ejpmr, 2016,3(5), 98-106

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

PREVALENCE RATE OF CMV INFECTION IN PATIENTS AFTER KIDNEY TRANSPLANTATION IN VIET NAM

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Article Received on 05/03/2016 **Article Revised on 26/03/2016** **Article Accepted on 17/04/2016**

ABSTRACT

We studied a cross-sectional survey on prevalence of CMV status (no-infection, infection and clinical disease) in 808 Vietnamese transplant recipients. The proportions of prevalence were 757 (93.7%) with no CMV infection; 48 (5.9%) CMV infection, and 3 (0.4%) CMV clinical disease. The VMV infection proportions were high as 9, and 10.8% for recipients with survival time after transplant < 100 days, and 100 – 540 days, respectively, higher than that for whom who had longer survival time after transplant, > 540 days (> 18 months), 4.0% (p=0.004). The routine risk factors as deceased donor, CMV-negative recipients, allograft rejection, young age at transplant (< 20 yrs.) were not found. Binary logistic analysis showed only the survival time after transplant (≤ 18 months) as independent risk factor for CMV infection with OR: 2.48 [95% CI: 1.3 – 4.74], p=0.006.

KEYWORDS: Cytomegalovirus; kidney transplantation; CMV infection; survival time; risk factor.

INTRODUCTION

In Viet Nam, the first kidney transplantation case from related living donor was done in June 1992 at the 103 Military Medical Institute, Ha Dong in the North and then 2 another cases in December 1992 at Cho Ray Hospital, Ho Chi Minh City. Up to year 2015, there are 15 kidney transplantation centers in Viet Nam, performing around 1300 kidney transplant in which 500 cases at Cho Ray Hospital. Beyond in-country kidney transplants, hundreds of case had kidney transplantation from outside countries. Both have been followed-up at kidney transplantation centers in Viet Nam. Most of kidney transplants in Vietnamese patients had allograft from living donor [LD].

Cytomegalovirus (CMV) infection is associated with significantly decreased outcomes of kidney transplantation.[1] To minimize CMV infection, all kidney transplant centers in Viet Nam apply routinely CMV prophylaxis of 100 days after transplantation, following to previous studies and guidelines.[2-5]

We reported herein the prevalence of CMV status, no CMV infection, CMV infection and CMV clinical disease, in a cross-sectional study on 808 Vietnamese recipients after kidney transplantation, carried from June-2013 to Dec-2014 in Viet Nam.

STUDY METHODS

Cross-sectional study

The cross-sectional study was carried out at 6 kidney transplantation centers: Cho Ray Hospital, Hospital 115 and Children Hospital 2 in Ho Chi Minh City, the South of Viet Nam; Hue Central Hospital in the Middle of Viet Nam, and Hospital 19-8 and Military Medical Institute 103 in the North of Viet Nam. The study was carried out from Jun-2013 to Dec-2014.

This study was a part of a national research, approved by Ministry of Health Board Review on 12 Apr 2013.

All kidney transplant recipients were investigated one time in the study, by chance based on their routine monitoring visits at one of 6 kidney transplantation

centers. Patients were reviewed on history of kidney transplant, immunosuppressive regimens applied, allograft rejection episodes, CMV prophylaxis regimens, CMV risk factors such as blood transfusion, sexual habit. The CMV infection was evaluated by serologic assays (CMV IgG, CMV IgM) with enzyme Immunoassay (EIA) in Biorad system or with Electrochemiluminescence immunoassay (ECLIA) in Cobas e-601 module, Roche; or by CMV virus load test with Real-Time PCR (IQ-5 BioRad). Clinical investigation was carefully performed to detect signs, symptoms of CMV disease. Data were recorded in electronic case record form (eCRF) per each patient. All eCRFs from study centers were transferred to central study site, Cho Ray Hospital, for final analysis.

Immunosuppressive protocols

There were 6 immunosuppressive protocols used for kidney transplant patients in Viet Nam. Immunosuppressants included Calcineurin inhibitors (CNIs: cyclosporine, tacrolimus), mTOR suppresses cytokine driven T-lymphocyte proliferation and activation (Sirolemus, Everolemus), antimetabolite (mycophenolate mophetil, azathioprine), steroids (prednisone). The 6 triple protocols were: 1-Sandimmum Neoral + steroids+ azathioprine; 2-Sandimmum Neoral+ steroids+ mycophenolate mophetil; 3-Tacrolimus+steroid+ azathioprine; 4- Tacrolimus+ mycophenolate mophetil + steroids; 5-mTOR (Everolemus)+ mycophenolate mophetil +steroids; 6-mTOR (Everolemus)+ Sandimmun Neoral/ Tacrolimus (low dose) + steroids. At the time of transplant, recipients received the antibody induction (with Baxilisimab), in combination with antimetabolite (Mycophenolate Mophetil) and steroids, with low dose of CNIs (Neoral/Tacrolimus/Sirolimus). Steroids can be discontinued early or late depending on immunosuppressive response of recipients, as guided from study of Matas AJ 2001.[6] The optimal immunosuppressive protocol was given per each individual case.

Mild to moderate allograft rejection was treated with a pulse steroids therapy; severe rejection was treated with immunosuppressant antibody (Antithymocyte Globulin [ATG]/Muromonab CD3 [OKT3]).

CMV prophylaxis and preemptive therapy

In Viet Nam the CMV prophylaxis was applied for all kidney transplant recipients, including CMV-seropositive recipients (D+/R+, D-/R+), seronegative recipients with seropositive donors (D+/R-) and also for both seronegative in recipient and donor (D-/R-), within 3 week after the transplant. Drugs used in CMV prophylaxis were acyclovir and valganciclovir as follows: valganciclovir 450mg orally twice per day in 100 days (or 200 days depending to the risk factors in patients); or acyclovir 200 mg orally 4 times per day in 100 days (or 200 days depending to the risk factor in patients).

The preemptive therapy has been applied only in Cho Ray Hospital where having the monitoring for early progressive evidence of CMV replication, more than 500 copies, by CMV- PCR combining with history of using immunosuppressant antibody. Patients with preemptive therapy were excluded in this survey.

CMV therapy

In our experience, we did treat only those recipients with symptomatic CMV viremia. Patients were treated with intravenous ganciclovir 5-10 mg/kg, dosage adjused to liver function, kidney function and complete blood count, until having negative CMV IgM and negative CMV PCR, followed by valganciclovir orally 900 mg/day until the completion of 100 days or 200 days depending to risk factor in patients. CMV therapy usually included reduction of immunosuppressive therapy.

Statistical analysis

Patients were grouped based on the timing from the transplant and prophylaxis protocol: (i) within ≤ 100 days after transplant (within 100 days of prophylaxis protocol); (ii) 101 to 540 days after transplant (within 15 months after completion of prophylaxis protocol), and (iii) > 540 days after transplant. Acute allograft rejection was diagnosed to the Banff 07 Classification of Renal Allograft Pathology 2008.[7] The statistical analysis was performed using the PASW software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). The quantitative results were expressed as mean ± standard deviation and were analyzed using independent Student t test. The statistical significance of differences was determined by the chi-square analysis for categorical variables. The binary logistic regression was applied to detect the independent risk factors for CMV infection. The survival life-table and Kaplan-Meier curve were used for calculation of cumulative no-infection rate at the end of observational periods and survival curve. Significance was defined as a p value less than .05.

RESULTS

Of the 808 kidney transplant recipients, 542 (67.8%) were followed up at Cho Ray Hospital and 410 (50.7%) having transplant recently in 5 yrs. There were no differences in characteristics on age, gender, occupation, year of transplant between 6 study sites (Table 1).The CMV status of donors and recipients at timing of transplant was presented in Table 2. Living donors were mainly as 607 (75.1%), in which family-related LD accounting for 267 (44.1%), 211 (36.4%) not related by blood. Of the 559 donors with CMV IgG information, 545 (97.5%) with CMV IgG (+). CMV status of recipients on time of kidney transplant were past- history CMV infection [CMV IgG(+)] in792/804 (98.5%); 8 (1%) cases with no CMV infection [CMV IgG -], and 4 (0.5%) with CMV infection [IgM+ and/or CMV PCR positive].

For immunosuppressive regimens, calcineurin inhibitors were accounted mainly 803/808 (99.4%), in which the triple regimen as Sandimmum Neoral+ steroids+ mycophenolate mophetil 381/803 (47.4%). The acute allograft rejection was recorded in 24 (3%) recipients, cellular rejection dominated as 21/24 (87.5%) (Table 3).

The prevalence rates of CMV status were 757 (93.7%) with no CMV infection (only CMV IgG +); 48 (5.9%) current CMV infection, and 3 (0.4%) CMV clinical disease. Distribution of recipients based on survival time from transplant were: 221 (27.4%) in time of 100 days of receiving CMV prophylaxis; 111 (13.7%) in follow-up time of 100-540 days after completion of CMV prophylaxis; and 476 (58.9%) after 540 days (> 18 months) from transplant (Table 4). Those 3 CMV clinical diseases: 2 cases in survival time of 100 days (0.9%); and 1 in survival time of more than 540 days (0.2%).

Risk factors for the development of CMV infection

It was due to only 3 recipients with CMV clinical disease, those cases were pooled together with CMV infection cases. Thus, the total number of patients with CMV infection were 51 (6.3%). Risk factors for the CMV infection (monovariable analysis) were recipient age ≤ 20 yrs. (p=0.04, OR: 3.5 [95% CI:1.2 – 10.8]; survival time after transplant ≤ 18 months (p = 0.002, OR: 2.5 [95%CI: 1.4 – 4.6]. There was no difference by CMV donor-recipient serostatus (p > 0.05), even all 51 (6.5%) CMV infections were only seen in D+/R+ group, no difference on donor status (LD versus DD) between no CMV infection and CMV infection groups (Table 5). The values of prevalence of CMV infection were 9, 10.8 and 4% in groups of survival times of □ 100 days, 100-540 days and > 540 days, respectively (p < 0.05). There was no difference in prevalence rates of CMV infection between study sites (p> 0.05), but this rate was different between 3 survival time groups of recipients based on time from transplant (p < 0.05).

Binary logistic analysis showed only the survival time after transplant (≤ 18 months) as independent risk factor for CMV infection with OR: 2.48 [95% CI: 1.3 – 4.74], p=0.006.

Mean time to CMV infection (± SD) for 20 patients in the survival time group of 100 days after transplant was 44.2 ± 23.8 days (median: 32.5 days, min-max: 21-100 days). Mean time to CMV infection (± SD) for 12 patients in the survival time group of 100 to 540 days (18 months) after transplant was 256 ± 146.8 days (median: 191 days, min-max: 110-510 days).

Mean time to CMV infection (± SD) for 19 patients in the survival time group > 540 days after transplant was 2248 ± 1468 days (6.2 ± 4.0 years) (median: 4.47 years, min-max: 1.73 – 15.46 years). Figure 1 to 3 showed the cumulative proportion of "no Infection" at the end of observation periods.

Table: 1 General characteristics of 808 post-kidney transplant recipients.

Characteristics		Post-kidney transplant monitoring sites						Total
		Hosp. 19-8	Hosp. 115	Hosp. Cho Ray	Hosp. Hue	Hosp. Children 2	MMI 103#	
n		9	104	542	71	15	67	808
Age (yr)	$\bar{X}$	38.7	47.6	42.7	42.1	15.6	39.3	42.5
	Median	35.0	46	42.0	39.0	15.0	37.0	42.0
	SD	10.1	11.1	12.4	11.7	4.2	11.8	12.7
	Min-max	27-58	17-76	17-81	22-64	11-23	17-74	11-81
Gender	female	0	34	193	16	5	19	267
	male	9	70	349	55	10	48	541
Occu-pation	Medicine	0	1	14	1	0	2	18
	Military	7	1	27	0	0	18	53
	CNV	0	37	91	50	0	5	183
	Education	0	5	57	4	14	8	88
	Business	0	36	108	1	0	3	148
	House work	0	0	22	0	0	4	26
	Farmer	0	15	75	13	0	7	110
	others	2	2	61	0	0	7	72
	None	0	7	87	2	1	13	110
Year of trans-plant	1993-2000	0	2	19	1	0	1	23
	2001-2005	0	26	133	5	2	5	171
	2006-2010	0	27	154	10	4	9	204
	2011-2015	9	49	236	55	9	52	410

MMI 103: Military Medical Institute 103.

Table: 2 Characteristics on CMV status of donors, recipients of 808 kidney transplant patients at timing of transplant.

Characteristics		Post-kidney transplant monitoring sites						Total
		Hosp. 19-8	Hosp. 115	Hosp. Cho Ray	Hosp. Hue	Hosp. Children 2	MMI 103#	
	n	9	104	542	71	15	67	808
Donors*	Living	9	63	390	71	15	59	607
	Deceased	0	41	152	0	0	8	201
Relation-ship donors-recipients	Father-Mother	1	0	101	8	7	25	142
	Brother-sister	0	3	113	0	0	9	125
	First cousins	0	1	13	14	5	0	33
	≥ second cousins	0	1	42	49	2	2	96
	Not related by blood	8	58	121	0	1	23	211
	Deceased donors	0	41	152	0	0	8	201
Site for kidney transplant	Hosp. Cho Ray	0	23	335	2	0	4	364
	Hosp. Viet Duc	0	0	17	0	0	0	17
	MMI 103	0	2	15	0	0	53	70
	Hops. Hue	0	8	16	59	0	2	85
	Hosp. 19-8	9	0	1	0	0	1	11
	Hosp. 115	0	37	3	0	0	0	40
	Hosp. Children 2	0	0	0	0	15	0	15
	From China	0	34	144	9	0	7	194
	Other countries	0	0	11	1	0	0	12
CMV donors*	CMV IgG (-)	1	3	8	0	0	2	14
	CMV IgG (+)	8	52	344	71	15	55	545
	No data	0	49	190	0	0	10	249
CMV recipients*	CMV IgG (-)	1	3	0	0	0	4	8
	CMV IgG (+)	8	99	536	71	15	63	792
	IgM CMV (+)	0	0	1	0	0	0	1
	PCR CMV (+)	0	2	1	0	0	0	3
	No data	0	0	4	0	0	0	4
CMV risk status*	extreme: D+/R-	0	2	4	0	0	2	8
	high: D+/R+	8	99	530	71	15	63	786
	moderate: D-/R+	0	2	8	0	0	0	10
	low: D-/R-	1	1	0	0	0	2	4

* significant difference between post-kidney transplant monitoring sites ($p < 0.05$, Chi-square Test)
# MMI 103: Military Medical Institute 103

Table: 3 Characteristics of immunosuppressive regimens of 808 recipients after kidney transplantation

Characteristics		Post-kidney transplant monitoring sites						Total
		Hosp. 19-8	Hosp. 115	Hosp. Cho Ray	Hosp. Hue	Hosp. Children 2	MMI 103#	
	n	9	104	542	71	15	67	808
Immunosuppressive regimens*	1. Sandimmun Neoral + steroids+ azathioprine	0	1	41	0	0	1	43
	2. Sandimmun Neoral+ steroids+ mycophenolate mophetil	3	34	239	68	1	36	381
	3. Tacrolimus+steroid+ azathioprine	0	2	13	0	0	0	15
	4. Tacrolimus+ mycophenolate mophetil + steroids	6	66	228	3	11	30	344
	5. mTOR (Everolemus)+ mycophenolate mophetil +steroids	0	0	5	0	0	0	5
	6. mTOR (Everolemus)+ Sandimmun Neoral/ Tacrolimus (low dose) + steroids	0	0	12	0	0	0	12
	Other regimens	0	1	3	0	0	0	4
	Regimen 1 and 2	0	0	1	0	0	0	1
	Regimen 2 and 4	0	0	0	0	3	0	3
Acute cellular rejection*	No	9	104	527	71	11	65	787
	Yes	0	0	15	0	4	2	21
Acute antibody mediated rejection*	No	9	104	540	71	14	67	805
	Yes	0	0	2	0	1	0	3

* significant difference between study sites ($p < 0.05$, Chi-square Test)
# MMI 103: Military Medical Institute 103.

Table: 4 The prevalence of different CMV status in a cross-sectional study on 808 recipients after kidney transplantation.

Characteristics		Post-kidney transplant monitoring sites						Total
		Hosp. 19-8	Hosp. 115	Hosp. Cho Ray	Hosp. Hue	Hosp. Children 2	MMI 103#	
	n	9	104	542	71	15	67	808
CMV status	No CMV Infection (IgG+)	9	104	492	71	15	66	757
	CMV Infection (IgM+ and/or PCR+)	0	0	47	0	0	1	48
	CMV clinical disease (CMV Infection + clinical symptoms)	0	0	3	0	0	0	3
Time from transplant*	≤ 100 days: within CMV prophylaxis protocol	9	25	116	35	7	29	221
	100 -540 days: follow-up time after completion of CMV prophylaxis	0	14	71	12	0	14	111
	> 540 days (> 18 mo.): after completion of follow-up time of CMV prophylaxis	0	65	355	24	8	24	476

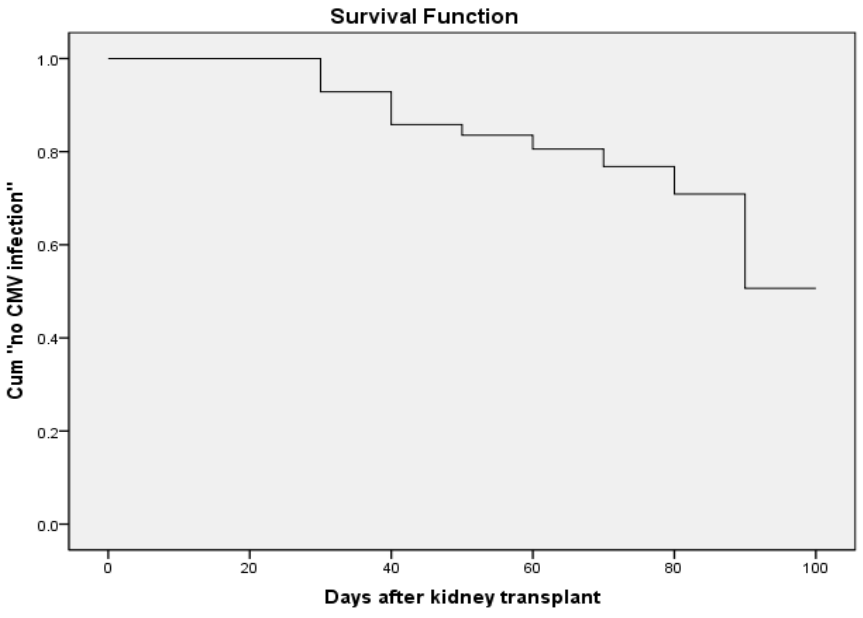
* significant difference between study sites.

Table: 5 The relationship between CMV status and potential risk factors.

Variables		CMV status			
		No CMV infection n = 757		CMV infection n = 51	
		n	%	n	%
Study sites*	Hospital 19-8	9	100	0	0
	Hospital 115	104	100	0	0
	Cho Ray Hospital	492	90.8	50	9.2
	Hue Central Hospital	71	100	0	0
	Children Hospital 2nd	15	100	0	0
	Military Medical Institute 103	66	98.5	1	1.5
Age groups*	<=20 yrs.	19	82.6	4	17.4
	21-30 yrs.	121	91.7	11	8.3
	31-40 yrs.	203	90.6	21	9.4
	41-50 yrs.	196	96.1	8	3.9
	51-60 yrs.	155	96.7	7	4.3
	>= 61 yrs.	63	100	0	0
Gender#	male	252	94.4	15	5.6
	female	505	93.3	36	6.7
Hospital for kidney transplant #	Cho Ray Hospital	329	90.4	35	9.6
	Viet Duc Hospital	16	94.1	1	5.9
	Military Medical Institute 103	66	94.3	4	5.7
	Hue Central Hospital	81	95.3	4	4.7
	Hospital 19-8	11	100	0	0.0
	Hospital 115	40	100	0	0.0
	Children Hospital 2	15	15	0	0.0
	In China	187	96.4	7	3.6
	In other countries	12	100	0	0.0
Relation-ships between donor-recipient#	"father-mother"	125	88	17	12
	"brother-sister"	116	92.8	9	7.2
	"first cousins relationship""	32	97.0	1	3.0
	"second cousin relationship""	91	94.8	5	5.2
	"not related by blood""	201	95.3	10	4.7
	Deceased donors	192	95.5	9	4.5

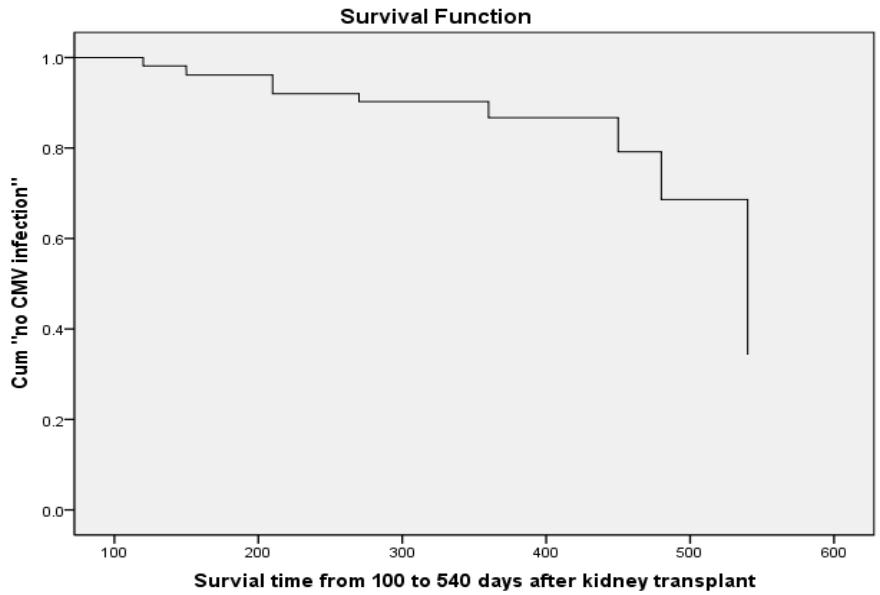
Table: 5 The relationship between CMV status and potential risk factors (cont.)

Variables investigated		CMV status: No (past) CMV infection n = 757		CMV infection n = 51	
		n	%	n	%
CMV donor-recipient risks #	Extreme (D+/R-)	8	100	0	0
	High (D+/R+)	735	93.5	51	6.5
	Moderate (D-/R+)	10	100	0	0
	Low (D-/R-)	4	100	0	0
Immunosuppressive regimens #	1: Neoral + steroids+ azathioprine	41	95.3	2	4.7
	2: Neoral+ steroids+ mycophenolate mophetil	354	92.9	27	7.1
	3: Tacrolimus+steroid+ azathioprine	15	100	0	0.0
	4: Tacrolimus+mycophenolate mophetil+ steroids	324	94.2	20	5.8
	5: Everolemus+mycophenolate mophetil+steroids	4	/	1	/
	6: Everolemus+Sandimmun Neoral/Tacrolimus (low dose)+ steroids	12	100	0	0.0
	Other regimens	3	/	1	/
	Regimen 1 and regimen 2	1	/	0	/
	Regimen 2 and regimen 4	3	/	0	/
Donor#	Living	565	93.1	42	6.9
	Deceased	192	95.5	9	4.5
Acute cellular rejection#	No	738	93.8	49	6.2
	Yes	19	90.5	2	9.5
Acute antibody mediated rejection#	No	754	93.7	51	6.3
	Yes	3	100	0	0.0
Survival time after transplant*	<= 100 days: prophylaxis protocol	201	91.0	20	9.0
	100 - 540 days: after prophylaxis	99	89.2	12	10.8
	> 540 days	457	96.0	19	4.0



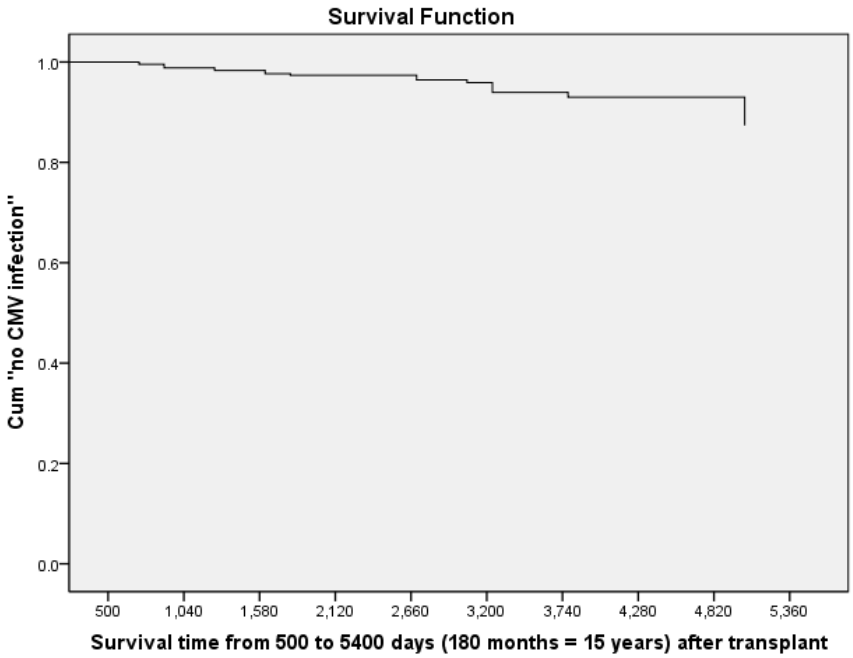
No CMV infection rate	
Time (days)	Cumulative rate
0	1.0
10	1.0
20	0.93
30	0.86
40	0.84
50	0.81
60	0.77
70	0.71
80	0.51
90	0.51
100	

Figure 1: Cumulative proportion at the end of interval time for the "no CMV infection" in patients with survival time after kidney transplant <= 100 days. The cumulative proportion of "no CMV infection" was 51% on day 90 after transplant.



No CMV infection rate	
Time (days)	Cumulative rate
50	1.0
100	0.96
150	0.93
200	0.91
250	0.91
300	0.91
350	0.87
400	0.80
450	0.67
500	0.40

Figure 2: Cumulative proportion at the end of interval time for the "no CMV infection" in patients with survival time after kidney transplant from 100 days to 540 days (18 months). The cumulative proportion of "no CMV infection" was 40% on day 500 after transplant.



No CMV infection rate	
Time (days)	Cumulative rate
540	1.0
720	0.98
1440	0.97
2160	0.96
2880	0.94
3600	0.92
4300	0.89
5040	0.8
5760	0.8

Figure 3: Cumulative proportion at the end of interval time for the "no CMV infection" in patients with survival time after kidney transplant from 540 days to 5760 days (16 years). The cumulative proportion of "no CMV infection" was 80% on day 5760 after transplant.

DISCUSSION

In this cross-sectional study on 808 Vietnamese kidney transplant recipients the prevalence of no CMV infection was highest at 93.7%, current CMV infection 5.94%, and CMV clinical disease 0.4%. Thus, the prevalence for total CMV infection was 6.3%. The overall incidences of CMV infection and CMV disease were 76/592 (12.8%) and 23/592 (3.9%), respectively in a report on 592 kidney recipients in a single center in Greece.[8] These rates were lower than that reported by Bouedjoro-Camus

and colleagues; the prevalence of CMV disease was 26.5% in sera of 192 kidney allograft recipients.[9] Watcharanan and colleagues showed symptomatic CMV infection in 18 Thai kidney transplant patients (4.6%)[10]. The discrepancies in prevalence of CMV infection in kidney transplant recipients between studies may be due to many factors, such as the study method as cohort[8], cross-sectional [our study], case-control[9], or retrospective[10]; as well as the difference in survival time after transplant of patients. In our study, the maximum survival time after transplant was 16 years and 476 (58.9%) recipients had survival time longer 540 days (> 18 months).

The CMV clinical disease had seen in 3 cases, in which 2 were in group of 100 days after kidney transplant (0.9%) and 1 in group of more than 540 days (18 months) after transplant. The majority of CMV replication and disease is reported early during the first 3 months after transplantation at the time of the highest immunosuppressive load (11-12). Symptomatic CMV infection occurred in 18 (4.6%) Thai patients within a median time of 12.1 (range, 3-30) weeks after kidney transplant in study of Watcharananan SP 2012.[10]

The values of prevalence of CMV infection were 9, 10.8 and 4% in groups of survival times of 100 days, 100-540 days and > 540 days, respectively ($p < 0.05$). This showed that there was a tendency of reducing incidence of CMV infection, 4% versus 9-11%, when recipients were out of time of CMV prophylaxis scheme (including drug taken time and follow- up time). Our result was similar to report on prevalence of CMV status in 2489 recipients, follow-up to maximum time of 17 years, in study of Barry J. Browne et al. 2010.[13] as follows: 77 (3.1%)

77 (3.1%) developed late CMV infection, 303 (12%) early infection, and 2190 (85%) no CMV infection. The low rate of CMV infection in recipients having long survival times after transplant may be due to the recovery of immune status.[13]

In our study, there was no presence of risk factors for CMV infection as transplantation into CMV-negative recipients, deceased donor, allograft rejection, age at transplant. This remark was different from study of Barry J Browne 2010.[13] but in agreement with other studies.[14] Of 427 recipients, 71 (16.6%) had CMV infection, of which 19 (4.4%) were recurrent infection. Donor source, dialysis duration before transplantation, recipient and donor age and sex, and administration of antithymocyte globulin and prophylactic treatment ganciclovir were not associated with CMV infection or recurrence.[14]

The only survival time after transplant was found as the risk factor for CMV infection in our cross-sectional study on 808 Vietnamese transplant patients.

For conclusion, CMV infection rates were different in recipients based on survival time after transplant and only this parameter was the independent risk factor for CMV infection.

ACKNOWLEDGMENTS

The study was supported by a grant from Ministry of Health, Viet Nam.

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