ORIGINAL ARTICLE

A Retrospective Cohort Single-Centre Study of Prophylactic Vs. Preemptive Valganciclovir Therapy in Cytomegalovirus-At-Risk Kidney Transplant Recipients in Malaysia

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ABSTRACT

INTRODUCTION: Valganciclovir is commonly used for prophylaxis or preemptive therapy to prevent post-transplant cytomegalovirus (CMV) infection and disease in kidney transplant recipients. However, there are a limited data on the outcome and the association between valganciclovir and clinical characteristics of kidney transplant recipients, particularly those who are CMV seronegative (R-) receiving a transplant from CMV seropositive donors (D+), as well as in populations with high CMV seroprevalence. **MATERIALS AND METHODS:** This retrospective, single-center cohort study collected clinical data from kidney transplantation recipients at a tertiary referral hospital from January 2020 to June 2022. The data on the recipients' demographics, CMV risk categories, clinical characteristics, and types of valganciclovir therapy were obtained. Associations between clinical data, CMV risk categories, and therapies were determined. **RESULTS:** Among 110 kidney recipients, 9 were classified as high-risk and 101 as intermediate-risk. There were no significant differences found in the recipients' demographics and underlying factors between the risk categories. CMV infection occurred significantly less in the prophylaxis group than in the preemptive group (22.2% vs. 59.4%, p=0.04). There were no significant differences in one-year graft outcomes or patient survival observed between prophylaxis and preemptive therapies. Leukopenia incidence was higher in patients receiving prophylaxis. The incidence of co-infection with CMV viremia was similar between high-risk and intermediate-risk recipients. A significant association was found between CMV risk categories and prophylactic therapy in relation to post-transplant complications, CMV viremia clearance duration, and peak titer. **CONCLUSION:** Valganciclovir was the preferred therapy to prevent CMV infection and disease in kidney transplant recipients, with prophylactic therapy showing particular benefit in high-risk groups without increasing complications.

Keywords
Cytomegalovirus, Kidney transplantation, Preemptive, Prophylaxis, Yalganciclovir

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INTRODUCTION

Valganciclovir, a prodrug of ganciclovir, is widely used in prevention and treatment of cytomegalovirus (CMV) infection in solid organ and bone marrow transplant recipients.[1] It is administered orally and is rapidly converted to ganciclovir, the active antiviral agent.[2] The drug acts by inhibiting viral DNA polymerase, thus preventing viral replication.[2]

Studies have demonstrated the effectiveness of valganciclovir in prevention of CMV infection in paediatric kidney transplant recipients[3], renal transplant recipients,[4] and thoracic organ transplant recipients.[5] However, its use is associated with adverse effects, including leukopenia, fever, abdominal pain, and an increased risk of opportunistic infections.[6] Studies also shown that there is a higher occurrence of CMV infection among high risk liver transplant recipients receiving valganciclovir prophylaxis compared to ganciclovir prophylaxis.[7] Additionally, a retrospective analysis by Brown et al. showed that low-dose

valganciclovir is both effective and safe for prevention of CMV disease in renal transplant recipients.[8] In a previous study that emphasized on the impact of CMV disease on solid organ transplant recipients, the adverse effect of vangiclacvir has also been explored.[9]

CMV infections are a major concern following kidney transplantation, as CMV is the most common opportunistic infection in this patient group. CMV infection can be classified into two categories, CMV infection and CMV disease. CMV infection refers to the presence of CMV replication, while CMV disease involves clinical signs and symptoms attributable to the infection. Despite effective antiviral therapy, studies have shown that CMV infections can persist after kidney transplant, leading to adverse outcomes.

The American Society of Transplantation guidelines emphasize on the importance of distinguishing between CMV replication and latency, with clinical signs and symptoms of CMV disease including fever, abdominal pain, and myelosuppression. Identifying factors that influence the development of CMV infection and disease after kidney transplantation is essential for effective prevention, management, and treatment. Wei & Yi (2020) highlight the importance of understanding the risk factors associated with CMV viremia, particularly the donor and recipient CMV serostatus (D+/R-) and recipients who have received anti-lymphocyte antibody therapy. Additionally, demographic and factors such as such as donor and recipient age, pre-transplant hemodialysis duration, estimated post-transplant glomerular filtration rate (eGFR), acute rejection, transplant type, non-white race, diabetes mellitus, and cyclosporine therapy contribute to CMV risk.[10] Post-transplant factors, including the use of thymoglobulin or anti-thymocyte globulin (ATG) for induction and maintenance of immunosuppression, also play a role in increasing the risk of CMV viremia.[11,12] These multifactorial risk factors highlight the complexity of managing and preventing CMV-related complications in kidney transplant recipients.

Immunosuppression following transplantation significantly increases the risk of cytomegalovirus (CMV) infection, leading to severe morbidity and mortality in solid organ transplant (SOT) recipients.[13] CMV infection in SOT recipients is associated with acute and chronic graft rejection, allograft dysfunction, heightened susceptibility to opportunistic infections, reduced patient survival, and increased healthcare costs.[13] The prevalence of CMV viremia among kidney transplant recipients further underscores the critical concern regarding the interplay between immunosuppression with CMV infection, and their implications on the health outcomes of transplant recipients.[14]

Prophylaxis and preemptive therapy are the primary strategies for prevention of cytomegalovirus (CMV) infection or disease in SOT recipients. Prophylaxis strategy by administration of antiviral agents in prevention of CMV infection, is particularly crucial in high-risk recipients with a CMV-positive (D+) donor and CMV-negative (R−) recipient.[15] In contrast, preemptive therapy by initiating antiviral treatment upon detecting the early signs of CMV replication has been shown to result in significantly lower rates of CMV disease compared to prophylaxis in certain specific transplant recipient groups.[15]

This approach allows for early intervention when viral replication is detected, effectively reducing the incidence and severity of CMV disease in SOT recipients. Additionally, preemptive therapy has proven effective in reducing the risk of prophylaxis failure

A key advantage of preemptive therapy is its ability to tailor treatment to individual patients through real-time PCR monitoring of CMV viral load. This approach allows for early intervention when viral replication is detected, effectively reducing the incidence and outcomes of CMV disease in SOT recipients.[15] Additionally, preemptive therapy has proven effective in reducing the risk of primary prophylaxis failure in preventing CMV infection and disease, positioning it as a targeted and efficient management strategy for CMV.[15]

This study aimed to compare the effectiveness of valganciclovir as prophylaxis or preemptive therapy in high-risk and intermediate-risk groups. It also sought

to examine the relationship between recipients' risk categories and their demographic and clinical characteristics.

MATERIALS AND METHODS

Data collection

This was a retrospective cohort study, conducted at a single centre by employing convenience sampling over a period of two and a half years, from January 2020 to June 2022, for collection of comprehensive data. Clinical data were gathered from recipients aged 13 to 70 years old who underwent kidney transplantation at the Nephrology Department of Kuala Lumpur Hospital. Recipients managed with valganciclovir as part of either prophylactic or pre-emptive therapies, following established guidelines to prevent CMV disease were included in the study, and recipients with a post-transplant follow-up period of fewer than 6 months were excluded.

Clinical outcomes including CMV infection and disease were monitored for 12 months post-transplantation. CMV infection was defined as the presence of CMV replication in blood without symptoms, detected by real-time PCR (>200 IU/ml), whilst CMV disease was defined as CMV infection with attributable symptoms including fever, malaise, leucopenia, thrombocytopenia, or evidence of tissue-invasive disease (e.g., colitis, pneumonitis, hepatitis). All recipients were followed up for a minimum of 12 months post-transplantation to assess both CMV-related outcomes and graft survival.

Graft outcomes were monitored over a period of one year, focusing on several key parameters such as acute kidney injury (defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or ≥1.5 times baseline within 7 days), acute allograft dysfunction (characterized by sustained decline in eGFR more than 25% from baseline, not attributable to acute rejection), and graft rejection (defined as biopsy-proven rejection according to the Banff 2013 criteria). Graft loss was described as a return to renal replacement therapy such as dialysis, graft removal, retransplantation, or the death of the recipients.

In terms of risk categorization, the recipients were divided into intermediate-risk and high-risk groups according to the their CMV donor/recipient serostatus as determined by the pretransplant CMV serology. The intermediate-risk group included recipients with a positive or negative CMV donor serostatus and a positive recipients serostatus, (D+/R+ or D-/R+). The high-risk group, included recipients with a positive CMV donor serostatus and a negative CMV recipient serostatus (D+/R-), or those within the intermediate-risk group (D+/R+ or D-/R+) who received anti-lymphocyte preparations as part of their treatment regimen.

Clinical data were meticulously collected and included several key variables. The recipients' demographic information, such as age at transplantation, race, gender, and the donor/recipient relationship, were recorded. Clinical characteristics that might influence CMV infection and disease were also examined, including the primary cause of end-stage renal disease (ESRD), pre-transplant CMV serostatus, duration of pre-transplant hemodialysis, baseline eGFR, and the use of antiviral therapy (prophylaxis or pre-emptive therapy with valganciclovir). For prophylaxis, recipients were administered 450 mg of oral valganciclovir daily for six months. In contrast, recipients on pre-emptive therapy received 900 mg of valganciclovir daily for the first 14 days, followed by secondary prophylaxis with 450 mg daily for three months, and the dosage of valganciclovir was adjusted based on renal function to ensure appropriate dosing.

Additional clinical data included the use of immunosuppressive induction therapy such as thymoglobulin or anti-thymocyte globulin [ATG], basiliximab; as well as the type of immunosuppressive drugs for maintenance such as mycophenolate; type of transplantation; presence of leucopenia, defined as white blood cell count less than 4.0x10^9^/L; co-morbidities including diabetes mellitus and hypertension; clinical outcomes such as co-infections with other microorganisms, graft rejection or graft loss and mortality rate) and post-transplant complications including oedema, anaemia, diarrhoea, dyslipidaemia, and relevant conditions.

The dependent variables for this study included the risk categories of the recipients, categorized as either high-risk or intermediate-risk, and the types of CMV viraemia, classified as either CMV infection or CMV disease. The independent variables examined in this study encompassed a wide range of factors, including the recipients' demographic characteristics and underlying factors, co-morbidities, clinical outcomes and complications, types of therapy administered, length of CMV therapy, and type of immunosuppressive drugs for maintenance, co-infections by other infectious agents, graft outcomes and patients' survival.

This study received ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia with approval number: NMRR-20-993-53201. In compliance with ethical standards, the confidentiality of all participants was maintained through data anonymization, and secure methods of data storage were employed. Additionally, all procedures followed the relevant institutional guidelines for research involving human subjects, ensuring the protection of participant rights throughout the study.

Statistical analysis

The percentage of independent variables was evaluated using frequency analysis. Unless otherwise specified, both dependent and independent variables are expressed as the median and interquartile range (IQR). To determine the associations between risk categories and demographics, the clinical characteristics and outcomes were assessed. P-values were determined by Mann–Whitney U-test and Student t-test for continuous variables, according to their distribution, and Fisher's exact test for categorical variables. All p-values were two-sided, with the p-values of <0.05 were considered statistical significance. Statistical analyses were conducted using SPSS software (Version 23.0, IBM Corp, Armonk, NY, United States).

RESULTS

Recipients' demography and underlying factors

Out of 115 kidney transplant recipients selected for the study, five were excluded due to an inadequate post-transplant follow-up duration (<6 months; range 2-4 months). Of the remaining 110 recipients included in the analysis, 9 (8.1%) were categorized as high-risk for CMV infection or disease [(D+/R-) and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations] and 101 (91.8%) were categorized as intermediate-risk (D+/R+) (Figure 1).

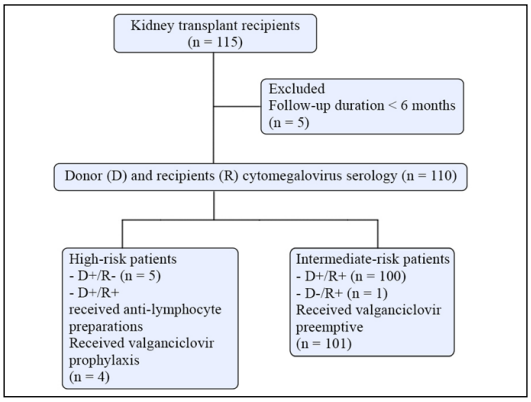

Figure 1 Distribution of the kidney recipients' risk categories

The baseline characteristics of the recipients are summarized in Table 1. Majority of the recipients were male, older than 35 years old, underwent ABO-incompatible (ABOi) transplantation, received a graft from a living donor, and treated with basiliximab as the immunosuppressant induction agent.

Regarding immunosuppressive induction therapy, all (100%) intermediate-risk recipients received basiliximab, while 55.6% of high-risk recipients did so (p=1.00). Additionally, 44.4% of high-risk recipients received thymoglobulin (p=1.00), whereas none of the intermediate-risk recipients were administered this therapy.

There was no significant difference between the high-risk and intermediate-risk recipients in terms of the age, sex, presence of diabetes mellitus, type of kidney transplantation, ABO-incompatible (ABOi) transplantation, pre-transplant donor-specific antibodies, or the donation from blood relatives. Regarding the immunosuppressive induction therapy, 100% of intermediate-risk recipients received basiliximab, while only 55.6% of high-risk recipients did so (p=1.00). Additionally, 44.4% of high-risk recipients received thymoglobulin (p=1.00), whereas none of the intermediate-risk recipients were administered with this therapy.

Regarding maintenance immunosuppressive therapy, nearly all recipients were treated with tacrolimus, mycophenolate mofetil, and methylprednisolone, with a slightly higher proportion of high-risk recipients receiving these therapies. The median duration of post-transplant follow-up was similar between the high-risk recipients and intermediate-risk recipients, 29 months (IQR 26.0-35.5 months) and 28 months (IQR 27.0-31.5 months), respectively (p=0.45)

Table 1 : Recipients' Demographics and Clinical Characteristics by Risk Category

Characteristics	High-risk recipients[a] (n=9)	Intermediate-risk recipients[b] (n=101)	p-value[c]
Demographics			
Age, years, mean+ SD	42.7+12	37.8+10	0.18[d]
Male sex, n (%)	7 (77.8)	65 (64.4)	0.72
Clinical Parameters			
Baseline eGFR, ml/ min/1.73m² (mean ± SD)	42.5 ± 10.2	43.2 ± 11.4	0.68
Diabetes mellitus, n (%)	3 (33.3)	11 (10.9)	0.09
Transplantation Details			
ABO-incompatible, n (%)	6 (66.7)	73 (72.3)	0.71
Related donor, n (%)	6 (66.7)	81 (80.2)	0.39
Immunosuppression Induction therapy			
Basiliximab, n (%)	5 (55.6)	100 (100.0)	0.00
Thymoglobulin n (%) Maintenance therapy	4 (44.4.)	0 (0.0)	1.00
TAC + MMF + MP, n (%)	9 (100.0)	99 (98.0)	1.00
TAC + EVR + MP, n (%)	0 (0.0)	2 (2.0)	1.00
Follow-up Duration, months, median (IQR)	29 (26.0-35.5)	28 (27.0-31.5)	0.45

D+. Donor CMV seropositive; R-, recipient CMV seronegative; D-, donor seronegative; R+, recipient seropositive; eGFR: Estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range; DSA, donor-specific antibody; TAC, tacrolimus; MMF, mycophenolate mofetil; EVR, everolimus; MP, methylprednisolone.

[a] High-risk: D+/R- and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations
[b] Intermediate-risk: D+/R+ or D-/R+
[c] P-values based on Mann-Whitney U-test unless otherwise specified
[d] By Student t-test

Clinical outcomes and complications

The incidence of cytomegalovirus (CMV) infection was significantly higher in high-risk recipients (5/9, 55.6%) compared to intermediate-risk recipients (22/101, 22.0%) (p=0.04). Although the incidence of CMV disease was also higher in high-risk recipients (1/9, 11.1%) than in intermediate-risk recipients (6/101, 5.9%), this difference was not statistically significant (p=0.46). One intermediate -risk patient experienced a series of CMV infections, beginning as early as one month post-transplant, which progressed to multiple CMV-related diseases, including colitis, acute hepatitis, diarrhea, acute gastritis, and esophagitis.

Valganciclovir was used as prophylactic therapy in high-risk recipients and preemptive therapy in intermediate-risk. The clinical outcomes are shown in Table 2. The incidence of CMV infection was significantly higher in high-risk recipients 5/9 (55.6%) than the intermediate-risk recipients 22/101 (22.0%) (p=0.04). Although CMV disease incidence was also higher in high-risk recipients, 1/9 (11.1%) than in the intermediate-risk recipients 6/101 (5.9%), this difference was not statistically significant (p=0.46). One intermediate-risk recipients experienced a series of CMV infections, beginning as early as one month psot transplantation which progressed into multiple CMV-related diseases, including colitis, acute hepatitis, diarrhoea, acute gastritis, and esophagitis.

There was no significant difference in the incidence of co-infectious pathogens other than CMV between the two-group; 2/9 (22.2%) in high-risk recipients and 23/101 (22.8%) in intermediate-risk recipients (p=1.00). Other pathogens that were isolated or detected included *Escherichia coli, Acinetobacter spp., Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas spp., Enterobacter cloacae* and *Burkholderia pseudomallei, Candida albicans, Tinea pedis* and BK polyomavirus (BKV).

The median estimated glomerular filtration rate (eGFR) at 12 months post transplantation was similar between the two groups: 46.4 (IQR 41.0–64.0)ml/min/1.73m² in high-risk recipients (n=9) and 46.5 (IQR 41.3–52.5)ml/ min/1.73m² in intermediate-risk recipients (n=101). There was no significant difference in leukopenia findings among both groups; high-risk recipients (n=1/9, 11.1%) and intermediate-risk recipients (n=4/101, 4.0%, p= 0.35).

Post-transplant complications were significantly higher in intermediate-risk recipients (50/101, 49.5%) than the high-risk recipients (1/9, 11.1%) with p value <0.05. The complications observed complications included delayed graft function, acute allograft dysfunction, dehydration, hypophosphatemia, dyslipidemia, hyponatremia, hypoalbuminemia, persistent proteinuria, acute tubular necrosis, pancytopenia, fever, cardiomyopathy, acute antibody-mediated rejection (ABMR), acute. T-cell–mediated rejection (TCMR), renal artery thrombosis,

Table 2: Clinical Outcomes with Valganciclovir Therapies at 12 Months Post-Transplant

Outcomes	Prophylaxis Valganciclovir High-risk Recipients[a] (n=9)	Preemptive Valganciclovir Intermediate-risk Recipients[b] (n=101)	P-value[c]
CMV Events			
CMV infection[d], n (%)	2 (22.2)	60 (59.4)	0.04
- Mean time to first infection, days (range)	185 (170-200)	85 (30-140)	0.02
CMV disease[e], n (%)	1 (11.1)	46 (45.5)	0.08
- Mean time to first disease, days (range)	250 (-)	120 (45-270)	0.03
Clinical Parameters			
Co-infection with other microorganisms[f], n (%)	2 (22.2)	23 (22.8)	1.00
eGFR at 12 months, ml/ min/1.73 m^2, median (IQR)	46.5 (41.3–52.5)	46.4 (41.0–64.0)	0.22
Leukopenia[g], n (%)	3 (33.3)	18 (17.8)	0.37
Co-infection with other microorganisms[7], n (%)	2 (22.2)	23 (22.8)	1.00
Post-transplant complication[h], n (%)	1 (11.1)	50 (49.5)	0.04
CMV Viremia Characteristics			
Duration of CMV viremia clearance, days, median (IQR)	14 (7-25)	26 (17-54)	0.02
Peak titer, 10^9/mL, median (IQR)	18 (7.0-43.0)	105 (18.0-213.0)	<0.01

D+. Donor CMV seropositive; R-, recipient CMV seronegative; D-, donor seronegative; R+, recipient seropositive; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a] High-risk: D+/R- and (D+/R+ or D-/R+) receiving anti-lymphocyte preparations
[b] Intermediate-risk: D+/R+ or D-/R+
[c] P-values: Mann-Whitney U-test for continuous variables; Fisher's exact test for categorical variables
[d] CMV infection defined as CMV replication in blood (>200 IU/ml) without symptoms
[e] CMV disease defined as CMV infection with attributable symptoms (fever, organ involvement)
[f] Including bacterial infections, BK virus, and fungal infections
[g] Leucopenia defined as white blood cell count <4.0 × 10^9/L
[h] Including delayed graft function, acute allograft dysfunction, dehydration, etc.

macrocytic anaemia, perinephric hematoma, gout, chronic diarrhoea, pedal oedema, recurrent focal segmental glomerulosclerosis (FSGS) and ischemic heart disease. The duration of CMV viremia clearance was significantly faster in high-risk recipients receiving prophylaxis than in intermediate-risk receiving preemptive therapy, 14 (7-25) vs 26 (17-54) days, respectively. The CMV viremia peak titers were significantly lower in high- than intermediate-risk recipients, 18 (7.0-43.0) vs 105 (18.0-213.0) CMV peak titres, respectively.

Valganciclovir as prophylaxis and preemptive therapy

The prophylaxis dose was 450 mg oral valganciclovir/day for 6 months. Pre-emptive therapy recipients received initial treatment with valganciclovir 900 mg/day for 14 days, followed by secondary prophylaxis consisting of valganciclovir 450 mg/day for 3 months. All valganciclovir dosages were adjusted according to renal function. At a median follow-up duration of 24 months, CMV infection developed significantly less in the prophylaxis therapy than in the pre-emptive group (22.2%, 2/9 vs 59.4%, 60/101, respectively; p=0.04). Lower percentages of CMV disease were also seen in the prophylaxis therapy than in the pre-emptive therapy, but the difference was not significant (11.1%, 1/9 vs 45.5%, 46/101 respectively, p=0.08). In intermediate-risk recipients with pre-emptive valganciclovir, CMV infection was developed within the first three months after transplantation and CMV disease within the first nine months after transplantation, while in the high-risk recipients with valganciclovir prophylaxis, CMV infection was developed after six months of transplantation and CMV disease within the first 12 months after transplantation.

Graft outcomes and patients' survival

Graft and recipient survival and graft rejection data are shown in Table 3 and. Acute kidney injury (AKI) was seen in 1/9 (11.1%) and 14/101 (13.9%) in high-risk and intermediate-risk recipients, respectively. Acute allograft dysfunction was observed in 1/9 (11.1%) and 11/101 (11.9%) in high-risk and intermediate-risk recipients, respectively. These graft dysfunction cases were predominantly due to causes other than rejection, including medication-related effects, infections, and haemodynamic factors. There were 0/9 (00.0%) cases and 2/101 (2.0%) cases of acute antibody-mediated rejection (ABMR) in high-risk and intermediate-risk recipients, respectively, and 1 case of acute T-cell–mediated rejection (TCMR) in the intermediate group. No incidence of death occurred in the current study group.

Table 3: Graft outcomes and patients' survival with valganciclovir therapies.

	Prophylaxis valganciclovir High-risk recipients (D+/ R-) and (D+/ R+, D-/R+) receiving anti-lymphocyte preparations (n = 9)	Preemptive valganciclovir Intermediate-risk recipients (D+/R+, D-/ R+) n = 101	P-value[a]
Acute kidney injury (AKI), n (%)	1 (11.1)	14 (13.9)	1.00
Acute allograft dysfunction, n (%)	1 (11.1)	11 (11.9)	1.00
Acute antibody-mediated rejection (ABMR), n (%)	0 (0.0)	2 (2.0)	1.00
Acute T-cell–mediated rejection (TCMR), n (%)	0 (0.0)	1 (1.0)	1.00
Death, n (%)	0 (0.0)	0 (0.0)	1.00

[a] P-values: Fisher's exact test for categorical variables.

DISCUSSION

Cytomegalovirus (CMV) viraemia significantly affects clinical outcomes post-solid organ transplantation, exacerbated by immunosuppression, leading to symptomatic CMV disease with severe morbidity and occasional mortality.[16] In this study, 115 kidney transplant recipients were initially included, with 5 excluded due to insufficient post-transplant follow-up (<6 months). The remaining 110 recipients showed an 8.1% high-risk (D+/R- and D+/R+ or D-/R+ with anti-lymphocyte preparations) and 91.8% intermediate-risk (D+/R+) distribution.

Immunosuppression modulates the risk of CMV infection, underscoring the need to comprehend the interplay between immunosuppression and CMV infection.[17] The prevalence of CMV disease in transplant recipients, without pre-emptive or prophylaxis therapy, remains a critical concern despite advancements, posing a substantial threat to solid-organ transplant recipients.[18] The selection between prophylaxis and pre-emptive therapy for preventing CMV in transplant recipients is a subject of continuous research and debate. Reports of high rates of delayed-onset post prophylaxis CMV disease emphasize the necessity for targeted and effective preventive strategies tailored to the specific transplant population.[19]

The baseline characteristics, including age, sex, and transplantation factors, were comparable between high-risk and intermediate-risk recipients, indicating a well-balanced study population. However, a significant disparity in immunosuppression induction strategies was observed, with 100.0% of intermediate-risk recipients receiving basiliximab compared to 55.6% in the high-risk group. Furthermore, thymoglobulin was administered to 44.4% of high-risk recipients, while none among the intermediate-risk recipients received this treatment.

In this study, valganciclovir played a crucial role in managing cytomegalovirus (CMV) in kidney transplant recipients through prophylactic and preemptive strategies. High-risk recipients, constituting 8.1% of the cohort, had a significantly higher incidence of CMV infection (22.0%) than intermediate-risk recipients. Although CMV disease rates were elevated in high-risk recipients (11.1%) compared to the intermediate-risk group (5.9%), statistical significance was not reached. Remarkably, an intermediate -risk case experienced early-onset CMV infections leading to multiple diseases. Co-infection rates with other pathogens were similar between high-risk and intermediate-risk recipients. Renal function, assessed by estimated glomerular filtration rate, was comparable at the 12-month post-transplant mark. However, intermediate-risk recipients had a significantly higher post-transplant complication rate (49.5%) than high-risk recipients (11.1%). Additionally, high-risk recipients showed faster CMV viremia clearance and lower peak titers, suggesting potential prophylaxis benefits.

The usage of prophylaxis therapy in this study showed a lower incidence of CMV infection and CMV disease (delayed-onset disease) by 6 months after transplant in high-risk recipients. Studies have shown that universal prophylaxis can reduce the initial risk of CMV infection and disease (20)(21). However, there is concern about the high risk of late-onset CMV disease, which usually begins with D+/R- recipients after discontinuing prophylaxis.[22] This may increase mortality and/or death.[22,23,24]

However, some studies show the benefits of universal prophylaxis[25] compared preemptive therapy and universal prophylaxis in high-risk kidney and liver transplant recipients (D+/R-). In their group, consistent with previous studies by[26], late-onset CMV disease was not severe or life-threatening. They also showed that CMV reactivation in the first two years post-transplant, regardless of the preventive measures used, was a risk factor for transplant failure 5 years post-transplant.[25]

No statistically significant differences between the two therapy strategies were observed for leukopenia. The cause of leukopenia is usually multifactorial. Besides, CMV infection or the disease itself is often caused by the side effects of CMV antivirals such as valganciclovir and immunosuppressive agents.[27] The CMV infection has marked myelosuppression effects in renal transplant recipients and has been reported to have leukopenia or neutropenia as a manifestation.[28] Age at transplantation was not associated with the development of leukopenia;

however, older recipients had a higher incidence of leukopenia[28], as observed in this study group.

The high-risk recipients demonstrated a significantly faster median clearance of CMV viremia compared to their intermediate-risk counterparts, aligning with the findings of a previous study[29] that reported a swifter clearance of CMV DNAemia in the prophylaxis group beyond the 12-month post-transplant period. Additionally, the median peak titer of CMV viremia was notably lower in high-risk recipients under prophylaxis compared to intermediate-risk recipients. However, it is worth noting that contrary findings have been reported;[30] observed a significantly higher median CMV antigenemia peak titer in high-risk patients compared to intermediate-risk patients, while[29] found no difference in the median peak titer between recipients undergoing prophylaxis and preemptive approaches. These variations in results may be attributed to factors such as differences in antiviral selection, immunosuppressive status, the presence, or absence of CMV-specific T-cell immunity, suboptimal antiviral drug levels, or resistance to antiviral medications.[31]

In this study, occurrences of acute kidney injury (AKI), acute allograft dysfunction, acute antibody-mediated rejection (ABMR), and acute T-cell–mediated rejection (TCMR) were observed at higher rates in intermediate-risk recipients compared to high-risk recipients, although these differences did not reach statistical significance. Numerous studies have established a connection between AKI and unfavorable long-term graft outcomes.[32] The delayed graft function observed in this study may signify post-transplant AKI. In solid organ transplant (SOT) recipients, CMV infection often manifests through indirect effects, contributing to outcomes like acute rejection, graft failure, and mortality, collectively termed the 'indirect effects of CMV infection.[33] Additional factors leading to AKI in transplant recipients, such as obstruction of a single-functioning kidney, vascular thrombosis, drug toxicity, and drug-induced thrombotic microangiopathy [34], were not specifically identified in this study.

Initiating preemptive therapy in intermediate-risk cases during the early post-transplant period may permit mild CMV replication, resulting in CMV infection.[35] Such infections could potentially contribute to graft rejection. In alignment with findings from other investigations, our study lends support to the universal prophylaxis approach, emphasizing its advantage in suppressing early CMV replication, as opposed to preemptive therapy, thereby reducing the risk of graft rejection, particularly within the initial 3 months following transplantation in high-risk (D+/R-) kidney transplant recipients.[25,35]

This study has several limitations, such as its retrospective design, leading to incomplete clinical and laboratory data. Additionally, the convenience sampling employed may introduce bias into the results. It is crucial to note that this study contributes new data specific to the Malaysian setting.

CONCLUSION

The use of valganciclovir as antiviral prophylaxis in high-risk kidney transplant recipients, compared to preemptive therapy in intermediate-risk kidney transplant recipients, demonstrated superior efficacy in prevention of CMV infection and slowing the progression of CMV disease in these groups. This strategy did not pose an increased risk of opportunistic infections, allograft rejection, graft loss, drug resistance development, or mortality.

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