MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS AND EFFECT OF TREATMENT IN PATIENTS WITH IGA NEPHROPATHY

Hiroyuki Komatsu, M.D.,[1] Shouichi Fujimoto, M.D., [1] Seiichiro Hara, M.D., [1] Hiroyuki Nakao, Ph.D., [2] Yuji Sato, M.D., [1] Kazuhiro Yamada, M.D., [1] Tanenao Eto, M.D. [1]

[1]First Department of Internal Medicine and [2]Department of Public Health,

Miyazaki Medical College, University of Miyazaki, Miyazaki, Japan

Corresponding author:

Hiroyuki Komatsu, M.D.

First Department of Internal Medicine,

Miyazaki Medical College, University of Miyazaki

5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan.

Tel.: 81-985-85-0872

Fax: 81-985-85-6596

E-mail: hkomatsu@fc.miyazaki-med.ac.jp

ABSTRACT

Background: Although the clinical and histological prognostic factors of IgA nephropathy have been investigated in detail, the value of treatment in terms of renal outcome is not well understood.

Methods: We examined data from 237 patients with IgA nephropathy (age 31.4±13.5 years, mean ± SD) who had been followed-up for at least six months (follow-up periods, 62.3±45.5 months). We initially tested the significance of prognostic factors (age, sex, systolic blood pressure, proteinuria, serum creatinine, and histological severity) and treatment strategies (steroid therapy, renin-angiotensin system inhibitors and tonsillectomy) on renal outcome with univariate analysis, then evaluated the findings using the Cox proportional hazards model.

Results: Univariate and multivariate analyses showed that among the prognostic variables, a high level of serum creatinine at renal biopsy, large amounts of proteinuria, and extensive histological injury were significant risk factors for end-stage renal failure. Kaplan-Meier analysis showed that the renal survival rates associated with these factors were significantly poorer depending on their severity. Univariate analysis revealed that tonsillectomy was the only significant treatment that contributes to the maintenance of renal survival. Moreover, urinary abnormalities disappeared at a significantly higher frequency when patients were treated by tonsillectomy. The Cox proportional hazards model showed that steroid therapy independently contributed to improve renal prognosis in addition to tonsillectomy, and the hazard ratios were 0.26 (95% CI, 0.07 to 0.93) and 0.37 (95% CI, 0.14 to 0.99), respectively.

Conclusion: Steroid therapy and tonsillectomy can independently improve renal outcome in patients with IgA nephropathy.

Key words: IgA nephropathy, Multivariate analysis, Renal prognosis, Tonsillectomy, Steroid therapy

INTRODUCTION

IgA nephropathy (IgAN) is the most frequent form of primary glomerulonephritis diagnosed worldwide (1, 2). Renal outcome is relatively poor, with 30 to 40 % of patients reaching end-stage renal failure (ESRF) within 20 years (3).

Many investigators have used multivariate analysis to determine the clinical and pathological prognostic factors of adult IgAN. These studies have found that hypertension, a large amount of proteinuria, impaired renal function at the time of renal biopsy, and severe histopathological lesions such as glomerulosclerosis or tubulointerstitial fibrosis are generally considered consistent and powerful predictors of poor renal outcome in IgAN (3, 4).

On the other hand, the criteria for treating IgAN are vague because the clinical course varies from spontaneous remission to rapid progression. Although some treatment strategies such as corticosteroids, immunosuppressants, fish oil, renin-angiotensin system inhibitors and tonsillectomy have been applied, the effects of treatment have not

been rigorously determined based on an adequate methodology (5). Two randomized controlled trials (RCTs) that address the effectiveness of corticosteroid therapy (6) and angiotensin-converting enzyme inhibitor (ACE-I) (7) on renal survival in patients with IgAN have been reported. However, RCT evaluations are not easy because IgAN usually progresses slowly, requiring long-term follow-up.

Here, we conducted a retrospective study with a multivariate analysis of 237 patients with IgAN to evaluate the validity of known reported prognostic factors and the value of treatment strategies. Our Cox proportional hazards model included the four main prognostic factors described above, and evaluated the benefits of steroid therapy, renin-angiotensin system inhibitors and tonsillectomy with respect to renal outcome.

METHODS

Patients

Between April 1985 and September 2002, 270 patients were diagnosed with IgAN by renal biopsy at our hospital. The histological diagnosis was based on light microscopy and immunofluorescence findings. None showed evidence of Henoch-Schoenlein purpura nephritis, systemic lupus erythematosus, liver cirrhosis, or other systemic diseases. We selected 237 of these patients who had been followed-up for over six months. The degree of proteinuria and hematuria, determined by qualitative urine test (dip-stick test), and the level of serum creatinine were confirmed from medical records.

Histological Classification

We assessed the histological lesions of the patients with IgAN according to the guidelines presented by the Special Study Group (IgA nephropathy) on Progressive Glomerular Disease in Japan (8). These guidelines separate patients with IgAN into four prognostic groups:

1) Grade 1 (good): Slight mesangial cell proliferation and increased matrix. Absence of glomerulosclerosis, crescent formation and adhesion to Bowman's capsule. No prominent changes in the interstitium, renal tubuli or blood vessels.

2) Grade 2 (relatively good): Slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in less than 10% of all glomerular biopsies. Interstitial and vascular findings the same as those of the good prognosis group.

3) Grade 3 (relatively poor): Moderate, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in 10-30% of all glomerular biopsies. Slight cellular infiltration in the interstitium, except around some sclerosed glomeruli, slight tubular atrophy and mild vascular sclerosis.

4) Grade 4 (poor): Severe, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in over 30% of all glomerular biopsies. When sclerosis sites are totaled and converted to global sclerosis, the sclerosis rate includes over 50% of glomeruli. Some glomeruli also show

compensatory hypertrophy, interstitial cellular infiltration and tubular atrophy and fibrosis. Hyperplasia or degeneration in some intrarenal arteriolar walls.

Definition of Clinical Findings

Hypertension was defined as systolic blood pressure (SBP) ≧ 140 mmHg, and/or diastolic blood pressure (DBP) ≧ 90 mmHg, or use of anti-hypertensive medication. Microscopic hematuria was defined as a positive dip-stick reaction (≧ 1+) and urinary sediment (> 5-10 / high power field). Disappearance of hematuria and/or proteinuria was defined as at least two consecutive negative dip-stick reactions (－ or ±). We defined ESRF as a state requiring some type of continual renal replacement therapy.

Initial Treatment

Oral prednisolone was administered to patients with moderate to severe mesangial cell proliferation and/or crescent formation, as well as interstitial cellular infiltration without a high degree of glomerulosclerosis and interstitial fibrosis. Initial doses were usually 0.5–0.8 mg/kg/day, and gradually tapered to zero over 18 to 24 months. We applied intravenous high-dose methylprednisolone (0.5–1.0 g/day for three days) when histological damage was more obvious, followed by oral prednisolone at an initial dose of 0.5 mg/kg/day. No other immunosuppressive drugs such as cyclophosphamide or azathioprine were used in any of the patients.

Angiotensin receptor blockers (ARB) and/or ACE-I were administered to patients with hypertension and/or moderate proteinuria at the attending physician's discretion. Antiplatelet drugs (dipyridamole, 150–300 mg/day; or dilazep dihydrochloride, 150–300 mg/day) were administered to all patients as initial treatment.

After IgAN was histologically confirmed, we consulted otolaryngologists about indications for tonsillectomy when patients had chronic tonsillitis or a history of macrohematuria with upper respiratory infection. Indications for tonsillectomy were ultimately decided based on otolaryngology findings of chronic hypertrophic tonsillitis or chronic atrophic tonsillitis, or a positive tonsil provocation test. The final decision of tonsillectomy was dependent on the will of the patients themselves. Patients underwent tonsillectomy before starting steroid therapy.

Seventy-eight (32.9 %), 57 (24.1 %) and 104 (43.9 %) patients were treated with steroids, ACE-I/ARB and tonsillectomy, respectively. Intravenous pulse therapy was first introduced to 40 of 78 patients treated with steroids. Twenty-nine patients received corticosteroids (17 by intravenous steroid pulse therapy and 12 by oral prednisolone) in addition to tonsillectomy.

Statistical Analysis

All continuous variables are presented as means ± standard deviation (SD). These continuous variables between patient groups with and without tonsillectomy were

compared using the Mann-Whitney U test. The chi-square test expresses differences in categorical variables between the two groups as percentages. Renal survival rate was analyzed by the Kaplan-Meier method, and the difference in survival curves was 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. Age, sex, histological severity, steroid therapy, ACE-I/ARB and tonsillectomy were regarded as categorical variables, whereas SBP, proteinuria, and serum creatinine were regarded as quantitative variables. The results of the multivariate analyses are expressed as a hazard ratio with 95% confidence intervals (CI), and a P-value.

In all analyses, a P-value below 0.05 was considered statistically significant. All statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) for Windows, Advance Statistical Release 11.0 (SPSS Inc. Chicago).

RESULTS

Univariate Analysis of the Prognostic Factors and Treatment Strategies

Table 1 summarizes the baseline characteristics of the patients. About 20 % of them had hypertension at the time of renal biopsy. The mean level of proteinuria in all patients

exceeded 1.0 g/day. All patients were observed for 62.3±45.5 months on an average, and 30 of them (12.7 %) reached ESRF during the follow-up period.

We examined the effects of two basic characteristics (age, sex), four major clinicopathological parameters (SBP, urinary protein, serum creatinine, and histological lesions) and three treatment strategies (steroid therapy, ACE-I/ARB administration, and tonsillectomy) on renal outcome using the univariate Cox regression model (Table 2). We excluded DBP because of its close correlation with SBP. A high SBP, large amounts of proteinuria, elevated serum creatinine at renal biopsy, and histological injury that indicated a poor prognosis were significant prognostic factors for ESRF. Among treatment strategies, only tonsillectomy had a significantly positive effect on renal survival (hazard ratio, 0.39; 95% CI, 0.18 to 0.86).

Comparison of Renal Survival Rates Stratified by Various Prognostic Factors

Figure 1 shows the renal survival curves of the four prognostic factors that univariate analysis found significant. Eleven and 19 patients reached ESRF in the grade 3 (n = 139) and grade 4 (n = 32), respectively. None of the patients in grade 1 and 2 (n = 66) reached ESRF. Kaplan-Meier analysis revealed that severe histological lesions were associated with a significantly poorer renal outcome ($p < 0.01$, log-rank test); the cumulative renal survival rate at 10 years was 100 % vs. 84.4 % vs. 27.4 % (Figure 1A). The renal outcome of hypertensive patients was significantly poorer than that of normotensive patients ($p < 0.01$, log-rank test); the cumulative renal survival rate at 10

years was 79.9 % vs. 61.6 % (Figure 1B). The renal outcome of patients with larger amounts of proteinuria was significantly poor. Renal survival rates stratified by amounts of <1.0, 1.0–3.0, and ≧3.0 g/day were 98.0 % vs. 62.2 % vs. 39.4 %, respectively (Figure 1C). The renal outcome of patients with elevated serum creatinine at renal biopsy was also significantly poor. Renal survival rates stratified by levels of <1.0, 1.0–1.5 and ≧1.5 mg/dl at 10 years were 87.9 % vs. 66.9 % vs. 23.4 %, respectively (Figure 1D).

Effect of Tonsillectomy on Renal Survival and Urinary Findings

Among the 237 patients, 104 (43.9 %) were treated with tonsillectomy or tonsillectomy combined with corticosteroid and/or ACE-I/ARB. Serum creatinine levels, degree of histological severity, and frequency of concomitant corticosteroid and ACE-I/ARB usage did not differ significantly between the patients treated with and without tonsillectomy. Amounts of proteinuria at renal biopsy were significantly lower in the patients treated with, than without tonsillectomy, but the values exceeded 1.0 g/day in both groups (Table 3).

Kaplan-Meier analysis revealed that the renal survival rate was significantly higher in patients with, than without tonsillectomy ($p = 0.016$, log-rank test; 87.8 and 64.2 % survival at 10 years, respectively) (Figure 2). At the final observation period, urinary abnormalities disappeared at a significantly higher proportion in patients treated with, than without tonsillectomy (31.7 % vs. 16.5 %, $p < 0.01$). Moreover, the proportion of

ESRF tended to decrease in patients treated with, than without tonsillectomy (Table 3).

Multivariate Analysis of Prognostic Factors and Treatment Strategies

The Cox proportional hazards model comprised the same nine variables that were used in the univariate analysis to assess the hazard for ESRF and treatment benefits (Table 4). Like the results of the univariate analysis, elevated serum creatinine at renal biopsy, large amounts of proteinuria, and severe histological injury were independent risk factors for ESRF. In contrast, SBP was not an independent risk factor in this model. To evaluate treatment efficacy, steroid therapy independently contributed to improve renal prognosis in addition to tonsillectomy, and those hazard ratios were 0.26 (95 % CI, 0.07 to 0.93) and 0.37 (95 % CI, 0.14 to 0.99), respectively. Univariate and multivariate analyses revealed that ACE-I/ARB was not a useful treatment strategy to improve renal prognosis.

DISCUSSION

The first aim of the present study was to test the validity of the four main prognostic factors (hypertension, proteinuria, impaired renal function, and severe histological injury), so that we could evaluate treatment effects by adjusting these factors after verification. The results of univariate and multivariate analyses indicated that a large amount of proteinuria, elevated serum creatinine at renal biopsy, and histological injury (grade 4) were significant prognostic indicators of ESRF. Furthermore, the renal

survival rates among the groups stratified according to severity were obviously separate with respect to all three factors. On the contrary, only hypertension at presentation was not an independent prognostic factor in multivariate analysis. D'Amico found a similar discrepancy between the univariate and multivariate results for hypertension (3), as did several others (9-14). One of the presumed causes is the correlation between hypertension and impaired renal function when both parameters estimated at one point in time are included in the multivariate analysis (3, 12, 14). In fact, our data suggested a significant correlation between SBP and serum creatinine level at renal biopsy ($r = 0.30$, $p < 0.01$; Pearson's correlation coefficient; data not shown). Thus, hypertension appears to be a weaker prognostic indicator of ESRF than serum creatinine level. However, blood pressure should also be evaluated because hypertension is a more precocious sign of disease progression than elevated serum creatinine (3, 9, 15-17). Moreover, Bartosik et al. (18) confirmed that persistent hypertension is a more important prognostic indicator than its existence at presentation. In addition, persistent proteinuria is also emphasized as playing a causative role in the progression of IgAN (6, 18, 19).

After we verified the validity of these four prognostic factors, we examined the effect of three treatment strategies using the Cox proportional hazards model in which all four important prognostic factors were embedded. Steroid therapy was a valuable treatment that helped improve renal survival according to the multivariate analysis, but not the univariate analysis. Tonsillectomy was also a positive treatment in both univariate and multivariate analyses. In contrast, neither procedure determined the influence of ACE-I/ARB on renal survival.

The discrepancy between the results of both analyses for steroid therapy might have been caused by the bias for treatment selection. In fact, steroid therapy was administered to patients with higher levels of proteinuria (2.18±2.33 vs. 1.02±1.25 g/day, $p < 0.05$; Mann-Whitney U test). Steroid therapy can reduce urinary protein, stabilize renal function, and ameliorate histological injury (20-22). Kobayashi et al. (20) indicate that oral prednisolone for 18 months helps to reduce proteinuria and stabilize renal function in patients with progressive IgAN and preserved initial creatinine clearance (more than 70 ml/min) during the 10 year follow-up period. The RCT described by Shoji et al. (21) found that corticosteroid significantly ameliorated mesangial cell proliferation, mesangial matrix accumulation and cellular crescents as compared with antiplatelet therapy after one year of treatment. The RCT described by Pozzi et al. found that a six-month course of steroid therapy protected against deteriorating renal function (22), and they recently demonstrated that the 10 year renal survival rates were significantly improved by steroid compared with the control group (6). These results support the findings of our multivariate analysis with respect to steroid therapy.

The effect of tonsillectomy on renal survival in patients with IgAN remains controversial. Rasche et al. (23) have reported that tonsillectomy does not prevent a progressive course in IgAN with renal survival estimates and multivariate analysis, but they treated only 16 patients with tonsillectomy and the mean observation time after renal biopsy was 3.4 years. On the contrary, a large cohort study (n = 329) by Hotta et al. (24) revealed that renal function did not progressively deteriorate in any of the patients

whose urinary abnormalities disappeared (clinical remission) during the observation period, and that tonsillectomy and high-dose methylprednisolone significantly impacted clinical remission. Xie et al. (25) have indicated that tonsillectomy benefits long-term renal survival in patients with a mean follow-up of over 15 years. Our study also showed that renal survival improved in patients with, than without tonsillectomy (87.8% vs. 64.2% at 10 years), and that tonsillectomy significantly contributed to improving renal survival in the multivariate analysis with a hazard ratio of 0.37. Additionally, the rate at which urinary abnormalities disappeared was significantly higher in patients with tonsillectomy. To determine the value of tonsillectomy using a RCT is actually difficult because tonsillectomy is an invasive surgical operation and long-term follow-up is needed to clarify the effect on renal survival. Hence, even a retrospective study is important if a large number of patients and long-term follow-up can be ensured.

Neither univariate nor multivariate analysis in the present study showed that ACE-I/ARB positively affected renal survival. The beneficial influence of ACE-I/ARB on IgAN patients appears to be mainly dependent on the reducing proteinuria, but the effect on renal function has not been defined (26, 27). Praga et al. (7) found from an RCT that the renal survival of patients with proteinuric IgAN treated with ACE-I is better than that of control groups. Our findings that ACE-I/ARB is ineffective might have resulted from differences in the study population and the dose of ACE-I, as well as other factors.

In conclusion, we reconfirmed proteinuria, impaired renal function at renal biopsy and

severe histological injury as important prognostic factors of IgAN. To evaluate the influence of hypertension on progression of the disease, future studies should focus on the duration of the hypertensive state. We also suggest that steroid therapy and tonsillectomy are independently effective according to the Cox proportional hazards model that included the four main prognostic factors described above. Details of the indication for tonsillectomy in stratified patients with IgAN and of the benefit of corticosteroid combined with tonsillectomy also require further study.

REFERENCES

1. D'Amico, G. The commonest glomerulonephritis in the world: IgA nephropathy. Q. J. Med. **1987**, *64* (245), 709-727.

2. Julian, B.A.; Waldo, F.B.; Rifai, A.; Mestecky, J. IgA nephropathy, the most common glomerulonephritis worldwide. A neglected disease in the United States? Am. J. Med. **1988**, *84* (1), 129-132.

3. D'Amico, G. Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am. J. Kidney Dis. **2000**, *36* (2), 227-237.

4. Donadio, J.V.; Grande, J.P. IgA nephropathy. N. Engl. J. Med. **2002**, *347* (10), 738-748.

5. Strippoli, G.F.; Manno, C.; Schena, F.P. An--Evidence-based--survey of therapeutic options for IgA nephropathy: Assessment and criticism. Am. J. Kidney Dis. **2003**, *41* (6), 1129-1139.

6. Pozzi, C.; Andrulli, S.; Del Vecchio, L.; Melis, P.; Fogazzi, G.B.; Altieri, P.; Ponticelli, C.; Locatelli, F. Corticosteroid effectiveness in IgA nephropathy: Long-term results of a randomized, controlled trial. J. Am. Soc. Nephrol. **2004**, *15* (1), 157-163.

7. Praga, M.; Gutierrez, E.; Gonzalez, E.; Morales, E.; Hernandez, E. Treatment of IgA nephropathy with ACE inhibitors: A randomized and controlled trial. J. Am. Soc. Nephrol. **2003**, *14* (6), 1578-1583.

8. Yasuhiko, T.; Sakai H.; Special Study group (IgA nephropathy) on Progressive Glomerular Disease. Clinical guidelines for immunoglobulin A (IgA) nephropathy in Japan, second version. Clin. Exp. Nephrol. **2003**, *7* (2), 93-97.

9. D'Amico, G.; Minetti, L.; Ponticelli, C.; Fellin, G.; Ferrario, F.; Belgioioso, G.; Imbasciati, E.; Ragni, A.; Bertoli, S.; Fogazzi, G. Prognostic indications in idiopathic IgA mesangial nephropathy. Q. J. Med. **1986**, *59* (228), 363-378.

10. Johnston, P.A.; Brown, J.S.; Braumholtz, D.A.; Davison, A.M. Clinico-pathological correlations and long-term follow-up of 253 United Kingdom patients with IgA nephropathy. A report from the MRC Glomerulonephritis Registry. Q. J. Med. **1992**, *84* (304), 619-627.

11. Radford, M.G. Jr.; Donadio, Jr.; Bergstralh, E.J.; Grande, J.P. Predicting renal outcome in IgA nephropathy. J. Am. Soc. Nephrol. **1997**, *8* (2), 199-207.

12. Frimat, L.; Briancon, S.; Hestin, D.; Aymard, B.; Renoult, E.; Huu, T.C.; Kessler, M. IgA nephropathy: prognostic classification of end-stage renal failure. Nephrol. Dial. Transplant. **1997**, *12* (12), 2569-2575.

13. Daniel, L.; Saingra, Y.; Giorgi, R.; Bouvier, C.; Pellissier, J.F.; Berland, Y. Tubular lesions determine prognosis of IgA nephropathy. Am. J. Kidney Dis. **2000**, *35* (1), 13-20.

14. Geddes, C.C.; Rauta, V.; Gronhagen-Riska, C.; Bartosik, L.P.; Jardine, A.G.; Ibels, L.S.; Pei, Y.; Cattran, D.C. A tricontinental view of IgA nephropathy. Nephrol. Dial. Transplant. **2003**, *18* (8), 1541-1548.

15. Alamartine, E.; Sabatier, J.C.; Guerin, C.; Berliet, J.M.; Berthoux, F. Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analyses. Am. J. Kidney Dis. **1991**, *18* (1), 12-19.

16. Rekola, S.; Bergstrand, A.; Bucht, H. Development of hypertension in IgA nephropathy as a marker of a poor prognosis. Am. J. Nephrol. **1990**, *10* (4), 290-295.

17. Payton, C.D.; McLay, A.; Jones, J.M. Progressive IgA nephropathy: the role of hypertension. Nephrol. Dial. Transplant. **1988**, *3* (2), 138-142.

18. Bartosik, L.P.; Lajoie, G.; Sugar, L.; Cattran, D.C. Predicting progression in IgA nephropathy. Am. J. Kidney Dis. **2001**, *38* (4), 728-735.

19. Donadio, J.V.; Bergstralh, E.J.; Grande, J.P.; Rademcher, D.M. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. Nephrol. Dial. Transplant. **2002**, *17* (7), 1197-1203.

20. Kobayashi, Y.; Hiki, Y.; Kokubo, T.; Horii, A.; Tateno, S. Steroid therapy during the early stage of progressive IgA nephropathy. A 10-year follow-up study. Nephron **1996**, *72* (2), 237-242.

21. Shoji, T.; Nakanishi, I.; Suzuki, A.; Hayashi, T.; Togawa, M.; Okada, N.; Imai, E.; Hori, M.; Tsubakihara, Y. Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. Am. J. Kidney Dis. **2000**, *35* (2), 194-201.

22. Pozzi, C.; Bolasco, P.G.; Fogazzi, G.B.; Andrulli, S.; Altieri, P.; Ponticelli, C.; Locatelli, F. Corticosteroids in IgA nephropathy: A randomized controlled trial. Lancet **1999**, *353* (9156), 883-887.

23. Rasche, F.M.; Schwarz, A.; Keller, F. Tonsillectomy does not prevent a progressive course in IgA nephropathy. Clin. Nephrol. **1999**, *51* (3), 147-152.

24. Hotta, O.; Miyazaki, M.; Furuta, T.; Tomioka, S.; Chiba, S.; Horigome, I.; Abe, K.; Taguma, Y. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am. J. Kidney Dis. **2001**, *38* (4), 736-743.

25. Xie, Y.; Nishi, S.; Ueno, M.; Imai, N.; Sakatsume, M.; Narita, I.; Suzuki, Y.;

Akazawa, K.; Shimada, H.; Arakawa, M.; Gejyo, F. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int. **2003**, *63* (5), 1861-1867.

26. Maschio, G.; Cagnoli, L.; Claroni, F.; Fusaroli, M.; Rugiu, C.; Sanna, G.; Sasdelli, M.; Zuccala, A.; Zucchelli, P. ACE inhibitor reduces proteinuria in normotensive patients with IgA nephropathy: A multicentre, randomized, placebo-controlled study. Nephrol. Dial. Transplant. **1994**, *9* (3), 265-269.

27. Bannister, K.M.; Weaver, A.; Clarkson, A.R.; Woodroffe, A.J. Effect of angiotensin-converting enzyme and calcium channel inhibition on progression of IgA nephropathy. Contrib. Nephrol. **1995**, *111*, 184-192.

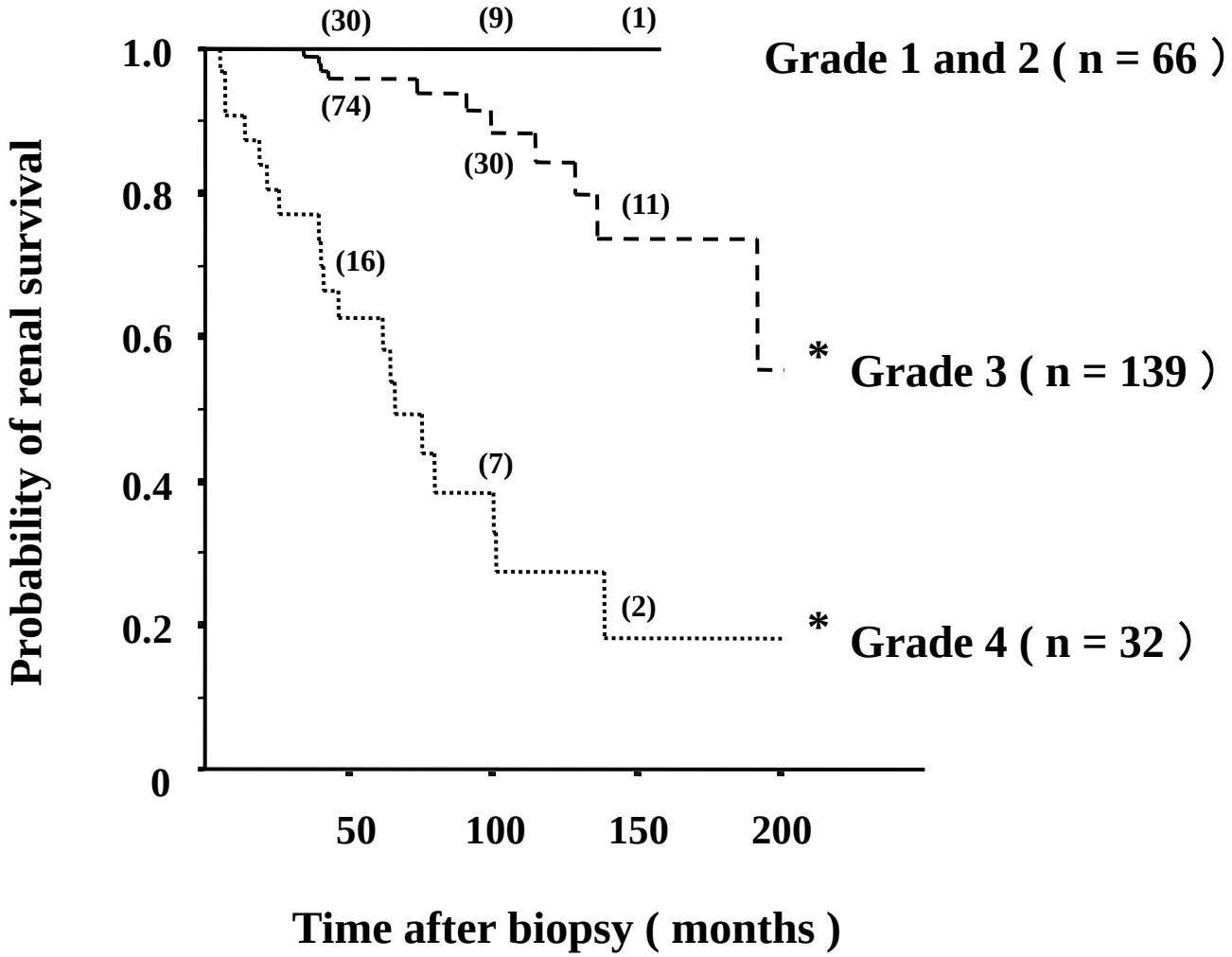
(30)
(9)
(1)
1.0
(74)
(30)
(11)
0.8
(16)
0.6
(7)
0.4
(2)
0.2
0
50
100
150
200
Probability of renal survival
Time after biopsy (months)
Grade 1 and 2 (n = 66)
*
Grade 3 (n = 139)
*
Grade 4 (n = 32)

Figure 1 (A)

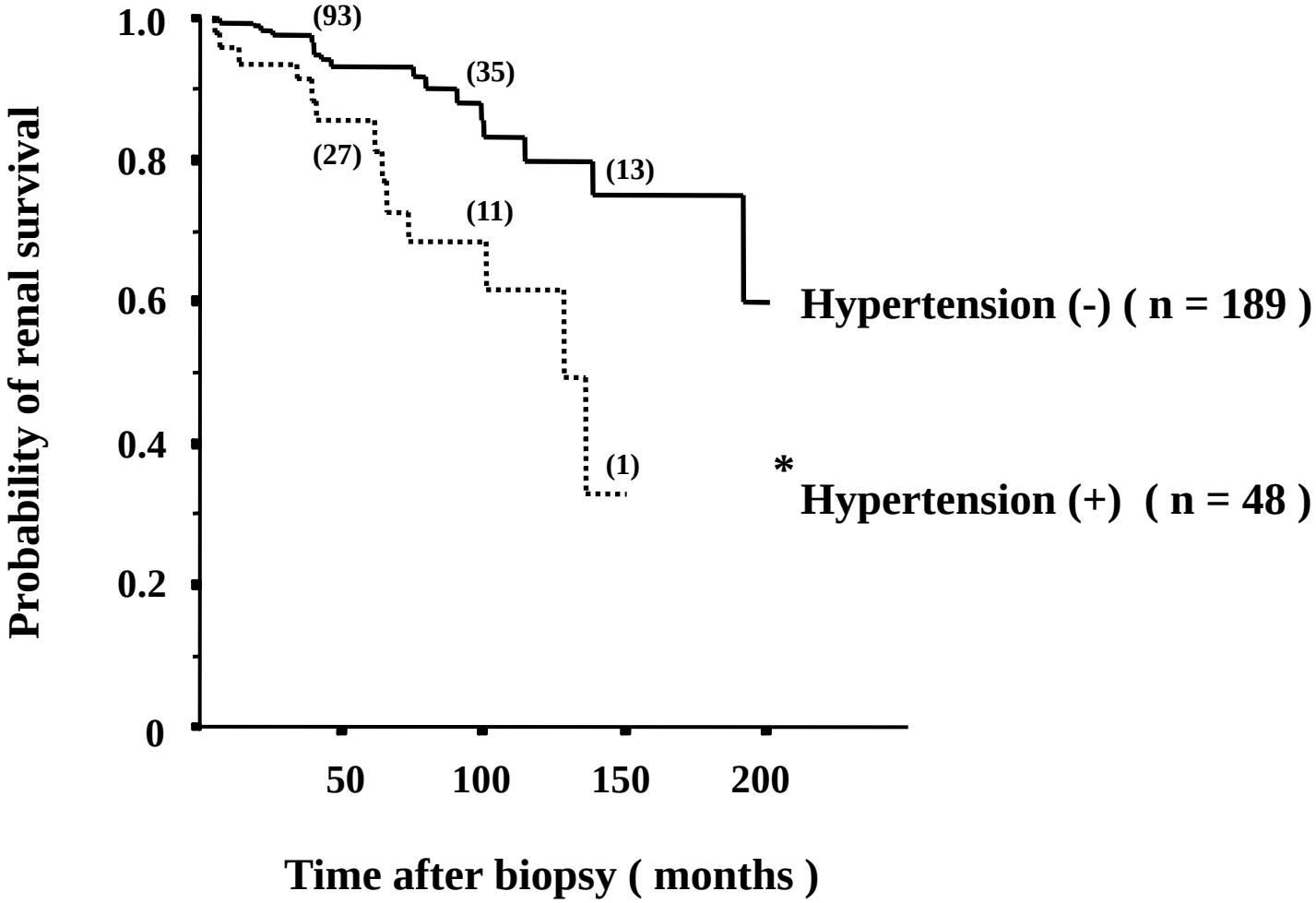
1.0
0.8
0.6
0.4
0.2
0
Probability of renal survival
(93)
(35)
(27)
(13)
(11)
(1)
Hypertension (-) (n = 189)
*
Hypertension (+) (n = 48)
50
100
150
200
Time after biopsy (months)

Figure 1 (B)

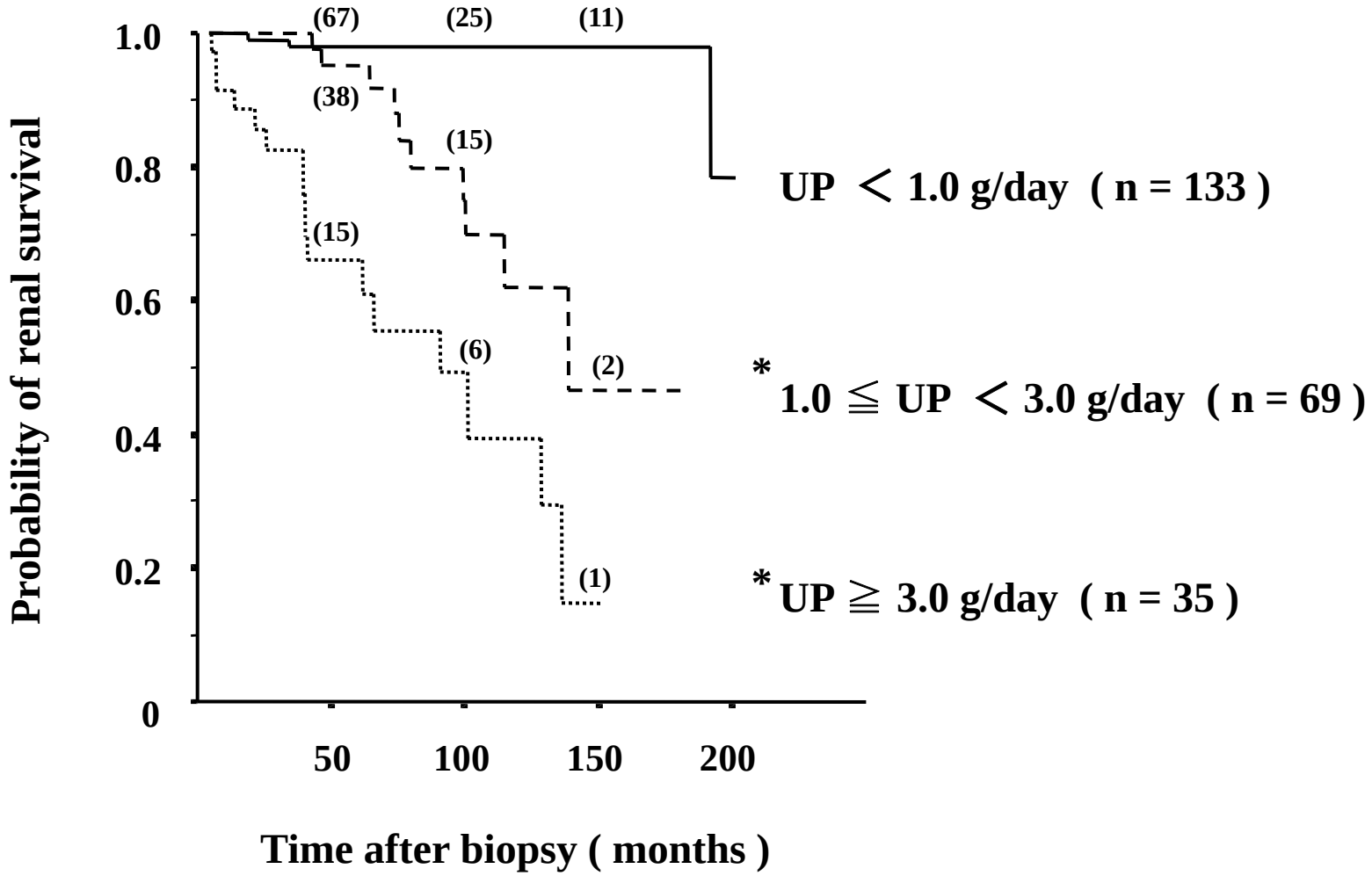
Probability of renal survival
1.0
0.8
0.6
0.4
0.2
0
50
100
150
200
Time after biopsy (months)
(67)
(25)
(11)
(38)
(15)
(15)
(6)
(2)
(1)
UP ＜ 1.0 g/day (n = 133)
* 1.0 ≦ UP ＜ 3.0 g/day (n = 69)
* UP ≧ 3.0 g/day (n = 35)

Figure 1 (C)

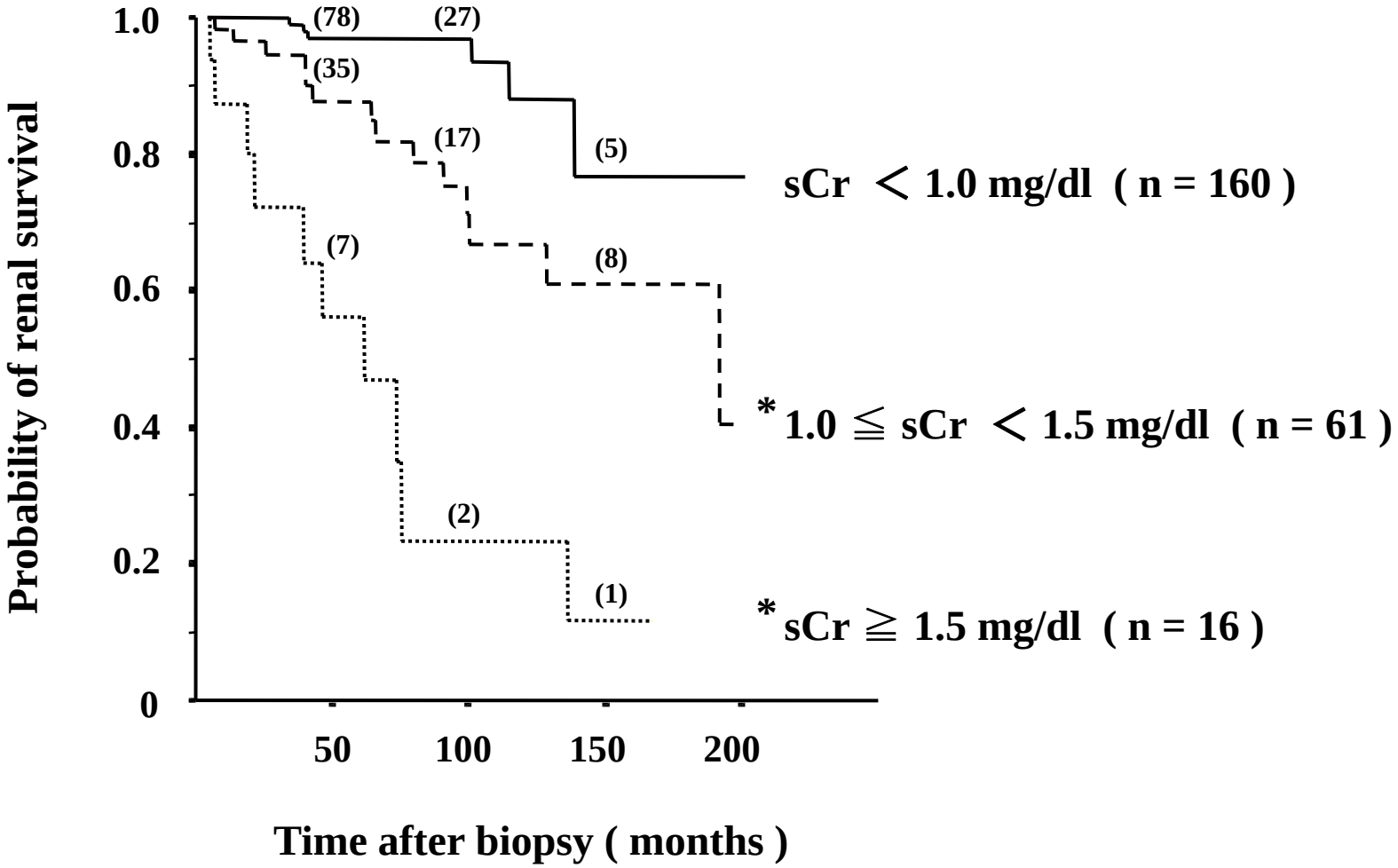
1.0
0.8
0.6
0.4
0.2
0
Probability of renal survival
(78)
(27)
(35)
(17)
(5)
(7)
(8)
(2)
(1)
50
100
150
200
Time after biopsy (months)
sCr ＜ 1.0 mg/dl (n = 160)
* 1.0 ≦ sCr ＜ 1.5 mg/dl (n = 61)
* sCr ≧ 1.5 mg/dl (n = 16)

Figure 1 (D)

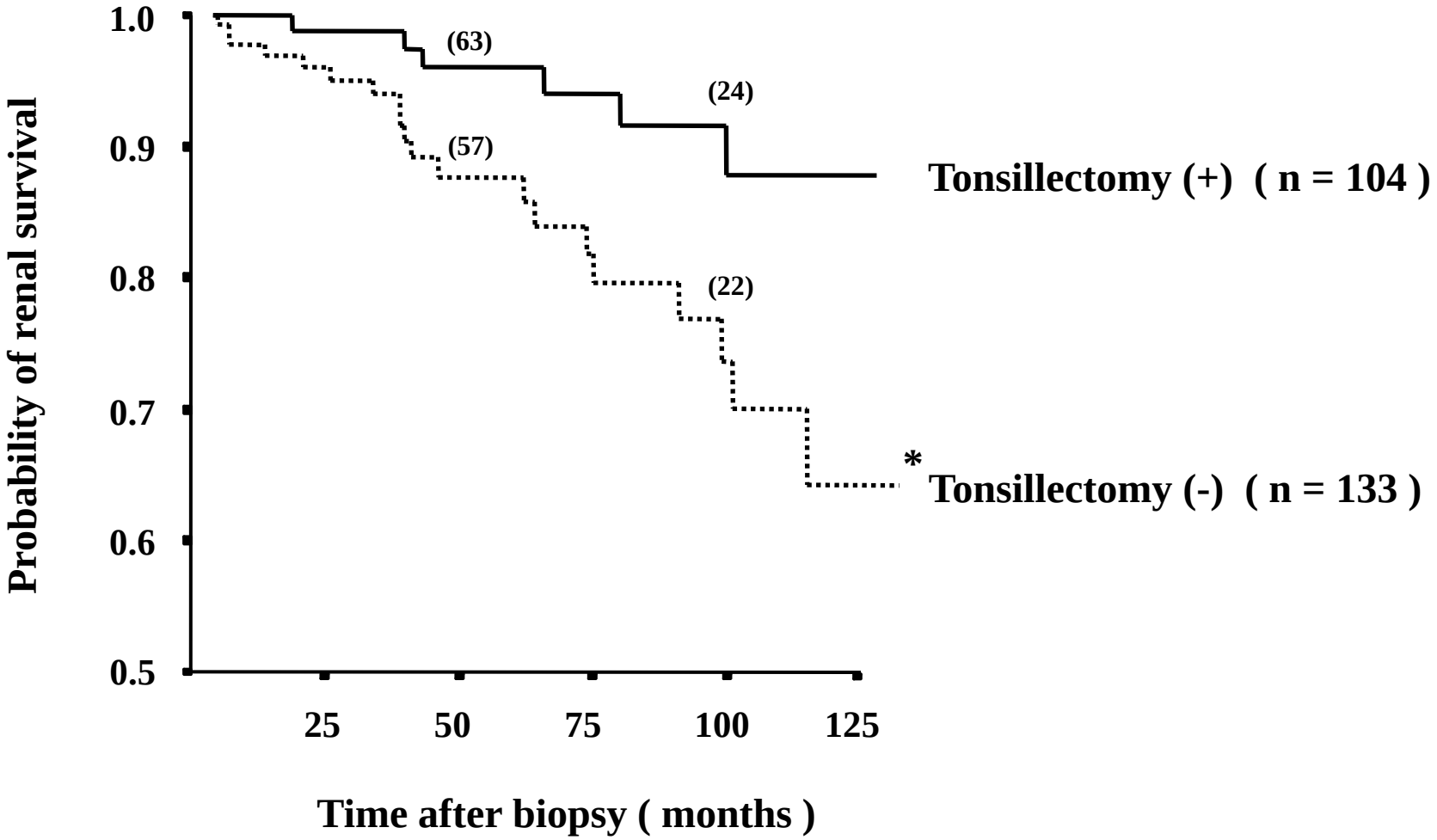
1.0
0.9
0.8
0.7
0.6
0.5
Probability of renal survival
(63)
(24)
(57)
(22)
Tonsillectomy (+) (n = 104)
*
Tonsillectomy (-) (n = 133)
25
50
75
100
125
Time after biopsy (months)

Figure 2

FIGURE LEGENDS (Manuscript ID# RNF 44919)

Figure 1. Renal survival rates of IgA nephropathy patients stratified by histological grading (A), presence of hypertension (B), amount of proteinuria (C) and serum creatinine level (D).

* indicates $p<0.05$ by log-rank test.

Numbers in parentheses indicate patients at risk at 50, 100, and 150 months.

Figure 2. Renal survival rates of patients treated with and without tonsillectomy.

* indicates $p<0.05$ by log-rank test.

Numbers in parentheses indicate patients at risk at 50 and 100 months.

Table 1. Baseline characteristics of 237 patients with IgA nephropathy

Characteristics	Data
Age (years)	31.4 ± 13.5
Sex (M / F)	112 / 125
Hypertension	48 (20.3 %)
Systolic BP (mmHg)	126.1 ± 18.7
Diastolic BP (mmHg)	75.3 ± 13.2
Urinary protein (g/day)	1.41 ± 1.78
Serum creatinine (mg/dl)	0.91 ± 0.47
Total choresterol (mg/dl)	208.6 ± 57.1
Urinary acid (mg/dl)	5.72 ± 1.51
Serum IgA (mg/dl)	345.0 ± 110.8
Serum C3 (mg/dl)	86.3 ± 21.2

Data shown as mean±SD or number (%).

Table 2. Univariate analysis of prognostic factors and treatments in IgA nephropathy patients

Variables		Hazard ratio	95% CI	P value
< Prognostic factors >				
Age	(per 10 years)	1.26	(0.97 - 1.63)	0.08
Male	(vs. female)	1.46	(0.71 - 3.00)	0.30
SBP	(per 10 mmHg)	1.31	(1.11 - 1.54)	< 0.01
Urinary protein	(per 1.0 g/day)	1.33	(1.19 - 1.49)	< 0.01
Serum creatinine	(per 0.5 mg/dL)	1.89	(1.49 - 2.39)	< 0.01
Histology of grade 4	(vs. other grade)	10.91	(5.19 - 23.0)	< 0.01
< Treatments >				
Tonsillectomy	(vs. no tonsillectomy)	0.39	(0.18 - 0.86)	0.02
Steroid therapy	(vs. no steroid therapy)	0.61	(0.23 - 1.60)	0.32
ACE-I / ARB	(vs. no ACE-I / ARB)	0.99	(0.29 - 3.43)	0.99

Table 3. Effect of tonsillectomy on urinary findings at the end of observation

	Tonsillectomy (n = 104)	No tonsillectomy (n = 133)	P value
< Baseline >			
Serum creatinine at renal biopsy (mg/dl)	0.85 ± 0.28	0.96 ± 0.57	0.14
Urinary protein at renal biopsy (g/day)	1.07 ± 1.27 *	1.67 ± 2.06	0.04[a]
No. of patients with histology of grade 3 and 4	70 (67.3 %)	101 (75.9 %)	0.14
No. of patients using corticosteroid	29 (27.9 %)	49 (36.8 %)	0.15
No. of patients using ACE-I and/or ARB	21 (20.2 %)	36 (27.1 %)	0.22
< Final follow up >			
Mean observation period (months)	69.5 ± 50.5	56.7 ± 40.5	0.07
No. of patients with disappearance of hematuria	56 (53.8 %) *	29 (21.8 %)	< 0.01[b]
No. of patients with disappearance of proteinuria	46 (44.2 %)	44 (33.1 %)	0.07
No. of patients with disappearance of hematuria and proteinuria	33 (31.7 %) *	22 (16.5 %)	< 0.01[b]
No. of patients who reached renal death	9 (8.7 %)	21 (15.8 %)	0.10

Data are compared by [a]Mann-Whitney U test and [b]chi-square test.

Asterisk indicates significant difference ($p < 0.05$).

Table 4. Multivariate analysis of prognostic factors and treatments in IgA nephropathy patients

Variables		Hazard ratio	95% CI	P value
< Prognostic factors >				
Age	(per 10 years old)	0.67	(0.47 - 1.00)	0.06
Male	(vs. female)	1.85	(0.82 - 4.19)	0.14
SBP	(per 10 mmHg)	1.07	(0.85 - 1.35)	0.56
Urinary protein	(per 1.0 g/day)	1.60	(1.31 - 1.95)	< 0.01
Serum creatinine	(per 0.5 mg/dl)	1.43	(1.12 - 1.81)	< 0.01
Histology of grade 4	(vs. other grade)	13.16	(5.05 - 34.3)	< 0.01
< Treatments >				
Tonsillectomy	(vs. no tonsillectomy)	0.37	(0.14 - 0.99)	0.04
Steroid therapy	(vs. no steroid therapy)	0.26	(0.07 - 0.93)	0.04
ACE-I / ARB	(vs. no ACE-I / ARB)	0.58	(0.11 - 2.99)	0.52