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Serum creatinine level at 1-month posttransplant can independently predict long-term graft survival and functional status

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Background: After the year 2000, kidney transplants with high immunologic risk and deceased donors increased rapidly in Korea. At the same time, the medical community developed special pretransplant and early posttransplantation management protocols. Our team evaluated the effect of early graft stabilization on long-term graft survival and functional status using databases from a high-volume kidney transplantation center.
Methods: We included 1,895 kidney transplant patients from a total of 1,976 performed between 2005 and 2018. Early graft failure within 1 month (n=9), loss to follow-up (n=2), pediatric recipient or donor (n=37), and combined organ transplantation (n=33) cases were excluded. We grouped the cases at 1-month posttransplantation by serum creatinine quantiles (1.0 mg%, 1.23 mg%, and 1.52 mg%).
Results: After an average of 95 months of follow-up (maximum 189 months), the high-serum creatinine group (4th quantile) showed significantly poorer graft survival than other groups (1st to 3rd quantile) (P<0.05). In multiple Cox regression analysis, a high serum creatinine level (4th quantile) at 1-month posttransplant is an independent risk factor for graft failure with a hazard ratio of 1.799 (P=0.013). The quantile group by serum creatinine shows a persistent, significant difference of functional graft status (glomerular filtration rate by Modification of Diet in Renal Disease method) among quantile groups beyond ten years posttransplant.
Conclusions: Serum creatinine level at 1-month posttransplant is a strong independent predictor of graft survival and functional graft status beyond ten years posttransplant.

Keywords: Creatinine; Kidney transplant; Graft survival

INTRODUCTION

Kidney transplantation (KT) has improved patient survival and quality of life compared to other modes of renal replacement therapy. It has become the treatment of choice in end-stage renal failure [1]. However, the gradual decline in renal function after transplantation is inevitable [2]. The rate may be influenced by numerous variables, including both donor- and recipient-related characteristics. Donor age, donor and recipient race, cold ischemia time, human leukocyte antibody (HLA) mismatching, and delayed graft function have all been shown to significantly influence short- and long-term graft survival [3-5]. Moreover, a calcineurin inhibitor (CNI) based immunosuppression regimens exhibit dose-related nephrotoxicity and could be a contributing factor in graft function decline [6].

Early identification of those patients at risk of graft function and subsequent timely therapeutic intervention is

HIGHLIGHTS

- One-month posttransplant serum creatinine level is related to long-term graft function.
- The glomerular filtration rate is associated with graft outcome.
- After the year 2000, higher risk kidney transplants increased rapidly in Korea.

necessary to improve outcomes in the kidney transplant patients.

Previous studies have shown that the parameters of renal function, mainly serum creatinine, creatinine clearance, and glomerular filtration rate (GFR), are valuable indicators of long-term outcomes. Early graft function, especially the 1 year posttransplant graft filtration rate or serum creatine level, is the most powerful predictor of long-term graft and patient survival [7-9]. However, these studies included patients who were treated in the early period of the transplantation era. Thus, the studies did not consider highly sensitized patients, ABO-incompatible transplantations, and marginal deceased donor.

After 2000, the number of kidney transplants of high immunologic risk patients (e.g., highly sensitized recipients, leucocyte cross-matching positive, and ABO-incompatible transplantation) and deceased donor transplantation, including marginal donors, rapidly increased in Korea. Special pretransplant and early posttransplantation management regimens were developed, such as plasmapheresis for antibody filtration and use of rituximab for antibody depletion [10]. At the same time, new immunosuppressive agents were rapidly developed [11,12].

Given the recent changes, early graft stabilization after transplantation is essential. Therefore, we evaluated the effect of early graft stabilization on long-term graft survival and functional status using the databases from a large-volume KT center.

METHODS

We accessed the data of 1,976 consecutive KT recipients between 2005 and 2018 performed at Severance Hospital, Korea. We identified 1,895 cases that met our inclusion criteria. We excluded the following cases: graft failure within 1 month (n=9), loss to follow-up (n=2), pediatric recipient or donor (age under 18 years old, n=37), or combined organ transplantation (n=33). We categorized the included patients into four groups defined by quartiles (Q) of serum creatinine levels at 1-month posttransplant. The cut points for the groups were 1.0 mg%, 1.23 mg%, and 1.52 mg%. We used CNI based triple regimen (mycophenolate mofetil, steroid) as an immunosuppressants protocol, and after 6 months, steroid withdrawal is considered.

Our purpose of this study was comparing of graft survival of each group and comparing graft function and failure rate. Graft function was measured by estimated GFR by Modification of Diet in Renal Disease equation. Graft failure was defined as returning to dialysis or renal retransplantation. Categorical variables are presented as frequencies. We used the chi-square test or Fisher's exact test to evaluate these data. Time-to-event data were compared by Kaplan-Meier survival curves with log-rank tests. For the adjusted model, we used a Cox regression analysis. All analyses were performed using standard statistical software (IBM SPSS ver. 25.0; IBM Corp., Armonk, NY, USA) and $P<0.05$ was considered statistically significant.

RESULTS

We had 450 individuals in the 1st Q (serum creatinine <1.0 mg%), 476 in the 2nd Q (serum creatinine <1.23 mg%), 489 in the 3rd Q (serum creatinine <1.52 mg%), and 480

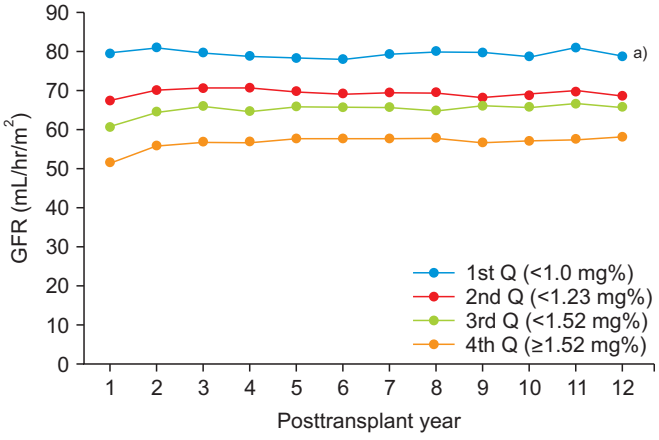

Fig. 1. Mean glomerular filtration rate (GFR) of functioning graft by quantile group of serum creatinine quantile at 1-month posttransplant. Q, quartile. [a)]P<0.05 vs. each other.

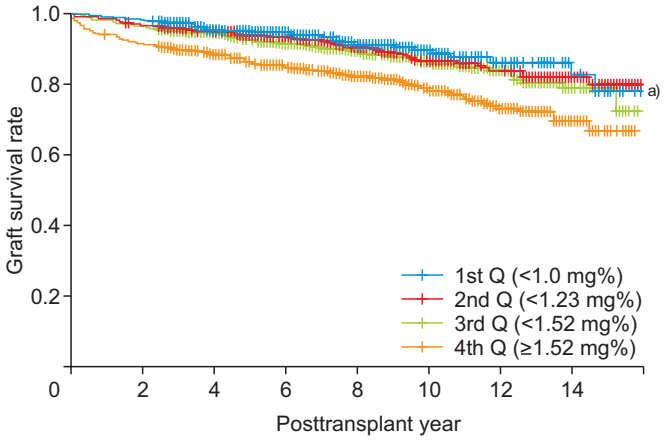

Fig. 2. Graft survival rate by quantile group of serum creatinine quantile at 1-month posttransplant. Q, quartile. [a)]P<0.05 vs. others.

in the 4th Q (serum creatinine ≥1.52 mg%). With respect to high-risk transplantation, there were 582 (30.7%) cases of ABO-incompatible transplants and 170 (9.0%) cases of retransplantation, including four cases of three transplants and one case of four transplants. Finally, 286 (15.1%) recipients underwent plasmapheresis at least one time (range, 1–7 times).

Serial changes of GFR for each group by year are shown in Fig. 1. The 1st Q group showed statistical significance compared to all other groups each year. Within the entire sample, there were 251 graft failure events in the 1st Q group with 35 (8.8%) cases, 2nd Q with 54 (11.3%) cases, 3rd Q with 63 (12.9%) case, and 4th Q with 99 (20.6%) cases. The graft survival rate of the 1st Q was significantly higher than that of all the other groups at posttransplant

Table 1. Multiple Cox regression analysis for graft failure

Variable	B	P-value	Hazard ratio	95% Confidential interval
Serum creatinine, posttransplant 1 month		0.023		
2nd Q (<1.23 mg%)	0.116	0.606	1.123	0.722–1.748
3rd Q (<1.52 mg%)	0.220	0.345	1.246	0.790–1.965
4th Q (≥1.52 mg%)	0.585	0.013	1.795	1.133–2.843
Retransplantation	0.136	0.530	1.146	0.749–1.754
Pretransplant desensitization	−0.264	0.461	0.768	0.382–1.547
ABO-incompatible	0.297	0.459	1.346	0.613–2.957
Recipient age (yr)		0.049		
25–34	−0.226	0.512	0.798	0.406–1.568
35–44	−0.567	0.101	0.567	0.288–1.117
45–54	−0.326	0.326	0.722	0.377–1.383
55–64	0.002	0.996	1.002	0.515–1.950
≥65	0.255	0.572	1.291	0.533–3.129
Donor age (yr)		0.109		
25–34	−0.017	0.951	0.983	0.567–1.703
35–44	−0.395	0.167	0.674	0.384–1.180
45–54	−0.146	0.586	0.864	0.511–1.462
≥55	0.148	0.597	1.159	0.670–2.005
Acute rejection within 1 year	0.651	0.000	1.918	1.355–2.715
HLA mismatching, zero-mismatching[a)]		0.015		
1–3 Ag mismatching	0.302	0.242	1.352	0.816–2.240
4–6 Ag mismatching	0.665	0.014	1.944	1.146–3.298
Donor sex, female	0.323	0.016	1.382	1.063–1.796
Recipient sex, female	0.126	0.403	1.134	0.844–1.523
Donor type, living related[a)]		0.000		
Living unrelated	0.109	0.579	1.116	0.758–1.643
Deceased	0.737	0.000	2.089	1.457–2.996

Q, quartile; HLA, human leukocyte antibody.
[a)]Reference value.

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every year (Fig. 2).

In the multivariate analysis, high serum creatinine level at 1-month posttransplant (4th quantile) is an independent risk factor for graft failure with a hazard ratio of 1.799 (P=0.013). Posttransplant 1-month serum creatinine (P=0.023), recipient age (P=0.049), HLA zero-mismatching (P=0.015), acute rejection within 1 year (P<0.001), and a living related donor (P<0.001) were shown to be statistically significant factors (Table 1).

DISCUSSION

This study showed that the 1-month posttransplant serum creatinine level is a strong predictor of long-term graft function for patients who had transplants after 2000. Moreover, the results reveal that some classical risk factors, such as HLA mismatching, donor type, and acute rejection within 1 year, affect long-term graft function. As the risk of early renal graft failure has substantially decreased over recent years, it is more critical to improve long-term graft function and the prevention of graft failure. It is also essential to find predictors of graft function to optimize the posttransplant care plan, including immunosuppressant combinations [13].

Previous studies have shown that 1-year posttransplant serum creatinine levels and GFR were strong predictive factors of long-term graft outcome [2-4]. However, these studies do not reflect the current state of KT as they were published one to two decades ago. There have been many changes in the transplantation field. High immunologic risk transplantation has been successfully performed, including ABO-incompatible transplantation. The finding of this study that renal and graft failures was not influenced by advanced donor age was unexpected and is inconsistent with that of a previous report [14]. A study by De la Vega et al. [15] found that kidneys from living donors aged 50 years or older had a lower GFR pre- and posttransplant. Our study showed that only the recipient's age was related to graft failure.

This study is meaningful since it evaluated the long-term graft function of a substantial study population, including high-risk transplant patients (752/1,895, 39.6%). However, our study has some limitations. First, this is a retrospective single-institution study. The patient treatment protocol, including the immunosuppressive drug regimen, has changed during the study period. In summary, the 1-month posttransplant serum creatinine level is the most relevant parameter in predicting long-term graft function. It is influenced by recipient age, acute rejection, and donor type.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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