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Clinical and virological features of SARS-CoV-2 Omicron variant-infected immunocompromised patients receiving immunosuppressive medications

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Abstract

Background The prognosis of immunocompromised individuals with COVID-19 remains a significant concern. Information regarding the clinical and virological characteristics of immunocompromised patients infected with SARS-CoV-2 during the Omicron variant period is limited.

Methods Medical records of patients admitted to our hospital with COVID-19 during the Omicron (BA.1–5) epidemic were retrospectively reviewed. Clinical, virological (nasopharyngeal swabs and blood), and serological data were compared between immunocompromised patients receiving immunosuppressive medications (calcineurin inhibitors, mycophenolate mofetil, or steroids) and control patients not receiving immunosuppressive medications.

Results Twenty-eight immunocompromised patients (25 transplant recipients) and 26 control patients were included. Fourteen of the immunocompromised patients (50%) received monoclonal antibodies. The immunocompromised group included 15 mild/moderate (53.6%), 10 severe (35.7%), and three critical (10.7%) disease severities. The mortality rate due to COVID-19 during hospitalization was 3.6% (1/28) in the immunocompromised group, with no difference between the two groups. Three cases of re-exacerbation after discharge occurred in the immunocompromised group and none in the control group. Linear regression based on nasopharyngeal real-time-PCR cycle threshold (Ct) values according to the time since symptom onset showed markedly slower viral clearance in the immunocompromised group than in the control group ($P_{\text{slope}} = 0.078$). In the immunocompromised group, patients who received monoclonal antibodies showed faster viral clearance than those who did not receive monoclonal antibodies. The convalescent anti-spike IgG titers were comparable to those in the control group in patients who received monoclonal antibodies and significantly lower than those in the control patients in patients who did not receive monoclonal antibodies ($P < 0.001$). The prevalence of viremia at onset was significantly higher in the immunocompromised group than in the control group (35.7%, [10/28] vs. 11.5%, [3/26]; $P = 0.003$). All three patients with critical disease severity in the immunocompromised group exhibited viremia, one of whom died. All three patients with viremia in the control group were critical, of whom two died.

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Conclusions Immunocompromised individuals receiving immunosuppressive medications are more likely to show delayed post-infection SARS-CoV-2 viral clearance and the development of viremia, potentially resulting in worsening severity and outcomes, especially in viremic patients, even during the Omicron epidemic.

Keywords COVID-19, SARS-CoV-2, Immunocompromised patients, Immunosuppressive medications, Viremia, Severity

Background

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was of concern due to its high mortality rate in immunocompromised patients [1–3]. Some studies reported a prolonged period of viral shedding of up to 70 days in immunocompromised patients [4, 5]. Since the end of 2021, Omicron variant lineages have been circulating worldwide. The association of Omicron variant infection with shorter symptom duration, lower severity, and lower hospitalization rates has been reported in the general population [6–8]. Regarding immunocompromised patients infected with SARS-CoV-2 after the Omicron wave, the mortality rate in those with hematologic malignancies has been reported to be approximately 8% [9], whereas a few studies on other immunocompromised patients infected with the Omicron variant reported lower mortality rates [10, 11]. However, limited information is available on the clinical and virological characteristics, and prognosis of immunocompromised patients infected with the Omicron variant.

In this study, we collected information on immunocompromised patients with COVID-19 admitted to our hospital after the Omicron wave, which started in January 2022 in Japan. Previous studies on the features of immunocompromised patients with COVID-19 seemed to be unclear regarding the definition of immunocompromised status, and most of the studies focused on patients with various conditions, including cancer and those receiving antitumor or immunosuppressive drugs [9–11]. Therefore, in this study, we defined immunocompromised patients as those receiving immunosuppressive medications to clarify their immunocompromised status. These patients are classified as moderately or severely immunocompromised in the US National Institute of Health (NIH) criteria [12]. In addition, we collected data on patients who did not receive immunosuppressive agents and were hospitalized during the same period, as a control group. We collected not only clinical data, such as background, severity, and outcome, but also virological data, including nasopharyngeal and serum viral loads, and serological data on antibody titers. These data were compared between the immunocompromised and control groups.

Methods

Patients

This was a retrospective clinical and virological evaluation of immunocompromised patients with SARS-CoV-2 infection. Patients with COVID-19 admitted to Kyushu University Hospital in Japan from January to October 2022 during the Omicron (BA.1–5) epidemic period [13] were included, and those with at least one nasopharyngeal real-time PCR (RT-PCR) cycle threshold (Ct) value obtained during hospitalization were selected. In this study, patients who had received immunosuppressive medications (calcineurin inhibitors, mycophenolate mofetil, or steroids) at the time of admission and those not receiving immunosuppressive medications were defined as the immunocompromised and control groups, respectively. In the immunocompromised group, the transplant recipients received standard doses of their immunosuppressive drugs that were administered after transplantation, and the remaining patients received NIH-defined steroid doses (≥ 20 mg/day) that potentially satisfied the immunosuppressive status.

Data collection

Patient information and laboratory test results, including nasopharyngeal SARS-CoV-2 RT-PCR Ct values, were collected from medical records. All records and tests were physician dependent. ‘Days after symptom onset’ in this study was based on the number of days from symptom onset at the time of admission, which was recorded by physicians. The severity of COVID-19 was defined based on the US NIH criteria [14]. ‘Mild/moderate’ was defined as $SpO_2 \geq 94\%$, ‘severe’ was defined as $SpO_2 < 94\%$, and ‘critical’ was defined as requiring mechanical ventilation.

RT-PCR

Two quantitative RT-PCR methods were used for the detection of SARS-CoV-2 in nasopharyngeal swab specimens: the cobas 6800 system (Roche Molecular Diagnostics, Pleasanton, CA, USA) targeting the E and ORF 1a/b genes, and the GeneXpert system (Cepheid, Sunnyvale, CA, USA) targeting the E and N genes. Samples with a Ct value of 40 or higher were considered negative (no amplification) for SARS-CoV-2 RNA and were treated as a result of a Ct value of 40 [15–17].

Qualitative RT-PCR detection of SARS-CoV-2 was performed using serum samples obtained at the time of admission for other biochemical tests. Amplification of the N gene in serum was performed using the amplification conditions described in the Centers for Disease Control and Prevention (CDC) 2019–Novel Coronavirus EUA protocol [18]. Viremia was defined as positive when at least one of the N1, N2, or N3 genes was detected.

Serological testing

Serum samples obtained within 6 days of symptom onset and 7 or more days after symptom onset were used as early and convalescent samples, respectively. Serological testing was performed using the serum samples. The quantitative levels of IgG antibodies for the spike (receptor-binding domain [RBD]) antigen of SARS-CoV-2 were examined using Abbott Architect immunoassays (SARS-CoV-2 IgG II Quant, Abbott, Park, IL, USA) according to the manufacturer's protocol.

Statistical analysis

Categorical variables were analyzed using the Chi-squared test or Fisher's exact test. Continuous variables were compared using the Wilcoxon signed-rank test. Spearman's rank correlation coefficient and linear regression analysis were used to analyze the correlation between SARS-CoV-2 RT-PCR Ct values and the number of days since symptom onset. For these analyses, one Ct value was randomly selected for each patient when multiple values were obtained. The linear regression analysis used Ct values as the outcome variable and included the following three explanatory variables: the number of days from symptom onset to sample collection, receiving immunosuppressive medications, monoclonal antibody therapy, or viremia; and an interaction term between the number of days from symptom onset and immunocompromised status, monoclonal antibody therapy, or viremia. The slope values were calculated using linear regression analysis. Two-sided P values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics and outcomes of immunocompromised patients

The demographics and clinical characteristics of the entire patient cohort are shown in Table 1. Of the 28 patients in the immunocompromised group, 25 (89.2%) were transplant recipients, including 15 kidney, 4 liver, 3 heart, 2 multiorgan, and 1 allogeneic hematopoietic stem cell transplant recipients. In the immunocompromised group, 25 patients (89.2%) received calcineurin inhibitors

and steroids, and all immunocompromised patients received multiple immunosuppressive drugs. Dose adjustments for immunosuppressive drugs after COVID-19 were conducted only for mycophenolate mofetil, excluding calcineurin inhibitors and steroids. Of the 18 patients treated with mycophenolate mofetil, 10 (55.6%) and 7 (38.9%) received dose reduction and cessation, respectively. There were no significant differences in the vaccination history between the immunocompromised and control groups. Regarding COVID-19 treatment, 14 patients (50%) in the immunocompromised group and none in the control group received monoclonal antibody therapy (sotrovimab or casirivimab/imdevimab). There were no significant differences in the use of remdesivir between the immunocompromised and control groups (75.0%, [21/28] vs. 57.7% [15/26], $P=0.25$).

The immunocompromised group included 15 mild/moderate (53.6%), 10 severe (35.7%), 3 critical (10.7%) diseases in the severity of COVID-19. There was no difference in the severity between the immunocompromised and control groups. The mortality rate due to COVID-19 during hospitalization was 3.6% (1/28) in the immunocompromised group, with no significant difference between the two groups. Three patients (10.7%) in the immunocompromised group were readmitted because of symptom exacerbation, with no readmission in the control group (Supplementary Table 1). The Ct values on admission and readmission were 14.3 on day 3 and 20.0 on day12 in Patient 1, 16.6 on day 2 and 24.0 on day20 in Patient 2, and 18.0 on day 1 and 25.0 on day15 in Patient 3. All three patients showed rapid improvement after readmission, with no symptom exacerbation after the second discharge.

Dynamics of SARS-CoV-2 RT-PCR Ct values and anti-spike antibody levels in immunocompromised patients

Changes in SARS-CoV-2 RT-PCR Ct values after symptom onset were compared between the two groups (Fig. 1A). The correlation between the Ct values and the number of days since symptom onset was significant for each group based on the linear regression line ($r=0.705$, $P<0.001$ in the immunocompromised group; $r=0.765$, $P<0.001$ in the control group). The slope of the linear regression line was markedly lower in the immunocompromised group than in the control group (0.37 vs. 0.75; interaction (B): -0.307 , 95% confidence interval (CI): -0.796 to 0.043 ; $P=0.078$), suggesting that the immunocompromised group showed a slower rate of viral clearance in the nasopharynx than the control group. The effects of monoclonal antibody therapy on Ct values were evaluated in the immunocompromised group (Fig. 1B). The slopes in the patients receiving and not receiving antibody therapies were 0.65 and

Table 1 Demographic and clinical characteristics in control and immunocompromised patients

Characteristic	control (n = 26)	immunocompromised (n = 28)	P value
Age, mean years (range)	53.5 (24–94)	55.0 (19–74)	0.591
Gender, male	16 (61.5)	12 (42.9)	0.17
Type of transplantation			
Kidney	N/A	15 (53.6)	N/A
Liver	N/A	4 (14.3)	N/A
Heart	N/A	3 (10.7)	N/A
Multiorgan (kidney and pancreas)	N/A	2 (7.1)	N/A
Hematologic stem cell	N/A	1 (3.6)	N/A
Immunosuppressive medication			
Calcineurin inhibitor	N/A	26 (92.9)	N/A
Mycophenolate mofetil	N/A	18 (64.3)	N/A
Steroids (Prednisolone or Methylprednisolone)	N/A	26 (92.9)	N/A
Calcineurin inhibitor + Mycophenolate mofetil + Steroids	N/A	16 (57.1)	N/A
Calcineurin inhibitor + Mycophenolate mofetil	N/A	1 (3.6)	N/A
Calcineurin inhibitor + Steroids	N/A	9 (32.1)	N/A
Chronic underlying disease			
Diabetes mellitus	2 (7.7)	18 (64.3)	< 0.001
Hypertension	7 (26.9)	21 (75.0)	< 0.001
Renal disease	3 (11.5)	5 (17.9)	0.396
Cardiac disease	3 (11.5)	4 (14.3)	0.543
Chronic pulmonary disease	2 (7.7)	2 (7.1)	0.666
Liver disease	2 (7.7)	2 (7.1)	0.666
Collagen disease	0 (0.0)	2 (7.1)	0.264
Hematologic malignancy	0 (0.0)	1 (3.6)	0.519
Solid cancer	1 (3.8)	0 (0.0)	0.481
Vaccination			
no vaccination	4 (15.4)	4 (14.3)	0.604
1 dose	0 (0.0)	1 (3.6)	0.519
2 doses	10 (38.5)	14 (50.0)	0.328
3 doses	4 (15.4)	7 (25.0)	0.381
4 doses	2 (7.7)	2 (7.1)	0.666
Unknown	6 (23.1)	0 (0.0)	0.009
Treatment for COVID-19			
Monoclonal antibody therapy	0 (0.0)	14 (50.0)	< 0.001
Sotrovimab	0 (0.0)	10 (35.7)	< 0.001
Casirivimab/imdevimab	0 (0.0)	4 (14.3)	0.065
Remdesivir	15 (57.7)	21 (75.0)	0.25
Molnupiravir	1 (3.8)	7 (25.0)	0.033
Steroids	7 (26.9)	10 (35.7)	0.487
Dexamethasone	6 (23.1)	7 (25.0)	0.869
Methylprednisolone	2 (7.7)	5 (17.9)	0.242
Severity of COVID-19 ¹⁾			
Asymptomatic	0 (0.0)	0 (0.0)	N/A
Mild/moderate	12 (46.2)	15 (53.6)	0.586
Severe	9 (34.6)	10 (35.7)	0.93
Critical	5 (19.2)	3 (10.7)	0.31
Clinical course			
Time from symptom onset to admission, mean days (range)	3.0 (0–17)	2.0 (0–22)	0.655
Length of stay, mean days (range)	9.0 (4–38)	17.5 (4–49)	0.001
Outcome			
Death	2 (7.7)	1 (3.6)	0.472
Readmission due to re-exacerbation	0 (0.0)	3 (10.7)	0.132

Table 1 (continued)

N/A not applicable, COVID-19 the coronavirus disease 2019

Data are no. (%) of individuals, unless indicated otherwise

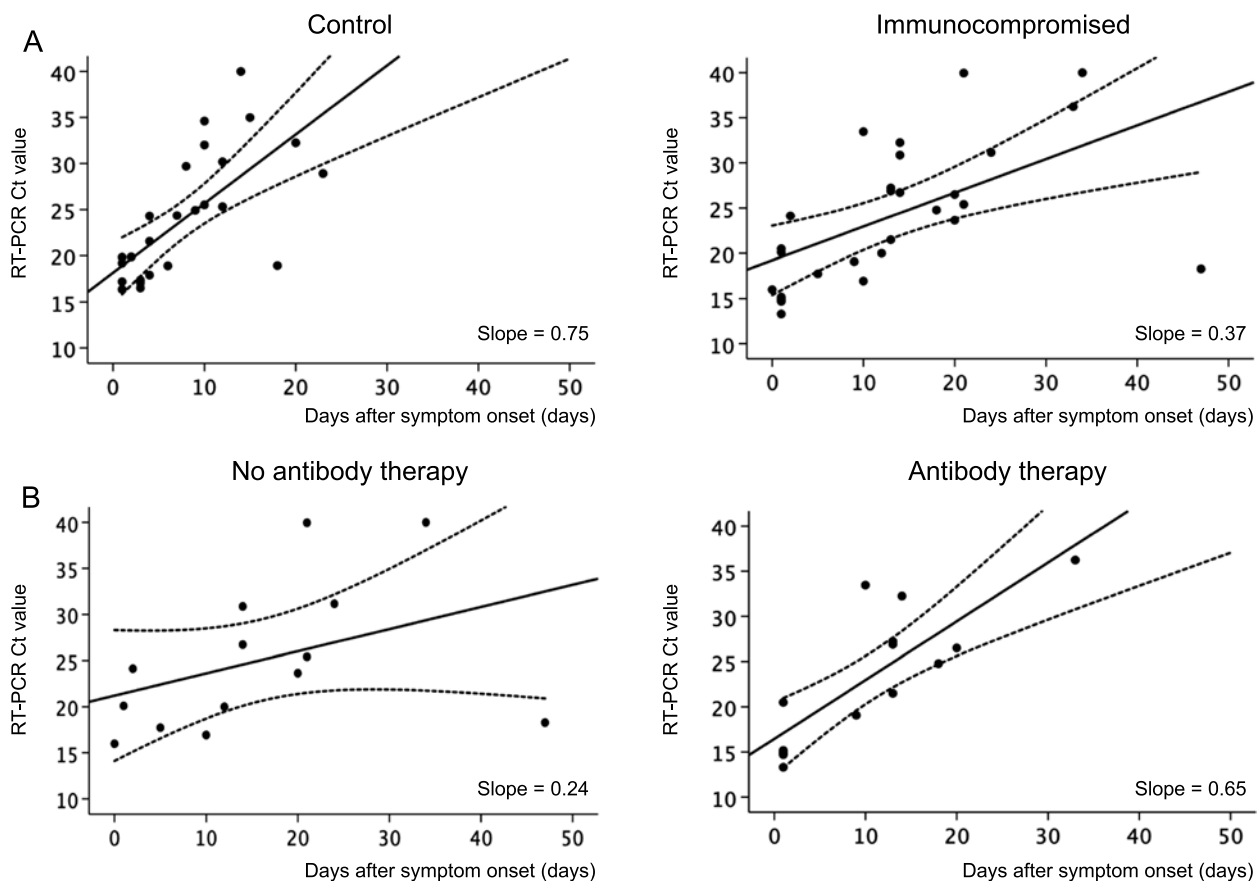
¹ The definition of severity of COVID-19 is based on reference no. 14

Fig. 1 Comparison of dynamics of nasopharyngeal SARS-CoV-2 RT-PCR Ct values after symptom onset between control and immunocompromised patients (A) and between immunocompromised patients receiving and not receiving monoclonal antibody therapies. The solid line represents the linear regression line for all plots, with the dotted curves indicating the 95% confidence interval (95% CI) for the regression line. The slope value of the linear regression line was calculated using linear regression analysis. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, real-time-PCR; Ct, cycle threshold

0.24, respectively (interaction (B): 0.41, 95% CI: -0.059 to 0.879 ; $P=0.083$).

The dynamics of anti-spike IgG titers in the immunocompromised and control groups are shown in Supplementary Fig. 1. The median anti-spike IgG titers in immunocompromised patients not receiving monoclonal antibody therapy were significantly lower than those in control patients, both in early serum samples (19.5 vs. 1683.0, $P<0.001$) and convalescent serum samples (900.8 vs. 5,000.0, $P<0.001$). The median anti-spike IgG titer in convalescent samples from immunocompromised patients receiving monoclonal antibodies

was comparable to that in control patients (2,300.0 vs. 5,000.0, $P=0.525$).

Clinical and virological characteristics

of immunocompromised patients with SARS-CoV-2 viremia

The incidence of SARS-CoV-2 viremia was significantly higher in the immunocompromised group than that in the control group (35.7% [10/28] vs. 11.5% [3/26]; $P=0.003$) (Fig. 2). The slope of the linear regression line based on the Ct values after symptom onset in immunocompromised patients with viremia tended to be considerably lower than that in patients without viremia (0.19

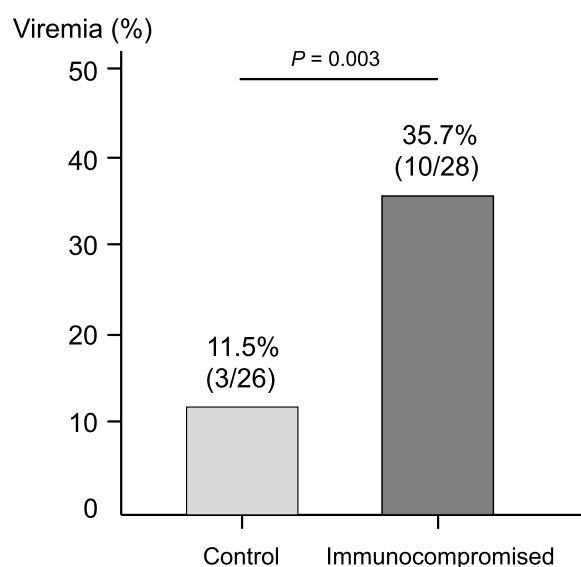


Fig. 2 Frequency of SARS-CoV-2 viremia in control and immunocompromised patients. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

vs. 0.65, $P=0.054$) (Supplementary Fig. 2). The demographic and clinical characteristics according to the presence or absence of viremia in the immunocompromised group are shown in Table 2. There were no differences in ages, types of organ transplantation, types of immunosuppressive medication, or comorbidities between the two groups. The frequency of booster (third and fourth) vaccinations was significantly higher in the patients without viremia than in those with viremia (50.0% [9/18] vs. 0.0% [0/10], $P=0.0098$). All three patients with critical disease in the severity of COVID-19 were included in the viremia group, of whom one died. All three patients with viremia in the control group were critical in terms of severity, of whom two died. The demographic and clinical characteristics of the 13 patients with viremia (10 in the immunocompromised group and 3 in the control group) are shown in Supplementary Table 2.

Discussion

Our study suggested that during the Omicron period of COVID-19, immunocompromised patients showed a slower decline in viral loads than control patients, based on nasopharyngeal SARS-CoV-2 PCR Ct values. This finding differs from that of a previous study with a larger number of immunocompromised patients [16] conducted during the Omicron epidemic. However, the definition of ‘immunocompromised’ used in the previous study included patients with a diverse mix of backgrounds. The immunocompromised group in our study consisted mainly of organ transplant recipients and was

limited to patients receiving immunosuppressive medications, which likely explains the difference in the results. Thus, our study suggests that a distinct immunosuppressed status results in slower SARS-CoV-2 clearance in individuals infected with the Omicron variants. Readmission, along with the re-exacerbation of symptoms observed in this study, may reflect delayed viral clearance. Previous reports have suggested virological and/or symptomatic re-exacerbations in immunocompromised patients with COVID-19 [19, 20]. In this study, immunocompromised patients receiving antibody therapy showed a faster reduction in viral load than those not receiving antibody therapy. Anti-spike IgG titers in immunocompromised patients who did not receive antibody therapy barely increased during the convalescent phase. In contrast, during the convalescent phase, anti-spike IgG titers in immunocompromised patients who received antibody therapy increased to levels comparable to those in the control group. These findings suggest that antibody therapy promotes viral clearance. Although half of the immunocompromised patients in our study received antibody therapy, the immunocompromised group in the overall analysis showed markedly slower viral clearance than the control group. In SARS-CoV-2 infected patients receiving immunosuppressive medications, viral clearance is likely to be significantly prolonged during the natural clinical course.

In terms of the comparison between the two groups in this study, a history of immunosuppressive medications did not appear to affect COVID-19 severity; however, the severity of severe and critical diseases accounted for approximately 50% of the immunocompromised group, potentially indicating a higher risk of disease severity. Notably, one-third of immunocompromised patients exhibited SARS-CoV-2 viremia. This likely reflected the depth of immunosuppression. In this study, no immunocompromised patients with viremia received a booster vaccination. It has been reported that SARS-CoV-2 vaccination is associated with protecting against the development of viremia [21]. The anti-spike antibody levels in our immunocompromised group were extremely low at the early onset of symptoms, regardless of the presence of viremia, suggesting that patients receiving immunosuppressive medications could not obtain sufficient antibody responses to SARS-CoV-2 vaccinations. Therefore, we cannot address whether SARS-CoV-2 booster vaccinations contribute to the prevention of viremia in an immunosuppressed state. Further investigation is required to address this issue.

In the overall analysis of this study, most patients with critical severity (6/8) and all patients with an outcome of death (3/3) were accompanied by SARS-CoV-2 viremia. Several studies have reported significant adverse effects

Table 2 Demographic and clinical characteristics according to the presence or absence of SARS-CoV-2 viremia in immunocompromised patients

Characteristic	no viremia (n = 18)	viremia (n = 10)	P value
Age, mean years (range)	57.0 (19–74)	49.5 (25–74)	0.487
Gender, male	8 (44.4)	4 (40.0)	0.57
Type of transplantation			
Kidney	10 (55.6)	5 (50.0)	0.544
Liver	2 (11.1)	2 (20.0)	0.452
Heart	3 (16.7)	0 (0.0)	0.249
Multiorgan (kidney and pancreas)	1 (5.6)	1 (10.0)	0.595
Hematologic stem cell	1 (5.6)	0 (0.0)	0.643
Immunosuppressive medication			
Calcineurin inhibitor	17 (94.4)	9 (90.0)	0.595
Mycophenolate mofetil	13 (72.2)	5 (50.0)	0.221
Steroids (Prednisolone or Methylprednisolone)	17 (94.4)	9 (90.0)	0.595
Calcineurin inhibitor + Mycophenolate mofetil + Steroids	12 (66.7)	4 (40.0)	0.103
Calcineurin inhibitor + Mycophenolate mofetil	0 (0.0)	1 (10.0)	0.357
Calcineurin inhibitor + Steroids	0 (0.0)	9 (90.0)	< 0.001
Chronic underlying disease			
Diabetes mellitus	12 (66.7)	6 (60.0)	0.519
Hypertension	14 (77.8)	7 (70.0)	0.491
Renal disease	2 (11.1)	3 (30.0)	0.228
Cardiac disease	3 (16.7)	1 (10.0)	0.548
Chronic pulmonary disease	0 (0.0)	2 (20.0)	0.119
Liver disease	1 (5.6)	1 (10.0)	0.595
Collagen disease	0 (0.0)	2 (20.0)	0.119
Hematologic malignancy	1 (5.6)	0 (0.0)	0.643
Vaccination			
no vaccination	3 (16.7)	1 (10.0)	N/A
1 dose	0 (0.0)	1 (10.0)	N/A
2 doses	6 (33.3)	8 (80.0)	N/A
3 doses	7 (38.9)	0 (0.0)	N/A
4 doses	2 (11.1)	0 (0.0)	0.01 ²⁾
Treatment for COVID-19			
Monoclonal antibody therapy	8 (44.4)	6 (60.0)	0.347
Sotrovimab	4 (22.2)	6 (60.0)	0.057
Casirivimab/imdevimab	4 (22.2)	0 (0.0)	0.149
Remdesivir	16 (88.9)	5 (50.0)	0.036
Molnupiravir	5 (27.8)	2 (20.0)	0.509
Steroids	6 (33.3)	4 (40.0)	0.519
Dexamethasone	5 (27.8)	2 (20.0)	0.509
Methylprednisolon	1 (5.6)	4 (40.0)	0.041
Severity of COVID-19 ¹⁾			
Asymptomatic	0 (0.0)	0 (0.0)	N/A
Mild/moderate	10 (55.6)	5 (50.0)	0.544
Severe	8 (44.4)	2 (20.0)	0.19
Critical	0 (0.0)	3 (30.0)	0.037
Clinical course			
Time from symptom onset to admission, mean days (range)	2.0 (0–22)	4.5 (1–20)	0.203
Length of stay, mean days (range)	19.5 (4–36)	12.0 (7–49)	0.962
Outcome			
Death	0 (0.0)	1 (10)	0.357
Readmission due to re-exacerbation	3 (16.7)	0 (0.0)	0.249

Table 2 (continued)

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, N/A not applicable, COVID-19 the coronavirus disease 2019

Data are no. (%) of individuals, unless indicated otherwise

¹ The definition of severity of COVID-19 is based on reference no. 14² The frequency of booster (third and fourth) vaccinations was compared

and mortality in COVID-19 patients with viremia [22–25]. These findings suggest that COVID-19 patients, particularly those with immunosuppressive conditions, are likely to be at potential risk of deteriorating the severity of COVID-19, along with viremia. Among the 13 patients with viremia in this study, most patients with critical severity did not receive monoclonal antibody therapy because they were not suitable for treatment at the time of admission. In contrast, most of the remaining patients with mild/moderate and severe severity received antibody therapy. This suggests that COVID-19 patients with viremia may worsen disease severity during the natural clinical course, possibly due to prolonged viral clearance, and that careful observation is necessary during the course of COVID-19, particularly in immunocompromised patients. In addition, this implies the contribution of antibody therapy to viral clearance and the reduction in severity and mortality, as reported previously [10]. After the Omicron variant wave, lower COVID-19 severity was reported in the general population [6–8]. However, for patients receiving immunosuppressive medications, categorized as moderately or severely immunocompromised [12], we need to recognize the possibility of a high risk for adverse severity and poor outcomes and the necessity of early treatment from onset, even during the Omicron epidemic.

There are several limitations in this study. The small sample size potentially results in a low statistical power, making it difficult to conclude the COVID-19 clinical course, severity, prognosis, and dynamics of SARS-CoV-2 viral loads in immunocompromised patients. In addition, it was difficult to adjust for potential confounding factors that could influence the outcomes, due to the small sample size. Large scale, multicenter, and international studies are required to resolve this issue. The study was not designed prospectively but was conducted retrospectively based on the physician-dependent collection of clinical information, laboratory data, and serum samples, which affects its reliability. The immunocompromised group in our study focused only on patients receiving immunosuppressive medications; however, this definition might restrict the applicability of the study findings because of the exclusion of patients receiving biological therapies such as rituximab. In this study, only serological immune responses were evaluated. A broader immunological analysis, including T-cell activity and cytokine profiles, should deepen the understanding of the virological and

clinical characteristics of immunocompromised patients infected with SARS-CoV-2. In this study, the long-term outcomes of COVID-19 in immunocompromised patients, such as the incidence of persistent symptoms (long COVID), were not evaluated. A longer follow-up period is required in future studies. The control group in this study was not prepared as immunocompetent individuals. Based on the study criteria, patients admitted to our hospital within a certain period were selected as controls. Severity in the control group did not reflect that of COVID-19 in the general population during the Omicron variant epidemic. Since the onset of SARS-CoV-2 pandemic, the Centers for Disease Control and Prevention (CDC) has recommended an isolation period of at least 20 days for moderately to severely immunocompromised patients [26]. Considering our findings, the duration of Omicron variant infectivity in immunocompromised patients treated with immunosuppressive drugs may be longer than that in non-immunocompromised patients. However, in this study, it was difficult to assess the isolation period based on infectivity because viral culture was not performed. The Omicron lineages that have mutated from the BA variants, during of which our study was conducted, have been circulating. Further studies on the relative effects of different Omicron subvariants are warranted.

Conclusions

Despite these limitations, the results of this study are clinically relevant. Even though the control patient was not necessarily immunologically competent, a history of immunosuppressive medications is likely to be associated with the prolongation of SARS-CoV-2 viral clearance and the development of viremia in immunocompromised patients, based on a comparison between the two groups. In addition, the virological features of immunocompromised patients receiving immunosuppressive medications may affect disease severity, symptom remission, and prognosis. Most immunocompromised patients in our study received multiple COVID-19 medications, including antiviral and antibody therapies. Monoclonal antibody therapies against the current Omicron variants are not available because of significant changes in antigenicity. It remains a concern that some immunocompromised patients receiving currently available antiviral medications experience

worsening symptoms, severity, and outcomes. Further information needs to be collected on the clinical course, including severity, mortality, and re-exacerbation of immunocompromised patients infected with currently circulating SARS-CoV-2 variants and receiving currently available medications.

Abbreviations

COVID-19	Coronavirus disease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
NIH	National Institute of Health
RT-PCR	Real-time-Polymerase chain reaction
Ct	Cycle threshold
CDC	Centers for Disease Control and Prevention
RBD	Receptor-binding domain
CI	Confidence interval
Ig	Immunoglobulin

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-024-09633-1>.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.

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Authors' contributions

KN and YC collected epidemiological data. TG, KS, AY and YE collected serological data. KN, TG and YC performed data analysis and interpretation. KN and YC drafted the manuscript, and YC, KA, and NS revised the manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials

The data analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The requirement for patient consent was waived because the study used de-identified data. The study was approved by the Ethics Committee of Kyushu University (Approval No: 22241–00).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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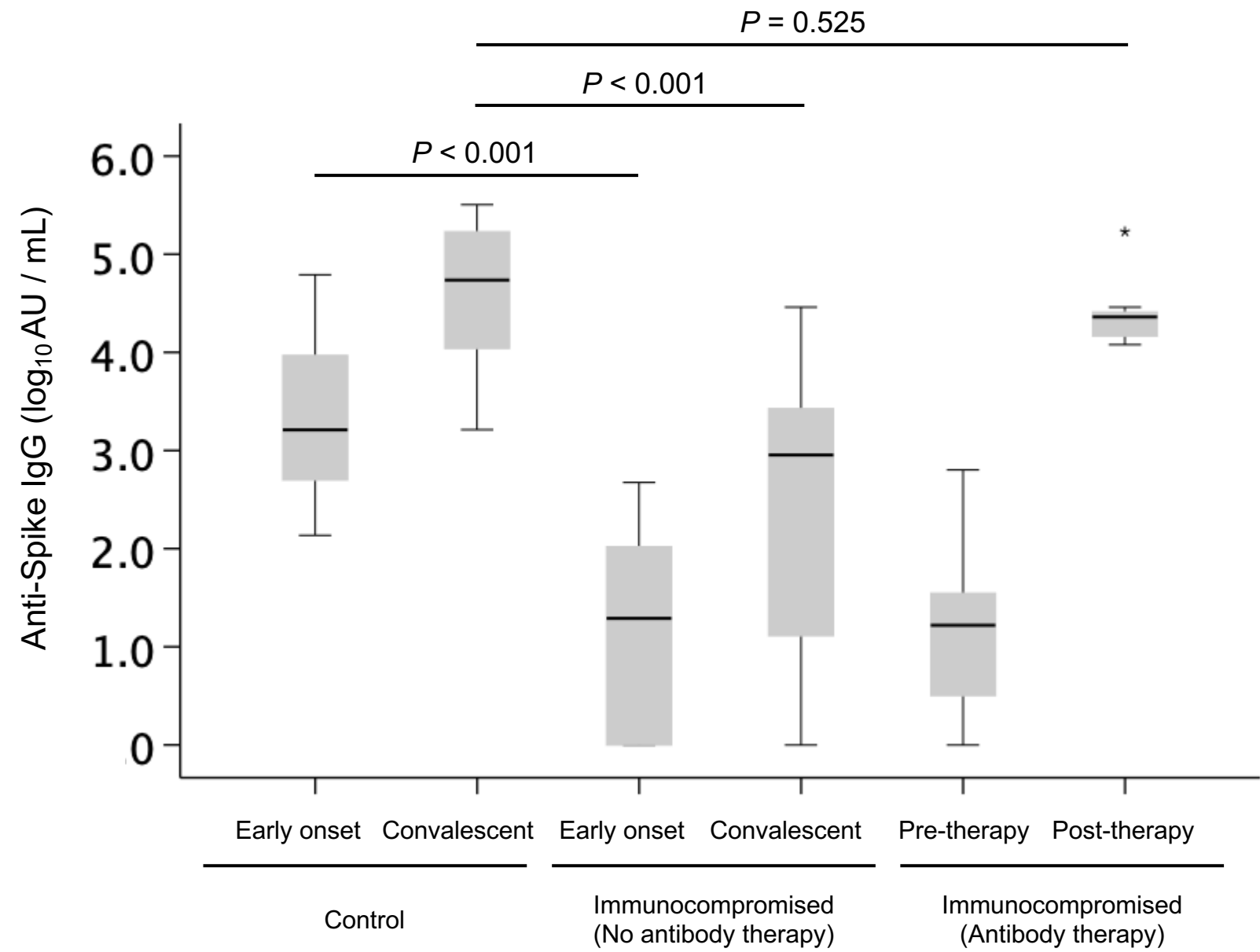
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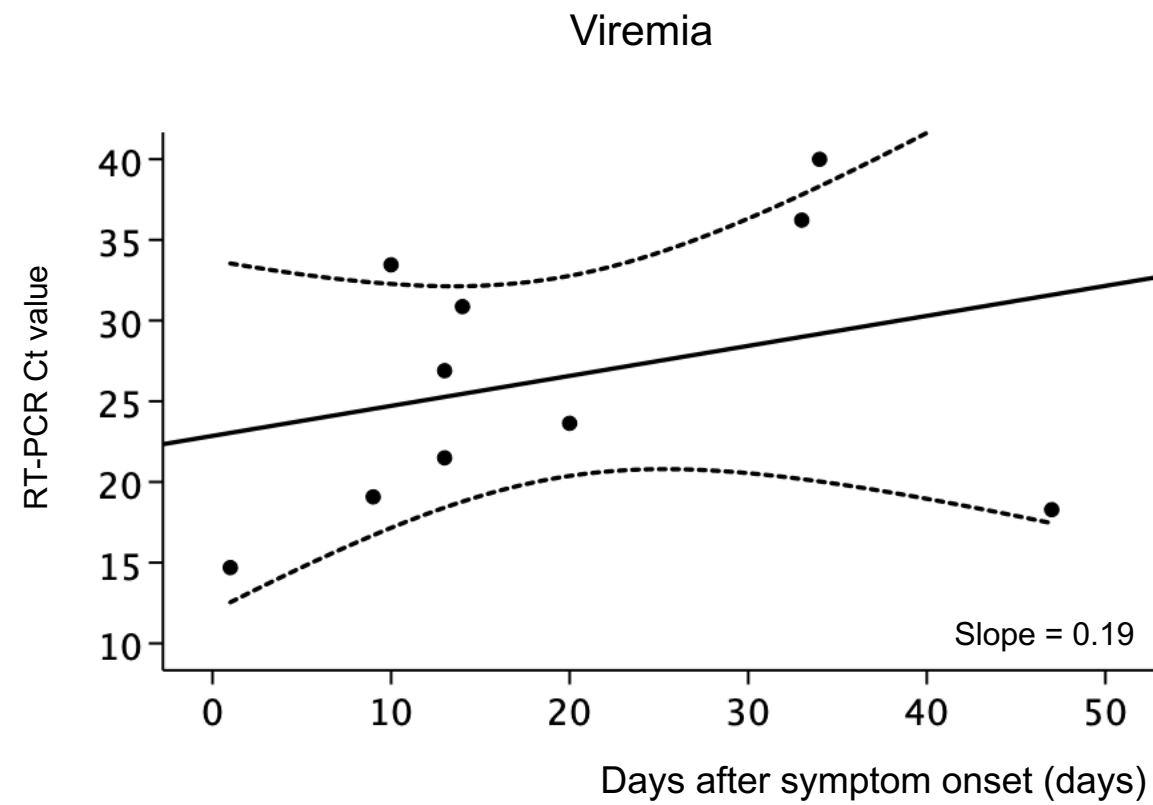
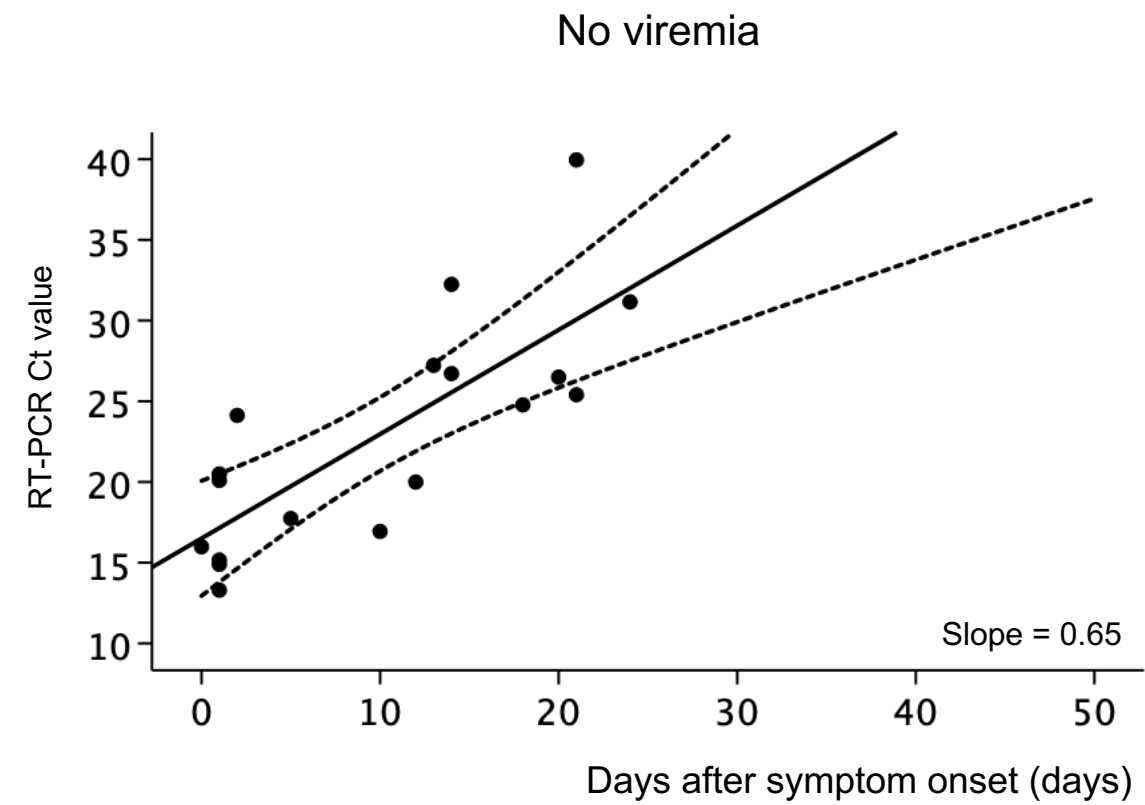
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Supplementary Figure 1



Supplementary Figure 2



Supplementary Table 1. Demographic and clinical characteristics in patients with readmission due to symptom re-exacerbation

Age/gender	Type of transplantation	Immunosuppressive medication	Chronic underlying disease	RT-PCR Ct value on 1st admission (days from symptom onset)	Severity (1st admission)	Treatment (1st admission)	Time from onset to 1st discharge	Time from onset to readmission	RT-PCR Ct value on readmission (days from initial symptom onset)	Severity (readmission)	Treatment (readmission)	Outcome
60/male	Kidney	Tac 4mg, MMF 1000mg, mPSL 4mg	DM, HT	14.3 (day 3)	Mild/moderate	Molnupiravir	10	12	20.0 (day 12)	Severe	Remdesivir	Improve
64/male	Kidney	Tac 0.5mg, MMF 500mg, mPSL 2mg	HT, Cardiac disease	16.6 (day 2)	Mild/moderate	C/I+Molnupiravir	10	20	24.0 (day 20)	Mild/moderate	Dexamethasone	Improve
55/female	Kidney	Tac 2mg, MMF 1000mg, mPSL 4mg	DM, HT	18.0 (day 1)	Mild/moderate	C/I+Molnupiravir	7	15	25.0 (day 15)	Mild/moderate	Remdesivir	Improve

RT-PCR, real-time-PCR; Ct, cycle threshold ; Tac, tacrolimus; MMF, mycophenolate mofetil; mPSL, methylprednisolone; DM, diabetes mellitus; HT, hypertension; C/I, casirivimab/imdevimab

Supplementary Table 2. Demographic and clinical characteristics in control and immunocompromised patients with SARS-CoV-2 viremia

Group	Age/gender	Type of transplantation	Immunosuppressive medication	Chronic underlying disease	Vaccination (dose)	Time from onset to admission (days)	Severity	Treatment	Length of stay (days)	Outcome
Control	61/male	N/A	N/A	Solid cancer (HCC)	2	7	Critical	Dexamethasone+mPSL	11	Death
Control	72/female	N/A	N/A	DM, Renal disease	Unknown	6	Critical	mPSL	28	Improve
Control	75/male	N/A	N/A	DM	Unknown	7	Critical	Remdesivir +mPSL	17	Death
Immunocompromised	53/female	Multiorgan	Tac 3mg, MMF 500mg, mPSL 4mg	DM, HT	2	20	Critical	Sotrovimab+Remdesivir	43	Improve
Immunocompromised	71/male	Liver	Tac 1mg, PSL 4mg	DM, HT, Renal disease	2	6	Critical	Dexamethasone +mPSL	49	Death
Immunocompromised	57/female	N/A	PSL 15mg	Collagen disease (RA)	None	6	Critical	Remdesivir+mPSL	32	Improve
Immunocompromised	38/female	Kidney	Tac 4mg, MMF 1000mg, mPSL 2mg	DM, HT, Renal disease	2	12	Severe	Sotrovimab+mPSL	44	Improve
Immunocompromised	74/female	N/A	Tac 0.5mg, PSL 4mg	Collagen disease (RA, SLE)	1	1	Severe	Remdesivir	10	Improve
Immunocompromised	41/male	Kidney	Tac 5mg, PSL 12.5mg	HT	2	2	Mild/moderate	Sotrovimab+Remdesivir	11	Improve
Immunocompromised	46/female	Kidney	Tac 4.5mg, mPSL 4mg	HT	2	3	Mild/moderate	Sotrovimab	7	Improve
Immunocompromised	25/male	Kidney	Tac 5mg, MMF 1250mg	DM	2	1	Mild/moderate	Sotrovimab	9	Improve
Immunocompromised	42/male	Kidney	Tac 2mg, MMF 1500mg, mPSL 4mg	DM, HT, Renal / Cardiac disease	2	20	Mild/moderate	Molnupiravir	13	Improve
Immunocompromised	62/female	Liver	CyA 50mg, MMF 1000mg, PSL 5mg	Liver disease	2	2	Mild/moderate	Sotrovimab+Remdesivir	9	Improve

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; N/A, not applicable; Tac, tacrolimus; MMF, mycophenolate mofetil; mPSL, methylprednisolone; PSL, prednisolone; CyA, cyclosporine A
HCC, hepatocellular carcinoma; DM, diabetes mellitus; HT, hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus