
ACUTE PHASE INFLAMMATORY RESPONSE IN PATIENTS WITH PULMONARY TUBERCULOSIS

By

Abdelrhman K. Ahmed*, **Ahmed M. Tahoun***, **Ahmed M. Ragheb***,
Mousa M. Mousa**, and **Mahmoud M. Metwally***

*Clinical Pathology and ** Chest, Departments Faculty of Medicine
Al-Azhar University

ABSTRACT

Introduction: Tuberculosis (TB) is a common infectious disease caused by *Mycobacterium tuberculosis* (MTB). Although no other current test is more reliable for determining the activity of PTB than culture growth of bacilli, some biochemical parameters that reflect the inflammation present in patients with this condition may provide guidance at the diagnostic stage. The mean platelet volume (MPV) reflects the size of platelets. It has been shown to be inversely correlated with level of the inflammation in some chronic inflammatory diseases. **Aim of the Work:** This study aims to evaluate the role of some inflammatory markers in patients with active pulmonary tuberculosis (PTB) and to investigate the relationship between the inflammatory markers with each other as well as with the sputum smear positivity for TB bacilli.

Methods: This cross sectional study included 50 patients who presented to the outpatient clinic of Qena general chest hospital and were diagnosed with active pulmonary tuberculosis and 50 healthy subjects (control group) who presented to the outpatient clinic for routine examination and presented no disease during the period between April 2017 to October 2017. Complete blood count, C-reactive protein (CRP) level, Erythrocyte sedimentation rate (ESR), ferritin level, and albumin level were compared between the two groups. In the PTB group, the relationship between inflammatory markers with each other as well as with sputum smear positivity for TB bacilli were investigated.

Results: The MPV was 7.46 ± 0.71 fl in the PTB group and 8.02 ± 0.56 fl in the control group ($p = .000$). The blood platelets count, CRP levels, ESR and ferritin levels were significantly higher in the active PTB group than in the control group ($p = .000$). In the PTB group, CRP levels ($p = .012$) and platelets count ($p = .026$) but not ESR ($p = .565$) and MPV ($p = .392$) were significantly correlated with the sputum smear positivity for TB bacilli.

Conclusions: The MPV was lower in patients with PTB than in healthy controls but the difference was limited. The MPV does not reflect the severity of the disease. The use of MPV as an inflammatory marker and a negative acute phase reactant in PTB does not seem to be reliable. The ESR and CRP proved to be good markers for the

severity of pulmonary tuberculosis. However CRP showed more significant results than ESR in determining the disease severity.

Key words: inflammatory response, pulmonary tuberculosis, sputum smear, TB bacilli

INTRODUCTION

Tuberculosis (TB) is a common infectious disease caused by mycobacterium tuberculosis (MTB), and it remains an important public health problem despite developments in its diagnosis and treatment. According to a world health organization (WHO) report, TB caused the death of 1.4 million people worldwide in 2010 (WHO, 2011). Delayed diagnosis and treatment are also important public health issues. The only definitive diagnostic method known for pulmonary TB (PTB) is the growth of MTB bacilli from pulmonary material (sputum or bronchoscopic lavage fluid) (Ozdemir et al., 1994). Although no other current test is more reliable for determining the activity of PTB than culture growth of bacilli, some biochemical parameters that reflect inflammation in patients with this condition may provide guidance at the diagnostic stage.

TB is an infectious disease characterised by a cellular immune response. MTB and its components activate macrophages and lymphocytes, which then secrete cytokines (TNF- α , IL-6, IL-8, and

IL-12) enabling the development of a cellular immune response (Poveda et al., 1999). Of these cytokines, TNF- α and IL-6 in particular affect maturation of thrombopoietic cells and secretion of platelets into the circulation (Kaushansky, 2005). The C-Reactive Protein (CRP) level, Erythrocyte Sedimentation Rate (ESR), presence of reactive thrombocytosis can reportedly be used to determine the disease activity and these values are correlated with the disease severity (Tozkoparan et al 2007).

The mean platelet volume (MPV) reflects the size of platelets. It can be measured during a routine automatic whole blood count. The importance of MPV has been emphasized as an inflammation marker in some chronic inflammatory disorders, such as inflammatory intestinal diseases, rheumatoid arthritis, and ankylosing spondylitis. An inverse correlation between disease activity and MPV has been demonstrated (Kapsoritakis et al., 2001).

This study aims to evaluate the role of some inflammatory markers in patients with active

pulmonary tuberculosis (PTB) and to investigate the relationship between the inflammatory markers with each other as well as with the sputum smear positivity for TB bacilli.

METHODS

This study was conducted on 50 patients (24 male and 26 female) who presented to the outpatient clinic of Qena general chest hospital between April 2017 and October 2017 and were diagnosed with pulmonary tuberculosis (PTB) based on clinical symptoms, radiological signs and examination of sputum smears and cultures for mycobacterium tuberculosis bacilli (Mtb), their ages ranged between 20-70 years old with a mean age of 41.7 years old in addition 50 apparently healthy subjects (23 male and 27 female) who presented to the outpatient clinic for routine examination and presented no disease and normal lung radiography findings during the examination were included in the study as control group.

The exclusion criteria were:

1. Children.
 2. Patients with history of receiving anti tuberculosis treatment.
 3. Patients known to have malignancy.
 4. Patients with extra pulmonary TB.
 5. Pregnancy
 5. Systemic arterial hypertension
 6. Endocrinal disorders, hematological disease, hepatic and renal disorders.
- Detailed histories of all patients and healthy subjects were obtained and their smoking status were noted. A physical examination of all participants was performed and weights and heights were measured to calculate their body mass index (BMI). 6 ml of Venous blood was drawn from all participants (pre-treatment samples in patients with PTB). Two ml blood was transferred to an evacuated tube containing ethylenediaminetetraacetic acid (EDTA) used to determine complete blood count (CBC) using swelab alfa plus hematology analyzer device (Boule Diagnostics, Sweden), 1.6 ml blood was transferred to sodium citrate tube to measure ESR using westergren method by adding 0.4 milliliter of sodium citrate anticoagulant was pipette into 1.6 milliliter of EDTA anticoagulated blood and mixed well. The cap of the container was removed and the sample placed in the ESR stand. The westergren pipette was inserted and was positioned

vertically. Using a safe suction method, the blood was drawn to the zero mark of the westergren pipette avoiding air bubbles. This was allowed to stand for 1 hour. At exactly 1 hour, the level at which the plasma meets the red cells was read in mm/hr, and the remaining 2.4 ml blood was put in plain tube and left to clot, then

centrifuged at 3000 rpm for 15 minute and serum separated for measurement of albumin using RIELE PHOTOMETER 5010 chemistry analyzer device on the same day, then serum was kept frozen at -20 C° for assay of CRP using Sunostik SBA-733 analyser device (China) and Ferritin using ELISA method.

The positive sputum smear were quantified by the number of acid fast bacilli in the sample (1+, 2+, 3+)

Number of Acid fast bacilli(AFB) seen	Result
1-9 AFB per 100 fields	Exact number
10-99 AFB per 100 fields	1+
1-10 AFB per field	2+
> 10 AFB per field	3+

(Karin Weyer, <https://pdfs.semanticscholar.org>)

Ethical Considerations:

1. Written informed consent was obtained from patients or their legal guardians.
2. An approval by the local ethical committee was obtained before the study.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
4. All the data of the patients and results of the study are confidential and the patients have the right to keep it.

5. The authors received no financial support for the research, author-ship, and/or publication of this article
6. The patient has the right to withdraw from the study at any time.

Statistical Analysis

Statistical Analysis was performed using the SPSS version 22 software. All the data were expressed as a mean \pm SD (mean and standard deviation). One-way analysis of variance (ANOVA) and independent-sample t test were applied where appropriate. $P < 0.05$ was considered statistically significant in all comparisons.

RESULTS

The study group comprised 50 patients with active PTB and 50 healthy subjects.

Table (1): Age, sex, BMI and smoking habits of the PTB patients and healthy subjects

TB		Mean \pm SD		P-value
		Patient (N=50)	Controls (N=50)	
<i>Age in years (Mean\pmSD)</i>		41.70 \pm 14.92	37.88 \pm 15.20	0.208
<i>Sex</i>	<i>Male</i>	24(48%)	23(46%)	0.841
	<i>Female</i>	26(52%)	27(54%)	
<i>BMI (Mean\pmSD)</i>		20.78 \pm 0.84	23.48 \pm 1.05	0.000*
<i>Smokers n(%)</i>		17 (34%)	15 (30%)	

The mean age, sex distribution, and number of individuals with smoking habits showed no statistically significant differences between the two groups. The BMI was lower in patients with active PTB than in the healthy controls, and the difference was statistically significant.

Table (2): Comparison of hematological parameters between PTB patients and healthy subjects.

	Mean \pm SD		P-value
	Patient (N=50)	Controls (N=50)	
<i>HGB (g/dl)</i>	11.60 \pm 1.99	13.12 \pm 1.40	.000*
<i>RBCs (10¹²/l)</i>	4.81 \pm 0.78	4.84 \pm 0.49	.805
<i>HCT (l/l)</i>	34.42 \pm 5.74	39.01 \pm 3.72	.000*
<i>MCV (fl)</i>	69.85 \pm 11.10	79.79 \pm 9.56	.000*
<i>MCH (pg)</i>	23.84 \pm 2.09	28.07 \pm 5.52	.000*
<i>WBCs (10⁹/l)</i>	10.07 \pm 4.60	8.20 \pm 1.83	.009*
<i>Platelets (10⁹/l)</i>	316.72 \pm 81.48	223.38 \pm 40.31	.000*
<i>MPV (fl)</i>	7.46 \pm 0.71	8.02 \pm 0.56	.000*

The MPV was significantly lower in the active PTB group than in the control group. The platelets and WBCs count were significantly higher in PTB group than in the control group. The hemoglobin level, RBCs, MCV and MCH were significantly lower in PTB group than the control group.

Table (3): Comparison of inflammatory markers between PTB patients and healthy subjects.

	Mean±SD		P-value
	Patient(N=50)	Controls(N=50)	
<i>ESR (mm/hr)</i>	76.70±10.74	12.82±3.28	.000*
<i>CRP (mg/l)</i>	103.88±38.00	3.88±1.28	.000*
<i>Ferritin (ng/ml)</i>	581.32±370.64	61.94±28.85	.000*
<i>Albumin (g/dl)</i>	3.56±0.48	4.20±0.47	.000*

The CRP level, ESR and ferritin level were significantly higher in PTB group than in the control group. The albumin level was significantly lower in PTB patients than in the control group.

Table (4): Correlation between the sputum smear positivity for TB bacilli and the hematological parameters of the patients.

Sputum smear Positivity of TB bacilli	Mean±SD			P-value
	1+(N=21)	2+(N=24)	3+(N=5)	
<i>HGB (g/dl)</i>	11.10± 1.93	12.02± 2.18	11.70±0.41	.309
<i>RBCs (10¹²/l)</i>	4.63± 0.80	5.01± 0.81	4.61±0.17	.221
<i>HCT (l/l)</i>	34.11± 5.92	35.19± 6.05	32.02±2.42	.515
<i>MCV (fl)</i>	68.23± 16.02	70.88± 5.90	71.72±1.62	.682
<i>MCH (pg)</i>	23.93± 2.01	23.92± 2.30	23.10±1.36	.710
<i>WBCs (10⁹/l)</i>	9.57± 5.01	10.23± 4.15	11.42±5.58	.710
<i>Platelets (10⁹/l)</i>	283.57± 64.03	347.83± 91.08	306.60±37.68	.026*
<i>MPV (fl)</i>	7.58± 0.79	7.44± 0.69	7.10±0.37	.392

There was a significant relationship between the sputum smear positivity for TB bacilli and the platelets count. No significant relationship was found between the sputum smear positivity for TB bacilli and the MPV. No significant relationship was found between the sputum smear positivity for TB bacilli and the WBCs count.

Table (5): Correlation between the sputum smear positivity for TB bacilli and the inflammatory markers of the patients.

Positivity	Mean±SD			P-value
	1+(N=21)	2+(N=24)	3+(N=5)	
<i>ESR (mm/hr)</i>	74.95± 9.03	77.54± 11.51	80.00±14.47	.565
<i>CRP (mg/l)</i>	87.75± 42.60	111.12± 28.88	136.86±27.87	.012*
<i>Ferritin (ng/ml)</i>	496.52± 368.76	601.12± 370.65	842.40±296.12	.162

Albumin (g/dl)	3.63± 0.620	3.54± 0.39	3.35±0.18	.493
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There was a significant relationship between the sputum smear positivity for TB bacilli and the CRP level. No significant relationship was found between the sputum smear positivity for TB bacilli and the ESR, ferritin and albumin.

Table (6): Correlation between inflammatory markers in active PTB patients

Correlations	MPV	ESR	CRP	Albumin	Ferritin
Platelets Pearson Correlation	-0.213	0.255	0.366	0.056	0.102
Sig. (2-tailed)	.137	.074	0.009*	.698	.481
MPV Pearson Correlation	-----	-0.261	-0.060	0.088	0.025
Sig. (2-tailed)		0.067	.678	.544	.864
ESR Pearson Correlation	-----	-----	0.120	-0.143	0.188
Sig. (2-tailed)			.406	.322	.190
CRP Pearson Correlation	-----	-----	-----	-0.110	0.491
Sig. (2-tailed)				.448	.000*
Albumin Pearson Correlation	-----	-----	-----	-----	-0.153
Sig. (2-tailed)					.288
Ferritin Pearson Correlation	-----	-----	-----	-----	-----
Sig. (2-tailed)					

There was a significant correlation between the platelet count and the CRP level. There was a significant correlation between the ferritin level and the CRP level. There was an inverse correlation between the MPV and platelet count but it was not statistically significant ($P=0.137$). There was an inverse correlation between the MPV and the CRP level but it was not statistically significant ($P=0.678$).

DISCUSSION

Active TB has been associated with an imbalance of the Th1/Th2 cytokine pattern. Effective induction of Th1 immunity is vital in the defence against Mtb. The major cytokines secreted in response to Mtb are IL-2, IFN gamma, IL-6, IL-12, and TNF- α (Zuniga et al., 2012). Animal

model have demonstrated the presence of cytokines in TB granulomas.

In addition, human studies have shown IL-1 beta, IL-6, and TNF- α , which are secreted from active macrophages in the broncho-alveolar lavage fluid of patients with active TB (Law et al., 1996). Nevertheless, a systemic inflam-

matory response is known to occur in patients with TB when these cytokines enter the systemic circulation, and as a result the CRP blood level and ESR increase.

Platelets are pulmonary immune cells as shown by their role in the pathogenesis in some pulmonary diseases and their immune cell characteristics (**Herd and Page, 1994**). In patients affected by PTB, microthromboses form in vessels around the tuberculous cavities, probably as a defence mechanism (**Kuhn and Askin, 1990**). These thromboses prevent the spread of Mtb, thus averting the occurrence of disseminated disease. Reactive thrombocytosis is seen in many chronic inflammatory diseases, including TB (**Baynes et al., 1987**) (**Feng et al., 2011**). The increased number of platelets in patients with PTB has also been linked to the disease extent, (**Sahin et al., 2012**) as in this study platelets count increased significantly in active TB disease (p value=.000) and had positive correlation with sputum smear positivity for TB bacilli (p value=.026).

The MPV reflects the size of platelets and is a marker used to determine platelet function. The size of platelet in the circulation is

associated with the intensity of inflammation (**Gasparyan et al., 2011**). In some chronic inflammatory disorders, the MPV has been used as an inflammatory marker of disease activity and to monitor the response to anti-inflammatory treatment (**Kapsoritakis et al., 2001**) (**Kisacik et al., 2008**) (**Purnak et al., 2013**). In acute exacerbations of chronic obstructive pulmonary disease, in which the intensity of inflammation also increases, the MPV has been found to be significantly lower while the serum leukocyte count and neutrophil percentage were higher than those during the stable period. It has been suggested that the MPV can be used as a negative acute-phase reactant (**Ulasli et al., 2012**). When various cytokines, including IL-6, enter the systemic circulation in patients with TB, systemic symptoms emerge and an acute-phase response occurs (**Unsal et al., 2005**). In such cases of TB, the lower MPV can be explained by the fact that megakaryopoiesis is affected by the excess production of proinflammatory cytokines and acute-phase reactants which decreases the size of platelets, therefore smaller platelets are released from the bone marrow (**Bath and Butterworth.,1996**). (**Baynes et al., 1987**), found that the MPV to be low in patients with

active PTB and suggested that although thrombopoiesis increased in patients with TB, the platelets' lifetime may have been shortened. In this study MPV was significantly lower in TB patients than healthy subjects (p value=.000). Similarly, **Gunluoglu et al. (2014)** found that MPV was significantly lower in TB patients than Healthy subjects. Platelets and their indices in active PTB have been addressed in several previous studies (**Tozkoparan et al., 2007**) (**Feng et al., 2011**) (**Sahin et al., 2012**). Contradictory to this study, **Lee et al. (2016)** found that the MPV in TB patients is higher than Healthy subjects but the difference was not significant. **Tozkoparan et al. (2007)** found that the MPV was significantly higher in patients with active TB than in control patients with inactive TB and non-specific pneumonia and decreased with anti-TB treatment. On the other hand, **Sahin et al. (2012)** showed that in patients with active TB MPV was identical to that of patients with non-specific pneumonia and healthy subjects.

Disease-specific characteristics and cardiovascular risk factors (diabetes, hypertension, smoking, obesity) may directly affect the MPV (**Gasparyan et al., 2011**). This is why participants with risk factors were excluded from the study. In the above mentioned

studies there were not enough data about the patients' characteristics that could have affected the MPV. Contradictory results may be related to the characteristics of the studied groups of patients. An association has been established between obesity and high MPV, and a positive correlation has been demonstrated between BMI and MPV (**Coban et al., 2005**). As expected, in this study BMI in the PTB patients was lower than in healthy controls but no relationship was found between BMI and MPV.

CRP is an acute-phase reactant secreted from hepatocytes in response to tissue damage or inflammation. It has been shown to increase in proportion to the severity of TB and decrease after treatment (**Taha and Thanoon, 2010**). It has also been linked to mortality (**Kim et al., 2012**). The ESR, another acute-phase reactant, has been found to be high in patients with active PTB and to have a correlation with the radiological extent of disease (**Caner et al., 2007**). This study also demonstrated that the CRP level and ESR increased significantly in active disease and CRP (p value=.012) alone not ESR(p value=.565) had a significant correlation with the sputum smear positivity for TB bacilli. This may be because of

many factors affecting ESR like the physiological state, body temperature, used drugs, smoking habits, physical activity, morphological characteristics of red blood cells. In assessing the correlation between ESR and CRP, it can be observed a moderate correlation between the two markers (p value=.120) which corroborates the findings of another study (**Furuhashi et al., 2012**). In contrast Jeremiah et al found no correlation between ESR and CRP in the early diagnosis of tuberculosis, describing that the CRP can not be used as a screening tool for the early diagnosis of tuberculosis (**Jeremiah et al., 2013**).

Albumin is significantly reduced in patient with PTB, and this is considered to be due to nutritional factors, enteropathy and acute phase reactants, as hepatic synthesis of acute phase proteins inhibit the production of serum albumin (**Kuppamuthu et al., 2008**) in this study serum albumin was significantly decreased in TB patients than healthy subjects (p value=.000).

Some reports indicated that ferritin synthesis is stimulated in pulmonary tuberculosis as a consequence of the inflammatory process (**Wessels et al., 1999**). Al-

Omar and Oluboyede attributed the rise in serum ferritin levels to two factors: first, increased production by monocytes and macrophages, monocytosis having been observed in pulmonary TB, second, serum ferritin is an acute phase protein that increases in inflammatory conditions (**Al-Omar and Oluboyede, 2002**). In favour of this conclusion, in this study the ferritin increased significantly in active disease (p value=.000) and had a positive correlation with CRP (p value=.000) but a non significant correlation with sputum smear positivity for TB bacilli (p value=.162).

CONCLUSIONS

The MPV, measured automatically during a whole blood count, in patients with active PTB was lower than in healthy controls and the MPV had no correlation with thrombocytosis, acute phase reactants or the sputum smear positivity for TB bacilli. Therefore, it does not reflect the disease severity. The ESR and CRP proved to be good markers for the severity of pulmonary tuberculosis treatment, they can be used in routine clinical practice of these patients, however CRP showed more significant results than ESR in determining the disease severity. It

is important to mention that these tests are not specific for tuberculosis, thus it is required the combined use of other parameters, such as clinical, radiological, and conventional microbiological data.

The increased levels of serum ferritin and the decreased levels of serum albumin indicate that PTB is associated with an inflammatory response.

RECOMMENDATION

MPV does not seem to be reliable as an inflammatory marker to determine the disease activity in patients with PTB and it is a negative acute-phase reactant. Thus, further prospective studies on this issue with the inclusion of larger numbers of patients are mandatory.

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الملخص العربي

مقدمة: مرض الدرن الرئوي يعتبر مرض عدوي شائع بسبب بواسطة بكتيريا الدرن على الرغم من عدم وجود أداة تشخيص المرض غير نمو البكتيريا في المزرعة، يوجد بعض الدلالات الكيميائية التي تعكس الالتهابات الموجودة في مرض الدرن يمكن أن تساعد في التشخيص. يوجد أن متوسط حجم الصفائح الدموية يتناسب عكسياً مع درجة الالتهابات في بعض الأمراض الالتهابية المزمنة.

الهدف من الدراسة: تقييم بعض دلالات الالتهاب في مرض الدرن الرئوي النشط (سرعة ترسيب كرات الدم الحمراء- بروتين سي الفعال- الفيرتين- الالومبين- الصفائح الدموية- متوسط حجم الصفائح الدموية- كرات الدم البيضاء) وإيجاد العلاقة بين دلالات الالتهاب وبعضها ودرجة الايجابية لبكتيريا الدرن.

طرق البحث: تمت الدراسة على 50 مريض بمرض الدرن الرئوي النشط والذين تقدموا للعيادة الخارجية لمستشفى قنا العام وتم تشخيصهم بالمرض و50 شخص سليم من الذين قدموا إلى العيادة الخارجية للفحص الروتيني خلال الفترة من ابريل 2017 إلى أكتوبر 2017. يتم مقارنة صورة الدم الكاملة وبروتين سي الفعال وسرعة ترسيب كرات الدم الحمراء والفيرتين والالبومين بين المرضى والحالات السليمة. وفي المرضى يتم إيجاد علاقة بين دلالات الالتهاب وبعضها ودرجة الايجابية لبكتيريا الدرن.

النتائج: متوسط حجم الصفائح الدموية في مرض الدرن الرئوي $7,46 + 0,71$ وفي الحالات السليمة $8.02 + 0.56$ عدد الصفائح الدموية، نسبة بروتين سي الفعال، سرعة ترسيب كرات الدم الحمراء ونسبة الفيرتين اعلي بدرجة كبيرة في مرض الدرن الرئوي عن الحالات السليمة. في مرض الدرن الرئوي توجد علاقة كبيرة بين (نسبة بروتين سي الفعال $P=0.12$) وعدد الصفائح الدموية ($P= 0.26$) ودرجة ايجابية بكتيريا الدرن وتوجد علاقة ولكن ليست كبيرة بين (سرعة ترسيب كرات الدم الحمراء $P=0.565$) ومتوسط حجم الصفائح الدموية ($P=0.392$) ودرجة ايجابية بكتيريا الدرن.

الاستنتاج: متوسط حجم الصفائح الدموية اقل في مرض الدرن الرئوي عن الحالات السليمة متوسط حجم الصفائح الدموية لا يعكس درجة تطور المرض لا يعتمد استخدام متوسط حجم الصفائح الدموية كدال عكسي للالتهاب سرعة ترسيب كرات الدم الحمراء وبروتين سي الفعال يعتبروا دلالات جيدة لدرجة تطور المرض ولكن بروتين سي الفعال بدرجة اعلي من سرعة ترسيب كرات الدم الحمراء في تحديد درجة تطور المرض.