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Original Article

Seroprevalence of CMV and HSV in Kidney Transplant Donor Candidates and Recipients at Ngoerah Hospital, Denpasar

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ABSTRACT

Background: Despite significant advancements in solid organ transplantation over recent decades, infections remain a leading cause of morbidity and mortality among transplant recipients. Herpesviruses, particularly Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV), are the most common viral pathogens affecting this patient population.

Objective: This study aims to evaluate the seroprevalence of CMV and HSV infections among kidney transplant donor and recipient candidates at RS. Ngoerah Denpasar.

Methods: This descriptive study involved 66 adult subjects, comprising 33 kidney transplant donor candidates and 33 recipient candidates, all aged over 18 years. The study participants were evaluated for CMV and HSV seroprevalence using serological tests, including IgG and IgM antibodies, to determine the presence of latent or active infections. The study population included patients with chronic kidney disease (CKD) stage V who were candidates for kidney transplantation.

Results: Among the 33 donor candidates, 39.4% were found to have both CMV and HSV infections, with 45.5% testing positive for IgG anti-CMV, indicating a latent CMV infection. In the recipient candidate group, 27.3% were infected with both CMV and HSV, with 42.4% showing seropositivity for IgG anti-CMV. Additionally, a small proportion of donor and recipient candidates were found to have reactivated HSV infections, as indicated by the presence of IgM antibodies. The study highlights the significant prevalence of CMV and HSV infections among kidney transplant donor and recipient candidates.

Conclusion: These findings underscore the importance of thorough serological screening prior to transplantation to identify latent infections that may influence post-transplant outcomes.

Keywords: Seroprevalence; Cytomegalovirus; Herpes Simplex Virus; Kidney Transplantation; Donor Screening.

Introduction

Despite the rapid development of solid organ transplantation in recent decades, infections remain a major cause of morbidity and mortality among solid organ transplant recipients. The herpesvirus family is the most common viral pathogen causing disease in this patient population. Herpesviruses are large enveloped DNA viruses that commonly reactivate during periods of severe immunosuppression. Currently, infections caused by herpesviruses complicate the clinical management of transplant patients. Two viruses belonging to this family are Cytomegalovirus (CMV) and Herpes simplex virus (HSV). This study aimed to assess the

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seroprevalence of CMV and HSV infections in kidney transplant candidates and recipients.[1]

CMV is a herpesvirus found in 40%-70% of the population, is common after solid organ transplantation, and is an independent risk factor for graft loss and mortality. Iatrogenic immunosuppression targeting T cells can result in uncontrolled CMV replication.[2] The risk of CMV infection in the first month after transplantation is generally minimal, despite the high-intensity immunosuppression used at the time of transplantation due to the lack of prolonged immunosuppressive exposure. The duration of immunosuppressive exposure is thought to be an important factor in the development of opportunistic infections such as CMV.[3–5] In a study of 5000 kidney transplants in one health center, the incidence of CMV infection in the first 30 days after kidney transplantation was 0.2%. Common clinical findings in patients were bleeding requiring reoperation and prolonged cold ischemic time (CIT). The outcomes of CMV infection in the first 30 days and later were similar. The study concluded that the results of the study can provide clinicians with information as a basis for confidence that the overall risk of CMV infection in the first 30 days is very low.[2]

HSV has 2 types, namely HSV type 1 and HSV type 2 (HSV-1, HSV-2), which belong to the alpha-herpesvirus family. These viruses are characterized by a short replication cycle, rapid growth in culture, host cell lysis during replication, and latency in nerve ganglia. Although HSV-1 and HSV-2 share 40% of their nucleotide sequence, they have distinct epidemiological profiles, biological features, and antigenic features.[1] The majority of the population is infected with HSV-1 during childhood or early adolescence via saliva. Primary infection is usually asymptomatic or presents as gingivostomatitis, while reactivation of the virus usually results in herpes labialis. Transmission to humans occurs through direct contact with lesions or secretions of an actively shedding person. The prevalence of HSV-1 in the United States has been reported to be 80% by age 60 years. HSV-2 infection is less common, usually acquired through sexual transmission and is usually associated with genital infections. The prevalence of HSV-2 infection increases with age, with prevalence rates in the United States for 14-19 and 40-49 year-olds being 1.6% and 26.3%, respectively.[6] Colitis in solid organ transplantation is more commonly caused by CMV than HSV.[7]

Screening of potential organ donors and recipients before transplantation is an essential part of solid organ transplantation. The goals of pretransplant infectious disease screening are as follows: (1) to identify donor or recipient eligibility; (2) to identify and treat active pretransplant infections; (3) to determine the level of risk for infection to determine posttransplant infection prevention strategies.[8] CMV serologic status of the donor and recipient is an important predictor of post-transplant events, with CMV-seronegative recipients of CMV-seropositive (D+/R-) donor organs being at greatest risk for developing tissue-invasive CMV, recurrent CMV, and ganciclovir-resistant CMV. However, D+/R- status is not generally considered a contraindication to transplantation, but rather an indication for a more intensive posttransplant monitoring and prevention strategy. Seropositive recipients, regardless of donor status, are also at risk for CMV and usually receive pre-emptive prophylaxis or monitoring. HSV screening is performed in some centers, while others do not perform screening but provide universal antiviral prophylaxis for at least the first month posttransplant.[8,9]

Methods

This study used a descriptive research design involving 66 samples, namely recipients (33 patients) and donors (33 patients) from the adult population aged >18 years at Ngoerah Hospital, Denpasar. The target population in this study were patients with chronic kidney failure (CKD) stage V who had become candidates for kidney transplant recipients and candidates for kidney organ donors. The accessible population in this study were patients who were candidates for kidney transplant recipients and donors who underwent procedures at Ngoerah Hospital, Denpasar. The sample of this study was candidate

donors and recipients who would undergo kidney transplantation and met the inclusion and exclusion criteria. The inclusion criteria in this study were patients aged >18 years, as candidates for kidney donors or recipients who were diagnosed with CKD stage V, and agreed to participate in the study by providing written informed consent, while the exclusion criteria in this study were incomplete patient data.

Results

The total subjects included in this study were 66 people, with 33 (50.0%) patients as donor candidates and 33 (50.0%) patients as recipient candidates, of which 12 (18.2%) were male, and 21 (31.8%) were female from the donor candidate group. The number of male subjects from the recipient candidate group was 22 (33.3%) and female subjects from the recipient candidate group were 11 (16.7%). The majority of patients were in the age group of 50-59 years and 60-69 years in the donor candidate group. (N=13; 19.7%), and in the recipient group were aged 18-29 years (N=15; 22.7%).

The majority of causes of CKD were chronic glomerulonephritis (GNC) (N=27; 40.9%). Subjects with candidate recipient status had chronic kidney failure (CKD) stage V. Most of the kidney transplant recipient candidates underwent renal replacement therapy in the form of hemodialysis (N=30; 45.5%). The majority of recipients underwent renal replacement therapy for 1 year (N=17; 25.8%) (Table 1).

Table 1. Subject characteristics

Characteristics	**Patient Status (%)**	
	Donor (n = 33)	**Recipient (n = 33)**
Age (years)		
- 18-29	2 (3.0)	15 (22.7)
- 30-39	0 (0.0)	14 (21.2)
- 40-49	5 (7.6)	3 (4.5)
- 50-59	13 (19.7)	0 (0.0)
- 60-69	13 (19.7)	1 (1.5)
Mean ± SD (Age)	52.4 ± 9.1	31.2 ± 10.8
Gender		
- Male	12 (18.2)	22 (33.3)
- Female	21 (31.8)	11 (16.7)
Etiologic of CKD		
- PNC	0 (0.0)	3 (4.5)
- GNC	0 (0.0)	27 (40.9)
- Nefrosclerotic	0 (0.0)	1 (1.5)
- DKD	0 (0.0)	1 (1.5)
- SN	0 (0.0)	1 (1.5)
- No CKD	33 (50.0)	0 (0.0)
Stage of CKD		
- V	0 (0.0)	33 (50.0)
- No CKD	33 (50.0)	0 (0.0)
Kidney Replacement Therapy		
- Hemodialysis	0 (0.0)	30 (45.5)
- Peritoneal dialysis	0 (0.0)	1 (1.5)

- Predialysis	0 (0.0)	1 (1.5)
- Unknown	0 (0.0)	1 (1.5)
- No CKD	33 (50.0)	0 (0.0)
Duration of Replacement Therapy (years)		
- <1	0 (0.0)	2 (3.0%)
- 1-3	0 (0.0)	25 (37.9%)
- 4-7	0 (0.0)	3 (4.5%)
- Unknown	0 (0.0)	3 (5.5%)
- No CKD	33 (50.0)	0 (0.0)
Mean ± SD (Therapy Duration)	N/A	1.67 ± 1.2

From the 33 patients with kidney transplant candidate donor status, 26 (39.4%) had CMV and HSV infections, while 6 (9.1%) had CMV infections only. A total of 30 (45.5%) patients in the candidate donor group had anti-CMV IgG seropositivity, while 2 (3.0%) had anti-CMV IgG and anti-CMV IgM seropositivity. IgG anti-HSV 1 seropositivity was found in 24 (36.4%) patients in the candidate donor group. IgG anti-HSV 1 seropositivity and IgM anti-HSV 1 seropositivity were found in 2 (3.0%) patients in the candidate donor group. Seronegative for HSV was found in 7 (10.6%) patients in the candidate donor group (Table 2).

Table 2. Seroprevalence of CMV and HSV in kidney transplant donors and recipients.

Variable	Patient Status		*p-value*
	Donor (N=3)	Recipient (N=33)	
Serology			0.042*
- HSV	0 (0.0)	1 (1.5)	
- CMV	6 (9.1)	13 (19.7)	
- CMV, HSV	26 (39.4)	18 (27.3)	
- Seronegative	1 (1.5)	1 (1.5)	
CMV			0.435
- Long-standing/latent infections	30 (45.5)	28 (42.4)	
(IgG +, IgM -)	2 (3.0)	2 (3.0)	
- Reactivation (IgG +, IgM +)	0 (0.0)	1 (1.5)	
- Acute infections (IgG -, IgM +)	1 (1.5)	2 (3.0)	
- Non-reactive (IgG -, IgM -)			
HSV 1			0.171
- Long-standing/latent infections	24 (36.4)	17 (25.8)	
(IgG +, IgM -)	2 (3.0)	2 (3.0)	
- Reactivation (IgG +, IgM +)	0 (0.0)	0 (0.0)	
- Acute infections (IgG -, IgM +)	7 (10.6)	14 (21.2)	
- Non-reactive (IgG -, IgM -)			

HSV 2			0.052
- Long-standing/latent infections	8 (12.1)	2 (3.0)	
(IgG +, IgM -)	0 (0.0)	0 (0.0)	
- Reactivation (IgG +, IgM +)	0 (0.0)	2 (3.0)	
- Acute infections (IgG -, IgM +)	25 (37.9)	29 (43.9)	
- Non-reactive (IgG -, IgM -)			

*p<0.05: significant relationship

In the candidate recipient patient group, out of 33 people, 18 (27.3%) experienced CMV and HSV infections, while 13 (19.7%) others only experienced CMV infections. There was 1 (1.5%) person in the candidate recipient group who experienced HSV infection. IgG anti-CMV seropositivity was found in 28 (42.4%) patients in the candidate recipient group, while IgG anti-CMV and IgM anti-CMV were found positive in 2 (3.0%) patients. IgM anti-CMV seropositivity was found in 1 (1.5%) patient in the candidate recipient group. Seropositivity for IgG anti-HSV 1 was found in 17 (25.8%) patients in the candidate recipient group, while seropositivity for IgG anti-HSV 1 and IgM anti-HSV 1 was found in 2 (3.0%) patients in the candidate recipient group, while seronegative for HSV was found in 14 (21.2%) patients in this group (Table 2).

Discussion

Cytomegalovirus (CMV) is a member of the Herpesviridae family that is known to be a major pathogen in patients with compromised immune systems, such as solid organ transplant recipients, hematopoietic cell transplant recipients, patients infected with Human Immunodeficiency Virus (HIV), and individuals undergoing immunomodulatory therapy. Although CMV infection is often asymptomatic in immunocompetent individuals, it can cause serious complications in immunosuppressed populations. In immunocompromised patients, the clinical manifestations of CMV are very diverse and can include unexplained febrile syndrome, hepatitis, pneumonitis, retinitis, encephalitis, esophagitis, and colitis. These complications not only worsen the patient's clinical condition but also potentially increase the risk of mortality if not treated adequately.[7]

The diagnosis of CMV infection is often challenging, especially because the signs and symptoms that appear can resemble other viral infections. Establishing a diagnosis of CMV requires a comprehensive approach, including evaluation of the patient's clinical history, careful physical examination, and confirmation by laboratory tests involving direct detection of the virus or through signs of viral activity. One of the major challenges in diagnosis is differentiating between latent infection, asymptomatic reactivation, and active CMV disease. Latent infection is a condition in which the virus remains in the body without causing symptoms, but can replicate again when the patient's immune system is weakened, causing reactivation that has the potential to progress to clinical disease.[10]

The terms "CMV infection" and "CMV disease" have important differences in clinical contexts. CMV infection refers to the presence of a virus in the body, which can be detected through virus isolation, detection of viral proteins (antigens), or their nucleic acids in body fluids or tissue specimens, even if no symptoms appear. In contrast, CMV disease refers to a condition in which a CMV infection causes noticeable clinical symptoms, as mentioned above. It is important for clinicians to differentiate between the two because treatment approaches and patient management differ based on whether the patient only has CMV infection or has developed CMV disease.[8]

Studies to determine the cut-off between CMV infection and disease have been conducted, with varying results. A study in Brazil found that a threshold value of 5010 copies/mL OF CMV DNA in the blood can be used to distinguish infections from CMV disease, although its sensitivity and specificity are not yet fully optimal.

Another study reported a lower threshold, which was 3800 copies/mL, with a sensitivity of 76.9% and a specificity of 91.6%. However, this variability suggests that there is no one universally reliable threshold, and clinical decisions often need to be tailored to the patient's specific context, including immunity status and other clinical conditions. By understanding the complexities of CMV infection diagnosis and management, clinicians can reduce the risk of serious complications in immunocompromised patients, as well as improve long-term outcomes post-transplant or in the management of immunosuppression-related diseases.[7,8]

Screening of donors and potential organ recipients before transplantation is a very crucial component of the solid organ transplant process. This process aims not only to ensure that the donor and recipient are in decent health, but also to identify and treat infections that may be present before the transplant takes place. The main objectives of pre-transplant infectious disease screening include three important aspects: first, to ensure the feasibility of donor and recipient conditions; second, identifying and managing existing active infections in the pre-transplant phase; and third, assessing the level of infection risk to develop effective post-transplant infection prevention strategies.[6]

The serological status of CMV of donors and recipients has an important role as a predictor of the risk of posttransplant complications. Recipients who are seronegative for CMV, but receive organs from donors who are seropositive for CMV (D+/R-), are at the highest risk of developing CMV infections that can be invasive, cause tissue damage, and even become recurrent or resistant to antiviral treatments such as gancyclovir. In this scenario, although D+/R- status increases the risk of posttransplant complications, this condition is not considered an absolute contraindication to transplantation. Instead, this status demands a more intensive and targeted monitoring and prevention strategy after transplantation.[11,12]

Prevention strategies that may be applied to recipients with seronegative status who receive organs from seropositive donors may include the use of long-term antiviral prophylaxis or pre-emptive monitoring approaches. Antiviral prophylaxis, such as gancyclovir or valgancyclovir, are generally given during the first 3 to 6 months posttransplant to reduce the risk of primary CMV infection. In addition, the pre-emptive monitoring approach involves routine monitoring of the viral load of CMV via PCR or other serological methods, with therapeutic interventions initiated immediately after virus detection, even if no clinical symptoms have yet emerged.[13,14]

Meanwhile, recipients who are already seropositive for CMV, regardless of the donor serological status, are also at risk of CMV reactivation. This risk necessitates the application of similar prophylaxis or pre-emptive monitoring, especially in the early post-transplant period when immunosuppression is at its peak. Prophylaxis in this group not only lowers the risk of primary or recurrent CMV infection, but also helps prevent further complications that can affect the long-term outcomes of the transplant, such as decreased graft function or even graft loss.[2,15]

In addition to CMV, screening for other infections such as Herpes Simplex Virus (HSV) is also important, although practices vary across different transplantation centers. Some health centers perform serological screening for HSV, while others prefer to administer universal antiviral prophylaxis, such as acyclovir or valacyclovir, to all recipients for at least the first month post-transplant. This prophylactic approach aims to reduce the risk of HSV reactivation, which can occur in recipients who are severely immunosuppressed.[13,16]

However, screening and treatment are not limited to CMV and HSV. Other active viral infections, such as hepatitis virus or community-acquired respiratory viruses, should also be considered. If an active viral infection is detected in a potential recipient, the decision to delay the transplant is often wiser until the infection improves. This delay allows the recipient's body to develop a natural immune response before

intensive immunosuppression is administered, which is an integral part of the transplant protocol.[2]

A similar approach is also applied to transplant candidates who show clinical symptoms leading to acute viral infections. Delaying transplantation in this situation not only helps in the recovery of the recipient's health condition, but also gives time for the transplant team to develop a more effective prevention strategy. These recommendations support a more cautious and targeted approach to managing the risk of infection before, during, and after solid organ transplantation.[8]

Overall, pre-transplant infectious screening and post-transplant infection risk management require a personalized approach based on each patient's risk profile. Careful attention to the patient's serological status and clinical condition allows the transplant team to minimize the risk of infection and ensure better outcomes for posttransplant patients. The strategy should be flexible and adapted to the development of the patient's condition, while taking into account the latest evidence and existing clinical guidance.[9]

Cytomegalovirus (CMV) infection is one of the major challenges in posttransplant management, especially in patients with high-risk serostatus. The main risk factors known to affect the occurrence of CMV infection include the patient's serostatus before transplantation and the presence of decreased lymphocyte count, which is an important marker in the immune system. Decreased lymphocytes, specifically T cells, may facilitate the reactivation of latent CMV or worsen primary infections, given the central role of T cells in controlling viral replication. When lymphocytes are significantly reduced due to immunosuppression used in transplants, the risk of CMV infection increases substantially.[11,17]

In addition, gender and impaired kidney function have also been identified as risk factors for CMV infection. A study showed that men had a higher risk of developing post-transplant CMV infection, with a hazard ratio (HR) of 1.92. This may be related to immunological differences between the sexes, where males tend to have different immune responses compared to females. In addition, decreased glomerular filtration rates, measured through estimated glomerular filtration rate (eGFR), were also found to be a risk factor with an HR of 0.98. A decrease in eGFR indicates more severe kidney damage, which can affect the body's ability to handle infections, including CMV.[13]

One of the interesting findings is the variability of CMV strains that can affect clinical outcomes in recipients who are seropositive for CMV. In patients with seropositive CMV status who receive kidneys from donors who are also seropositive (D+/R+), there is a possibility of pseudoprimary infection. This pseudoprimary infection occurs when a recipient who already has antibodies to CMV is re-exposed to a different strain of CMV from the donor, which can lead to reactivation of the infection with higher virulence. This condition is often associated with poorer clinical outcomes compared to recipients who receive kidneys from seronegative donors (D-/R+), where there is no exposure to new CMV strains.[1,8,10]

However, not all studies conclude that CMV seropositivity always has a negative impact. A retrospective cohort evaluating the high prevalence of CMV IgG antibodies found no significant association between CMV disease and the risk of death or graft loss in kidney transplant recipients. These findings suggest that although CMV may increase the risk of complications, not all patients with seropositive CMV will experience poor outcomes. Other factors, such as immunosuppression management and the use of antiviral prophylaxis, are also likely to play a role in influencing long-term outcomes.[6,9,11]

Nevertheless, other studies have shown that rapid episodes of deteriorating clinical conditions, often due to CMV infection, can significantly increase the risk of graft loss and long-term mortality. Uncontrolled CMV infection, especially in the early posttransplant period, can cause severe damage to graft tissue as well as interfere with the function of the newly

transplanted kidney. Therefore, close monitoring and early intervention are essential to prevent complications that can have long-term consequences.

The study conducted by Strivastava et al. provides further insight into the risk of CMV infection in recipients who receive kidneys from donors with D+/R+ status. This study showed that recipients who did not receive routine CMV prophylaxis were more susceptible to late CMV infection. These infections are often invasive and destructive, which directly affects graft function and is associated with poor long-term outcomes. This emphasizes the importance of antiviral prophylaxis in high-risk patients, especially in those with D+/R+ status.[10,11]

Antiviral prophylaxis, as recommended in various clinical guidelines, aims to suppress CMV replication during the critical post-transplant period. Without prophylaxis, the risk of reactivation of CMV or primary infection can increase, which can trigger serious complications such as pneumonia, gastroenteritis, and even other life-threatening diseases. In recipients with D+/R+ status, long-term antiviral prophylaxis is often necessary to reduce this risk, and regular viral load monitoring can help detect CMV replication at an early stage.[15]

Overall, the management of CMV infections in kidney transplant recipients is complex and requires a personalized approach. Identification of risk factors such as serostatus, lymphocyte decrease, sex, and eGFR is essential for assessing individual risk and designing effective prevention strategies. With proper monitoring and the timely use of antiviral prophylaxis, the risk of complications due to CMV infection can be minimized, thereby increasing the chances of long-term success of kidney transplantation.[13]

Herpes Simplex Virus (HSV) infection has complex and unique infection mechanisms, especially in the context of primary infection and reactivation. During primary infection, HSV replicates in the mucocutaneous layer, such as the skin or mucous membranes, which is where the virus first enters and begins its life cycle. The virus then moves retrogradely through the axons of sensory neurons to the nerve ganglion, where it settles in a latent state. This latent state allows the virus to hide from the immune system and survive in the body for the lifetime of the infected individual.[14,18]

Although there have been many studies on the pathogenesis of HSV, to date, there is no effective method to stop or control viral latency at the cellular molecular level. This latency is one of the biggest challenges in the management of HSV infection, as the virus can remain dormant for years and then undergo reactivation, especially when individuals experience a decline in immune systems, such as in organ transplant recipients.[5,6,9]

HSV reactivation is generally endogenous, meaning that the virus that has been dormant in the body for a long time becomes reactivated, rather than the occurrence of a new exogenous infection from the outside. This reactivation can be triggered by a variety of factors, including stress, illness, or immunosuppression that is often used in organ transplant patients. In kidney transplant recipients, the risk of HSV reactivation is significantly increased due to the use of immunosuppressive drugs necessary to prevent organ rejection, but it can also weaken the immune system that protects against latent viral reactivation.[15]

Although rare, there have been reports of transmission of HSV through kidney transplant grafts. This occurs when the donor has an active or latent HSV infection, and the virus is transmitted to the recipient through the transplanted organ. This is one of the reasons why screening for infectious diseases in organ donors is so important, even though HSV infection is usually considered less critical compared to other infections such as CMV.[13]

Studies assessing the seroprevalence of HSV-2 in kidney transplant recipients provide important insights into the spread of this infection among patients with immuno-

suppression. In the study, it was found that 5.4% of kidney transplant recipients had anti-HSV-2 IgG antibodies, indicating prior or latent infection with HSV-2. Interestingly, these patients did not show clinical manifestations of genital herpes, which is the most common form of HSV-2 infection. This suggests that HSV-2 infection in transplant recipients may often be subclinical or clinically undetectable, although the presence of this virus can have significant clinical implications, especially in the event of reactivation.[19]

The study also noted that there was no significant association between HSV-2 seropositivity and factors such as age, sex, history of hemodialysis and transplantation, blood transfusions, or immunosuppression regimens used. These findings suggest that HSV-2 infection in kidney transplant recipients may be more influenced by other factors, such as the individual's immunity status or previous exposure to the virus, rather than demographic or clinical variables typically considered.[20]

Although HSV-2 is often associated with genital herpes, in the kidney transplant recipient population, the clinical manifestations of the infection may be more varied or unclear. HSV reactivation can lead to a wide range of complications, ranging from mild mucocutaneous lesions to more serious diseases such as meningoencephalitis or hepatitis, especially in patients with severe immunosuppression. Therefore, although the prevalence of HSV-2 infection may appear low, it is important for clinicians to remain vigilant of possible reactivation and associated complications in kidney transplant recipients.[21]

In the management of transplant recipients, the prevention and control of HSV reactivation is generally carried out through antiviral prophylaxis. Medications such as acyclovir or valacyclovir are used routinely in the early posttransplant period to prevent reactivation of herpesvirus infections, including HSV. The administration of this prophylactic is especially important in patients who are known to have seropositivity against HSV, as they have a higher risk of experiencing reactivation of the infection.[21,22]

Overall, although HSV infection may appear to be less dangerous than other infections such as CMV, the potential complications it poses in kidney transplant recipients should not be underestimated. A comprehensive approach to screening, prevention, and management of HSV infection is needed to ensure that the risk of viral reactivation and its clinical impact can be minimized, thereby improving long-term outcomes for posttransplant patients.[2,23]

If antiviral prophylaxis is not given, the risk of infection in solid organ transplant recipients increases significantly, with an estimated 40-50% of them developing infection within the first month post-transplant. In this period, clinical manifestations of infections, including Herpes Simplex Virus (HSV), generally appear within 2-3 weeks after transplantation, coinciding with the intensive phase of immunosuppression administered to prevent organ rejection. This condition shows how critical the administration of antiviral prophylaxis is in preventing opportunistic infections that can threaten patient safety in the early posttransplant phase.

HSV, in particular, has the ability to reactivate quickly after the start of immunosuppression therapy. This risk of reactivation and infection is greatly influenced by the intensity of immunosuppression administered. Powerful immunosuppressive drugs, such as OKT3 (anti-CD3 monoclonal antibody), mycophenolate mofetil, or anti-thymocyte globulin, are known to be associated with high rates of HSV reactivation. Studies show that patients who receive this therapy have a higher risk of developing severe HSV disease, including mucocutaneous and visceral complications.[20]

Gingivostomatitis, a condition in which HSV causes inflammation of the gums and oral mucosa, is more commonly found in patients undergoing hematopoietic cell transplants than solid organ transplant recipients. However, solid organ recipients are also susceptible to other

forms of HSV infection, such as anogenital herpes, which is usually caused by HSV-2. HSV-2 can undergo reactivation from latent conditions in the sacral ganglia, especially when the immune system is suppressed by immunosuppression therapy. Although these mucocutaneous infections are often considered mild, they can cause significant morbidity, especially if left untreated.[16,18,19]

Without therapeutic intervention, HSV can spread and cause much more serious complications. For example, in patients with uncontrolled HSV infections, especially those with HSV-induced hepatitis, mortality rates can reach 60%-80%. In the most severe cases, when the infection causes intravascular coagulopathy to be disseminated, mortality can be close to 100%. In these situations, a liver transplant may be necessary for patients who have fulminant liver failure due to HSV infection. These extreme cases highlight the importance of aggressive and timely management of HSV infection in this highly vulnerable patient population.[21]

The use of antiviral drugs such as acyclovir, valacyclovir, and valgancyclovir has been shown to be effective in preventing most HSV reactivations. This antiviral prophylaxis should be an integral part of the management of solid organ transplant patients, especially for those who have been identified as seropositive against HSV-1 or HSV-2. In cases where the patient does not receive antiviral prophylaxis against CMV (Cytomegalovirus), special consideration should be given to initiating prophylaxis against HSV, given the high risk of reactivation and the complications that can occur.[23]

Some researchers also argue that HSV prophylaxis may also be necessary in patients with seronegative HSV, although this evidence still requires further confirmation. This approach is based on the potential risk of HSV primary infection which can be particularly severe in individuals who are severely immuno-suppressed.[21]

The efficacy of HSV prophylactic administration has been proven in various studies, particularly in recipients receiving OKT3. Administration of acyclovir, which is the standard of therapy, is recommended at a dose of 400-800 mg twice daily for at least the first month posttransplant. In patients with a history of severe HSV reactivation, higher doses may be necessary to prevent further reactivation. In addition, dosage adjustments should be made based on the patient's kidney function, since the clearance of this drug is highly dependent on kidney function. Kidney failure can lead to drug accumulation and increase the risk of toxicity, so close monitoring and careful dosage adjustment are essential.[11,20]

In conclusion, the administration of antiviral prophylaxis should be considered a key element in posttransplant protocols to prevent potentially fatal opportunistic infections such as HSV. A coordinated and personalized approach in immunosuppression management and infection prevention can improve overall clinical outcomes and reduce morbidity and mortality in solid organ transplant recipients. Thus, the integration of comprehensive prevention strategies into clinical practice can provide significant protection for patients in the critical post-transplant phase.[20,29]

Conclusion

This study evaluated the seroprevalence of Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV) infections in donor candidates and kidney transplant recipients in hospitals. Ngoerah Denpasar. The results showed that among the donor candidates, as many as 39.4% were infected with both CMV and HSV, with 45.5% of them showing anti-CMV IgG seropositives, indicating latent CMV infection. In addition, some donor candidates also showed seropositive for anti-HSV-1 IgG, with a small proportion showing viral reactivation characterized by the presence of anti-HSV-1 IgM. On the other hand, in the recipient candidate group, as many as 27.3% were infected by CMV and HSV. Of this group, 42.4% showed anti-CMV IgG

seropositives, signaling a latent infection that may require special posttransplant attention. Some recipients also showed seropositive for anti-HSV-1 IgG and anti-HSV-1 IgM, indicating a risk of postoperative infection reactivation. The conclusion of this study confirms the importance of serological screening before kidney transplantation to detect the presence of latent infections that can affect post-transplant clinical outcomes. By knowing the serological status of CMV and HSV in donors and recipients, medical teams can implement more targeted and intensive prevention strategies, especially in high-risk recipients, to reduce the likelihood of complications of post-transplant infection. This is important to improve the long-term success of kidney transplants and maintain the health of postoperative patients.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee of the Ngoerah Hospital, Denpasar.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: NNAT. Design: NNAT. Control/supervision: IKS, YK. Data collection/ processing: NNAT. Analysis/interpretation: NNAT. Literature review: NNAT. Writing the article: NNAT. Critical review: IKS, YK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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