with in-hospital follow-up, albeit the size is not limited. Second, a markedly reduced mortality of Wuhan-outside patients compared to those in Wuhan[16] may indicate a viral evolution towards host adapation. Therefore, whether the host risk score applies to Wuhan patients is not clear.

In summary, by identifying host risk factors assciated with severe COVID-19, this study shed light on the underlying mechanisms of disease progression and provides a useful tool to identify high risk individuals, which is helpful for designing specific strategies for prevention and treatment of this disease. But further studies, particlularly those enrolling Wuhan patients, are needed to validate the findings.

Conclusions

This study identifis elder age, male sex and presence of hypertension are associated with host susceptibility to developing severe COVID-19. A host risk score was also establishd, which is helpful to reflect the intrinstic susceptiblity to develop severe type of this disease but requires further validation.

Declarations

Ethics approval and consent to participate

The ethics committee of First Affiliated Hospital of Zhejiang University reviewed and approved this study. Written consent was obtained from each patient or his/her authorized representatives following a full explanation of the study.

Consent for publication: Not applicable.

Availability of data and materials

The datasets and materials used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J.S and Y.S conceptualized the idea and design the study. Y.S and X.Y draft the manuscript and J.S revised it. X.Y, H.Z, H.W, R.Z, Q.C, S.S, H.F, Y.W, Z.H, X.L, H.T and S.T participated int data collection, analysis and interpretation. All authors read and approved the final manuscript.

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Tables

Table.1 Demographic, epidermological characteristics and underlying comorbidities of patients with confirmed 2019-ncov infection

Variables	Total (N=487)	Mild (N=438)	Severe (N=49)	*P* value
Age (years)	46(19)	45(19)	56(17)	<0.001
Sex				
Male	259(53.2%)	223(50.9%)	36(73.5%)	
Female	228(46.8%)	215(49.1%)	13(26.5%)	0.003
Occupation				
Agricultural worker	140(28.7%)	122(27.9%)	18(36.7%)	
Self-employed	219(45.0%)	203(46.3%)	16(32.7%)	
Employee	82(16.8%)	79(18.0%)	3(6.1%)	
Retired	38(7.8%)	26(5.9%)	12(24.5%)	
Students	8(1.6%)	8(1.8%)	0(0%)	<0.001
Smoking history				
Yes	40(8.2%)	34(7.8%)	6(12.2%)	
No	434(89.1%)	391(89.3%)	43(87.8%)	
Unknown	13(2.7%)	13(2.7%)	0(0%)	0.331
Comorbidities				
Hypertension	99(20.3%)	73(16.7%)	26(53.1%)	<0.001
Diabetes	29(6.0%)	22(5.0%)	7(14.3%)	0.009
Cardiovascular disease	11(2.3%)	7(1.6%)	4(8.2%)	0.003
Malignancy	5(1%)	3(0.7%)	2(4.1%)	0.025
Chronic liver diseases	22(4.5%)	20(4.6%)	2 (4.1%)	0.877
Chronic renal diseases	7(1.4%)	5(1.1%)	2(4.1%)	0.101
Others	32(6.6%)	27(6.1%)	5(10.2%)	0.279
Exposure to confirmed cases	186(38.2%)	173(39.5%)	13(26.5%)	0.077
Family cluster				
0	392(80.5%)	352(80.4%)	40(81.6%)	
1	67(13.8%)	63(14.4%)	4 (8.2%)	
2	12(2.5%)	12(2.7%)	0 (0%)	
>=3	16(3.3%)	11(2.5%)	5(10.2%)	0.031
Recent travel or residence to/in epidemic area	309(63.4%)	285(65.1%)	24(49.0%)	0.027
Time from onset of symptom to admission	2(3)	2(3)	3(5)	0.10

Data are expressed as mean ± standard deviation (SD), median (interquartile range) or number (percent). Comparisons between mild and severe cases were performed by the Mann-Whitney u test or a Chi-square test.

Table.2 Factors associated with severe COVID-19 at admission

Variables	Unadjusted by time to admission			Adjusted by time to admission		
	OR	95%CI	P value	OR	95%CI	P value
Age	1.06	1.03-1.08	<0.001	1.06	1.03-1.09	<0.001
Male	3.68	1.75-7.75	0.001	3.60	1.69-7.63	0.001
Presence of hypertension	2.71	1.32-5.59	0.007	2.73	1.32-5.65	0.007
Piror exposure to confirmed patients	0.39	0.16-0.89	0.026	----	----	----

Statistical analysis was performed using a step-wise multivariable logistic regression model. Either adjusted by time to admission or not, variables entering multivariate analysis were age, sex, occupation, smoking history, any comorbidity, exposure history, family cluster and epidemic area travel or residence history. Only variables remaining in the final step with statistical significance ($P<0.05$) were represented.

Table.3 Definition of host risk factor score

Variables	Scores
Age	
≥50 (years)	1
<50 (years)	0
Sex	
Male	1
Female	0
Hypertension	
Presence	1
Absence	0

Figures

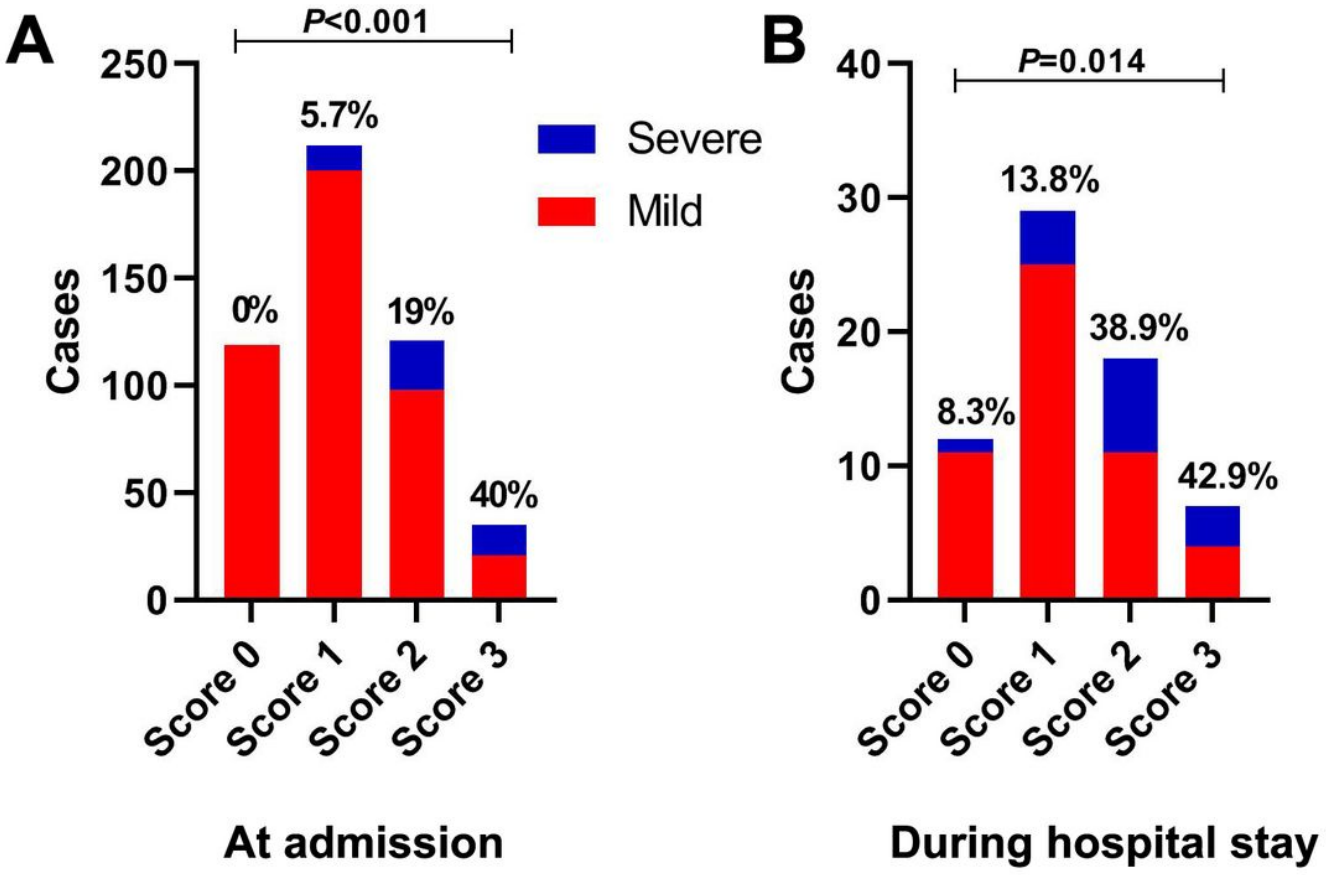

Figure 1

Incidences of severe cases by host risk score. The incidences of severe cases at admission (A) or developing during hospitalizaiton (B) was compared across the different score groups by a linear-by-

linear association test.