

Article

Dynamic Biochemical Phenotypes in Hospitalized Patients with Pulmonary Tuberculosis

Juan C. Polo ¹, Jesus M. Angulo-Mercado ¹ , Sandra M. Coronado-Ríos ¹ , Fernando de la Vega ², Edwin D. Correa ³ and Nelson E. Arenas ^{2,*} 

¹ Faculty of Medicine, Universidad de Cartagena, Cartagena 130014, Colombia; jpolod@unicartagena.edu.co (J.C.P.); jangulom@unicartagena.edu.co (J.M.A.-M.); scoronador@unicartagena.edu.co (S.M.C.-R.)

² Department of Infectious Diseases, E.S.E. (Public Institution) Caribbean University Hospital, Cartagena 130014, Colombia; fdelavegar@unicartagena.edu.co

³ Faculty of Agricultural Sciences, Universidad de Cundinamarca, Fusagasugá 252211, Colombia; edcorrea@ucundinamarca.edu.co

* Correspondence: narenas@unicartagena.edu.co

Abstract

Pulmonary tuberculosis (TB) produces systemic alterations that can be reflected in biochemical parameters beyond microbiological resolution. Early characterization of the biochemical response to treatment could provide additional criteria for following up with hospitalized patients. A retrospective observational study was conducted focusing on patients with pulmonary TB from a tertiary care hospital, based on biochemical parameters upon admission (“before”) and between 2 and 10 days after starting anti-tuberculosis treatment (“after”). The patients were grouped into three clusters according to the results of the clinical tests: mild (70.1%), inflammatory (26.7%), and severe (3.2%). After the start of treatment, 30% of the patients migrated toward the most biochemically compromised phenotype (Cluster 3). Sixty-one percent showed deterioration in at least one of the three key parameters; only 12.8% improved simultaneously. Significant associations were identified between unfavorable biochemical evolution and HIV ($p = 0.004$) or patients with public health coverage ($p = 0.01$). Overall, after antituberculous therapy, a reduction in CRP and leukocytes was observed ($p < 0.001$), and progressive anemia (ΔHb : -1.7 g/dL) and renal deterioration (ΔCr : $+0.52$ mg/dL) were identified. The identification of dynamic phenotypes in patients with pulmonary TB can be used to establish early risk markers and contribute to individualized clinical surveillance.

Keywords: pulmonary tuberculosis; clinical outcome; prognosis; biochemical parameter; hepatotoxicity; antituberculous treatment



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1. Introduction

Pulmonary tuberculosis (TB) is indeed the main form responsible for the spread of *Mycobacterium tuberculosis* in community settings. Consistently, TB remains a major global health problem despite the availability of effective antibiotic therapy, and its clinical management in hospitalized patients requires an integrated understanding of the host’s biochemical and immune environment. Within the framework of the Sustainable Development Goals, the World Health Organization (WHO) has set a goal to eliminate the TB epidemic by 2030, aiming for an 80% reduction in incidence and a 90% reduction in mortality compared to 2015 rates [1]. However, progress toward these goals has been hindered by factors such

as the COVID-19 pandemic, migration, and health system crises, resulting in a decline in global indicators [2,3]. In Colombia, approximately 20,832 new cases of TB have been reported, representing an approximate incidence of 50 cases per 100,000 inhabitants in 2024 [4]. Although TB must be diagnosed at the first level of care, a significant proportion of patients are diagnosed late at a higher level of complexity, especially patients with extrapulmonary TB and nonspecific presentations or patients who do not receive health services promptly [5–7].

In hospitalized patients with pulmonary TB, infection not only compromises the general clinical state but also induces detectable systemic alterations in biochemical and hematological parameters. These include erythrocyte count, hemoglobin concentration, C-reactive protein (CRP) and serum creatinine, as well as electrolytes and total serum proteins [8,9]. Thus, early identification of favorable biochemical shifts could potentially help in tailoring therapy and predicting outcomes.

Anemia, in particular, constitutes one of the most frequent alterations: for example, the prevalence of microcytic anemia (mean corpuscular volume, MCV < 80 fL) in pulmonary TB ranges between 32% and 93% and is associated with a higher risk of mortality and slower clinical recovery [10]. This adverse hematological state usually reflects the combination of chronic inflammation, malnutrition, and the effects of tubercle bacillus on bone marrow and iron metabolism [11]. In addition, other biochemical alterations, such as hypoalbuminemia, hyponatremia, or elevated transaminases, can be indirect markers of the severity of the disease and predictors of unfavorable outcomes [12].

Prior to the initiation of antituberculosis therapy, hospitalized TB patients exhibit a biochemical signature characteristic of an active acute-phase response. Studies have consistently demonstrated that at the time of diagnosis, markers such as CRP and ESR are markedly elevated. Similarly, before treatment, biochemical analyses in TB patients frequently reveal disturbances in liver function tests. Increased levels of liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) indicate a degree of hepatic involvement, either from the infection itself or from the systemic inflammatory response [11]. Concurrently, lipid profiles are often disrupted; for example, patients may exhibit decreased high-density lipoprotein (HDL) levels and altered triglyceride concentrations, which are thought to be secondary to the inflammatory state and malnutrition [9].

Similarly, antituberculous therapy, although highly effective at controlling and eliminating infection in most cases, can also induce transient or persistent changes in the biochemical and hematological profile, both because of its potential toxicity, including hepatotoxicity, nephrotoxicity, and electrolyte alterations due to the modulation of the systemic inflammatory response that results in bacterial death, and the release of antigens [13–15]. Changes such as a decrease in hemoglobin levels, an increase in creatinine levels or the persistence of elevated CRP levels during the first days of treatment may indicate a vulnerable biological profile with a greater risk of complications [16,17].

Although the evaluation of the therapeutic response in pulmonary TB has historically focused on microbiological and clinical indicators measured at 2–8 weeks, recent evidence suggests that certain immunoinflammatory biomarkers, such as IP-10, IL-6 and CRP, may undergo changes detectable from the first days after starting therapy, while biochemical alterations such as hyponatremia or hypoalbuminemia have been associated with early mortality in hospitalized patients [12,18]. Despite extensive research on drug-induced hepatotoxicity and renal impairment associated with first-line antituberculosis therapy, few studies have systematically characterized the early biochemical response within the first 0–7 days of treatment in hospitalized patients. Most available data describe alterations in liver enzymes, bilirubin, and renal markers after prolonged exposure, typically beyond the

second week, leaving a critical gap in understanding the initial metabolic and homeostatic adaptations triggered by the RIPE (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol) regimen [19,20]. This early phase is biologically relevant, as transient fluctuations in hepatic and renal function, electrolyte balance, or hematologic parameters may precede overt toxicity or predict treatment intolerance.

Based on previous clinical findings, this study aims to characterize the early dynamic biochemical and hematological profiles in hospitalized patients with pulmonary TB during the first seven days of treatment as a complementary tool to identify individuals at risk of biochemical worsening beyond clinical and microbiological or molecular tests.

2. Materials and Methods

2.1. Population and Variables

A retrospective observational and analytical study was conducted on hospitalized patients with pulmonary TB at Hospital Universitario del Caribe (HUC), a tertiary care facility, between 2023 and 2024. The study included patients who had complete clinical examinations upon admission (referred to as “Before”) and again between 2 and 10 days after starting treatment (referred to as “After”). Patients were excluded if they had extra-pulmonary TB, incomplete data, untreated bacterial coinfections, or if they did not have follow-up clinical evaluations.

Sociodemographic characteristics, clinical (comorbidities such as HIV or cancer) and clinical variables were collected and classified as follows: hematological (hemoglobin, hematocrit, MCV, HCM, leukocytes, and platelets), kidney (creatinine and blood urea nitrogen-BUN), liver (ALT, AST, total bilirubin, direct and indirect) and inflammatory (C-reactive protein). All tests were conducted in a clinical laboratory level III, which supports diagnostic services at HUC.

2.2. Definition of Biochemical Deterioration

Clinically relevant deterioration was defined as a decrease in hemoglobin ≥ 1 g/dL, an increase in CRP ≥ 2 mg/L or an increase in creatinine ≥ 0.3 mg/dL. Sixty-one percent of the patients presented worsening trends in at least one of these three parameters, and 19.8% did so in two or more simultaneously. In contrast, only 12.8% of the patients showed joint improvement in the three markers.

2.3. Statistical Analysis

Statistical analyses were conducted using R software (version 4.2.2). Mixed clinical and laboratory data were analyzed using Factorial Analysis of Mixed Data (FAMD), implemented in the FactoMineR package version 2.12. Quantitative variables comprised hematological, biochemical, and inflammatory parameters, while qualitative variables included demographic and clinical characteristics (e.g., sex, HIV status, comorbidities, and health insurance regime). Consistent with FAMD requirements, quantitative variables were maintained on their original scale, whereas qualitative variables were treated as factors.

The FAMD model retained three principal dimensions (ncp = 3, graph = FALSE), accounting for 13.6% of the total variance (Dim 1: 6.38%; Dim 2: 4.10%; Dim 3: 3.17%). The individual coordinates derived from these dimensions served as input for subsequent clustering analyses.

Ascending Hierarchical Clustering (AHC) was performed on the Euclidean distance matrix of the FAMD coordinates using Ward’s minimum variance method (Ward.D2). The optimal number of clusters was determined through visual inspection of the dendrogram and assessment of cluster interpretability, yielding a three-cluster solution. Cluster membership was assigned using tree cutting ($k = 3$).

To visualize the data structure, Uniform Manifold Approximation and Projection (UMAP) was applied to standardized laboratory variables (z-scores) [21]. Prior to UMAP embedding, data preprocessing included robust numeric parsing, median imputation for missing values, and the exclusion of zero-variance variables. The UMAP embedding was generated using the umap package with a Euclidean distance metric (metric = “Euclidean”), a minimum distance of 0.20 (min_dist = 0.20), and a neighborhood size of $n_neighbors = \min(15, n - 1)$, where n denotes the number of patients. To ensure reproducibility, a fixed random seed (set.seed = 123) was employed. Identical preprocessing steps and parameters were applied to both baseline (“Before”) and post-treatment (“After”) datasets.

The paired Wilcoxon test was used to evaluate changes “Before” and “After” treatment, defining clinically relevant deterioration as a decrease in hemoglobin concentration ≥ 1 g/dL, an increase in CRP concentration ≥ 2 mg/L, or an increase in creatinine concentration ≥ 0.3 mg/dL. The redistribution between clusters was classified as stable, improved or worse. Comparisons between groups were made with ANOVA, the Kruskal–Wallis test or the chi-square test, with $p < 0.05$ indicating statistical significance.

2.4. Bioethical Aspects

The Bioethics Committee for clinical research at HUC approved this study. The HUC authorized access to the medical records of the included patients, guaranteeing the confidentiality of the information at all times. The patient data were anonymized (prior to data analysis) and used exclusively for research purposes. This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and current Colombian regulations governing research in human health.

3. Results

3.1. Study Population

The clinical records of 382 patients were reviewed, and those whose clinical data were incomplete were discarded; 187 hospitalized patients with a confirmed diagnosis of pulmonary TB were included (average age 42 years old), each with full availability of clinical examinations in the pre-treatment stage (“Before”) and between 2 and 10 days after the start of antituberculous therapy (“After”) (Figure 1).

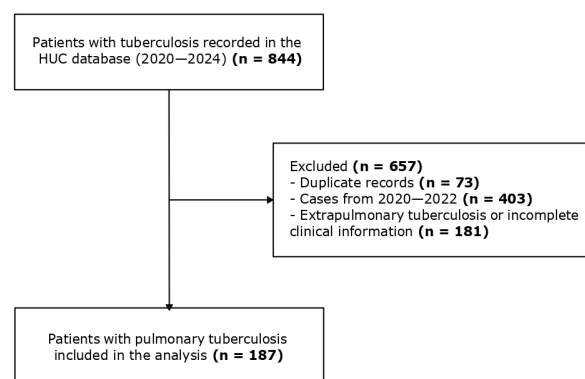


Figure 1. Flowchart of TB patient sampling.

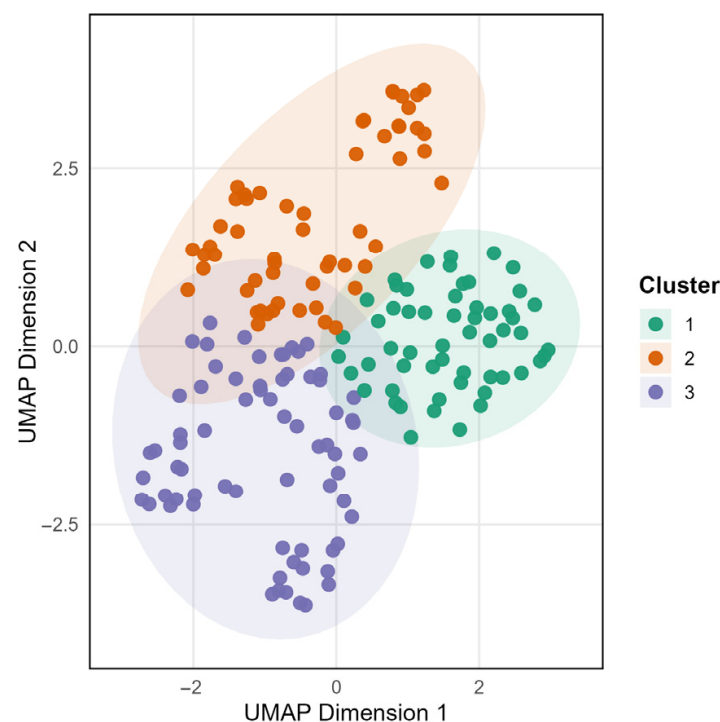
A total of 187 patients hospitalized for pulmonary TB were analyzed, and clinical examinations were performed at two time points: at hospital admission (“Before”) and after the start of antituberculous treatment (“After”). The variables included hematological, inflammatory, liver and kidney parameters (Table 1). Symptomatic variables were not evaluated.

Table 1. Biochemical parameters evaluated in TB patients ($n = 187$).

Parameters	Media Before	Media After	Change	p	Interpretation
Hemoglobin (g/dL)	10.69	8.11	−1.7	<0.001	Progressive anemia
Hematocrit (%)	32.8	23.2	−9.6	<0.001	Progressive anemia
Leukocytes ($\times 10^9$ /L)	11.6	8.5	−3.1	<0.001	Inflammatory reduction
CRP (mg/L)	9.9	6.6	−2.4	<0.001	Inflammatory improvement
Creatinine (mg/dL)	1.03	1.82	+0.52	<0.001	Renal impairment
BUN (mg/dL)	12.97	11.38	−1.14	0.003	Mild kidney improvement

3.2. Baseline Classification and Grouping (Before)

Three distinct clinical–biological phenotypes were identified at the time of hospital admission using FAMD analysis, UMAP algorithm, and ascending hierarchical grouping (Figure 2).

**Figure 2.** UMAP analysis for TB patients clustering based on the similarity of biochemical parameters.

Cluster 1 ($n = 131$; 70.1%) showed a mild clinical profile with more conserved hemoglobin (mean: 11.7 g/dL), hematocrit (36.8%), and CRP (6.2 mg/L) values.

Cluster 2 ($n = 50$; 26.7%) showed a marked inflammatory response, with a mean CRP concentration of 14.1 mg/L, mild anemia (hemoglobin concentration of 10.5 g/dL), and a high percentage of patients subsidized under the health system (58%).

Cluster 3 ($n = 6$; 3.2%) showed a severe clinical profile, including renal impairment (creatinine concentration: 1.9 mg/dL), elevated CRP (22.8 mg/L), and significant anemia (hemoglobin concentration: 7.4 g/dL). Comorbidities, particularly HIV and active cancer, were prevalent in this group.

Statistical analysis revealed significant differences between clusters in hemoglobin, hematocrit, CRP, creatinine and bilirubin levels ($p < 0.001$ in all cases).

The chi-square test revealed a significant association between membership in clusters and affiliation with a government health regime ($p = 0.0027$) and HIV positivity ($p = 0.027$).

3.3. Post-Treatment Grouping (After)

After the initiation of antituberculosis treatment and biochemical reassessment, three clusters were again identified by the same statistical procedure (FAMD + hierarchical grouping), revealing relevant changes in the distribution of TB patients ($\chi^2 = 89.4$; $p < 0.001$).

Cluster 1 ($n = 92$; 49.2%) included TB patients with stable values or partial improvement in hematological, inflammatory and renal parameters, and cluster 2 ($n = 39$; 20.9%) included patients with persistent inflammation accompanied by mild anemia.

The clinical profile of Cluster 3 ($n = 56$; 29.9%) was impaired, showing signs of progressive renal impairment, including marked anemia (mean Hb concentration: 8.1 g/dL), elevated CRP (13.9 mg/L), and elevated creatinine (1.82 mg/dL). This distribution showed that a substantial number of patients moved toward more compromised profiles, even though a sizable portion of patients remained in favorable biochemical states.

Overall, clusters 1 and 2 were slightly different compared with cluster 3 (Figure 3).

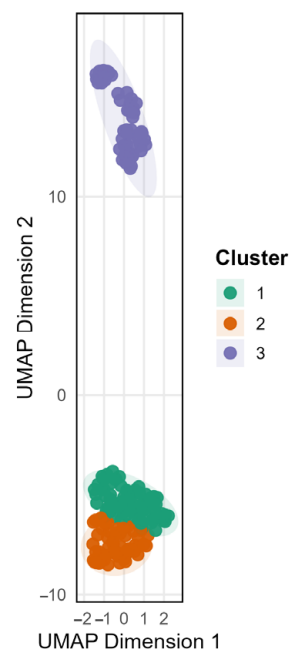


Figure 3. Comparison between clusters for TB patients based on the UMAP algorithm.

3.4. Individual Changes in Biochemical Parameters

Paired comparisons between the “Before” and “After” stages using the Wilcoxon test revealed significant changes in several markers. No statistically significant changes were observed in bilirubin or transaminases ($p > 0.1$), although a slight increase in these values was recorded in patients belonging to Cluster 3.

These results show a general trend toward a decrease in hemoglobin and, in a significant subgroup, toward a decrease in creatinine clearance, despite an overall improvement in inflammation markers (reductions in leukocytes and CRP).

3.5. Migration Between Groups

Analysis of the redistribution of patients between the two stages revealed that approximately half of the cohort experienced biochemical worsening. In total, 92 patients (49.2%) remained in the same classification group or migrated to clusters with a more favorable biochemical profile, while 95 patients (50.8%) experienced deterioration, either because of migration to a cluster of greater commitment or because of deterioration in at least one of the parameters considered critical (Figure 4).

For this analysis, clinically relevant biochemical worsening was defined as a decrease in hemoglobin concentration ≥ 1 g/dL, an increase in CRP concentration ≥ 2 mg/L, or an increase in creatinine concentration ≥ 0.3 mg/dL. Under these criteria, 114 patients (61%) met at least one of these conditions, 37 patients (19.8%) presented simultaneous deterioration in two or more parameters, and only 24 patients (12.8%) achieved a parallel improvement in hemoglobin, CRP, and creatinine levels.

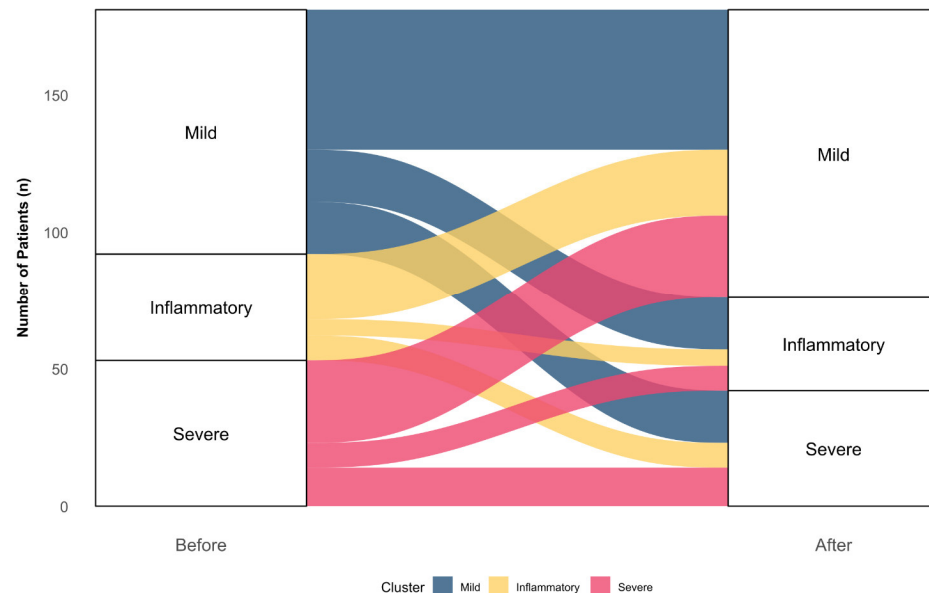


Figure 4. Migration of pulmonary TB patients among clusters of biochemical parameters from hospitalized individuals.

4. Discussion

Pulmonary TB remains a major global health challenge despite the availability of effective treatment, and its clinical management in hospitalized patients demands an integrated understanding of the host's biochemical and immunological milieu [22]. Thus, the evolution of the biochemical profile in hospitalized patients with pulmonary TB during the first days of antituberculous treatment reflects the intersection between host immunity, pathogen elimination and the pharmacological effects of treatment. Initially, biochemical alterations, such as alterations in CRP levels, erythrocyte sedimentation rate (ESR), and proinflammatory cytokines; alterations in iron metabolism that cause anemia; and metabolic alterations are characteristic of an acute phase response triggered by *M. tuberculosis* infection [23,24].

The rapid decrease in CRP after the start of the antituberculosis treatment probably reflects the reduction in bacillary load and the modulation of the systemic inflammatory response mediated by cytokines such as IL-6 and TNF- α [25–27]. Given its short half-life (~19 h) and its hepatic synthesis as an acute phase reactant [28], CRP responds quickly to the resolution of inflammatory stimuli, allowing the detection of significant changes even during the first 5–7 days of treatment [29]. In our hospital cohort, a significant decrease in CRP was observed during the first 10 days, accompanied by a mean reduction of 1.7 g/dL in hemoglobin and an increase of 0.52 mg/dL in creatinine. The magnitude and speed of the decrease in CRP are consistent with prospective studies that report reductions of 40–60% in the first or second week of treatment, associated with conversion of the smear test and early clinical improvement [30–32], supporting its usefulness as an early biomarker, especially when microbiological confirmation is delayed or difficult to obtain [33–37]. Regarding hemoglobin, the decrease observed in the initial phase reflects the anemia of inflammation typical of TB which is supported by concurrent findings of low albumin and transferrin levels, which are reflective of the broader metabolic disruptions [38,39]. This anemia is

characterized by elevated serum hepcidin levels, functional hypoferremia, suppression of erythropoiesis, and even impaired T cell response limiting hematological recovery in the short term [40–42]. Additional factors such as malnutrition, some antitubercular antibiotics (e.g., rifampicin), chronic bleeding or coinfections can accentuate this delay [43,44]. Therefore, the early decrease in hemoglobin should not be interpreted as therapeutic failure but it might be part of the expected course of anemia of inflammation.

The initial increase in creatinine may be due to prerenal mechanisms such as dehydration, hypotension or fever, previously undiagnosed kidney disease and, to a lesser extent, early effects of drugs such as pyrazinamide and rifampin [45–47]. Other possible factors include drug interactions, protein overload due to immobilization, or rhabdomyolysis [48,49]. Although these agents usually cause nephrotoxicity between 4 and 8 weeks after exposure, cases of acute kidney injury have been reported earlier [50,51]. These results highlight the importance of closely monitoring renal function from the beginning of treatment, particularly in high-risk subgroups, and ideally incorporating early biomarkers of tubular damage [52,53].

The quick drop in CRP levels supports its potential as an early response biomarker in TB patients, with reductions of more than 50–55% at 7–14 days linked to faster bacterial conversion and a better overall prognosis [54–56]. The interpretation of CRP should always be complemented by clinical and microbiological evolution, since persistent values may reflect coinfections or inflammation not related to TB [36,37]. On the other hand, the early decrease in hemoglobin reflects the pathophysiology of anemia of inflammation and should not motivate premature interventions such as changes in the scheme or unnecessary transfusions [57–59]. Initial elevations in creatinine require careful interpretation: although drug-induced nephrotoxicity tends to appear later, an early increase may indicate dehydration, hypotension, or previous kidney disease [50]. Surveillance should prioritize patients with risk factors and avoid unnecessary interventions for those who are at low risk [60]. Similarly, other clinical parameters such as ALT, AST, ALP, and GGT tend to stabilize as the inflammatory drive diminishes, although caution is warranted since antituberculosis drugs themselves can impose hepatotoxic stress and complicate the biochemical picture [27]. Likewise, alterations in lipid profiles manifested as low HDL and dysregulated triglyceride levels may begin to normalize slowly in response to the reversal of systemic inflammation, although these changes generally occur over a more extended timeline [61].

The identification of combined patterns of biochemical response such as a rapid decrease in CRP with hematological and renal stability or inflammatory persistence with deterioration of other parameters is a tool to stratify follow-up and personalize monitoring. This approach requires external validation and additional statistical analysis before its routine implementation [24,62]. Ultimately, early improvement in the biochemical profile is not only a marker of therapeutic efficacy but also an essential component of the patient's overall recovery process. As clinicians and researchers continue to refine the understanding of these early biochemical changes, there is hope that such insights will lead to the development of more precise and rapid diagnostic and prognostic tools that can be used at the bedside to guide treatment decisions for patients with pulmonary TB [23,32].

One asset of this study is the early evaluation of biochemical parameters between days 2 and 10 of treatment in a hospital cohort, providing information little explored in the literature [30,32,34]. In addition, routine laboratory tests were used, which are easily accessible in clinical practice, and a cluster analysis was performed to identify response phenotypes that are rare in TB and have the potential for patient stratification [63,64]. As this investigation was carried out in a single tertiary care hospital in Colombia, the external applicability of these findings to other settings or TB populations may be limited. Among other limitations, the wide time window (2–10 days) could mask important dynamic

variations; the single-center design and moderate sample size limit generalizability, and the study was not adjusted for relevant clinical confounders such as HIV, diabetes, chronic kidney disease, or baseline bacillary burden [65]. Corrections were not applied for multiple comparisons nor was the stability of the clusters evaluated by internal methods such as bootstrapping.

In future research, shortening the sampling window (e.g., 0–3, 4–7, and 8–10 days) and applying multivariate models that adjust for comorbidities and relevant clinical factors are recommended [66]. Furthermore, statistically validating the identified phenotypes and complementing the analysis with additional biomarkers, such as ferritin, IL-6, uric acid, and lipopolysaccharide-binding protein, could enrich the characterization of response profiles. Finally, assessing whether early changes in CRP, hemoglobin, and creatinine can predict better clinical outcomes, including mortality, time to bacteriological negativity, and relapses, would provide evidence of their prognostic value and their potential to inform therapeutic decisions for TB patients.

Author Contributions: Conceptualization, N.E.A. and S.M.C.-R.; methodology, J.C.P. and J.M.A.-M.; software, J.M.A.-M. and E.D.C.; validation, E.D.C.; formal analysis, J.C.P., J.M.A.-M. and N.E.A.; investigation, S.M.C.-R.; resources, F.d.l.V.; data curation, J.C.P. and J.M.A.-M.; writing—original draft preparation, J.C.P., J.M.A.-M. and E.D.C.; writing—review and editing, S.M.C.-R., F.d.l.V. and N.E.A.; supervision, N.E.A. and F.d.l.V.; project administration, S.M.C.-R.; funding acquisition, S.M.C.-R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the International Council of Medical Sciences (CIOMS) (protocol code: DB-FM-CERT 05; date of approval: 18 May 2025).

Informed Consent Statement: Since this study only included medical records, the Informed Consent Statement does not apply.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AHC	Ascending hierarchical clustering
BUN	Blood Urea Nitrogen
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
FAMD	Factorial Analysis of Mixed Data
HUC	Hospital Universitario del Caribe
MCV	Mean corpuscular volume
RIPE	Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol
TB	Tuberculosis
UMAP	Uniform Manifold Approximation and Projection
WHO	World Health Organization

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