Kidney Function and Urine LAM Detection in HIV-Negative Adults with Pulmonary Tuberculosis Disease

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Abstract

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Background: Urine lipoarabinomannan (uLAM) is a glycolipid biomarker for tuberculosis (TB) disease in resource-limited settings, and uLAM testing is approved for use in people living with HIV (PLHIV). uLAM is detectable among HIV-negative adults, and the impact of kidney function on uLAM detectability remains unclear. We investigated the association between estimated glomerular filtration rate (eGFR), a measure of kidney function, and uLAM detection in patients with microbiologically confirmed pulmonary TB disease (PTB).

Methods: Adults with presumptive TB disease were enrolled in a diagnostic cohort study at the National Lung Hospital in Hanoi, Vietnam, between October 2021 and April 2022. Each participant provided two sputum samples, one tested with Xpert MTB/RIF Ultra and the other with Mycobacterial Growth Indicator Tube (MGIT) culture, to confirm pulmonary TB (PTB) microbiologically. We restricted analyses to HIV-negative adults who provided a urine specimen for testing. We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and determined uLAM positivity by an electrochemiluminescence assay (S4-20: A194-01 antibody pair). Univariate analyses were conducted to evaluate associations between participant characteristics and uLAM positivity, while multivariable logistic regression was used to assess the relationship between eGFR and uLAM positivity, adjusting for key covariates.

Results: Among 780 enrolled participants, mean age was 44 years, 72.5% were male, and 324 (41.5%) had microbiologically confirmed PTB. Among 324 adults with PTB, 57 participants (17.6%) had decreased renal function (eGFR <90 mL/min/1.73ml). In univariate analysis, higher HbA1c levels (OR = 1.22, 95% CI: 1.07–1.41), urine protein positivity (OR = 2.37, 95% CI: 1.27–4.46), and sputum smear positivity (OR for 3+ vs. smear-negative = 8.43, 95% CI: 2.78–31.47) were significantly associated with uLAM positivity. In multivariable analysis, sputum smear grade (aOR for 3+ = 6.96, 95% CI: 2.21–26.58) and HbA1c (aOR = 1.18, 95% CI: 1.03–1.38) remained significant predictors of uLAM positivity. eGFR was not significantly associated with uLAM positivity in either the univariate analyses or multivariable models.

Conclusion: Among HIV-negative adults with microbiologically confirmed PTB in Vietnam, uLAM detectability was associated with bacillary load and diabetes status. Kidney function, as measured by eGFR, was not a significant determinant of uLAM positivity. uLAM testing may be suitable for HIV-negative people with acute kidney injury or chronic kidney disease in resource-limited settings.

Keywords: Tuberculosis, Urine LAM, Kidney Function, eGFR, Pulmonary TB, Diagnostic Biomarkers

Introduction

In 2023, an estimated 10.8 million people had tuberculosis (TB) disease worldwide.[1,2] TB remains the world's leading cause of death from a single infectious agent, following three years in which it was replaced by coronavirus disease (COVID-19).[3] Roughly one in four people with TB were either undiagnosed or not reported.[2]

In many high TB burden settings, sputum-based testing remains the primary diagnostic technique for evaluating individuals presenting with the signs and symptoms of TB.[4] While obtaining a sputum sample may be possible for some individuals, collecting a high-quality sample suitable for diagnosis can be challenging due to both intrinsic and extrinsic factors.[5] Also, sputum collection can be difficult in certain populations, such as children and individuals with low bacillary burden (e.g., people living with HIV).[6,7] WHO recommends that in adults with signs and symptoms of pulmonary TB, molecular assays like Xpert MTB/RIF should be used as the initial diagnostic test, irrespective of sputum quality.[8] However, the feasibility of these molecular diagnostics remains constrained in many low- and middle-income countries (LMICs) due to health system barriers.[7,9]

Given these challenges, tests based on the detection of Mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as an alternative diagnostic tool for TB disease, offering a non-invasive and more accessible option in resource-limited settings.[10] LAM is a glycolipid integral to the Mycobacterium tuberculosis cell wall and is excreted into urine in a soluble form.[11] LAM (~17.5 kDa when unbound) is secreted in exosomes from bacteria and infected macrophages.[12,13] In circulation, it typically binds to immune complexes and high-density lipoproteins.[14,15] Urine lipoarabinomannan (uLAM) testing has demonstrated significant utility in diagnosing TB among people living with HIV, particularly those with advanced immunosuppression, and has been included in TB diagnostic guidelines.[10,16,17,18]

Our primary goal was to understand how kidney function affects uLAM detectability to refine the diagnostic utility of uLAM testing for TB disease in HIV-negative individuals. Therefore, we sought to evaluate the role of renal function on uLAM detection among HIV-negative adults with microbiologically confirmed pulmonary TB (PTB). We also sought to assess whether reduced filtration capacity, measured by estimated glomerular filtration rate (eGFR), and increased glomerular permeability, indicated by urine protein positivity, correlate with increased uLAM detection.

Methods

Study Design and Setting

We conducted a secondary analysis of cross sectional data from a prospective longitudinal cohort study, the PROVE-TB-VN Study.[19] The primary study aimed to evaluate uLAM concentrations as a biomarker for TB diagnosis among HIV-uninfected adults in Vietnam. This analysis builds upon the primary study's findings to further explore factors associated with detectable uLAM concentrations among adults diagnosed with TB.[19] We recruited adults 18 years of age or older who had TB-related symptoms at the National Lung Hospital (NLH) in Vietnam. TB testing data was analyzed in the National TB Reference Laboratory (NTRL), which is part of the research lab located within the NLH. Participants were enrolled between October 2021 and April 2022 and followed for 6 months to confirm whether TB was diagnosed following evaluation. This analysis includes data collected at baseline, including clinical assessments, laboratory results, demographic information, and treatment history.

Ethical Approval for the Primary study

Ethical approvals were obtained from the National Lung Hospital (NLH) and the Vietnam Ministry of Health, with additional approval from the PATH Office of Research Affairs. Written informed consent was obtained from all participants. This secondary analysis used de-identified data, and therefore, no additional IRB review was required.

Participants

Participants were recruited from the pulmonary TB ward (PR-PTBW), including both outpatients and hospitalized respiratory inpatients, as well as the extra-pulmonary TB ward (PR-EPTBW), exclusively from the EPTB inpatient ward. Participants were eligible for inclusion if they were 18 years or older and had TB-related symptoms. Exclusion criteria included receipt of isoniazid preventive therapy within the last 3 months, prior anti-TB treatment for more than 24 hours before enrollment, or a confirmed TB diagnosis at the time of recruitment.[19]

This analysis included HIV-negative adults diagnosed with PTB through positive Xpert MTB/RIF Ultra (Xpert Ultra) and/or Mycobacterial Growth Indicator Tube (MGIT) liquid culture results on sputum specimens, which served as microbiological reference standard (MRS) in the primary study. Specifically, each participant contributed two separate sputum samples—one for Xpert Ultra and one for MGIT, and was classified as having microbiologically confirmed PTB if at least one of those tests was positive. Conversely, a participant was deemed negative only if both Xpert Ultra and MGIT results were negative.[19] Xpert Ultra provides rapid molecular detection of MTB with an overall sensitivity of approximately 85–90% and a specificity of ≥98%, making it an effective diagnostic tool.[20,21] MGIT liquid culture is considered a gold-standard method and has reported sensitivity of 90–95% and specificity of ≥98%.[21,22] By using this approach, cases that might be missed by one method could still be captured by the other.

Primary Exposure

The primary exposure in this study is kidney function as assessed using the eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:[23]

$$eGFR = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.018 \text{ (if female)}$$

where:

- Scr represents the serum creatinine concentration (mg/dL).
- κ (kappa) is 0.7 for females and 0.9 for males.
- α (alpha) is -0.329 for females and -0.411 for males.
- Age is the participant's age in years.
- 1.018 is a multiplicative factor applied only for females.

Further, kidney function was categorized using a modified version of the CKD-EPI classification, adjusted to reflect the distribution of eGFR values within our study population.[24] Due to the limited number of participants with eGFR < 60 mL/min/1.73m², stages 3 and 4 were merged into a single "Moderate to Severe" category to enhance statistical power and improve interpretability. Further details are provided in Supplementary Table S3.

Outcome Measure

The primary study utilized electrochemiluminescence (ECL) immunoassays to measure uLAM concentrations and compared them against microbiological reference standards (MRS), GeneXpert Ultra and TB culture.[19] uLAM concentration was measured Pa (S4-20 from Otsuka Pharmaceuticals, Tokyo, Japan[25] , and A194-01 from Rutgers University[26]). Assay performance was optimized using U-PLEX plates (Mesoscale Diagnostics [MSD], Rockville, MD, USA) and a recombinant detector antibody labeled with GOLD SULFO-TAG NHS-Ester (Mesoscale Diagnostics [MSD]). Calibration curves were generated from seven-point serial dilutions of LAM standards (40,000 pg/mL to 2.44 pg/mL), derived from in vitro culture of the TB strain Aoyama B.[20] The plate-specific LOD was determined for each assay run, ensuring greater accuracy compared to fixed cutoff values.[25,27]

In this study, uLAM was analyzed as a binary variable, where samples were classified as uLAM-positive if their ECL signal exceeded the plate-specific LOD and uLAM-negative if it fell below.

Statistical Analysis

Study Variables

TB disease variables

TB diagnosis and severity were evaluated using multiple diagnostic tools. Sputum smear microscopy results were recorded as an ordinal variable, categorized as negative, scanty, 1+, 2+, or 3+, based on the presence and quantity of acid-fast bacilli (AFB). 'Negative' smear status served as the reference category.

Both MGIT liquid culture and the GeneXpert MTB/RIF assay served as MRS for TB diagnosis: a positive result from any test was considered positive. If Xpert result was negative and culture result was missing (and vice-versa), then the microbiologic status was considered missing. MGIT results were classified as either positive or negative, while the GeneXpert MTB/RIF assay, a molecular diagnostic test, was recorded as positive or negative as well.[19]

Clinical variables

Glycated hemoglobin (HbA1c) levels were measured as a continuous variable, expressed as a percentage, to provide an indicator of long-term blood glucose regulation. Based on HbA1c classification using the American Diabetes Association (ADA) criteria, the participants were classified into three categories: (Normal (HbA1c $<$5.7%), Pre-diabetes (HbA1c 5.7%–6.4%), and Diabetes ((HbA1c $\geq$6.5%).[28]

Urine protein detection was assessed using standard clinical urinalysis procedures with reagent test strips analyzed in an automated urinalysis system.[19] Urine protein status was modeled as a binary predictor, with 'absence of urine protein' as the reference category. Positive results indicated the presence of detectable urine protein, serving as an indicator of impaired glomerular integrity.

Univariate Analysis

Univariate analyses were conducted to evaluate the relationship between participant characteristics with uLAM positivity (i.e. any LAM reading above the LOD). Due to the non-normal distribution of HbA1c, eGFR, and age, as determined by visualization of histograms and boxplots, the non-parametric Mann-Whitney U test was used for comparisons. Pearson's chi-squared test was used for determining the association between categorical variables (gender, culture results, GeneXpert results, and urine protein status) and uLAM positivity. Fisher's exact test was used for smear results due to low expected cell counts in some categories. To further quantify associations, univariate logistic regression was conducted for selected predictors to generate odds ratios (ORs), and 95% confidence intervals (CIs) were estimated for these predictors. A conceptual model was developed to illustrate the relationships between eGFR, uLAM positivity, and key covariates. (See Supplementary Figure S1 for conceptual model)

Multivariable Analysis

Covariates with a p-value $\leq$0.2 in the univariate logistic regression analysis were included in the multivariable logistic regression model. This model assessed the association between eGFR, the primary exposure, and uLAM positivity, while adjusting for urine protein, smear result, and

HbA1c. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived by exponentiating the regression coefficients to provide interpretable effect estimates. Statistical significance was defined as a p-value ≤0.05. A multivariable logistic regression model was constructed to assess the association between uLAM positivity and eGFR, adjusting for, urine protein, smear result, and HbA1c. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by exponentiating the regression coefficients. A p-value threshold of ≤0.05 was considered statistically significant.

A complete case analysis approach was used for univariate and multivariable logistic regression. All analyses were conducted using R software.

Results

Participant Characteristics

We enrolled 780 participants in the primary study. Of these, 11 participants were excluded due to urine collection outside the protocol window, and 3 participants were excluded due to HIV-positive status. Among the remaining participants, 693 had presumptive PTB and 73 had presumptive EPTB. One presumptive PTB case was excluded due to pleural fluid specimen collection, leaving 692 presumptive PTB participants for microbiological analysis.
Among these, 335 were MRS-positive. Of the MRS-positive cases, 10 participants were excluded due to non-tuberculous mycobacteria (NTM), and 1 participant was excluded due to negative GeneXpert and culture results, leaving 324 microbiologically confirmed PTB cases.
A total of 103 participants were excluded from the univariate and multivariable analyses due to missing data. Specifically, 27.5% (n = 89) participants were missing eGFR values, 5.2% (n = 17) participants were missing HbA1c values, and 0.6% (n = 2) participants were missing sputum smear results. Although these individual counts sum to 108, some participants were missing data in multiple categories. Specifically, 3 participants were missing both eGFR and HbA1c, and 2 were missing both eGFR and sputum smear result. Accounting for these overlaps reduced the total number of exclusions to 103. (See Appendix Figure 1 for the Participant Flowchart.)

Among 324 participants included in the analysis, the mean age of the evaluated participants was 44 years, and the majority (72.5%) were male. Urine LAM positivity was detected in 39% (n = 126) of the participants. 22.5% (n = 73) of participants had diabetes, 26.2% (n = 85) had prediabetes, and 46% (n = 149) did not have diabetes. Sputum smear results were as follows: 60.8% (n = 197) negative, 3.7% (n = 12) scanty, 19.1% (n = 62) 1+, 9.3% (n = 30) 2+, and 6.5% (n = 21) 3+. The study population comprised 54.9% (n = 178) with Stage 1 CKD, 14.5% (n = 47) with Stage 2 CKD, and 3.1% (n = 10) with Stage 3 CKD. No participants had Stage 4 CKD. Urine protein positivity was observed in 23.1% (n = 75) of participants, while 76.9% tested negative (n = 249). (See Table 1 for details)

Univariate Analysis

Non-Parametric Tests

In the non-parametric tests, higher HbA1c levels ($p < 0.001$), urine protein positivity ($p < 0.01$), and sputum smear positivity ($p < 0.001$) were significantly associated with uLAM positivity. However, eGFR ($p = 0.84$), age ($p = 0.53$), and gender ($p = 0.11$) were not associated with uLAM positivity. (See Table 2 for details)

Univariate Logistic Regression Analysis

In univariate logistic regression analysis, several factors demonstrated significant associations with uLAM positivity. Higher HbA1c levels were associated with increased odds of uLAM positivity (OR = 1.22, 95% CI: 1.07–1.41). Urine protein positivity also showed a strong positive association (OR = 2.37, 95% CI: 1.27 - 4.46). Sputum smear positivity exhibited a dose-dependent relationship with uLAM positivity. Compared to smear-negative participants, the odds of uLAM positivity increased with higher smear grades: 1+ (OR = 2.37, 95% CI: 1.17–4.80), 2+ (OR = 6.05, 95% CI: 2.25–18.20), and 3+ (OR = 8.43, 95% CI: 2.78–31.47). eGFR was not significantly associated with uLAM positivity in univariate analysis (OR = 1.01, 95% CI: 1.0–1.0).

Multivariable Analysis

In multivariable logistic regression analysis, we assessed the association between uLAM positivity and eGFR, adjusting for HbA1c levels, sputum smear results and urine protein. We found that the odds of uLAM positivity were 4.22 times greater (aOR: 4.22, 95% CI: 1.49–13.17) among participants with 2+ sputum smear grades and 6.96 times greater (aOR: 6.96, 95% CI: 2.21–26.58) among participants with 3+ sputum smear grades, when compared to smear-negative participants. Participants with elevated HbA1c levels were 1.18 times more likely to have uLAM positivity (aOR: 1.18, 95% CI: 1.03–1.38). Urine protein positivity was associated with a 2-fold increase in the odds of uLAM positivity compared to those without urine protein (aOR: 2.00, 95% CI: 0.95–4.19); however, this association did not reach statistical significance. eGFR was not significantly associated with uLAM detection (aOR: 1.01, 95% CI: 1.00–1.02). (See Table 3 for details). A comparison between the full cohort (n=324) and the regression subset (n=221) is provided in Supplementary Table S2. The subset included in regression analyses was comparable to the full cohort in key characteristics.

Discussion

In our cohort of HIV-negative adults with PTB in Vietnam, higher sputum smear grades and elevated HbA1c levels were significantly associated with increased odds of uLAM positivity. While urine protein positivity showed a positive trend toward increased uLAM positivity, this association did not reach statistical significance. However, renal function as measured by eGFR was not associated with uLAM positivity.

eGFR and urine protein are valuable markers of kidney dysfunction, but they capture distinct physiological processes.[29] Given that eGFR is widely used to assess overall kidney function and classify CKD, we examined urine protein as a marker of impaired glomerular permeability, which could theoretically allow for increased LAM filtration.[30,31] A study conducted in HIV-positive populations reported a higher proportion of LAM-positive patients with abnormal renal function (GFR of <60 mL/min/1.73 m²), compared to LAM-negative patients.[32] The strength of this finding was modest. Additionally, there was a higher proportion LAM-positive patients with nephrotic-range proteinuria, trending toward statistical significance.[32] Another study found that urine protein above trace levels was significantly associated with LAM positivity, suggesting a potential link between urinary protein and LAM detection in urine.[33] Similarly, in our study of HIV-negative individuals, we observed a positive trend between urine protein positivity and uLAM status, though this association did not reach statistical significance. However, we did not find a significant association between eGFR and uLAM positivity. Sputum smear grading is a rough indicator of pulmonary TB burden, with higher grades reflecting greater bacillary load.[34] Our findings suggest that a higher bacillary load may increase the likelihood of uLAM detection. Elevated HbA1c levels were associated with increased uLAM. Given that diabetes is a well-established risk factor for TB, especially in endemic regions, these results highlight the need for careful monitoring of TB biomarkers in diabetic populations.[35,36,37]

This study has some strengths and limitations. As a secondary analysis of existing data, certain constraints were inherent in the dataset, missing data were encountered in high proportions for serum creatinine, a key variable necessary for calculating eGFR. While the laboratory case report form (CRF) at baseline included fields for creatinine measurement, testing was not mandated by the study protocol and was ordered at the clinical team's discretion as part of routine care. If conducted, the test result and date were recorded in the CRF; however, there was no variable capturing the rationale for why a creatinine test may not have been performed. In addition, the study did not attempt to compare an HIV-negative cohort to PLHIV. Another limitation was the classification of urine protein as a binary variable (positive vs. negative) rather than as a continuous measure. This approach captured only the presence of detectable urine protein without quantifying proteinuria, potentially limiting the ability to detect a stronger association. Furthermore, the cohort primarily consisted of participants with normal renal function, with only 3.1 % having an eGFR below 60 mL/min/1.73m^2—meeting the clinical threshold for CKD. The limited representation of moderate to severe renal dysfunction may have reduced the study's ability to detect the impact of renal impairment on LAM filtration

In conclusion, this study demonstrates that uLAM positivity is significantly associated with higher sputum smear grades and elevated HbA1c levels, highlighting a potential link between bacillary load, diabetes, and uLAM detectability. In contrast, kidney function, as measured by eGFR, was not a determining factor in uLAM positivity. Efforts are underway to refine uLAM assays.[13,38] However, the relevance of uLAM in HIV-negative populations remains less well understood.[19] Addressing this gap is crucial, especially in resource-limited settings.[39] Our study contributes to filling this knowledge gap by providing insights into factors potentially influencing uLAM detection. Future research should further investigate the detectability of uLAM across distinct subgroups of TB patients, carefully evaluating the effects of renal function and diabetes on LAM excretion. Comparative studies that include HIV-negative individuals with

CKD versus those with normal renal function, and specifically account for diabetes as a comorbidity, are necessary. This approach could clarify whether renal dysfunction and diabetes independently or synergistically affect uLAM detectability, informing the refinement and application of uLAM-based diagnostic strategies in diverse patient populations, particularly in TB-endemic regions.

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Appendix

Table1: Baseline characteristics of participants stratified by LAM status (LAM Negative vs LAM Positive)

Variable	LAM Negative (n=198)	LAM Positive (n=126)	Total (n=324)
Age, mean (SD)	44 (16)	46 (16)	44 (16)
Sex, n (%)			
Female	66(33.3)	23(18.3)	89(27.5)
Male	132 (66.7)	103 (81.7)	235 (72.5)
AFB Smear Positivity, n (%)			
Negative	143(72.2)	54 (42.9)	197 (60.8)
Scanty	6 (3.0)	6 (4.8)	12 (3.7)
1+	32 (16.2)	30 (23.8)	62 (19.1)
2+	9 (4.5)	21 (16.7)	30 (9.3)
3+	7 (3.5)	14 (11.1)	21 (6.5)
Xpert Ultra, n(%)			
Positive	170 (85.9)	119 (94.4)	289 (89.2)
Negative	28 (14.1)	7(5.6)	35 (10.8)
Mtb Culture, n (%)			
Positive	168 (84.8)	112 (88.9)	280 (86.4)
Negative	30 (15.2)	12 (9.5)	42 (13.0)
Urine protein positivity, n (%)			
Positive	31 (15.7)	44 (34.9)	75 (23.1)
Negative	167 (84.3)	82 (65.1)	249 (76.9)
HbA1c Category, n (%)			
Normal	109 (55.1)	40 (31.7)	149 (46.0)
Pre-diabetes	49 (24.7)	36 (28.6)	85 (26.2)
Diabetes	32 (16.2)	41 (32.5)	73 (22.5)
missing	*8 (4.0)*	*9 (7.1)*	*17 (5.2)*
eGFR Category, n (%)			
Stage 1	105 (53.0)	73 (57.9)	178 (54.9)
Stage 2	28 (14.1)	19 (15.1)	47 (14.5)
Stage 3	6 (3.0)	4 (3.2)	10 (3.1)
Stage 4	0 (0.0)	0 (0.0)	0 (0.0)

missing	*59 (29.8)*	*30 (23.8)*	*89 (27.5)*
Serum Creatinine, mean (SD)	83.11 (35.55)	77.41 (24.78)	80.78 (31.66)
Glycated hemoglobin (HbA1c), mean (SD)	5.99 (1.71)	7.15 (2.61)	6.43 (2.17)

Note: Number and percent missing are presented for variables where at least 5% were missing. Number and percent missing for other variables are as follows: AFB Smear Positivity, n=2 (0.6%), Mtb culture, n=2 (0.6%)

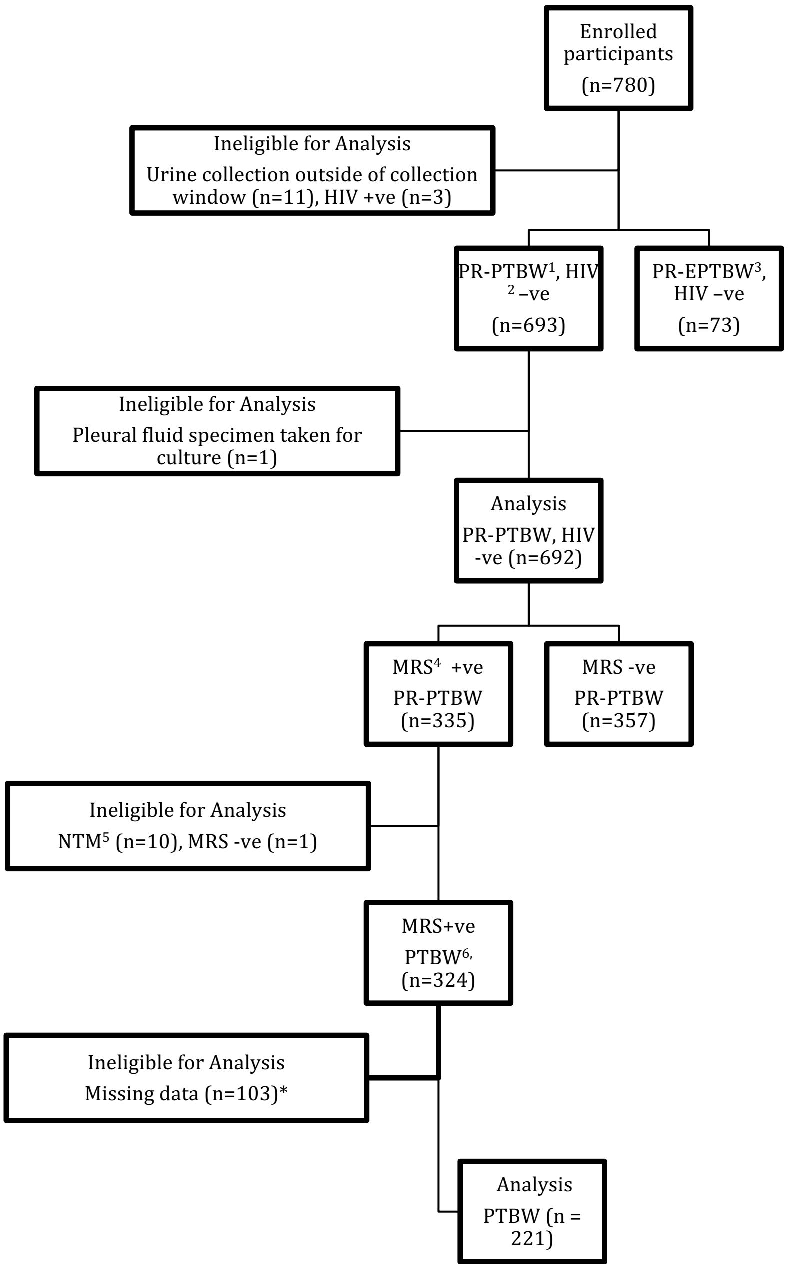
Table 2: Results of Non-Parametric Tests Assessing Factors Associated with uLAM Positivity

Variable	**Test Statistic**	**p-value**
eGFR vs. uLAM	U = 5800	0.84
Age vs. uLAM	U = 5601.5	0.53
HbA1c vs. uLAM	U = 4129	< 0.001
Gender vs. uLAM	$\chi 2 = 2.5605$	0.11
Urine Protein vs. uLAM	$\chi 2 = 6.7013$	< 0.01
Sputum Smear vs. uLAM	—	< 0.001

Table 3: Multivariable Logistic Regression Analysis of Factors Associated with Urine LAM positivity

Predictor Variable	Univariate OR [95% CI]	p-value (unadjusted)	Adjusted OR [95% CI]	p-value (adjusted)
eGFR (mL/min/1.73 m²)	1.01 [1.0, 1.02]	0.13	1.01 [1.00, 1.02]	0.21
Urine Protein				
Negative	*ref*	*ref*	*ref*	*ref*
Positive	2.37 [1.27, 4.46]	0.01	1.91 [0.95, 3.84]	0.07
Smear Result				
Negative	*ref*	*ref*	*ref*	*ref*
Scanty	1.04 [0.14, 5.05]	0.97	1.01 [0.13, 5.17]	0.99
1+	2.37 [1.17, 4.80]	0.02	2.00 [0.95, 4.19]	0.06
2+	6.05 [2.25, 18.20]	<0.001	4.22 [1.49 13.17]	0.01
3+	8.43 [2.78, 31.47]	<0.001	6.96 [2.21, 26.58]	< 0.01
HbA1c (%)	1.22 [1.07, 1.41]	<0.01	1.18 [1.03, 1.38]	0.02

Figure 1: Study Participant Flowchart



Note: A total of 103 participants were excluded due to missing data on any of the following: eGFR (89), HbA1c (17), and sputum smear result (2). While these counts add up to 108, there was overlap among missing categories. Specifically, 3 participants were missing both eGFR and HbA1c, and 2 participants were missing both eGFR and sputum smear. These overlaps reduce the total number of excluded participants to 103.*

[1]Presumptive Pulmonary Tuberculosis from the wards
[2]Human Immuno-deficiency Virus
[3]Presumptive Extra-pulmonary Tuberculosis from the wards
[4]Medical Reference Standard- Xpert Ultra or MGIT
[5]Non- Tuberculous Mycobacteria
[6]Pulmonary Tuberculosis from the wards

Supplementary Table S1. Comparison of Baseline Characteristics Between the Full Cohort and Regression Subset

Variable	Total (n=324)	Regression Subset (n=221)	Excluded (n=103)	p-value
Age, mean (SD)	44 (16)	45(16)	42 (16)	0.13
Sex, n (%)				
Female	89 (27.5)	57 (25.8)	32 (31.1)	
Male	235 (72.5)	164 (74.2)	71 (68.9)	0.39
AFB Smear Positivity, n (%)				
Negative	197 (60.8)	133 (60.2)	64 (62.1)	
Scanty	12 (3.7)	7 (3.2)	5 (4.9)	
1+	62 (19.1)	44 (19.9)	18 (17.5)	
2+	30 (9.3)	20 (9.0)	10 (9.7)	
3+	21 (6.5)	17 (7.7)	4 (3.9)	0.24
Urine protein positivity, n (%)				
Positive	75 (23.1)	53 (24.0)	22 (21.4)	
Negative	249 (76.9)	168 (76.0)	81 (78.6)	0.70
Serum Creatinine, mean (SD)[1]	80.78(31.7)	80.55 (31.7)	84.39 (31.8)	0.66
Glycated Hemoglobin (HbA1c), mean (SD)[2]	6.43 (2.17)	6.45 (2.14)	6.38 (2.26)	0.81
MRS (Omitted from Regression)				
Xpert Ultra, n (%)				
Positive	289 (89.2)			
Negative	35 (10.8)	-	-	-
Mtb Culture, n (%)				
Positive	280 (86.4)			
Negative	42 (13.0)	-	-	-

Note: GeneXpert Ultra and Mtb Culture were included in the total cohort characteristics but omitted from regression analysis as they are part of the Medical Reference Standard (MRS).

[1]Serum Creatinine missing in 27.5% of cases
[2]HbA1c missing in 5.2% of cases

Supplementary Table S2. Modified CKD-EPI Classification

CKD-EPI Classification	**CKD-EPI Term**	**Modified Classification**	**Modification Details**
G1 (≥90)	Normal	Stage 1: Normal (≥90)	Unchanged
G2 (60-89)	Mildly decreased	Stage 2: Mild (60-89)	Unchanged
G3a (45-59)	Mildly to moderately decreased	Stage 3: Moderate to Severe (15-60)	Merged into Stage 3
G3b (30-44)	Moderately to severely decreased	Stage 3: Moderate to Severe (15-60)	Merged into Stage 3
G4 (15-29)	Severely decreased	Stage 3: Moderate to Severe (15-60)	Merged into Stage 3
G5 (<15)	Kidney failure	Stage 4: Kidney Failure (<15)	Unchanged

Supplementary Figure S1: Conceptual Model Depicting the Relationships Between Kidney Function, uLAM Detection, and Key Factors