Early predictors and screening tool developing for severe patients with COVID-19

Le Fang
Zhejiang Provincial Center for Disease Control and Prevention

Huashan Xie
Jingmen Center for Disease Control and Prevention

Lingyun Liu
Jingmen Center for Disease Control and Prevention

Shijun Lu
Dongyang Center for Disease Control and Prevention

Fangfang Lv
Sir Run Run Shaw hospital, School of medicine, Zhejiang University

Jiancang Zhou
Sir Run Run Shaw hospital, School of medicine, Zhejiang University

Yue Xu
Zhejiang Provincial Center for Disease Control and Prevention

Huiqing Ge
Sir Run Run Shaw hospital, School of medicine, Zhejiang University

Min Yu (✉ minyucdc@163.com)
Zhejiang Provincial Center for Disease Control and Prevention

Limin Liu
Sir Run Run Shaw hospital, School of medicine, Zhejiang University

Research Article

Keywords: coronavirus disease 2019, predictor, screening, severe patient

DOI: https://doi.org/10.21203/rs.3.rs-38399/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

Coronavirus disease 2019 (COVID-19) is a declared global pandemic, causing a lot of death. How to quickly screen risk population for severe patients is essential for decreasing the mortality.

Methods

This retrospective study included all the 813 confirmed cases diagnosed with COVID-19 before March 2\textsuperscript{nd}, 2020 in a city of Hubei Province in China. Data of the COVID-19 patients including clinical and epidemiological features were collected through Chinese Disease Control and Prevention Information System. Predictors were selected by logistic regression, and then categorized to four different level risk factor. A screening tool for severe patient with COVID-19 was developed and tested by ROC curve.

Results

Seven early predictors for severe patients with COVID-19 were selected, including chronic kidney disease ($OR=14.7$), age above 60 ($OR=5.6$), lymphocyte count less than $<0.8 \times 10^9$ per L ($OR=2.5$), Neutrophile to Lymphocyte Ratio larger than 4.7 ($OR=2.2$), high fever with temperature $\geq 38.5^\circ C$ ($OR=2.2$), male ($OR=2.2$), cardiovascular related diseases ($OR=2.0$). The Area Under the Curve of the screening tool developed by above seven predictors was 0.798 (95\%CI: 0.747~0.849), and its best cut-off value is $>4.5$, with sensitivity 72.0\% and specificity 75.3\%.

Conclusions

This newly developed screening tool can be a good choice for early prediction and alert for severe case especially in the condition of overload health service.

Background

An unknown pneumonia emerged in Wuhan city, the capital of Hubei province in China, in December, 2019. A novel coronavirus was isolated by Chinese scientists from these patients with above unknown pneumonia in January, 2020, and this pneumonia was later designated coronavirus disease 2019 (COVID–19) in February, 2020, by World Health Organization (WHO)\textsuperscript{1–3}. COVID–19 spread quickly in China and later became an international public health event. On March 11\textsuperscript{th}, WHO declared COVID–19 as a pandemic. As of April 5\textsuperscript{th}, there were more than 1.1 million cases with COVID–19 worldwide and 62784 of them died. The fatality rates of COVID–19 varied a lot in different countries: Italy 12.33\%, France 11.14\%, The United Kingdom 10.29\%, China 4.03\%, United States 2.56\%, Japan 2.14\%, Australia 0.60\%.\textsuperscript{4} There were many reasons for these fatality differences, including prevention strategy, health resource, proportion of elder population and others. However, one of the key measure to decrease the fatality rate is to strengthen early screening for severe patient with COVID–19 and timely medical treatment. Although
there were several studies had demonstrate several predictors for severe patient with COVID–19, such as higher Sequential Organ Failure Assessment (SOFA), d-dimer greater than 1µ/mL, decrease of CD8+ T cells, involvement of multiple lung lobes and pleural effusion, some of the data of these predictors might not available for all hospitals or all patients because of inadequate health facilities and professionals especially during a pandemic \(^5\textsuperscript{-7}\). What's more, some of these predictor were not early enough to prevent patients from becoming worse. It is very necessary to find early simple predictors for quick risk assessment to screen more potential severe patients with COVID–19 and give them timely treatment to decrease the number of severe patients and death \(^1\textsuperscript{,8\textsuperscript{-11}}\).

**Methods**

**Participants**

This retrospective study included all the confirmed cases diagnosed with COVID–19 before March 2\(^{\text{nd}}\), 2020 in Jingmen city, a city of Hubei Province in China, which was 220 kilometers far away from Wuhan city. Totally 813 cases were enrolled, excluding clinical diagnostic cases. The confirmed cases were divided into three groups including common cases, severe cases and fatal cases for characteristic comparison.

**Data collection**

Data of patients with COVID–19 were collected through Chinese Disease Control and Prevention Information System which was the official disease reporting system for COVID–19 in China. All the data collection for COVID–19 control and prevention by local Center for Disease Control and Prevention and hospitals was legal, and all the patients with COVID–19 had the obligation to cooperate with epidemiological survey according to ‘Law of the People's Republic of China on prevention and control of infectious diseases’. Each case had two parts of disease information, one was the disease report card which included demographic information, hospital visit, disease onset time, diagnose time, death time and clinical category of patient with COVID–19, and another one was epidemiological survey questionnaire which was consisted of exposure history, risk factors, symptoms, routine blood test and laboratory test results. The disease report card was fulfilled by doctors in hospitals, and epidemiological survey was conducted and inputted by health professionals in local county level Center for Disease and Prevention. All the disease information was examined and verified step by step from county level then by city level and finally by provincial level Center for Disease and Prevention. Following disease information including laboratory test, disease progress, clinical category and clinical severity should be updated timely according to ‘Chinese COVID–19 surveillance programme’ in ‘Chinese prevention and control guideline for COVID–19’\(^1\textsuperscript{11}\), and the last time of updating was March 1\(^{\text{st}}\), 2020.

**Definitions**
All the definitions about COVID–19 were according to the Chinese management guideline for COVID–19.

Confirmed case was defined as a suspected case with laboratory test COVID–19 positive from respiratory specimen by the Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay.

Suspected case was a case with at least one epidemiological exposure and at least two clinical signs, or a case with no explicit epidemiological exposure but at least three clinical signs as followings. 1. Epidemiological exposure during 14 days before disease onset: (1) travel to or living in Wuhan city or places around in Hubei province or other places with COVID–19 case, (2) exposure to people infected with COVID–19, (3) exposure to people with fever or respiratory symptoms from Wuhan city or places around in Hubei province or other places with COVID–19 case, (4) coming from family, work place and school where occurred more than two COVID–19 cases. 2. Clinical signs: (1) having fever or respiratory symptoms, (2) radiographic evidence of COVID–19 pneumonia, (3) subnormal or normal white-cell count or subnormal lymphocyte count during early stage of disease onset.

For the confirmed case, it could be classified into four different clinical categories. 1. Mild type: with mild clinical symptoms or signs, without radiographic evidence of pneumonia. 2. Common type: having fever, respiratory and other symptoms, and with radiographic evidence of pneumonia. 3. Severe type: at least having one of following signs: (1) dyspnea, respiration frequency $\geq 30/ \text{min}$, (2) finger oxygen saturation in resting condition $\leq 93\%$, (3) partial Pressure of arterial oxygen ($\text{PaO}_2$) to Fraction of inspired oxygen ($\text{FiO}_2$) ratio $\leq 300 \text{mmHg}$, (4) radiographic evidence of lung infiltrates more than 50% within 24 to 48 hours. 4. Critical type: at least having one of following conditions: (1) respiratory failure and in need of mechanical ventilation, (2) shock, (3) complication of other organ failure and in need of Intensive Care Unit (ICU) treatment. In this study, common case included cases of mild and common types, severe case included severe and critical types, and fatal case referred to all the dead cases of above four types.

**Statistical analysis**

The continuous variables were expressed as median ($1^{\text{st}}$ quartile, $3^{\text{rd}}$ quartile) and were compared by Kruskal-Wallis test. And the categorical variables were presented as percentage and analyzed by Chi-square test. Logistic regression was used for multi-factors analysis. All the predictors selected by the logistic regression were categorized to five different level risk factor according to their Odds Ratio (OR) values: (1) Not discernible: $0.9 \leq \text{OR} < 1.1$, (2) weak: $1.1 \leq \text{OR} < 1.50$, (3) moderate:$1.50 \leq \text{OR} < 3.0$, (4) strong:$3.0 \leq \text{OR} < 7.0$, (5) very strong: $\text{OR} \geq 7.0$. For the not discernible, weak, middle, strong and very strong level risk factors, they were weighted as 0, 1, 2, 3 and 4 respectively, and then a screening tool for severe patient with COVID–19 was developed by these predictors and tested by Receiver Operating Characteristic (ROC) curve. All statistical analysis was performed with SPSS software version 18.0, and $P$ value less than 0.05 was considered statistically significant.
Results

There were 37 fatal cases, 123 severe cases and 653 common cases in this study. Among these three different groups of COVID–19 patients, the age, gender and comorbidity were different ($P<0.05$). The median ages of fatal cases, severe cases and common cases were 61.0, 57.0 and 47.0 years old. The percentage of male in severe case group was 63.4%, higher than fatal case group (54.1%) and common case group (49.0%). Only 5.4% of fatal cases had no comorbidity, while the proportions of patient without comorbidity among severe cases and common cases was 59.1%, 77.8% respectively. The proportions of patients with two and three comorbidities in fatal cases was 21.6%, 8.1%, higher than the same proportion among severe case and common case groups. The exposures to Wuhan patients, diagnosed patients and symptomatic patients in the past 14 days, days from illness onset to visit hospital, days from visit hospital to be defined and the proportion of cluster case showed no statistical differences among above three groups of patient with COVID–19 (Table 1).

Except chronic lung disease and liver disease, the proportions of underlying comorbidities such as hypertension, diabetes, cardiovascular disease, chronic kidney disease and other diseases were significantly different among COVID–19 patients with different severity ($P<0.05$). In the fatal cases, 59.5% cases were with hypertension, 21.6% with diabetes, 21.6% with cardiovascular diseases and 16.2% with chronic kidney disease, higher than the same prevalence rates of the same comorbidity among severe cases and common cases (Table 2).

There were more than 18 symptoms among COVID–19 patients (Table 3). The most prevalent symptoms in common cases were fever (81.2%), cough (36.3%), sputum (23%) and fatigue (18.5%), and these symptoms were also very common in severe and fatal cases. Besides above symptoms, headache (16.7%), vomiting (13.9%), nausea (11.1%) and myalgia (13.9%) were another frequently reported symptoms in fatal cases. By comparison, the proportions of higher fever (temperature $\geq$38.5°C), vomiting, nausea were significantly different among fatal cases, severe cases and common cases ($P<0.05$).

White blood count showed no significant difference among fatal, severe and common cases, and 55.7% to 69.2% patients had normal level white blood cell count. However, lymphocyte count, lymphocyte constituent ratio, neutrophile granulocyte constituent ratio, Neutrophile to Lymphocyte Ratios (NLR) and the proportion of NLR > 4.7 were different among above three groups of COVID–19 patients ($P<0.05$). There were 78.3% of fatal cases and 68.4% of severe cases with subnormal lymphocyte count, while only 46.1% patients had subnormal (or significant decreased) lymphocyte count in common cases. The lymphocyte constituent ratios of fatal, severe and common cases were 18.7%, 21.3% and 26.0%, while neutrophile granulocyte constituent ratios of these three groups of COVID–19 patients were 75.4%, 67.3% and 62.1% respectively. The Neutrophile to Lymphocyte Ratios (NLR) in fatal and severe case groups were 4.2 and 3.1, larger than the NLR (2.4) in common case group. The proportions of NLR > 4.7 among fatal, severe and common cases were 44.4%, 34.7% and 15.0% (Table 4).
The variables showed statistical significance in the table 1–4, such as age group (age above or below 60), gender (male proportion), chronic kidney disease, cardiovascular related diseases, other diseases, higher fever, vomiting, nausea, lymphocyte count group, Neutrophile to Lymphocyte Ratio group were included in the following logistical regression analysis. It showed that chronic kidney disease and age above 60 were very important indicators for severe patients with COVID–19, and their OR values were 14.7 and 5.6 respectively. Other risk factors such as lymphocyte count less than <0.8 × 10^9 per L (OR = 2.5), NLR larger than 4.7 (OR = 2.2), high fever with temperature ≥ 38.5°C (OR = 2.2), male (OR = 2.2), cardiovascular related diseases (OR = 2.0) were also good predictors for severe patients (Table 5).

According to the OR values of above predictors, all the selected predictors were categorized into different level risk factor (Table 6): (1) very strong risk factor: chronic kidney disease, weighted as 4, (2) strong risk factor: age above 60, weighted as 3; (3) moderate risk factors: male, with at least one cardiovascular related disease, high fever (temperature ≥ 38.5°C), lymphocyte count < 0.8 × 10^9 per L, NLR > 4.7, all weighted as 2. The total risk of a COVID–19 patient for becoming severe was the total score of these seven predictors by this screening tool. The Area Under the Curve (AUC) was 0.798 (95% Confidence Internal (CI): 0.747~0.849), and its best cut-off value is >4.5, with sensitivity 72.0% and specificity 75.3%.

Discussions

COVID–19 is a rapidly progressive disease. Wang's study showed that the median time from disease onset to dyspnea, hospital admission and Acute Respiratory Distress Syndrome (ARDS) was 5, 7, and 8 days, respectively. Zhou et al found that the non-survivor of COVID–19 usually developed more complications by day 15, and died by day 19. So it is crucial to screen risk population for severe patient with COVID–19 as early as possible. During a pandemic or in an inadequate health resource condition, it is unfeasible to do lots of expensive or time-cost laboratory tests and physical examination for all patients. It is very important to find quick and low-cost screening tool to predict the possibility of becoming severe patient with COVID–19.

Most epidemiological data such as age, gender, underlying chronic diseases can be easily obtainable by inquiry, and health professionals should make full use of these data for risk evaluation and early warning for severe patient. Similar to most other previous reports, elder age (usually elder than 60 years old), male, underlying chronic diseases including cardiovascular disease, diabetes, kidney disease were more likely to suffer from a severe COVID–19 infection and death. What needs to stressed is that elder age is an independent risk factor for severe patient when considering the confounding effect of underlying chronic diseases. This information should be emphasized among those elder population without underlying medical condition who usually have overconfidence of their health and weak awareness of self-protection. In comparison to other studies, the difference of this research was that kidney disease demonstrated more risk than other chronic disease and the OR value reached 14.7. The mechanism of kidney disease involvement in patients with COVID–19 is likely to be multidimensional. First, the novel coronavirus may exert direct cytopathic effects on kidney tissue and worsen its organ
function. Second, deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-cell lymphocyte or antibody) may further damage the kidney. Third, virus-induced cytokines or mediators might exert indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis\textsuperscript{7,20,21}. Clinicians should increase their awareness of kidney disease treatment in hospitalized patients with COVID–19. Early detection and effective intervention of kidney involvement may help to reduce deaths of patients with COVID–19.

Symptoms (and signs) are another valuable health data which may be available for all patient. The most common onset symptoms of COVID–19 onset are fever, cough, sputum, fatigue, headache, vomiting, nausea, et al, and most of them are not specific\textsuperscript{3,8,19,22,23}. However, high fiver was proved to be good predictors for severe case. This finding is extremely important for guide the public to self-judge whether he/she needs to go to hospital for treatment. In addition, routine blood test is quite prevalent in all level hospitals even in developing countries, and it is another good choice for quick risk evaluation. Along with most other studies, this research showed that lymphocyte count less than \(<0.8 \times 10^9\) per L, NLR larger than 4.7 were early predictors for severe patient with COVID–19. The decrease of lymphocyte which finally leads to immune disorder is due to the sustained responses of cytokines and chemokines (namely cytokine storm) caused by novel coronavirus\textsuperscript{24–26}. The NLR was an important supplement for lymphocyte count, reflecting the inflammation of the patient which indicated the possibility of bacteria infection\textsuperscript{9,27}.

Different countries have difference health resource. Even in the developed countries with enough health resource reserve, they may also confront the shortage of health resource and fail to response to COVID–19 pandemic\textsuperscript{9}. By early screening, more current mild patients at risk of becoming severe can be arranged together for early intervention, and it also helps to make full use of health facilities and professionals. Early intervention including antibiotics, glucocorticoid and supportive respiratory treatment can decrease the number of severe patients and death, and also reduce the time of hospitalization of patients and increase the hospitalization capacity of hospitals. What’s more, risk assessment can help mild patient treat their illness properly and release from anxiety and worry. The screening tool developed by this study only needs seven predictors which can be easily obtained from quick epidemiological inquiry and routine blood test, and it is very cost-effective..

The strengths of this study were: (1) the predictors were easily accessed and the screening could be broadly used. (2) the representative of COVID–19 in this study was good. It included all the patients with COVID–19 in the whole city while most other studies only recruited COVID–19 cases based on hospitals. The limitations were just as followings: laboratory tests were limited and not dynamic, so the predictors may not be comprehensive. The predictors for severe case and death were not stratified for multifactor analyses due to the small amount of death, and the differences between sever case and death were not further explored.

Conclusions
The screening tool developed by seven indicators including chronic kidney disease, age, lymphocyte count, Neutrophile to Lymphocyte Ratio, high fever, male and cardiovascular related diseases, can used for early predicting severe patients with COVID–19. All the information for prediction can be easily obtained from quick epidemiological inquiry and routine blood test. It can help screen more potential risk patient by limited health resource and offer timely treatment to save more patients. It is very cost-effective and deserve widely application in the condition of overload health service.

**Abbreviations**

COVID–19: Coronavirus disease 2019; WHO: World Health Organization; SOFA: Sequential Organ Failure Assessment; RT-PCR: Real-Time Reverse Transcription Polymerase Chain Reaction; PaO2: Pressure of arterial oxygen; FiO2: Fraction of inspired oxygen; ICU: Intensive Care Unit; OR: Odds Ratio; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve; CI: Confidence Interval; NLR: Neutrophile to Lymphocyte Ratios; ARDS: Acute Respiratory Distress Syndrome

**Declarations**

**Ethics approval and consent to participate**

The study was approved by Ethics Committee of Zhejiang Provincial Center for Disease Control and Prevention (No.2020–009). Informed consent was obtained from each participant.

**Consent for publication**

No applicable.

**Availability of data and material**

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

**Competing interests**

All authors declare no competing interests.

**Funding**

This study was supported by Zhejiang Provincial Medical Science Project (NO. 2020388945). The funder had no further role in the design of the study and collection, analysis, and interpretation of data, or in
writing the manuscript.

**Authors’ contributions**

LF contributed to data analysis and paper writing. LYL collected the data and analyzed the data. HX and MY designed the study and took responsibility for the whole research work. SL collected and check the data. FL, JZ, YX, HG and LML contributed to the data collection and interpretation. All authors read and approved the final manuscript.

**Acknowledgements**

We thank all the professional staff in Jingmen city in Hubei province for their investigation, lab test, prevention and control work of COVID–19. We thank Ms. Xi Yang from Taizhou Central Hospital for her guidance in the data analysis and interpretation.

**References**

1. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. *JAMA* 2020.

2. Alexander E. Gorbalenya SCB, Ralph S. Baric, Raoul J. de Groot, Christian Drosten, Anastasia A. Gulyaeva, Bart L. Haagmans, Chris Lauber, Andrey M Leontovich, Benjamin W. Neuman, Dmitry Penzar, Stanley Perlman, Leo L. M. Poon, Dmitry Samborskiy, Igor A. Sidorov, Isabel Sola, John Ziebuhr. Severe acute respiratory syndrome-related coronavirus: The species and its viruses—a statement of the Coronavirus Study Group. *bioRxiv* 2020.

3. Siordia JA, Jr. Epidemiology and clinical features of COVID–19: A review of current literature. *J Clin Virol* 2020;127:104357.

4. World Health Orgnization. Coronavirus disease 2019 (COVID–19) situation report–76. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200405-sitrep–76-covid–19.pdf?sfvrsn = 6ecf0977_4.

5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID–19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–1062.

6. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, Xiong W, Yang D, Chen R, Lu F, Lu Y, Liu X, Chen Y, Li X, Li Y, Summah HD, Lin H, Yan J, Zhou M, Lu H, Qu J. COVID–19 with Different Severity: A Multi-center Study of Clinical Features. *Am J Respir Crit Care Med* 2020.
7. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, Song S, Ma Z, Mo P, Zhang Y. Characteristics of peripheral lymphocyte subset alteration in COVID–19 pneumonia. *J Infect Dis* 2020.

8. Kakodkar P, Kaka N, Baig MN. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID–19). *Cureus* 2020;12(4):e7560.

9. Ivers LC, Walton DA. Novel Coronavirus Disease (COVID–19): Global Health Equity in Pandemic Response. *Am J Trop Med Hyg* 2020.

10. Sahu KK, Mishra AK, Lal A. COVID–2019: update on epidemiology, disease spread and management. *Monaldi Arch Chest Dis* 2020;90(1).

11. National Health Commission of the People's Republic of China. Chinese prevention and control guideline for COVID–19 (version 6.0). [http://www.nhc.gov.cn/jkj/s3577/202003/4856d5b0458141fa9f376853224d41d7.shtml](http://www.nhc.gov.cn/jkj/s3577/202003/4856d5b0458141fa9f376853224d41d7.shtml) (accessed April 6, 2020; in Chinese).

12. National Health Commission of the People's Republic of China. Chinese management guideline for COVID–19 (version 6.0). [http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8ae0c2.shtml](http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8ae0c2.shtml) (accessed April 6, 2020; in Chinese).

13. Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, Hunter DJ. Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. *Cancer Causes Control* 2000;11(6):477–88.

14. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.

15. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A, Network C-LI. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV–2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020.

16. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID–19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.

17. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID–19) with a focus on congenital heart disease. *Int J Cardiol* 2020.

18. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID–19 in China. *Clin Res Cardiol* 2020.
19. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID–19) infection: a systematic review and meta-analysis. *Int J Infect Dis* 2020.

20. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. *Immunol Res* 2014;59(1–3):118–28.

21. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID–19. *Kidney Int* 2020.

22. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, Li GC, Liu HG. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020.

23. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, Chen H, Wang D, Liu N, Liu D, Chen G, Zhang Y, Li D, Li J, Lian H, Niu S, Zhang L, Zhang J. Characteristics of COVID–19 infection in Beijing. *J Infect* 2020;80(4):401–406.

24. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, Qu J. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. *Front Microbiol* 2019;10:2752.

25. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–513.

26. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Lye DC, Singapore Novel Coronavirus Outbreak Research T. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV–2 in Singapore. *JAMA* 2020.

27. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID–19. *J Infect* 2020.

Tables

**Table 1. Characteristic comparison among COVID-19 patients with different severity**
| Characteristic                                                                 | Fatal cases n=37 | Severe cases n=123 | Common cases n=653 | $c^2$ | $P$     |
|-------------------------------------------------------------------------------|------------------|--------------------|--------------------|------|--------|
| **Age**                                                                       | 61.0             | 57.0               | 47.0               | 78.7 | <0.001 |
|                                                                                | [55.0, 74.5]     | [47.0, 68.0]       | [35.0, 56.0]       |      |        |
| **Age groups**                                                                |                  |                    |                    | 74.8 | <0.001 |
| <45                                                                           | 2.7%             | 20.3%              | 44.0%              |      |        |
| 45-59                                                                         | 37.8%            | 34.1%              | 36.8%              |      |        |
| >60                                                                           | 59.5%            | 45.6%              | 19.2%              |      |        |
| **Male**                                                                      | 54.1%            | 63.4%              | 49.0%              | 8.7  | 0.013  |
| **Exposure in the past 14 days**                                              |                  |                    |                    |      |        |
| Have been to Wuhan or other places with patient                               | 60.0%            | 55.0%              | 51.2%              | 1.3  | 0.524  |
| Exposure to diagnosed patient                                                 | 30.6%            | 21.7%              | 30.4%              | 3.6  | 0.166  |
| Exposure to symptomatic patient                                               | 33.3%            | 24.8%              | 33.9%              | 3.5  | 0.177  |
| Days from illness onset to visit hospital                                     | 3.0              | 3.0                | 3.0                | 0.1  | 0.953  |
|                                                                                | [1.0, 4.0]       | [1.0, 5.0]         | [1.0, 5.8]         |      |        |
| Days from visit hospital to be defined                                        | 6.9              | 7.5                | 7.9                | 0.9  | 0.653  |
|                                                                                | [5.2, 9.4]       | [5.0, 9.9]         | [5.4, 10.9]        |      |        |
| Cluster case                                                                  | 24.1%            | 19.6%              | 28.5%              | 3.5  | 0.177  |
| **Comorbidity**                                                               |                  |                    |                    | 103.4| <0.001 |
| None                                                                          | 5.4%             | 59.1%              | 77.8%              |      |        |
| One disease                                                                   | 64.9%            | 26.1%              | 15.0%              |      |        |
| Two diseases                                                                  | 21.6%            | 13.0%              | 6.0%               |      |        |
| Three diseases and more                                                       | 8.1%             | 1.8%               | 1.2%               |      |        |
Table 2. Comorbidity comparison among COVID-19 patients with different severity

| Comorbidity                | Fatal cases n=37 | Severe cases n=123 | Common cases (n=653) | c²   | P    |
|----------------------------|------------------|---------------------|----------------------|------|------|
| Hypertension               | 59.5%            | 17.4%               | 12.6%                | 58.7 | <0.001|
| Diabetes                   | 21.6%            | 7.0%                | 3.9%                 | 22.8 | <0.001|
| Cardiovascular diseases    | 21.6%            | 5.2%                | 4.1%                 | 22.2 | <0.001|
| Chronic kidney disease     | 16.2%            | 7.0%                | 0.3%                 | 58.6 | <0.001|
| Chronic lung disease       | 2.7%             | 2.6%                | 2.0%                 | 0.3  | 0.874 |
| Chronic liver disease      | 0                | 1.7%                | 0.7%                 | 1.8  | 0.412 |
| Other diseases             | 13.5%            | 16.5%               | 7.0%                 | 12.0 | 0.002 |

Table 3. Symptom comparison among COVID-19 patients with different severity
| Symptoms                          | Fatal cases [n=37] | Severe cases [n=123] | Common cases (n=653) | c²   | P    |
|----------------------------------|--------------------|----------------------|---------------------|------|------|
| Fever (temperature >37.3°C)      | 94.4%              | 84.3%                | 81.2%               | 4.5  | 0.107|
| High Fever (temperature ≥38.5°C) | 47.1%              | 43.2%                | 31.4%               | 7.7  | 0.022|
| Cough                            | 30.6%              | 45.2%                | 36.3%               | 4.1  | 0.132|
| Sputum                           | 25.0%              | 18.3%                | 23.0%               | 1.4  | 0.492|
| Fatigue                          | 25.0%              | 20.9%                | 18.5%               | 1.2  | 0.548|
| Headache                         | 16.7%              | 9.6%                 | 8.0%                | 3.4  | 0.185|
| Vomiting                         | 13.9%              | 6.1%                 | 2.6%                | 14.5 | 0.001|
| Nausea                           | 11.1%              | 7.0%                 | 3.3%                | 7.8  | 0.020|
| Myalgia                          | 13.9%              | 13.9%                | 9.5%                | 2.6  | 0.278|
| Arthralgia                       | 8.3%               | 3.5%                 | 3.4%                | 2.4  | 0.313|
| Breathlessness                   | 8.3%               | 3.5%                 | 4.1%                | 1.7  | 0.427|
| Dyspnea                          | 5.6%               | 3.5%                 | 2.6%                | 1.2  | 0.543|
| Chest distress                   | 8.3%               | 5.2%                 | 9.2%                | 1.9  | 0.382|
| Chest pain                       | 0                  | 0.9%                 | 0.8%                | 0.3  | 0.859|
| Nasal obstruction                | 0                  | 0.9%                 | 3.8%                | 3.9  | 0.144|
| Runny nose                       | 2.8%               | 5.2%                 | 4.9%                | 0.4  | 0.830|
| Diarrhoea                        | 2.8%               | 9.6%                 | 7.7%                | 1.8  | 0.410|
| Stomach ache                     | 0                  | 0                    | 1.0%                | 1.5  | 0.474|
| Conjunctival congestion          | 0                  | 0                    | 0.2%                | 0.3  | 0.884|

Table 4. White blood cell comparison among COVID-19 patients with different severity
|                          | Fatal cases n=37 | Severe cases n=123 | Common cases n=653 | \( \chi^2 \) | \( P \) |
|--------------------------|------------------|-------------------|-------------------|----------|------|
| **White blood cell count,** \( \times 10^9 \) per L |                  |                   |                   |          |      |
| Subnormal (<4)           | 23.1%            | 36.1%             | 35.1%             | 8.0      | 0.094|
| Normal (4-10)            | 69.2%            | 55.7%             | 61.9%             |          |      |
| Above normal (>10)       | 7.7%             | 8.2%              | 3.1%              |          |      |
| **Lymphocyte count,** \( \times 10^9 \) per L |                  |                   |                   |          |      |
| Significant decreased (<0.8) | 43.5%           | 49.5%             | 21.1%             | 43.9     | <0.001|
| Subnormal (0.8-1.09)     | 34.8%            | 18.9%             | 25.0%             |          |      |
| Normal (1.1-3.2)         | 17.4%            | 28.4%             | 52.2%             |          |      |
| Above normal (>3.2)      | 4.3%             | 3.2%              | 1.7%              |          |      |
| **Lymphocyte constituent ratio (%)** |                  |                   |                   |          |      |
| Subnormal (<20%)         | 59.3%            | 46.4%             | 29.9%             | 19.8     | 0.001|
| Normal (20%-40%)         | 37.0%            | 49.5%             | 59.7%             |          |      |
| Above normal (>40%)      | 3.7%             | 4.1%              | 10.4%             |          |      |
| **Neutrophile granulocyte constituent ratio (%)** |                  |                   |                   |          |      |
| Subnormal (<20%)         | 3.7%             | 11.3%             | 6.8%              | 41.6     | <0.001|
|                               | 44.4% | 60.8% | 80.4% |
|-------------------------------|-------|-------|-------|
| **Normal** (40%-75%)          |       |       |       |
| **Above normal** (>75%)       | 51.9% | 27.8% | 12.8% |
| **Neutrophile-to-Lymphocyte Ratio (NLR)** | 4.2 (2.6, 7.4) | 3.1 (2.0, 6.2) | 2.4 (1.7, 3.8) |
| **Increased NLR (>4.7)**      | 44.4% | 34.7% | 15.0% |

Table 5. Early predictors for severe patients with COVID-19 a

|                              | B     | S.E.  | Walds   | P      | OR (95% CI)       |
|------------------------------|-------|-------|---------|--------|-------------------|
| **Age above 60**             | 1.714 | 0.297 | 33.348  | <0.001 | 5.6(3.1-9.9)      |
| **Gender (male)**            | 0.777 | 0.274 | 8.016   | 0.005  | 2.2(1.3,3.7)      |
| **Chronic kidney disease**   | 2.690 | 1.208 | 4.960   | 0.026  | 14.7(1.4,157.1)   |
| **Cardiovascular related diseases** b | 0.687 | 0.316 | 4.721   | 0.030  | 2.0(1.1,3.7)      |
| **High Fever** (temperature ≥38.5°C) | 0.792 | 0.281 | 7.931   | 0.005  | 2.2(1.3,3.8)      |
| **Significant decreased lymphocyte count (< 0.8 × 10^9 per L)** | 0.932 | 0.295 | 9.994   | 0.002  | 2.5(1.4,4.5)      |
| **Increased NLR (>4.7)**     | 0.776 | 0.310 | 6.256   | 0.012  | 2.2(1.3,3.8)      |

a Multifactor logistic regression conducted in this analysis. Due to the small sample size of fatal cases, severe patients with COVID-19 in this model included both severe cases and fatal cases. Common case was used as reference group.

b Cardiovascular related diseases included hypertension, diabetes and cardiovascular diseases in table 2.
Table 6. Screening tool for severe patients with COVID-19

| Predictor                                                                 | Score |
|---------------------------------------------------------------------------|-------|
|                                                                            | No    | Yes   |
| Age above 60                                                              | 0     | 3     |
| Male                                                                      | 0     | 2     |
| With chronic kidney disease                                              | 0     | 4     |
| With at least one cardiovascular related disease (hypertension, diabetes, stroke, heart disease) | 0     | 2     |
| High Fever (temperature $\geq 38.5^\circ C$)                             | 0     | 2     |
| Lymphocyte count $< 0.8 \times 10^9$ per L                                | 0     | 2     |
| Neutrophile-to-lymphocyte ratio $> 4.7$                                   | 0     | 2     |

Figures
Figure 1

The ROC curve for the screening tool for severe patients with COVID-19

Diagonal segments are produced by ties.