BMJ Open

# Fibrosis-4 Index as a Predictor for Mortality in Hospitalized Patients with COVID-19



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-041989 |
| Article Type: | Original research |
| Date Submitted by the Author: | 23-Jun-2020 |
| Complete List of Authors: | Park, Jung Gil; Yeungnam University School of Medicine and College of Medicine, Internal Medicine<br>Kang, Min Kyu; Yeungnam University School of Medicine and College of Medicine, Internal Medicine<br>Lee, Yu Rim; Kyungpook National University School of Medicine, Internal Medicine<br>Song, Jeong Eun; Catholic University of Daegu School of Medicine, Internal Medicine<br>Kim, Na Young; Keimyung University School of Medicine, Internal Medicine<br>Kweon, Young Oh; Kyungpook National University School of Medicine, Internal Medicine<br>Tak, Won Young; Kyungpook National University School of Medicine, Internal Medicine<br>Jang, Se Young; Kyungpook National University School of Medicine, Internal Medicine<br>Lee, Changhyeong; Catholic University of Daegu School of Medicine, Internal Medicine<br>Kim, Byung Seok; Catholic University of Daegu School of Medicine, Internal Medicine<br>Hwang, Jae Seok; Keimyung University School of Medicine, Internal Medicine<br>Jang, Byoung Kuk; Keimyung University School of Medicine, Internal Medicine<br>Bae, Jinmok; Keimyung University School of Medicine, Internal Medicine<br>Lee, Ji Yeon; Keimyung University School of Medicine, Internal Medicine<br>Suh, Jeong Ill; Dongguk University Gyeongju Hospital, Internal Medicine<br>Park, Soo Young; Kyungpook National University School of Medicine, Internal Medicine<br>Chung, Woo Jin; Keimyung University School of Medicine, Internal Medicine |
| Keywords: | Respiratory infections < THORACIC MEDICINE, VIROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, INTERNAL MEDICINE |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

**Title: Fibrosis-4 Index as a Predictor for Mortality in Hospitalized Patients with COVID-19**

**Short title: Fibrosis-4 Index in COVID-19**

Jung Gil Park[a*], Min Kyu Kang[a*], Yu Rim Lee[b], Jeong Eun Song[c], Na Young Kim[d], Young Oh Kweon[b], Won Young Tak[b], Se Young Jang[b], Changhyeong Lee[c], Byung Seok Kim[c], Jae Seok Hwang[d], Byoung Kuk Jang[d], Jinmok Bae[d], Ji Yeon, Lee[d], Jeong Ill Suh[e], Soo Young Park[†], Woo Jin Chung[d†], for the Daegu-Gyeongbuk Liver Study Group (DGLSG)

[a]Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, South Korea

[b]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea

[c]Department of Internal Medicine, School of Medicine, Daegu Catholic University, Daegu, South Korea

[d]Department of Internal Medicine, School of Medicine, Keimyung University, Daegu, South Korea

[e]Department of Internal Medicine, College of Medicine, Dongguk University, Dongguk University Gyeongju Hospital, Gyeongju, South Korea

[*]These authors contributed equally to this study

[†]These authors contributed equally as corresponding authors

**Correpondence**: Soo Young Park, Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, 130 Dongdeok-

ro, Jung-gu 41940, Daegu, South Korea, Email: psyoung0419@gmail.com

Woo Jin Chung, Department of Internal Medicine, School of Medicine, Keimyung University, 1035 Dalgubol-daero, Dalseo-gu, Daegu, South Korea, Email: chung50@dsmc.or.kr

## ABSTRACT

**Objective** Risk for mortality of Coronavirus 2019 (COVID-19) has not evaluated in well controlled cohort. The reliable risk factors for mortality in patients with severe infection of COVID-19 is required to be investigated.

**Methods** This retrospective multicenter cohort study was undertaken to identify risk factors for in-hospital mortality in COVID-19 confirmed patients aged >19 years in five tertiary hospitals of Daegu, South Korea. The clinical and laboratory features of patients with COVID-19 receiving respiratory support were analyzed to ascertain the risk factors for mortality.

**Results** Of the1005 patients with a confirmed diagnosis of COVID-19, 289 (28.8%) received respiratory support and of these, 70 patients (24.2%) died. In multivariate analysis, high fibrosis-4 index (HR 2.784; 95% CI 1.691–4.585; $P < 0.001$), low lymphocyte count (HR 0.480; 95% CI 0.271–0.852; P = 0.012), diabetes (HR 1.917; 95% CI 1.181–3.111; P = 0.009), and systemic inflammatory response syndrome (HR 1.714; 95% CI 1.048–2.802; P = 0.032) were found to be independent risk factors for mortality in patients with COVID-19 receiving respiratory support. Regardless of respiratory support, fibrosis-4 index was found to be a robust predictive marker for mortality in patients with COVID-19 (P < 0.001). A number of risk factors were also significantly related to survival in patients with COVID-19 regardless of respiratory support ($P < 0.001$).

**Conclusion** Fibrosis-4 index is a useful predictive marker for mortality in COVID-19 patients regardless of its severity.


*Keywords: Coronavirus, COVID-19, risk factors, fibrosis, mortality, survival*

**Strengths and limitations of this study**

- Though FIB-4 is originally used to predict liver fibrosis in patients with chronic liver

disease, it is a most single reliable predictor of mortality in patients with COVID-19 regardless of respiratory support.

- This study has very low probability of sampling bias, because all tertiary hospitals in the area, where approximately three fourths of COVID-19 patients were diagnosed in South Korea, enrolled entire cohort.
- Further studies for validation with other cohorts would be required to consolidate these results.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), is one of the most important healthcare concerns worldwide [1]. It was first identified in Wuhan City, Hubei province, central China, and linked to Wuhan's Huanan Seafood Wholesale Market in December 2019 [2]. To investigate the causative pathogen, pan-CoV polymerase chain reaction (PCR) was performed initially. followed by metagenomics analysis using next-generation sequencing [3]. After commercial real time quantitative PCR-based detection methods became available, the number of patients with confirmed COVID-19 rapidly increased [4]. Subsequently, this outbreak spread internationally, and was recognized as a pandemic by the World Health Organization (WHO) on 11 March 2020 [5].

Despite measures such as immediate isolation of patients diagnosed with COVID-19 in designated hospitals, contact tracing, and quarantine of people suspected of being infectious, 2294222 cases of COVID-19 have been confirmed and 202,597 deaths have been reported globally as of April 28 2020 [6]. In South Korea, 3705 patients were diagnosed in the Daegu and Gyeongsangbuk-do area among a total of 4212 patients diagnosed in South Korea from January 19 to March 2, 2020 [7]. Epidemiological surveillance revealed that 2333 (63.0%) of cases in this area were related to the religious group Shincheonji [7]. At that time, the mortality rate was only 0.5% in South Korea and 0.6% in the Daegu and Gyeongsangbuk-do area [8]. However, by April 28, the mortality rate had increased to 224 of 10752 confirmed cases (2.3%) [9].

At the time of writing, due to lockdowns in most countries, including the United States and Europe, the exponential increase in cases appears to have been brought under control [6]. However, as a result of unprecedented demand, most countries are experiencing a shortage of medical resources. The difficulty of dealing with this emergency would be assisted by earlier

diagnosis, as well as forecasts of mortality. Several Chinese studies of clinical characteristics and risk factors relating to COVID-19 have been published [4 10-14], and recently, the clinical and epidemiological experience of several other countries have been reported [15 16]. However, few reports of risk modeling and prediction are awaiting peer review and publication [17], and most of these studies have limited sample size or high risk of bias [17]. The risk prediction models in these studies were established using conventional scoring systems, risk nomograms, or advanced machine learning models [18-20]. Although the performance of such models is relatively good, no COVID-19 risk prediction model can currently be recommended for clinical use, due to a number of limitations [21].

This study aims to evaluate the predictive risk factors for mortality by analyzing epidemiologic and laboratory features in patients with COVID-19 receiving respiratory support in tertiary hospitals within the Daegu and Gyeongsangbuk-do area. Most cases in South Korea were concentrated in this area, the most severe cases being admitted to five tertiary hospitals.

## MATERIALS AND METHODS

### Patients and their public involvement

After the beginning of the COVID-19 outbreak on February 18, 2020, in Daegu, all COVID-19 patients were admitted to one designated tertiary hospital. Because of limited medical resources, efficient allocation was required. Therefore, from March 2, the disinfection team of Daegu classified all new COVID-19 patients on the basis of severity of respiratory symptoms and oxygen demand to transfer to one of four other tertiary hospitals in accordance with regional policy. Accordingly, from February 20 to April 14, 2020, we enrolled 1005

hospitalized patients aged >19 years with COVID-19 confirmed by PCR in five tertiary hospitals of Daegu, South Korea.

This study was performed in accordance with the ethical guidelines of the revised Helsinki Declaration of 2013 and approved by the Institutional Review Board of all tertiary hospitals. Written informed consent by the patients was waived due to the retrospective nature of our study. It was not possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of this study.

**Data collection**

The medical records of anthropometric and epidemiological data, patients' clinical characteristics, radiologic and laboratory data, treatments, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and clinical outcomes, were collected retrospectively by each hospital and reviewed by two independent reviewers. Laboratory tests included complete blood cell and lymphocyte count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), liver and kidney function tests, electrolytes, and serum ferritin on admission day. All patients underwent chest radiography with or without computed tomography (CT). The treatment patients received included antivirals, hydroxychloroquine, systemic glucocorticoid, intravenous immunoglobulin, respiratory support, continuous renal replacement therapy, and extracorporeal membrane oxygenation (ECMO). The data collection terminated on April 14, 2020.

**Definition**

In accordance with the WHO interim guidance, all COVID-19 cases were diagnosed by detection of SARS-CoV-2 sequence using real-time PCR from nasopharyngeal and

oropharyngeal swabs. Fever was defined as tympanic temperature of 37.5 °C or higher. Systemic inflammatory response syndrome (SIRS) on admission was defined by satisfaction of any two of the criteria: (a) white blood cell count < 4000 cells/mm$^3$ or > 12000 cells/mm , (b) body temperature < 36 °C or > 38 °C, (c) heart rate >90 beats/min, and (d) tachypnea >20 breaths/min. Shock and acute respiratory distress syndrome (ARDS) were defined in accordance with the WHO interim guidance [22]. Acute kidney injury was defined either from the highest serum creatinine level (>0.3 mg/dl within 48 hours or 1.5 times of the baseline level within 7 days), and/or from decreased urine output (<0.6 ml/kg/h for 6 hours) on admission.

**Study outcomes**

The primary objective of this study was to identify clinical and laboratory risk factors predictive of in-hospital mortality for any reason within 56 days in patients with COVID-19 receiving respiratory support. The secondary objectives were identification of risk factors predictive of mortality in patients with COVID-19 regardless of respiratory support.

**Statistical analysis**

All continuous data were expressed as mean and standard deviation (mean ± SD) or median with range, and compared using Student's t-test or the Mann-Whitney U test. Categorical data were compared using a χ-squared test or Fischer's exact test. The predictive factors for mortality were assessed using the Cox proportional hazards regression model with hazards ratio (HR). Receiver operating characteristic (ROC) analysis was conducted to assess the predictive performance of assessed risk factors. The best cut-off values were calculated based on the Youden index. The relationship between overall survival and fibrosis-4 index (FIB-4) was calculated using the Kaplan-Meier method. *P*-value <0.05 was considered statistically

significant. All statistical analyses were performed using R software (version 3.0.2, Vienna, Austria).

## RESULTS

### Baseline characteristics

Of 1,005 patients with COVID-19, 289 (28.8%) received respiratory support and were included in this study. Of these, 162 (56.1 %) were treated with low-dose oxygen therapy using a nasal or venturi mask, while 127 (43.9%) were treated with a high-flow nasal mask, invasive mechanical ventilation and/or ECMO. Patient disposition is shown in Figure 1. The baseline characteristics of the COVID-19 patients receiving respiratory support are shown in Table 1. The median age was 72.0 years (range: 62.0–80.0 years) and 156 subjects (54.0%) were females. The two most common comorbidities were hypertension (45.8%) and diabetes (32.3%), followed by cardiovascular disease (6.9%) and chronic liver disease (5.2%). The two most common symptoms on admission were fever and/or chills (67.9%), cough (61.2%), followed by shortness of breath (53.0%), myalgia (30.8%), and gastrointestinal symptoms (25.4%). The median time from symptom onset to admission was 6 days (range, 3-9). Radiologic abnormality and bilateral involvement on chest radiographs were 269 (93.1%) and 225 (83.6%), respectively.

There were several differences in demographics and past history between fatal cases and survivors, including older age, preponderance of males, and more frequent diabetes among fatal cases. However, there was no significant difference in the use of ACE inhibitors or ARBs. Duration of symptoms before admission was shorter in survivors but the presence of fever or

respiratory symptoms on admission did not differ between survivors and non-survivors. There was no significant difference in viral signs on admission except for frequent SIRS in fatal cases. Some differences in laboratory tests on admission were also significant, including higher white blood cell count, CRP, procalcitonin, aspartate aminotransferase (AST), gamma glutamyl transferase, prothrombin time, blood urea nitrogen, serum creatinine, and lower lymphocyte count, platelet count, serum albumin, and serum sodium in fatal cases compared with survivors.

**Treatments and clinical outcomes**

The treatments and clinical outcomes of patients with COVID-19 receiving respiratory support are shown in Table 2. Of these, 57 (19.7%) and 70 (24.2%) were treated with high-flow nasal cannula and invasive mechanical ventilation, respectively. Analysis of clinical outcomes revealed that 113 patients (11.2%) had ARDS, 93 (33.2%) were admitted to an intensive care unit (ICU), and 18 (6.2%) underwent ECMO. The median duration of hospital stay was 25 days (range 8-33). Survivors were less frequently treated with darunavir/cobicistat, systemic glucocorticoid, high-flow nasal cannula, invasive mechanical ventilation, or continuous renal replacement therapy compared with fatal cases. Survivors had a longer median duration of hospital stay compared with fatal cases, were less frequently admitted to an ICU, and less frequently developed septic shock, ARDS or acute kidney injury.

**Risk factors for mortality in COVID-19 patients receiving respiratory support**

Univariate analysis identified age, sex, diabetes, chronic obstructive pulmonary disease, lymphocyte count, AST, ESR, and SIRS as significant variables relating to mortality in patients with COVID-19 receiving respiratory support (Table 3). Multivariate analysis identified age (HR 1.054; 95% CI 1.028–1.082; $P < 0.001$), diabetes (HR 2.226; 95% CI 1.357–3.652; $P =$

0.002), low lymphocyte count (HR 0.999; 95% CI 0.998–1.000; $P = 0.005$), and high AST (HR 1.002; 95% CI 1.000–1.003; $P = 0.033$) as independent predictors of mortality. Lower platelet count (HR 0.997; 95% CI 0.994–1.000, $P = 0.069$) and presence of SIRS on admission (HR 1.968; 95% CI 1.199–3.230; $P = 0.074$) tended to be associated with severe COVID-19, but this did not reach statistical significance.

**Risk factors for mortality, including fibrosis-4 index**

The fibrosis-4 index (FIB-4), which is calculated from age, AST, alanine aminotransferase (ALT), and platelet counts, was originally used to predict liver fibrosis in patients with chronic liver disease [23]. Based on multivariate analysis, we used FIB-4 as a predictive risk factor candidate. In multivariate analysis including FIB-4 as a continuous variable, diabetes (HR 1.998; 95% CI 1.202–3.321; $P = 0.008$), lower lymphocyte count (HR 0.999; 95% CI 0.998–1.000; $P = 0.003$), and FIB-4 (HR 1.115; 95% CI 1.069–1.163; $P < 0.001$) were identified as independent predictors of mortality in COVID-19 patients receiving respiratory support (Table S1). To set a cut-off value of FIB-4 and lymphocyte count, ROC analysis was performed (Figure 2). The Areas under the ROC curves (AUCs) of FIB-4 and lymphocyte counts were 0.702 and 0.647 with sensitivity of 48.5% and 78.6%, specificity of 87.6% and 45.8%, positive predictive value (PPV) of 55.0% and 32.0%, and negative predictive value (NPV) of 84.4% and 86.9%, respectively (all $P$ <0.001). The optimal cut-off values (COVs) of FIB-4 and lymphocyte count were 4.95 and 1010, respectively.

In multivariate analysis after converting FIB-4 and lymphocyte count to categorical variables, diabetes (HR 1.917; 95% CI 1.181–3.111; $P = 0.009$), low lymphocyte count (HR 0.480; 95% CI 0.271–0.852; $P = 0.012$), SIRS (HR 1.714; 95% CI 1.048–2.802; $P = 0.032$), and high FIB-4 (HR 2.784; 95% CI 1.691–4.585; $P < 0.001$) were identified as independent predictors of

mortality (Table 4).

**FIB-4 and other predictive risk factors for survival in COVID-19 patients receiving respiratory support**

Among the four predictive risk factors, FIB-4 was the best predictor of mortality in COVID-19 patients receiving respiratory support. Therefore, we performed survival analysis to compare mortality in the high FIB-4 group (FIB-4 ≥ 4.95) and low FIB-4 group (FIB-4 < 4.95). Survival in the high FIB-4 group was significantly better than in the low FIB-4 group (high FIB-4, 28.8 days [23.8–33.8]; low FIB-4, 44.0 days [41.9–46.1], $P < 0.001$) (Figure 3a.) Using the four variables diabetes, lymphocyte count, SIRS on admission, and FIB-4, we performed survival analysis to predict mortality in COVID-19 patients receiving respiratory support. As the number of risk factors increased, survival of the patients significantly deteriorated ($P = 0.0016$, Figure 3b, Figure S1).

To explore additional predictive performance for mortality in the entire group of patients with COVID-19, we performed survival analysis to compare mortality in the high and low FIB-4 groups using the same cut-off. Survival in the high FIB-4 group was significantly better than in the low FIB-4 group (high FIB-4, 32.5 days [27.7–37.2]; low FIB-4, 50.0 days [49.3–50.6], $P < 0.001$) (Figure 4a.) Using four variables, we also performed survival analysis to predict mortality in the entire group of patients with COVID-19. As the number of risk factors increased, survival significantly deteriorated ($P < 0.0001$, Figure 4b, Figure S2).

**DISCUSSION**

In this retrospective cohort study, predictive risk factors for mortality were evaluated in 289 patients with confirmed COVID-19 receiving respiratory support in the Daegu and Gyeongsangbuk-do area. After the initial outbreak, immediate isolation of patients diagnosed with COVID-19 in designated hospitals and intensive contact tracing with quarantine of suspected virus carriers commenced. Despite absence of lockdown, the numbers of new patients in this area declined. This probably implied that most patients had been successfully isolated and treated in designated hospitals. Most patients requiring respiratory support were allocated to five tertiary hospitals.

The present study revealed that diabetes, low lymphocyte count, SIRS, and FIB-4 were independent risk factors for mortality. A recent meta-analysis found that the main laboratory abnormalities in COVID-19 patients included low lymphocyte count, and elevated CRP and lactate dehydrogenase (LDH) [24]. In non-survivors, or severely ill patients requiring ICU care or suffering from ARDS, laboratory abnormalities including high WBC count, low lymphocyte count, prolonged prothrombin time, low albumin, elevated AST, ALT, total bilirubin, LDH, creatinine, troponin I, CRP, procalcitonin, ferritin, and D-dimer were identified as risk factors in previous studies [10 11 13]. However, numbers of enrolled patients were small and multivariate analyses were not performed. In a recent study, logistic regression analysis identified age, Sequential Organ Failure Assessment (SOFA) score, and D-dimer as predictive risk factors for death in patients with COVID-19 pneumonia [14]. SOFA score is derived from $PaO_2/FiO_2$, use of mechanical ventilator, platelets count, Glasgow Coma scale, bilirubin, mean arterial pressure or requirement for vasoactive agents, and serum creatinine or urine output. The score is related to the cytokine storm in sepsis [25], and we think some of the risk factors in our study, including platelets as a component of the FIB-4 index, and SIRS, were also associated with this serious

inflammatory condition. This recent study included patients similar to those in the present study, as judged from the proportion of patients receiving respiratory support (82.1% versus 100% in the present study) and the mortality rate (28.3% versus 24.2% in the present study) [14]. Multivariate analysis in two recent studies showed that neutrophil-to-lymphocyte ratio, CD4 T cell count, and age were independent risk factors of in-hospital mortality and ICU admission for COVID-19 [26] [27]. Severe inflammation dysregulates the immune response and is characterized by decreased memory helper T (Th) cells and regulatory T cells with increased naive Th cells in patients with COVID-19 [28]. These findings are consistent with low lymphocyte count as an independent risk factor for mortality in our study. However, in previous studies, survival analysis was not performed, and the enrolled patients were somewhat different from those in the present study.

Liver injury in COVID-19 was observed more frequently in severe cases than in mild cases [4] [13]. Though the mechanism is unclear, elevated AST and ALT may be related to the immune response in severe pneumonia, which may result from inflammatory cytokines following COVID-19 infection [29]. Elevated liver enzyme can be also associated with drug induced liver injury (DILI), which may result from antibacterial and antiviral drugs, anti-inflammatory drugs, and vasopressors in severe cases [30]. As there has been no study of DILI in COVID-19 infection, its prevalence should be investigated. However, in this study, laboratory tests performed at the time of admission did not indicate an association between AST elevation and DILI. Also in this study, although FIB-4 was originally used in patients with liver disease, it was identified as a predictor of mortality in patients with COVID-19, whether or not they were receiving respiratory support. Elevated LDH has been reported as a promising predictor for severe COVID infection [19] [31] [32]. However, it was only identified as a risk factor by univariate analysis,

not by multivariate analysis. We suggest that the ratio of AST to ALT in FIB-4 may be a better predictor of mortality than the level of LDH, due to its non-specificity of cause. In addition, the common finding of elevated AST in patients with severe disease in several other studies supports the present study [4 13 33].

When FIB-4 is analyzed with other risk factors including lymphocyte count, SIRS, and diabetes, as number of risk factors increases, survival deteriorates in patients with COVID-19 regardless of respiratory support. There are several published or preprinted studies of prediction models for the prognosis of patients with COVID-19 [17]. Albumin, direct bilirubin, and red blood cell distribution width have been suggested as diagnostic or prognostic indicators of severe disease or mortality in COVID-19 [17]. However, among these three factors, albumin was not a significant risk factor, and the other two factors were not evaluated in the present study. Most of the proposed models have been open to criticism on the grounds of severe sampling bias due to rarely reported length of follow-up and prevalence of COVID-19 with or without severe infection. A strength of the present study is the low probability of sampling bias, because approximately three fourths of patients with COVID-19 in South Korea have been diagnosed in the Daegu and Gyeongsangbuk-do area, and our entire cohort was derived from tertiary hospitals in that area.

This study has some limitations. First, there was no validation with another cohort. As described above, most of the COVID-19 cases were enrolled in this study. Thus, it would be impossible to validate these results without undertaking an international study. Improved assessments of international data on COVID-19 will require data sharing, using a reporting protocol specified by WHO [34]. Second, detailed radiologic assessment of CT scans was not performed. To our knowledge, there are only a few reports at preprint stage which include

clinical features and radiologic features from CT scan with artificial intelligence techniques to develop prediction models [35]. However, this study also has sampling bias as well as an inadequate sample size [21 35]. Therefore, advanced machine learning combining radiologic image analysis with clinical risk factors would be needed to develop a robust prediction model. Third, prediction of severe COVID-19 including ICU admission or ARDS was not analyzed in this study. However, we think prediction of severe COVID-19 was not appropriate for our cohort, because transfer to a tertiary hospital may introduce the possibility of sampling bias. Thus, we used the objective outcome of mortality in this study.

In conclusion, FIB-4, diabetes, low lymphocyte count, and SIRS are independent risk factors of mortality in patients with COVID-19 receiving respiratory support. Among these risk factors, FIB-4 is a robust predictor of mortality in patients with COVID-19 regardless of respiratory support. A number of risk factors are significantly related to survival in patients with COVID-19 regardless of respiratory support.

**Author Contributions:** Conceptualization, Soo Young Park and Woo Jin Chung; Formal analysis, Min Kyu Kang; Data curation, Min Kyu Kang, Yu Rim Lee, Jeong Eun Song and Na Young Kim; Investigation, Jung Gil Park, Min Kyu Kang, Yu Rim Lee, Jeong Eun Song, Na Young Kim, Young Oh Kweon, Won Young Tak, Se Young Jang, Changhyeong Lee, Byung Seok Kim, Jae Seok Hwang, Byoung Kuk Jang, Jinmok Bae, Ji Yeon Lee, Jeong Ill Suh and Soo Young Park; Supervision, Soo Young Park and Woo Jin Chung; Visualization, Jung Gil Park; Writing – original draft, Jung Gil Park and Min Kyu Kang; Writing – review & editing, Soo Young Park and Woo Jin Chung.

**Funding:** There was no external funding for this work.

**Acknowledgements:** We appriciate all dedicated doctors and epidemiologist who contribute declining trends of patients with COVID-19 in the Daegu and Gyeongsangbuk-do area and Editage (www.editage.co.kr) for English language editing.

**Conflict of interest:** The authors declare no conflicts of interest about this work.

References

1. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J* 2020;55(4) doi: 10.1183/13993003.00607-2020 [published Online First: 2020/04/10]

2. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020;92(4):401-02. doi: 10.1002/jmv.25678 [published Online First: 2020/01/18]

3. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579(7798):270-73. doi: 10.1038/s41586-020-2012-7 [published Online First: 2020/02/06]

4. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020 doi: 10.1056/NEJMoa2002032 [published Online First: 2020/02/29]

5. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020". World Health Organization. 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

6. World Health Organization. Coronavirus disease 2019 (COVID-19) situation reports - 89, April 28, 2020 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200428-sitrep-99-covid-19.pdf?sfvrsn=119fc381_2.

7. Korean Society of Infectious D, Korean Society of Pediatric Infectious D, Korean Society of E, et al. Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci* 2020;35(10):e112. doi: 10.3346/jkms.2020.35.e112 [published

Online First: 2020/03/17]

8. Korean Society of Infectious D, Korea Centers for Disease C, Prevention. Analysis on 54 Mortality Cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020. *J Korean Med Sci* 2020;35(12):e132. doi: 10.3346/jkms.2020.35.e132 [published Online First: 2020/04/02]
9. Korea Centers for Disease Control and Prevention. The update of COVID-19 in Korea as of April 28. *http://ncovmohwgokr/en/bdBoardListdo?brdId=16&brdGubun=161&dataGubun=&ncvContSeq=&contSeq=&board_id=&gubun=*
10. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020 doi: 10.1001/jamainternmed.2020.0994 [published Online First: 2020/03/14]
11. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020 doi: 10.1001/jama.2020.1585 [published Online First: 2020/02/08]
12. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7 [published Online First: 2020/02/03]
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5 [published Online First: 2020/01/28]

14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3 [published Online First: 2020/03/15]

15. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020 doi: 10.1001/jama.2020.5394 [published Online First: 2020/04/07]

16. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med* 2020 doi: 10.1056/NEJMoa2006100 [published Online First: 2020/04/15]

17. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ* 2020;369:m1328. doi: 10.1136/bmj.m1328 [published Online First: 2020/04/09]

18. Shi Y, Yu X, Zhao H, et al. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Crit Care* 2020;24(1):108. doi: 10.1186/s13054-020-2833-7 [published Online First: 2020/03/20]

19. Gong J, Ou J, Qiu X, et al. A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa443 [published Online First: 2020/04/17]

20. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality - preliminary results: medRxiv [Preprint] 2020.

21. Sperrin M, Grant SW, Peek N. Prediction models for diagnosis and prognosis in Covid-

19. *BMJ* 2020;369:m1464. doi: 10.1136/bmj.m1464 [published Online First: 2020/04/16]

22. Organization WH. Clinical management of severe acute respiratory infection (SARI) when Covid-19 disease is suspected. Interim guidance, 2020.

23. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43(6):1317-25. doi: 10.1002/hep.21178 [published Online First: 2006/05/27]

24. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect* 2020 doi: 10.1016/j.jinf.2020.03.041 [published Online First: 2020/04/14]

25. Marik PE, Taeb AM. SIRS, qSOFA and new sepsis definition. *J Thorac Dis* 2017;9(4):943-45. doi: 10.21037/jtd.2017.03.125 [published Online First: 2017/05/20]

26. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect* 2020 doi: 10.1016/j.jinf.2020.04.002 [published Online First: 2020/04/14]

27. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect* 2020;80(5):e1-e6. doi: 10.1016/j.jinf.2020.03.004 [published Online First: 2020/03/17]

28. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa248 [published Online First: 2020/03/13]

29. Fan Z, Chen L, Li J, et al. Clinical Features of COVID-19-Related Liver Damage.

*Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2020 doi: 10.1016/j.cgh.2020.04.002 [published Online First: 2020/04/14]

30. Qi X, Liu C, Jiang Z, et al. Multicenter analysis of clinical characteristics and outcome of COVID-19 patients with liver injury. *Journal of hepatology* 2020 doi: 10.1016/j.jhep.2020.04.010 [published Online First: 2020/04/20]
31. Yan L, Zhang H-T, Xiao Y, et al. Prediction of survival for severe Covid-19 patients with three clinical features: development of a machine learning-based prognostic model with clinical data in Wuhan: medRxiv [Preprint] 2020.
32. Xie J, Hungerford D, Chen H, et al. Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19: medRxiv [Preprint] 2020.
33. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;20(4):425-34. doi: 10.1016/S1473-3099(20)30086-4 [published Online First: 2020/02/28]
34. Moorthy V, Henao Restrepo AM, Preziosi MP, et al. Data sharing for novel coronavirus (COVID-19). *Bull World Health Organ* 2020;98(3):150. doi: 10.2471/BLT.20.251561 [published Online First: 2020/03/07]
35. Bai X, Fang C, Zhou Y, et al. Predicting COVID-19 malignant progression with AI techniques: medRxiv [Preprint] 2020.

Table 1. Baseline characteristics of patients with COVID-19 receiving respiratory support

| | All (n = 289, 100%) | Survivors (n = 219, 75.8%) | Fatal cases (n = 70, 24.2%) | *P* value* |
|---|---|---|---|---|
| **Demographic and clinical characteristics** | | | | |
| Age, years | 72.0 (62.0-80.0) | 70.0 (60.0–79.0) | 77.0 (71.0–84.0) | <0.001 |
| Female gender | 156 (54.0) | 128 (58.4) | 28 (40.0) | 0.011 |
| Body mass index, kg/m$^2$ | 24.3 (22.2–26.3) | 24.2 (22.2–26.2) | 24.5 (22.2–26.8) | 0.577 |
| **Comorbidity** | | | | |
| Hypertension | 132 (45.8) | 96 (44.0) | 36 (51.4) | 0.346 |
| Diabetes | 93 (32.3) | 59 (27.1) | 34 (48.6) | 0.001 |
| Cardiovascular disease | 20 (6.9) | 14 (6.4) | 6 (8.6) | 0.723 |
| Chronic obstructive pulmonary disease | 9 (3.1) | 4 (1.8) | 5 (7.1) | 0.067 |
| Chronic kidney disease | 11 (3.8) | 9 (4.1) | 2 (2.9) | 0.906 |
| Chronic liver disease | 15 (5.2) | 9 (4.1) | 6 (8.6) | 0.248 |
| Liver cirrhosis | 8 (2.8) | 4 (1.8) | 4 (5.7) | 0.191 |
| Hepatocellular carcinoma | 2 (0.7) | 1 (0.5) | 1 (1.4) | 0.979 |
| ACE inhibitors or ARBs use | 61 (24.8) | 47 (24.1) | 14 (27.5) | 0.756 |
| **Symptoms on admission** | | | | |
| Fever/chills | 195 (67.9) | 145 (66.5) | 50 (72.5) | 0.438 |
| Cough | 175 (61.2) | 139 (63.8) | 36 (52.9) | 0.145 |
| Shortness of breath | 152 (53.0) | 112 (51.4) | 40 (58.0) | 0.413 |
| Gastrointestinal symptoms (Vomiting/Diarrhea) | 73 (25.4) | 67 (30.7) | 6 (8.7) | <0.001 |
| Myalgia | 88 (30.8) | 73 (33.5) | 15 (22.1) | 0.103 |
| Headache | 46 (16.1) | 43 (19.7) | 3 (4.4) | 0.005 |
| Duration of symptom before admission, days | 6 (3–9) | 6 (3–9) | 4.5 (2–7) | 0.031 |
| **Vital signs at presentation** | | | | |
| Temperature, °C | 36.9 (36.5–37.6) | 37.0 (36.5–37.6) | 36.7 (36.5–37.3) | 0.070 |
| Respiratory rate, breath/min | 20 (20–22) | 20 (20–22) | 20 (20–23) | 0.101 |
| Saturation, % | 95 (92–98) | 95 (93–98) | 95 (90–100) | 0.948 |

| | | | | |
|---|---|---|---|---|
| Systolic pressure, mm Hg | 130 (116–145) | 130 (120–144) | 122 (108–146) | 0.062 |
| Heart rate, /min | 86 (72–100) | 85 (72–97) | 92 (72–102) | 0.140 |
| **SIRS on admission** | 102 (35.7) | 65 (30.1) | 37 (52.9) | 0.001 |
| **Radiologic and laboratory findings** | | | | |
| **Radiologic findings** | | | | |
| Abnormal chest radiograph | 269 (93.1) | 201 (91.8) | 68 (97.1)) | 0.205 |
| Bilateral involvement on chest radiographs | 225 (83.6) | 163 (81.1) | 62 (91.2) | 0.080 |
| **Laboratory findings** | | | | |
| White blood cell count, $\times 10^3$/uL | 6140 (4695–8065) | 6000 (4690-7420) | 7320 (5100–12020) | 0.001 |
| Lymphocyte count, $\times 10^3$/uL | 895 (611–1260) | 952 (661–1321) | 702 (490–980) | <0.001 |
| Haemoglobin, g/dL | 12.4 (11.1–13.6) | 12.4 (11.2–13.6) | 12.6 (10.9–13.9) | 0.510 |
| Platelet count, $\times 10^9$/L | 192 (146–267) | 200 (150–277) | 166 (132–239) | 0.029 |
| Erythrocyte sedimentation rate, mm/h | 57 (39–76) | 57 (39–76) | 51 (40–70) | 0.592 |
| C–reactive protein, mg/L | 10.1 (4.8–21.5) | 9.3 (4.0–20.4) | 13.4 (7.4–24.8) | 0.015 |
| Procalcitonin, ng/mL | 0.1 (0.1–0.4) | 0.1 (0.1–0.2) | 0.4 (0.1–1.1) | <0.001 |
| Aspartate aminotransferase, U/L | 38 (26–53) | 34 (25–50) | 49 (34–65) | <0.001 |
| Alanine aminotransferase, U/L | 21 (15–33) | 20 (15–32) | 23 (16–38) | 0.528 |
| Total bilirubin, mg/dL, mg/dL | 0.6 (0.4–0.9) | 0.6 (0.4–0.9) | 0.7 (0.4–0.9) | 0.240 |
| Alkaline phosphatase, U/L | 71 (57–92) | 71 (57–91) | 72 (58–104) | 0.488 |
| Gamma glutamyl transferase, U/L | 35 (22–61) | 27 (16.5–48.5) | 60 (40–101) | 0.001 |
| Serum albumin, g/dL | 3.4 (3.2–3.7) | 3.5 (3.2–3.8) | 3.2 (3.0–3.4) | <0.001 |
| Prothrombin time, second | 12.4 (11.8–13.3) | 12.4 (11.7–13.1) | 12.8 (11.9–14.8) | 0.026 |
| Prothrombin time, INR | 1.1 (1.0–1.1) | 1.0 (1.0–1.1) | 1.1 (1.0–1.3) | 0.015 |
| Blood urea nitrogen, mg/dL | 17 (12–24) | 15 (12–21) | 22 (16–37) | <0.001 |
| Creatinine, mg/dL | 0.8 (0.7–1.1) | 0.8 (0.7–1.0) | 1.0 (0.8–1.7) | <0.001 |
| Estimated glomerular filtration rate, mL/min/1.73㎡ | 80 (58–98) | 84 (64–100) | 63 (39–91) | 0.001 |

| | | | | |
|---|---|---|---|---|
| Sodium, mmol/L | 137 (134–141) | 138 (134–141) | 136 (133–140) | 0.006 |
| Potassium, mmol/L | 4.1 (3.7–4.5) | 4.1 (3.7–4.5) | 4.2 (3.5–4.7) | 0.870 |
| Lactate dehydrogenase, U/L | 558 (405–753) | 560 (404–753) | 556 (410–762) | 0.969 |
| Creatine kinase, U/L | 79 (52–155) | 73 (51–149) | 86 (54–172) | 0.307 |
| Serum ferritin, ng/mL | 552 (327–975) | 430 (308–941) | 659 (521–1432) | 0.115 |

Data are expressed as median and interquartile range (IQR) or numbers (%).
*Calculated by Student's t test (or the Mann-Whitney U test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; SIRS, systemic inflammatory response syndrome

Table 2. Treatments and clinical outcomes of patients with COVID-19 receiving respiratory support

| | All (n = 289) | Survivors (n = 219) | Fatal cases (n = 70) | *P* value* |
|---|---|---|---|---|
| **Treatments** | | | | |
| Antiviral therapy | | | | |
| Lopinavir/ritonavir | 235 (81.3) | 182 (83.1) | 53 (75.7) | 0.228 |
| Darunavir/cobicistat | 42 (14.5) | 26 (11.9) | 16 (22.9) | 0.038 |
| Hydroxychloroquine | 187 (64.7) | 137 (62.6) | 50 (71.4) | 0.227 |
| Systemic glucocorticoid | 152 (52.6) | 96 (43.8) | 56 (80.0) | <0.001 |
| Intravenous immunoglobulin | 26 (9.0) | 16 (7.3) | 10 (14.3) | 0.124 |
| High–flow nasal cannula | 57 (19.7) | 19 (8.7) | 38 (54.3) | <0.001 |
| Invasive mechanical ventilation | 70 (24.2) | 38 (17.4) | 32 (45.7) | <0.001 |
| Continuous renal–replacement therapy | 22 (7.6) | 5 (2.3) | 17 (24.3) | <0.001 |
| ECMO | 18 (6.2) | 10 (4.6) | 8 (11.4) | 0.074 |
| **Clinical outcomes** | | | | |
| ICU admission | 96 (33.2) | 59 (26.9) | 37 (52.9) | <0.001 |
| Septic shock | 77 (26.6) | 40 (18.3) | 37 (52.9) | <0.001 |
| ARDS | 113 (39.1) | 49 (22.4) | 64 (91.4) | <0.001 |
| Acute kidney injury | 52 (18.0) | 16 (7.3) | 36 (51.4) | <0.001 |
| Hospital stay, days | 25 (14–33) | 27 (19–37) | 10 (6–19) | <0.001 |

Data are expressed as median and interquartile range (IQR) or numbers (%).
*Calculated by Student's t test (or the Mann-Whitney U test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; ARDS, acute respiratory distress
syndrome

Table 3. Risk factors for mortality in patients with COVID-19 receiving respiratory support

| Variable | Univariate | Multivariate analysis | |
|---|---|---|---|
| | *P* value* | *P* value* | Hazard ratio (95% CI) |
| Age, yr | <0.001 | <0.001 | 1.054 (1.028–1.082) |
| Male (yes/no) | 0.014 | | |
| Comorbidities (yes/no) | | | |
| Hypertension | 0.392 | | |
| Diabetes | 0.001 | 0.002 | 2.226 (1.357-3.652) |
| Chronic obstructive pulmonary disease | 0.009 | | |
| Chronic kidney disease | 0.841 | | |
| Chronic liver disease | 0.226 | | |
| ACE inhibitor/ARB use (yes/no) | 0.871 | | |
| Lymphocyte count, $\times 10^3$/uL | <0.001 | 0.005 | 0.999 (0.998-1.000) |
| Platelet count, $\times 10^9$/L | 0.087 | 0.069 | 0.997 (0.994-1.000) |
| C-reactive protein, mg/L | 0.584 | | |
| Aspartate aminotransferase, U/L | 0.050 | 0.033 | 1.002 (1.000-1.003) |
| Alanine aminotransferase, U/L | 0.552 | | |
| Total bilirubin, mg/dL | 0.831 | | |
| Alkaline phosphatase, U/L | 0.725 | | |
| Gamma glutamyl transferase, U/L | 0.263 | | |
| Serum albumin, g/dL | 0.773 | | |
| Prothrombin time, INR | 0.444 | | |
| Estimated glomerular filtration rate, mL/min/1.73㎡ | 0.002 | | |
| SIRS on admission (yes/no) | <0.001 | 0.074 | 1.968 (1.199-3.230) |

*Calculated by Cox proportional hazards regression test

COVID-19, coronavirus disease 2019; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; INR, international normalized ratio; SIRS, systemic inflammatory response syndrome

Table 4. Risk factors including fibrosis-4 score for mortality in patients with COVID-19 receiving respiratory support

| Variable | Univariate | Multivariate analysis | |
|---|---|---|---|
| | *P* value* | *P* value* | Hazard ratio (95% CI) |
| Male (yes/no) | 0.143 | | |
| Comorbidities (yes/no) | | | |
| Hypertension | 0.392 | | |
| Diabetes | 0.001 | 0.009 | 1.917 (1.181-3.111) |
| Chronic obstructive pulmonary disease | 0.087 | | |
| Chronic kidney disease | 0.841 | | |
| Chronic liver disease | 0.226 | | |
| ACE inhibitor/ARB use (yes/no) | 0.871 | | |
| Lymphocyte count, /uL | | | |
| <1010 | | | 1 (ref) |
| ≥1010 | 0.012 | 0.012 | 0.480 (0.271-0.852) |
| C-reactive protein, mg/L | 0.584 | | |
| Total bilirubin, mg/dL | 0.831 | | |
| Alkaline phosphatase, U/L | 0.725 | | |
| Gamma glutamyl transferase, U/L | 0.263 | | |
| Serum albumin, g/dL | 0.773 | | |
| Prothrombin time, INR | 0.444 | | |
| Estimated glomerular filtration rate, mL/min/1.73㎡ | 0.002 | | |
| SIRS on admission (yes/no) | <0.001 | 0.032 | 1.714 (1.048-2.802) |
| Fibrosis-4 score | | | |
| <4.95 | | | 1 (ref) |
| ≥4.95 | <0.001 | <0.001 | 2.784 (1.691-4.585) |

*Calculated by Cox proportional hazards regression test

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; INR, international normalized ratio, SIRS, systemic inflammatory response syndrome

**Figure 1.** Flow diagram of the study

**Figure 2.** Predictive performance of risk factors for mortality in patients with COVID-19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the curve for lymphocyte counts

**Figure 3.** Survival of patients with COVID-19 receiving respiratory support plotted against fibrosis-4 index (a) and number of risk factors (b)

**Figure 4.** Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and number of risk factors (b)

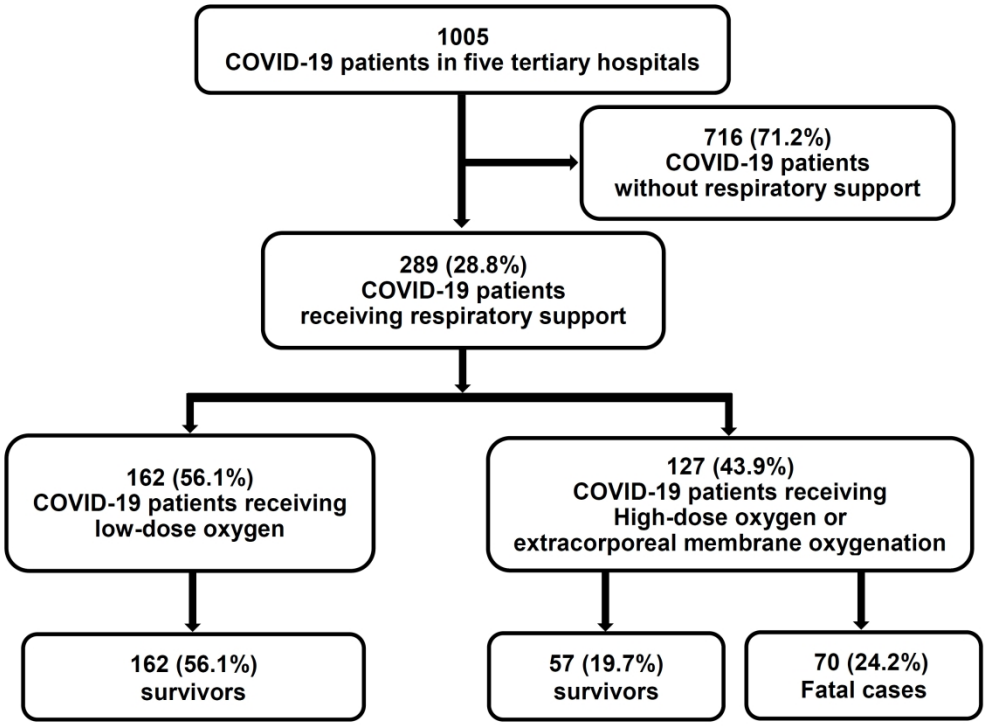



Figure 1. Flow diagram of the study

264x194mm (300 x 300 DPI)

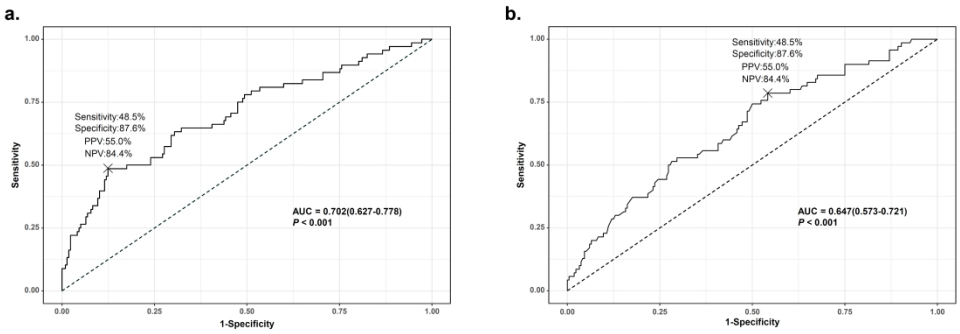



Figure 2. Predictive performance of risk factors for mortality in patients with COVID-19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the curve for lymphocyte counts

669x250mm (300 x 300 DPI)

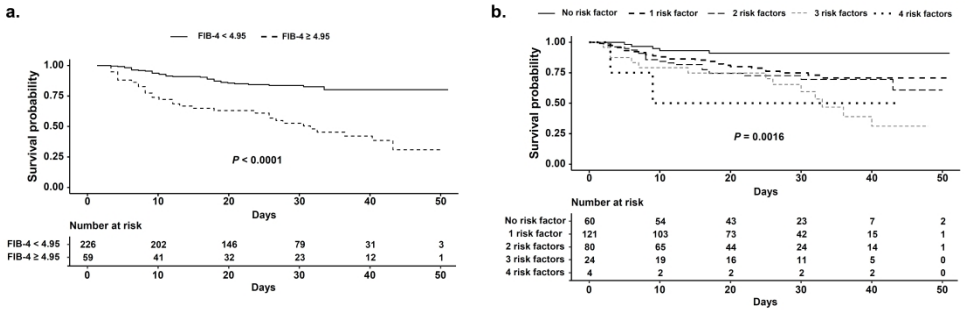



Figure 3. Survival of patients with COVID-19 receiving respiratory support plotted against fibrosis-4 index (a) and number of risk factors (b)

600x199mm (300 x 300 DPI)

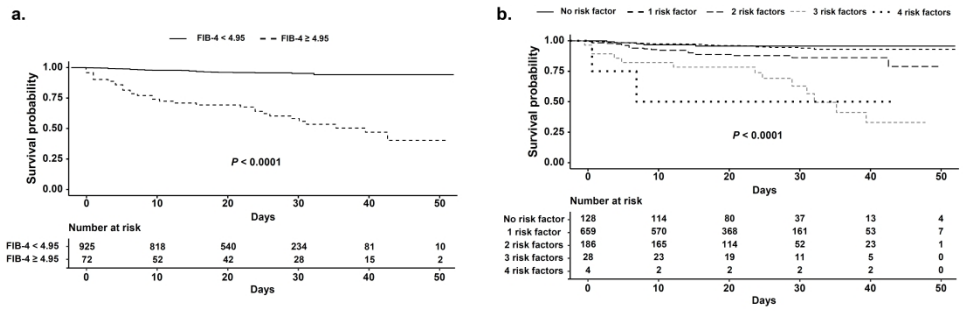



Figure 4. Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and number of risk factors (b)

600x199mm (300 x 300 DPI)

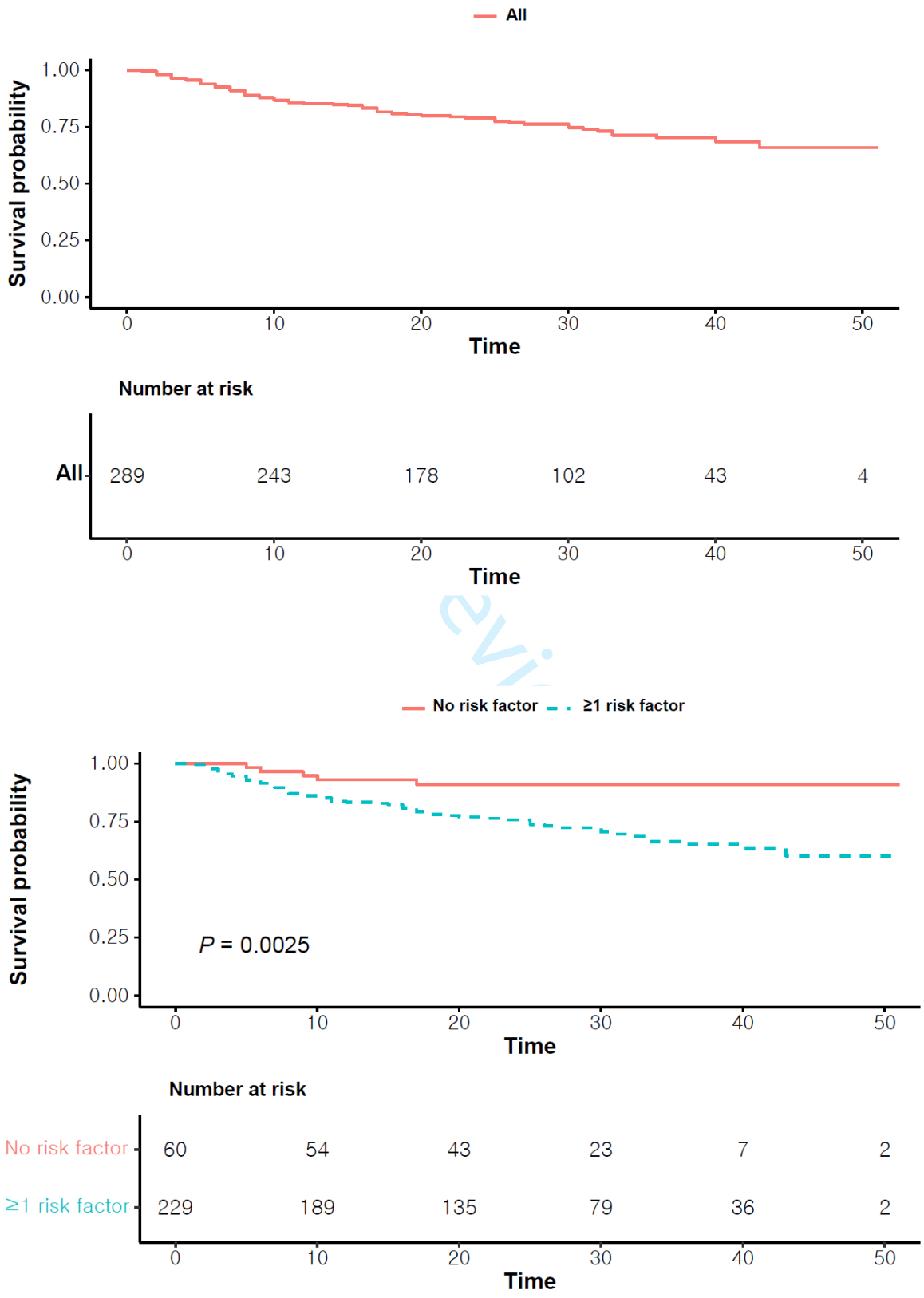
Table S1. Risk factors with Fibrosis-4 score for mortality in patients with COVID-19 receiving respiratory support

| Variable | Univariate | Multivariate analysis | |
|---|---|---|---|
| | *P* value* | *P* value* | Hazard ratio (95% CI) |
| Sex (male/female) | 0.143 | | |
| Comorbidities (yes/no) | | | |
| Hypertension | 0.392 | | |
| Diabetes | 0.001 | 0.008 | 1.998 (1.202-3.321) |
| Chronic obstructive pulmonary disease | 0.087 | | |
| Chronic kidney disease | 0.841 | | |
| Chronic liver disease | 0.226 | | |
| ACE inhibitor/ARB use (yes/no) | 0.871 | | |
| Lymphocyte count, $\times 10^3$/uL | <0.001 | 0.003 | 0.999 (0.998-1.000) |
| C-reactive protein, mg/L | 0.584 | | |
| Total bilirubin, mg/dL | 0.831 | | |
| Alkaline phosphatase, U/L | 0.725 | | |
| Gamma glutamyl transferase, U/L | 0.263 | | |
| Serum albumin, g/dL | 0.773 | | |
| Prothrombin time, INR | 0.444 | | |
| Estimated glomerular filtration rate, mL/min/1.73 ㎡ | 0.002 | | |
| SIRS on admission (yes/no) | <0.001 | | |
| Fibrosis-4 score | <0.001 | <0.001 | 1.115 (1.069-1.163) |

*Calculated by Cox proportional hazards regression test

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; INR, international normalized ratio, SIRS, systemic inflammatory response syndrome.

Figure S1. Survival of the patients with COVID-19 receiving respiratory support as the number of risk factors



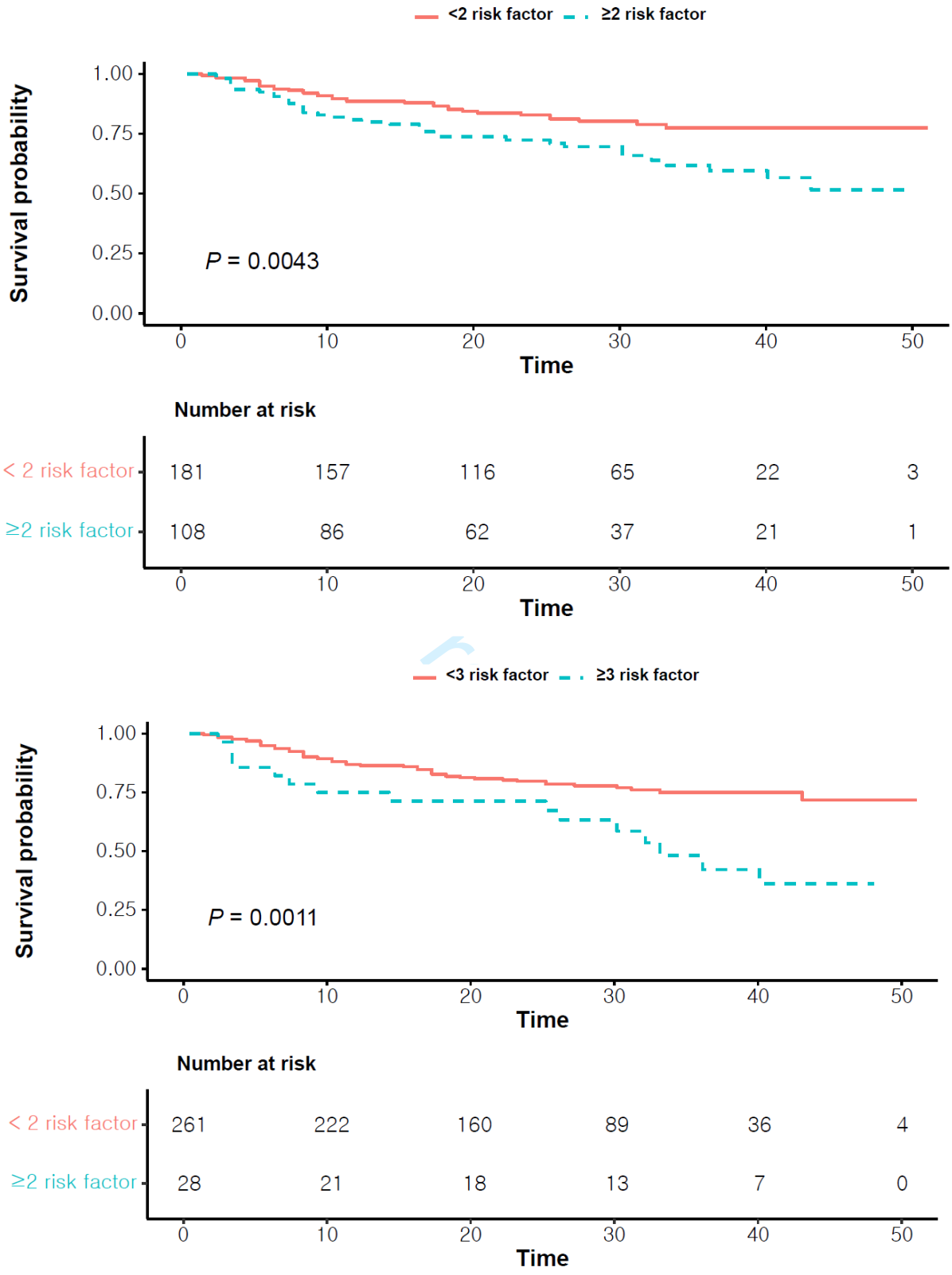
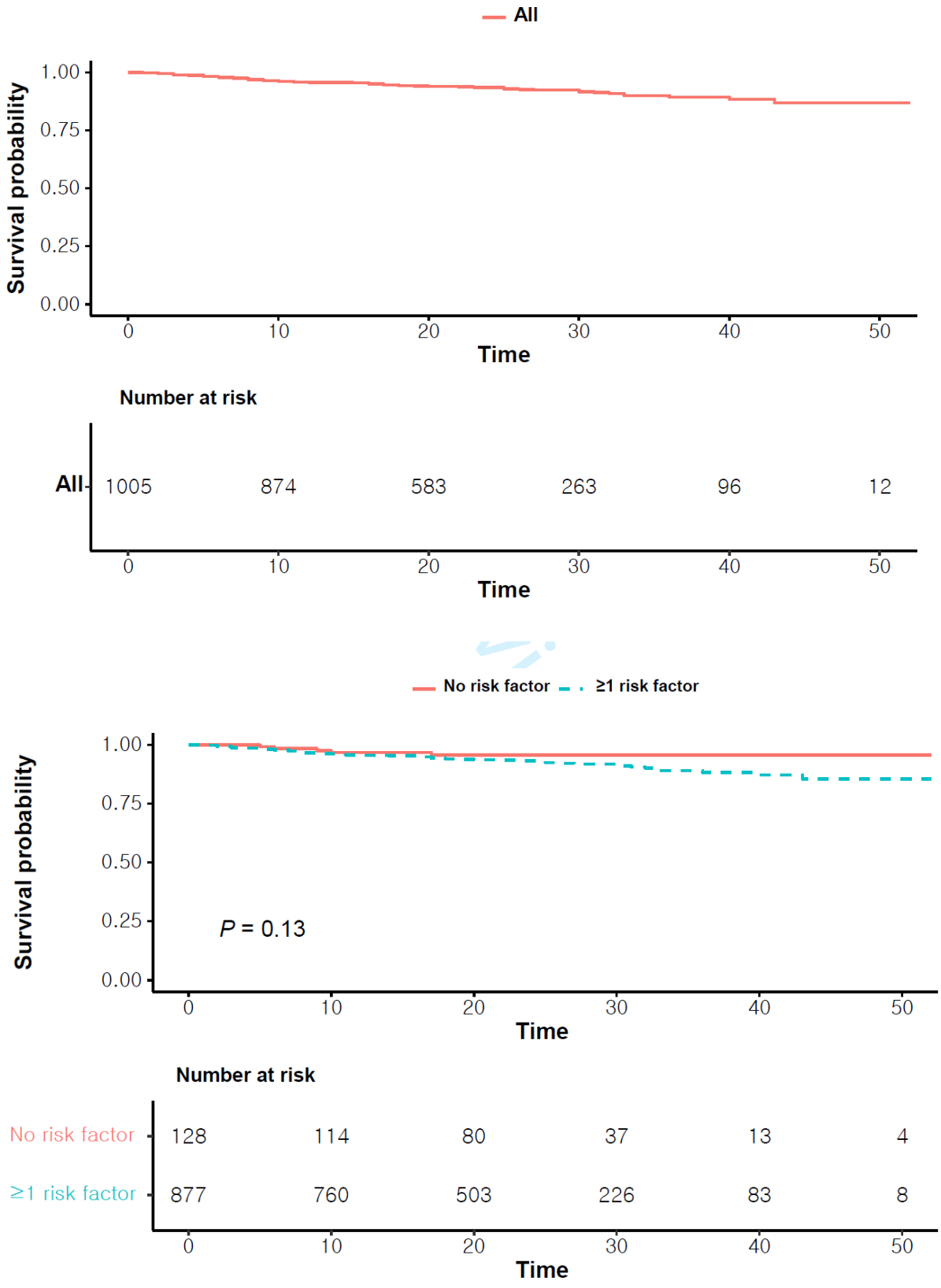
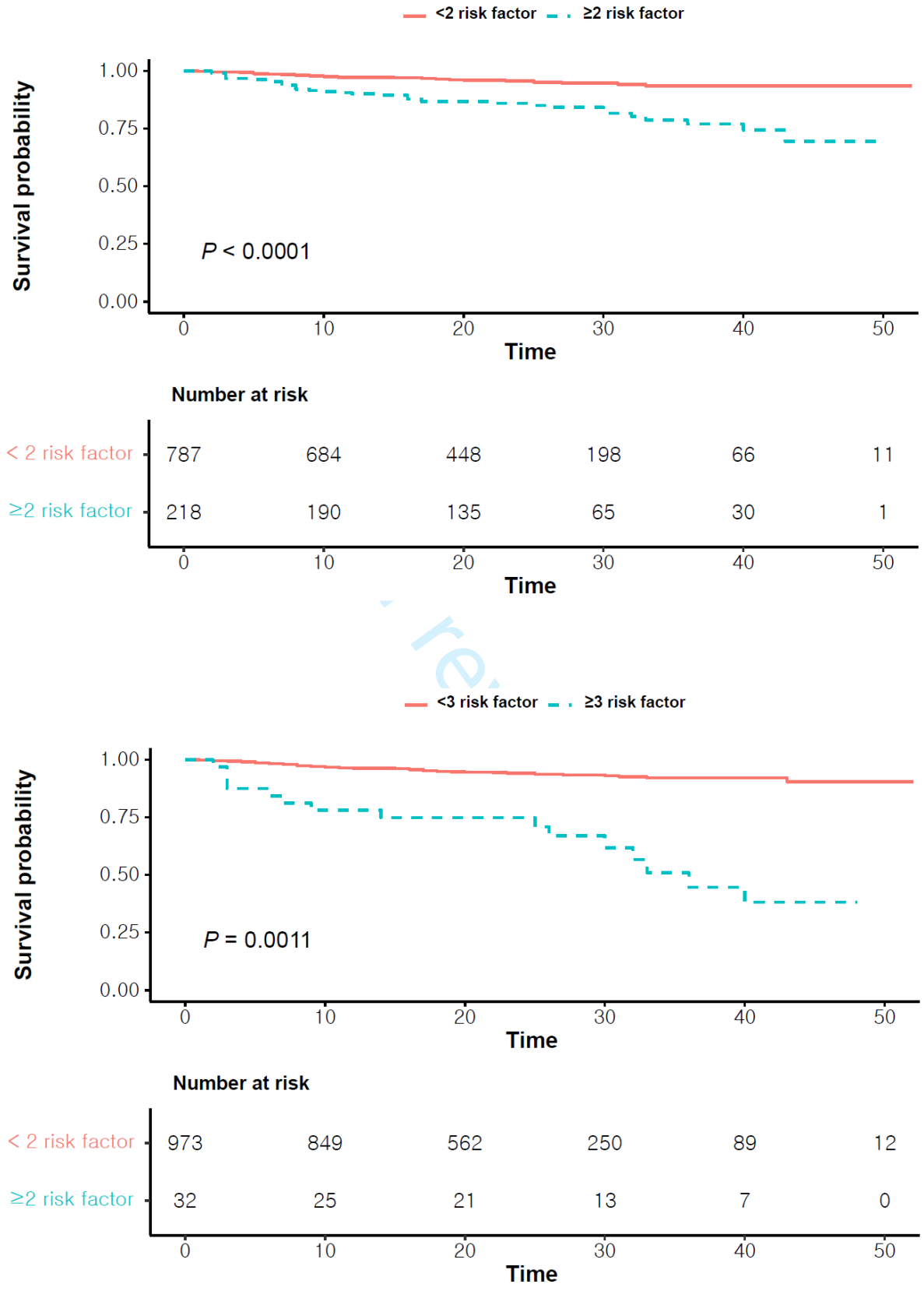

<2 risk factor
≥2 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P = 0.0043
0
10
20
30
40
50
Time
Number at risk
< 2 risk factor
181
157
116
65
22
3
≥2 risk factor
108
86
62
37
21
1
Time
<3 risk factor
≥3 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P = 0.0011
Time
Number at risk
< 2 risk factor
261
222
160
89
36
4
≥2 risk factor
28
21
18
13
7
0
Time

Figure S2. Survival of the entire group of patients with COVID-19 as the number of risk factors




<2 risk factor
≥2 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P < 0.0001
0
10
20
30
40
50
Time
Number at risk
< 2 risk factor
787
684
448
198
66
11
≥2 risk factor
218
190
135
65
30
1
Time
<3 risk factor
≥3 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P = 0.0011
Time
Number at risk
< 2 risk factor
973
849
562
250
89
12
≥2 risk factor
32
25
21
13
7
0
Time

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6-7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 5-6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 14-15 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | 8 |
| | | (c) Consider use of a flow diagram | 8 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8-9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 8 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 10 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 9-11<br>9-11<br>9-11 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11-14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 14-15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 15 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# Fibrosis-4 Index as a Predictor for Mortality in Hospitalized Patients with COVID-19: a retrospective multicenter cohort study



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-041989.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 01-Sep-2020 |
| Complete List of Authors: | Park, Jung Gil; Yeungnam University School of Medicine and College of Medicine, Internal Medicine<br>Kang, Min Kyu; Yeungnam University School of Medicine and College of Medicine, Internal Medicine<br>Lee, Yu Rim; Kyungpook National University School of Medicine, Internal Medicine<br>Song, Jeong Eun; Catholic University of Daegu School of Medicine, Internal Medicine<br>Kim, Na Young; Keimyung University School of Medicine, Internal Medicine<br>Kweon, Young Oh; Kyungpook National University School of Medicine, Internal Medicine<br>Tak, Won Young; Kyungpook National University School of Medicine, Internal Medicine<br>Jang, Se Young; Kyungpook National University School of Medicine, Internal Medicine<br>Lee, Changhyeong; Catholic University of Daegu School of Medicine, Internal Medicine<br>Kim, Byung Seok; Catholic University of Daegu School of Medicine, Internal Medicine<br>Hwang, Jae Seok; Keimyung University School of Medicine, Internal Medicine<br>Jang, Byoung Kuk; Keimyung University School of Medicine, Internal Medicine<br>Bae, Jinmok; Keimyung University School of Medicine, Internal Medicine<br>Lee, Ji Yeon; Keimyung University School of Medicine, Internal Medicine<br>Suh, Jeong Ill; Dongguk University Gyeongju Hospital, Internal Medicine<br>Park, Soo Young; Kyungpook National University School of Medicine, Internal Medicine<br>Chung, Woo Jin; Keimyung University School of Medicine, Internal Medicine |
| Primary Subject Heading: | Gastroenterology and hepatology |
| Secondary Subject Heading: | Infectious diseases |
| Keywords: | Respiratory infections < THORACIC MEDICINE, VIROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, INTERNAL MEDICINE |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

**Title: Fibrosis-4 Index as a Predictor for Mortality in Hospitalized Patients with COVID-19: a retrospective multicenter cohort study**

**Short title: Fibrosis-4 Index in COVID-19**

Jung Gil Park[a*], Min Kyu Kang[a*], Yu Rim Lee[b], Jeong Eun Song[c], Na Young Kim[d], Young Oh Kweon[b], Won Young Tak[b], Se Young Jang[b], Changhyeong Lee[c], Byung Seok Kim[c], Jae Seok Hwang[d], Byoung Kuk Jang[d], Jinmok Bae[d], Ji Yeon, Lee[d], Jeong Ill Suh[e], Soo Young Park[†], Woo Jin Chung[d†], for the Daegu-Gyeongbuk Liver Study Group (DGLSG)

[a]Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, South Korea

[b]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea

[c]Department of Internal Medicine, School of Medicine, Daegu Catholic University, Daegu, South Korea

[d]Department of Internal Medicine, School of Medicine, Keimyung University, Daegu, South Korea

[e]Department of Internal Medicine, College of Medicine, Dongguk University, Dongguk University Gyeongju Hospital, Gyeongju, South Korea

[*]These authors contributed equally to this study

[†]These authors contributed equally as corresponding authors

**Correpondence**: Soo Young Park, Department of Internal Medicine, School of

Medicine, Kyungpook National University, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu 41940, Daegu, South Korea, Email: psyoung0419@gmail.com

Woo Jin Chung, Department of Internal Medicine, School of Medicine, Keimyung University, 1035 Dalgubol-daero, Dalseo-gu, Daegu, South Korea, Email: chung50@dsmc.or.kr

## ABSTRACT

**Objective** The reliable risk factors for mortality of Coronavirus 2019 (COVID-19) has not evaluated in well characterized cohort. This study aimed to identify risk factors for in-hospital mortality within 56 days in patients with severe infection of COVID-19.

**Design** Retrospective multicenter cohort study

**Setting** Five tertiary hospitals of Daegu, South Korea

**Participants** 1005 participants over 19 years old confirmed COVID-19 using real-time polymerase chain reaction from nasopharyngeal and oropharyngeal swabs.

**Methods** The clinical and laboratory features of patients with COVID-19 receiving respiratory support were analyzed to ascertain the risk factors for mortality using the Cox proportional hazards regression model. The relationship between overall survival and risk factors was analyzed using the Kaplan-Meier method.

**Outcome** In-hospital mortality for any reason within 56 days

**Results** Of the 1005 patients, 289 (28.8%) received respiratory support and of these, 70 patients (24.2%) died. In multivariate analysis, high fibrosis-4 index (FIB-4, hazard ratio [HR] 2.784), low lymphocyte count (HR 0.480), diabetes (HR 1.917), and systemic inflammatory response syndrome (HR 1.714) were found to be independent risk factors for mortality in patients with COVID-19 receiving respiratory support (all $P < 0.05$). Regardless of respiratory support, survival in the high FIB-4 group was significantly lower than in the low FIB-4 group (28.8 days vs. 44.0 days, respectively, $P < 0.001$). A number of risk factors were also significantly related to survival in patients with COVID-19 regardless of respiratory support (0-4 risk factors, 50.2 days; 49.7 days; 44.4 days; 32.0 days; 25.0 days, $P < 0.001$).

**Conclusion** Fibrosis-4 index is a useful predictive marker for mortality in COVID-19 patients regardless of its severity.

*Keywords: Coronavirus, COVID-19, risk factors, fibrosis, mortality, survival*

**Strengths and limitations of this study**

- Use of simple scoring system widely used in clinical practice
- Predict mortality regardless of its severity
- Very low probability of sampling bias
- Requiring further studies for validation with other cohorts
- Relatively early cohort before outbreak caused by newer variant of COVID-19

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), is one of the most important healthcare concerns worldwide.[1] It was first identified in Wuhan City, Hubei province, central China, and linked to Wuhan's Huanan Seafood Wholesale Market in December 2019.[2] To investigate the causative pathogen, pan-CoV polymerase chain reaction (PCR) was performed initially. followed by metagenomics analysis using next-generation sequencing.[3] After commercial real time quantitative PCR-based detection methods became available, the number of patients with confirmed COVID-19 rapidly increased.[4] Subsequently, this outbreak spread internationally, and was recognized as a pandemic by the World Health Organization (WHO) on 11 March 2020.[5]

In South Korea, 3705 patients were diagnosed in the Daegu and Gyeongsangbuk-do area among a total of 4212 patients diagnosed in South Korea from January 19 to March 2, 2020.[6] Epidemiological surveillance revealed that 2333 (63.0%) of cases in this area were related to the religious group Shincheonji.[6] At that time, the mortality rate was only 0.5% in South Korea and 0.6% in the Daegu and Gyeongsangbuk-do area.[7] However, by April 28, the mortality rate had increased to 224 of 10752 confirmed cases (2.3%).[8]

As a result of unprecedented demand, most countries are experiencing a shortage of medical resources. The difficulty of dealing with this emergency would be assisted by earlier diagnosis, as well as forecasts of mortality. Several Chinese studies of clinical characteristics and risk factors relating to COVID-19 have been published[4 9-13], and recently, the clinical and epidemiological experience of several other countries have been

reported.[14 15] However, few reports of risk modeling and prediction are awaiting peer review and publication[16], and most of these studies have limited sample size or high risk of bias[16]. The risk prediction models in these studies were established using conventional scoring systems, risk nomograms, or advanced machine learning models[17-19]. Although the performance of such models is relatively good, no COVID-19 risk prediction model can currently be recommended for clinical use, due to a number of limitations.[20].

This study aims to evaluate the predictive risk factors for mortality by analyzing epidemiologic and laboratory features in patients with COVID-19 receiving respiratory support in tertiary hospitals within the Daegu and Gyeongsangbuk-do area. Most cases in South Korea were concentrated in this area, the most severe cases being admitted to five tertiary hospitals.

## MATERIALS AND METHODS

### Patients and their public involvement

After the beginning of the COVID-19 outbreak on February 18, 2020, in Daegu, all COVID-19 patients were admitted to one designated tertiary hospital. Because of limited medical resources, efficient allocation was required. Therefore, from March 2, the disinfection team of Daegu classified all new COVID-19 patients on the basis of severity of respiratory symptoms and oxygen demand to transfer to one of four other tertiary hospitals in accordance with regional policy. Accordingly, from February 20 to April 14, 2020, we enrolled 1005 hospitalized patients aged >19 years with COVID-19 confirmed

by PCR in five tertiary hospitals of Daegu, South Korea.

This study was performed in accordance with the ethical guidelines of the revised Helsinki Declaration of 2013 and approved by the Institutional Review Board of all tertiary hospitals. Written informed consent by the patients was waived due to the retrospective nature of our study. It was not possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of this study.

**Data collection**

The medical records of anthropometric and epidemiological data, patients' clinical characteristics, radiologic and laboratory data, treatments, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and clinical outcomes, were collected retrospectively by each hospital and reviewed by two independent reviewers. Laboratory tests included complete blood cell and lymphocyte count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), liver and kidney function tests, electrolytes, and serum ferritin on admission day. All patients underwent chest radiography with or without computed tomography (CT). Antivirals, hydroxychloroquine, systemic glucocorticoid, intravenous immunoglobulin, respiratory support, continuous renal replacement therapy, and extracorporeal membrane oxygenation (ECMO) were included on the treatment of COVID-19. The data collection terminated on April 14, 2020.

**Definition**

In accordance with the WHO interim guidance, all COVID-19 cases were diagnosed by

detection of SARS-CoV-2 sequence using real-time PCR from nasopharyngeal and oropharyngeal swabs. Fever was defined as tympanic temperature of 37.5 °C or higher. Systemic inflammatory response syndrome (SIRS) on admission was defined by satisfaction of any two of the criteria: (a) white blood cell count < 4000 cells/mm$^3$ or > 12000 cells/mm, (b) body temperature < 36 °C or > 38 °C, (c) heart rate >90 beats/min, and (d) tachypnea >20 breaths/min. Persistent hypotension was defined by MAP < 65 mmHg despite volume resuscitation, requiring vasopressors to maintain MAP. Acute respiratory distress syndrome (ARDS) were defined in accordance with the WHO interim guidance. Acute kidney injury was defined either from the highest serum creatinine level (>0.3 mg/dl within 48 hours or 1.5 times of the baseline level within 7 days), and/or from decreased urine output (<0.6 ml/kg/h for 6 hours) on admission. In accordance with oxygen demand, two groups of respiratory support were defined as low-dose oxygen group using nasal cannula or venturi mask and high-dose oxygen group using high–flow nasal cannula, invasive mechanical ventilation and/or ECMO.

Chronic liver disease was defined by chronic hepatitis B or C infection, liver cirrhosis, and hepatocellular carcinoma by history taking or serology test. The fibrosis-4 index (FIB-4), which is calculated from age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet counts, was originally used to predict liver fibrosis in patients with chronic liver disease. FIB-4 was assessed as: age (year) × AST (U/L)/ [platelet count ($10^9$/L) × √ALT (U/L)].[21]

**Study outcomes**

The primary objective of this study was to identify predictive risk factors for in-hospital

mortality for any reason within 56 days in patients with COVID-19 receiving respiratory support. The secondary objective was to evaluate whether FIB-4 index is associated with mortality in patients with COVID-19 regardless of respiratory support.

**Statistical analysis**

All continuous data were expressed as mean and standard deviation (mean ± SD) or median with range, and compared using Student's t-test or the Mann-Whitney U test. Categorical data were compared using a χ-squared test or Fischer's exact test. The predictive factors for mortality were assessed using the Cox proportional hazards regression model with hazards ratio (HR) using backward selection method. Receiver operating characteristic (ROC) analysis was conducted to assess the predictive performance of assessed risk factors. The best cut-off values were calculated based on the Youden index. The relationship between overall survival and FIB-4 was calculated using the Kaplan-Meier method. The valuables including age, AST, ALT, and platelet, which were used for calculation of FIB-4, were not included in the multivariate analysis to avoid multicollinearity. *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using R (version 3.0, http://cran.r-project.org/, install. packages("devtools")) software.

**RESULTS**

**Baseline characteristics**

Of 1,005 patients with COVID-19, 289 (28.8%) received respiratory support and were

included in this study. Of these, 162 (56.1 %) were treated with low-dose oxygen therapy using a nasal or venturi mask, while 127 (43.9%) were treated with a high-flow nasal mask, invasive mechanical ventilation and/or ECMO. Patient disposition is shown in Figure 1. The baseline characteristics of the COVID-19 patients receiving respiratory support are shown in Table 1. There were several differences in demographics and past history between fatal cases and survivors, including older age, preponderance of males, and more frequent diabetes among fatal cases. However, there was no significant difference in the use of ACE inhibitors or ARBs. Duration of symptoms before admission was shorter in survivors but the presence of fever or respiratory symptoms on admission did not differ between survivors and non-survivors. There was no significant difference in viral signs on admission except for frequent SIRS in fatal cases. Some differences in laboratory tests on admission were also significant, including higher white blood cell count, CRP, procalcitonin, AST, gamma glutamyl transferase, prothrombin time, blood urea nitrogen, serum creatinine, and lower lymphocyte count, platelet count, serum albumin, and serum sodium in fatal cases compared with survivors.

**Treatments and clinical outcomes**

The treatments and clinical outcomes of patients with COVID-19 receiving respiratory support are shown in Table 2. Of these, 57 (19.7%) and 70 (24.2%) were treated with high-flow nasal cannula and invasive mechanical ventilation, respectively. Analysis of clinical outcomes revealed that 113 patients (39.1%) had ARDS, 93 (33.2%) were admitted to an intensive care unit (ICU), and 18 (6.2%) underwent ECMO. The median duration of hospital stay was 25 days (range 8-33). Survivors were less frequently treated

with darunavir/cobicistat, systemic glucocorticoid, high-flow nasal cannula, invasive mechanical ventilation, or continuous renal replacement therapy compared with fatal cases. Survivors had a longer median duration of hospital stay compared with fatal cases, were less frequently admitted to an ICU, and less frequently developed persistent hypotension, ARDS or acute kidney injury.

**Risk factors for mortality in COVID-19 patients receiving respiratory support**

Univariate analysis identified age, sex, diabetes, chronic obstructive pulmonary disease, lymphocyte count, AST, ESR, and SIRS as significant variables relating to mortality in patients with COVID-19 receiving respiratory support (Table 3). Multivariate analysis identified age (HR 1.054; 95% CI 1.028–1.082; $P < 0.001$), diabetes (HR 2.226; 95% CI 1.357–3.652; $P = 0.002$), low lymphocyte count (HR 0.999; 95% CI 0.998–1.000; $P = 0.005$), and high AST (HR 1.002; 95% CI 1.000–1.003; $P = 0.033$) as independent predictors of mortality. Lower platelet count (HR 0.997; 95% CI 0.994–1.000, $P = 0.069$) and presence of SIRS on admission (HR 1.968; 95% CI 1.199–3.230; $P = 0.074$) tended to be associated with severe COVID-19, but this did not reach statistical significance.

**Risk factors for mortality, including Fibrosis-4 index**

Based on multivariate analysis, we used FIB-4 as a predictive risk factor candidate. In multivariate analysis including FIB-4 as a continuous variable, diabetes (HR 1.998; 95% CI 1.202–3.321; $P = 0.008$), lower lymphocyte count (HR 0.999; 95% CI 0.998–1.000; $P = 0.003$), and FIB-4 (HR 1.115; 95% CI 1.069–1.163; $P < 0.001$) were identified as independent predictors of mortality in COVID-19 patients receiving respiratory support (Table S1). To set a cut-off value of FIB-4 and lymphocyte count, ROC analysis was

performed (Figure 2). The Areas under the ROC curves (AUCs) of FIB-4 and lymphocyte counts were 0.702 and 0.647 with sensitivity of 48.5% and 78.6%, specificity of 87.6% and 45.8%, positive predictive value (PPV) of 55.0% and 32.0%, and negative predictive value (NPV) of 84.4% and 86.9%, respectively (all $P$ <0.001). The optimal cut-off values (COVs) of FIB-4 and lymphocyte count were 4.95 and 1010, respectively.

In multivariate analysis after converting FIB-4 and lymphocyte count to categorical variables, diabetes (HR 1.917; 95% CI 1.181–3.111; $P$ = 0.009), low lymphocyte count (HR 0.480; 95% CI 0.271–0.852; $P$ = 0.012), SIRS (HR 1.714; 95% CI 1.048–2.802; $P$ = 0.032), and high FIB-4 (HR 2.784; 95% CI 1.691–4.585; $P$ < 0.001) were identified as independent predictors of mortality (Table 4). In addition, the results of high FIB-4 as a predictor of survival was consistent in stepwise multivariate analysis (Table S2)

**FIB-4 and other predictive risk factors for survival in COVID-19 patients receiving respiratory support**

Among the four predictive risk factors, FIB-4 was the best predictor of mortality in COVID-19 patients receiving respiratory support. Therefore, we performed survival analysis to compare mortality in the high FIB-4 group (FIB-4 ≥ 4.95) and low FIB-4 group (FIB-4 < 4.95). Survival in the high FIB-4 group was significantly lower than in the low FIB-4 group (high FIB-4, 28.8 days [23.8–33.8]; low FIB-4, 44.0 days [41.9–46.1], $P$ < 0.001) (Figure 3a.) Using the four variables diabetes, lymphocyte count, SIRS on admission, and FIB-4, we performed survival analysis to predict mortality in COVID-19 patients receiving respiratory support. As the number of risk factors increased, survival of the patients significantly deteriorated (no risk factor, 47.3 days [44.2-50.4]; 1 risk

factor, 40.7 days [37.4-44.0]; 2 risk factors, 38.0 days [33.8-42.2]; 3 risk factors, 30.7 days [23.9-37.5]; 4 risk factors, 25.0 days [6.3-43.7], $P = 0.0016$, Figure 3b, Figure S1).

To explore additional predictive performance for mortality in the entire group of patients with COVID-19, we performed survival analysis to compare mortality in the high and low FIB-4 groups using the same cut-off. Survival in the high FIB-4 group was significantly lower than in the low FIB-4 group (high FIB-4, 32.5 days [27.7–37.2]; low FIB-4, 50.0 days [49.3–50.6], $P < 0.001$) (Figure 4a.) Using four variables, we also performed survival analysis to predict mortality in the entire group of patients with COVID-19. As the number of risk factors increased, survival significantly deteriorated (no risk factor, 50.2 days [48.6-51.7]; 1 risk factor, 49.7 days [48.8-50.5]; 2 risk factors, 44.4 days [42.2-46.6]; 3 risk factors, 32.0 days [25.7-38.3]; 4 risk factors, 25.0 days [6.3-43.7], $P < 0.001$, Figure 4b, Figure S2). In COVID-19 patients receiving high-dose oxygen, survival in the high FIB-4 group was significantly lower than in the low FIB-4 group (high FIB-4, 16.5 days [7.0–32.0]; low FIB-4, 20.0 days [10.0–33.0], $P = 0.011$) (Data not shown).

## DISCUSSION

In this retrospective cohort study, predictive risk factors for mortality were evaluated in 289 patients with confirmed COVID-19 receiving respiratory support in the Daegu and Gyeongsangbuk-do area. Diabetes, low lymphocyte count, SIRS, and FIB-4 were revealed as independent risk factors for mortality in COVID-19. Furthermore, survival of patients with low FIB-4 and number of risk factors is better than those with high FIB-4

and number of risk factors. A recent meta-analysis found that the main laboratory abnormalities in COVID-19 patients included low lymphocyte count, and elevated CRP and lactate dehydrogenase (LDH).[22] In non-survivors, or severely ill patients requiring ICU care or suffering from ARDS, laboratory abnormalities including high WBC count, low lymphocyte count, prolonged prothrombin time, low albumin, elevated AST, ALT, total bilirubin, LDH, creatinine, troponin I, CRP, procalcitonin, ferritin, and D-dimer were identified as risk factors in previous studies.[9 10 12] However, numbers of enrolled patients were small and multivariate analyses were not performed. In a recent study, logistic regression analysis identified age, Sequential Organ Failure Assessment (SOFA) score, and D-dimer as predictive risk factors for death in patients with COVID-19 pneumonia.[13] SOFA score is derived from $PaO_2/FiO_2$, use of mechanical ventilator, platelets count, Glasgow Coma scale, bilirubin, mean arterial pressure or requirement for vasoactive agents, and serum creatinine or urine output. The score is related to the cytokine storm in sepsis[23], and we think some of the risk factors in our study, including platelets as a component of the FIB-4 index, and SIRS, were also associated with this serious inflammatory condition. This recent study included patients similar to those in the present study, as judged from the proportion of patients receiving respiratory support (82.1% versus 100% in the present study) and the mortality rate (28.3% versus 24.2% in the present study).[13] Multivariate analysis in two recent studies showed that neutrophil-to-lymphocyte ratio, CD4 T cell count, and age were independent risk factors of in-hospital mortality and ICU admission for COVID-19.[24 25] Severe inflammation dysregulates the immune response and is characterized by decreased memory helper T (Th) cells and regulatory T cells with increased naive Th cells in patients with COVID-

19 [26]. These findings are consistent with low lymphocyte count as an independent risk factor for mortality in our study. However, in previous studies, survival analysis was not performed, and the enrolled patients were somewhat different from those in the present study.

Liver injury in COVID-19 was observed more frequently in severe cases than in mild cases.[4 12] Though the mechanism is unclear, elevated AST and ALT may be related to the immune response in severe pneumonia, which may result from inflammatory cytokines following COVID-19 infection.[27] Elevated liver enzyme can be also associated with drug induced liver injury (DILI), which may result from antibacterial and antiviral drugs, anti-inflammatory drugs, and vasopressors in severe cases.[28] As there has been no study of DILI in COVID-19 infection, its prevalence should be investigated. However, in this study, laboratory tests performed at the time of admission did not indicate an association between AST elevation and DILI. Also in this study, although FIB-4 was originally used in patients with liver disease, it was identified as a predictor of mortality in patients with COVID-19, whether or not they were receiving respiratory support. Elevated LDH has been reported as a promising predictor for severe COVID infection.[18 29 30] However, it was only identified as a risk factor by univariate analysis, not by multivariate analysis. We suggest that the ratio of AST to ALT in FIB-4 may be a better predictor of mortality than the level of LDH, due to its non-specificity of cause. In addition, the common finding of elevated AST in patients with severe disease in several other studies supports the present study.[4 12 31] Recently, association of FIB-4 with ICU admission in patients with COVID-19 was reported in Spain.[32] They calculated FIB-4 using laboratory tests at the same time of SARS-CoV-2 detection to assess presence of advanced fibrosis. However,

although they exclude previously diagnosed patients with myopathies and platelets disorders to avoid non-specificity of FIB-4, values of AST, ALT, and platelets can be affected by COVID-19 infection itself. Furthermore, as described above, severe cause of COVID-19 infection can affect AST and platelet more than mild case. If they overcome these, we think they should use laboratory test to estimate advanced fibrosis before patients had COVID-19.

When FIB-4 is analyzed with other risk factors including lymphocyte count, SIRS, and diabetes, as number of risk factors increases, survival deteriorates in patients with COVID-19 regardless of respiratory support. There are several published or preprinted studies of prediction models for the prognosis of patients with COVID-19.[16] Albumin, direct bilirubin, and red blood cell distribution width have been suggested as diagnostic or prognostic indicators of severe disease or mortality in COVID-19.[16] However, among these three factors, albumin was not a significant risk factor, and the other two factors were not evaluated in the present study. Most of the proposed models have been open to criticism on the grounds of severe sampling bias due to rarely reported length of follow-up and prevalence of COVID-19 with or without severe infection. A strength of the present study is the low probability of sampling bias, because approximately three fourths of patients with COVID-19 in South Korea have been diagnosed in the Daegu and Gyeongsangbuk-do area, and our entire cohort was derived from tertiary hospitals in that area.

This study has some limitations. First, there was no validation with another cohort. As described above, most of the COVID-19 cases were enrolled in this study. Thus, it would

be impossible to validate these results without undertaking an international study. Improved assessments of international data on COVID-19 will require data sharing, using a reporting protocol specified by WHO.[33] Second, detailed radiologic assessment of CT scans was not performed. To our knowledge, there are only a few reports at preprint stage which include clinical features and radiologic features from CT scan with artificial intelligence techniques to develop prediction models.[34] However, this study also has sampling bias as well as an inadequate sample size.[20 34] Therefore, advanced machine learning combining radiologic image analysis with clinical risk factors would be needed to develop a robust prediction model. Third, prediction of severe COVID-19 including ICU admission or ARDS was not analyzed in this study. However, we think prediction of severe COVID-19 was not appropriate for our cohort, because transfer to a tertiary hospital may introduce the possibility of sampling bias. Thus, we used the objective outcome of mortality in this study.

In conclusion, FIB-4, diabetes, low lymphocyte count, and SIRS are independent risk factors of mortality in patients with COVID-19 receiving respiratory support. Among these risk factors, FIB-4 is a robust predictor of survival in patients with COVID-19 regardless of respiratory support. A number of risk factors are significantly related to survival in patients with COVID-19 regardless of respiratory support.

**Author Contributions:** Conceptualization, Soo Young Park and Woo Jin Chung; Formal analysis, Min Kyu Kang; Data curation, Min Kyu Kang, Yu Rim Lee, Jeong Eun Song and Na Young Kim; Investigation, Jung Gil Park, Min Kyu Kang, Yu Rim

Lee, Jeong Eun Song, Na Young Kim, Young Oh Kweon, Won Young Tak, Se Young Jang, Changhyeong Lee, Byung Seok Kim, Jae Seok Hwang, Byoung Kuk Jang, Jinmok Bae, Ji Yeon Lee, Jeong Ill Suh and Soo Young Park; Supervision, Soo Young Park and Woo Jin Chung; Visualization, Jung Gil Park; Writing – original draft, Jung Gil Park and Min Kyu Kang; Writing – review & editing, Soo Young Park and Woo Jin Chung.

**Funding:** There was no external funding for this work.

**Acknowledgements:** We appriciate all dedicated doctors and epidemiologist who contribute declining trends of patients with COVID-19 in the Daegu and Gyeongsangbuk-do area and Editage (www.editage.co.kr) for English language editing.

**Conflict of interest:** The authors declare no conflicts of interest about this work.

**Data Availability:** The data that support the findings of this study are also available from the corresponding author (SYP and WJC) upon reasonable request.

References

1. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J* 2020;55(4) doi: 10.1183/13993003.00607-2020 [published Online First: 2020/04/10]

2. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020;92(4):401-02. doi: 10.1002/jmv.25678 [published Online First: 2020/01/18]

3. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579(7798):270-73. doi: 10.1038/s41586-020-2012-7 [published Online First: 2020/02/06]

4. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020 doi: 10.1056/NEJMoa2002032 [published Online First: 2020/02/29]

5. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020". World Health Organization. 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

6. Korean Society of Infectious D, Korean Society of Pediatric Infectious D, Korean Society of E, et al. Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci* 2020;35(10):e112. doi: 10.3346/jkms.2020.35.e112 [published Online First: 2020/03/17]

7. Korean Society of Infectious D, Korea Centers for Disease C, Prevention. Analysis

on 54 Mortality Cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020. *J Korean Med Sci* 2020;35(12):e132. doi: 10.3346/jkms.2020.35.e132 [published Online First: 2020/04/02]

8. Korea Centers for Disease Control and Prevention. The update of COVID-19 in Korea as of April 28. https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=00300030

9. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020 doi: 10.1001/jamainternmed.2020.0994 [published Online First: 2020/03/14]

10. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020 doi: 10.1001/jama.2020.1585 [published Online First: 2020/02/08]

11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7 [published Online First: 2020/02/03]

12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5 [published Online First: 2020/01/28]

13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.

*Lancet* 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3 [published Online First: 2020/03/15]

14. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020 doi: 10.1001/jama.2020.5394 [published Online First: 2020/04/07]
15. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med* 2020 doi: 10.1056/NEJMoa2006100 [published Online First: 2020/04/15]
16. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ* 2020;369:m1328. doi: 10.1136/bmj.m1328 [published Online First: 2020/04/09]
17. Shi Y, Yu X, Zhao H, et al. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Crit Care* 2020;24(1):108. doi: 10.1186/s13054-020-2833-7 [published Online First: 2020/03/20]
18. Gong J, Ou J, Qiu X, et al. A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa443 [published Online First: 2020/04/17]
19. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality - preliminary results: medRxiv [Preprint] 2020.
20. Sperrin M, Grant SW, Peek N. Prediction models for diagnosis and prognosis in

Covid-19. *BMJ* 2020;369:m1464. doi: 10.1136/bmj.m1464 [published Online First: 2020/04/16]

21. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43(6):1317-25. doi: 10.1002/hep.21178 [published Online First: 2006/05/27]

22. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect* 2020 doi: 10.1016/j.jinf.2020.03.041 [published Online First: 2020/04/14]

23. Marik PE, Taeb AM. SIRS, qSOFA and new sepsis definition. *J Thorac Dis* 2017;9(4):943-45. doi: 10.21037/jtd.2017.03.125 [published Online First: 2017/05/20]

24. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect* 2020 doi: 10.1016/j.jinf.2020.04.002 [published Online First: 2020/04/14]

25. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect* 2020;80(5):e1-e6. doi: 10.1016/j.jinf.2020.03.004 [published Online First: 2020/03/17]

26. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa248 [published Online First: 2020/03/13]

27. Fan Z, Chen L, Li J, et al. Clinical Features of COVID-19-Related Liver Damage. *Clinical gastroenterology and hepatology : the official clinical practice journal*

*of the American Gastroenterological Association* 2020 doi: 10.1016/j.cgh.2020.04.002 [published Online First: 2020/04/14]

28. Qi X, Liu C, Jiang Z, et al. Multicenter analysis of clinical characteristics and outcome of COVID-19 patients with liver injury. *Journal of hepatology* 2020 doi: 10.1016/j.jhep.2020.04.010 [published Online First: 2020/04/20]
29. Yan L, Zhang H-T, Xiao Y, et al. Prediction of survival for severe Covid-19 patients with three clinical features: development of a machine learning-based prognostic model with clinical data in Wuhan: medRxiv [Preprint] 2020.
30. Xie J, Hungerford D, Chen H, et al. Development and external validation of a prognostic multivariable model on admission for hospitalized patients with COVID-19: medRxiv [Preprint] 2020.
31. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;20(4):425-34. doi: 10.1016/S1473-3099(20)30086-4 [published Online First: 2020/02/28]
32. Ibanez-Samaniego L, Bighelli F, Uson C, et al. Elevation of Liver Fibrosis Index FIB-4 Is Associated With Poor Clinical Outcomes in Patients With COVID-19. *J Infect Dis* 2020;222(5):726-33. doi: 10.1093/infdis/jiaa355 [published Online First: 2020/06/21]
33. Moorthy V, Henao Restrepo AM, Preziosi MP, et al. Data sharing for novel coronavirus (COVID-19). *Bull World Health Organ* 2020;98(3):150. doi: 10.2471/BLT.20.251561 [published Online First: 2020/03/07]
34. Bai X, Fang C, Zhou Y, et al. Predicting COVID-19 malignant progression with AI

techniques: medRxiv [Preprint] 2020.

Table 1. Baseline characteristics of patients with COVID-19 receiving respiratory support

| | All (n = 289, 100%) | Survivors (n = 219, 75.8%) | Fatal cases (n = 70, 24.2%) | *P* value* |
|---|---|---|---|---|
| **Demographic and clinical characteristics** | | | | |
| Age, years | 72.0 (62.0-80.0) | 70.0 (60.0–79.0) | 77.0 (71.0–84.0) | <0.001 |
| Female gender | 156 (54.0) | 128 (58.4) | 28 (40.0) | 0.011 |
| Body mass index, kg/m$^2$ | 24.3 (22.2–26.3) | 24.2 (22.2–26.2) | 24.5 (22.2–26.8) | 0.577 |
| **Comorbidity** | | | | |
| Hypertension | 132 (45.8) | 96 (44.0) | 36 (51.4) | 0.346 |
| Diabetes | 93 (32.3) | 59 (27.1) | 34 (48.6) | 0.001 |
| Cardiovascular disease | 20 (6.9) | 14 (6.4) | 6 (8.6) | 0.723 |
| Chronic obstructive pulmonary disease | 9 (3.1) | 4 (1.8) | 5 (7.1) | 0.067 |
| Chronic kidney disease | 11 (3.8) | 9 (4.1) | 2 (2.9) | 0.906 |
| Chronic liver disease | 15 (5.2) | 9 (4.1) | 6 (8.6) | 0.248 |
| Liver cirrhosis | 8 (2.8) | 4 (1.8) | 4 (5.7) | 0.191 |
| Hepatocellular carcinoma | 2 (0.7) | 1 (0.5) | 1 (1.4) | 0.979 |
| ACE inhibitors or ARBs use | 61 (24.8) | 47 (24.1) | 14 (27.5) | 0.756 |
| **Symptoms on admission** | | | | |
| Fever/chills | 195 (67.9) | 145 (66.5) | 50 (72.5) | 0.438 |
| Cough | 175 (61.2) | 139 (63.8) | 36 (52.9) | 0.145 |
| Shortness of breath | 152 (53.0) | 112 (51.4) | 40 (58.0) | 0.413 |
| Gastrointestinal symptoms (Vomiting/Diarrhea) | 73 (25.4) | 67 (30.7) | 6 (8.7) | <0.001 |
| Myalgia | 88 (30.8) | 73 (33.5) | 15 (22.1) | 0.103 |
| Headache | 46 (16.1) | 43 (19.7) | 3 (4.4) | 0.005 |
| Duration of symptom before admission, days | 6 (3–9) | 6 (3–9) | 4.5 (2–7) | 0.031 |
| **Vital signs at presentation** | | | | |
| Temperature, °C | 36.9 (36.5–37.6) | 37.0 (36.5–37.6) | 36.7 (36.5–37.3) | 0.070 |

| | | | | |
|---|---|---|---|---|
| Respiratory rate, breath/min | 20 (20–22) | 20 (20–22) | 20 (20–23) | 0.101 |
| Saturation, % | 95 (92–98) | 95 (93–98) | 95 (90–100) | 0.948 |
| Systolic pressure, mm Hg | 130 (116–145) | 130 (120–144) | 122 (108–146) | 0.062 |
| Heart rate, /min | 86 (72–100) | 85 (72–97) | 92 (72–102) | 0.140 |
| **SIRS on admission** | 102 (35.7) | 65 (30.1) | 37 (52.9) | 0.001 |
| **Radiologic and laboratory findings** | | | | |
| **Radiologic findings** | | | | |
| Abnormal chest radiograph | 269 (93.1) | 201 (91.8) | 68 (97.1)) | 0.205 |
| Bilateral involvement on chest radiographs | 225 (83.6) | 163 (81.1) | 62 (91.2) | 0.080 |
| **Laboratory findings** | | | | |
| White blood cell count, $\times 10^3$/uL | 6140 (4695–8065) | 6000 (4690-7420) | 7320 (5100–12020) | 0.001 |
| Lymphocyte count, $\times 10^3$/uL | 895 (611–1260) | 952 (661–1321) | 702 (490–980) | <0.001 |
| Haemoglobin, g/dL | 12.4 (11.1–13.6) | 12.4 (11.2–13.6) | 12.6 (10.9–13.9) | 0.510 |
| Platelet count, $\times 10^9$/L | 192 (146–267) | 200 (150–277) | 166 (132–239) | 0.029 |
| Erythrocyte sedimentation rate, mm/h | 57 (39–76) | 57 (39–76) | 51 (40–70) | 0.592 |
| C–reactive protein, mg/L | 10.1 (4.8–21.5) | 9.3 (4.0–20.4) | 13.4 (7.4–24.8) | 0.015 |
| Procalcitonin, ng/mL | 0.1 (0.1–0.4) | 0.1 (0.1–0.2) | 0.4 (0.1–1.1) | <0.001 |
| Aspartate aminotransferase, U/L | 38 (26–53) | 34 (25–50) | 49 (34–65) | <0.001 |
| Alanine aminotransferase, U/L | 21 (15–33) | 20 (15–32) | 23 (16–38) | 0.528 |
| Total bilirubin, mg/dL, mg/dL | 0.6 (0.4–0.9) | 0.6 (0.4–0.9) | 0.7 (0.4–0.9) | 0.240 |
| Alkaline phosphatase, U/L | 71 (57–92) | 71 (57–91) | 72 (58–104) | 0.488 |
| Gamma glutamyl transferase, U/L | 35 (22–61) | 27 (16.5–48.5) | 60 (40–101) | 0.001 |
| Serum albumin, g/dL | 3.4 (3.2–3.7) | 3.5 (3.2–3.8) | 3.2 (3.0–3.4) | <0.001 |
| Prothrombin time, second | 12.4 (11.8–13.3) | 12.4 (11.7–13.1) | 12.8 (11.9–14.8) | 0.026 |
| Prothrombin time, INR | 1.1 (1.0–1.1) | 1.0 (1.0–1.1) | 1.1 (1.0–1.3) | 0.015 |
| Blood urea nitrogen, mg/dL | 17 (12–24) | 15 (12–21) | 22 (16–37) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Creatinine, mg/dL | 0.8 (0.7–1.1) | 0.8 (0.7–1.0) | 1.0 (0.8–1.7) | <0.001 |
| Estimated glomerular filtration rate, mL/min/1.73㎡ | 80 (58–98) | 84 (64–100) | 63 (39–91) | 0.001 |
| Sodium, mmol/L | 137 (134–141) | 138 (134–141) | 136 (133–140) | 0.006 |
| Potassium, mmol/L | 4.1 (3.7–4.5) | 4.1 (3.7–4.5) | 4.2 (3.5–4.7) | 0.870 |
| Lactate dehydrogenase, U/L | 558 (405–753) | 560 (404–753) | 556 (410–762) | 0.969 |
| Creatine kinase, U/L | 79 (52–155) | 73 (51–149) | 86 (54–172) | 0.307 |
| Serum ferritin, ng/mL | 552 (327–975) | 430 (308–941) | 659 (521–1432) | 0.115 |

Data are expressed as median and interquartile range (IQR) or numbers (%).
*Calculated by Student's t test (or the Mann-Whitney U test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; SIRS, systemic inflammatory response syndrome

Table 2. Treatments and clinical outcomes of patients with COVID-19 receiving respiratory support

| | All (n = 289) | Survivors (n = 219) | Fatal cases (n = 70) | *P* value* |
|---|---|---|---|---|
| **Treatments** | | | | |
| Antiviral therapy | | | | |
| Lopinavir/ritonavir | 235 (81.3) | 182 (83.1) | 53 (75.7) | 0.228 |
| Darunavir/cobicistat | 42 (14.5) | 26 (11.9) | 16 (22.9) | 0.038 |
| Hydroxychloroquine | 187 (64.7) | 137 (62.6) | 50 (71.4) | 0.227 |
| Systemic glucocorticoid | 152 (52.6) | 96 (43.8) | 56 (80.0) | <0.001 |
| Intravenous immunoglobulin | 26 (9.0) | 16 (7.3) | 10 (14.3) | 0.124 |
| High–flow nasal cannula | 57 (19.7) | 19 (8.7) | 38 (54.3) | <0.001 |
| Invasive mechanical ventilation | 70 (24.2) | 38 (17.4) | 32 (45.7) | <0.001 |
| Continuous renal–replacement therapy | 22 (7.6) | 5 (2.3) | 17 (24.3) | <0.001 |
| ECMO | 18 (6.2) | 10 (4.6) | 8 (11.4) | 0.074 |
| **Clinical outcomes** | | | | |
| ICU admission | 96 (33.2) | 59 (26.9) | 37 (52.9) | <0.001 |
| Persistent hypotension | 77 (26.6) | 40 (18.3) | 37 (52.9) | <0.001 |
| ARDS | 113 (39.1) | 49 (22.4) | 64 (91.4) | <0.001 |
| Acute kidney injury | 52 (18.0) | 16 (7.3) | 36 (51.4) | <0.001 |
| Hospital stay, days | 25 (14–33) | 27 (19–37) | 10 (6–19) | <0.001 |

Data are expressed as median and interquartile range (IQR) or numbers (%).
*Calculated by Student's t test (or the Mann-Whitney U test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; ARDS, acute respiratory distress
syndrome

Table 3. Risk factors for mortality in patients with COVID-19 receiving respiratory support

| Variable | Univariate | Multivariate analysis | |
|---|---|---|---|
| | *P* value* | *P* value* | Hazard ratio (95% CI) |
| Age, years | <0.001 | <0.001 | 1.054 (1.028–1.082) |
| Male (yes/no) | 0.014 | | |
| Comorbidities (yes/no) | | | |
| Hypertension | 0.392 | | |
| Diabetes | 0.001 | 0.002 | 2.226 (1.357-3.652) |
| Chronic obstructive pulmonary disease | 0.009 | | |
| Chronic kidney disease | 0.841 | | |
| Chronic liver disease | 0.226 | | |
| ACE inhibitor/ARB use (yes/no) | 0.871 | | |
| Lymphocyte count, $\times 10^3$/uL | <0.001 | 0.005 | 0.999 (0.998-1.000) |
| Platelet count, $\times 10^9$/L | 0.087 | 0.069 | 0.997 (0.994-1.000) |
| C-reactive protein, mg/L | 0.584 | | |
| Aspartate aminotransferase, U/L | 0.050 | 0.033 | 1.002 (1.000-1.003) |
| Alanine aminotransferase, U/L | 0.552 | | |
| Total bilirubin, mg/dL | 0.831 | | |
| Alkaline phosphatase, U/L | 0.725 | | |
| Gamma glutamyl transferase, U/L | 0.263 | | |
| Serum albumin, g/dL | 0.773 | | |
| Prothrombin time, INR | 0.444 | | |
| Estimated glomerular filtration rate, mL/min/1.73㎡ | 0.002 | | |
| SIRS on admission (yes/no) | <0.001 | 0.074 | 1.968 (1.199-3.230) |

*Calculated by Cox proportional hazards regression test

COVID-19, coronavirus disease 2019; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; INR, international normalized ratio; SIRS, systemic inflammatory response syndrome

Table 4. Risk factors including Fibrosis-4 index for mortality in patients with COVID-19 receiving respiratory support

| Variable | Univariate | Multivariate analysis | |
|---|---|---|---|
| | *P* value* | *P* value* | Hazard ratio (95% CI) |
| Male (yes/no) | 0.143 | | |
| Comorbidities (yes/no) | | | |
| Hypertension | 0.392 | | |
| Diabetes | 0.001 | 0.009 | 1.917 (1.181-3.111) |
| Chronic obstructive pulmonary disease | 0.087 | | |
| Chronic kidney disease | 0.841 | | |
| Chronic liver disease | 0.226 | | |
| ACE inhibitor/ARB use (yes/no) | 0.871 | | |
| Lymphocyte count, /uL | | | |
| <1010 | | | 1 (ref) |
| ≥1010 | 0.012 | 0.012 | 0.480 (0.271-0.852) |
| C-reactive protein, mg/L | 0.584 | | |
| Total bilirubin, mg/dL | 0.831 | | |
| Alkaline phosphatase, U/L | 0.725 | | |
| Gamma glutamyl transferase, U/L | 0.263 | | |
| Serum albumin, g/dL | 0.773 | | |
| Prothrombin time, INR | 0.444 | | |
| Estimated glomerular filtration rate, mL/min/1.73㎡ | 0.002 | | |
| SIRS on admission (yes/no) | <0.001 | 0.032 | 1.714 (1.048-2.802) |
| Fibrosis-4 index | | | |
| <4.95 | | | 1 (ref) |
| ≥4.95 | <0.001 | <0.001 | 2.784 (1.691-4.585) |

*Calculated by Cox proportional hazards regression test

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; INR, international normalized ratio, SIRS, systemic inflammatory response syndrome

**Figure 1.** Flow diagram of the study

**Figure 2.** Predictive performance of risk factors for mortality in patients with COVID-19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the curve for lymphocyte counts

**Figure 3.** Survival of patients with COVID-19 receiving respiratory support plotted against fibrosis-4 index (a) and number of risk factors (b)

**Figure 4.** Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and number of risk factors (b)

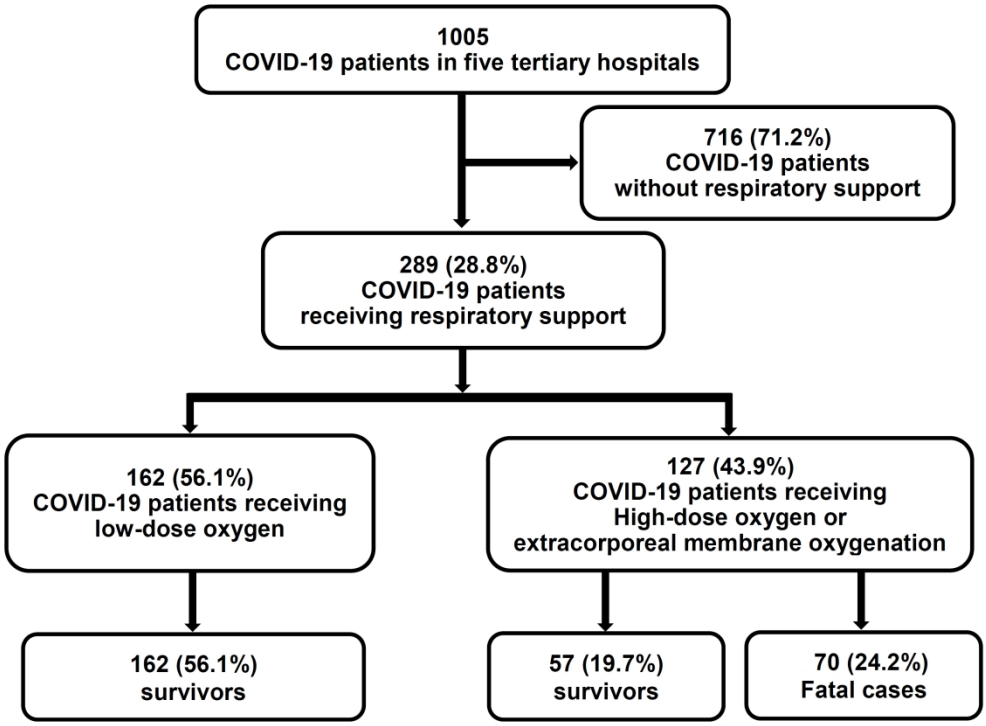



Figure 1. Flow diagram of the study

264x194mm (300 x 300 DPI)

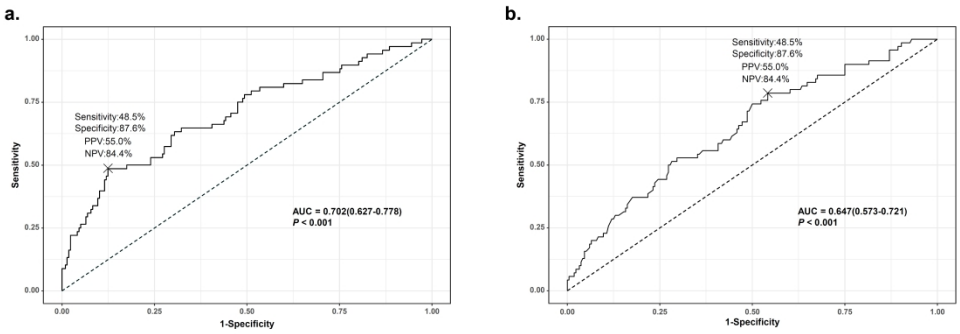



Figure 2. Predictive performance of risk factors for mortality in patients with COVID-19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the curve for lymphocyte counts

669x250mm (300 x 300 DPI)

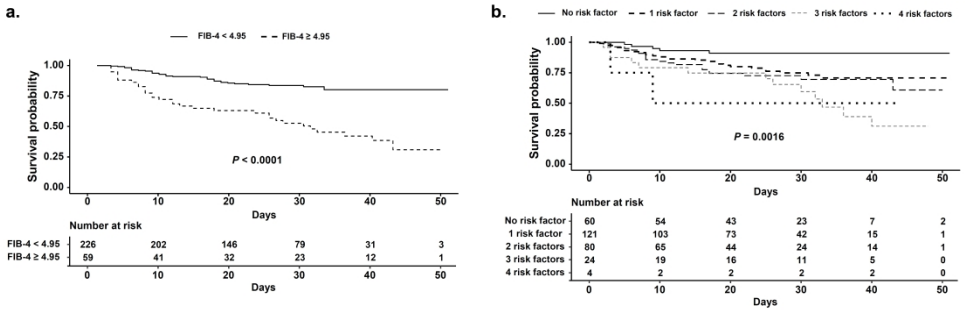



Figure 3. Survival of patients with COVID-19 receiving respiratory support plotted against fibrosis-4 index (a) and number of risk factors (b)

600x199mm (300 x 300 DPI)

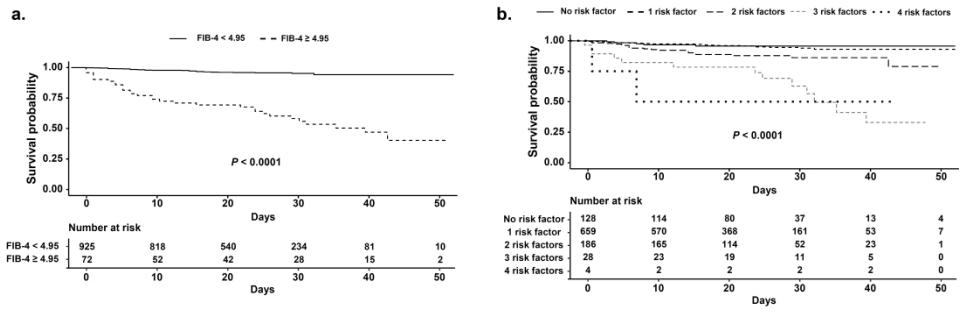



Figure 4. Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and number of risk factors (b)

600x199mm (300 x 300 DPI)

Table S1. Risk factors with Fibrosis-4 score for mortality in patients with COVID-19 receiving respiratory support

| Variable | Univariate | Multivariate analysis | |
|---|---|---|---|
| | *P* value* | *P* value* | Hazard ratio (95% CI) |
| Male (yes/no) | 0.143 | | |
| Comorbidities (yes/no) | | | |
| Hypertension | 0.392 | | |
| Diabetes | 0.001 | 0.008 | 1.998 (1.202-3.321) |
| Chronic obstructive pulmonary disease | 0.087 | | |
| Chronic kidney disease | 0.841 | | |
| Chronic liver disease | 0.226 | | |
| ACE inhibitor/ARB use (yes/no) | 0.871 | | |
| Lymphocyte count, $\times 10^3$/uL | <0.001 | 0.003 | 0.999 (0.998-1.000) |
| C-reactive protein, mg/L | 0.584 | | |
| Total bilirubin, mg/dL | 0.831 | | |
| Alkaline phosphatase, U/L | 0.725 | | |
| Gamma glutamyl transferase, U/L | 0.263 | | |
| Serum albumin, g/dL | 0.773 | | |
| Prothrombin time, INR | 0.444 | | |
| Estimated glomerular filtration rate, mL/min/1.73 ㎡ | 0.002 | | |
| SIRS on admission (yes/no) | <0.001 | | |
| Fibrosis-4 score | <0.001 | <0.001 | 1.115 (1.069-1.163) |

*Calculated by Cox proportional hazards regression test

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; INR, international normalized ratio, SIRS, systemic inflammatory response syndrome.

Table S2. Adjusted hazard ratio of high Fibrosis-4 index for mortality in patients with COVID-19 receiving respiratory support

| | Death | |
|---|---|---|
| | HR (95% CI) | *P*-value |
| High Fibrosis-4 index (≥ 4.95) (yes vs. no) | | |
| Unadjusted | 3.93 (2.44-6.33) | <0.001 |
| Model 1 | 3.01 (1.84-4.93) | <0.001 |
| Model 2 | 3.02 (1.84-4.96) | <0.001 |
| Model 3 | 2.80 (1.64-4.65) | <0.001 |

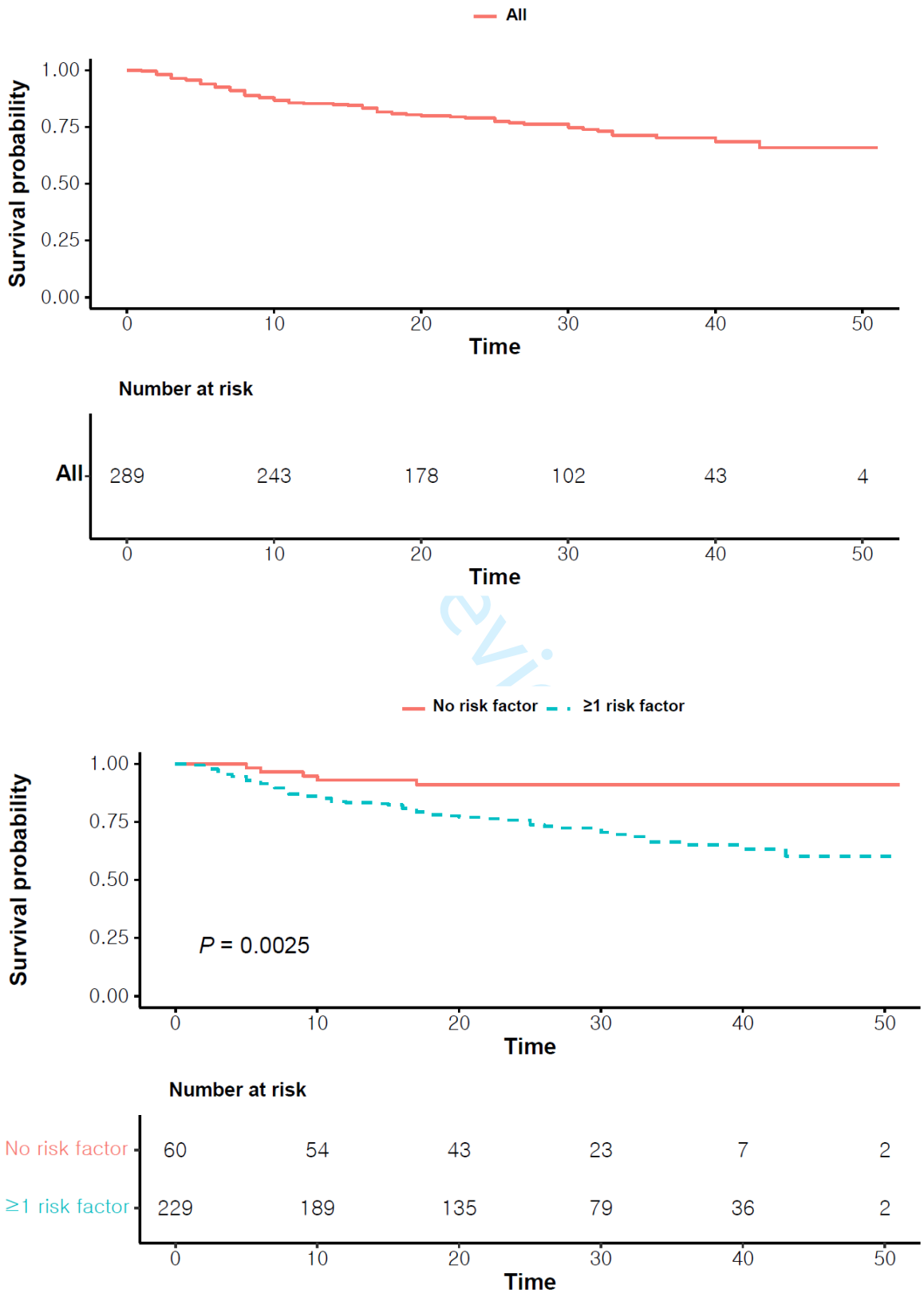
HR, hazard ratio; CI, confidential interval

Model 1 was adjusted for age, gender.

Model 2 was adjusted for chronic liver disease, diabetes, hypertension, chronic kidney disease, and chronic obstructive pulmonary disease inclusive of model 1.

Model 3 was adjusted for lymphocyte count, C-reactive protein, and presence of systemic inflammatory response syndrome inclusive of model 2.

Figure S1. Survival of the patients with COVID-19 receiving respiratory support as the number of risk factors



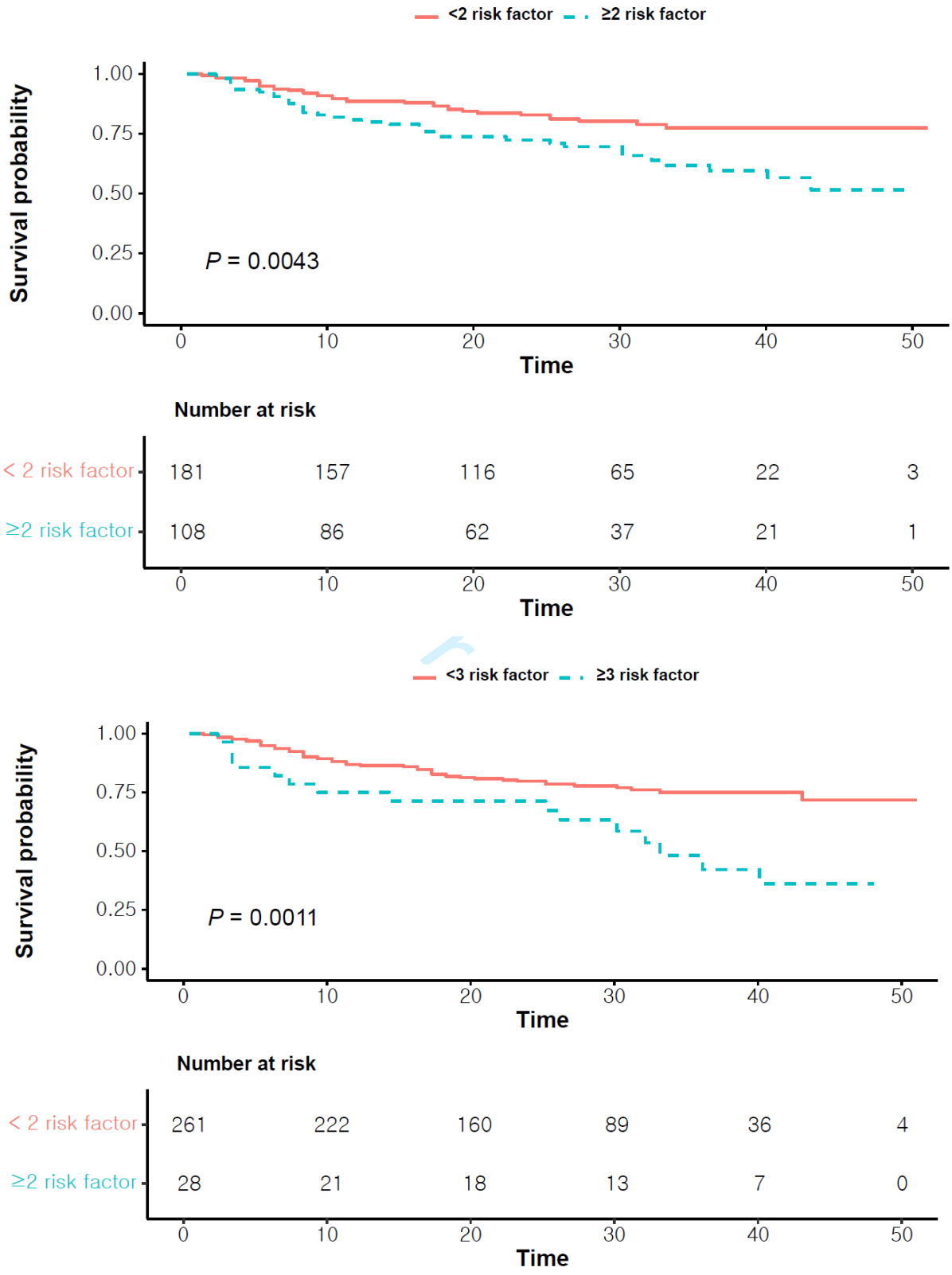
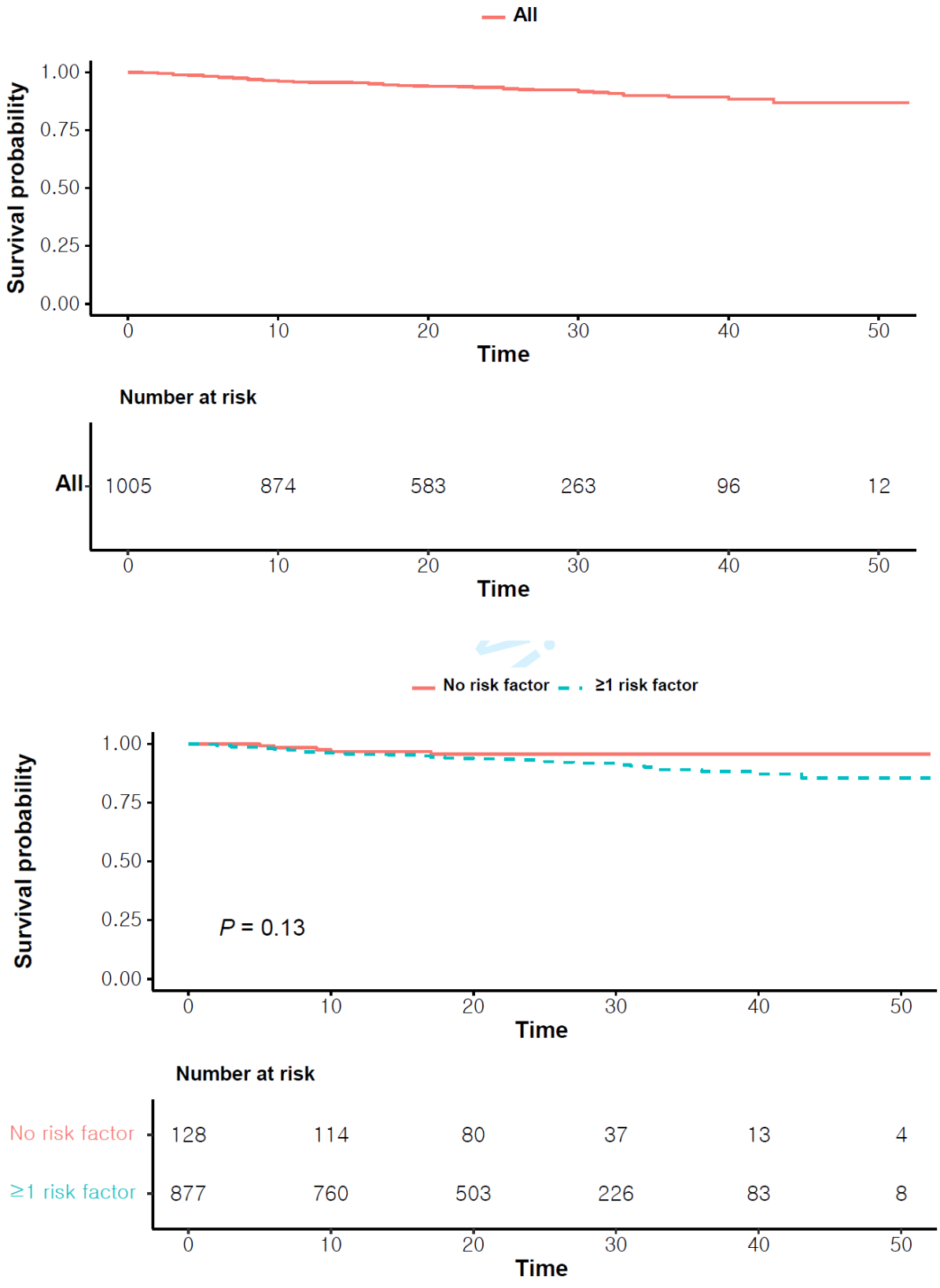
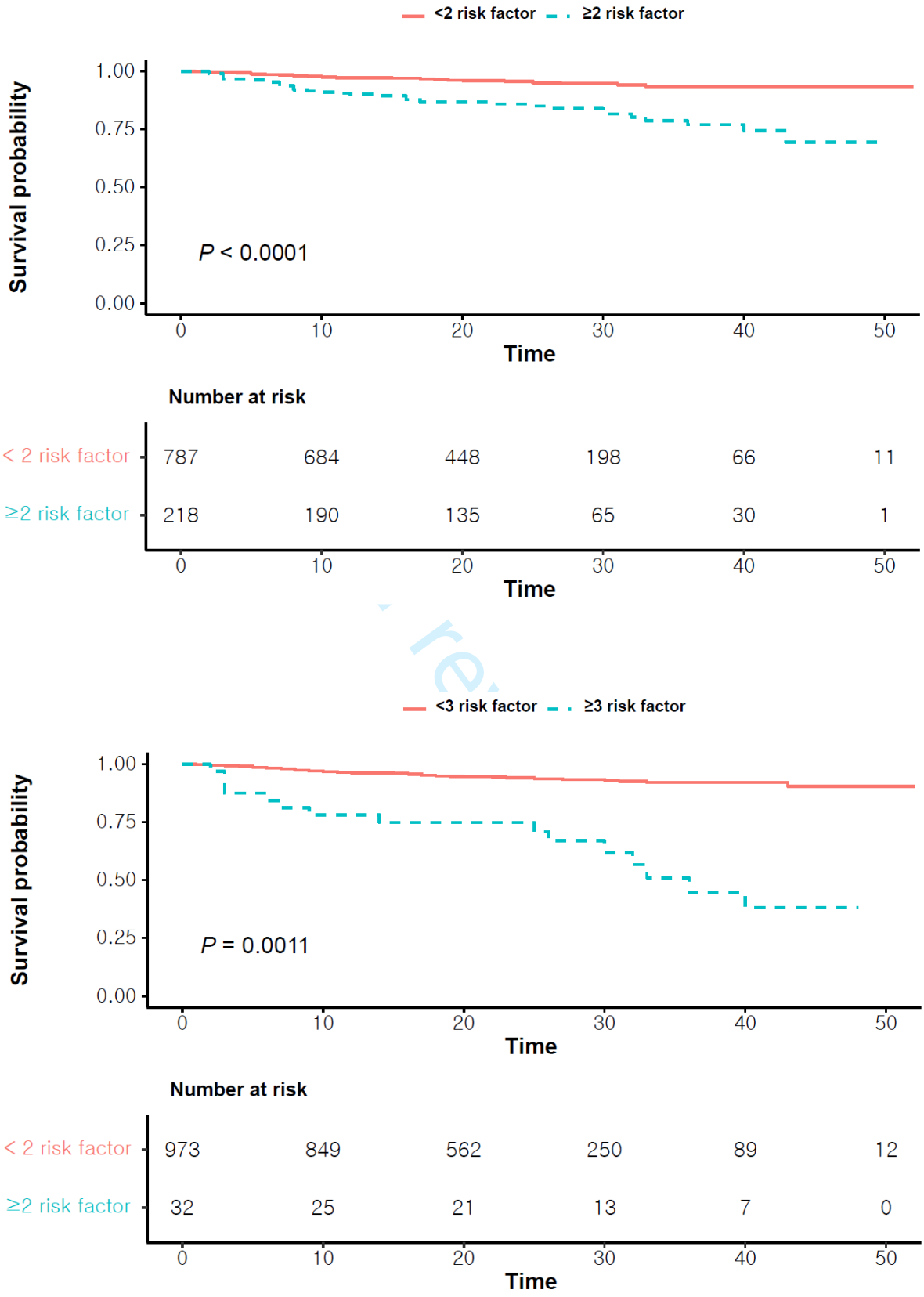

<2 risk factor
≥2 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P = 0.0043
0
10
20
30
40
50
Time
Number at risk
< 2 risk factor
181
157
116
65
22
3
≥2 risk factor
108
86
62
37
21
1
Time
<3 risk factor
≥3 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P = 0.0011
Time
Number at risk
< 2 risk factor
261
222
160
89
36
4
≥2 risk factor
28
21
18
13
7
0
Time

Figure S2. Survival of the entire group of patients with COVID-19 as the number of risk factors




<2 risk factor
≥2 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P < 0.0001
0
10
20
30
40
50
Time
Number at risk
< 2 risk factor
787
684
448
198
66
11
≥2 risk factor
218
190
135
65
30
1
Time
<3 risk factor
≥3 risk factor
Survival probability
1.00
0.75
0.50
0.25
0.00
P = 0.0011
Time
Number at risk
< 2 risk factor
973
849
562
250
89
12
≥2 risk factor
32
25
21
13
7
0
Time

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6-7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 5-6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 14-15 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | 8 |
| | | (c) Consider use of a flow diagram | 8 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8-9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 8 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 10 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 9-11<br>9-11<br>9-11 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11-14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 14-15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 15 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.