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Risk factors for severity on admission and the disease progression during hospitalisation in a large cohort of patients with COVID-19 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 An observational cohort study using data entered in a Japan nationwide COVID-19 inpatient registry, COVIREGI-JP.

Setting As of 28 September 2020, 10480 cases from 802 facilities have been registered. Participating facilities cover a wide range of hospitals where patients with COVID-19 are admitted in Japan.

Participants Participants who had a positive test result on any applicable SARS-CoV-2 diagnostic tests were admitted to participating healthcare facilities. A total of 3829 cases were identified from 16 January to 31 May 2020, of which 3376 cases were included in this study.

Primary and secondary outcome measures Primary outcome was severe or nonsevere on admission, determined by the requirement of mechanical ventilation or oxygen therapy, SpO2 or respiratory rate. Secondary outcome was the worst severity during hospitalisation, judged by the requirement of oxygen and/orinvasive mechanical ventilation/extracorporeal membrane oxygenation.

Results Risk factors for severity on admission were older age, men, cardiovascular disease, chronic respiratory disease, diabetes, obesity and hypertension. Cerebrovascular disease, liver disease, renal disease or dialysis, solid tumour and hyperlipidaemia did not influence severity on admission; however, it influenced worst severity. Fatality rates for obesity, hypertension and hyperlipidaemia 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, hyperlipidaemia 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.

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 hospitalisation and fatality, whereas previous studies have predominantly reported worst severity.
- ► Categorisation used for worst severity may differ from those used in other studies as most cases in our data set did not include lung infiltration rate judged from radiological examination, SpO_2:FiO_2 ratio or PaO_2:FiO_2 ratio.
- ► The data set 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 hospitalisation.

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

INTRODUCTION

COVID-19, caused by SARS-CoV-2, has caused a major global public health crisis. As of 3 October 2020, >34 million people had been infected in over 230 countries.[1 2] Japan experienced two pandemic waves after the first case reported on 16 January 2020. During the first wave, a state of emergency was declared on 7th April, which ended on 25th May, 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 used 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 their illness.[9] However, some cases initiated nonsevere may instantly plunge into a serious state and require aggressive care.[10] Therefore, public health centres 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 at 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 uses the data accumulated in the nationwide 'COVID-19 REGISTRY JAPAN (COVIREGI-JP)'. As of 28 September 2020, 10 048 cases from 802 facilities have been registered. Participating facilities cover a wide range of hospitals where patients with COVID-19 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 2 March 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] On modification, we elaborated on data collection, especially on treatments, comorbidities and symptoms. In addition, as of 26 October 2020, this CRF underwent revisions two times 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 ≥3 mg/dL, nephropathy, postrenal transplantation or on dialysis) and maintenance haemodialysis or peritoneal dialysis before hospitalisation and solid tumour—solid tumour 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 hospitalisation

Steroids, chemotherapy and immunosuppressants administered prior to hospitalisation were collected as prehospitalisation treatments. Steroids included those equivalent to 20 mg/day prednisolone for ≥1 month and are not considered as immunosuppressants. Chemotherapy and immunosuppressants were applicable if administered 3 months prior to hospitalisation. Treatment during hospitalisation 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 from 16 January to 31 May 2020,[16] and cases from the first wave were included in this analysis. Therefore, data extraction conditions were (1) cases admitted to healthcare facilities between 16 January and 31 May 2020 and (2) all CRF items completed on data set generation. The data set was generated and fixed on 2 September 2020.

Definitions of severity

Severity on admission

Severity on admission was converted into bivariate variables: severe and nonsevere. Cases met at least one of the following criteria were categorised as severe: (1) requiring invasive or non-invasive mechanical ventilation (IMV), (2) requiring supplemental oxygen, (3) SpO_2 ≤94% in room air or (4) tachypnea with respiratory rate ≤24 bpm.[17] Those who did not meet the aforementioned were classified as nonsevere.

Worst severity

The worst severity was grouped into three categories: no-oxygen, oxygen and IMV/extracorporeal membrane oxygenation (ECMO). The worst state during hospitalisation was adopted on categorisation, and each was defined as follows:

No-oxygen—no requirement of supplemental oxygen throughout hospitalisation.

Oxygen—required supplemental oxygen (including high-flow oxygen devices) or non-IMV during hospitalisation.

IMV/ECMO—required IMV or ECMO during hospitalisation.

Statistical analysis

Continuous variables are presented in median and 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 χ^2 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 tumours, leukaemia, lymphoma, hypertension and hyperlipidaemia), use of systemic steroids in the past month, chemotherapy in the past 3 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 V.3.6.3 (R core team, 2020)[21] was used for all the analyses performed in this study.

RESULTS

Within the study period, 3829 cases were identified and 3376 cases from 299 facilities were included in this study. Of them, 2199 cases (65.1%) were nonsevere, and 1181 cases (34.9%) were severe at the time of admission. After categorising the two groups further into no-oxygen, oxygen and IMV/ECMO by worst severity, compositions were 1758 (81.5 %), 357 (16.5%) and 43 (2.0%) for the nonsevere group and 190 (16.1%), 677 (57.5%) and 311 (26.4%) for the severe group, respectively. While categorising 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 (nonsevere 6.0 vs severe 7.0 days). Over 10 times as many severe cases on admission underwent IMV/ECMO than nonsevere 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 leukaemia, compared with the nonsevere group. The most prevalent symptoms in both groups were fever (nonsevere 49.5%, severe 73.7%), cough (nonsevere 53.8%, severe 64.9%) and fatigue (nonsevere 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 nonsevere group.

Results of univariate analyses about factors associated with being severe cases on admission are described in table 2. 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 3. Older age (OR 1.04 (1.03–1.04)) and men (OR 2.09 (1.76–2.48)) were considered a risk among the demographics and comorbidities including 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 nonsignificant (p=0.960); the timing of admission did not affect the severity on admission. Cerebrovascular disease and hyperlipidaemia were not associated with the severity at admission after other confounding factors were considered, although they showed different results in univariate analyses.

Table 4 depicts the study population from a different angle and is categorised by the worst severity (n=3336) and fatality (n=3376). 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 were longer in nonfatal cases (5 days vs 7 days).

More nonsevere cases with any comorbidity underwent treatment with oxygen or IMV/ECMO compared with nonsevere cases with no comorbidities. In figure 1, only 11.9% underwent oxygen therapy or IMV/ECMO in nonsevere cases without any comorbidities. However, among the nonsevere 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 tumour (27.3%), hypertension (31.2%) and hyperlipidaemia (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—five times higher when the following comorbidities were present: renal disease or dialysis (44%), CVD (40.5%), cerebrovascular disease (39.5%), CRD (30.4%),

Table 1 Characteristics of patients included in the present study

	Nonsevere (n=2196)	Severe (n=1180)
Fatal cases	39 (2)	204 (17)
Worst severity during hospitalisation		
No oxygen	1796 (82)	192 (16)
Oxygen	357 (16)	678 (58)
IMV/ECMO	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 tumour	66 (3)	79 (7)
Leukaemia	10 (1)	3 (0)
Lymphoma	16 (1)	9 (1)
Hypertension	292 (13)	331 (28)
Hyperlipidaemia	176 (8)	157 (13)
Treatments prior to COVID-19		
Use of steroid in 1 month	6 (0)	10 (1)
Chemotherapy in 3 months	32 (2)	24 (2)
Immunosuppressants** use in 3 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)
Diarrhoea	251 (12)	164 (16)

Continued

Table 1 Continued

	Nonsevere (n=2196)	Severe (n=1180)
Dysgeusia	494 (26)	113 (13)
Dysosmia	422 (23)	96 (12)

*Immunosupprenssants other than steroids.
BMI, body mass index; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation.

solid tumour (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 tumour, CRD, cerebrovascular disease, CVD, and renal disease or dialysis, with fatality rates ranging from 8.1% to 11.1%. Collectively, obesity, hypertension and hyperlipidaemia 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 online supplemental figures 12. 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, online 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 (online supplemental 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

Table 2 Factors associated with being 'severe' at the time of admission (univariate analysis)

	OR	95% CI	P value
Days between onset and admission	1.0	0.99 to 1.01	0.897
Age	1.04	1.04 to 1.05	<0.001
Male	1.85	1.59 to 2.16	<0.001
Comorbidities			
Cardiovascular disease	3.93	2.84 to 5.48	<0.001
Cerebrovascular disease	3.18	2.33 to 4.38	<0.001
Chronic respiratory disease	5.80	3.90 to 8.78	<0.001
Asthma	1.18	0.84 to 1.64	0.318
Liver disease	1.50	0.95 to 2.34	0.070
Diabetes	2.52	2.08 to 3.04	<0.001
Obesity diagnosed by physicians	1.67	1.22 to 2.29	0.001
Severe renal disease or dialysis	2.14	1.15 to 4.00	0.013
Solid tumour	2.32	1.63 to 3.29	<0.001
Leukaemia	0.56	0.10 to 2.17	0.562
Lymphoma	1.05	0.41 to 2.53	0.999
Hypertension	2.54	2.12 to 3.05	<0.001
Hyperlipidaemia	1.76	1.39 to 2.23	<0.001
Treatments prior to COVID-19			
Use of steroid in 1 month	3.12	1.02 to 10.47	0.032
Chemotherapy in 3 months	1.40	0.79 to 2.47	0.258
Immunosuppressants* use in 3 months	1.29	0.67 to 2.46	0.428

*Immunosupprenssants other than steroids.

Table 3 Factors associated with being 'severe' at the time of admission

	OR	95% CI	P value
Days between onset and admission	1	0.99 to 1.01	0.96
Age	1.04	1.03 to 1.04	<0.001
Male	2.09	1.76 to 2.48	<0.001
Comorbidities			
Cardiovascular disease	1.48	1.04 to 2.10	0.028
Cerebrovascular disease	1.33	0.95 to 1.85	0.097
Chronic respiratory disease	2.51	1.67 to 3.78	<0.001
Asthma	1.24	0.87 to 1.77	0.24
Liver disease	0.97	0.61 to 1.54	0.892
Diabetes	1.34	1.09 to 1.64	0.006
Obesity diagnosed by physicians	1.75	1.26 to 2.45	0.001
Severe renal disease or dialysis	1	0.54 to 1.88	0.991
Solid tumour	1.2	0.82 to 1.77	0.351
Leukaemia	0.34	0.08 to 1.39	0.132
Lymphoma	0.42	0.16 to 1.11	0.081
Hypertension	1.33	1.08 to 1.64	0.008
Hyperlipidaemia	0.91	0.70 to 1.19	0.49
Treatments prior to COVID-19			
Use of steroid in 1 month	1.65	0.52 to 5.22	0.394
Chemotherapy in 3 months	1.47	0.72 to 3.0	0.286
Immunosuppressants* use in 3 months	1.35	0.69 to 2.64	0.384

*Immunosupprenssants other than steroids.

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, while 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 hyperlipidaemia was relatively favourable. In contrast to our results, hypertension and obesity are reportedly related to an increased risk of severity and mortality.[22–25] A large cohort reported a trend similar to our results,[18] whereas other studies reported that obesity is being confounded by age and sex.[26 27] The presence of hypertension and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers act contrarily,[28–30] while ACE2 mediates the entry of SARS-CoV-2 into host cells[31 32]; thus, COVID-19 pathophysiology in hypertensive patients becomes intricate.

In accordance with previous studies, CVD, CRD, liver disease, diabetes, cerebrovascular disease, renal disease or dialysis and solid tumour were associated with fatality and worst severity. Two meta-analyses have reported common risk factors for worst severity during hospitalisation, which include diabetes, COPD, malignancy, CVD and cerebrovascular disease.[33 34] Other studies have also reported chronic liver disease and renal disease as risk factors.[35–37] 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.[38–40] Clinical and nonclinical 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.[40–43] Elevated blood glucose is also associated with mortality.[44] Although risk factors vary among studies, the comorbidities we identified are highly likely associated with fatality, backed up by clinical and nonclinical 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, hyperlipidaemia 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

Table 4 Characteristics of patients stratified by non-fatal/fatal cases and severity during hospitalisation

	Nonfatal (n=3129)	Fatal (n=243)	No oxygen (n=1988)	Oxgen (n=1035)	IMV/ECMO (n=353)
Fatal cases			6 (0)	137 (13)	100 (28)
Severity on admission					
Nonsevere	2155 (69)	39 (16)	1796 (90)	357 (35)	43 (12)
Severe	974 (31)	204 (84)	192 (10)	678 (66)	310 (88)
Worst severity during hospitalisation					
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 tumour	114 (4)	31 (13)	60 (3)	63 (6)	22 (6)
Leukaemia	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)
Hyperlipidaemia	305 (10)	26 (11)	148 (7)	124 (12)	61 (17)
Use of steroid in 1 month	10 (0)	5 (2)	4 (0)	8 (1)	4 (1)
Chemotherapy in 3 months	38 (1)	18 (7)	21 (1)	30 (3)	5 (1)
Immunosuppressants** use in 3 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)
Diarrhoea	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)

*Immunosupprenssants other than steroids.
IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation.

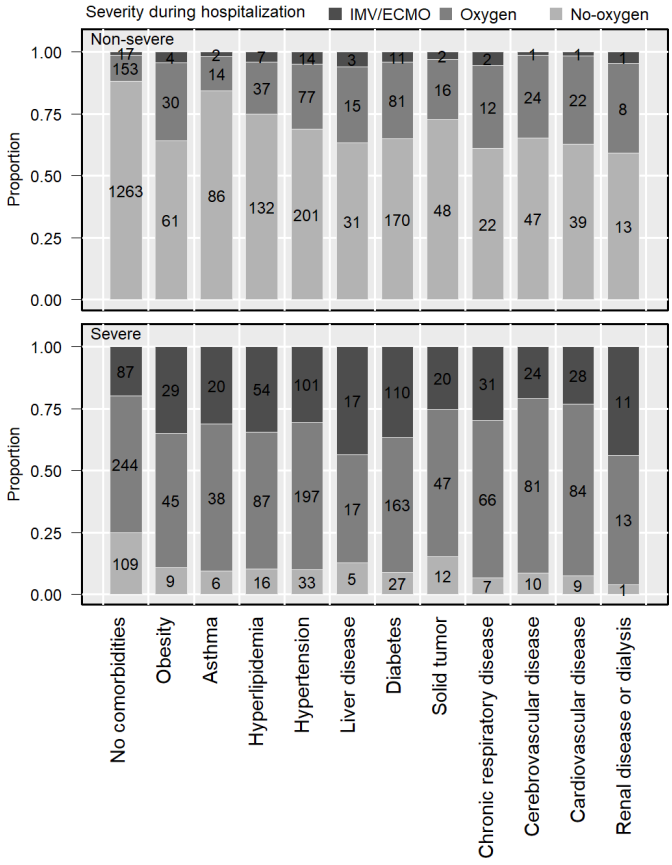

Figure 1 Distribution of the worst severity arranged by severe/nonsevere at admission and presence/absence of comorbidities. Top bars represent nonsevere cases at admission and bottom bars represent severe cases at admission. Each group of cases was divided based on the presence of comorbidities. Bars represent different categories of worst severity: light grey—no-oxygen, darker grey—oxygen and darkest grey—IMV/ECMO. IMV/ECMO, invasivemechanical ventilation/extracorporeal membrane oxygenation.

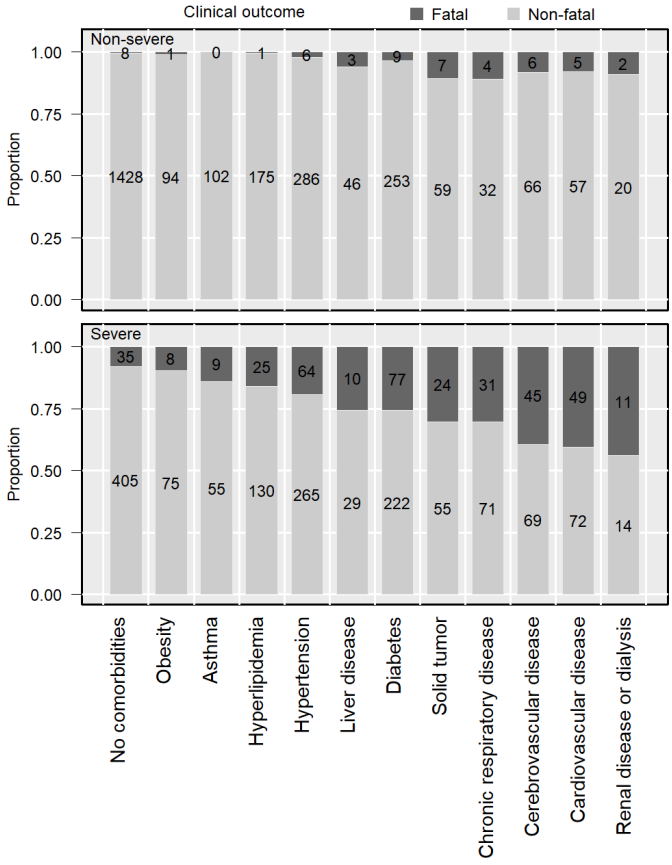

Figure 2 Distribution of the fatality arranged by severe/nonsevere at admission and presence/absence of comorbidities. Top bars represent nonsevere cases at admission and bottom bars represent severe cases at admission. Each group of cases was divided based on the presence of comorbidities. Dark grey represents fatal cases while light grey represents nonfatal cases.

dysfunction, tumour 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 tumour, 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,[45] and, thus, intubation may have been unperformed due to a medical judgement. A detailed examination of these issues is necessary in the future.

Our results did not show prominent difference in fatality between men and women. Oftentimes, men are considered to develop severe conditions and increased fatality.[36 37 46–48] However, according to Global Health 5050, sexual disparity in incidence of COVID-19 is low.[49] Additionally, ACE2 expression is affected by sexual hormones, whereby higher expression is observed in men, possibly explaining the sexual disparity.[50–52] Moreover, the immunological response to produce antibodies is more favourable in women.[53] These studies support the rationale that men 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 patients with asthma. A viral respiratory infection is presented as relatively worse and causes asthma exacerbation.[54 55] Asthmatic patients reportedly require a longer duration of mechanical ventilation when intubated[56]; however, no study, including ours, has found strong evidence on severity or mortality.[57–60] Inhaled corticosteroids (ICS) are known to downregulate ACE2[61 62] and are being investigated for treating COVID-19.[63] ICS may have impeded aggravation in patients with asthma with COVID-19.[64] 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 65] 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.[66]Second, 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 leucocyte antigen (HLA) proteins to SARS-CoV-2 virus peptides are less likely become severe or fatal,[67–70] and ethnic differences are present in HLA allele frequency.[71] A few strong binder alleles were more frequent in Northeast Asians; however, the complete picture is complicated. ACE1 polymorphism[72] and Neanderthal haplotype[73] 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.[74] Within the elderly population, higher rates of deficiencies were observed in North America and Europe compared with Japan.[75] 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.[76] Similar trend was observed in other countries.[77 78] 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 data set 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 were not a risk factor; early hospitalisation 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.[79–81] However, these use 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 nonsevere 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 categorisation of worst severity also differs from other definitions.[82 83] We did not adopt radiological criteria as lung infiltration rate was not collected in the registry where our data set was extracted. Ratio of arterial oxygen saturation or arterial partial oxygen pressure (PaO2) to the fraction of inspired oxygen (FiO2) was not used as data were available for limited number of cases. This fact may have caused differences in risk factors. We did not consider treatments prior to and during hospitalisation 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 are required before usage of these data; thus, we did not include them in the current analysis. Moreover, hotels were used 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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Competing interests HO reports personal fees as a statistician and as an external consultant for clinical trials from EPS International, outside the submitted work.

Patient consent for publication Obtained.

Ethics approval 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 (https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanbou kouseikagakuka/0000080278.pdf). 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 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000045453).

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