Validation of the revised Oxford classification for IgA nephropathy considering treatment with corticosteroids/immunosuppressors

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The Oxford classification for IgA nephropathy (IgAN) was updated in 2017. We have validated the revised Oxford classification considering treatment with corticosteroids/immunosuppressors. In this retrospective analysis, 871 IgAN patients were enrolled. Patients were divided into two groups, those treated with or without corticosteroids/immunosuppressors. The 20-year renal prognosis up to end-stage renal disease was assessed using the Oxford classification. In all patients, the renal survival rate was 87.5% at 10 years and 72.6% at 20 years. The T score alone was significantly related to renal prognosis in the Kaplan–Meier analysis and multivariate Cox regression analysis. In the non-treatment group (n = 445), E, S, T, and C scores were significantly related to renal survival rates, however, in the treatment group (n = 426), T score alone was significantly related to renal prognosis on Kaplan–Meier analysis, indicating that corticosteroids/immunosuppressors improved renal prognosis in E1, S1, and C1. In patients with E1, S1, or C1, the treatment group showed significantly better renal prognosis than the non-treatment group in univariate and multivariate analysis. The Oxford classification and T score were used to determine renal prognosis in IgAN patients. Corticosteroids/immunosuppressors improved renal prognosis, especially E1, S1, and C1 scores.

IgA nephropathy (IgAN) was first reported 50 years ago by Berger1. IgAN was initially labelled as a benign disease; however, it was later shown to have a poor long-term prognosis2–5. Although the prognostic risk factors of IgAN have not been clearly defined, hypertension, deterioration of renal function, and increased levels of proteinuria are known prognostic factors2–5. Histological findings may also inform prognosis6–9, although these factors have not achieved worldwide acceptance.

In 2009, the Oxford classification was reported by the International IgAN Network and International Renal Pathology Society10,11. In the Oxford classification, mesangial hypercellularity (M), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and endothelial hypercellularity (E) were selected as prognostic factors against corticosteroids/immunosuppressors (MEST score). After this report of the Oxford classification, several validation studies were performed, with different results among those studies12–25. Using a multivariate analysis, it was determined that the T score was the most valuable marker of progression; however, other factors differed according to the clinical background (race, age), inclusion criteria (estimated glomerular filtration rate [eGFR] > 30 mL/min/1.73 m², proteinuria > 0.5 g/day, minimum follow-up > 1 year), duration of follow-up, treatment, and endpoint of each study (eGFR slope, 50% reduction of eGFR, or end-stage renal disease [ESRD]). Interestingly, several reports validated not only the MEST score but also the crescent formation (as the C score), and multivariate analysis indicated that the C score was an independent factor for progression12,17,18. One meta-analysis of 16 validation studies with 2,893 patients confirmed that the M, S, T, and C scores were strongly related to renal prognosis26. Considering those reports and the previous exclusion criterion of eGFR < 30 mL/min/1.73 m², which meant excluding rapid progressive cases, the MEST...
score was improved when cellular crescent and fibrocellular crescent formations (MEST-C score) were included. The C score was defined as C0 (no crescents), C1 (crescent in >0% but <25% of glomeruli), and C2 (crescents in at least 25% of glomeruli). Corticosteroids/immunosuppressors improved the prognosis of patients with C1 lesions but not of those with C2 lesions; therefore, corticosteroids/immunosuppressors were recommended for treating IgAN patients with C1 lesions.

It is important to note, however, that validation studies of the MEST score have generally excluded patients with rapidly progressing IgAN, defined by an eGFR < 30 mL/min/1.73 m². Moreover, validation data on the revised Oxford classification are lacking. Accordingly, our aim in this study was to validate the revised Oxford classification (MEST-C score) among patients with IgAN, confirmed by renal biopsy.

Results
Clinical and histological findings, initial treatment, and prognosis in all IgAN patients. The study group included 871 patients with IgAN, who had > 8 glomeruli and were observed over a period of ≥ 1 year. The renal prognosis was evaluated using the revised Oxford classification and compared between patients treated with and without corticosteroids/immunosuppressants. The baseline data of all patients are shown in Table 1. The median age was 31.0 years, and there were 356 (40.9%) male and 515 (59.1%) female patients. The median systolic blood pressure (SBP) was 120.0 mmHg, and the median diastolic blood pressure (DBP) was 74.0 mmHg. The median duration of follow-up was 8.0 years. Regarding the laboratory findings, the median eGFR was 77.0 mL/min/1.73 m², and the median urinary protein excretion (U-Prot) was 0.68 g/day. Notably, in our study group, 11 patients (1.2%) had an eGFR < 30 mL/min/1.73 m², with 323 patients (37.0%) having a U-Prot level <0.5 g/day. Histological findings were as follows: 49.4% had M1, 44.9% had E1, 72.0% had S1, 21.7/5.9% had T1/T2, and 45.3/5.3% had C1/C2. Several major treatments for IgAN were started within 1 year after renal biopsy as the initial treatment (Table 1b); 426 patients (48.9%) were treated with corticosteroids/immunosuppressors. Among those 426 patients, 424 patients were treated with corticosteroids alone, and 13 patients were treated with corticosteroids and/or other immunosuppressive agents. One-hundred-and-ninety-two (22.0%) patients underwent tonsillectomy, 293 (33.6%) were treated with renin-angiotensin system (RAS) inhibitors, and 177 (20.3%) were treated with fish oil (Table 1b). One-hundred-and-fifteen patients (13.2%) progressed to ESRD during the follow-up period, and five patients died before reaching ESRD.

The 10-year renal survival rate was 87.5%, and the 20-year renal survival rate was 72.6% (Fig. 1a). There were significant differences in the 20-year renal survival rates for each Oxford classification based on the T score (T0, 82.1%; T1, 59.1%; T2, 38.0%; p < 0.0001), but not based on the M, E, S, or C scores (Fig. 1b–f).

Clinical and histological findings and prognosis in the treatment and non-treatment groups. The Oxford baseline data of the treatment group and the non-treatment group is shown in Table 2, as well as comparisons between the data in the two groups (Table 2). There were significant differences in the median SBP (p = 0.0473), total protein (TP) (p < 0.0001), eGFR (p = 0.0133), T-Cho (p < 0.0001), U-Prot (p < 0.0001), and U-RBC (p = 0.0045) between the groups. Regarding the histological findings used to determine the Oxford classification, M1, E1, S1, and C1/2 were found significantly more often in the treatment group than in the non-treatment group (M1: 57.0 vs. 42.0%, p < 0.0001; E1: 59.6 vs. 30.8%, p < 0.0001; S1: 75.8 vs. 68.5%, p = 0.0164; C1/C2: 55.4/9.6 vs. 30.1/1.1%, p < 0.0001); however, T1 and T2 were similar in both groups. The renal survival rate in the non-treatment group was 85.1% at 10 years and 69.4% at 20 years (Fig. 2a). There were significant differences in the renal survival rate based on E scores (E0, 72.6%; E1, 62.7%; p = 0.0222), S scores (S0, 76.0%; S1, 66.4%; p = 0.0219), T scores (T0, 77.3%; T1, 60.0%; T2, 29.0%; p < 0.0001), and C scores (C0, 73.5%; C1 + C2, 60.3%; p = 0.0075), but not in those based on M score (Fig. 2b–f). The renal survival rate of the treatment group was 90.6% at 10 years and 78.0% at 20 years (Fig. 3a). There were only significant differences between the renal survival rate based on the T score (T0, 90.6%; T1, 55.4%; T2, 51.7%; p < 0.0001). Interestingly, the renal survival rate based on E1, S1, and C1 increased more than that based on E0, S0, and C0, respectively, when corticosteroids/immunosuppressors were used as treatment (E0, 73.4%; E1, 80.5%; p = 0.8183) (S0, 73.8%; S1, 78.4%; p = 0.9111) (C0, 74.9%; C1, 82.6%; p = 0.6672); however, these increases were not significant, and moreover, the renal survival rate based on C2 was still low (64.2%), despite treatment (Fig. 3b–f).

The Cox regression multivariate analysis indicated that lower eGFR and higher U-Prot and mean arterial pressure (MAP) were independent risk factors for progression to ESRD in all patients (Table 3). According to the Oxford classification, only the T score was an independent risk factor for progression in all patients (HR, 1.48; 95% CI, 1.10–1.99; p = 0.0085) and the treatment group (HR, 1.76; 95% CI, 1.05–2.92; p = 0.0287).

Comparison of renal prognosis between the treatment and non-treatment group patients in the E1, S1, or C1 categories. Treatment with corticosteroids/immunosuppressors significantly improved the renal prognosis among IgAN patients in the E1, S1, and C1 categories compared to no treatment (Fig. 4; E1, p = 0.008; S1, p = 0.0064; and C1, p = 0.0014). In the univariate analysis (Table 4, Model 1) and the multivariate analyses considering the clinical and histological findings (Table 4, Model 2), and the clinical and histological findings and treatment (Table 4, Model 3), the use of corticosteroids/immunosuppressors decreased the risk of progression to ESRD in IgAN patients in the E1 (Model 1: HR 0.41, p = 0.0011; Model 2: HR 0.34, p = 0.0008; Model 3: HR 0.50, p = 0.0409), S1 (Model 1: HR 0.55, p = 0.0061; Model 2: HR 0.37, p < 0.0001; Model 3: HR 0.48, p = 0.0032), and C1 (Model 1: HR 0.41, p = 0.0019; Model 2: HR 0.29, p < 0.0001; Model 3: HR 0.39, p = 0.0054) categories.

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Discussion

This report is a validation study of the Oxford analysis of all 871 IgAN patients treated with or without corticosteroids/immunosuppressors. In our analysis, we included IgAN patients with eGFR < 30 mL/min/1.73 m² and progression to ESRD within 1 year who were excluded from the original Oxford classification because it seemed important to include rapidly progressive glomerulonephritis (RPGN) and deteriorated cases at the time of renal biopsy to analyse the risk of cellular and fibrocellular crescents, which were newly included in the Oxford classification as C scores. We also included IgAN patients with U-Prot < 0.5 g/day who were excluded from the original Oxford classification because, in Japan, many IgAN patients are found in the relatively early stages of the
disease by health screening checks; therefore, those mild cases were important to the analysis of IgAN diagnosed in Japan. Moreover, IgAN is generally considered a slowly progressing disease, and those mild cases should be considered in the long-term renal prognosis as in our analysis.

Salient features of our study cohort that are important to note include a relatively young age (median: 30 years old), a greater proportion of females (59.1%), well-controlled blood pressure (120/74 mmHg), relatively good renal function (eGFR 77.0 mL/min/1.73 m²), and mild U-Prot (0.68 g/day), including 37.0% of patients with a U-Prot level < 0.5 g/day. The distribution of Oxford classification categories, based on histological findings, were as follows: M1, 49.4%; E1, 44.9%; S1, 72.0%; T1:T2, 21.7:5.9%; and C1:C2, 45.4:5.3%. Almost half of the patients (48.9%) were treated using corticosteroids/immunosuppressants, with corticosteroids being used in the majority of patients (424 of 426). In our institution, corticosteroids are generally used in the treatment of IgAN for patients with higher U-Prot and U-RBC levels, stable renal function, and presence of active histological findings; these criteria are reflected in Table 2. The indications for the use of immunosuppressants in the other 13 cases included rapid disease progression, presence of comorbidities, patient's request for a reduction of the dose and/or duration of corticosteroids or the detection of adverse effects of corticosteroid therapy, and the physician's decision. The RAS-I was used in 33.6% of patients. This rate of use of RAS-I does not reflect the current standard treatment for IgAN. This lower than expected percentage of RAS-I use does, however, reflect the extended relevant period for our study, which included patients from as far back as 1974. The first RAS-I (captopril) was used for the treatment of hypertension in the mid-1980s in Japan. We began using RAS-I for the treatment of IgAN at our institution in the 1990s, at a rate of 19.2% up to the year 2000, with this rate having since increased to 44.5%. The lower than expected rate of RAS-I use also reflects the characteristics of our study group, with a relatively young age (median age, 31 years), larger proportion of women than men, and the majority of patients being non-hypertensive (MAP ≤ 100 mmHg, 669 (76.8%) patients, and ≤ 90 mmHg, 461 (52.9%) patients). Therefore, there was no significant indication for the use of RAS-I in our study group. We used ESRD as the endpoint of our study, although 37% of our cohort was relatively early cases of IgAN, with a U-Prot level < 0.5 g/day and slow disease progression. As such, the longer period of observation to ESRD was deemed to be more appropriate for analysis than the change in eGFR that was used for the validation of the Oxford classification for IgAN (VALIGA) in the European multicentre cohort trial19,20. Use of the delta eGFR was appropriate in the VALIGA study as patients in that study cohort had more severe IgAN than our cohort and, as such, eGFR is a good predictor of short-term renal survival.
Table 2. Comparison of baseline characteristics between patients with or without corticosteroids/immunosuppressors. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TP, serum total protein; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; UA, serum uric acid; T-cho, serum total cholesterol; TG, triglyceride; U-Prot, urinary protein excretion; U-RBC, urinary red blood cells; MAP, mean arterial pressure; TP, serum total protein; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; UA, serum uric acid; T-cho, serum total cholesterol; TG, triglyceride; U-Prot, urinary protein excretion; U-RBC, urinary red blood cells; MAP, mean arterial pressure; TP, serum total protein; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; UA, serum uric acid; T-cho, serum total cholesterol; TG, triglyceride; U-Prot, urinary protein excretion; U-RBC, urinary red blood cells. The P-values were calculated using the Student t-test for continuous variables and Fisher’s exact test for categorical variables. The results are expressed as the mean (95% confidence interval) or as percentages.

| Baseline data | Unit | Non-treatment group | Treatment group | P-value |
|---------------|------|---------------------|-----------------|---------|
| Age           | Year | 31.0 (24.0–41.0)    | 30.0 (24.0–41.0) | 0.8199  |
| Sex           | Male/female | 174/271     | 182/244         | 0.2771  |
| BMI           | kg/m² | 21.3 (19.6–23.3)   | 21.4 (19.6–23.7) | 0.9953  |
| SBP           | mmHg | 120.0 (110.0–132.0) | 118.0 (110.0–130.0) | 0.0473  |
| DBP           | mmHg | 75.0 (66.0–84.0)    | 74.0 (66.0–82.0)  | 0.4872  |
| MAP           | mmHg | 90.0 (80.8–100.0)   | 88.3 (81.5–98.0)  | 0.2391  |

Laboratory findings

| TP            | g/dL  | 6.9 (6.5–7.3) | 6.7 (6.2–7.1) | <0.0001 |
| Cr            | mg/dL | 0.80 (0.69–1.07) | 0.78 (0.66–0.98) | 0.1492  |
| eGFR          | ml/min/1.73 m² | 73.3 (59.1–93.2) | 79.8 (63.1–96.9) | 0.0133  |
| UA            | mg/dL | 5.4 (4.4–6.7)  | 5.6 (4.7–6.7)  | 0.2996  |
| T-Chol        | mg/dL | 188.0 (164.0–212.0) | 201.0 (173.2–232.0) | <0.0001 |
| TG            | mg/dl | 101.0 (71.0–147.0) | 100.0 (75.0–143.0) | 0.7707  |
| U-Prot        | g/day | 0.54 (0.24–1.08) | 0.88 (0.39–1.83) | <0.0001 |

Histological findings

| M0/M1         | Count/HPF | 57, 186, 57, 59, 82 | 28, 179, 83, 60, 75 | 0.0045  |
| E0/E1         | Count/HPF | 258/187            | 183/243            | <0.0001 |
| S0/S1         | Count/HPF | 308/137            | 172/254            | <0.0001 |
| T0/T1/T2      | Count/HPF | 140/305            | 103/323            | 0.0164  |
| C0/C1/C2      | Count/HPF | 324/94/27          | 307/95/24          | 0.8934  |

In all patients, only the T score was an independent risk factor for progression to ESRD in the multivariate Cox regression analysis. In previous reports of validation studies of the Oxford classification, the results varied because of differences in clinical backgrounds, treatments, and endpoints; however, the T score was shown to be the most important predictive factor for progression in almost all those reports. These previous studies are in support of our results. For IgAN patients treated with corticosteroids/immunosuppressors, we found that the T score was an independent risk factor according to the multivariate Cox regression analysis. For IgAN patients without corticosteroids/immunosuppressors treatment, the E, S, T, and C scores were predictive factors for progression to ESRD according to the univariate analysis (Kaplan–Meier analysis and log-rank test). Moreover, among patients with E1, S1, or C1 lesions, renal prognosis was significantly better among those treated than in those without corticosteroids/immunosuppressors on univariate analysis (Fig. 4 and Model 1 in Table 4) as well as on multivariate analysis considering the clinical and histological background (Model 2 in Table 4) and treatment (Model 3 in Table 4). These results are indicative of the possibility that corticosteroids/immunosuppressors can improve E1, S1, and C1 lesions. The renal survival rate of IgAN patients with a C1 score increased slightly more than that of IgAN patients with a C0 score, but it did not increase in IgAN patients with a C2 score. These results indicate that treatment with corticosteroids/immunosuppressors could improve the renal prognosis of IgAN patients with crescents in less than 25% of glomeruli, but it was difficult to improve the prognosis of IgAN patients with crescents in more than 25% of glomeruli. Recent validation studies of the Oxford classification, including the C score, showed varying results. In results from the VALIGA study, for all patients (n = 1,130), the C score was not a predictive risk factor for a 50% decrease in eGFR or ESRD, and was not a predictive risk factor for the eGFR slope according to the multivariate analysis; however, for IgAN patients without corticosteroids/immunosuppressors treatment during follow-up (n = 582), the C score was an independent risk factor for the eGFR slope. These results indicated that corticosteroids/immunosuppressors improve the prognosis of IgAN patients with C scores. Furthermore, a multicentre validation study involving 3,380 IgAN patients performed in Korea indicated that C1 and C2 scores were valid predictive risk factors for progression to ESRD and decreased eGFR according to univariate and multivariate analyses. In a sub-analysis of the STOP-IgAN trial involving 70 IgAN patients, for IgAN patients without corticosteroids/immunosuppressors treatment, significantly more patients with C1/C2 (38%; 3/8 patients) experienced progression to ESRD compared to patients with C0 (4%; 1/24 patients) (p = 0.0039); however, this was not true for IgAN patients treated with corticosteroids/immunosuppressors (C1/2 vs. C0: 7% [1/14 patients] vs. 13% [3/23 patients]; not significant) or for all patients (C1/2 vs. C0: 18% [4/22 patients] vs. 9% [4/47 patients]; not significant) during the 3-year analysis. A validation study performed in China involving two centres with 1,152 patients showed
that the 10-year renal survival rate was not significantly different among patients with C0, C1, and C2 scores, regardless of whether patients were treated with corticosteroids/immunosuppressors. However, in this study, for the patients with nephrotic syndrome, the C score was an independent factor for progression according to the multivariate analysis after adjusting for age, sex, eGFR, MAP, pathological findings, and immunosuppressors32. Considering all of these reports and our results, the C score is indicated to be a significant predictive factor for progression to ESRD, and the C1 score was reversible with corticosteroids/immunosuppressors, which is a good indication for this treatment.

Interestingly, our results showed that treatment with corticosteroids/immunosuppressors also improved the prognosis of IgAN patients with E1 or S1 score. Endocapillary hypercellularity (E1) was considered as the active lesion leading to the inflammation of capillaries and crescent formation. The beneficial effects of corticosteroids/immunosuppressors were seen as a reasonable result, like the previous VALIGA study28. When segmental sclerosis (S1) was considered as the chronic lesion, it was difficult to obtain a good response using corticosteroids/immunosuppressors. However, chronic lesions can result from continuous inflammation in the glomeruli; therefore, some IgAN patients with chronic lesions also had active lesions, and immunosuppressors improved their renal outcomes. These results were also shown in a sub-analysis of the STOP-IgAN trial31 and a sub-analysis34 of the randomized controlled trial by the IgAN study group in Japan that compared tonsillectomy combined with steroid pulse therapy and steroid pulse monotherapy33. In the STOP-IgAN trial, the renal survival rate for IgAN patients with T scores with progression to ESRD was improved by corticosteroids/immunosuppressors (T1/2 vs. T0: 18% [3/17 patients] vs. 7% [1/15 patients]; p = 0.0603) but not supportive therapy (T1/2 vs. T0: 33% [4/12 patients] vs. 0% [0/25 patients]; p = 0.008)31. A randomized controlled trial performed by the IgAN study group indicated that only the S score was an independent factor for the disappearance of both proteinuria and haematuria by steroid pulse therapy combined with tonsillectomy; however, the M, E, and T scores were not33,34. These results were observed during the short-term (only 1 to 3 years); therefore, we propose that our long-term observation study shows clearer results.

This study has some limitations. First, it was performed at a single centre in Japan. Therefore, almost all of the patients in our cohort were Japanese, which means that these results might not apply to other ethnicities than
Figure 3. Renal survival rates of the treatment group. (a) The renal survival rate of treatment group was 90.6% at 10 years and 78.0% at 20 years, and they were similar for the (b) M0 (83.0%) and M1 (70.5%) categories (p = 0.2125), (c) E0 (73.4%) and E1 (80.5%) categories (p = 0.8183) and (d) S0 (73.8%) and S1 (78.4%) categories (p = 0.9111). (e) The 20-year renal survival rates were 90.6% for T0, 55.4% for T1, and 51.7% for T2, which were significantly different among the three groups (p < 0.0001). The renal survival rate for T1 was significantly higher than for T2 (p = 0.0165). (f) The 20-year renal survival rate was not significantly different among the three C-score groups (C0, 74.9%; C1, 82.6%; C2, 64.2%; p = 0.4954). The renal survival rate for the C0 category was similar to that for C1 (p = 0.6672) and for C2 (p = 0.4924). The renal survival rate for C1 was similar to that for C2 (p = 0.2219).

Table 3. Independent risk factors for progression to ESRD in the multivariate Cox regression analysis. BMI body mass index, MAP mean arterial pressure, TP serum total protein, eGFR estimated glomerular filtration rate, U-Protein urinary protein excretion, U-RBC urinary red blood cells, M mesangial hypercellularity, E endocapillary hypercellularity, S segmental sclerosis, T interstitial fibrosis/tubular atrophy, C crescents.
Asian. Second, we did not exclude cases of deteriorated renal function and/or mild proteinuria cases at diagnosis because our aim was also to evaluate the rapid progressive cases (cases of deteriorated renal function), which seem to have more crescent formation, and also evaluate early-stage cases (mild proteinuria cases) especially those diagnosed in Japan. We have shown the cohort results when applying the inclusion criteria stated in the original Oxford classification (Supplemental Materials). However, the results were clearer in the cohort where our criteria were applied than in the cohort with the criteria of the original Oxford classification. In Japan, IgAN was mainly found in health screening checks, and the criterion for biopsy was the early stage of the disease; therefore, the evaluation criteria of the Oxford classification might be different. Specifically, although delta eGFR might be the most appropriate marker to evaluate the short-term renal prognosis among patients with more than mild IgAN, the Oxford Classification was useful in our study, in which we included cases with a wide range of IgAN disease severity, from mild (slowly progressing) to deteriorating IgAN. Third, this study was a retrospective cohort analysis. To establish strong evidence, large multicentre prospective control trials, including patients of other races, should be performed.

Conclusions
In this study, we report a validation of the Oxford analysis and found that the T score was the most important predictive factor of renal survival in all IgAN patients despite treatment with corticosteroids/immunosuppressors. However, corticosteroids/immunosuppressors improved the long-term renal prognosis for IgAN patients with E1, S1, and C1 scores.

Methods
Study population and study design. In this study, 1,147 primary IgAN patients were diagnosed via renal biopsy at Tokyo Women’s Medical University between 1974 and 2015. In those patients, 871 patients had more than eight glomeruli according to the renal biopsy. They were observed for at least 1 year after renal biopsy unless ESRD occurred within 1 year and were not diagnosed with a systemic disease, such as systemic lupus erythematosus, liver cirrhosis, and IgA vasculitis with nephritis. The patients with eGFR < 30 mL/min/1.73 m² and/or proteinuria < 0.5 g/day were not excluded from evaluating the rapid progressive cases at diagnosis and mild cases. Of those 871 patients, 426 patients began treatment with corticosteroids/immunosuppressors within...
1 year after renal biopsy as the initial treatment (treatment group), and 445 patients did not (non-treatment group). Validation of the Oxford classification was determined using all patients, and comparisons were made between the two groups.

This retrospective cohort study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Tokyo Women’s Medical University (reference #5104). Written informed consent to perform a renal biopsy was obtained from all patients; patients were able to opt-out of this study by visiting our institution’s website.

**Diagnosis of IgAN and histological evaluation of renal biopsy specimens.** The indication for renal biopsy generally depended on a higher amount of proteinuria (>1.0 g/day), U-RBC (>50/HPF), stable renal function (chronic kidney disease (CKD) grade 1 or 2), and/or severe histological active lesions, such as endocapillary hypercellularity and cellular and fibro-cellular crescents. The criteria for renal biopsy included rapid progressive glomerulonephritis, with deteriorating renal function, and patients’ background and assessment/treatment goals in cases with mild urinary and/or histological findings.

All renal biopsy specimens were obtained using a percutaneous needle biopsy. Specimens were fixed in 10% phosphate-buffered formalin (pH 7.2), embedded in paraffin, and cut into 4-μm-thick sections. The sections were stained with haematoxylin and eosin, periodic acid–Schiff, silver methenamine, and Masson trichrome; then, they were examined by light microscopy. For the immunofluorescence analysis, the specimens were fixed with cold acetone, and frozen sections were routinely subjected to fluorescence by IgG, IgA, IgM, C3, C4, Clq, fibrinogen, and fibronectin. IgAN was diagnosed based on mesangial proliferative changes in light microscopic findings, mesangial IgA and C3 deposition in immunofluorescence findings, and mesangial electron-dense deposits in electron microscopic findings.

Histological findings were graded according to the Oxford classification.10,11,27.

**Clinical and laboratory data.** Patient sex, age, body mass index (BMI), SBP, DBP, MAP, and duration of the observation period were recorded. Laboratory data included serum TP, creatinine (Cr), eGFR, uric acid (UA), total cholesterol (T-Cho), triglycerides, U-Prot, and urinary red blood cells (U-RBC) at the time of renal biopsy; these were evaluated as baseline data. The eGFR was calculated using the modified isotope dilution mass spectrometry-modification of diet in renal disease (IDMS-MDRD) study for Japanese individuals [eGFR = 194 × S-Cre-1.094 × age-0.287 × 0.739 [if female]]28. Time to progression to ESRD, defined as requiring dialysis or renal transplantation, was evaluated as the endpoint, and the risk factors associated with progression to ESRD were evaluated.

**Statistical analysis.** Data were expressed as mean ± standard deviation (SD) for normally distributed data and as the median and interquartile range (IQR) for skewed data. Cumulative renal survival rates until ESRD were calculated according to the Kaplan–Meier method and compared using the log-rank test. The unpaired Student’s t-test for normally distributed data and Mann–Whitney’s U test for skewed data were used to compare the clinical findings of patients treated with or without corticosteroids/immunosuppressors. The chi-squared test was used to compare the sex distribution, the number of patients with each grade of U-RBC at the time of renal biopsy, and the Oxford classification of groups treated with or without corticosteroids/immunosuppressors. Univariate and multivariate Cox regression analyses were performed to evaluate the risk of deterioration to ESRD. The univariate analyses indicated that sex (male/female) and Oxford classification were categorical variables, and that age, BMI, MAP, eGFR, UA, T-Cho, U-Prot, and U-RBC were quantitative variables. The results of these univariate and multivariate analyses are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). In all analyses, p < 0.05 was considered statistically significant. All analyses were performed using JMP Pro 13.0.0 (SAS Institute Inc., Cary, NC, USA).

**Data availability**
The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

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