Long-term Progression Pattern of Chronic Allograft Dysfunction Among Kidney Transplant Recipients

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Introduction. There is little data about the pattern of disease progression in kidney transplant recipients with chronic allograft dysfunction (CAD). Extrapolating the current classification of chronic kidney disease for CAD, we studied the pattern of progression of CAD in 5 stages among our kidney transplant recipients.
Materials and Methods. We performed a retrospective cohort study on 214 kidney transplant recipients with CAD. The selection criteria were a functioning kidney allograft for at least 1 year after transplantation and a progressive decline in allograft function. An event history analysis in survival data was carried out based on the stages of CAD at baseline and the end of the study.
Results. At the beginning of the study, 54.7% of the patients had CAD stage 1; 37.9%, stage 2, and 7.5%, stage 3. At the end of study, 10.3% were in stage 2; 39.7%, stage 3; 23.4%, stage 4; and 26.6%, stage 5. Patients with CAD stage 5 were 17.1% of those in stage 1, 32.1% of those in stage 2, and 67.7% of those in stage 3 at baseline. There was a significant correlation between stage of CAD at the beginning of the study and the stage of CAD at the end ($r = 0.465$, $P < .001$).
Conclusions. Because the decline in kidney allograft function was relatively faster in advanced stages of CAD, strategies to increase allograft survival by improving the baseline level of allograft function can be more effective than strategies to slow down progression of advanced stages of CAD.

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INTRODUCTION

Graft loss due to chronic allograft dysfunction (CAD) is a major concern in kidney transplant recipients. Introduction of new immunosuppressive medications has led to improvement of short-term kidney allograft survival. However, long-term survival rates have not been improved substantially.[1] There is little information about the CAD progression in this patient population. One of the reasons is that we need special data to show history of disease progression, which is called *multistate data*.[2,3] The multistate data analysis is one method of survival analysis that helps us to understand the process of chronic diseases.[2-4]

In this study, we recoded history of disease progression in kidney transplant recipients with CAD. We hypothesized that the Kidney Disease Quality Outcome Initiative (KDOQI) classification of chronic kidney disease (CKD) is applicable to these patients, and applied this staging system to determine the pattern of disease progression per stage of kidney dysfunction in this group of patients. The cured rate of pass from one stage to the next stage and death-censored graft loss were estimated, and probability stage-survival and overall death-censored graft survival were determined

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in these patients. The effect of predictability for kidney function at the initiation of CAD process (considered as assessing kidney function in the first year) on probability stage-survival and overall death-censored graft survival was assessed in these patients.

MATERIALS AND METHODS

Patients

We performed a retrospective cohort study on 214 patients with CAD among 1534 kidney transplant recipients at Urmia University Hospital from 1997 to 2005. The selection criteria were a functional renal allograft (patients who did not need permanent dialysis) for at least 1 year after transplantation and a progressive decline in allograft function.

Kidney Function Staging

The Cockcroft-Gault estimation of creatinine clearance was used to estimate kidney function.[5] The patients had regularly been visited at the clinic during the study period by nephrologists. They were staged using the values of the estimated glomerular filtration rate (GFR) based on the KDOQI classification of chronic kidney disease. In this classification scheme, stage 1 (GFR, ≥ 90 mL/min/1.73 m^2) indicates kidney damage with normal or increased GFR; stage 2 (GFR, 60 mL/min/1.73 m^2 to 89 mL/min/1.73 m^2), kidney damage with mildly decreased GFR; stage 3 (GFR 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2), moderate kidney disease; stage 4 (GFR 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2), severe kidney disease; and stage 5 (GFR, < 15 mL/min/1.73 m^2), kidney failure.[6]

Disease Progression

The pattern of disease progression was assessed by defining the probability of stage-survival, mean waiting times of progression from one stage to the next one, and death-censored graft loss by the Kaplan-Meier survival analysis. The log-rank test was used to compare the probability of stage-survival and death-censored graft survival between the groups.

RESULTS

Patients

Of 1534 kidney transplant recipients, 214 fulfilled the CAD criteria, of whom 152 (71%) were men and 62 (29%) were women. The mean time of starting CAD process (to enter the CAD stage 1) was 9.8 ± 2.4 months posttransplant. The mean of patient-visits during the follow-up period was 32.1 ± 9.9 times (range, 12 to 56 times).

Kidney Function Stages

At the beginning of the study, 117 patients (54.7%) were in stage 1, 81 (37.9%) in stage 2, and 16 (7.5%) in stage 3 of chronic kidney disease, and no one was in stages 4 and 5. At the end of the study, none of the patients could be categorized in stage 1, while 22 (10.3%) were in stage 2, 85 (39.7%) in stage 3, 50 (23.4%) in stage 4, and 57 (26.6%) in stage 5. Patients in stage 5 were 20 (17.1%) from stage 1, 26 (32.1%) from stage 2, and 11 (67.7%) from stage 3 at the beginning of the study (Table 1).

The pattern of progression of kidney disease from one stage to the next stage is shown in Table 2.

Table 2. Pattern of Progression of Chronic Allograft Dysfunction (CAD) From One Stage to Next Stage

Baseline CAD Stage	CAD Stage at the End of Study			
	2	3	4	5
1	22 (18.8)	54 (46.2)	21 (17.9)	20 (17.1)
2	0	31 (38.3)	24 (29.6)	26 (32.1)
3	0	0	5 (31.2)	11 (68.8)

Table 1. Stage of Chronic Allograft Dysfunction (CAD) and Follow-up of Kidney Transplant Recipients

CAD Stage	Number of Patients		Mean Follow-up, mo	Patient Visits	Crude Death-censored Graft Loss, %
	Start of CAD	End of Study			
1	117 (54.7)	0	68.6 ± 14.6	32.7 ± 10.0	20 (17.1)
2	81 (37.9)	22 (10.3)	58.7 ± 15.9	32.7 ± 9.1	26 (32.1)
3	16 (7.5)	85 (39.7)	35.3 ± 18.6	24.7 ± 11.0	11 (68.8)
4	0	50 (23.4)	…	…	…
4	0	57 (26.6)	…	…	…
All	214	214	67.3 ± 17.8	32.1 ± 9.9	57 (26.6)

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Most patients reached stage 4 or 5 at the end of the study. There was a significant correlation (nonparametric Kendall's correlation) between stage of CAD at the beginning of the study and the stage of CAD at the end of study (r = 0.465, $P < .001$). Probabilities of stage-survival and death-censored graft survival are shown in Figure 1. The censored and noncensored waiting time observations, rate of progression, and mean, standard error, and median of progression waiting time from stage 1 to 2, 2 to 3, 3 to 4, and 4 to 5 are shown in Table 3. The crude death-censored graft survival and the mean waiting time were 26.6% and 81.7 months, respectively. All of the patients progressed from stage 1 to stage 2 within a mean waiting time of 26.3 months, 88.9% from stage 2 to stage 3 within a mean waiting time of 23.5 months, 55.7% from stage 3 to stage 4 within a mean waiting time of 27.9 months, and 53.3% from stage 4 to stage 5 within a mean waiting time 18.2 months. To examine whether the CAD stage in the start of CAD process can be a predictor of long-term kidney function, we assessed stage-survival probability and death-censored graft survival using the log-rank tests.

Probability Survival From Stage 2 to 3

The mean waiting time for progression from stage 2 to 3 was 23.7 ± 1.1 months (median, 21.3 months) and 23.7 ± 1.2 months (median, 24.1 months) for patients with stage 1 and stage 2 at the start of CAD process, respectively. There was no significant difference between patients with CAD stage 1 and 2 in terms of progression from stage 2 to 3 ($P = .90$). Probability survival curves to pass from stage 2 to stage 3 are shown in Figure 2.

Probability Survival From Stage 3 to 4

The mean waiting time for progression from stage 3 to 4 was 29.3 ± 1.9 months (median, 23.6 months), 28.9 ± 1.7 months (median, 26.3 months) and 18.7 ± 2.5 months (median, 13.3 months) for patients with stage 1, 2, and 3 at the start of CAD process, respectively. Probability survival curves to pass from stage 3 to stage 4 are demonstrated

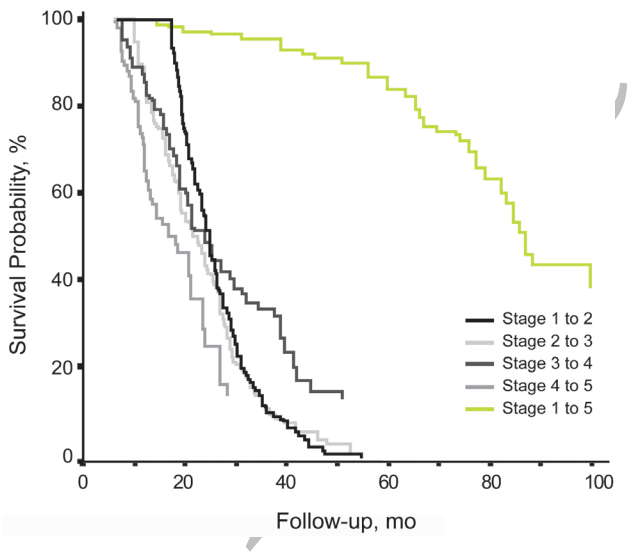

Figure 1. Stage-survival curves and death-censored graft survival.

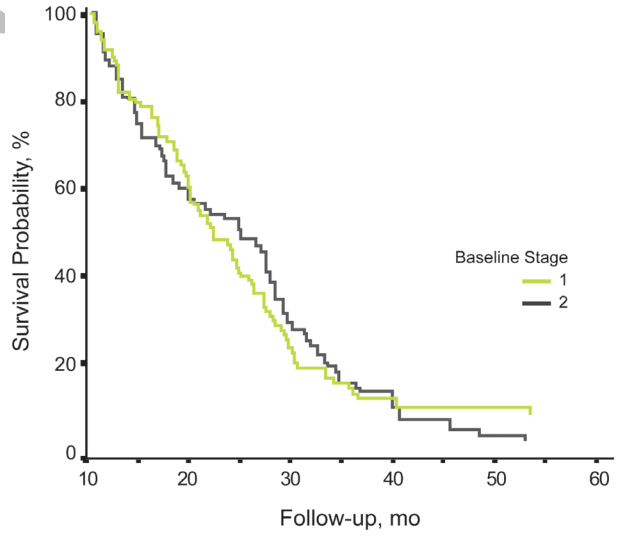

Figure 2. Probability survival curves to pass from stage 2 to 3 by chronic allograft survival stages at the start of the disease process.

Table 3. Waiting Time Censoring and Descriptive Information

Stage Transition	No Censoring	Right Censoring	Total Number of Transitions	Progress Rate, %	Mean Waiting Time (Median), mo
1 to 2	117	0	117	100	26.4 ± 0.7 (24.7)
2 to 3	176	22	198	88.9	23.5 ± 0.7 (22.5)
3 to 4	107	85	192	55.7	27.9 ± 1.2 (24.4)
4 to 5	57	50	107	53.3	18.2 ± 0.8 (18.1)
1 to 5	57	157	214	26.6	81.7 ± 1.8 (85.1)

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in Figure 3. There was a significant difference between patients with CAD stages 1, 2, and 3 in terms of progression from stage 3 to 4 (P = .002). Patients with stage 3 had a shorter waiting time to progress to stage 4.

Probability Survival From Stage 4 to 5

The mean waiting time for progression from stage 4 to 5 was 17.1 ± 1.3 months (median, 14.7 months), 19.9 ± 1.1 months (median, 21.2 months), and 13.3 ± 1.8 months (median, 12.2 months) for patients with CAD stage 1, 2, and 3, respectively. The probability survival curves to pass from stage 4 to stage 5 are shown in Figure 4. There was a significant difference between patients with CAD stages 1, 2, and 3 in terms of progression from stage 4 to 5 (P = .03), with patients with stage 3 having a shorter waiting time to progress to stage 5.

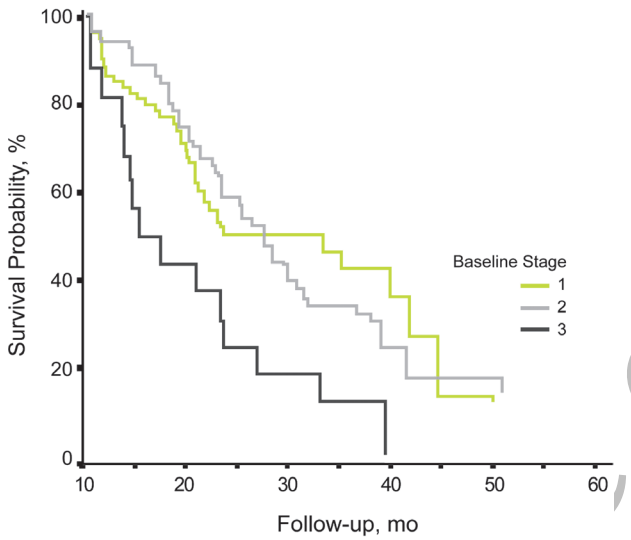

Figure 3. Probability survival curves to pass from stage 3 to 4 by chronic allograft survival stages at the start of the disease process.

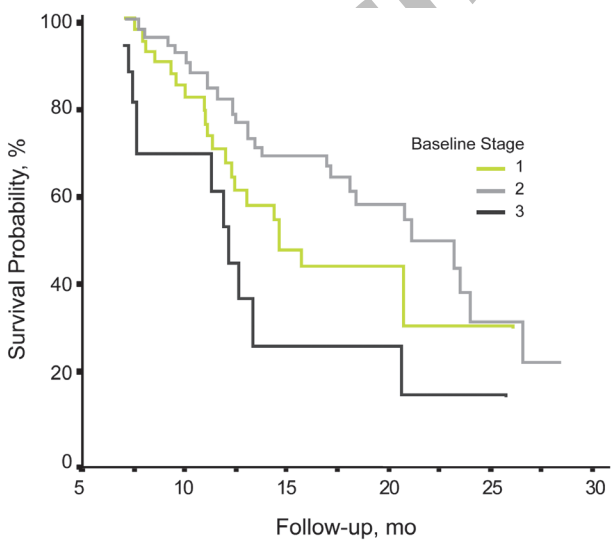

Figure 4. Probability survival curves to pass from stage 4 to 5 by chronic allograft survival stages at the start of the disease process.

Overall Death-censored Graft Survival

The overall death-censored graft survival is depicted in Figure 5. Patients with stage 3 at the beginning of CAD process had a shorter waiting time to progress to stage 5 (P < .001). The mean waiting time to graft loss was 89.5 ± 1.8 months, 76.1 ± 3.1 months, and 35.3 ± 4.5 months in patients with CAD stages 1, 2, and 3, respectively.

DISCUSSION

The most common complication of kidney transplantation is CAD, which, in some cases, leads to graft loss.[16] Although there is a wide intercenter variability, data from the United States indicate that the overall 1-year unadjusted survival of a kidney allograft is approximately 92% for a deceased donor kidney transplant and approximately 96% for a living donor kidney transplant.[8] The excellent short-term outcomes in kidney transplantation have created the need for more meaningful markers of treatment efficacy among recipients with long-term allograft survival. The most common cause of CAD is an incompletely understood clinicopathological

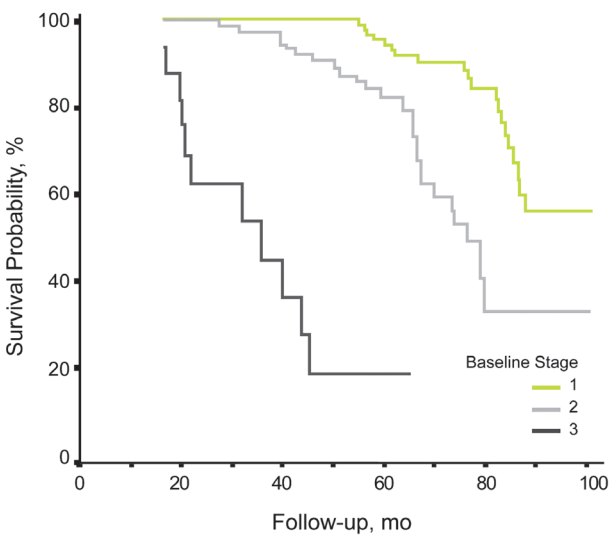

Figure 5. Death-censored graft survival curves by chronic allograft survival stages at the start of the disease process.

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entity, variously called *chronic rejection*, *transplant nephropathy*, *chronic renal allograft dysfunction*, *transplant glomerulopathy*, or *chronic kidney allograft nephropathy*.[9-18] Understanding the pathophysiology and management of CAD is an important issue in kidney transplantation.

The frequency of late allograft loss remains excessive; approximately 7% of kidney transplants fail each year, with approximately half of the losses being due to patient's death and the remainder being due to loss of functioning grafts.[7] In studying the failures that are due to loss of kidney function, transplant population studies have usually examined outcomes such as graft survival and half-life. However, these approaches are limited because they give information only about grafts that have failed completely and do not describe the pattern of progression of allograft dysfunction. Additional information can be gained by looking at the pattern of progression of CAD and changes in function. We describe the alterations in GFR after kidney transplantation among patients with CAD and allograft survival of at least 1 year in our center.

In the present study, we assessed the pattern of progression of CAD through different stages and determined the rate of progression, survival probability per stage, waiting time per stage, and overall survival rate. In our cohort, 26.6% of patients with CAD reached end-stage renal disease during the follow-up period. The 1-, 5-, and 8-year death-censored graft survival were 100%, 85%, and 45%, respectively. Among patients with CAD, the mean, standard error, and median of death-censored graft survival were 81.7 months, 1.8 months, and 85.1 months, respectively. The mean time to initiation of CAD was 9.8 ± 2.4 months. Our results showed that the rate of progression between stages become greater in more advanced stages, which means that the rate of progression from stage 1 to 2 is slower than progression from stage 2 to 3, and so on. This finding is compatible with the hyperfiltration theory in chronic kidney disease. According to this theory, loss of a number of glomeruli leads to hyperfiltration in the remaining glomeruli. This hyperfiltration could destroy the remaining glomeruli and this process becomes more serious when the number of the remaining glomeruli becomes less and less. Thus, CAD is not a linear, but an accelerating process.

CONCLUSIONS

This study describes the change in GFR among transplant recipients with CAD. Because GFR decline after transplantation was relatively faster in more advanced stages of CAD, strategies to increase allograft survival by improving the baseline level of allograft function may be more effective than strategies to slow down the progression of advanced stages of CAD in kidney transplant recipients.

CONFLICT OF INTEREST

None declared.

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