Renal outcome after tonsillectomy plus corticosteroid pulse therapy in patients with Immunoglobulin A nephropathy : Results of a multicenter cohort study

year	2016
	IgA +
	(University of Tsukuba)
	2016
	12102 2797
URL	http://hdl.handle.net/2241/00145212

筑 波 大 学

博 士 （ 医 学 ） 学 位 論 文

Renal outcome after tonsillectomy plus corticosteroid pulse therapy in patients with Immunoglobulin A nephropathy: Results of a multicenter cohort study

（IgA 腎症における扁桃腺摘出＋ステロイドパルス療法が腎予後に与える影響：多施設コホート研究）

２０１６

筑波大学

星　野　純　一

Table of contents

Background

Definition of Immunoglobulin A nephropathy

Immunoglobulin A nephropathy (IgAN) was first described by Berger and Hinglains in 1968. It is diagnosed by the predominance of IgA deposits, either alone or with IgG or IgM in the glomerular mesangium, with no evidence of other underlying disease [1]. So although the presence of glomerular hematuria and proteinuria suggests glomerulonephritis, renal biopsy is needed to confirm the diagnosis of IgAN.

After immunohistological examination became widely accepted as a routine in the majority of institutions by the end of the 1960s, IgAN has been recognized as the most common cause of end-stage renal disease (ESRD) around the world—most markedly in Japan and other Asian countries, [2-4].

Pathological findings in IgAN

As noted, histological evaluation is essential for diagnosis of IgAN, while mesangial hypercellularity and expansion of the mesangial matrix are the main histological changes with IgAN. In addition to these findings in the mesangium, various changes may be observed such as injury to podocytes and capillary loops as well as

tubular, interstitial and vascular lesions.

Although various classifications have been reported, the Oxford classification published in 2009 is now the most widely accepted worldwide [5]. Its scoring system—derived from Oxford's analysis of patients' renal outcome—is based on four biopsy findings: (1) the mesangial hypercellularity score, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity, and (4) tubular atrophy/interstitial fibrosis (Table 1). In Japan, however, a domestic histological classification based on a multicenter case-control study of IgAN was proposed in 2004 and published in 2013 [1, 6] (Tables 2 A-C). It remains unclear which classification is more suitable for Japanese patients with IgAN.

Pathogenesis of IgAN

Pathogenesis of IgA nephropathy has not been fully elucidated, probably due to lack of adequate animal models. However it is well known that IgAN frequently recurs after kidney transplantation, suggesting that IgAN is a systemic disease in which the kidney sustains damage as an innocent bystander. Furthermore, in over 40% of patients with IgAN, a history of painless recurrent macroscopic hematuria is observed 1 to 2 days following an infectious illness, most commonly pharyngitis or tonsillitis and less

often gastroenteritis or pneumonia [7, 8]. In IgAN, an increased fraction of circulatory

IgA1 has a galactose deficiency in some carbohydrate side chains that are attached to

the hinge-region segment of the heavy chain. Synthesis of poorly galactosylated IgA1,

which is produced mainly in mucosal tissues, leads to the formation of immune

complexes in the circulation or glomeruli. Although poorly galactosylate IgA1 is

considered to be synthesized mainly by tonsillar B cells, and the serum level of the

abnormal IgA1 was decreased after tonsillectomy in IgAN patients [9], recent study has

suggested that the abnormal IgA1-producing plasma cells were also present in the bone

marrow, not only in the mucosal tissues [10]. In turn, the complexed galactose-deficient

IgA1 activates mesangial cells and leads to expansion of mesangial matrix, to mesangial

hypercellularity, apoptosis, oxidative stress, activation of complement, and injury to

podocytes [11]. It is generally thought that these renal injuries will lead to hypertension,

proteinuria, hematuria, and reduced renal function.

Epidemiology of IgAN

In Japan, the incidence of IgAN is estimated to be 3.9 to 4.5 per 100,000

persons per year. An estimated 33,000 persons have IgAN (95% confidence interval

(CI): 28,000-37,000). IgAN has been found in every age group, though one third of

Japanese IgAN patients were diagnosed while teenagers [1]. The male to female ratio of IgAN varies among countries, reported as 1:1 in Asia, and 2:1 in North America [11]. Many studies in Asian and Western countries published in the 1980s to the 2010s showed very similar 10-year overall renal survival among IgAN patients—between 80% and 85%—no matter which one of many therapies was used [12, 13].

Clinical predictors of IgAN at the time of initial examination were the amount of proteinuria, blood pressure levels, degree of renal dysfunction, and histological severity. And it is reported that a remission of urinary findings, defined as an improvement or disappearance of hematuria and proteinuria, is associated with improved renal prognosis. As a result, the remission of urinary findings is often used as a proxy outcome in trials, though the definition of the remission of urinary findings has not been fully confirmed [1, 14].

Treatment of IgAN

Several registry data suggest that proteinuria < 1.0g/day, either at the time of biopsy or after therapy, leads to a better prognosis with IgAN [15, 16]. It has been reported that renin-angiotensin system inhibitors (RAS) can reduce proteinuria and slow the decline in the estimated glomerular filtration rate (eGFR) [14]. In addition, several

studies, including controlled trials, reported that corticosteroid treatment was more effective than just RAS, especially for IgAN patients with proteinuria $\geqq$ 1g/day and eGFR >50 ml/min/1.73m^2 [17-20]. Based on these findings, the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis recommended use of corticosteroids as oral steroids (OS) or steroid pulse (SP) for patients with persistent proteinuria at that level, even after 3-6 months of optimal supportive care including RAS and blood pressure control [14].

Since episodes of macroscopic hematuria are not uncommon in patients with IgAN after bouts of recurrent tonsillitis, tonsillectomy is considered one of the treatment options for these patients, removing potential antigen stimuli [21]. The relationship between hematuria and tonsillar is supported by the findings that the abnormal polymeric IgA1 is mainly produced by mucosal tissues [9]. Nevertheless, in many countries—especially those in the West—it is considered unlikely that a dysregulated mucosal immune system in IgAN could be affected by tonsillectomy alone [22], because of the association between gastrointestinal mucosal immune systems and IgAN [23], and also because of the presence of the abnormal IgA1-producing plasma cells in the bone marrow[10]. For these reasons, tonsillectomy alone is not recommended in the 2012 KDIGO clinical practice guideline [14], even though it is listed as a treatment

option in the Japanese clinical practice guideline for IgAN 2014 [1].

In 2001, Hotta et al. reported that tonsillectomy and steroid pulse (TSP) therapy was more effective in achieving clinical remission than SP, alone [24]; other such reports followed, including a controlled trial, suggesting good clinical remission rates in patients who received TSP [25-29]. In addition, a recent meta-analysis suggested a better clinical remission rate for patients with TSP than for those without tonsillectomy [30]. These reports showed that the effect of TSP on clinical remission of IgAN was superior to that of corticosteroid treatments, including SP; but the evidence showing the preventive effect of TSP on ESRD was not strong, mainly because this hard outcome takes a long follow-up with an inherently large drop-out rate, hence requires a particularly large sample size for stable analysis. In fact, a recent randomized controlled trial, comparing TSP with SP, concluded that TSP's impact on renal function remains unknown [4].

Study Objective

As noted above, there is a distinct difference between the treatment of IgAN in Japan and the United States. In the KDIGO guideline, TSP therapy is *not* recommended routinely for treatment of IgAN whereas the Japanese Clinical Practice Guideline for

IgAN recommends it as grade C1. In addition, as written in the KDOGO guideline, there are *no* trials showing that RAS or other treatments actually decrease the risk of ESRD from IgAN. All these findings—sometimes inconclusive and even contradictory—impelled the present multicenter, long-term cohort study designed to investigate the comparative effect of TSP and other therapies in preventing ESRD.

Methods

Patient population

The data were obtained from medical records of patients treated at our four hospitals in the Tokyo metropolitan area March 1981-December 2013. The patients had biopsy-proven IgAN with an eGFR $\geqq 30$ ml/min/1.73m^2, and were 18 years or older. Patients with a history of renal transplantation or of any other renal disease were excluded.

Pathological diagnosis had been performed by at least two observers, with histological grading of biopsy specimens evaluated using the Oxford IgAN classification [5] and the Japanese criteria published by the Japanese IgAN Study Group, with pathological grades (H-grades) I to IV representing, respectively, <25%, 25-49%,

50-74%, and $\geqq$75% of glomeruli that exhibit cellular/fibrocellular crescents (active

lesions) or fibrous crescents or global/segmental sclerosis (chronic lesions) [6]—or a

combination thereof.

Patients' demographic data had been obtained at the time of renal biopsy. All

laboratory data and medications—including serum albumin (Alb), serum creatinine,

total cholesterol, hemoglobin (Hb), systolic and diastolic blood pressure, proteinuria,

hematuria, body weight, use and dose of prednisone, use of RAS, anticoagulants, and/or

antiplatelets—had been noted before treatment, at 3, 6, and 12 months after treatment,

and every subsequent year until the end of follow-up. All laboratory values had been

measured by the automated, standardized methods used in our hospitals within 24h after

drawing blood samples. If the Jaffe method had been used to measure serum creatinine,

the values were converted, for our analyses, to those for enzyme assays. Proteinuria was

categorized into three groups: <0.5 g/gram creatinine (gCre) or urine dipstick with (-) or

($\pm$); 0.5-0.99 g/gCre or (+); and $\geqq$1.0 g/gCre or (2+). Hematuria was categorized into

four groups: <5/high power field (HPF) or urine dipstick with (-) or ($\pm$); 5-10/HPF or

(+); 10-29/HPF or (2+); and $\geqq$30/HPF or (3+). Renal-biopsy year was categorized as

the 1980s, 1990s, or 2000s. The primary outcome of this study was initiation of dialysis

as indication of ESRD, with all patients followed until ESRD, death, or end of

follow-up. The eGFR was calculated by the formula for Japanese patients devised by

Matsuo et al. [31]. The study's protocol was approved by institutional review boards in

each hospital.

Statistical analysis

We categorized patients into four groups—TSP, SP, OS, and RAS—based on

their initial treatment and/or the treatment in use at >50% of their follow-ups. The TSP

protocol was three courses of a 3-day pulse of methylprednisolone, 0.5g/day,

administered 2-4 weeks after tonsillectomy, followed by oral corticosteroid at an initial

dose of 30mg every other day, gradually tapered by 5mg every two months, then

discontinued 12 months after the initial therapy. The original SP protocol was a 3-day

pulse of methylprednisolone administered in months 1, 3, and 5 in addition to 0.5 mg/kg

of oral prednisone every other day.   With both TSP and SP, however, the number of

methylprednisolone pulses could be reduced to one or two courses depending on the

patient's condition or clinician's preference. Data were summarized using proportions

and means (±SD) as appropriate. Categorical variables were analyzed with the

chi-squared or Fisher's exact test, continuous variables compared using Student's t-test,

the Mann-Whitney U test, or ANOVA. Cumulative survival was estimated with

Kaplan-Meier survival curves, and compared by log-rank test. Cox proportional hazard

models were used to obtain hazard ratios (HRs) and a 95% confidence interval (95% CI)

for ESRD. In the Cox model 1, each HR was adjusted for the risk grade calculated by

the IgA scoring system [32], medications (use of RAS, anticoagulants, and/or

antiplatelets), and renal-biopsy year (RBY). In model 2, each HR was adjusted for sex,

age, body mass index (BMI), eGFR, Alb, proteinuria, hematuria, blood pressure control,

medications and RBY. In model 3, each HR was adjusted for model-2 factors plus

pathological grade.

To minimize selection bias for IgAN treatment, propensity score-matched

analyses were performed to balance patients' background characteristics, including

treatment group, age, sex, eGFR, Alb, proteinuria, hematuria, Hb, blood pressure

control, medications, RBY, and pathological grade. To estimate the propensity score, we

used a logistic regression model for the choice of treatment as a function of the

background characteristics detailed above. Each patient with RAS was matched with a

patient with TSP, SP, and OS with nearest-neighbor matching on the logit scale. All

analyses used Stata® SE version 13.1 (StataCorp, College Station, TX).

Results

Characteristics of patients in this study

Of the 1,840 patients screened, 1,127 met the study criteria. Table 3 shows the

characteristics of eligible IgAN patients who received TSP (n=209), SP (n=103), OS

(n=300), and RAS, alone (n=515). Mean age was lower in the TSP and OS groups

(p<0.01) than in the other two.   The proportion of chronic kidney disease (CKD),

stages G1 and 2 (eGFR $\geqq$60 ml/min/1.73m^2), and proteinuria <1.0g/gCre was highest

in the TSP group while the proportion of CKD, G3 (eGFR 30~59 ml/min/1.73m^2), and

proteinuria $\geqq$1.0g/gCre was highest in the SP group (p<0.01). Of those in the TSP

group, 65.1% also received RAS, as did 77.7% with SP, and 56.3% with OS (p<0.01).

The mean initial dose of daily oral prednisolone with TSP, SP, and OS was, respectively,

17±6mg, 26±13mg, and 28±11mg (p<0.001). Methylprednisolone pulse courses were

reduced for 33% of the TSP patients, 66% with SP. The mean follow-up duration was

8.3±6.4 years overall, 7.0±4.4 years with TSP, 6.6±5.4 with SP, 10.4±7.3 with OS, and

8.0±6.4 with RAS, alone.

Renal survival by decade

As shown in Table 4, overall 5, 10, 15, and 20-year survival was, respectively,

93.3% (95% CI, 91.8-94.5), 85.3% (83.0-87.3), 78.2% (75.1-80.9), and 74.0%

(70.3-77.4). The 10-year survival with TSP of 96.3% (90.3-98.6) was significantly

better than OS's 79.7% (73.8-84.4) or RAS's 84.8% (80.2-88.4) (p<0.05), that trend

holding throughout the observation period. Survival with SP was better than with OS or

RAS, but worse than with TSP.

Next, we compared renal survival of patients who received renal biopsy in the

1980s, the 1990s, and 2000s (2000-present). Overall survival was, respectively, 79.6%

(72.8-84.9), 84.6% (81.3-87.4), and 89.6% (86.0-92.4) (Table 4), indicating that renal

outcome for IgAN patients improved over the decades. Interestingly, this survival rate

was similar to that reported in European and Asian countries in the 1980s and 1990s

(around 80-85%) [12]. Better renal outcome with TSP/SP may contribute to the overall

improvement of renal outcome by decade.

Renal survival with each treatment

Comparing renal survival after renal biopsy for each group, 10- and 15-year

survival was, respectively, with TSP, 96.3% (90.3-98.6) and 86.3% (68.8-94.3); with SP,

85.7% (73.0-92.7) and 85.7% (73.0-92.7); with OS, 79.7% (73.8-84.4) and 71.3%

(64.3-77.1); and with RAS, 84.8% (80.2-88.4) and 73.6% (64.3-77.1) (Table 4). The

overall renal survival curve with TSP was significantly better than with other groups by

log rank: p=0.04 vs. SP; p<0.001 vs. OS or RAS (Figure 1a). When analyzing patients

by proteinuria, the curves of all four groups were similar with proteinuria <1.0g/gCre or

<0.5g/gCre, but when proteinuria was ≧1.0g/gCre, renal survival with TSP was better

than with OS (p=0.02) or RAS (p=0.03) (Figure 1b-1d), and 10-year survival better with

TSP than with SP (p=0.02) although, after 10 years, the curves of those two groups

became similar—partially due to the limited number of patients with TSP and SP who

were followed up >10 years. In addition, similar renal outcomes were observed when

we divided patients treated with TSP and SP by the number of methylprednisolone

pulses they received, whether one or two. However, the adjusted HR of patients treated

with three or more pulses in model 3—with one or two as referent—was 0.09 (0.02-0.51,

p=0.006), suggesting that treatment with three or more courses of pulse may be

beneficial.

Then we compared HRs of ESRD in each treatment group using Cox models

with TSP as referent (Figure 2). With SP, the HR of ESRD was 2.10 (0.73-6.01) in

model 1, 1.33 (0.44-4.04) in model 2, and 2.05 (0.60-7.03) in model 3. With OS, the HR

of ESRD was 3.62 (1.51-8.65) in model 1, 3.56 (1.45-8.71) in model 2, and 4.19

(1.47-11.99) in model 3. With RAS, the HR was 3.89 (1.63-9.30) in model 1, 3.64

(1.48-8.96) in model 2, and 4.67 (1.66-13.12) in model 3. Although the HRs were not

significantly different between TSP and SP, these data suggested better renal prognosis

for patients with TSP than with the other treatments, and were consistent throughout the

models.

Since use of TSP was wide-spread after the end of the '90s, and many kinds of

RAS appeared after 2000, we did sub-analyses of patients after the year 2000 (n=550).

In these sub-analyses, the survival curve of TSP was significantly better than that of

RAS (p<0.01), and showed a better trend than those of SP (p=0.13) and OS (p=0.11)

(Figure 3). Also, in the Cox analyses, with TSP as referent, the overall HRs in model 2

were, for SP, 0.95 (0.18-4.90), for OS, 4.32 (1.08-17.25), and for RAS, 5.41

(1.43-20.44). The outcome of TSP was similar to that of SP, and significantly better than

those of OS or RAS, which was consistent with our overall analyses.

Comparison of treatments by renal function and proteinuria

Next, to determine the best candidates for TSP, we analyzed the HR of each

treatment by CKD stage and level of proteinuria with TSP as referent. As detailed in

Figure 2, when proteinuria was $\geqq$1.0g/gCre, the HR with TSP was significantly better

than with OS or RAS—e.g., in model 2, respectively, 5.04 (1.44-17.67) and 7.23

(1.98-26.40)—and showed a better trend than with SP, which was 2.99 (0.71-12.54), the

results consistent across the models.   However, for patients whose proteinuria was <1.0g/gCre—or whose CKD was G3—the HR with TSP was only slightly better than with OS or RAS and similar to that with SP, suggesting that tonsillectomy, in addition to SP, may not confer any additional benefit to those patients.

Propensity score-matched analyses

Since we did not control the assignment of treatments, the treatment groups may have differences in their observed covariates that could lead to biased estimates of the treatment effect. So to minimize selection bias for choice of treatment, we performed propensity-score matching to balance patients' background characteristics, including age, sex, eGFR, Alb, Hb, proteinuria, hematuria, blood pressure control, medications (use of RAS, anticoagulants or antiplatelets), and pathological grade. After matching, a similar distribution of characteristics was observed between TSP and other treatments (Table 5). As noted above, and shown in Figure 4, renal survival curves were slightly better with TSP than with SP up to10 years—especially in patients with proteinuria $\geqq$1.0g/gCre (p=0.08)—but the difference became small after 10 years. The curves were significantly better with TSP than with OS or RAS, alone, especially in patients with proteinuria $\geqq$1.0g/gCre.,

Finally, we compared HRs for ESRD in each treatment group with Cox models. When compared with TSP as referent, HRs for ESRD in propensity score-matched patients were, for SP, 1.86 (0.59-5.91) in model 1, 1.28 (0.32-5.10) in model 2, and 3.79 (0.69-20.83) in model 3; for OS, 2.93 (1.11-7.78) in model 1, 2.70 (0.92-7.91) in model 2, and 3.80 (1.10-13.15) in model 3; for RAS, 7.41 (2.38-23.06) in model 1, 4.65 (1.40-15.50) in model 2, and 18.51 (3.67-93.41) in model 3 (Table 6). So the HRs in the propensity score-matched population were very similar to those in the whole population, and those of TSP were the best among the four treatments in patients with proteinuria $\geqq 1.0$ g/gCre, but similar to those of the other treatments in patients with proteinuria<1.0 g/gCre.

Discussion

In this multicenter cohort study, we found that TSP was more strongly associated with lower HR of ESRD than SP, OS, or RAS in IgAN patients whose proteinuria was $\geqq 1.0$g/gCre, but not in patients with proteinuria <1.0g/gCre. In addition, we found that corticosteroid treatments (SP or OS) were better than RAS, alone, in patients with proteinuria $\geqq 1.0$ g/gCre, which is consistent with previous findings [17-20] and what is suggested in the 2012 KDIGO clinical practice guideline

[14].

There had been some reports showing that the effect of TSP on clinical

remission of IgAN was superior to that of corticosteroid treatments, including SP

[24-26]; but the evidence showing the preventive effect of TSP on ESRD was not strong,

mainly because those studies lacked statistical power due to their short observation

periods and limited number of participants. Recently, the first meta-analysis was

reported showing that the effect of TSP on clinical remission was superior to that of SP,

and showing the possible preventive effect of tonsillectomy on ESRD [30]. Although

this was the first study suggesting the possible preventive effect of TSP on ESRD, the

number of patients was limited (n=873) and diverse treatment procedures were included.

To our knowledge, the present study is the largest ever conducted comparing treatments

of IgAN with ESRD targeted as an outcome. Moreover, because our cohort, while

large-scale, was treated at only four hospitals, treatment regimens were relatively well

controlled compared with nationwide or meta-analysis cohorts. Interestingly, the HR of

ESRD this study found when TSP was the treatment—with corticosteroid (SP or OS) as

referent—was 0.19 (0.06-0.64), which is very similar to the reported pooled odds ratio

of 0.25 (0.12-0.52) in the meta-analysis [30].

There are several new findings in this study. First, the patients who are most

probably the best candidates for TSP were identified. Our study showed that they were the patients with CKD G1 and G2 whose proteinuria was $\geqq$1.0g/gCre; it also showed that TSP may be better than—and at least equal to—SP for patients with CKD G3 and proteinuria $\geqq$1.0 g/gCre, and distinctly better than OS and RAS. Going by one finding in the meta-analysis cited above that suggested tonsillectomy to reduce the rate of ESRD [30], TSP may be more effective than SP, alone, in patients with IgAN. But, at this point, we cannot posit the superiority of TSP over SP because, in our study, the difference was not significant due to the wide range in HRs of 95% CI. And in patients with proteinuria <1.0g/gCre, the HRs with TSP, SP and OS were not significantly better than with RAS, again due to the wide range of 95% CI, suggesting that there is not enough evidence at this point to choose TSP over RAS for those patients. Second, our study showed an improvement in overall 10-year renal survival during the last three decades. In the 1980s, 1990s and 2000s, 10-year renal survival for our cohort was, respectively, 79.6% (72.8-84.9), 84.6% (81.3-87.4), and 89.5% (85.9-92.3). The reason for this may be that, in addition to improvement of the various treatment regimens (TSP, SP, etc.), the clinical trend toward total CKD management of IgAN has contributed to better renal prognosis in these patients because improvement of renal survival was also seen in within each treatment group. Therefore, third, a general trend in overall 10-year

renal survival with TSP may be inferred. Our multicenter large-scale cohort may represent patients in general who have undergone TSP because the numbers showing our patients' condition and survival were very similar to those of other multicenter cohorts [4, 24, 25]. Note that our consistent results among analyses in the multiple models—adjusted for possible confounders—and among propensity score-matched analyses, show the robustness of our results.

The benefit of TSP to patients with mild IgAN has not been confirmed. Our study did not find that TSP was superior to SP for these patients. Perhaps the effect of TSP over SP in patients with mild IgAN may be small because such patients have less immune abnormality associated with mucosa; or an inability to detect the difference between these two treatments may be inherent to the situation. Because the reported annual eGFR decline in patients with proteinuria <1.0 g/day was only -1.0 ml/min/1.73m2/year (5), the instance of ESRD among such patients may be small—which, in our study, may have compromised detection of the difference between the TSP and SP groups. Recently, Komatsu et al. reported that TSP led to clinical remission more effectively than other treatments for IgAN patients with mild proteinuria (0.4-1.0g/day) [33]. In their study, the rate of clinical remission was significantly higher with TSP than with SP (71.7% vs. 44.4%). However, because the number of patients in

their study was very limited (especially in the SP group: n=9), and they merged patients

who had received SP and OS in the same group, one must await larger studies to assess

the efficacy of TSP over SP in patients with mild IgAN. Furthermore, although

tonsillectomy is a relatively non-invasive operation, one patient in our cohort who

received TSP experienced postoperative hemorrhage, requiring blood transfusion. And it

has been reported that the rate of post-tonsillectomy hemorrhage was 2.3~7.7% [34, 35].

Therefore, at this point, SP might be the better choice for patients with mild IgAN.

There are several limitations to this study. First, selection biases in treatment

may exist. Because of the nature of cohort studies, treatment protocols were not

uniformly defined, which may obscure the actual effect of treatment. Indeed, younger

patients with preserved renal function were more likely to receive TSP than other

therapies—and more likely to receive it than were other groups—which may affect

renal outcome in this study. However, the consistent results—including propensity

score-matched analyses—may overcome this inherent disadvantage of cohort studies.

Second, since the follow-up continued for many years, selection bias involving drop-out

or trend of treatment in each era may exist. For example, steroid use was initiated in the

1980s and TSP in the early 2000s. Although we adjusted by renal-biopsy years, and

observed similar results in propensity score-matched analyses, one needs to be careful

in assessing these results. Finally, the 95% CIs of our HRs were relatively widely

ranged. Although ESRD is considered the gold standard for renal-outcome studies,

because it takes so long to become definite, this hard outcome needs a particularly large

sample size for stable analysis, so its use may decrease study power in long follow-up

studies with their inherently large drop-out rate. Some soft outcomes have been

proposed as proxies for ESRD. But there is no direct evidence that, for instance, the

doubling of serum creatinine or any other soft outcome is surely predictive of ESRD.

Recently, the association of decline in eGFR with subsequent risk of ESRD was

reported in the general CKD population [36], and this may be another possible factor in

identifying the best candidates for TSP, though it is still unclear whether this association

is same among different races or renal diseases. In any case, while ESDR remains the

standard, analyses that involve an even larger IgAN population than ours are needed to

confirm the best candidates for TSP in greater detail.

In conclusion, our multicenter large-scale cohort study demonstrated the

effectiveness of TSP for patients with IgAN, and, for now, identified the best candidates

for the treatment. If IgAN patients have CKD G1 or G2 with proteinuria $\geqq 1.0$g/gCre,

TSP should be considered if they are not otherwise contraindicated for it, while SP,

alone, may be the best option for patients with proteinuria <1.0g or CKD G3.

Future plans

For our study, we had to create a multicenter, large-sale cohort with

biopsy-proven IgAN. Since the database of this cohort of course contains various

clinical information in detail, it may be possible to use it to clarify unsolved clinical

problems in treating IgAN patients. Indeed, as our next studies, we are now analyzing

this cohort, focusing on the disappearance of proteinuria 1 or 2 years after treatment as

an early detection marker of sustained renal function, and also focusing on the effect of

blood pressure control during the treatment by stratifying CKD stage and level of

proteinuria.

With this cohort, it may also be possible to answer other questions, including

what the best treatment option is for recurrent IgAN patients who once experienced

complete remission, and which pathological classification—Oxford or Japanese—is

better for predicting prognosis in IgAN patients.

Our study also showed how little evidence there exists about IgAN patients

with CKD G3. So we plan to use our collaborative network for a new randomized

controlled study of IgAN patients with CKD G3 and proteinuria $\geqq 1.0$g/gCre to

determine the most effective treatment option for them by comparing renal survival

between patients who received SP versus OS when RAS and fish oil were used in both

groups. Since these CKD G3 patients face the highest risk of ESRD, there is great

urgency about identifying the optimum treatment strategy for them.

Table 1: Definition of pathological variables in the Oxford classification (Quoted from reference 5)

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area =0 4-5 Mesangial cells/mesangial area =1 6-7 Mesangial cells/mesangial area =2 $\geqq$8 Mesangial cells/mesangial area =3 The score is the mean score for all glomeruli	M0 - $\leqq$0.5 M1 - >0.5[a]
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 - present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 - present
Tubular atrophy / interstitial fibrosis	Percentage of cortical area involving by the tubular atrophy or interstitial fibrosis, whichever is greater	T0 – 0-25% T1 – 26-50% T2 - >50%

[a] Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

Table 2: Histological classification in Japan (Quoted from reference 1)

A. Histological grade

Histological grade	Percent glomeruli with pathological variables* predicting progression to ESRD	Acute lesion only	Acute and chronic lesion	Chronic lesion only
H-Grade I	0-24.9%	A	A/C	C
H-Grade II	25-49.9%	A	A/C	C
H-Grade III	50-74.9%	A	A/C	C
H-Grade IV	>75%	A	A/C	C

*Acute lesion (A): cellular crescent, tuft necrosis, fibrocellular crescent

Chronic lesion (C): global sclerosis, segmental sclerosis, fibrous crescent

B. Clinical grade

Clinical grade	Proteinuria (g/day)	eGFR (ml/min/1.73m^2)
C-Grade I	<0.5	—
C-Grade II	$\geqq 0.5$	$\geqq 60$
C-Grade III	$\geqq 0.5$	<60

C. Grading system for prediction progression to ESRD

	H-Grade I	H-Grade II	H-Grade III
C-Grade I	Low	Moderate	High
C-Grade II	Moderate	Moderate	High
C-Grade III	High	High	Super High

Table 3: Baseline characteristics of patients who had biopsy-proven IgA nephropathy with estimated glomerular filtration rate (eGFR)≧30 ml/min/1.73m²

Variables		Total cohort					
		Total (n=1,127)	TSP (n=209)	SP (n=103)	OS (n=300)	RAS (n=515)	p-value
Age (years)		44.1±15.5	36.4±11.7	46.2±18.3	40.6±15.7	48.8±14.4	<0.001
Sex (female %)		43.4%	47.4%	52.4%	44.7%	39.2%	0.03
Mean eGFR (ml/min/1.73m²)		64.9±26.9	73.6±25.3	62.7±33.5	66.8±30.3	60.6±26.9	<0.001
CKD stage (eGFR)	G1&2 (eGFR≧60)	76.0%	86.5%	64.1%	76.7%	74.5%	<0.001
	G3a (eGFR45-60)	15.4%	10.1%	16.5%	14.7%	17.7%	
	G3b (eGFR30-45)	8.6%	3.4%	19.4%	9.7%	7.8%	
Albumin (g/dl)		3.7±0.6	3.6±0.4	3.4±0.6	3.6±0.7	3.8±0.5	<0.001
Total cholesterol (mg/dl)		205±50	196±39	213±59	214±64	202±40	<0.001
Hemoglobin (mg/dl)		13.3±1.9	13.3±1.5	12.3±2.0	13.3±2.2	13.6±1.8	<0.001
Blood pressure	systolic (mmHg)	129±19	125±17	131±18	127±18	133±19	<0.001
	diastolic (mmHg)	78±13	76±13	77±11	76±12	80±13	<0.001
Proteinuria (g/gCre)	median [IQR]	0.6 [0.30-1.30]	0.74 [0.32-1.50]	1.80 [0.72-2.80]	1.20 [0.51-2.29]	0.60 [0.33-1.20]	<0.001
	<0.5 (g/gCre)	17.5%	22.4%	9.3%	12.1%	20.1%	<0.001
	0.5-0.99 (g/gCre)	31.3%	36.3%	25.8%	23.2%	34.8%	
	≧1.0 (g/gCre)	51.2%	41.3%	65.0%	64.6%	45.1%	
Hematuria	<5/HPF or (−)	25.6%	16.5%	17.7%	22.2%	32.9%	<0.001
	5-10/HPF or (+)	15.0%	16.5%	13.7%	10.7%	17.2%	
	10-29/HPF or (2+)	27.3%	33.0%	24.5%	24.5%	27.2%	
	≧30/HPF or (3+)	32.1%	34.0%	44.1%	42.6%	22.7%	
Pathological grade (H-grade)	I	65.2%	68.0%	57.8%	69.6%	63.0%	0.31
	II	21.1%	19.4%	27.5%	20.5%	20.9%	

	Ⅲ	10.9%	9.7%	12.8%	8.2%	12.6%	
	Ⅳ	2.8%	2.9%	2.0%	1.7%	3.5%	
	Active lesion	29.8%	28.5%	51.1%	41.1%	18.7%	<0.001
Oxford classification	M	14.5%	8.4%	25.3%	19.6%	12.0%	<0.001
	E	28.3%	51.2%	52.6%	26.5%	18.0%	<0.001
	S	63.9%	76.5%	80.7%	68.0%	52.7%	<0.001
	T1/T2	24.3%/6.4%	24.3%/5.5%	28.3%/8.1%	21.5%/3.4%	25.1%/8.2%	0.10
Medication	RAS inhibitors	79.9%	65.1%	77.7%	56.3%	100.0%	<0.001
	Anticoagulants	8.6%	1.0%	19.4%	16.3%	5.1%	<0.001
	Antiplatelets	54.8%	33.5%	50.5%	71.0%	54.8%	<0.001
	PSL dose (mg/day)	24±11	17±6	26±13	28±11		<0.001

Abbreviations: TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; RAS, inhibitors of the renin-angiotensin system; IQR, interquartile range; HPF, high-power field.

Table 4: Renal outcomes among treatment groups

Variables	Total (n=1,127)	TSP (n=209)	SP (n=103)	OS (n=300)	RAS (n=515)	p-value
Mean follow-up years	8.3±6.4	7.0±4.4	6.6±5.4	10.4±7.3	8.0±6.4	<0.001
Proportion of ESRD	13.6%	3.4%	8.7%	22.0%	13.8%	<0.001
5-year renal survival (%)	93.3 [91.8-94.5]	99.3 [94.9-99.9]	90.6 [81.1-95.5]	89.8 [85.4-93.0]	93.1 [90.1-95.2]	<0.001
10-year renal survival (%)	85.3 [83.0-87.3]	96.3 [90.3-98.6]	85.7 [73.0-92.7]	79.7 [73.8-84.4]	84.8 [80.2-88.4]	<0.001
15-year renal survival (%)	78.2 [75.1-80.9]	86.3 [68.8-94.3}	85.7 [73.0-92.7]	71.3 [64.3-77.1]	73.6 [67.0-79.1]	<0.001
20-year renal survival (%)	74.0 [70.3-77.4]	86.3 [68.8-94.3}	85.7 [73.0-92.7]	65.3 [56.8-72.5]	69.1 [60.6-76.2]	<0.001
10-year renal survival (%)						
1980s	79.6 [72.8-84.9]	n/a	n/a	71.1 [51.6-83.9]	80.7 [56.3-92.3]	0.89
1990s	84.6 [81.3-87.4]	100	85.2 [60.2-95.1]	78.6 [70.6-84.6]	86.7 [80.3-91.1]	0.02
2000s	89.6 [86.0-92.4]	95.3 [87.9-98.3]	87.8 [74.2-94.5]	87.1 [76.5-93.2]	83.3 [75.3-88.8]	0.002

Abbreviations: TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; RAS, inhibitors of the renin-angiotensin system; ESRD, end-stage renal disease; n/a, not applicable.

Table 5: Baseline characteristics of propensity score-matched pairs of patients, TSP and. other treatment groups.

(a) Propensity score-matching, TSP and RAS

Variables		Total (n=254)	TSP (n=127)	RAS (n=127)	p−value
Age (years)		41.1±12.3	40.0±11.7	42.3±12.7	0.14
Gender (female %)		39.8%	41.7%	37.8%	0.90
Mean eGFR (ml/min/1.73m²)		67.7±25.9	67.1±25.9	68.4±25.9	0.69
CKD stage (eGFR)	G1&2 (eGFR≧60)	80.3%	81.1%	79.5%	0.14
	G3a (eGFR45−60)	14.6%	15.0%	14.2%	
	G3b (eGFR30−45)	5.1%	3.9%	6.3%	
Albumin (g/dl)		3.5±0.5	3.5±0.4	3.5±0.6	0.97
Total cholesterol (mg/dl)		199±39	199±41	199±39	0.97
Hemoglobin (mg/dl)		13.4±1.8	13.3±1.6	13.5±1.9	0.51
Blood pressure	systolic (mmHg)	128±17	128±16	128±17	97
	diastolic (mmHg)	78±13	78±13	78±12	0.33
Proteinuria (g/gCre)	median [IQR]	0.74 [0.38−1.51]	0.86 [0.44−1.64]	0.62 [0.35−1.32]	0.06
	<0.5 (g/gCre)	18.1%	15.8%	20.5%	0.35
	0.5−1.0 (g/gCre)	37.4%	35.4%	39.4%	
	>1.0 (g/gCre)	44.5%	48.8%	40.2%	
Hematuria	<5/HPF or (−)	22.1%	17.3%	26.8%	0.32
	5−10/HPF or (+)	15.0%	16.5%	13.4%	
	10−29/HPF or (2+)	32.3%	33.1%	31.5%	
	≧30/HPF or (3+)	30.7%	33.1%	28.4%	
Pathological grade (H−grade)	I	59.1%	57.5%	60.6%	0.55
	II	22.4%	25.2%	19.7%	
	III	15.4%	13.4%	17.3%	
	IV	3.2%	3.9%	2.4%	
	Active lesion	28.4%	31.4%	25.3%	0.33
Oxford	M	14.8%	10.3%	19.4%	0.04

	E	34.9%	45.0%	30.2%	0.25
	S	67.0%	80.8%	54.4%	0.003
	T1/T2	27.3%/8.8%	29.6%/7.2%	25.0%/10.5%	0.53
Medication	RAS inhibitors	100.0%	100.0%	100.0%	1.00
	Anticoagulants	0.0%	0.0%	0.0%	1.00
	Anti-platelets	35.8%	37.0%	34.7%	0.70

(b) Propensity score-matching, TSP and SP

Variables		Total (n=190)	TSP (n=95)	SP (n=95)	p-value
Age (years)		45.1±14.6	44.5±11.0	45.8±17.5	0.54
Sex (female %)		50.5%	48.4%	52.6%	0.56
Mean eGFR (ml/min/1.73m^2)		62.4±28.7	61.3±23.6	63.5±33.1	0.60
CKD stage (eGFR)	G1&2 (eGFR≧60)	71.1%	76.0%	66.3%	0.03
	G3a (eGFR45-60)	16.3%	17.9%	14.7%	
	G3b (eGFR30-45)	12.6%	6.3%	19.0%	
Albumin (g/dl)		3.4±0.5	3.5±0.4	3.4±0.6	0.24
Total cholesterol (mg/dl)		208±50	203±38	214±60	0.16
Hemoglobin (mg/dl)		12.7±1.8	12.9±1.6	12.5±2.0	0.07
Blood pressure	systolic (mmHg)	130±18	129±17	131±18	0.59
	diastolic (mmHg)	78±12	79±14	77±11	0.34
Proteinuria (g/gCre)	median [IQR]	1.13 [0.60-2.3]	0.95 [0.54-1.79]	1.60 [0.67-2.70]	0.005
	<0.5 (g/gCre)	10.5%	11.6%	9.5%	0.26
	0.5-1.0 (g/gCre)	31.1%	35.8%	26.3%	
	>1.0 (g/gCre)	58.4%	52.6%	64.2%	
Hematuria	<5/HPF or (−)	19.5%	21.1%	17.9%	0.25
	5-10/HPF or (+)	17.9%	21.1%	14.7%	
	10-29/HPF or (2+)	26.3%	28.4%	24.2%	
	≧30/HPF or (3+)	36.3%	29.5%	43.2%	

Pathological grade	I	59.5%	60.0%	59.0%	0.79
(H-grade)	II	25.3%	25.3%	25.3%	
	III	12.1%	10.5%	13.7%	
	IV	3.2%	4.2%	2.1%	
	Active lesion	39.1%	24.0%	53.1%	0.001
Oxford	M	17.8%	9.7%	26.1%	0.004
	E	51.5%	62.5%	48.1%	0.31
	S	81.0%	82.1%	80.3%	0.83
	T1/T2	31.0%/7.6%	35.9%/7.6%	26.1%/7.6%	0.34
Medication	RAS inhibitors	80.5%	84.2%	76.8%	0.20
	Anticoagulants	11.1%	2.1%	20.0%	<0.001
	Antiplatelets	45.3%	41.1%	49.5%	0.24

(c) Propensity score-matching, TSP and OS

Variables		Total (n=394)	TSP (n=197)	OS (n=197)	p-value
Age (years)		38.7±14.1	36.7±11.9	40.7±15.7	0.01
Sex (female %)		46.5%	47.7%	45.2%	0.61
Mean eGFR (ml/min/1.73m^2)		71.2±27.6	74.1±25.5	68.4±29.3	0.04
CKD stage (eGFR)	G1&2 (eGFR≧60)	82.0%	86.8%	77.2%	0.01
	G3a (eGFR45-60)	11.7%	10.2%	13.2%	
	G3b (eGFR30-45)	6.4%	3.1%	9.6%	
Albumin (g/dl)		3.7±0.6	3.6±0.4	3.7±0.7	0.24
Total cholesterol (mg/dl)		202±52	195±39	209±61	0.01
Hemoglobin (mg/dl)		13.3±1.9	13.3±1.5	13.3±2.2	0.92
Blood pressure	systolic (mmHg)	125±17	125±17	126±17	0.34
	diastolic (mmHg)	76±13	76±13	76±12	0.67
Proteinuria (g/gCre)	median [IQR]	0.83 [0.35-1.57]	0.69 [0.30-1.22]	1.00 [0.42-1.66]	0.003
	<0.5 (g/gCre)	19.3%	22.8%	15.7%	0.001

	0.5–1.0 (g/gCre)	31.0%	36.6%	25.4%	
	>1.0 (g/gCre)	49.8%	40.6%	58.9%	
Hematuria	<5/HPF or (−)	20.3%	17.3%	23.4%	0.05
	5–10/HPF or (+)	14.2%	16.8%	11.7%	
	10–29/HPF or (2+)	28.7%	33.0%	24.4%	
	≧30/HPF or (3+)	36.8%	33.0%	40.6%	
Pathological grade (H–grade)	I	70.6%	69.0%	72.1%	0.71
	II	19.0%	18.8%	19.3%	
	III	8.1%	9.6%	6.6%	
	IV	2.3%	2.5%	2.0%	
	Active lesion	34.7%	28.5%	42.3%	0.01
Oxford	M	14.5%	8.8%	20.4%	0.001
	E	38.5%	50.0%	33.7%	0.07
	S	71.0%	75.9%	67.5%	0.20
	T1/T2	21.3%/4.5%	23.8%/4.7%	18.7%/4.3%	0.45
Medication	RAS inhibitors	64.2%	64.5%	64.0%	0.92
	Anticoagulants	4.3%	1.0%	7.6%	0.001
	Antiplatelets	45.9%	31.0%	60.9%	<0.001

Abbreviations: TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; RAS, inhibitors of the renin-angiotensin system; IQR, interquartile range; HPF, high-power field.
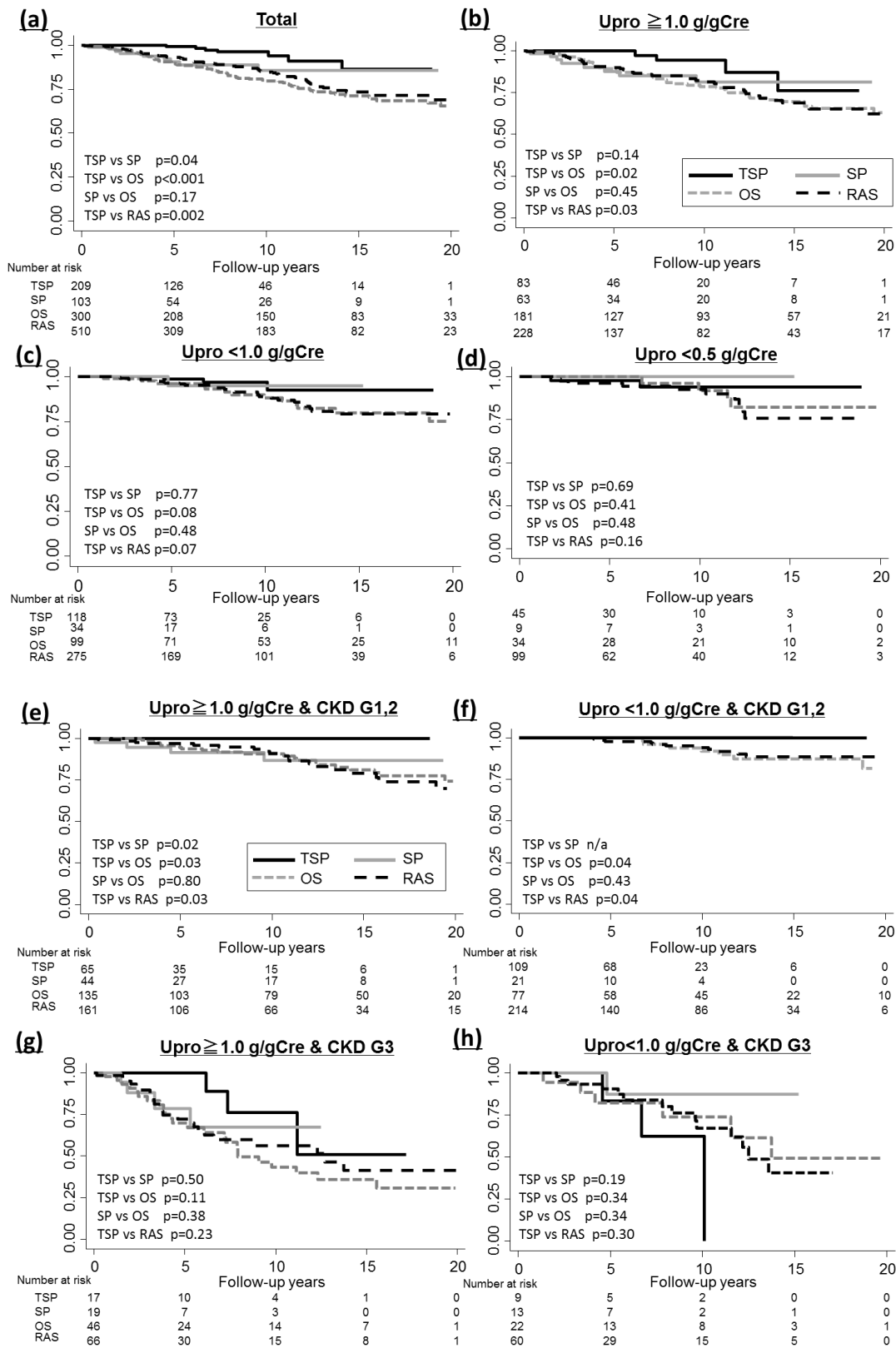
Table 6: Hazard ratios (HRs) of end-stage renal disease in propensity score-matched cohorts by treatment regimens, proteinuria, and CKD stages

	Model 1	Model 2	Model 3
TSP	1.00 (referent)	1.00 (referent)	1.00 (referent)
SP	1.86 [0.59-5.91]	1.28 [0.32-5.10]	3.79 [0.69-20.83]
OS	2.93 [1.11-7.76]	2.70 [0.92-7.91]	3.80 [1.10-13.15]
RAS	7.41 [2.38-23.06]	4.65 [1.40-15.50]	18.51 [3.67-93.41]

Each HR was adjusted in model 1, for IgA scoring system, medications (use of RAS, anticoagulants, and/or antiplatelets), and year of renal-biopsy; in model 2, for sex, age, body mass index (BMI), eGFR, Alb, proteinuria, hematuria, blood pressure, medications and year of renal biopsy; and in model 3, for factors in model 2 plus pathological grade.
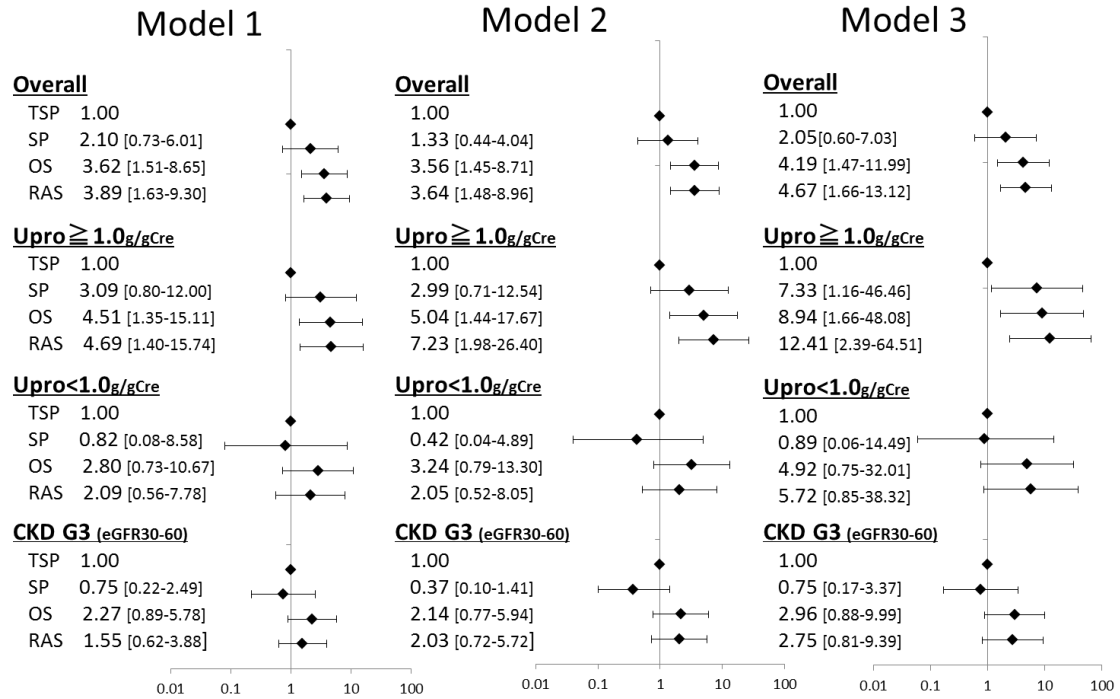
Abbreviations: Upro, proteinuria g/gCre; TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; and RAS, inhibitors of renin-angiotensin system; eGFR, estimated glomerular filtration rate.

Figure 1: Renal survival by treatment group, level of proteinuria, and renal function

(a) Total

TSP vs SP   p=0.04
TSP vs OS   p<0.001
SP vs OS   p=0.17
TSP vs RAS p=0.002

Number at risk

	0	5	10	15	20
TSP	209	126	46	14	1
SP	103	54	26	9	1
OS	300	208	150	83	33
RAS	510	309	183	82	23

(b) Upro ≧1.0 g/gCre

TSP vs SP   p=0.14
TSP vs OS   p=0.02
SP vs OS   p=0.45
TSP vs RAS p=0.03

	0	5	10	15	20
	83	46	20	7	1
	63	34	20	8	1
	181	127	93	57	21
	228	137	82	43	17

(c) Upro <1.0 g/gCre

TSP vs SP   p=0.77
TSP vs OS   p=0.08
SP vs OS   p=0.48
TSP vs RAS p=0.07

Number at risk

	0	5	10	15	20
TSP	118	73	25	6	0
SP	34	17	6	1	0
OS	99	71	53	25	11
RAS	275	169	101	39	6

(d) Upro <0.5 g/gCre

TSP vs SP p=0.69
TSP vs OS p=0.41
SP vs OS   p=0.48
TSP vs RAS p=0.16

	0	5	10	15	20
	45	30	10	3	0
	9	7	3	1	0
	34	28	21	10	2
	99	62	40	12	3

(e) Upro≧1.0 g/gCre & CKD G1,2

TSP vs SP p=0.02
TSP vs OS p=0.03
SP vs OS   p=0.80
TSP vs RAS p=0.03

Number at risk

	0	5	10	15	20
TSP	65	35	15	6	1
SP	44	27	17	8	1
OS	135	103	79	50	20
RAS	161	106	66	34	15

(f) Upro <1.0 g/gCre & CKD G1,2

TSP vs SP n/a
TSP vs OS p=0.04
SP vs OS   p=0.43
TSP vs RAS p=0.04

Number at risk

	0	5	10	15	20
	109	68	23	6	0
	21	10	4	0	0
	77	58	45	22	10
	214	140	86	34	6

(g) Upro≧1.0 g/gCre & CKD G3

TSP vs SP p=0.50
TSP vs OS p=0.11
SP vs OS   p=0.38
TSP vs RAS p=0.23

Number at risk

	0	5	10	15	20
TSP	17	10	4	1	0
SP	19	7	3	0	0
OS	46	24	14	7	1
RAS	66	30	15	8	1

(h) Upro<1.0 g/gCre & CKD G3

TSP vs SP p=0.19
TSP vs OS p=0.34
SP vs OS   p=0.34
TSP vs RAS p=0.30

Number at risk

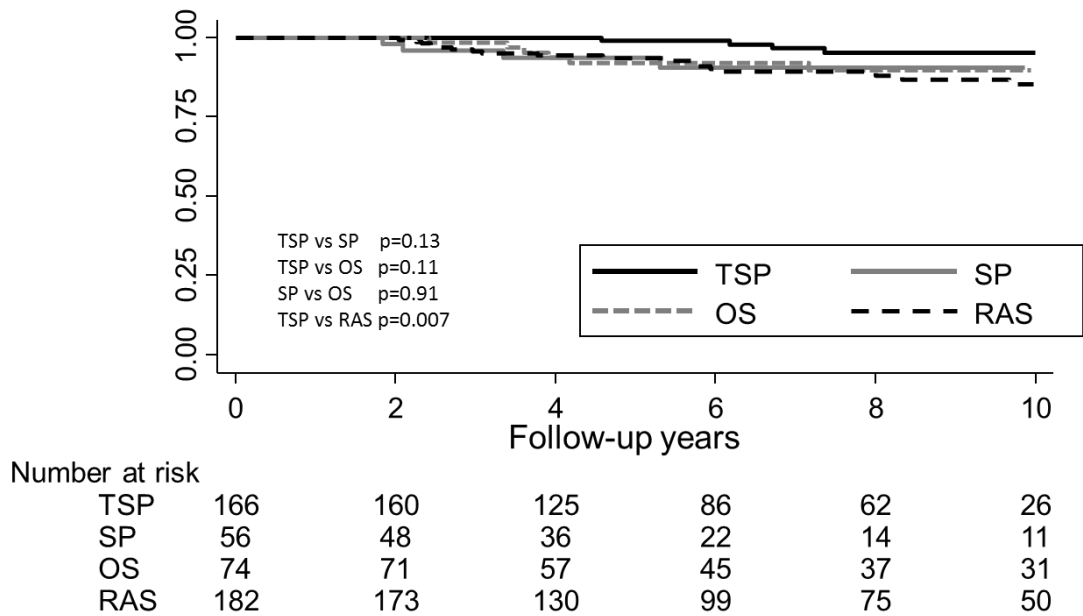|	0	5	10	15	20
	9	5	2	0	0
	13	7	2	1	0
	22	13	8	3	1
	60	29	15	5	0

Legend: TSP, SP, OS, RAS

Abbreviations: Upro, proteinuria g/gCre; TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; and RAS, inhibitors of renin-angiotensin system; eGFR, estimated glomerular filtration rate.

Figure 2: Hazard ratios (HRs) of end-stage renal disease by treatment regimen, proteinuria, and CKD stages.

Each HR was adjusted in model 1, for IgA scoring system, medications (use of RAS, anticoagulants, and/or antiplatelets), and year of renal-biopsy; in model 2, for sex, age, body mass index (BMI), eGFR, Alb, proteinuria, hematuria, blood pressure, medications and year of renal biopsy; and in model 3, for factors in model 2 plus pathological grade.

Abbreviations: Upro, proteinuria g/gCre; TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; and RAS, inhibitors of renin-angiotensin system; eGFR, estimated glomerular filtration rate.

Figure 3: Renal survival by treatment group in 2000's

Number at risk						
TSP	166	160	125	86	62	26
SP	56	48	36	22	14	11
OS	74	71	57	45	37	31
RAS	182	173	130	99	75	50

The p-values were calculated by log-rank test.

Abbreviations: TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; and RAS, inhibitors of renin-angiotensin system.

Figure 4: Comparison of renal survival in propensity score-matched cohorts by treatment.
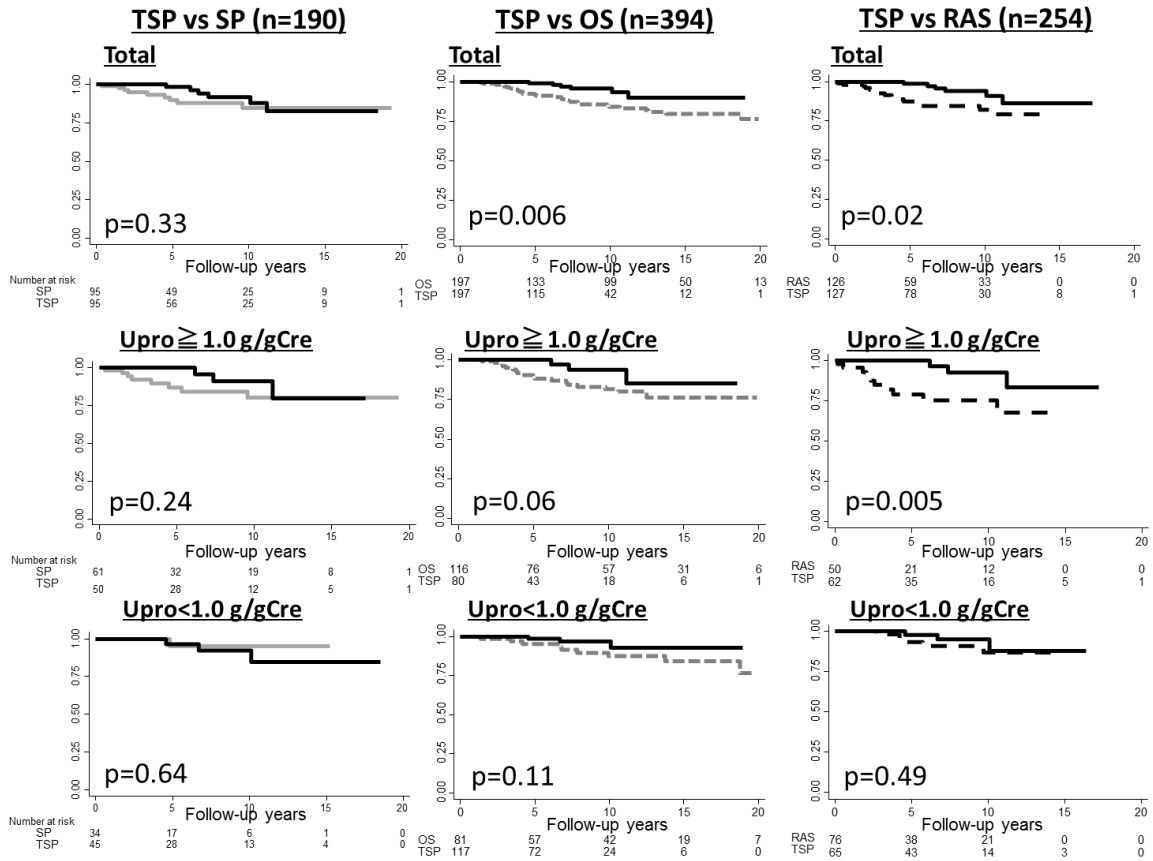
The p-values were calculated by log-rank test.

Abbreviations: Upro, proteinuria g/gCre; TSP, tonsillectomy plus steroid pulse therapy; SP, steroid pulse therapy; OS, oral steroid therapy; and RAS, inhibitors of renin-angiotensin system.

Acknowledgements

References

1. Matsuo, S., et al., *Evidence-Based Clinical Practice Guideline for IgA nephropathy 2014.* Jpn J Nephrol, 2015. **57**(1): p. 5-137.

2. Zeng, C.H., et al., *A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult chinese patients.* Am J Kidney Dis, 2012. **60**(5): p. 812-20.

3. D'Amico, G., *The commonest glomerulonephritis in the world: IgA nephropathy.* Q J Med, 1987. **64**(245): p. 709-27.

4. Kawamura, T., et al., *A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy.* Nephrol Dial Transplant, 2014. **29**(8): p. 1546-53.

5. Cattran, D.C., et al., *The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification.* Kidney Int, 2009. **76**(5): p. 534-45.

6. Kawamura, T., et al., *A histologic classification of IgA nephropathy for predicting long-term prognosis: emphasis on end-stage renal disease.* J Nephrol, 2013. **26**(2): p. 350-7.

7. Galla, J.H., *IgA nephropathy.* Kidney Int, 1995. **47**(2): p. 377-87.

8. Ibels, L.S. and A.Z. Gyory, *IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature.* Medicine (Baltimore), 1994. **73**(2): p. 79-102.

9. Xie, Y., et al., *Relationship between tonsils and IgA nephropathy as well as indications of tonsillectomy.* Kidney Int, 2004. **65**(4): p. 1135-44.

10. Barratt, J., et al., *Immune complex formation in IgA nephropathy: a case of the 'right' antibodies in the 'wrong' place at the 'wrong' time?* Nephrol Dial Transplant, 2009. **24**(12): p. 3620-3.

11. Wyatt, R.J. and B.A. Julian, *IgA nephropathy.* N Engl J Med, 2013. **368**(25): p. 2402-14.

12. D'Amico, G., *Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome.* Semin Nephrol, 2004. **24**(3): p. 179-96.

13. Le, W., et al., *Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population.* Nephrol Dial Transplant, 2012. **27**(4): p. 1479-85.

14. Beck, L., et al., *KDOQI US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis.* Am J Kidney Dis, 2013. **62**(3): p. 403-41.

15. Radford, M.G., Jr., et al., *Predicting renal outcome in IgA nephropathy.* J Am Soc Nephrol, 1997. **8**(2): p. 199-207.

16. Reich Hn Fau - Troyanov, S., et al., *Remission of proteinuria improves prognosis in IgA nephropathy.* J Am Soc Nephrol, 2007. **18**(12): p. 3177-83.

17. Pozzi, C., et al., *Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial.* J Am Soc Nephrol, 2004. **15**(1): p. 157-63.

18. Manno, C., et al., *Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy.* Nephrol Dial Transplant, 2009. **24**(12): p. 3694-701.

19. Kobayashi, Y., et al., *Steroid therapy during the early stage of progressive IgA nephropathy. A 10-year follow-up study.* Nephron, 1996. **72**(2): p. 237-42.

20. Moriyama, T., et al., *The effectiveness of steroid therapy for patients with advanced IgA nephropathy and impaired renal function.* Clin Exp Nephrol, 2004. **8**(3): p. 237-42.

21. Haas, M., *Chapter 10: IgA Nephrology and Henoch-Schonlein Purpura Nephritis*, in *Heptinstall's Pathology of the Kidney*. 6th edition, Lippincott Williams & Wilkins, 2007. p. 421-457.

22. Coppo, R., *Can a dysregulated mucosal immune system in IgA nephropathy be controlled by tonsillectomy?* Nephrol Dial Transplant, 2010. **25**(8): p. 2395-7.

23. de Moura, C.G., et al., *Inflammatory bowel disease, ankylosing spondylitis, and IgA nephropathy.* J Clin Rheumatol, 2006. **12**(2): p. 106-7.

24. Hotta, O., et al., *Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy.* Am J Kidney Dis, 2001. **38**(4): p. 736-43.

25. Komatsu, H., et al., *Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study.* Clin J Am Soc Nephrol, 2008. **3**(5): p. 1301-7.

26. Kawaguchi, T., et al., *Clinical effectiveness of steroid pulse therapy combined with tonsillectomy in patients with immunoglobulin A nephropathy presenting glomerular haematuria and minimal proteinuria.* Nephrology (Carlton), 2010. **15**(1): p. 116-23.

27. Sato, M., et al., *Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy.* Nephron Clin Pract, 2003. **93**(4): p. c137-45.

28. Chen, Y., et al., *Long-term efficacy of tonsillectomy in Chinese patients with IgA nephropathy.* Am J Nephrol, 2007. **27**(2): p. 170-5.

29. Xie, Y., et al., *The efficacy of tonsillectomy on long-term renal survival in patients*

with IgA nephropathy. Kidney Int, 2003. **63**(5): p. 1861-7.

30.   Liu, L.L., et al., *Tonsillectomy for IgA Nephropathy: A Meta-analysis.* Am J Kidney Dis, 2015. **65**(1): p. 80-7.

31.   Matsuo, S., et al., *Revised equations for estimated GFR from serum creatinine in Japan.* Am J Kidney Dis, 2009. **53**(6): p. 982-92.

32.   Goto, M., et al., *A scoring system to predict renal outcome in IgA nephropathy: a nationwide 10-year prospective cohort study.* Nephrol Dial Transplant, 2009. **24**(10): p. 3068-74.

33.   Komatsu, H., et al., *Significance of tonsillectomy combined with steroid pulse therapy for IgA nephropathy with mild proteinuria.* Clin Exp Nephrol, 2015.

34.   Arora, R., et al., *Post tonsillectomy hemorrhage: who needs intervention?* Int J Pediatr Otorhinolaryngol, 2015. **79**(2): p. 165-9.

35.   Cadd, B., et al., *(Ton)silly seasons? Do atmospheric conditions actually affect post-tonsillectomy secondary haemorrhage rates?* J Laryngol Otol, 2015. **129**(7): p. 702-5.

36.   Coresh, J., et al., *Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality.* JAMA, 2014. **311**(24): p. 2518-31.