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ORIGINAL ARTICLE

Clinical Burden of Cytomegalovirus Infection Post-kidney Transplantation in Japan

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Abstract

Objective：Cytomegalovirus（CMV）infection is a major complication following kidney transplantation（KTx）. We aimed to investigate the clinical burden of CMV infection in KTx patients in Japan.

Methods：KTx patients were identified using an administrative claims database（JMDC Inc.）. Patients who underwent KTx without CMV prophylaxis between January 1, 2012 and December 31, 2021 with 12-month follow-up date were divided into 2 groups based on the presence or absence of CMV episode during the follow-up period：patients with CMV infection requiring prescription for anti-CMV drugs（i.e., CMV episode）, and patients without any CMV episode.

Results：In total, 291 KTx patients were identified；36.4% experienced at least one CMV episode. Among patients with CMV episode(s), 56.6% had recurrent episode(s), with a mean of 2.2 recurrences. Significantly more patients with CMV episode(s) experienced myelotoxicity（31.1% vs. 9.7%；$p<0.01$）. Additionally, patients with CMV episode(s) had more hospitalizations（2.9 vs. 2.3；$p<0.01$）and longer hospital stays（49.1 vs. 35.2 days；$p<0.01$）compared to those without CMV episode.

Conclusion：This study demonstrated that CMV infection occurred in more than one third of KTx patients in Japan and caused a significant burden after KTx in terms of clinical outcomes and healthcare resource utilization.

Introduction

Cytomegalovirus（CMV）infection is one of the most common infections after kidney transplant（KTx）and such complications can negatively impact post-transplantation outcomes[1]. The cumulative morbidity of complications resulting from the direct and indirect consequences of CMV infection is considerable and is thought to partially derive from the immunomodulating effects of such infections[2]. The indirect effects of this infection include elevated risks for poor outcome such as bacterial, fungal and viral infections, immunosenescence, acute transplant rejection and graft loss. The main risk factor for CMV infection in organ transplantation depend on the CMV serostatus of donors and recipients[3]. Other risk factors for infection after transplant include the intensity of immunosuppression, advanced age and comorbidities which vary depending on the demographics of the transplant population in question.

Although the number of KTx in Japan is still small compared to other high income countries, the relative number of KTx in Japan is increasing and 1782 KTx were conducted in 2022[4)5)]. In 2022, out of the 1488 live KTx with CMV-antibody testing results, 180（12.1%）were in seronegative recipients（R－）with seropositive donors（D＋）and 923（62.0%）were R＋transplants[5]. Ganciclovir（GCV）is indicated for treatment and valganciclovir（VGCV）is indicated for both prevention and treatment of CMV infection/disease in KTx in Japan. However, these two conventional antiviral drugs can cause myelosuppression and therefore require regular hematological monitoring[6] and renal function-based dose adjustments due to the fluctuation of kidney function. In CMV management, VGCV prophylaxis is associated with similar life expectancy and renal loss compared with preemptive therapy in patients at high（D＋/R－）and intermediate（R＋）risk for CMV infection[7)8)]. Since the development of CMV infection is associated with poor outcomes and increased health care costs, practice guideline for solid organ transplantation-related CMV disease from the Japan Society for Transplantation recommends VGCV prophylaxis not only for patients at high risk for CMV infection but also for patients at intermediate risk although preemptive therapy for CMV infection is as effective as prophylaxis[9]. Nonetheless, preemptive therapy is still a useful option and has been widely used to manage CMV infection after solid organ transplantation including KTx in Japan.

Despite the growing body of evidence on CMV infection in the international transplant population[10)11)], there is a paucity of data from Japan on the clinical burden of CMV infection under preemptive therapy after KTx. Understanding the clinical burden of CMV infection which requires treatment with anti-CMV drugs（i.e., CMV episode）is vital for optimizing management strategies and improving patient outcomes in this population.

Abbreviations：CMV；cytomegalovirus, KTx；kidney transplant, ER；emergency room, GCV；ganciclovir, VGCV：valganciclovir, HCRU；healthcare resource utilization, ICU；intensive care unit, ICD-10；international statistical classification of diseases and related health problems, 10th revision, S.D.；standard deviation, IQR；interquartile range, STROBE；strengthening the reporting of observational studies in epidemiology, CONSORT；consolidated standards of reporting trials

Using one of the largest medical claims databases available in Japan, this study investigated the clinical burden and health care resource utilization (HCRU) associated with CMV episode(s) post-KTx in clinical settings in Japan.

Ⅰ Methods

1. Data Source

Patients who underwent KTx during an identification period of January 1, 2012 to 12 months prior to the end of the study period (December 31, 2021) were retrospectively identified from an anonymized employer-based health insurance claims database provided by JMDC Inc. This database includes inpatient, outpatient, medication dispensing services and annual health check results from about 14 million patients in Japan. Data can be used to follow patients longitudinally between medical institutions as long as the patients remain with the same health insurance association.

2. Study population

To be included in this analysis patients must have met all of the following criteria : 1) aged ≥18 years on the index date, 2) had at least one procedure claim for KTx during the identification period, 3) can be followed for ≥12 months from the index date. The date of first procedure claim for KTx was defined as the index date. For patients whose first claim for KTx had missing date, patients must have met at least one of the additional criteria to identify the index date : 4a) had a claim for basiliximab, which has been widely used as an induction therapy on the day and 4 days after KTx, in the same month as a claim for KTx[12] or 4b) had a claim for anesthesia in the same month as the KTx claim. Patients were excluded if they had received CMV prophylaxis (defined as VGCV prescription within 10 days after index date), as well as a claim for letermovir or simultaneous pancreas-kidney transplant during the study period.

Patients were then categorized into those who experienced at least one CMV episode and those who did not. More specifically, patients with CMV episode(s) were those who experienced at least one CMV infection [International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) : B25x, B271] during the 12-month follow-up period and at least one claim for any anti-CMV drug (GCV and VGCV) in the same month to exclude patients who received anti-CMV drugs to treat other herpes virus as well as patients who may have had a claim code for CMV infection for suspected CMV infection to receive examinations. Anti-CMV drugs for treatment purposes was defined as administration of VGCV at least 11 days after index date, or the administration of GCV on/after index date. Patients who did not experience a CMV episode were those without any claim for CMV infection and without any anti-CMV drug during the 12-month follow-up period. It should be noted that another anti-CMV drug, foscarnet, is not reimbursed for the purpose of CMV treatment in KTx patients by Japanese health insurance (i.e., off-label use) and therefore this prescription could not be captured from the claims database.

The follow-up period was defined as 12 months from the index date to ensure sufficient time to capture CMV episodes as well as HCRU associated with CMV infection.

The date of the first claim for any anti-CMV drug administration during the follow-up period, with a record of any specified ICD-10 diagnosis code during the same month, was defined as the start date of the CMV episode. The first date of the prescription claim for the same or different treatment administered at least 8 days after the last prescription of the previous treatment was considered the start date of a separate CMV episode.

3. Outcome measures

Clinical outcomes included HCRU for the applicable patient groups calculated per patient for those with at least one relevant claim during the follow-up period. These endpoints included number of outpatient visits, hospitalizations, emergency room (ER) visits, intensive care unit (ICU) admissions as well as length of hospitalization and ICU stay. Additionally, anti-CMV drug utilization was examined along with laboratory testing related to CMV infection.

Secondary clinical endpoints for each patient group included graft loss, transplant rejection, time to CMV infection and recurrent CMV episodes. Exploratory endpoints were calculated per patient for both patient groups, as applicable, during the 12-month follow-up period. These endpoints included mean daily dosage of immunosuppressant drugs as well as frequencies of myelotoxicities.

Only anonymized secondary data was used in this analysis, and additionally, informed consent was not required according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan (MHLW)[13]. This study received ethical approval (Takahashi Clinic Ethics Committee Approval Number : NIS100264) in order to establish alignment with those guidelines.

4. Statistical analysis

Continuous variables were summarized using mean, standard deviation (S.D.) and, where appropriate, median and interquartile range (IQR). Categorical variables were summarized using frequency and percentage. As the study objectives were descriptive in nature, missing data was not imputed. Statistical comparison between patients with and without CMV episode was performed for the primary, secondary and exploratory endpoints when applicable to both groups. T-tests were used to compare continuous outcomes, and chi-square or Fisher's exact test was used for categorical variables. For median values of continuous variables, the Wilcoxon rank sum test was conducted. Time-to-event outcomes were calculated as the number of days from index date to the first occurrence date of an event plus one for those with an event and follow-up was truncated at 1 year to ensure comparability and that all events could be captured within the enrollment period. A two-sided significance level was set at $\alpha = 0.05$ (p-value< 0.05) for all statistical testing. All data analyses were performed using SAS® version 9.4 or higher and in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and applicable sections of the Consolidated Standards of Reporting Trials (CONSORT) guidelines[14)15)].

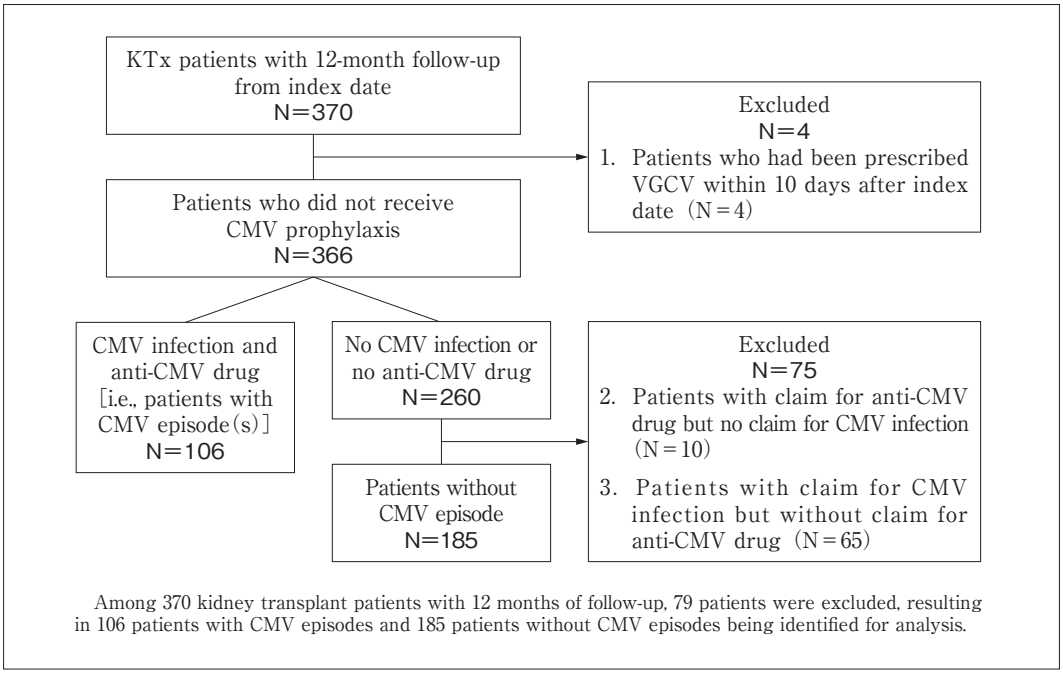


Figure 1 Selection of study population

Ⅱ Results

Of the 370 patients initially identified with KTx and had 12 months of follow-up date, a total of 79 patients were excluded from the analysis. The reasons for exclusions included four patients who were prescribed VGCV within 10 days of KTx, 10 patients who had a claim for an anti-CMV drug but without a diagnosis claim for CMV infection during the follow-up period, and 65 patients who had a diagnosis claim for CMV infection without a claim for any anti-CMV drug occurring during the follow-up period. Overall, 106 patients with CMV episode(s) and 185 patients without CMV episode were identified (**Figure 1**).

The mean age was similar across patient groups (approximately 45 years-old) with females accounting for slightly more than one third of each group. Modified Charlson Comorbidity Index scores were slightly higher in patients with CMV episode(s) compared to patients without CMV episode (2.86 vs. 2.59, respectively). Most patients in both groups received basiliximab (98.11% for patients with CMV episode(s) vs. 96.22% for patients without CMV episode) (**Supplementary Table 1**).

Included in this analysis 36.42% (106/291) of patients experienced CMV infection which required treatment with anti-CMV drug(s) at least once (**Table 1**). Patients with CMV episode(s) had their first CMV episode on mean 63.95 days following KTx, with 73.58% of episodes occurring on or within 90 days. Additionally, 56.60% of patients with CMV episode(s) experienced recurrent CMV episodes and the mean number of recurrent CMV episodes was 2.15.

Table 1 CMV infection episode

	Patients with CMV episode(s) (n＝106)
Time from KTx to first CMV episode, days；mean（S.D.）	63.95（49.82）
Number of patients with initial onset of CMV episode	
Occurring ≤90 days from KTx, n（%）	78（73.58）
Occurring ＞90 days from KTx, n（%）	28（26.42）
Number of patients who experienced CMV diseases and/or syndrome, n（%）	11（10.38）
Number of patients who experienced recurrent CMV episode, n（%）	60（56.60）
Number of recurrent CMV episodes, mean（S.D.）	2.15（1.60）

S.D.；standard deviation

In this study, 36.42% of patients experienced CMV episode(s) with the first CMV episode occurring on mean 63.95 days following KTx. Furthermore, 56.60% of patients with CMV episodes experienced recurrent episodes, with an mean of 2.15 recurrent episodes.

Table 2 Clinical conditions of patients over the 12-month follow-up period

	Patients with CMV episode(s) (n＝106)	Patients without CMV episode (n＝185)
Number of patients with graft loss, n（%）	2（ 1.89）	0（ 0.00）
Number of patients with transplant rejection, n（%）	38（35.85）	47（25.41）
Number of patients with tubulointerstitial nephritis, not specified as acute or chronic, n（%）	25（23.58）	29（15.68）

The most common clinical condition reported was transplant rejection, and less than 2% of patients in either group experienced graft loss.

During their first CMV episode, patients received an mean（S.D.）of 28.14（27.71）days of anti-CMV treatment. However, the mean number of days to treat a recurrent infection was 3 days longer than a first CMV episode [31.15 (31.65)]. Patients with CMV episode(s) had significantly more claims than patients without CMV episode for laboratory tests such as CMV pp65 antigen（16.16 vs. 11.23, $p<0.01$）and viral antibody titer（1.87 vs. 1.24, $p<0.05$；**Supplementary Table 2**）.

Among the clinical conditions listed in **Table 2**, the most common condition reported was transplant rejection. While not statistically significant, more patients with CMV episode(s) tended to experience kidney rejection than patients without CMV episode（35.85% vs. 25.41%）. Less than 2% of patients in either

Table 3 Immunosuppressive drug utilization

	Patients with CMV episode(s) (n = 106)	Patients without CMV episode (n = 185)
Tacrolimus, n (%)	94 (88.68)	163 (88.11)
Mean daily dosage of tacrolimus per patient (mg), mean (S.D.)	3.61 (1.69)	3.63 (1.81)
Cyclosporin, n (%)	21 (19.81)	19 (10.27)
Mean daily dosage of cyclosporin per patient (mg), mean (S.D.)	101.42 (54.52)	126.14 (77.63)
Everolimus, n (%)	40 (37.74)	49 (26.49)
Mean daily dosage of everolimus per patient (mg), mean (S.D.)	1.16 (0.33)*	1.41 (0.60)*
Mycophenolate mofetil, n (%)	104 (98.11)	161 (87.03)
Daily dosage of mycophenolate mofetil per patient (mg), mean (S.D.)	1198.96 (309.63)*	1288.52 (287.56)*

*：$p<0.05$；**：$p<0.01$
IQR；Interquartile range, S.D.；standard deviation

Note：The mean daily dosage of methylprednisolone will be adjusted (multiplied by 1.25) and reported as part of the mean daily dosage for prednisolone.

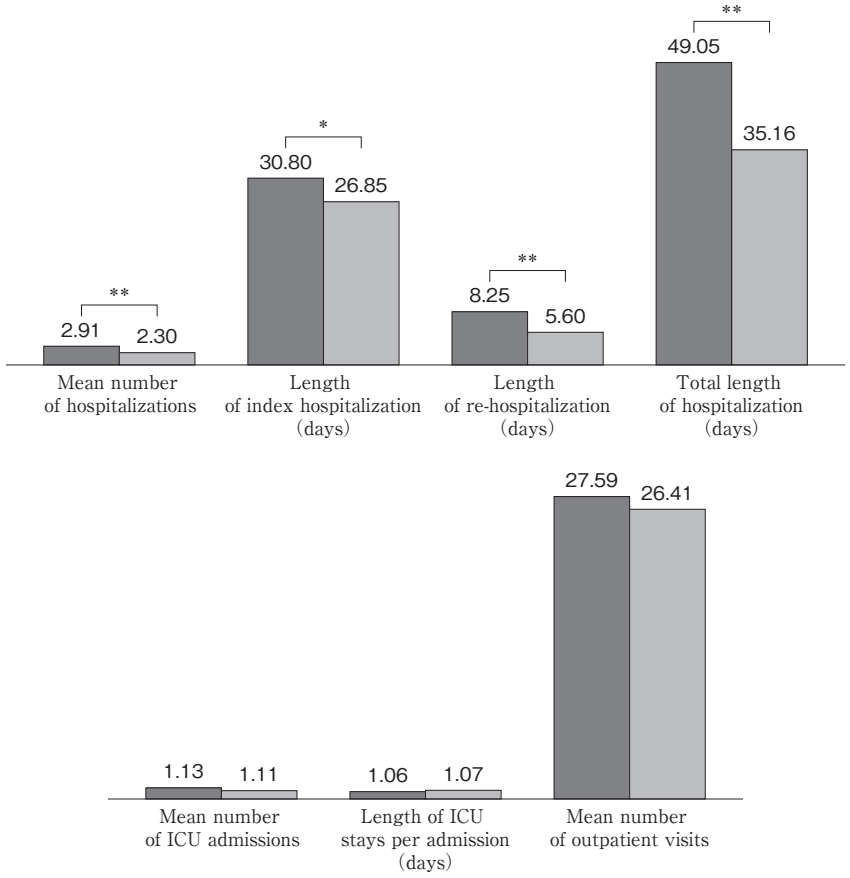
In the standard immunosuppressive regimen, most patients received tacrolimus and mycophenolate mofetil.

group experienced graft loss.

The proportion of patients with experiences of myelotoxicity was significantly higher among patients with CMV episode(s) (31.13% vs. 9.73%, $p<0.01$). A similar trend was observed for frequency of neutropenia (29.25% vs. 7.57%, $p<0.01$) (**Supplementary Table 3**).

As a standard immunosuppressive regimen, most patients received tacrolimus and mycophenolate mofetil (**Table 3**) regardless of patient groups although the proportion of patients who received mycophenolate mofetil was slightly less in patients without CMV episode(s) than in patients with CMV episode(s) (98.11% vs. 87.03%, no statistical analysis was conducted). However, prescription of everolimus was more common among patients with CMV episode(s) (37.74%, no statistical analysis was conducted) than among those without (26.49%) (**Table 3**). The mean daily dose of immunosuppressants was lower for everolimus (1.16 vs. 1.41 mg/day, $p<0.05$) and mycophenolate mofetil (1198.96 vs. 1288.52 mg/day, $p<0.05$) among patients with CMV episode(s).

In terms of HCRU, patients with CMV episode(s) had significantly more hospitalization admissions (2.91 vs. 2.30；$p<0.01$), longer length of index hospitalization (30.80 vs. 26.85 days；$p<0.05$) and re-hospitalization (8.25 vs. 5.60 days；$p<0.01$), and total hospitalization (49.05 vs. 35.16 days；$p<0.01$) during follow up (**Figure 2**). The number of outpatient visits, as well as ICU admissions, did not significantly differ



Patients with CMV episodes had significantly more hospitalization admissions, longer length of index hospitalization, and re-hospitalization, resulting in increased total hospitalization during follow-up, while the number of outpatient visits and ICU admissions did not significantly differ between the groups.

Figure 2 Healthcare resource utilization over the 12-month follow-up period

between the groups.

Ⅲ Discussion

In this study, we observed a substantial increase in the clinical burden among KTx recipients with CMV episode(s) in Japan, particularly in terms of direct/indirect CMV treatment effects (e.g. side effects due to anti-CMV drugs and dose adjustment of immunosuppression) and HCRU (e.g. hospitalizations). Approximately 36% of KTx patients in this analysis developed CMV episode(s), with more than 70% of these cases occurring within the first 90 days post-transplantation without CMV prophylaxis. Although the data of CMV serostatus were not available in the database,

and the risk status of CMV infection in each patient was unknown, these findings are consistent with previous studies conducted in Japan and Brazil, where CMV infection rates were reported to be 38% in high-risk transplant patients (D+/R−)[16] and 39% in intermediate-risk transplant patients (R+) who received preemptive anti-CMV treatment[17], respectively. In another study from Japan, median duration from KTx to CMV infection was 69 days[18]. Importantly, the patient groups included in our analysis exhibited similar age distributions and comorbidity profiles at the time of KTx, regardless of subsequent CMV infection status. These similar groups provided a valuable baseline for assessing the differential post-KTx outcomes associated with CMV episode(s).

This study focused on patients who experienced CMV episode(s), which is CMV infection requiring treatment with anti-CMV drugs, and it was observed that a significantly higher proportion of patients with CMV episode(s) experienced myelotoxicity compared to those without CMV episode, potentially attributable to the use of anti-CMV drugs. It is important to note that only patients with CMV episode(s) received anti-CMV drugs (GCV or VGCV), which have been reported to cause myelotoxicity in transplant recipients[2].

Recurrent CMV episodes among KTx recipients were observed in more than half of the patients (56.60%) with CMV episode(s) in this study and the frequency of recurrent CMV episodes was relatively high compare to those previously reported, which further emphasized the necessity of improvement of current CMV management in Japan. A study conducted in the United States involving 170 solid organ transplant patients reported that 29% of the participants experienced recurrent CMV episodes. Among these cases, 67% occurred within 6 months (with a median of 3 months) after completing treatment for their initial CMV episode[19]. Similarly, in an observational study involving 282 transplant patients who had experienced a CMV infection, 30.5% of patients subsequently developed recurrent CMV episodes. The median time to recurrence was 51 days after discontinuation of treatment for CMV infection[20]. Besides additional treatment, adjustment of immunosuppression and resource use, recurrent CMV can also negatively affect graft function and promote viral resistance to anti-CMV drugs.

In Japan, basiliximab is the most common induction therapy and triple therapy with calcineurin inhibitors (tacrolimus or cyclosporin), mycophenolate mofetil and steroid is a standard immunosuppression regimen in KTx patients as shown in this study[21]. Patients with CMV episode(s) received lower daily doses of some immunosuppressants and were more likely to receive everolimus than those without CMV episode. Mycophenolate mofetil is an immunosuppresaant, which is commonly reduced or stopped when CMV infection occurs. This immunosuppressant is then usually replaced with another immunosuppressive mTOR inhibitor, everolimus, that has effective anti-CMV activity. A pooled analyses of 3 randomized controlled trials in kidney transplant patients, showed that patients who received everolimus had significantly fewer CMV events than those who received mycophenolate, with or

without prophylaxis[22]. Therefore, it is reasonable to speculate that other immunosuppressants were switched to everolimus when patients experienced CMV episode. A study conducted on a large cohort of KTx recipients in Brazil reported that changes in immunosuppression and acute transplant rejection were significantly more common in patients with CMV infection compared to those without (63% vs. 31%)[23]. These findings suggest that immunosuppressants were modified, reduced or discontinued to manage CMV infection, which may have led to the increased frequency of poor outcomes such as transplant rejection in patients with CMV episode(s) although the exact date of rejection occurred was not able to be captured and the incidence of rejection before CMV infection/disease was unknown in this study. In the real-world clinical setting it is important to carefully balance the duration and intensity of immunosuppressive therapy to minimize the risk of CMV infections and their recurrence, while still maintaining adequate immunosuppression to prevent rejection[24]. Implementing CMV prophylaxis rather than preemptive therapy helps to simplify the management of immunosuppression especially during the period when CMV infection frequently happens in high-risk patients for CMV infection, which may reduce the burden of CMV infection in terms of patients' clinical outcomes and HCRU. In this study, the mean daily dose of steroid, which is commonly used in KTx patients together with a calcineurin inhibitor (i.e., tacrolimus or cyclosporin) and mycophenolate mofetil for maintenance immunosuppressive therapy, was not calculated. High doses of steroid can be used for steroid pulse therapy when KTx patients experience rejection. However, it was not possible to distinguish the use of steroid for immunosuppressive maintenance from for treatment of rejection due to the nature of the database and calculating the mean daily dose of steroid was considered not informative.

The clinical burden of CMV infection in KTx patients extends beyond the direct impact on patient health, as it also leads to increased HCRU. Our findings in Japan align with this observation, as we found that patients with CMV episode(s) had a significantly higher mean length of hospitalizations compared to those without CMV episode (49.05 vs. 35.16 days). Another study in Japan found a similar length of hospitalization post-KTx (median : 37 days, IQR : 29-63) for a cohort that included CMV-infected patients[16]. Although the actual health care cost related to CMV infection was not calculated in this study, the prolonged length of hospitalizations would have contributed to the increased health care cost. In addition, unlike CMV prophylaxis, preemptive therapy does not require routine administration of VGCV but the cost of VGCV for prophylaxis may be less expensive than the treatment of CMV infection overall in some patients. Further studies are warranted to minimize HCRU related to CMV infection by optimizing CMV management.

Finally, there are several limitations to this analysis that should be noted. The JMDC database is comprised of health insurance claims for reimbursement. Records of diagnoses in the JMDC data may include an apparent disease (so-called disease name for claims) as a diagnosis in order to charge

medical fees or examination of medical practice performed（drug prescription, etc.）. Therefore, administrative health records may not accurately reflect the actual clinical status of patients due to the limitations of claims data processing. In some cases, higher-level disease is coded rather than specific disease typology.

Approximately 1800 KTx are annually conducted in Japan[5] and the number of KTx patients included in this study was much smaller than the actual number of KTx conducted during the study period. However, a sufficient number of KTx recipients were captured in this analysis which allowed statistical comparison based on CMV episode status. Patients included in the JMDC database are collected through participating employer health insurance associations. Unfortunately, the number of institutions included in this study was unknown. However, KTx is performed at only 138 hospitals in Japan and large variations in KTx procedures and management among institutions were not expected[5]. Few individuals over 60 years of age, who may have more comorbidities and worse outcomes, are included. However, as the age range of the majority of insured individuals enrolled in the JMDC database（18-64 years old：74%）is adequately aligned with the basic age criterion（between 20 and 70 years）for adult transplant eligibility in Japan[5], this database can be considered to be appropriate for use to understand real-world trends in CMV infection in KTx.

Conclusions

CMV infections occurred in a considerable proportion of KTx patients in Japan. Such infection complicates post-transplantation recovery and management, leading to increased myelosuppression and inappropriate dose adjustment of immunosuppressive drugs. The side effects of treatment for CMV infection and inadequate immunosuppression due to CMV infection may have been associated with worse transplant outcomes. Furthermore, CMV infection was linked with increased clinical burden including HCRU. These real-world outcomes highlight that there is a room for improvement of current CMV management using preemptive therapy in Japan, and optimizing the frequency of CMV monitoring and implementing CMV prophylaxis with anti-CMV drugs in high-risk KTx patients for CMV infection may help to reduce the incidence and burden of CMV infection in KTx.

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Funding/Support and Conflict of Interest

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The publication of study results was not

contingent on the sponsor's approval or censorship of the manuscript.

Author Contributions

R.O., J.H. and M.F. conceived the idea of this study. Employees of Syneos Health developed the statistical analysis plan and conducted statistical analyses. R.O., J.H. and M.F. interpreted the results. R.M. drafted the original manuscript. All authors reviewed the manuscript draft and approved the final version of the manuscript.

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原著

日本の腎移植患者におけるCMV感染の臨床的疾病負担の検討

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要　旨

目的：サイトメガロウイルス（CMV）感染は腎移植（KTx）後の主要な合併症である。本研究では，日本のKTx患者におけるCMV感染の臨床的負担を検討した。

方法：JMDC社の保険者データベースを用いて2012～2021年の間にKTxを受けCMV予防を受けなかった患者のうち，12カ月間の追跡が可能であった患者を対象とした。追跡期間中に抗CMV薬の処方が必要なCMV感染があった患者をCMVエピソードを有する患者とした。CMVエピソードの有無によって分けた2群間で臨床的アウトカムと医療資源利用を比較した。

結果：合計291人のKTx患者が同定され，36.4％の患者が少なくとも1回のCMVエピソードを経験し，56.6％が平均2.2回の再発CMVエピソードを経験した。CMVエピソードを経験した患者のうち，有意に多くの患者が骨髄毒性を経験した（31.1％ vs. 9.7％；$p<0.01$）。さらに，CMVエピソードを有する患者は，有しない患者と比較して入院回数が多く（2.9回 vs. 2.3回；$p<0.01$），入院期間も長かった（49.1日 vs. 35.2日；$p<0.01$）。

結論：本研究により，CMV感染は日本におけるKTx患者の3分の1以上で発生し，KTx後の臨床的アウトカムおよび医療資源利用の面で大きな負担をもたらすことが示唆された。

Supplementary Table 1 Baseline patient characteristics

	Patients with CMV episode(s) (n = 106)	Patients without CMV episode (n = 185)
Age at index date, mean (S.D.)	44.93 (12.49)	45.62 (11.13)
Female (%)	40 (37.74)	64 (34.59)
Modified Charlson Comorbidity Index, mean (S.D.)	2.86 (1.76)	2.59 (1.62)
Use of basiliximab, n (%)	104 (98.11)	178 (96.22)
Use of plasma exchange, double filtration plasma-pheresis, or apheresis, n (%)	37 (34.91)	60 (32.43)

S.D.；standard deviation

The average age was similar across patient groups while females accounted for slightly more than one third of each group.

Supplementary Table 2 Drug utilization and testing over the 12-month follow-up period

	Patients with CMV episode(s) (n = 106)	Patients without CMV episode (n = 185)
Number of days of prescriptions of anti-CMV drug (GCV or VGCV) for treatment purposes for first CMV episode, mean (S.D.)	28.14 (27.71)	N/A
Number of days of prescriptions of anti-CMV drug (GCV or VGCV) for treatment purposes for recurrent CMV episode, mean (S.D.)	31.15 (31.65)	N/A
Number of days of prescriptions across all CMV episodes per patient, mean (S.D.)	61.60 (55.04)	N/A
Number of claims for CMV pp65 antigen, mean (S.D.)	16.16 (6.44)**	11.23 (5.28)**
Number of claims for viral antibody titer by globulin class for CMV, mean (S.D.)	1.87 (1.30)*	1.24 (0.75)*

*：$p<0.05$；**：$p<0.01$

S.D.；standard deviation, N/A；not applicable

Patients received an average of 28.14 days of anti-CMV treatment during their first CMV episode. Patients with CMV episodes had significantly more claims than patients without CMV episodes for laboratory tests such as CMV pp65 antigen and viral antibody titer.

Supplementary Table 3 Toxicities among patients who underwent KTx

	Patients with CMV episode(s) (n = 106)	Patients without CMV episode (n = 185)
Patients with myelotoxicity, n (%)	33 (31.13)**	18 (9.73)**
Patients with neutropenia, n (%)	31 (29.25)**	14 (7.57)**

*：$p<0.05$；**：$p<0.01$

The proportion of patients experiencing myelotoxicity and neutropenia was significantly higher among patients with CMV episodes.

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