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## **Association of baseline white blood cell counts with tuberculosis treatment outcome: a prospective multicentered cohort study**

Carole Chedid, Eka Kokhreidze, Nestani Tukvadze, Sayera Banu, Mohammad Khaja Mafij Uddin, Samanta Biswas, Graciela Russomando, Chyntia Carolina Díaz Acosta, Rossana Arenas, Paulo Pr. Ranaivomanana, et al.

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1 **Association of baseline white blood cell counts with tuberculosis treatment**  
2 **outcome: a prospective multicentered cohort study.**

3  
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40

41 **Abstract**

42 **Objectives.** Tuberculosis (TB) is the leading infectious cause of death in the world. **Cheaper**  
43 **and more accessible** TB treatment monitoring methods are needed. Here, **we evaluated white**  
44 **blood cell (WBC) absolute counts, lymphocyte, and monocyte proportions during TB**  
45 **treatment, and characterized their association with treatment failure.**

46 **Methods.** This multicentered prospective cohort study was based in Bangladesh, Georgia,  
47 Lebanon, Madagascar, and Paraguay. Adult, non-immunocompromised patients with culture  
48 confirmed pulmonary TB were included and followed up after 2 months of treatment and at the  
49 end of therapy. Blood counts were compared to treatment outcome using **descriptive statistics,**  
50 **logistic regression,** and Receiver Operating Characteristic (ROC) analyses.

51 **Results.** Between December 2017 and **August 2020, 198 participants were enrolled and 152**  
52 **completed treatment, including 28 (18.5%) drug-resistant patients. The rate of cure at the end**  
53 **of treatment was 90.8% (138/152). WBC absolute counts decreased and lymphocyte**  
54 **proportions increased over the course of treatment. In multivariate analyses, baseline high WBC**  
55 **counts and low lymphocyte proportions were associated with positive sputum culture results at**  
56 **the end of treatment (WBC > 11,450 cells/mm<sup>3</sup>: p=0.048; lymphocytes < 16.0%: p=0.039;**  
57 **WBC > 11,450 cells/mm<sup>3</sup> and lymphocytes < 16.0%: p=0.024).**

58 **Conclusion.** High WBC counts and low lymphocyte proportions **at baseline are significantly**  
59 **associated with risk of TB treatment failure.**

60

61 **Keywords:** tuberculosis; multi-drug resistance; treatment monitoring; white blood cells;  
62 **lymphopenia; immunomonitoring.**

63

## 64 **Introduction**

65 Tuberculosis (TB) is the leading cause of death by infectious disease in the world, responsible  
66 for 1.5 million deaths in 2018 (World Health Organization Geneva 2019a). The treatment of  
67 active pulmonary TB lasts at least 6-months and can cause heavy side effects (World Health  
68 Organization Geneva 2017, 2019b). As a consequence, treatment adherence is poor, particularly  
69 in primary care settings (Woimo et al. 2017).

70 *Mycobacterium tuberculosis* culture from sputum samples is the gold standard for TB treatment  
71 monitoring (Wallis et al. 2016). However, it is time-consuming and requires high level biosafety  
72 laboratories (Horne et al. 2010). Sputum smear microscopy is quicker for treatment monitoring,  
73 but it has limited accuracy (Ngabonziza et al. 2016). Hence, blood-based tests are a promising  
74 alternative. A variety of blood-based immunoassays, from interferon (IFN)- $\gamma$  release assays to  
75 T cell activation tests, are being evaluated for treatment monitoring (Cingolani et al. 2012; Sali  
76 et al. 2018). However, in low-resource countries, these tests need to be adapted to limited  
77 laboratory equipment (MacLean et al. 2017) and with a simple output (Goletti et al. 2018).

78 Hematological abnormalities - such as leukocytosis, neutrophilia, or lymphopenia - during  
79 pulmonary TB disease have been described in the literature since the eighties (Morris et al.  
80 1989). Low monocyte proportions have been associated with higher rates of progression  
81 towards active TB (Rakotosamimanana et al. 2015). Neutrophilia and lymphopenia have been  
82 associated with higher risks of mortality during TB treatment (Lowe et al. 2013). However,  
83 many these studies were either small case-control studies (Abay et al. 2018), focused on the  
84 risk of developing active TB disease (Kurup et al. 2016), or assessed kinetics during treatment  
85 and not association with treatment failure (Morris et al. 1989; Rakotosamimanana et al. 2015).  
86 Most available comprehensive studies were in low-burden, high-healthcare standards areas  
87 (Ritchie et al. 2016).

88 Here, we describe a prospective multicentered cohort study conducted in five low- and middle-  
89 income countries across four continents: Bangladesh, Georgia, Lebanon, Madagascar, and

90 Paraguay. Four of these countries are on the 2019 WHO high incidence TB country list ( $\geq 20$   
91 cases per 100,000 population), with the exception of Lebanon (11 cases per 100,000 population)  
92 (World Health Organization Geneva 2019a). The target population was adult, HIV-uninfected,  
93 drug-susceptible (DS-TB) and drug-resistant (DR-TB) pulmonary TB patients.

94 The primary objective of this study was to monitor the evolution of simple hematological  
95 parameters during pulmonary TB treatment in higher TB incidence settings: absolute WBC  
96 counts, lymphocyte, and monocyte proportions. These markers of inflammation were chosen  
97 because they are routinely monitored in primary care settings. The focus was kept on cellular  
98 parameters.

99 A secondary objective was to characterize their association with treatment failure, defined by  
100 sputum culture positivity (the gold standard) at the end of treatment, in relation with clinical  
101 and sociodemographic factors.

102

## 103 **Materials and methods**

### 104 **Study design and sample population**

#### 105 *Study design*

106 This *descriptive* study was nested within a multicentered prospective cohort study *evaluating*  
107 *the prognostic value of blood-based immunological markers for TB treatment monitoring,*  
108 based in five partner institutions from the Mérieux Foundation GABRIEL network (Komurian-  
109 Pradel et al. 2013). with the approval of national TB programs: the international center for  
110 diarrheal diseases and research, Bangladesh (icddr,b) in Dhaka, Bangladesh; the National  
111 Center for Tuberculosis and Lung Diseases (NTCLD) in Tbilisi, Georgia; the *Laboratoire*  
112 *Microbiologie, Santé et Environnement (LMSE, Université Libanaise)*, in Tripoli, Lebanon; the  
113 *Institut Pasteur de Madagascar* in Antananarivo, Madagascar; and the *Instituto de*  
114 *Investigaciones en Ciencias de la Salud (Universidad Nacional de Asunción; IICS-UNA)* in  
115 Asunción, Paraguay.

116 ***Ethical considerations***

117 This study was conducted with the approval of the ethical boards of: in Bangladesh, the  
118 Research Review Committee and the Ethical Review Committee of icddr,b; in Georgia, the  
119 Institutional Review Board of the NTCLD (IORG0009467); in Lebanon, the institutional  
120 review board of NINI hospital (IRB-F-01); in Madagascar, the Ministry of Public Health and  
121 the Ethical Committee for Biomedical Research (reference number: n°099 –  
122 MSANP/CERBM); in Paraguay, the Research Ethics Committee and the Scientific Committee  
123 of the IICS-UNA (IRB number: IRB00011984; Federalwide Assurance number:  
124 FWA00029097). All recruited patients provided written informed consent.

125 ***Cohort recruitment, TB diagnosis and patient follow-up***

126 We calculated that a sample size of 156 was required to reach a level of significance of 95%  
127 and a power of 80%, assuming an average rate of treatment failure of 10% (World Health  
128 Organization Geneva 2019a), a baseline prevalence of lymphopenia (<15% of total WBC) of  
129 30%, and that treatment failure was three times more likely in patients with lymphopenia (Lowe  
130 et al. 2013). We aimed to include 200 participants to account for lower prevalence values, rates  
131 of failure, or missing data.

132 Patients were recruited if diagnosed with microbiologically confirmed pulmonary TB (positive  
133 culture and/or sputum smear and/or GeneXpert; see “Microbiological diagnosis” section for  
134 further detail). Patients with HIV or diabetes mellitus (defined by HBA1C levels > 6.5%; Cobas  
135 (Roche) automated analyzer) and children under 15 years were excluded. In downstream  
136 analyses, patients under immunocompromising treatment (corticosteroids, calcineurin  
137 inhibitors, biologics, or other chemotherapeutic agents), patients with negative cultures at  
138 inclusion, and patients who were lost-to-follow-up were excluded.

139 Patients were followed up: at inclusion (T0), after two months of treatment (T1), at the end of  
140 therapy (T2; 6 months for drug-susceptible (DS-TB) patients, 9 to 24 months for drug-resistant  
141 (DR-TB) patients), and two months after the end of therapy when possible (T3). All patients

142 were on Directly Observed Treatment, Short Course (DOTS) and received treatment according  
143 to standard protocols (Aung K.J.M. et al. 2014; World Health Organization Geneva 2017,  
144 2019b). Detail of therapeutic regimens can be found in Supp. Table 1.

145

#### 146 **Microbiological diagnosis and definition of treatment outcome**

147 At each visit, at least one sputum sample per patient was collected for culture (solid and/or  
148 liquid media) and smear microscopy (Ziehl-Neelsen and/or Auramine O staining). Molecular  
149 amplification of *M. tuberculosis* DNA was conducted at inclusion (GeneXpert MTB/RIF,  
150 Cepheid, Sunnyvale, CA). Drug susceptibility testing (DST) and diagnosis of multi-drug  
151 resistance were performed according to standard protocols (World Health Organization Geneva  
152 2019b). Microbiological methods and DST protocols are detailed in Supp. Table 2.

153 Treatment outcomes were defined as follows: failed (positive sputum culture at T2); cured  
154 (negative sputum culture at T2 and no evidence of positive culture at T3); relapse or reinfection  
155 (culture conversion at T2 but positive culture recorded at T3); completed (patient not lost to  
156 follow up, but no available culture data at T2 or T3) (World Health Organization (WHO) 2013).

157

#### 158 **On-site whole blood collection and cell count**

159 At each visit, 10 mL of whole blood were drawn, 1 mL of which was collected in EDTA tubes  
160 used for the present study. Complete blood counts were performed on automated analyzers  
161 (details of manufacturing references per study site are in Supp. Table 2).

162

#### 163 **Clinical data collection and standardization**

164 Data collection forms were created with clinicians from partner sites and standardized to ensure  
165 dataset homogeneity. Follow-up sheets were used to track sample handling and time flow from  
166 collection in health centers to receipt in laboratories. All forms were translated into the local

167 official language upon request from staff. Data were entered into the cloud-based database  
168 system CASTOR (CASTOR Electronic Data Capture, Version 1.4, Netherlands).

169

### 170 **Descriptive statistical analysis**

171 Data were cleaned and analyzed in R (version 3.6.2). As sample size was small, discrete  
172 variables were analyzed using Fisher's Exact test with Bonferroni's post-hoc test (Kim 2017).  
173 Normality was assessed using the Shapiro-Wilk Normality Test (test statistics available in  
174 Supp. Table 3). Normal, continuous variables were analyzed with Student's t-test. Non-normal,  
175 continuous variables were analyzed with the Mann-Whitney test, or the Kruskal-Wallis rank  
176 sum test with Dunn's Kruskal-Wallis Multiple Comparisons post-hoc test (Dunn 1964).  
177 Repeated measures of non-independent continuous variables were analyzed using the Friedman  
178 rank sum test, with Wilcoxon-Nemenyi-McDonald-Thompson's post-hoc (Paro Pedro et al.  
179 2015).

180

### 181 **Logistic regression and Receiver Operating Characteristic (ROC) analyses**

182 For these analyses, the assessed outcome was a recorded positive *M. tuberculosis* culture result  
183 at T2. Patients with unavailable culture data at T2 and patients with relapse were excluded from  
184 the analyses. The evaluated variables were leukocyte counts, lymphocyte proportions, and  
185 monocyte proportions at T0 or T1. If missing data exceeded 10% of the sample size, the variable  
186 was not considered. Otherwise, missing data were replaced by the most frequent group  
187 (categorical variables) or the mean (continuous variables). Highly skewed, non-normal  
188 continuous variables were log-transformed prior to analyses. Variables were first evaluated in  
189 univariate logistic regression analyses, then multivariate analyses were performed. Adjustment  
190 variables were selected as follows: sociodemographic variables of known clinical importance  
191 (e.g. sex, country of origin), TB risk factors (e.g. smoking), and additional sociodemographic  
192 variables that were at least moderately associated ( $p < 0.10$ ) with the outcome in univariate

193 analyses (*e.g.* prison). Irrelevant adjustment variables were then removed by backward model  
194 selection. The combination of variables that minimized the Akaike Information Criterion (AIC)  
195 for most tested predictors, while including important adjustment variables, was selected (age,  
196 sex, smoking habit, drug sensitivity, country of origin). For lymphocyte proportions, odds ratios  
197 (OR) were calculated for each increase of 5.0% because the total range of measured values was  
198 5.0–70.0%. Similarly, for absolute WBC counts, OR were calculated for each increase of 1000  
199 cells per mm<sup>3</sup>.

200 For both ROC analyses and logistic regression, since the sample size was small, model  
201 performance metrics (respectively the Area Under the Curve (AUC) and the C-statistic) were  
202 corrected for optimism using bootstrap to assess model validity as described elsewhere (Smith  
203 et al. 2014).

204

## 205 **Results**

### 206 **Demographic and clinical characteristics of the cohort.**

207 Between December 2017 and February 2020, 198 eligible patients with culture confirmed  
208 active pulmonary TB were recruited in Dhaka (Bangladesh), Tbilisi (Georgia), Tripoli and  
209 Akkar (Lebanon), Antananarivo (Madagascar), and Asunción (Paraguay). As of July 2020, 152  
210 of them were followed at least until the end of treatment and had available blood count data  
211 (Figure 1). As the T3 timepoint was later than the local TB program visits, the dropout rate was  
212 highest between T2 and T3 (26%).

213 Among patients followed until T2 at least, 18.4% (28/152) were diagnosed with DR-TB. The  
214 sociodemographic and clinical characteristics of DS-TB and DR-TB patients were comparable  
215 at inclusion (Table 1). The characteristics of patients at inclusion were compared between study  
216 sites (Supp. Table 4.). There was no significant difference in baseline absolute WBC counts  
217 and lymphocyte proportions between cohorts, but several other parameters differed. Monocyte  
218 counts were significantly higher in the Lebanon and Madagascar cohorts than in the other sites.

219 Patients in Bangladesh were younger than those recruited in Georgia and Paraguay. The body  
220 mass index (BMI) at inclusion of patients from Bangladesh and Madagascar was significantly  
221 lower than in the other study sites. Finally, BCG vaccination rates were significantly lower in  
222 the Georgia and Lebanon cohorts.

223

#### 224 **Microbiological characterization of treatment response over time and assessment of** 225 **treatment outcome.**

226 All enrolled patients were positive for sputum culture at inclusion. Most patients were also  
227 positive for sputum smear microscopy (78.2%, 119/152) and/or GeneXpert (98.6%, 150/152).  
228 Culture positivity rates decreased significantly upon treatment (Table 2). No significant  
229 difference was detected between DR-TB and DS-TB patients (data not shown). At the end of  
230 treatment, 90.8% (138/152) of patients were cured, and eight had unavailable culture data and  
231 were classified as having completed treatment with no evidence of cure (5.3%, 8/152). One  
232 patient (0.7%, 1/152) was culture negative at T2 but had a positive culture result at T3, which  
233 was classified as relapse or reinfection. Treatment failure was observed in five DS-TB patients  
234 (3.3%, 5/152; Supp. Table 5 for demographic and microbiological characteristics).  
235 Interestingly, 80% (4/5) of treatment failure patients had high sputum smear microscopy grades  
236 at baseline (2+ or 3+). At T1, two of them were culture positive and one was microscopy  
237 positive.

238

#### 239 **Absolute WBC counts and lymphocyte proportions vary significantly over the course of** 240 **therapy.**

241 In all cohorts (n=152), we observed a significant decrease in median absolute WBC counts  
242 during treatment (Figure 2.A.), and a significant increase in median lymphocyte proportions  
243 (Figure 2.B.). Monocyte proportions were heterogeneous between study sites and increased  
244 significantly only in the Bangladesh and Georgia cohorts (Figure 2.C.). At all timepoints, they

245 were significantly higher in the Lebanon and Madagascar cohorts. Neutrophil responses were  
246 assessed in a subset of the cohort (n = 129) and also decreased significantly during treatment  
247 (Supp. Figure 1).

248

249 **Early absolute WBC counts and lymphocyte proportions were significantly different**  
250 **between successfully and unsuccessfully treated TB patients.**

251 Absolute WBC counts, lymphocyte and monocyte proportions were then compared between  
252 successfully and unsuccessfully treated patients with available culture data at T2 (n = 143;  
253 Figure 3). At baseline and after 2 months, unsuccessfully treated patients had significantly  
254 higher absolute WBC counts (Figure 3.A.) and significantly lower lymphocyte proportions than  
255 successfully treated patients (Figure 3.B.). No significant difference was observed for monocyte  
256 proportions (Figure 3.C.).

257 As the majority of treatment failure patients had high AFB at baseline (2+ or 3+), we compared  
258 WBC absolute counts and lymphocyte proportions according to AFB results. in a subset of all  
259 patients presenting with high AFB at baseline (51.7%, 74/143). In this subset, median WBC  
260 and lymphocyte counts were similar at baseline, but at T1, WBC counts were higher and  
261 lymphocyte proportions were lower in unsuccessfully than in successfully treated patients  
262 (Supplementary Figure 2).

263

264 **Low baseline lymphocyte proportions are significantly associated with a positive sputum**  
265 **culture at the end of treatment**

266 Sociodemographic characteristics and blood counts at T0 and T1 were compared between cured  
267 (n = 138) and failed (n = 5) patients, and logistic regression was performed (Table 3). In  
268 univariate analyses, significant associations with treatment failure were detected for  
269 lymphocyte proportions at baseline (OR 0.32, 95% CI 0.10-0.80, p = 0.032) and at 2 months  
270 (OR 0.32, 95% CI 0.11-0.68, p = 0.0091). No significant association was detected for absolute

271 WBC counts or monocytes proportions at T0 and T1. In multivariate analyses, low lymphocyte  
272 proportions at T0 remained moderately associated with treatment failure (adjusted OR 0.090,  
273 95% CI 0.0040-0.52,  $p = 0.042$ ).

274 ROC analyses were then performed to identify a threshold discriminating successfully and  
275 unsuccessfully treated patients based on baseline WBC counts and lymphocyte proportions  
276 diction (Supp. Table 6). Baseline WBC counts predicted treatment outcome performed with an  
277 AUC of 0.788 (95% CI: 0.664-0.912; optimal cutoff  $>11,435$  cells/mm<sup>3</sup>). Baseline lymphocyte  
278 proportions performed with an AUC of 0.807 (95% CI: 0.671-0.943; optimal cutoff  $<16\%$  of  
279 total WBC). The AUC of both variables combined into a new parameter performed better (AUC  
280 0.841 95% CI 0.722-0.959).

281 Data was then stratified according to the ROC obtained cutoffs. Significant associations were  
282 observed in univariate analyses for patients absolute WBC  $> 11,450$  cells/mm<sup>3</sup> (OR 8.45, 95%  
283 CI 1.21 – 168,  $p = 0.031$ ), and for patients with both WBC  $> 11,450$  cells/mm<sup>3</sup> and lymphocytes  
284  $< 16.0\%$  at baseline (OR 877, 95% CI 1.37 – 69.8,  $p = 0.019$ ), but not for lymphocytes  $< 16.0\%$   
285 alone ( $p = 0.061$ ). These variables remained moderately associated in multivariate analyses  
286 (WBC  $> 11,450$  cells/mm<sup>3</sup>:  $p = 0.048$ ; lymphocytes  $< 16.0\%$ :  $p = 0.039$ ; WBC  $> 11,450$   
287 cells/mm<sup>3</sup> and lymphocytes  $< 16.0\%$ :  $p = 0.024$ ).

288

## 289 **Discussion**

290 In this multicentered prospective study, we monitored the evolution of absolute WBC counts,  
291 lymphocyte and monocyte proportions during pulmonary TB treatment, and described their  
292 association with treatment failure in five cohorts (Bangladesh, Georgia, Lebanon, Madagascar,  
293 and Paraguay), four of which were in high-incidence TB countries. We included 152 HIV-  
294 negative, culture confirmed pulmonary TB patients, including 28 drug-resistant TB cases.

295 We showed that during treatment, the lymphocyte proportions increased significantly, whereas  
296 the absolute WBC counts decreased significantly. These trends are indicative of general clinical

297 improvement in response to treatment, and are consistent with characteristics of successful  
298 therapy. WBC counts are usually higher in TB patients than in healthy individuals, with distinct  
299 lymphocyte rates before and after TB treatment (Morris et al. 1989; Rakotosamimanana et al.  
300 2015). No significant evolution of monocyte proportions during treatment was detected in our  
301 cohort, which is consistent with previous works (Rakotosamimanana et al. 2015).  
302 Five patients had positive culture results at the end of treatment and were classified as treatment  
303 failure. Two of them had negative smears or cultures at T1, which was likely due to poor sputum  
304 quality. The main finding is that at baseline and after two months of treatment, unsuccessfully  
305 treated patients had significantly higher WBC counts and lower lymphocyte proportions than  
306 those successfully treated. In adjusted logistic regression analyses, treatment failure was  
307 significantly associated with high WBC counts and low lymphocyte proportions at baseline.  
308 This result is important because WBC counts are usually evaluated in TB patients at baseline  
309 and along the therapy course. They are cheap, quick tests that are used routinely in health care  
310 centers worldwide. They require a small volume of blood, their output is easy to interpret, and  
311 they can be performed without automated equipment. Therefore, they may be a helpful point-  
312 of-care tool to help clinicians identify which patients might be less responsive to treatment.  
313 Larger studies on this topic are needed to assess whether early WBC or lymphocyte counts  
314 should be taken into account when considering changes to treatment composition or duration.  
315 We hypothesize that patients with high baseline WBC counts and low lymphocyte proportions  
316 had highly inflammatory clinical patterns. In the context of mycobacterial infection, WBC  
317 counts are mostly reflective of neutrophil counts as markers of persisting inflammation or  
318 failure to clear the bacteria (Srivastava et al. 2014). Sustained inflammation in chronic TB  
319 infection has been described as an impairment of the TB-specific immune response, and a  
320 marker of active disease (Sia and Rengarajan 2019). Previous studies have highlighted a  
321 correlation between elevated neutrophils, lymphopenia, and TB disease severity, based on chest  
322 X-rays (Naghavi et al. 2017; Panteleev et al. 2017). Therefore, a hypothesis is that in this cohort,

323 patients with high baseline WBC and low lymphocytes also had more severe TB manifestations  
324 and were less likely to achieve cure.

325 We observed that in the subset of our cohort with high smear microscopy grades (n=74), WBC  
326 counts and lymphocyte proportions at baseline were not associated to the treatment outcome;  
327 however, significant associations were detected at T1. This suggests that in patients who  
328 possibly had a higher bacterial burden, cellular inflammatory markers did not stratify risks of  
329 failure at baseline, but persistent cellular differences between failed and cured patients were  
330 noticeable after the intensive phase of treatment. A limitation is that TB disease severity at  
331 baseline could not be assessed in our cohort other than with microscopy (through chest X-rays,  
332 Erythrocyte Sedimentation Rate (ESR) or hemoglobin measurements). Further work is needed  
333 to assess the relevance of the association of WBC and lymphocytes with treatment failure in  
334 cohorts with better defined disease severity.

335 Moreover, a feature of TB infection is a delayed initiation of adaptive response after infection,  
336 and lymphocyte anergy during chronic infection (Urdahl et al. 2011). This could indicate that  
337 *M. tuberculosis* specific adaptive immunity might be hindered during treatment in the patients  
338 with high WBC or low lymphocyte proportions. Alternatively, as blood counts are measured in  
339 the periphery, this may suggest that *M. tuberculosis* specific lymphocytes are localized in the  
340 lungs for infection clearance: their decreased frequency in peripheral blood would indicate a  
341 persisting infection. We observed that the majority of unsuccessfully treated patients (80%, 4/5)  
342 presented either high WBC counts or low lymphocyte proportions at baseline, and 60% (3/5)  
343 with both, suggesting that the mechanisms behind a persistently activated innate immune  
344 response and an anergic adaptive immune response during anti-TB therapy might be linked.  
345 Consequently, whether systemic inflammation hinders TB treatment needs to be further  
346 investigated.

347 Our cohort included patients from developing countries, in diverse geographical areas, with  
348 varying sociodemographic backgrounds and living standards. In addition, we have enrolled

349 both DS-TB and DR-TB patients, which implies different clinical presentations of the disease.  
350 This design suggests similar trends might be occurring in heterogeneous settings and clinical  
351 contexts. However, it creates major limitations and analytical challenges as it hinders the  
352 control of some patient- and pathogen-dependent factors such as antibiotic regimens,  
353 malnutrition levels, untested infections (*e.g.* parasites), mycobacterial strains, and genetic  
354 background. Moreover, the sample size was small. To account for these limitations, adjustment  
355 with the available patient-dependent factors as well as optimism corrections with a method  
356 adapted to small sample sizes (Smith et al. 2014) was performed. However, the clinical  
357 interpretation of these results should remain cautious given the heterogeneity and size of the  
358 cohort. Another limitation was the important dropout rate, especially between T2 and T3 (26%,  
359 40/152) as T3 was not a timepoint that fell within the time frame of national TB programs. As  
360 a consequence, it is likely that occurrences of TB relapse could not be recorded in our study.  
361 In conclusion, this study confirms that WBC counts and lymphocyte proportions are simple  
362 biomarkers for TB treatment monitoring. In this cohort, early measurements of these  
363 parameters were associated with treatment failure; these results are encouraging but need to be  
364 confirmed on larger cohorts.

365

## 366 **Author contributions**

367 JH is the principal investigator, and initiated the project together with DG, NT, SBa, GR, NR,  
368 and MH. Data was collected by EK, MU, SBi, CA, PR, CR, PH, and RB. CC performed all  
369 statistical analyses and wrote the manuscript. All authors have contributed to the content and  
370 have given their final approval.

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378 **Conflicts of interest**

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382 Conflicts of Interest.

383

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480 **Tables**

481 **Table 1. Sociodemographic and clinical characteristics of drug-susceptible and drug-**  
 482 **resistant patients at inclusion.**

N	ALL 152	DS-TB 124	DR-TB 28	<i>p</i> DS-TB vs DR-TB
<b>Patient demographics</b>				
Age (years)	28 (22-37.25)	28 (22-39)	27.5 (19.75-33.25)	0.22
Sex (male)	63.2% (96/152)	64.5% (80/124)	57.1% (16/28)	0.52
Country of origin				
<i>Bangladesh</i>	25% (38/152)	16.9% (21/124)	60.7% (17/28)	>0.001
<i>Georgia</i>	21.7% (33/152)	18.5% (23/124)	35.7% (10/28)	0.072
<i>Lebanon</i>	11.8% (18/152)	14.5% (18/124)	0	0.045
<i>Madagascar</i>	23.7% (36/152)	29% (36/124)	0	>0.001
<i>Paraguay</i>	17.8% (27/152)	21% (26/124)	3.6% (1/28)	0.028
BMI at inclusion	18.8 (17.1-21.4)	18.9 (16.9-21.4)	18.8 (17.5-21.0)	0.87
<b>Sputum smear microscopy at inclusion</b>				
<i>High grade (2+ or 3+)</i>	51.1% (76/149)	50.4% (61/121)	53.6% (15/28)	0.83
<i>Low grade (1+ or scanty)</i>	18.8% (43/149)	29.8% (36/121)	25% (7/28)	0.81
<i>Negative</i>	20.1% (30/149)	19.8% (24/121)	21.4% (6/28)	0.79
WBC absolute count at inclusion (/mm <sup>3</sup> )	9590 (7468-11770)	9500 (7365-11640)	10150 (7725-11850)	0.54
Lymphocytes at inclusion (% of WBC)	18 (14-24)	18 (14-23.2)	17 (13.8-24.5)	0.65
Monocytes at inclusion (% of WBC)	5 (2-7.48)	5 (2-8.23)	4 (3-5.25)	0.35
Number of household contacts	4 (3-6)	4 (3-6)	4 (3.75-6.25)	0.91
BCG vaccination	81.1% (99/122)	80.2% (81/101)	85.7% (18/21)	0.64
<b>Risk factors and comorbidity</b>				
Smoking	47.7% (72/151)	48% (59/123)	46.4% (13/28)	1
Alcohol abuse	21.9% (33/151)	23.6% (29/123)	14.3% (4/28)	0.55
Injectable drug use	3.3% (5/150)	2.4% (3/123)	7.4% (2/27)	0.36
Jail detention history	10.1% (15/149)	11.6% (14/121)	3.6% (1/28)	0.44
Chronic HCV infection	2.1% (3/146)	2.5% (3/118)	0	1
Other disease <sup>1</sup>	5.5% (7/128)	6.7% (7/105)	0	0.35
<b>History of TB</b>				
Previous TB	18.9% (28/148)	16.4% (20/122)	30.8% (8/26)	0.1
<i>Of which are documented</i>	78.5% (22/28)	70.0% (14/20)	88.9% (8/9)	0.05
Prior exposure to active TB patients	30.9% (46/149)	31.4% (38/121)	28.6% (8/28)	0.22
<b>Previous TB treatment outcome</b>				
Cured and completed	57.1% (12/21)	56.2% (9/16)	60% (3/5)	1
Completed	14.3% (3/21)	12.5% (2/16)	20% (1/5)	1
Treatment failure	14.3% (3/21)	18.8% (3/16)	0	-
Outcome not evaluated or unknown	14.3% (3/21)	12.5% (2/16)	20% (1/5)	1

483 **Footnotes:** DS-TB: drug-susceptible tuberculosis. DR-TB: drug-resistant tuberculosis. BMI:  
 484 body mass index. IQR: interquartile range. WBC: white blood cells. 1: asthma, hypertension,  
 485 inflammation. No patients presented with either pregnancy, renal disease, solid tumors or  
 486 other cancers, HIV infection, chronic pulmonary disease, or chronic HBV infection. Data  
 487 were given as % (N) or median (IQR).

488

489 **Table 2. Microbiological characterization of treatment response and outcome definition.**

<b>Sputum culture results</b>	<b>Positive</b>	<b>Negative</b>	<b>Unavailable</b>
<i>Timepoint</i>			
T0	100% (152/152)	0	0
T1	13.8% (21/152)	70.4% (107/152)	15.8% (24/152)
T2	3.3% (5/152)	94.8% (144/152)	1.9% (3/152)
T3	0.9% (1/112)	43.8% (49/112)	55.4% (62/112)
	<b>All patients</b>	<b>DS-TB</b>	<b>DR-TB</b>
<i>Treatment outcome</i>			
Cured and completed <sup>1</sup>	90.8% (138/152)	88.7% (110/124)	100% (28/28)
Completed <sup>2</sup>	5.3% (8/152)	6.5% (8/124)	0
Failed <sup>4</sup>	3.3% (5/152)	4% (5/124)	0
Relapse or reinfection <sup>5</sup>	0.7% (1/152)	0.8% (1/124)	0

490

491 **Footnotes:** T0: baseline. T1: baseline + 2 months. T2: end of treatment. T3: end of treatment + 2

492 months. DS-TB: drug-susceptible tuberculosis. DR-TB: drug-resistant tuberculosis.

493 1: positive culture at T2. 2: negative culture at T2 but positive culture at T3. 3: negative culture at T2

494 and no evidence of positive culture at T3. 4: patients not lost to follow-up, but with no available

495 culture data at T2 or T3. Unavailable culture data were caused by contaminations or failure to

496 expectorate sputum. Unavailable sputum smear microscopy results were caused either by technical

497 issues or failure to expectorate enough sputum for both culture and smear.

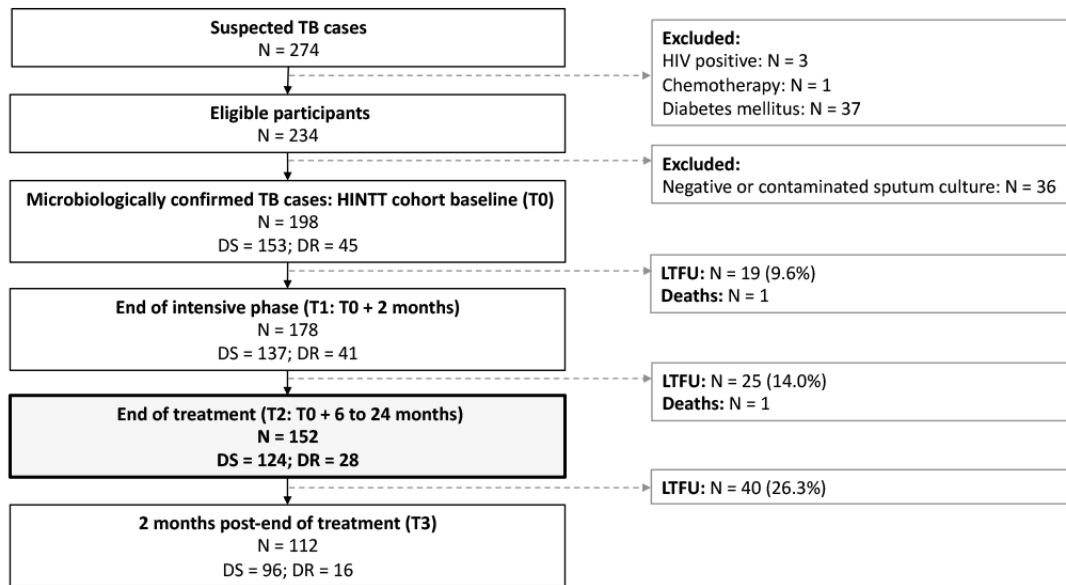
498

499 **Table 3. Association of selected baseline sociodemographic and clinical factors with treatment outcome.**

Sociodemographic factors and clinical parameters at baseline and at 2 months	Descriptive analysis (n = 143)			Logistic regression - association with treatment failure					
	Cured (n = 138)	Failed (n = 5)	p	Univariate analysis		Multivariate analysis <sup>1</sup>			
				OR (95% CI)	p	aOR	p	AIC	Corrected C-statistic
Age (years)	27.5 (21-37)	31 (29-45)	0.22	1.02 (0.96 - 1.08)	0.38	-	-	-	-
Sex (male)	62.3% (86/138)	100% (5/5)	0.15	-	-	-	-	-	-
Drug resistance	20.3% (28/138)	0	0.58	-	-	-	-	-	-
Smoking habit	45.3% (62/137)	100% (5/5)	0.021	-	-	-	-	-	-
BMI at inclusion	18.8 (17.1-21.4)	16.0 (15.8-20.9)	0.31	0.87 (0.61 - 1.15)	0.39	0.74 (0.46 - 1.05)	0.14	44.68	0.862
Alcohol consumption	21.9% (30/137)	40% (2/5)	0.32	2.38 (0.3 - 14.9)	0.35	0.52 (0.02 - 8.55)	0.66	47.23	0.861
History of prison	8.9% (12/135)	40% (2/5)	0.075	6.94 (0.85 - 46.1)	0.047	1.96 (0.14 - 25.81)	0.59	47.16	0.856
Previous TB episode	19.4% (26/134)	20% (1/5)	1	1.07 (0.05 - 7.59)	0.95	1.72 (0.06 - 29.24)	0.71	47.30	0.860
Absolute WBC count at T0 (cells/mm <sup>3</sup> ) <sup>2</sup>	9500 (7403-11575)	12100 (11470-12300)	0.032	1.26 (0.97-1.64)	0.080	1.4 (0.99-2.23)	0.092	43.87	0.862
Lymphocytes at T0 (% of WBC) <sup>3</sup>	18 (14-25)	14 (10-15)	0.019	0.32 (0.10-0.80)	0.032	0.09 (0.0040-0.52)	0.042	37.85	0.866
Monocytes at T0 (% of WBC)	4.9 (2-7.8)	3 (1-4)	0.12	0.75 (0.49 - 1.03)	0.13	0.21 (0.01 - 0.78)	0.12	40.57	0.861
Absolute WBC count at T1 (cells/mm <sup>3</sup> ) <sup>2</sup>	7385 (5907-9382.5)	11440 (11200-11600)	0.014	1.04 (0.94-1.11)	0.23	4.75 (1.45-55.6)	0.081	35.03	0.860
Lymphocytes at T1 (% of WBC) <sup>3</sup>	25 (20.25-31)	13 (11-20)	0.0079	0.32 (0.11-0.68)	0.0091	0.18 (0.02-0.68)	0.063	39.25	0.864
Monocytes at T1 (% of WBC)	6 (3-8.4)	4 (3-6)	0.41	0.89 (0.66 - 1.16)	0.40	0.9 (0.4 - 1.95)	0.79	47.36	0.866
Baseline WBC > 11,450/ mm <sup>3</sup>	26.8% (37/138)	80% (4/5)	0.024	11.2 (1.60 - 223.5)	0.031	16.38 (1.52 - 592)	0.048	41.94	0.867
Baseline lymphocytes < 16%	31.9% (44/138)	80% (4/5)	0.044	8.45 (1.21 - 168.0)	0.061	12.08 (1.44 - 264)	0.039	42.06	0.858
Baseline WBC > 11,450/ mm <sup>3</sup> and lymphocytes < 16%	14.5% (20/138)	60% (3/5)	0.029	8.77 (1.37 - 69.9)	0.019	29.85 (2.19 - 1088)	0.024	40.73	0.864

500 **Footnotes:** Data are given as % (n) or median (interquartile range). Treatment failure was defined as a positive sputum culture result at T2 or T3. BMI: body  
501 mass index. OR: odds ratio. aOR: adjusted odds ratio. AIC: Akaike Information Criterion. C-statistic: concordance statistic (corrected for optimism). WBC: white  
502 blood cells. T0: baseline. T1: baseline + 2 months. T2: end of treatment. T3: end of treatment + 2 months. 1: adjusted for age, sex, country of origin, drug  
503 resistance strain, and smoking habit. 2: OR or aOR given for each increase in 1,000 units. 3: OR or aOR given for each increase in 5 units.

504 **Figure legends**



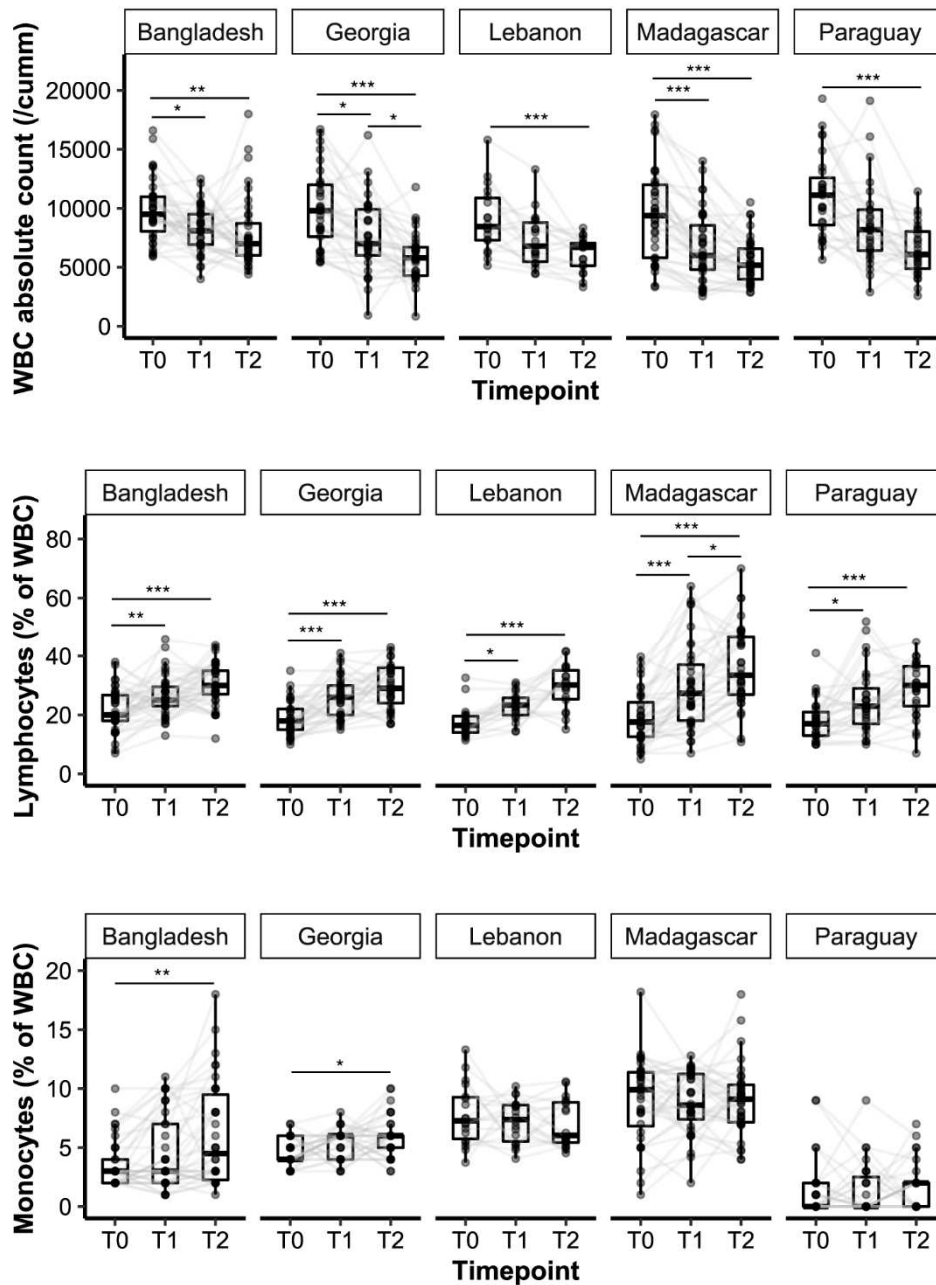
505

506 **Figure 1. Inclusion and data collection process between December 2017 and July 2020.**

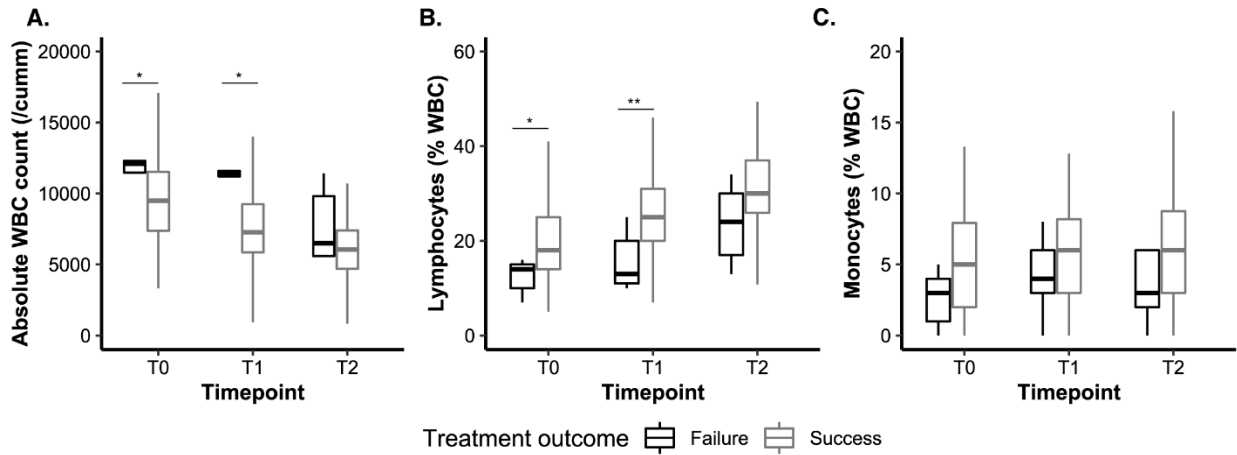
507 DR: drug resistant. DS: drug-susceptible. LTFU: lost to follow-up. TB: tuberculosis. HIV:

508 human immunodeficiency virus. Treatment for DS-TB patients lasted 6 months. Treatment for

509 DR-TB patients lasted 9 to 24 months.



510  
 511 **Figure 2. Dynamics of main white blood cell types over the course of TB treatment.**  
 512 **A.** White blood cell (WBC) absolute count. cumm: cubic millimeter of whole blood. **B.**  
 513 Lymphocyte percent of WBC. **C.** Monocyte percent of WBC. Data are given as median +  
 514 interquartile range. Each dot represents one patient at one timepoint. Grey lines connect data  
 515 points from a same patient. T0: baseline. T1: baseline + 2 months. T2: end of treatment. Data  
 516 were analyzed using Friedman's test, with the Wilcoxon-Nemenyi-McDonald-Thompson test as  
 517 a post-hoc correction for pairwise multiple comparisons. \*:  $p < 0.05$ . \*\*:  $p < 0.01$ . \*\*\*:  $p < 0.001$ .



519

520 **Figure 3. Main white blood cell types over time stratified by sputum smear microscopy and**  
 521 **treatment outcome.**

522 White blood cell (WBC) absolute counts (A.), lymphocyte percent of WBC (B.), and monocyte  
 523 percent of WBC (C.) were assessed over time in cured (n=138) and treatment failure patients

524 (n=5). Data are given as median + interquartile range. T0: baseline. T1: baseline + 2 months. T2:  
 525 end of treatment. T3: end of treatment + 2 months. cumm: cubic millimeter of whole blood.

526 Treatment failure was defined as a positive sputum culture result at T2 . Treatment success was  
 527 defined as a negative sputum culture result at T2 and no evidence of positive culture at T3. Data

528 were analyzed using the Mann-Whitney U test at each timepoint. \*: p<0.05. \*\*: p<0.01.

529