

### **Original Article**

# **A PROSPECTIVE CLINICAL INVESTIGATIONAL STUDY OF ACUTE KIDNEY INJURY ON USING ANTI TUBERCULAR DRUGS IN GERIATRIC POPULATION**

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Tuberculosis is a global disease affecting one-third of the world's population. This study aimed to calculate the incidence of AKI due to anti TB drugs and analyze the outcomes and predictors of renal recovery, to assess the onset of AKI and to assess the status of renal recovery. All TB patients received a standard anti-TB treatment of daily INH, RIF, EMB, and pyrazinamide (PZA) for the first two months, and daily INH and RIF for the next four months. For patients with an estimated creatinine clearance of < 30 ml/minute, the frequencies of EMB and PZA were changed to once every two days with the unit dose unchanged. The regimen was modified by the primary care physician if necessary, e.g. when there were adverse drug effects. Within a follow-up period of 180 days since the onset of AKI, No one died. Nine did not recover from AKI (AKI-unrecovered group), (median age, 68.5 years [IQR 59–81.5 years]) who required long-term renal replacement therapy. Very few had hypoalbuminemia. Among the 31 patients who recovered from AKI (AKI-recovered group), 44 recovered within 100 days. Serum BUN level ( $p=0.005$ ) and the prevalence of hematuria ( $p=0.033$ ) and proteinuria ( $p=0.048$ ) at the onset of AKI were significantly higher in the AKI-unrecovered group, whereas thrombocytopenia was less common ( $p=0.064$ ). The AKI recovery rate was not different among the different AKIN stages. Anti-tuberculosis drug-induced acute kidney injury is not rare in an aging population. It usually develops within two months of treatment and resolves within three months after onset. Although about some of patients with AKI will have permanent renal impairment, those who present with fever, rash, and GI disturbance at the onset of AKI have better renal recovery. Of the 51 patients who had recovery of renal function, successfully continued rifampicin or had rifampicin re-introduced.

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## **1. INTRODUCTION**

The present study was conducted to investigate the incidence of aki during anti-tb treatment in india and to determine outcomes and predictive factors for renal recovery<sup>[1]</sup>. Acute renal failure

(ARF) is an abrupt and usually reversible decline in the glomerular filtration rate (gfr). This results in an elevation of serum blood urea nitrogen (BUN), creatinine, and other metabolic waste products that are normally excreted by the kidney<sup>[2-6]</sup>. The term acute kidney injury (AKI)

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rather than ARF, is increasingly used by the nephrology community to refer to the acute loss of kidney function. This term also highlights that injury to the kidney that does not result in "failure" is also of great clinical significance<sup>[7]</sup>. In this topic review, the acute loss of kidney function will be referred to as AKI. The initial assessment of patients with aki and management of the major complications of AKI are discussed here. The incidence, causes, diagnosis, and prevention of AKI are presented separately<sup>[8,9]</sup>. Patients who are hypotensive due to surgery, sepsis, bleeding, or other causes are at risk of developing postischemic (also called ischemic) Acute Tubular Necrosis (ATN), especially if the impairment in renal perfusion is either severe or prolonged in duration. This disorder is characterized by a rising plasma creatinine concentration, a urine volume that may be reduced or normal, and a characteristic set of changes in the urinalysis, including many granular casts and a fractional excretion of sodium above 1 percent and fractional excretion of urea above 35 percent<sup>(10-12)</sup>. Serum and urine biomarkers of tubular injury have been proposed as early biomarkers for the diagnosis of ATN. The pathogenesis and etiology of postischemic ATN will be reviewed here. The diagnosis of ATN, potential therapies for postischemic ATN, and other causes of ATN are discussed separately.

The study aimed to calculate the incidence of AKI due to Anti TB drugs and analyze the outcomes and predictors of renal recovery.

## **2. MATERIALS AND METHODS:**

This prospective study was observed Om Sai hospitals Balapur Hyderabad. The hospital's Research Ethics Committee approved the study protocol. Patients were included if they met the following criteria: (1) age  $\geq 18$  years; (2) clinical diagnosis or suspicion of TB; (3) under rifampin-containing anti-TB treatment; and (4) had onset of AKI during anti-TB treatment. Acute kidney injury (AKI) was defined according to the criteria

established by the Acute Kidney Injury Network (AKIN) and was classified into three stages (Stages 1 to 3) based on serial changes in serum creatinine level. Stage 1 was defined as an increase in serum creatinine  $\geq 26.52 \mu\text{mol/L}$  or by 1.5-fold but less than twice the baseline level. Stage 2 was defined as a two-fold increase but less than three-fold increase from baseline, while Stage 3 was defined as a three-fold increase from the baseline level. All TB patients received a standard anti-TB treatment of daily INH, RIF, EMB, and pyrazinamide (PZA) for the first two months, and daily INH and RIF for the next four months. For patients with an estimated creatinine clearance of  $< 30 \text{ ml/minute}$ , the frequencies of EMB and PZA were changed to once every two days with the unit dose unchanged. The regimen was modified by the primary care physician if necessary, e.g. when there were adverse drug effects. Patients were excluded if they: 1) had shock or urinary tract infection; 2) were under potentially nephrotoxic drugs other than rifampin at the onset of AKI; 3) had other conditions possibly resulting in AKI, such as hypercalcemia and nephrotic syndrome; 4) had end-stage renal disease and was under renal replacement therapy; and 5) had non-tuberculous mycobacteria infection.

## **3. Data collection**

Demographic data, including sex, age, smoking status, excessive alcohol consumption (defined according to a single-question alcohol screening test), co-morbidities, results of sputum acid-fast bacilli (AFB) smear and mycobacterial culture, anti-TB regimen, laboratory results, onset, and management of AKI, were collected. Chronic kidney disease was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines, with an estimated glomerular filtration rate (eGFR) of  $< 60 \text{ mL/min/1.73 m}^2$  for three months or more. Baseline laboratory tests included a hemogram, renal function (blood urea

nitrogen [BUN], creatinine) tests, and levels of liver enzymes (aspartate aminotransferase and alanine aminotransferase), total bilirubin, albumin, and uric acid. The patients were classified into two groups based on hemoglobin < or  $\geq 100$  g/L, leukocyte > or  $\leq 10 \times 10^9$ /L, eosinophil count > or  $\leq 0.5 \times 10^9$ /L, and platelet < or  $\geq 100 \times 10^9$ /L. Hepatitis was defined as increased serum alanine aminotransferase >3 times the upper limit of normal (ULN) in symptomatic patients, or >5 times the ULN in asymptomatic patients, or serum total bilirubin >51.3  $\mu\text{mol/L}$  [17, 20]. Hypoalbuminemia was defined as albumin < 35 g/L, hematuria as urine red blood cell >5 per high-power field (HPF), sterile leukocyturia as urine leukocyte >5 per HPF with negative urine bacterial culture, and proteinuria as urine protein >30 mg/dL. TB laboratory tests were repeated every two weeks in the first two months and every eight weeks thereafter or when the primary care physician deemed it necessary. The time to AKI was defined as the interval between the start of anti-TB treatment and the onset of AKI. Renal recovery was defined as a return of serum creatinine to baseline and the absence of AKI features. Time to recovery was defined as the interval between the onset of AKI and renal recovery. If renal recovery was not achieved after 180 days from the onset of AKI, the AKI was considered “unrecovered”.

#### 4. Statistical analysis

All data were expressed as either mean  $\pm$  standard deviation or median [inter-quartile range]. Inter-group difference was compared using the *t*-test or Mann–Whitney *U*-test for continuous variables based on their normality, and the *chi*-square test or Fisher’s exact test for categorical variables, as appropriate. Time to renal recovery for each variable was compared. All variables with a *p* value  $\leq 0.1$  in univariate analysis were entered into a multivariate Cox proportional hazards regression analysis to compute the adjusted hazard ratios (HR) and 95% confidence intervals (CI. Statistical

significance was set at *p* < 0.05. Sensitivity analysis was performed in the sub-population without CKD, since it was difficult to differentiate an “acute-on-chronic” disease from progression of CKD.

## 5. RESULTS AND DISCUSSION:

### Patient characteristics

From 2015-2016, 200 TB patients were identified, including 150 with serum creatinine data before and after the start of anti-TB treatment. Of the 80 patients with increased serum creatinine level  $\geq 17.68$   $\mu\text{mol/L}$ , 30 were excluded and only 50 (7.1%) were included for further analysis. In terms of severity, 45 (84%) patients were in AKIN Stage 1, 10 in Stage 2, and 5(6%) in Stage 3. The patients’ median age was 68 years ( 56–76 years), and there was a male predominance (71%). The diagnosis of TB was culture-confirmed in 11. Of the 60AKI patients, 16 had regular alcohol intake and 48 were smokers (Table 1). The most common underlying co-morbidities were pre-existing chronic kidney disease, diabetes mellitus, and malignancy.

**6. Table 1: Demographic data based on recovery status of AKI**

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Male	49	41 (72)	8 (69)
Age $\geq 65$	49	43 (59)	6 (62)
Smoking	18	17 (52)	1(38)
Alcoholism	6	3 (18)	3 (8)
Malnutrition	29	25 (34)	4 (54)

**7. Table 2: Data of comorbidities based on recovery status of AKI**

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Old TB history	3	2 (3)	1 (4)
CKD	30	21 (30)	9 (35)
DM	25	15 (21)	10 (38)
Malignancy	25	19 (27)	6 (19)
Gout	15	10 (14)	5 (19)
Autoimmune disease	6	4 (6)	2 (8)
HIV	2	2 (3)	0 (0)
AFB-positive	29	22 (31)	7 (23)
Culture-positive	39	38 (79)	1 (81)

**8. Table 3: ADR data based on recovery status of AKI**

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Rash	21	18 (25)	3 (12)
Gastro-intestinal upset	17	14 (20)	3 (12)
Fever	6	5 (7)	1 (3.8)
Arthralgia	4	4 (6)	0 (0)

**9. Table 4: Data of patients based on stages of AKI**

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Stage 1	25	24 (89)	1 (73)
Stage 2	10	6 (8)	4 (12)
Stage 3	5	1 (6)	4(15)

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Onset of AKI after ATT (days)	44 [20–102]	40 [15–104]	4[27–91]
<b>Management after AKI</b>			
Hold rifampin	34 (34)	24 (31)	10 (38)
Hold pyrazinamide	35 (51)	24 (28)	11 (42)
Re-challenge rifampin	21 (21)	14 (20)	7 (27)

**10. Table 5: Patient characteristics based on recovery status of acute kidney injury (AKI)**

**11.**

*Abbreviations:* AFB acid-fast bacilli smear, AKI acute kidney injury, ATT anti-TB treatment, TB tuberculosis. Note: Data are either number or median . There was no statistically significant difference between the AKI-recovered and -unrecovered groups. \*Re-treatment meant that AKI recurred after re-exposure to rifampin. #Only 69 patients received pyrazinamide-containing anti-TB regimen at the onset of AKI.

**12. Onset of AKI**

Within six months after anti-TB treatment, there was a continuous probability of developing AKI (Figure 2). The median interval in all of the study subjects between the start of anti-TB treatment and the onset of AKI was 44 days]. Moreover, 61% of AKI episodes happened in the first two months of treatment. In all patients taking rifampin at the onset of AKI, some were also taking isoniazid, ethambutol, and pyrazinamide. The most common presenting symptoms at the onset of AKI were skin

rash (21%) and gastro-intestinal disturbance (17%), followed by fever (6%) and arthralgia (4%) (Table 1). The most common laboratory findings were hypoalbuminemia, increased eosinophil count ( $>0.5 \times 10^9/L$ ), and anemia (hemoglobin  $<100$  g/L) (Table 2). Urinalysis showed proteinuria in 20%, sterile leukocyturia in 17%, and hematuria in 5%. Aside from elevated serum creatinine level, serum uric acid level was also elevated during AKI compared to baseline ( $p < 0.001$ ).

### 13. Table 6: Laboratory data of patients who did and did not recover from acute kidney injury (AKI)

	No. of patients with data	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Uric Acid ( $\mu\text{mol/L}$ )	22	37.7 [285.5-440.2]	34.7 [267.7-434.2]	3.0 [339.0-493.7]
Creatinine ( $\mu\text{mol/L}$ )	29	12.8 [97.2-246.8]	11.2 [97.2-159.1]	1.6 [106.1-238.7]
Blood urea nitrogen (mmol/L)	46	8.4 [6.0-15.4]	7.5 [5.6-13.3]	1.4 [7.9-20.7]*
Uric Acid (mmol/L)	23	29.4 [386.6-678.1]	25.2 [386.6-695.9]	4.2 [350.9-565.1]
Hemoglobin $<100$ (g/L)	24	22 (26)	15 (25)	7 (33)
Eosinophil $>0.5$ ( $10^9/L$ )	33	21 (29)	14 (25)	7 (44)
White blood cell $>10$ ( $10^9/L$ )	35	15 (18)	11 (18)	4 (19)
Platelet $<100$ ( $10^9/L$ )	25	9 (11)	9 (15)	0 (0)**
Hepatitis #	17	4 (4)	3 (4)	1 (4)
Jaundice §	11	3 (4)	2 (3)	1 (6)
Hypoalbuminemia	24	17 (41)	14 (36)	3 (54)
Hematuria	25	5 (5)	2 (7)	3 (38)*
Proteinuria	25	20 (20)	13 (48)	7 (88)*
Sterile leukocyturia	25	17 (17)	13 (48)	4 (50)

14.

Note: Data are either median [inter-quartile range] or number (%) unless otherwise stated. \*Significantly different ( $p < 0.05$ ) between the AKI-recovered and -unrecovered groups. \*\* $p = 0.064$ . # Hepatitis was defined as increased serum alanine aminotransferase  $>3$  times the upper limit of normal (ULN) in symptomatic, or  $>5$  times the ULN in asymptomatic patients.

§Jaundice was defined as serum total bilirubin level  $>51.3$   $\mu\text{mol/L}$ .

### 15. Modifications of anti-TB treatment during AKI

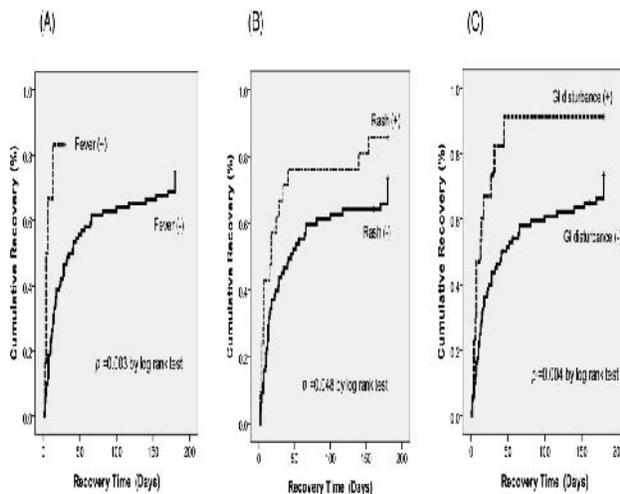
After the onset of AKI, rifampin was discontinued in some patients. Among them, re-challenge was performed in few. Of the remaining few patients who did not undergo rifampin re-challenge, few were treated with regimens not including rifampin, while some had clinical observation only (without anti-TB medication). Overall, rifampin was successfully re-introduced or continued without interruption in 60 of the 31 AKI-recovered patients and 9 AKI-unrecovered patients. Pyrazinamide was discontinued in some patients after the onset of AKI. Anti-TB drugs were interrupted in some, including few who failed to complete the trail, no one died. In the remaining few patients, the median duration of treatment interruption was 14 days (IQR, 7–28 days).

### 16. Outcome and prognostic factors of AKI

Within a follow-up period of 180 days since the onset of AKI, No one died. Nine did not recover from AKI (AKI-unrecovered group), (median age, 68.5 years [IQR 59–81.5 years]) who required long-term renal replacement therapy. Very few had hypoalbuminemia. Among the 31 patients who recovered from AKI (AKI-recovered group), 44 recovered within 100 days. Serum BUN level ( $p = 0.005$ ) and the prevalence of hematuria ( $p = 0.033$ ) and proteinuria ( $p = 0.048$ ) at the onset of AKI were significantly higher in the AKI-

unrecovered group, whereas thrombocytopenia was less common ( $p = 0.064$ ). The AKI recovery rate was not different among the different AKIN stages ( $p = 0.061$ ). In the Kaplan-Meier analysis, fever (HR 3.65 [1.43-9.37]), gastro-intestinal disturbance (HR 2.32 [1.27-4.27]), and thrombocytopenia (HR 2.20 [1.08-4.50]) at the onset of AKI were significant predictors of renal recovery, whereas skin rash (HR 1.69 [0.99-2.90]) and arthralgia (HR 2.78 [0.99-7.78]) had borderline significance. Multivariate Cox proportional hazard regression analysis including all of these five variables revealed that the VIFS of all variables were  $< 3$ . The independent predictors of renal recovery were fever, gastro-intestinal disturbance, and skin rash.

Variables	Median days for AKI recovery	Pvalue	HR	95% CI
AKI: yes vs. No				
Rash at onset of AKI: yes vs. No	17 vs. 45	0.044	1.79	1.02-3.14
GI disturbance at onset of AKI: yes vs. No	13 vs. 41	0.023	2.07	1.11-3.89



17. Figure 3

**Kaplan-Meier curves for time to recovery from acute kidney injury among patients with or without (A) fever, (B) rash, and (C) gastro-intestinal (GI) disturbance.** Sub-group difference was compared by log-rank test.

18. Table 7: Predictive factors of recovery from acute kidney injury (AKI), by multivariate Cox proportional hazard regression analysis

Variables	Median days for AKI recovery	Pvalue	HR	95% CI
Fever at onset of	4 vs. 40	0.013	3.43	1.29-9.12

19. Sensitivity analysis focusing on the sub-population without CKD revealed that fever at AKI onset remained a significant predictor of renal recovery ( $p = 0.002$ ; HR 11.99 [2.43-59.19]), whereas thrombocytopenia ( $p = 0.051$ ; HR 2.40 [1.00-5.78]) and gastro-intestinal disturbance ( $p = 0.091$ ; HR 1.94 [0.90-4.17]) had borderline significance. The definition of rifampin-induced renal impairment varies in previous studies. The exact incidence rate is unknown. Only the review article from Romania reports that 0.05% of patients receiving rifampin (mean age, 45 years) develop acute renal failure, defined as elevated serum creatinine  $> 44.2 \mu\text{mol/L}$  or  $> 20\%$  of baseline in two weeks. Using the criteria established by the AKIN, AKI during anti-TB treatment in the current study is not uncommon (7.1%), probably reflecting the old age (mean age, 65.9 years) and high prevalence of systemic co-morbidity, such as DM and CKD, that can predispose to more kidney damage. The findings that 60% of patients are older than 65 years and 80% have positive mycobacterial culture are similar to the country-wide epidemiologic data reported by the Taiwan Center of Disease Control (TCDC) (age  $> 65$  years, 52%; culture-positive rate, 80%), implying that the study subjects here are representative of the whole TB population in Taiwan. With the global trend of aging,

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determining the local incidence rate of AKI is necessary to improve the quality of TB care and to determine the frequency and duration of monitoring. The mechanism of rifampin-induced AKI is not well established. Several studies suggest that it is either a type II or type III hypersensitivity reaction induced by rifampin antigens in which anti-rifampin antibodies form immune complexes that are deposited in renal vessels, the glomerular endothelium, and the interstitial area. These reactions cause two different pathologic changes in the kidneys. The deposition of immune complexes in the vessels causes vascular constriction and tubular ischemia, leading to acute tubular necrosis, whereas the deposition of immune complexes in the interstitial area leads to acute interstitial nephritis. Renal biopsies performed in several studies with a total of 106 patients reveal that the most common pathologies are acute interstitial nephritis (54%) and acute tubular necrosis (38%)<sup>[4,11-13]</sup>. The immune reaction is indirect proof by the Romania study of a positive correlation between the duration of anuria and serum gamma-globulin level. In previous studies, more than 80% of patients recover from AKI within 120 days<sup>[4,11-13]</sup>. The recovery rate in the present study (73%) is slightly lower, probably due to the older age and the presence of underlying co-morbidities. Because AKIN stage includes mild renal impairment, some patients who improve their renal function but still fulfill the stage I criteria of AKI may be classified as “unrecovered”. One report reveals that age may predict delayed renal function recovery in patients with drug-induced acute interstitial nephritis<sup>[15]</sup>. However, the present study has different findings. The recovery time of AKI-recovered patients is similar to those of previous reports, with 90% recovery within 100 days. Thus, close monitoring and avoidance of further kidney injury for three-to-four months after the onset of AKI during anti-

TB treatment are necessary. The prognostic factors of AKI during anti-TB treatment are rarely investigated. Only the duration of anuria and leukocytosis have been associated with renal recovery. The current study lacks data on the duration of anuria and few patients (n= 33) underwent urinalysis. After including clinical symptoms, demographic data, and laboratory results into the statistical model, the multivariate Cox regression analysis reveals that the presence of fever, rash, and GI disturbance at the onset of AKI are associated with better renal recovery. Because fever and skin rash are common manifestation of acute interstitial nephritis<sup>[16]</sup>, the underlying pathophysiology of AKI in patients with these two symptoms is more likely to be acute interstitial nephritis. Since acute interstitial nephritis has better prognosis than acute tubular necrosis, these patients also have better renal recovery<sup>[17,18]</sup>. For patients with GI disturbance, AKI may be partly due to dehydration and hypo-perfusion. With careful fluid management, renal impairment may be quickly overcome. More than 50% of the AKI events occurred within two months of anti-TB treatment, indicating that an acute phase reaction may be contributory. The findings also suggest that patients with CKD and hypoalbuminemia maybe more vulnerable to severe and permanent renal damage. After AKI develops, more physicians decide to discontinue pyrazinamide, rather than rifampin, implying that they do not know which of the first-line anti-TB drugs is the most common offending drug for AKI. Continuous medical education on the correct regimen modification is necessary to prevent further renal damage in TB patients with AKI. In this study, the diagnosis of AKI is not confirmed because renal biopsy was not performed. However, the results of previous studies suggest that even without histology studies, the diagnosis of rifampin-induced AKI can be made based on the typical time course

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and by excluding other etiologies<sup>[19]</sup>. In the present study, the medical records were reviewed extensively to exclude other possible causes of AKI like sepsis, hypotension, or use of other nephrotoxic medication. Seven patients had a second AKI episode after rifampin re-challenge, further confirming that rifampin may be the leading cause of AKI. Re-treatment or re-exposure to rifampin causes repeat antigen exposure, which can lead to a high antibody surge and subsequent severe immune response<sup>[11,12]</sup>. This theory is supported by the finding that a high percentage of patients with rifampin-induced AKI are re-treatment cases<sup>[4,11-13]</sup>. However, the findings here are different from previous observations and show that only 11% of AKI patients are re-treatment cases. Rifampin has been successfully re-introduced in 71%. The possible explanation is drug desensitization<sup>[26]</sup>. Although the rifampicin desensitization protocol varies, success rates (80-82%) of re-introducing rifampin are high in some studies<sup>[19,20]</sup>. Further large-scale studies are needed to address whether re-exposure to rifampin is an independent risk factor of developing AKI, and to determine the method of rifampin re-introduction. The present study has some limitations. First, there is no strong evidence to confirm rifampin as the cause of AKI due to the lack of pathology results. Only seven patients had a second AKI episode after re-challenge rifampin. However, this may not be a serious problem because possible causes other than anti-TB medication have been excluded and AKI due to first-line anti-TB drugs other than rifampin is rarely reported<sup>[5,6]</sup>. Second, in this retrospective study, there is no standard protocol of laboratory follow-up for every TB patient during anti-TB treatment. Follow-up depends on the primary care physicians. Patients who did not have any symptoms or signs suggestive for AKI usually had no follow-up data on renal function. Therefore, risk factors of AKI during anti-TB

treatment were not identified. Furthermore, asymptomatic patients with AKI may be missed, resulting in lower incidence and recovery rates of AKI. Third, although some characteristics of the study subjects are similar as those of the general TB population, the results here may not be applicable to all TB patients because this is a retrospective study conducted in a medical center.

## 20. CONCLUSION:

Anti-tuberculosis drug-induced acute kidney injury is not rare in an aging population. It usually develops within two months of treatment and resolves within three months after onset. Although about some of patients with AKI will have permanent renal impairment, those who present with fever, rash, and GI disturbance at the onset of AKI have better renal recovery. Of the 51 patients who had recovery of renal function, successfully continued rifampicin or had rifampicin re-introduced.

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