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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Original Article

Clinical characteristics and prognosis of immunosuppressed inpatients with COVID-19 in Japan

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ABSTRACT

Introduction: We aimed to analyze the clinical characteristics and outcomes of immunosuppressed inpatients with coronavirus disease 2019 (COVID-19).

Methods: In this observational study, we utilized a large nationwide registry of hospitalized patients with COVID-19 in Japan. Patients' baseline characteristics and outcomes were compared according to the immunosuppressed states of the patients. The impact of different therapeutic agents on the clinical courses of the patients was evaluated.

Results: Data of 14,760 patients were included, and 887 (5.9%) were immunosuppressed. The immunosuppressed state of the patient resulted from solid tumor (43.3%, n = 384), chemotherapy within 3 months (15.6%, n = 138), collagen disease (16.9%, n = 150), use of immunosuppressive agents (16.0%, n = 142), and metastatic solid tumor (13.5%, n = 120). Immunosuppressed patients were older and had a higher severity of illness at admission and during hospitalization than non-immunosuppressed patients. The mortality rates for major diseases causing immunosuppression were as follows: solid tumor, 12.5% (48/384; P < 0.001; relative risk [RR], 3.41); metastatic solid tumor, 31.7% (38/120; P < 0.001; RR, 8.43); leukemia, 23.1% (9/39; P < 0.001; RR, 5.87); lymphoma, 33.3% (20/60; P < 0.001; RR, 8.63); and collagen disease, 15.3% (23/150; P < 0.001; RR 3.97). Underlying diseases with high mortality rates were not necessarily associated with high rates of invasive supportive care.

Conclusions: The prognosis of immunosuppressed COVID-19 inpatients varied according to the different immunosuppressed states. Multiple factors, including the severity of the underlying diseases, might have affected their invasive supportive care indications.

1. Introduction

During this global pandemic, concerns have been raised regarding the impact of coronavirus disease 2019 (COVID-19) on immunosuppressed patients [1]. COVID-19 causes the release of potent cytokines in the host, and an excessive immune response is implicated in the progression of the disease [2]. However, it is not fully understood how the suppression of biological responses due to an originally immunosuppressed state affects the patients' clinical course. Several studies that focused on individual diseases found that certain immunosuppressed states, such as those due to solid organ tumor, hematological malignancies, and solid organ transplantation, were associated with a risk of

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease; DMARDs, disease-modifying anti-rheumatic drugs; ECMO, extracorporeal membranous oxygenation; IMV, invasive mechanical ventilation; IQR, interquartile range; OR, odds ratio; SpO_2, oxygen saturation; HIV, human immunodeficiency virus.

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severe illness, comorbidities, and poor prognosis [3]. In collagen diseases, the use of biologics may not worsen the prognosis, although chronic use of moderate-to-high doses of steroids is associated with severe COVID-19 [4]. Nevertheless, there is a lack of comprehensive studies investigating the effects of multiple immunosuppressed states on the clinical course and outcomes of COVID-19. Such a study is important for prioritizing medical management and determining the optimal allocation of medical resources to overcome severe outbreaks [5].

In this study, we aimed to descriptively analyze the epidemiological characteristics of immunosuppressed COVID-19 patients and to compare their clinical courses between different immunosuppressed states using a large nationwide registry of hospitalized COVID-19 patients.

2. Materials and methods

2.1. Study design and data collection

This was an observational study that utilized data from the COVID-19 Registry Japan (COVIREGI-JP) [6]. The clinical courses of immunosuppressed COVID-19 patients were descriptively analyzed, and the effects of the major immunosuppressive agents on the clinical course of each disease were examined. Data were collected and managed using Research Electronic Data Capture (REDCap), which is a secure, web-based data capture application hosted at the JCRAC Data Center of the National Center for Global Health and Medicine [7]. We used data from patients who were admitted before October 31, 2020, and all major data items as of December 28, 2020.

2.2. Immunosuppressed states and immunosuppressive treatment

Patients were defined as immunosuppressed if they have 1) following comorbidities: neutropenia (neutrophil count <500/μL), solid tumor (no metastasis except for those diagnosed >5 years ago), metastatic solid tumor, leukemia, lymphoma, collagen disease, human immunodeficiency virus, asplenia, primary immunodeficiency syndrome, hematopoietic cell transplantation, and organ transplant; or 2) following drugs or therapies prior to their infection: steroids (20 mg/day or higher prednisolone equivalent for at least 1 month), any chemotherapy, radiotherapy or immunosuppressive agents other than steroids, within the past 3 months [8,9]. Immunosuppressive treatment was also defined as having received steroids (≥20 mg of prednisolone or equivalent) for at least 1 month and receiving chemotherapy or immunosuppressive agents other than steroids within the past 3 months.

2.3. Severity at admission, supportive care during hospitalization, and outcomes

"Severe disease" at admission was defined as a condition requiring supplemental oxygen or invasive or noninvasive mechanical ventilation or characterized by oxygen saturation (SpO_2) of 94% or less on room air or tachypnea (respiratory rate ≥24 breaths per minute). Respiratory support during hospitalization was categorized into three groups: no oxygen, oxygen required, and invasive mechanical ventilation (IMV)/extracorporeal membranous oxygenation (ECMO). The groups and the corresponding intervention of supplementary oxygen provided were: no oxygen (i.e., no respiratory support was provided during hospitalization), oxygen (oxygen was supplied, except for IMV/ECMO), and IMV/ECMO (IMV or ECMO was required). In addition, supportive care through IMV or ECMO was defined as invasive supportive care. Patients' deaths were captured at each facility at the time of data collection and were not followed-up after transfer or discharge.

2.4. Statistical analysis

Continuous variables are described as the median (interquartile range [IQR]), and categorical variables are described as the number of cases and percentages. Wilcoxon's rank sum test was performed for continuous variables, and the Chi-square test was performed for categorical variables. The 95% confidence intervals for the rate of symptomatic cases were obtained using the Clopper-Pearson method. All statistical analyses were conducted using R version 4.0.2 (R Core Team) [10].

2.5. Ethics

This study was approved by the National Center for Global Health and Medicine Ethics Review.

3. Results

3.1. Patients' baseline demographics

Data of 14,760 patients from 444 hospitals were included in this study, and 887 (5.9%) were immunosuppressed (Table 1). Patients with underlying diseases with less than 20 registrations were shown separately (Supplementary Table 1). The common reasons for immunosuppressed state included solid tumor (43.3%, n = 384), chemotherapy (15.6%, n = 138), collagen disease (16.9%, n = 150), immunosuppressive agents (16.0%, n = 142), and metastatic solid tumor (13.5%, n = 120). Among the immunosuppressed patients, 60.0% (n = 532) were male. Immunosuppressed patients were older than non-immunosuppressed patients (median age, 70 years; IQR [57, 79] vs 50 years; IQR [32, 68]). The percentage of patients admitted with severe disease was higher in immunosuppressed (n = 332, 37.4%) than in non-immunosuppressed (n = 3337, 24.1%) patients. Hypertension, diabetes mellitus, and hyperlipidemia were common in both immunosuppressed and non-immunosuppressed patients.

Collagen disease tended to be more prevalent among women than men (62.7% [94/150] for women in collagen disease). For all immunosuppressed categories except HIV infection, immunosuppressed patients were likely to be older than non-immunosuppressed patients. The median number of days from symptom onset to hospitalization was shortest for patients with metastatic solid tumor (3 days; IQR [1,7]), leukemia (3 days; IQR [0.5, 6]), lymphoma (3 days; IQR [0.75, 5]), and patients under chemotherapy (3 days; IQR [0, 5.75]).

The comparison of baseline demographics in five major immunosuppressed states in the presence or absence of treatment for underlying diseases is summarized in Supplementary Table 2. For solid tumor, metastatic solid tumor, and collagen disease, the patients in the treatment group for underlying diseases were younger than those in the no treatment group (solid tumor, $P = 0.001$; metastatic solid tumor, $P < 0.001$; collagen disease, $P = 0.001$). Conversely, there was no difference in age between the groups with and without treatment for lymphoma and leukemia. For all five diseases, the severity at admission was not affected by the presence or absence of the specific treatments.

3.2. Symptoms in immunosuppressed patients

Symptoms at admission in immunosuppressed patients compared with non-immunosuppressed patients are shown in Fig. 1. Fever and shortness of breath tended to occur more frequently in immunosuppressed than in non-immunosuppressed patients, whereas headache, dysgeusia, and olfactory abnormalities were less frequent.

3.3. Outcomes and supportive care during hospitalization

A higher number of immunosuppressed patients needed oxygen and IMV/ECMO than non-immunosuppressed patients (Table 2). Of the immunosuppressed and non-immunosuppressed patients, 146 (16.5%) and 439 (3.2%) died, respectively. The highest proportions of deceased patients were among those with a history of using steroids within 1 month (25.4%), chemotherapy within 3 months (21.7%), metastatic

Table 1
Patients' baseline demographics.

	Non-immunosuppressed	All Immunosuppressed	Immunosuppressed status								
			Steroids within 1 month	Chemotherapy within 3 months	Use of immunosuppressive agents	Solid tumor	Metastatic solid tumor	Leukemia	Lymphoma	Collagen disease	HIV
Number of cases[a]	13873	887	59	138	142	384	120	39	60	150	33
Demographics											
Sex, Male (%)	8072 (58.2)	532 (60)	32 (54.2)	88 (63.8)	65 (45.8)	243 (63.3)	75 (62.5)	25 (64.1)	39 (65)	56 (37.3)	32 (97)
Age, Median [IQR]	50 [32, 68]	70 [57, 79]	69 [53, 78.75]	69 [57.25, 73]	63 [47, 72]	73 [63.75, 82]	71 [63.75, 79.25]	69 [53, 76]	71 [60, 79.25]	68 [56, 76]	38 [30, 51]
Conditions at admission											
Severe disease at admission (%)	3337 (24.1)	332 (37.4)	31 (52.5)	51 (37)	43 (30.3)	152 (39.6)	55 (45.8)	9 (23.1)	20 (33.3)	57 (38)	4 (12.1)
Symptomatic cases (%)	12292 (91.5)	761 (89.2)	49 (86)	114 (86.4)	121 (90.3)	338 (91.8)	97 (82.2)	29 (78.4)	50 (86.2)	130 (89.7)	33 (100)
Days from onset to admission, Median [IQR][b]	5 [3,8]	5 [2,8]	4 [0.25, 8.75]	3 [0, 5.75]	4 [2,7]	5 [2,8]	3 [1,7]	3 [0.5, 6]	3 [0.75, 5]	5 [2,7]	5 [4,7]
Comorbidities											
Cardiovascular disease (%)[c]	491 (3.5)	69 (7.8)	7 (11.9)	4 (2.9)	7 (4.9)	36 (9.4)	9 (7.5)	2 (5.1)	4 (6.7)	6 (4)	0 (0)
Peripheral Vascular disease (%)	141 (1)	24 (2.7)	2 (3.4)	1 (0.7)	4 (2.8)	10 (2.6)	4 (3.3)	1 (2.6)	1 (1.7)	5 (3.3)	0 (0)
Cerebrovascular disease (%)	673 (4.9)	76 (8.6)	6 (10.2)	8 (5.8)	8 (5.6)	33 (8.6)	14 (11.7)	4 (10.3)	8 (13.3)	15 (10)	0 (0)
Dementia (%)	770 (5.6)	75 (8.5)	5 (8.5)	5 (3.6)	6 (4.2)	43 (11.2)	11 (9.2)	3 (7.7)	3 (5)	9 (6)	0 (0)
Chronic respiratory disease (%)[d]	402 (2.9)	84 (9.5)	19 (32.2)	10 (7.2)	13 (9.2)	34 (8.9)	10 (8.3)	1 (2.6)	2 (3.3)	17 (11.3)	0 (0)
Liver disease (%)[e]	263 (1.9)	36 (4.1)	2 (3.4)	5 (3.6)	3 (2.1)	20 (5.2)	7 (5.8)	0 (0)	2 (3.3)	2 (1.3)	1 (3)
Hypertension (%)	2932 (21.1)	268 (30.2)	15 (25.4)	23 (16.7)	38 (26.8)	134 (34.9)	32 (26.7)	7 (17.9)	13 (21.7)	48 (32)	5 (15.2)
Hyperlipidemia (%)	1471 (10.6)	108 (12.2)	7 (11.9)	7 (5.1)	20 (14.1)	48 (12.5)	14 (11.7)	3 (7.7)	5 (8.3)	19 (12.7)	4 (12.1)
Diabetes mellitus (%)	1813 (13.1)	195 (22)	17 (28.8)	33 (23.9)	22 (15.5)	94 (24.5)	27 (22.5)	9 (23.1)	11 (18.3)	33 (22)	0 (0)
Obesity (%)	742 (5.3)	40 (4.5)	7 (11.9)	5 (3.6)	8 (5.6)	16 (4.2)	2 (1.7)	0 (0)	2 (3.3)	9 (6)	0 (0)
Renal disease on dialysis (%)[f]	147 (1.1)	48 (5.4)	3 (5.1)	3 (2.2)	17 (12)	14 (3.6)	5 (4.2)	0 (0)	6 (10)	8 (5.3)	0 (0)
Solid tumor (%)	0 (0)	384 (43.3)	2 (3.4)	33 (23.9)	5 (3.5)	384 (100)	12 (10)	4 (10.3)	3 (5)	6 (4)	0 (0)
Metastatic solid tumor (%)	0 (0)	120 (13.5)	3 (5.1)	46 (33.3)	1 (0.7)	12 (3.1)	120 (100)	1 (2.6)	1 (1.7)	2 (1.3)	0 (0)
Leukemia/Lymphoma (%)	0 (0)	99 (11.2)	3 (5.1)	49 (35.5)	15 (10.6)	7 (1.8)	2 (1.7)	39 (100)	60 (100)	1 (0.7)	0 (0)
Collagen disease (%)	0 (0)	150 (16.9)	13 (22)	2 (1.4)	60 (42.3)	6 (1.6)	2 (1.7)	1 (2.6)	0 (0)	150 (100)	0 (0)

Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus.

[a] The denominator in each category may vary owing to missing values.

[b] The median and IQR include negative values due to those who were admitted before symptom onset; the numbers are not shown.

[c] Myocardial infarction and congestive heart failure.

[d] Chronic obstructive pulmonary disease (COPD) and chronic lung disease.

[e] Mild liver disease and moderate-to-severe liver dysfunction.

[f] Moderate-to-severe renal disorder and maintenance hemodialysis before hospitalization.

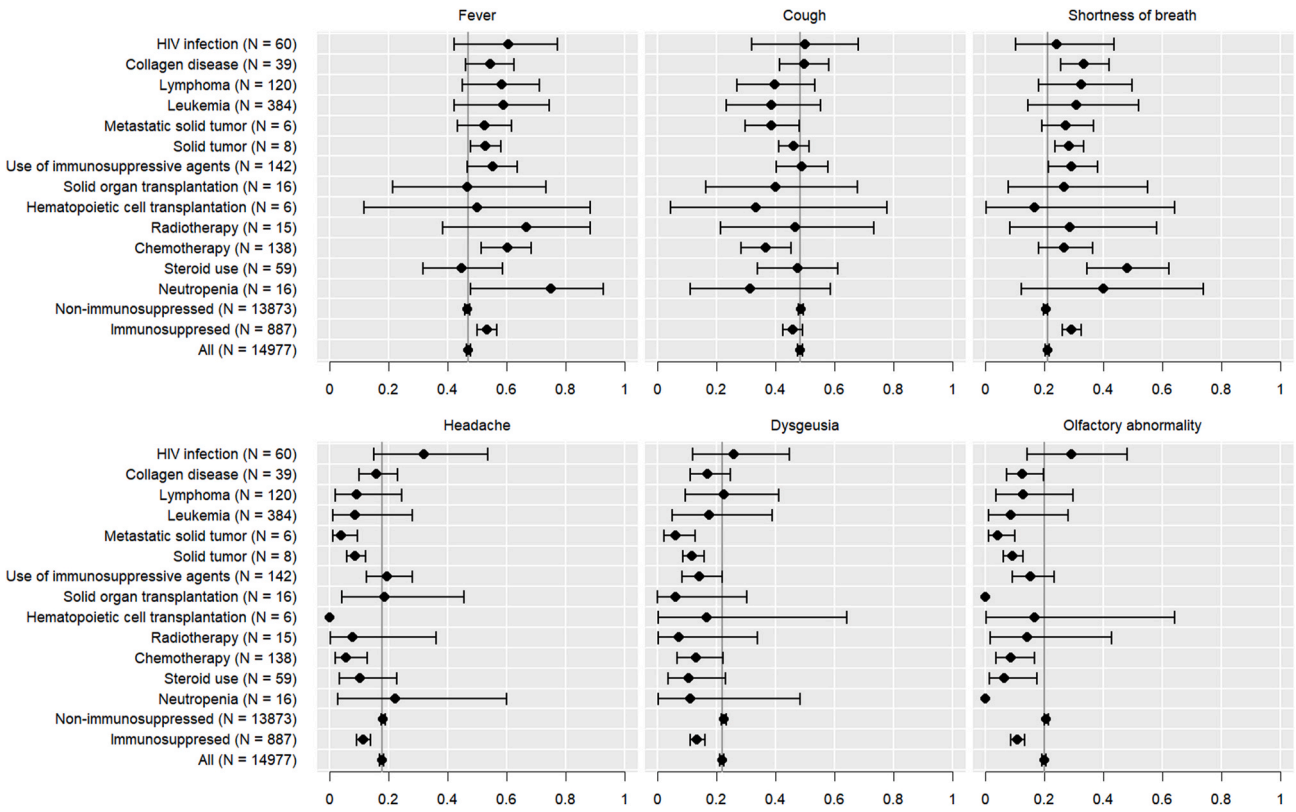

Fig. 1. Symptoms associated with Coronavirus Disease in each immunosuppressed state at admission. HIV, human immunodeficiency virus.

solid tumor (31.7%), leukemia (23.1%), and lymphoma (33.3%). A total of 136 (15.3%) immunosuppressed patients and 993 (7.2%) non-immunosuppressed patients were admitted to an intensive care unit. The most common complication in immunosuppressed patients was bacterial pneumonia (11.3%, n = 100), followed by acute respiratory distress syndrome (ARDS) (11.2%, n = 99).

The outcomes and impact of supportive therapy for the five major immunosuppressed states are shown in Table 3. The mortality rates for each immunosuppressed state were 12.5% (48/384; $P < 0.001$; relative risk [RR], 3.41) in solid tumor; 31.7% (38/120; $P < 0.001$; RR, 8.43) in metastatic tumor; 23.1% (9/39; $P < 0.001$; RR, 5.87) in leukemia; 33.3% (20/60; $P < 0.001$; RR, 8.63) in lymphoma; and 15.3% (23/150; $P < 0.001$; RR, 3.97) in collagen disease. Coexistence of these diseases also increased the proportion of more serious complications during hospitalization. Patients with solid tumors were likely to be placed on IMV/ECMO compared with those without solid tumors.

A comparison of the outcomes and supportive care during hospitalization in each immunosuppressed state in the presence or absence of treatment for underlying diseases is summarized in Supplementary Table 3. These specific treatments for underlying diseases did not affect the rate of IMV/ECMO or mortality during hospitalization. For many complications during hospitalization, coexistence of immunosuppressed states increased the prevalence of complications, but treatments for underlying diseases did not have a significant effect on that prevalence.

3.4. Medication administered during hospitalization based on immunosuppressed states

Information on the medication used during hospitalization is summarized in Supplementary Table 4. The drugs used to treat COVID-19 and anticoagulants were more frequently administered to immunosuppressed patients, such as those with solid tumors, metastatic solid tumors, and collagen diseases (Supplementary Table 5). Antibiotics were more commonly used in immunosuppressed than in non-immunosuppressed patients.

4. Discussion

In this study, we used a multicenter registry from Japan to comprehensively evaluate the clinical epidemiological characteristics of immunosuppressed patients. Immunosuppressed COVID-19 inpatients tended to have a worse prognosis than non-immunosuppressed COVID-19 inpatients. Patients with metastatic tumors, leukemia, and lymphoma had relatively high mortality rates compared with those having solid tumors and collagen diseases. However, IMV/ECMO was not always applied to patients with underlying conditions with higher mortality rates. Use of invasive therapies for patients with COVID-19 may depend on several factors, including the severity of underlying conditions. Therapeutic options may also depend on the condition of medical infrastructure, although it was not explicitly documented in the present study. In addition, government policies changed over time during the pandemic, influencing the indications for hospitalization. Although further research is necessary to determine the indications for supportive therapies for immunosuppressed COVID-19 patients, our study highlighted that underlying health conditions might influence the indications for invasive therapies.

Immunosuppressed patients were more likely to present with fever and shortness of breath at admission than non-immunosuppressed patients. Hospitalization is usually indicated for patients with COVID-19 showing these symptoms. Moreover, immunosuppressed patients presented with more severe disease at admission. Therefore, these two symptoms suggest the severity of COVID-19 in immunosuppressed patients. Conversely, dysgeusia, olfactory abnormality, and headache were less prevalent in patients with solid tumors and metastatic solid tumors in our study. These sensory abnormalities are common among cancer patients receiving chemotherapy [11], and tumors could cause a variety of headaches [12]. However, our results showed that only 8.6% and 38.3% of patients with solid and metastatic solid tumors, respectively,

Table 2
Supportive care during hospitalization and outcomes.

	Non-immunosuppressed	All Immunosuppressed	Immunosuppressed status								
			Steroid within 1 month	Chemotherapy within 3 months	Use of immunosuppressive agents	Solid tumor	Metastatic solid tumor	Leukemia	Lymphoma	Collagen disease	HIV
Number of cases[a]	13873	887	59	138	142	384	120	39	60	150	33
Respiratory support											
No oxygen (%)[b]	9923 (71.6)	445 (50.3)	22 (37.3)	65 (47.8)	73 (51.4)	186 (48.7)	51 (42.9)	22 (56.4)	24 (40)	74 (49.3)	28 (84.8)
Oxygen required (%)[c]	3234 (23.3)	352 (39.8)	30 (50.8)	59 (43.4)	54 (38)	152 (39.8)	59 (49.6)	16 (41)	30 (50)	61 (40.7)	5 (15.2)
IMV/ECMO (%)[d]	709 (5.1)	87 (9.8)	7 (11.9)	12 (8.8)	15 (10.6)	44 (11.5)	9 (7.6)	1 (2.6)	6 (10)	15 (10)	0 (0)
Outcome at discharge[e]											
Discharge (%)	10692 (77.1)	531 (59.9)	29 (49.2)	75 (54.3)	94 (66.2)	232 (60.4)	57 (47.5)	20 (51.3)	24 (40)	96 (64.4)	29 (87.9)
Transfer to another facility (%)	2739 (19.7)	209 (23.6)	15 (25.4)	33 (23.9)	30 (21.1)	104 (27.1)	25 (20.8)	10 (25.6)	16 (26.7)	30 (20.1)	4 (12.1)
Dead (%)	439 (3.2)	146 (16.5)	15 (25.4)	30 (21.7)	18 (12.7)	48 (12.5)	38 (31.7)	9 (23.1)	20 (33.3)	23 (15.3)	0 (0)
Supportive therapy during admission											
Stay in ICU (%)	993 (7.2)	136 (15.3)	13 (22)	15 (10.9)	26 (18.3)	66 (17.2)	14 (11.7)	1 (2.6)	7 (11.7)	24 (16)	0 (0)
ECMO (%)	84 (0.6)	11 (1.2)	1 (1.7)	2 (1.5)	2 (1.4)	4 (1)	2 (1.7)	0 (0)	1 (1.7)	2 (1.3)	0 (0)
Complications during admission											
Bacterial pneumoniae (incl. HAP/VAP) (%)	610 (4.4)	100 (11.3)	17 (28.8)	15 (11)	8 (5.7)	45 (11.8)	18 (15.1)	4 (10.3)	7 (11.7)	17 (11.4)	0 (0)
ARDS (%)	641 (4.6)	99 (11.2)	8 (13.6)	15 (11)	20 (14.2)	39 (10.2)	11 (9.2)	3 (7.9)	14 (23.3)	22 (14.8)	0 (0)
Deep vein thrombosis (%)	83 (0.6)	9 (1.1)	1 (1.8)	1 (0.8)	0 (0)	4 (1.1)	2 (1.8)	0 (0)	0 (0)	3 (2.1)	0 (0)
Bacteremia (%)	111 (0.8)	16 (1.8)	4 (6.8)	1 (0.7)	2 (1.4)	4 (1)	3 (2.5)	2 (5.1)	1 (1.7)	5 (3.4)	0 (0)
Gastrointestinal bleeding (%)	74 (0.5)	13 (1.5)	3 (5.1)	2 (1.5)	3 (2.1)	4 (1)	0 (0)	1 (2.6)	3 (5)	3 (2)	0 (0)
C. difficile infection (%)	31 (0.2)	6 (0.7)	0 (0)	1 (0.7)	1 (0.7)	3 (0.8)	2 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary thromboembolism (%)	25 (0.2)	4 (0.5)	1 (1.8)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.4)	0 (0)

Abbreviations: IQR, interquartile range; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; ARDS, acute respiratory distress syndrome.

[a] The denominator in each category may vary owing to missing values.

[b] Myocardial infarction and congestive heart failure.

[c] Chronic obstructive pulmonary disease (COPD) and chronic lung disease.

[d] Mild liver disease and moderate-to-severe liver dysfunction.

[e] Moderate-to-severe renal disorder and maintenance hemodialysis before hospitalization.

Table 3
Comparison of supportive care during hospitalization and outcomes by comorbidities.

	Solid tumor			Metastatic solid tumor			Leukemia			Lymphoma			Collagen disease		
	No	Yes	p-value	No	Yes	p-value	No	yes	p-value	No	Yes	p-value	No	Yes	p-value
Number of cases[a]	14593	384		14857	120		14938	39		14917	60		14827	150	
Respiratory support															
IMV/ECMO (%)	773 (5.3)	44 (11.5)	<0.001	808 (5.4)	9 (7.6)	0.3066	816 (5.5)	1 (2.6)	0.723	811 (5.4)	6 (10)	0.1421	802 (5.4)	15 (10)	0.0272
Outcome at discharge															
Dead (%)	548 (3.8)	48 (12.5)	<0.001	558 (3.8)	38 (31.7)	<0.001	587 (3.9)	9 (23.1)	<0.001	576 (3.9)	20 (33.3)	<0.001	573 (3.9)	23 (15.3)	<0.001
Self-care ability[b]															
Worsened (%)	968 (7)	55 (16.7)	<0.001	1008 (7.2)	15 (18.8)	<0.001	1019 (7.1)	4 (13.3)	0.2736	1015 (7.2)	8 (21.6)	0.0043	1005 (7.2)	18 (14.4)	0.0047
Supportive therapy during admission															
Stay in ICU (%)	1090 (7.5)	66 (17.2)	<0.001	1142 (7.7)	14 (11.7)	0.119	1155 (7.7)	1 (2.6)	0.3647	1149 (7.7)	7 (11.7)	0.2266	1132 (7.6)	24 (16)	<0.001
ECMO (%)	97 (0.7)	4 (1)	0.3306	99 (0.7)	2 (1.7)	0.187	101 (0.7)	0 (0)	1	100 (0.7)	1 (1.7)	0.3345	99 (0.7)	2 (1.3)	0.2689
Complications during admission															
Bacterial pneumoniae (incl. HAP/VAP) (%)	684 (4.8)	45 (12.2)	<0.001	711 (4.9)	18 (16.5)	<0.001	725 (5)	4 (11.1)	0.1022	722 (4.9)	7 (12.1)	0.0244	712 (4.9)	17 (11.5)	0.0016
ARDS (%)	714 (4.9)	39 (10.4)	<0.001	742 (5)	11 (9.4)	<0.001	750 (5.1)	3 (8.1)	0.4348	739 (5)	14 (24.1)	<0.001	731 (5)	22 (15.2)	<0.001
Deep vein thrombosis (%)	91 (0.7)	4 (1.2)	0.2934	93 (0.7)	2 (1.9)	0.1638	95 (0.7)	0 (0)	1	95 (0.7)	0 (0)	1	92 (0.7)	3 (2.1)	0.0711
Bacteremia (%)	129 (0.9)	4 (1.1)	0.5801	130 (0.9)	3 (2.5)	0.0896	131 (0.9)	2 (5.3)	0.0454	132 (0.9)	1 (1.7)	0.418	128 (0.9)	5 (3.4)	0.0101
C. difficile infection (%)	34 (0.2)	3 (0.8)	0.0643	35 (0.2)	2 (1.7)	0.0346	37 (0.3)	0 (0)	1	37 (0.3)	0 (0)	1	37 (0.3)	0 (0)	1
Pulmonary thromboembolism (%)	30 (0.2)	0 (0)	1	30 (0.2)	0 (0)	1	30 (0.2)	0 (0)	1	30 (0.2)	0 (0)	1	28 (0.2)	2 (1.4)	0.0358

Abbreviations: IQR, interquartile range; PIS, primary immunodeficiency syndrome; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; ARDS, acute respiratory distress syndrome.

[a] The denominator in each category may vary owing to missing values.

[b] The p-value was calculated based on the aggregate values for "Stable," "Worsened," "Improved," and "Unknown."

were receiving chemotherapy. Therefore, we could not fully evaluate the impact of treatments for underlying diseases on the symptoms in these patients. Detailed studies will be needed to investigate the effects of underlying diseases on COVID-19 patients' symptoms.

In our study, patients with solid tumor and metastatic solid tumors were associated with higher mortality rates than those without tumors, as in a previous study [13]. However, the presence of specific tumor treatment did not affect the severity and the outcomes of COVID-19, or other indicators, such as symptoms and supportive therapies. Whether chemotherapies should be withheld during the COVID-19 epidemic is a crucial question. Studies including a small number of patients with solid tumors showed that chemotherapies had an undesirable effect on COVID-19 prognosis and infectious risk [14–16]. However, according to more recent large studies, chemotherapies were not shown to have any effect on the prognosis of COVID-19 [17–19], which was consistent with the results of our study. Consequently, large-scale studies to date have suggested that there has not been remarkable evidence to withhold treatments for solid tumors. Regarding metastatic solid tumor, the mortality rate was quite high at 31.7%, but again, there was no difference between the treatment and no treatment groups for underlying diseases. Notably, the rate of IMV/ECMO was not high, although this population was likely to be more severely ill. One possible explanation is that patients with untreated metastatic solid tumors were suggested palliative care, meaning that this population was unlikely to receive invasive treatments at the end of their lives.

In our study, the mortality rate of patients with COVID-19 with hematologic malignancies was relatively higher than that of patients with other immunosuppressed states. The mortality rates of COVID-19 patients with hematologic malignancies were likely to be high, but they vary widely among studies [20–23]. The mortality rates for leukemia and lymphoma in our study were similar to those in existing studies on COVID-19 inpatients with hematologic malignancies [20], although a small number of patients was included in our study and selection bias may have affected the result. Despite these high mortality rates, the rate of IMV/ECMO was not significantly higher in hematologic malignancies in our study. More than half of the patients with hematologic malignancies received chemotherapy, meaning these patients received active treatments for the underlying diseases, but only few of them received IMV/ECMO when they became severely ill. This discrepancy between the severity of COVID-19 and indications for invasive treatments was similar in COVID-19 patients with metastatic solid tumors. In contrast, patients with hematological malignancies in our study had a shorter time to admission with a median of 3 days from the onset of symptoms to admission compared to a median of 5 days for all the patients. Patients with hematological malignancies often need meticulous treatment by specialists, and the shorter time to admission for these patients might reflect the accessibility of specialized medical institutions.

Among the patients with collagen disease in our study, 45.3% received immunosuppressive therapy, of whom 19.1% used steroids and 88.2% used other immunosuppressive agents, suggesting that the treatment group for underlying diseases almost exclusively received immunosuppressive therapies other than steroids. Patients with collagen diseases presented higher mortality rates, and more of these patients received IMV/ECMO than those without collagen diseases. Nevertheless, there was no differences in invasive respiratory support and mortality rates between the patients under treatment for collagen diseases and those without such treatment. Our cohort lacked an informative breakdown of collagen disease, severity, and the details of immunosuppressive agents. Therefore, we were unable to assess whether specific treatments were associated with a worse prognosis in this population. Previous cohort studies have also reported that patients with collagen diseases tend to be more severely ill [24], but considerable variation has been observed in correlation between medications for collagen disease and poor prognosis by COVID-19 [4,25]. According to a large cohort study [26,27], prednisolone $\geq$10 mg/day was associated with a high rate of hospitalization. Conversely, use of biological or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), conventional synthetic DMARDs, and a combination of both might not be associated with hospitalization. These studies should be interpreted with caution because case-reporting bias and hidden confounders need to be addressed. The accumulation of pathophysiological findings on medications that may pose a risk of exacerbating COVID-19 is still insufficient, and the causal relationship between medications used for collagen diseases and the prognosis of COVID-19 remains to be further investigated.

5. Limitations

There are some limitations in our study. First, due to the definition of diseases or states in the original registry data, some potential immunosuppressed states might have been excluded. Several patients with solid tumor did not undergo chemotherapy, and other underlying diseases might have resulted in their poor clinical outcomes. Second, we believe that our study provided useful clinico-epidemiological information of immunosuppressed COVID-19 patients in Japan, but we did not adjust for the already-known risk factors, such as age, while investigating the effect of immunosuppressed status on the outcomes. Therefore, it is difficult to make simple and meaningful comparisons between our study and previous studies. Third, due to the nature of the registry study, some detailed information about the cases was lacking; thus, it was difficult to determine the extent to which each specific disease and immunosuppressive agent contributed to the outcomes. Future research will be necessary to elucidate this point. Fourth, as our study included only a few cases of some diseases, we could not investigate all cases associated with COVID-19. Finally, the data entered in this registry were from discharged patients; the data for outpatients and patients with prolonged hospitalization were not included.

6. Conclusions

In this comprehensive analysis, the prognosis of immunosuppressed COVID-19 inpatients varied according to the different states of immunosuppression. Although COVID-19 inpatients with metastatic tumors and hematologic malignancies tended to have a worse prognosis, invasive treatments were not necessarily applied to these patients. Multiple factors, including the severity of the underlying diseases, might have affected the indications for invasive supportive care for immunosuppressed COVID-19 inpatients.

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Authors' contributions

All authors meet the ICMJE authorship criteria. HN, SS, and KH contributed to the concept, study design, and data interpretation. YA contributed to the statistical analysis. HG contributed to the concept and study design. MT, KS, HO, and AT contributed to the data acquisition. NO provided supervision. All authors contributed to critical revision of the manuscript for important intellectual content.

Declaration of competing interest

H. Ohtsu reports personal fees as a statistician and as an external consultant for clinical trials from EPS International outside the submitted work. The other authors report no 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.2021.10.021.

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