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A Cohort Study: Urine Interferon Gamma-Induced Protein 10 As A Non-Sputum Biomarker in Diagnostic and Treatment Monitoring in Patients with Active Pulmonary Tuberculosis

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ABSTRACT

There are still limitations in the diagnosis of tuberculosis (TB), and developing monitoring tools to predict treatment outcomes for TB patients is important. Sputum collection is not only challenging but also has low sensitivity when used as a diagnostic specimen. Interferon gamma-inducible protein 10 (IP-10) is a potential biomarker of diagnosis and treatment response in tuberculosis. In this study, we measured IP-10 levels in urine samples taken at diagnosis, following the intensive treatment period, and post-treatment from patients with active tuberculosis. This was a comparative observational cohort study on new active pulmonary TB patients who were >18 years old at the TB Clinic of Dr. Hasan Sadikin General Hospital Bandung. IP-10 was measured using enzyme-linked immunosorbent assays in urine samples collected from 39 patients with active TB (26 patients with drug-resistant and 13 patients with drug-sensitive tuberculosis) and 34 healthy adults (73 total individuals). Thirty-nine patients who met the inclusion criteria were followed up until completion of TB treatment. There was a decrease in urine ip-10 levels in both the DR-TB vs DS-TB groups at diagnosis, after the intensive phase, and after treatment. (16.1 vs 13.3 pg/mL; 11.7 vs 8.4 pg/mL; 3.6 vs 3.2 pg/mL). IP-10 in urine has good accuracy with an AUC value of 0.847 in detecting Active TB with a cutoff value of 8.3 pg/mL, sensitivity of 97.4%, specificity of 61.8%, PPV 74.5%, NPV 95.5%, LR+ 2.55, and LR- 0.04. Urine IP-10 levels in active pulmonary TB patients decreased significantly after intensive phase and at the end of treatment ($p<0.001$), and urine IP-10 levels have the potential as a non-sputum-based marker for treatment-related TB monitoring.

Keywords: *biomarker; pulmonary tuberculosis; diagnosis; monitoring; urine IP-10.*

1. INTRODUCTION

Tuberculosis (TB) is a prevalent infectious disease and a significant contributor to morbidity and mortality worldwide. TB is caused by the bacillus *Mycobacterium tuberculosis.* People who have TB transmit the bacteria into the air through coughing or other respiratory secretions. Approximately 25% of the global population is believed to have experienced a TB infection; nevertheless, most individuals affected are expected to recover from the infection. An estimated 90% of tuberculosis cases occur in adults, with a greater incidence rate in males compared to females. The disease typically affects the lungs (pulmonary TB) but can affect other sites as well.[1]

There are still limitations in the diagnosis of TB, and developing monitoring tools to predict treatment outcomes for TB patients is important. Sputum collection is not only challenging but also has low sensitivity when used as a diagnostic

specimen. Urine specimens are used as they are easier to garner. IP-10 (CXCL-10), a pro-inflammatory chemokine implicated in various disease processes, is among the most promising molecules linked to therapy responses. IP-10 is involved in the recruitment of natural killer (NK) cells, macrophages, and activated T lymphocytes.[2,3,4]

Mycobacterium tuberculosis is transmitted through the air in the form of droplets from patients with active pulmonary TB. Droplets containing M. tuberculosis inhaled into the lung are trapped in the upper respiratory tract and removed by ciliated mucosal cells, and only <10% can pass through the ciliated mucosal cell defenses of the bronchi and settle in the alveolus terminalis. Mycobacterium tuberculosis is phagocytized by alveolar macrophages and dendritic cells, then presented directly to naive CD4+ T cells via MHC class II.[5,6,7]

Naive CD4+ T cells differentiate into CD4+ effector T cells. CD4+ effector T cells then proliferate into Th17, Th1, Th2 and Treg cells. Th17 cells secrete IL-17, which plays a role in the activation of polymorphonuclear leucocytes, which plays a role in the beginning of the inflammatory process in the lung. Th1 cells secrete IFN-γ, which activates macrophages. Activated macrophages have better bactericidal or bacteriostatic ability and play a major role in granuloma formation. Th1 cells proliferate into Th1 T memory (Th1 Tm) cells. Th1 Tm cells secrete IL-2, IFN-γ and TNF, which play a role in the activation of macrophages and T cells.[8,9,10]

Naive CD8+ T cells differentiate into CD8+ effector T cells. CD8+ effector T cells proliferate into CD8+ memory T cells and CD8+ cytolytic cells. CD8+ memory T cells secrete IFN-γ, which activates macrophages. CD8+ cytotoxic T lymphocytes cells secrete perforin and granulisin, which lyse host cells and directly attack M. tuberculosis.[7,8,10]

Interferon gamma secreted by Th_1 cells, Th_1 Tm cells, and $CD8^+$ T memory cells in the inflammatory area will influence antigen presenting cells (APCs) to secrete IP-10.[11,12,13,14]

IP-10 plays a role in immune system regulation by binding to the CXCR3 receptor to induce chemotaxis, apoptosis, cell growth, and angiostasis. IP-10 expression abnormalities are linked to inflammatory disorders, such as autoimmune, infectious, and tumor development.[2,3,4,13,14]

IP-10 has been extensively studied as a tuberculosis biomarker, and it has been found to be expressed at 100 times the levels of IFN-γ.[15] Researchers have examined IP-10 in peripheral blood samples[13,16-34], bronchoalveolar lavage[24], pleural fluid[35-37], and urine[2,13], from patients at different phases of tuberculosis infection.

IP-10 is one of the biomarkers in urine that can be utilized to identify pulmonary tuberculosis and is a potential biomarker of diagnosis and treatment response in tuberculosis. Urine levels of IP-10 have been found to be elevated in patients with active pulmonary tuberculosis as compared to healthy individuals. However, following the completion of anti-tuberculosis medication treatment, these levels have considerably decreased.[2,4,12] In this study, we measured IP-10 levels in urine samples taken at diagnosis, following the intensive treatment period, and post-treatment from patients with active tuberculosis.

2. MATERIALS AND METHODS

Study population

For this comparative observational cohort study, we recruited new active pulmonary TB patients who were >18 years old at the TB Clinic of Dr. Hasan Sadikin General Hospital Bandung, West Java, Indonesia, between September 2021 and April 2024. Eligible for participation were newly diagnosed adult pulmonary TB patients (>18 years old) who visit TB clinic Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The patients who met the following exclusion criteria were not eligible for enrollment in the study: they had to be diagnosed with extrapulmonary tuberculosis (TB) or have been diagnosed with clinical TB without laboratory confirmation; received treatment for hepatitis with interferon treatment, which is known to exacerbate tuberculosis infection; received chemotherapy and immunomodulators; received treatment for TB within the previous week; and not used oral steroids for longer than two weeks. Ethics approval for this study was provided by the Bioethical Committee of the Dr. Hasan Sadikin General Hospital, and written informed consent was obtained from each participant before enrolment (approval no. 077/UN6.KEP/EC/2021; Bandung, Indonesia).

Clinical and laboratory procedures

Demographics, history, and clinical findings were recorded systematically using a case report form. All participants underwent peripheral blood and urine testing. Adults suspected of active pulmonary TB underwent standard diagnostic procedures encompassing the chest X-ray and bacteriological evaluation (microscopy, Xpert MTB/RIF, and culture). All participants with active pulmonary TB received standard combined anti-tuberculosis treatment.

IP-10 measurement

Urine samples were collected to measure serial IP-10 levels from all patients before treatment (0 months, T0), after intensive phase (T2), and at 6-12 months after the treatment was completed (T6). IP-10 concentration was measured using the Elabscience® Human IP-10/CXCL10 ELISA Kit (Elabscience, Texas, USA) with catalog number E-EL-H0050, E-EL-H6154, and E-EL-H0099 according to the manufacturer's instructions. All samples were measured in duplicate. The lower

limit of detection (sensitivity) was 4.69 pg/mL. IP-10 concentrations are expressed in pg/mL.[38]

Statistical analysis

Data were analyzed using SPSS 27.0 and Medcalc 22.0 (MedCalc Software, Ostend, Belgium). The data were presented as the median and interquartile range (IQR). For quantitative data, the Shapiro-Wilk normality test was performed, followed by the Mann-Whitney test. To compare more than two independent groups of normally distributed data, the one-way ANOVA test was performed, followed by the Kruskal-Wallis test. The Friedman test was performed to test for differences at three different time points in one group (baseline, after intensive phase, after treatment). The diagnostic performance of IP-10 was assessed using receiver operating characteristic curve (ROC) analysis and the area under the curve (AUC). Finally, to predict the likelihood of an event occurring based on multiple predictor variables, logistic regression analysis was used. All tests were two-sided, and a *p*-value of <0.05 was considered significant.

3. RESULTS

This research was conducted from September 2021 and April 2024. This was a comparative observational cohort study on active pulmonary TB patients who were >18 years old at the TB Clinic of Dr. Hasan Sadikin General Hospital Bandung. IP-10 was measured using enzyme-linked immunosorbent assays in urine samples collected concomitantly from 39 patients with active TB (26 patients with drug-resistant TB and 13 patients with drug-sensitive TB) and 34 healthy adults (73 total individuals).

Characteristics of the study population

In our study, there are no differences in the characteristics of the research subjects based on gender and age (Table I). The active TB group was 48.7% male and 51.3% female, and the healthy control group was 38.2% male and 61.8% female. The mean age in the active TB group was 38 years, which was similar to the healthy group at 36 years.

Table I. Characteristics of the study population

Variable	**Group (n=73)**		**p value**
	Active TB (n = 39)	**Healthy Controls (n = 34)**	
Sex			
Male	19 (48.7)	13 (38.2)	0.368[a]
Female	20 (51.3)	21 (61.8)	
Age (year)			
Mean ± SD	38 ± 18	36 ± 10	0.335[b]
Median (IQR)	36 (27 – 50)	34 (21 – 65)	
Min – Max	20 – 64	21 – 65	

Analysis using the [a]*Chi Square*, [b]*Paired t-test*, *significant. SD, standard deviation; IQR, inter quartile range.

There are no differences in the characteristics of the study population based on gender and age between the DR-TB, DS-TB, and healthy control groups (Table II). There were no significant differences in BMI characteristics, clinical symptoms, smoking history, and AFB smear results, between the DR-TB and DS-TB groups.

Tabel II. Characteristics of the study population in DR-TB, DS- TB, and healthy controls

Variable	**Active Pulmonary TB (n=39)**		**Healthy Controls (n = 34)**	**p value**	
	DR-TB (n = 26)	**DS-TB (n = 13)**			
Sex					
Male	13	6	13	0.650[a]	
Female	13	7	21		

Age (year)					
Mean ± SD	41 ± 15	34 ± 10	36 ± 10	0.177[c]	
Median	38	34	34		
BMI (kg/m^2)					
Mean ± SD	18.2 ± 2.58	19.1 ± 3.0	21.3 ± 2.21	0.358[d]	
Median	18.3	19.3			
BMI criteria					
Underweight	14	5	0	0.365[a]	
Normal Overweight Obese	12 0 0	8 0 0	33 1 0		
Clinical Symptoms					
Productive Cough	26	11	0	0.105[b]	
Dyspnoe	13	5	0	0.496[a]	
Weight Loss	18	12	0	0.225[b]	
Night sweats	14	9	0	0.357[a]	
Smoking History					
Yes	11	6	0	0.819[a]	
No	15	7	34		
Acid Fast Bacilli (AFB)					
Negative	12	6	Negative	1.000[a]	
Positive	14	7			
AFB					
+/-	3	2		0.594[a]	
+1	7	4			
+2	3	0			
+3	1	1			
Xpert MTB/RIF Result					
Sensitive	0	13	NA	-	
Resistant	26	0			
MODS Culture					
Positive	19	8	NA	0.462[a]	
Negative	7	5			

Analysis using [a]*Chi Square*, [b]*Fisher Exact*, [c]*One Way ANOVA*, [d]*Paired t-test*, [e]*Mann Whitney*, *significant. SD, standard deviation; DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis; BMI, body mass index; MODS, microscopic observation drug susceptibility assay.

Statistical analysis of IP-10 levels between active TB patients and healthy controls

Table III shows the differences in IP-10 levels in urine between active TB and healthy controls. Normality test results showed that urine IP-10 data were not normally distributed ($p<0.05$), so the difference test used non-parametric analysis with the Mann Whitney test. IP-10 levels were higher in subjects with active TB than healthy controls, significantly different (median: 18.3 pg/mL vs. 8.0 pg/mL, $p<0.001$).

Table III. IP-10 difference between active TB and healthy controls

Variable	**Group (n=73)**		**p value**
	Active TB (n = 39)	**Healthy Controls (n = 34)**	
Urine IP-10 (pg/mL)			
Mean ± SD	18.3 ± 11.3	8.0 ± 5.4	<0.001*
Median (IQR)	14.6 (13.1 – 20.3)	6.0 (3.5 – 12.7)	
Min – Max	5.6 – 63.6	0.8 – 20.3	

Analysis using Mann Whitney test, *significant. SD, standard deviation; IQR, inter quartile range.

The results in Table IV show the ROC analysis of urine IP-10 for predicting active TB. IP-10 in urine has good accuracy with an AUC value of 0.847 in detecting active TB with a cutoff value of 8.3 pg/mL, sensitivity of 97.4%, specificity of 61.8%, PPV 74.5%, NPV 95.5%, LR+ 2.55, and LR- 0.04 (Fig. 1.).

Tabel IV. ROC analysis of urine IP-10 to predict active TB

Predicted Value	**Urine IP-10 (pg/mL) n=39**
AUC value (95% CI)	0.847 (0.744 – 0.921)
Cutoff value	>8.3
Sensitivity	97.4%
Specificity	61.8%
PPV	74.5%
NPV	95.5%
LR+	2.55
LR-	0.04

AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive, LR-; likelihood ratio negative.

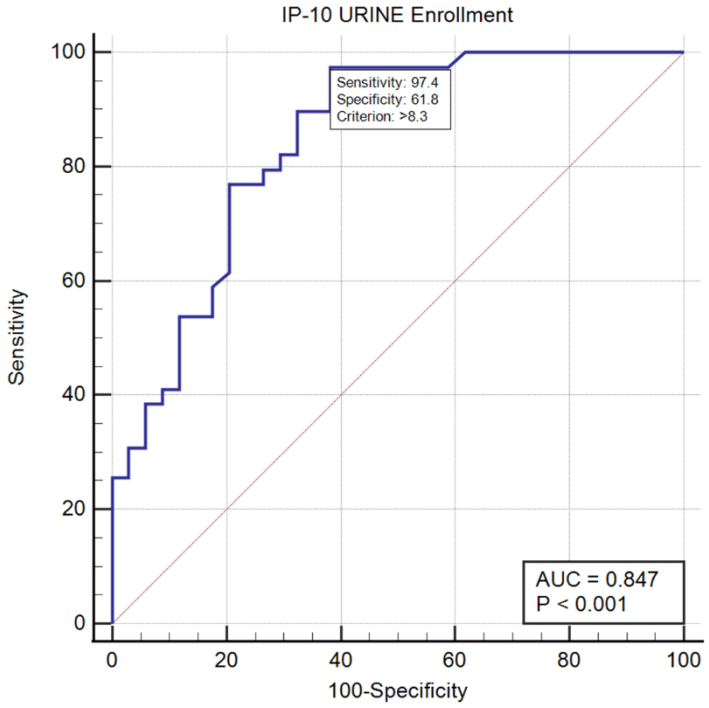

Figure 1. ROC curve of urine IP-10 in detecting active TB. AUC, area under curve.

Individuals with urine IP-10 >8.3 pg/mL have a 61.39 times higher chance of developing active TB (Table V).

Table V. Association between urine IP-10 and active TB

Variable	Group		p value	OR (95% CI)
	Active TB (n=39)	Healthy Controls (n=34)		
Cut off value Urine IP-10 (pg/mL)				
>8.3	38 (97.4)	13 (38.2)	<0.001*	61.39 (7.50 – 502.59)
≤8.3	1 (2.6)	21 (61.8)		

Analysis using the Chi Square test, *significant. OR, odds ratio; CI, confidence interval.

IP-10 levels were highest in subjects with DR-TB, then DS-TB, and the lowest in healthy controls (Table VI), significantly different (median: 18.8 pg/mL vs. 17.2 pg/mL vs. 8.0 pg/mL, p<0.001).

Table VI. Difference in IP-10 between active TB and healthy controls

Variable	Active TB (n=39)		Healthy Controls (n = 34)	p value
	DR-TB (n = 26)	DS-TB (n = 13)		
Urine IP-10 (pg/mL)				
Mean ± SD	18.8 ± 9.8	17.2 ± 14.1	8.0 ± 5.4	<0.001*

Median (IQR)	16.1 (13.6 – 23.1)	13.3 (12.3 – 13.6)	6.0 (3.5 – 12.7)	
Min – Max	5.6 – 52.7	10.3 – 63.6	0.8 – 20.3	

Analysis using *Kruskall-Wallis*, *significant. DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis.

The urine IP-10 results showed an AUC value of 0.847 (good criteria) in detecting active DR TB with a cutoff value of 14.5 pg/mL, sensitivity of 73.1%, specificity of 88.2%, PPV 82.6%, NPV 81.1%, LR+ 6.21, and LR- 0.31 (Fig. 2.).

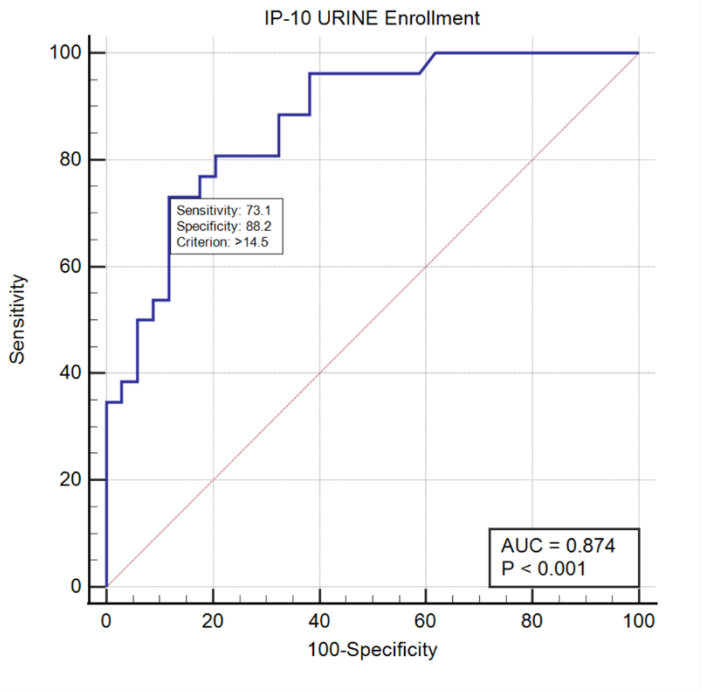

Figure 2. ROC curve of Urine IP-10 in detecting DR-TB. AUC, area under curve.

The urine IP-10 results showed an AUC value of 0.793 (good criteria) in detecting active DS TB with a cutoff value of 8.3 pg/mL, sensitivity of 100%, specificity of 61.8%, PPV 50.0%, NPV 100.0%, LR+ 2.62, and LR- 0.0 (TableVII) (Fig. 3.).

Table VII. ROC analysis of urine IP-10 for predicting DR-TB and DS-TB

Predicted Value	**Urine IP-10 (pg/mL)**	
	DR-TB (n = 26)	**DS-TB (n = 13)**
AUC value (95% CI)	0.874 (0.763 – 0.946)	0.793 (0.650 – 0.897)
Cutoff	>14.5	>8.3
Sensitivity	73.1%	100.0%
Specificity	88.2%	61.8%
PPV	82.6%	50.0%
NPV	81.1%	100.0%
LR+	6.21	2.62
LR-	0.31	0.00

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR-, likelihood ratio negative; DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis.

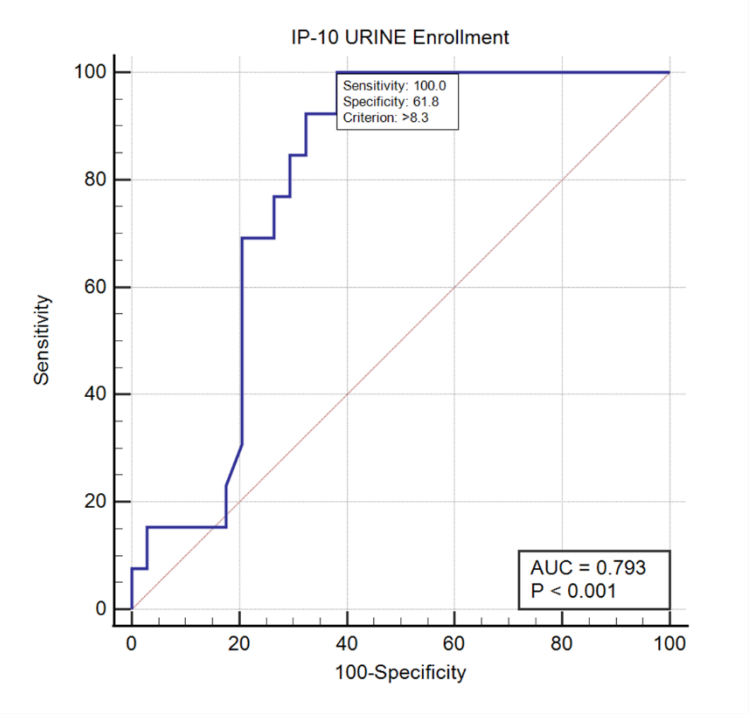

Figure 3. ROC curve of Urine IP-10 in detecting DS-TB. AUC, area under curve.

The results in Table VIII show differences in urine IP-10 levels in the examination before Anti-TB Drugs treatment (baseline), after intensive phase and after treatment (Fig. 4.). The normality test with the Shapiro-Wilk test was conducted before the difference test, it was found that the data was not normally distributed, so the difference test used non-parametric analysis with the Friedman test, then continued posthoc analysis with Bonferroni correction for multiple tests.

Table VIII. Differences in urine IP-10 levels after anti-TB drugs treatment

Variable					p value
		Baseline	**After Intensive phase**	**After Treatment**	
Urine IP-10 (pg/mL)					
DR-TB	Mean ± SD	18.8 ± 9.8	11.8 ± 3.5	3.8 ± 1.2	<0.001*
(n= 26)	Median (IQR)	16.1 (13.6 – 23.1)	11.7 (10.0 – 14.3)	3.6 (2.8 – 5.2)	
DS-SO	Mean ± SD	17.2 ± 14.1	8.4 ± 2.7	3.5 ± 1.3	<0.001*
(n=13)	Median (IQR)	13.3 (12.3 – 13.6)	8.4 (6.8 – 9.2)	3.2 (2.6 – 4.3)	

Analysis using *Friedman's test*; *significant. SD, standard deviation; IQR, inter quartile range; DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis.

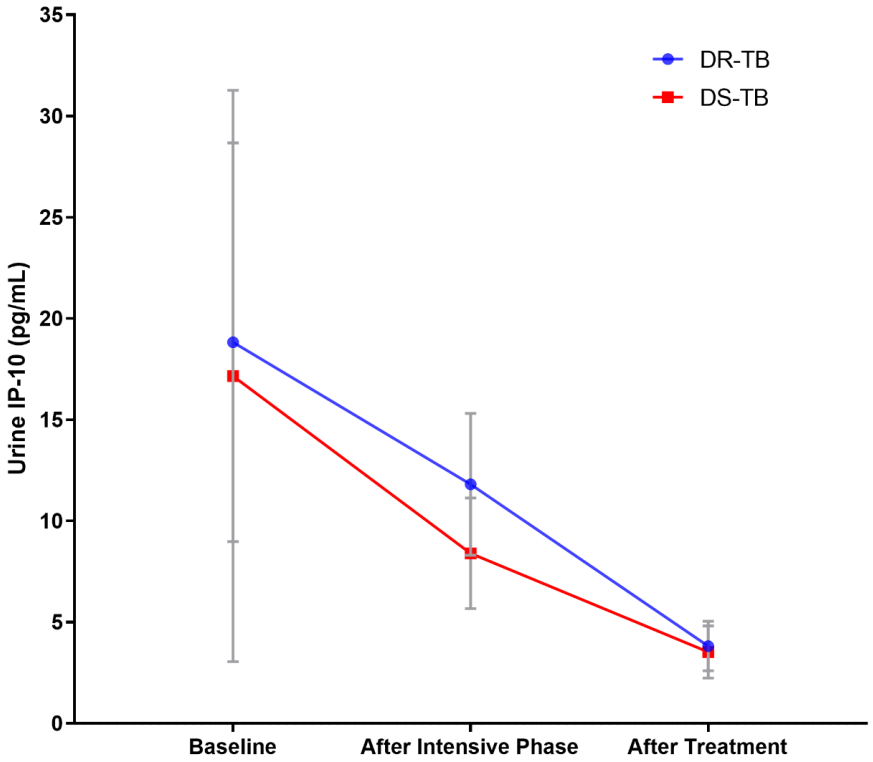

Figure 4. Differences in median urine IP-10 levels at baseline, after intensive phase and after treatment. DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis.

DR-TB group subjects had a median baseline urine IP-10 level of 16.1 pg/mL (IQR: 13.6-23.1 pg/mL), then after intensive phase decreased to 11.7 pg/mL (IQR: 10.0-14.3 pg/mL) and completed treatment to 3.6 pg/mL (IQR: 2.8-5.2 pg/mL). Statistical test results showed that there was a significant difference in median urine IP-10 levels between baseline examination, after intensive phase, and after treatment in subjects with TB ($p<0.001$). Posthoc analysis showed that there was a significant difference in urine IP-10 levels between baseline and after intensive phase ($p = <0.001$), then baseline and after treatment ($p<0.001$), and after intensive phase and after treatment ($p = <0.001$) (Fig. 5.).

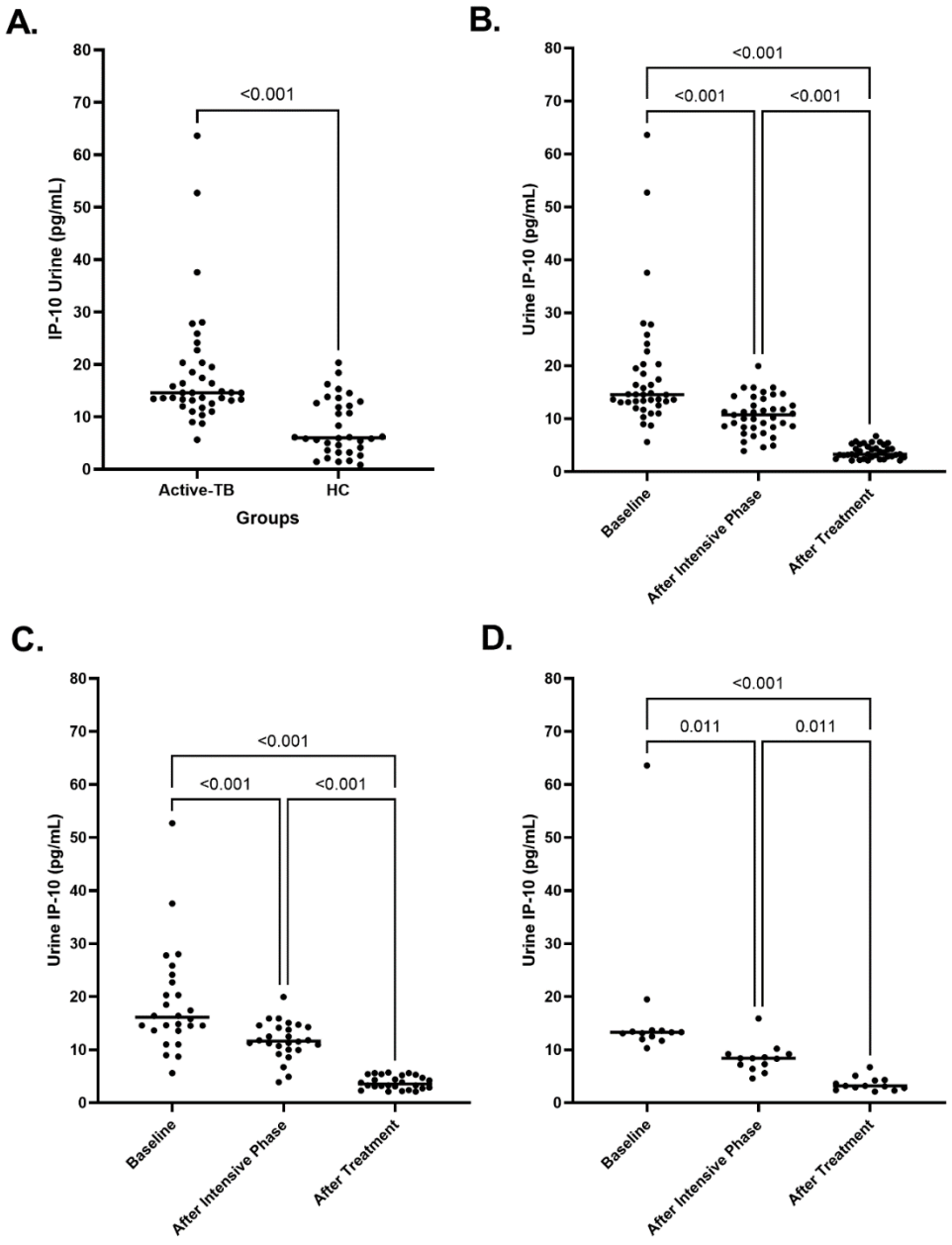

Figure 5. Urine IP-10 levels in healty control (A), patient with active TB (B), DR-TB (C), and DS-TB (D). DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis.

IP-10 levels in the urine of patients with TB obtained at the time of diagnosis (baseline), after intensive phase, and after treatment.

DS-TB group subjects had a median baseline urine IP-10 level of 13.3 pg/mL (IQR: 12.3-13.6 pg/mL), then after intensive phase decreased to 8.4 pg/mL (IQR: 6.8-9.2 pg/mL) and after treatment to 3.2 pg/mL (IQR: 2.6-4.3 pg/mL). Statistical test results showed that there was a significant difference in median urine IP-10 levels between baseline examination, after intensive phase, and after treatment in subjects with TB ($p<0.001$). Posthoc analysis showed that there was a significant difference in urine IP-10 levels between baseline and after intensive phase ($p = 0.011$), then baseline and after treatment ($p<0.001$), as well as after intensive phase with after treatment ($p = 0.011$) (Fig. 5.).

Urine IP-10 levels at baseline showed similar values between culture-positive (14.7 pg/mL) and negative (14.5 pg/mL) patients, with no significant difference (p value = 0.951) (Table IX). After the intensive phase, urine IP-10 levels decreased to 11.4 pg/mL in the culture-positive group and 10.2 pg/mL in the culture-negative group, with no significant difference (p value = 0.113). At the end of treatment, urine IP-10 levels further decreased to 4.2 pg/mL in the culture-positive group and

3.2 pg/mL in the culture-negative group, with no significant difference (p value = 0.377). However, the change in urine IP-10 levels during treatment was highly significant in both groups (p value < 0.001), indicating a significant decrease as treatment progressed.

Table IX. Differences in urine IP-10 levels based on MODS culture

Variable	MODS Culture (n=39)		p[a] value
	Positive (n = 27)	Negative (n = 12)	
Urine IP-10 (pg/mL)			
Baseline	14.7 (13.1 – 19.3)	14.5 (12.0 – 20.3)	0.951
After intensive phase	11.4 (9.2 – 15.6)	10.2 (7.2 – 12.5)	0.113
After treatment	4.2 (2.9 – 5.0)	3.2 (2.4 – 4.7)	0.377
p[b] value	<0.001*	<0.001*	

Analysis using: [a]*Mann Whitney test*, [b]*Friedman*, *significant. MODS, microscopic observation drug susceptibility assay.

Urine IP-10 levels at the initial stage of treatment showed similar values between sputum AFB smear-positive (15.3 pg/mL) and negative (13.6 pg/mL), with no significant difference (p value = 0.693) (Table X). After the intensive phase, urine IP-10 levels decreased to 11.4 pg/mL in sputum AFB smears positive and 10.0 pg/mL in sputum AFB smears negative, with no significant difference (p value = 0.297). At the end of treatment, urine IP-10 levels further decreased to 4.3 pg/mL in AFB smear-positive and 3.2 pg/mL in AFB smear-negative sputum, with no significant difference (p value = 0.080). However, the change in urine IP-10 levels during treatment was highly significant in both groups (p value < 0.001), indicating a significant response to treatment.

Table X. Differences in urine IP-10 levels based on AFB smear

Variable	AFB Smear (n=39)		p[a] value
	Positive (n = 21)	Negative (n = 18)	
Urine IP-10 (pg/mL)			
Baseline	15.3 (12.8 – 20.3)	13.6 (12.8 – 20.6)	0.693
After intensive phase	11.4 (8.3 – 15.0)	10.0 (8.4 – 12.0)	0.297
After treatment	4.3 (2.8 – 5.2)	3.2 (2.6 – 4.0)	0.080
p[b] value	<0.001*	<0.001*	

Analysis using: [a]*Mann Whitney test*, [b]*Friedman*, *significant. AFB, acid-fast bacilli.

4. DISCUSSION

In this cohort study, we analyzed the diagnostic performance of urine IP-10 and assessed its potential as a non-sputum biomarker in patients with active pulmonary tuberculosis in a country with a high TB incidence. Several things that can cause IP-10 levels to increase are infectious or inflammatory conditions such as pulmonary infections other than TB, HIV, hepatitis, DM, and malignancy, but in this study several factors have been excluded, including: pulmonary infections other than TB (through thoracic photo examination), hepatitis B and hepatitis C (through HBsAg and anti-HCV examination), HIV infection (through anti-HIV examination), UTI (through routine urine examination), DM (through fasting and 2 hours of postprandial blood sugar), and malignancy (history and physical examination). All possible inflammation and infections that might raise the IP-10 level and affect the measurement outcome were ruled out. To confirm that the urinary IP-10 response was from TB infection, a serum creatinine test was performed at diagnosis as abnormal serum creatinine levels can indicate kidney disease. This served to ensure that the urinary IP-10 levels detected in this study were not influenced by kidney disease.

The majority of participants in this study who fulfilled the inclusion and exclusion criteria had DR-TB. However, there was

no statistically significant difference in IP-10 levels between DR-TB and DS-TB patients. This is in accordance with research by García-Basteiro et al. which states that there is no difference in IP-10 levels between DR-TB and DS-TB.[39]

Blood IP-10 levels may affect urine IP-10 detection. IP-10 is a small molecular weight protein (8.6 kDa), so when passing through the glomerulus, IP-10 will undergo a filtration process and reabsorb easily in the renal tubules.[13] In this study, there was an increase in baseline (at diagnosis) urine IP-10 levels in active pulmonary TB patients compared to healthy controls (median: 18.3 pg/mL vs. 8.0 pg/mL, p<0.001). This is consistent with the studies by Kim et al. and Petrone et al.[2,13] We found that individuals with urine IP-10 >8.3 pg/mL had a 61.39 times higher chance of developing active TB.

After the patient received OAT treatment, the urinary IP-10 level decreased in the intensive phase and continued to decrease until after treatment, reflecting a decrease in the patient's bacteriological load, and activated T cells that decrease due to treatment.[13] This is consistent with the study by García-Basteiro et al. but different from the study by Kim et al., where urine IP-10 levels in the intensive phase increased compared to urine IP-10 levels at diagnosis.[2,13]

Higher IP-10 levels at baseline and a significant decrease during treatment suggest that urine IP-10 are markers that are responsive to TB therapy, although urine IP-10 levels did not show a significant difference between the culture-positive and negative groups and AFB smear-positive and negative goups at any stage of treatment (Table IX and Table X).

The limitation of this study is that there is no comparison of urine IP-10 levels after the intensive phase of treatment with AFB smear and MODS culture results, so whether the decrease in IP-10 levels after intensive phase illustrates laboratory improvements (bacteriological load and inflammation status). To evaluate inflammatory changes in response to tuberculosis treatment, CRP levels should be measured and their associations with IP-10 levels examined.

In conclusion, urine IP-10 levels might be utilized as a predictive factor because they are simpler to obtain and examine than sputum or blood samples. According to our findings, an early decline in urine IP-10 levels could be a biomarker for the effectiveness of anti-TB medications. For this reason, urine IP-10 detection could be a helpful monitoring technique to assess if TB patients are benefiting from anti-TB medication therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HS, IP, BA, CR designed the study. HS, IP, BA, CR confirm the auntheticity of all the raw data. HS, IP, BA, and CR recruited study participants. HS, IP, BA, and CR conducted experiments and collect study data. HS, IP, BA, CR and JNM analyzed the study data. HS, IP, BA, CR and JNM wrote the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by The Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (approval no. 077/UN6.KEP/EC/2021; Bandung, Indonesia) and conducted in accordance with the Declaration of Helsinki. Written info

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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