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Early Post-transplant Renal Functions Predict Incidence of Acute Rejection in Kidney Transplantation

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Authors' contributions

This work was carried out in collaboration among all authors. Authors KA, WA and AA collected data from medical report. Author RKA shared in writing the draft manuscript. Author YAR provided the detailed patient notes and managed the literature searches and author SV did the statistical analysis and designed the figures, tables. Author MM managed the literature searches and contributed to correction of the draft. All authors read and approved the final version of the manuscript.

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ABSTRACT

Objectives: After renal transplantation, a remarkable improvement of impaired patient's kidney function is often observed. Preserving improved kidney function ensures long-term renal allograft survival. However, there are different risk factors; the acute rejection is the major risk factor. Therefore, the aim of the present study was to examine renal function within the first six months as independent variables in predicting long-term survival and incidence of acute rejection.
Methods: Fifty-three patients who underwent kidney transplantation in 2016 and 2017 in King Abdulaziz Medical City- National Guard were evaluated consecutively1 and 2-month pre-transplant

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up to six months' post-transplant. Time course of changes in kidney functions; measurements of serum creatinine (Scr), blood urea nitrogen(BUN), albumin, calcium, sodium and potassium were recorded. Estimated glomerular filtration rate (eGFR) and anion gap (AGAP) were also reported. In addition, age, anthropometric factors and causes of ESRD were analyzed.

Results: Lower level of calcium was observed in 40% of patient's two-month pre-transplantation and 69% of patients one month before. Normalization of calcium was achieved in all patients starting from second month post-transplantation. All patients presented elevated serum potassium level in pre-transplant months, however, renal transplant normalize potassium level starting from first month. A remarkable higher level of serum BUN was observed in all pre-transplant patients followed by dramatically decreased after renal transplant for first four months and remain in normal level starting from month 5. Likewise, serum creatinine was highly elevated in all pre-transplant patients. A profound reduction in serum creatinine started from month 1 post-transplant and normalizes at month 4. Moreover, both eGFR and AGAP were kept in normal level immediately after renal transplantation. All patients with early acute rejection during mean follow-up period have a remarkable elevated level of serum creatinine and profound decrease in eGFR starting from first month. While a significant higher level of serum BUN observed in fifth month only and serum albumin in third month.

Conclusion: Significant elevation of serum creatinine and reduction in eGFR starting from first month were associated with post-transplanted patients with early acute rejection. The clinical use of eGFR and serum creatinine may aid in predicting incidence of early acute rejection.

Keywords: Biochemical parameters; renal transplant; allograft survival.

1. INTRODUCTION

The treatment of choice in end-stage renal disease (ESRD) patients is kidney transplantation (KT) as it confers a significant survival advantage over dialysis [1]. It has been reported that KT can help to restore patients" quality of life and can reduce the mortality and morbidity in patients with renal failure, as it compared to dialysis [2,3,4]. This hypothesis was confirmed by Mehrabi et al. [5] who showed that KT is the safest method among patients with ESRD as it is associated with a high patient survival rate and a low morbidity [6,7]. Therefore, renal transplantation is still the treatment of choice for patients with end-stage renal disease and kidney failure, because of the expectancy of prolonged life as compared with those maintained on dialysis and/or hemodialysis [8]. In general, successful transplantation should correct or should significantly improves patient's impaired kidney function during the first year of post-transplant.

A previous large study about 18 years ago, involving 220,000 patients treated with long-term dialysis or cadaveric transplant showed a larger benefit about mortality in transplant patients after 18 months from the graft [1]. These results have also been shown even in elderly patients; as the kidney, transplantation in these patients can get survival advantages over dialysis treatment [9].

There are several reasons involved in kidney transplant grafts failure. Identification of the predominant cause could facilitate the development of strategies that stave off that process and improve graft survival potentially. Medical complications include organ/tissue rejection, drug toxicity related to anti-rejection treatments (e.g., cyclosporine), acute tubular necrosis (ATN), infection, and transplantation-related malignancies (e.g., post-transplantation lymphoproliferative disorder or lymphoma) are the most important challenge in kidney transplantation [10]. Acute rejection and cyclosporine toxicity are the most common causes of early transplant failure [11]. These complications may result in deterioration of renal function as a late permanent event. Several reports discussed the incidence of chronic kidney disease in transplanted kidney which may be due to early inflammatory events such as release of pro-inflammatory cytokines mediated from T-cell that occur during delayed graft function, which often leads to acute rejection [12,13].

New advances in immunosuppressive therapy have reduced incidence of rejection (cases of acute rejection) and have improved short-term graft survival [14]. The availability of non-nephrotoxic immunosuppressive drugs may further improve graft and patient survival. Therefore, the accurate immunosuppressive dosage as adequate pharmacological treatment

is required to improve the outcome of transplant kidney [15].

It has been shown that graft function measured by kidney function test especially serum creatinine early after transplantation was an important predictive factor of graft survival [16]. Consequently, follow-up the kidney function in post-transplant patients may improve and maintain early graft function and decrease incidence of late graft failure. Therefore, careful monitoring of kidney transplant patients is highly required to detect complications before severe damage occurs [17,18].

The relationship between renal function during the first year post-transplantation, and long-term graft survival and mortality was investigated to increase awareness of the importance of preserving renal function in kidney transplant recipients. Elevation of serum creatinine and change in GFR during first year following kidney transplantation has improved over the time. Although, the level is still far from normal value [19]. Hariharan and co-workers [19] has confirmed the correlation between the risk of graft loss and higher serum creatinine level as it reflects severity of renal dysfunction. Moreover, it has been reported that post-transplanted patient with higher serum creatinine (more than 2.5 mg/dl) during first year had a fourfold increase in risk of infection related death compared with patients who had normal serum creatinine (less than 1.2 mg\dl) [20].

Therefore, the aim of the present study was to assess renal function in the first 6 month after renal transplantation. Making special emphasis on the monthly follow-up of serum level of different kidney parameters in subset of patients with great risk of acute rejection. Furthermore, the effect of different immunosuppressive drugs on baseline graft function in post-transplant patients.

2. METHODS

2.1 Study Design

This is a retrospective cohort study carried out on Fifty-three patients who underwent kidney transplantation in 2016 and 2017 in the renal transplantation unit of King Abdulaziz Medical city, National Guard; the largest tertiary hospital in the Middle East, located in the city of Al-Riyadh, Saudi Arabia. The study were performed by reviewing pre- and post-renal transplant patients' medical record sheet.

The initial data were taken during the year 2019 from database of the hospital management system that performs the routine collection of health data from local programs. Therefore, all included patients had the possibility of graft loss or acute rejection or even exposure to the risk for at least one consecutive year after transplantation. Patients of any age were eligible for this cohort at the time of transplantation, including pediatric recipients, and geriatric recipients. The exclusion criteria were as follows: patients underwent kidney transplant combined with another solid organ (simultaneous with the liver or pancreas, or heart).

2.2 Variables and Outcomes

Medical record review was performed according to clinical data confidentiality protection. A blinded number (ID) was assigned to each patients in order to take into consideration confidentiality. The demographic data concerned recipients were age, gender, height, weight and body mass index and other variables follow-up for 6 months Table 1. In addition data concerning, primary renal diseases, early or late acute rejections, information about urinary infections, primary immunosuppressive treatment data, treatment changes, biopsy results, major complications, donor characteristics, causes of graft losses, metabolic parameters, and renal functions at the end of the follow-up period were recorded.

The outcomes considered were incidence of acute rejection with their date, graft loss, defined as the need for the permanent return to dialysis after transplantation and death.

All recipients with graft failure was categorized into early or accelerated acute rejection, which occurred with the first days post-transplantation. The reason behind accelerated rejection was reported as thrombosis, patients with arterial or venous renal thrombosis of the renal graft or those with evidence of an immune-mediated vascular injury.

We have collected biochemical variables like calcium, potassium, sodium, BUN, Serum Creatinine and albumin. Furthermore, data of eGFR and AGAP were also collected at every month for three months' post-transplant until the end of the follow-up.

Table 1. Distribution of socio-demographic variables among the kidney transplantation patients (N = 53)

Socio-demographic variables	No. of patients N (%)
Gender	
Male	32 (60.4%)
Female	21 (39.6%)
Age (in years) Mean ± SD	37.6 ± 16.6 (4-72)
Height (in Cms.) Mean ± SD	158.5 ± 15.5 (91.8 – 182.0)
Weight (in Kgs.) Mean ± SD	65.4 ± 21.0 (15.1 – 122.0)
BMI (Kg/m^2)	25.7 ± 6.1 (15.8 – 44.4)

Table 2. Distribution of patients among consuming medications (N = 53)

Medications	No. of Patients	Percentage
(Mycophenolate Mofetil, Prednisolone, Tacrolimus)	47	88.7
Prednisolone, Tacrolimus, Azathioprine	2	3.77
Prednisolone, Tacrolimus	4	7.54

2.3 Statistical Analysis

Quantitative variables were expressed like descriptive statistics as Mean±Standard deviation (SD) on the data for the study sample. For categorical variables, they were expressed as frequency and proportions. Statistical comparisons between different various data were made. The distribution of all continuous data was examined. For continuous variables with normal distribution, paired t-test was used for comparisons between pre and post data. For funding the influencing factors we have used multivariate COX regression analysis approach.

The statistical significance was fixed as $p<0.05$. Data were entered in Microsoft Excel 2010 and all statistical analyses were done by using SPSS 21.0 version [IBM Ltd., USA].

3. RESULTS

3.1 Characteristic of the Patients

In the present study, we collected data from 53 patients who underwent kidney transplantation in our center in 2016 and 2017.

There was a predominance of male recipients (60.4%, n=32) while female was (39.6%, n=21). The mean age of the patients was 37.6 ± 16.6 years. The mean BMI was 25.7 ± 6.1 (15.8 – 44.4) Kg/m^2 as shown in Table 1. At the time of transplantation, 11.3% of the patients were less than 18 years old, 49% were between 18 and less than 40 years old, 33% were between 40 and 64 years old, and 5.5% (n=3) were 65 years old or older. The follow-up time was 6 months, in this period, 7 patients have early acute rejection with a primary absence of function, three had acute T cell mediated rejection 3 to 14 days post-transplant while others had antibody mediated rejection 2 month after transplantation. The majority of transplanted patients 88.7% were treated with triple therapy: Mycophenolate Mofetil, Prednisolone, Tacrolimus, while 3.77 of the patients treated with Azathioprine instead of mycophenolate Mofetile, and 5.77 received both Prednisolone, Tacrolimus only (Table 2).

3.2 Graft Function in Kidney Transplant Recipients

A highly significant elevated level of serum creatinine, blood urea nitrogen (BUN), AGAP and slightly increase in serum potassium was reported in all pre-transplant patients (one and two months). These biochemical changes in kidney function were parallel with a remarkable decrease in eGFR, and slightly reduced level of serum calcium and albumin. The statistical significance differences were $p<0.05$.

After renal transplantation, serum calcium declined significantly during the 1st month post-transplant, followed by a profound rise from second month until month six (Fig. 1A). Regarding serum potassium level, there is a significant increase in pre-transplant patients; however, serum potassium level tends to be

normalized after transplantation (data not shown). Moreover, the mean serum sodium level remains stable within normal range along the follow-up period before and after renal transplantation (data not shown). As expected the mean serum BUN were highly elevated about three times of the normal level. After renal transplantation, a remarkable decrease in serum BUN level starting immediately after transplantation and normalized in month 5 and 6 (Fig. 1B). The comparison of the mean values of serum creatinine between two months before renal transplantation and different months follow-up after transplantation had shown that serum creatinine were 8 times more than control, started immediately after transplantation to decrease, and normalized after month 4 (Fig. 1C). Serum albumin has been decreased significantly one month after transplantation. However, a remarkable increase in serum albumin started from month 3 and remains high until month 6 (Fig. 1D). The improvement in kidney function was confirmed by amelioration in eGFR level. A progressive decrease in eGFR level had been shown in all pre-transplanted patients ranging from 4-13 ml/min/ 1.73 m^2 with mean level 7.13±0.67 ml/min/1.73 m^2 two month and 6.46±0.5 ml/min/1.73 m^2 one month before transplantation. A remarkable increase in eGFR starting from first month after transplantation was noted to reach 71.4+3.8 ml/min/1.73m^2 and remain stable along the follow-up period (Fig. 1E).

In an attempt to further, elaborate the effect of kidney transplantation on AGAP. The comparison between mean values of AGAP before transplantation and the different follow-up values after transplantation were studied. AGAP levels were noticeably elevated in pre-transplanted patients. A marked reduction in AGAP levels were shown in all patients after transplantation although it is still higher than normal values (Fig. 1F).

Table 3. Multivariate cox regression analysis of kidney function parameters in long-term survival and acute rejection

Variables in the equation	β	SE	OR	95.0% CI	
				Lower	Upper
BUN	0.008	0.089	1.01	0.85	1.20
Serum Creatinine	0.037	0.031	1.04	0.98	1.10
Albumin	0.370	0.273	1.45	0.85	2.47
eGFR	0.035	0.058	1.04	0.93	1.16
AGAP	-0.081	0.435	0.92	0.39	2.16

β – Regression value; SE – Standard Error value; OR – Odds Ratio; CI – Confidence Interval

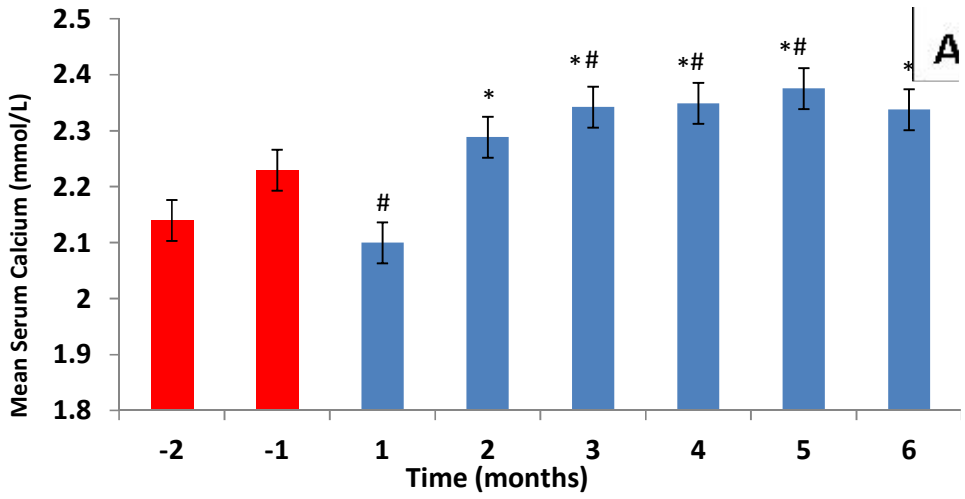

Fig. 1A. Monthly changes in serum calcium levels two months before transplantation (red) and six month after transplantation (blue)

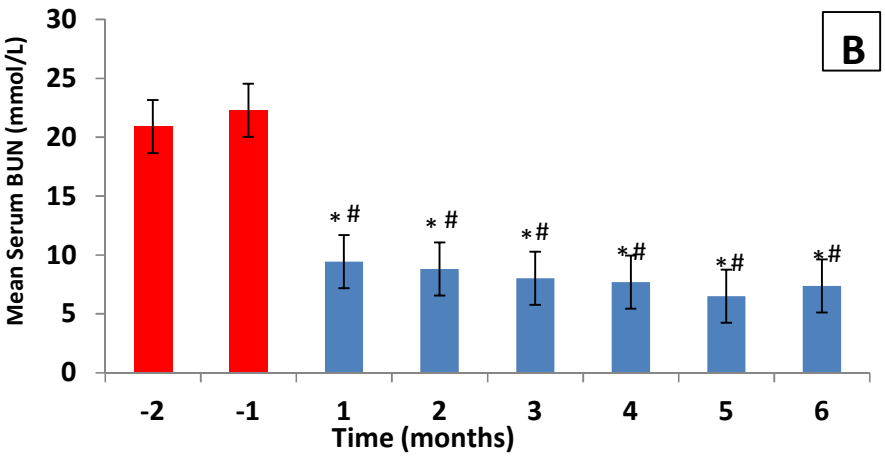

Fig. 1B. Changes of Blood urea nitrogen (BUN) during two month pre-transplant and six month post-transplant period

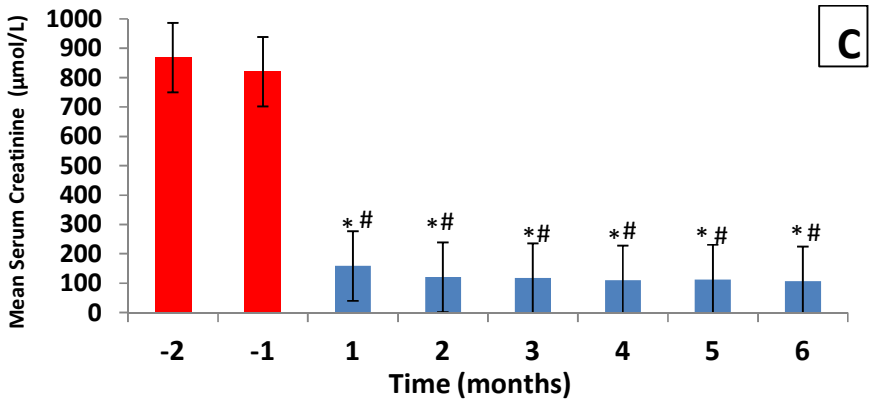

Fig. 1C. Serum creatinine during the follow-up two-month before and six month after renal transplantation

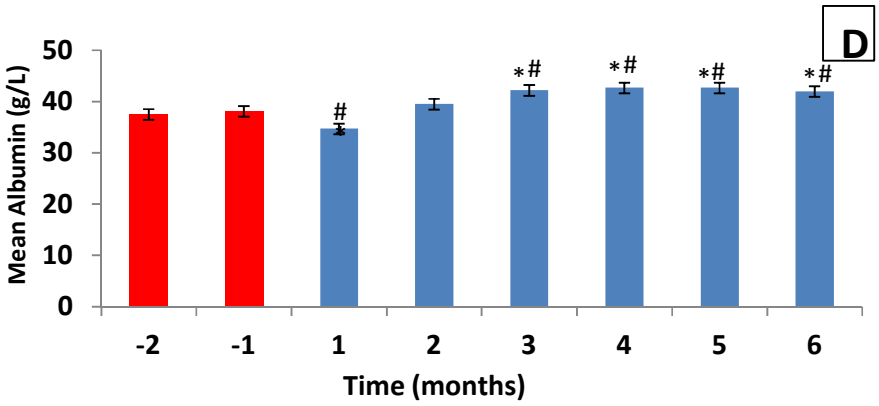

Fig. 1D. Serum albumin mean values during the follow-up before and after renal transplantation

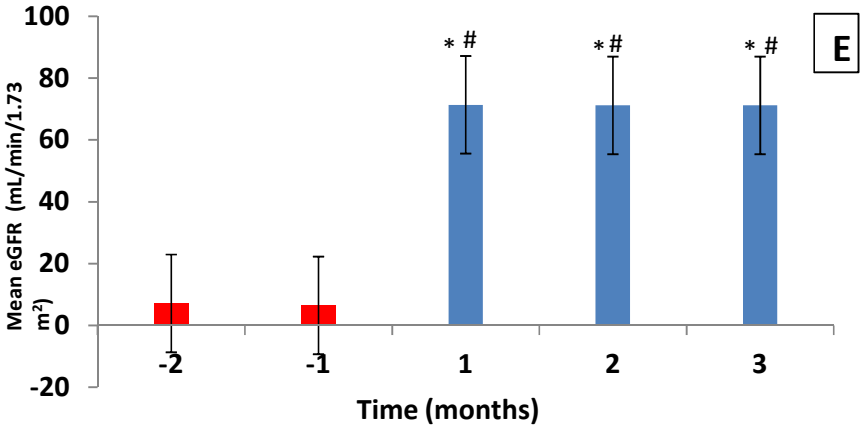

Fig. 1E. eGFR during the follow-up two-month before and three month after renal transplantation

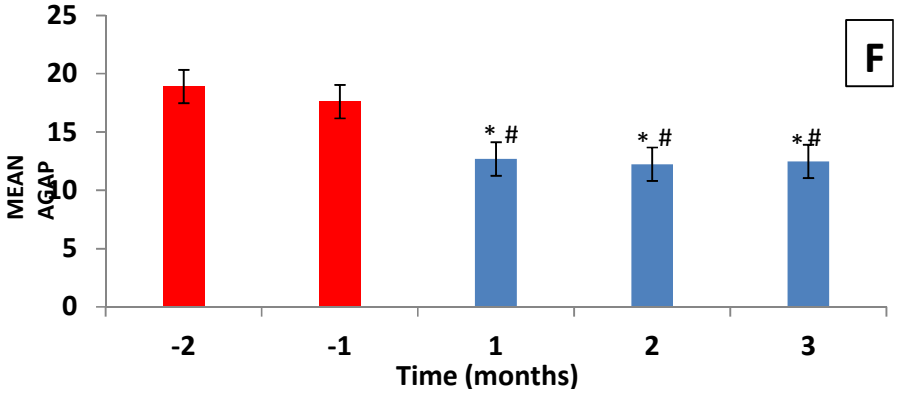

Fig. 1F. Changes of AGAP during the follow-up two-month before and three month after renal transplantation

** Statistically significant from one month Pre-transplant -1 P>0.05*
 # Statistically significant form two month Pre-transplant -2 P>0.05

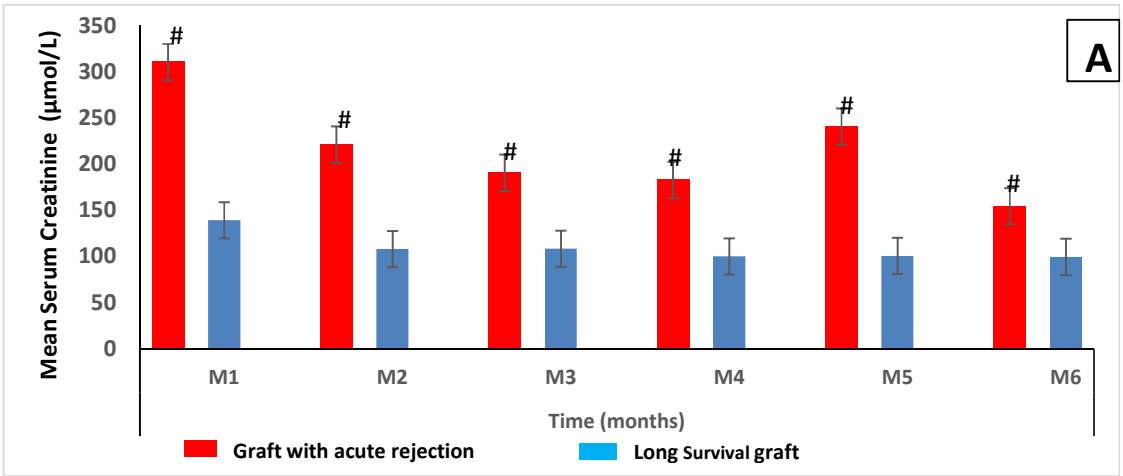

Fig. 2A. Post-transplant creatinine level in patients with acute rejection (red) and long survival graft (blue)

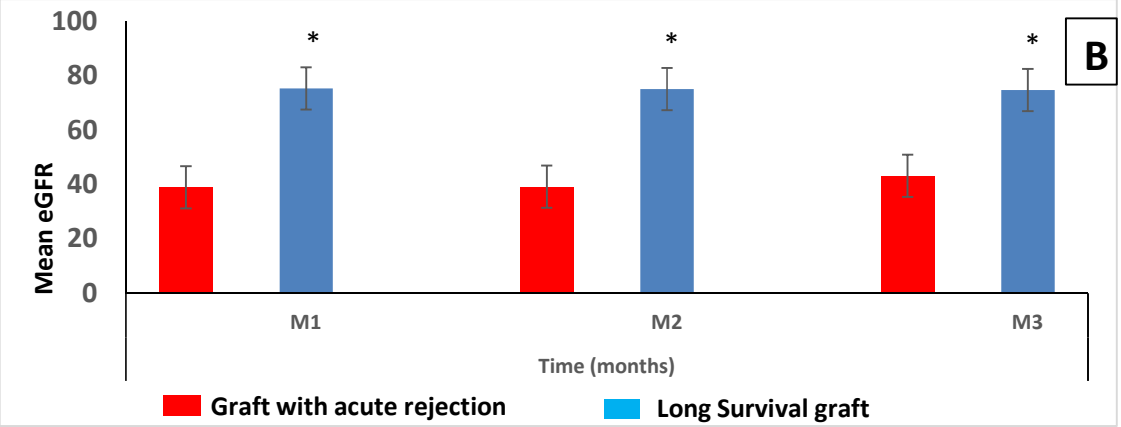

Fig. 2B. Post-transplant eGFR level in patients with acute rejection (red) and long survival graft (blue)

 # statistically significant difference between acute rejection (red) and long survival graft (blue) P>0.05

3.3 Graft Function in Acute Rejection

Renal functions deterioration in patients with acute rejection started from first month after transplantation, 13.8% of our patients suffering from early acute rejection, have a remarkable increment of serum creatinine (Fig. 2A). While serum BUN elevated significantly at fifth month (data not shown). Furthermore, there is a reduction in serum albumin during follow-up period reach significant difference at third month. The gold standard to measure renal functions is eGFR, which roughly represent early adaptation of allograft after transplantation. There is a profound reduction from first month until third month in the calculated eGFR in all patients with acute rejection (Fig. 2B).

According to Multivariate COX regression analysis, the variables BUN, Odds Ratio = 1.01; 95% CI: (0.85 – 1.20); Serum Creatinine, OR = 1.04; 95% CI: (0.98 – 1.10);, Albumin, OR = 1.45;95% CI: (0.85 – 2.47);, eGFR, OR = 1.04; 95% CI: (0.93 – 1.16);, and AGAP, OR = 0.92; 95% CI: (0.39 – 2.16). All OR values exceeding 1 except AGAP and hence we conclude that the kidney functions are independent predictors of the renal function in the kidney transplantation patients.

4. DISCUSSION

The treatment of choice for advanced kidney disease is renal transplantation, even when compared with more sophisticated dialysis modalities [21-24]. Moreover, there has been a substantial improvement in adverse outcomes related to renal transplantation in the short term in recent decades. As the incidence of acute rejection is highly improved [25], and there has been a better management of delayed graft function [26,27]. However, the improvement in long-term outcomes is still far, even in the most recent eras [28]. Based on results of previous studies, the major primary causes of renal graft loss are death with the functioning kidney, recurrence of the underlying disease, and acute rejection [29-31].

In a previous American study evaluating the outcomes of 1,317 kidney transplants patients, they were unable to determine the different causes of death in 31.2%of the patients evaluated, and the follow-up of the cohort was not available El-Zoghby et al. [31]. However, long-term follow up of transplanted patients does not occur in the transplant center in several countries, but non specialized teams [30] may perform it. Hariharan et al. [19], showed that elevated kidney functions occurring within the first year are of critical importance for long-graft survival. Using values, creatinine≥1.5 and ∧creatinine ≥ 0.3 values, groups of patients with markedly reduced graft half-life can be identified. Controversy, transplant recipients with creatinine level less than 1.5 mg\dl and ∧ creatinine less than 0.3 in the first year have an excellent long-term survival rate. The author concluded that, one-year creatinine and ∧ creatinine values are the variables that correlate best with long-term renal graft survival.

To date, little is known about the role of eGFR, proteinuria, together with kidney function tests

(serum creatinine and blood urea nitrogen) as an independent variables influencing long-term survival. The results of the present study clearly demonstrate that successful kidney transplantation associated with significantly improvement in kidney function test gradually within the first six months. As expected, impaired kidney function were confirmed by the highest level of serum creatinine and BUN within last two months before transplantation. Furthermore, deterioration in renal function reflected by, a significant decrease in eGFR, serum albumin and serum calcium in last two months pre-transplant too. After renal transplantation, a remarkably reduction in both serum creatinine and BUN together with elevated level of serum albumin, eGFR and calcium were improved after transplantation. This confirms the value of regular measurement of kidney functions during first months after transplantation. From the current study, post-transplant serum creatinine and estimated eGFR from first month emerges as important variables, which influences long-term graft survival. Based on current analysis of our study, a progressive increment of serum creatinine (two to three fold) together with remarkable decline (50%) in eGFR from first month post-transplant were associated with patients suffering from early acute rejection. While serum creatinine and estimated eGFR values in renal transplant patient with long-term graft survival were within normal ranges. In our study, there was an increment in serum BUN started from first month, but reach significant level only in fifth month. While, there was a significant lower level of serum albumin during third month after transplantation. Elevated level of serum creatinine, urea and decline in estimated eGFR are an indicator of renal damage and subsequent decline in renal survival. Based on multivariate COX regression analysis all tested parameters (Serum creatinine, eGFR, BUN and albumin) are significant except AGAP. In our previously study, we assess weekly proteinuria as an important measure to follow-up kidney function and allograft survival in post-transplanted patients. We claimed that the highest reduction of proteinuria was noticed at week 8 (second month) post transplantation in long-term graft survival and we recommended that, the prime target to be achieved after renal transplantation is the reduction of proteinuria for nephron-protection [32]. Taken together, evaluation of serum creatinine, eGFR and microalbuminuria should be a systematic request by nephrologist and should be performed by the kidney recipient annually. Our results can confirm previously published data showing, graft function measured as serum creatinine early after transplantation was an important predictive factor of graft survival [19]. Moreover, the Kidney Disease Outcome Quality Initiative (K/DOQI) [K/DOQI 2002] [33] guidelines have recommended measuring graft function in primary renal diseases by estimated creatinine clearance (eCrCl) or estimated glomerular filtration rate (eGFR). Monitoring changes in eGFR has been established as the recommended method for assessing the progression of kidney disease (K/DOQI).

Since the first use of mycophenolate mofetil and tacrolimus, δ GFR improved significantly [34]. The improvement were based on superior immunosuppressive belong to these drugs allowing reduction in the incidence of acute rejection. In our study, the majority of renal-transplanted patients (88.4%) were treated with Mycophenolate Mofetil, prednisolone, tacrolimus regimen as immunosuppressive drugs. While the rest of the patients treated with either triple therapy regimen prednisolone, tacrolimus, azathioprineor prednisolone, tacrolimusonly. All post-transplanted patients with early acute rejection in our study treated with Mycophenolate Mofetil, prednisolone, tacrolimus regimen. Gill et al. [34] reported a slower decline in GFR in patients receiving mycophenolate mofetil (cellcept) and tacrolimus. Furthermore, Mayer et al. [35], reported that incidence of acute rejection in 12 month was 24.1% with the tacrolimus based regimen and 43.4% with ciclosporin. These results confirmed by Margreiter [36] who showed acute rejection happen in 19.6% of tacrolimus-treated patients and in 37.3% of patients receiving ciclosporin. Still lower 12-month incidences of acute rejection were reported by Johnson et al. [37] with regimens of tacrolimus and corticosteroids in combination with either azathioprine (17.1%) or mycophenolate mofetil (MMF; 15.3%), compared with 20.0% for ciclosporin microemulsion, corticosteroids plus MMF. Marcén et al. [38] examined the effects of immunosuppression on graft function, and concluded that cyclosporine-treated recipients had a more rapid decline than tacrolimus-treated. In our study, patients treated with incidence of acute rejection were 13.2% in patients treated with tacrolimus. Together with the previous finding, this could confirm the belief that tacrolimus induce lower toxicity than cyclosporine. However, this data was contradicted by other data stated that no differences in recipients treated with tacrolimus

when compared with those on treatment with cyclosporine in graft survival [39] nor with chronic allograft nephropathy [40]. However, other study declared that renal function deteriorated in patients receiving calcineurin inhibitor based regimen (ciclosporine, mycophenolate mofetil and prednisolone) as compared with calcineurin inhibitor free regimen (sirolimus, mycophenolate mofetil and prednisolone) [41].

5. CONCLUSION

Measurement of serum creatinine and estimated GFR from the first month after renal transplantation are the ideal variables that predict incidence of early acute rejection and long term renal graft survival. The improvement of the allograft half-life is due to the preservation of renal function in the first 6 month after transplantation. Further studies are highly needed to investigate allograft function in long-term to better clarify the causes of long-term graft loss in those patients who had a good clinical course in the first year.

DATA AVAILABILITY

The data that support the findings of this study are available from the King Abdul-Aziz Medical City (KAMC), National Guard, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Medical record review was performed according to clinical data confidentiality protection. A blinded number (ID) was assigned to each patients in order to take into consideration confidentiality. Data are however available for the authors upon reasonable request and with permission.

CONSENT

Written informed consent was obtained from all patient for publication. Medical record review was performed according to clinical data confidentiality protection. A blinded number (ID) was assigned to each patients in order to take into consideration confidentiality

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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