Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Predictors associated with clinical improvement of SARS-CoV-2 pneumonia

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ABSTRACT

Background: There are few agents that have been proven effective for COVID-19. Predicting clinical improvement as well as mortality or severity is very important.
Objectives: This study aimed to investigate the factors associated with the clinical improvement of COVID-19.
Methods: Overall, 74 patients receiving treatment for COVID-19 at Tokyo Medical and Dental University Hospital from April 6th to May 15th, 2020 were included in this study. Clinical improvement was evaluated, which defined as the decline of two levels on a six-point ordinal scale of clinical status or discharge alive from the hospital within 28 days after admission. The clinical courses were particularly investigated and the factors related to time to clinical improvement were analyzed with the log-rank test and the Cox proportional hazard model.
Results: Forty-nine patients required oxygen support during hospitalization, 22 patients required invasive mechanical ventilation, and 5 patients required extracorporeal membrane oxygenation. A total of 83% of cases reached clinical improvement. Longer period of time from onset to admission (≥10 days) (HR, 1.057; 95% CI, 1.002–1.114), no hypertension (HR, 2.077; 95% CI, 1.006–4.287), and low D-dimer levels (<1 μg/ml) (HR, 2.372; 95% CI, 1.229–4.576) were confirmed to be significant predictive factors for time to clinical improvement. Furthermore, a lower SARS-CoV-2 RNA copy number was also a predictive factor for clinical improvement.
Conclusions: Several predictors for the clinical improvement of COVID-19 pneumonia were identified. These results may be important for the management of COVID-19 pneumonia.

1. Introduction

A novel coronavirus disease (COVID-19) caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) infection has spread rapidly worldwide since it was first reported in December 2019 in Wuhan, China. While clinical trials of antiviral agents approved for other viruses [1–5], anti-inflammatory agents [6–8], plasma and

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antibody therapy [9–11], and vaccines [12] are ongoing [13,14], few agents have been confirmed to be effective so far, and empirical treatments are being performed practically.

A variety of clinical courses are shown in COVID-19. While some patients are discharged from the hospital within 10 days, severe cases prolong the treatment duration [15]. Several predictive factors for mortality and severity have been reported [6,15–20]. On the other hand, shortages of medical and human resources have become apparent in many regions of the world [21]. These findings suggest that evaluation of factors affecting clinical improvement is critical in the treatment of COVID-19.

Here, this study aimed to investigate the factors associated with the clinical improvement of COVID-19 with empiric treatments. In this manuscript, the detailed clinical behavior of COVID-19 was reported for the first time in Japan and the factors that affected the time to clinical improvement were analyzed. The findings should be important for predicting disease course.

2. Methods

2.1. Enrolled patients

Seventy-four patients who were treated for COVID-19 in Tokyo Medical and Dental University (TMDU) Hospital from April 6th to May 15th in 2020 were enrolled. These patients were retrospectively reviewed to assess the clinical course. This study was approved by the Institutional Review Board at TMDU hospital (M2020-027).

2.2. The definition of clinical improvement

Clinical improvement was defined as the decline of two levels on a six-point ordinal scale of clinical status or discharge alive from hospital within 28 days after admission, whichever came first [20,22]. The six-category scale was defined as follows according to previous reports [22,23], death = 6; hospital admission for extracorporeal membrane oxygenation or mechanical ventilation = 5; hospital admission for noninvasive ventilation or high-flow oxygen therapy = 4; hospital admission for oxygen therapy (not requiring high-flow or noninvasive ventilation) = 3; hospital admission not requiring oxygen therapy = 2; and discharged = 1.

2.3. Treatment agents

Treatments for COVID-19 with ciclesonide, favipiravir, hydroxychloroquine, nafamostat mesylate, tocilizumab, glucocorticoid, intravenous immunoglobulin (IVIG), heparin, and antibacterial drugs were chosen according to the guide issued by the Ministry of Health, Labor and Welfare in Japan and the National Institutes of Health. Non-insurance-approved drugs against COVID-19 were used only after obtaining approval from the Unapproved New Drug Evaluation Committee in TMDU.

2.4. Clinical course

The clinical courses of all patients with any degree of respiratory support were shown and the time from admission to clinical improvement were analyzed. The oxygen support for patients during hospitalization is displayed with several color bars in Fig. 1. The criteria for discharge were as follows: 1) patients with symptom improvement and with two consecutive negative virus tests by SARS-CoV-2 PCR were discharged to their home; 2) patients under the age of 65 who had no coexisting disorder (diabetes, heart disease, respiratory disease, or renal failure requiring dialysis), immunosuppression, pregnancy, or fever of more than 37.5° in the past 24 h and whose symptoms improved were discharged to a hotel and continued isolation.

2.5. Quantitative reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 on admission

RT–PCR used targets in the open reading flame 1a (ORF1a) and spike (S) of SARS-CoV-2 according to the guideline [24] from the National Institute of Infectious Diseases in Japan. Total RNA was extracted using an EZ1 Virus Mini Kit v2.0 (Qiagen, Tokyo, Japan) according to the manufacturer's instructions. RT-PCR was performed using a QuantiTect Probe RT-PCR Kit (Qiagen) and an N2 primer set.

2.6. Statistical analysis

Continuous and categorical variables are presented as the median (interquartile range [IQR]) and n (%), respectively. The time to clinical improvement were portrayed with a Kaplan-Meier plot and compared it with a log-rank test. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for clinical improvement. A multivariate analysis was performed to predict the clinical improvement. The cutoff values of age [16], neutrophil-to-lymphocyte ratio [25], and D-dimer [15], C-reactive protein (CRP) [26], and lactate dehydrogenase [17] levels, were identified according to previous reports. The cutoff values of white blood cell counts and procalcitonin levels were set at the upper limit of clinical laboratory values. The cut-off value of body mass index (BMI) was identified according definition of overweight by World Health Organization. The cutoff value of RNA copy number was identified following Youden's index of receiver operator characteristic (ROC) curve with a sensitivity of 77.8% and a specificity of 76.9% (Suppl. Fig. 1). For multivariable analysis, the total number was considered in this study to avoid overfitting in the models, and chosen 5 variables with a P-value of less than 0.05 and a low correlation coefficient with other factors in the univariate analysis. The Fisher's exact test was used to compare the rate of 6 − category scale on admission by separated by each predictor.

A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Result

3.1. Baseline characteristics of the patients on admission

Table 1 shows demographic clinical characteristics at baseline of the 74 patients. The median age was 56 yr (IQR, 43–70 yr), and 52 patients (70%) were men. The median body mass index (BMI) was 24 (IQR, 21–26). Forty-five percent had a history of smoking. Among the overall population, 39% had hypertension, 11% had diabetes, 12% had dyslipidemia, 9% had heart disease, 9% had asthma, and 7% had COPD. The median time from onset to admission was 10 days (IQR, 7.3–13.8 days). Laboratory data showed mild increases in CRP, lactate dehydrogenase, and D-dimer levels. On admission, the proportions of patients with six-category scale values of 2, 3, and 5 were 53%, 23%, and 24%, respectively.

3.2. Treatment options in TMDU hospital

Table 2 shows treatment experiences in TMDU hospital. A majority of the patients (74%) received ciclesonide. Fifty-one percent

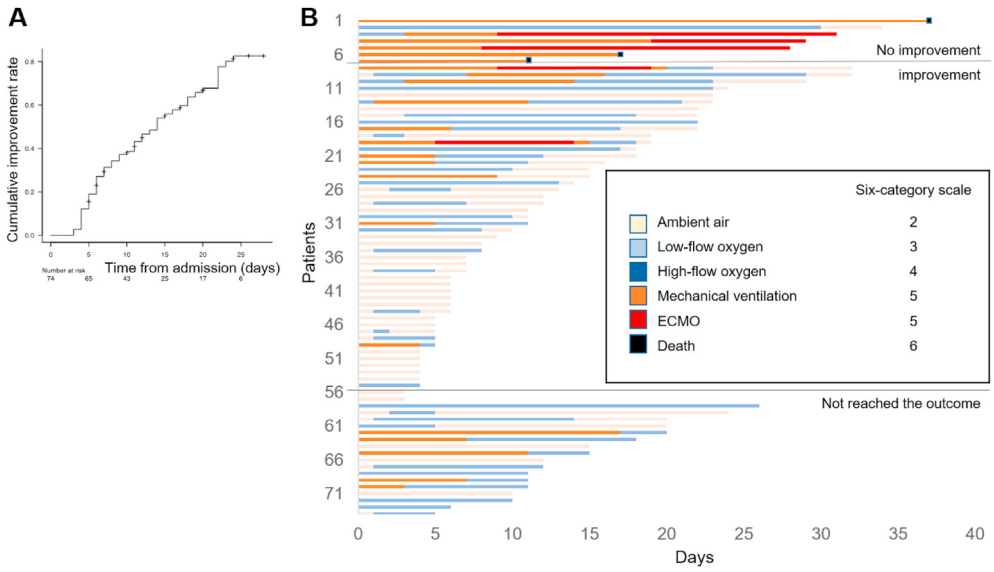

Fig. 1. Cumulative improvement rate and oxygen support during admission. (A) Kaplan-Meier plot showing the cumulative improvement rate since admission in all patients. (B) Changes in oxygen support status from admission in 74 patients. For each patient, the colors in the line represent the oxygen-support status and death of the patient over time.

Table 1
Baseline characteristics of patients.

	Total N = 74
Age, median (IQR) – yr	56 (43–70)
Sex	52 (70%)
Men	22 (30%)
Women	
BMI, median (IQR)	24 (21–26)
Smoking history never/ex/current	41/25/8
Any comorbidities	29 (39%)
Hypertension	8 (11%)
Diabetes	9 (12%)
Dyslipidemia	7 (9%)
Heart disease	7 (9%)
Asthma	5 (7%)
COPD	
Time from symptom onset to admission, median (IQR) - days	10 (6–28)
Laboratory data at admission	5750 (1650–7275)
WBC, median (IQR) -/μl	18 (12–67)
Lymphocytes, median (IQR) - %	22 (17–30)
Platelet, median (IQR) - 10,000/μl	5 (1–11)
CRP, median (IQR) - mg/dl	69 (53–84)
Creatinine, median (IQR) - μmol/l	303 (227–420)
LDH, median (IQR) - U/l	1.06 (0.38–2.45)
D-dimer, median (IQR) - μg/ml	0.07 (0.04–0.22)
Procalcitonin (IQR) – ng/ml	
Six-category scale on admission	39 (53%)
2—hospital admission, not requiring supplemental oxygen	17 (23%)
3—hospital admission, requiring supplemental oxygen	0 (0%)
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	18 (24%)
5—hospital admission, requiring extracorporeal membrane oxygenation or mechanical ventilation	

IQR, interquartile rang; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase.

received favipiravir, and 19% received hydroxychloroquine. Hydroxychloroquine was received in severe COVID-19 patients until the U.S. Food and Drug Administration (FDA) warned us of a potential serious heart risk [27]. Fourteen percent received nafamostat mesylate. Eighteen percent and 19% received tocilizumab and glucocorticoid, respectively, after maximum possible exclusion of infectious diseases other than COVID-19. One percent received IVIG, which was administered in a critical patient with poor response to glucocorticoid and tocilizumab. Thirty-five percent received heparin. Heparin was administered to all severe patients with mechanical ventilation and 6 mild patients, including 5 with overweight (BMI > 25) and 1 with low activities of daily living (ADL) transferred from another hospital. Oxygen support was required for 66%. Low-flow oxygen, mechanical ventilation and extracorporeal membrane oxygenation (ECMO) were required for 36%, 30%, and 7%, respectively. Six patients received renal replacement therapy, including 2 patients with maintenance dialysis.

Table 2
Treatment options in this population.

	Total N = 74
Receiving treatments	55 (74%)
Ciclesonide	38 (51%)
Favipiravir	14 (19%)
Hydroxychloroquine	10 (14%)
Nafamostat mesilate	13 (18%)
Tocilizumab	14 (19%)
Glucocorticoid	1 (1%)
Intravenous immunoglobulin	26 (35%)
Heparin	35 (48%)
Antibacterial drugs	
Oxygen support	49 (66%)
Low-flow oxygen	27 (36%)
Invasive mechanical ventilation	22 (30%)
Extracorporeal membrane oxygenation	5 (7%)
Renal replacement therapy	6 (8%)

3.3. Clinical courses

The median duration of hospital stay was 10 days (IQR: 6.3–20.0 days). The clinical improvement rate of all patients is shown in Fig. 1A. Eighty-three percent of patients achieved clinical improvement by day 28. Fig. 1B shows the details of the clinical courses and oxygen support for 74 individual patients. Patients who required mechanical ventilation and ECMO were predominant in groups with poor clinical improvement. Among all cases, 20 patients were discharged to their home, and 23 patients were discharged to hotels. Four patients were transferred to another hospital. Three patients died during the observation period. Pulmonary embolism was a complication in 4 cases.

3.4. The clinical variables associated with time to clinical improvement

The time to clinical improvement has been shown with dichotomy by cutoff values of each factor with univariate analysis using Cox regression and with the log-rank test (Table 3, Fig. 2, and Suppl. Fig. 2). In baseline characteristics, younger age (<60 yr) (hazard ratio [HR], 3.428; 95% CI, 1.787–6.576) and longer time from onset to admission (≥10 days) (HR, 1.933; 95% CI, 1.092–3.423) were significantly associated with earlier clinical improvement. However, “discharge alive from hospital within 28 days” was included as an indicator of clinical improvement in this study. In addition, the discharge to hotel criteria includes “patients under 65 years old without underlying disease”. These affect duration of hospital stay of young cases. Therefore, we performed the analysis excluding the cases discharged to the hotel. As a result, clinical improvement tended to be faster in cases younger than 60 years, but there was no statistically significant difference. Sex, body mass index, smoking, and body temperature were not significant factors. In comorbidities, no hypertension (HR, 2.493; 95% CI, 1.301–4.777) was significantly associated with early clinical improvement. None of the patients were treated with ACE inhibitors, and the presence or absence of antihypertensive drugs did not affect clinical improvement (Suppl. Fig. 3). Diabetes, dyslipidemia, heart disease, and bronchial asthma were not significant factors. In laboratory data, low D-dimer (<1 μg/ml) (HR, 3.107; 95% CI, 1.721–5.610) and low procalcitonin levels (<0.05 ng/ml) (HR, 2.310; 95% CI, 1.253–4.261) were significantly associated with early clinical improvement. White blood cell count, neutrophil-to-lymphocyte ratio, platelet count, CRP level, and lactate dehydrogenase level were not significant factors. The six – category scale for groups with longer period of time from onset to admission (≥10 days), low D-dimer levels (<1 μg/ml), and low procalcitonin (<0.05 ng/mL) were low (Suppl. Table 1).

Next, multivariate analysis using Cox regression including 5 factors (Table 3) with a p value < 0.05 were performed. Pearson's product moment correlation coefficient between predictive factors for clinical improvement is shown in Suppl. Table 2. Multivariate analysis demonstrated that younger age (<60 yr) (HR, 3.501; 95% confidence Interval [CI], 1.636–7.492), longer period of time from onset to admission (≥10 days) (HR, 1.057; 95% CI, 1.002–1.114), no hypertension (HR, 2.077; 95% CI, 1.006–4.287), and low D-dimer levels (<1 μg/ml) (HR, 2.372; 95% CI, 1.229–4.576) remained statistically significant. Of these, age (<60 yr) was a factor affected by the criteria for discharge to hotels. Therefore, age (<60 yr) was included in the variables of multivariate analysis as an adjustment factor rather than a predictive factor. In severe patients who required mechanical ventilation, category 5 on the 6-category scale, only shorter time from onset to admission was associated with early clinical improvement (Suppl. Fig. 4). Younger age, no hypertension, and lower D-dimer levels were not associated with clinical improvement.

3.5. SARS-CoV-2 RNA copy number on admission was also associated with clinical improvement

The SARS-CoV-2 RNA copy numbers of 49 patients with samples taken by nasopharyngeal swabs performed within 10 days of hospitalization were analyzed. The median copy number was 46,455 copies/swab (IQR, 5040–8,133,000 copies/swab). The distribution of viral load shows in Suppl. Fig. 5. Using Kaplan–Meier and Cox analysis, RNA copy number was significantly associated with early clinical improvement (HR, 2.075; 95% CI, 1.027–4.193) (Fig. 3). However, the discharge criteria included “two consecutive negative virus tests by SARS-CoV-2 PCR ". This accelerated the discharge of patients with low RNA copy number. Therefore, we performed the analysis excluding the cases discharged by two consecutive negative virus tests. As a result, RNA copy number was significantly associated with early clinical improvement (HR, 2.693; 95% CI, 1.087–6.673). RNA copy number was an independent factor for clinical improvement with low correlation with other factors (Suppl. Table 3).

4. Discussion

In this study, the clinical course of COVID-19 in Tokyo, Japan, which is the center of the outbreak in Japan were detailed. A total of 83% of patients improved, and only three patients died during hospitalization, while the proportion of severe cases requiring invasive mechanical ventilation was fairly high, at 30% in the cohort. From this population, several predictive factors for the clinical improvement of COVID-19 pneumonia were identified.

Several models have been proposed to predict mortality and severity [6,15–20,28]. However, time to clinical improvement is extremely useful information in the clinical setting of COVID-19 in the absence of standard treatment and shortages of medical care and human resources [29]. This study confirmed that longer time from onset to admission, no hypertension, and low D-dimer levels were significant factors related to earlier clinical improvement. And younger cases, excluding discharge to the hotel, tended to shorted time to clinical improvement. Older age, hypertension, and high D-dimer levels are also known predictive factors of mortality and severity [6,15,16,18,19,30]. Lower D-dimer levels were associated with time to clinical improvement in this study, which was consistent with previous reports that COVID-19 caused abnormal coagulation and thrombosis [15,31–36]. The updated NIH guidelines also recommended caution and treatment for complications

Table 3
Univariate and multivariate analysis, using cox regression for relating to time to clinical improvement.

	HR	95% CI	P value
Univariate analysis			
Baseline characteristics			
Age (<60 yr)	3.428	1.787–6.576	**<0.001**
Age (<60 yr), excluding the cases discharged to the hotel	2.158	0.966–4.819	0.061
Sex, Female	1.365	0.752–2.478	0.287
Body mass index	1.768	0.858–3.643	0.110
Smoking	1.878	0.917–3.848	0.073
Never vs Ex	1.034	0.414–2.580	0.940
Never vs Current			
Body temperature (°C)	1.670	0.870–3.208	0.107
Time from onset to admission (≥10 days)	1.933	1.092–3.423	**0.017**
Comorbidities			
No hypertension	2.493	1.301–4.777	**0.003**
No diabetes	1.568	0.699–3.519	0.256
No dyslipidemia	1.768	0.691–4.489	0.209
No heart disease	1.247	0.449–3.468	0.661
No asthma	0.966	0.381–2.450	0.939
Laboratory data			
White blood cell (<8600/μl)	1.018	0.477–2.174	0.961
Neutrophil − to − lymphocyte ratio	1.627	0.927–2.857	0.077
Platelet (≥150.000/μl)	1.546	0.724–3.304	0.241
D-dimer (<1 μg/ml)	3.107	1.721–5.610	< **0.001**
C-reactive protein (<4.2 mg/dl)	1.503	0.858–2.636	0.138
Lactate dehydrogenase (<365 IU/l)	1.792	1.253–4.261	0.055
Procalcitonin (<0.05 ng/ml)	2.310	1.253–4.261	**0.004**
Multivariate analysis			
Age (<60 yr)	3.501	1.636–7.492	**0.001**
No hypertension	2.077	1.006–4.287	**0.048**
Time from onset to admission (≥10 days)	1.057	1.002–1.114	**0.031**
Procalcitonin (<0.05 ng/ml)	1.299	0.652–2.589	0.053
D-dimer (<1 μg/ml)	2.372	1.229–4.576	**0.007**

HR, hazard ratio; CI, Confidence Interval.

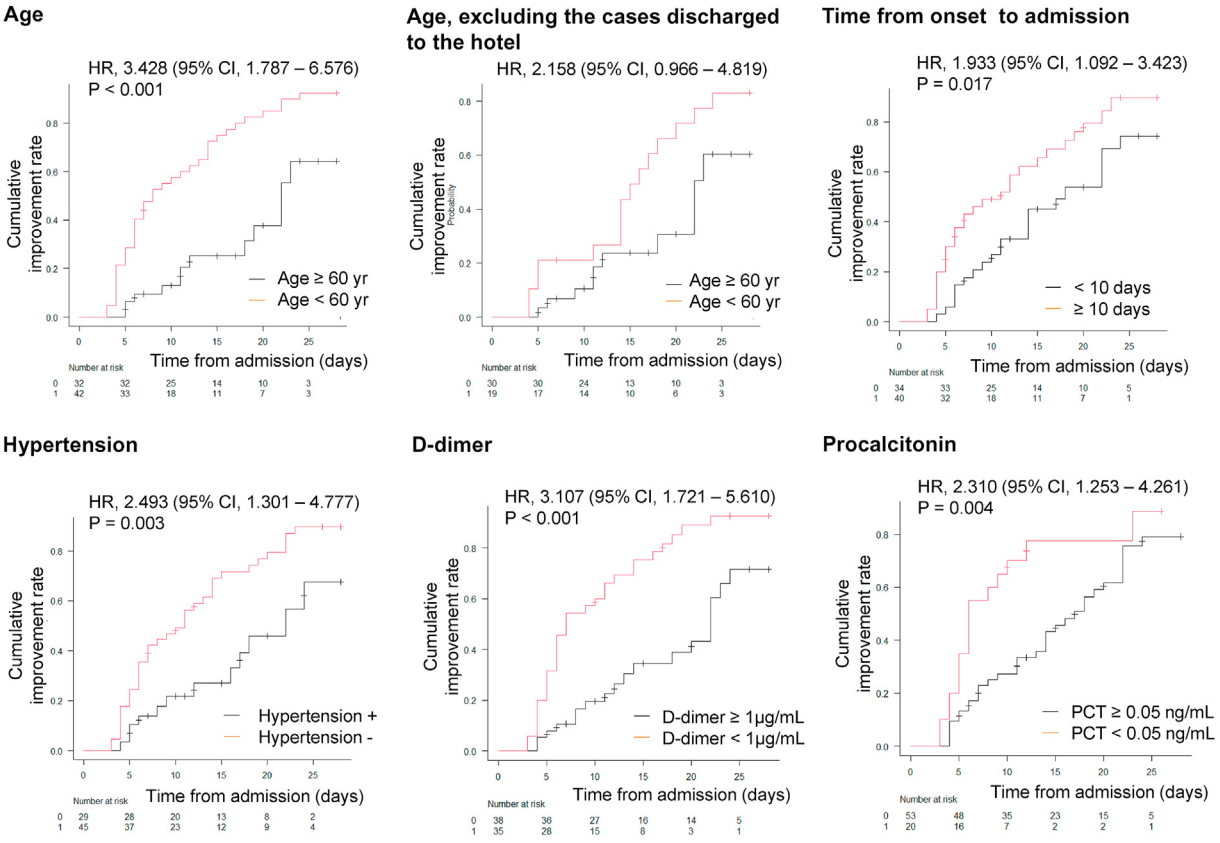

Fig. 2. The associations between clinical variables and time to clinical improvement. Kaplan-Meier plot showing the cumulative improvement rate since admission in each group by baseline characteristics, comorbidities and, laboratory data.

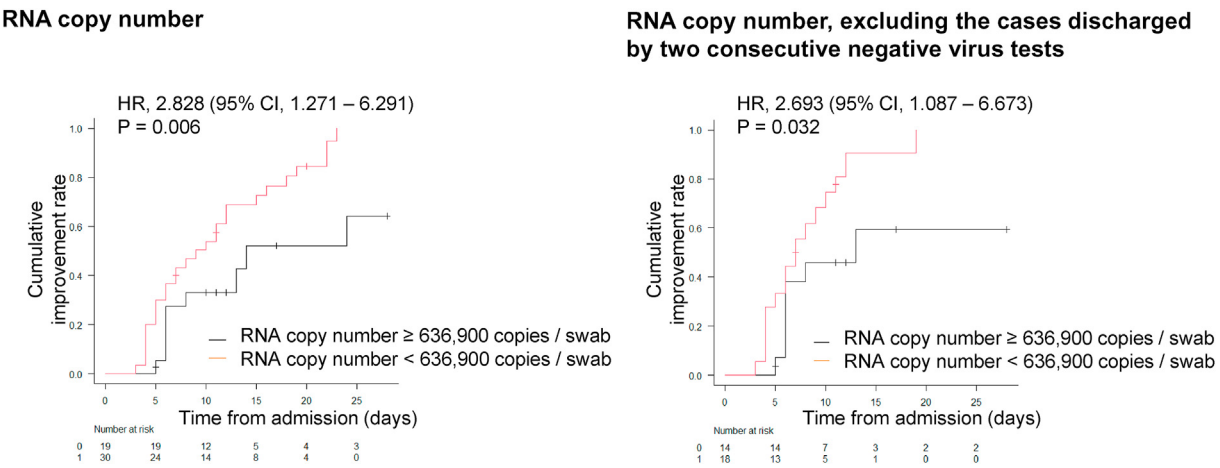

Fig. 3. Cumulative improvement rate in each group by RNA copy number. Kaplan-Meier plot showing the cumulative improvement rate since admission in each group by RNA copy number. Forty-nine patients who underwent SARS-CoV-2 PCR within 10 days after hospitalization were included.

of thrombosis. In this study, heparin was administered to patients with embolism or at high risk of thrombosis (with mechanical ventilation, overweight, or low ADL). A longer time from onset to admission was a significant predictor for clinical improvement in all cases and even in severe cases (Suppl. Fig. 4). Some severe cases take a long time from onset to admission. Previous reports showed no difference in the time from onset to admission between survivors and non-survivors between [15]. On the other hand, another report showed that the time from onset to admission in the critical group was shorter than in the mild and severe groups [37]. In our study, the group with shorter period of time from onset to admission (<10 days) had already had poor respiratory status at admission. In addition, all deaths were included in the group with shorter period of time from onset to admission (<10 days). These suggested that the group with a shorter time from onset to admission (<10 days) progressed quickly and was refractory to treatment.

In this study, a higher RNA copy number was a predictive factor for a longer time to clinical improvement. This result is consistent with a previous report showing that the ΔCt values of severe cases remained significantly lower for the first 12 days after onset than those of corresponding mild cases [36]. SARS-CoV-2 RNA copy number was reported to peak 4 days after onset [38]. PCR was purportedly performed after peak virus shedding in mild cases. This finding is also consistent with the result that a longer time from onset to admission predicts a longer time to clinical improvement. These findings suggest that patients with higher viral copy numbers and shorter time from onset to admission need to be managed more carefully. Measurement of SARS-CoV-2 RNA copy number can predict the clinical improvement of COVID-19 and provide better care in each region of the world where viral epidemics with different genomic variants are prevalent [39,40].

The limitations of this study are as follows. First, this study was a single-institution retrospective study with a small sample size. In a previous report, many bias interventions had been pointed out in the COVID-19 diagnosis and prognosis prediction models [19], and more accurate data will be required in the future. Second, most treatments for COVID-19 were based on empirical experience. Remdesivir [2–4], which was approved with emergency authorization by the U.S. Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan as a treatment for COVID-19, was not used in this study. Furthermore, this study is not large enough to prove the efficacy and safety of each agent.

Findings identified that real-world COVID-19 clinical information in Japan were shown and several factors, including age, hypertension, D-dimer level, time to admission, and SARS-CoV-2 RNA copy number, predicted time to improvement of COVID-19 pneumonia were identified. These results are beneficial in the management of COVID-19 pneumonia. More detailed elucidation of disease states and more effective treatment methods are desired.

Authorship

All authors meet the ICMJE authorship criteria. TM and TO designed this study. TM wrote the first draft of this manuscript. TM, TO, TS, YI, RS, TH, MI, JA, and TT provided medical care to the patients. MT, HS, HA, YO, ST, TA, KT, and SY developed the trial design. YM was the chief investigator and responsible for the data analysis. All authors commented on the manuscript and approved the final version.

Declaration of competing interest

YM received funding from Chugai Pharmaceutical Co. Ltd. SY received research grant/speakers fee from Chugai Pharmaceutical Co. Ltd. None of the other co-authors have any conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.02.012.

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