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Risk factors for severity on admission and the disease progression during hospitalization in a large cohort of COVID-19 patients in Japan

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Title: Risk factors for severity on admission and the disease progression during hospitalization in a large cohort of COVID-19 patients in Japan

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52 **Word Count:** 3025
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Abstract

Objectives: To investigate the risk factors contributing to severity on admission.

Additionally, risk factors on worst severity and fatality were studied. Moreover, factors were compared based on three points: early severity, worst severity, and fatality.

Design: An observational cohort study utilizing data entered in a Japan nationwide COVID-19 inpatient registry, COVIREGI-JP.

Setting: As of August 31, 2020, 7,546 cases from 780 facilities have been registered. Participating facilities cover a wide range of hospitals where COVID-19 patients are admitted in Japan.

Participants: Participants who had a positive test result on any applicable SARS-CoV-2 diagnostic tests, and were admitted to participating healthcare facilities. A total of 3,829 cases were identified from January 16 to May 31, 2020, of which 3,376 cases were included in this study.

Primary and secondary outcome measures: Primary outcome was severe or non-severe on admission, determined by the requirement of mechanical ventilation or oxygen therapy, SpO₂, or respiratory rate. Secondary outcome was the worst severity during hospitalization, judged by the requirement of oxygen and/or IMV/ECMO.

Results: Risk factors for severity on admission were older age, male, cardiovascular disease,

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6 chronic respiratory disease, diabetes, obesity, and hypertension. Cerebrovascular disease, liver
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9 disease, renal disease or dialysis, solid tumor, and hyperlipidemia did not influence severity on
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12 admission ; however it influenced worst severity. Fatality rates for obesity, hypertension, and
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15 hyperlipidemia were relatively lower.
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18 **Conclusions:** This study segregated the comorbidities driving severity and death. It is
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20 possible that risk factors for severity on admission, worst severity, and fatality are not consistent
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22 and may be propelled by different factors. Specifically, while hypertension, hyperlipidemia, and
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24 obesity had major effect on worst severity, their impact was mild on fatality in the Japanese
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26 population. Some studies contradict our results; therefore, detailed analyses, considering in-
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28 hospital treatments, are needed for validation.
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36 **Trial registration:** UMIN000039873. [https://upload.umin.ac.jp/cgi-open-](https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453)
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45 **Strengths and limitations of this study**

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48 • In this article, we studied the disease progression of COVID-19, by comparing the risk
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50 factors on three points: early severity, worst severity, and fatality.
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54 • Our results are useful from a public health perspective, as we provide risk factors for
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56 predicting the severity on admission and disease progression from patients' background
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6 factors.

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- 10 • This study pointed out the possibility that risk factors of the severity on admission, worst
11 severity, and fatality are not consistent and may be propelled by different factors.
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 - 13 • Our data were collected from hundreds of healthcare facilities; thus data accuracy may be
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 - Also, treatment type, dosage, duration, and combination varied immensely across the
facilities and we did not consider treatments prior to and during hospitalization in the analysis.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused a major global public health crisis. As of October 3, 2020, >34 million people had been infected in over 230 countries^{1,2}. Japan experienced two pandemic waves after the first case reported on January 16, 2020. During the first wave, a state of emergency was declared on April 7, which ended on May 25, settling the first wave. Nearly thrice as many SARS-CoV-2 positive cases were detected in the second wave, which emerged from the end of June³. The fatality rate in the second wave has generally been lower in many countries, including Japan⁴.

When the number of patients explodes, hospital beds were in great shortage; hotels were utilized as isolation facilities in many countries⁵⁻⁷. Likewise, in Japan, mild patients were transferred to hotels from April 2020⁸. About two-thirds of cases did not require oxygen support throughout their illness⁹. However, some cases initiated non-severe may instantly plunge into a serious state and require aggressive care¹⁰. Therefore, public health centers are in demand for indicators to identify those at a higher risk of aggravation in the early phase and determine the destination—hospital, hotel, or home. Depicting the clinical course—from onset to worst severity and the outcome—is imperative to appropriately allocate patients to healthcare resources. Analyses considering the severity on admission and the disease progression thereafter

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6 has not been conducted are of interest to physicians globally.
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9 We obtained nationwide data from a COVID-19 inpatient registry, "COVID-19 REGISTRY
10 JAPAN (COVIREGI-JP)"¹¹, and conducted a study to identify the independent risk factors
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12 contributing towards severity on admission. We aimed to determine the risk factors on
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14 admission, namely demographics and comorbidities. Progression of severity was inspected in
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16 detail on different time points. Cases identified within the period of the first pandemic wave
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18 were studied.
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30 **Methods**

31 **Study design and patients**

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33 This is an observational cohort study that utilizes the data accumulated in the
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35 nationwide "COVID-19 REGISTRY JAPAN (COVIREGI-JP)"¹¹. As of September 28, 2020,
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37 10,048 cases from 802 facilities have been registered. Participating facilities covers a wide
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39 range of hospitals where COVID-19 patients are admitted in Japan. Enrolled cases satisfied two
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41 eligibility criteria: a positive test result for COVID-19 and being admitted to a healthcare
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43 facility. Registration started on March 2, 2020, and is ongoing, at present.
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57 **Data collection and case report form**

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6 Data were collected in a case report form (CRF) developed for COVIREGI-JP. This CRF
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9 includes modified information of the International Severe Acute Respiratory and Emerging
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12 Infection Consortium CRF on COVID-19¹². Upon modification, we elaborated on data collection,
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15 especially on treatments, comorbidities, and symptoms. In addition, as of October 26, 2020, this
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18 CRF underwent revisions twice to update therapeutic options or definitions, as new evidence
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21 emerges. Study data were collected and managed using Research Electronic Data Capture
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24 (REDCap) electronic data capture tools^{13,14}, hosted at the datacenter in National Center for Global
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27 Health and Medicine. Data were either recorded on a CRF hard-copy or were entered directly into
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30 REDCap at each facility.
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36 **Comorbidities**

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39 Comorbidities were collected based on Charlson comorbidity index^{15,16} with modifications.
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42 Some comorbidities were combined as follows: Cardiovascular disease (CVD)—myocardial
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45 infarction, congestive heart failure, and peripheral vascular disease; Chronic respiratory disease
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48 (CRD)—chronic obstructive pulmonary disease (COPD) and other chronic lung diseases; Renal
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51 disease or dialysis—moderate to severe renal disorder (creatinine \geq 3mg/dL, nephropathy, post-
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54 renal transplantation, or on dialysis), and maintenance hemodialysis or peritoneal dialysis before
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57 hospitalization; and Solid tumor—solid tumor with or without metastasis. Obesity was
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6 diagnosed based on physician's judgement, and body mass index (BMI) was not considered in
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9 this study.
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11 12 13 14 15 **Drug administration prior to and during hospitalization** 16

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18 Steroids, chemotherapy, and immunosuppressants administered prior to hospitalization were
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20 collected as pre-hospitalization treatments. Steroids included those equivalent to 20 mg/day
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22 prednisolone for ≥ 1 month and are not considered as immunosuppressants. Chemotherapy and
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24 immunosuppressants was applicable if administered 3 months prior to hospitalization. Treatment
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26 during hospitalization was studied on systemic steroids, favipiravir, ciclesonide, heparin, and
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28 tocilizumab, due to the frequent use in Japan. Heparin use included those given for both
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30 prophylactic and treatment purposes.
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43 **Dataset** 44

45 We defined the first wave period as January 16 to May 31, 2020¹⁷, and cases from the first
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47 wave was included in this analysis. Therefore, data extraction conditions were: (1) cases
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49 admitted to healthcare facilities between January 16 and May 31, 2020, and (2) all CRF items
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51 completed on dataset generation. The dataset was generated and fixed on September 2, 2020.
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Definitions of severity

1) Severity on admission

Severity on admission was converted into bivariate variables: severe and non-severe. Cases met at least one of the following criteria were categorized as severe: (1) requiring invasive or non-invasive mechanical ventilation, (2) requiring supplemental oxygen, (3) $SpO_2 \leq 94\%$ in room air, or (4) tachypnea with respiratory rate (RR) ≤ 24 breaths per minute¹⁸. Those who did not meet the aforementioned were classified as non-severe.

2) Worst severity

The worst severity was grouped into three categories: no-oxygen, oxygen, and IMV/ECMO. The worst state during hospitalization was adopted on categorization, and each was defined as follows:

No-oxygen—No requirement of supplemental oxygen throughout hospitalization.

Oxygen—Required supplemental oxygen (including high-flow oxygen devices) or non-invasive mechanical ventilation during hospitalization.

IMV/ECMO—Required invasive mechanical ventilation or extracorporeal membrane oxygenation during hospitalization.

Statistical analysis

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Continuous variables are presented in median and interquartile range (IQR) and categorical variables in number of cases and percentages. We classified the disease progression into three stages: severity on admission, worst severity, and clinical outcomes. We used Mann-Whitney U tests (for two groups) or Kruskal-Wallis tests (for three groups) for continuous variables and chi-squared tests for categorical variables.

We conducted a multivariable logistic regression analysis to identify the factors associated with the patients' severity on admission. We included age, sex, comorbidities (CVD, cerebrovascular disease, CRD, asthma, liver disease, diabetes, obesity diagnosed by physicians, renal disease or dialysis, solid tumors, leukemia, lymphoma, hypertension, and hyperlipidemia), use of systemic steroids in the past month, chemotherapy in the past three months, and use of immunosuppressants other than steroids as independent variables. Multicollinearity was evaluated using the variance inflation factor (VIF). Variables of $VIF > 3$ were excluded from the model; however, no variables demonstrated obvious multicollinearity.

R version 3.6.3 (R core team, 2020)¹⁹ was used for all the analyses performed in this study.

Ethics

The National Center for Global Health and Medicine ethics board approved this study (referral

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6 number NCGM-G-003494-08), and waived the need for informed consent from individual
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8 patients owing to the non-invasive, non-interventional nature of this observational study
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10 according to the local Ethical Guidelines²⁰. Information regarding opting out of our study is
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12 available on the website¹¹. Although it is not mandatory, the study is also being registered on trial
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14 registration website (Unique ID: UMIN000039873, [https://upload.umin.ac.jp/cgi-open-](https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453)
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16 [bin/ctr_e/ctr_view.cgi?recptno=R000045453](https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453)).
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28 Results

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30 Within the study period, 3,829 cases were identified and 3,376 cases from 299
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32 facilities were included in this study. Of them, 2,199 cases (65.1%) were non-severe, and 1,181
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34 cases (34.9%) were severe at the time of admission. After categorizing the two groups further
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36 into no-oxygen, oxygen, and IMV/ECMO by worst severity, compositions were 1,758 (81.5 %),
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38 357 (16.5%), and 43 (2.0%) for the non-severe group and 190 (16.1%), 677 (57.5%), and 311
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40 (26.4%) for the severe group, respectively. While categorizing the cases, 44 (1.3%) were
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42 unavailable due to missing values.
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51 Demographics and clinical characteristics of the study population are shown in Table

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54 1. Days between onset and admission were similar in both groups (non-severe 6.0 vs severe 7.0
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56 days). Over ten times as many severe cases on admission underwent IMV/ECMO than non-
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6 severe cases (2.0% vs 26.4%). Severe cases were older (50.0 vs 67.0), had higher BMI (22.9 vs
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9 24.1), greater male dominance (56.3% vs 70.5%), and a higher prevalence of comorbidities
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12 excluding leukemia, compared to the non-severe group. The most prevalent symptoms in both
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15 groups were fever (non-severe 49.5%, severe 73.7%), cough (non-severe 53.8%, severe 64.9%),
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18 and fatigue (non-severe 40.3%, 59.9%), but was greater in the severe group. Conversely,
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21 prevalence of dysgeusia (25.9% vs 13.2%), dysosmia (22.6% vs 11.5%), headache (18.1% vs
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24 14.7%), and runny nose (11.9% vs 8.9%) was higher in the non-severe group.
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28 Results of the multivariate logistic regression to determine the risk of severity on
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30 admission are shown in Table 2. Older age (OR 1.038 [1.032—1.044]) and male (OR 2.06
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32 [1.69—2.51]) were considered a risk among the demographics and comorbidities included CVD
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34 (OR 1.61 [1.07—2.43]), respiratory disease (OR 2.59 [1.63—4.13]), diabetes (OR 1.39 [1.09—
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36 1.76]), obesity (OR 1.62 [1.12—2.35]), and hypertension (OR 1.31 [1.03—1.67]). Days
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39 between onset to admission were non-significant ($p = 0.376$); the timing of admission did not
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42 affect the severity on admission.
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49 Table 3 depicts the study population from a different angle and is categorized by the
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51 worst severity (n=3,336) and fatality (n=3,376). Oxygen and IMV/ECMO cases were
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54 predominantly severe at admission (65.5% and 87.9%, respectively), whereas most no-oxygen
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57 cases come from non-severe group (90.2%). Prevalence of comorbidities was lowest in no-
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6 oxygen cases; however, prominent difference was not observed for asthma. Similarly, fatal
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9 cases were more severe at admission (84.0% vs 31.1%) and had higher prevalence of oxygen
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12 and IMV/ECMO cases (oxygen: 56.4% vs 29.0%, IMV/ECMO: 41.9% vs 8.2%, respectively).
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15 Days between onset and admission was longer in non-fatal cases (5-days vs 7-days).
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18 More non-severe cases with any comorbidity underwent treatment with oxygen or
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21 IMV/ECMO compared to non-severe cases with no comorbidities. In figure 1, only 11.9%
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24 underwent oxygen therapy or IMV/ECMO in non-severe cases without any comorbidities.
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27 However, among the non-severe cases with comorbidity, the rates of oxygen or IMV/ECMO
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30 were higher in most comorbidities, including CVD (34.7%), CRD (38.9%), liver disease
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33 (36.7%), diabetes (35.1%), obesity (35.8%), cerebrovascular disease (34.7%), renal disease
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36 (40.9%), solid tumor (27.3%), hypertension (31.2%), and hyperlipidemia (25.0%). Asthma
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39 alone followed a different trend; the chances of oxygen and IMV/ECMO requirement was
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42 lower.
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45 Among the cases without comorbidity, 75.2% of cases that were severe on admission
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48 required oxygen or IMV/ECMO; however, the fatality rate was low, and only 8.0% resulted in
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51 death (Figure 2). Fatality rates were approximately 3—5 times higher when the following
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54 comorbidities were present: renal disease or dialysis (44%), CVD (40.5%), cerebrovascular
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57 disease (39.5%), CRD (30.4%), solid tumor (30.4%), diabetes (25.8%), and liver disease
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6 (25.6%). Even among non-severe cases, relatively high fatality rate was observed in cases with
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9 solid tumor, CRD, cerebrovascular disease, CVD, and renal disease or dialysis, with fatality
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11 rates ranging from 8.1% to 11.1%. Collectively, obesity, hypertension, and hyperlipidemia
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13 influenced the worst severity; however, their influence on fatality was relatively lower than that
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15 mentioned earlier.
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21 Older age was relevant to both worst severity and fatality, as shown in supplemental
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23 figures 1 and 2. The combined proportion of oxygen and IMV/ECMO increased gradually by
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25 age from 5.3% in 20s to 69.3% in ≥ 80 s. Conversely, the fatality rate leaped between 60s (2.2%)
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27 and 70s (8.6%). Likewise, supplemental figure 3 shows the combined proportion of oxygen and
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29 IMV/ECMO and fatality rates as higher in older individuals, irrespective of underlying
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31 comorbidities.
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39 Predominant comorbid cases required more drug administration than those without
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41 comorbidities (Supplementary Table 1). Systemic steroids were most frequently used in cases
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43 with CRD (27.9%). Heparin was used most often in renal disease (12.8%), hypertension
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45 (11.2%), diabetes (10.9%), and CVD (10.4%).
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54 Discussion

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57 We took disease progression into consideration and evaluated the study population
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6 based on severity on admission, worst severity, and the outcome. To our knowledge, studies
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9 have predominantly reported worst severity, whereas disease progression has not been
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12 considered. Our findings, therefore, are novel, augmenting the evidence needed to depict the
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15 clinical course and trajectory from onset to worsening condition. Specifically, this study
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18 segregated the comorbidities influencing severity and death. Based on our findings, it may be
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21 possible that the early severity, worst severity, and death are propelled by different factors,
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24 whilst confirmation is necessary by multivariate analysis.
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27 The majority of comorbidities we studied did not influence severity on admission. On
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30 admission, severity was driven by age, sex, CVD, CRD, diabetes, obesity, and hypertension.
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33 The trend was similar for the worst severity, as cases with these factors had higher rate of
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36 oxygen or IMV/ECMO. However, all comorbidities appeared to influence the worst severity.
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39 Within the comorbidities, the prognosis of cases with obesity, hypertension, or
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42 hyperlipidemia was relatively favorable. In contrast to our results, hypertension and obesity are
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45 reportedly related to an increased risk of severity and mortality²¹⁻²⁴. However, a large cohort
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48 reported a trend similar to our results²⁵. Another study reported that obesity is be confounded by
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51 age and sex^{26,27}. Obesity was judged by a physician in our study, and the results may change
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54 after incorporating BMI. Several other evidences suggest that the association of these
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57 comorbidities with poorer outcome of COVID-19 needs further investigation. BMI, on average,
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6 is lower in the Asia-Pacific region than in other global regions²⁸; therefore, the degree of obesity
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9 may have been milder in our study population. Extreme obesity may worsen the prognosis, and
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12 confounders should be addressed in consecutive analyses. On the other hand, the presence of
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15 hypertension and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II
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18 receptor blockers act contrarily²⁹⁻³¹, while ACE2 mediates the entry of SARS-CoV-2 into host
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21 cells^{32,33}, making the COVID-19 pathophysiology in hypertensive patients intricate. Our study
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24 suggested that hypertension, hyperlipidemia, and obesity could be less detrimental on fatality.
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28 In accordance with previous studies, CVD, CRD, liver disease, diabetes,
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30 cerebrovascular disease, renal disease or dialysis, and solid tumor were associated with to
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33 fatality and worst severity. Two meta-analyses have reported common risk factors for worst
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36 severity during hospitalization, which include, diabetes, COPD, malignancy, CVD, and
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39 cerebrovascular disease^{34,35}. Other studies have also reported chronic liver disease and renal
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42 disease as risk factors³⁶⁻³⁸. Studies have elucidated that acute respiratory distress syndrome and
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45 coagulation dysfunction are related to the renin-angiotensin-aldosterone system and blood
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48 coagulation pathways, which are altered by SARS-CoV-2 host cell invasion via ACE2³⁹⁻⁴¹.
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51 Clinical and non-clinical studies revealed an association between these comorbidities; while
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54 SARS-CoV-2 infection decreases ACE2 expression, ACE2 deficiency is reported to cause
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57 cardiac overload and kidney inflammation⁴¹⁻⁴⁴. Elevated blood glucose is also associated with
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6 mortality⁴⁵. Although risk factors vary among studies, the comorbidities we identified are highly
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8 likely associated with fatality, backed up by clinical and non-clinical results.
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12 Different trends were seen in the rates of IMV/ECMO and death for each comorbidity.
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15 Although rates of IMV/ECMO were comparable in all comorbid cases, those with obesity,
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17 asthma, hyperlipidemia, and hypertension showed a lower fatality rate, suggesting that the
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19 fatality rates within the IMV/ECMO cases with these comorbidities were lower than expected.
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24 Contrarily, fatality rates in cases with CVD, cerebrovascular disease, renal dysfunction, tumor,
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26 and CRD were comparable or higher than IMV/ECMO rates. The number of death actually
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28 exceeded the number of IMV/ECMO cases in patients with tumor, cerebrovascular disease, or
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30 CVD. These comorbidities likely have caused a higher risk of death and some even died without
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32 intubation. Healthcare nearly overwhelmed in the first wave in Japan but ICU capacity was
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34 maintained⁴⁶, and thus intubation may have been unperformed due to a medical judgment. A
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36 detailed examination of these issues is necessary in the future.
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45 Our results did not show prominent difference in fatality between males and females.
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48 Oftentimes, males are considered to develop severe conditions and increased fatality^{37,38,47-49}.
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51 However, according to Global Health 5050, sexual disparity in incidence of COVID-19 is low⁵⁰.
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54 Additionally, ACE2 expression is affected by sexual hormones, whereby higher expression is
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56 observed in men, possibly explaining the sexual disparity⁵¹⁻⁵³. Moreover, the immunological
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6 response to produce antibodies is more favorable in females⁵⁴. These studies support the
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9 rationale that males are more susceptible to severe COVID-19, which contravene our results.
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12 The lower-than-expected fatality rate in our male population may be attributed to comorbidity
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15 prevalence, treatments, age, and/or degree of obesity.
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19 Fatality rates were comparable between asthmatic and cases without comorbidities in
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21 our results. Theoretically, COVID-19 can be a risk for asthmatic patients. A viral respiratory
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23 infection is presented as relatively worse and causes asthma exacerbation^{55,56}. Asthmatic
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25 patients reportedly require a longer duration of mechanical ventilation when intubated⁵⁷;
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28 however, no study, including ours, has found strong evidence on severity or mortality⁵⁸⁻⁶¹.
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31 Inhaled corticosteroids (ICS) are known to downregulate ACE2^{62,63} and are being investigated
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33 for treating COVID-19⁶⁴. ICS may have impeded aggravation in asthmatic patients with
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36 COVID-19⁶⁵. Overall, further studies are needed to elucidate the true risk of asthma on COVID-
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Our results could be useful to roughly identify those at a risk of aggravation or death.
Days from onset to admission was not a risk factor; early hospitalization will not influence the
disease progression or outcome, and severity on admission was mostly driven by age and the
presence of a few comorbidities. Several studies have created a scoring system to predict the
risk of severity or mortality⁶⁶⁻⁶⁸. However, these utilize laboratory data collected on admission

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6 and are seldom practical for estimating the severity of illness prior to medical visits or when test
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9 results are not promptly available. While these are useful to predict prognosis more precisely,
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12 our results are useful from a public health perspective, as they provide risk factors for predicting
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15 the severity on admission and disease progression from patients' background factors.
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18 Our study has several limitations. In some of our analyses, confounders were not
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21 eliminated. We did not consider treatments prior to and during hospitalization. As our data were
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24 collected from hundreds of healthcare facilities, treatment type, dosage, duration, and
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27 combination varied immensely. We plan to deliberate the analytical methodology further to
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30 evaluate the outcomes which are prone to be affected by in-hospital treatments. Data were
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33 collected from numerous facilities; therefore, accuracy may be questionable. Additionally,
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36 hotels were utilized as isolation facilities from April 2020, and participant selection might have
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39 altered thereafter. COVIREGI-JP is continuously open for new entry; the number of
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42 registrations is increasing, and subsequent results may vary from ours.
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48 **Conclusion**

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51 On admission, factors that influence severity were age, sex, and comorbidities,
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54 including CVD, CRD, diabetes, obesity, and hypertension. Risk factors for severity on
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57 admission, worst severity, and fatality were not consistent, and it is likely that they are each
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6 propelled by different factors. Our results are practically useful for predicting the progression
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9 and preparing for the worst, based on patients' backgrounds. Moreover, based on our
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12 predictions, healthcare resources can be allocated to patients in the most suitable way.
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18 **Acknowledgments**

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21 We thank all the participating facilities for their care towards COVID-19 patients and
22
23
24 cooperation during data entry. We are especially grateful for the 299 facilities that contributed
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26
27 to the dataset used in this study.
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33 **Contributorship statement**

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35
36 MT conceived and HO, SS, KH, ST and MT designed the study. ST, YA, SS, KH, and
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38
39 MT analyzed and interpreted the data. MT and ST drafted the first version of the manuscript.
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42 All the authors contributed to, read, and approved the final manuscript. The corresponding
43
44
45 author attests that all listed authors meet authorship criteria and that no others meeting the
46
47
48 criteria have been omitted. SS is the guarantor.
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9 emerging infectious diseases”, provided by the Japanese Ministry of Health, Labour, and
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12 Welfare. The funding agency did not assume any role in this study or COVIREGI-JP.
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18 **Competing Interests**

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20
21 All authors have completed the ICMJE uniform disclosure form at
22
23 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
24
25 submitted work; H.O. reports personal fees as a statistician and as an external consultant for
26
27 clinical trials from EPS International, outside the submitted work; no other relationships or
28
29 activities that could appear to have influenced the submitted work.
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40 **Transparency Statement**

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42 The corresponding author affirms that this manuscript is an honest, accurate, and
43
44 transparent account of the study being reported; that no important aspects of the study have been
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46 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
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48 been explained.
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58 **Data sharing**

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6 Data on an individual level is shared with limitation to participating healthcare facilities
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9 through applications to COVIREGI-JP¹¹.
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15 **Patient and Public Involvement**

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18 No patient was involved in the setting of research question, outcome measures, or study
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21 design, nor were they involved in the recruitment to and conduct of the study.
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28 **Dissemination to participants and related patients and public communities**

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30 The study results will be shared with all the healthcare facilities which participated and
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33 registered data in COVIREGI-JP. It will also be shared with the public on the website¹¹.
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Table 1. Characteristics of patients included in the present study

	Non-severe (n=2196)	Severe (n=1180)
Fatal cases	39 (2)	204 (17)
Worst severity during hospitalization		
No oxygen	1796 (82)	192 (16)
Oxygen	357 (16)	678 (58)
IMV/ECMO^a	43 (2)	310 (26)
Days between onset and admission		
(median [IQR])	6 [4, 10]	7 [4, 10]
Age (median [IQR])	50 [35, 64]	67 [53, 78]
Male	1232 (56)	830 (71)
BMI (median [IQR])	22.9 [20.3, 25.7]	24.1 [21.5, 27.1]
Comorbidities		
Cardiovascular disease	62 (3)	121 (10)
Respiratory disease	36 (2)	104 (9)
Liver disease	49 (2)	39 (3)
Cerebrovascular disease	72 (3)	115 (10)
Asthma	102 (5)	64 (5)

	Diabetes	262 (12)	300 (25)
	Obesity	95 (4)	83 (7)
	Severe renal disease or dialysis	22 (1)	25 (2)
	Solid tumor	66 (3)	79 (7)
	Leukemia	10 (1)	3 (0)
	Lymphoma	16 (1)	9 (1)
	Hypertension	292 (13)	331 (28)
	Hyperlipidemia	176 (8)	157 (13)
Treatments prior to COVID-19			
	Use of steroid in one month	6 (0)	10 (1)
	Chemotherapy in three months	32 (2)	24 (2)
	Immunosuppressants^b use in three months	26 (1)	18 (2)
Symptoms on admission			
	Fever ($\geq 37.5^{\circ}\text{C}$)	1078 (49)	862 (74)
	Cough	1167 (54)	716 (65)
	Sore throat	340 (17)	142 (16)
	Runny nose	239 (12)	86 (9)
	Chest pain	95 (5)	44 (5)

	Myalgia	172 (9)	79 (9)
	Headache	361 (18)	136 (15)
	Confusion	21 (1)	68 (6)
	Fatigue	834 (40)	595 (60)
	Abdominal pain	60 (3)	24 (3)
	Vomit	88 (4)	59 (6)
	Diarrhea	251 (12)	164 (16)
	Dysgeusia	494 (26)	113 (13)
	Dysosmia	422 (23)	96 (12)

^ainvasive mechanical ventilation/extracorporeal membrane oxygenation

^bimmunosuppressants other than steroids

Table 2. Factors associated with being “severe” at the time of admission

	Odds ratio	95% CI ^a	<i>P</i> value
Days between onset and admission	1.0	0.99-1.01	0.960
Age	1.04	1.03-1.04	< 0.001
Male	2.09	1.76-2.48	< 0.001
Comorbidities			
Cardiovascular disease	1.48	1.04-2.10	0.028
Cerebrovascular disease	1.33	0.95-1.85	0.097
Chronic respiratory disease	2.51	1.67-3.78	< 0.001
Asthma	1.24	0.87-1.77	0.240
Liver disease	0.97	0.61-1.54	0.892
Diabetes	1.34	1.09-1.64	0.006
Obesity diagnosed by physicians	1.75	1.26-2.45	0.001
Severe renal disease or dialysis	1.0	0.54-1.88	0.991
Solid tumor	1.20	0.82-1.77	0.351
Leukemia	0.34	0.08-1.39	0.132
Lymphoma	0.42	0.16-1.11	0.081
Hypertension	1.33	1.08-1.64	0.008

	Hyperlipidemia	0.91	0.70-1.19	0.490
Treatments prior to COVID-19				
	Use of steroid in one month	1.65	0.52-5.22	0.394
	Chemotherapy in three months	1.47	0.72-3.0	0.286
	Immunosuppressants^b use in three months	1.35	0.69-2.64	0.384

^aconfidence interval

^bimmunosuppressants other than steroids

Table 3. Characteristics of patients stratified by non-fatal/fatal cases and severity during hospitalization

	Non-fatal (n=3129)	Fatal (n=243)	No-oxygen (n=1988)	Oxygen (n=1035)	IMV/ECMO^a (n=353)
Fatal cases			6 (0)	137 (13)	100 (28)
Severity on admission					
Non-severe	2155 (69)	39 (16)	1796 (90)	357 (35)	43 (12)
Severe	974 (31)	204 (84)	192 (10)	678 (66)	310 (88)
Worst severity during hospitalization					
No-oxygen	1980 (63)	6 (3)			
Oxygen	897 (29)	137 (56)			
IMV/ECMO	252 (8)	100 (41)			
Days between onset and admission (median [IQR])	7 [4, 10]	5 [2, 8]	7 [4, 10]	6 [3, 9]	7 [5, 10]
Age (median [IQR])	54 [40, 68]	80 [71, 86]	48 [33, 61]	68 [53, 80]	65 [56, 74]
Male	1899 (61)	161 (66)	1083 (55)	694 (67)	285 (81)

BMI (median [IQR])	23.3 [20.8, 26.3]	22.7 [19.4, 25.7]	22.6 [20.2, 25.5]	24.0 [21.5, 27.0]	24.8 [22.6, 27.8]
Cardiovascular disease	129 (4)	54 (22)	48 (2)	106 (10)	29 (8)
Respiratory disease	103 (3)	35 (14)	29 (2)	78 (8)	33 (9)
Liver disease	75 (2)	13 (5)	36 (2)	32 (3)	20 (6)
Cerebrovascular disease	135 (4)	51 (21)	57 (3)	105 (10)	25 (7)
Asthma	157 (5)	9 (4)	92 (5)	52 (5)	22 (6)
Diabetes	475 (15)	86 (35)	197 (10)	244 (24)	121 (34)
Obesity	169 (5)	9 (4)	70 (4)	75 (7)	33 (9)
Severe renal disease or dialysis	34 (1)	13 (5)	14 (1)	21 (2)	12 (3)
Solid tumor	114 (4)	31 (13)	60 (3)	63 (6)	22 (6)
Leukemia	9 (0)	4 (2)	6 (0)	7 (1)	0 (0)
Lymphoma	13 (0)	12 (5)	6 (0)	16 (2)	3 (1)
Hypertension	551 (18)	70 (29)	234 (12)	274 (27)	115 (33)
Hyperlipidemia	305 (10)	26 (11)	148 (7)	124 (12)	61 (17)

Use of steroid in one month	10 (0)	5 (2)	4 (0)	8 (1)	4 (1)
Chemotherapy in three months	38 (1)	18 (7)	21 (1)	30 (3)	5 (1)
Immunosuppressants^b use in three months	37 (1)	7 (3)	18 (1)	18 (2)	8 (2)
Fever ($\geq 37.5^{\circ}\text{C}$)	1737 (56)	199 (82)	897 (45)	758 (74)	285 (82)
Cough	1770 (58)	112 (52)	1034 (53)	643 (64)	206 (69)
Sore throat	459 (17)	23 (16)	316 (18)	125 (15)	41 (16)
Runny nose	311 (11)	13 (7)	224 (12)	79 (9)	22 (8)
Chest pain	136 (5)	3 (2)	88 (5)	46 (6)	5 (2)
Myalgia	242 (9)	9 (7)	148 (8)	84 (10)	19 (7)
Headache	486 (18)	11 (8)	333 (18)	138 (17)	26 (10)
Confusion	60 (2)	29 (14)	19 (1)	54 (6)	16 (5)
Fatigue	1323 (46)	104 (62)	709 (38)	560 (62)	160 (58)
Abdominal pain	79 (3)	5 (3)	53 (3)	25 (3)	6 (2)
Vomit	139 (5)	8 (5)	80 (4)	51 (6)	16 (6)
Diarrhea	397 (14)	18 (9)	236 (13)	143 (15)	36 (13)

Dysgeusia	128 (17)	25 (10)	454 (26)	128 (17)	25 (10)
Dysosmia	103 (14)	13 (6)	402 (23)	103 (14)	13 (6)

^ainvasive mechanical ventilation/extracorporeal membrane oxygenation

^bimmunosuppressants other than steroids

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Figure Legends

Figure 1. Distribution of the worst severity arranged by severe/non-severe at admission and presence/absence of comorbidities.

Top bars represent non-severe cases at admission and bottom bars represent severe cases at admission.

Each group of cases was divided based on the presence of comorbidities. Bars represent different categories of worst severity: light gray – no-oxygen, darker gray – oxygen, and darkest gray – IMV/ECMO.

Figure 2. Distribution of the fatality arranged by severe/non-severe at admission and presence/non-presence of comorbidities

Top bars represent non-severe cases at admission and bottom bars represent severe cases at admission.

Each group of cases was divided based on the presence of comorbidities. Dark gray represents fatal cases while light gray represents non-fatal cases.

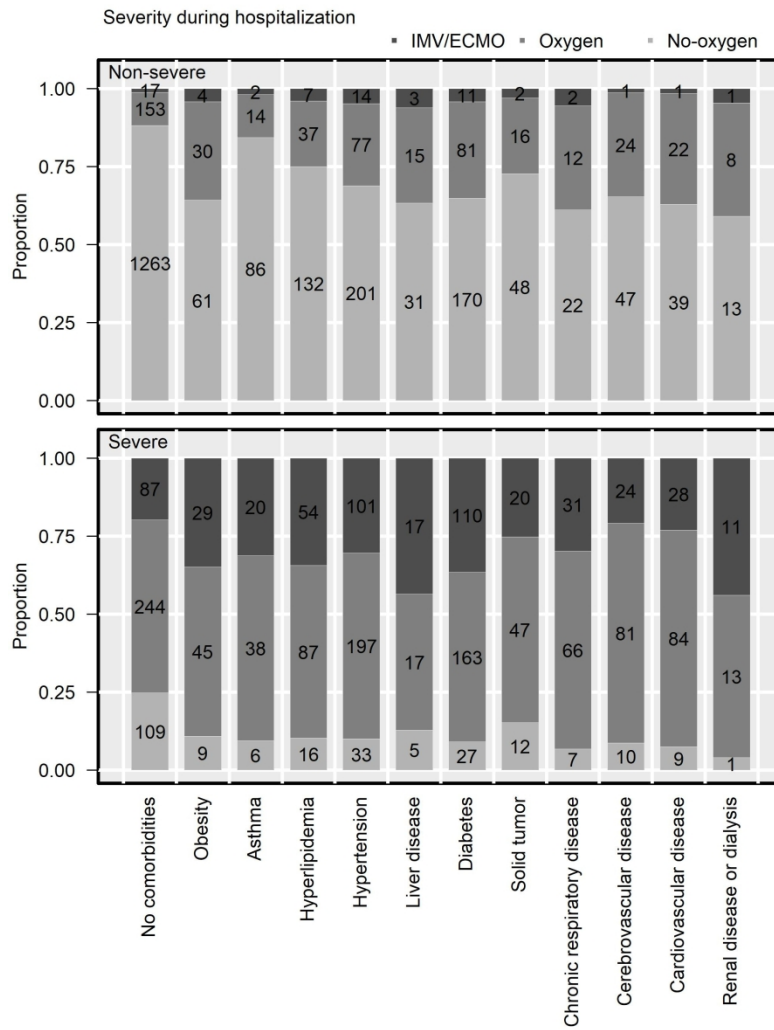
Supplementary Figure 1. Distribution of worst severity by age group

Supplementary Figure 2. Distribution of fatality by age group

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6 **Supplementary Figure 3. (a) Worst severity of cases aged <65 and ≥65 with no comorbidities**
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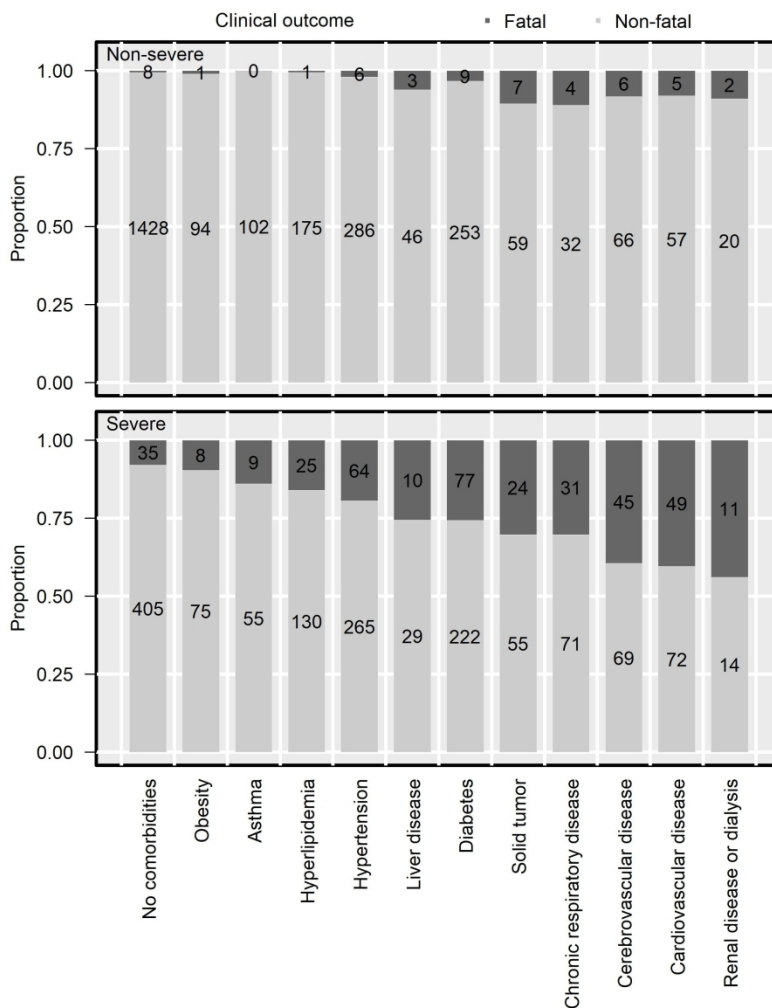
9 **(b) Fatality in cases aged <65 and ≥65 with no comorbidities**
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Distribution of the worst severity arranged by severe/non-severe at admission and presence/absence of comorbidities

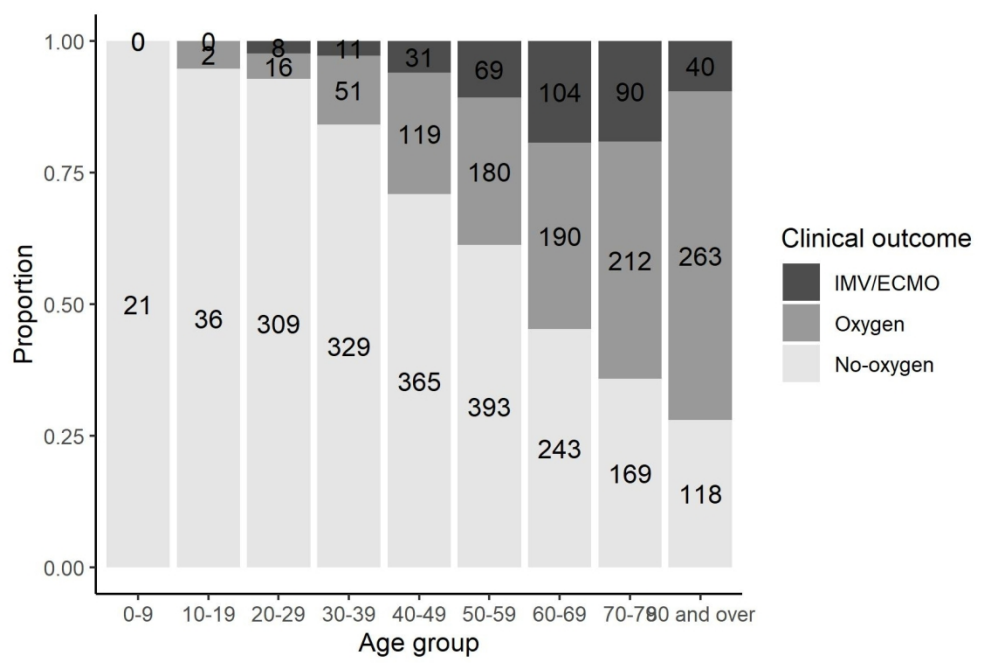
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Distribution of the fatality arranged by severe/non-severe at admission and presence/non-presence of comorbidities

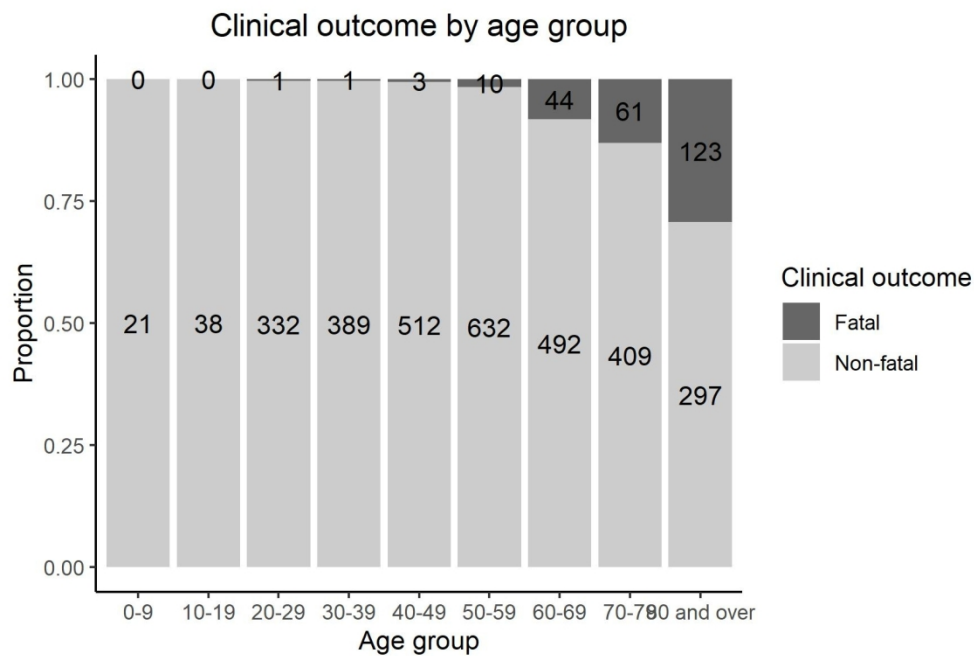
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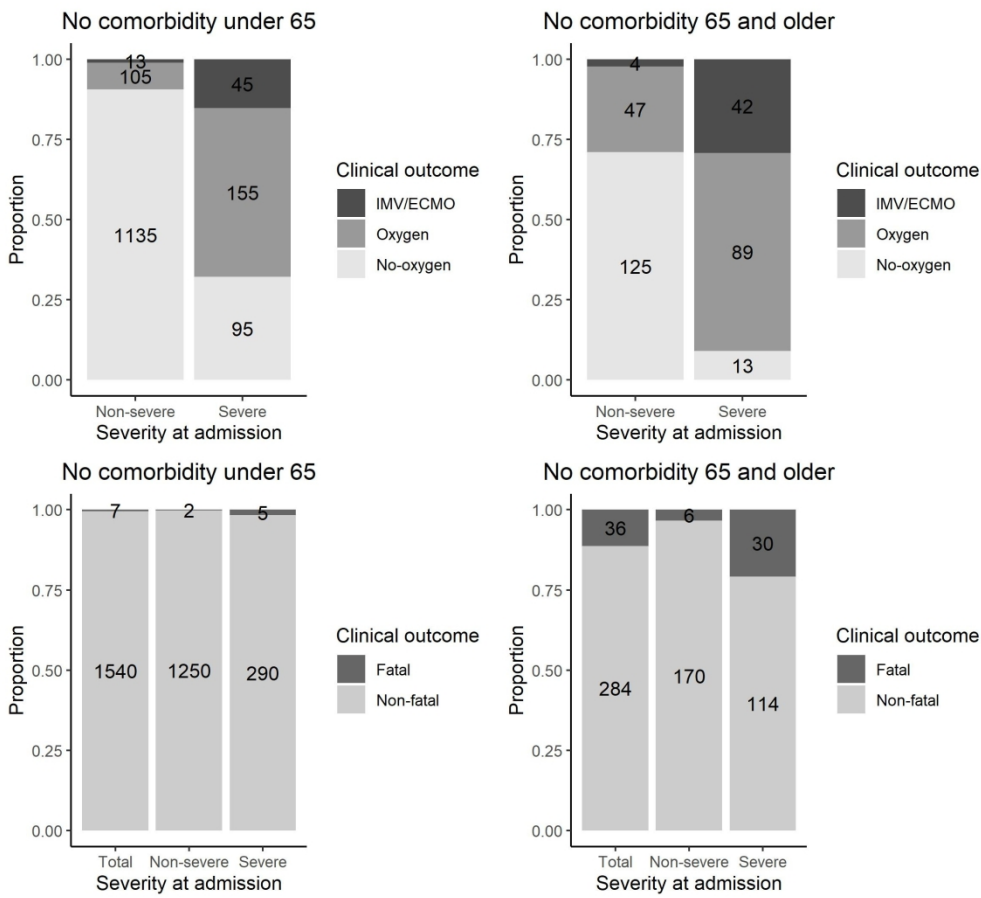
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Supplementary Table. Proportion of therapeutics used for each comorbidity

	Number of patients	Systemic steroid	Favipiravir	Ciclesonide	Heparin	Tocilizumab
No comorbidity	1873	105 (6)	606 (32)	562 (30)	48 (3)	22 (1)
Obesity	178	34 (19)	109 (61)	72 (40)	17 (10)	5 (3)
Cardiovascular disease	183	30 (16)	86 (47)	46 (25)	19 (10)	6 (3)
Chronic respiratory disease	140	39 (28)	94 (67)	52 (37)	10 (7)	5 (4)
Diabetes	562	98 (17)	325 (58)	197 (35)	61 (11)	12 (2)
Hypertension	623	120 (19)	338 (54)	200 (32)	70 (11)	20 (3)
Cerebrovascular disease	187	34 (18)	93 (50)	42 (23)	15 (8)	7 (4)
Liver disease	88	15 (17)	57 (65)	32 (36)	5 (6)	3 (3)
Severe renal disease or dialysis	47	9 (19)	21 (45)	12 (26)	6 (13)	3 (6)
Solid tumor	145	20 (14)	68 (47)	34 (23)	6 (4)	1 (1)

Numbers in brackets represent percentages.

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	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
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	9
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	12 12 13
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	14 13 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

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	14
2			(b) Report category boundaries when continuous variables were categorized	14
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	17
7	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	21
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	21
10	Other information			
11	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	22

*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>.

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Risk factors for severity on admission and the disease progression during hospitalization in a large cohort of COVID-19 patients in Japan

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1 **Title: Risk factors for severity on admission and the disease progression during**
2 **hospitalization in a large cohort of COVID-19 patients in Japan**

3
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6 **55 Abstract**
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9 **56 Objectives:** To investigate the risk factors contributing to severity on admission.
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12 **57** Additionally, risk factors of worst severity and fatality were studied. Moreover, factors were
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15 **58** compared based on three points: early severity, worst severity, and fatality.
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18 **59 Design:** A observational cohort study utilizing data entered in a Japan nationwide COVID-
19
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21 **60** 19 inpatient registry, COVIREGI-JP.
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24 **61 Setting:** As of August 31, 2020, 7,546 cases from 780 facilities have been registered.
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27 **62** Participating facilities cover a wide range of hospitals where COVID-19 patients are admitted in
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30 **63** Japan.
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33 **64 Participants:** Participants who had a positive test result on any applicable SARS-CoV-2
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36 **65** diagnostic tests, and were admitted to participating healthcare facilities. A total of 3,829 cases
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39 **66** were identified from January 16 to May 31, 2020, of which 3,376 cases were included in this
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42 **67** study.
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46 **68 Primary and secondary outcome measures:** Primary outcome was severe or non-severe on
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48
49 **69** admission, determined by the requirement of mechanical ventilation or oxygen therapy, SpO₂,
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51
52 **70** or respiratory rate. Secondary outcome was the worst severity during hospitalization, judged by
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55 **71** the requirement of oxygen and/or IMV/ECMO.
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58 **72 Results:** Risk factors for severity on admission were older age, male, cardiovascular disease,
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6 73 chronic respiratory disease, diabetes, obesity, and hypertension. Cerebrovascular disease, liver
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9 74 disease, renal disease or dialysis, solid tumor, and hyperlipidemia did not influence severity on
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12 75 admission ; however it influenced worst severity. Fatality rates for obesity, hypertension, and
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15 76 hyperlipidemia were relatively lower.
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18 77 **Conclusions:** This study segregated the comorbidities influencing severity and death. It is
19
20
21 78 possible that risk factors for severity on admission, worst severity, and fatality are not consistent
22
23
24 79 and may be propelled by different factors. Specifically, while hypertension, hyperlipidemia, and
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27 80 obesity had major effect on worst severity, their impact was mild on fatality in the Japanese
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30 81 population. Some studies contradict our results; therefore, detailed analyses, considering in-
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33 82 hospital treatments, are needed for validation.
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36 83 **Trial registration:** UMIN000039873. [bin/ctr_e/ctr_view.cgi?recptno=R000045453](https://upload.umin.ac.jp/cgi-open-
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39 84 <a href=)
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41 42 43 44 45 86 **Strengths and limitations of this study**

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48 87 • This study investigated the disease progression of COVID-19, by comparing the risk factors
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50
51 88 on three points: early severity, worst severity throughout hospitalization, and fatality,
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54 89 whereas previous studies have predominantly reported worst severity.
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57 90 • Categorization used for worst severity may differ from those used in other studies as most
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6 91 cases in our dataset did not include lung infiltration rate judged from radiological
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9 92 examination, SpO₂:FiO₂ ratio or PaO₂:FiO₂ ratio.
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12 93 • The dataset was derived from a large COVID-19 patient registry in Japan which involves
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15 94 299 facilities in Japan, which is both a strength and a limitation, as treatment methods and
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18 95 severity may vary.
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21 96 • As treatment type, dosage, duration, and combination varied immensely across the facilities,
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24 97 we did not consider treatments prior to and during hospitalization.
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99 Introduction

100 Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome
101 coronavirus-2 (SARS-CoV-2), has caused a major global public health crisis. As of October 3,
102 2020, >34 million people had been infected in over 230 countries^{1,2}. Japan experienced two
103 pandemic waves after the first case reported on January 16, 2020. During the first wave, a state
104 of emergency was declared on April 7, which ended on May 25, settling the first wave. Nearly
105 thrice as many SARS-CoV-2 positive cases were detected in the second wave, which emerged
106 from the end of June³. The fatality rate in the second wave has generally been lower in many
107 countries, including Japan⁴.

108 When the number of patients explodes, hospital beds were in great shortage; hotels were
109 utilized as isolation facilities in many countries⁵⁻⁷. Likewise, in Japan, mild patients were
110 transferred to hotels from April 2020⁸. About two-thirds of cases did not require oxygen support
111 throughout their illness⁹. However, some cases initiated non-severe may instantly plunge into a
112 serious state and require aggressive care¹⁰. Therefore, public health centers are in demand for
113 indicators to identify those at a higher risk of aggravation in the early phase and determine the
114 destination—hospital, hotel, or home. Depicting the clinical course—from onset to worst
115 severity and the outcome—is imperative to appropriately allocate patients to healthcare
116 resources. Analyses considering the severity on admission and the disease progression thereafter

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6 117 has not been conducted are of interest to physicians globally.
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9 118 We obtained nationwide data from a COVID-19 inpatient registry, "COVID-19 REGISTRY
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12 119 JAPAN (COVIREGI-JP)", and conducted a study to identify the independent risk factors
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15 120 contributing towards severity on admission. We aimed to determine the risk factors on
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18 121 admission, namely demographics and comorbidities. Progression of severity was inspected in
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21 122 detail on different time points. Cases identified within the period of the first pandemic wave
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23
24 123 were studied.
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27 124

30 125 **Methods**

33 126 **Study design and patients**

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36 127 This is an observational cohort study that utilizes the data accumulated in the
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39 128 nationwide "COVID-19 REGISTRY JAPAN (COVIREGI-JP)". As of September 28, 2020,
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41
42 129 10,048 cases from 802 facilities have been registered. Participating facilities covers a wide
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44
45 130 range of hospitals where COVID-19 patients are admitted in Japan. Enrolled cases satisfied two
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48 131 eligibility criteria: a positive test result for COVID-19 and being admitted to a healthcare
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51 132 facility. Registration started on March 2, 2020, and is ongoing, at present.
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57 134 **Patient and Public Involvement**

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6 135 No patient involved.
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12 137 **Data collection and case report form**
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15 138 Data were collected in a case report form (CRF) developed for COVIREGI-JP. This CRF
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18 139 includes modified information of the International Severe Acute Respiratory and Emerging
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21 140 Infection Consortium CRF on COVID-19¹¹. Upon modification, we elaborated on data
22
23
24 141 collection, especially on treatments, comorbidities, and symptoms. In addition, as of October
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27 142 26, 2020, this CRF underwent revisions twice to update therapeutic options or definitions, as
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29
30 143 new evidence emerges. Study data were collected and managed using Research Electronic Data
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32
33 144 Capture (REDCap) electronic data capture tools^{12,13}, hosted at the datacenter in National Center
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36 145 for Global Health and Medicine. Data were either recorded on a CRF hard-copy or were entered
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39 146 directly into REDCap at each facility.
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45 148 **Comorbidities**
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48 149 Comorbidities were collected based on Charlson comorbidity index^{14,15} with modifications.
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51 150 Some comorbidities were combined as follows: Cardiovascular disease (CVD)—myocardial
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54 151 infarction, congestive heart failure, and peripheral vascular disease; Chronic respiratory disease
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57 152 (CRD)—chronic obstructive pulmonary disease (COPD) and other chronic lung diseases; Renal
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6 153 disease or dialysis—moderate to severe renal disorder (creatinine \geq 3mg/dL, nephropathy, post-
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9 154 renal transplantation, or on dialysis), and maintenance hemodialysis or peritoneal dialysis before
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12 155 hospitalization; and Solid tumor—solid tumor with or without metastasis. Obesity was
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15 156 diagnosed based on physician’s judgement, and body mass index (BMI) was not considered in
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17
18 157 this study.
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23 24 159 **Drug administration prior to and during hospitalization**

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27 160 Steroids, chemotherapy, and immunosuppressants administered prior to hospitalization were
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30 161 collected as pre-hospitalization treatments. Steroids included those equivalent to 20 mg/day
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33 162 prednisolone for \geq 1 month and are not considered as immunosuppressants. Chemotherapy and
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36 163 immunosuppressants was applicable if administered 3 months prior to hospitalization.
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39 164 Treatment during hospitalization was studied on systemic steroids, favipiravir, ciclesonide,
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42 165 heparin, and tocilizumab, due to the frequent use in Japan. Heparin use included those given for
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45 166 both prophylactic and treatment purposes.
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49 50 51 168 **Dataset**

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54 169 We defined the first wave period as January 16 to May 31, 2020¹⁶, and cases from the first
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57 170 wave was included in this analysis. Therefore, data extraction conditions were: (1) cases
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6 171 admitted to healthcare facilities between January 16 and May 31, 2020, and (2) all CRF items

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9 172 completed on dataset generation. The dataset was generated and fixed on September 2, 2020.

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15 174 **Definitions of severity**

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18 175 **1) Severity on admission**

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21 176 Severity on admission was converted into bivariate variables: severe and non-severe. Cases

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23
24 177 met at least one of the following criteria were categorized as severe: (1) requiring invasive or

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27 178 non-invasive mechanical ventilation, (2) requiring supplemental oxygen, (3) $SpO_2 \leq 94\%$ in

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30 179 room air, or (4) tachypnea with respiratory rate (RR) ≤ 24 breaths per minute¹⁷. Those who did

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33 180 not meet the aforementioned were classified as non-severe.

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36 181 **2) Worst severity**

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39 182 The worst severity was grouped into three categories: no-oxygen, oxygen, and IMV/ECMO.

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42 183 The worst state during hospitalization was adopted on categorization, and each was defined as

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45 184 follows:

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48 185 No-oxygen—No requirement of supplemental oxygen throughout hospitalization.

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51 186 Oxygen—Required supplemental oxygen (including high-flow oxygen devices) or non-

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54 187 invasive mechanical ventilation during hospitalization.

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57 188 IMV/ECMO—Required invasive mechanical ventilation or extracorporeal membrane

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6 189 oxygenation during hospitalization.
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12 191 **Statistical analysis**
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15 192 Continuous variables are presented in median and interquartile range (IQR) and
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18 193 categorical variables in number of cases and percentages. We classified the disease progression
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21 194 into three stages: severity on admission, worst severity, and clinical outcomes. We used Mann-
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24 195 Whitney U tests (for two groups) or Kruskal-Wallis tests (for three groups) for continuous
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27 196 variables and chi-squared tests for categorical variables.
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30 197 We conducted univariate analyses and a multivariable logistic regression analysis to
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33 198 identify the factors associated with the patients' severity on admission. We included age, sex,
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36 199 comorbidities (CVD, cerebrovascular disease, CRD, asthma, liver disease, diabetes, obesity
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39 200 diagnosed by physicians, renal disease or dialysis, solid tumors, leukemia, lymphoma,
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42 201 hypertension, and hyperlipidemia), use of systemic steroids in the past month, chemotherapy in
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44
45 202 the past three months, and use of immunosuppressants other than steroids as independent
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48 203 variables. As for univariate analysis, we conducted logistic regression analysis about days
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51 204 between onset and admission and age. As for multivariate analysis, multicollinearity was
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54 205 evaluated using the variance inflation factor (VIF). Variables of $VIF > 3$ were excluded from
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57 206 the model; however, no variables demonstrated obvious multicollinearity. The variables
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6 207 included in the model were chosen based on the previous findings¹⁸⁻²⁰, and expert opinions.
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9 208 R version 3.6.3 (R core team, 2020)²¹ was used for all the analyses performed in this
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12 209 study.
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18 211 **Ethics**

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21 212 The National Center for Global Health and Medicine ethics board approved this study (referral
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23
24 213 number NCGM-G-003494-08), and waived the need for informed consent from individual
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26
27 214 patients owing to the non-invasive, non-interventional nature of this observational study
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30 215 according to the local Ethical Guidelines²². Information regarding opting out of our study is
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33 216 available on the COVIREGI-JP website (<https://covid-registry.ncgm.go.jp/>). Although it is not
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36 217 mandatory, the study is also being registered on trial registration website (Unique ID:
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39 218 UMIN000039873, [https://upload.umin.ac.jp/cgi-open-](https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453)
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42 219 [bin/ctr_e/ctr_view.cgi?recptno=R000045453](https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453)).
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45 220

48 221 **Results**

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51 222 Within the study period, 3,829 cases were identified and 3,376 cases from 299
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54 223 facilities were included in this study. Of them, 2,199 cases (65.1%) were non-severe, and 1,181
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57 224 cases (34.9%) were severe at the time of admission. After categorizing the two groups further
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6 225 into no-oxygen, oxygen, and IMV/ECMO by worst severity, compositions were 1,758 (81.5 %),
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9 226 357 (16.5%), and 43 (2.0%) for the non-severe group and 190 (16.1%), 677 (57.5%), and 311
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12 227 (26.4%) for the severe group, respectively. While categorizing the cases, 44 (1.3%) were
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15 228 unavailable due to missing values.
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18 229 Demographics and clinical characteristics of the study population are shown in Table
19
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21 230 1. Days between onset and admission were similar in both groups (non-severe 6.0 vs severe 7.0
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24 231 days). Over ten times as many severe cases on admission underwent IMV/ECMO than non-
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27 232 severe cases (2.0% vs 26.4%). Severe cases were older (50.0 vs 67.0), had higher BMI (22.9 vs
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30 233 24.1), greater male dominance (56.3% vs 70.5%), and a higher prevalence of comorbidities
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33 234 excluding leukemia, compared to the non-severe group. The most prevalent symptoms in both
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36 235 groups were fever (non-severe 49.5%, severe 73.7%), cough (non-severe 53.8%, severe 64.9%),
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38
39 236 and fatigue (non-severe 40.3%, 59.9%), but was greater in the severe group. Conversely,
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42 237 prevalence of dysgeusia (25.9% vs 13.2%), dysosmia (22.6% vs 11.5%), headache (18.1% vs
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45 238 14.7%), and runny nose (11.9% vs 8.9%) was higher in the non-severe group.
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48 239 Results of univariate analyses about factors associated with being severe cases on
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51 240 admission was described in Table 2-a. In most variables, univariate analysis showed similar
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54 241 results compared with the multivariate analysis. Results of the multivariate logistic regression to
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57 242 determine the risk of severity on admission are shown in Table 2-b. Older age (OR 1.04 [1.03—
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6 243 1.04]) and male (OR 2.09 [1.76—2.48]) were considered a risk among the demographics and
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9 244 comorbidities included CVD (OR 1.48 [1.04—2.10]), respiratory disease (OR 2.51 [1.67—
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12 245 3.78]), diabetes (OR 1.34 [1.09—1.64]), obesity (OR 1.75 [1.26—2.45]), and hypertension (OR
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15 246 1.33 [1.08—1.64]). Days between onset to admission were non-significant ($p = 0.960$); the
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18 247 timing of admission did not affect the severity on admission. Cerebrovascular disease and
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21 248 hyperlipidemia were not associated with the severity at admission after other confounding
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24 249 factors were considered, although they showed different results in univariate analyses.
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27 250 Table 3 depicts the study population from a different angle and is categorized by the
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30 251 worst severity ($n=3,336$) and fatality ($n=3,376$). Oxygen and IMV/ECMO cases were
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33 252 predominantly severe at admission (65.5% and 87.9%, respectively), whereas most no-oxygen
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36 253 cases come from non-severe group (90.2%). Prevalence of comorbidities was lowest in no-
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39 254 oxygen cases; however, prominent difference was not observed for asthma. Similarly, fatal
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42 255 cases were more severe at admission (84.0% vs 31.1%) and had higher prevalence of oxygen
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45 256 and IMV/ECMO cases (oxygen: 56.4% vs 29.0%, IMV/ECMO: 41.9% vs 8.2%, respectively).
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48 257 Days between onset and admission was longer in non-fatal cases (5-days vs 7-days).
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51 258 More non-severe cases with any comorbidity underwent treatment with oxygen or
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54 259 IMV/ECMO compared to non-severe cases with no comorbidities. In figure 1, only 11.9%
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57 260 underwent oxygen therapy or IMV/ECMO in non-severe cases without any comorbidities.
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6 261 However, among the non-severe cases with comorbidity, the rates of oxygen or IMV/ECMO
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9 262 were higher in most comorbidities, including CVD (34.7%), CRD (38.9%), liver disease
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12 263 (36.7%), diabetes (35.1%), obesity (35.8%), cerebrovascular disease (34.7%), renal disease
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15 264 (40.9%), solid tumor (27.3%), hypertension (31.2%), and hyperlipidemia (25.0%). Asthma
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18 265 alone followed a different trend; the chances of oxygen and IMV/ECMO requirement was
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21 266 lower.

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24 267 Among the cases without comorbidity, 75.2% of cases that were severe on admission
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27 268 required oxygen or IMV/ECMO; however, the fatality rate was low, and only 8.0% resulted in
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30 269 death (Figure 2). Fatality rates were approximately 3—5 times higher when the following
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33 270 comorbidities were present: renal disease or dialysis (44%), CVD (40.5%), cerebrovascular
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36 271 disease (39.5%), CRD (30.4%), solid tumor (30.4%), diabetes (25.8%), and liver disease
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39 272 (25.6%). Even among non-severe cases, relatively high fatality rate was observed in cases with
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42 273 solid tumor, CRD, cerebrovascular disease, CVD, and renal disease or dialysis, with fatality
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45 274 rates ranging from 8.1% to 11.1%. Collectively, obesity, hypertension, and hyperlipidemia
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48 275 influenced the worst severity; however, their influence on fatality was relatively lower than that
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51 276 mentioned earlier.

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54 277 Older age was relevant to both worst severity and fatality, as shown in supplemental
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57 278 figures 1 and 2. The combined proportion of oxygen and IMV/ECMO increased gradually by
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6 279 age from 5.3% in 20s to 69.3% in \geq 80s. Conversely, the fatality rate leaped between 60s (2.2%)
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9 280 and 70s (8.6%). Likewise, supplemental figure 3 shows the combined proportion of oxygen and
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12 281 IMV/ECMO and fatality rates as higher in older individuals, irrespective of underlying
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15 282 comorbidities.
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18 283 Predominant comorbid cases required more drug administration than those without
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21 284 comorbidities (Supplementary Table 1). Systemic steroids were most frequently used in cases
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24 285 with CRD (27.9%). Heparin was used most often in renal disease (12.8%), hypertension
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27 286 (11.2%), diabetes (10.9%), and CVD (10.4%).
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32 33 288 **Discussion**

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36 289 We took disease progression into consideration and evaluated the study population
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39 290 based on severity on admission, worst severity, and the outcome. To our knowledge, studies
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42 291 have predominantly reported worst severity, whereas disease progression has not been
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45 292 considered. Our findings, therefore, are novel, augmenting the evidence needed to depict the
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48 293 clinical course and trajectory from onset to worsening condition. Specifically, this study
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51 294 segregated the comorbidities influencing severity and death. Based on our findings, it may be
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54 295 possible that the early severity, worst severity, and death are propelled by different factors,
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57 296 whilst confirmation is necessary by multivariate analysis.
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6 297 The majority of comorbidities we studied did not influence severity on admission. On

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9 298 admission, severity was driven by age, sex, CVD, CRD, diabetes, obesity, and hypertension.

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12 299 The trend was similar for the worst severity, as cases with these factors had higher rate of

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15 300 oxygen or IMV/ECMO. However, all comorbidities appeared to influence the worst severity.

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18 301 Within the comorbidities, the prognosis of cases with obesity, hypertension, or

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21 302 hyperlipidemia was relatively favorable. In contrast to our results, hypertension and obesity are

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24 303 reportedly related to an increased risk of severity and mortality²³⁻²⁶. A large cohort reported a

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27 304 trend similar to our results¹⁸, whereas other studies reported that obesity is being confounded by

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30 305 age and sex^{27,28}. The presence of hypertension and the use of angiotensin-converting enzyme

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33 306 (ACE) inhibitors and angiotensin II receptor blockers act contrarily²⁹⁻³¹ while ACE2 mediates

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36 307 the entry of SARS-CoV-2 into host cells^{32,33}; thus, COVID-19 pathophysiology in hypertensive

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39 308 patients become intricate.

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42 309 In accordance with previous studies, CVD, CRD, liver disease, diabetes,

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45 310 cerebrovascular disease, renal disease or dialysis, and solid tumor were associated with to

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48 311 fatality and worst severity. Two meta-analyses have reported common risk factors for worst

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51 312 severity during hospitalization, which include, diabetes, COPD, malignancy, CVD, and

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54 313 cerebrovascular disease^{34,35}. Other studies have also reported chronic liver disease and renal

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57 314 disease as risk factors³⁶⁻³⁸. Studies have elucidated that acute respiratory distress syndrome and

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6 315 coagulation dysfunction are related to the renin-angiotensin-aldosterone system and blood
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9 316 coagulation pathways, which are altered by SARS-CoV-2 host cell invasion via ACE2³⁹⁻⁴¹.
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12 317 Clinical and non-clinical studies revealed an association between these comorbidities; while
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15 318 SARS-CoV-2 infection decreases ACE2 expression, ACE2 deficiency is reported to cause
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18 319 cardiac overload and kidney inflammation⁴¹⁻⁴⁴. Elevated blood glucose is also associated with
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21 320 mortality⁴⁵. Although risk factors vary among studies, the comorbidities we identified are highly
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24 321 likely associated with fatality, backed up by clinical and non-clinical results.
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27 322 Different trends were seen in the rates of IMV/ECMO and death for each comorbidity.
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30 323 Although rates of IMV/ECMO were comparable in all comorbid cases, those with obesity,
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33 324 asthma, hyperlipidemia, and hypertension showed a lower fatality rate, suggesting that the
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36 325 fatality rates within the IMV/ECMO cases with these comorbidities were lower than expected.
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39 326 Contrarily, fatality rates in cases with CVD, cerebrovascular disease, renal dysfunction, tumor,
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42 327 and CRD were comparable or higher than IMV/ECMO rates. The number of death actually
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45 328 exceeded the number of IMV/ECMO cases in patients with tumor, cerebrovascular disease, or
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48 329 CVD. These comorbidities likely have caused a higher risk of death and some even died without
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51 330 intubation. Healthcare nearly overwhelmed in the first wave in Japan but ICU capacity was
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54 331 maintained⁴⁶, and thus intubation may have been unperformed due to a medical judgment. A
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57 332 detailed examination of these issues is necessary in the future.
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6 333 Our results did not show prominent difference in fatality between males and females.
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9 334 Oftentimes, males are considered to develop severe conditions and increased fatality^{37,38,47-49}.
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12 335 However, according to Global Health 5050, sexual disparity in incidence of COVID-19 is low⁵⁰.
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15 336 Additionally, ACE2 expression is affected by sexual hormones, whereby higher expression is
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18 337 observed in men, possibly explaining the sexual disparity⁵¹⁻⁵³. Moreover, the immunological
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21 338 response to produce antibodies is more favorable in females⁵⁴. These studies support the
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24 339 rationale that males are more susceptible to severe COVID-19, which contravene our results.
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27 340 The lower-than-expected fatality rate in our male population may be attributed to comorbidity
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30 341 prevalence, treatments, age, and/or degree of obesity.
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33 342 Fatality rates were comparable between asthmatic and cases without comorbidities in
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36 343 our results. Theoretically, COVID-19 can be a risk for asthmatic patients. A viral respiratory
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39 344 infection is presented as relatively worse and causes asthma exacerbation^{55,56}. Asthmatic
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42 345 patients reportedly require a longer duration of mechanical ventilation when intubated⁵⁷;
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45 346 however, no study, including ours, has found strong evidence on severity or mortality⁵⁸⁻⁶¹.
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48 347 Inhaled corticosteroids (ICS) are known to downregulate ACE2^{62,63} and are being investigated
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51 348 for treating COVID-19⁶⁴. ICS may have impeded aggravation in asthmatic patients with
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54 349 COVID-19⁶⁵. Overall, further studies are needed to elucidate the true risk of asthma on COVID-
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6 351 The variability in the risk factors may be explained by the differences in study
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9 352 population, definition for comorbidities, and ethnicity. First, the rate of comorbid patients had
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12 353 been lower in our cohort as suggested by extensive cohort studies^{19,20,66}. The degree of obesity
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15 354 may also have been milder, as the average BMI is lower in the Asia-Pacific region than in other
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18 355 global regions⁶⁷. Secondly, obesity was judged by a physician in our study, and the results may
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21 356 change if BMI was incorporated. Ethnic differences due to genetic properties are also plausible.
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24 357 Individuals with stronger binding affinities of human leukocyte antigen (HLA) proteins to
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27 358 SARS-CoV-2 virus peptides are less likely become severe or fatal⁶⁸⁻⁷¹, and ethnic differences
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30 359 are present in HLA allele frequency⁷². A few strong binder alleles were more frequent in
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33 360 Northeast Asians; however, the complete picture is complicated. ACE1 polymorphism⁷³ and
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36 361 Neanderthal haplotype⁷⁴ were also suggestive of lower risk of COVID-19 among Asians and
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39 362 East Asians, respectively. Additionally, ethnic differences other than genetic traits are also
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42 363 anticipated. Vitamin D deficiency is postulated to increase COVID-19 severity, whereas vitamin
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45 364 D deficiency is correlated to Northern latitude⁷⁵. Within the elderly population, higher rates of
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48 365 deficiencies were observed in North America and Europe compared to Japan⁷⁶. Although our
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51 366 study did not examine vitamin D, these facts also allow us to expect lower severity and fatality
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54 367 in Japan.

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57 368 The period of when the COVID-19 occurred, and the situation of pandemic and
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6 369 healthcare provision should also be noted when discussing severity and fatality. The longer our
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9 370 struggle against COVID-19 pandemic becomes, the more complicated interpretation be required
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12 371 due to chronological, regional, and viral transition. In the two pandemic waves of COVID-19 in
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15 372 Japan, the patient population altered; median age, rates of comorbidities, and fatality rate had
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18 373 become smaller in the second than the first⁷⁷. Similar trend was observed in other countries^{78,79}.
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21 374 These differences might be explained, at least partially, by the timing of drug approval for
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24 375 remdesivir (approved in May, 2020) and newly revealed efficacy of dexamethasone against
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27 376 COVID-19 in June. Our dataset includes nationwide data during the first wave, and articles
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30 377 referred elsewhere for comparison included data from a period close to ours.

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33 378 Our results could be useful to roughly identify those at a risk of aggravation or death.
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36 379 Days from onset to admission was not a risk factor; early hospitalization will not influence the
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39 380 disease progression or outcome, and severity on admission was mostly driven by age and the
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42 381 presence of a few comorbidities. Several studies have created a scoring system to predict the
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45 382 risk of severity or mortality⁸⁰⁻⁸². However, these utilize laboratory data collected on admission
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48 383 and are seldom practical for estimating the severity of illness prior to medical visits or when test
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51 384 results are not promptly available. While these are useful to predict prognosis more precisely,
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54 385 our results are useful from a public health perspective, as they provide risk factors for predicting
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57 386 the severity on admission and disease progression from patients' background factors.
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6 387 Our study has several limitations. Although the definition of severe and non-severe
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9 388 was adopted from a previous study¹⁷, such definition is not common as worst severity is used
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12 389 frequently or otherwise point of evaluation is unspecified. Our categorization of worst severity
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15 390 also differs from other definitions^{83,84}. We did not adopt radiological criteria as lung infiltration
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18 391 rate was not collected in the registry where our dataset was extracted. Ratio of arterial oxygen
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21 392 saturation (SaO₂) or arterial partial oxygen pressure (PaO₂) to the fraction of inspired oxygen
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24 393 (FiO₂) was not utilized as data was available for limited number of cases. This fact may have
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27 394 caused differences in risk factors. We did not consider treatments prior to and during
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30 395 hospitalization nor did we incorporate laboratory test results in the analysis which may be
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33 396 persisting as confounders. As our data were collected from hundreds of healthcare facilities,
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36 397 treatment type, dosage, duration, and combination varied immensely; laboratory tests also
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39 398 varied as reporting units and standard reference ranges were different across facilities.
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42 399 Treatments may be confounding also in terms of drug approval, as explained elsewhere.
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45 400 Thorough data verification and analytical deliberation is required before usage of these data;
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48 401 thus, we did not include it in the current analysis. Moreover, hotels were utilized as isolation
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51 402 facilities from April 2020, and participant selection might have altered thereafter. COVIREGI-
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54 403 JP is continuously open for new entry; the number of registrations is increasing, and subsequent
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57 404 results may vary from ours.
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9 406 **Conclusion**

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12 407 On admission, factors that influence severity were age, sex, and comorbidities,
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15 408 including CVD, CRD, diabetes, obesity, and hypertension. Risk factors for severity on
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18 409 admission, worst severity, and fatality were not consistent, and it is likely that they are each
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21 410 propelled by different factors. Our results are practically useful for predicting the progression
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24 411 and preparing for the worst, based on patients' backgrounds. Moreover, based on our
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27 412 predictions, healthcare resources can be allocated to patients in the most suitable way.
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33 414 **Acknowledgments**

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36 415 We thank all the participating facilities for their care towards COVID-19 patients and
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39 416 cooperation during data entry. We are especially grateful for the 299 facilities that contributed
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42 417 to the dataset used in this study.
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48 419 **Contributorship statement**

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51 420 MT conceived and HO, SS, KH, ST and MT designed the study. ST, YA, SS, KH, and
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54 421 MT analyzed and interpreted the data. MT and ST drafted the first version of the manuscript.
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57 422 All the authors including NM, SK, SW, NO, and those stated above contributed to, read, and
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6 423 approved the final manuscript. The corresponding author attests that all listed authors meet
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9 424 authorship criteria and that no others meeting the criteria have been omitted. SS is the guarantor.
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23
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30 431 or COVIREGI-JP.
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36 433 **Competing Interests**

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39 434 All authors have completed the ICMJE uniform disclosure form at
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41
42 435 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
43
44
45 436 submitted work; H.O. reports personal fees as a statistician and as an external consultant for
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47
48 437 clinical trials from EPS International, outside the submitted work; no other relationships or
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51 438 activities that could appear to have influenced the submitted work.
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57 440 **Transparency Statement**
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6 441 The corresponding author affirms that this manuscript is an honest, accurate, and
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9 442 transparent account of the study being reported; that no important aspects of the study have been
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12 443 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
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21 446 **Data sharing**
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24 447 Data on an individual level is shared with limitation to participating healthcare
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27 448 facilities through applications to COVIREGI-JP.
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33 450 **Dissemination to participants and related patients and public communities**
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36 451 The study results will be shared with all the healthcare facilities which participated
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39 452 and registered data in COVIREGI-JP. It will also be shared with the public on the website.
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Table 1. Characteristics of patients included in the present study

	Non-severe (n=2196)	Severe (n=1180)
Fatal cases	39 (2)	204 (17)
Worst severity during hospitalization		
No oxygen	1796 (82)	192 (16)
Oxygen	357 (16)	678 (58)
IMV/ECMO^a	43 (2)	310 (26)
Days between onset and admission		
(median [IQR])	6 [4, 10]	7 [4, 10]
Age (median [IQR])	50 [35, 64]	67 [53, 78]
Male	1232 (56)	830 (71)
Ethnicity		
Japanese	2074 (94)	1135 (96)
Non-Japanese Asian	75 (3)	33 (3)
Others	29 (1)	8 (1)
Unknown	11 (1)	4 (0)
BMI (median [IQR])	22.9 [20.3, 25.7]	24.1 [21.5, 27.1]
Comorbidities		

Cardiovascular disease	62 (3)	121 (10)
Respiratory disease	36 (2)	104 (9)
Liver disease	49 (2)	39 (3)
Cerebrovascular disease	72 (3)	115 (10)
Asthma	102 (5)	64 (5)
Diabetes	262 (12)	300 (25)
Obesity	95 (4)	83 (7)
Severe renal disease or dialysis	22 (1)	25 (2)
Solid tumor	66 (3)	79 (7)
Leukemia	10 (1)	3 (0)
Lymphoma	16 (1)	9 (1)
Hypertension	292 (13)	331 (28)
Hyperlipidemia	176 (8)	157 (13)
Treatments prior to COVID-19		
Use of steroid in one month	6 (0)	10 (1)
Chemotherapy in three months	32 (2)	24 (2)
Immunosuppressants^b use in three months	26 (1)	18 (2)
Symptoms on admission		

Fever ($\geq 37.5^{\circ}\text{C}$)	1078 (49)	862 (74)
Cough	1167 (54)	716 (65)
Sore throat	340 (17)	142 (16)
Runny nose	239 (12)	86 (9)
Chest pain	95 (5)	44 (5)
Myalgia	172 (9)	79 (9)
Headache	361 (18)	136 (15)
Confusion	21 (1)	68 (6)
Fatigue	834 (40)	595 (60)
Abdominal pain	60 (3)	24 (3)
Vomit	88 (4)	59 (6)
Diarrhea	251 (12)	164 (16)
Dysgeusia	494 (26)	113 (13)
Dysosmia	422 (23)	96 (12)

^ainvasive mechanical ventilation/extracorporeal membrane oxygenation

^bimmunosuppressants other than steroids

Table 2-a. Factors associated with being “severe” at the time of admission (univariate analysis)

	Odds ratio	95% CI^a	P value
Days between onset and admission	1.0	0.99-1.01	0.897
Age	1.04	1.04-1.05	< 0.001
Male	1.85	1.59-2.16	< 0.001
Comorbidities			
Cardiovascular disease	3.93	2.84-5.48	< 0.001
Cerebrovascular disease	3.18	2.33-4.38	< 0.001
Chronic respiratory disease	5.80	3.90-8.78	< 0.001
Asthma	1.18	0.84-1.64	0.318
Liver disease	1.50	0.95-2.34	0.070
Diabetes	2.52	2.08-3.04	< 0.001
Obesity diagnosed by physicians	1.67	1.22-2.29	0.001
Severe renal disease or dialysis	2.14	1.15-4.00	0.013
Solid tumor	2.32	1.63-3.29	< 0.001
Leukemia	0.56	0.10-2.17	0.562
Lymphoma	1.05	0.41-2.53	0.999

	Hypertension	2.54	2.12-3.05	< 0.001
	Hyperlipidemia	1.76	1.39-2.23	< 0.001
Treatments prior to COVID-19				
	Use of steroid in one month	3.12	1.02-10.47	0.032
	Chemotherapy in three months	1.40	0.79-2.47	0.258
	Immunosuppressants^b use in three months	1.29	0.67-2.46	0.428

^aconfidence interval

^bimmunosuppressants other than steroids

Table 2-b. Factors associated with being “severe” at the time of admission

	Odds ratio	95% CI ^a	<i>P</i> value
Days between onset and admission	1.0	0.99-1.01	0.960
Age	1.04	1.03-1.04	< 0.001
Male	2.09	1.76-2.48	< 0.001
Comorbidities			
Cardiovascular disease	1.48	1.04-2.10	0.028
Cerebrovascular disease	1.33	0.95-1.85	0.097
Chronic respiratory disease	2.51	1.67-3.78	< 0.001
Asthma	1.24	0.87-1.77	0.240
Liver disease	0.97	0.61-1.54	0.892
Diabetes	1.34	1.09-1.64	0.006
Obesity diagnosed by physicians	1.75	1.26-2.45	0.001
Severe renal disease or dialysis	1.0	0.54-1.88	0.991
Solid tumor	1.20	0.82-1.77	0.351
Leukemia	0.34	0.08-1.39	0.132
Lymphoma	0.42	0.16-1.11	0.081
Hypertension	1.33	1.08-1.64	0.008

	Hyperlipidemia	0.91	0.70-1.19	0.490
Treatments prior to COVID-19				
	Use of steroid in one month	1.65	0.52-5.22	0.394
	Chemotherapy in three months	1.47	0.72-3.0	0.286
	Immunosuppressants^b use in three months	1.35	0.69-2.64	0.384

^aconfidence interval

^bimmunosuppressants other than steroids

Table 3. Characteristics of patients stratified by non-fatal/fatal cases and severity during hospitalization

	Non-fatal (n=3129)	Fatal (n=243)	No-oxygen (n=1988)	Oxygen (n=1035)	IMV/ECMO^a (n=353)
Fatal cases			6 (0)	137 (13)	100 (28)
Severity on admission					
Non-severe	2155 (69)	39 (16)	1796 (90)	357 (35)	43 (12)
Severe	974 (31)	204 (84)	192 (10)	678 (66)	310 (88)
Worst severity during hospitalization					
No-oxygen	1980 (63)	6 (3)			
Oxygen	897 (29)	137 (56)			
IMV/ECMO	252 (8)	100 (41)			
Days between onset and admission (median [IQR])	7 [4, 10]	5 [2, 8]	7 [4, 10]	6 [3, 9]	7 [5, 10]
Age (median [IQR])	54 [40, 68]	80 [71, 86]	48 [33, 61]	68 [53, 80]	65 [56, 74]
Male	1899 (61)	161 (66)	1083 (55)	694 (67)	285 (81)

BMI (median [IQR])	23.3 [20.8, 26.3]	22.7 [19.4, 25.7]	22.6 [20.2, 25.5]	24.0 [21.5, 27.0]	24.8 [22.6, 27.8]
Cardiovascular disease	129 (4)	54 (22)	48 (2)	106 (10)	29 (8)
Respiratory disease	103 (3)	35 (14)	29 (2)	78 (8)	33 (9)
Liver disease	75 (2)	13 (5)	36 (2)	32 (3)	20 (6)
Cerebrovascular disease	135 (4)	51 (21)	57 (3)	105 (10)	25 (7)
Asthma	157 (5)	9 (4)	92 (5)	52 (5)	22 (6)
Diabetes	475 (15)	86 (35)	197 (10)	244 (24)	121 (34)
Obesity	169 (5)	9 (4)	70 (4)	75 (7)	33 (9)
Severe renal disease or dialysis	34 (1)	13 (5)	14 (1)	21 (2)	12 (3)
Solid tumor	114 (4)	31 (13)	60 (3)	63 (6)	22 (6)
Leukemia	9 (0)	4 (2)	6 (0)	7 (1)	0 (0)
Lymphoma	13 (0)	12 (5)	6 (0)	16 (2)	3 (1)
Hypertension	551 (18)	70 (29)	234 (12)	274 (27)	115 (33)
Hyperlipidemia	305 (10)	26 (11)	148 (7)	124 (12)	61 (17)

Use of steroid in one month	10 (0)	5 (2)	4 (0)	8 (1)	4 (1)
Chemotherapy in three months	38 (1)	18 (7)	21 (1)	30 (3)	5 (1)
Immunosuppressants^b use in three months	37 (1)	7 (3)	18 (1)	18 (2)	8 (2)
Fever ($\geq 37.5^{\circ}\text{C}$)	1737 (56)	199 (82)	897 (45)	758 (74)	285 (82)
Cough	1770 (58)	112 (52)	1034 (53)	643 (64)	206 (69)
Sore throat	459 (17)	23 (16)	316 (18)	125 (15)	41 (16)
Runny nose	311 (11)	13 (7)	224 (12)	79 (9)	22 (8)
Chest pain	136 (5)	3 (2)	88 (5)	46 (6)	5 (2)
Myalgia	242 (9)	9 (7)	148 (8)	84 (10)	19 (7)
Headache	486 (18)	11 (8)	333 (18)	138 (17)	26 (10)
Confusion	60 (2)	29 (14)	19 (1)	54 (6)	16 (5)
Fatigue	1323 (46)	104 (62)	709 (38)	560 (62)	160 (58)
Abdominal pain	79 (3)	5 (3)	53 (3)	25 (3)	6 (2)
Vomit	139 (5)	8 (5)	80 (4)	51 (6)	16 (6)
Diarrhea	397 (14)	18 (9)	236 (13)	143 (15)	36 (13)

Dysgeusia	128 (17)	25 (10)	454 (26)	128 (17)	25 (10)
Dysosmia	103 (14)	13 (6)	402 (23)	103 (14)	13 (6)

^ainvasive mechanical ventilation/extracorporeal membrane oxygenation

^bimmunosuppressants other than steroids

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Figure Legends

Figure 1. Distribution of the worst severity arranged by severe/non-severe at admission and presence/absence of comorbidities.

Top bars represent non-severe cases at admission and bottom bars represent severe cases at admission.

Each group of cases was divided based on the presence of comorbidities. Bars represent different categories of worst severity: light gray – no-oxygen, darker gray – oxygen, and darkest gray – IMV/ECMO.

Figure 2. Distribution of the fatality arranged by severe/non-severe at admission and presence/non-presence of comorbidities

Top bars represent non-severe cases at admission and bottom bars represent severe cases at admission.

Each group of cases was divided based on the presence of comorbidities. Dark gray represents fatal cases while light gray represents non-fatal cases.

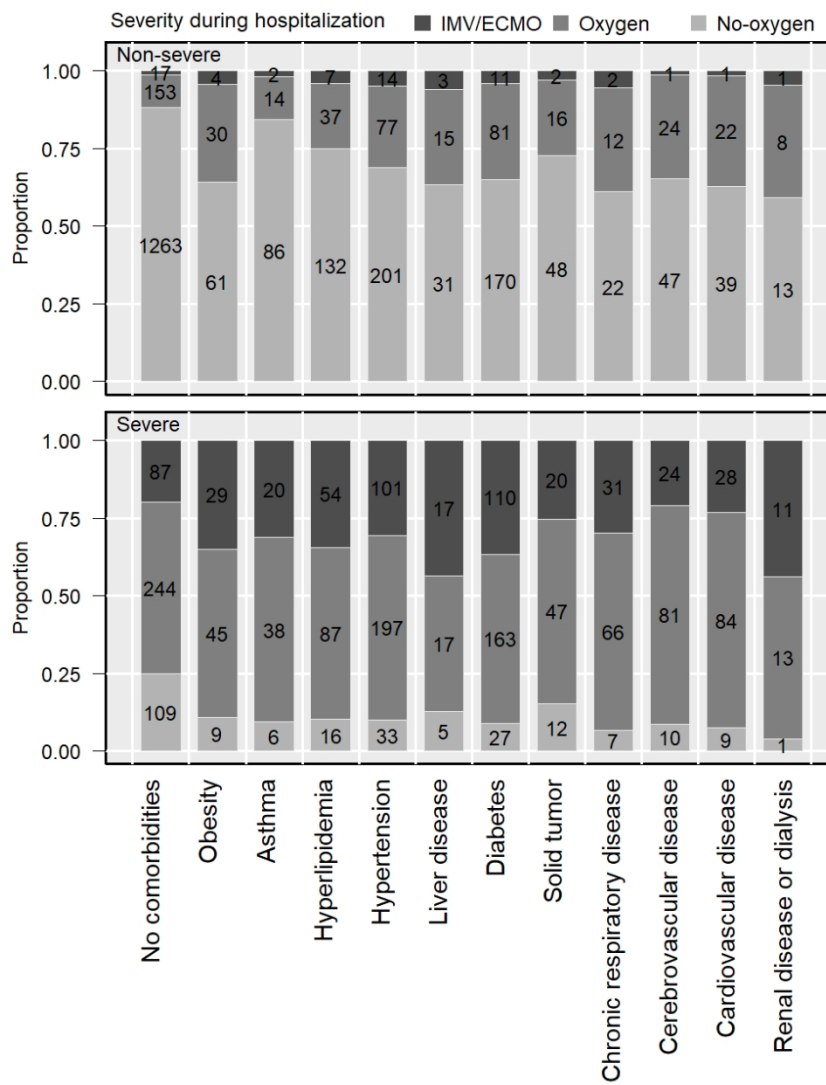
Supplementary Figure 1. Distribution of worst severity by age group

Supplementary Figure 2. Distribution of fatality by age group

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6 **Supplementary Figure 3. (a) Worst severity of cases aged <65 and ≥65 with no comorbidities**
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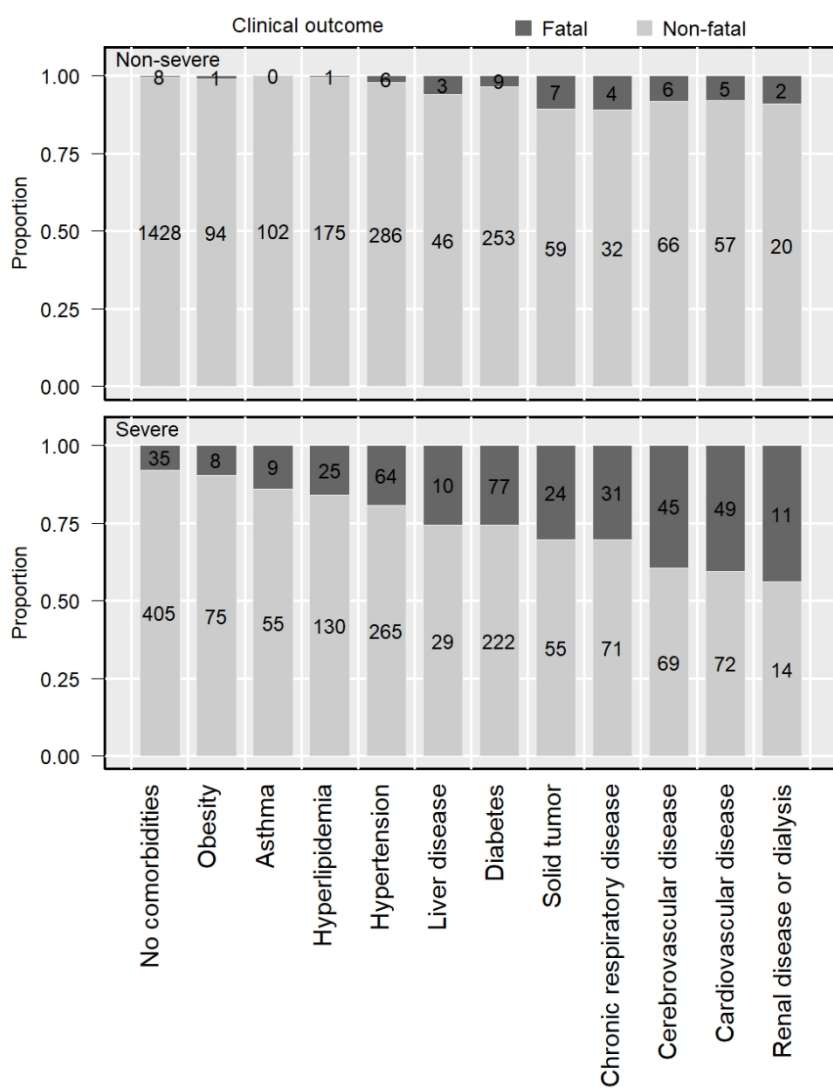
9 **(b) Fatality in cases aged <65 and ≥65 with no comorbidities**
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Distribution of the worst severity arranged by severe/non-severe at admission and presence/absence of comorbidities.

352x493mm (72 x 72 DPI)



Distribution of the fatality arranged by severe/non-severe at admission and presence/non-presence of comorbidities

352x493mm (72 x 72 DPI)

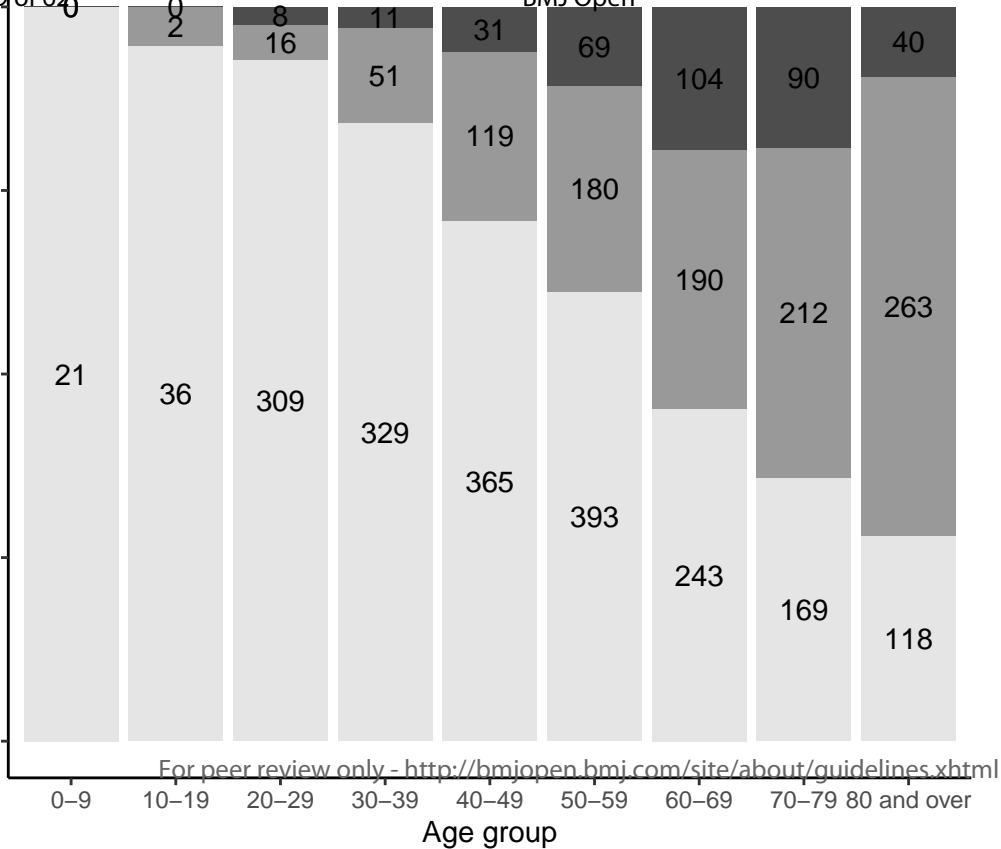
Supplementary Table. Proportion of therapeutics used for each comorbidity

	Number of patients	Systemic steroid	Favipiravir	Ciclesonide	Heparin	Tocilizumab
No comorbidity	1873	105 (6)	606 (32)	562 (30)	48 (3)	22 (1)
Obesity	178	34 (19)	109 (61)	72 (40)	17 (10)	5 (3)
Cardiovascular disease	183	30 (16)	86 (47)	46 (25)	19 (10)	6 (3)
Chronic respiratory disease	140	39 (28)	94 (67)	52 (37)	10 (7)	5 (4)
Diabetes	562	98 (17)	325 (58)	197 (35)	61 (11)	12 (2)
Hypertension	623	120 (19)	338 (54)	200 (32)	70 (11)	20 (3)
Cerebrovascular disease	187	34 (18)	93 (50)	42 (23)	15 (8)	7 (4)
Liver disease	88	15 (17)	57 (65)	32 (36)	5 (6)	3 (3)
Severe renal disease or dialysis	47	9 (19)	21 (45)	12 (26)	6 (13)	3 (6)
Solid tumor	145	20 (14)	68 (47)	34 (23)	6 (4)	1 (1)

Numbers in brackets represent percentages.

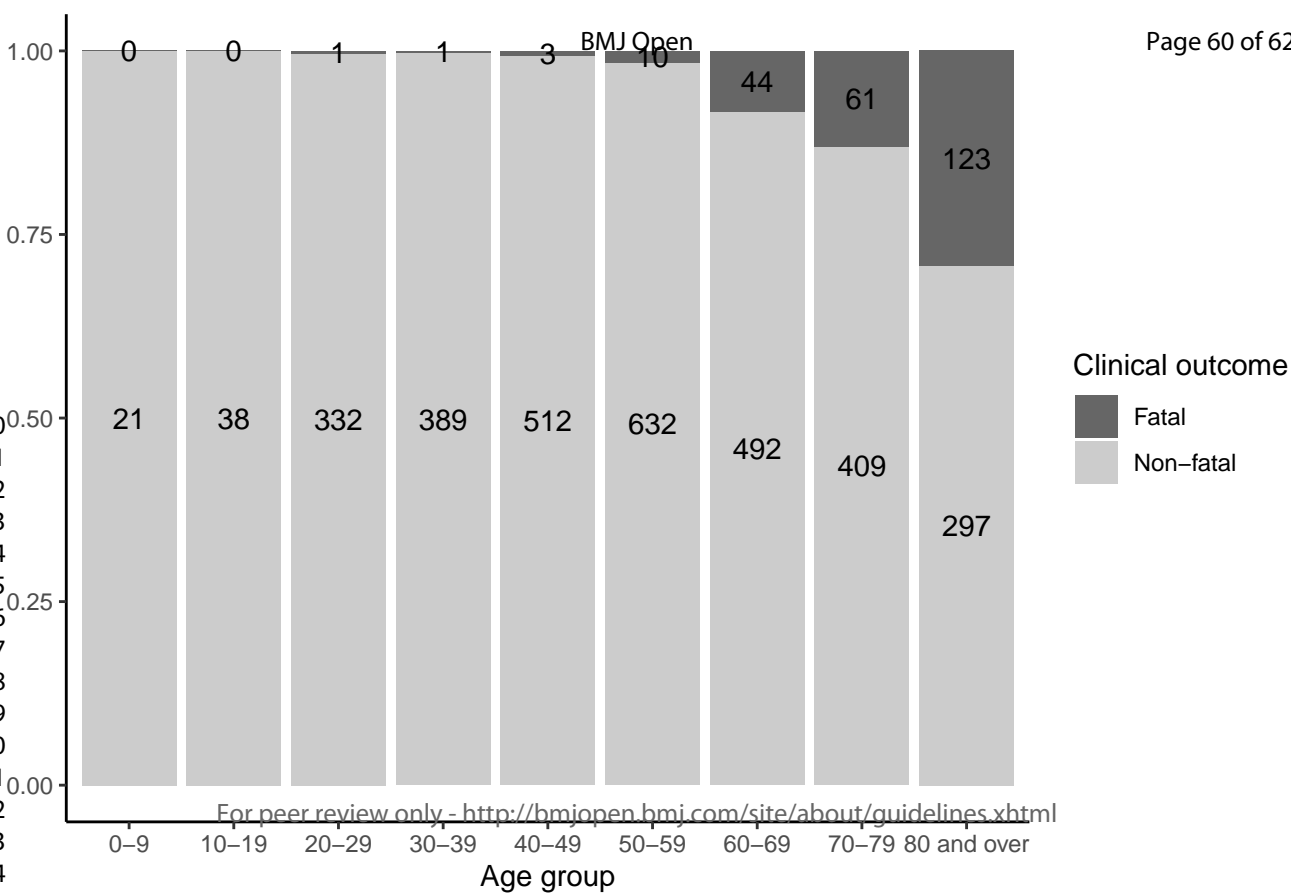
Convalescent Plasma therapy was not utilized in Japan at the time of data collection.

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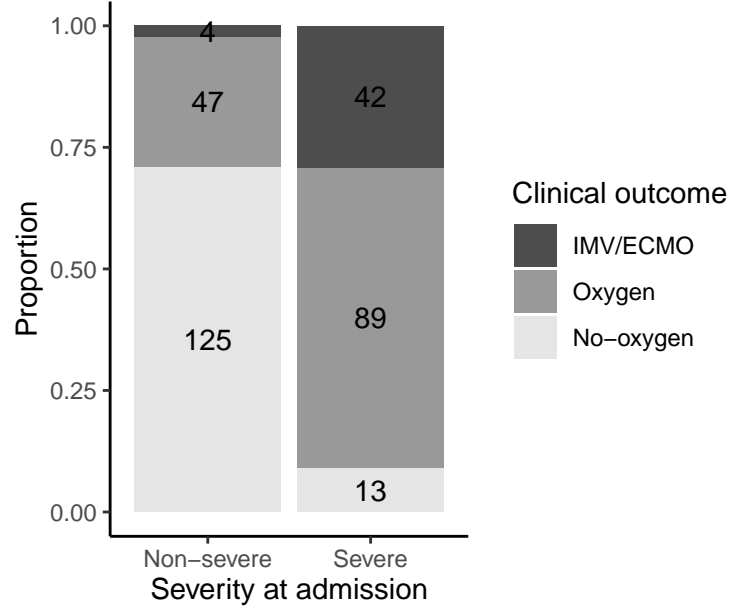
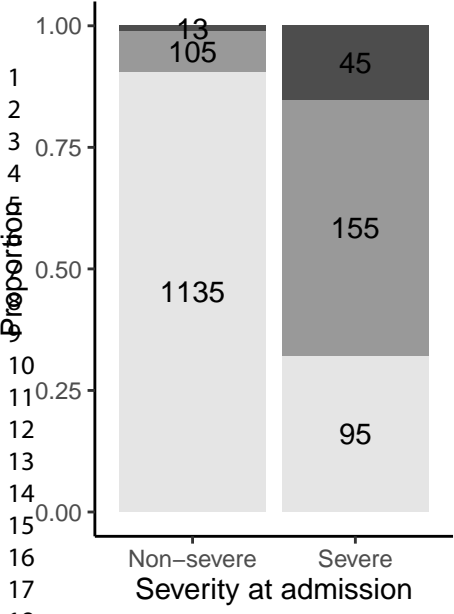
Clinical outcome

- IMV/ECMO
- Oxygen
- No-oxygen

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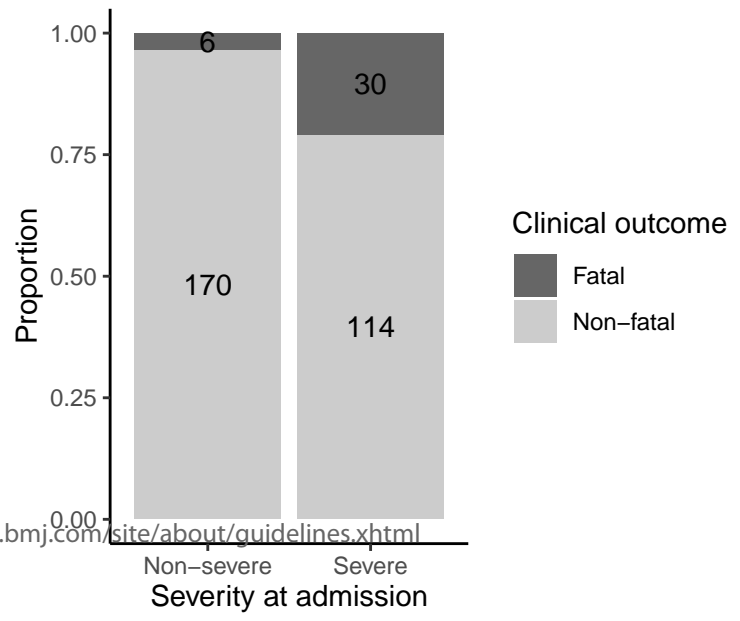
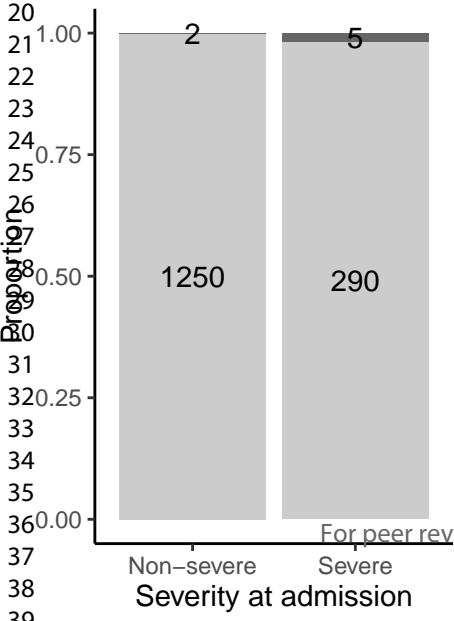
No comorbidity under 65

No comorbidity 65 and older



No comorbidity under 65

No comorbidity 65 and older



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	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
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	9
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	12 12 13
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	14 13 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

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	14
2			(b) Report category boundaries when continuous variables were categorized	14
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	17
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	21
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	21
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	21
20				
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	22
23				
24				

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26 *Give information separately for exposed and unexposed groups.

27
28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
32 available at <http://www.strobe-statement.org>.
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