Original Article

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Evaluation of Influential Factors in the Incidence Period of Cytomegalovirus after Renal Transplantation

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Abstract

BACKGROUND AND OBJECTIVES: Cytomegalovirus (CMV) infection is one of the most frequent infectious complications, which results in renal transplant failure. In this study, we aimed to evaluate the demographic characteristics and risk factors associated with the incidence period of CMV infection after renal transplant.

METHODS: This cross-sectional study was conducted in renal transplant recipients during 2010-2015 in kidney transplant unit of Shahid Beheshti Hospital of Babol, Iran. The evaluated demographics included body mass index (BMI), smoking status, type of underlying disease leading to end-stage renal disease, hepatitis B, hepatitis C, and type of dialysis. Data analysis was performed using Kaplan-Meier estimator, log-rank test, and Cox regression.

FINDINGS: In total, 242 patients received renal transplant, among whom 73 (30.2%) cases had CMV infection with median and mean survival of 41 and 48.09±23.50, respectively. In this study, there was no correlation between demographic variables (e.g., gender, place of residence, marital status, educational level, BMI, smoking status, hepatitis B, and type of dialysis) and incidence period of CMV. However, a significant relationship was observed between the incidence period of CMV and age (mean: 45 years, P=0.04), as well as etiology of ESRD urology (P=0.03).

CONCLUSION: The prevalence of CMV infection is reported to be high in elderly patients with history of urologic diseases. Therefore, performing short-term follow-ups four months after transplantation, with emphasis on the first two months is recommended.

KEY WORDS: *Cytomegalovirus, Kaplan-Meier estimator, Renal transplantation, Survival analysis.*

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Introduction

Annually, numerous infections lead to transplant rejection or death of thousands of transplant patients (1-3). Cytomegalovirus (CMV) is a genus of viruses in the order Herpesvirales, (4) which can be transmitted through blood transfusion, organ transplantation, sexual intercourse, and hemodialysis (3,5-7). Antibodies against this virus were identified in 80% of healthy adults, which is indicative of previous infection, virus latency, and possibility of reactivation (8). Suppression of the immune system by various factors results in reactivation of CMV in transplant recipients (9), which might even lead to patient death (10). CMV can produce primary and secondary infections. In this regard, the incidence of primary infection is observed in patients without serum viral infection; however, secondary infection indicates reactivation of a latent virus.

The third form of CMV infection is observed in transplant recipients in the form of super-infection or reinfection and occurs when seropositive recipients (R+) receive latent infected cells from seropositive donors (D+); in other words, the donor is the source of the activated virus (11, 12). A study by Taherimahmoudi et al. on the incidence and risk factors of CMV revealed that mean incidence period of CMV infection was 4.7 weeks, with the consumption of antithymocyte globulins as an independent risk factor (13).

Moreover, history of corticosteroid therapy was considered as one of the risk factors of CMV incidence in a study by Viot et al. (14). Clinical manifestations of CMV infection in transplant recipients include damaged implanted organ, transplant rejection, or even mortality. Therefore, early diagnosis of CMV infection is of paramount importance to prevent disease progression (15). Several researchers performed patient follow-ups until discovering a malfunction in the patient. In survival studies, the target variable is monitored until a specific condition is observed, and the interval is recorded. Given that CMV might not occur in some of the studied patients, the observations are accompanied with censoring (16).

In the current study, survival is considered as lack of CMV infection after renal transplantation. Polymerase chain reaction (PCR) method was applied to evaluate the incidence of CMV. In this study, we aimed to evaluate demographics and risk factors associated with the incidence of CMV after renal transplantation using survival analysis.

Methods

This cross-sectional study was conducted in renal transplant recipients in the renal transplant unit of Shahid Beheshti Hospital of Babol, Iran. Medical records of 242 patients were selected and evaluated during 2010-2015.

The evaluated demographics included age at the time of transplantation, gender, marital status (married or single), educational level (illiterate, below diploma, diploma, or above diploma), place of residence (rural or urban), biological variables such as body max index (BMI), smoking status (smoker or non-smoker), type of underlying disease leading to kidney failure (urologic diseases, diabetes, hypertension, glomerulonephritis, and renal cysts), type of dialysis (hemodialysis, peritoneal, both, or without dialysis), hepatitis B, hepatitis C, and age of the recipient. Survival time was considered as the interval between renal transplantation and incidence of CMV infection, calculated in days.

The exclusion criteria of this study were loss to followed-up and lack of virus reactivation until the end of the evaluation period (120 days after transplantation). Survival curves were plotted using Kaplan-Meier estimator. In addition, log-rank test and Cox regression were utilized to evaluate and compare survival rates (17).

Data analysis was performed using STATA version 12 and SPSS version 20 and $p<0.05$ was considered statistically significant.

Results

In this study, of the 242 renal transplant recipients, 156 (64.5%) were male, and total mean age of the patients was 41.58±14.06 years (table 1). In terms of the admission year, frequency of referrals was 53, 51, 51, 49, and 38 cases during 2010-2015, respectively. CMV was activated in 69 (28.5%) cases during the first 120 days of the post-transplant period. All the donors were alive, with total mean age of 29.1±5.26 years. Moreover, the mean age of the patients affected by CMV was 30±6 years. In the pre-transplant evaluations, immunoglobulin M (IgM) was not found in any of the donors or recipents.

On the other hand, immunoglobulin G (IgG) was reported negative in seven (4.7%) donors, and eight (3.8%) recipents, and positive for the other cases (seven cases in the form of D-/R- and one case in the form of D-/R+).

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Table 1. Demographics of the transplant recipients (total study population and patients with cytomegalovirus)

Demographics	Patients with cytomegalovirus N(%)	All the patients N(%)
Age		
Mean	45	41.58
Domain	(10-66)	(8-79)
Standard deviation	14	14.06
Gender		
Male	49(67.1)	156(64.5)
Female	24(32.9)	86(35.5)
Educational level		
Illiterate	21(29.2)	43(17.8)
Below diploma	22(30.6)	108(44.6)
Diploma	14(19.4)	52(21.5)
Above diploma	15(20.8)	35(14.5)
Place of residence		
Urban	49(67.1)	152(62.8)
Rural	24(32.9)	90(37.2)
Marital status		
Married	60(82.2)	194(80.2)
Single	13(17.8)	48(19.8)
Type of dialysis		
Hemodialysis	60(83.3)	205(84.7)
Peritoneal	7(9.7)	19(7.9)
Both	0	2(0.8)
Without dialysis	5(6.9)	15(6.2)
Body mass index*		
Underweight	7(13.2)	29(12.0)
Normal	24(54.3)	88(36.4)
Overweight	14(26.4)	54(22.3)
Obese	8(15.1)	29(12.0)
Smoking status	10(13.9)	38 (15.7)
Underlyingdiseases		
Diabetes	8(12.1)	27(11.2)
Hypertension	4(6.1)	65(26.9)
Glomerulonephritis	22(33.3)	12(5.0)
Urologic	10(15.2)	16(6.6)
Renal cysts	10(15.2)	26(10.7)
Others	12(18.2)	69(28.5)

The highest incidence rate of CMV was observed in the second post-transplantation month (table 2). Survival rates (lack of CMV infection post-transplant) in the first, second, third, and fourth post-transplantation months were 95%, 78%, 74%, and 71%, respectively (fig 1). Median of survival in patients with CMV infection was calculated to be 41 days. In addition, the medians of the first and third quarters were 31 and 57 days, respectively. Furthermore, mean duration of survival was 48.09±23.50 (CI, 2.02-94.15) days. A significant association was observed between some variables including age of the patients at the time of transplantation (p=0.04) and etiology of kidney failure (p=0.03) and the interval between transplant and CMV infection. These relationships were noted through evaluation of survival rates in subgroups (patients with CMV infection) using log-rank test. Therefore, CMV incidence might increase by advancing age (fig 2).

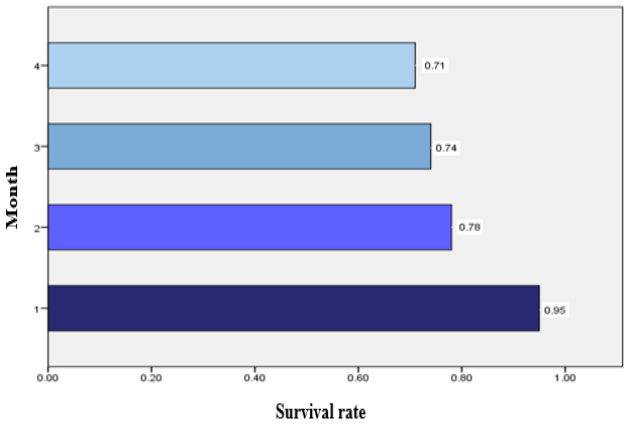

Figure 1. Survival rate (lack of cytomegalovirus infection)

Table 2. Prevalence of cytomegalovirus based on post-transplant period (in month)

Month after transplantation	Compared to total patients N(%)	Compared to cytomegalovirus N(%)
1	15(6.2)	15(20.2)
2	39(16.1)	39(52.7)
3	10(4.1)	10(13.5)
4	5(2.1)	5(8.1)
Others	4(1.7)	4(5.4)
Not activated	169(69.8)	—

Our results indicated that the rate of early activation of CMV in patients with kidney failure due to urologic diseases was higher, compared to patients with other etiologies (e.g., diabetes, hypertension, glomerulonephritis, and renal cysts; fig 3). However, no significant relationship was observed between the incidence period of CMV, demographic characteristics (i.e., gender, place of residence, marital status, smoking status, and educational level), and histopathologic variables (i.e., BMI, hepatitis B, and

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type of dialysis). Similarly, no significant association (including cross-border) was recognized between incidence period of CMV and hepatitis C and age of donors (p=0.1). Thus, Cox regression was not run, as the proportional hazard assumption did not hold.

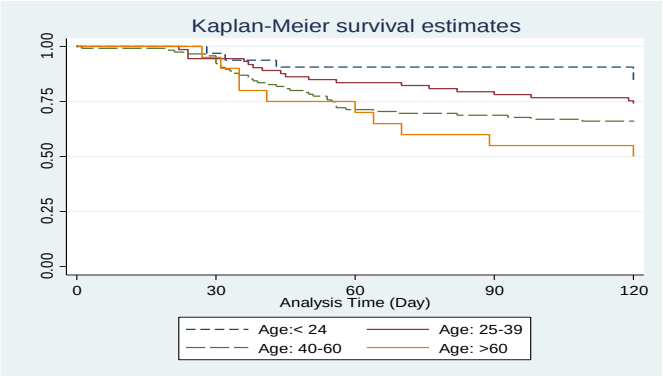

Figure 2. Estimation of the survival curve based on age using the Kaplan–Meier method

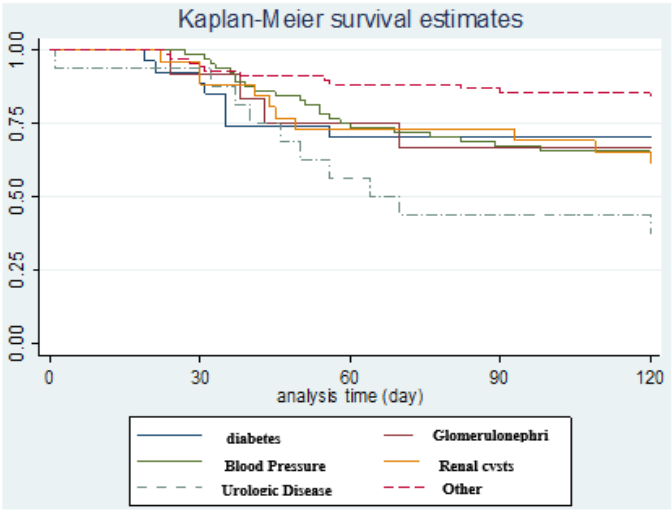

Figure 3. Kaplan-Meier survival curves according to etiology of kidney failure

Discussion

According to the results of the present study, the most important risk factors for the development of CMV disease were advanced age and history of urologic diseases. The incidence of CMV after renal transplantation is still recognized as one of the leading causes of morbidity and mortality (7, 15). According to the literature, the incidence rate of CMV is significantly different around the globe (4, 15). Our findings revealed that the total incidence rate of this infection was 30.2%, which is consistent with the results of Mandel et al. and Tarabadi et al. (9, 11). The prevalence rate of CMV was 10.4% in the study by Bal et al.; moreover, in a study by Hartmann et al., this rate was 6.04% in each one thousand cases per month (18). In general, the incidence rate of CMV was reported to be 8-32% in the studies by Hartmann et al. and Weikert et al. (18, 19). In another retrospective study conducted in Australia and New Zealand, the incidence rate of CMV in a 12-month period was found to be 38% (20). The results of Peterson et al. revealed a 31% incidence rate (21), while this rate was reported to be 26.5% six months after transplantation in a study by Chiaskul et al. (22). This difference in the incidence rate of CMV might be due to distinct conditions of patients in terms of seroprevalance, type of immunosuppression, and various diagnostic methods. In the present study, 49 (67.1%) CMV cases were male and 24 (32.9%) were female.

Male to female ratio was 2:1, which is in congruence with the findings of Erdbruegger et al. (2). However, this ratio was reported to be 4:25 in a study by Kute et al. (1). In addition, the male to female ratio was equal to 0:9 in a study by Chiasakul, while this ratio was reported to be 1:5 (23) in a study by Nafar et al. and 1:7 (24) in a study by Cordero et al. Total mean age of the recipients in this study was 41.6±14.1 years, and mean age of the recipients with CMV infection was 45±14 years, which was less than the calculated mean age in the studies by Chiasakul et al. and Cordero et al. (22, 24), and higher than the findings of Kute et al., Bal et al., and Nafar et al. (1, 15, 23).

The highest prevalence of this disease was observed in the first and sixth months post-transplantation, which reaches its highest rate between the second and third months (25). In a study by Peterson et al., it was indicated that the highest incidence of CMV occurred in the fourth month after renal transplantation (21). Similarly, in a study by Cordero et al., CMV incidence rate in the third post-transplantation month was 50% (24).

In another study conducted in Thailand, 86% of CMV infections happened in the third post-transplantation month (22). However, our results demonstrated a 94.5% incidence rate in the first-fourth post-transplantation months, with the highest rate belonging to the second month. Considering dispersion in the primary studies, the duration of this study was decided to be 120 days. Although risk factors for CMV infection were formerly evaluated in transplant recipients, there is a scarcity of studies on the survival analysis of these patients. Among the evaluated factors, age of the recipients (4, 22, 23, 26) and donors (15, 23) had the highest association with CMV

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infection, even though no such relationship was found in other studies (27). While no significant link was observed between CMV incidence and gender of donors or recipients in the study by Falahi et al. (27), the significant role of donors (4, 23) and recipients' (23) gender was revealed in other studies. On the other hand, Motamedifar et al. identified educational level, financial status, and hygiene status as risk factors of CMV infection (4). Another reported risk factor for this disease was seropositivity of donors (15, 24, 26). Similarly, incompatibility of serum index was proposed to be a risk factor in the study by Cordero (24). However, no relationship was observed between seropositivity of recipients and CMV incidence in the study by Diaz et al. (26); additionally, kinship of donors and recipients was considered as a risk factor in that study (24).

Above all, the most common risk factor for CMV infection is known to be immunodeficiency, which mostly leads to severe clinical symptoms (7, 8). In this regard, there is a direct relationship between immunosuppression (23), which is due to the type and dosage of the immunosuppressant (15), and the incidence rate of CMV. Nevertheless, even standard or lower doses of rATC lead to the incidence of CMV in the study by Chiasakul et al. (22).

Oliaei et al. indicated that prophylaxis injection before transplantation does not affect the incidence of CMV (28). Additionally, in the present study, only age and urologic etiology of kidney failure were significantly associated with patient survival. There was no relationship between CMV infection and variables such as gender, educational level, place of residence, hepatitis B, hypertension, diabetes, and seropositivity. Merely a cross-border link was found between incidence of CMV and hepatitis C and age of donors. Therefore, conducting broader studies on this subject is recommended. Given the use of similar medication protocols for all the patients in the present study, it was presumed that there was an almost equal level of immunosuppression among patients. However, further evaluations of level of cyclosporine in other studies revealed the effects of immunosuppression on incidence period of CMV.

Accordingly, assessment of cyclosporine level in specific time intervals is highly suggested. The latency of diagnosis in serological test is considered as a major problem in diagnosis of CMV. Accordingly, transplant patients should be followed-up for early diagnosis of CMV. Based on our findings, patients' age plays a pivotal role in the incidence of CMV. Considering the high prevalence of CMV in the second post-transplantation month, conducting short-term follow-ups in the first-fourth post-transplantation months, with a greater focus on the first and second months, especially in the elderly with urologic diseases, is highly recommended.

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