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

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Keywords:	Respiratory infections < THORACIC MEDICINE, VIROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, INTERNAL MEDICINE

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

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For peer review only

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 the 1005 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

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4 disease, it is a most single reliable predictor of mortality in patients with COVID-19
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6 regardless of respiratory support.
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- 10 ● This study has very low probability of sampling bias, because all tertiary hospitals in
11 the area, where approximately three fourths of COVID-19 patients were diagnosed in
12 South Korea, enrolled entire cohort.
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 - 15 ● Further studies for validation with other cohorts would be required to consolidate these
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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

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

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

30 31 32 33 34 35 36 37 38 **MATERIALS AND METHODS**

39 40 41 **Patients and their public involvement**

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44 After the beginning of the COVID-19 outbreak on February 18, 2020, in Daegu, all COVID-
45 19 patients were admitted to one designated tertiary hospital. Because of limited medical
46 resources, efficient allocation was required. Therefore, from March 2, the disinfection team of
47 Daegu classified all new COVID-19 patients on the basis of severity of respiratory symptoms
48 and oxygen demand to transfer to one of four other tertiary hospitals in accordance with
49 regional policy. Accordingly, from February 20 to April 14, 2020, we enrolled 1005
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4 hospitalized patients aged >19 years with COVID-19 confirmed by PCR in five tertiary
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6 hospitals of Daegu, South Korea.
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10 This study was performed in accordance with the ethical guidelines of the revised Helsinki
11 Declaration of 2013 and approved by the Institutional Review Board of all tertiary hospitals.
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13 Written informed consent by the patients was waived due to the retrospective nature of our
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15 study. It was not possible to involve patients or the public in the design, conduct, reporting, or
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17 dissemination plans of this study.
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20 21 22 **Data collection**

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24 The medical records of anthropometric and epidemiological data, patients' clinical
25 characteristics, radiologic and laboratory data, treatments, use of angiotensin-converting
26 enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and clinical outcomes,
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28 were collected retrospectively by each hospital and reviewed by two independent reviewers.
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30 Laboratory tests included complete blood cell and lymphocyte count, erythrocyte
31 sedimentation rate (ESR), c-reactive protein (CRP), liver and kidney function tests, electrolytes,
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33 and serum ferritin on admission day. All patients underwent chest radiography with or without
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35 computed tomography (CT). The treatment patients received included antivirals,
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37 hydroxychloroquine, systemic glucocorticoid, intravenous immunoglobulin, respiratory
38 support, continuous renal replacement therapy, and extracorporeal membrane oxygenation
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40 (ECMO). The data collection terminated on April 14, 2020.
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50 51 **Definition**

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53 In accordance with the WHO interim guidance, all COVID-19 cases were diagnosed by
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55 detection of SARS-CoV-2 sequence using real-time PCR from nasopharyngeal and
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4 oropharyngeal swabs. Fever was defined as tympanic temperature of 37.5 °C or higher.
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6 Systemic inflammatory response syndrome (SIRS) on admission was defined by satisfaction
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8 of any two of the criteria: (a) white blood cell count < 4000 cells/mm³ or > 12000 cells/mm³ ,
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10 (b) body temperature < 36 °C or > 38 °C, (c) heart rate >90 beats/min, and (d) tachypnea >20
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12 breaths/min. Shock and acute respiratory distress syndrome (ARDS) were defined in
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14 accordance with the WHO interim guidance ²². Acute kidney injury was defined either from
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16 the highest serum creatinine level (>0.3 mg/dl within 48 hours or 1.5 times of the baseline level
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18 within 7 days), and/or from decreased urine output (<0.6 ml/kg/h for 6 hours) on admission.
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23 **Study outcomes**

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

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39 All continuous data were expressed as mean and standard deviation (mean ± SD) or median
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41 with range, and compared using Student's t-test or the Mann-Whitney U test. Categorical data
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43 were compared using a χ -squared test or Fischer's exact test. The predictive factors for
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45 mortality were assessed using the Cox proportional hazards regression model with hazards ratio
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47 (HR). Receiver operating characteristic (ROC) analysis was conducted to assess the predictive
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49 performance of assessed risk factors. The best cut-off values were calculated based on the
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51 Youden index. The relationship between overall survival and fibrosis-4 index (FIB-4) was
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53 calculated using the Kaplan-Meier method. *P*-value <0.05 was considered statistically
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4 significant. All statistical analyses were performed using R software (version 3.0.2, Vienna,
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6 Austria).

11 12 **RESULTS**

13 14 15 **Baseline characteristics**

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18 Of 1,005 patients with COVID-19, 289 (28.8%) received respiratory support and were included
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20 in this study. Of these, 162 (56.1 %) were treated with low-dose oxygen therapy using a nasal
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22 or venturi mask, while 127 (43.9%) were treated with a high-flow nasal mask, invasive
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24 mechanical ventilation and/or ECMO. Patient disposition is shown in Figure 1. The baseline
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26 characteristics of the COVID-19 patients receiving respiratory support are shown in Table 1.
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28 The median age was 72.0 years (range: 62.0–80.0 years) and 156 subjects (54.0%) were
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30 females. The two most common comorbidities were hypertension (45.8%) and diabetes
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32 (32.3%), followed by cardiovascular disease (6.9%) and chronic liver disease (5.2%). The two
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34 most common symptoms on admission were fever and/or chills (67.9%), cough (61.2%),
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36 followed by shortness of breath (53.0%), myalgia (30.8%), and gastrointestinal symptoms
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38 (25.4%). The median time from symptom onset to admission was 6 days (range, 3-9).
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40 Radiologic abnormality and bilateral involvement on chest radiographs were 269 (93.1%) and
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42 225 (83.6%), respectively.

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49 There were several differences in demographics and past history between fatal cases and
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51 survivors, including older age, preponderance of males, and more frequent diabetes among
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53 fatal cases. However, there was no significant difference in the use of ACE inhibitors or ARBs.
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56 Duration of symptoms before admission was shorter in survivors but the presence of fever or
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4 respiratory symptoms on admission did not differ between survivors and non-survivors. There
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6 was no significant difference in viral signs on admission except for frequent SIRS in fatal cases.
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8 Some differences in laboratory tests on admission were also significant, including higher white
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10 blood cell count, CRP, procalcitonin, aspartate aminotransferase (AST), gamma glutamyl
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12 transferase, prothrombin time, blood urea nitrogen, serum creatinine, and lower lymphocyte
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14 count, platelet count, serum albumin, and serum sodium in fatal cases compared with survivors.
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17 18 19 **Treatments and clinical outcomes**

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21 The treatments and clinical outcomes of patients with COVID-19 receiving respiratory support
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23 are shown in Table 2. Of these, 57 (19.7%) and 70 (24.2%) were treated with high-flow nasal
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25 cannula and invasive mechanical ventilation, respectively. Analysis of clinical outcomes
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27 revealed that 113 patients (11.2%) had ARDS, 93 (33.2%) were admitted to an intensive care
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29 unit (ICU), and 18 (6.2%) underwent ECMO. The median duration of hospital stay was 25 days
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31 (range 8-33). Survivors were less frequently treated with darunavir/cobicistat, systemic
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33 glucocorticoid, high-flow nasal cannula, invasive mechanical ventilation, or continuous renal
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35 replacement therapy compared with fatal cases. Survivors had a longer median duration of
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37 hospital stay compared with fatal cases, were less frequently admitted to an ICU, and less
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39 frequently developed septic shock, ARDS or acute kidney injury.
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45 46 **Risk factors for mortality in COVID-19 patients receiving respiratory support**

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48 Univariate analysis identified age, sex, diabetes, chronic obstructive pulmonary disease,
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50 lymphocyte count, AST, ESR, and SIRS as significant variables relating to mortality in patients
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52 with COVID-19 receiving respiratory support (Table 3). Multivariate analysis identified age
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54 (HR 1.054; 95% CI 1.028–1.082; $P < 0.001$), diabetes (HR 2.226; 95% CI 1.357–3.652; $P =$
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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 disease²³. 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

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4 mortality (Table 4).
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7 **FIB-4 and other predictive risk factors for survival in COVID-19 patients receiving**
8 **respiratory support**
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12 Among the four predictive risk factors, FIB-4 was the best predictor of mortality in COVID-
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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

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4 In this retrospective cohort study, predictive risk factors for mortality were evaluated in 289
5 patients with confirmed COVID-19 receiving respiratory support in the Daegu and
6 Gyeongsangbuk-do area. After the initial outbreak, immediate isolation of patients diagnosed
7 with COVID-19 in designated hospitals and intensive contact tracing with quarantine of
8 suspected virus carriers commenced. Despite absence of lockdown, the numbers of new
9 patients in this area declined. This probably implied that most patients had been successfully
10 isolated and treated in designated hospitals. Most patients requiring respiratory support were
11 allocated to five tertiary hospitals.
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23 The present study revealed that diabetes, low lymphocyte count, SIRS, and FIB-4 were
24 independent risk factors for mortality. A recent meta-analysis found that the main laboratory
25 abnormalities in COVID-19 patients included low lymphocyte count, and elevated CRP and
26 lactate dehydrogenase (LDH) ²⁴. In non-survivors, or severely ill patients requiring ICU care
27 or suffering from ARDS, laboratory abnormalities including high WBC count, low lymphocyte
28 count, prolonged prothrombin time, low albumin, elevated AST, ALT, total bilirubin, LDH,
29 creatinine, troponin I, CRP, procalcitonin, ferritin, and D-dimer were identified as risk factors
30 in previous studies ^{10 11 13}. However, numbers of enrolled patients were small and multivariate
31 analyses were not performed. In a recent study, logistic regression analysis identified age,
32 Sequential Organ Failure Assessment (SOFA) score, and D-dimer as predictive risk factors for
33 death in patients with COVID-19 pneumonia ¹⁴. SOFA score is derived from PaO₂/FiO₂, use
34 of mechanical ventilator, platelets count, Glasgow Coma scale, bilirubin, mean arterial pressure
35 or requirement for vasoactive agents, and serum creatinine or urine output. The score is related
36 to the cytokine storm in sepsis ²⁵, and we think some of the risk factors in our study, including
37 platelets as a component of the FIB-4 index, and SIRS, were also associated with this serious
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4 inflammatory condition. This recent study included patients similar to those in the present study,
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6 as judged from the proportion of patients receiving respiratory support (82.1% versus 100% in
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8 the present study) and the mortality rate (28.3% versus 24.2% in the present study) ¹⁴.
9
10 Multivariate analysis in two recent studies showed that neutrophil-to-lymphocyte ratio, CD4 T
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12 cell count, and age were independent risk factors of in-hospital mortality and ICU admission
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14 for COVID-19 ^{26 27}. Severe inflammation dysregulates the immune response and is
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16 characterized by decreased memory helper T (Th) cells and regulatory T cells with increased
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18 naive Th cells in patients with COVID-19 ²⁸. These findings are consistent with low
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20 lymphocyte count as an independent risk factor for mortality in our study. However, in previous
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22 studies, survival analysis was not performed, and the enrolled patients were somewhat different
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24 from those in the present study.
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30 Liver injury in COVID-19 was observed more frequently in severe cases than in mild cases ⁴
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32 ¹³. Though the mechanism is unclear, elevated AST and ALT may be related to the immune
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34 response in severe pneumonia, which may result from inflammatory cytokines following
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36 COVID-19 infection ²⁹. Elevated liver enzyme can be also associated with drug induced liver
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38 injury (DILI), which may result from antibacterial and antiviral drugs, anti-inflammatory drugs,
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40 and vasopressors in severe cases ³⁰. As there has been no study of DILI in COVID-19 infection,
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42 its prevalence should be investigated. However, in this study, laboratory tests performed at the
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44 time of admission did not indicate an association between AST elevation and DILI. Also in
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46 this study, although FIB-4 was originally used in patients with liver disease, it was identified
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48 as a predictor of mortality in patients with COVID-19, whether or not they were receiving
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50 respiratory support. Elevated LDH has been reported as a promising predictor for severe
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52 COVID infection ^{19 31 32}. However, it was only identified as a risk factor by univariate analysis,
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4 not by multivariate analysis. We suggest that the ratio of AST to ALT in FIB-4 may be a better
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6 predictor of mortality than the level of LDH, due to its non-specificity of cause. In addition,
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8 the common finding of elevated AST in patients with severe disease in several other studies
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10 supports the present study ^{4 13 33}.

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14 When FIB-4 is analyzed with other risk factors including lymphocyte count, SIRS, and diabetes,
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16 as number of risk factors increases, survival deteriorates in patients with COVID-19 regardless
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18 of respiratory support. There are several published or preprinted studies of prediction models
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20 for the prognosis of patients with COVID-19 ¹⁷. Albumin, direct bilirubin, and red blood cell
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22 distribution width have been suggested as diagnostic or prognostic indicators of severe disease
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24 or mortality in COVID-19 ¹⁷. However, among these three factors, albumin was not a
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26 significant risk factor, and the other two factors were not evaluated in the present study. Most
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28 of the proposed models have been open to criticism on the grounds of severe sampling bias due
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30 to rarely reported length of follow-up and prevalence of COVID-19 with or without severe
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32 infection. A strength of the present study is the low probability of sampling bias, because
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34 approximately three fourths of patients with COVID-19 in South Korea have been diagnosed
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36 in the Daegu and Gyeongsangbuk-do area, and our entire cohort was derived from tertiary
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38 hospitals in that area.
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45 This study has some limitations. First, there was no validation with another cohort. As
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47 described above, most of the COVID-19 cases were enrolled in this study. Thus, it would be
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49 impossible to validate these results without undertaking an international study. Improved
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51 assessments of international data on COVID-19 will require data sharing, using a reporting
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53 protocol specified by WHO ³⁴. Second, detailed radiologic assessment of CT scans was not
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55 performed. To our knowledge, there are only a few reports at preprint stage which include
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4 clinical features and radiologic features from CT scan with artificial intelligence techniques to
5 develop prediction models³⁵. However, this study also has sampling bias as well as an
6 inadequate sample size^{21 35}. Therefore, advanced machine learning combining radiologic
7 image analysis with clinical risk factors would be needed to develop a robust prediction model.
8
9 Third, prediction of severe COVID-19 including ICU admission or ARDS was not analyzed in
10 this study. However, we think prediction of severe COVID-19 was not appropriate for our
11 cohort, because transfer to a tertiary hospital may introduce the possibility of sampling bias.
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13 Thus, we used the objective outcome of mortality in this study.
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23 In conclusion, FIB-4, diabetes, low lymphocyte count, and SIRS are independent risk factors
24 of mortality in patients with COVID-19 receiving respiratory support. Among these risk factors,
25 FIB-4 is a robust predictor of mortality in patients with COVID-19 regardless of respiratory
26 support. A number of risk factors are significantly related to survival in patients with COVID-
27 19 regardless of respiratory support.
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43 Suh and Soo Young Park; Supervision, Soo Young Park and Woo Jin Chung; Visualization,
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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%)	<i>P</i> 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, $\times 10^3/\mu\text{L}$	6140 (4695–8065)	6000 (4690–7420)	7320 (5100–12020)	0.001
Lymphocyte count, $\times 10^3/\mu\text{L}$	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, $\times 10^9/\text{L}$	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/1.73m ²	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)	<i>P</i> 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	
	<i>P</i> value*	<i>P</i> 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, ×10 ³ /uL	<0.001	0.005	0.999 (0.998–1.000)
Platelet count, ×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/1.73m ²	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	
	<i>P</i> value*	<i>P</i> 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 m ²	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

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4 **Figure 1.** Flow diagram of the study
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10 **Figure 2.** Predictive performance of risk factors for mortality in patients with COVID-19
11 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the
12 curve for lymphocyte counts
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19 **Figure 3.** Survival of patients with COVID-19 receiving respiratory support plotted against
20 fibrosis-4 index (a) and number of risk factors (b)
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28 **Figure 4.** Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and
29 number of risk factors (b)
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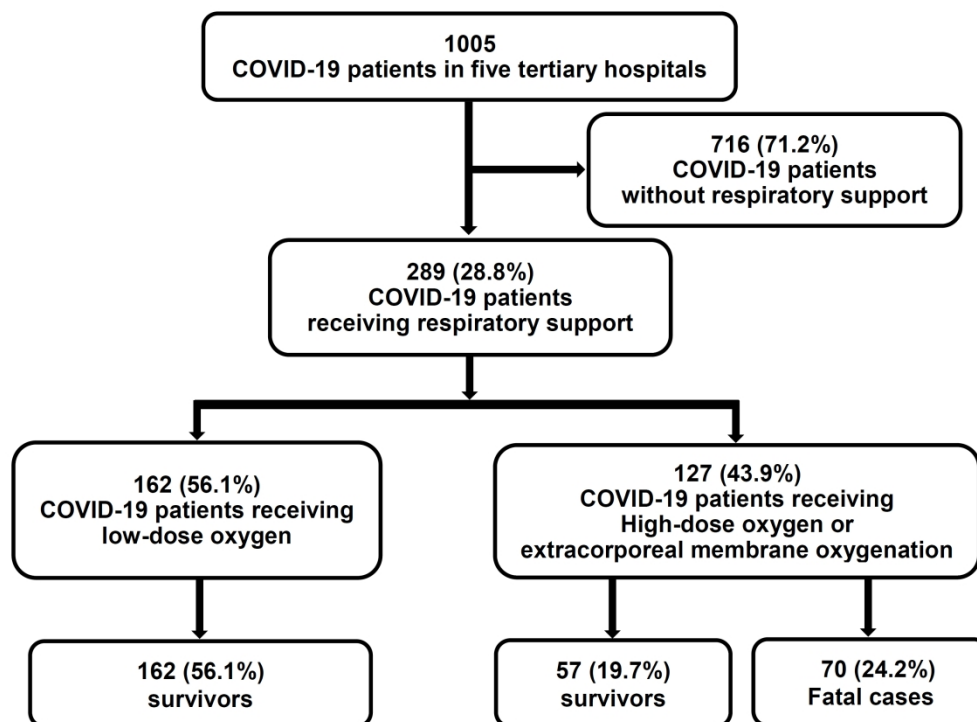


Figure 1. Flow diagram of the study

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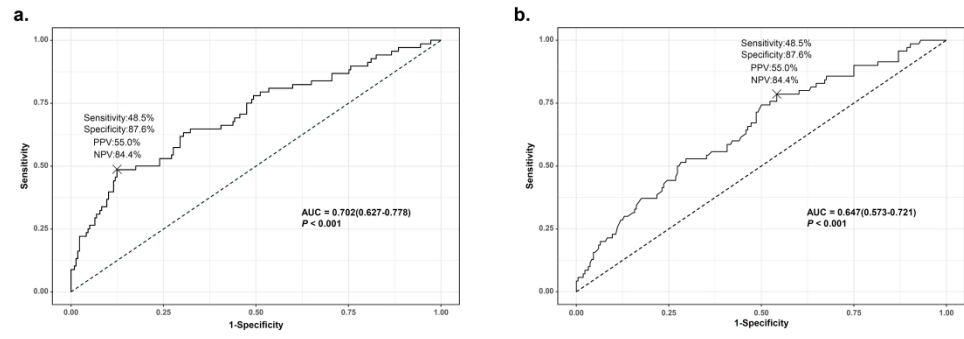


Figure 2. Predictive performance of risk factors for mortality in patients with COVID-19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the curve for lymphocyte counts

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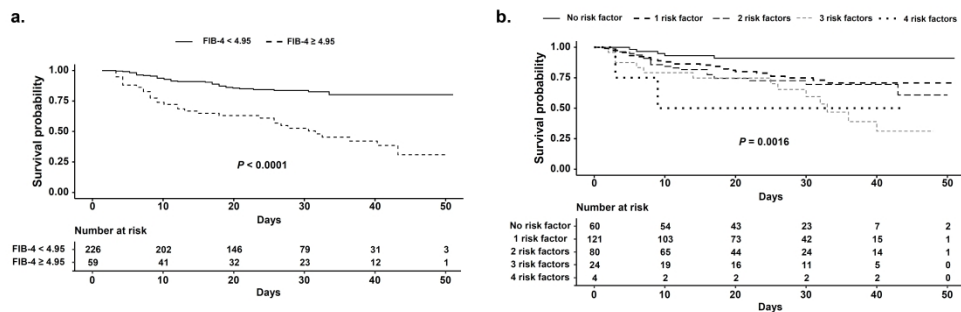


Figure 3. Survival of patients with COVID-19 receiving respiratory support plotted against fibrosis-4 index (a) and number of risk factors (b)

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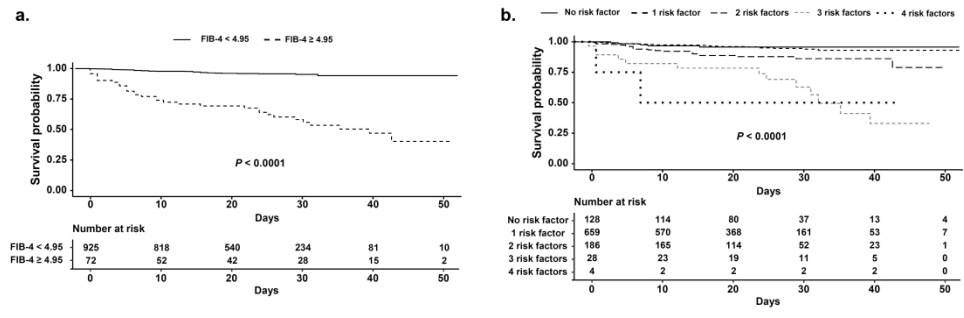


Figure 4. Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and number of risk factors (b)

600x199mm (300 x 300 DPI)

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

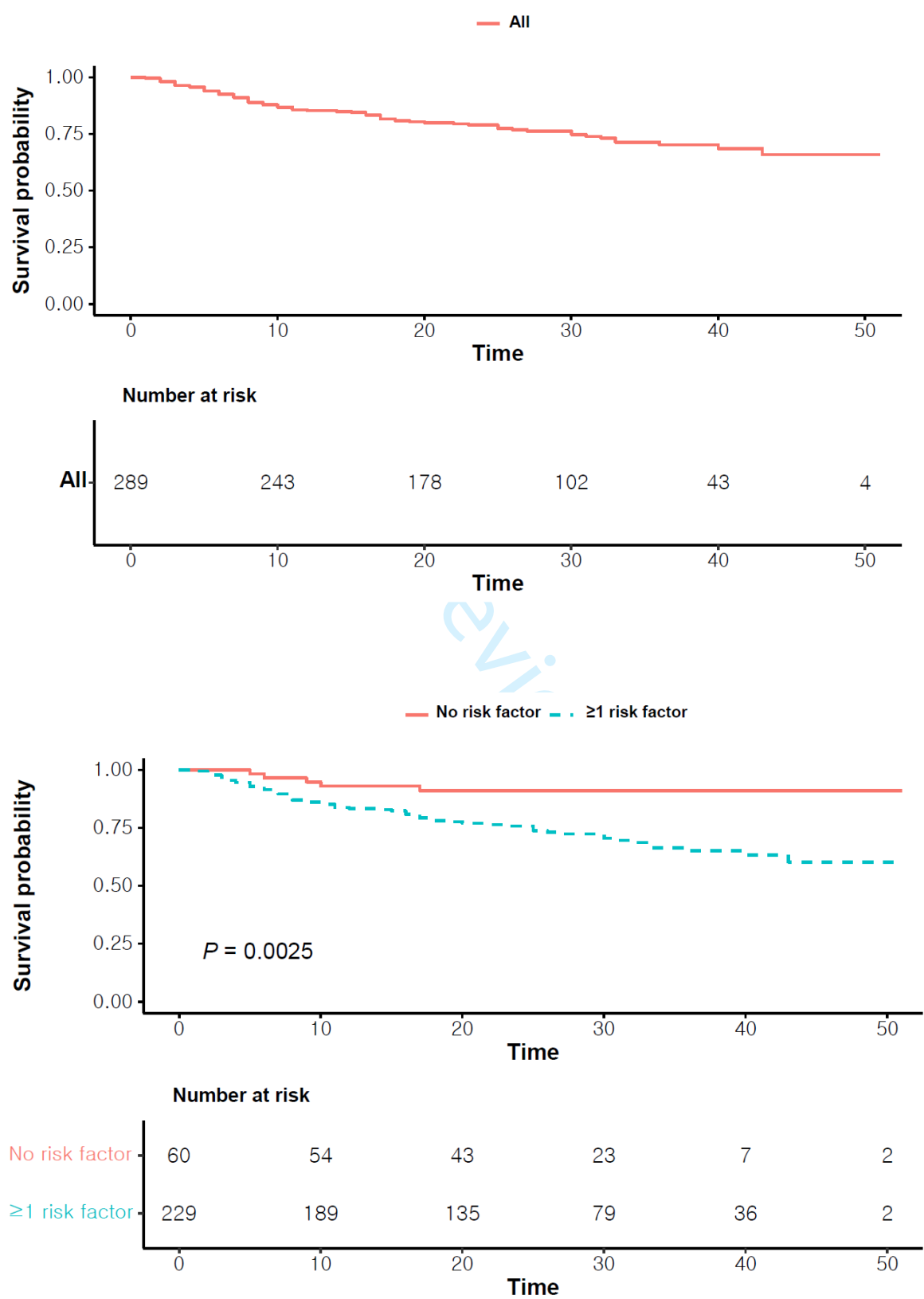
Variable	Univariate	Multivariate analysis	
	<i>P</i> value*	<i>P</i> value*	Hazard ratio (95% CI)
Sex (male/female)	0.143		
Comorbidities (yes/no)			
Hypertension	0.392		
Diabetes	0.001	0.008	1.998 (1.202-3.321)
Chronic obstructive pulmonary disease	0.087		
Chronic kidney disease	0.841		
Chronic liver 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 m ²	0.002		
SIRS on admission (yes/no)	<0.001		
Fibrosis-4 score	<0.001	<0.001	1.115 (1.069-1.163)

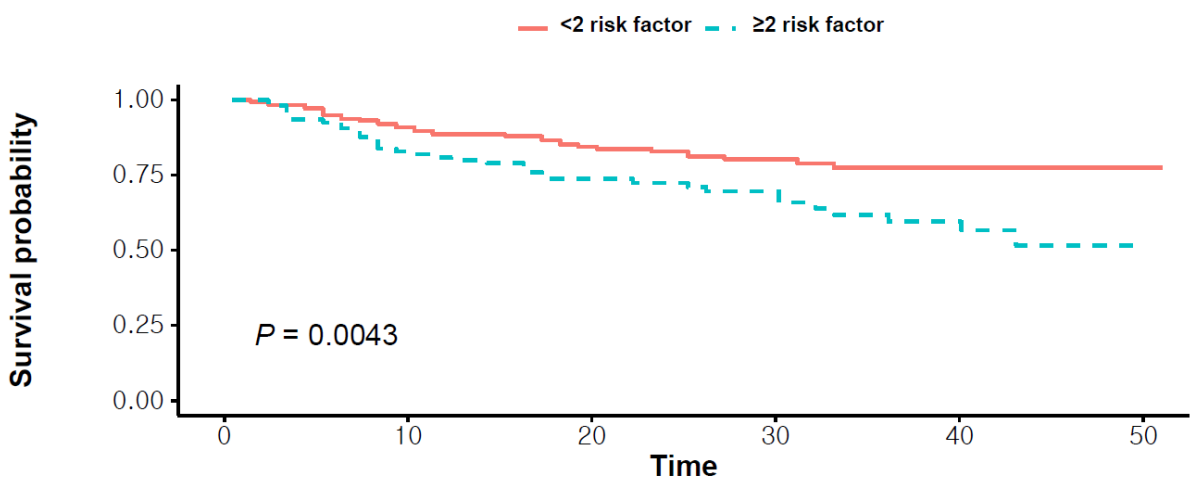
*Calculated by Cox proportional hazards regression test

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

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

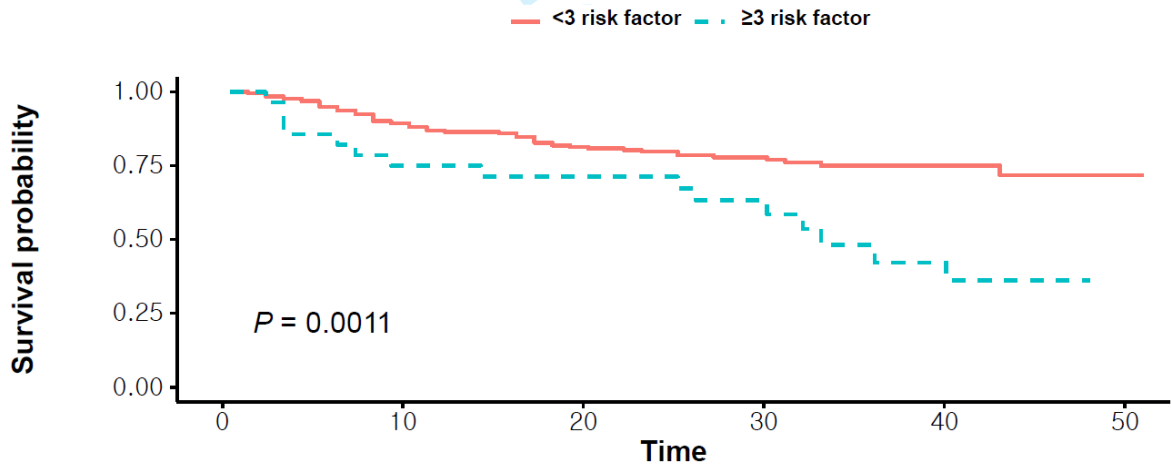




Number at risk

< 2 risk factor	181	157	116	65	22	3
≥2 risk factor	108	86	62	37	21	1

Time

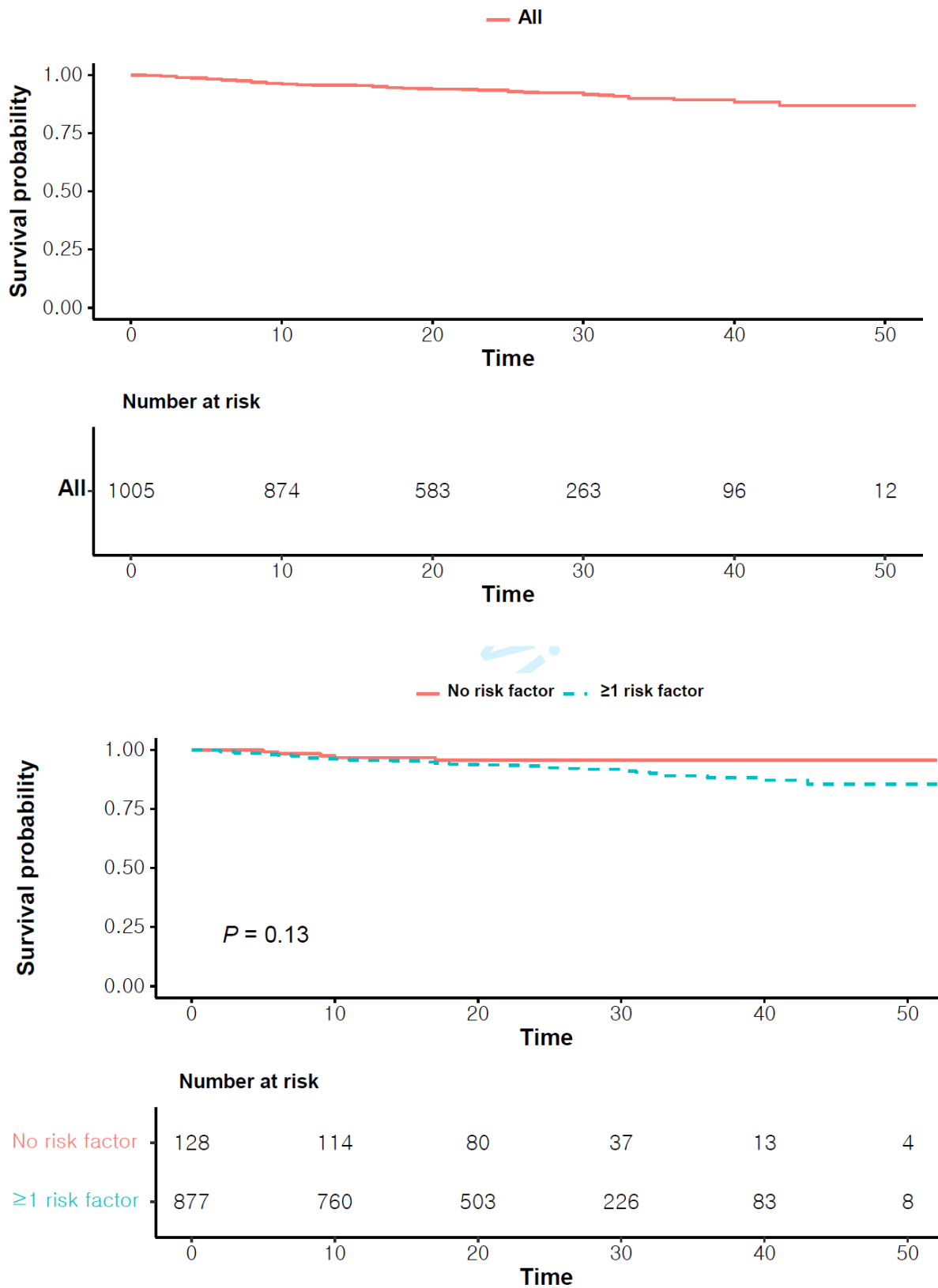


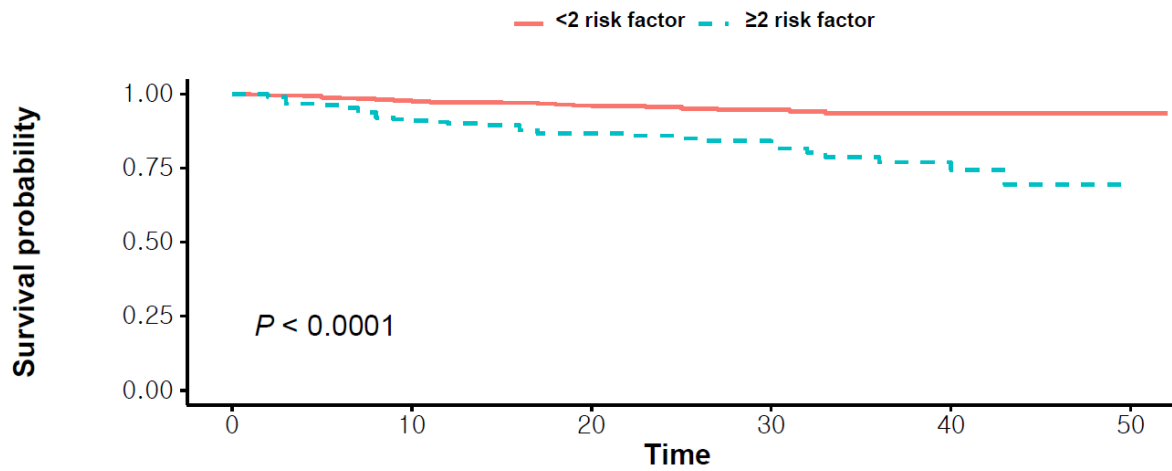
Number at risk

< 3 risk factor	261	222	160	89	36	4
≥3 risk factor	28	21	18	13	7	0

Time

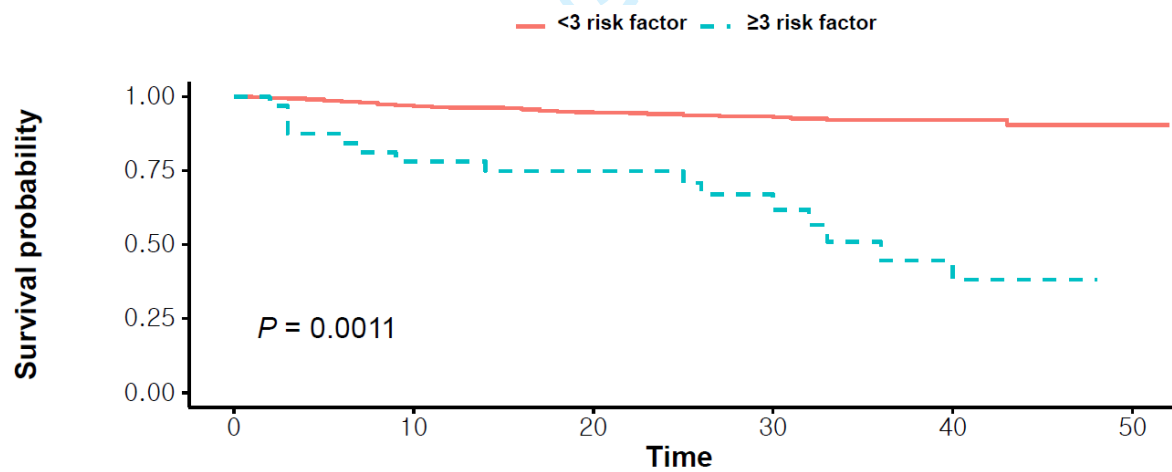
Figure S2. Survival of the entire group of patients with COVID-19 as the number of risk factors





Number at risk

	0	10	20	30	40	50
< 2 risk factor	787	684	448	198	66	11
≥2 risk factor	218	190	135	65	30	1



Number at risk

	0	10	20	30	40	50
< 2 risk factor	973	849	562	250	89	12
≥2 risk factor	32	25	21	13	7	0

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

1	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	9-11
2			(b) Report category boundaries when continuous variables were categorized	9-11
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	11-14
13				
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
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
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18	Generalisability	21	Discuss the generalisability (external validity) of the study results	15
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21	Other information			
22	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
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*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

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Infectious diseases
Keywords:	Respiratory infections < THORACIC MEDICINE, VIROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, INTERNAL MEDICINE

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5 **Title: Fibrosis-4 Index as a Predictor for Mortality in Hospitalized Patients with**
6 **COVID-19: a retrospective multicenter cohort study**
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10 **Short title: Fibrosis-4 Index in COVID-19**
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13 Jung Gil Park^{a*}, Min Kyu Kang^{a*}, Yu Rim Lee^b, Jeong Eun Song^c, Na Young Kim^d,
14 Young Oh Kweon^b, Won Young Tak^b, Se Young Jang^b, Changhyeong Lee^c, Byung Seok
15 Kim^c, Jae Seok Hwang^d, Byoung Kuk Jang^d, Jinmok Bae^d, Ji Yeon, Lee^d, Jeong Ill Suh^e,
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49 *These authors contributed equally to this study

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For peer review only

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, $P < 0.001$).

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5 **Conclusion** Fibrosis-4 index is a useful predictive marker for mortality in COVID-19
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7 patients regardless of its severity.
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12 *Keywords: Coronavirus, COVID-19, risk factors, fibrosis, mortality, survival*
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15 16 17 **Strengths and limitations of this study**

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

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5 reported.^{14 15} However, few reports of risk modeling and prediction are awaiting peer
6 review and publication¹⁶, and most of these studies have limited sample size or high risk
7 of bias¹⁶. The risk prediction models in these studies were established using conventional
8 scoring systems, risk nomograms, or advanced machine learning models¹⁷⁻¹⁹. Although
9 the performance of such models is relatively good, no COVID-19 risk prediction model
10 can currently be recommended for clinical use, due to a number of limitations.²⁰

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

25 26 27 28 29 30 31 32 33 34 35 **MATERIALS AND METHODS**

36 37 38 **Patients and their public involvement**

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41 After the beginning of the COVID-19 outbreak on February 18, 2020, in Daegu, all
42 COVID-19 patients were admitted to one designated tertiary hospital. Because of limited
43 medical resources, efficient allocation was required. Therefore, from March 2, the
44 disinfection team of Daegu classified all new COVID-19 patients on the basis of severity
45 of respiratory symptoms and oxygen demand to transfer to one of four other tertiary
46 hospitals in accordance with regional policy. Accordingly, from February 20 to April 14,
47 2020, we enrolled 1005 hospitalized patients aged >19 years with COVID-19 confirmed

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6 by PCR in five tertiary hospitals of Daegu, South Korea.
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9 This study was performed in accordance with the ethical guidelines of the revised
10 Helsinki Declaration of 2013 and approved by the Institutional Review Board of all
11 tertiary hospitals. Written informed consent by the patients was waived due to the
12 retrospective nature of our study. It was not possible to involve patients or the public in
13 the design, conduct, reporting, or dissemination plans of this study.
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20 21 **Data collection**

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23 The medical records of anthropometric and epidemiological data, patients' clinical
24 characteristics, radiologic and laboratory data, treatments, use of angiotensin-converting
25 enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and clinical
26 outcomes, were collected retrospectively by each hospital and reviewed by two
27 independent reviewers. Laboratory tests included complete blood cell and lymphocyte
28 count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), liver and kidney
29 function tests, electrolytes, and serum ferritin on admission day. All patients underwent
30 chest radiography with or without computed tomography (CT). Antivirals,
31 hydroxychloroquine, systemic glucocorticoid, intravenous immunoglobulin, respiratory
32 support, continuous renal replacement therapy, and extracorporeal membrane
33 oxygenation (ECMO) were included on the treatment of COVID-19. The data collection
34 terminated on April 14, 2020.
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51 52 **Definition**

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54 In accordance with the WHO interim guidance, all COVID-19 cases were diagnosed by
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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/mm³ 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 (10⁹/L) × √ALT (U/L)].²¹

Study outcomes

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

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

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

51 **Baseline characteristics**

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55 Of 1,005 patients with COVID-19, 289 (28.8%) received respiratory support and were
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5 included in this study. Of these, 162 (56.1 %) were treated with low-dose oxygen therapy
6 using a nasal or venturi mask, while 127 (43.9%) were treated with a high-flow nasal
7 mask, invasive mechanical ventilation and/or ECMO. Patient disposition is shown in
8 Figure 1. The baseline characteristics of the COVID-19 patients receiving respiratory
9 support are shown in Table 1. There were several differences in demographics and past
10 history between fatal cases and survivors, including older age, preponderance of males,
11 and more frequent diabetes among fatal cases. However, there was no significant
12 difference in the use of ACE inhibitors or ARBs. Duration of symptoms before admission
13 was shorter in survivors but the presence of fever or respiratory symptoms on admission
14 did not differ between survivors and non-survivors. There was no significant difference
15 in viral signs on admission except for frequent SIRS in fatal cases. Some differences in
16 laboratory tests on admission were also significant, including higher white blood cell
17 count, CRP, procalcitonin, AST, gamma glutamyl transferase, prothrombin time, blood
18 urea nitrogen, serum creatinine, and lower lymphocyte count, platelet count, serum
19 albumin, and serum sodium in fatal cases compared with survivors.
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40 **Treatments and clinical outcomes**

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43 The treatments and clinical outcomes of patients with COVID-19 receiving respiratory
44 support are shown in Table 2. Of these, 57 (19.7%) and 70 (24.2%) were treated with
45 high-flow nasal cannula and invasive mechanical ventilation, respectively. Analysis of
46 clinical outcomes revealed that 113 patients (39.1%) had ARDS, 93 (33.2%) were
47 admitted to an intensive care unit (ICU), and 18 (6.2%) underwent ECMO. The median
48 duration of hospital stay was 25 days (range 8-33). Survivors were less frequently treated
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5 with darunavir/cobicistat, systemic glucocorticoid, high-flow nasal cannula, invasive
6 mechanical ventilation, or continuous renal replacement therapy compared with fatal
7 cases. Survivors had a longer median duration of hospital stay compared with fatal cases,
8 were less frequently admitted to an ICU, and less frequently developed persistent
9 hypotension, ARDS or acute kidney injury.
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16 17 **Risk factors for mortality in COVID-19 patients receiving respiratory support**

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20 Univariate analysis identified age, sex, diabetes, chronic obstructive pulmonary disease,
21 lymphocyte count, AST, ESR, and SIRS as significant variables relating to mortality in
22 patients with COVID-19 receiving respiratory support (Table 3). Multivariate analysis
23 identified age (HR 1.054; 95% CI 1.028–1.082; $P < 0.001$), diabetes (HR 2.226; 95% CI
24 1.357–3.652; $P = 0.002$), low lymphocyte count (HR 0.999; 95% CI 0.998–1.000; $P =$
25 0.005), and high AST (HR 1.002; 95% CI 1.000–1.003; $P = 0.033$) as independent
26 predictors of mortality. Lower platelet count (HR 0.997; 95% CI 0.994–1.000, $P = 0.069$)
27 and presence of SIRS on admission (HR 1.968; 95% CI 1.199–3.230; $P = 0.074$) tended
28 to be associated with severe COVID-19, but this did not reach statistical significance.
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42 **Risk factors for mortality, including Fibrosis-4 index**

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45 Based on multivariate analysis, we used FIB-4 as a predictive risk factor candidate. In
46 multivariate analysis including FIB-4 as a continuous variable, diabetes (HR 1.998; 95%
47 CI 1.202–3.321; $P = 0.008$), lower lymphocyte count (HR 0.999; 95% CI 0.998–1.000;
48 $P = 0.003$), and FIB-4 (HR 1.115; 95% CI 1.069–1.163; $P < 0.001$) were identified as
49 independent predictors of mortality in COVID-19 patients receiving respiratory support
50 (Table S1). To set a cut-off value of FIB-4 and lymphocyte count, ROC analysis was
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5 performed (Figure 2). The Areas under the ROC curves (AUCs) of FIB-4 and lymphocyte
6 counts were 0.702 and 0.647 with sensitivity of 48.5% and 78.6%, specificity of 87.6%
7 and 45.8%, positive predictive value (PPV) of 55.0% and 32.0%, and negative predictive
8 value (NPV) of 84.4% and 86.9%, respectively (all $P < 0.001$). The optimal cut-off values
9 (COVs) of FIB-4 and lymphocyte count were 4.95 and 1010, respectively.

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18 In multivariate analysis after converting FIB-4 and lymphocyte count to categorical
19 variables, diabetes (HR 1.917; 95% CI 1.181–3.111; $P = 0.009$), low lymphocyte count
20 (HR 0.480; 95% CI 0.271–0.852; $P = 0.012$), SIRS (HR 1.714; 95% CI 1.048–2.802; P
21 = 0.032), and high FIB-4 (HR 2.784; 95% CI 1.691–4.585; $P < 0.001$) were identified as
22 independent predictors of mortality (Table 4). In addition, the results of high FIB-4 as a
23 predictor of survival was consistent in stepwise multivariate analysis (Table S2)

24 25 26 27 28 29 30 31 32 **FIB-4 and other predictive risk factors for survival in COVID-19 patients receiving** 33 **respiratory support**

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37 Among the four predictive risk factors, FIB-4 was the best predictor of mortality in
38 COVID-19 patients receiving respiratory support. Therefore, we performed survival
39 analysis to compare mortality in the high FIB-4 group (FIB-4 ≥ 4.95) and low FIB-4
40 group (FIB-4 < 4.95). Survival in the high FIB-4 group was significantly lower than in
41 the low FIB-4 group (high FIB-4, 28.8 days [23.8–33.8]; low FIB-4, 44.0 days [41.9–
42 46.1], $P < 0.001$) (Figure 3a.) Using the four variables diabetes, lymphocyte count, SIRS
43 on admission, and FIB-4, we performed survival analysis to predict mortality in COVID-
44 19 patients receiving respiratory support. As the number of risk factors increased, survival
45 of the patients significantly deteriorated (no risk factor, 47.3 days [44.2–50.4]; 1 risk
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5 factor, 40.7 days [37.4-44.0]; 2 risk factors, 38.0 days [33.8-42.2]; 3 risk factors, 30.7
6 days [23.9-37.5]; 4 risk factors, 25.0 days [6.3-43.7], $P = 0.0016$, Figure 3b, Figure S1).

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10 To explore additional predictive performance for mortality in the entire group of patients
11 with COVID-19, we performed survival analysis to compare mortality in the high and
12 low FIB-4 groups using the same cut-off. Survival in the high FIB-4 group was
13 significantly lower than in the low FIB-4 group (high FIB-4, 32.5 days [27.7–37.2]; low
14 FIB-4, 50.0 days [49.3–50.6], $P < 0.001$) (Figure 4a.) Using four variables, we also
15 performed survival analysis to predict mortality in the entire group of patients with
16 COVID-19. As the number of risk factors increased, survival significantly deteriorated
17 (no risk factor, 50.2 days [48.6-51.7]; 1 risk factor, 49.7 days [48.8-50.5]; 2 risk factors,
18 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-
19 43.7], $P < 0.001$, Figure 4b, Figure S2). In COVID-19 patients receiving high-dose
20 oxygen, survival in the high FIB-4 group was significantly lower than in the low FIB-4
21 group (high FIB-4, 16.5 days [7.0–32.0]; low FIB-4, 20.0 days [10.0–33.0], $P = 0.011$)
22 (Data not shown).
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46 **DISCUSSION**

47 In this retrospective cohort study, predictive risk factors for mortality were evaluated in
48 289 patients with confirmed COVID-19 receiving respiratory support in the Daegu and
49 Gyeongsangbuk-do area. Diabetes, low lymphocyte count, SIRS, and FIB-4 were
50 revealed as independent risk factors for mortality in COVID-19. Furthermore, survival of
51 patients with low FIB-4 and number of risk factors is better than those with high FIB-4
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5 and number of risk factors. A recent meta-analysis found that the main laboratory
6 abnormalities in COVID-19 patients included low lymphocyte count, and elevated CRP
7 and lactate dehydrogenase (LDH).²² In non-survivors, or severely ill patients requiring
8 ICU care or suffering from ARDS, laboratory abnormalities including high WBC count,
9 low lymphocyte count, prolonged prothrombin time, low albumin, elevated AST, ALT,
10 total bilirubin, LDH, creatinine, troponin I, CRP, procalcitonin, ferritin, and D-dimer
11 were identified as risk factors in previous studies.^{9 10 12} However, numbers of enrolled
12 patients were small and multivariate analyses were not performed. In a recent study,
13 logistic regression analysis identified age, Sequential Organ Failure Assessment (SOFA)
14 score, and D-dimer as predictive risk factors for death in patients with COVID-19
15 pneumonia.¹³ SOFA score is derived from PaO₂/FiO₂, use of mechanical ventilator,
16 platelets count, Glasgow Coma scale, bilirubin, mean arterial pressure or requirement for
17 vasoactive agents, and serum creatinine or urine output. The score is related to the
18 cytokine storm in sepsis²³, and we think some of the risk factors in our study, including
19 platelets as a component of the FIB-4 index, and SIRS, were also associated with this
20 serious inflammatory condition. This recent study included patients similar to those in the
21 present study, as judged from the proportion of patients receiving respiratory support
22 (82.1% versus 100% in the present study) and the mortality rate (28.3% versus 24.2% in
23 the present study).¹³ Multivariate analysis in two recent studies showed that neutrophil-
24 to-lymphocyte ratio, CD4 T cell count, and age were independent risk factors of in-
25 hospital mortality and ICU admission for COVID-19.^{24 25} Severe inflammation
26 dysregulates the immune response and is characterized by decreased memory helper T
27 (Th) cells and regulatory T cells with increased naive Th cells in patients with COVID-
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19²⁶. 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,

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5 although they exclude previously diagnosed patients with myopathies and platelets
6 disorders to avoid non-specificity of FIB-4, values of AST, ALT, and platelets can be
7 affected by COVID-19 infection itself. Furthermore, as described above, severe cause of
8 COVID-19 infection can affect AST and platelet more than mild case. If they overcome
9 these, we think they should use laboratory test to estimate advanced fibrosis before
10 patients had COVID-19.
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20 When FIB-4 is analyzed with other risk factors including lymphocyte count, SIRS, and
21 diabetes, as number of risk factors increases, survival deteriorates in patients with
22 COVID-19 regardless of respiratory support. There are several published or preprinted
23 studies of prediction models for the prognosis of patients with COVID-19.¹⁶ Albumin,
24 direct bilirubin, and red blood cell distribution width have been suggested as diagnostic
25 or prognostic indicators of severe disease or mortality in COVID-19.¹⁶ However, among
26 these three factors, albumin was not a significant risk factor, and the other two factors
27 were not evaluated in the present study. Most of the proposed models have been open to
28 criticism on the grounds of severe sampling bias due to rarely reported length of follow-
29 up and prevalence of COVID-19 with or without severe infection. A strength of the
30 present study is the low probability of sampling bias, because approximately three fourths
31 of patients with COVID-19 in South Korea have been diagnosed in the Daegu and
32 Gyeongsangbuk-do area, and our entire cohort was derived from tertiary hospitals in that
33 area.
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52 This study has some limitations. First, there was no validation with another cohort. As
53 described above, most of the COVID-19 cases were enrolled in this study. Thus, it would
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5 be impossible to validate these results without undertaking an international study.
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7 Improved assessments of international data on COVID-19 will require data sharing, using
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9 a reporting protocol specified by WHO.³³ Second, detailed radiologic assessment of CT
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11 scans was not performed. To our knowledge, there are only a few reports at preprint stage
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13 which include clinical features and radiologic features from CT scan with artificial
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15 intelligence techniques to develop prediction models.³⁴ However, this study also has
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17 sampling bias as well as an inadequate sample size.^{20 34} Therefore, advanced machine
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19 learning combining radiologic image analysis with clinical risk factors would be needed
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21 to develop a robust prediction model. Third, prediction of severe COVID-19 including
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23 ICU admission or ARDS was not analyzed in this study. However, we think prediction
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25 of severe COVID-19 was not appropriate for our cohort, because transfer to a tertiary
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27 hospital may introduce the possibility of sampling bias. Thus, we used the objective
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29 outcome of mortality in this study.
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36 In conclusion, FIB-4, diabetes, low lymphocyte count, and SIRS are independent risk
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38 factors of mortality in patients with COVID-19 receiving respiratory support. Among
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40 these risk factors, FIB-4 is a robust predictor of survival in patients with COVID-19
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42 regardless of respiratory support. A number of risk factors are significantly related to
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44 survival in patients with COVID-19 regardless of respiratory support.
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50 **Author Contributions:** Conceptualization, Soo Young Park and Woo Jin Chung;
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52 Formal analysis, Min Kyu Kang; Data curation, Min Kyu Kang, Yu Rim Lee, Jeong
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54 Eun Song and Na Young Kim; Investigation, Jung Gil Park, Min Kyu Kang, Yu Rim
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6 Jang, Changhyeong Lee, Byung Seok Kim, Jae Seok Hwang, Byoung Kuk Jang,
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8 Jinmok Bae, Ji Yeon Lee, Jeong Ill Suh and Soo Young Park; Supervision, Soo Young
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10 Park and Woo Jin Chung; Visualization, Jung Gil Park; Writing – original draft, Jung
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12 Park and Woo Jin Chung; Writing – review & editing, Soo Young Park and Woo Jin
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29
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36 **Conflict of interest:** The authors declare no conflicts of interest about this work.
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42 **Data Availability:** The data that support the findings of this study are also available from
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44 the corresponding author (SYP and WJC) upon reasonable request.
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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%)	<i>P</i> 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, $\times 10^3/\text{uL}$	6140 (4695–8065)	6000 (4690–7420)	7320 (5100–12020)	0.001
Lymphocyte count, $\times 10^3/\text{uL}$	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, $\times 10^9/\text{L}$	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

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6	Creatinine, mg/dL	0.8 (0.7–1.1)	0.8 (0.7–1.0)	1.0 (0.8–1.7)	<0.001
7	Estimated glomerular				
8	filtration rate,	80 (58–98)	84 (64–100)	63 (39–91)	0.001
9	mL/min/1.73m ²				
10					
11	Sodium, mmol/L	137 (134–141)	138 (134–141)	136 (133–140)	0.006
12	Potassium, mmol/L	4.1 (3.7–4.5)	4.1 (3.7–4.5)	4.2 (3.5–4.7)	0.870
13	Lactate dehydrogenase,				
14	U/L	558 (405–753)	560 (404–753)	556 (410–762)	0.969
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16	Creatine kinase, U/L	79 (52–155)	73 (51–149)	86 (54–172)	0.307
17	Serum ferritin, ng/mL	552 (327–975)	430 (308–941)	659 (521–1432)	0.115
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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)	<i>P</i> 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	
	<i>P</i> value*	<i>P</i> 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, $\times 10^3/\mu\text{L}$	<0.001	0.005	0.999 (0.998–1.000)
Platelet count, $\times 10^9/\text{L}$	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/1.73m ²	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	
	<i>P</i> value*	<i>P</i> 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/1.73m ²	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

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6 **Figure 1.** Flow diagram of the study
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11 **Figure 2.** Predictive performance of risk factors for mortality in patients with COVID-
12 19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area
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14 under the curve for lymphocyte counts
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21 **Figure 3.** Survival of patients with COVID-19 receiving respiratory support plotted
22 against fibrosis-4 index (a) and number of risk factors (b)
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29 **Figure 4.** Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and
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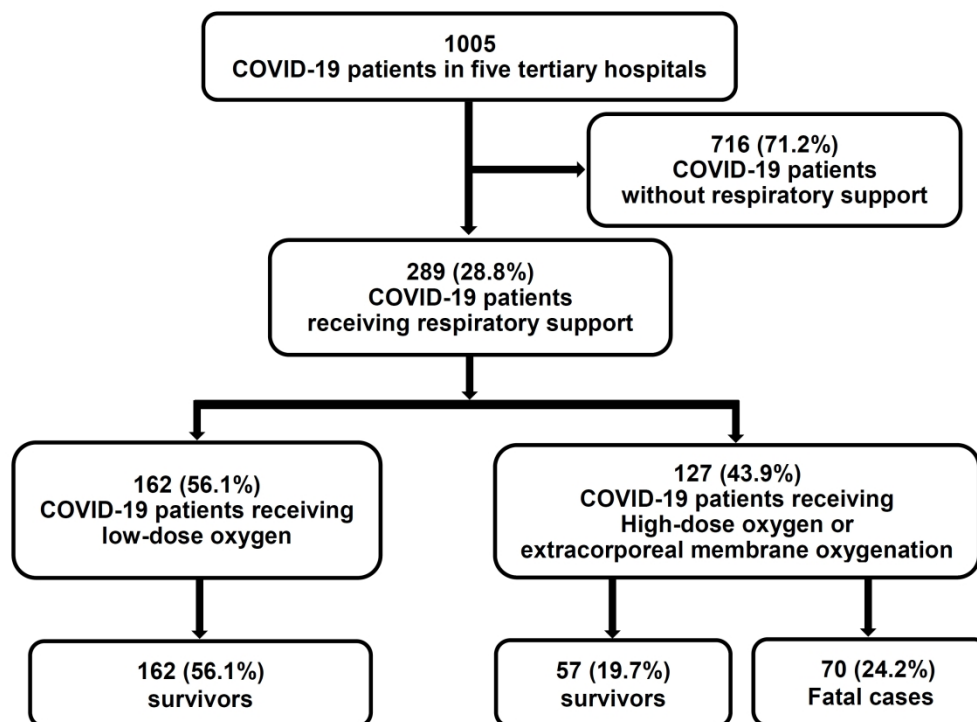


Figure 1. Flow diagram of the study

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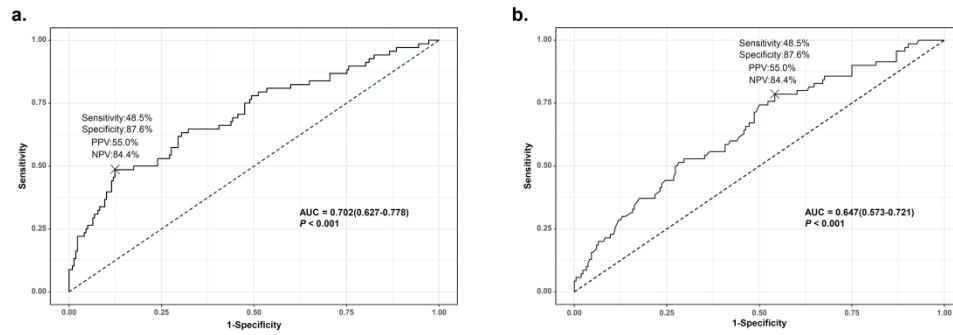


Figure 2. Predictive performance of risk factors for mortality in patients with COVID-19 receiving respiratory support. a. Area under the curve for fibrosis-4 index; b. Area under the curve for lymphocyte counts

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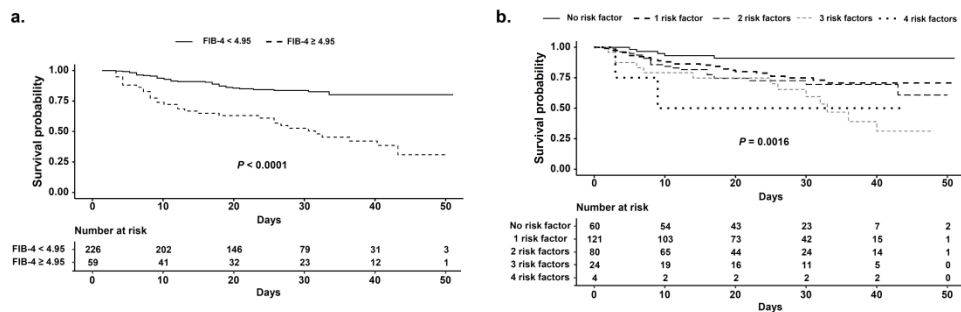


Figure 3. Survival of patients with COVID-19 receiving respiratory support plotted against fibrosis-4 index (a) and number of risk factors (b)

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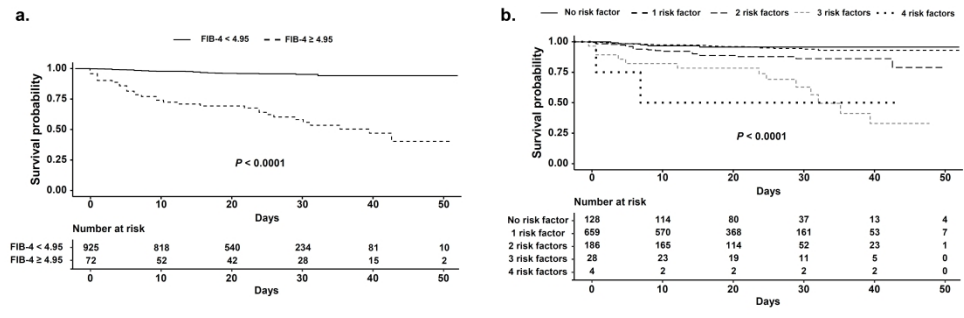


Figure 4. Survival of patients with COVID-19 plotted against fibrosis-4 index (a) and number of risk factors (b)

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	
	<i>P</i> value*	<i>P</i> 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, $\times 10^3/\mu\text{L}$	<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 m ²	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)	<i>P</i> -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

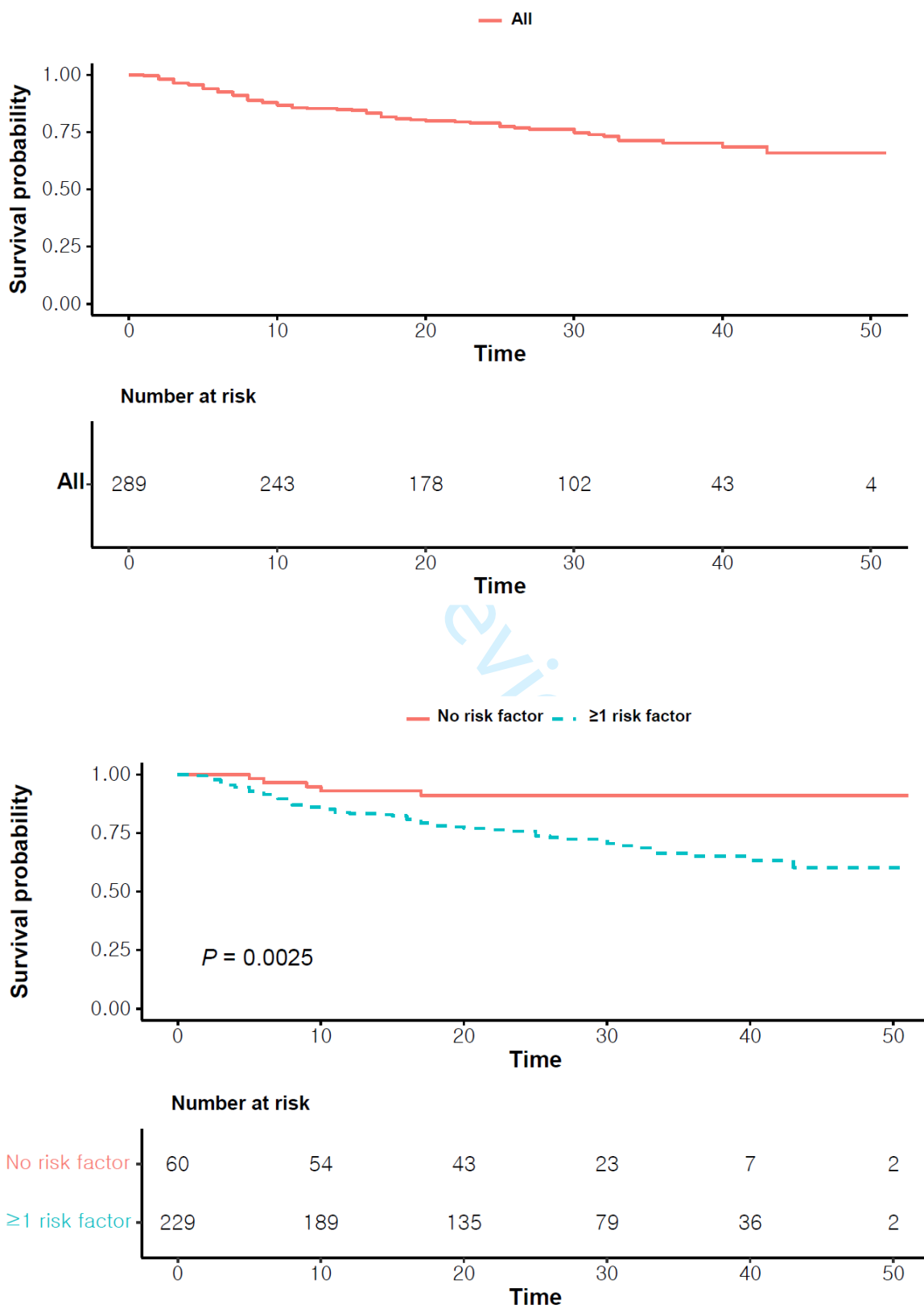
HR, hazard ratio; CI, confidential interval

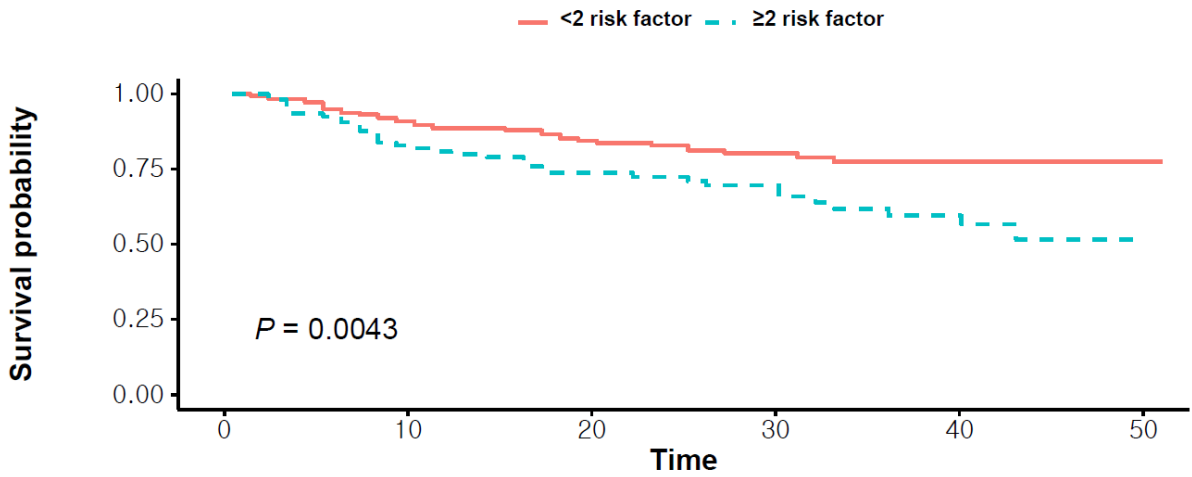
Model 1 was adjusted for age, gender.

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

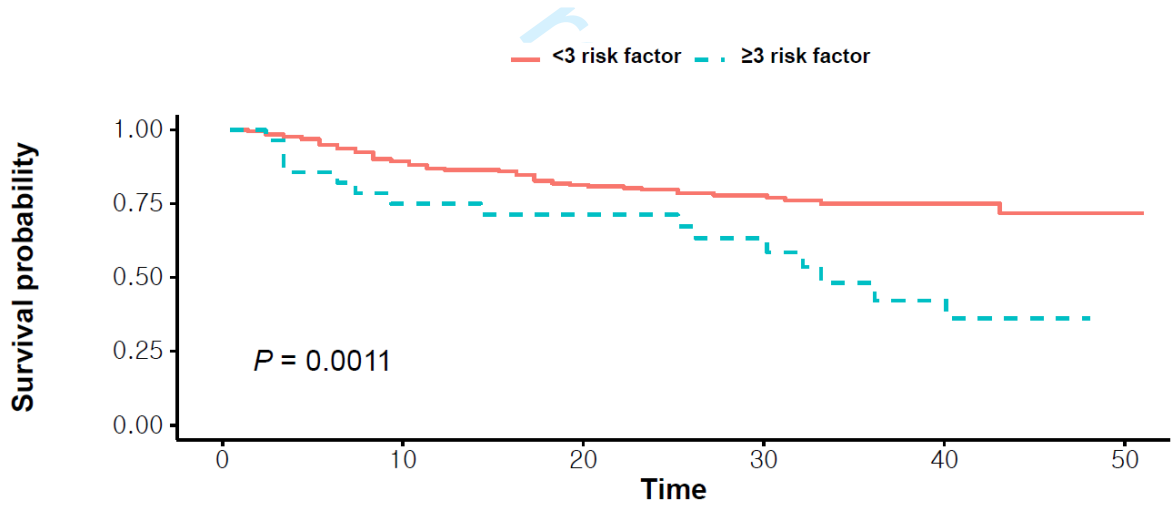




Number at risk

< 2 risk factor	181	157	116	65	22	3
>=2 risk factor	108	86	62	37	21	1

Time

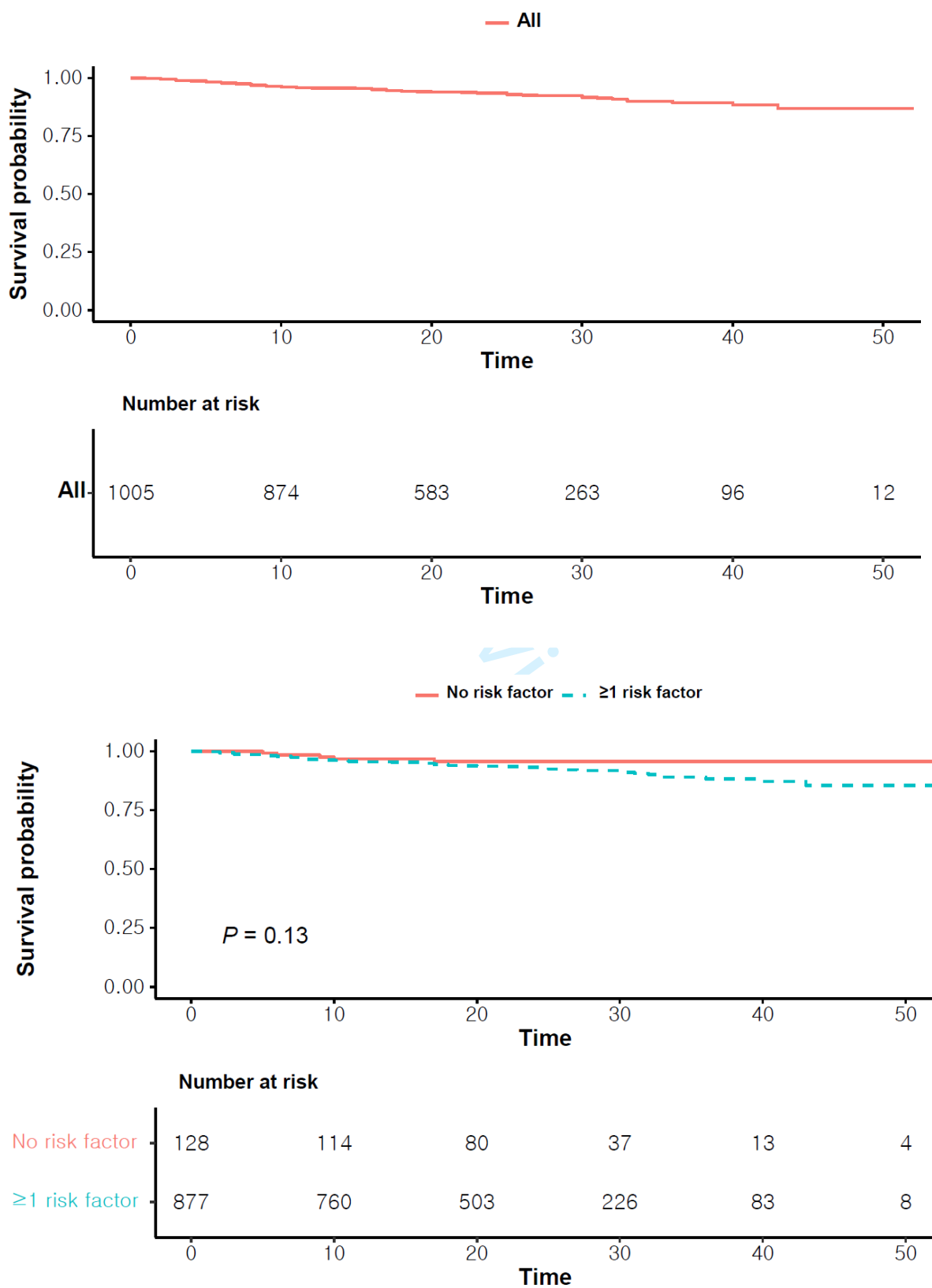


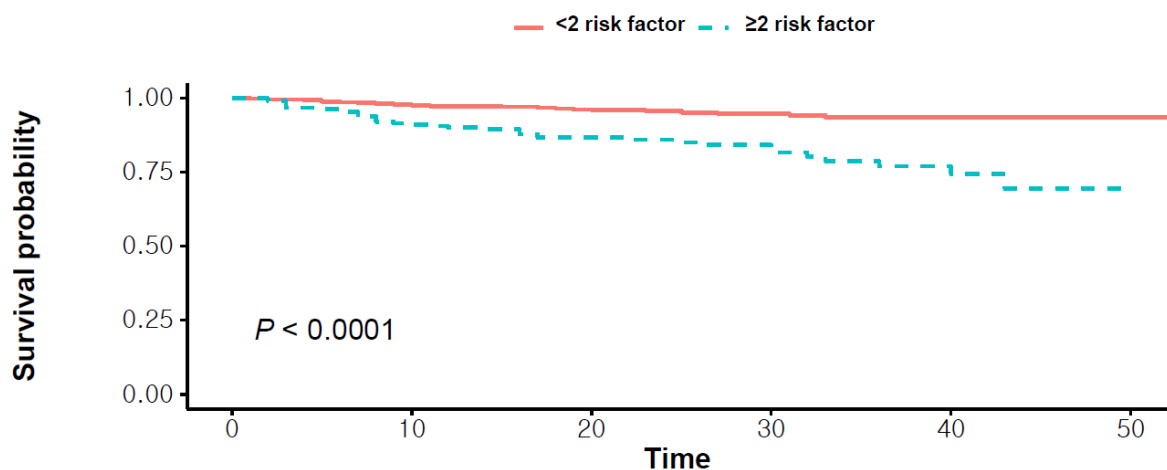
Number at risk

< 3 risk factor	261	222	160	89	36	4
>=3 risk factor	28	21	18	13	7	0

Time

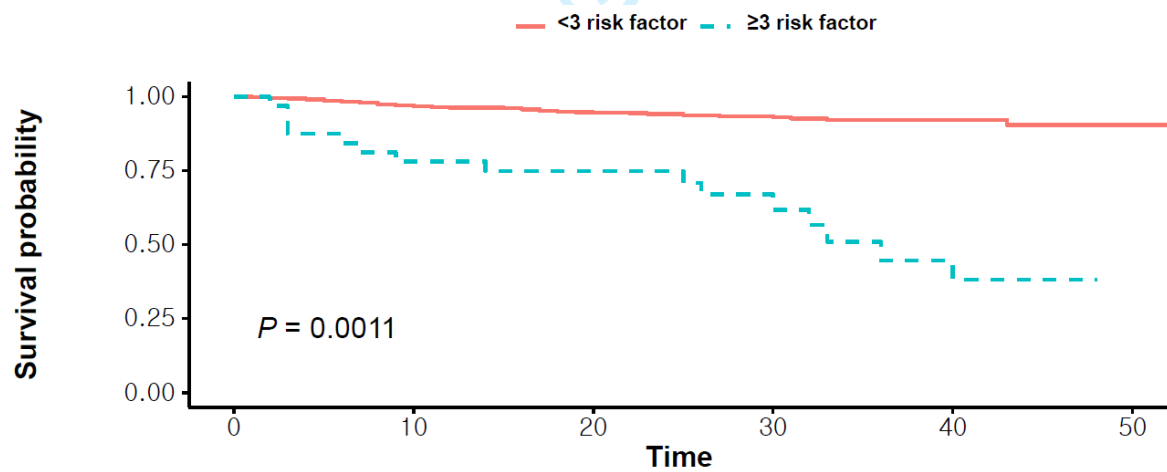
Figure S2. Survival of the entire group of patients with COVID-19 as the number of risk factors





Number at risk

	0	10	20	30	40	50
< 2 risk factor	787	684	448	198	66	11
≥2 risk factor	218	190	135	65	30	1



Number at risk

	0	10	20	30	40	50
< 2 risk factor	973	849	562	250	89	12
≥2 risk factor	32	25	21	13	7	0

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

1	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	9-11
2			(b) Report category boundaries when continuous variables were categorized	9-11
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	11-14
13	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
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	15
16				
17	Other information			
18	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
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*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>.