Incidence of and risk factors for acute kidney injury during antituberculosis treatment: A prospective cohort study and literature review

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Abstract

Aims: Acute kidney injury (AKI) is occasionally detected in patients receiving anti tuberculosis (TB) treatment. This prospective cohort study is the first to investigate the true incidence, risk factors, and renal outcomes. Methods: This study was conducted from January 1, 2016, to May 31, 2018, and patients with a new diagnosis of TB and receiving standard anti-TB treatment were enrolled; the patients received regular laboratory monitoring. AKI was defined according to the Kidney Disease: Improving Global Outcome (KDIGO) criteria. Urinalysis, measurements for blood erythrocyte morphology and the fractional excretion of sodium, and renal ultrasonography were performed at AKI onset. Anti-TB drugs were adjusted by the primary physician. Risk factors for AKI were identified using a Cox regression analysis. Results: In total, 106 patients were recruited (mean age: 52.6 years, 71.7% men). Eleven (10.3%) patients experienced AKI. An increase in serum uric acid and hemoglobin levels was noted at AKI onset. All patients with AKI exhibited renal function recovery and completed rifampin-containing anti-TB treatment. Age (hazard ratio (HR): 1.06 [1.02–1.11]), a higher baseline estimated glomerular filtration rate (eGFR; HR: 1.04 [1.02–1.06]), and a blood eosinophil count >350 (109/L) (HR: 10.99 [2.28–53.02]) were associated with AKI development during anti-TB treatment. Conclusions: Under regular pharmacovigilance monitoring, the incidence of renal function impairment during anti-TB treatment was higher than expected. AKI frequently occurred in older patients with a higher eGFR and blood eosinophil count. However, the complication had no influence on anti-TB treatment completion, and no permanent renal impairment occurred.

Introduction

Currently, more than 1.7 billion people (approximately 22% of the world population) have a *Mycobacterium tuberculosis* (MTB) infection [1]. Tuberculosis (TB) caused 1.5 million deaths in 2020 and is the 13th leading cause of death worldwide. Age is a major risk factor for pulmonary TB [2] and is associated with a longer treatment delay and higher mortality rate [3]. Because of the global increase in the aging population, TB must be diagnosed and treated quickly. However, the risk of adverse reactions during anti-TB treatment is higher in older adults, especially in patients receiving rifampin (RIF) or pyrazinamide (PZA) [4, 5]. The situation is worse in Taiwan because Taiwan's population is aging at a rate more than twice that in Western countries [6]. The occurrence of adverse reactions may compromise drug adherence and worsen anti-TB treatment outcomes [7].

Acute kidney injury (AKI) is a rare and severe complication that can interrupt anti-TB treatment and cause permanent kidney damage [8]. Among first-line anti-TB drugs, the most common offending drug for AKI

is RIF [8-10]. However, other drugs, such as isoniazid (INH) and ethambutol (EMB), are also associated with AKI [11, 12]. So far prospective studies evaluating the incidence of AKI during anti-TB treatment have not been conducted. Retrospective cohort studies on TB treatment have reported an AKI incidence of approximately 0.05% to 7.1% [13, 14]. However, these studies have not followed renal function regularly, and one study performed a laboratory survey only when patients exhibited gastrointestinal (such as nausea and vomiting) or flu-like symptoms [15]. Furthermore, the definition of kidney injury has differed between these studies [8, 13, 16]. Predictive factors for AKI, especially in an aging population, also remained unclear. Therefore, we conducted this prospective cohort study to evaluate the incidence of AKI during first-line anti-TB treatment and explored the risk factors for this complication.

Methods

Study design and participants

This prospective cohort study was conducted at the National Taiwan University Hospital Hsin-Chu branch from January 1, 2016, to May 31, 2018. Approval from the institute's research ethics committee was obtained prior to study initiation. Patients aged [?]18 years, who received first-line anti-TB treatment for culture-confirmed or clinically diagnosed TB, and who could be followed up regularly according to the directives of the *Taiwan Guidelines for TB Diagnosis & Treatment* were included in this study [17]. All patients with TB received a standard anti-TB treatment comprising daily INH, RIF, EMB, and PZA for the first 2 months and daily INH and RIF for the next 4 months. For patients with an estimated creatinine clearance of $<$ 30 ml/min, the frequencies of EMB and PZA were changed to once every 2 days with the unit dose kept unchanged. If necessary, the regimen was modified by the primary care physician; for example, in cases with adverse drug reactions or the presence of resistant MTB strains.

Patients with urinary tract infection; who received potentially nephrotoxic drugs other than anti-TB drugs at AKI onset; with other conditions possibly resulting in AKI, such as hypercalcemia, dehydration, hypotension, and nephrogenic cause; or with an end-stage renal disease receiving renal replacement therapy were excluded.

Laboratory surveillance

According to the directives of the *Taiwan Guidelines for TB Diagnosis & Treatment* , a basic laboratory survey, including measurements of complete blood count with differential count, tests of liver function (aspartate transaminase, alanine transaminase, and total bilirubin), and tests of renal function (blood urea nitrogen, creatinine, and uric acid), must be performed before initiating anti-TB treatment and at 2, 4, and 8 weeks after initiating anti-TB treatment [17]. Further laboratory surveys are allowed if the primary care physician deems it to be necessary.

AKI definition and intervention

AKI was defined according to the Kidney Disease: Improving Global Outcome (KDIGO) guidelines [18]. Urinalysis, renal ultrasonography, measurements for blood erythrocyte morphology, and measurements of the fractional excretion of sodium (FENa) performed at AKI onset. Time to AKI was defined as the interval between anti-TB treatment initiation and AKI onset. Renal recovery was defined as the return of serum creatinine level to the baseline level when the initial serum creatinine level had not fit the KDIGO AKI criteria. AKI duration was defined as the interval between AKI onset and renal recovery.

Data collection and statistical analysis

Data on characteristics, including sex, age, smoking status, alcohol consumption, comorbidities, the results of acid-fast bacilli (AFB) smear and mycobacterial culture, laboratory results, anti-TB regimen, anti-TB drug related side effects, and the onset and management of AKI, were collected. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula [19].

All data are expressed as the number (%), mean $\pm$ standard deviation, or median (interquartile range). Intergroup differences were determined using a t test or Mann–Whitney U test for continuous variables based on their normality, and the chi-square test or Fisher's exact test was used for categorical variables,

as appropriate. Time to AKI for each variable was compared using the Kaplan–Meier method with the log-rank test. All variables with a p value [?]0.1 in univariate analysis were subjected to a multivariate Cox proportional hazards regression analysis to compute the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were conducted using the Statistical Package for the Social Sciences 24.0 ([SPSS]; SPSS Inc, Chicago, IL, USA). Statistical significance was set at $p< 0.05$.

Results

Patient characteristics

A total of 259 patients with pulmonary TB were identified during the study period, and 111 (42.9%) were enrolled (Figure 1). Among them, three patients withdrew their consent, one had a diagnosis of *M. abscessus* lung disease, and another died before the initiation of anti-TB treatment. Therefore, a total of 106 patients were included for further analysis. Among them, 11 (10.3%) patients experienced AKI during anti-TB treatment.

The mean age of 106 patients was 52.6 +- 21.1 years, and 71.7% were men (Table 1). The average body mass index (BMI) was 21.6 +- 3.2, and 52 (49.1%) patients had a current or previous smoking history. The most common comorbidities were hypertension (22; 20.8%) and diabetes mellitus (20; 18.9%). The mycobacterial culture results revealed that 39 (36.8%) patients had a positive AFB smear result and 85 (80.2%) had a positive culture report for MTB complex. The most common side effects of anti-TB treatment were gastrointestinal symptoms (19; 17.9%) and skin rashes (16; 15.1%).

The completion rates of laboratory follow-up were 95.3%, 97.2%, and 96.2% at 2, 4, and 8 weeks, respectively, after anti-TB treatment initiation. Eleven (10.3%) patients experienced AKI (Table 1). Compared with the non-AKI group, the AKI

group had a greater number of patients with a current or previous smoking history (72.7% versus 46.3%, $p = 0.097$) and exhibited a higher risk of fever and gastrointestinal symptoms. The two groups were similar in baseline hemogram and biochemistry survey results; however, eGFR was higher in the AKI group (112.3 +- 38.1 versus 92.5 +- 29.6,$p = 0.018$; Table 2).

Clinical course of AKI

Among 11 patients with AKI, the time to AKI ranged from 6 to 68 days and AKI duration ranged from 8 to 286 days (Table 3). Most AKI events were classified as KDIGO stage 1, except for one patient who had stage 3 AKI. After AKI onset, four patients continued with the previous anti-TB regimen, six discontinued all anti-TB drugs, and one discontinued EMB. Among six patients who discontinued RIF, four restarted full-dose RIF 2 to 8 weeks after discontinuation. In another patient, RIF was replaced with rifabutin after 2 weeks of dissimulation. For the remaining one patient, RIF was reintroduced at a dose of 150 mg daily and increased 150mg every 2 days to full dose.

Urinalysis revealed no overt pyuria or hematuria; however, two patients exhibited mild proteinuria (1+; Table 3). The FENa value ranged from 0.2% to 2.9%, suggesting a prerenal AKI etiology in five (45%) patients and a renal etiology in six (55%) patients. A renal echography revealed an enlarged kidney in two patients, renal

stones in two patients, and renal atrophy in one patient. A morphological analysis of red blood cells (RBCs) revealed the presence of abnormal RBCs in 10 patients, with anisocytosis in eight and teardrop cells, target cells, and fragmented RBCs in one patient each. All patients recovered their renal function and completed the anti-TB treatment. The laboratory findings revealed higher serum uric acid (0.58+-0.14 versus 0.30+-0.12 mmol/L, $p < 0.001$) and hemoglobin levels (135+-20 versus 127+-19 g/L, $p = 0.034$) at AKI onset than at baseline (Table 2).

Predictors for AKI

The Kaplan–Meier analysis revealed that a higher eGFR (HR: 1.02 [1.00–1.04]) and blood eosinophil count

>350/μL (HR: 4.3 [1.21–15.25]) were associated with a higher risk of AKI during anti-TB treatment. Other risk factors, such as BMI, smoking status, hypertension, diabetes mellitus, mycobacterial culture results (a positive AFB smear or positive TB culture), other baseline laboratory data, and treatment-related side effects, were not statistically significant (Table 4).

The multivariate Cox regression analysis revealed that older age (HR: 1.06 [1.02–1.11]), a higher baseline eGFR (HR: 1.04 [1.02–1.06] per unit increase in eGFR), and a blood eosinophil count >350 (10^9/L) (HR: 10.99 [1.28–53.02]) were significant predictors for AKI development during anti-TB treatment (Table 4).

Discussion

This is the first prospective study to investigate the risk of AKI in patients receiving anti-TB treatment by regularly monitoring their renal function; we reported three major findings. First, the incidence of AKI during anti-TB treatment was 10.3%, which was higher than that of our previous retrospective study (7.1%). Second, old age, a higher eGFR, and a blood eosinophil count >350 (10^9/L) were the three independent predictors for AKI. Third, all patients with AKI completed anti-TB treatment with no or one-drug modification in the treatment regimen and exhibited renal recovery within 1 year.

The literature review revealed four retrospective studies and one case series that focused on AKI occurrence during anti-TB treatment; the studies are summarized in Table 5 [8, 13-16]. Three studies enrolled patients receiving anti-TB treatment [13-15], and two have focused on patients receiving RIF [8, 16]. The incidences of AKI in Romania [13] and Taiwan are 0.05% and 7.4%–10.4%, respectively. The lower incidence of AKI in Romania may be due to underestimation because of missing data in the Iasi Hemodialysis Centre registry database [13]. The higher incidence of AKI in Taiwan may be attributed to the aging population (median age between 52 and 68 years) and the application of the KDIGO definition that includes patients with mild (stage 1) AKI also [14]. Moreover, we adopted a prospective study design and performed a regular follow-up of renal function that could precisely capture patients with mild AKI and without clinical symptoms, thereby providing a true estimation of AKI incidence in patients receiving anti-TB treatment.

Among first-line anti-TB drugs, RIF, INH, and EMB are associated with AKI development during treatment [8-12]. EMB-induced acute renal failure is rare, and only three cases of EMB-induced tubulointerstitial nephritis have been reported [11]. Similarly, INH-induced kidney injury has only been reported in a few pediatric cases [12]. Therefore, the most common offending drug for AKI is RIF [8-10]. The definite pathophysiology of RIF-induced AKI is not well documented. However, a study suggested that RIF antigens may induce either a type II or type III hypersensitivity reaction in which anti-RIF antibodies form immune complexes that deposit in the renal vessels, glomerular endothelium, and interstitial area [16]. These reactions cause two different pathologic changes in the kidneys. Immune complex deposition in the vessels causes vascular constriction and tubular ischemia, leading to acute tubular necrosis (ATN), whereas the deposition of immune complexes in the interstitial area leads to acute tubulointerstitial nephritis (ATIN) [16]. The hypothesis is further supported by the current study finding demonstrating that ATIN and ATN are the most common histopathological findings in anti-TB related AKI (Table 5) [8, 13, 15, 16].

In this study, the average time to AKI was 35 days, and the mean AKI duration was 89 days; the results were similar to those of our previous retrospective study [14], where most patients experienced mild AKI (stage 1). Although anti-TB treatment was interrupted in seven (63.6%) patients, RIF was reintroduced successfully. All patients experiencing AKI completed anti-TB treatment with an RIF-containing regimen. On the basis of the FENa value, the etiology of AKI was classified as prerenal (45%) and intrinsic (55%). Prerenal AKI may have been caused by a decrease in food intake due to gastrointestinal side effects. Because few patients undergo renal biopsy, identifying definite causes of intrinsic AKI remains challenging. Renal function recovery was achieved within 9 months, and patients with prerenal or intrinsic AKI exhibited similar recovery rates (Table 3). Compared with the recovery rate of previous studies, our recovery rate of 100% was much higher [8, 13-16]. Because of the prospective setting and nearly all patients adhering to the follow-up protocol, renal function decline could be detected and intervention in the early phase could be performed before patients exhibited AKI symptoms, such as oliguria or generalized edema.

The multivariate Cox regression analysis revealed that older age, a higher baseline eGFR, and a blood eosinophil count >350 (10^9/L) were the three significant predictors for AKI development during anti-TB treatment. The higher incidence of AKI in older individuals may be attributed to the following: 1) comorbidities that accumulate with age; 2) comorbidities that necessitate interventions (e.g., drugs) that function as kidney stressors or nephrotoxins; and 3) the kidney undergoes age-dependent transcriptomic, hemodynamic, physiologic, and structural alterations over time [20, 21]. Therefore, clinicians should follow renal function regularly during anti-TB treatment, especially in older patients.

A higher eGFR was associated with a higher risk of AKI; however, this finding is contradictory. Previous studies have demonstrated that patients with chronic kidney disease (CKD) or a higher baseline serum creatinine level (the injured kidney) were more vulnerable to AKI [22-24]. Therefore, the finding that a high eGFR is a risk factor for AKI may be because the percentage changes in serum creatinine level after AKI onset are partly confounded by baseline kidney function; therefore, AKI diagnosis in patients with CKD based on the KDIGO guidelines remains challenging [25]. Nevertheless, our results suggested that regular renal monitoring during anti-TB treatment is necessary even in patients with normal renal function.

Eosinophilia is an uncommon presentation in drug-induced AKI, whereas urine eosinophilia is a common finding in drug-induced AKI, especially of ATIN [26]. Although urine eosinophils cannot be used to effectively distinguish ATIN from ATN or other kidney diseases [27], substantial eosinophilia often reflects an allergic drug reaction and may assist in diagnosing patients with hospital-acquired AKI [28, 29]. Higher eosinophil counts may induce a higher immune reaction during anti-TB treatment, thereby inducing kidney injury.

Our study has some limitations. First, a histopathological examination was not performed for a definite AKI diagnosis. Instead, we used FENa values for identifying AKI caused by prerenal or intrinsic factors. Second, the small sample size may not be representative of the population with TB and may not delineate AKI characteristics during anti-TB treatment. Third, because all patients with AKI completed anti-TB treatment with an RIF-containing regimen, whether these episodes of AKI were drug-induced remains uncertain. In our previous retrospective study, RIF was successfully reintroduced in 71% of patients [14]. The high successful reintroduction rate may be attributed to drug desensitization. A study reported that the RIF desensitization protocol led to a high successful drug reintroduction rate (80%–82%) [30, 31].

In conclusion, the incidence of AKI during anti-TB treatment is not rare (10.3%) and occurs frequently in older patients with normal renal function and a blood eosinophil count >350 (10^9/L). The kidney injury is usually mild, and patients recover without permanent renal damage. Moreover, most patients with AKI complete the standard anti-TB treatment.

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Table 1. Patient characteristics, stratified by status of acute kidney injury (AKI)

Variable	**Overall (n=106)**	**AKI (n=11)**	**Non-AKI (n=95)**	p **value**
Male	76 (71.7)	6 (54.5)	70 (73.7)	0.182
Age	52.6±21.1	62.2±15.9	55.1±21.2	0.282
Age [?]65	42 (39.6)	6 (54.5)	36 (37.9)	0.285
Body-mass index	21.6±3.2	21.1±2.4	21.6±3.3	0.261
<18.5	20 (18.9)	2 (18.2)	18 (18.9)	0.951
Current or ex-smoker	52 (49.1)	8 (72.7)	44 (46.3)	0.097
Alcohol consumption	32 (30.2)	4 (36.4)	28 (29.5)	0.637
Co-morbidity				
Old TB history	3 (2.8)	1 (9.1)	2 (2.1)	0.186
Diabetic mellitus	20 (18.9)	1 (9.1)	19 (20.0)	0.381
Hypertension	22 (20.8)	3 (27.3)	19 (20.0)	0.573
Hepatitis B	6 (5.7)	0 (0.0)	6 (6.3)	0.329
Malignancy	6 (5.7)	0 (0.0)	6 (6.3)	0.391
Autoimmune	2 (1.9)	0 (0.0)	2 (2.1)	0.627
Mycobacterial study				
Positive acid-fast smear	39 (36.8)	4 (36.4)	35 (36.8)	0.975
Culture-positive	85 (80.2)	8 (72.7)	77 (81.1)	0.512
Side effect*	19 (17.9)	3 (27.3)	16 (16.8)	0.393
Fever	1 (0.9)	1 (9.1)	0 (0)	0.003
Rash	16 (15.1)	3 (27.3)	13 (13.7)	0.233

Variable	Overall (n=106)	AKI (n=11)	Non-AKI (n=95)	p value
Arthralgia	4 (3.8)	0 (0)	4 (4.2)	0.488
Gastrointestinal symptoms	19 (17.9)	4 (36.4)	15 (15.8)	0.092

Note: Data are either number (%) or mean±standard deviation.

* Including anyone of fever, rash, arthralgia, or gastrointestinal symptoms.

Table 2. Laboratory data of patients, stratified by status and course of acute kidney injury (AKI)

	Overall (n=106) Baseline	AKI (n=11)	AKI (n=11)	AKI (n=11)	Non-AKI (n=95) Baseline	p value[#]
		Baseline	During AKI	p value*		
Blood urea nitrogen (mmol/L)	5.3±2.4	5.2±2.9	5.2±2.0	0.698	5.4±2.4	0.839
Creatinine (μmol/L)	80.44±34.48	61.88±24.75	129.06±102.54	0.063	82.21±35.36	0.075
estimate GFR (mL/min)[&]	92.5±29.6	112.3±38.1	58.6±24.5	<0.001	90.2±27.8	**0.018**
estimate GFR < 60	14 (13.2)	1 (9.1)	7 (63.6)	0.428	13 (13.7)	0.670
Uric acid (mmol/L)	0.35±0.11	0.30±0.12	0.58±0.14	**<0.001**	0.35±0.11	0.201
Hemoglobin (g/L)	131±20	127±19	135±20	**0.034**	131±21	0.494
Platelet (10^9/L)	304±110	276±112	242±103	0.387	308±110	0.370
Leukocyte (10^9/L)	8.00±3.15	8.98±6.49	7.21±2.15	0.935	7.89±2.55	0.591
Eosinophil (10^9/L)	186±185	286±404	281±254	0.260	175±141	0.385
Alanine transaminase (U/L)	24.9±21.3	29.9±21.9	43.2±61.9	0.530	24.3±21.3	0.412
Total bilirubin (μmol/L)	8.72±5.30	11.63±14.02	10.09±4.62	0.696	8.55±4.28	0.520

Note: Data are either mean±standard deviation or number (%).

* Comparing laboratory data between baseline and during AKI.

[#] Comparing baseline laboratory data between AKI and non-AKI groups.

[&] Estimated Glomerular Filtration Rate (eGFR) was estimated by Modification of Diet in Renal Disease

(MDRD) formula: [GFR = 175 × Serum $Cr^{-1.154}$ × $age^{-0.203}$ × 1.212 (if patient is black) × 0.742 (if female)]

Table 3. Brief Summary of Patient with AKI during anti-TB Treatment

Case	Age/Sex	Baseline eGFR*	Time to AKI (Days)	Duration of AKI (Days)	KDIGO stage#	Managing during AKI	Laboratory findings during AKI	Laboratory findings during AKI	Laboratory findings during AKI	Laboratory findings during AKI	Laboratory findings during AKI	Laboratory findings during AKI	Laboratory findings during AKI
							Worst eGFR*	Urine WBC	Urine RBC	Urine protein	Renal echography	FENA (%)	RBC Morphology
1	50s/M	172	56	217	1	Observation	100	2-5	0-1	Trace	Enlarged kidneys	0.2%	Anis
2	70s/M	164	56	269	1	Hold HREZ	83	0-2	0-2	-	Renal stone	1.2%	Tear cell
3	60s/M	139	47	49	1	Hold HREZ	81	0-2	0-2	Trace	Parenchymal renal disease	1.1%	Anis
4	40s/F	124	68	8	3	Hold HREZ	9	5-10	5-10	-	Normal	0.5%	Anis
5	60s/F	123	35	56	1	Hold HREZ	55	0-2	0-2	-	Parenchymal renal disease	1.1%	Anis
6	40s/F	110	11	15	1	Observation	69	0-2	0-1	-	Normal	1.4%	Norm
7	40s/F	108	6	10	1	Observation	50	0-2	0-2	-	Parenchymal renal disease	2.9%	Anis
8	70s/M	90	39	27	1	Hold E	49	0-2	10-25	Trace	Enlarged left kidney	0.6%	Targ cells
9	70s/F	82	44	286	1	Hold HREZ	54	2-5	2-5	1+	Parenchymal renal disease	0.5%	Anis frag-ment RBC
10	80s/M	71	14	14	1	Observation	52	0-2	5-10	1+	Left kidney atrophy	0.6%	Anis
11	70s/M	48	11	29	1	Hold HREZ	37	0-2	0-2	Trace	Renal stone	1.1%	Anis

Abbreviation: AKI, acute kidney injury; FENA, fractional excretion of sodium; E, ethambutol; eGFR, estimated glomerular filtration rate; H, isoniazid; KDIGO, kidney disease: improving global outcome; R, rifampin; RBC, red blood cell; TB, tuberculosis; WBC, white blood cell; Z, pyrazinamide

All received standard four-combined treatment after TB diagnosis.

* Estimated Glomerular Filtration Rate (eGFR) was estimated by Modification of Diet in Renal Disease (MDRD) formula: [GFR = 175 × Serum $Cr^{-1.154}$ × $age^{-0.203}$ × 1.212 (if patient is black) × 0.742 (if female)][19]

KDIGO staging criteria:[18]

Stage 1, Increase in serum creatinine of [?]26.53 μmol/L or 1.5 to 1.9 times baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours

Stage 2, Increase in serum creatinine to 2.0 to 2.9 times baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours

Stage 3, Increase in serum creatinine to [?]3.0 times baseline OR Increase in serum creatinine of [?]26.53 μmol/L to [?]353.68 μmol/L OR Urine output of <0.3 mL/kg/hour for [?]24 hours or anuria for [?]12 hours OR Initiation of kidney replacement therap

Table 4. Predictors for acute kidney injury (AKI), by multivariate cox proportional hazards regression analysis

Variable	**Kaplan-Meier Analysis**	**Kaplan-Meier Analysis**	**Kaplan-Meier Analysis**	**Multivariate Cox Regression**	**Multivariate Cox Regression**	**Multivariate Cox Regression**
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Male	0.56	0.16-1.98	0.366			
Age	1.02	0.99-1.06	0.189	1.06	1.02-1.11	0.007
Body-mass index	0.99	0.82-1.20	0.897			
Smoking	2.43	0.62-9.41	0.198			
Alcoholism	0.94	0.24-3.64	0.930			
Co-morbidities						
Diabetes mellitus	0.47	0.06-3.70	0.472			
Hypertension	1.67	0.43-6.45	0.459			
Baseline eGFR (mL/min)	1.02	1.00-1.04	0.047	1.04	1.02-1.06	<0.001
Mycobacterial study						
Positive acid-fast smear	1.16	0.33-4.10	0.823			
Culture-positive	0.55	0.14-2.12	0.385			
Side Effect	2.02	0.52-7.82	0.308			
Baseline laboratory data						
Blood urea nitrogen (mg/dL)	1.01	0.93-1.10	0.769			

Variable	Kaplan-Meier Analysis	Kaplan-Meier Analysis	Kaplan-Meier Analysis	Multivariate Cox Regression	Multivariate Cox Regression	Multivariate Cox Regression
Creatinine (mg/dL)	0.04	0.001-1.46	0.080			
Uric acid (mg/dL)	0.66	0.43-1.02	0.063			
Hemoglobin (g/dL)	0.92	0.68-1.23	0.564			
Platelet (K/μL)	1.00	0.99-1.01	0.656			
Leukocyte (K/μL)	1.08	0.94-1.25	0.272			
Eosinophil >350 (/μL)	4.30	1.21-15.25	0.024	10.99	2.28-53.02	0.003
Alanine transaminase (U/L)	1.004	0.98-1.03	0.777			
Total bilirubin (mg/dL)	2.66	0.73-9.73	0.139			

Abbreviation: CI, confidence interval; eGFR, Estimated Glomerular Filtration Rate; HR, hazards ratio

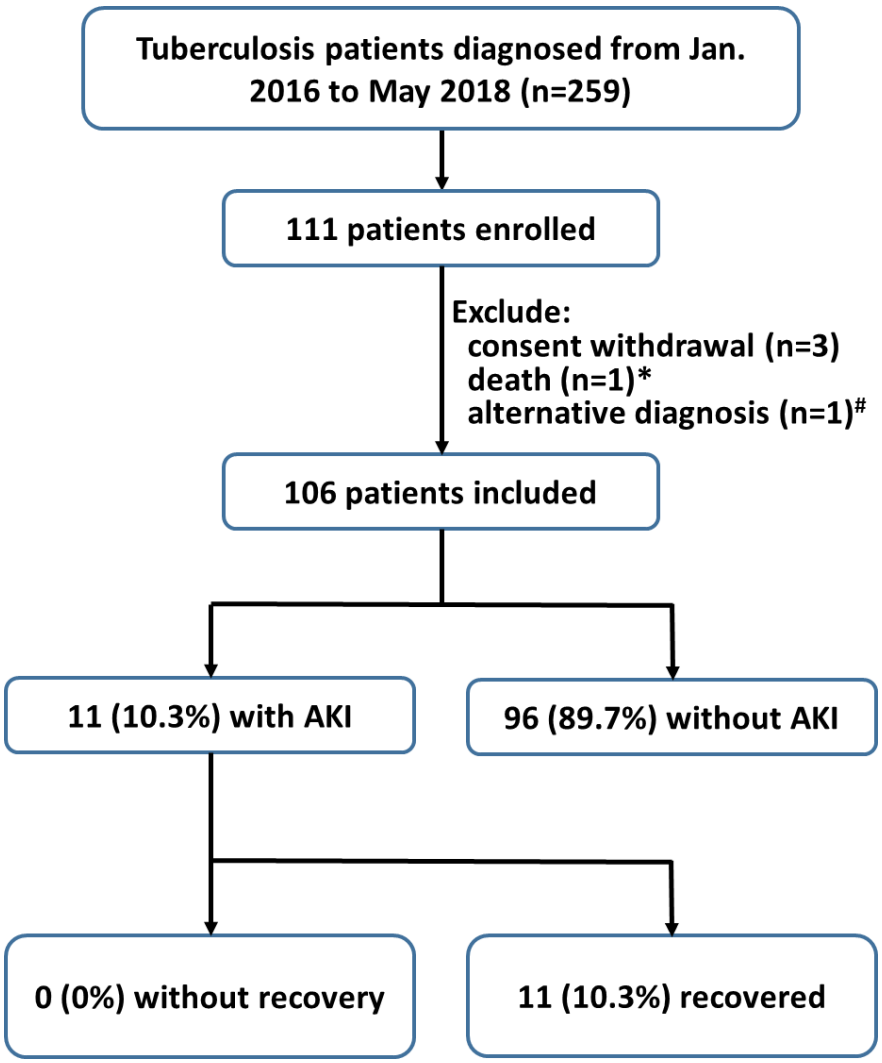
Table 5. Literature review of acute kidney injury (AKI) during anti-tuberculous (TB) or rifampin treatment

Study Design Reference	Country	Study population	No. of patients* (AKI/Overall)	Incidence* (%)	Age (Mean/Median)	Biopsy-confirmed diagnosis (n)	Recovery (%)	Retrea (%)
Retrospective[12]	Romania	Patients under anti-TB treatment (outcome only in retreatment group)	55/120,132	0.05	45	ATIN (4), ATN (1)	96	100
Retrospective[8]	Worldwide	AKI after rifampin	48/NA	NA	47.4	ATIN (4), ATN (11), crescentic GN (2)	87	64

Study Design Reference	Country	Study population	No. of patients* (AKI/Overall)	Incidence* (%)	Age (Mean/Median)	Biopsy-confirmed diagnosis (n)	Recovery (%)	Retrea (%)
Retrospective[16]	India	Rifampin-associated AKI	25/NA	NA	41.6	ATIN (7), ATN (2), crescentic GN (1), mesangial proliferation (3)	100	80
Retrospective[15]	South Africa	Biopsy-proven AIN under anti-TB treatment	41/NA	NA	42.2	ATIN (41)	83	83
Retrospective[14]	Taiwan	Patients under anti-TB treatment	99/1,394	7.1	68	NA	73	11
Prospective (current study)	Taiwan	Patients under anti-TB treatment	11/106	10.4	52.6	NA	100	2.8

Abbreviations: ATIN, acute interstitial nephritis; AKI, acute kidney injury; ATIN, acute tubulointerstitial nephritis; ATN, acute tubular necrosis; GN, glomerulonephritis; NA, not applicable

* Some studies only recruited patients with AKI.



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