Predictors of early remission of proteinuria in adult patients with minimal change disease: a retrospective cohort study

Ryohei Yamamoto1,2*, Enyu Imai3, Shoichi Maruyama4, Hitoshi Yokoyama5, Hitoshi Sugiyama6, Asami Takeda7, Shunya Uchida8, Tatsuo Tsukamoto9, Kazuhiko Tsuruya10, Yasuhiro Akai11, Kosaku Nitta12, Megumu Fukunaga13, Hiroki Hayashi14, Kosuke Masutani15, Takashi Wada16, Tsuneo Konta17, Ritsuko Katafuchi18, Saori Nishio19, Shunsuke Goto20, Hiroyoshi Tama21, Arimasa Shirasaki22, Tatsuya Shoji23, Kojiro Nagai24, Tomoya Nishino25, Kunihiro Yamagata26, Junichiro J. Kazama27, Keiju Hiromura28, Hideo Yasuda29, Makoto Mizutani30, Tomohiko Naruse31, Takeyuki Hiramatsu32, Kunio Morozumi33, Hiroshi Sobajima34, Yusuke Saka35, Eiji Ishimura36, Daisuke Ichikawa37, Takashi Shigematsu38, Tadashi Sato39, Shouichi Fujimoto40, Takanori Ito41, Hiroshi Sato42, Ichiei Narita43, Yositaka Isaka2 & JNSCS Investigators*

Previous studies reported conflicting results regarding an association between serum albumin concentration and the cumulative incidence of remission of proteinuria in adult patients with minimal change disease (MCD). The present study aimed to clarify the clinical impact of serum albumin concentration and the cumulative incidence of remission and relapse of proteinuria in 108 adult patients with MCD at 40 hospitals in Japan, who were enrolled in a 5-year prospective cohort study of primary nephrotic syndrome, the Japan Nephrotic Syndrome Cohort Study (JNSCS). The association between serum albumin concentration before initiation of immunosuppressive treatment (IST) and the cumulative incidence of remission and relapse were assessed using multivariable-adjusted Cox proportional hazards models. Remission defined as urinary protein < 0.3 g/day (or g/gCr) was observed in 104 (96.3%) patients. Of 97 patients with remission within 6 month of IST, 42 (43.3%) developed relapse defined as ≥ 1.0 g/day (or g/gCr) or dipstick urinary protein of ≥ 2+. Serum albumin concentration was significantly associated with remission (multivariable-adjusted hazard ratio [95% confidence interval] per 1.0 g/dL, 0.57 [0.37, 0.87]), along with eGFR (per 30 mL/min/1.73 m²: 1.43 [1.08, 1.90]), whereas they were not associated with relapse. A multivariable-adjusted model showed that patients with high eGFR level (≥ 60 mL/min/1.73 m²) and low albumin concentration (≤ 1.5 g/dL) achieved significantly early remission, whereas those with low eGFR (< 60 mL/min/1.73 m²) and high albumin concentration (> 1.5 g/dL) showed significantly slow remission. In conclusion, lower serum albumin concentration and higher eGFR were associated with earlier remission in MCD, but not with relapse.

1Health and Counseling Center, Osaka University, 1-17 Machikaneyama-cho, Toyonaka, Osaka 560-0043, Japan. 2Department of Nephrology, Osaka University Graduate School of Medicine, 2-2-D11 Yamadaoka, Suita, Osaka 565-0871, Japan. 3Nakayamadera Imai Clinic, 2-8-18 Nakayamadera, Takarazuka, Hyogo 665-0861, Japan. 4Department of Nephrology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. 5Department of Nephrology, Kanazawa Medical University School of Medicine, 1-1 Daigaku, Uchinada, Kahoku, Ishikawa 920-0293, Japan. 6Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikatacho, Kita-ku, Okayama, Okayama 700-8558, Japan. 7Kidney Disease Center, Japanese Red Cross Nagoya Daini Hospital, 2-9 Myokencho, Showa-ku, Nagoya, Aichi 466-8650, Japan. 8Department of Internal Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8606, Japan.
Minimal change disease (MCD) is one of the major primary nephrotic syndromes1-3. MCD in adults is highly steroid-sensitive, but steroid resistance is seen in 5–20% of adult patients with MCD4. Epidemiological studies have showed that the incidence of end-stage kidney disease (ESKD) is remarkably lower in patients with MCD than in those with MN and FSGS4,5, concluding that MCD typically has favorable outcomes. However, compared with the general population, patients with MCD were at significantly higher risk of ESKD and thromboembolism6. Because steroid resistance predicts the incidence of ESKD in adult patients with MCD7, clinical characteristics associated with steroid sensitivity should be clarified to stratify the patients with MCD into several groups with different levels of steroid sensitivity.

Early small retrospective cohort studies published between the 1980s and the 2000s including ≤ 62 adult patients with MCD, suggested that several clinical factors were associated with steroid sensitivity in adult patients with MCD without controlling for potential clinical confounders, including age9,10, serum concentrations of creatinine11 and albumin10, selectivity index of proteinuria11, microscopic hematuria11, and acute kidney injury (AKI)12. However, their results may be biased without controlling for potential confounding factors. Recent Japanese retrospective cohort studies, including 142-15 or 125-15 patients aged ≥ 15 years with MCD, confirmed that young age13,14, low serum creatinine concentration13,14, and low urinary protein level14 independently predicted early remission, even after adjusting for clinically relevant factors. Another Japanese retrospective cohort study identified low serum albumin concentration, not urinary protein level, as a significant predictor of early remission, besides young age and no AKI15. The findings of these two studies strongly suggest that high glomerular filtration rate (GFR) level is a predictor of early remission. In contrast, the impacts of urinary protein level and serum albumin concentration on remission were conflicting, which should be examined in a multicenter cohort study with external validity.
The aim of the present cohort study was to identify the clinical predictors of remission and relapse of proteinuria in adult patients with MCD, with great interest in serum albumin concentration, urinary protein level, and GFR. We used the clinical data collected prospectively in 108 adult patients with MCD in 40 hospitals, who were enrolled in a 5-year prospective cohort study, the Japan Nephrotic Syndrome Cohort Study (JNSCS)\(^1\)–\(^5\).

The results of the present study provide useful clinical information to identify patients at a high risk of steroid resistance, who might need intensive immunosuppressive therapy (IST).

### Results

Clinical characteristics of 108 adult patients with MCD included in the present study were listed in Table 1. Medina age was 43 years (interquartile range 30, 64) and 61.1% were male patients. Numbers (proportions) of the patients with eGFR of < 30, 30–59, 60.0–89.0, and ≥ 90.0 mL/min/1.73 m\(^2\) were 11 (10.2%), 28 (25.9%), 48 (44.4%), and 21 (19.4%), respectively. Serum albumin concentration was 1.7 ± 0.6 g/dL, and the urinary protein level was 7.8 (5.1, 10.7) g/day or g/gCr. The cumulative incidence of remission within 6 months of IST was 89.8% (95.7% for the Wilcoxon rank-sum test, the chi-square test, or Fisher's exact test).

The aim of the present cohort study was to identify the clinical predictors of remission and relapse of proteinuria in adult patients with MCD, with great interest in serum albumin concentration, urinary protein level, and GFR. We used the clinical data collected prospectively in 108 adult patients with MCD in 40 hospitals, who were enrolled in a 5-year prospective cohort study, the Japan Nephrotic Syndrome Cohort Study (JNSCS)\(^1\)–\(^5\).

The results of the present study provide useful clinical information to identify patients at a high risk of steroid resistance, who might need intensive immunosuppressive therapy (IST).

### Results

Clinical characteristics of 108 adult patients with MCD included in the present study were listed in Table 1. Medina age was 43 years (interquartile range 30, 64) and 61.1% were male patients. Numbers (proportions) of the patients with eGFR of < 30, 30–59, 60.0–89.0, and ≥ 90.0 mL/min/1.73 m\(^2\) were 11 (10.2%), 28 (25.9%), 48
The clinical characteristics of 108 adult patients with MCD stratified by serum albumin levels were listed in Table S1, including 12 (11.1%), 41 (38.0%), 28 (25.9%), and 27 (25.0%) patients with serum albumin concentrations of ≤ 1.00, 1.01–1.50, 1.51–2.00, and > 2.00 g/dL, respectively. Age, urinary protein level, and intravenous albumin administration at initiating IST were significantly different among 4 groups of serum albumin concentration. After categorizing 108 patients into 2 groups of ≤ 1.50 (n = 53 [49.1%]) and > 1.50 g/dL (n = 55 [50.9%]) of serum albumin concentration, no significant difference was observed between these groups in baseline characteristics and use of immunosuppressive drugs within one month of IST, except intravenous albumin administration (Table 1). Table S2 shows the clinical characteristics stratified by estimated GFR (eGFR) groups, including 11 (10.2%), 28 (25.9%), 48 (44.4%), and 21 (19.4%) patients with eGFR < 30.0, 30.0–59.9, 60.0–89.9, and ≥ 90.0 mL/min/1.73 m², respectively. Age, age category, body mass index (BMI), and systolic and diastolic blood pressure, serum creatinine concentration, dipstick hematuria, renin-angiotensin system (RAS) blockade at initiating IST were significantly different among the eGFR groups. Between the patients with eGFR ≥ 60 mL/min/1.73 m² and those with eGFR < 60 mL/min/1.73 m², age, age category, systolic blood pressure, serum creatinine concentration, urinary protein level, dipstick hematuria, RAS blockade, and intravenous albumin administration at initiating IST were significantly different (Table 1). The clinical characteristics stratified by urinary protein groups are listed in Table S3. Age, age category, BMI, serum creatinine concentration at initiating IST were significantly different among 4 groups of urinary protein, besides use of intravenous mPSL within 1 month of IST.

During the median (interquartile range) observational period of 15 (10, 28) days, remission was observed in 12 (100.0%), 40 (97.6%), 28 (100.0%), and 24 (88.9%) patients with serum albumin levels of ≤ 1.00, 1.01–1.50, 1.51–2.00, and > 2.00 g/dL, respectively (Table S1). Patients with lower serum albumin concentrations were likely to achieve remission more rapidly (P_{rend} = 0.007) (Fig. 1a). Compared with patients with > 2.00 g/dL of serum albumin concentration, those with 1.01–1.50 g/dL had a significantly lower cumulative probability of remission (P = 0.046) and those with ≤ 1.00 g/dL had lower cumulative probability of remission at marginally significant level (P = 0.060). In patients with eGFR of < 30.0, 30.0–59.9, 60.0–89.9, and ≥ 90.0 mL/min/1.73 m², 10 (90.9%), 28 (100.0%), 46 (95.8%), and 20 (95.2%) patients achieved remission, respectively (Table S2). Patients with a higher eGFR were more likely to achieve remission more rapidly (P_{rend} < 0.001) (Fig. 1b). Compared with patients with eGFR < 30.0 mL/min/1.73 m², those with eGFR ≥ 30.0 mL/min/1.73 m² had a significantly higher cumulative probability of remission. In contrast, no significant difference was observed in the cumulative incidence of remission among the four groups of urinary protein levels (Fig 1c). Unadjusted Cox proportional hazards (CPH) models showed that younger age, lower systolic blood pressure, lower serum albumin concentration, and higher eGFR levels were significantly associated with remission (Table 2). A multivariable-adjusted model identified serum albumin (per 1.0 g/dL, adjusted hazard ratio [HR] 0.57 [95% confidence interval 0.37, 0.87]) and eGFR (per 30 mL/min/1.73 m², 1.43 [1.08, 1.90]) as significant predictors of remission (Table 2).

To clarify the dose-dependent association of serum albumin concentration and eGFR with remission, the unadjusted and adjusted HR of each group of serum albumin and eGFR was calculated. Compared with patients with serum albumin concentration of > 2.00 g/dL, those with serum albumin concentration of ≤ 1.00 and 1.01–1.50 g/dL had significantly higher unadjusted and adjusted HR, and their HRs were very comparable (adjusted HRs of serum albumin concentration of ≤ 1.00, 1.01–1.50, 1.51–2.00, and > 2.00 g/dL: 2.47 [1.14, 5.34], 2.32 [1.31, 4.14], 1.51 [0.83, 2.73], and 1.00 [reference], respectively) (Table 3). A multivariable-adjusted restricted cubic spline model confirmed the non-linear association between serum albumin concentration and remission (Fig. 2a). A similar non-linear association was observed between eGFR and remission. Compared with patients with eGFR of < 30.0 mL/min/1.73 m², those with eGFR of 60.0–89.9 and ≥ 90.0 mL/min/1.73 m² were significantly associated with remission at the similar level (adjusted HRs of eGFR of < 30.0, 30.0–59.9, 60.0–89.9, and ≥ 90.0 mL/min/1.73 m²: 1.00 [reference], 1.21 [0.54, 2.70], 2.59 [1.18, 5.70], and 2.73 [1.09, 6.84], respectively) (Table 3). The non-linear association between eGFR and remission was verified in a multivariable-adjusted restricted cubic spline model (Fig. 2b). According to the non-linear association of serum albumin concentration and eGFR, we categorized the patients into four groups based on eGFR (< 60.0 vs. ≥ 60.0 mL/min/1.73 m²) and serum albumin concentration (> 1.50 vs. ≤ 1.50 g/dL) and calculated their HRs. Compared with patients with eGFR ≥ 60.0 mL/min/1.73 m² and serum albumin concentration > 1.50 g/dL, those with eGFR < 60.0 mL/min/1.73 m² and serum concentration > 1.50 g/dL achieved remission significantly more slowly (0.48 [0.23, 1.00]), whereas those with eGFR ≥ 60.0 mL/min/1.73 m² and serum concentration ≤ 1.50 g/dL did significantly more rapidly (2.20 [1.28, 3.81]) (Table 3).

Predictors of relapse of proteinuria were assessed in 97 patients with remission within 6 months of IST. During the median (interquartile range) observational period of 2.2 (0.9, 4.7) years, relapse was observed in 3 (25.0%), 21 (53.8%), 11 (45.8%), and 7 (31.8%) patients with serum albumin concentration of ≤ 1.00, 1.01–1.50, 1.51–2.00, and > 2.00 g/dL, respectively (Table S1). No significant difference was observed in the cumulative probability of relapse among the four groups of serum albumin concentrations (P_{rend} = 0.407). Regarding the four eGFR groups, 3 (50.0%), 12 (44.4%), 18 (40.0%), and 9 (47.4%) patients with eGFR of < 30.0, 30.0–59.9, 60.0–89.9, and ≥ 90.0 mL/min/1.73 m² relapsed after remission, respectively (Table S2). The cumulative probability of relapse was comparable among these eGFR groups (P_{rend} = 0.633). Unadjusted and adjusted CPH models showed that no variable was associated with relapse (Table 2).
Figure 1. Cumulative probability of remission stratified by serum albumin concentration (a), eGFR level (b), and urinary protein level (c). *P < 0.05, vs. serum albumin concentration > 2.00 g/dL and eGFR < 30.0 mL/min/1.73 m². †P < 0.10, vs. serum albumin concentration > 2.00 g/dL.
Discussion

The present study clarified that serum albumin and eGFR were associated with remission of proteinuria in a non-linear fashion in 108 adult patients with MCD, whereas they were not associated with relapse of proteinuria. Patients with lower serum albumin concentrations, especially ≤ 1.5 g/dL, were likely to achieve remission more rapidly. Lower eGFR, especially < 60 mL/min/1.73 m², was associated with slower remission. An advantage of the present study was the detailed assessment of the multivariable-adjusted non-linear association of serum albumin and eGFR with remission, providing clinically useful information to identify the patients who are resistant to IST, namely, those with serum albumin concentration > 1.5 g/dL or eGFR < 60 mL/min/1.73 m².

Table 2. Predictors of remission and relapse. CI confidence interval, eGFR estimated glomerular filtration rate, HR hazard ratio, mPSL methylprednisolone, UP urinary protein. *P < 0.05. † Including 97 patients with remission of proteinuria within 6 months of IST. ‡ Adjusted for all variables listed in the table.

| Category | N (%) | Unadjusted HR (95% CI) | Adjusted HR (95% CI)‡ |
|----------|-------|------------------------|-----------------------|
| Serum albumin |       |                        |                       |
| ≤ 1.00 g/dL | 12   | 12 (100.0)              | 2.18 (1.07, 4.46)*    | 2.47 (1.14, 5.34)* |
| 1.01–1.50 | 41   | 40 (97.6)               | 1.79 (1.06, 3.01)*    | 2.32 (1.31, 4.16)* |
| 1.51–2.00 | 28   | 28 (100.0)              | 1.27 (0.73, 2.20)     | 1.51 (0.83, 2.73)  |
| > 2.00   | 27   | 24 (88.9)               | 1.00 (reference)      | 1.00 (reference)   |
| eGFR     |       |                        |                       |
| < 30.0 mL/min/1.73 m² | 11 | 10 (90.9) | 1.00 (reference) | 1.00 (reference) |
| 30.0–59.9 | 28  | 28 (100.0)              | 1.69 (0.81, 3.52)     | 1.21 (0.54, 2.70)  |
| 60.0–89.9 | 48  | 46 (95.8)               | 2.90 (1.45, 5.81)*    | 2.59 (1.18, 5.70)  |
| ≥ 90.0   | 21   | 20 (95.2)               | 2.81 (1.30, 6.05)*    | 2.73 (1.09, 6.84)  |
| eGFR and serum albumin |       |                        |                       |
| < 60.0 mL/min/1.73 m² and > 1.50 g/dL | 19 | 18 (94.7) | 0.50 (0.28, 0.89)* | 0.48 (0.23, 1.00)* |
| < 60.0 and ≥ 1.50 | 20 | 20 (100.0) | 0.82 (0.47, 1.43) | 0.85 (0.45, 1.59) |
| ≥ 60.0 and > 1.50 | 36 | 34 (94.4) | 1.00 (reference) | 1.00 (reference) |
| ≥ 60.0 and ≥ 1.50 | 33 | 32 (97.0) | 1.84 (1.13, 3.02)* | 2.20 (1.28, 3.81)* |

Table 3. Serum albumin, eGFR, and the incidence of remission. CI confidence interval, eGFR estimated glomerular filtration rate, IRR incidence rate ratio. *P < 0.05. † Adjusted for age (18–40, 41–64, and ≥ 65 years), sex, body mass index (kg/m²), systolic blood pressure (mmHg), serum albumin (g/dL, if eGFR), eGFR (mL/min/1.73 m², if serum albumin), urinary protein (log g/day or log g/gCr), dipstick hematuria (− or ±, 1+, and ≥ 2+), use of intravenous albumin before immunosuppressive therapy, and use of intravenous methylprednisolone and cyclosporine within 1 month after initiating immunosuppressive therapy.
Conflicting associations between serum albumin concentration and remission of proteinuria in patients with MCD have been reported in some retrospective cohort studies. A retrospective single-center cohort study in the UK, including 51 adult patients with MCD at a single hospital, reported that the time to remission was positively correlated with serum albumin concentration, compatible with the results of the present study. A Japanese retrospective single-center cohort study, including 53 adult patients with MCD, verified the inverse association between serum albumin concentration and remission, even after adjusting for potential clinical confounding factors. In contrast, two cohort studies reported no significant association between serum albumin concentration and remission. A retrospective single-center cohort study in the UK, including 52 adult patients with MCD, showed that serum albumin concentration was not associated with remission in an unadjusted CPH model. Another Japanese retrospective multicenter cohort study, the STOP-MCD study, including 142 adult patients with MCD in five hospitals showed no significant association between serum albumin concentration and remission in a multivariable-adjusted CPH model. In the STOP-MCD study, high prevalence of intravenous albumin administration (62.0% in the STOP-MCD study vs. 11.1% in the JNSCS) might have blunted the association between serum albumin concentration and remission. The present multicenter prospective cohort study with higher external validity than previous studies, including 108 adult patients with MCD in 40 hospitals in Japan, showed that serum albumin concentration was inversely associated with remission.

Previous studies have reported contradictory impacts of kidney function on remission of proteinuria in patients with MCD. A retrospective single-center cohort study, including 52 patients with MCD in UK, reported that eGFR was not associated with remission in an unadjusted CPH model. Inclusion of suspected secondary MCD (11.5%) might potentially dilute the association between eGFR and remission. In contrast, a Japanese single-center retrospective cohort study suggested that higher serum creatinine level was associated with slower remission in 53 adult patients with MCD. Another Japanese retrospective multicenter cohort study, the STOP-MCD study, including 142 adult patients with MCD in 5 hospitals, confirmed the inverse association between serum creatinine level and remission using a multivariable-adjusted CPH model. In the STOP-MCD study, high prevalence of intravenous albumin administration (62.0% in the STOP-MCD study vs. 11.1% in the JNSCS) might have blunted the association between serum albumin concentration and remission. The present multicenter prospective cohort study with higher external validity than previous studies, including 108 adult patients with MCD in 40 hospitals in Japan, showed that serum albumin concentration was inversely associated with remission.

The present study has several limitations. First, the association between low eGFR and slower remission might be confounded by AKI. Of 716 patients with MCD included in 13 reports, AKI was commonly observed in 235 (33.3%) patients. A Taiwanese retrospective cohort study of MCD reported that 23 patients with no AKI and creatinine clearance of 88.3 ± 23.6 mL/min had a significantly higher cumulative probability of remission than 20 patients with AKI and creatinine clearance of 31.6 ± 19.2 mL/min. Another Japanese cohort study, including 53 adult patients with MCD, clarified a dose-dependent association between AKI stage of the Kidney Disease Improving Global Outcomes (KDIGO) criteria and remission, using CPH model adjusting for clinically relevant factors except for eGFR. In the present study, patients with AKI and, therefore, lower eGFR might achieve remission more slowly than those with no AKI and higher eGFR. The limited number of eGFR measurements available in the present study hindered the identification of the incidence of AKI during the clinical course of each patient. The clinical impact of AKI on the association between eGFR and remission should be assessed in more detail in future studies.
future studies. Second, details of IST, including the time between the onset of symptomatic edema and IST, the initial dose of PSL, and the total duration of prednisolone use, were not available in the present study. Because of the observational nature of the present study, the lack of IST protocol potentially led to biased results. Thus, the associations of use of intravenous mPSL and cyclosporine with remission and relapse in the present study should be interpreted with great caution. The JNSCS is planning to retrieve all laboratory and drug data of each patient during the observational period, which will enable statistical methods for modeling time-updated exposure to IST to estimate precise effectiveness of IST in a real-world setting.

In conclusion, this multicenter prospective cohort study clarified that higher serum albumin concentrations and lower eGFR levels were independently associated with a lower cumulative probability remission in adult patients with MCD. The findings of the present study provide a simple risk stratification system for remission in adult patients with MCD, which should be verified in different cohorts.

Methods
The JNSCS, a 5-year multicenter prospective cohort study of primary nephrotic syndrome, aimed to clarify the incidence rates of major clinical outcomes and assess the effectiveness of IST in Japan. Of 455 nephrotic patients who were diagnosed with primary nephrotic syndrome between January 2009 and December 2010 in 56 hospitals and registered in the JNSCS, 81 patients including those with no kidney biopsy (n = 20), kidney biopsy before or the entry period (n = 32), no history of nephrotic syndrome (n = 1), diagnosis of secondary nephrotic syndrome (n = 13), sclerosing glomerulonephritis with unknown etiology (n = 1), incomplete informed consent (n = 7), duplicate registration (n = 3), and unknown reasons (n = 4) were excluded (Fig. 3). Finally, the JNSCS enrolled 374 patients with primary nephrotic syndrome in 55 hospitals, including those with MCD (n = 155), MN (n = 148), FSGS (n = 38), IgA nephropathy (n = 15), membranoproliferative glomerulonephritis (n = 9), mesangial proliferative glomerulonephritis (n = 5), endocapillary proliferative glomerulonephritis (n = 2), and crescentic glomerulonephritis (n = 2). Of 155 patients with MCD, 108 adult patients aged 18 years or older with urinary protein ≥ 3.5 g/day at initiating IST in 40 hospitals were included to identify the predictors of remission of proteinuria after initiating IST, after excluding two patients without IST during the observational period, 16 patients aged < 18 years, 17 patients with urinary protein < 3.5 g/day at initiating IST, 7 patients with use of antidiabetic drugs at initiating IST, and 5 patients with missing baseline data at initiating IST. To identify predictors of relapse of proteinuria, 97 patients with remission within 6 months of IST were included after excluding 11 patients with no remission within 6 months of IST, because 93.3% of patients with remission during the entire observational period achieved remission within 6 months of IST.

The study protocol of the JNSCS was approved by the ethics committee of Osaka University Hospital (approval number 17035-4) and the Institutional Review Board of each participating hospital. All procedures performed in the JNSCS involving human participants were in accordance with the ethical standards of the research committee of the institute at which the studies were conducted and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants and the legal representatives of the participants under 20 years of age in 54 hospitals. A single hospital used an opt-out approach to provide informed consent, according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Measurements
Baseline characteristics at initiation of IST included age, sex, BMI, systolic and diastolic blood pressure, serum creatinine and albumin concentration, eGFR, 24 h urinary protein (or urinary protein-to-creatinine ratio if 24 h urinary protein was missing), and RAS blockade, including use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, and intravenous albumin administration. The Japanese equation was used to calculate eGFR: eGFR = 194 × age (year)−0.287 × serum creatinine (mg/dL)−0.094 × 0.739 (if female)24. Data pertaining to the use of immunosuppressive drugs within 1 month of IST were also collected, including oral prednisolone, intravenous mPSL, cyclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil, mizoribine, and rituximab.

The outcome of interest was (i) remission of proteinuria defined as 24-h urinary protein < 0.3 g/day or urinary protein-to-creatinine ratio < 0.3 g/gCr, and (ii) relapse of proteinuria defined as 24-h urinary protein ≥ 1.0 g/day, urinary protein-to-creatinine ratio ≥ 1.0 g/gCr, and/or dipstick urinary protein ≥ 2+ continued two or more times. The observational period to identify the predictors of remission was defined as the period from the initiation of IST to (i) the incidence of remission, (ii) the end of the 5-year study period of the JNSCS, or (iii) loss to follow-up, whichever came first. To identify the predictors of relapse, the observational period was defined as the period from the incidence of remission to (i) the incidence of relapse, (ii) the end of the 5-year study period of the JNSCS, or (iii) loss to follow-up, whichever came first.

Statistics. After categorizing serum albumin concentration into four groups of ≤ 1.00, 1.01–1.50, 1.51–2.00, and > 2.00 g/day; eGFR into 4 groups of < 30.0, 30.0–59.9, 60.0–89.9, and ≥ 90.0 mL/min/1.72 m²; and urinary protein into 4 groups of 3.5–4.9, 5.0–7.4, 7.5–9.9, ≥ 10.0 g/day or g/gCr, baseline characteristics, use of immunosuppressive drugs within 1 month of IST, and the cumulative incidence of remission and relapse were compared among these 4 groups using analysis of variance, the Kruskal–Wallis test, the chi-square test, and the Fisher’s exact test, as appropriate. We also compared these clinical characteristics after categorizing the patients into two categories of serum concentration of ≤ 1.50 and > 1.50 g/dL and eGFR of < 60.0 and ≥ 60.0 mL/min/1.73 m², using the unpaired t-test, the Wilcoxon rank-sum test, or the chi-square test, as appropriate.

Cumulative probabilities of remission in the four groups of serum albumin concentration, eGFR level, and urinary protein level were calculated using the Kaplan–Meier method and compared using log-rank test for
Figure 3. Flow diagram of inclusion and exclusion of study participants.
trend. To identify predictors of remission and relapse, we used unadjusted and multivariable-adjusted CPH models, including age (18–39, 40–64, and ≥ 65 year), sex, BMI (kg/m²), systolic blood pressure (mmHg), serum albumin (g/dL), eGFR (mL/min/1.73 m²), urinary protein (log g/day or log g/Cre), dipstick hematuria (− or ±, 1+, and ≥ 2+), intravenous albumin administration, and use of intravenous mPSL and cyclosporine within 1 month of SST as covariates. Because of its skewed distribution, urinary protein was included in CPH models after logarithmic transformation.

To clarify a dose-dependent association of serum albumin and eGFR with remission, we used restricted cubic spline functions using 4 knots placed at 5th, 35th, 65th, and 95th percentiles of serum albumin (0.85, 1.40, 1.80, and 2.70 g/dL, respectively) and eGFR (16, 59, 80, and 107 mL/min/1.73 m², respectively). The cutoff values between the second and third groups, namely serum albumin of 1.5 g/dL and eGFR of 60 mL/min/1.73 m², were used as the reference, which were very close to the median values of these two variables (1.59 g/dL and 70 mL/min/1.73 m², respectively).

Continuous variables were expressed as the mean ± standard deviation or median and interquartile range, as appropriate, and categorical variables were expressed as numbers and proportions. Statistical significance was set at P < 0.05. Statistical analyses were performed using Stata, version 17.0 (Stata Corp, www.stata.com).

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request and with permission of the Steering Committee for the JNSCS.

Received: 3 October 2021; Accepted: 20 May 2022
Published online: 13 June 2022

References
1. Yokoyama, H., Taguchi, T., Sugiyama, H. & Sato, H. Membranous nephropathy in Japan: Analysis of the Japan Renal Biopsy Registry (J-RBR). Clin. Exp. Nephrol. 16, 557–563 (2012).
2. Gipson, D. S. et al. Complete remission in the Nephrotic Syndrome Study Network. Clin. J. Am. Soc. Nephrol. 11, 81–89 (2016).
3. Wada, T. et al. A digest of the evidence-based clinical practice guideline for nephrotic syndrome 2020. Clin. Exp. Nephrol. 25, 1277–1285 (2021).
4. Korbet, S. M. & Whittier, W. L. Management of adult minimal change disease. Clin. J. Am. Soc. Nephrol. 14, 911–913 (2019).
5. Chou, Y. H. et al. Clinical outcomes and predictors for ESRD and mortality in primary GN. Clin. J. Am. Soc. Nephrol. 7, 1401–1408 (2012).
6. Lee, H. et al. Mortality and renal outcome of primary membranulonephritis in Korea: Observation in 1,943 biopsied cases. Am. J. Nephrol. 37, 74–83 (2013).
7. Go, A. S. et al. Primary nephrotic syndrome and risks of ESKD, cardiovascular events, and death: The Kaiser Permanente Nephrotic Syndrome Study. J. Am. Soc. Nephrol. 32, 2303–2314 (2021).
8. Sztco, C.-C. et al. Long-term outcome of biopsy-proven minimal change nephropathy in Chinese adults. Am. J. Kidney Dis. 65, 710–718 (2015).
9. Korbet, S. M., Schwartz, M. M. & Lewis, E. J. Minimal-change glomerulopathy of adulthood. Am. J. Nephrol. 8, 291–297 (1988).
10. Mak, S. K., Short, C. D. & Mallick, N. P. Long-term outcome of adult-onset minimal-change nephropathy. Nephrol. Dial. Transplant. 11, 2192–2201 (1996).
11. Nakayama, M. et al. Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. Am. J. Kidney Dis. 39, 503–512 (2002).
12. Chen, C.-L. et al. Increased endothelin 1 expression in adult-onset minimal change nephropathy with acute renal failure. Am. J. Kidney Dis. 45, 818–825 (2005).
13. Shinzawa, M. et al. Age and prediction of remission and relapse of proteinuria and corticosteroid-related adverse events in adult-onset minimal-change disease: A retrospective cohort study. Clin. Exp. Nephrol. 17, 839–847 (2013).
14. Shinzawa, M. et al. Comparison of methylprednisolone plus prednisolone with prednisolone alone as initial treatment in adult-onset minimal change disease: A retrospective cohort study. Clin. J. Am. Soc. Nephrol. 9, 1040–1048 (2014).
15. Komukai, D. et al. Influence of acute kidney injury on the time to complete remission in adult minimal change nephrotic syndrome: A single-centre study. Nephrol. Dial. Transplant. 21, 887–892 (2016).
16. Yamamoto, R. et al. Regional variations in immunosuppressive therapy in patients with primary nephrotic syndrome: The Japan Nephrotic Syndrome Cohort Study. Clin. Exp. Nephrol. 22, 1266–1280 (2018).
17. Yamamoto, R. et al. Incidence of remission and relapse of proteinuria, end-stage kidney disease, mortality, and major outcomes in primary nephrotic syndrome: The Japan Nephrotic Syndrome Cohort Study (JNSCS). Clin. Exp. Nephrol. 24, 526–540 (2020).
18. Yokoyama, H. et al. Better remission rates in elderly Japanese patients with primary membranous nephropathy in nationwide real-world practice: The Japan Nephrotic Syndrome Cohort Study (JNSCS). Clin. Exp. Nephrol. 24, 893–909 (2020).
19. Nishihi, K. et al. Incidence and factors associated with prescribing renin–angiotensin-system inhibitors in adult idiopathic nephrotic syndrome: A nationwide cohort study. J. Clin. Hypertens. 23, 999–1007 (2021).
20. Yamamoto, R. et al. Time to remission of proteinuria and incidence of relapse in patients with steroid-sensitive minimal change disease and focal segmental glomerulosclerosis: The Japan Nephrotic Syndrome Cohort Study. J. Nephrol. 35(4), 1135–1144 (2022).
21. Fenton, A., Smith, S. W. & Hewins, P. Adult minimal-change disease: Observational data from a UK centre on patient characteristics, therapies, and outcomes. BMC Nephrol. 19, 207 (2018).
22. Meyrier, A. & Niaudet, P. Acute kidney injury complicating nephrotic syndrome of minimal change disease. Kidney Int. 94, 861–869 (2018).
23. Xie, D. et al. Statistical methods for modeling time-updated exposures in cohort studies of chronic kidney disease. Clin. J. Am. Soc. Nephrol. 12, 1892–1899 (2017).
24. Matsuo, S. et al. Revised equations for estimated GFR from serum creatinine in Japan. Am. J. Kidney Dis. 53, 982–992 (2009).
25. Orsini, N. & Greenland, S. A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. Statist. J. 11, 1–29 (2011).

Author contributions
Research idea and study design: E.I., S.M., and Y.I.; data acquisition: all authors; Data analysis/interpretation: R.Y.; Statistical analysis: R.Y.; Supervision or mentorship: E.I., S.M., and Y.I. Each author contributed important intellectual content during manuscript drafting and agrees to be personally accountable for the individual's own
contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Funding
JNSCS was supported by a Grant-in-Aid for Intractable Renal Diseases Research, Research on Rare and Intractable Diseases, Health and Labor Sciences Research Grants for the Ministry of Health, Labor, and Welfare of Japan.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-13067-7.

Correspondence and requests for materials should be addressed to R.Y.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022

JNSCS Investigators

Saori Nishio44, Yasunobu Ishikawa44, Daigo Nakazawa44, Tasuku Nakagaki44, Toshinobu Satō45, Mitsuhiro Satō45, Satoru Sanada45, Hiroshi Sato46, Mariko Miyazaki46, Takashi Nakamichi46, Tae Yamamoto46, Kaori Narumi46, Gen Yamada46, Tsuneo Konta47, Kazunobu Ichikawa47, Junichiro James Kazama48, Tsuyoshi Watanabe48, Koichi Asahi48, Yuki Kusano48, Kimio Watanabe48, Kunihiro Yamagata49, Joichi Usui49, Shuzo Kaneko49, Tetsuya Kawamura49, Keiju Hiromura49, Akiyoshi Nakamura50, Yoriaki Kaneko50, Hidekazu Ikeuchi50, Toru Sakai50, Masao Nakasatomi50, Hajime Hasegawa51, Takatsugu Iwashita51, Taisuke Shimizu51, Koichi Kanozawa51, Tomonari Ogawa51, Kaori Takayanagi51, Tetsuya Mitara51, Hirokazu Okada52, Tsutomu Inoue52, Hiromichi Suzuki52, Kouji Tomori52, Kosaku Nitta53, Takahito Moriyama53, Akemi Ino53, Masayo Sato53, Shunya Uchida54, Hideaki Nakajima54, Hitoshi Homma54, Nichito Nagura54, Yoshifuru Tamura54, Shigeru Shibata54, Yoshihide Fujigaki54, Yusuke Suzuki55, Yukihiko Takeda55, Isao Osawa55, Teruo Hidaka55, Daisuke Ichikawa55, Yugo Shibagaki56, Sayuri Shirai56, Tsutomu Sakurada56, Tomo Suzuki56, Mikako Hisamichi56, Ichiee Narita57, Naohumi Imai57, Yumi Ito57, Shin Goto57, Yosikazu Sato57, Rohohei Kaseda57, Hitoshi Yokoyama58, Keiji Fujimoto58, Norifumi Hayashi58, Takashi Wada59, Miho Shimizu59, Kengo Furuchi59, Norihiko Saka59, Yasunori Iwata59, Tadashi Toyama59, Shinji Kitajima59, Kiyoki Kitagawa60, Hiroshi Sobaijima60, Norimi Ohashi60, So Oshitan60, Kiyohito Kawashima61, Tetsuo Mimura62, Hideo Yasuda63, Akira Hishida63, Yoshihide Fujigaki63, Satoshi Tanaka64, Noriko Mori64, Toshikazu Nakahori65, Yutaka Fujita65, Shoichi Maruyama66, Naotake Tsuboi66, Tomoki Kosugii66, Takuji Ishimoto66, Takayuki Katsuno66, Noritoshi Kato66, Waichi Satō66, Asami Takeda66, Kunio Morozumi66, Yasuhiro Ohtsuka67, Hiibiki Shinjo67, Akihito Tanaka67, Hiroki Hayashi68, Yukio Yuzawa68, Midori Hasegawa68, Daijo Inaguma68, Shigehisa Koide68, Kazuo Takahashi68, Takeyuki Hiramatsu69, Shinya Furuta69, Hideaki Ishikawa69, Hirofumi Tama69, Takatoshi Morinaga70, Arimasa Shirasaki71, Toshiaki Kimura71, Mina Kato71, Shizunori Ichida72, Nobuhide Endo72, Tomohiko Naruse73, Yuzo Watanabe73, Yusuke Saka74, Satoshi Suzuki74, Michiko Yamazaki74, Rieko Morita74, Kunio Morozumi75, Kunio Morozumi75, Kaoru Yasuda75, Chiaki Kondo75, Takahiro Morohiro75, Rho Sato75, Yuichiro Hirasawa75, Yoshiro Fujita76, Hideaki Shimizu76, Tatsuhito Tomino76, Makoto text/
Mizutani77, Yosuke Saka78, Hiroshi Nagaya78, Makoto Yamaguchi78, Tatsuo Tsukamoto79, Eri Muso79, Hiroyuki Suzuki79, Tomomi Endo79, Hiroko Kakita79, Megumu Fukunaga80, Tatsuya Shoji81, Terumasa Hayashi82, Eiji Ishimura82, Akihiro Tsuda82, Shinya Nakatani82, Ikue Kobayashi82, Mitsuru Ichii82, Akinobu Ochi82, Yoshiteru Ohno82, Yoshitaka Isaka83, Enyu Imai83, Yasuyuki Nagasawa83, Hirotsugu Iwatan83, Ryoei Yamamoto83, Tomoko Namba83, Shunsuke Goto84, Shinichi Nishi84, Yasuhiro Akai85, Ken-ichi Samejima85, Masaru Matsui85, Miho Tagawa85, Koari Tanabe85, Hideo Tsushima85, Takashi Shigematsu86, Masaki Ohya86, Shigeo Negi86, Toru Mima86, Takafumi Ito87, Hitoshi Sugiyama88, Keiko Tanaka88, Toshiro Yamanari88, Masashi Kitagawa88, Akifumi Onishi88, Koki Mise88, Naoki Kashihara88, Tamaki Sasaki89, Sohachi Fujimoto89, Hajime Nagasa89, Kojiro Nagai90, Toshio Doi90, Tadashi Sofue91, Hideyasu Kiyomoto91, Kumi Moriiwaki91, Taiga Haro91, Yoko Nishijima91, Yoshio Kushida91, Tetsuo Minamino91, Yoshio Terada92, Taro Horino92, Yoshinori Taniguchi92, Kosuke Inoue92, Yoshiko Shimamura92, Tatsuki Matsumoto92, Kazuhiko Tsuruya93, Hisako Yoshida93, Naoki Haruyama93, Shunsuke Yamada93, Akihiro Tsuchimoto93, Yuta Matsukuma93, Kosuke Masutani94, Yasuhiro Abe94, Aki Hamauchi94, Tetsuhiro Yasuno95, Kenji Ito96, Kei Fukami96, Junko Yano96, Chika Yoshida96, Yuka Kurokawa96, Nao Nakamura96, Ritsuko Katafuchi96, Hiroshi Nagae96, Shumei Matsueda96, Kazuto Abe96, Tomoya Nishino97, Tadashi Uramatsu97, Toshiyuki Okada97, Shouichi Fujimoto98, Yuji Sato98, Masao Kikuchi98, Ryuzo Nishizono98, Takashi Ikawari98 & Hiroyuki Komatsu98

44Hokkaido University Hospital, Sapporo, Hokkaido, Japan. 45JCHO Sendai Hospital, Sendai, Miyagi, Japan. 46Tohoku University Hospital, Sendai, Miyagi, Japan. 47Yamagata University Hospital, Yamagata, Yamagata, Japan. 48Fukushima Medical University Hospital, Fukushima, Fukushima, Japan. 49University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan. 50Gunma University Hospital, Maebashi, Gunma, Japan. 51Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan. 52Department of Nephrology, Saitama Medical University, Irumagun, Saitama, Japan. 53Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan. 54Teikyo University School of Medicine, Itabashi-ku, Tokyo, Japan. 55Juntendo Faculty of Medicine, Bunkyo-ku, Tokyo, Japan. 56St. Marianna University, Kawasaki, Kanagawa, Japan. 57Niigata University Medical and Dental Hospital, Niigata, Niigata, Japan. 58Kanazawa Medical University, Uchinada, Ishikawa, Japan. 59Kanazawa University Hospital, Kanazawa, Ishikawa, Japan. 60National Hospital Organization Kanazawa Medical Center, Kanazawa, Ishikawa, Japan. 61Ogaki Municipal Hospital, Ogaki, Gifu, Japan. 62Gifu Prefectural Tajimi Hospital, Tajimi, Gifu, Japan. 63Hamamatsu University Hospital, Hamamatsu, Shizuoka, Japan. 64Shizuoka General Hospital, Shizuoka, Shizuoka, Japan. 65Chuo Toen General Medical Center, Kakegawa, Shizuoka, Japan. 66Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan. 67Japanese Red Cross Nagoya Daini Hospital, Nagoya, Aichi, Japan. 68Fujita Health University School of Medicine, Toyoake, Aichi, Japan. 69Kanouchi Hospital, Konan, Aichi, Japan. 70Anjo Kosei Hospital, Anjo, Aichi, Japan. 71Ichinomiya Municipal Hospital, Ichinomiya, Aichi, Japan. 72Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Aichi, Japan. 73Kasugai Municipal Hospital, Kasugai, Aichi, Japan. 74Kainan Hospital, Yatomi, Aichi, Japan. 75Masuko Memorial Hospital, Nagoya, Aichi, Japan. 76Chubu Rosai Hospital, Nagoya, Aichi, Japan. 77Handa City Hospital, Handa, Aichi, Japan. 78Yokkaichi Municipal Hospital, Yokaichi, Mie, Japan. 79Kitano Hospital, Osaka, Osaka, Japan. 80Toyonaka Municipal Hospital, Toyonaka, Osaka, Japan. 81Osaka General Medical Center, Osaka, Osaka, Japan. 82Osaka City University Hospital, Osaka, Osaka, Japan. 83Osaka University Hospital, Suita, Osaka, Japan. 84Kobe University Hospital, Kobe, Hyogo, Japan. 85Nara Medical University Hospital, Kashiwara, Nara, Japan. 86Kawamura Medical University Hospital, Wakayama, Wakayama, Japan. 87Shimane University Hospital, Izumo, Shimane, Japan. 88Okayama University Hospital, Okayama, Okayama, Japan. 89Kawasaki Medical School, Kurashiki, Okayama, Japan. 90Graduate School of Medicine, The University of Tokushima, Tokushima, Tokushima, Japan. 91Kagawa University, Mi-cho, Kamakura, Japan. 92Kochi Medical School, Kochi, Kochi, Japan. 93Kyushu University Hospital, Fukuoka, Fukuoka, Japan. 94Fukuoka University Hospital, Fukuoka, Fukuoka, Japan. 95Kumamoto University Hospital, Kumamoto, Kumamoto, Japan. 96National Hospital Organization Fukuoka Medical Center, Fukuoka, Japan. 97Nagasaki University Hospital, Nagasaki, Nagasaki, Japan. 98Miyazaki University Hospital, Miyazaki, Miyazaki, Japan.