

Original article

Clinical outcomes of coronavirus disease 2019 and seasonal influenza in patients with hematological disorders: a retrospective study

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Abstract

Objective: The differences in clinical outcomes in hospitalized patients with hematological disorders (HD) who developed either coronavirus disease 2019 (COVID-19) or seasonal influenza (SI) are not fully understood. To examine these differences, we retrospectively analyzed the baseline characteristics and clinical outcomes of hospitalized patients with HD admitted from 2016 to 2021.

Patients and Methods: Patients with HD who developed COVID-19 (in the past 1 year) (n=21) or SI (in the past 5 years) (n=23) in the Department of Hematology/Oncology, Asahikawa Kosei General Hospital were evaluated.

Results: The median ages of the patients with HD with either COVID-19 or SI were 80 and 68 years, respectively ($P=0.03$). The groups showed no significant differences in sex ratio, body mass index, or Eastern Cooperative Oncology Group performance status. In the COVID-19 and SI groups, the most common primary diseases were diffuse large B-cell lymphoma (43%) and multiple myeloma (39%), respectively. The median numbers of days of oxygen administration (8 vs. 0 days), quarantine (25 vs. 6 days), and hospitalization (72 vs. 21 days) were significantly higher in HD patients with COVID-19 than those in HD patients with SI (all $P<0.001$). The overall 90-day survival of patients with HD and COVID-19 was significantly shorter than that of patients with HD and SI ($P=0.019$). Moreover, patients with HD and COVID-19 had a higher risk of in-hospital mortality (43% vs. 9%; odds ratio, 7.50; 95% confidence interval, 1.26–82.4; $P=0.01$) compared to patients with HD and SI.

Conclusion: Patients with HD and COVID-19 required longer periods of in-hospital medical and showed poorer survival than those with SI. During the COVID-19 pandemic, hematologists should closely monitor the condition of patients with COVID-19 to closely monitor their condition to prevent deaths.

Key words: coronavirus disease 2019, seasonal influenza, hematological disorder, nosocomial infection, patient outcome

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Introduction

Coronavirus disease 2019 (COVID-19) which first emerged in Wuhan, China, in December 2019, has spread worldwide, including Japan¹. Since then, the COVID-19 pandemic has negatively impacted routine medical practice.

Seasonal influenza (SI) is a medical concern, especially

during the winter season. In 2020, when the COVID-19 epidemic raged, a few SI outbreaks were recorded. In the Northern Hemisphere, more SI outbreaks were reported in October 2021 than in the previous year². These two respiratory infections are concerning because of their severity in immunocompromised patients. The clinical presentations of COVID-19, such as fever, cough, and malaise, are similar to those of SI; however, their clinical outcomes differ. Patients with hematological malignancies (HMs), who are typically immunocompromised, such as those with leukemia or who have received allogeneic or autologous hematological stem cell transplantation, can develop serious SI infections^{3–5}. In addition, adult COVID-19 patients with HMs have a high risk of mortality⁶.

Several studies comparing both infections in the general population revealed that COVID-19 was more likely to progress to severe disease than SI^{7–10} and that COVID-19 patients tended to have longer periods of hospitalization^{8, 10}

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and increased in-hospital mortality^{7–9}). Although Modemann *et al.*¹⁰ recently reported a comparative analysis of COVID-19 or SI in patients with HM in Germany, the differences in clinical outcomes in patients with hematological disorders (HDs) who developed either COVID-19 or SI in Japan remain to be elucidated.

The third wave of the COVID-19 pandemic in Hokkaido Prefecture began in October 2020 and generated an extensive burden on the regional medical care facilities in the Asahikawa area. We encountered COVID-19 outbreaks among HD and non-HD inpatients at our hospital during the winter season (from 2020 to 2021). Based on this experience, this study elucidated the differences in the clinical outcomes of patients with HD who developed one of these two viral infections by comparing their baseline characteristics and clinical outcomes such as duration of oxygen administration or hospitalization, survival, and mortality.

Patients and Methods

Study design and patients

This retrospective study investigated the clinical backgrounds and outcomes of patients with HD with confirmed COVID-19 or SI. We reviewed HD in inpatients who were confirmed as COVID-19-positive in the Department of Hematology/Oncology, Asahikawa Kosei General Hospital from November 2020 to January 2021, when a COVID-19 outbreak occurred in our hospital. All COVID-19 cases reported in our department were confirmed during the aforementioned period. We also collected data from HD patients with SI who were hospitalized or admitted to our department between January 2016 and January 2021. This study was approved by our institutional ethics committee (approval number 2020059) and conducted in accordance with the 1975 Declaration of Helsinki. The requirement for informed consent was waived owing to the retrospective design of the study.

Definitions and data collection

COVID-19 patients were defined as persons confirmed to be positive for the presence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by reverse-transcriptase polymerase chain reaction (RT-PCR). COVID-19 patients were also hospitalized for at least 24 hours with one or more systemic symptoms (e.g., fever, cough, rhinorrhea, sore throat, malaise, dysosmia, and dysgeusia) or if they had come into close contact with a person diagnosed with COVID-19. Patients with SI were defined as those who tested positive by influenza antigen rapid detection kit (Imunoace flu®; TAUNS, Shizuoka, Japan) and had at least one clinical symptom, including fever, malaise, headache, and cough, on admission or during hospitalization.

The COVID-19 quarantine regulations, based on the dis-

charge criteria of the Ministry of Health, Labor, and Welfare¹², were as follows: 1) at least 10 days from the onset of symptoms and 72 h after the relief from symptoms, or 2) confirmation by two consecutive negative RT-PCR SARS-CoV-2 test results performed at least 24 h apart, after 24 h of relief from symptoms. Based on our institutional infection control manual, the discharge criteria for quarantined SI patients were as follows: 1) more than 5 days after symptom onset and 2) fever resolution for 2 days.

The clinical data of all patients were retrospectively collected from their medical records. The collected clinical data included patient background such as age, body mass index (BMI, weight in kilograms divided by the square of the height in meters), Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary disease type or status, treatment histories for HD, comorbidities, symptoms or laboratory data at the onset of COVID-19 or SI, use of antiviral drugs, and outcome indicators such as the duration of oxygen administration, quarantine, hospitalization, and mortality or survival.

Statistical analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics¹³. Mann–Whitney *U* and Fisher's exact tests were performed for the comparisons of continuous and categorical variables, respectively, between the two groups. Overall survival (OS) from the onset of COVID-19 or SI was estimated using the Kaplan–Meier method. Univariate analyses were performed. $P < 0.05$ and 95% confidence intervals (CIs) of the odds ratios (ORs) that did not cross 1 were considered statistically significant for all analyses.

Results

Cases of COVID-19 or SI

This study included 21 COVID-19 cases out of patients with 23 HD and 23 patients with HD who developed SI during hospitalization or who had been admitted to our department over the past 5 years. The median follow-up days (range) of patients with COVID-19 or SI were 79 (5–108) and 376 (0–1,504), respectively. Of the 23 patients with SI, 20 and 3 were positive for influenza A and influenza B, respectively. There were no cases of coinfection with COVID-19 or SI. All patients with HD with COVID-19 were diagnosed during hospitalization and none of the patients were vaccinated. Of the 23 patients with SI, 11 (48%) were diagnosed with SI either on the same day of admission or 3 days after admission, whereas 12 (52%) were diagnosed 4

days after admission. The distribution of the influenza cases over the past 5 years was five, seven, five, four, and two cases in 2016, 2017, 2018, 2019, and 2020, respectively. The exact numbers of patients who were vaccinated against influenza could not be determined from medical records.

Baseline characteristics of patients with HD and COVID-19 or SI

Table 1 shows the backgrounds of the patients in both groups. The median ages of patients with HD with COVID-19 or SI were 80 and 68 years, respectively ($P=0.03$). In the COVID-19 and SI groups, the most common primary diseases were diffuse large B-cell lymphoma (9/21, 43%) and multiple myeloma (9/23, 39%), respectively. The sex ratio, BMI, and ECOG PS did not differ significantly between

the groups. Patients with SI experienced cardiovascular disease more frequently compared to those with COVID-19 (43% vs. 10%, $P=0.02$).

Table 2 shows the baseline symptoms and in-hospital laboratory data associated with both diseases. Fever (86% and 100% in the COVID-19 and SI groups, respectively) and cough (24% and 30%, respectively) were the two most common symptoms, followed by dyspnea and dysgeusia (COVID-19 group) and malaise and sputum production (SI group). Laboratory data at the onset of both infections revealed hypoalbuminemia and pancytopenia. The other laboratory data did not differ significantly between the groups.

Table 1 Baseline characteristics of patients with hematological disorders who developed coronavirus disease (COVID-19) or seasonal influenza

	COVID-19 (n=21)	Influenza (n=23)	P-value
Age, median [range]	80 (50–93)	68 (46–93)	0.03
Sex (%)			1
Male	10 (48)	12 (52)	
Female	11 (52)	11 (48)	
Body mass index, median [range]	21.2 (16.2–30.1)	21.8 (15.2–34.8)	0.64
ECOG PS, median [range]	2 (1–4)	1 (1–4)	0.07
Primary disease (%)			
Benign disease			
Autoimmune hemolytic anemia	0 (0)	3 (13)	
Idiopathic thrombocytopenic purpura	1 (5)	0 (0)	
Vitamin B12 deficiency anemia	1 (5)	1 (4)	
Hematological malignancy			
Acute lymphocytic leukemia	0 (0)	1 (4)	
Acute myelogenous leukemia	2 (10)	0 (0)	
Acute promyelocytic leukemia	1 (5)	0 (0)	
Chronic lymphocytic lymphoma	0 (0)	1 (4)	
Diffuse large B-cell lymphoma	9 (43)	4 (17)	
Essential thrombocythemia	1 (5)	0 (0)	
Follicular lymphoma	0 (0)	1 (4)	
Hodgkin's lymphoma	1 (5)	0 (0)	
Mucosa-associated lymphoid tissue lymphoma	1 (5)	0 (0)	
Myelodysplastic syndrome	1 (5)	3 (13)	
Multiple myeloma	2 (10)	9 (39)	
Waldenström macroglobulinemia	1 (5)	0 (0)	
Comorbidity (%)			
Hypertension	12 (52)	19 (83)	0.1
Diabetes mellitus	6 (29)	7 (30)	1
Dyslipidemia	4 (19)	3 (13)	0.69
Cardiovascular disease*	2 (10)	10 (43)	0.02
Chronic kidney disease	3 (14)	5 (22)	0.7

Data are presented as number, % or median. Bold text indicates a statistically significant difference with a P -value <0.05 . N: sample size; ECOG PS: Eastern Cooperative Oncology Group Performance Status. *Cardiovascular disease includes chronic heart failure, old myocardial infarction, arteriosclerosis obliterans, angina, valvular disease, and arrhythmia.

Table 2 Clinical symptoms and in-hospital laboratory data associated with coronavirus disease (COVID-19) or seasonal influenza

	COVID-19 (n=21)	Influenza (n=23)	P-value
Symptoms at onset (%)			
Fever	18 (86)	23 (100)	0.1
Cough	5 (24)	7 (30)	0.74
Sputum	0 (0)	3 (13)	0.23
Nasal discharge	1 (5)	2 (9)	1
Sore throat	2 (10)	3 (13)	1
Malaise	1 (5)	6 (26)	0.1
Dyspnea	3 (14)	1 (4)	0.33
Dysgeusia	3 (14)	0 (0)	0.1
Gastrointestinal symptoms	2 (10)	1 (4)	0.6
Laboratory data (range)			
White blood cell counts (/μL)	3,300 (1,500–45,000)	4,300 (200–15,200)	0.36
Neutrophil counts (/μL)	2,082 (783–40,050)	2,496 (20–12,540)	0.34
Lymphocyte counts (/μL)	756 (255–2,836)	594 (36–5,375)	0.35
Hemoglobin (g/dL)	9.2 (5.3–15)	9.5 (4.2–13)	0.91
Platelet counts (×10 ³ /μL)	71 (14–829)	99 (10–288)	0.9
Albumin (g/dL)	3.2 (2.1–4.1)	3.5 (2.4–4.2)	0.07
Lactate dehydrogenase (U/L)	205 (87–2,815)	198 (105–1,594)	0.58
Creatinine (g/dL)	0.73 (0.38–2.22)	0.8 (0.44–1.57)	0.15
C-reactive protein (g/dL)	1.18 (0.04–20.99)	4.61 (0.05–16.82)	0.05

Data are presented as number, % or median. *P*-value <0.05 was considered statistically significant. n: sample size.

Table 3 Treatment history and disease status of patients with hematological malignancies who developed coronavirus disease (COVID-19) and seasonal influenza

	COVID-19 (n=19)	Influenza (n=19)	P-value
Any chemotherapies within 3 months prior to COVID-19 or SI onset (%)			
Yes	14 (74)	15 (79)	1
No	5 (26)	4 (21)	
Use of rituximab within 3 months prior to COVID-19 or SI onset (%)			
Yes	7 (37)	4 (21)	0.48
No	12 (63)	15 (79)	
Number of regimens for hematological malignancies (%)			
0–1	13 (68)	5 (26)	0.02
>1	6 (32)	14 (74)	
Complete remission of hematological malignancies (%)			
CR	3 (16)	1 (5)	0.6
non-CR	16 (84)	18 (95)	

Data are presented as number, % or median. Bold text indicates a statistically significant difference with a *P*-value <0.05. n: sample size; SI: seasonal influenza; CR: complete remission.

Treatment history and disease status of patients with HM and COVID-19 or SI

Although the patients in this study had various primary HDs, most (19/21 with COVID-19 and 19/23 with SI) had HM. Therefore, we focused only on patients with HMs and examined the treatment histories and disease status of HM between the two groups. As shown in Table 3, >80% of patients in both groups did not achieve complete remission.

The numbers of patients treated with chemotherapy or rituximab within 3 months did not differ significantly between the groups. However, significantly more patients with HM with a history of treatment with two or more regimens developed SI compared to those who developed COVID-19 (74% vs. 32%, *P*=0.02).

Treatments for patients with HD and COVID-19 or SI

According to the treatment strategies for COVID-19 based on the Ministry of Health, Labor, and Welfare's discharge criteria¹²⁾, we administered antiviral drugs (favipiravir, 17 cases; and remdesivir, one case) to patients with COVID-19 with pneumonia or hypoxemia (<93% oxygen saturation) who consented to the use of these drugs. In accordance with the recommendations of the Japanese Society of Infectious Diseases¹⁴⁾, all 23 patients with SI were promptly administered antiviral drugs (oseltamivir, five cases; laninamivir, three cases; and peramivir, 15 cases).

In-hospital clinical parameters associated with COVID-19 or SI

Several in-hospital clinical parameters associated with the treatment of patients with COVID-19 or SI are shown in Figure 1. The median duration of oxygen administration and the duration from symptom onset to the start of oxygen administration in the COVID-19 group were significantly longer than those in the SI group (8 vs. 0 days; 6 vs. 0 days;

$P=0.00005$ and $P=0.00011$, respectively) (Figure 1a, 1b). The median quarantine period of patients with COVID-19 was also significantly longer than that of patients with SI (25 vs. 6 days; $P=0.0000008$; Figure 1c). The median duration of hospitalization for patients with COVID-19 was significantly longer than that for patients with SI (72 vs. 21 days; $P=0.0003$; Figure 1d).

Clinical outcomes of patients with COVID-19 and SI

The number of patients requiring oxygen administration was higher in the COVID-19 group than in the SI group (81% vs. 26%; OR, 0.09; 95% CI, 0.02–0.41; $P=0.0004$), while there was no difference in intensive care unit (ICU) use between the groups (N=1 [5%] vs. N=2 [9%]; $P=1$) (Table 4). Although seven patients with COVID-19 clinically required ICU admission or were dependent on mechanical ventilation, six eventually died of COVID-19 pneumonia without mechanical ventilation or treatment in the ICU, based on the decision of the patients or their families. The number of patients discharged was significantly lower in the

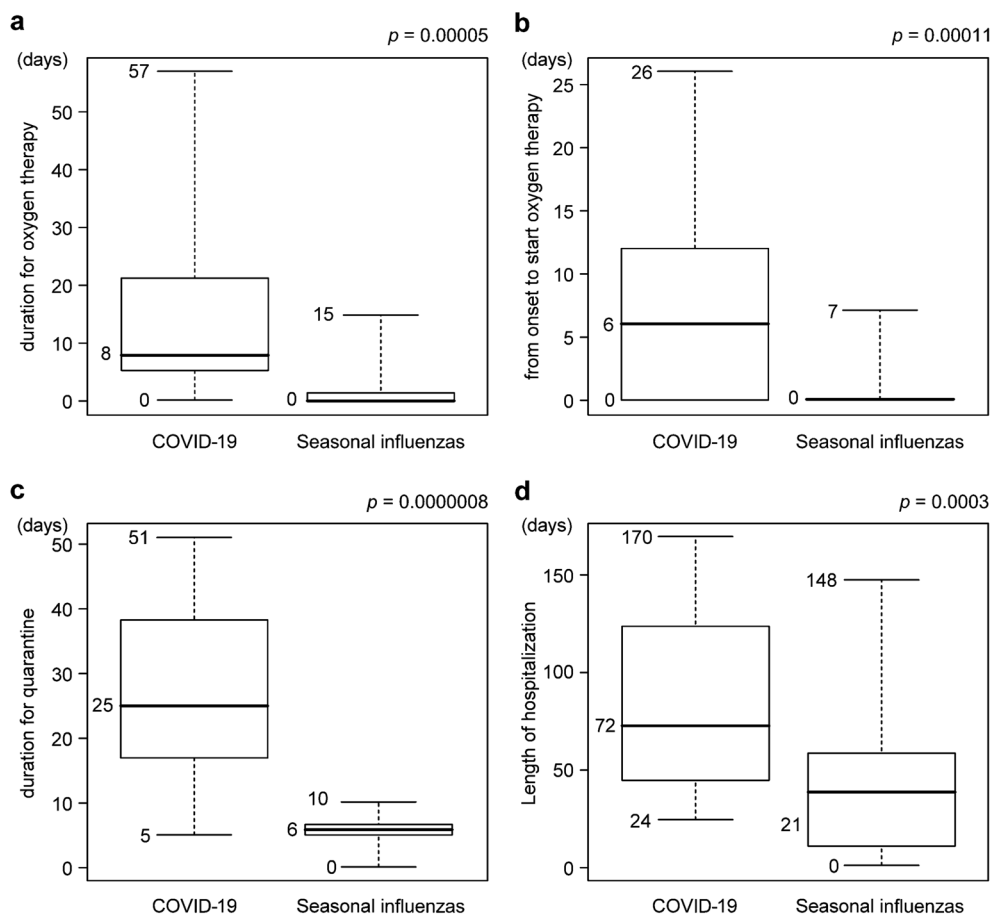


Figure 1 Duration of oxygen administration overall (a), from onset to start of oxygen administration (b), quarantine (c), and length of hospitalization (d) in patients with coronavirus disease (COVID-19) and seasonal influenza. The box plots show the medians and interquartile ranges (IQRs).

Table 4 Clinical outcomes of patients with coronavirus disease (COVID-19) and seasonal influenza

	COVID-19 (n=21)	Influenza (n=23)	P-value	OR [95%CI]
Use of oxygen therapy (%)			0.0004	0.09 [0.02–0.41]
Yes	17 (81)	6 (26)		
No	4 (19)	17 (74)		
Intensive care unit therapy (%)			1	1.88 [0.09–117.8]
Yes	1 (5)	2 (9)		
No	20 (95)	21 (91)		
Outcomes (%)				
Discharge	8 (38)	20 (87)	0.001	0.1 [0.01–0.49]
Hospitalization	2 (10)	0 (0)	0.22	Inf [0.21–Inf]
Changing hospital	2 (10)	1 (4)	0.6	2.27 [0.11–142.6]
Death in hospital	9 (43)	2 (9)	0.01	7.5 [1.26–82.4]

Data are presented as number, % or median. Bold text indicates a statistically significant difference with a P-value <0.05. n: sample size; OR: odds ratio; CI: confidence interval; Inf: infinity.

COVID-19 group than that in the SI group [38% vs. 87%; OR, 0.1; 95% CI, 0.01–0.49; P=0.001]. Moreover, inpatient mortality was significantly higher in patients with HD and COVID-19 than in those with SI (43% vs. 9%; OR, 7.50; 95% CI, 1.26–82.4; P=0.01) (Table 4). Similarly, the 90-day OS after symptom onset in patients with HD and COVID-19 was significantly shorter than that in patients with HD and SI (P=0.019) (Figure 2).

Discussion

The result of our study of hospitalized patients with HD demonstrated significantly higher numbers of days of oxygen administration, quarantine, and hospitalization in patients with COVID-19 compared to those in patients with SI. Moreover, patients with COVID-19 had lower 90-day survival and were at a higher risk for in-hospital mortality compared to those with SI.

Several reports have compared patient backgrounds and outcomes between COVID-19 and SI in the general population^{7–10, 15}). However, to our knowledge, no comprehensive comparative study of COVID-19 and influenza infections in patients with HD has been conducted in Japan. Thus, this is the first study in Japan to report the clinical outcomes of patients with HD who developed either COVID-19 or SI.

Several studies comparing both infections in the general population have shown that patients with COVID-19 tend to have longer periods of hospitalization^{8, 10}) and increased in-hospital mortality^{7–9}). While our findings were limited to patients with HD, they showed trends similar to those in the general population.

Recently, Modemann *et al.*¹¹) compared the prognosis of COVID-19 and SI in patients with HD in Germany. They reported virus-associated 90-day mortalities of patients with COVID-19 (n=29) and SI (n=50) in a single institute of 41%

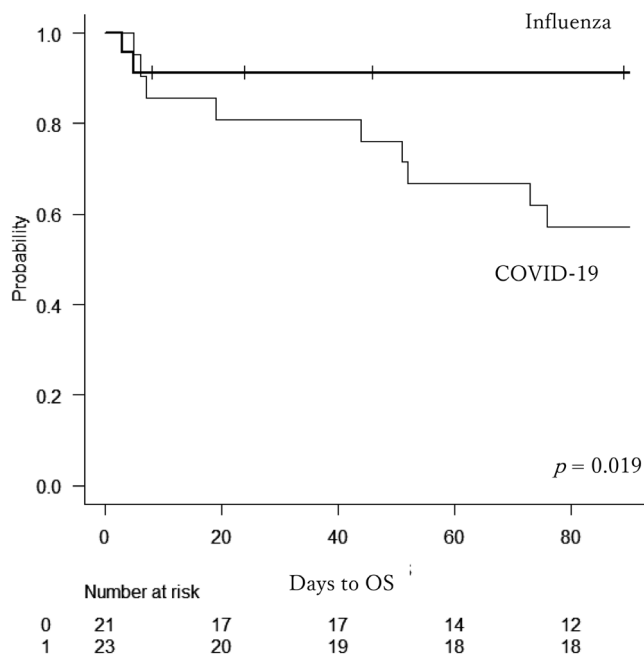


Figure 2 Overall survival from the onset of coronavirus disease (COVID-19) or seasonal influenza in patients with hematological disorders.

Overall survival after patients were diagnosed with COVID-19 or seasonal influenza during hospitalization in our department. The survival data were cut off on March 2021 in the COVID-19 group and on day 90 from the onset of SI in the seasonal influenza group to match the follow-up periods of patients with COVID-19.

and 12%, respectively. This finding was comparable to that of our study (in-hospital deaths: 43% and 9%, respectively, as shown in Table 4). In addition, a large cohort study of patients with COVID-19 (n=3,641) and SI (n=12,676) in the general population demonstrated relatively low mortality

rates (8.6% vs. 5.3%, respectively)¹⁰. These results suggested that HD may be associated with higher mortality rates due to COVID-19 or SI compared to the general population, even in different races and medical environments.

In addition, our patients with COVID-19 required a higher frequency and longer duration of oxygen administration, along with longer quarantine periods, than patients with SI. These results suggested that patients with COVID-19 not only faced longer periods of distress but also required more medical care by health care professionals compared to patients with SI.

We previously reported that a history of multiple chemotherapeutic regimens was a significant risk factor for the severity of nosocomial COVID-19 in patients with HM⁶. In the present study, a significantly higher number of patients in the SI group had received two or more chemotherapy regimens during disease onset compared to the COVID-19 group. Furthermore, patients with SI had a higher prevalence of cardiovascular disease compared to those with COVID-19. Despite this background, patients with HD and SI had significantly lower in-hospital mortality rates (9% vs. 43%; $P=0.01$) compared to those with COVID-19. There are two clinical explanations for these differences in virological characteristics. First, there are no highly effective medications for the prevention of COVID-19, such as peramivir, oseltamivir, and laninamivir. Second, COVID-19 vaccination was not performed in this study population. Moreover, the median age of patients with COVID-19 (80 years) in this study was significantly higher than that of patients with SI (68 years). Physicians may need to focus their attention on HD patients of all ages until there is a specific medication or sufficient vaccination against COVID-19.

In the current study, significantly more patients with HM had a history of treatment with two or more regimens developed SI compared to those who developed COVID-19 (74% vs. 32%, $P=0.02$ in Table 3), indicating that significantly more patients treated with one or fewer regimens for HM developed COVID-19 compared to those who developed SI (68% vs. 26%). As shown in Table 1, the patients who developed COVID-19 were significantly older ($P=0.03$) than those who developed SI. In addition, concerning treatment history with one or fewer regimens for HM, the mean age of the 13 patients who developed COVID-19 tended to be higher than that of the five patients who developed SI (78.1 vs. 65.4 years, respectively; data not shown in Table 3). The proportion of hospitalized elderly patients aged >60 years who developed COVID-19 was more than twice that of patients who developed SI (45.2% vs. 22.5%)¹⁷ and the relative number of elderly patients developing COVID-19 was higher than that in the population¹⁸. Some of the reasons for the higher susceptibility of elderly patients to COVID-19 can be explained by immune system dysregulation, including reduced innate and adaptive immune responses

and angiotensin-converting enzyme 2 (ACE2) overexpression¹⁹. However, the association of these factors with the above-mentioned significant differences requires clarification by accumulating more cases and conducting future investigations.

The results of the present study showed a higher number of median days from symptom onset to the start of oxygen therapy in patients with COVID-19 compared to patients with SI (6 [0–26] vs. 0 [0–7] days; $P=0.00011$) (Figure 1b). In the general population, the deterioration of COVID-19 pneumonia appears later than that of influenza in the general population¹⁴. Our findings suggested that it could take more days for COVID-19 to become more severe in patients with HD, similar to that in the general population. Therefore, attention should be paid to the progression of COVID-19 pneumonia, not only during disease onset but also a week or more later, even in patients with HD.

Patients with HD and COVID-19 have a worse prognosis than patients without HD^{6, 20}. Furthermore, nosocomial infection can also be a poor prognostic factor. The present study included 21 patients with HD and nosocomial COVID-19, who showed a high 90-day mortality rate (43%). Uchida *et al.*²¹ reported that patients with HD and nosocomial COVID-19 exhibited poor outcomes compared to those in patients with HD (52.5% vs. 35.1%, respectively). Vijenthira *et al.*⁶ reported a higher risk of mortality in hospitalized patients with HD (39%) compared to that in all HD patients (34%), whereas the in-hospital mortality in patients aged >60 years (47%) was significantly higher. A cohort including outpatients with HD and COVID-19 reported a mortality rate of only 26.5%²². Thus, physicians should take care in treating patients with HD, especially those who are or may be hospitalized during the COVID-19, pandemic to limit their risk of exposure to COVID-19.

This study had several limitations. First, this was a retrospective study with inherent risks of physician-related selection biases such as treatment strategies. Second, this study was analyzed based on daily clinical practice in a single institute comprising a small number of patients with HD, including those with various backgrounds. Third, the patient backgrounds of the two groups were not matched; all COVID-19 cases were nosocomial infections that had developed within 3 months, while the SI cases had developed in the past 5 years and included both nosocomial and community-acquired infections that resulted in hospitalization. Fourth, the COVID-19 outbreak occurred before the spread of SARS-CoV-2 mutants in our study area and the use of the SARS-CoV-2 vaccine. Therefore, the implications of mutant strains and vaccinations against SARS-CoV-2 in patients with HD and COVID-19 or SI have not been elucidated. These issues should be clarified in larger sample sizes and prospective, multi-institutional studies.

Conclusion

Patients with HDs who develop COVID-19 may have an increased need for oxygen administration and a longer treatment period. Their infections are also likely to become more serious compared to patients with HDs who develop SI. During the COVID-19 pandemic, hematologists must pay more attention to these infections compared to past influenza seasons. Although there has been a progressive accumulation of treatment strategies for COVID-19, the anticipated increased vaccine use shortly will help to strengthen the effectiveness of prevention and treatment strategies for COVID-19, similar to those for SI.

Data availability: The data supporting the findings of this study are available from the corresponding author upon

reasonable request.

Authors' contributions: NT designed this study. NT, JI, IS, and KS recruited and treated the patients. NT, JI, and KS collected the data. NT, JI, and KS analyzed and interpreted the data. NT wrote the manuscript. KS supervised this study. All authors contributed to the manuscript writing.

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