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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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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: A 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 outcoe 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,

chronic respiratory disease, diabetes, obesity, and hypertension. Cerebrovascular disease, liver disease, renal disease or dialysis, solid tumor, and hyperlipidemia did not influence severity on admission ; however it influenced worst severity. Fatality rates for obesity, hypertension, and hyperlipidemia were relatively lower.

Conclusions: This study segregated the comorbidities driving severity and death. It is possible that risk factors for severity on admission, worst severity, and fatality are not consistent and may be propelled by different factors. Specifically, while hypertension, hyperlipidemia, and obesity had major effect on worst severity, their impact was mild on fatality in the Japanese population. Some studies contradict our results; therefore, detailed analyses, considering in-hospital treatments, are needed for validation.

Trial registration: UMIN000039873. https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453

Strengths and limitations of this study

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

factors.

- This study pointed out the possibility that risk factors of the severity on admission, worst severity, and fatality are not consistent and may be propelled by different factors.
- Our data were collected from hundreds of healthcare facilities; thus data accuracy may be questionable.
- 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 June[3]. The fatality rate in the second wave has generally been lower in many countries, including Japan[4].

When the number of patients explodes, hospital beds were in great shortage; hotels were utilized as isolation facilities in many countries[5-7]. Likewise, in Japan, mild patients were transferred to hotels from April 2020[8]. About two-thirds of cases did not require oxygen support throughout thier illness[9]. However, some cases initiated non-severe may instantly plunge into a serious state and require aggressive care[10]. 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

has not been conducted are of interest to physicians globally.

We obtained nationwide data from a COVID-19 inpatient registry, "COVID-19 REGISTRY JAPAN (COVIREGI-JP)"[11], and conducted a study to identify the independent risk factors contributing towards severity on admission. We aimed to determine the risk factors on admission, namely demographics and comorbidities. Progression of severity was inspected in detail on different time points. Cases identified within the period of the first pandemic wave were studied.

Methods

Study design and patients

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

Data collection and case report form

Data were collected in a case report form (CRF) developed for COVIREGI-JP. This CRF includes modified information of the International Severe Acute Respiratory and Emerging Infection Consortium CRF on COVID-19[12]. Upon modification, we elaborated on data collection, especially on treatments, comorbidities, and symptoms. In addition, as of October 26, 2020, this CRF underwent revisions twice to update therapeutic options or definitions, as new evidence emerges. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools[13,14], hosted at the datacenter in National Center for Global Health and Medicine. Data were either recorded on a CRF hard-copy or were entered directly into REDCap at each facility.

Comorbidities

Comorbidities were collected based on Charlson comorbidity index[15,16] with modifications. Some comorbidities were combined as follows: Cardiovascular disease (CVD)—myocardial infarction, congestive heart failure, and peripheral vascular disease; Chronic respiratory disease (CRD)—chronic obstructive pulmonary disease (COPD) and other chronic lung diseases; Renal disease or dialysis—moderate to severe renal disorder (creatinine ≥ 3mg/dL, nephropathy, post-renal transplantation, or on dialysis), and maintenance hemodialysis or peritoneal dialysis before hospitalization; and Solid tumor—solid tumor with or without metastasis. Obesity was

diagnosed based on physician's judgement, and body mass index (BMI) was not considered in this study.

Drug administration prior to and during hospitalization

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

Dataset

We defined the first wave period as January 16 to May 31, 2020[17], and cases from the first wave was included in this analysis. Therefore, data extraction conditions were: (1) cases admitted to healthcare facilities between January 16 and May 31, 2020, and (2) all CRF items completed on dataset generation. The dataset was generated and fixed on September 2, 2020.

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 ≤94% in room air, or (4) tachypnea with respiratory rate (RR) ≤24 breaths per minute[18]. 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

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 version3.6.3 (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

number NCGM-G-003494-08), and waived the need for informed consent from individual patients owing to the non-invasive, non-interventional nature of this observational study according to the local Ethical Guidelines[20]. Information regarding opting out of our study is available on the website[11]. Although it is not mandatory, the study is also being registered on trial registration website (Unique ID: UMIN000039873, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453).

Results

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

Demographics and clinical characteristics of the study population are shown in Table 1. Days between onset and admission were similar in both groups (non-severe 6.0 *vs* severe 7.0 days). Over ten times as many severe cases on admission underwent IMV/ECMO than non-

severe cases (2.0% *vs* 26.4%). Severe cases were older (50.0 *vs* 67.0), had higher BMI (22.9 *vs* 24.1), greater male dominance (56.3% *vs* 70.5%), and a higher prevalence of comorbidities excluding leukemia, compared to the non-severe group. The most prevalent symptoms in both groups were fever (non-severe 49.5%, severe 73.7%), cough (non-severe 53.8%, severe 64.9%), and fatigue (non-severe 40.3%, 59.9%), but was greater in the severe group. Conversely, prevalence of dysgeusia (25.9% *vs* 13.2%), dysosmia (22.6% *vs* 11.5%), headache (18.1% *vs* 14.7%), and runny nose (11.9% *vs* 8.9%) was higher in the non-severe group.

Results of the multivariate logistic regression to determine the risk of severity on admission are shown in Table 2. Older age (OR 1.038 [1.032—1.044]) and male (OR 2.06 [1.69—2.51]) were considered a risk among the demographics and comorbidities included CVD (OR 1.61 [1.07—2.43]), respiratory disease (OR 2.59 [1.63—4.13]), diabetes (OR 1.39 [1.09—1.76]), obesity (OR 1.62 [1.12—2.35]), and hypertension (OR 1.31 [1.03—1.67]). Days between onset to admission were non-significant ($p = 0.376$); the timing of admission did not affect the severity on admission.

Table 3 depicts the study population from a different angle and is categorized by the worst severity (n=3,336) and fatality (n=3,376). Oxygen and IMV/ECMO cases were predominantly severe at admission (65.5% and 87.9%, respectively), whereas most no-oxygen cases come from non-severe group (90.2%). Prevalence of comorbidities was lowest in no-

oxygen cases; however, prominent difference was not observed for asthma. Similarly, fatal cases were more severe at admission (84.0% *vs* 31.1%) and had higher prevalence of oxygen and IMV/ECMO cases (oxygen: 56.4% *vs* 29.0%, IMV/ECMO: 41.9% *vs* 8.2%, respectively). Days between onset and admission was longer in non-fatal cases (5-days *vs* 7-days).

More non-severe cases with any comorbidity underwent treatment with oxygen or IMV/ECMO compared to non-severe cases with no comorbidities. In figure 1, only 11.9% underwent oxygen therapy or IMV/ECMO in non-severe cases without any comorbidities. However, among the non-severe cases with comorbidity, the rates of oxygen or IMV/ECMO were higher in most comorbidities, including CVD (34.7%), CRD (38.9%), liver disease (36.7%), diabetes (35.1%), obesity (35.8%), cerebrovascular disease (34.7%), renal disease (40.9%), solid tumor (27.3%), hypertension (31.2%), and hyperlipidemia (25.0%). Asthma alone followed a different trend; the chances of oxygen and IMV/ECMO requirement was lower.

Among the cases without comorbidity, 75.2% of cases that were severe on admission required oxygen or IMV/ECMO; however, the fatality rate was low, and only 8.0% resulted in death (Figure 2). Fatality rates were approximately 3—5 times higher when the following comorbidities were present: renal disease or dialysis (44%), CVD (40.5%), cerebrovascular disease (39.5%), CRD (30.4%), solid tumor (30.4%), diabetes (25.8%), and liver disease

(25.6%). Even among non-severe cases, relatively high fatality rate was observed in cases with solid tumor, CRD, cerebrovascular disease, CVD, and renal disease or dialysis, with fatality rates ranging from 8.1% to 11.1%. Collectively, obesity, hypertension, and hyperlipidemia influenced the worst severity; however, their influence on fatality was relatively lower than that mentioned earlier.

Older age was relevant to both worst severity and fatality, as shown in supplemental figures 1 and 2. The combined proportion of oxygen and IMV/ECMO increased gradually by age from 5.3% in 20s to 69.3% in ≥80s. Conversely, the fatality rate leaped between 60s (2.2%) and 70s (8.6%). Likewise, supplemental figure 3 shows the combined proportion of oxygen and IMV/ECMO and fatality rates as higher in older individuals, irrespective of underlying comorbidities.

Predominant comorbid cases required more drug administration than those without comorbidities (Supplementary Table 1). Systemic steroids were most frequently used in cases with CRD (27.9%). Heparin was used most often in renal disease (12.8%), hypertension (11.2%), diabetes (10.9%), and CVD (10.4%).

Discussion

We took disease progression into consideration and evaluated the study population

based on severity on admission, worst severity, and the outcome. To our knowledge, studies have predominantly reported worst severity, whereas disease progression has not been considered. Our findings, therefore, are novel, augmenting the evidence needed to depict the clinical course and trajectory from onset to worsening condition. Specifically, this study segregated the comorbidities influencing severity and death. Based on our findings, it may be possible that the early severity, worst severity, and death are propelled by different factors, whilst confirmation is necessary by multivariate analysis.

The majority of comorbidities we studied did not influence severity on admission. On admission, severity was driven by age, sex, CVD, CRD, diabetes, obesity, and hypertension. The trend was similar for the worst severity, as cases with these factors had higher rate of oxygen or IMV/ECMO. However, all comorbidities appeared to influence the worst severity.

Within the comorbidities, the prognosis of cases with obesity, hypertension, or hyperlipidemia was relatively favorable. In contrast to our results, hypertension and obesity are reportedly related to an increased risk of severity and mortality[21-24]. However, a large cohort reported a trend similar to our results[25]. Another study reported that obesity is be confounded by age and sex[26,27]. Obesity was judged by a physician in our study, and the results may change after incorporating BMI. Several other evidences suggest that the association of these comorbidities with poorer outcome of COVID-19 needs further investigation. BMI, on average,

is lower in the Asia-Pacific region than in other global regions[28]; therefore, the degree of obesity may have been milder in our study population. Extreme obesity may worsen the prognosis, and confounders should be addressed in consecutive analyses. On the other hand, the presence of hypertension and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers act contrarily[29-31], while ACE2 mediates the entry of SARS-CoV-2 into host cells[32,33], making the COVID-19 pathophysiology in hypertensive patients intricate. Our study suggested that hypertension, hyperlipidemia, and obesity could be less detrimental on fatality.

In accordance with previous studies, CVD, CRD, liver disease, diabetes, cerebrovascular disease, renal disease or dialysis, and solid tumor were associated with to fatality and worst severity. Two meta-analyses have reported common risk factors for worst severity during hospitalization, which include, diabetes, COPD, malignancy, CVD, and cerebrovascular disease[34,35]. Other studies have also reported chronic liver disease and renal disease as risk factors[36-38]. Studies have elucidated that acute respiratory distress syndrome and coagulation dysfunction are related to the renin-angiotensin-aldosterone system and blood coagulation pathways, which are altered by SARS-CoV-2 host cell invasion via ACE2[39-41]. Clinical and non-clinical studies revealed an association between these comorbidities; while SARS-CoV-2 infection decreases ACE2 expression, ACE2 deficiency is reported to cause cardiac overload and kidney inflammation[41-44]. Elevated blood glucose is also associated with

mortality[45]. Although risk factors vary among studies, the comorbidities we identified are highly likely associated with fatality, backed up by clinical and non-clinical results.

Different trends were seen in the rates of IMV/ECMO and death for each comorbidity. Although rates of IMV/ECMO were comparable in all comorbid cases, those with obesity, asthma, hyperlipidemia, and hypertension showed a lower fatality rate, suggesting that the fatality rates within the IMV/ECMO cases with these comorbidities were lower than expected. Contrarily, fatality rates in cases with CVD, cerebrovascular disease, renal dysfunction, tumor, and CRD were comparable or higher than IMV/ECMO rates. The number of death actually exceeded the number of IMV/ECMO cases in patients with tumor, cerebrovascular disease, or CVD. These comorbidities likely have caused a higher risk of death and some even died without intubation. Healthcare nearly overwhelmed in the first wave in Japan but ICU capacity was maintained[46], and thus intubation may have been unperformed due to a medical judgment. A detailed examination of these issues is necessary in the future.

Our results did not show prominent difference in fatality between males and females. Oftentimes, males are considered to develop severe conditions and increased fatality[37,38,47-49]. However, according to Global Health 5050, sexual disparity in incidence of COVID-19 is low[50]. Additionally, ACE2 expression is affected by sexual hormones, whereby higher expression is observed in men, possibly explaining the sexual disparity[51-53]. Moreover, the immunological

response to produce antibodies is more favorable in females[54]. These studies support the rationale that males are more susceptible to severe COVID-19, which contravene our results. The lower-than-expected fatality rate in our male population may be attributed to comorbidity prevalence, treatments, age, and/or degree of obesity.

Fatality rates were comparable between asthmatic and cases without comorbidities in our results. Theoretically, COVID-19 can be a risk for asthmatic patients. A viral respiratory infection is presented as relatively worse and causes asthma exacerbation[55,56]. Asthmatic patients reportedly require a longer duration of mechanical ventilation when intubated[57]; however, no study, including ours, has found strong evidence on severity or mortality[58-61]. Inhaled corticosteroids (ICS) are known to downregulate ACE2[62,63] and are being investigated for treating COVID-19[64]. ICS may have impeded aggravation in asthmatic patients with COVID-19[65]. Overall, further studies are needed to elucidate the true risk of asthma on COVID-19.

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 mortality[66-68]. However, these utilize laboratory data collected on admission

and are seldom practical for estimating the severity of illness prior to medical visits or when test results are not promptly available. While these are useful to predict prognosis more precisely, our results are useful from a public health perspective, as they provide risk factors for predicting the severity on admission and disease progression from patients' background factors.

Our study has several limitations. In some of our analyses, confounders were not eliminated. We did not consider treatments prior to and during hospitalization. As our data were collected from hundreds of healthcare facilities, treatment type, dosage, duration, and combination varied immensely. We plan to deliberate the analytical methodology further to evaluate the outcomes which are prone to be affected by in-hospital treatments. Data were collected from numerous facilities; therefore, accuracy may be questionable. Additionally, hotels were utilized as isolation facilities from April 2020, and participant selection might have altered thereafter. COVIREGI-JP is continuously open for new entry; the number of registrations is increasing, and subsequent results may vary from ours.

Conclusion

On admission, factors that influence severity were age, sex, and comorbidities, including CVD, CRD, diabetes, obesity, and hypertension. Risk factors for severity on admission, worst severity, and fatality were not consistent, and it is likely that they are each

propelled by different factors. Our results are practically useful for predicting the progression and preparing for the worst, based on patients' backgrounds. Moreover, based on our predictions, healthcare resources can be allocated to patients in the most suitable way.

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Contributorship statement

MT conceived and HO, SS, KH, ST and MT designed the study. ST, YA, SS, KH, and MT analyzed and interpreted the data. MT and ST drafted the first version of the manuscript. All the authors contributed to, read, and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SS is the guarantor.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; H.O. reports personal fees as a statistician and as an external consultant for clinical trials from EPS International, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Transparency Statement

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

Data sharing

Data on an individual level is shared with limitation to participating healthcare facilities through applications to COVIREGI-JP[11].

Patient and Public Involvement

No patient was involved in the setting of research question, outcome measures, or study design, nor were they involved in the recruitment to and conduct of the study.

Dissemination to participants and related patients and public communities

The study results will be shared with all the healthcare facilities which participated and registered data in COVIREGI-JP. It will also be shared with the public on the website[11].

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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 (≥37.5℃)	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)

[a]invasive mechanical ventilation/extracorporeal membrane oxygenation

[b]immunosupprenssants other than steroids

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

	Odds ratio	95% CI[a]	*P* 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

[a]confidence interval

[b]immunosuppresssants 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)	Oxgen (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 (≥37.5℃)	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)

[a]invasive mechanical ventilation/extracorporeal membrane oxygenation

[b]immunosupprenssants other than steroids

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

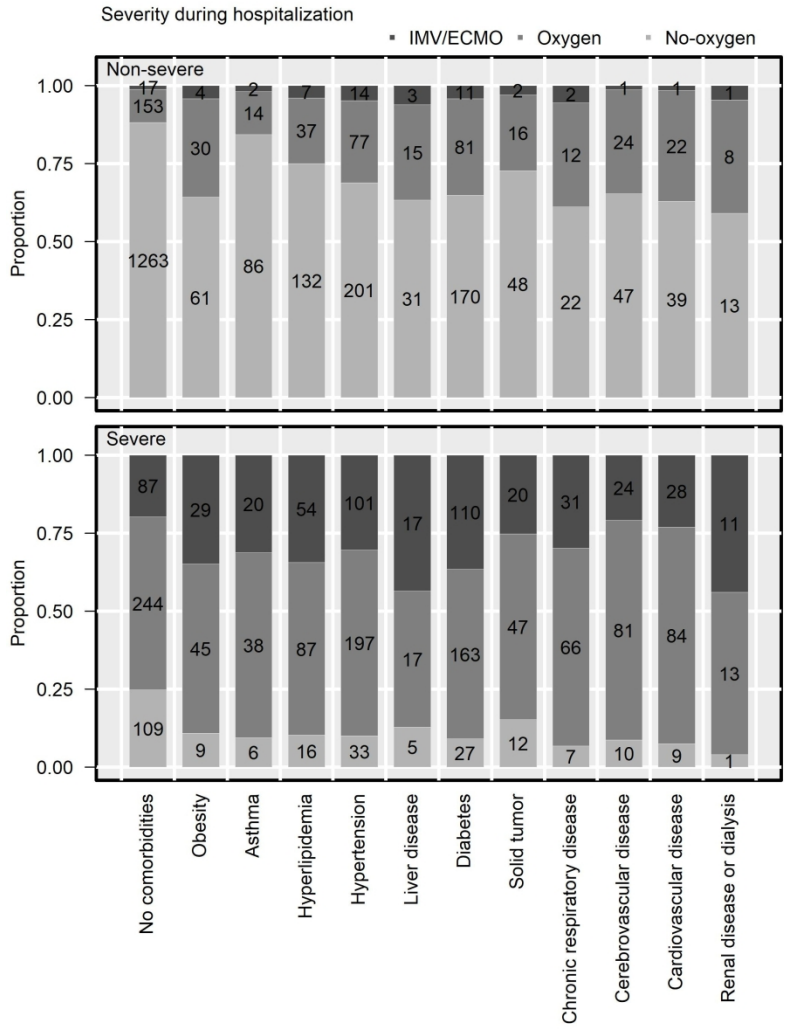
Top bars represent non-severe cases at admission and bottom bars represent severe cases at admission. Each group of cases was divided based on the presence of comorbidities. Dark gray represents fatal cases while light gray represents non-fatal cases.

Supplementary Figure 1. Distribution of worst severity by age group

Supplementary Figure 2. Distribution of fatality by age group

Supplementary Figure 3. (a) Worst severity of cases aged <65 and ≥65 with no comorbidities

(b) Fatality in cases aged <65 and ≥65 with no comorbidities



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

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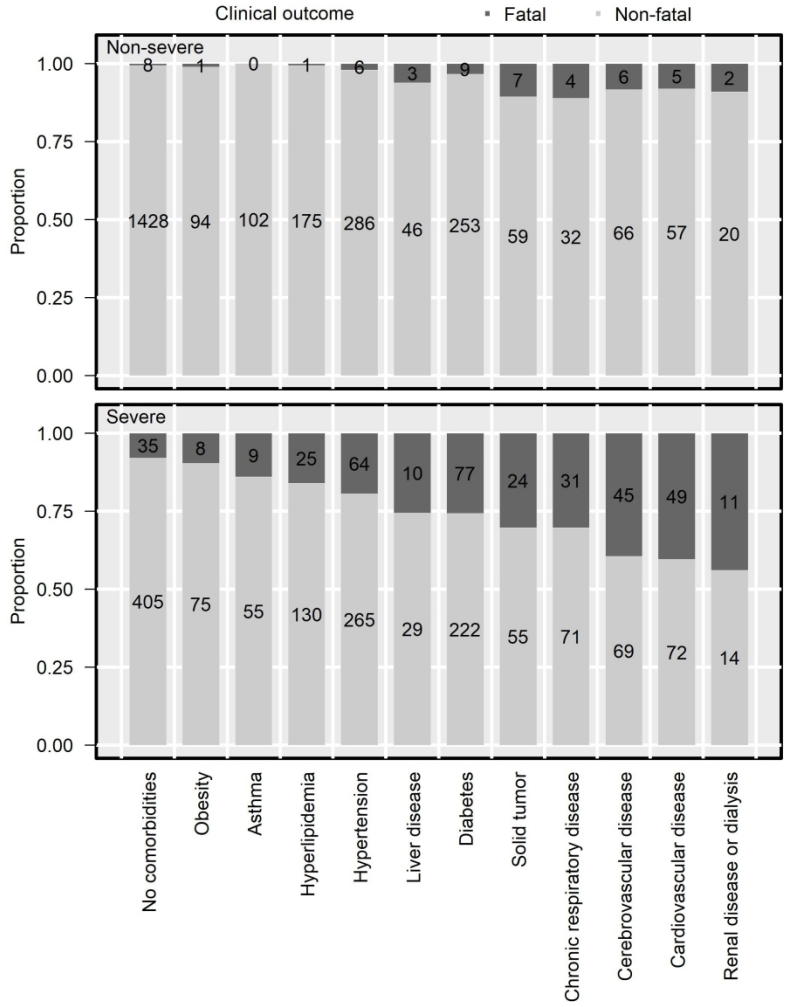

Distribution of the fatality arranged by severe/non-severe at admission and presence/non-presence of comorbidities

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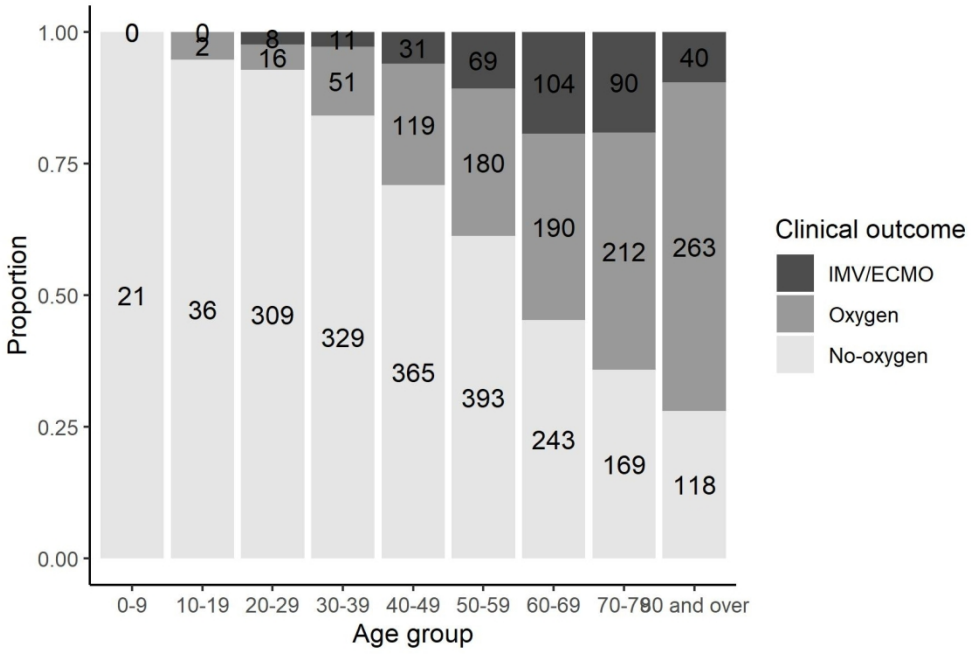

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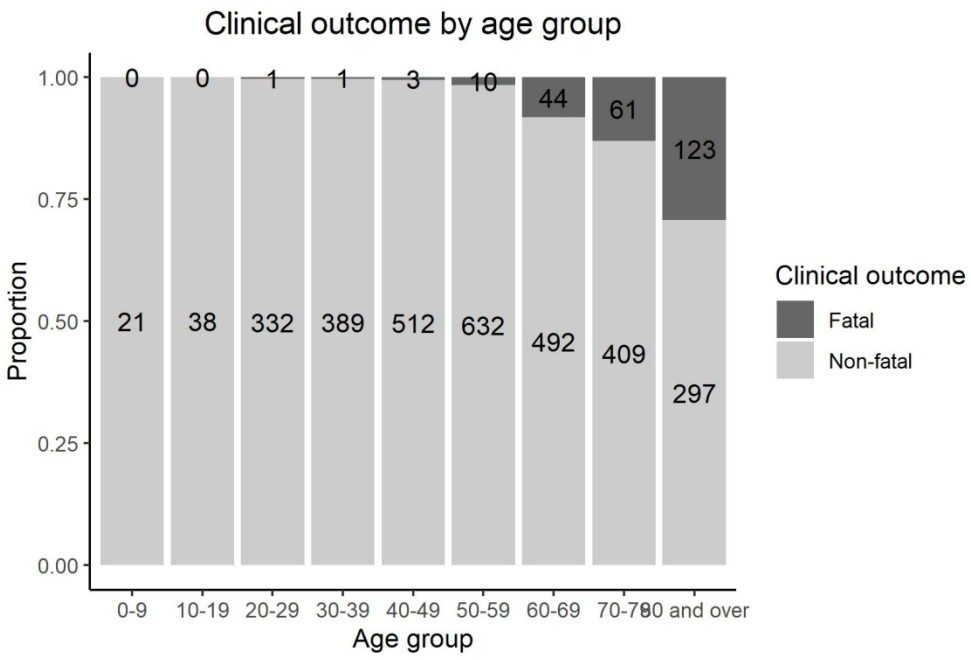

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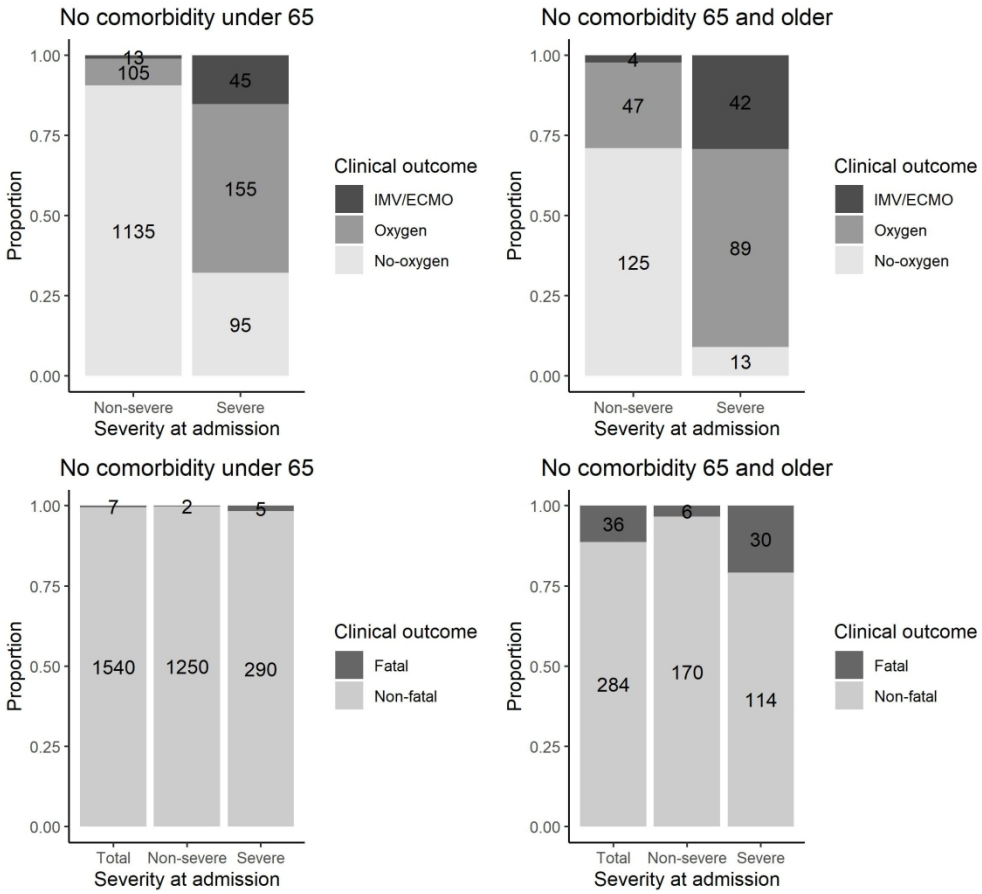

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Supplementary Table. Proportion of therapeutics used for each comorbidity

	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	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
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	13
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	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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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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Abstract

Objectives: To investigate the risk factors contributing to severity on admission. Additionally, risk factors of worst severity and fatality were studied. Moreover, factors were compared based on three points: early severity, worst severity, and fatality.

Design: A 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 outcoe 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,

chronic respiratory disease, diabetes, obesity, and hypertension. Cerebrovascular disease, liver disease, renal disease or dialysis, solid tumor, and hyperlipidemia did not influence severity on admission ; however it influenced worst severity. Fatality rates for obesity, hypertension, and hyperlipidemia were relatively lower.

Conclusions: This study segregated the comorbidities influencing severity and death. It is possible that risk factors for severity on admission, worst severity, and fatality are not consistent and may be propelled by different factors. Specifically, while hypertension, hyperlipidemia, and obesity had major effect on worst severity, their impact was mild on fatality in the Japanese population. Some studies contradict our results; therefore, detailed analyses, considering in-hospital treatments, are needed for validation.

Trial registration: UMIN000039873. https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453

Strengths and limitations of this study

- This study investigated the disease progression of COVID-19, by comparing the risk factors on three points: early severity, worst severity throughout hospitalization, and fatality, whereas previous studies have predominantly reported worst severity.
- Categorization used for worst severity may differ from those used in other studies as most

cases in our dataset did not include lung infiltration rate judged from radiological examination, SpO_2:FiO_2 ratio or PaO_2:FiO_2 ratio.

- The dataset was derived from a large COVID-19 patient registry in Japan which involves 299 facilities in Japan, which is both a strength and a limitation, as treatment methods and severity may vary.
- As treatment type, dosage, duration, and combination varied immensely across the facilities, we did not consider treatments prior to and during hospitalization.

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 June[3]. The fatality rate in the second wave has generally been lower in many countries, including Japan[4].

When the number of patients explodes, hospital beds were in great shortage; hotels were utilized as isolation facilities in many countries[5-7]. Likewise, in Japan, mild patients were transferred to hotels from April 2020[8]. About two-thirds of cases did not require oxygen support throughout thier illness[9]. However, some cases initiated non-severe may instantly plunge into a serious state and require aggressive care[10]. 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

has not been conducted are of interest to physicians globally.

We obtained nationwide data from a COVID-19 inpatient registry, "COVID-19 REGISTRY JAPAN (COVIREGI-JP)", and conducted a study to identify the independent risk factors contributing towards severity on admission. We aimed to determine the risk factors on admission, namely demographics and comorbidities. Progression of severity was inspected in detail on different time points. Cases identified within the period of the first pandemic wave were studied.

Methods

Study design and patients

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

Patient and Public Involvement

No patient involved.

Data collection and case report form

Data were collected in a case report form (CRF) developed for COVIREGI-JP. This CRF includes modified information of the International Severe Acute Respiratory and Emerging Infection Consortium CRF on COVID-19[11]. Upon modification, we elaborated on data collection, especially on treatments, comorbidities, and symptoms. In addition, as of October 26, 2020, this CRF underwent revisions twice to update therapeutic options or definitions, as new evidence emerges. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools[12,13], hosted at the datacenter in National Center for Global Health and Medicine. Data were either recorded on a CRF hard-copy or were entered directly into REDCap at each facility.

Comorbidities

Comorbidities were collected based on Charlson comorbidity index[14,15] with modifications. Some comorbidities were combined as follows: Cardiovascular disease (CVD)—myocardial infarction, congestive heart failure, and peripheral vascular disease; Chronic respiratory disease (CRD)—chronic obstructive pulmonary disease (COPD) and other chronic lung diseases; Renal

disease or dialysis—moderate to severe renal disorder (creatinine ≥ 3mg/dL, nephropathy, post-renal transplantation, or on dialysis), and maintenance hemodialysis or peritoneal dialysis before hospitalization; and Solid tumor—solid tumor with or without metastasis. Obesity was diagnosed based on physician's judgement, and body mass index (BMI) was not considered in this study.

Drug administration prior to and during hospitalization

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

Dataset

We defined the first wave period as January 16 to May 31, 2020[16], and cases from the first wave was included in this analysis. Therefore, data extraction conditions were: (1) cases

admitted to healthcare facilities between January 16 and May 31, 2020, and (2) all CRF items completed on dataset generation. The dataset was generated and fixed on September 2, 2020.

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 ≤94% in room air, or (4) tachypnea with respiratory rate (RR) ≤24 breaths per minute[17]. 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

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 univariate analyses and 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. As for univariate analysis, we conducted logistic regression analysis about days between onset and admission and age. As for multivariate analysis, multicollinearity was evaluated using the variance inflation factor (VIF). Variables of VIF > 3 were excluded from the model; however, no variables demonstrated obvious multicollinearity. The variables

included in the model were chosen based on the previous findings[18-20], and expert opinions.

R version3.6.3 (R core team, 2020)[21] 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 number NCGM-G-003494-08), and waived the need for informed consent from individual patients owing to the non-invasive, non-interventional nature of this observational study according to the local Ethical Guidelines[22]. Information regarding opting out of our study is available on the COVIREGI-JP website (https://covid-registry.ncgm.go.jp/). Although it is not mandatory, the study is also being registered on trial registration website (Unique ID: UMIN000039873, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453).

Results

Within the study period, 3,829 cases were identified and 3,376 cases from 299 facilities were included in this study. Of them, 2,199 cases (65.1%) were non-severe, and 1,181 cases (34.9%) were severe at the time of admission. After categorizing the two groups further

into no-oxygen, oxygen, and IMV/ECMO by worst severity, compositions were 1,758 (81.5 %), 357 (16.5%), and 43 (2.0%) for the non-severe group and 190 (16.1%), 677 (57.5%), and 311 (26.4%) for the severe group, respectively. While categorizing the cases, 44 (1.3%) were unavailable due to missing values.

Demographics and clinical characteristics of the study population are shown in Table 1. Days between onset and admission were similar in both groups (non-severe 6.0 *vs* severe 7.0 days). Over ten times as many severe cases on admission underwent IMV/ECMO than non-severe cases (2.0% *vs* 26.4%). Severe cases were older (50.0 *vs* 67.0), had higher BMI (22.9 *vs* 24.1), greater male dominance (56.3% *vs* 70.5%), and a higher prevalence of comorbidities excluding leukemia, compared to the non-severe group. The most prevalent symptoms in both groups were fever (non-severe 49.5%, severe 73.7%), cough (non-severe 53.8%, severe 64.9%), and fatigue (non-severe 40.3%, 59.9%), but was greater in the severe group. Conversely, prevalence of dysgeusia (25.9% *vs* 13.2%), dysosmia (22.6% *vs* 11.5%), headache (18.1% *vs* 14.7%), and runny nose (11.9% *vs* 8.9%) was higher in the non-severe group.

Results of univariate analyses about factors associated with being severe cases on admission was described in Table 2-a. In most variables, univariate analysis showed similar results compared with the multivariate analysis. Results of the multivariate logistic regression to determine the risk of severity on admission are shown in Table 2-b. Older age (OR 1.04 [1.03—

1.04]) and male (OR 2.09 [1.76—2.48]) were considered a risk among the demographics and comorbidities included CVD (OR 1.48 [1.04—2.10]), respiratory disease (OR 2.51 [1.67—3.78]), diabetes (OR 1.34 [1.09—1.64]), obesity (OR 1.75 [1.26—2.45]), and hypertension (OR 1.33 [1.08—1.64]). Days between onset to admission were non-significant ($p = 0.960$); the timing of admission did not affect the severity on admission. Cerebrovascular disease and hyperlipidemia were not associated with the severity at admission after other confounding factors were considered, although they showed different results in univariate analyses.

Table 3 depicts the study population from a different angle and is categorized by the worst severity (n=3,336) and fatality (n=3,376). Oxygen and IMV/ECMO cases were predominantly severe at admission (65.5% and 87.9%, respectively), whereas most no-oxygen cases come from non-severe group (90.2%). Prevalence of comorbidities was lowest in no-oxygen cases; however, prominent difference was not observed for asthma. Similarly, fatal cases were more severe at admission (84.0% *vs* 31.1%) and had higher prevalence of oxygen and IMV/ECMO cases (oxygen: 56.4% *vs* 29.0%, IMV/ECMO: 41.9% *vs* 8.2%, respectively). Days between onset and admission was longer in non-fatal cases (5-days *vs* 7-days).

More non-severe cases with any comorbidity underwent treatment with oxygen or IMV/ECMO compared to non-severe cases with no comorbidities. In figure 1, only 11.9% underwent oxygen therapy or IMV/ECMO in non-severe cases without any comorbidities.

However, among the non-severe cases with comorbidity, the rates of oxygen or IMV/ECMO were higher in most comorbidities, including CVD (34.7%), CRD (38.9%), liver disease (36.7%), diabetes (35.1%), obesity (35.8%), cerebrovascular disease (34.7%), renal disease (40.9%), solid tumor (27.3%), hypertension (31.2%), and hyperlipidemia (25.0%). Asthma alone followed a different trend; the chances of oxygen and IMV/ECMO requirement was lower.

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

Older age was relevant to both worst severity and fatality, as shown in supplemental figures 1 and 2. The combined proportion of oxygen and IMV/ECMO increased gradually by

age from 5.3% in 20s to 69.3% in ≥80s. Conversely, the fatality rate leaped between 60s (2.2%) and 70s (8.6%). Likewise, supplemental figure 3 shows the combined proportion of oxygen and IMV/ECMO and fatality rates as higher in older individuals, irrespective of underlying comorbidities.

Predominant comorbid cases required more drug administration than those without comorbidities (Supplementary Table 1). Systemic steroids were most frequently used in cases with CRD (27.9%). Heparin was used most often in renal disease (12.8%), hypertension (11.2%), diabetes (10.9%), and CVD (10.4%).

Discussion

We took disease progression into consideration and evaluated the study population based on severity on admission, worst severity, and the outcome. To our knowledge, studies have predominantly reported worst severity, whereas disease progression has not been considered. Our findings, therefore, are novel, augmenting the evidence needed to depict the clinical course and trajectory from onset to worsening condition. Specifically, this study segregated the comorbidities influencing severity and death. Based on our findings, it may be possible that the early severity, worst severity, and death are propelled by different factors, whilst confirmation is necessary by multivariate analysis.

The majority of comorbidities we studied did not influence severity on admission. On admission, severity was driven by age, sex, CVD, CRD, diabetes, obesity, and hypertension. The trend was similar for the worst severity, as cases with these factors had higher rate of oxygen or IMV/ECMO. However, all comorbidities appeared to influence the worst severity.

Within the comorbidities, the prognosis of cases with obesity, hypertension, or hyperlipidemia was relatively favorable. In contrast to our results, hypertension and obesity are reportedly related to an increased risk of severity and mortality[23-26]. A large cohort reported a trend similar to our results[18], whereas other studies reported that obesity is being confounded by age and sex[27,28]. The presence of hypertension and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers act contrarily[29-31] while ACE2 mediates the entry of SARS-CoV-2 into host cells[32,33]; thus, COVID-19 pathophysiology in hypertensive patients become intricate.

In accordance with previous studies, CVD, CRD, liver disease, diabetes, cerebrovascular disease, renal disease or dialysis, and solid tumor were associated with to fatality and worst severity. Two meta-analyses have reported common risk factors for worst severity during hospitalization, which include, diabetes, COPD, malignancy, CVD, and cerebrovascular disease[34,35]. Other studies have also reported chronic liver disease and renal disease as risk factors[36-38]. Studies have elucidated that acute respiratory distress syndrome and

coagulation dysfunction are related to the renin-angiotensin-aldosterone system and blood coagulation pathways, which are altered by SARS-CoV-2 host cell invasion via ACE2[39-41]. Clinical and non-clinical studies revealed an association between these comorbidities; while SARS-CoV-2 infection decreases ACE2 expression, ACE2 deficiency is reported to cause cardiac overload and kidney inflammation[41-44]. Elevated blood glucose is also associated with mortality[45]. Although risk factors vary among studies, the comorbidities we identified are highly likely associated with fatality, backed up by clinical and non-clinical results.

Different trends were seen in the rates of IMV/ECMO and death for each comorbidity. Although rates of IMV/ECMO were comparable in all comorbid cases, those with obesity, asthma, hyperlipidemia, and hypertension showed a lower fatality rate, suggesting that the fatality rates within the IMV/ECMO cases with these comorbidities were lower than expected. Contrarily, fatality rates in cases with CVD, cerebrovascular disease, renal dysfunction, tumor, and CRD were comparable or higher than IMV/ECMO rates. The number of death actually exceeded the number of IMV/ECMO cases in patients with tumor, cerebrovascular disease, or CVD. These comorbidities likely have caused a higher risk of death and some even died without intubation. Healthcare nearly overwhelmed in the first wave in Japan but ICU capacity was maintained[46], and thus intubation may have been unperformed due to a medical judgment. A detailed examination of these issues is necessary in the future.

Our results did not show prominent difference in fatality between males and females. Oftentimes, males are considered to develop severe conditions and increased fatality[37,38,47-49]. However, according to Global Health 5050, sexual disparity in incidence of COVID-19 is low[50]. Additionally, ACE2 expression is affected by sexual hormones, whereby higher expression is observed in men, possibly explaining the sexual disparity[51-53]. Moreover, the immunological response to produce antibodies is more favorable in females[54]. These studies support the rationale that males are more susceptible to severe COVID-19, which contravene our results. The lower-than-expected fatality rate in our male population may be attributed to comorbidity prevalence, treatments, age, and/or degree of obesity.

Fatality rates were comparable between asthmatic and cases without comorbidities in our results. Theoretically, COVID-19 can be a risk for asthmatic patients. A viral respiratory infection is presented as relatively worse and causes asthma exacerbation[55,56]. Asthmatic patients reportedly require a longer duration of mechanical ventilation when intubated[57]; however, no study, including ours, has found strong evidence on severity or mortality[58-61]. Inhaled corticosteroids (ICS) are known to downregulate ACE2[62,63] and are being investigated for treating COVID-19[64]. ICS may have impeded aggravation in asthmatic patients with COVID-19[65]. Overall, further studies are needed to elucidate the true risk of asthma on COVID-19.

The variability in the risk factors may be explained by the differences in study population, definition for comorbidities, and ethnicity. First, the rate of comorbid patients had been lower in our cohort as suggested by extensive cohort studies[19,20,66]. The degree of obesity may also have been milder, as the average BMI is lower in the Asia-Pacific region than in other global regions[67].Secondly, obesity was judged by a physician in our study, and the results may change if BMI was incorporated. Ethnic differences due to genetic properties are also plausible. Individuals with stronger binding affinities of human leukocyte antigen (HLA) proteins to SARS-CoV-2 virus peptides are less likely become severe or fatal[68-71], and ethnic differences are present in HLA allele frequency[72]. A few strong binder alleles were more frequent in Northeast Asians; however, the complete picture is complicated. ACE1 polymorphism[73] and Neanderthal haplotype[74] were also suggestive of lower risk of COVID-19 among Asians and East Asians, respectively. Additionally, ethnic differences other than genetic traits are also anticipated. Vitamin D deficiency is postulated to increase COVID-19 severity, whereas vitamin D deficiency is correlated to Northern latitude[75]. Within the elderly population, higher rates of deficiencies were observed in North America and Europe compared to Japan[76]. Although our study did not examine vitamin D, these facts also allow us to expect lower severity and fatality in Japan.

The period of when the COVID-19 occurred, and the situation of pandemic and

healthcare provision should also be noted when discussing severity and fatality. The longer our struggle against COVID-19 pandemic becomes, the more complicated interpretation be required due to chronological, regional, and viral transition. In the two pandemic waves of COVID-19 in Japan, the patient population altered; median age, rates of comorbidities, and fatality rate had become smaller in the second than the first[77]. Similar trend was observed in other countries[78,79]. These differences might be explained, at least partially, by the timing of drug approval for remdesivir (approved in May, 2020) and newly revealed efficacy of dexamethasone against COVID-19 in June. Our dataset includes nationwide data during the first wave, and articles referred elsewhere for comparison included data from a period close to ours.

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 mortality[80-82]. However, these utilize laboratory data collected on admission and are seldom practical for estimating the severity of illness prior to medical visits or when test results are not promptly available. While these are useful to predict prognosis more precisely, our results are useful from a public health perspective, as they provide risk factors for predicting the severity on admission and disease progression from patients' background factors.

Our study has several limitations. Although the definition of severe and non-severe was adopted from a previous study[17], such definition is not common as worst severity is used frequently or otherwise point of evaluation is unspecified. Our categorization of worst severity also differs from other definitions[83,84]. We did not adopt radiological criteria as lung infiltration rate was not collected in the registry where our dataset was extracted. Ratio of arterial oxygen saturation (SaO2) or arterial partial oxygen pressure (PaO2) to the fraction of inspired oxygen (FiO2) was not utilized as data was available for limited number of cases. This fact may have caused differences in risk factors. We did not consider treatments prior to and during hospitalization nor did we incorporate laboratory test results in the analysis which may be persisting as confounders. As our data were collected from hundreds of healthcare facilities, treatment type, dosage, duration, and combination varied immensely; laboratory tests also varied as reporting units and standard reference ranges were different across facilities. Treatments may be confounding also in terms of drug approval, as explained elsewhere. Thorough data verification and analytical deliberation is required before usage of these data; thus, we did not include it in the current analysis. Moreover, hotels were utilized as isolation facilities from April 2020, and participant selection might have altered thereafter. COVIREGI-JP is continuously open for new entry; the number of registrations is increasing, and subsequent results may vary from ours.

Conclusion

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

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Contributorship statement

MT conceived and HO, SS, KH, ST and MT designed the study. ST, YA, SS, KH, and MT analyzed and interpreted the data. MT and ST drafted the first version of the manuscript. All the authors including NM, SK, SW, NO, and those stated above contributed to, read, and

approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SS is the guarantor.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; H.O. reports personal fees as a statistician and as an external consultant for clinical trials from EPS International, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Transparency Statement

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

Data sharing

Data on an individual level is shared with limitation to participating healthcare facilities through applications to COVIREGI-JP.

Dissemination to participants and related patients and public communities

The study results will be shared with all the healthcare facilities which participated 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 (≥37.5℃)	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)

[a]invasive mechanical ventilation/extracorporeal membrane oxygenation

[b]immunosupprenssants 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

[a]confidence interval

[b]immunosupprenssants other than steroids

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

	Odds ratio	95% CI[a]	*P* 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

[a]confidence interval

[b]immunosuppresssants 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)	Oxgen (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 (≥37.5℃)	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)

[a]invasive mechanical ventilation/extracorporeal membrane oxygenation

[b]immunosupprenssants other than steroids

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

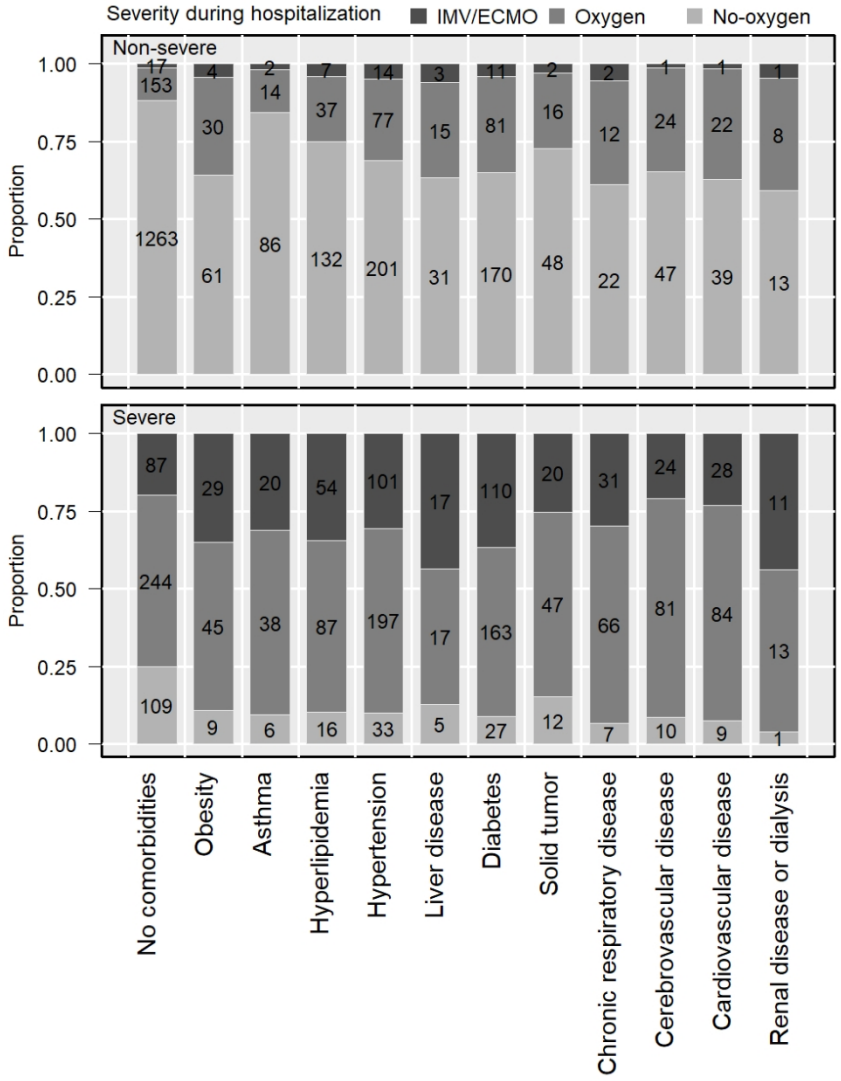
Top bars represent non-severe cases at admission and bottom bars represent severe cases at admission. Each group of cases was divided based on the presence of comorbidities. Dark gray represents fatal cases while light gray represents non-fatal cases.

Supplementary Figure 1. Distribution of worst severity by age group

Supplementary Figure 2. Distribution of fatality by age group

Supplementary Figure 3. (a) Worst severity of cases aged <65 and ≥65 with no comorbidities

(b) Fatality in cases aged <65 and ≥65 with no comorbidities



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

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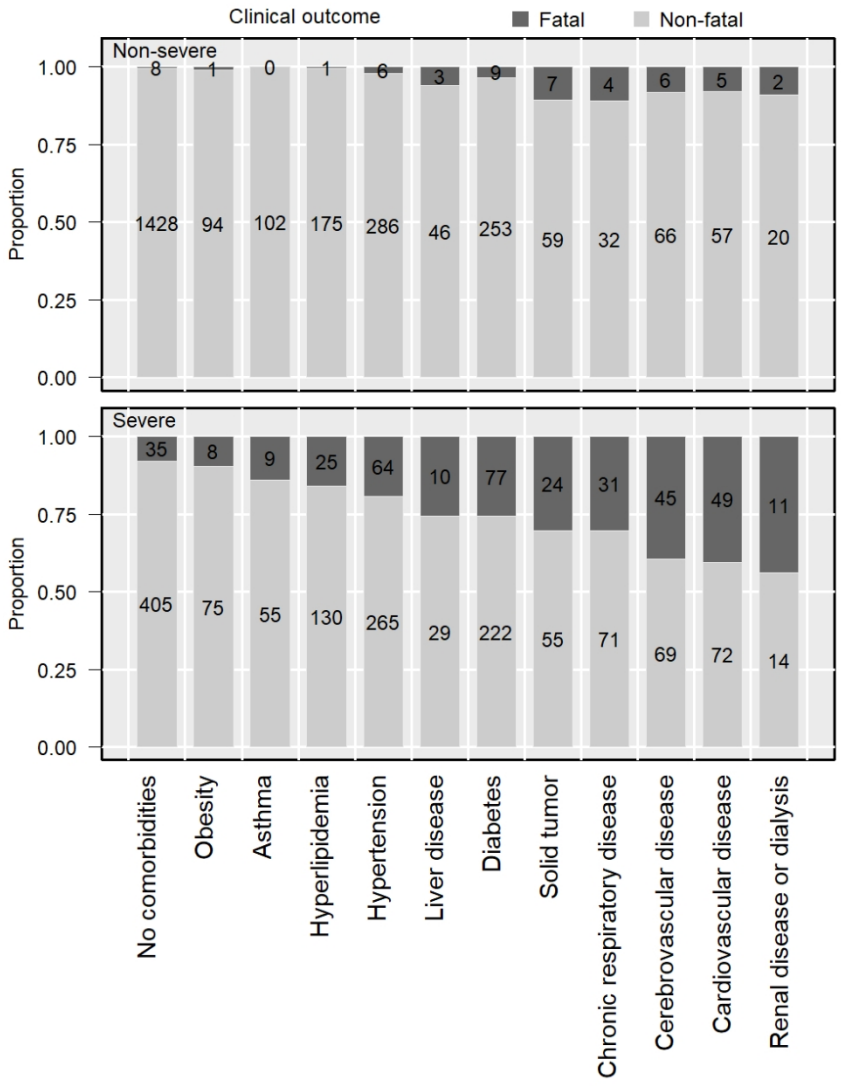

Distribution of the fatality arranged by severe/non-severe at admission and presence/non-presence of comorbidities

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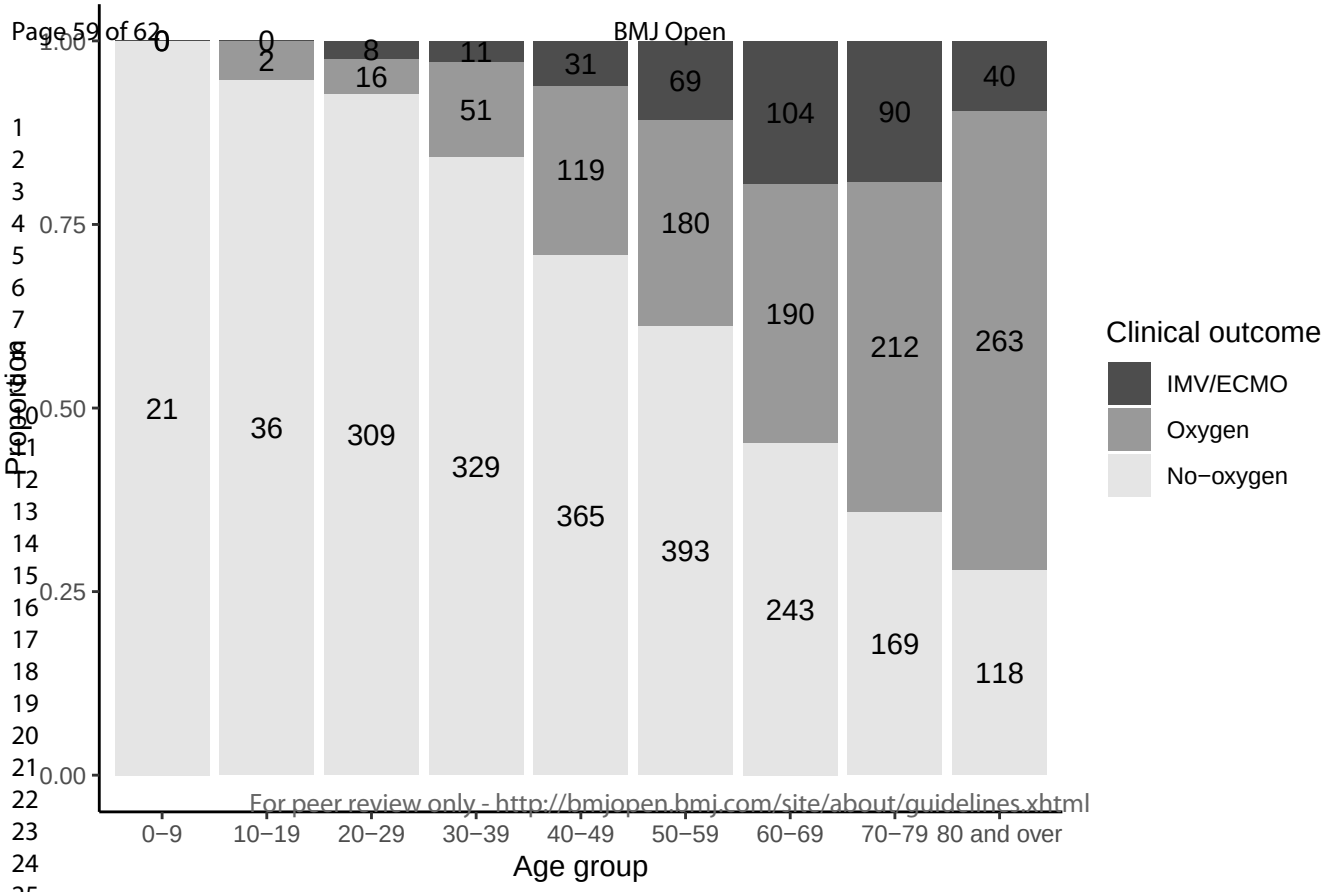
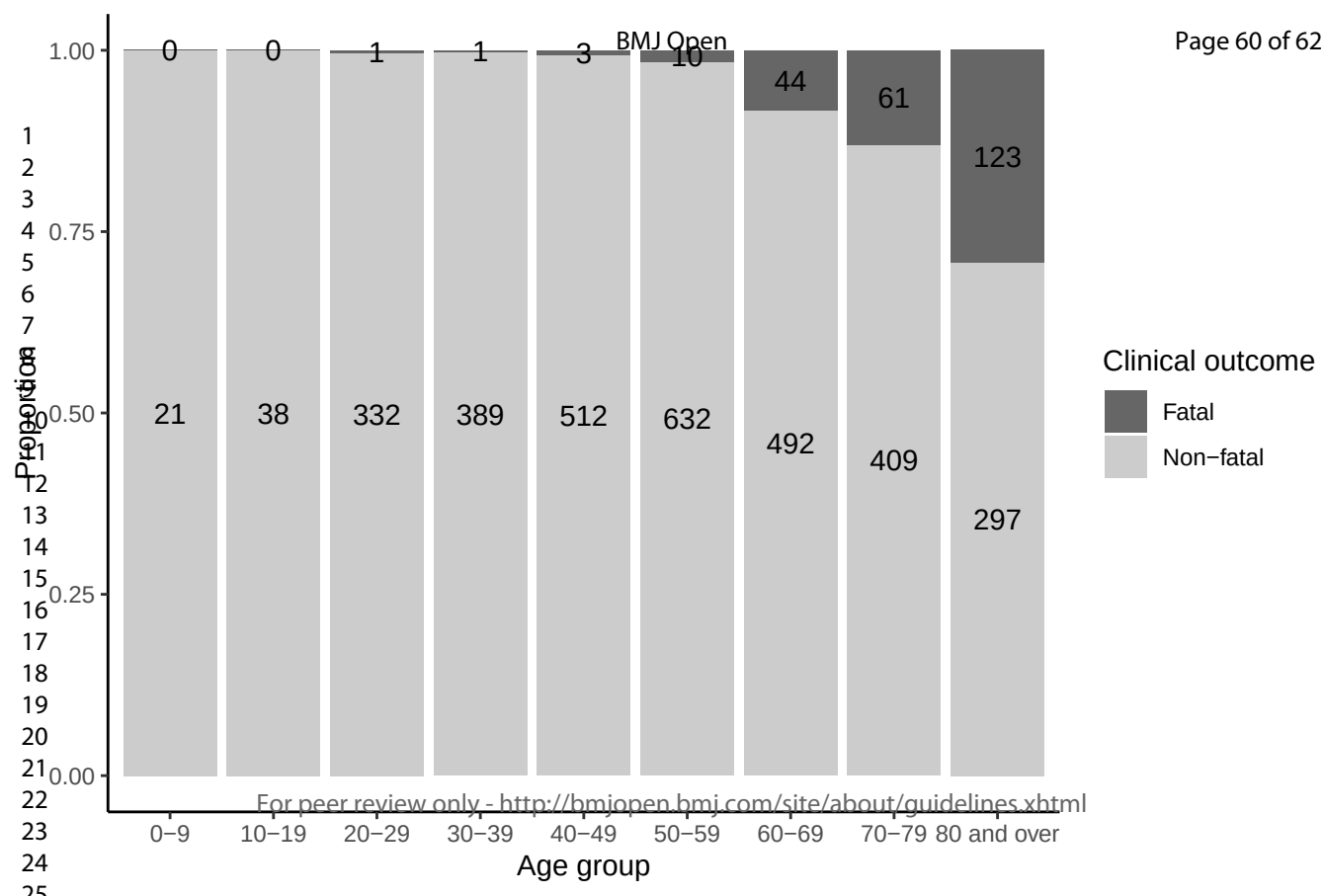
Supplementary Table. Proportion of therapeutics used for each comorbidity

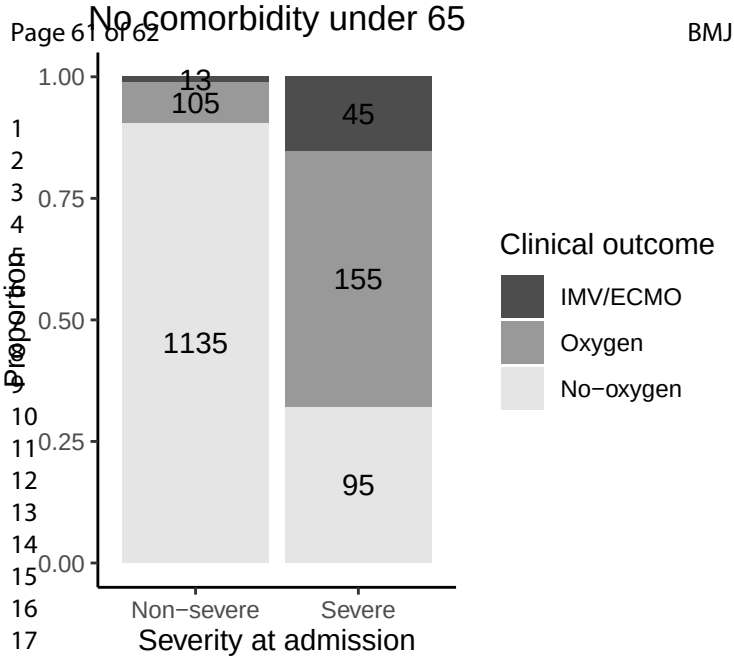
	Number of patients	Systemic steroid	Favipiravir	Ciclesonide	Heparin	Tocilizumab
No comorbidity	**1873**	**105 (6)**	**606 (32)**	**562 (30)**	**48 (3)**	**22 (1)**
Obesity	**178**	**34 (19)**	**109 (61)**	**72 (40)**	**17 (10)**	**5 (3)**
Cardiovascular disease	**183**	**30 (16)**	**86 (47)**	**46 (25)**	**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)**

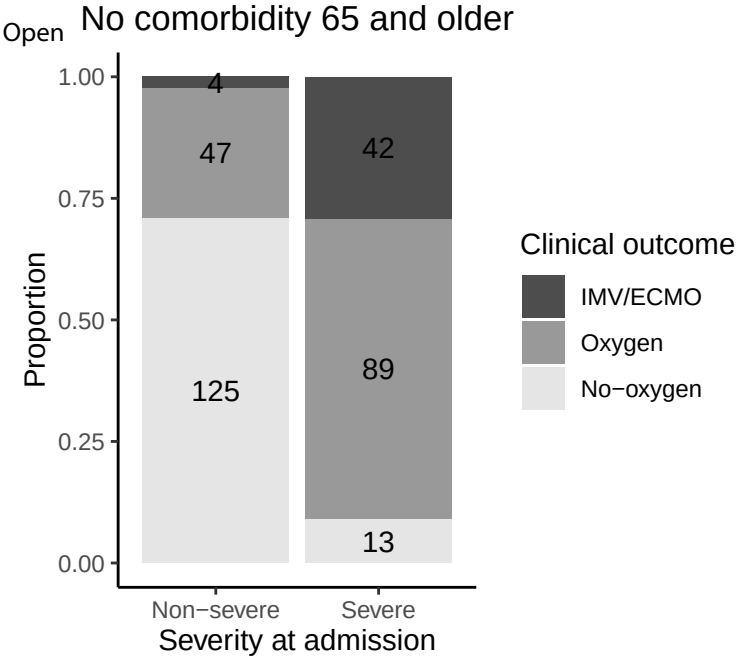
Numbers in brackets represent percentages.

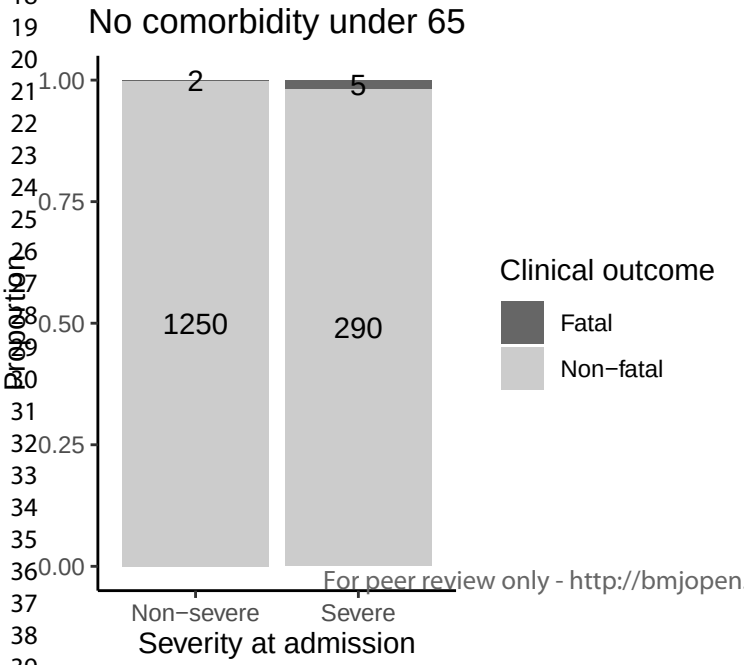
Convalescent Plasma therapy was not utilized in Japan at the time of data collection.

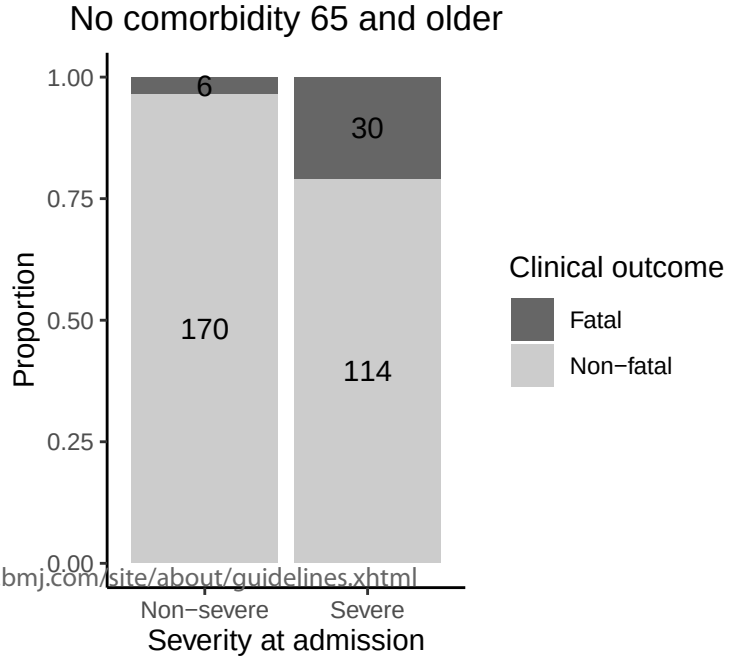












STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	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	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
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	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
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	13
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	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.