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Clinicopathological Characteristics and Kidney Outcomes in Biopsy-Confirmed Acute Interstitial Nephritis

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Introduction: Acute interstitial nephritis (AIN) is a significant cause of acute kidney injury, with varying etiologies and outcomes. This study aimed to examine the causes, clinical characteristics, management, and kidney outcomes in patients with biopsy-confirmed AIN.

Methods: A retrospective review was conducted on 166 patients diagnosed with AIN through kidney biopsy at Mayo Clinic between 2012 and 2023. Demographic, clinical, laboratory, and pathological data were collected. The primary outcome was kidney function recovery within the first 6 months. Statistical analyses included univariable and multivariable logistic regression, Kaplan-Meier survival analysis, and Cox proportional hazards modeling.

Results: Medications were the primary cause of AIN (67%), followed by autoimmune diseases (20%) and infections (6%). Within 6 months, 76% of patients achieved kidney recovery. Multivariable analysis indicated that moderate to severe interstitial fibrosis and tubular atrophy (IFTA) and dialysis requirement were associated with nonrecovery, whereas a prebiopsy diagnosis of AIN was positively associated with kidney recovery. Drug-related AIN had higher recovery rates compared to all other causes (81% vs. 66%, $P = 0.04$), and moderate to severe IFTA and dialysis need remained significant predictors of decreased recovery. Steroid therapy, used in 81% of patients, did not significantly influence kidney recovery in the overall cohort or in drug-induced AIN.

Conclusion: This study provides insights into the characteristics and outcomes of biopsy-confirmed AIN. IFTA and dialysis requirement were significant factors associated with worse kidney outcomes. These findings may help inform clinical management and prognostication in patients with AIN.

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AIN is a significant and potentially reversible cause of acute kidney injury, particularly among hospitalized individuals, accounting for 15% to 27% of cases.[1,2] Whereas some patients experience full recovery of kidney function, a considerable proportion, ranging from 30% to 70% may not achieve complete recovery and instead progress to chronic kidney disease (CKD).[3] Studies show that individuals with biopsy-confirmed AIN have a 5% to 7% risk of advancing to end-stage kidney disease (ESKD), requiring dialysis.[4,5]

The etiology of AIN is diverse, with drugs implicated in over two-thirds (70%–75%) of cases, followed by autoimmune diseases (10%–20%), and infections (4%–10%).[6,7] Consequently, the clinical, laboratory, and histopathological presentations of AIN can vary significantly.[8] Treatment typically involves the cessation of any offending agents and the administration of immunosuppressive therapy, mainly steroids, although the efficacy of this regimen is currently under debate.[1,3–5,9–11] The clinical management of patients with AIN presents significant challenges due to its frequently uncharacteristic and atypical manifestations in many cases. It remains unclear whether specific clinical and laboratory characteristics can predict response to steroids and improved kidney outcomes. An in-depth exploration of the clinicopathological attributes, including the effects of steroid therapy and kidney outcomes, is critically needed.

In this retrospective analysis, we explored the etiology, clinical presentation, histopathological features,

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laboratory findings, and steroid treatment in a cohort of 166 patients diagnosed with biopsy-confirmed AIN over the past 10 years. Our aim was to pinpoint prognostic indicators associated with kidney outcomes.

METHODS

Study Population

This study was approved by the Institutional Review Board of Mayo Clinic. We conducted a retrospective chart review of patients diagnosed with biopsy-confirmed AIN at Mayo Clinic between January 1, 2012, and December 31, 2023. We used Mayo Data Explorer to search and identify eligible patients in Renal Pathology Laboratory database. Subsequently, we manually reviewed kidney pathology reports to confirm AIN diagnosis. The study excluded patients aged <18 years, those diagnosed with glomerulonephritis or primary vascular disease, and those with transplant biopsies.

Data Collection

We reviewed and collected demographic, clinical, laboratory, and pathological data. A pathologic diagnosis of AIN is based on the presence of prominent interstitial inflammation in the nonfibrotic cortex and tubulitis.[1] Biopsy time was established as the baseline. Leukocytosis was defined by a leukocyte count greater than 10.5×10^9/L, eosinophilia was defined by an eosinophil count exceeding 0.5×10^9/L, and eosinophiluria was defined by more than 1% urine eosinophils. The estimated glomerular filtration rate was calculated using the CKD-Epidemiology Collaboration formula, expressed in ml/min per 1.73 m^2.

Kidney Outcomes

The primary outcome assessed was the recovery of kidney function, determined by the available serum creatinine (sCr) measurement within the first 6 months. Complete recovery was achieved when the sCr level returns to within 25% of its baseline or to below 1.4 mg/dl if the baseline is unknown. Partial recovery was defined as a reduction in sCr by at least 50% from its peak, without returning to within 25% of the baseline. No recovery included cases that did not meet the criteria for complete or partial recovery or those remaining on kidney replacement therapy.

The secondary outcome, evaluated at the 6-month follow-up, included normal kidney function, progression to CKD, and ESKD. Normal kidney function was characterized by a final sCr level < 1.4 mg/dl, progressive CKD by an sCr level ≥ 1.4 mg/dl, and ESKD if the patient continued on dialysis therapy or had received a kidney transplant. The definitions for kidney recovery and secondary kidney outcomes in this study aligned with those used in our institution's previous study, which covered the period from 1993 to 2011,[1] to facilitate a comparison of AIN outcomes between the 2 timeframes.

Statistical Analysis

Data were expressed as either mean ± SD or median with interquartile range for continuous variables, and as counts with percentages for categorical variables. Categorical characteristics between groups were compared using either Fisher exact test or chi-square test. For continuous variables, the t test or Wilcoxon rank sum test was employed for comparisons between 2 groups, whereas 1-way ANOVA was used to assess differences across multiple groups. Kidney recovery was analyzed using Kaplan-Meier survival analysis. Univariable and multivariable logistic regression analyses were conducted to identify factors associated with kidney recovery. In addition, a Cox proportional hazards model was employed to assess the association between steroid treatment and kidney recovery. Results from the logistic and Cox models were presented as odds ratios and hazard ratios with 95% confidence intervals (CI), respectively. Statistical significance was set at $P < 0.05$. Statistical analyses were carried out using JMP Pro software, version 14.3.0 (SAS Institute Inc., NC).

RESULTS

Comparative clinical characteristics of patients achieving versus those not achieving kidney recovery within 6 months.

A total of 166 patients with AIN were identified in this study. In Table 1, we display the demographic and clinical data for the entire cohort. The average age was 59 ± 17 years, with approximately half being male. The incidence of rash, fever, and oliguria was notably low within the cohort, affecting less than 16% of patients. Only 2 patients exhibited the triad of these symptoms, representing 1.2% of the study group.

Within the cohort, a significant portion of the patients (76%; 126 out of 166) experienced kidney recovery either complete ($n = 85$) or partial ($n = 25$), with a median recovery time of 1.7 months. Approximately 18% of patients in the nonrecovery group had an unknown cause of AIN, a proportion significantly larger than the 6% observed in the recovery group ($P = 0.05$). The baseline sCr did not differ between those who recovered and those who did not (1.2 ± 0.5 vs. 1.4 ± 0.7, $P = 0.58$). Compared to patients with recovery, those without recovery had a higher incidence of moderate to severe IFTA (59% vs. 22%, $P < 0.001$) and global glomerulosclerosis (44% vs. 17%, $P = 0.003$), presence of granulomas (33% vs. 17%, $P = 0.04$), and a need for dialysis (40% vs. 7%, $P < 0.001$); however,

Table 1. Clinical, laboratory, histopathological, and treatment comparisons in the entire acute interstitial nephritis cohort: recovery versus nonrecovery

Characteristics	All patients (N = 166)	Recovery (n = 126)[a]	Nonrecovery (n = 40)	P value
Age at the biopsy (yr)	58.6 ± 17.0	59.0 ±16.7	56.4 ± 17.6	0.78
Male sex, *n* (%)	83 (49.7)	63 (50.0)	20 (50.0)	>0.99
White race, *n* (%)[b]	152 (93.2)	122 (97.6)	30 (79.0)	<0.001
BMI (kg/m^2)	29.6 ± 7.7	29.5 ± 7.0	29.5 ± 9.8	0.53
Comorbidities, *n* (%)	158 (95.2)	119 (94.4)	39 (97.5)	0.68
Prebiopsy AIN diagnosis, *n* (%)	130 (78.3)	106 (84.1)	24 (60.0)	0.003
Causes of AIN				
Drug-related, *n* (%)	111 (66.9)	90 (71.4)	21 (52.5)	0.03
Autoimmune-related, *n* (%)	33 (19.9)	27 (21.4)	6 (15.0)	0.49
Infection-related, *n* (%)	10 (6.0)	6 (4.9)	4 (10.0)	0.52
Unknown, *n* (%)	15 (9.0)	8 (6.4)	7 (17.5)	0.05
Other, *n* (%)	4 (2.4)	2 (1.6)	2 (5.0)	na
Multiple causes, *n* (%)	7 (4.2)	7 (5.6)	0	na
Clinical presentation				
Rash, *n* (%)	21 (12.7)	16 (12.7)	5 (12.5)	>0.99
Fever, *n* (%)	23 (13.9)	16 (12.7)	7 (17.5)	0.44
Oliguria, *n* (%)	27 (16.3)	16 (12.7)	11 (27.5)	0.046
Triad sign, *n* (%)	2 (1.2)	2 (1.6)	0	>0.99
CKD prior to biopsy, *n* (%)	59/161 (36.6)	41/123 (33.9)	18/38 (47.4)	0.13
Baseline sCr (mg/dl)	1.3 ± 0.5	1.2 ± 0.5	1.4 ± 0.7	0.58
Baseline sCr in CKD (mg/dl)	1.8 ± 0.6	1.7 ± 0.5	1.9 ± 0.7	0.31
Baseline eGFR in CKD (ml/min per 1.73 m^2)	42 (32–50)	42 (33–50)	26 (25– 50)	0.34
Baseline sCr without CKD (mg/dl)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.12	>0.99
Baseline eGFR without CKD (ml/min per 1.73m^2)	78 (71–90)	78 (69–89)	79 (74–94)	0.43
Kidney size, *n*	137	103	34	0.23
Normal, *n* (%)	123 (89.8)	95 (92.2)	28 (82.4)	
Small, *n* (%)	4 (2.9)	2 (1.9)	2 (5.9)	
Large, *n* (%)	10 (7.3)	6 (5.8)	4 (11.8)	
AKI stage	165	126	39	0.78
Stage 1	33 (20.0)	26 (20.6)	7 (18.0)	
Stage 2	32 (19.4)	23 (18.3)	9 (23.1)	
Stage 3	100 (60.6)	77 (61.1)	23 (59.0)	
Kidney biopsy				
IFTA, *n*	163	125	39	<0.001
None, *n* (%)	44 (27.0)	41 (32.8)	3 (7.7)	
Mild, *n* (%)	69 (41.7)	56 (44.8)	13 (33.3)	
Moderate, *n* (%)	35 (21.5)	23 (18.4)	12 (30.8)	
Severe, *n* (%)	16 (9.8)	5 (4.0)	11 (28.2)	
Globally glomerulosclerosis, *n*	163	125	39	0.003
None, *n* (%)	77 (47.2)	64 (51.2)	14 (35.9)	
Mild, *n* (%)	48 (29.4)	40 (32.0)	8 (20.5)	
Moderate, *n* (%)	26 (16.0)	16 (12.8)	10 (25.6)	
Severe, *n* (%)	12 (7.4)	5 (4.0)	7 (18.0)	
Granuloma present, *n* (%)	34 (20.5)	21 (16.5)	13 (32.5)	0.04
Laboratory test				
sCr at biopsy (mg/dl)	3.0 (2.0–4.7)	2.9 (2.0–4.7)	3.1 (2.1–5.6)	0.21
Peak sCr (mg/dl)	3.8 (2.5–6.2)	3.8 (2.5–5.9)	4.4 (2.3–7.4)	0.43
Albumin at biopsy (g/dl)	3.7 ± 0.74	3.73 ± 0.76	3.62 ± 0.69	0.45
24h proteinuria at biopsy (g/24-h)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.6 (0.2–2.2)	0.10
CRP at biopsy (mg/dl)	17.1 (5.0–61.3)	22.9 (5.9–68.4)	10.4 (2.9–15.4)	0.02
ESR at biopsy (mm/h)	48 (30–85)	49 (31–92)	35 (17–58)	0.33
Neutrophil count (x 10^9/L)	5.2 (3.5–7.0)	5.4 (3.6–7.1)	4.3 (2.8–6.7)	0.04
Lymphocytes count (x 10^9/L)	1.3 (0.9–1.8)	1.3 (1.0–1.8)	1.2 (0.7–1.7)	0.53
Leukocytosis, *n* (%)	31 (18.7)	27 (21.4)	4 (10.0)	0.16
Eosinophilia, *n* (%)	22/151 (14.6)	19/118 (16.1)	3/33 (9.1)	0.41
Urine WBC present, *n* (%)	135/163 (82.8)	105/125 (84.0)	30/38 (78.9)	0.47
Urine RBC present, *n* (%)	111/164 (67.7)	86 (68.3)	25/38 (65.8)	0.84
Urine WBC cast present, *n* (%)	5/163 (3.1)	4/125 (3.2)	1/38 (2.6)	>0.99

(Continued on following page)

Table 1. (Continued) Clinical, laboratory, histopathological, and treatment comparisons in the entire acute interstitial nephritis cohort: recovery versus nonrecovery

Characteristics	All patients ($N = 166$)	Recovery ($n = 126$)[a]	Nonrecovery ($n = 40$)	*P* value
Urine RBC cast present, *n* (%)	1/163 (0.6)	1/125 (0.8)	0	>0.99
Eosinophiluria, *n* (%)	13/102 (12.7)	10/72 (13.9)	3/30 (10.0)	0.75
Urine RTE cell present, *n* (%)	20/164 (12.2)	18 (14.3)	2/38 (5.3)	0.17
Urine RTE cast present, *n* (%)	3/162 (1.9)	3/124 (2.4)	0	>0.99
Urine granular cast present, *n* (%)	35/164 (21.3)	24 (19.1)	11/38 (29.0)	0.26
Treatment				
Steroid therapy, *n* (%)	134 (80.7)	104 (82.5)	30 (75.0)	0.36
Time to start steroid after biopsy (d)	2 (1–5)	2 (1–5)	2 (1–14)	0.26
Duration of steroids (weeks)	10 (6–24)	10 (6–24)	9 (5–23)	0.71
IV steroids given initially, *n* (%)	25/138 (18.1)	22/107 (20.6)	3/31 (9.7)	0.20
MMF, *n* (%)	8 (4.8)	7 (5.6)	1 (2.5)	0.68
Dialysis required, *n* (%)	25 (15.1)	9 (7.1)	16 (40.0)	<0.001
Death, *n* (%)	8 (4.8)	3 (2.4)	5 (12.5)	0.02
Kidney outcome				
Recovery within the first 6 mo				na
Complete recovery, *n* (%)	85 (51.2)[c]	na	na	
Partial recovery, *n* (%)	41 (24.7)	na	na	
No recovery, *n* (%)	40 (24.1)	na	na	
Time to recovery (mo)	na	1.7 (0.8, 3.1)	na	
Outcome at 6-mo follow-up, *n*	128[d]	97	31	<0.0001
Normal kidney function, *n* (%)	50 (39.0)[e]	50 (51.6)	0	
Progressive CKD, *n* (%)	63 (49.2)	47 (48.5)	16 (51.6)	
ESKD, *n* (%)	15 (11.7)	0	15 (48.4)	

AIN, acute interstitial nephritis; AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESR, erythrocyte sedimentation rate; ICIs, immune checkpoint inhibitors; IFTA, interstitial fibrosis and tubular atrophy; IQR, interquartile range; MMF, mycophenolate mofetil; na, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; RTE, renal tubule epithelial; sCr, serum creatinine; WBC, white blood cell; RBC, red blood cell.
Results are presented as mean ± SD or median (IQR) for continuous variables and as *n* (%) for categorical variables.
[a]The recovery indicates either complete or partial recovery.
[b]Unreleased in 2 patients did not acieve recovery.
[c]Patients who achieved complete recovery had their sCr levels decrease from a peak of 4.5 ± 2.9 mg/dl (median 3.7 mg/dl, IQR: 2.4–5.6) to 1.4 ± 0.4 mg/dl, which was not statistically different from their baseline level of 1.3 ± 0.5 mg/dl ($P = 0.23$).
[d]Eight patients died, and 30 patients were lost to follow-up at the 6-month end point (26 from the recovery group and 4 from the nonrecovery group). Thus, there were 128 patients in total at the 6-month end point.
[e]In patients who reached normal kidney function, their sCr levels decreased from a peak of 4.7 ± 3.1 mg/dl (median 3.7 mg/dl, IQR: 2.3–6.0) to 1.1 ± 0.2 mg/dl, with no significant difference compared to their baseline value of 0.98 ± 0.24 mg/dl ($P = 0.36$).

they had lower levels of C-reactive protein (CRP; 10 mg/dl vs. 23 mg/dl, $P = 0.02$) and neutrophil counts (4.3×10^9/L vs. 5.4×10^9/L, $P = 0.04$). Among patients who achieved kidney recovery, 71% had drug-related AIN, compared to 53% in those who did not recover ($P = 0.03$). At the 6-month follow-up, kidney function normalized in half of the patients who achieved kidney recovery. In contrast, all patients who did not recover experienced either progressive CKD (52%) or progressed to ESKD (48%).

Causes of AIN

In Table 2, we outline the various causes of AIN. Medications emerged as the predominant cause, responsible for 67% of cases; with autoimmune diseases contributing to 20%; and infections contributing to 6%. In 9% of cases, the cause of AIN could not be determined. In addition, 4.2% of patients had multiple causes for their AIN, such as a combination of drug-related and autoimmune or infectious diseases. In the category of autoimmune-related AIN, Sjogren's syndrome and sarcoidosis were the most common causes (33% and 21%, respectively). Among the infectious-related AIN, bacterial and fungal infections were the primary causes, accounting for 50% and 40% of these cases, respectively. Within the drug-related category, antibiotics were the most common cause, making up 36% of these cases, followed by proton pump inhibitors (PPIs) at 29%, immune checkpoint inhibitors (ICIs) at 18%, and nonsteroidal antiinflammatory drugs (NSAIDs) at 14%. Notably, 14% of the drug-related cases involved multiple drugs, and other drugs were implicated in 21% of cases. Further details on specific medications are provided in Supplementary Table S1.

Predictors for Kidney Recovery in the Entire Cohort

Across the entire cohort, univariable analysis identified White race, prebiopsy AIN diagnosis, a known cause of AIN, drug-related AIN, and CRP levels as factors associated with increased kidney recovery

Table 2. All causes of acute interstitial nephritis

Causes	Number of patients, *n* (%)
Drug-induced	111 (66.9)[a]
Antibiotics	40 (36.0)
PPIs	32 (28.8)
ICIs	20 (18.0)
NSAIDs	15 (13.5)
Other drugs	23 (20.7)
Multiple drugs	16 (14.4)
Autoimmune related	33 (19.9)[a]
Sjogren syndrome[b]	11 (33.3)
Sarcoidosis	7 (21.2)
TINU	3 (9.1)
VEXAS syndrome	3 (9.1)
IgG4-related	2 (6.1)
IBD	2 (6.1)
SLE	1 (3.0)
GPA	1 (3.0)
CVID	1 (3.0)
Crohn disease	1 (3.0)
RA and allergic rhinitis	1 (3.0)
Infectious	10 (6.0)[a]
Bacterial[c]	5 (50.0)
Viral[d]	1 (10.0)
Fungal[e]	4 (40.0)
Other	4 (2.4)[a]
Malignancy[f]	3 (75.0)
Calcium oxalate deposit	1 (25.0)
Multiple causes	7 (4.2)
Drug and autoimmune[g]	6 (85.7)
Drug and infectious disease[h]	1 (14.3)
Unknown	15 (9.0)[a]

CVID, common variable immunodeficiency; GPA, granulomatosis with polyangiitis; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; ICIs, immune checkpoint inhibitors; NSAIDs, nonsteroidal antiinflammatory drugs; PPIs, proton pump inhibitors; SLE, systemic lupus erythematosus; TINU, tubulointerstitial nephritis and uveitis syndrome.
[a]The percentage in the entire cohort.
[b]One patient also had rheumatoid arthritis.
[c]One *Escherichia coli*, 1 *Klebsiella aerogenes*, 1 methicillin-sensitive *Staphylococcus aureus* (MSSA), 1 mycobacterium infection, and 1 *Streptococcus agalactiae*.
[d]BK virus.
[e]One candida, 2 histoplasmosis, and 1 unidentified.
[f]One B cell chronic lymphocytic leukemia, 1 B cell lymphoma, and 1 multiple myeloma.
[g]One combination of antibiotic (sulfonamides) and Sjogren syndrome, 1 combination of antibiotic (penicillin and z-pak/azithromycin), PPI (omeprazole) and Sjogren syndrome, 1 combination of NSAID (ibuprofen) and Sjogren syndrome, 1 combination of PPI (esomeprazole) and IgG4-related disease, 1 combination of PPI (omeprazole) and SLE, and 1 combination of mesalamine and Crohn disease.
[h]Combination of antibiotic (fluroquinolones) and *E coli*.

Table 3. Univariable and multivariable analysis of predictors influencing kidney recovery in the entire cohort

	Univariable analysis		Multivariable analysis	
Variables	OR (95% CI)[a]	*P value*	OR (95% CI)[a,b]	*P* value
Age[c]	1 (0.99–1.02)	0.39	-	-
Male	0.98 (0.48–2.00)	0.97	-	-
White race	10.9 (3.0–52.2)	<0.0001	0.12 (0–136)	0.55
Prebiopsy AIN diagnosis	3.36 (1.53–7.42)	0.003	10.8 (1.7–69.3)	0.01
Drug-related	2.2 (1.1–4.6)	0.04	1.52 (0.31–7.52)	0.61
Known cause	3.2 (1.0–9.4)	0.04	1.13 (0.08–17.00)	0.93
Oliguria	0.38 (0.16–0.92)	0.033	1.69 (0.15–19.3)	0.78
IFTA (moderate/severe)	0.20 (0.09–0.42)	<0.0001	0.15 (0.03–0.70)	0.02
Global glomerulosclerosis (moderate/severe)	0.26 (0.11–0.58)	0.001	0.32 (0.07–1.52)	0.15
Granuloma present	0.4 (0.2–0.9)	0.04	0.71 (0.11–4.42)	0.71
24-h proteinuria	0.64 (0.46–0.85)	0.001	0.54 (0.21–1.35)	0.18
CRP[c]	1.01 (1.00–1.03)	0.046	1.01 (0.99–1.04)	0.16
Neutrophil count[c]	1.01 (0.94–1.21)	0.33	-	-
Dialysis required	0.11 (0.04–0.28)	<0.0001	0.07 (0.01–0.64)	0.02
Steroid treatment	1.4 (0.6–3.3)	0.41	-	-

AIN, acute interstitial nephritis; CI, confidence interval; CRP, C-reactive protein; IFTA, interstitial fibrosis and tubular atrophy.
[a]Odds ratios (OR) with 95% CI and *P* values calculated using logistic regression model to identify factors associated with recovery in the entire cohort.
[b]The variables with $P < 0.05$ in univariable analysis were used for multivariable analysis.
[c]OR is per unit change in regression.

(Table 3). Conversely, the presence of oliguria, IFTA, global glomerulosclerosis, and granulomas, as well as 24-hour proteinuria and the need for dialysis, were factors associated with decreased kidney recovery. Within the study cohort, 134 patients (81%) received steroid therapy. Univariable analysis indicated that steroid therapy was not significantly associated with kidney recovery ($P = 0.41$). Subsequent multivariable analysis indicated that only IFTA (OR: 0.15; 95% CI: 0.03–0.70; $P = 0.02$) and dialysis requirement (OR: 0.07; 95% CI: 0.01–0.64; $P = 0.02$) were significant predictors for decreased kidney recovery, whereas prebiopsy diagnosis of AIN was a strong indicator (OR: 10.8; 95% CI: 1.7–69.3; $P = 0.01$) for increased kidney recovery.

We further assessed the effectiveness of steroid therapy on kidney outcomes by comparing these results with those of patients who did not receive steroid treatment (Supplementary Table S2). Most variables, including kidney outcomes within the first 6 months and the time to recovery, did not differ between the 2 groups; exceptions were lower peak sCr (3.6 mg/dl vs. 7 mg/dl, $P = 0.002$), need of dialysis (12% vs. 28%, $P = 0.03$), and incidence of ESKD (8% vs. 32%, $P = 0.004$), as well as higher albumin levels (3.8 ± 0.6 g/l vs. 3.2 ± 1.0 g/l, $P = 0.02$) observed in the steroid-treated group.

Effects of Steroid Therapy on Kidney Recovery in the Entire Cohort

Within the entire cohort, survival analysis demonstrated that steroid treatment did not influence kidney recovery (log-rank test: $P = 0.84$) (Figure 1). Further analysis, both unadjusted and adjusted for various variables revealed no significant difference in kidney recovery between patients who received steroid therapy and those who did not (Table 4).

Kidney Outcomes of Drug-Related AIN

Upon diagnosis of AIN, all drugs implicated in the condition were discontinued. According to the data in Supplementary Table S3, drug-induced AIN was

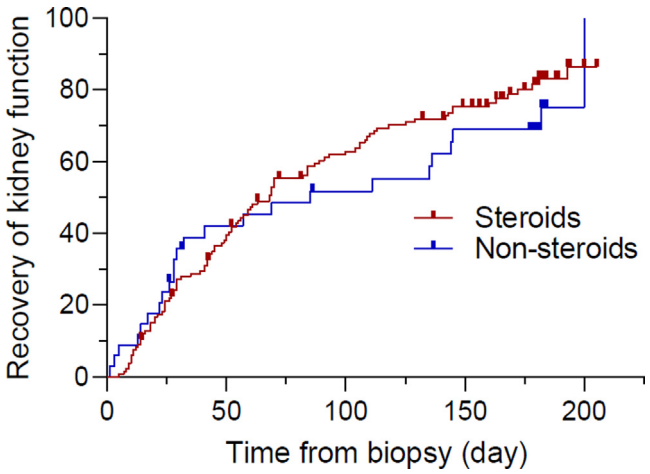

Figure 1. Kidney recovery between steroid and nonsteroid treatment in patients with AIN. One hundred thirty-three patients were treated with steroid, whereas 32 were not. The effectiveness of steroid therapy in achieving either complete or partial kidney recovery was evaluated through Kaplan-Meier analysis, with a log-rank test result of $P = 0.84$. The average recovery time for kidneys in patients receiving steroid treatment was 62 days, similar to the 64 days observed in patients who did not receive steroid treatment.

associated with a higher incidence of rash (17% vs. 4%, $P = 0.01$) and elevated CRP (23 mg/dl vs. 12 mg/dl, $P = 0.04$) and neutrophils (5.6×10^9/L vs. 4.3×10^9/L, $P = 0.01$). In addition, these patients had a lower prevalence of CKD prior to biopsy (30% vs. 51%, $P = 0.01$), as well as reduced granuloma formation (14% vs. 33%, $P = 0.01$). Although the proportion of drug-induced AIN with steroid therapy was comparable to those with other causes (85% vs. 73%, $P = 0.09$), the duration of steroid use was significantly shorter (median 8 weeks vs. 16 weeks, $P = 0.002$) in drug-induced AIN. Of the patients with drug-induced AIN, 81% achieved kidney recovery, significantly higher than the 66% observed in patients with other causes of AIN ($P = 0.04$). Approximately half of the patients with drug-induced AIN had normal kidney function at the 6-month follow-up, in contrast to the 79% of patients with other causes who developed ESKD or progressive CKD ($P = 0.004$).

Table 4. Comparative likelihood of kidney recovery in AIN: steroid vs. nonsteroid therapy

Variables	HR (95% CI)[a]	*P* value
Nonadjusted	1.32 (0.64–2.71)	0.46
Adjusted for		
Sex	1.41 (0.68–2.93)	0.35
White race	1.57 (0.71–3.52)	0.27
Prebiopsy AIN diagnosis	1.37 (0.66–2.89)	0.56
Oliguria	1.38 (0.66–2.88)	0.39
IFTA	1.29 (0.61–2.72)	0.50
Global glomerulosclerosis	1.44 (0.67–3.1)	0.35
Granuloma present	1.32 (0.64–2.72)	0.45
Known cause	1.25 (0.59–2.66)	0.56
Drug related	1.34 (0.64–2.78)	0.44
CRP	1.3 (0.41–4.19)	0.66
Dialysis required	1.39 (0.65–2.98)	0.39
All the above variables	3.86 (0.19–79.9)	0.38

AIN, acute interstitial nephritis; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IFTA, interstitial fibrosis and tubular atrophy.
[a]HR and 95% CI calculated using proportional Cox hazard model.

We also conducted a comparison of the clinical characteristics between patients with drug-induced AIN who achieved recovery and those who did not recover (Supplementary Table S4). Compared to patients who experienced recovery, those without recovery exhibited a higher incidence of moderate to severe IFTA (57% vs. 19%, $P = 0.003$) and global glomerulosclerosis (43% vs. 15%, $P = 0.03$), along with a greater dialysis need (33% vs. 7%, $P = 0.003$). Conversely, their levels of CRP were lower (7.5 mg/dl vs. 32 mg/dl, $P = 0.03$). At the 6-month follow-up, kidney function normalized in 61% of the patients who achieved kidney recovery, whereas every patient who did not recover experienced either progressive CKD or progressed to ESKD.

The proportion of patients undergoing steroid therapy was consistent between the recovery and nonrecovery groups in cases of drug-related AIN (83% vs. 91%, $P = 0.52$), as shown in Supplementary Table S4. We evaluated kidney outcomes in patients with drug-induced AIN who received steroid therapy versus those who did not (Table 5). The proportion of kidney recovery was comparable between the 2 groups (80% vs. 88%, $P = 0.59$). Kidney outcomes at the 6-month follow-up were also similar ($P = 0.99$).

In this study, the distribution of patients with drug-induced AIN was as follows: 30 associated solely with antibiotics, 16 with PPIs, 18 with ICIs, and 7 with NSAIDs. Supplementary Table S5 details comparisons of clinicopathological features across these 4 categories. Most variables showed no significant differences between the groups. However, NSAID-related AIN exhibited a lower incidence of comorbidities compared to the other groups (57% vs. 97%–100%, $P = 0.001$). Nearly all patients in the ICI-related AIN group had normal or mild IFTA, whereas approximately one-third of patients in the other groups displayed moderate to severe IFTA ($P = 0.02$). Kidney interstitial eosinophils were also less prevalent in the ICI-related group compared to the other groups (33% vs. 50%–86%, $P = 0.002$). Only 43% of NSAID-related AIN received steroid therapy, compared to 80% in antibiotics and 94% in PPI or ICI groups ($P = 0.01$). The duration of steroid use was shortest in the antibiotics group (6 weeks vs. 8–10 weeks in other groups, $P = 0.02$). All patients with ICI-related AIN achieved recovery and none developed ESKD, whereas 29% of patients within NSAID group did not achieve recovery and 40% progressed to ESKD ($P = 0.03$).

Table 5. Kidney outcomes in drug and autoimmune-induced AIN: comparisons of steroid therapy and nonsteroid therapy

	Drug-induced AIN (n = 111)			Autoimmune-induced AIN (n = 27)	
	Steroid therapy (n = 94)	Nonsteroid therapy (n = 17)	P value	Steroid therapy (n = 27)	P value[a]
Mycophenolate mofetil, n (%)	3 (3.2)	0	>0.99	5 (18.5)	0.01
Recovery within 6 mo, n	94	17	0.59	27	0.06
Complete recovery, n (%)	49 (52.1)	11 (64.7)		14 (51.9)	
Partial recovery, n (%)	26 (27.7)	4 (23.5)		7 (25.9)	
No recovery, n (%)	19 (20.2)	2 (11.8)		6 (22.0)	
Time to recovery (d)	43 (21–84)	28 (17–135)	0.78	82 (44–166)	0.04
Time to start steroids (d)	1 (1–3)	na	na	6 (1–16)	0.03
Outcome at 6-month follow-up, n	69	12	0.99	26	0.06
Normal kidney function, n (%)	34 (49.3)	6 (50.0)		6 (23.1)	
Progressive CKD, n (%)	30 (43.5)	5 (41.7)		18 (69.2)	
ESKD, n (%)	5 (7.3)	1 (8.3)		2 (7.7)	

AIN, acute interstitial nephritis; CKD, chronic kidney disease; ESKD, end stage kidney disease; IQR, interquartile range; na, not applicable.
Results are presented as median (IQR) for continuous variables and as n (%) for categorical variables.
[a]The P value for comparisons of patients with steroid therapy between drug- and autoimmune-related AIN.

In addition, all 27 patients with AIN solely affected by autoimmune disease were treated with steroids. Significantly, 5 patients with autoimmune-related AIN were treated with mycophenolate mofetil, in contrast to just 3 patients with drug-induced AIN who underwent steroid therapy ($P = 0.01$). Table 5 shows that for autoimmune-related AIN, steroids were initiated at a median of 6 days after biopsy. Of these cases, 78% ($n = 21$) experienced kidney recovery, with a median recovery period of 82 days. The time to initiate steroid therapy and the duration of kidney recovery for autoimmune-related AIN were considerably longer than for drug-induced AIN, where the median time were 1 day and 43 days, respectively, with statistically significant differences ($P = 0.03$ and $P = 0.04$). Notably, among patients who received steroid treatment, kidney recovery and outcomes were similar between drug-induced and autoimmune-related AIN ($P = 0.06$ for both).

Characteristics of Patients With AIN who Underwent Dialysis

Within the entire cohort, 25 patients required dialysis; of these, 36% (9 out of 25) achieved either complete or partial recovery. Meanwhile, 61% (11 out of 18) progressed to ESKD at the 6-month follow-up (Supplementary Table S6). Medications were the primary cause of AIN necessitating dialysis, representing more than half of the cases (52%, 13 out of 25). Importantly, 64% of patients who progressed to ESKD exhibited severe IFTA, whereas none of the patients without ESKD presented with severe IFTA ($P = 0.02$).

Predictors of Kidney Recovery in Drug-Induced AIN

Univariable analysis revealed that factors such as moderate to severe IFTA, global glomerulosclerosis, CKD prior to biopsy, and the necessity for dialysis were associated with decreased kidney recovery; whereas steroid treatment was not a predictor of kidney recovery (Supplementary Table S7). Further multivariable analysis demonstrated that only moderate to severe IFTA (OR: 0.24; 95% CI: 0.06–0.85; $P = 0.03$) and the need for dialysis (OR: 0.17; 95% CI: 0.04–0.79; $P = 0.02$) remained significant predictors for decreased recovery.

Effects of Steroid Therapy on Kidney Recovery Within 6 Months in Drug-Induced AIN

Survival analysis, which included all 111 patients with drug-related AIN, showed that steroid treatment did not significantly affect kidney recovery within the initial 6 months (log-rank test: $P = 0.42$) (Figure 2). The results from both unadjusted and adjusted analyses (either sex, kidney size, IFTA, global glomerulosclerosis, CKD prior to biopsy, dialysis required, or all these variables) indicated that there was no significant difference in kidney recovery between patients who received steroids and those who did not (Table 6).

DISCUSSION

This study offers significant insights into the etiology, clinicopathological manifestations, and prognostic factors associated with AIN, as well as the impact of steroid therapy on kidney outcomes in the last decade. Our research demonstrates that the primary cause of AIN continues to be drug-induced, aligning with earlier studies that identify medications as the foremost contributors to AIN (Supplementary Table S8).[1,8,12] Among these agents, antibiotics remain the most frequently implicated in AIN, although there is a decreasing tread compared to the previous period (24% versus 35%, $P = 0.07$). Notably, the incidence of AIN related to PPIs is increasing (19% vs. 10%, $P = 0.01$). Importantly, AIN associated with ICIs is emerging and

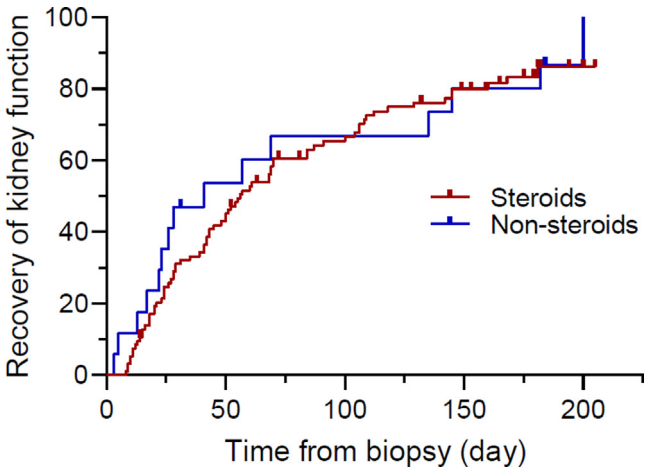

Figure 2. Kidney recovery between steroid and nonsteroid treatment in patients with drug-related AIN. Among 111 patients with drug-induced AIN, 94 received steroid therapy, whereas 17 did not. The effectiveness of steroid therapy in achieving either complete or partial kidney recovery was evaluated through Kaplan-Meier analysis, with a log-rank test result of $P = 0.42$. The average recovery time for kidneys in patients receiving steroid treatment was 56 days, similar to the 64 days observed in patients who did not receive steroid treatment.

now represents 12% of the entire cohort and 18% of drug-related AIN, paralleling the rising prevalence of cancer and the expanded use of ICIs.[13-15] In our cohort, AIN related to ICIs has already surpassed that associated with NSAIDs. In addition, AIN related to ICI treatment frequently involves concurrent use of other drugs such as PPIs.[16] In this study, 2 patients received both ICIs and additional drugs, accounting for 10% (2 out of 20) of ICI-related AIN. Specifically, one used a PPI, and the other was on antibiotics, a PPI, and an NSAID. Interestingly, the incidence of AIN with an unknown cause has increased from 1% during the 1993 to 2011 period to 9% currently ($P = 0.0001$), whereas the rate of prebiopsy diagnosis of AIN has also increased (78% compared to 55%, $P < 0.0001$). The percentage of patients receiving steroid therapy remained similar (86% during 1993–2011 vs. 81% in the current period, $P = 0.21$). Whereas 6-month outcomes were comparable between the periods, the time to recovery appears to be shorter in the current period, with a median of 6.8 weeks compared to 12 weeks previously. These findings indicate a shift in etiology, characterized by increased use of PPIs and especially ICIs. Steroid therapy continues to be extensively utilized in patients with AIN. Whereas kidney outcomes were similar to those in earlier periods, recovery time has decreased in the current period, likely due to improved early recognition of this condition.

Table 6. Comparative likelihood of kidney recovery in drug-related AIN: steroid versus nonsteroid therapy

Variables	HR (95% CI)[a]	*P* value
Nonadjusted	2.64 (0.61–11.45)	0.20
Adjusted for		
Sex	2.74 (0.63–11.92)	0.18
Kidney size	3.56 (0.48–26.2)	0.21
IFTA	2.72 (0.62–11.84)	0.18
Global glomerulosclerosis	2.67 (0.61–11.68)	0.19
CKD prior to biopsy	2.63 (0.60–11.56)	0.20
Dialysis required	2.61 (0.60–11.36)	0.20
All the above variables	3.24 (0.41–25.9)	0.27

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IFTA, interstitial fibrosis and tubular atrophy.
[a]HR and 95% CI calculated using proportional Cox hazard model.

This retrospective analysis underscores the complexity and varied etiology of AIN, highlighting the significant variability in kidney outcomes among affected patients. The pivotal findings of this study elucidate the differential impact of underlying causes—predominantly drugs, autoimmune conditions, and infections—on kidney recovery. Significantly, drug-induced AIN was more amenable to recovery, contrasting with cases attributed to autoimmune diseases or infections, which were less likely to see kidney function restitution. The disparity in recovery rates might be attributable to the direct reversibility of drug effects upon cessation compared to the often-progressive nature of autoimmune or infectious etiologies.[2,12] Remarkably, in cases of drug-induced AIN, patients recovered faster, typically within 1.7 months, compared to 3 months for other causes of AIN. Furthermore, a larger proportion of patients with drug-induced AIN reached recovery, whereas fewer progressed to ESKD relative to those with AIN from other causes. It is important to note that within the drug-induced AIN group, about 20% of patients who did not recover eventually died, and 40% advanced to ESKD.

As previously reported,[17] the clinical presentation of AIN was varied, with only a minority of patients exhibiting the classic triad of rash, fever, and eosinophilia as well as relatively bland urine. This underscores the diagnostic challenge posed by AIN, necessitating a high index of suspicion and often reliance on kidney biopsy for definitive diagnosis.[7] Laboratory findings such as elevated CRP and neutrophil counts were more pronounced in drug-related AIN, potentially reflecting a more robust inflammatory response in these cases.

Histopathologically, the presence of moderate to severe IFTA was significantly associated with worse kidney outcomes, consistent with previous studies.[1,18,19] Nevertheless, a prebiopsy diagnosis of AIN was positively associated with kidney recovery. These findings underscore the critical need for early detection and intervention to prevent irreversible kidney damage. Although some studies have reported

that greater interstitial inflammation correlates with better kidney function recovery,[18,20] we were unable to assess this in our study due to the lack of a consistent quantification of the nonscarred cortex involved by inflammation. In addition, our data show that the need for dialysis at presentation strongly predicted poor recovery, reflecting the severity of kidney impairment in these patients. Notably, over half of those with severe IFTA progressed to ESKD by the 6-month follow-up. Other potential clinical or histological factors affecting AIN prognosis include advanced age, severity of tubulitis, and the presence of granulomas, though their impact remains uncertain.[1,11,21,22]

Steroid therapy, frequently used for AIN, was promptly initiated in 80% of the cohort within 2 days after biopsy. The majority of patients with AIN related to antibiotics, PPIs, and ICIs were treated with steroids. In contrast, only 43% of those with NSAID-related AIN received steroid therapy. Although steroids are traditionally believed to mitigate the inflammatory process in AIN, kidney outcomes over the initial 6 months were similar across these groups; analysis using proportional Cox regression and survival analysis indicated that steroid treatment had no impact on kidney recovery outcomes in both the overall AIN cohort and specifically within the drug-related AIN subgroup. This observation is especially pertinent in light of the current discussions surrounding the effectiveness of steroids in managing AIN.[1] Notably, several studies have demonstrated the benefits of employing steroids, especially when used early in cases of drug-induced AIN.[5,23–25] It is important to recognize that the limited number of patients who did not receive steroids in the cohort, both for drug-related AIN and overall, complicates any comparative analysis and firm conclusion drawing; selection bias persists even after adjustments. Furthermore, the small size of the subgroup with non–drug-related AIN precluded analyses of prognostic factors and the effectiveness of steroids. Consequently, it is difficult to definitively conclude that steroids have no potential benefit in AIN. Further clinical trials are necessary to better determine the role of steroids in the treatment of AIN. The lack of significant benefit observed in this study may prompt a reevaluation of current treatment protocols and encourage exploration of alternative or adjunctive therapies.[21]

Although kidney outcomes did not differ between the steroid-treated group and the untreated group within the initial 6 months, by the end of this period, only 8% of the patients in the steroid-treated group developed ESKD, compared to 29% in the nonsteroid group. This indicates that steroids may have a prolonged protective effect against the progression of AIN.[9] A recent randomized clinical trial suggested that prednisolone may improve long-term outcomes of CKD in patients with an unknown etiology.[26] Notably, all patients with ICI-related AIN experienced some level of kidney recovery, either complete or partial. This group also displayed minimal or absent IFTA and had the lowest presence of eosinophils compared to those with AIN related to antibiotics, PPIs, and NSAIDs. By the end of the 6-month follow-up, 40% of the NSAID-related AIN group had progressed to ESKD, whereas none in the ICI and PPI groups did, and only a small portion of the antibiotic-related group developed ESKD. In cases of drug-related AIN, the presence of IFTA and the necessity for dialysis were also identified as risk factors impacting kidney recovery. This observation calls into question the conventional reliance on corticosteroids for managing AIN, particularly when considering the risks associated with long-term steroid use, such as infections and metabolic disturbances. This aspect of treatment demands a reevaluation, potentially paving the way for clinical trials to establish more refined criteria for steroid administration in patients with AIN.

We acknowledge several limitations of this study. First, the retrospective design inherently limits our ability to ascertain causal relationships and may be subject to biases related to data collection and selection. Second, the identification of AIN was exclusively dependent on biopsy, potentially excluding patients with clinical AIN who did not undergo this procedure, thereby introducing selection bias. The variability in treatment approaches, because not all patients received standardized therapy, could influence the outcomes independently of the disease process itself. Furthermore, the study may not have adequately controlled for all potential confounding variables that could influence the outcomes, such as variations in the severity of initial kidney injury, patient comorbidities, or the precise timing and dosage of steroid therapy.

In conclusion, the study offers crucial insights into the determinants of kidney recovery in AIN, demonstrating that though the cessation of causative agents and management strategies, including steroid therapy, are standard, their effectiveness varies substantially across different patient subgroups. The potential benefits of steroid therapy in patients with AIN cannot be ruled out, underscoring the necessity of additional clinical trials. Crucially, the extent and severity of irreversible kidney damage present at the time of biopsy significantly influences outcomes. Although this assumption is widely held, data from large cohorts underscore the importance of early intervention and setting realistic expectations for recovery. Future research should focus on refining treatment protocols,

exploring novel therapies, and conducting long-term follow-up studies to enhance kidney recovery in patients with AIN. These findings contribute to a deeper understanding of AIN and provide a foundation for improving patient care and outcomes in this challenging clinical condition.

DISCLOSURE

All the authors declared no competing interests.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

JM and WC conceptualized and designed the study. JM and PK acquired the data. JM and CT performed data analysis. JM wrote the initial draft, with WC performing primary revisions. AB and IMC contributed to the discussion of the results. All the authors revised the manuscript and approved the final version of the article.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Causes of drug-related AIN.

Table S2. Clinical, laboratory, histopathological, and outcome comparisons in the entire AIN cohort: steroid therapy vs. nonsteroid therapy.

Table S3. Clinical, laboratory, histopathological, treatment and outcome comparisons between drug-related and all other causes related AIN.

Table S4. Clinical, laboratory, histopathological, and treatment comparisons in the drug-related AIN cohort: recovery vs. nonrecovery.

Table S5. Clinical, laboratory, histopathological, treatment and outcome comparisons among different drug-related AIN.

Table S6. Characteristics of patients with AIN on dialysis.

Table S7. Univariable and multivariable analysis of predictors influencing kidney recovery in the drug-related AIN.

Table S8. Comparison of the etiology spectrum, clinicopathological features, and kidney outcomes between the current period (2012–2023) and the previous period (1993–2011).

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