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Research Article

"Cytomegalovirus Infection in Renal Transplant Recipients: Incidence, Risk Factors, Clinical Profile and Outcomes"

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Introduction

The reported prevalence of CKD in India, in different regions ranges from <1% to 13%, and recently, data from the International Society of Nephrology's Kidney Disease Data Centre Study reported a prevalence of 17% [1]. Renal transplantation is the preferred modality of renal replacement therapy as it offers longer survival and better quality of life when compared to dialysis. In the recent years, with the increased access to transplantation both live related as well as deceased donor, we need to focus on the infectious complications in post renal transplant recipients, which on prompt treatment can prevent allograft dysfunction. Infections in a post renal transplant recipient can be bacterial, viral, fungal, parasitic or caused by other atypical organisms. They can be community acquired, reactivation of past infection or donor derived. Cytomegalovirus (CMV) is one of the commonly encountered opportunistic infection following renal transplantation, usually seen in the first 6 months of transplant. CMV infection in transplant patients may be symptomatic or asymptomatic. CMV disease refers to symptomatic acute CMV infection [2]. CMV infection remains an important challenge in the early as well as late phase after kidney transplantation. Despite routine use of preventive strategies nowadays, several recent studies still confirm the negative impact of CMV on kidney transplant outcomes such as acute rejection, graft survival, mortality and cardiovascular events. These so-called indirect effects of CMV are thought to be due to its immunomodulating effects, and the chronic low-grade viral persistence in the allograft [3].

Risk factors include, CMV-seronegative recipients of a CMV-seropositive donor, older donor age, exposure to induction agents (depleting/non-depleting agents), prior rejection episodes and impaired graft function, PTDM. The risk of CMV infection is maximum in kidney transplant among CMV seropositive donor/ CMV seronegative recipient (D+/R–) as compared to kidney transplants among D–/R–. The risk is moderate in D+/R + and D–/R+ transplants. The incidence of CMV infection in D+/R+ patients varies from 5 to 30% [4]. In India, most of the population is exposed to CMV and have a D+/R+ serology at transplant. In this study we compare the risk factors and outcomes of early vs late CMV infection in renal transplant recipients.

Material and Methods

This is a retrospective, observational study of patients who underwent renal transplant between January 2010 to December 2020 and developed CMV infection in a nephrology unit at a tertiary care hospital in south India. Patients who had CMV infection diagnosed with detection of viral replication through CMV DNA PCR method and had a minimum of 6 months follow up post CMV infection were included in the study.

The baseline characteristics such as age at transplant, sex, pre-

morbid conditions, cause of CKD, dialysis vintage, date of transplantation, type of transplant (live related/ deceased donor), time of CMV infection post-transplant were noted from hospital records.

Immunosuppression details – according to the Institute protocol, recipients of kidney from a parent and siblings with haplomatch on HLA analysis i.e. low immunological risk were not given induction therapy, recipients of kidney from siblings without haplomatch, spouse, deceased donor were considered intermediate to high immunological risk, induction therapy with either intravenous rabbit ATG in a dose of 1-3mg/kg or two doses of Basiliximab 40mg on day 0 and day4 were given. Maintenance therapy with triple immunosuppression – oral prednisolone 20mg tapered over 6 months, calcineurin inhibitor like tacrolimus (0.089mg/kg/day for those who received induction and 0.1mg/kg/day for those who did not receive induction therapy) and mycophenolate mofetil (1200mg/m^2/day). Prophylaxis for CMV with oral Valganciclovir 450mg daily or alternate day was prescribed according to institute protocol in patients who received induction therapy.

Screening for CMV infection, serostatus of donor and recipient were done prior to transplant and recipients were tested for CMV if they present with symptoms suggestive of infection such as mononucleosis syndrome with fever, flu-like symptoms, lymphadenopathy, hepatomegaly or organ specific symptoms suggestive of gastroenteritis, lower respiratory tract infection, cranial nerve palsy, etc were recorded. Asymptomatic viremia was suspected when they have unexplained transaminitis or leukopenia and were tested for CMV DNA by PCR method either qualitative or quantitative analysis was done. The diagnosis of CMV infection is based on detection of viral replication using a CMV DNA polymerase chain reaction (PCR) of serum or broncho-alveolar lavage fluid in case of pneumonia, cerebrospinal fluid in case of central nervous system infection, bone marrow aspirate in haematological involvement, histological diagnosis by endoscopy or colonoscopy and biopsy in case of gastrointestinal involvement.

CMV viremia was defined as detection of DNA viral load of >150 copies without presence of symptoms and CMV disease as detection of viral load > 150 copies with clinical symptoms suggestive of viral syndrome and/or organ system involvement. Early CMV infection was defined as CMV infection within 3 months of transplant, whether detected on routine screening or when patients had features suggestive of CMV infections. Late CMV infection was defined as CMV infection after 3 months of transplant, again whether detected on routine screening or detected once patients had features suggestive of CMV infections.

Treatment of CMV according to standard guidelines with either intravenous Ganciclovir 5mg/kg in two divided doses for 14-21 days followed by oral Valganciclovir 900mg once a day for 90 days or oral Valganciclovir 900mg alone as induction therapy was given to our patients. Graft dysfunction was defined as rise in serum creatinine of 15% from baseline. We defined graft loss as progressive rise in serum creatinine and return to renal replacement therapy. Immediate outcomes were recorded up to 3 months after CMV infection and long-term outcomes were recorded up to the date of last follow up.

Statistical Analysis

Statistical analysis was done using SPSS 17 Software (IBM, Chicago, IL). Continuous variables were expressed as mean and standard deviation (SD). Categorical data will be expressed as percentages. For comparison of clinical and pathological features of patients, the student's t-test, Chi-square test will be used. Kaplan-Meier curves will be used to analyse the patients' survival analysis. Statistical significance will be considered as $P<0.05$.

Results

A total of 480 patients underwent renal transplantation in a unit of Nephrology between 2010 to 2021 among which 67.1% (n=322) had a live donor and 32.9% (n=158) had a deceased donor renal transplant. Incidence of CMV infection among these patients was 11.45% (n=55) with 61 episodes of infection. CMV viremia was seen in 36.1% (n=22) and CMV disease in 63.9% (n=39). Early CMV infection episodes were seen in 40.9% (n=25) and Late CMV infection episodes were seen in 59.1% (n=36) Table 1.

Parameters	Total	Early CMV	Late CMV	P value
Number of recipients	55	25 (45.6%)	30 (54.4%)	-
Number of episodes	61	25(40.9%)	36 (59.1%)	-
Mean age at transplant (years)	33.5+9.03	33.5+10.6	33.6+11.0	0.96
Gender (M: F)	46:9	19:6	27:3	0.162
Mean duration of dialysis (Months)	19.54+24.9	22.5+25.4	17+24.5	0.42
LDRT DDRT	39 (70.9%) 16 (29.1%)	17 (68%) 8 (32%)	22 (73.3%) 8 (26.7%)	0.66
Mean cold ischemia time (Hours)	3.21+3.4	3.56+3.8	2.9+3.2	0.51
Delayed graft function (%)	12 (21.8%)	7 (23%)	5 (20%)	
Induction regimen No induction (N%) ATG (N%) Basiliximab (N%)	 30 (54.6%) 7 (12.7%) 18 (32.7%)	 12 (48%) 4 (16%) 9 (36%)	 18 (60%) 3 (10%) 9 (30%)	 0.89
CMV prophylaxis given (N%)	32 (58.1%)	11 (34.3%)	21 (65.6%)	0.027
Mean follow up	51.6+35.8	47.6+39.9	54.9+32.3	0.45

Table 1: Baseline characteristics of patients are shown.

There is a higher preponderance of male recipients in both early and late CMV groups. Most of the patients were Hypertensive (86.5%) in our study group and the most common native kidney disease was Chronic Glomerulonephritis seen in 55.8% of cases followed by Chronic interstitial nephritis in 19.2%. The relatively higher mean dialysis vintage (22.5 months) and cold ischemia time (3.56 hours) which predispose to delayed graft function were higher in the early CMV group. The details of the risk factor for early and late CMV infection are shown in Table 2.

Risk factors	Early CMV	Late CMV	P value
Induction received	13 (52%)	12 (40%)	0.45
HCV infection	3 (12%)	2 (6.6%)	
Acute rejection prior to CMV	1 (4%)	8 (22.3%)	0.02
Other infections prior to CMV	0.4+0.65	1.2+1.19	0.004
Dose of immunosuppressants (mg/day) Steroid Tac MMF	 18.4+2.59 4.3+0.99 1727.6+315.9	 8.8+4.1 2.34+1.3 1271.6+430.1	 0.001 0.001 0.001
Mean Tac levels	11.2+5	6.6+6.5	0.004
PTDM	10 (40%)	11 (30.6%)	0.44
CMV prophylaxis	11 (34.3%)	21 (65.6%)	0.027

CMV donor status D+/R+ D+/R-	 17 0	 21 1	

Table 2: Risk factors for CMV.

In the early CMV infection group 52% (n=13) received induction therapy, higher rate of pre-transplant HCV infection (12%) when compared to late CMV infection. The mean dose of immunosuppressive drugs like steroid, tacrolimus & MMF were significantly higher in the early CMV group with p=0.001.

The mean Tacrolimus levels were higher in early group 11.2ng/dl (p=0.004). The incidence of PTDM was higher 40% in early group. In the early group, lesser number of patients received CMV prophylaxis 34.3% (p=0.02). In the late CMV group, 22.3% had an acute rejection episode prior to CMV infection when compared to 4% in early group (p=0.02). Other infections prior to CMV infection was higher in late CMV group compared to early group (p=0.004) Table 3.

Clinical features	Early CMV	Late CMV
Time of onset of CMV (Months-mean+SD)	2.09+0.5	27.7+23.52
Clinical presentation Asymptomatic Symptoms with tissue diagnosis Symptoms with no tissue diagnosis	 10 (40%) 9 (60%) 6 (40%)	 12 (33.3%) 7 (29.1%) 17 (70.9%)
Viral load copies/ml (mean+SD)	10114.4+19883.8	20916.6+29747.6
Graft function At CMV After 3 months	 1.81+1.06 1.27+0.43	 2+0.88 1.61+0.7
Relapses	3 (33.4%)	6 (66.6%)

Table 3: Clinical features of patients with early and late CMV infection.

All the patients included in the study were diagnosed CMV infection with DNA PCR qualitative or quantitative method. Those who had symptoms suggestive of CMV were treated according to standard protocol after PCR confirmation. Only those who had severe disease not promptly responding to therapy underwent invasive tissue diagnosis with colonoscopy and biopsy in colitis, bronchoscopy in pneumonia Table 4.

Outcome variables	Early CMV	Late CMV	P value
Mean duration of follow up (months)	47.6+39.9	54.9+32.3	0.45
Mean creatinine at last follow-up	2.04+1.4	2.73+1.74	0.106
Graft dysfunction	1 (4%)	11 (36.6%)	
Graft loss	1 (4%)	3 (10%)	
Patient loss	7 (28%)	3 (10%)	

Table 4: Outcomes in early and late CMV infection.

Discussion

This is a retrospective analysis of recipients with CMV infection comparing early vs late CMV infection and assessing their risk factors and outcomes. A total of 55 patients had 61 episodes of infection with CMV. A total of 25 patients (45.4%) received induction therapy among which 13 recipients (52%) in the early group and 12 recipients (48%) in the late group (p=0.48) received induction, suggesting that induction therapy has no significant effect on the timeline of development of CMV infection. Basiliximab as induction agent was used in majority of our patients (72%). Rabbit ATG as induction agent was used in only 28% of recipients hence its impact on infection rate could not be assessed. In two Indian studies, one by VB Kute et.al [5] of 42 patients with predominant D+/R+ (59.5%)

CMV serology, majority of infections occurred after 3 months of transplant, ATG induction (54.8%) was identified as a risk factor for CMV infection. One study by Bhaduria D et al. of 521 patients, 74 (14.2%) patients developed CMV infection, majority of them had late infection with median time to CMV of 7.18 ± 4.35 months among which 58% received induction [6]. In two studies by San Juan R *et al.* and Schroeder R et al. use of ATG as induction agent was significantly associated with development of early CMV infection, OR 2.1, 95% CI 1.1-3.8,) and (73% vs 41%, $P = 0.022$) respectively [7,8].

According to this study, high-risk patients may be more susceptible to primary CMV infection if their cold ischemia duration is prolonged [9]. Notably, immunosuppression, donor-recipient serostatus, and advanced age are more relevant risk factors for CMV infection in transplant patients than cold ischemia time, even though the latter may play a role. In our study mean cold ischemia time was 3.2+3.4 hours, with the early group experiencing 3.56+3.8 hours and the late group experiencing 2.9+3.2 hours. Wieteke Kleinherenbrink's study found a strong association between DGF and an increased risk of CMV illness. The immunological dysregulation and inflammation associated with DGF may be the reason for this, as they create an environment favourable to viral multiplication. However, the risk of CMV illness is not only determined by DGF. Other significant risk factors include immunosuppression, donor-recipient serostatus, and advanced age. Twenty percent of the late group and twenty-three percent of the early group of our transplant recipients developed DGF, making up 21.8%.

About 20% of kidney transplant recipients get CMV disease, and 60% of them have an active CMV infection if preventive measures are not taken [11]. 58% of the CMV patients in our study received CMV prophylaxis; the early group received it at a percentage of 34.3, while the late group received it at a rate of 65.6%. Majority of our patients in both the groups were of D+/R+ serostatus. With 61 episodes of infection, the CMV infection rate among these patients was 11.45% (n=55). 36.1% (n=22) had CMV viremia, and 63.9% (n=39) had CMV disease. 40.9% (n=25) experienced early CMV infection episodes, while 59.1% (n=36) experienced late CMV infection episodes. While prophylactic treatment significantly lowers the incidence of CMV illness, 18–31% of KTR still get CMV illness after stopping antiviral prophylaxis [12-15].

Acute rejection (AR) after solid organ donation has been linked to cytomegalovirus (CMV) infection. The incidence of CMV infection did not differ significantly across the groups (AR group, 13% [10/75] vs. non-AR group, 10% [92/917], P = 0.37), per the study by Y-M Lee et al15. However, the late CMV group in our study had statistically significant CMV infections.

Prophylactic treatment with an anti-CMV medication was more effective than pre-emptive therapy in preventing CMV diseases, but there were no appreciable differences between the two approaches in terms of acute rejection or graft loss, according to a recent meta-analysis comparing the evidence for prophylaxis against pre-emptive therapy for CMV infections in renal transplant recipients [16].

Additionally, prophylaxis may be better than pre-emptive therapy for preventing CMV while treating acute graft rejection [16,17]. Barry et al [18]. found that the mean time to CMV infection (±SE) was 3.4 ± 2.6 months for those with early CMV and 54 ± 46 months for those with late CMV. At 2.09+0.5 months for early CMV and 27.7=23.52 months for late CMV, on the other hand, the mean+sd onset of CMV was earlier in our group.

The results of our investigation concur with those of Atul Srivastava et al [4].

Of the 172 individuals who got CMV in the study by Atul Srivastava et al [4], 90 (52.3%) had an early infection and 82 (47.7%) had a late infection. Every patient in the study had a CMV status of D+/R +. While 54.8% of the late CMV group experienced CMV symptoms without a tissue diagnosis, the majority of the early CMV group (63.3%) was asymptomatic. While the majority of our patients in early group had symptoms with a tissue diagnosis (60%) while the late group had symptoms without a tissue diagnosis (70.9%).

Our study showed greater viral loads in both the early and late CMV groups, and patients with late CMV had higher viral loads than those in the early CMV group, in contrast to the study by Atul Srivastava et al [4]. According to a study [4], the mean creatinine values in the early and late CMV groups were 1.3±0.4 and 1.6±0.6, respectively, over a mean follow-up of 22.8±22.1 months in the early group and 49.7±40.9 months in the late group. Graft dysfunction was experienced by 4.4% of patients in the early group and by 9.7% in the late group, while graft loss was experienced by 2.2% and 6.1% in the early and late groups. In contrast, the early and late cmv groups in our study had mean serum creatinine levels of 2.04+1.4 and 2.73+1.74 mg/dl, respectively. Graft loss occurred in 10% of the late group and 4% of the early group, whereas 36.6% of the late group experienced persistent graft dysfunction following CMV.

Conclusions

- The incidence of CMV infection during the study period in renal transplant recipients was 11.45%.
- CMV disease was more common (63.9%) in our group of patients compared to CMV viremia (36.1%).
- There is a change in the traditional risk factors for developing CMV infection such as CMV serostatus and induction therapy. As majority of our patients were D+/R+ and received no induction therapy.
- Persistent graft dysfunction was seen in 4.4% in the early

group and 9.7% in the late group, while graft loss was seen in 2.2% and 6.1% in the early and late groups respectively.

Limitations

- It is a Retrospective Observational study with a small sample size and lacks comparison group.
- As it is a single centre study so results cannot be generalised to other Population.
- Prophylaxis for CMV was given according to institute protocol.

References

1. Ene-Iordache B, Perico N, Bikbov B, Carminati S, Remuzzi A, et al (2016) Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study. The Lancet Global Health. 4: e307-19.
2. Jutta KP, Daniel CB, Jay F, Upton A. (2005) Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. American Journal of Transplantation. 5:218-27.
3. Hellemans R, Abramowicz D. (2022) Cytomegalovirus after kidney transplantation in 2020: moving towards personalized prevention. Nephrology Dialysis Transplantation. 37:810-6.
4. Srivastava A, Bagchi S, Singh S, Balloni V, Agarwal SK. (2022) Assessment of Risk Factors and Outcome of Early Versus Late Cytomegalovirus Infection Infection in Living-related D+/R+ Renal Allograft Recipients. Indian Journal of Nephrology. 32:47-53.
5. et al (2012) Post–Renal Transplant Cytomegalovirus Infection: Study of Risk Factors. InTransplantation proceedings. 44: 706-709.
6. Bhadauria D, Sharma RK, Kaul A, Prasad N, Gupta A, et al (2012) Cytomegalovirus disease in renal transplant recipients: a single-center experience. Indian journal of microbiology. 52:510-5.
7. San Juan R, Aguado JM, Lumbreras C, Fortun J, Munoz P, et al (2008) Impact of current transplantation management on the development of cytomegalovirus disease after renal transplantation. Clinical infectious diseases. 47:875-82.
8. Schroeder R, Michelon T, Fagundes I, Bortolotto A, Lammerhirt E, et al (2004) Cytomegalovirus disease latent and active infection rates during the first trimester after kidney transplantation. In Transplantation proceedings 36:896-898.
9. Falk C, Schlott F, Katsrintaki K, Steubl D, Puppe W, et al (2017) Primary Cytomegalovirus Infection in Seronegative Kidney Transplant Patients is Associated with Prolonged Cold Ischemic Time of Seropositive Donor Organs.
10. Kleinherenbrink W, Baas M, Nakhsbandi G, Hesselink DA, Roodnat JI, et al (2021) Delayed graft function and rejection are risk factors for cytomegalovirus breakthrough infection in kidney transplant recipients. Pharmacological Research. 167:105565.
11. Sagedal S, Nordal KP, Hartmann A, Degré M, Holter E, et al (2000) A prospective study of the natural course of cytomegalovirus infection and disease in renal allograft RECIPIENTS1. Transplantation. 70:1166-74.
12. Doyle AM, Warburton KM, Goral S, Blumberg E, Grossman RA, et al (2006) 24-week oral ganciclovir prophylaxis in kidney recipients is associated with reduced symptomatic cytomegalovirus disease compared to a 12-week course. Transplantation. 81:1106-11.
13. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, et al (2008) Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. American Journal of Transplantation. 8:975-83.
14. Helanterä I, Kyllönen L, Lautenschlager I, Salmela K, Koskinen P. (2010) Primary CMV infections are common in kidney transplant recipients after 6 months valganciclovir prophylaxis. American Journal of Transplantation. 10:2026-32.
15. Lee YM, Kim YH, Han DJ, Park SK, Park JS, et al (2014) Cytomegalovirus infection after acute rejection therapy in seropositive kidney transplant recipients. Transplant Infectious Disease. 16:397-402.
16. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, et al (2018) The Transplantation Society International CMV Consensus Group. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 102:900-31.
17. Felipe C, Ferreira AN, de Paula M, Viana L, Cristelli M, et al (2019) Incidence and risk factors associated with cytomegalovirus infection after the treatment of acute rejection during the first year in kidney transplant recipients receiving pre-emptive therapy. Transplant Infectious Disease. 21: e13106.
18. Browne BJ, Young JA, Dunn TB, Matas AJ. (2010) The impact of cytomegalovirus infection≥ 1 year after primary renal transplantation. Clinical transplantation. 24:572-7.