

Morbidity Pattern in End Stage Renal Disease Patients Before And After Renal Transplantation

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Abstract

Introduction: To effectively and efficiently plan programmes for prevention and control of End Stage Renal Disease (ESRD)/ chronic kidney disease, there is a need for basic epidemiological and clinical data. This hospital-based descriptive study on renal transplant patients attempted to provide some information on their morbidity pattern before and after renal transplantation.

Methods: A hospital-based study was conducted at the Teaching Hospital, Kandy. The study sample consisted of 305 patients who had undergone renal transplant and attended the clinic during the three month period of data collection. Interviewer administered questionnaire was used as the data collection tool.

Results: Renal transplant patients are prone to infections mainly due to iatrogenic immunosuppression. Cytomegalovirus infection was the commonest. Other common infections observed were upper respiratory tract infections, gastroenteritis and urinary tract infections. All the patients who participated in the study developed at least one non-communicable disease during the follow up period. Anaemia (54%) was the most common problem encountered, followed by rejection, both acute and chronic (50%) and dyslipidaemia (44%). Almost all the participants had hypertension developed before or after the transplantation. This suggests that hypertension is leading to ESRD, resulting from ESRD or just a co-morbidity.

Conclusion: Cytomegalovirus infection was the commonest infectious disease reported. Other common infections observed in this study were upper respiratory tract infections, gastroenteritis and urinary tract infections. All the patients developed at least one non-communicable disease during the follow up period.

Keywords – Morbidity, Renal Transplant, Non Communicable Disease.

I. INTRODUCTION

Sri Lanka is facing the double burden of disease i.e. non-communicable and communicable diseases due to the demographic and epidemiological transitions, currently the country undergoes. There is an epidemic of diabetes mellitus which resulted in high prevalence of diabetes in young population also. The long duration of disease in these patients invariably lead to high incidence of complications including the End Stage Renal Disease (ESRD). In addition, there are also patients with end stage renal disease due to other known aetiological factors such as chronic hypertension. There are also cases of ESRD, where the aetiology is not clear.¹ All these resulted in a high demand for renal transplantation.

The Government of Sri Lanka spend considerable amount of resources for dialysis, renal transplantation and for follow up of patients with end stage renal disease. According to a recent statistic, 4.6% of the annual health budget was spent on management of chronic kidney disease patients.¹ After renal transplantation, these patients should lead a reasonable quality of life. However, the quality of life is often disturbed by co-morbidity conditions, which were there before transplantation or acquired after transplantation. As the post-renal transplantation patients are on immunosuppressant drugs, they are more prone to get infectious diseases, cardiovascular diseases, malignancy etc.

To effectively and efficiently plan programmes for prevention and control of chronic kidney disease, there is a need for basic epidemiological and clinical data. This study on renal transplant patients attempted to provide some information on their socio-demographic characteristics, aetiological factors and morbidity pattern.

Dialysis is a procedure that is performed routinely on persons who suffer from acute or chronic renal failure, or who have ESRD. The process involves removing waste substances and fluid from the blood that are normally eliminated by the kidneys. Dialysis may also be used for individuals who have been exposed to or ingested toxic substances to prevent renal failure from occurring. There are two types of dialysis that may be performed, that are peritoneal dialysis and haemodialysis.^{2,3} However, the preferred modality for renal replacement is renal transplantation, and its superiority in prolonging the longevity of patients with ESRD is well established.⁴ Renal transplantation is a surgical procedure to remove a healthy, functioning kidney from a living or brain-dead donor and implant it into a patient with nonfunctioning kidneys.⁵ In terms of quality of life, patient surveys have consistently indicated a clear preference for transplantation over other replacement therapies.⁴

Economically also transplant is a more feasible method of replacement therapy an important factor when considering the increasing health care costs and the government's continued commitment to providing coverage of end stage renal disease therapies such as dialysis. In Sri Lanka demand for renal transplantation is growing but only a few centers do transplantation and follow-up. Some patients got transplantation done in India, but most of these patients also depend on services available in Sri Lanka for the follow-up.

Causes for end stage renal disease may differ from region to region and country to country. However, diabetes and hypertension are the dominant factors leading to ESRD, followed by glomerular and vascular causes. According to global studies, diabetes (43.2%), hypertension (23.0%), glomerulonephritis (12.3%), and polycystic kidneys (2.9%) are the leading causes for ESRD.⁶

In Sri Lanka, end stage renal disease can be considered as one of the growing health problems as well as a public health issue.¹ The demographic and epidemiological transition currently the country undergoes, contribute significantly to this situation. Further, in some part of the country, especially in the North Central Province and its surroundings, high prevalence of chronic kidney disease has been reported in the recent past.¹ Adequate graft function requires lifelong immunosuppressive treatment, and the resultant modification of the immune system is associated with an increased risk of various complications.^{7,8}

Rarely, active infection is conveyed with the allograft, although, unusual cases of disseminated toxoplasmosis or herpes simplex infection have resulted from the transplantation of organs from donors with active systemic infections.⁸ Untreated infection in the recipient can have a major impact after transplantation. In particular, transplantation of an organ into a patient with pneumonia or lung injury from pulmonary aspiration or infarction almost guarantees super infection with nosocomial gram-negative bacilli, fungi, or both.^{8,9}

During the first decade of renal transplantation era, severe infections developed in up to 70% of patients following transplantation resulting in fatal outcomes in as many as 11% to 40% of cases.⁹ In the late 90s, the incidence of infections declined to 15% - 44% with a mortality rate of less than 5%.⁹ This trend is probably attributable to a number of factors, including refinement of the actual surgical technique, better and more appropriately tailored immunosuppressive regimens, the use of prophylactic antimicrobial agents, improved methods for diagnosis, more effective therapies and avoidance of prolonged intravenous lines.⁴ However, despite improved outcomes in kidney transplant patients over the years, infectious complications remain a significant cause of morbidity and mortality in this population. Even in the current era infection remains the third largest cause of death in renal transplant patients⁹

The incidence and distribution of infections differs from country to country, region to region. A study done in at Iran showed an overall incidence of 54.2% among renal transplant patients. According to this study, most common sites of infections were the urinary tract (41.5%) and the respiratory tract (6.3%), and the most frequent causes of infections agents were Klebsiella (24%) and cytomegalovirus (CMV) (17.6%).¹⁰ Another study done in India found tuberculosis in 10 - 15%, deep mycosis in 3.8 - 6%, hepatitis B in 40%, hepatitis C in 15%, CMV in 20%, and Plasmodium falciparum in 22.5% of renal transplant patients.¹¹

The immunosuppressive programs used in all forms of solid-organ transplantation are quite similar. As a result, there are similar patterns of infection in all forms of organ transplantation and a consistent timetable for when different infections occur

after transplantation This timetable is most easily organized into three segments: the first month, one to six months, and more than six months after transplantation.^{8,9}

More than 90 percent of the infections occurring in the first month are nosocomial bacterial or fungal infections of the surgical wound, lungs, urinary tract, or vascular-access devices.⁸ These occur even in surgical patients who are not in a state of immunosuppression.

The nature of infections in transplant recipients changes after the first month. In addition to residual effects of earlier events, new types of infection appear. The immunomodulating viruses, particularly cytomegalovirus (CMV), but also Epstein Bar Virus (EBV), other human herpes viruses, hepatitis B and C viruses (HBV and HCV) and human immunodeficiency virus (HIV) if present, begin to exert clinically significant effects.⁸ The combination of sustained immunosuppression and viral infection makes possible opportunistic infections also.^{8,9}

Six months after transplantation, patients can be divided into three categories in terms of their infectious-disease problems. More than 80 percent of patients have a good result from transplantation and are maintained on minimal long-term immunosuppressive therapy with good allograft function. Their infectious disease problems are similar to those of the general community and are primarily respiratory infections. Opportunistic infection is unusual unless a particularly intense environmental exposure has occurred (e.g. aspergillosis after digging in the garden).⁸

Approximately 10% of patients will have a chronic or progressive infection with HBV, HCV, CMV, EBV, or HPV (Human Papilloma Virus). Such viral infection may cause injury to the infected organ (the liver in the case of the hepatitis viruses and the retina in the case of CMV) or contribute to cancer (e.g., hepatocellular carcinoma following HBV or HCV infection, lymphoma due to EBV, and squamous-cell cancer due to HPV).⁷

Among all infectious agents, cytomegalovirus (CMV) is one of the most common, encountered in the renal transplant patient population with an incidence of 34% to 55%.⁴ The typical onset of infection is within the first 1 to 4 months after transplant. Tuberculosis is well reported in the worldwide transplant community literature that end-stage renal disease, dialysis, and renal transplant patients are at an increased risk for both primary and reactivated tuberculosis.^{12, 13} Tuberculosis, pulmonary as well as disseminated, is a major opportunistic infection after renal transplantation, especially in tropical countries.¹⁴ The risk of TB in renal transplant recipients is reported to be 20 – 74 times higher than that in the general population.¹⁵ The decreased cellular immunity of patients with end-stage renal disease, secondary to uremia, and the iatrogenic immunocompromised state post-transplant are commonly believed to be the contributors.¹³ Tuberculosis can occur any time after transplantation, but the majority of infections occur in the first 18 months.⁹

Urinary tract infection (UTI) is also among the common infections in the transplant recipients with an incidence of more than 30% in the first 3 months following transplantation.⁴ A study has reported an incidence of 5% - 36% among patients not receiving antimicrobial prophylaxis.⁹ Prat and his team reported a very high UTI incidence of 62% in the first month after transplantation.¹⁶ Beyond three months after transplantation, the incidence of UTI decreases progressively.⁹

Upper respiratory tract infection is common after a transplant. Though, the incidence did not show much difference than that of general population, those with transplant may get these infections more frequently, or may take longer to recover after an infection than expected.⁸ Pneumonia is also among the most common infections after transplantation and causes high mortality.⁹

Herpes virus infection is often seen following kidney transplantation and it is mainly due to immunosuppression. Most of the infected patients remain asymptomatic while some present with unexplained fever, skin rash, stomatitis, and even pneumonia.⁸ Primary chickenpox infection in adults is usually associated with increased morbidity and mortality.⁹

Renal transplant recipients were at higher risk for cardiovascular disease than the general population.^{4,18} According to a study, the incidence of ischemic heart disease in transplant population is 15% which is four times greater than expected in the general population.⁴ Anaemia is another complication commonly seen after renal transplantation. According to a study, anemia was found among 30% - 40% of kidney transplant patient and 10% - 15% had severe anaemia.^{19,20} Studies also show that anaemia raises mortality risk by 69% in these patients.¹²

Post transplant diabetes (PTDM) is an additional disease burden as many appear to be developing diabetes for the first time following kidney transplantation.²¹ Further, this condition increases the risk of transplant complications and death. According to a study, cumulative incidence of PTDM was 9.1%, 16% and 24% at 3, 12 and 36 months post transplant respectively.²¹

Hypertension is common after renal transplantation. Use of certain drugs including cyclosporine and corticosteroids, presence of native kidneys, and renal allograft dysfunction (including renal artery stenosis) are the likely causes of high prevalence of post-transplant hypertension.²² Post-transplant hypertension appears to be a risk for both rejection and eventual graft loss.²³ A study found a prevalence of 50% - 70% for hypertension among transplant patients treated with azathioprine and prednisone.²²

Avascular osteonecrosis (AVN) of femoral head is one of the most common skeletal complications seen in kidney transplant patients.²⁴ A cumulative incidence of 7.1% was reported between 1994 and 1998.²⁵ It is generally accepted that corticosteroids play a crucial role in the pathogenesis of this condition. Prevalence of this complication decreased following the introduction of cyclosporine but the effect of recently introduced immunosuppressive agents is not so well documented.²⁴

II. METHODS

The study was conducted at the Kandy Teaching Hospital. The study population included patients who underwent renal transplant. The following patients were excluded from the study

- Those with failed graft
- Those who underwent renal transplantation more than once
- Those who didn't have proper medical records since the time of transplantation
- Children and adolescents less than 18 years

All the patients who satisfied the selection criteria were included into the study and the sample consisted of 305 subjects recruited during the study period of three months.

An interviewer-administered questionnaire was used as the study instrument. The questionnaire included five sections namely; Socio-demographic characteristics, Morbidity pattern before transplantation and Details of transplantation.

Prior approval was obtained from the Director, Teaching Hospital, Kandy to conduct this study. Permission to get access to the relevant clinic records and other necessary information was obtained from the Consultant Medical Officers. The medical officers conducting the clinic sessions were briefed about the objectives of the study and their cooperation was solicited. Ethical approval was obtained from the Ethical Committee, Teaching Hospital, Kandy before starting the study. An information sheet about the study was given to all participants and their queries about the study were answered. Informed consent was obtained from each of the respondents.

III. RESULTS

Details about the chronic diseases renal transplant patients had before the onset of end-stage renal diseases for a period of one year or more were obtained from the patients by interviewing them and by reviewing the available medical records.

Though 124 patients (40.0%) had hypertension and 38 patients (12.4%) had diabetes before the onset of end-stage renal disease, only for 17 (5.6%) and 35 patients (11.5%) respectively hypertension and diabetes were mentioned as the aetiological factors responsible for ESRD. Further, the medical history of renal transplant patients showed that around the time of diagnosis as end-stage renal disease (i.e. within one year of diagnosis) 179 patients (58.6%) had hypertension.

Table 1: Renal transplant patients by chronic diseases before the onset of ESRD

Disease	Number	%
Hypertension	124	40.0
Diabetes Mellitus	38	12.4
Ischaemic Heart Disease	02	0.6

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Nephrotic Syndrome	18	5.9
Systemic Lupus Erythematosus	01	0.3
Others	07	2.2
Total	192	64.4

The minimum waiting period for renal transplantation after developing end stage renal disease was one month while the maximum was 106 months. The mean waiting period was 13.6 months (95% CI: 12.4, 14.8) while the median was 12 months. Almost all the patients (98%) received kidney from live donors. In 52.5% of cases, donors were related to the recipients (first degree relationship/ blood relation).

After renal transplantation, some patients developed infectious diseases as well as non-communicable diseases during their follow-up period.

All the renal transplant patients who participated in the study had at least one infectious disease during the follow up period. Some patients got more than one type of infectious disease, thus the total was more than 305. As shown in the table the most common infection in this group of patients was cytomegalovirus infection (38.6%), followed by upper respiratory tract infection (34.7%) and gastroenteritis (18.3%).

Table 2: Renal transplant patients by infectious diseases after transplantation

Infectious disease	Number	%
Simple fever/ flu like illness	54	17.7
Cytomegalovirus infection	118	38.6
Urinary tract infection	51	16.7
Pneumonia	07	2.2
Tuberculosis	09	2.9
Upper respiratory tract infection	106	34.7
Chickenpox	22	7.2
Gastroenteritis	55	18.3
Herpes zoster	24	7.8
Total	446	-

Among the common infectious diseases, renal transplant patients comparatively often get repeated attacks of cytomegalovirus infections, upper respiratory tract infections and urinary tract infections. The difference in the occurrence of reaction to allograft in relation to history of cytomegalovirus infection was found to be statistically not significant (chi square = 3.018, p = 0.0824).

All the renal transplant patients who participated in the study developed at least one non-communicable disease/ condition during the follow up period. Some patients got more than one type of non-communicable disease/ condition, thus the total was more than 305. Anaemia (54%) was the most common problem encountered by these patients, followed by rejection, both acute and chronic (50.17%) and dyslipidaemia (44.3%).

Among renal transplant patients participated in the study, 124 had hypertension at least one year before the onset of ESRD and another 179 developed hypertension within one year of the onset of ESRD. Among the balance 2 patients, one developed hypertension after surgery and one remained free of hypertension throughout.

Table 3: Renal transplant patients by non-communicable diseases developed after transplantation

Disease	Number	%
Anaemia	165	54.0
Rejection (acute and chronic)	155	50.1
Dyslipidaemia	135	44.3
Diabetes Mellitus	49	16.0
Cataract	27	8.6
Polycythaemia	17	5.6
Ischaemic Heart Disease	15	4.9
Menstrual disorders	14	15.6
Avascular necrosis/ Osteoporosis	10	3.2
Depression	07	2.3
IgA Nephropathy	02	0.6
Hypertension	01	0.3

The difference in the occurrence of rejection of allograft in relation to the type of donor was found to be statistically not significant (chi-square = 0.94, p = 0.33). When the donor was not a blood relation (53.3%) the risk for rejection was more than when the donor was a blood relation (47.7%). However, this observation was not significant (Odds Ratio = 1.25, 95% CI: 0.78 - 2.01).

The difference in the occurrence of ischaemic heart disease in relation to the duration of dialysis patients underwent before transplantation was found to be statistically not significant (chi-square = 1.80, p = 0.772). The odds ratios also failed to confirm the “dose-response effect” i.e. according to literature, with increasing duration of dialysis, chances for ischaemic heart disease also increase.

Out of 305 participants, 124 patients had hypertension for at least one year before the diagnosis of ESRD and 179 patients developed hypertension within one year before the diagnosis of ESRD. One patient developed hypertension after renal transplantation and the balance one patient remained free of hypertension throughout.

The hypertensive state improved (19.4%) or remained unchanged (78.6%) in 98% of patients, while in 2% of patients the condition got deteriorated after renal transplantation.

A review of patients’ own perceptions of their health status revealed that 90.2% of patients felt that their health status had improved after renal transplantation. About 7% did not feel any difference in their health status despite the surgery, while 2.6% felt that their condition had deteriorated since the transplantation.

IV. DISCUSSION

The mean waiting period for renal transplantation (since the diagnosis of ESRD) was 13.6 months (95% CI: 12.4, 14.8) with a minimum waiting period of one month and a maximum of 106 months. According to the United States Renal Data System (USRDS), the average waiting period for a kidney transplant for patients aged 20 years or less was 10 months and for adults approximately two years.³⁴ The analysis of the relationship between the age of the patients and waiting time was not done in this study.

Almost all (98%) who were interviewed received the kidney from live donors. In United States, percentage of live donors was 47% but in Spain it was only 3%.⁵ The availability of live donors (importantly willingness) and the advancement in the surgical

techniques are some of the factors determining the type of donor i.e. live or cadaver. According to literature, the 4 years survival rate for cadaveric recipients was 66% and for living-related recipients, it was 81%.³⁵

According to the data available for this study, among the live donors, 53% were “blood relations” (i.e. first degree relationship). A related donor has a better chance of strong biological match for the patient. However, the difference in the occurrence of rejection of allograft in relation to the type of live donor (i.e. “blood relation” or not) was found to be statistically not significant (chi square = 0.94, df = 1, p = 0.33) in this study. In this study, rejection, both acute and chronic, was reported in 50% of patients, which was higher than what was reported in the literature. Generally, a rejection rate of between 32% and 50% was reported from other transplantation centers.²⁶

Renal transplant patients are prone to infections mainly due to iatrogenic immunosuppression. The net state of immunosuppression is the sum of several factors including the nature of immunosuppressive therapy, presence of underlying immune deficiency, metabolic condition and infection with immune-modulating viruses like CMV.²⁷ Cytomegalovirus (CMV) infection was the commonest infectious disease reported among renal transplant patients with an incidence of 34% to 55%.⁴ In this study also, a total of 118 episodes of CMV infection were reported among study subjects. A detailed analysis showed that 92 patients had a single episode and another 26 had recurrent episodes of CMV infection. High incidence of reaction to allograft was observed in transplant patients who had CMV infection (8). This study failed to confirm such finding (chi square = 3.018, p = 0.0824). Though those with a history of CMV infection had more risk for reaction to allograft (56.7%) compared to those without CMV infection ((46.5%), this observation was statistically not significant (Odds Ratio = 1.5, 95% CI: 0.92 - 2.46).

Other common infections observed in this study were upper respiratory tract infections (106 episodes), gastroenteritis (55 episodes), and urinary tract infections (51 episodes). Often these patients experienced recurrent attacks of the above diseases. A similar trend was observed in other studies also.^{4,10,1}

Non-communicable disease is a growing problem in the transplant population due to factors such as conventional risk factors, the net effect of immunosuppressants and infections like CMV. All the patients who participated in the study developed at least one non-communicable disease/ condition during the follow-up period. Some patients got more than one type of non-communicable disease/ condition. Anemia (54%) was the most common problem encountered by renal transplant patients, followed by rejection, both acute and chronic (50%), and dyslipidemia (44%).

Anemia is significantly associated with mortality and graft failure.²⁸ The literature describes a prevalence of between 30% and 40% for anemia among renal transplant patients.²⁶ The prevalence found in this study (54%) was comparatively high. Further, dyslipidemia was found in 44% of patients, which is an important cardiovascular risk factor and also a risk factor for graft loss.

Literature describes a prevalence of 70% to 90% for hypertension among ESRD patients.^{22,29,30} In this study, out of 305 participants interviewed, 124 patients (41%) had hypertension for at least one year before the diagnosis of ESRD and 179 patients (58%) developed hypertension within one year of the diagnosis of ESRD. One patient developed hypertension after renal transplantation and the remaining patient was free of hypertension throughout. These findings suggest that hypertension is leading to ESRD, resulting from ESRD or just a co-morbidity. Among those who had hypertension, the hypertensive state improved in 19% and remained unchanged in 79% of patients, while in 2% the condition got deteriorated with renal transplantation.

During the waiting period for renal transplantation, patients with ESRD should undergo dialysis for survival. According to the literature, there is a “dose-response effect” i.e. with increasing duration of dialysis, chances of getting ischaemic heart disease (IHD) increase due to calcification and intima-media thickening of vessels.^{31,32,33} In this study, however, the difference in the occurrence of ischaemic heart disease in relation to the duration of dialysis was found to be statistically not significant (chi-square = 1.80, p = 0.772). The odds ratios also failed to confirm this (with increasing duration of dialysis, odds ratios were 1, 1.5, 0.9, 3.5, and zero respectively). The effect of possible confounders and less number of patients in each category may be the reasons for this observation.

Despite whatever morbidity they developed after transplantation, 77% of the renal transplant patients felt very good improvement in their health status and another 13% felt moderate improvement with transplantation. Only 3% of patients complained that after transplantation their condition got deteriorated.

V. CONCLUSIONS

Cytomegalovirus infection was the commonest infectious disease reported. Other common infections observed in this study were upper respiratory tract infections, gastroenteritis, and urinary tract infections. All the patients developed at least one non-communicable disease during the follow-up period. Anemia was the most common problem encountered by renal transplant patients, followed by rejection, both acute and chronic, and dyslipidemia. About 41% of patients had hypertension for at least one year before the diagnosis of ESRD and another 58% developed hypertension within one year of the diagnosis of ESRD.

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