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Risk Factors Associated with Post-Transplant Cytomegalovirus Infection in Renal Transplant Recipients in Lagos, Nigeria

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ABSTRACT

Background: Cytomegalovirus (CMV) infection is an important infection in renal transplant recipients and has significant impact on long-term recipients and graft survival.

Objective: This study aimed to determine the risk factors associated with post-transplant CMV infection in renal transplant recipients in Lagos, Nigeria.

Subjects and Methods: The study subjects were 40 renal transplant recipients aged 16 to 58 years and kidney graft donorsto 22 of the transplant recipients.One hundred normal subjects from the general population and 36 patients with either stage 4 or 5 chronic kidney disease (CKD) who matched the transplant recipients for age and gender served as controls.Enzyme Linked Immunosorbent Assay (ELISA) was employed to detect CMV IgM antibodiesfor the diagnosis of post-transplant CMV infection. Risk factors for CMV infection among the renal transplant recipients were assessed by means of a structured pre-tested self-administered questionnaire. Statistical analyses were done using EPI-INFO 2002. Unconditional logistic regression and multiple logistic regression analyses were done to identify risk factors associated with CMV infection in study subjects and controls.

Results: Exposure to multiple sexual partners, blood transfusion, haemodialysis and immunosuppressive drug therapy were identified as risk factors for CMV infection from unconditional logistic regression analysis. Exposure to multiple sexual partners was the only risk factor significantly associated with CMV infection after multiple logistic regression analysis (odds ratio= 3.05, 95% confidence interval = 1.02 - 9.12, p = 0.045).

Conclusion: Exposure to multiple sexual partners is an independent risk factor for post-transplant CMV infection in renal transplant recipients.

Keywords: *Post-transplant Cytomegalovirus infection, risk factors, renal transplant recipients, Nigeria*

INTRODUCTION

Cytomegalovirus (CMV) is an important infection in renal transplant recipients[1,2]. Renal transplant recipients may become infected with CMV through personal contact with medical care staff, through medical procedures such as transplanted organs, haemodialysis and blood transfusion [3- 10]. They may also become infected through the same traditional routes as healthy people such as sexual transmission [11-12].Studies have demonstrated serologic evidence implicating the graft kidney as a transmitting vehicle for CMV infection[3-5]. Other studies suggested that the importance of blood transfusion in causing CMV infection in renal transplant recipients was probably low[6-8]. Adler[9] in his review of transfusion associated CMV infection suggested that individuals perfused with large volumes of whole blood experience subsequent changes in their cell-mediated immunity that allow the expression of latent CMV virus.

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Tegtmeier[10] observed that storage leucodepletion of blood components may be as effective as the use of CMV-seronegative blood components.

Also, studies have shown that cytomegalovirus can be sexually transmitted and the prevalence is high among patients examined at sexually transmitted infection (STI) clinics[11-12.] Chandler *et al*[11] in a study of 347 non-pregnant women attending a sexually transmitted infection (STI) Clinic in the United States, in 1985 showed that CMV seropositivity correlated with indices of sexual activity. Theyalso observed that the risk of primary infection and seropositivity correlated strongly with indices of sexual activity such as the number of sexual partners and age at onset of sexual activity[11]. A young age at onset of sexual activity was found to be the strongest determinant of CMV seropositivity[11]. Moreover, age specific rates of seropositivity were lower in celibate woman than in those who were sexually active. The study employed complement fixation test for diagnosis of CMV. Handsfield et al[12]noted that heterosexual contact was a major mode of transmission of CMV infection young adults [12].

Prevalence rates based on the frequency of seropositive individuals in the general population have shown an inverse correlation between acquisition of CMV infection and the socio-economic condition of the population[13]. Mustakangas et al[13]in a population-based cohort study in Finland, studied seroprevalence of IgG and IgM antibodies to CMV, and IgG avidity by ELISA in a population of 1,088 pregnant women at 9 to 12 weeks of gestation from three different socio-economic areas. They found an overall CMV-IgG seropositivity of 70.7% with the prevalence higher in the lower socio-economic area compared with the upper socioeconomic area (76% vs. 61%). The prevalence of specific IgM seropositivity was also higher in the lower socio-economic area (4.6% vs. 3.8%)[13]. On the other hand, Ogbaini-Emovon et al in a study of seroprevalence and risk factors for cytomegalovirus infection among pregnant women in Benin City, Southern Nigeria found no significant association between socio-economic class and CMV infection[14].Chandler et al[11] in a study involving women attending an STI Clinic in the United Statessimilarly found that low socio-economic status (SES) was not predictive of CMV seropositivity in their study group as a whole. It was nonetheless positively correlated with seropositivity instudy subjects who were 18 years old or younger[17]. Chandler et al noted that although SES was a strong determinant of childhood CMV infection, in some populations, SES-related differences might be obscured by later sexually acquired infection [11].

Again, the requirements of a patient for cytotoxic drugs, anti-lymphocyte and anti-thymocyte globulin superimposed on the underlying disease, can lead to expression of varying degrees of virulence and reactivation of latent virus[3]. Rubin[15] noted that the critical exogenous factor influencing CMV reactivation following transplantation was the type and intensity of immunosuppressive therapy. The level of immunosuppression in any given patient is determined by the dose, duration, and temporal sequence in which immunosuppressive medications are administered, which in turn influences the course of CMV infection in the post-transplant period [16]. The addition of high doses of corticosteroid to anti-lymphocyte therapy has been associated with a higher incidence and increased severity of CMV disease[17]. Studies have shown that while the use of mycophenolate mofetil (MMF) has dramatically reduced the incidence of rejection in renal transplant patients, a slight increase in CMV invasive disease has been noted in MMF-treated patients (especially those given high doses) compared to those receiving conventional azathioprine-containing immunosuppressive regimens[18-21]. However, Sarmiento et al[22]reported that recipients treated with cyclosporine/prednisolone/MMF based immunosuppressive regimen did not differ from cyclosporine/prednisolone/ azathioprine regimen in relation to initial CMV infection episode after renal transplantation.

Other studies have shown that the use of immunosuppressive agents such as anti-thymocyte or anti-lymphocyte globulin and muromonab anti-CD3 [OKT3] monoclonal antibodies, either as induction therapy or for allograft rejection treatment, enhances the risk of symptomatic CMV infection, especially in CMV-seropositive individuals [23-25].Monoclonal antibodies not only diminish the capability of the host to mount immune surveillance but also increase reactivation of latent CMV from infected cells [23-25]. Kanter et al[26] in a retrospective study of 207 patients who received a renal allograft from May 2003 to December 2007 with a mean follow-up period of 27.8 +/- 17 months observed that 32 (15.7%) of the 207 transplant recipients had active CMV infections and

another 35 (17.2%) had CMV disease. Cytomegalovirus (CMV) infection was defined by the detection of two or more positive tests for pp65 antigenemia, and CMV disease by evidence of related symptoms requiring antiviral treatment. Logistic regression analysis showed that transplant recipients older than 55 years, induction therapy with thymoglobulin, and maintenance immunosuppression with cyclosporine were the major risk factors associated with the development of CMV disease[26].

The absence of a published study on CMV infection and its risk factors in renal transplant recipients from the study environment till date prompted this paper especially in the face of a growing renal transplant population in Nigeria [27-30].

Subjects and Methods

Study Population

The subjects were 40 renal transplant recipients and kidney graft donors to 22 of the transplant recipients attending post-transplant follow-up clinics at the Lagos University Teaching Hospital (LUTH) Lagos, Saint Nicholas Hospital (SNH) Lagos and Life Support Medical Centre (LSMC) Ikeja, Lagos between October 2004 and July 2005. One hundred normal subjects from the general population resident in different parts of Lagos metropolis, and chronic kidney disease (CKD) patients with either stage 4 or 5 disease attending renal clinic or dialyzing at LUTH Lagos, SNH Lagos and LSMC Ikeja, Lagos who matched the transplant recipients for age and gender served as study control population.

Study Design

The was a cross-sectional case-control study employing a structured pre-tested self-administered questionnaire to evaluate the risk factors associated with cytomegalovirus infection in the study subjects and controls. Diabetic individuals were excluded from the general population control subjects. Non- diabetic status was determined in the general population control subjects using the One Touch ™ Basic Plus Glucometer manufactured by Life Scan Inc. 2000, Milpitas CA 95035 U.S.A, to test for random blood sugar (RBS). An upper limit of 140 mg/dl in subjects not on diabetic diet or taking diabetic medication was accepted as non-diabetic in the study.

Sample Size Determination

The equation used to calculate minimum sample size in the study was [31]:

$$n = Z^2 Pq / d^2$$

Where:

n = minimum sample size
Z = normal standard deviation (Which corresponds to the desired confidence for the study at a 95% confidence interval) [Z = 1.96]
P = Prevalence
q = 1-Prevalence
d = Precision set at 0.05

The sample size was determined from 80% prevalence rate in the following equation:

$$n = ((1.96)^2 x\ 0.8\ x\ 0.2) / (0.05)^2 = 246$$

However, using the equation [28]:

$$nf = n \div \{1 + (n / N)\}$$

Where:

nf = the desired sample size when the entire study population size is less than 10,000
N = the estimate of the study population size which was 85 renal transplant recipients in the study area

$$nf = 246 \div \{1 + (246 / 85)\} = 63$$

The sample size was thus determined as 63. However, a pilot study of the three centres following up renal transplant recipients in Lagos showed the following number of recipients being followed up at the respective centres during the period of study:

Saint Nicholas Hospital, Lagos - 40
Lagos University Teaching Hospital, Lagos - 5
Life Support Medical Centre, Ikeja, Lagos - 7

One (1) recipient was reporting to all three centres.

This gave a total of 53 transplant recipients being followed up in the study environment at the time of the study.

Of this number, 40 consented to and participated in the study. The break down from the centres was as followed:

Saint Nicholas Hospital, Lagos - 33
Lagos University Teaching Hospital, Lagos. - 4
Life Support Medical Centre, Ikeja, Lagos - 2

One recipient who participated in the study was reporting to all three centers.

Twenty-two renal graft donors consented to and participated in the study. The control population comprised of 136 subjects who matched the recipients for age and gender. One hundred of them who fulfilled the inclusion criteria were selected from the general population residing in the Lagos metropolis. They were selected from randomly recruited 114 persons residing in different parts of Lagos Island and Mainland. The remaining 36 were patients with either stage 4 or 5 chronic kidney disease (NKF/DOQI Classification)[32], as defined in the inclusion criteria.

The pre-transplant qualitative CMV-IgG screening results of 27 recipients and their donors were obtained from their hospital records.

Study Procedures for Detection of CMV Infection in Subjects and Controls

Blood sample specimen of 4 to 5ml was obtained from each study subject and control by simple venipuncture at the cubital fossa after observing appropriate aseptic precautions. Each sample was centrifuged to obtain serum specimen, which was stored at -80^0C in a deep freezer at the Nigerian Institute of Medical Research (NIMR) Human Virology Laboratory, Lagos until tested.

Samples were collected and pooled between October 2004 and February 2005 for the first batch, and in March 2005 for the second batch. The third batch of specimen samples was collected between April and June 2005 while the fourth batch was collected in July 2005. The serological tests on the samples were done on the four batches on 9th March 2005, 4th April 2005, 29th June 2005, and 25th July 2005 respectively.

The ELISA technique was performed using kits intended for semi-quantitative determination of CMV-IgM (Capita ™ CMV-IgM)) antibodies in the test sera. The kits used were from Trinity Biotech Plc (Bray, Ireland)[33]. The technique for CMV ELISA was performed according to the manufacturer's instructions. The CMV-IgM test kit was designed to eliminate errors introduced by the rheumatoid factor, which in the presence of CMV-specific IgG may result in a false positive CMV-IgM reaction. The absorbent solution used in the IgM test kit diminishes competing virus-specific IgG and minimizes rheumatoid factor interference in samples.

Test Interpretation

CMV-IgM

For each test sample specimen, the sample absorbance was determined by subtracting the control antigen well absorbance from the antigen well absorbance.

The calibration cut off value was then determined from the mean optical densities of each pair of calibrator wells and correction factor as contained in the manufacturer's instructions.

ISR was then calculated as follows:

$$\frac{\text{Sample Absorbance}}{\text{COV}} = \text{ISR}$$

ISR < 0.90	= Negative
0.91-1.09	= Equivocal
> 1.10	= Positive

Sensitivity and Specificity of ELISA Test

For the CMV-IgM ELISA, the relative sensitivity of the Trinity Biotech kits has been determined as 97.2% while the relative specificity was determined as 99.2% [33].

The ELISA tests conducted in this study satisfied all the quality control indices outlined in the manufacturer's instructional manual accompanying each of the test kits.

Study Procedure for Assessment of Risk Factors Associated with CMV infection in the Study population

The assessment of risk factors for CMV infection among the renal transplant recipients was done by means of a structured pre-tested self-administered questionnaire which evaluated blood transfusion history, haemodialysis history, history of sexual exposure and number of lifetime sexual partners (Appendices I and II). The questionnaire was in English language which is Nigeria's lingua franca and was pre-tested in a pilot study involving 114 study subjects and controls comprising 33 recipients, 18 kidney graft donors, 33subjects from the general populationand 30 chronic kidney disease patients.

The duration of renal transplant, andthe immunosuppressive drug history of the transplant recipients as at the time of the study were also evaluated. Furthermore, data on acute rejection episodes in the transplant recipients were obtained from recipients' case records. The pre-transplant qualitative CMV-IgG screening results of 27 recipients and their donors as well as data on the use

of CMV prophylaxis were obtained from the hospital case records of the transplant recipients. Information on immunosuppressive drug regimens of the study participants were obtained from the hospital case records of the transplant recipients.

The questionnaire also evaluated the socio-economic classes of the subjects and controls (Appendices I and II). The classification was adapted from the United Kingdom Office of Statistics socio-economic status classification of 2001[34]. It was based on professional occupation of the respondents. Classes 1 and 2 were grouped as high group, 3 and 4 as middle group, and 5-8 as the low socio-economic group. Students and the long-term unemployed (greater than two years) were grouped as unclassified.

Data Analysis and Interpretation of Results

The Microsoft Excel and EPI-Info 2002 statistical software were used for data entry and analysis. Frequency distributions were generated for nominal and ordinal variables while measures of central tendency i.e. mean plus standard deviation were computed for quantitative variables. Variability was expressed as the standard deviation (SD). The Chi-square (two-tailed) and Fisher exact tests were employed where applicable for comparison of prevalence indices between the study subjects and controls while the analysis of variance (ANOVA) was used for the comparison of the means between the study and control groups. Unconditional logistic regression and multiple logistic regression analyses were performed to identify risk factors that were associated with the prevalence of CMV infection in the study subjects and controls. Statistical significance was attained when p value was less than 0.05 ($p < 0.05$).

RESULTS

Characteristics of Study Subjects and Controls

A total of 40 renal transplant recipients and 22 graft donors were studied. Thirty-two recipients (80%) were males and eight (20%) were females giving a male to female ratio of 4:1. The donor group consisted of 14 males (63.6%) and 8 females (36.4%) with a male to female ratio of 1.75:1.

The study control population consisted of 100 persons from the general population and 36 patients with either stage 4 or 5 CKD. The general population controls were made up of 75 males (75%) and 25 females (25%) giving a male to female ratio of 3:1; while the CKD group comprised 28 males (78%) and 8 females (22%)with a male to female ratio of 3.5:1.

The mean age of thetransplant recipients was 39.0$\pm$ 11.6 years, and was similar to those of general population controls (39.1$\pm$10.5 years) and CKD patients (39.0$\pm$ 10.8 years). The mean age of the graft donors was 36.1$\pm$11.3 years. The age range distribution of the recipients (16 to 58 years) was also similar to that of the general population controls (17 to 57 years) and for the CKD control group (17 to 57 years). The age range of the donors was 22 to 60 years.

Seroprevalence of CMV-IgM and CMV-IgG in Study Subjects and Controls

The seroprevalence of CMV-IgM in entire study population of 198 subjects and controls was 9.6%. The seroprevalence for transplant recipients was 22.5%; 6.0% for the general population controls and 11.1% for the CKD group. None of the kidney graft donors was positive for CMV-IgM. There were statistically significant differences between the seroprevalence of CMV-IgM in transplant recipients and their graft donors (Fisher exact p=0.01), and between the transplant recipients and the general population controls (Fisher exact p=0.007). However, there was no significant difference in the seroprevalence between the transplant recipients and the CKD control group (Fisher exact p=0.13).

The seroprevalence of CMV-IgG in the entire study population of 198 subjects and controls was 97.5%. The seroprevalence for transplant recipients was 97.5% while that of the graft donors was 90.9%. For the general population controls, it was 99.0%, and 97.2% for CKD controls. The seroprevalence was similar in the recipients, donors and controls (recipients versus donors, Fisher exact p=0.29; recipients versus general population controls, Fisher exact p=0.49; recipients versus CKD patients, Fisher exact p=0.72).

Risk Factors for CMV Infection:
Blood transfusion

Table 1 shows the pattern of exposure of study subjects and controls to blood transfusions prior to the study. Exposure to blood transfusion was similar between the recipients and CKD control group (p= 0.13) but differed between the transplant recipients

and general population controls (p=0.00001). Only one kidney graft donor (4.5%) had a history of blood transfusion. Each of the seven subjects from the general population with a history of blood transfusion as well as the only donor with a history of blood transfusion was transfused for a total of less than five times prior to the study (Table 1). Each time of transfusion represented two units of packed cells transfused, giving an average of 500 to 600 ml of blood transfused per session or one time of transfusion.

Also, 24 (75.0%) of the 32 recipients with a positive history of blood transfusions were last transfused more than 6 months before the study while eight recipients (25.0%) were last transfused six months or less before the study. Only four (17.4%) of the 23 CKD controls with a positive history of blood transfusion had their last transfusion more than six months before the study. The remaining 19 (82.6%) were transfused within six months prior to the study. All the seven general population control subjects who had a prior history of blood transfusion were last transfused more than six months before the study. The only donor with a prior history of blood transfusion was last transfused less than six months before the study (Table 1).

Haemodialysis

All 40 recipients had been exposed to haemodialysis prior to the study (Table 2). Thirty-four of the thirty-six CKD patients had also been exposed to haemodialysis prior to the study. Exposure to haemodialysis was similar in transplant recipients and CKD controls (p=0.22). Twenty-seven (67.5%) of the recipients had dialyzed for 12 months or less prior to the study (including one recipient who had just one session of dialysis prior to renal transplantation) while 13 (32.5%) had dialyzed for more than 12 months. Frequency of haemodialysis was two times or less per week in 33 (82.5%) of the recipients including one recipient who had just one session of dialysis prior to renal transplantation. The remaining seven (17.5%) had dialyzed more frequently than twice per week (Table 2).

Twenty-seven (79.4%) of the CKD patients had dialyzed for 12 months or less prior to the study including three who had just one session of dialysis prior to the study, while seven (20.6%) had dialyzed for more than 12 months before the study. Frequency of haemodialysis was two times or less per week in 28 (82.4%) of the CKD controls including the three patients who had just one session of haemodialysis prior to the study. Six (17.6%) of the CKD patients had dialyzed more frequently than twice per week prior to the study (Table 2). The frequency of weekly haemodialysis sessions was also similar in the transplant recipients and CKD controls (p=0.94).

Sexual Exposure

Table 3 shows the pattern of sexual exposure in the study subjects and controls. The general population controls had the least proportion of multiple sex partners (20.5%) and the highest proportion of single partners (79.5%). For the transplant recipients 71.4% had single partners and 28.6% had multiple partners, while 77.8% of the donors had single partners and 22.2% had multiple partners. Among the CKD control group 63.6% had single sexual partners while 36.4% had multiple partners. There were no statistically significant differences in sexual exposure between transplant recipients and general population controls (p=1.0), and between transplant recipients and CKD controls (p=0.715). There were also no statistically significant differences in the distribution of single and multiple sex partners between transplant recipients and general population controls (p=0.348), and between recipients and CKD controls (p=0.606).

Regarding duration of sexual, one subject in the general control group did not provide information relating to duration of sexual exposure. In all three study groups i.e. the study subjects and the controls, majority had been sexually exposed for more than 10 years with no statistically significant differences between the study subjects and control groups. (χ^2=0.83, p=0.18, df=4).

Socio-Economic Class

The distribution of study subjects and controls in high/medium versus low socioeconomic classes (SEC) showed that 27 of 30 the classified transplant recipients (90%) were of the high/medium SEC while three (10%) were of the low SEC. Ten (10) recipients were unclassified. In the general population group, 56 (68.3%) of 82 classified persons were in the high/medium SEC and 26 (31.7%) in the low SEC. Eighteen persons from the general population controls (18%) were unclassified. Also 20 classified CKD patients (90.9%) were of the high/medium SEC while two (9.1%) were of low SEC. The remaining 14 were in the unclassified SEC group. In the donor group,

there were 17 subjects in the high/medium SEC and none in the low SEC. Five of the donors were in the unclassified group.The socio-economic class distribution of the study subjects and controls was similar between the transplant recipients and CKD control group (Fisher exact p=0.432) but differed significantly between the transplant recipients and the general population group (Fisher exact p=0.04).

Immunosuppressive Drug Therapy

All the 40 renal transplant recipients studied were on immunosuppressive drugs at the time of the study. Twenty-two recipients (55%) were on cyclosporine, prednisolone and mycophenolate mofetil combination while 14 (35%) were on cyclosporine, prednisolone and azathioprine.Three recipients (10%) were on other medications such as sirolimus or tacrolimus plus cyclosporine and prednisolone combination. One recipient was on a two-drug combination regimen of cyclosporine and prednisolone.

Acute Rejection Episodes (AREs)

Twenty transplant recipients (50%) had a history of one or more acute rejection episodes post transplantation. The other 20 recipients did not experience any episodes. Most episodes occurred within the first week of transplantation and responded to a three to five-day course of pulse methylprednisolone. One transplant recipient required treatment with anti-lymphocyte globulin (ALG) as she failed to respond to methylprednisolone.

Duration of Renal Transplant

The post-transplant duration in the recipients studied ranged from 2 to 80 months (mean: 17.6$\pm$18.6 (SD) months). Thirty-one recipients (77.5%) had been transplanted for more than four months before the study. Nine (22.5%) had their transplants two to four months before the study.

Pre-transplant CMV Status of Transplant Recipients and their Graft Donors

The pre-transplant qualitative CMV-IgG screening test records were available for 27 of the recipients and their donors. In the 27 recipients, 26 (96.3%) were seropositive, and one (3.7%) was seronegative. For the graft donors, 25 of the 27 (92.6%) were seropositive for CMV-IgG while two (7.4%) were seronegative. The graft donor to the sole pre-transplant CMV-IgG seronegative recipient in the study was also seronegative for CMV-IgG prior to the transplant.

Use of CMV Prophylaxis

Cytomegalovirus prophylaxis was used by 16 (40%) of the recipients. Fifteen of them had acyclovir (200 mg bid) for six months, and one had intravenous ganciclovir for three weeks. Twenty-four recipients (60%) received no prophylaxis.

The prevalence of seropositive CMV-IgM did not differ between those who used CMV prophylaxis (oral acyclovir 200mg three times daily for six months) and the recipients who did not (Fisher exact p=0.45) . One recipient, who received intravenous ganciclovir for three weeks following therapy with basilximab for acute rejection episode in the first week of transplantation, was seronegative for CMV-IgM in the study.

Association of Risk Factors with Seropositive CMV-IgM

In the univariate analysis of the association of risk factors with seropositive CMV-IgM in the individual study groups, the closest to a significant association was exposure to multiple sexual partners in the general population control group (p=0.05). Exposure to either blood transfusion or haemodialysis was not significantly associated with seropositive CMV-IgM in either the transplant recipients or the CKD control (Tables 1 and 2 respectively). Also, there were no significant differences between the low socio-economic class and the high /medium socioeconomic class in any of the study groups with respect to seropositive CMV-IgM (transplant recipients -Fisher exact p=0.53; general population controls -Fisher exact p= 0.58; CKD controls-Fisher exact p= 0.27).

In the donor group none of the subjects studied was in the low socio-economic class.

In the transplant recipient group, there was no significant difference between the use of CPM and CPA immunosuppressive regimens with respect to seropositive CMV-IgM (Fisher exact p=0.44) .Neither was a statistically significant difference in seropositive CMV-IgM observedbetween transplants recipients who had one or more acute rejection episodes and those who did not (p=0.22).

Transplant recipients with post-transplant duration of four months or less did not differ significantly with respect to CMV-IgM seropositivity

from those with post-transplant duration of more than four months (Fisher exact p= 0.96).

Unconditional logistic regression analysis of the combined data of study subjects and control subjects for association of risk factors with seropositive CMV-IgM showed that statistically significant risk factors were exposure to blood transfusion (p=0.004), haemodialysis (p=0.006), multiple sexual partners (p=0.03), and immunosuppressive drug therapy (p=0.003) (Table 4). However, following multiple logistic regression analysis of the data, only exposure to multiple sexual partners showed a statistically significant association with seropositive CMV-IgM (p=0.045, OR 3.05, 95% CI 1.02-9.12) (Table 5).

Table 1: Exposure to Risk Factors for CMV infection in Subjects and Controls (Blood transfusion)

Risk factor	Recipients n=40	Donors n=22	CKD n=36	Gen. Pop. n=100
Blood transfusion				
Yes	32(80%)	1(4.5%)	23(63.9%)	7(7%)
No	8(20%)	21(95.5%)	13(36.1%)	93(93%)
Frequency of blood transfusion				
<5 times	16(50%)	1(100%)	19(82.6%)	7(100%)
>5 times	16(50%)	Nil	4(17.4%)	Nil
Time last transfused (months)				
<6	8(25%)	1(100%)	19(82.6%)	Nil
>6	24(75%)	Nil	4(17.4%)	7(100%)

n - Number of Subjects and Controls
CKD - Chronic kidney disease controls
Gen. Pop. - General Population controls

Association between exposure to blood transfusion and seropositive CMV-IgM: Transplant Recipients (Fisher exact p=0.38); CKD controls (Fisher exact p=0.15).
Exposure to more frequent blood transfusion: Recipients (Fisher exact p=0.11); CKD controls (Fisher exact p=0.42).

Table 2: Exposure to Risk Factors for CMV infection in Subjects and Controls (Haemodialysis)

Risk factor	Recipients n=40	Donors n=22	CKD n=36	General Population n=100
Haemodialysis				
Yes	40(100%)	N/A	34(94.4%)	N/A
No	Nil		2(5.6%)	
Haemodialysis duration				
<12 months	27(67.5%)	N/A	27(79.4%)	N/A
>12 months	13(32.5%)		7(20.6%)	
Haemodialysis frequency				
<2 times per week	33(82.5%)	N/A	28(82.4%)	N/A
>2 times per week	7(17.5%)		6(17.6%)	

N/A - Not Applicable
Association between seropositive CMV-IgM and haemodialysis duration: Transplant Recipients (Fisher exact p=0.68); CKD controls (Fisher exact p=0.21).
Association between seropositive CMV-IgM and haemodialysis frequency: Transplant Recipients (Fisher exact p= 0.45); CKD controls (Fisher exact p= 0.37).

Table 3: Exposure to Risk Factors for CMV infection in Subjects and Controls (Sexual Exposure)

Risk factor	Recipients n=40	Donors n=22	CKD n=36	General Population n=100
Sexual history				
Yes	35(87.5%)	18(81.8%)	33(91.7%)	88(88%)
No	5(12.5%)	4(18.2%)	3(8.3%)	12(12%)
No of partners	**n=35**	**n=18**	**n=33**	**n=88**
Single	25(71.4%)	14(77.8%)	21(63.6%)	70(79.5%)
Multiple	10(28.6%)	4(22.2%)	12(36.4%)	18(20.5%)
Duration of sexual exposure				
<10 years	7(20%)	7(38.9%)	9(27.3%)	31(35.6%)
>10 years	28(80%)	11(61.1%)	24(72.7%)	56(64.4%)

Association between sexual exposure and seropositive CMV-IgM: Differences between transplant recipients and general population controls (p=1.0); between transplant recipients and CKD controls (p=0.715). There were also no statistically significant differences in the distribution of single and multiple sex partners between transplant recipients and general population controls (p=0.348), and between recipients and CKD controls (p=0.606).

**Statistically significant association with seropositive CMV-IgM*
(Fisher exact p= 0.05, Odds Ratio [OR] = 0.14, 95% CI = 0.02-0.91

Table 4: Association of Risk Factors with Seropositive CMV-IgM in Study Subjects and Controls (Unconditional logistic regression analysis)

Risk Factor	Odds Ratio	95% CI	Co-eff.	S.E.	Z-Statistic	P-Value
Blood Transfusion (Yes/No)	4.33	1.61-11.66	1.47	0.5	2.91	0. 004*
Frequency of Blood transfusion (>5/<5 times)	2.77	0.76-10.13	1.02	0.66	1.54	0.12
Time last Transfused (>6/<6months)	1.45	0.41-5.15	0.37	0.65	0.57	0.57
Haemodialysis (Yes/No)	4.19	1.51-11.58	1.43	0.52	2.76	0.006*
Haemodialysis frequency per week (>2 times/<2 times)	0.82	0.16-4.28	-0.2	0.84	0.81	0.81
Haemodialysis Duration (>12/<12months)	3.03	0.87-10.61	1.11	0.64	1.74	0.08
Sexual History (Yes/No)	0.66	0.17-2.47	-0.42	0.67	-0.62	0.53
Multiple/Single Partners	3.28	1.15-9.35	1.19	0.53	2.22	0.03*
Duration of sexual exposure (>10 /<-10 years)	2.17	0.59-7.95	0.77	0.66	1.17	0.24
Low vs. High to/medium Socio-Economic Class	1.85	0.53-6.46	0.61	0.63	0.96	0.34
Immunosuppressive Drugs (Yes/No)	4.47	1.67-11.97	1.5	0.5	2.98	0.003*

**Statistically significant*
S.E. - Standard error; Co-eff. - Coefficient

Table 5: Association of Risk Factors with Seropositive CMV-IgM in Subjects and Controls (Multiple logistic regression analysis)

Risk Factor	Odds Ratio	95% CI	Co-eff.	S.E.	Z-Statistic	P-Value
Haemodialysis (Yes/No)	1.14	0.26-7.78	0.34	0.87	0.39	0.69
Sex Partners Multiple/single	3.05	1.02-9.12	1.12	0.56	2	0.045*
Immunosuppressive drug (Yes/No)	1.68	0.42 -6.81	0.52	0.71	0.73	0.47
Blood Transfusion (Yes/No)	2.78	0.60-12.86	1.02	0.78	1.31	0.19
Constant			-2.33	0.57	-4.09	0

**Statistically significant*

DISCUSSION

This study was part of a study on the prevalence of cytomegalovirus infection among renal transplant recipients and their donors in Lagos, Nigeria for a nephrology fellowship dissertation[35]. The absence of a published study on CMV infection and its risk factors in renal transplant recipients from our study environment till date prompted this paper especially in the face of a growing renal transplant population in Nigeria[27- 30].

The renal transplant recipients' characteristics in this study were similar to those of renal transplant recipients reported from other Nigerian studies[27,28]. Majority of the transplant recipients in this study were males with male: female (M: F) ratio of 4:1. This was similar to the male: female ratio of 3:1 reported by Arogundade[27], and 4:1 reported by Okafor[28]. The mean age of age recipients in this study was 39 $\pm$ 11.6 years and was similar to 45.4 $\pm$ 13.6 years reported by Okafor[28] and 47.0 $\pm$ 11.11 years reported by Ulasi *et al*[29]. The majority of renal transplant recipients in this study were in the age groups of 21-40 and 41-60 years.

In this study, post-transplant CMV infection was diagnosed by the detection of seropositive CMV-IgM in the study subjects' test samples. The seroprevalence of CMV-IgM for transplant recipients was 22.5%. It was 6.0% for the general population controls, and 11.1% for the CKD group. None of the kidney graft donors was seropositive for CMV-IgM. There were statistically significant differences between the seroprevalence of CMV-IgM in transplant recipients and their graft donors, and between the transplant recipients and the general population controls. However, there was no significant difference in the seroprevalence between the transplant recipients and the CKD control group.

In a study of 1,450 renal transplant recipients in Northern Iran who were followed up for post-transplant CMV infection over a period of 70 months, Babazadeh *et al*[36] observed that incidence of CMV disease in the 41-60 age group was four-fold compared to those under 20 years of age group.CMV disease in the study was identified by polymerase chain reaction (PCR) and/or PP65 antigen in peripheral blood leukocytes along with clinical manifestations[49]. Kanter *et al*[26] also showed that older age (> 55 years) was a major risk factor for developing post-transplant CMV disease. In this study, the relationship between transplant recipients' age and post-transplant CMV infection was not evaluated. Moreover, unlike the studies by Kanter *et al*[26] and Babazadeh *et al*[36], none of the transplant recipients in this study developed CMV disease. Nevertheless, future studies in the study environment could examine the relationship between age of transplant recipients and the development of post-transplant CMV infection.

In the univariate analysis of study data for transplant recipients and CKD controls respectively, there was no significant association between exposure to blood transfusion and the prevalence of seropositive CMV-IgM. The observed lack of significance of blood transfusion as a risk factor for post-transplant CMV infection in the recipients agrees with similar observations from other studies[6-9]. However, it could also be related to the small number of recipients and CKD controls in this study. Moreover, this study showed that blood transfusion was significantly associated with CMV infection

when all the study groups were combined in unconditional logistic regression analysis. This improved the statistical power of the analysis. Adler [9] suggested that individuals transfused with large volumes of whole blood experience subsequent changes in their cell-mediated immunity, which allows the expression of latent CMV virus. Patients with end-stage renal disease (ESRD) in the pre-transplant period in the study environment are frequently transfused. However, blood transfusion is typically with packed cells rather than whole blood. Forty percent of transplant recipients and 18% of CKD controls in this study had received more than a total 10 units of blood (about 2.5 litres to 3litres of packed redblood cells) prior to the study. The use of recombinant human erythropoietin for the treatment of anaemia should be encouraged in CKD patients in the pre-transplant period to minimize frequency of blood transfusions although the high cost of recombinant erythropoietin treatment may be a limitation to its routine use in the study environment. Tegtmeier[10] suggested that storage leucodepletion of blood components may be as effective as the use of CMV-seronegative blood components risk factor for CMV infection in the transplant.In this study however, multiple logistic regression analysis of study data failed to demonstrate that exposure to blood transfusion is an independent risk factor for post-transplant CMV infection in transplant recipients.

Transplant recipients and the CKD control group in this study had similar haemodialysis exposures. The similarity in seroprevalence of CMV-IgM between transplant recipients and CKD subjects in this study, which differs significantly from those of kidney graft donors and general population control groupsuggests that exposure to haemodialysis is a risk factor for CMV infection. This observation is supported by the findings in the unconditional logistic regression analysis of study subjects and controls in which haemodialysis showed significant association with seropositive CMV-IgM. The observation in this study however differs from findings in studies by Duran etal[37] in Turkey and Korcakova et al[38] in the Czech Republic. In both studies, unlike in this study there were no significant differences in prevalence of seropositive CMV-IgM between haemodialysis patients and healthy controls. In this study however, multiple logistic regression analysis of study data showed that exposure to haemodialysis is not an independent risk factor for post-transplant CMV infection. The reason for this might be the already deficient immune status of transplant recipients and CKD patients[39].

Again, in this study, when the study subjects and controls population data were subjected to multiple logistic regression analysis, only exposure to multiple sexual partners was significantly associated with seropositive CMV-IgM. This finding agrees with the findings of Chandler *et al*[11] who showed that the risk of primary CMV infection and seropositivity for CMV correlated strongly with indices of sexual activity such as the number of sexual partners and age of onset of sexual activity. Although longer duration of sexual exposure could be a reflection of early age of onset of sexual exposure, in this study however, it was not significantly associated with increased prevalence of seropositive CMV-IgM.

Low socio-economic class did not correlate with prevalence of seropositive CMV-IgM in the transplant recipients or in the control groups; neither did it correlate with seropositive CMV-IgM in the unconditional nor multiple logistic analyses of the study population in this study. This agrees with the finding ina previous study in an obstetric population in the study environment[14]. The relatively greater number of recipients in the high/medium class compared to the low SEC could be attributed to the fact that more affluent individuals are better placed to afford the high cost of renal transplants in the study environment as there are no functional national health insurance schemes covering renal replacement therapy in study environment[30]. Similarly, the fewer number of CKD controls in the low SEC group in comparison with the high/medium SEC is also a reflection of the fact that due to its high cost, haemodialysis treatment is mostly affordable to the more affluent CKD population in the study environment.

In the unconditional logistic regression analysis of the study data, the use of immunosuppressive drugs by transplant recipients was associated with a greater than four times likelihood of CMV infection in transplant recipients ($p = 0.003$, odds ratio: 4.47, 95% CI 1.67 – 11.97). However, this difference was not statistically significant after multiple logistic regression analysis indicating that immunosuppressive therapy is not an independent risk factor for post-transplant CMV infection.

In the transplant recipients study group, there was no difference in the prevalence of seropositive CM-IgM between MMF-based (Cyclosporine/ Prednisolone/Mycophenolate mofetil) and azathioprine-based (Cyclosporine/Prednisolone/ Azathioprine) immunosuppressive regimens. This finding is consistent with that of Sarmiento *et al*[22] who noted that recipients treated with cyclosporine/ prednisolone/MMF based immunosuppressive regimen did not differ from those treated with cyclosporine/prednisolone/azathioprine-based regimen with respect to initial CMV infection episode after renal transplantation. The finding of Sarmiento et al was based on presence of CMV viraemia or tissue-biopsy proven CMV infection. On the other hand, Hodge[18] Gonwa[19] and Matthew[20] showed that mycophenolate-containing immunosuppressive regimen was associated with increased symptomatic CMV infection. None of the transplant recipients in this study experienced symptomatic CMV infection. Also, in this study, the use of MMF in transplant recipients was associated with reduction in the dose of prednisolone and this steroid sparing effect might have partly explained the observed lack of association with increased risk of recent CMV infection.

The findings in this study also showed that acute rejection episodes were not associated with increased risk of post-transplant CMV infection. Eighteen (18) recipients who experienced acute rejection episodes in the immediate post-transplant period were treated with a five-day course of pulse methylprednisolone. Another recipient who experienced late acute rejection at one-year post transplantation was treated with pulse methylprednisolone and temporary discontinuation of MMF. The temporary discontinuation of MMF was in order to avoid heavy immunosuppression that could predispose to potential occurrence of opportunistic infections. The lack of association between acute rejection episodes (AREs) and post-transplant CMV infection observed in this study differs from findings of Sarmiento *et al*[22] who observed that prior history of acute graft rejection was associated with post-transplant CMV infection as a result of heavier immunosuppression in the affected patients. The fact that all the recipients who had acute rejection episodes participated in this study long after the episodes occurred might explain the lack of a positive association between acute rejection episodes and recent CMV infection as indicated by seropositive CMV-IgM as at the time of this study. However, these recipients did have antecedent CMV infection as indicated by their seropositive CMV-IgG in the study.

This study also showed that pre-transplant seropositive CMV-IgG donor status did not correlate with transplant recipient post-transplant CMV infection. Chou[3] noted that seropositive recipients could be re-infected by a new CMV strain from the donor following renal transplantation. Ho *et al*[4] also observed a high incidence of CMV infection in 12 seronegative recipients who received a kidney graft from seropositive donors while Sarmiento et al demonstrated that positive CMV serology in donors was associated with CMV infection in transplant recipients[22]. However, in this study all of the 27 transplant recipients whose pre-transplant CMV-IgG screening results were available were seropositive except for one recipient. Similarly, of the 27 graft donors whose pre-transplant CMV-IgG screeningresults were available, 25 were seropositive while two graft donors were seronegative for CMV-IgG. Thus, the high rate of antecedent CMV infection in transplant recipients and their graft donors (R+D+ combination) in the pre-transplant period might have obscured the impact of CMV positive donor on transplant recipient post-transplant CMV infection.

CONCLUSIONS

Thisstudy identified exposure to blood transfusion, haemodialysis and multiple sexual partners as well as immunosuppressive drug therapyas risk factors for post-transplant CMV infection in renal transplant recipients. However, exposure to multiple sexual partners was the only independent risk factor for post-transplant CMV infection.The use of CMV prophylaxis with acyclovir was not associated with prevention of post-transplant CMV infection in transplant recipients in the study environment.

Limitations of the Study

Serological method of CMV diagnosis was employed in this study due to limited resources. Serological diagnosis has limited sensitivity in the post-transplant diagnosis of CMV infection compared to more sensitive diagnostic techniques such as polymerase chain reaction and pp65 antigenaemia assay. Giving that more renal transplant centres are now actively carrying out renal transplants,and the increasing

number of transplant recipients in the study environment, future studies could employ the more sensitive diagnostic methods for CMV diagnosis.

Also, most of the transplant recipients in this study were at the stage well beyond the first four months of transplantation, the period the risk of CMV infection is greatest.

Again, the relatively low number of available transplant recipients and graft donors in this study could be a limitation. However, the study adjusted for this potential limitation by increasing the number of age and gender-matched control subjects and by using two sets of control populations.

REFERENCES

1. Rubin RH. Infectious disease complications of renal transplantation. Kidney International. 1993; 44: 221.
2. Liapis H, Storch GA, Ashley Hill D, Rueda J, Brennan DC. CMV infection of the renal allograft is much more common than the pathology indicates: A Retrospective Analysis of Qualitative and Quantitative Buffy Coat CMV-PCR, Renal Biopsy Pathology and Tissue CMV-PCR. Nephrol Dial Transplant. 2003; 18: 397-402.
3. Chou S.acquisition of donor strains of cytomegalovirus by renal transplant recipients. New England Journal of Medicine. 1986; 314:1418-1423.
4. Ho M, Suwansirikul S, Dowling JN, Youngblood LA, Armstrong JA. The transplanted kidney as a source of cytomegalovirus infection. New England Journal of Medicine. 1975; 293:1109-1112.
5. Orsi EV, HowardJL, Baturay N, Ende N, Ribot S, Eslami H. High Incidence of Virus Isolation from Donor and Recipients Tissue Associated with Renal Transplantation. Nature. 1978; 272: 372-373.
6. Kane RC, Rousseau WE, Noble GR, Tegtmeier GE, Wulff H, Herdon HB, Chin TDY, Bayer WL,Cytomegalovirus infection in a volunteer blood donor population. Infect Immune. 1975; 11:719-723.
7. Diosi PE, Tomescu N. Latent cytomegalovirus infection in blood donors. British Medical Journal. 1979; 41: 600-662.
8. Preiksaitis JK, Strautman TM, The risk of transfusion acquired cytomegalovirus (CMV) infection in seronegative solid organ transplant recipients receiving unscreened blood products (1984-1996). Transfusion. 2002; 42: 396-402.
9. Adler S.Transfusion - Associated Cytomegalovirus Infection. Review of Infectious Diseases. 1983; 5:977-993.
10. TegtmeirGE. Transfusion-acquired cytomegalovirus infection. In: Linden JV, Bianco E, Editors. Blood safety and surveillance. New York: Marcel Dekker; 2001.p315-333.
11. Chandler SH, Holmes KK, Wentworth BB, Gutman LT, Wiesner PJ, Alexander ER, et al. The epidemiology of cytomegaloviral infection in women attending a sexually transmitted disease clinic. Journal of Infectious Diseases. 1985; 152: 597-605.
12. Handsfield HH, Chandler SH, Caine VA, Meyers JD, Corey L, Medeiros E, et al. Cytomegalovirus infection in sex partners: Evidence for sexual transmission. Journal of Infectious Diseases. 1985; 151: 344-368.
13. Mustakangas P, SurnasAmmala P, Multilainen M, Koskela P, Koskiniemi M. Human cytomegalovirus: seroprevalence in three socioeconomically different urban areas during the first trimester; a population based cohort study. International Journal of Epidemiology. 2000; 29: 587-591.
14. Ogbaini-Emovon E,Oduyebo O,Lofor PV, Onakewhor JU, Elikwu CJ. Seroprevalence and risk factors for cytomegalovirus infection among pregnant women in Southern Nigeria. Journal of Microbiology and Infectious Diseases. 2013; 3(3): 123-127. doi: 10.5799/ ahinjs.02.2013.03.0094
15. Rubin RH. Impact of cytomegalovirusinfection on organ transplant recipients. Review of Infectious Diseases. 1990; 12(7): S754-S766.
16. Brennan DC, Singer GG. Infections complications in renal transplantation. In: Malluche HH, Sawaya BP, Hakim RM, Sayegb MH, Ismail N. Editors. Clinical Nephrology Dialysis and Transplantation. 1999; Landshut Germany; Bosch-Druck: 1-24.

17. Lewis RM, Johnson PC, Golden D, Van Buren, CT, Kerman RH, Kahan BD. The adverse impact of cytomegalovirus infection on clinical outcome in cyclosporine-prednisone treated renal allograft recipients. Transplantation. 1998; 45:353-359.

18. Hodge EE.The role of mycophenolate mofetil in clinical renal transplantation. World Journal Urology. 1996; 14: 249-255.

19. Gonwa TA. Mycophenolate mofetil for maintenance therapy in kidney transplantation. Clinical Transplantation. 1996; 10: 128-130.

20. Matthew TH. A blinded long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years. Transplantation. 1998; 65: 1450-1454.

21. Moreso F, Seron D, Morales JM, Cruzado JM, Gilvernet S, Perez JL, et al. Incidence of leukopenia and cytomegalovirus disease in kidney transplants treated with mycophenolate mofetil combined with low cyclosporinee and steroid doses. Clinical Transplantation. 1998; 12: 198-205.

22. Sarmiento JM, Munn SR, Paya CV, Velosa JA, Nguyen J. Is cytomegalovirus infection related to mycophenolate mofetil (MMF) after kidney transplantation? A Case – Control Study. Clinical Transplantation. 1998; 5: 371-374.

23. Akposso K, Rondeau E, Haymann JP, Peraldi MN, Marlin C, Sraer JD. Long-term prognosis of renal transplantation after preemptive treatment of cytomegalovirus infection. Transplantation. 1997; 63: 984-976.

24. Boland GJ, Hene RJ,Ververs C, de Gast GC. Factors influencing the occurrence of active cytomegalovirus infections after organ transplantation. Clinical and Experimental Immunology. 1993; 94: 306-312.

25. Pass RF, Whitley RJ, Diethelm AG, Whelchel JD, Reynolds DW, Alford CA. cytomegalovirus infection in patients with renal transplants: Potentation by antithymocyte globulin and an incompatible graft. Journal of Infectious Diseases. 1980; 142: 9-17.

26. Kanter J, Pallardó L, Gavela E,Escudero V, Beltrán S, Morales A, Avila A, Crespo JF. Cytomegalovirus infection renal transplant recipients: risk factors and outcome. Transplant Proceedings. 2009; 41(6): 2156-2158. doi: 10.1016/ j.transproceed.2009.06.057.

27. Arogundade FA. Kidney transplantation in a low-resource setting: Nigeria experience. Kidney International. 2013; 3(2): 241–245.

28. Okafor UH. Kidney transplant in Nigeria: a single centre experience. Pan African Medical Journal. 2016; 25: 112, 1-7. doi: 10.11604/pamj.2016.25.112.7930.

29. Ulasi II, Ijoma C, Onodugo O, Arodiwe E, Okoye J, Onu U et al. Post-transplant care of kidney transplant recipients and their donors in Nigeria. Experimental and Clinical Transplantation. 2019; 17(1): 50-56.

30. Ulasi II, Ijoma CK. Organ transplantation in Nigeria. Transplantation. 2016; 100(4): 695-697.

31. Araoye MO. Subjects selection. In: Araoye, M.O., Ed., Research methodology with statistics for health and social sciences. Ilorin: Nathadex Publishers; 2004.p115-129.

32. K/DOQI. Clinical practice guidelines for chronic kidney disease evaluation, classification and stratification. American Journal of Kidney Diseases. 2002; 39: S1-S66.

33. Trinity Biotech Capita TM. Cytomegalovirus IgG and IgM ELISA test instructional manual. Trinity Biotech Plc. Bray Ireland; 2001 ISO 9001 certified.

34. The United Kingdom Office of Statistics. 2001; Revised classification of socioeconomic status.

35. Menakaya NC. Prevalence of Cytomegalovirus Infection among Renal Transplant Recipients and Their Donors in Lagos, Nigeria. Nephrology Fellowship Dissertation, National Postgraduate Medical College of Nigeria. November 2006.

36. Babazadeh A, Javanian M, Oliaei F, Akbari R, Akbarzadepasha A, Bijani A, et al. Incidence and risk factors for cytomegalovirus in kidney transplant patients in Babol, Northern Iran, Caspian Journal of Internal Medicine. 2017; 8(1): 23–29.

37. Duran N, Ocak S, Eskyocak AF. Seroprevalence of cytomegalovirus antibodies in haemodialysis patients. Turkish Journal of Medical Sciences. 2006; 36: 155-158.

38. Korcakova L, Kaslik J, Svobodova J, Kaslikova J, Blaha J, Sedlackova E, et al. CMV infection in patients with chronic renal failure and in those following transplantation. Czech Medicine. 1988; 11: 131-136.

39. Syed-Ahmed M and Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. Advances in chronic kidney disease. 2019: 26(1), 8–15. https://doi.org/10.1053/j.ackd.2019.01.004

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Ethics Declaration: The Research and Ethics Committee of Lagos University Teaching Hospital Lagos, The Management of Saint Nicholas Hospital Lagos, and The Management of Life Support Medical Centre Ikeja approved the study.

Informed Consent: Informed written consent was obtained from all the study participants after explaining the main purpose of the study to them.

Consent for Publication: The authors give their consent for this study to be published.

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