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Acute Kidney Injury as a Predictor of Remission and Relapse in Adult Minimal Change Disease: A Cohort Study Using Time-to-Event Analysis

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ABSTRACT

Acute kidney injury (AKI) is a common complication in adult minimal change disease (MCD), yet its influence on remission and relapse remains insufficiently characterized. This observational cohort study evaluated the association of AKI at presentation with time to complete remission and relapse in 174 adults with biopsy-proven MCD. Patients were classified according to AKI status at diagnosis. Time to complete remission and time to relapse after remission were assessed using Kaplan–Meier analysis and compared with the log-rank test, while Cox proportional hazards models were used to identify predictors of relapse. AKI was present in 40.8% of patients. All patients achieved complete remission during follow-up, with cumulative remission rates of 66.7% at 4 weeks and 87.4% at 8 weeks. Patients without AKI achieved remission more rapidly than those with AKI, with higher remission rates at 4 weeks (77.7% vs. 50.7%) and 8 weeks (92.2% vs. 80.3%), and a shorter median time to remission (24 vs. 28 days; log-rank $p < 0.001$). Relapse occurred in 64.9% of patients and was less frequent in the non-AKI group than in the AKI group (55.3% vs. 78.9%). Patients without AKI also experienced later relapse, with a longer median time to relapse (132 vs. 108 days; log-rank $p < 0.001$). In multivariable analysis, AKI remained independently associated with relapse (HR 1.65, 95% CI 1.14–2.39), whereas older age was protective and low serum albumin increased relapse risk. These findings indicate that AKI is a clinically relevant prognostic factor in adult MCD, associated with delayed remission and a higher and earlier risk of relapse.

Keywords: minimal change disease, acute kidney injury, remission, relapse, survival analysis

1. Introduction

Minimal change disease (MCD) is a leading cause of idiopathic nephrotic syndrome in adults, accounting for approximately 10–15% of cases worldwide [1]. In this population, MCD typically presents with abrupt onset of heavy proteinuria, hypoalbuminemia, and generalized edema. In addition, a subset of patients may exhibit hypertension, microscopic hematuria, and acute kidney injury (AKI) [2]. Despite its generally favorable response to corticosteroid therapy, with most patients achieving remission, the clinical course is frequently complicated by a high rate of relapse, reported in up to 50–75% of cases, often necessitating repeated or prolonged immunosuppressive treatment [3].

AKI occurs in approximately 20–35% of adult patients with MCD and is commonly attributed to hemodynamic disturbances, including intravascular volume depletion and impaired renal perfusion, often accompanied by varying degrees of tubular injury [4–6]. Histological evidence of acute tubular damage has been reported in a substantial proportion of these patients. Several clinical factors, such as older age, male sex, more severe proteinuria, and lower serum albumin, have been associated with the development of AKI. Importantly, previous studies have shown that AKI may delay the time to remission in adult MCD [7,8]. However, existing evidence has largely focused on pathophysiological mechanisms and short-term outcomes, whereas its role in long-term disease course remains less clearly defined. In particular, the impact of AKI on relapse, especially when assessed using time-to-event approaches, has not been systematically evaluated. Moreover, previously reported predictors of relapse, including age, serum albumin, and baseline renal function, have shown inconsistent associations across different cohorts. Given the substantial relapse burden and the increasing need for individualized treatment strategies, there is a clear need to identify reliable prognostic factors. In this

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context, AKI at presentation may represent a distinct clinical phenotype characterized by hemodynamic instability and tubular stress. Therefore, evaluating its association with both remission and relapse using survival analysis may provide important insights into disease trajectory and support improved risk stratification in adult MCD.

Research Objectives

This study aimed to evaluate the clinical characteristics of acute kidney injury in adult patients with minimal change disease and to investigate its association with time to complete remission and relapse using survival analysis.

2. Methodology

2.1. Study design and setting

This study was conducted as an observational cohort at the Kidney and Urology Center of Bach Mai Hospital between 2023 and 2024. Patients were identified at the time of diagnosis and followed longitudinally to evaluate clinical outcomes, including time to complete remission and subsequent relapse.

2.2. Population and Sample

Adult patients aged 18–60 years with newly diagnosed nephrotic syndrome were consecutively enrolled during the study period. The diagnosis of nephrotic syndrome was established based on standard clinical and laboratory criteria, including generalized edema, proteinuria greater than 3.5 g/day, and hypoalbuminemia (serum albumin <30 g/L). All patients underwent percutaneous ultrasound-guided renal biopsy, and only those with histopathologically confirmed MCD were included in the final analysis. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [9]. AKI was diagnosed if any of the following conditions were met: (1) an increase in serum creatinine to ≥1.5 times baseline; (2) an absolute increase in serum creatinine of ≥0.3 mg/dL (26.5 μmol/L) within 48 hours; or (3) a urine output of <0.5 mL/kg/h for at least 6 hours.

Exclusion criteria included a prior diagnosis of diabetes mellitus, chronic kidney disease, or systemic diseases associated with secondary nephrotic syndrome, such as systemic lupus erythematosus or amyloidosis. Patients with other glomerular diseases identified on biopsy, as well as those with acute nephritic syndrome or rapidly progressive glomerulonephritis, were also excluded. These criteria were applied to ensure a homogeneous cohort of patients with primary MCD. A total of 174 patients with biopsy-proven MCD were included in the final analysis.

2.3. Research variables

Demographic, clinical, and laboratory data were systematically collected at the time of admission. Demographic variables included age, sex, height, and body weight. Clinical parameters comprised blood pressure measurements, including systolic and diastolic blood pressure, as well as comorbid conditions such as hypertension and history of allergy. Urine output over 24 hours was recorded to assess volume status. Laboratory evaluations included complete blood count, with measurements of hemoglobin and white blood cell count. Renal function was assessed using serum creatinine, estimated glomerular filtration rate (eGFR), and serum urea levels. Serum albumin was measured as an indicator of nephrotic severity. Lipid profiles, including total cholesterol and triglycerides, were obtained for all patients. Additional laboratory parameters included complement levels (C3 and C4) and urinalysis findings such as microhematuria. Information on medication use at baseline, particularly renin–angiotensin system inhibitors, was also recorded.

2.4. Outcome definitions

- Complete remission (CR) was defined as a 24-hour urinary protein excretion of <0.3 g/day or a urine protein-to-creatinine ratio of <300 mg/g (or <30 mg/mmol) following corticosteroid therapy.
- Relapse was defined as a recurrence of proteinuria after achieving complete remission, indicated by a 24-hour urinary protein excretion of ≥1.0 g/day, a urine protein-to-creatinine ratio of ≥1.0 g/gCr, or a urine protein level of ≥2+ on dipstick testing for at least two consecutive days.
- Time to complete remission was defined as the interval from the date of diagnosis (or initiation of corticosteroid therapy) to the first documentation of complete remission.
- Time to relapse was defined as the interval from the date of complete remission to the first documented relapse or the last follow-up visit for patients without relapse. Patients who did not experience relapse were censored at the end of the observation period.

2.5. Statistical analysis

All statistical analyses were performed using Stata software (StataCorp, College Station, TX, USA). Continuous variables were summarized as means with standard deviations or medians with interquartile ranges, while categorical variables were presented as counts and percentages. Time-to-event outcomes, including time to complete remission and time to relapse after complete remission, were analyzed using the Kaplan–Meier method. Differences between groups were assessed using the log-rank test. Cox proportional hazards regression analysis was performed to evaluate factors associated with time to relapse. Variables considered clinically relevant were included in the multivariable model. Results were reported as hazard ratios with 95% confidence intervals. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

2.6. Ethics Statement

The study protocol was approved by the institutional review board, and all procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

3. RESULTS

A total of 174 patients with MCD were included, of whom 71 (40.8%) had acute kidney injury. The mean age of the study population was 40.12 ± 18.96 years, and

62 (35.63%) were female. Patients with AKI were older than those without AKI (41.53 ± 18.78 vs. 39.71 ± 19.21 years). At admission, systolic blood pressure was higher in the AKI group compared with the non-AKI group (119.89 ± 15.47 vs. 110.36 ± 15.02 mmHg), while urine output was lower (382.41 ± 254.35 vs. 670.19 ± 508.96 mL/24 h). Laboratory parameters showed similar levels of serum albumin (17.11 ± 4.71 vs. 16.28 ± 4.19 g/L), serum creatinine (74.80 ± 32.20 vs. 69.31 ± 28.75 μmol/L), and eGFR (115.42 ± 35.32 vs. 116.24 ± 21.76 mL/min) between the AKI and non-AKI groups. Lipid profiles were also comparable, with total cholesterol of 8.87 ± 4.11 vs. 9.91 ± 3.07 mmol/L and triglycerides of 1.82 ± 0.78 vs. 2.14 ± 1.44 mmol/L. The proportion of patients receiving renin–angiotensin system inhibitors was higher in the AKI group than in the non-AKI group (25.4% vs. 13.6%). (Table 1)

The cumulative probability of complete remission increased over time, with 66.7% and 87.4% of patients achieving remission at 4 and 8 weeks, respectively. Notably, all patients eventually achieved complete remission during the follow-up period. Patients without AKI achieved remission more rapidly than those with AKI, with a higher proportion reaching remission at both 4 weeks (77.7% vs. 50.7%) and 8 weeks (92.2% vs. 80.3%). The median time to remission was shorter in the non-AKI group (24 [95% CI 22–25] days) compared with the AKI group (28 [95% CI 26–35] days; log-rank $p < 0.001$) (Figure 1).

During follow-up, relapse occurred in 113 of 174 patients (64.9%). The proportion of relapse was higher in the AKI group compared with the non-AKI group (78.9% vs. 55.3%). The cumulative incidence of relapse increased over time and was consistently higher in patients with AKI. At 14 weeks, 21.1% of patients in the AKI group had relapsed compared with 5.8% in the non-AKI group. At 18 weeks, the corresponding proportions were 71.3% and 46.5%, and at 22 weeks, 82.0% and 60.9%, respectively. Kaplan–Meier analysis demonstrated a significantly higher risk of relapse in the AKI group compared with the non-AKI group (log-rank $p < 0.001$). The median time to relapse was shorter in patients with AKI than in those without AKI (108 [95% CI 105–112] vs. 132 [95% CI 123–140] days) (Figure 2).

In univariate Cox regression analysis, AKI, age, serum albumin, and total cholesterol were significantly associated with time to relapse. In the multivariable model, AKI remained independently associated with an increased risk of relapse (HR 1.65, 95% CI 1.14–2.39, $p < 0.01$). Older age was associated with a lower risk of relapse (HR 0.97 per year, 95% CI 0.96–0.99, $p < 0.01$). Low serum albumin (<25 g/L) was also independently associated with a higher risk of relapse (HR 1.42, 95% CI 1.00–2.02, $p = 0.049$). Total cholesterol showed a trend toward an increased risk of relapse, although this did not reach statistical significance (HR 1.36, 95% CI 0.95–1.95, $p = 0.09$). Sex, eGFR and hypertension were not independently associated with relapse in the multivariable analysis (Table 2).

4. Discussion

To our knowledge, this is among the first studies to demonstrate that AKI independently predicts not only delayed remission but also earlier and more frequent relapse in adult MCD. Beyond a mere complication, our findings suggest that AKI may represent a distinct disease phenotype linking tubular injury with glomerular immune dysregulation, thereby predisposing to disease recurrence. While prior studies have largely focused on the mechanisms and short-term outcomes of AKI, its role in shaping long-term disease trajectory has remained unclear. By applying a time-to-event framework, our study provides novel evidence that integrates AKI into the continuum of disease activity, with important implications for risk stratification and future mechanistic research.

In our cohort of 174 adults with biopsy-proven MCD, AKI was observed in 40.8% of patients, consistent with the upper range reported in prior studies (Waldman et al., 2007; Maas et al., 2017) [10,11]. Patients with AKI exhibited higher systolic blood pressure and reduced urine output, supporting the role of hemodynamic alterations such as hypertension and oliguria. Notably, serum albumin, renal function, and lipid profiles were comparable between groups, suggesting that AKI may not simply reflect greater nephrotic severity. Similar observations have been reported by Smith et al. (2020) and Abraham et al. (2017) [12,13]. The predominance of hemodynamic features, together with higher use of renin–angiotensin system inhibitors in the AKI group, points toward a prerenal mechanism driven by altered intrarenal perfusion rather than profound volume depletion alone. These findings support the concept that AKI in adult MCD may represent a distinct clinical phenotype, relatively independent of proteinuria severity. Proposed mechanisms include tubular ischemia due to vasoconstriction, podocyte–tubular cross-talk, and interstitial edema impairing tubular flow [5,14]. However, the role of RAS inhibition remains incompletely defined and warrants further investigation.

In our cohort, 87.4% of adult patients with MCD achieved complete remission within 8 weeks, consistent with previously reported rates of 80–98% (Waldman et al., 2007; Fenton et al., 2018) [11,15]. The presence of AKI was associated with a modest but significant delay in remission, with a median prolongation of approximately 4 days. This finding aligns with prior studies showing that AKI is associated with a lower likelihood of early proteinuria resolution (Nagasawa et al., 2017; Komukai et al., 2015) [16,17]. Importantly, this delay is unlikely to reflect intrinsic steroid resistance but may instead indicate transient intrarenal hemodynamic disturbances or subclinical tubular injury that impair podocyte recovery [18,19].

Patients with AKI also experienced a higher relapse burden, characterized by both increased cumulative incidence and earlier recurrence compared with those without AKI. Although overall relapse rates were consistent with prior reports in adult MCD (Waldman et al., 2007; Fenton et al., 2018; Shakeel et al., 2024), our findings suggest that AKI may influence not only relapse risk but also its timing [11,15,20]. Evidence directly linking AKI to relapse dynamics remains limited, and our results support its role as a potential

independent determinant of both outcomes, consistent with emerging data from Lee et al. (2016) and Wang et al. (2024) [8,21]. Mechanistically, AKI may reflect intrarenal hemodynamic disturbance and tubular injury, which can impair glomerular recovery and promote instability during steroid tapering [7,13].

In multivariable analysis, AKI remained independently associated with relapse, while older age was protective and low serum albumin increased relapse risk, consistent with observations that younger adults tend to relapse more frequently, possibly due to greater immune reactivity or podocyte vulnerability (Lee et al., 2016; Waldman et al., 2007) [8,11]. These findings are consistent with prior studies suggesting that younger patients are more prone to relapse and that hypoalbuminemia reflects greater disease severity. In contrast, total cholesterol lost significance after adjustment, likely reflecting confounding by nephrotic severity, while sex, eGFR, and hypertension were not independently associated, in line with the heterogeneous evidence reported in the literature. For instance, Uchida et al. (2016) suggested that AKI may prolong disease activity through impaired tubular recovery, potentially leading to maladaptive repair and persistent immune dysregulation [17]. Low serum albumin was also independently associated with relapse, reinforcing its role as a marker of disease severity and podocyte injury, as reported in previous cohorts (Dias et al., 2012; Lee et al., 2016) [8,22]. In contrast, the association between total cholesterol and relapse was attenuated after adjustment, suggesting confounding by disease severity. Sex, baseline eGFR, and hypertension were not independently associated with relapse, in line with the heterogeneous and inconclusive evidence in the literature [5,6]. Overall, these findings highlight the multifactorial nature of relapse and the need for larger prospective studies to better define risk predictors in adult MCD.

This study has several limitations. First, as an observational cohort conducted at a single center, the findings may be subject to residual confounding and may limit generalizability to other populations. Second, although time-to-event analysis was applied, the sample size remained moderate, which may have limited the statistical power to detect weaker associations. Third, important mechanistic biomarkers related to tubular injury or immune dysregulation were not assessed, precluding deeper exploration of the underlying pathways linking to relapse. Finally, treatment regimens and follow-up strategies were not standardized, which may have influenced clinical outcomes.

5. Conclusion

In this cohort of adults with biopsy-proven MCD, AKI was common and associated with distinct clinical features characterized by hemodynamic alterations. Importantly, AKI was independently associated with delayed remission and a higher risk of earlier and more frequent relapse. These findings suggest that AKI may represent a clinically relevant prognostic phenotype and highlight its potential role in risk stratification and management in adult MCD.

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