‘Point of No Return (PNR)’ in Progressive IgA Nephropathy:

Significance of Blood Pressure and Proteinuria Management Up to PNR

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Short title:

Point of no return in IgA nephropathy

ABSTRACT

Background: Based on observations of the clinical course of patients with IgA nephropathy (IgAN), D'Amico et al. proposed the concept of the 'point of no return (PNR)', after which progression to end-stage renal disease (ESRD) becomes inevitable. They reported that the approximate PNR is 3.0 mg/dl serum creatinine (sCr).

Methods: To confirm the PNR and to clarify the factors affecting the deterioration of renal function in IgAN patients, we analyzed the sequential data of those with 1.2≦ sCr <2.0 mg/dl at renal biopsy. Forty-seven patients with moderate to severe histological lesions and whose 36 month follow-up did not require renal replacement therapy, were enrolled in this study.

Results: None of the patients who once exceeded a sCr value of 2.0 mg/dl could return to below 2.0 mg/dl during the observation period. Kaplan-Meier analysis revealed that the renal outcome of patients with average values of MBP ≧102 mmHg and/or UP score ≧2.0 until 2.0 mg/dl sCr was significantly poor. Multivariate analysis using the Cox proportional hazards model, identified only MBP and UP during the course until 2.0 mg/dl sCr as independent prognostic factors for ESRD, having hazard ratios of 2.56 (per 10mmHg; 95% CI, 1.08 to 6.05) and 4.37 (per 0.5 point; 1.36 to 14.1), respectively.

Conclusions: We confirmed PNR as a sCr level of 2.0 mg/dl (equivalent to estimated glomerular filtration rate of 30 to 35 ml/min/1.73m^2) during the course of IgAN in Japan. The management of both BP and UP until sCr has reached PNR is essential to arrest the progression to ESRD in IgAN.

KEY WORDS:

end-stage renal disease,

hypertension,

IgA nephropathy,

point of no return,

proteinuria

INTRODUCTION

IgA nephropathy (IgAN) is the most widespread type of glomerulonephritis, and it has a relatively poor renal outcome with 30 to 40 % of patients reaching end-stage renal disease (ESRD) within 20 years (1, 2). The clinical course of IgAN ranges from spontaneous remission to rapid progression, and clinical factors such as hypertension, heavy proteinuria, and impaired renal function at presentation are considered as the determinant prognostic predictors of patients with this disease (3-5).

D'Amico et al. (6) first proposed the concept of 'point of no return (PNR)' in the irreversible clinical progression of IgAN. Based on the long-term observations of seven IgAN patients in whom a slow disease progression abruptly became rapid, they described the PNR as a sCr value of approximately 3.0 mg/dl. Schöll et al. (7) recently confirmed the same value for the PNR in 115 patients with chronic IgAN in the German Glomerulonephritis Therapy Study. The concept of PNR is important to determine a suitable treatment strategy for IgAN patients during follow-up, but little is understood about differences in race, gender or other factors that might affect the PNR.

We conducted a retrospective long-time follow-up cohort study of IgAN, and verified the PNR among Japanese patients. We additionally studied the relationship between variations in predictors during the course, especially until sCr reaches the supposed PNR, and disease progression.

SUBJECTS AND METHODS

Selection of subjects

Between April 1985 and September 2002, 270 patients were diagnosed with IgAN by renal biopsy at our hospital. Two-hundred and thirty-seven of them were followed-up for over six months. The distribution of the sCr levels at the final observation period (range, 6 - 237 months) in these patients revealed that the number of patients with stable renal function (sCr < 2.0 mg/dl at final observation period) and with ESRD were 197 and 35, respectively. In contrast, only five patients remained in the range of 2.0≦ sCr <6.0 mg/dl. Based on these findings, we initially surmised that the PNR is in the vicinity of 2.0 mg/dl sCr.

IgAN patients with normal renal function at renal biopsy take a long time to progress to ESRD. We therefore selected patients with sCr ≧1.2 mg/dl or estimated glomerular filtration rate (GFR) of ≦75 ml/min/1.73m^2, but who did not exceed the sCr of 2.0 mg/dl at renal biopsy. All of them were contingent upon an observation period of over 36 months without renal replacement therapy to assess the factors affecting the long-term clinical course of IgAN. To align the histopathological conditions of the subjects, we also selected patients with moderate to severe histological lesions that were equivalent to relatively poor (grade III) or poor (grade IV) prognoses according to the Japanese clinical guidelines for IgAN (8). We ultimately selected 47 patients for this study who satisfied these conditions.

Collection and evaluation of data

We measured the blood pressure (BP), urinary findings and sCr determined using an ambulatory BP machine, dip-stick test and blood samples, respectively. All of the sCr values were measured using Jaffé method in this study. These data were collected once every three months between over the first year, once every half year between one and ten years, then once every year over ten years after IgAN had been diagnosed. The qualitative reactions of urinary protein (UP) and urinary occult blood (UOB) were converted into scores as follows: (-) and (±) to 0 points, (1+) to 1 point, (2+) to 2 points, (3+) to 3 points. The averages of BP, UP, and UOB scores were calculated by leveling all of these data.

Hypertension was defined as systolic BP (SBP) ≧140 mmHg, and/or diastolic BP (DBP) ≧90 mmHg, or the use of anti-hypertensive medication. Mean BP (MBP) was calculated as (SBP + 2×DBP) / 3. The estimated GFR was calculated using a prediction equation of the Modification of Diet in Renal Disease (MDRD) Study that uses sCr concentration, demographic characteristics (age, sex, and ethnicity), and other serum measurements (urea nitrogen and albumin concentrations):

GFR (ml/min/1.73m^2) = $170 \times [\text{sCr}]^{-0.999} \times [\text{Age}]^{-0.176} \times [\text{urea nitrogen (mg/dl)}]^{-0.170} \times [\text{albumin (g/dl)}]^{+0.318} \times [0.762 \text{ if patient is female}]$ (9).

Statistical analysis

All continuous variables are presented as means ± standard deviation (SD). We

compared clinical parameters of the two groups at renal biopsy by the Mann-Whitney U test for non-parametric variables or by the chi-square test for categorical data. We also compared the average values of the MBP and UP scores of the two groups by Welch's t-test. Renal survival rates between high and low MBP or UP score groups were analyzed by the Kaplan-Meier method, and differences in survival curves were analyzed by the log-rank test. We used the Cox proportional hazards model to assess the impact of multiple covariates for renal prognosis. All of the independent variables used in multivariate analyses are expressed in a categorical (such as absent/present, coded as 0/1) or quantitative form. Gender was regarded as a categorical variable, whereas age, MBP, proteinuria, GFR, UP and UOB scores were regarded as quantitative variables. The results of the multivariate analyses are expressed as hazard ratios with 95% confidence intervals (CI) and a P-value.

A P-value below 0.05 was considered statistically significant in all analyses, which were performed by the Statistical Package for the Social Sciences (SPSS) for Windows, Advance Statistical Release 11.0 (SPSS Inc. Chicago, IL, USA).

RESULTS

Patient's characteristics

We investigated data from 22 male and 25 female patients aged 44.4±14.8 and 39.8±7.80 years. The mean body weight of all patients was 58.5±9.72 kg (male,

64.3±9.55 kg; female, 53.5±6.66 kg), and the mean body mass index (BMI) was 22.8±2.74 (male, 23.6±3.01; female, 22.1±2.34). Sixteen (34.0%), 10 (21.3%) and 17 (36.2%) patients were initially treated with steroids, angiotensin-converting enzyme (ACE) inhibitors and by tonsillectomy, respectively. Intravenous pulse therapy was first introduced to only three of the 16 patients treated with steroids. Fourteen patients did not receive any of these initial treatments. Anti-hypertensive medications were administrated to patients with hypertension at the attending physician's discretion during the observation period.

Cross-sectional comparison

We compared a cross-section of the clinical parameters of the two groups divided by the sCr value (cut-off: 2.0 mg/dl) at the final observation period (Table 1). Twenty-six of the 47 IgAN patients (group A) exceeded a sCr value of 2.0 mg/dl at the final observation period while the remainder (n=21, group B) were below 2.0 mg/dl. The mean observation periods of groups A and B were 94.8±55.8 and 113.8±51.8 months, respectively. The level of MBP, number of patients with hypertension, renal function and amounts of proteinuria at renal biopsy did not significantly differ between the groups.

Survey of PNR

Figure 1 shows the entire sCr courses of the studied patients. The mean

observation period was 103.3±54.3 (36 – 237) months. None of the patients who once exceeded the sCr level of 2.0 mg/dl could return to a value below 2.0 mg/dl during the observation period. The sCr value of 2.0 mg/dl was equivalent to the estimated GFR, calculated by the MDRD Study prediction equation, of 30 to 35 ml/min/1.73m^2 in these patients. From the viewpoint of the sCr courses, the patients could be categorized into three groups: short-term renal survivors who exceeded 2.0 mg/dl sCr within seven years and progressed to ESRD (n=18; straight lines), long-term renal survivors whose sCr stabilized at the level of less than 2.0 mg/dl throughout seven years and over (n=13; large broken lines), and other patients with a clinical course that could not be categorized or who were observed for less than seven years and did not develop ESRD (small broken lines). The level of MBP at renal biopsy did not significantly differ between short-term progressive and long-term stable groups, but the average values of MBP before sCr had reached 2.0 mg/dl were significantly lower in the stable group compared with the progressive group (96.4±7.0 vs. 105.3±8.3 mmHg, p=0.004). As with MBP, the average value of the UP score until reaching 2.0 mg/dl sCr in the stable group was significantly lower than that in the progressive group (1.11±0.64 vs. 2.63±0.37 points, p<0.001).

Effect of BP and UP during the course on renal survival

We examined the relationship between the MBP or UP levels and renal survival in 47 IgAN patients. Because the respective mean MBP and UP scores at renal biopsy were 102.6±13.2 mmHg and 2.43±0.68 points, we compared the renal survival rates of

the two groups based on those values. Kaplan-Meier analysis revealed that the renal survival rate was significantly higher among patients with an average MBP value of <102 mmHg (equivalent to 135/85 mmHg), than ≧102 mmHg until reaching 2.0 mg/dl sCr (p= 0.041, log-rank test; Figure 2). Moreover, none of the patients with an average UP score of <2.0 points (equivalent to < 1.0 g/day proteinuria) proceeded to ESRD (p <0.001, log-rank-test; Figure 2). The percentage of patients with an average MBP value of ≧102 mmHg was significantly less in group B than that in group A (14.3 % vs. 53.8 %, p = 0.005). The number of patients with an average UP score of ≧2.0 was only six out of 21 in group B; meanwhile all 26 patients exceeded the value in group A. With regard to anti-hypertensive therapy, the percentage of the patients treated with ACE inhibitors at initial therapy or during the course of the disease was significantly higher in group B than that in group A (61.9 % vs. 26.9 %, p = 0.016).

The Cox proportional hazards model included age, gender and three established prognostic factors (MBP, proteinuria, and estimated GFR) at renal biopsy, as well as three factors (MBP, UP score, UOB score until 2.0 mg/dl sCr) during the course of the disease to assess the risk of ESRD. Univariate regression analysis revealed that proteinuria at renal biopsy, average value of MBP, UP and UOB scores during the course until 2.0 mg/dl sCr were associated with poor renal outcome. In contrast, only the average MBP and UP scores during the course until reaching 2.0 mg/dl sCr were identified as independent prognostic factors with multivariate analysis, and those hazard ratios were 2.56 (per 10 mmHg; 95% CI, 1.08 to 6.05) and 4.37 (per 0.5 point; 95% CI, 1.36 to 14.1), respectively (Table 2).

DISCUSSION

This present study revealed that none of the patients who once exceeded a sCr value of 2.0 mg/dl could return to below 2.0 mg/dl during the observation period. Therefore, the PNR for Japanese IgAN patients might be around a sCr value of 2.0 mg/dl. Moreover, high levels of BP and UP throughout the course until sCr had reached 2.0 mg/dl were independent risk factors that significantly affected the renal prognosis.

D'Amico et al. (6) found 17 patients whose renal functions stabilized for a long time despite having impaired renal function from the beginning (sCr levels between 1.5 to 2.3 mg/dl), and a final sCr value that did not exceed 3.0 mg/dl. They also found seven more patients whose courses of renal disease suddenly and rapidly deteriorated after the sCr value exceeded 3.0 mg/dl, and they called this value the 'PNR'. Schöll et al. (7) followed 115 patients, and confirmed that the PNR was 3.0 mg/dl sCr. From the viewpoint of the sCr values, they suggested a progressive segment with fast and continuously increasing sCr, a chronically stable segment with constantly normal or up to 3.0 mg/dl of sCr that remained elevated for years, and an early restitution segment with a short-term increase of sCr and a rapid decrease to the normal range. We also identified patients with progressive (n=18) or chronically stable (n=13) courses, but none of the patients were suited to early restitution.

The PNR at a sCr level of 2.0 mg/dl found in this study differed from the published findings from Italy (6) and Germany (7). This might be caused by differences in the physical constitution between Japanese and European peoples. The levels of creatinine produced intrinsically correlate with the amounts of muscle in the body. In

fact, the sCr courses of some patients were relatively slow between the level of 2.0 and 3.0 mg/dl as shown Figure 1, and these patients weighed more than the mean value of the 47 patients. The sCr value of 2.0 mg/dl was equivalent to the estimated GFR, calculated by the MDRD Study prediction equation, of 30 to 35 ml/min/1.73m^2 in this study. The PNR might be presumed as being at the same level worldwide if physical constitution and ethnicity are taken into account.

Our previous study of 38 Japanese patients with impaired renal function at renal biopsy and with various underlying renal diseases including eight with IgAN, also reached the PNR at a sCr value of 2.0 mg/dl (10). The PNR of all chronic renal diseases might be the same with respect to the sCr level, and it might indicate an interchange point from the process of disease-specific progression to the final common pathway that results from the glomerular hyperfiltration of residual nephrons. Further studies will be needed to confirm the PNR in various renal diseases as well as in IgAN.

Many multivariate analyses have shown that the clinical prognostic factors for IgAN are hypertension, heavy proteinuria, and elevated sCr at presentation (3, 4). In some studies, however, predictors such as hypertension (11-14) and proteinuria (12, 15) that were significant in univariate analysis were not so in multivariate analysis. This discrepancy was mainly attributable to the study subjects being at different stages of the disease, especially if the correlation between hypertension and the level of sCr at presentation was significant. Meanwhile, recent studies have indicated that hypertension and proteinuria are more powerful predictors during follow-up than at the beginning of the observation period (16-18).

We selected patients who were at relatively similar stages of disease, especially in

consideration of renal function at the beginning of observation period (between 1.2 to 2.0 mg/dl sCr) and histological lesions (Grade III and IV according to the Japanese guidelines), to minimize lead-time bias (13). We also excluded patients who were followed-up for less than 36 months to more precisely assess the clinical factors during the course of the disease. We did not find any differences in the predictors at renal biopsy when we cross-sectionally compared patients with stable and progressive clinical courses. In addition, multivariate analysis could not determine the significance of high BP or UP values at renal biopsy as a risk for poor renal outcome. In contrast, high BP and UP levels during follow-up, until sCr reached 2.0 mg/dl, were significant independent risk factors for ESRD. High BP and UP levels notably affected the prognosis of IgAN, even when these factors were assessed only during the period until sCr reaches the PNR. This finding is very important when considering treatment strategies that focus on the term until PNR and control BP and UP levels. Two recent studies (15, 19) have indicated that obvious microscopic hematuria is also a prognostic factor of IgAN. We found that the UOB score was a significant predictor in univariate, but not in multivariate analysis. This was due to the relatively close correlation between the UP and UOB findings (r=0.55, Pearson's correlation coefficient; data not shown).

We could not refer to the contributing factors that define the difference between the stable and progressive clinical courses. Some factors such as treatment intervention or predisposing factors of patients might have affected the clinical courses. In fact, the percentage of the patients who had received anti-hypertensive therapy with ACE inhibitor is higher in group A, than that in group B. However, we could not assess the

more accurate effect of ACE inhibitor on the BP and UP control during the observation period because of this small number and retrospective study. For predisposing factors, Li et al. (20) indicated that IgAN patients with a family history of hypertension had a poor renal survival rate according to Kaplan-Meier analyses, and a family history of hypertension was a significant predictor of poor renal prognosis according to multivariate analysis. In our study, the proportion of patients with a family history of hypertension was higher in the group whose course was progressive, rather than stable (66.7% vs. 30.8%), but the difference was not statistically significant. This might be caused by the small sample size in our study. Further studies should also focus on the association between a family history of hypertension and disease progression.

In conclusion, we confirmed PNR at a sCr level of 2.0 mg/dl (equivalent to estimated GFR of 30 to 35 ml/min/1.73m^2) during the course of IgAN in Japan. Both BP and UP must be managed before sCr reaches the PNR to arrest the progression to ESRD in IgAN. Further studies are required to confirm the PNR in a larger sample cohort and to clarify the effect of treatment on renal function, BP, and proteinuria until the level of sCr reaches the PNR.

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Table 1. Cross-sectional comparison of clinical parameters at renal biopsy between two groups

	group A * (n = 26)	group B * (n = 21)	P value **
Age (years)	40.0 ± 10.7	44.4 ± 12.7	0.210
Sex (M / F)	12 / 14	10 / 11	0.920
MBP (mmHg)	103.5 ± 14.0	101.6 ± 12.7	0.628
Number of hypertension (%)	10 (38.5 %)	8 (38.1 %)	0.980
Serum albumin (g/dl)	3.63 ± 0.43	3.65 ± 0.66	0.893
Serum urea nitrogen (mg/dl)	21.3 ± 5.83	18.7 ± 4.69	0.195
sCr (mg/dl)	1.30 ± 0.25	1.17 ± 0.21	0.069
Estimated GFR (ml/min/1.73m^2)	57.2 ± 14.9	62.2 ± 12.9	0.231
Proteinuria (g/day)	2.84 ± 1.66	2.30 ± 1.60	0.280

* group A, sCr over 2.0 mg/dl at final observation; group B, sCr below 2.0 mg/dl at final observation

** Data compared by Mann-Whitney U test and chi-square test.

Table 2. Multivariate analysis of prognostic factors during development to ESRD in 47 IgAN patients

Variables		Hazard ratio	95% CI	P value
At renal biopsy				
Age	(per 10 years old)	1.31	(0.77 - 2.22)	0.318
Male	(vs. female)	1.80	(0.32 - 10.1)	0.504
MBP	(per 10 mmHg)	1.03	(0.61 - 1.74)	0.901
Proteinuria	(per 0.1 g/day)	1.29	(0.73 - 2.26)	0.380
Estimated GFR	(per 10 ml/min/1.73m^2)	0.57	(0.28 - 1.17)	0.124
Until 2.0 mg/dl sCr				
MBP	(per 10 mmHg)	2.56	(1.08 - 6.05)	0.032*
UP score	(per 0.5 points)	4.37	(1.36 - 14.1)	0.013*
UOB score	(per 0.5 points)	0.73	(0.47 - 1.13)	0.159

LEGENDS TO FIGURES

Figure 1. Whole sCr courses of 47 IgAN patients during observation periods.

Straight and large broken lines indicate patients with progressive (n=18) and stable (n=13) clinical courses, respectively. Small broken lines indicated patients with clinical courses that could not be categorized or with observation periods of less than seven years without ESRD.

Figure 2. Effect of MBP and UP scores until reaching 2.0 mg/dl sCr on renal survival.

MBP: asterisk (*) indicates statistical significance by log-rank test ($p= 0.041$).

UP score: asterisk (*) indicates statistical significance by log-rank test ($p< 0.001$).

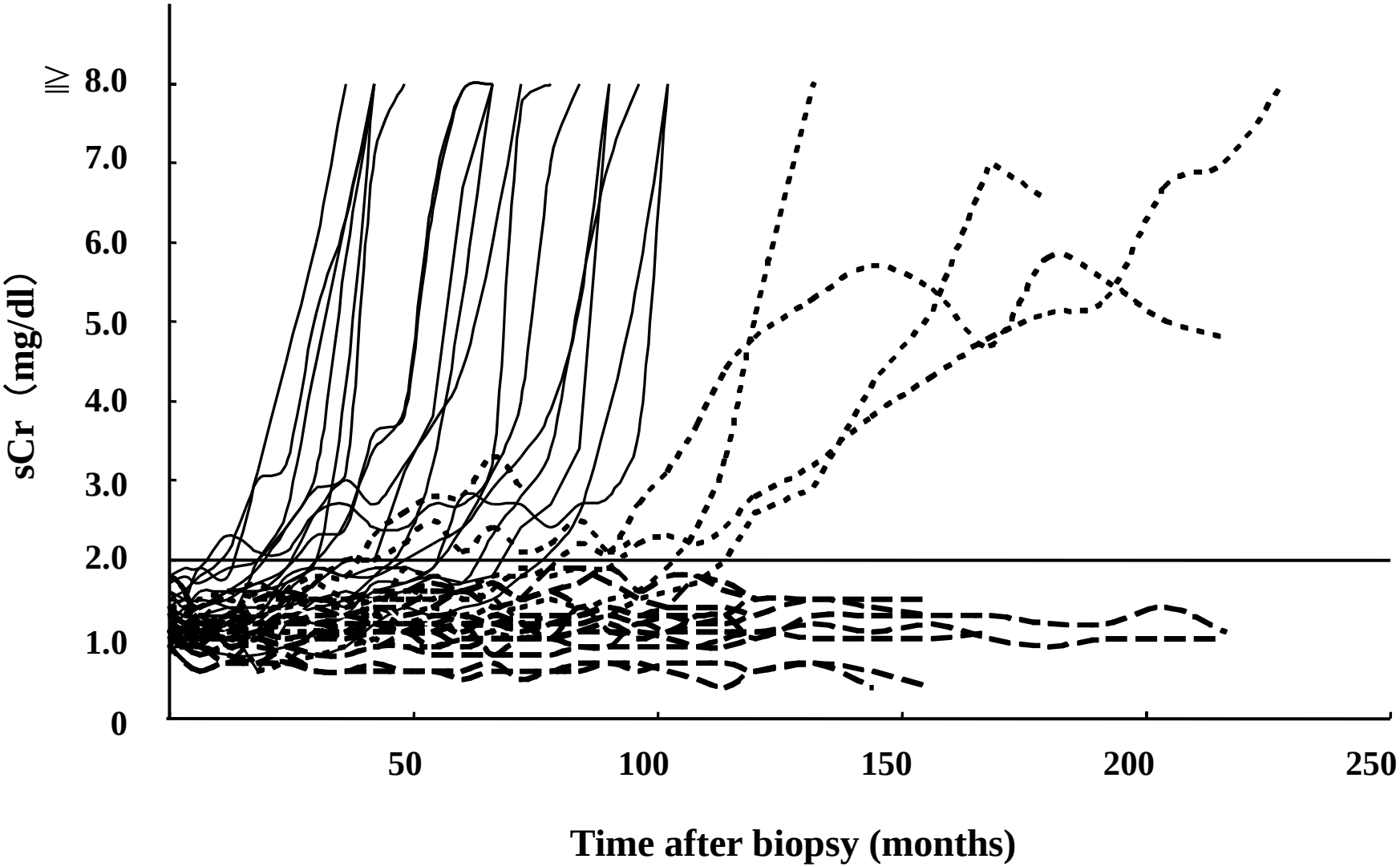
≧ 8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
sCr（mg/dl）
50
100
150
200
250
Time after biopsy (months)

Figure 1

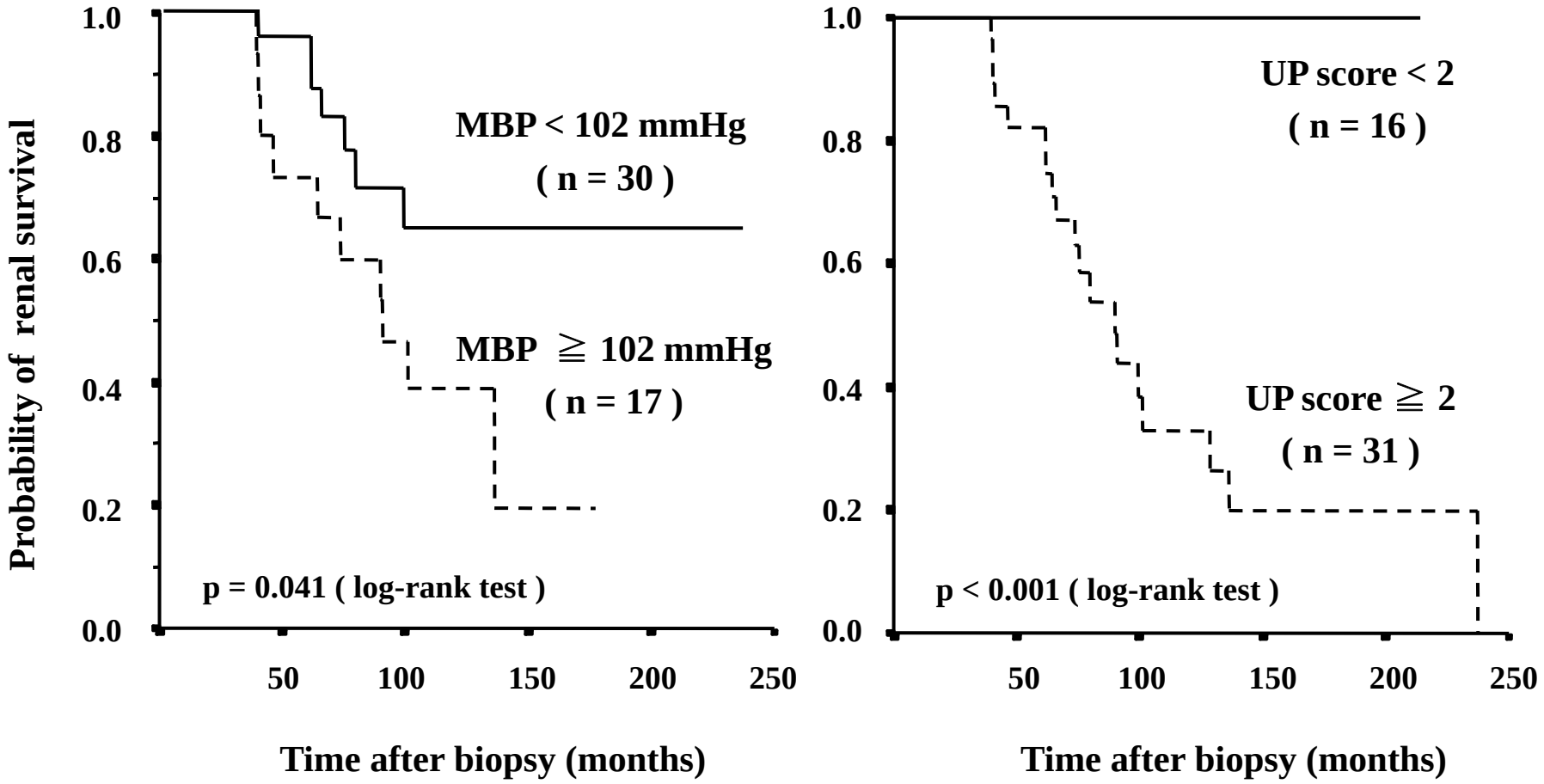
Probability of renal survival
1.0
0.8
0.6
0.4
0.2
0.0
MBP < 102 mmHg
(n = 30)
MBP ≧ 102 mmHg
(n = 17)
p = 0.041 (log-rank test)
50
100
150
200
250
Time after biopsy (months)
UP score < 2
(n = 16)
UP score ≧ 2
(n = 31)
p < 0.001 (log-rank test)
Time after biopsy (months)

Figure 2