

Bedside inflammatory mediators in pulmonary tuberculosis

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Background Monitoring of pulmonary tuberculosis (PTB) especially in poor countries is a major challenge aiming to find cheap valuable indices.

Objective The objective of this study was to evaluate the use of simple laboratory parameters as complete blood count (CBC), especially platelet (PLT) indices, for assessment and monitoring of PTB activity.

Patients and methods Totally, 140 PTB patients in addition to 30 healthy individuals as a control group were included in this case-control study. Patients were divided into three groups: 66 newly diagnosed active patients (group I), 39 patients after sputum and culture conversion (group II), and 35 patients defined as cured cases (group III). On the basis of chest radiography, only active PTB patients were classified into minimal, moderate, and far advanced cases. Laboratory parameters including CBC with PLT indices, erythrocyte sedimentation rate, and C-reactive protein (CRP) were performed for all enrolled participants.

Results Compared with the control group, hemoglobin, mean PLT volume, and platelet distribution width (PDW) were significantly lower in group I and increased after treatment in groups II and III. On the other hand, PLT count, platelet crit %, CRP, and erythrocyte sedimentation rate were significantly

higher in group I compared with the control group and decreased after treatment. In addition, there were significant correlations between CRP and all PLT indices. Regarding radiological extension, hemoglobin and mean PLT volume were significantly lower in far advanced PTB compared with both moderate and mild PTB, whereas PLT crit was significantly higher in moderate PTB compared with minimal PTB.

Conclusion CBC, especially PLT indices, could be considered valuable cheap markers in assessment and monitoring of PTB activity.

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Introduction

Tuberculosis (TB) is a common infectious disease caused by *Mycobacterium tuberculosis*, and despite developments in its diagnosis and treatment it remains an important public health problem. The presence of 9.6 million new TB cases has been reported in 2014 and 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people). To control TB efficiently, proper identification and cure of infectious pulmonary tuberculosis (PTB) patients should be done [1]. In addition, monitoring TB patients during treatment is important to establish patients' treatment outcomes [2].

Because of activation of the immune system in TB patients, excessive cytokines such as interleukin (IL)-1, IL-2, interferon- γ , and tumor necrosis factor- α (TNF- α) are produced. These cytokines enhance hepatic synthesis of acute-phase proteins, such as C-reactive protein (CRP), as well as in the erythrocyte sedimentation rate (ESR). CRP and ESR have been used in the diagnosis and follow-up of patients with TB beside the routinely done sputum for acid-fast bacilli (AFB) and sputum culture [3]. These cytokines also have a role in maturation of thrombopoietic cells and secretion of platelets (PLTs) into the circulation [4]. In recent years, it has been shown that PLTs can act as inflammatory cells releasing various

chemokines and cytokines. Changes in PLT counts may be associated with the severity of TB infection and mortality. A change in PLT size has been shown to be associated with numerous inflammatory diseases including TB [5–9]. To the best of our knowledge, these changes in PLTs were not studied as inflammatory markers on monitoring patients on anti-TB treatment.

Objectives

The objectives of this study were to evaluate the use of simple laboratory parameters such as complete blood count (CBC), especially PLT indices, as markers for assessment and monitoring of PTB activity.

Patients and methods

Participants

This case-control study was carried out on 140 PTB patients who were selected from chest outpatient clinic in a tertiary hospital. The study included patients with

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PTB with positive sputum smear for AFB and positive culture [1]. PTB patients included 66 patients who were newly diagnosed (active TB - in which a biological specimen obtained from the patient is positive by smear microscopy or culture) [1] and about to begin treatment (group I), 39 patients after sputum and culture conversion (the point at which samples taken from a patient infected with TB can no longer produce TB cell cultures) [10] (group II), and 35 patients defined as cured cases (a PTB patient with bacteriologically confirmed TB at the beginning of treatment who was smear-negative or culture-negative in the last month of treatment and on at least one previous occasion) [1](group III). In addition, 30 apparently healthy, age-matched and sex-matched individuals were included in this study as a control group. Informed written consent was obtained from each participants, and the study was approved by the Faculty of Medicine Ethics Committee. Patients who had other respiratory diseases, thromboembolic disorders, valvular or ischemic heart disease, associated hepatic or renal diseases, acute inflammatory disease, immunological disease, recent surgery and malignancy, receiving anticoagulant, anti-PLT, nonsteroidal anti-inflammatory, or antidepressant medications were excluded from the study.

Sputum collection, sputum analysis, and culture

Morning sputum specimens submitted to the laboratory were processed for AFB microscopy and mycobacterial culture. Direct smears were stained by Ziehl-Neelsen technique. A smear was declared to be positive if at least 1-9 AFB in 100 fields were found on microscopy [11,12].

For sputum culture, specimens were treated with 2% *N*-acetyl-l-cysteine-sodium hydroxide, followed by centrifugation [12]. The sediment was inoculated on Lowenstein-Jensen medium and incubated at 37°C for a maximum of 8 weeks. Cultures were read weekly for 2 months. Buffy, granular colonies appearing after 3-7 weeks were confirmed for their acid fastness. Culture was declared to be positive if colonies appear on AFB-positive smears. Liquefied or discolored Lowenstein-Jensen medium indicated contamination. Cultures that showed no growth after 8 weeks of incubation were reported as negative [13].

Clinical and radiological assessment

All the enrolled participants had their medical history taken and underwent physical examination. Chest radiography was performed for the PTB patients to assess severity of radiological involvement. On the basis of chest radiography, PTB patients were classified into

minimal (radiography lesion of slight to moderate density, no cavitation, lesions in one or both lungs, and extent of the lesion less than the part above the second chondrosternal junction of lung on one side), moderate (lesions were in one or both lungs, lesions of slight to moderate density involved total volume of one lung or equivalent in both lung cavities, whereas dense lesions were limited to one-third of one lung cavity; when it was present its diameter was less than 4 cm), and far advanced PTB, which included lesions more extensive than moderate [14].

Laboratory assessment

On the day of testing, patients were resting, fasting, and were refrained from smoking and any caffeine ingestion where a 7 ml sample of venous blood was collected from both patients and control groups by venipuncture of the antecubital fossa under complete antiseptic protocol with minimum tourniquet pressure using 19-21 G syringes. After discarding specimens containing any evidence of clotting, other specimens were maintained at room temperature (20-25°C), not placed on ice, refrigerator, or water bath. Tubes were kept capped upright at room temperature not exposed to vibration, excessive mixing, or agitation [15]. The samples were divided into three parts for analysis of CBC and biochemical analysis of CRP and ESR.

For estimation of CBC, 2 ml of venous blood was placed in standard tubes containing K3 EDTA anticoagulant. Samples were processed within 1 h to avoid bias due to excessive PLT swelling and to minimize variation due to sample aging [16,17]. CBC for patients and control was done by ABX Pentra XL80 (HORIBA group, Montpellier, France). To obtain serum for CRP, 3 ml of venous blood was placed in plain tubes and left to clot at room temperature for at least 30 min, and then centrifuged at 1500 rpm for 15 min. It was determined by using AVITEX CRP Ref OD037/OD023/OD023/E (Omega Diagnostics, UK) according to the methods described by the manufacturer (in-vitro diagnostic reagent for the quantitative determination of CRP). The last 2 ml of venous blood was directly collected in 0.5 ml of 3.8% trisodium citrate for estimation of ESR. Samples were processed within 6 h of collection, and blood was collected to the mark in the tube, as specified by the manufacturer.

Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences, version 20, software (SPSS; SPSS Inc., Chicago, Illinois, USA). The results were expressed as mean±SD or frequencies.

Kruskal–Wallis one-way analysis of variance was used for comparison of continuous variables among the study groups. Spearman's correlation analysis was used to evaluate the correlations between both CRP and ESR and CBC parameters; *P*-values less than 0.05 were considered significant.

Results

This study included 66 newly diagnosed active TB patients (group I), 39 patients after sputum and culture conversion (group II), and 35 cured patients after completion of anti-TB treatment (group III). These three groups are matched as regards age, sex, smoking habit, and BMI (*P*>0.05). Demographic data are shown in Table 1.

Table 2 demonstrated the laboratory parameters among the study groups. Hemoglobin (HB) was significantly lower in group I than in the control group (11.57±2.25 vs. 13.39±1.58 gm/dl, *P*=0.001) but relatively higher in other groups after treatment. Total leukocytic count was also significantly lower in group I than in the control group (5.39±1.23 vs. 7.00±1.76×10⁹/l, *P*=0.038) and significantly increased with treatment. Among PLT indices, total PLT count and platelet crit (PCT) % were significantly higher in group I compared with the

control group (365.2±184.2 vs. 235.17±60.98, *P*=0.001; 0.299±0.098 vs. 0.21±0.07, *P*=0.008, respectively) but showed a relative decrease in group II (365.2±184.2 vs. 295.9±106.57, *P*=0.212; 0.27±0.12 vs. 0.299±0.098, *P*=0.545, respectively) and group III (365.2±184.2 vs. 341.71±147.07, *P*=0.755; 0.299±0.098 vs. 0.27±0.12, *P*=0.0626, respectively). On the other hand, mean platelet volume (MPV) was significantly lower in group I than in the control group (7.5±1.198 vs. 8.597±1.199, *P*=0.001) but significantly increased after completion of anti-TB treatment in group III compared with group I (8.43±0.68 vs. 7.5±1.198, *P*=0.021). In addition, PDW % was significantly lower in group I compared with the control group (14.73±2.54 vs. 16.42±1.97, *P*=0.005). As expected, CRP and ESR first and second were significantly higher in group I compared with the control group (16.56±14.79 vs. 3.77±1.22, *P*=0.004; 58.65±27.88 vs. 10.53±5.44, *P*<0.001; 90.53±29.90 vs. 22.20±11.36, *P*<0.001, respectively) and lower in both group II (16.56±14.79 vs. 9.22±8.42, *P*=0.168; 58.65±27.88 vs. 34.27±19.96, *P*=0.010; 90.53±29.90 vs. 57.0±20.16, *P*=0.01, respectively) and group III (16.56±14.79 vs. 2.29±0.76, *P*=0.002; 58.65±27.88 vs. 17.0±9.73, *P*<0.001; 90.53±29.90 vs. 22.20±11.36, *P*<0.001, respectively) compared with group I (i.e. significantly decreased with treatment).

Table 1 Demographic data of the study groups

	Group I (n=66)	Group II (n=39)	Group III (n=35)	Control (n=30)	<i>P</i> ₁	<i>P</i> ₂	<i>P</i> ₃	<i>P</i> ₄	<i>P</i> ₅	<i>P</i> ₆
Age (years)	41.2±11.1	41.9±13.6	45.1±14.7	41.5±11.9	0.887	0.581	0.924	0.631	0.919	0.490
Sex										
Male	42 (60)	24 (61.5)	12 (42.9)	13 (46.4)	0.923	0.403	0.283	0.423	0.368	0.865
Smoking										
Smoker	12 (17.1)	4 (7.7)	5 (14.3)	4 (13.5)	0.122	0.116	0.209	0.896	0.421	0.664
BMI	20.4±3.8	22.1±2.6	22.1±2.5	21.3±4.1	0.179	0.275	0.485	0.982	0.539	0.610

Data expressed as number (%) or mean±SD. *P*₁, group I versus group II; *P*₂, group I versus group III; *P*₃, group I versus controls; *P*₄, group II versus group III; *P*₅, group II versus control IV; *P*₆, group III versus controls.

Table 2 Laboratory data of the study groups

	Group I (n=66)	Group II (n=39)	Group III (n=35)	Control (n=30)	<i>P</i> ₁	<i>P</i> ₂	<i>P</i> ₃	<i>P</i> ₄	<i>P</i> ₅	<i>P</i> ₆
HB (g/dl)	11.57±2.25	12.94±2.18	11.93±1.82	13.39±1.58	0.023*	0.639	<0.001*	0.162	0.293	0.004*
WBC (×10 ⁹ /l)	5.39±1.23	8.01±4.5	8.01±2.6	7.00±1.76	0.008*	0.003*	0.038*	0.0349	0.248	0.165
PLT (×10 ⁹ /l)	365.2±184.2	295.9±106.57	341.71±147.07	235.17±60.98	0.277	0.794	<0.001*	0.705	0.015*	0.106
MPV (fl)	7.5±1.198	7.98±1.28	8.43±0.68	8.597±1.199	0.242	0.002*	0.001*	0.427	0.090	0.889
PDW (%)	14.73±2.54	14.7±2.86	14.97±1.97	16.42±1.97	0.951	0.754	0.006*	1.000	0.056	0.044*
PCT (%)	299±0.098	0.25±0.101	0.27±0.12	0.21±0.07	0.859	0.362	0.015*	0.393	0.029*	<0.001*
CRP (mg/l)	16.56±14.79	9.22±8.42	2.29±0.76	3.77±1.22	0.002*	0.002*	<0.001	0.039*	<0.001*	0.004*
ESR first	58.65±27.88	34.27±19.96	17.0±9.73	10.53±5.44	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.871
ESR second	90.53±29.90	57.0±20.16	39.29±17.18	22.20±11.36	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.248

Data are expressed as mean±SD. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, Hemoglobin; MPV, mean platelet volume; *P*₁, group I versus group II; *P*₂, group I versus group III; *P*₃, group I versus controls; *P*₄, group II versus group III; *P*₅, group II versus control IV; *P*₆, group III versus controls; PCT, platelet crit; PDW, platelet distribution width; PLT, platelet count; WBC, white blood cell count. *Significant.

According to radiological extension in group I, we observed that HB was significantly lower in far advanced PTB compared with minimal and moderate PTB (9.95 ± 1.37 vs. 12.8 ± 2.46 gm/dl, $P=0.003$; 9.95 ± 1.37 vs. 12.06 ± 1.9 , $P=0.005$, respectively). No significant differences were detected between radiological groups regarding total leukocytic count ($P>0.05$). Among PLT indices, MPV was significantly lower in far advanced and moderate PTB compared with minimal PTB (6.7 ± 1.84 vs. 8.18 ± 0.79 fl, $P=0.019$; 7.4 ± 0.95 vs. 8.18 ± 0.79 , $P=0.045$, respectively), whereas PCT% was significantly higher in moderate PTB compared with minimal PTB (0.29 ± 0.12 vs. 0.22 ± 0.072 , $P=0.24$). Although it was not significant, PLT count increased and PDW% decreased with increased radiological extension (Table 3).

Moreover, significant positive correlations were observed between CRP and each of total PLT count ($r=0.512$, $P=0.009$) (Fig. 1a) and PCT% ($r=0.444$, $P=0.001$) (Fig. 1b). However, CRP was negatively correlated with each of MPV (although not significant) ($r=-0.260$, $P=0.060$) (Fig. 1c) and PDW% ($r=-0.362$, $P=0.008$) (Fig. 1d). ESR second showed only a significant positive correlation with total PLT count ($r=0.269$, $P=0.019$) (Fig. 2a) and negative correlation with MPV ($r=-0.369$, $P=0.001$) (Fig. 2c), with no significant correlation with other PLT indices (Fig. 2b and d).

Discussion

TB is an infectious common disease affecting as many as one-third of the world population, with population growth number of new cases continuing to increase [1]. Proper identification and monitoring of TB patients during treatment are important to establish patients' treatment outcomes [2].

Many markers of acute inflammation are available to assess activity and monitoring of PTB, but specific markers

are expensive [18] and cannot be done routinely. Hematological changes have been documented in PTB infection [19]. In recent years, PLTs are considered inflammatory cells releasing chemokines and cytokines [5–9]. CBC is a simple laboratory test and PLT indices (MPV, PCT%, PDW) are readily measured by clinical hematology analyzers and are indicators of PLT activation. Thus, this study was designed to investigate the simple CBC parameters, especially PLT indices, in assessment of activity and in follow-up of PTB patients.

Out of the hematological abnormalities, HB was significantly lower in group I (active PTB) than in the control group and relatively increased in other groups after anti-TB therapy. The prevalence of anemia was observed in previous studies [20–22], and it was thought to be due to a blunted response of bone marrow to anemia or suppression of erythropoietin production by TNF- α and other cytokines released by activated monocytes [23]. Total leukocytic count was also significantly lower in group I than in the control group (5.39 ± 1.23 vs. 7.00 ± 1.76 , $P=0.038$) and significantly increased with treatment. Mild leukocytosis was documented in 8–40% [24] and leukopenia in 1–4% [24] of patients with PTB. Leukopenia in active PTB was thought to be a consequence of marrow granulopoietic failure or associated malnutrition. Nevertheless, the role of cytokine including TNF in the pathogenesis of lymphocytopenia has been suggested [24].

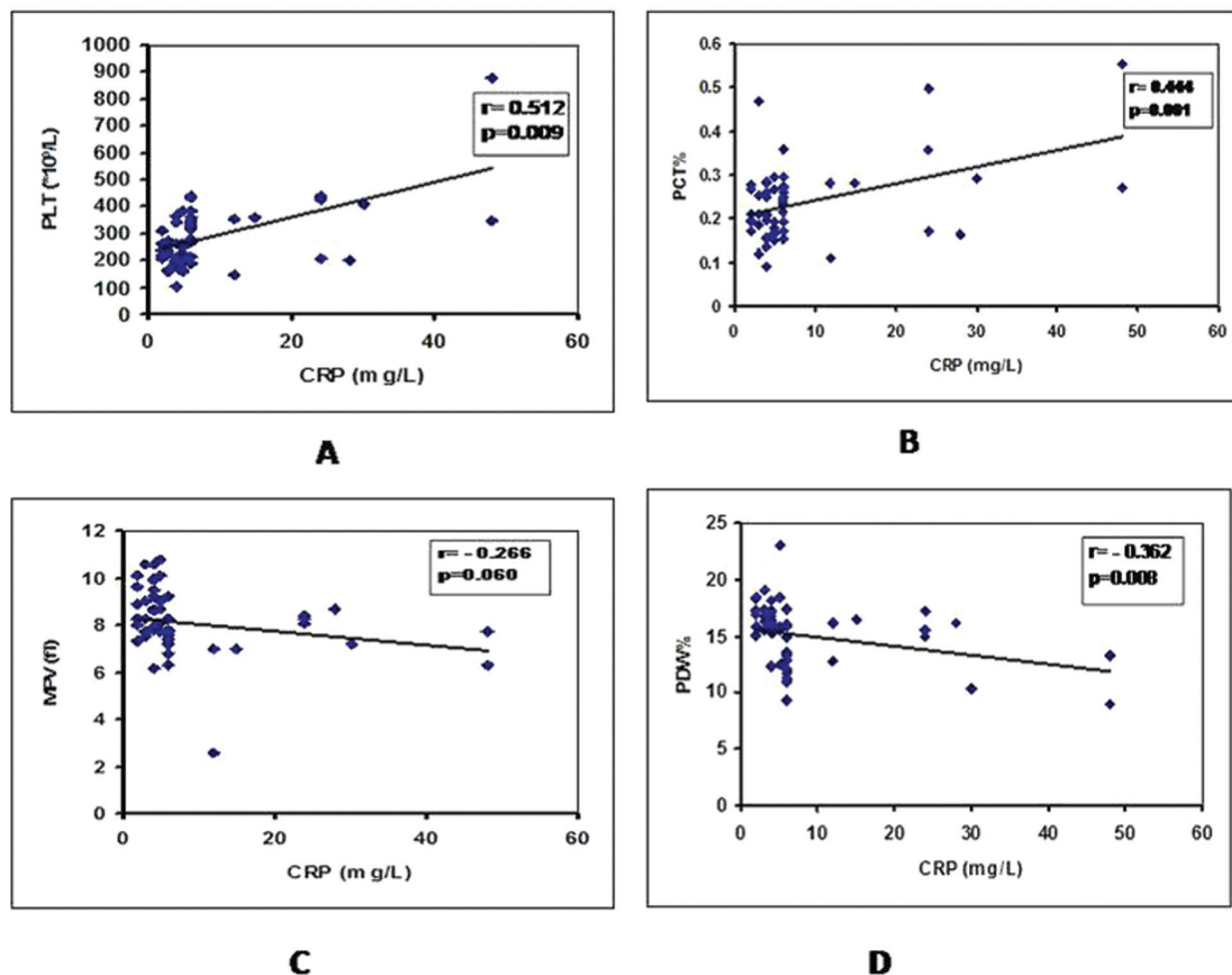
Among PLT indices, total PLT count was significantly higher in group I compared with the control group (365.2 ± 184.2 vs. 235.17 ± 60.98 , $P=0.001$), but it showed a relative decrease with treatment. Thrombocytosis was commonly reported in active PTB patients [20,21,25]. Increased PLT count before treatment would usually return to normal after anti-TB therapy [26,27]. Inflammatory cytokines, especially IL-6 (one of the inflammatory markers involved in TB granuloma

Table 3 Comparison of laboratory data among different groups of radiological extension

Variables	Radiographic groups			P_1 value	P_2 value	P_3 value
	Mild ($n=22$)	Moderate advanced ($n=25$)	Far advanced ($n=19$)			
HB (m/dl)	12.8 ± 2.46	12.06 ± 1.9	9.95 ± 1.37	0.095	<0.001*	0.005*
WBC ($\times 10^9/l$)	15.07 ± 2.32	7.31 ± 4.68	7.6 ± 2.6	0.566	0.853	0.158
PLT ($\times 10^9/l$)	290.5 ± 118.7	361.25 ± 159.28	407.44 ± 241.00	0.038*	0.126	0.459
MPV (fl)	8.18 ± 0.79	7.4 ± 0.95	6.7 ± 1.84	<0.001*	0.240	0.001*
PDW (%)	15.07 ± 2.3	15.01 ± 2.5	13.73 ± 3.33	1.000	0.094	0.139
PCT (%)	0.22 ± 0.072	0.29 ± 0.12	0.29 ± 0.15	0.006*	0.191	0.614
CRP (mg/l)	10.4 ± 10.99	12.92 ± 12.62	20 ± 18.05	0.497	0.075	0.340
ESR first	52.38 ± 26.74	49.52 ± 28.15	67.33 ± 26.57	0.919	0.028*	0.021*
ESR second	82.15 ± 25.01	80.095 ± 33.15	98.44 ± 25.29	0.686	0.028*	0.061

Data are expressed as mean \pm SD. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, hemoglobin; MPV, mean platelet volume; P_1 , mild versus moderate advanced; P_2 , mild versus far advanced; P_3 , moderate versus far advanced; PCT, platelet crit; PDW, platelet distribution width; PLT, platelet count; WBC, white blood cell count. *Significant.

Figure 1



Correlations between C-reactive protein (mg/l) and each of (a) platelet count ($\times 10^9/l$), (b) platelet crit percentage, (c) mean platelet volume (fl), and (d) platelet distribution width percentage. CRP, C-reactive protein; PCT, platelet crit; PDW, platelet distribution width; PLT, platelet

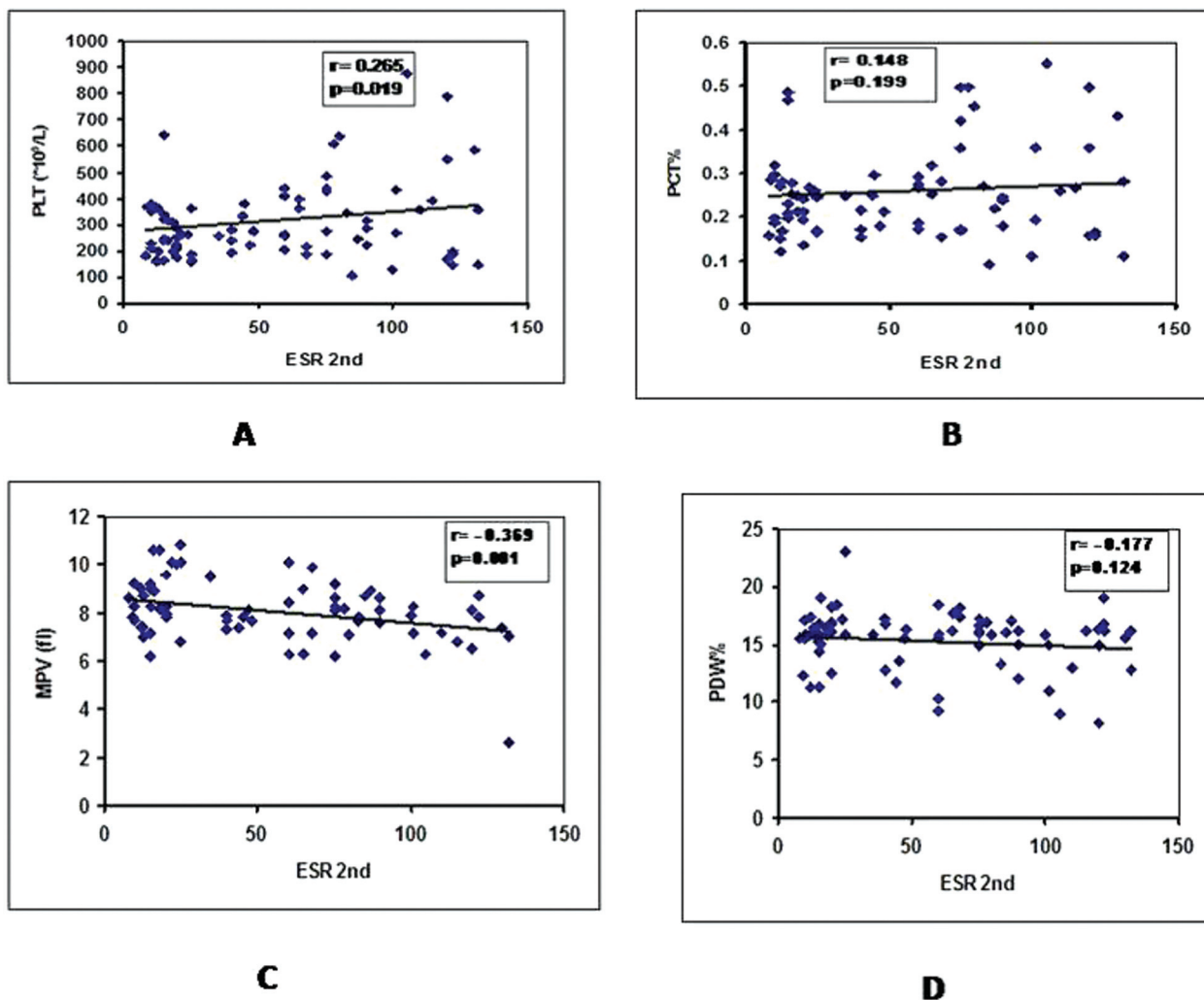
formation), have been known to stimulate PLT production [28].

On the other hand, the present study revealed significantly lower MPV in group I compared with the control group (7.5 ± 1.198 vs. 8.597 ± 1.199 , $P = 0.001$), which relatively increased with treatment in group III compared with group I (8.43 ± 0.68 vs. 7.5 ± 1.198 , $P = 0.021$). Gunluoglu *et al.* [29] agree with our results; they observed that MPV significantly reduced in PTB patients compared with healthy controls. Similarly, Baynes *et al.* [30] found the MPV to be low in patients with active PTB and suggested that although thrombopoiesis increased in patients with TB the PLTs' lifetime may have been shortened and that this may simply reflect the thrombocytosis, as there is normally an inverse correlation between the number and volume of PLTs. As they suppress other blood elements, excessive production of cytokines and acute-phase reactants affect megakaryopoiesis and decrease PLT size released from bone marrow [31]. Contrary to our study, Tozkoparan *et al.* [26] found that the MPV was significantly higher in

patients with active PTB than in control patients and decreased with anti-TB treatment. However, Sahin *et al.* [32] observed no significant difference between healthy control and active PTB. Variability of these results may be attributed to the difference in patient characteristics – e.g. BMI or comorbidities – which could affect the results of PLT indices.

In addition, the current study demonstrated significantly higher PCT% in group I compared with the control group (0.299 ± 0.098 vs. 0.21 ± 0.07 , $P = 0.008$), which relatively decreased with treatment but had significantly lower PDW compared with the control group. PCT is an expression of a percentage that reflects the volume occupied by PLTs in blood [33] and thus it depends on both size and number of PLTs [34]. PDW refers to the variability or the change in uniformity in the PLT size [35]. It might reflect the active role of PLTs in active PTB. Microthrombi (which denoted activity of PLTs) were observed around the cavity of PTB, which prevented dissemination of the disease, and it was suggested as an immunological defense mechanism [36,37].

Figure 2



Correlations between erythrocyte sedimentation rate second and each of (a) platelet count ($\times 10^9/l$), (b) platelet crit percentage, (c) mean platelet volume (fl), and (d) platelet distribution width percentage. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, platelet crit; PDW, platelet distribution width; PLT, platelet

As observed in previous studies [20,29,38–42], we showed a significant increase in markers of acute-phase reactants CRP and ESR in group I compared with the healthy control group and a significant decrease with treatment. Th_1 immunity, which is activated in PTB, results in systemic release of IL-2, IL-6, IL-12, INF- γ , and TNF- α with subsequent increase in ESR and CRP levels [43,44]. Moreover, there are significant correlations between CRP and all PLT indices in our study. Significant correlation was observed between CRP and total PLT count in previous studies [29,30]. Sahin *et al.* [32] also found that CRP and PCT% significantly increased in PTB patients with thrombocytosis compared with those with normal PLT count. Similarly, Unsal *et al.* [45] observed an increased level of IL-6 in addition to CRP in tuberculous patients with thrombocytosis.

According to radiological extension, HB was significantly lower in severe PTB compared with minimal and

moderate PTB (9.95 ± 1.37 vs. 12.8 ± 2.46 , $P = 0.003$; 9.95 ± 1.37 vs. 12.06 ± 1.9 , $P = 0.005$, respectively). Among PLT indices, MPV (fl) was significantly lower in far advanced and moderate PTB compared with minimal PTB (6.7 ± 1.84 vs. 8.18 ± 0.79 , $P = 0.019$; 7.4 ± 0.95 vs. 8.18 ± 0.79 , $P = 0.045$, respectively), whereas PCT% was significantly higher in moderate PTB compared with minimal PTB (0.29 ± 0.12 vs. 0.22 ± 0.072 , $P = 0.24$). Although it was not significant, PLT count increased and PDW% decreased with increased radiological extension. In their study, Sahin *et al.* [32] confirmed that PLT count, PCT%, ESR, and CRP were higher in advanced TB compared with minimal TB, and HB was lower; also, they documented that thrombocytosis in PTB correlated with the disease severity. MPV was also significantly correlated with radiological extent [26]. PLT activation also evaluated by PLT factor 4 was well correlated with radiological extent [46]. On the other hand, Gunluoglu *et al.* [29] showed no correlation between radiological extent and

each of MPV and PLT count. However, they use radiological classification involving pleural abnormalities that did not match with our study that assess radiology depending only on lung extension and cavitation.

This study concluded that CBC and PLT indices could be considered as simple valuable nonexpensive markers in assessment of activity, extension, and follow-up of PTB patients.

The strength of the current study is as follows: first, it evaluates PTB at three different stages of treatment; second, it evaluates PTB with different radiological extensions; and third, we included healthy individuals as a control group for comparison.

Limitations of this study are as follows: first, we did not study the modifying role of other comorbidities (e.g. diabetes, renal impairment, hepatic disease, and others) in CBC, ESR, and CRP, and thus further studies concentrated on these points may be useful; second, we did not compare inflammation in PTB with other diseases - e.g. pneumonia, chronic obstructive pulmonary disease, and others. Further studies are recommended to evaluate PLT index parameters in extra-PTB.

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Conflicts of interest

There are no conflicts of interest.

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