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Association between diuretic administration before diagnosis and incidence of acute kidney injury in patients with minimal change disease

A single-center observational study

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Abstract

We examined the association between diuretic administration before the diagnosis of minimal change disease and the incidence of acute kidney injury. Moreover, we examined whether the use of diuretics affected the time to complete remission in adults with such disease.

The present study was a single-center, retrospective, observational cohort study. We included 107 patients with biopsy-proven minimal change disease who were treated at a tertiary referral center in Japan between January 1, 2000 and March 31, 2019. All biopsy specimens were examined by a board-certified renal pathologist. The patients were considered to have minimal change disease when the kidney biopsy specimen had no glomerular lesions or only mild focal mesangial prominence (not exceeding 3 or 4 cells per segment) by light microscopy and/or foot process effacement by electron microscopy. Logistic regression and Kaplan–Meier curve analyses were performed, comparing the data of patients who received diuretics or not.

The median age was 47 (28–66) years, 52% of patients were women, and the median proteinuria dosage was 8.3 (5.3–11.2) g/d. When minimal change disease was diagnosed, 27% of patients were taking diuretics. Within 30 days after the diagnosis, acute kidney injury occurred in 27% of patients. On multivariable logistic regression analysis, the use of diuretics was significantly associated with a higher risk of acute kidney injury. The use of diuretics was also associated with a longer time to complete remission.

Diuretic administration can be associated with an elevated acute kidney injury risk and longer remission time in adult patients with newly diagnosed minimal change disease.

Abbreviations: AKI = acute kidney injury, CI = confidence interval, eGFR = estimated glomerular filtration rate, IQI = interquartile interval, MCD = minimal change disease, NSAIDs = non-steroidal anti-inflammatory drugs, OR = odds ratio, RASi = renin-angiotensin system inhibitor, RRT = renal replacement therapy, sCr = serum creatinine.

Keywords: acute kidney injury, complete remission, diuretics, minimal change disease, remission

1. Introduction

Minimal change disease (MCD) is a common cause of idiopathic nephrotic syndrome, accounting for approximately 15% of adult patients with idiopathic nephrotic syndrome.[1,2] Edema is a major clinical manifestation in MCD,[3,4] which often requires treatment with diuretics, such as furosemide, thiazides, and spironolactone.[4–6]

Although diuretics have an important role in volume management, they may increase the risk of acute kidney injury

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(AKI)[7] by inducing volume depletion.[8,9] AKI affects approximately 20% of adults with MCD and, thus, is an important complication.[2] As many risk factors of AKI (e.g., older age and hypoalbuminemia) are not readily modifiable at the time of MCD diagnosis, it is important to assess whether diuretics increase the risk of AKI in patients with MCD. However, to our knowledge, an association between the administration of diuretics before MCD diagnosis and the incidence of AKI has not yet been reported in such patients. Additionally, approximately 80% of adult patients with MCD reach complete remission (proteinuria of $\leq$0.3 g/d) with steroid treatment by 16 weeks[1,2]; however, it is also uncertain whether diuretic administration before diagnosis could affect the time to reach complete remission.

We conducted a retrospective cohort study to investigate the association between diuretic administration before diagnosis and the subsequent risk of AKI in adult patients with newly diagnosed MCD. In addition, we explored whether the use of diuretics was associated with a prolonged time to complete remission.

2. Methods

2.1. Study design and population

This study was conducted, and is reported, according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10] This retrospective observational study was based on clinical data obtained at the Teine Keijinkai Medical Center, a 650-bed tertiary reference center, in Sapporo, Hokkaido, Japan. We reviewed all the clinical records of patients with nephrotic syndromes in the Teine Keijinkai Renal Biopsy Registry (TK-RBR). The inclusion criteria of this study were the following: age $\geq$18 years and biopsy-proven MCD diagnosed between January 1, 2000 and March 31, 2019. We also restricted the analytic sample to patients with at least 1 month of follow-up from the time of MCD diagnosis to capture AKI events. All biopsy specimens were examined by a board-certified renal pathologist (YO). Patients were considered to have MCD when the kidney biopsy specimen had no glomerular lesions or only mild focal mesangial prominence (not exceeding 3 or 4 cells per segment) by light microscopy and/or foot process effacement by electron microscopy.[1] Among the 125 eligible patients who were registered to the TK-RBR between January 1, 2000 and March 31, 2019, we excluded 15 and 3 patients with missing baseline laboratory data and age <18 years, respectively. Therefore, 107 patients with newly diagnosed MCD were included in this study (Fig. 1).

This study was conducted in compliance with the Declaration of Helsinki. The institutional review board of Teine Keijinkai Medical Center approved the study (approval number 2019–006). Written informed consent for publication was obtained from all participants at treatment initiation, but consent was not required for the analyses because of the retrospective study design.

2.2. Exposure

The primary exposure of interest was the use of diuretics before diagnosing MCD, which was defined by the records in the medical charts or referral letters from primary care physicians, indicating the use of loop diuretics, thiazides, or aldosterone blockers within 1 month prior to MCD diagnosis.

2.3. Outcomes

The primary outcome of interest was the incidence of AKI within 30 days after MCD diagnosis; the date of renal biopsy was used to define the date of diagnosis. AKI was defined according to the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline on AKI as follows[11]: an increase in serum creatinine (sCr) by $\geq$0.3 mg/dL within 48 hours or an increase in sCr $\geq$1.5 times the baseline. Baseline sCr was defined as the latest sCr value available in 6 months prior to the date of renal biopsy. AKI was staged as follows[11]: stage 1, an increase in sCr levels to 1.5 to 1.9 times the baseline; stage 2, an increase in sCr levels to 2.0 to 2.9 times the baseline; and stage 3, an increase in sCr levels to $\geq$3.0 times the baseline or the need for renal replacement therapy (RRT). sCr was measured 1 day after the renal biopsy and, thereafter, every 2 days until the date of discharge.

The secondary outcome was the time (in days) from the initiation of steroid and/or other immunosuppressive treatment (cyclosporine, tacrolimus, mizoribine, mycophenolate mofetil, or

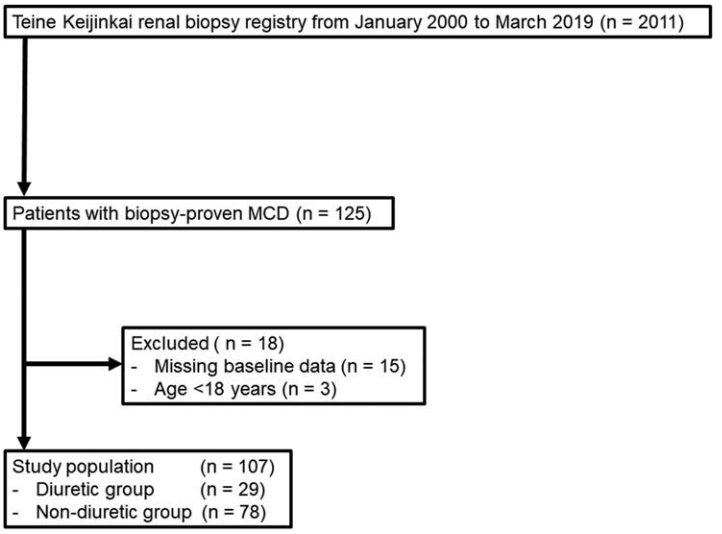

Figure 1. Flow chart showing the patient selection process. MCD = minimal change disease.

cyclophosphamide) to complete remission. Treatment was initiated on the day of, or 1 day after the diagnosis. Complete remission was defined as the first record of proteinuria <0.3 g per 24 hours or <.3 g/gCr after treatment initiation.

2.4. Covariates

We collected data on covariates by reviewing the participant medical records. The evaluated patient characteristics included age, sex, body mass index, comorbidities (i.e., hypertension, diabetes mellitus, heart failure, and coronary heart disease), and prescribed medications (non-steroidal anti-inflammatory drugs [NSAIDs] and renin-angiotensin system inhibitors [RASi]). Laboratory data were based on the closest measurement within 6 months of MCD diagnosis and included 24-hour urinary protein and serum levels of uric acid, hemoglobin, serum albumin (sAlb), and total cholesterol. The estimated glomerular filtration rate (eGFR) was calculated using the 3-variable equation for Japanese individuals ($eGFR = 194 \times \text{serum creatinine [mg/dL]}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ [if female]).[12] The treatment regimen[13] was classified into oral prednisolone, steroid pulse therapy (methylprednisolone 0.5 g/d for 3 consecutive days), cyclosporine, and other immunosuppressive medications including tacrolimus, mizoribine, mycophenolate mofetil, and cyclophosphamide. Hypertension was defined by a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or antihypertensive drug use. Diabetes mellitus was defined as hemoglobin A1c (HbA1c) level ≥6.5%[14] or the use of anti-diabetic drugs.

2.5. Statistical analyses

We compared the baseline characteristics between patients who did and did not use pre-diagnosis diuretics using the chi-squared test, Student *t* test, and Wilcoxon rank-sum test for categorical, normally distributed continuous, and non-normally distributed continuous variables, respectively.

Kaplan–Meier curve analyses, with the log-rank test, were performed to compare freedom from AKI and the time to complete remission between patients who did and did not receive diuretics before MCD diagnosis. Additionally, univariable and multivariable logistic regression analyses were performed to estimate the odds ratio (OR) and 95% confidence interval (CI) for developing AKI within 30 days of MCD diagnosis. Independent variables analyzed by univariable logistic regression were as follows: diuretic use, age, hypertension, urine protein levels, eGFR, and sAlb. The multivariate model included the use of diuretics, age, eGFR, and hypertension, which were selected a priori based on previous studies.[2,8,9,15–17]

As patient characteristics may differ between patients who did and did not receive diuretics (i.e., a selection bias by indication), we additionally calculated a propensity score for the use of diuretics using logistic regression analysis, including age, hypertension, urine protein levels, eGFR, sAlb, and heart failure in the regression model.[2,8,9,15–17] Subsequently, a weighted logistic regression model adjusted for the propensity score was used to estimate the OR for developing AKI within 30 days of MCD diagnosis.

Table 1

Baseline characteristics of the patients.

Patient characteristics	All (n = 107)	Diuretic (+) (n = 29)	Diuretic (–) (n = 78)	*P* value
Age, y, median [25%, 75%]	47 [28, 66]	65 [42, 72]	42 [25, 61]	.0005
Women, n (%)	56 (52)	15 (52)	41 (53)	.873
BMI, kg/m^2 [25%, 75%]	20.5 [18.5, 24.2]	21.3 [18.6, 25.2]	20.4 [18.5, 22.4]	.3757
Hypertension, n (%)	24 (22)	12 (41)	12 (15)	.004
Diabetes mellitus, n (%)	5 (5)	3 (10)	2 (3)	.09
Congestive heart failure, n (%)	5 (5)	3 (10)	2 (3)	.005
Coronary heart disease, n (%)	2 (2)	1 (4)	1 (1)	.444
Urine protein, g/gCr, median [25%, 75%]	8.3 [5.3, 11.2]	8.9 [5.5, 10.5]	8.2 [5.3, 12.1]	.7877
Uric acid, mg/dL, median [25%, 75%]	5.9 [4.7, 7.0]	6.6 [5.4, 7.8]	5.8 [4.6, 6.9]	.1428
Hemoglobin, g/dL, median [25%, 75%]	14.3 [12.9, 15.9]	13.5 [12.6, 14.7]	15.1 [13.2, 16.0]	.0116
Baseline serum creatinine, mg/dL, median [25%, 75%]	0.84 [0.69, 1.10]	1.10 [0.68, 1.72]	0.82 [0.69, 1.0]	.0473
Baseline eGFR, mL/min/1.73 m^2 median [25%, 75%]	78 [50, 102]	56 [34, 78]	86 [64, 113]	.0004
Serum albumin, mg/dL, median [25%, 75%]	1.9 [1.6, 2.3]	2.0 [1.7, 2.3]	1.9 [1.6, 2.4]	.7115
Total cholesterol, mg/dL, median [25%, 75%]	399 [318, 500]	349 [298, 461]	410 [333, 505]	.1433
Oral prednisolone, no. (%)	107 (100)	29 (100)	78 (100)	–
Oral prednisolone initial dose, mg/dL, median [25%, 75%]	40 [40, 50]	40 [40, 45]	42.5 [40, 50]	.231
Methylprednisolone pulse therapy, no. (%)	29 (27)	8 (30)	21 (27)	.905
Courses of pulse therapy (n = 1/2/3)	28/1/0	7/1/0	21/0/0	–
Furosemide, n (%)	29 (27)	29 (100)	0 (0)	–
Doses of furosemide, mg/d, median [25%, 75%]	40 [20, 60]	40 [20, 60]	0 (0)	–
Thiazides, n (%)	3 (3)	3 (10)	0 (0)	–
Doses of thiazides, mg/d, median [25%, 75%]	1 [1, 2]	1 [1, 2]	0 (0)	–
Spironolactone, n (%)	6 (6)	6 (21)	0 (0)	–
Doses of spironolactone, mg/d, median [25%, 75%]	50 [25, 50]	50 [25, 50]	0 (0)	–
NSAIDs, n (%)	5 (5)	2 (7)	3 (4)	.479
Renin angiotensin system inhibitors, n (%)	20 (19)	9 (33)	11 (14)	.058
Cyclosporine, n (%)	17 (16)	7 (26)	10 (13)	.181
*Other immunosuppressive medications, n (%)	0 (0)	0 (0)	0 (0)	–

BMI = body mass index, eGFR = estimated glomerular filtration rate, NSAIDs = non-steroidal anti-inflammatory drugs.
* Mizoribine, mycophenolate mofetil, and cyclophosphamide.

STATA version 15.1 (Stata Corp LLC, College Station, TX) was used to perform the statistical analyses. A 2-sided *P*-value $<.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

The median age of the 107 included patients was 47 (interquartile interval [IQI], 28–66) years, 52% of patients were women, and the median proteinuria level was 8.3 g/gCr (IQI, 5.3–11.2) g/d (Table 1). All patients received oral prednisolone at an initial median dose of 40 mg/d (IQI, 40–50 mg/d) on the day of, or 1 day after MCD diagnosis. In total, 29 patients (27%) additionally received steroid pulse therapy, with the number of steroid pulse courses ranging between 1 and 3. As a part of the initial therapy, 16% of the patients received cyclosporine.

Moreover, 29 patients (27%) used one or more classes of diuretics before diagnosis (i.e., the diuretic group), all of whom received furosemide (median dose, 40 [IQI, 20–60] mg/d). Three patients also used thiazides (median dose, 1 [IQI, 1–2] mg/d) and 6 patients also used spironolactone (median dose, 50 [IQI, 25–50] mg/d). Patients who received diuretics were more likely to be older, have hypertension and heart failure, and have lower hemoglobin levels and eGFR than those who did not receive diuretics. Other baseline characteristics, such as immunosuppressive agent (methylprednisolone pulse therapy, cyclosporine) and RASi use did not statistically differ between the 2 groups (Table 1).

3.2. Primary outcome: incidence of AKI using diuretics

Within 30 days after diagnosis, AKI occurred in 29 of 107 (27%) patients, comprising 18 of 29 (62%) and 11 of 78 (14%) patients who received diuretics or not, respectively. According to the AKI stage, 9, 0, and 20 patients had AKI stage 1, 2, and 3 (including 12 patients who required RRT) (Table 2), respectively.

Kaplan–Meier curve analysis showed that the diuretic group had a statistically higher risk of developing AKI than the non-diuretic group (log-rank test, $P<.001$) (Fig. 2). As shown in Table 3, the use of diuretics was significantly associated with a higher risk of developing AKI (OR, 9.97; 95% CI, 3.72–26.7) on univariable logistic regression analysis. Among the other evaluated factors, older age (OR, 1.04; 95% CI, 1.01–1.06) and lower eGFR (OR, 0.96; 95% CI, 0.94–0.98) were also significantly associated with the development of AKI. Although patients with hypertension had a higher risk of developing AKI, statistical significance was not reached (OR, 2.37; 95% CI, 0.91–6.12). On multivariable logistic regression analysis, the use of diuretics remained significantly associated with a higher risk of developing AKI (OR, 6.89; 95% CI, 2.29–20.6).

In the propensity score-matched analysis, patient characteristics were balanced between those who did and did not receive diuretics, as indicated by a standardized mean difference <0.1 for all variables. The weighted logistic regression model revealed that the use of diuretics remained significantly associated with a higher risk of developing AKI (OR, 5.50; 95% CI, 1.71–17.8).

3.3. Secondary outcome: time to reach complete remission using diuretics

All patients reached complete remission during the follow-up period (range, 2–396 days). The median time to complete remission was 34 (IQI, 17–63) days in the diuretic group and 16 (IQI, 12–26) days in the non-diuretic group ($P<.001$ by Wilcoxon rank-sum test). The Kaplan–Meier survival curve analysis showed that the time to reach complete remission was longer in the diuretic than in the non-diuretic group (log-rank test, $P<.001$) (Fig. 3). At 90 days of treatment, 23 (79%) and 77 (99%) patients in the diuretic and in the non-diuretic group, respectively, had achieved complete remission. At baseline, the levels of proteinuria were comparable between the 2 groups. At 30 days after treatment initiation, the median reduction in urinary protein from baseline was 7.3 (IQI, 2.8–8.5) and 8.1 (IQI, 5.0–12.1) g/d in the diuretic and in the non-diuretic group, respectively (Fig. 4).

4. Discussion

This single-center, retrospective observational study of 107 patients with MCD demonstrated that diuretic administration before MCD diagnosis was significantly associated with the development of AKI. Additionally, during treatment, patients who received diuretics before diagnosing MCD required a significantly longer time to reach complete remission than those who did not receive diuretics.

To the best of our knowledge, the present study was the first to identify the use of diuretics as a potential risk factor for AKI among patients with MCD. Our results were in line with findings from prior studies that reported an association between the use of loop diuretics and AKI in patients with other conditions, including cardiac disease, post-surgical status, and cancer.[17–20] For instance, a secondary analysis of data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization trial found that patients with heart failure who received a higher dose of loop diuretics had an increased risk of worsening kidney function compared with those who received a lower dose.[17]

Table 2

Primary and secondary outcomes of the patients.

	All (n = 107)	Diuretic (+) (n = 29)	Diuretic (−) (n = 78)
Acute kidney injury, n (%)	29/107 (27)	18/29 (62)	11/78 (14)
Stage 1, (%)	9/29 (31)	2/18 (11)	7/11 (64)
Stage 2, n (%)	0 (0)	0 (0)	0 (0)
Stage 3, n (%)	20/29 (69)	16/18 (89)	4/11 (36)
Renal replacement therapy, n (%)	12/20 (60)	12/16 (75)	0 (0)
Complete remission, n (%)	107 (100)	29 (100)	78 (100)
Time to complete remission, days*	17 [2–396]	34 [17–63]	16 [12–26]

* Median (range).

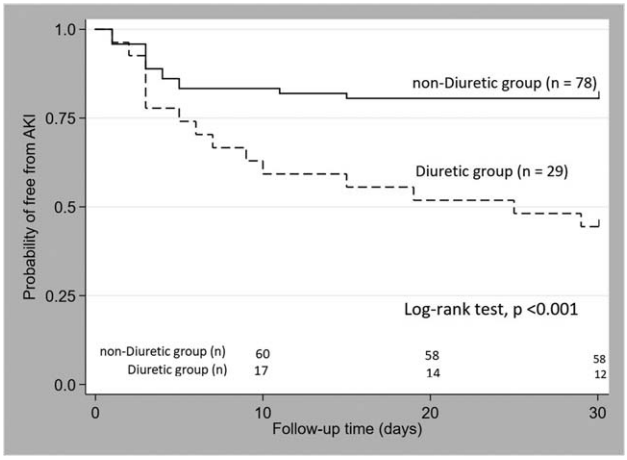

Figure 2. Comparison of the Kaplan–Meier curves of the probability of freedom from acute kidney injury (AKI) between the diuretic and non-diuretic groups. The curve analysis shows that the diuretic group had a statistically higher risk of developing AKI than the non-diuretic group.

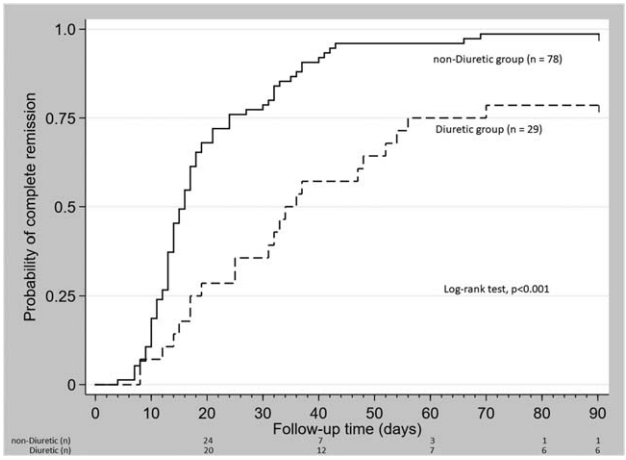

Figure 3. Comparison of the Kaplan–Meier curves of the time to complete remission between the diuretic and non-diuretic groups. The curve analysis shows that the time to reach complete remission was longer in the diuretic group than in the non-diuretic group. Follow-up time for the first 90 days after treatment initiation is shown.

There are several potential mechanisms linking the use of diuretics to an increased risk of AKI in patients with MCD. For example, a higher AKI risk among patients receiving diuretics may be related to patient characteristics, as the patients in the present study who received diuretics prior to MCD diagnosis tended to be older and had more comorbidities, such as hypertension, compared with those who did not receive diuretics. Additionally, patients who received diuretics had a lower eGFR. However, we observed a significant and robust association between the use of diuretics and the risk of AKI, even after accounting for these confounders. Furthermore, diuretics can cause extracellular fluid volume contraction, increasing the risk of pre-renal AKI.[21] Patients with MCD may be especially susceptible to this nephrotoxic effect of diuretics, as they have intravascular volume depletion and decreased oncotic pressure because of low sAlb levels.[1–3]

We also found that patients who used diuretics had a delay in reaching complete remission during the study period compared with the course in patients who did not use diuretics, although all patients achieved complete remission by the end of the follow-up period. The pathophysiologic explanations for this association remain unclear. However, a retrospective study by Komukai et al[22] showed that the presence of AKI was significantly associated with a longer time to achieve complete remission in adult patients with MCD. Additionally, endothelial dysfunction and inflammation induced by AKI can cause prolonged damage to the glomerular permeability barrier, resulting in delayed complete remission.[23,24] Thus, it is possible that the longer time to reach complete remission among patients who used diuretics may be partly mediated by their higher risk of developing AKI. Indeed, among those on diuretics, the median time to complete remission was longer in those who developed AKI compared with those who did not (42 vs 33 days, $P = .04$ by Wilcoxon rank-sum test).

The present results have several clinical and research implications. First, given the higher risk of AKI in patients who receive diuretics, careful weighing of the risks and benefits is needed when patients with nephrotic syndrome have a diuretic use history. Although the causes of nephrotic syndrome may not be determined at the moment of decision-making, MCD is often suspected as the underlying cause, based on the typical clinical manifestations. In addition, clinicians should minimize the exposure to other nephrotoxic agents, such as NSAIDs, antibiotics, and radiocontrast media, when patients with MCD receive diuretics. These implications may be broadly applicable to other causes of nephrotic syndrome, such as membranous nephropathy, because the role of diuretics is likely to be similar among pathophysiological conditions that cause nephrotic syndrome. Nonetheless, this should be explored in future studies.

Table 3

Clinical factors affecting the incidence of acute kidney injury.

	Univariable logistic regression analysis			Multivariable logistic regression analysis		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Diuretics	9.97	3.72–26.7	<.001	6.89	2.29–20.6	.001
Age	1.04	1.01–1.06	.002	1.00	0.97–1.03	.852
eGFR	0.96	0.94–0.98	<.001	0.97	0.95–0.99	.004
Hypertension	2.37	0.91–6.12	.078	1.28	0.36–4.63	.704
Urine protein	1.05	0.97–1.13	.259			
sAlb	0.64	0.29–1.40	.264			

CI = confidence interval, eGFR = estimated glomerular filtration rate, sAlb = serum albumin.

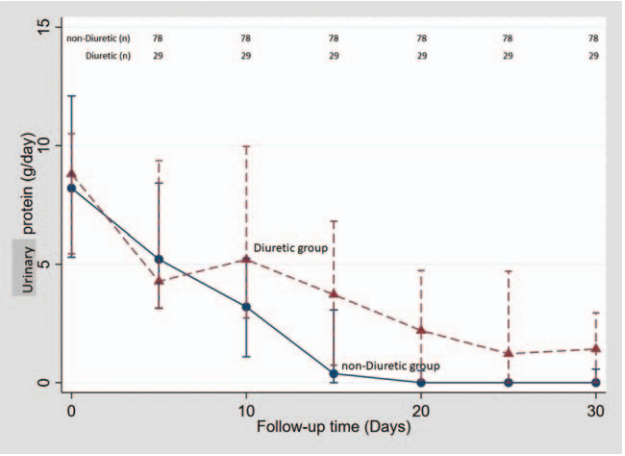

Figure 4. Comparison of the longitudinal change in urinary protein between the diuretic and non-diuretic groups. The median reduction in urinary protein from baseline was 7.3 g/d in the diuretic group and 8.1 g/d in the non-diuretic group.

The present study had several limitations. First, because of the relatively small sample size, some estimates had wide 95% CIs. Although we observed a strong and robust association, our findings should be replicated in future larger-scale studies to further confirm the robustness of the association between diuretic use and AKI risk in patients with MCD. Second, this study was conducted at a tertiary referral institution; therefore, as severe cases of MCD might have been more likely to be referred to our institution, our results may not be widely generalizable to cases with lower severity. However, MCD usually requires hospitalization for diagnosis and the initial treatment, and our center is solely responsible for providing such care in the area. Third, because of the study's retrospective design, there is a possibility that the history of diuretic use prior to MCD diagnosis could have been underreported, and that the sCr levels before the diagnosis of MCD might not have been an accurate index of baseline kidney function but might have reflected the initial stages of the index kidney disease. Finally, our study population was limited to Japanese adults with MCD, and, thus, the generalizability of our findings to other populations may be limited.

In conclusion, this study showed that diuretic administration before MCD diagnosis can be associated with a higher AKI risk and a longer time to complete remission in adult patients with MCD. Our results suggested that clinicians should carefully assess the benefits and risks of using diuretics, and minimize the use of other nephrotoxic medications, in such patients. Future studies are needed to determine whether these results can be applied to other causes of nephrotic syndrome or other racial groups.

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