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Platelet Indices in Drug Resistant Tuberculosis Patients in Ibadan

Pelumi Daniel Adewole[1], Ogundipe Tosin Deborah[2]

[1] Department of Medical Laboratory Science, Faculty of Basic and Applied Sciences, Elizade University, Ilara-Mokin, Ondo State, Nigeria
[2] Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, Kwara State University, Malete, Kwara State, Nigeria
[*]**Corresponding Author**
Department of Medical Laboratory Science, Faculty of Basic and Applied Sciences
Elizade University
Ilara-Mokin, Ondo State
Nigeria
Email: daniel.adewole@elizadeuniversity.edu.ng

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Abstract

Background: Tuberculosis remains a leading infectious cause of death. Drug resistant tuberculosis (DR-TB) which serves as a major problem for TB control thereby serves as a major hindrance to the recent achievements. Although, there has been an increase in TB and DR-TB cases, the gaps in case detection and treatment remain a problem due to under reporting and diagnosis, but the literature about the platelets indices associated with Drug Resistance Tuberculosis is scarce. This study aimed to determine the association between Platelet indices and drug Resistant Tuberculosis.

Materials and Methods: This study conducted a prospective case-control study to evaluate Platelets indices among 30 patients with DR-TB, 30 DS-TB and 30 healthy individuals. Sputum and Blood samples were analyzed using Gene Xpert and Mindary- BG5380 5-part automated full blood count analyzer respectively together with their Erythrocyte Sedimentation Rate using Westergren method.

Results: There was a statistically significant difference in Platelet counts, PCT (Plateletcrit), MPV (Mean Platelet Volume), and ESR (Erythrocytes Sedimentation Rate) among DR-TB. Among DS-TB patients, there was a statistically significant difference in PCT, MPV among DR-TB when compared to DS-TB at p-value < 0.05. There was a statistically significant difference in Platelet counts, PCT, MPV, ESR between DS-TB and Healthy controls at p-value < 0.05. The sensitivity of DR-TB for platelet count, MPV and PCT were 36%, 47%, and 47% respectively. Also, the specificity of the platelet count, MPV and PCT were 47%, 55% and 55% respectively. The sensitivity of DS-TB for platelet count, MPV and PCT were 77%, 68%, and 72% respectively. Also, the specificity of the platelet count, MPV and PCT were 53%, 63% and 58% respectively.

Conclusion: MPV and ESR were significantly reduced among DR-TB; Platelet count and PCT were significantly increased. MPV was significantly reduced among DS-TB; Platelet count, PCT and ESR were

significantly increased. The evaluation of the platelet indices among the DR-TB could be used as a marker during the course of diagnosis, prognosis and treatment of patients. Among DS-TB, the estimation of platelet indices and ESR could be used as a diagnostic tool for DS-TB patients.

Keywords: Drug resistant tuberculosis, Platelet indices, Erythrocyte sedimentation rate, Ibadan

1. Introduction

Tuberculosis (TB) is one of the most problematic and important diseases threatening Public Health in Africa and caused by a single pathogen called Mycobacterium tuberculosis [1]. Epidemiologically, tuberculosis remains a leading infectious cause of death, with an estimated 10 million incident cases per year [2]. In the year 2012, an estimated 1.3 million people died of this disease. However, more than 80% of TB patients are in the economically productive age of 15 to 49 years [3].

Drug resistant tuberculosis (DR-TB) can be defined as resistance to either rifampicin or isoniazid which is of the first line anti- tuberculosis drug. This serves as a major Problem for TB control that may weakened the recent achievements [4]. Nigeria is one of the 14 countries on the high burden lists for TB [5; 6]. Although, there is an increase in TB and DR-TB cases, the gaps in the case detection and treatment remain a problem due to under reporting and misdiagnosis [7].

Platelet is well known to be deeply involved in homeostasis [8]. Platelets have been extensively studied in inflammation -induced atherosclerosis as well as in thrombosis [9]. Platelet indices have been studied in several infectious diseases such as hepatitis B or other infections [10; 11]. Platelet indices are biomarker of platelet activation. The Abnormality of platelets count indicate inflammation [12; 13; 14]

A few studies have investigated the relations between drug resistant tuberculosis and platelets indices [15; 16; 17; 18]. The study aims to determine the association between platelet indices and DR-TB patients also investigating the sensitivity and specificity of platelet indices in determining the activity of DR-TB by comparing it with erythrocyte sedimentation rate as an inflammatory marker in other to validate platelet indices as drug resistant tuberculosis diagnostic marker.

2. Materials and Methods

2.1 Ethical approval/Inform consent

Ethical approval was obtained from Oyo state ministry of health and informed consent was obtained from all the participants. The principles of privacy and confidentiality were upheld.

2.2 Research design

A prospective case control study was carried out. About 5mls of blood was obtained using sterile syringe and needle for Haematological Parameters and Erythrocyte Sedimentation Rate.

2.3 Study Population

The study population consists of patients suffering from normal TB, Drug Resistant Tuberculosis Patients and healthy control group.

2.4 Study site

Blood and Sputum samples were collected among the patients attending Government Chest Hospital, Jericho, Ibadan and the analysis was done in Clina-Lancet laboratories Ibadan.

2.5 Sample Size

A total of 90 blood and sputum samples were collected. The sample size was computed using the formula designed Bamigboye et al., (2013):

$$n = \frac{2\left(Z\alpha + Z\beta\right)^2 \times \pi\left(1-\pi\right)}{\left(P1 - P2\right)/2}$$

Where n = the minimum sample size

Z^{α} = standard normal deviation at 80% of power set at 0.84, P1 is the prevalence of DR-TB = 2.2% (From WHO, 2011).

e is the level of error tolerance (10%), P2=Prevalence rate of mycobacterium tuberculosis is 50%

2.6 Sample Technique

A convenience sampling method is used to select patients who attended Tuberculosis clinic and

meet the inclusion criteria for case study and random sampling method was used to select those that meet the inclusion criteria for healthy control group.

2.7 Blood Sample Collection

Sputum samples were collected from each participant in to a leak proof, screw capped specimen containers and was transported at 4^{o} c to the tuberculosis laboratory and within 24 hours of collection it was analyzed. while 5ml of the blood sample was withdrawn from the antecubital fossa of the study participants into vacutainer EDTA tubes for full blood count and ESR analysis.

2.8 Laboratory Investigations

Sputum samples were analyzed using gene Xpert machine (Cepheid in-cooperation, California USA). Blood samples were analyzed for platelet indices using Mindary- BG5380 5-part automated full blood count analyzer.

2.9 Data Collection

Data Collection was done with the aid of a structured questionnaire to obtain the socio-demographic characteristics of respondents and TB history.

Inclusion/Exclusion criteria: DR-TB cases, confirmed by gene expert was enrolled into the study, while the individuals that belong to any high-risk group (example homeless, drug user and other) was excluded in this study.

2.10 Data analysis

SPSS version Statistical package was used. Descriptive statistics (Means, standard deviations and frequency) was used to describe the data. Statistical Comparison was Calculated by an unpaired t-Test. The association was evaluated using ANOVA, Pearson Correlation Coefficient. Regression analysis was preformed to make regression equation and calculate coefficient of determination, Sensitivity and specificity at P value < 0.05.

3. Results

3.1 Relationship between Platelet Indices and Drug Resistant Tuberculosis

Mean value for platelet count, PCT (plateletcrit) and MPV (mean platelet volume) has a statistically significance difference at P-value < 0.05. The platelet count was significantly increase in the DR-TB Patients ($293.47 \times 10^{\wedge 9}$ /L) than in the healthy controls ($197.73 \times 10^{\wedge 9}$ /L), PCT was significantly increase in the DR-TB Patients (2.78%) than in the controls (1. 72%). However, MPV was significantly decreased in the DR-TB Patients (10.04fL) than in the controls (12.10fL) (Table 1).

The mean value for PCT, MPV when compared in DR-TB and DS-TB patient, were statistically significant. For instance, PCT is 2.78%, MPV is 10.04Fl among DR-TB than DS-TB with PCT of 2.22% and MPV of 9.02 fl respectively (Table 2). The comparison of DS-TB and Healthy control shows statistically significance difference at P-value <0.05: platelet count ($282.43 \times 10^{\wedge 9}$ /L), PCT (2.22%), while the MPV (9.02fL) was decrease than in control individuals (Table 3). There was a statistically significant association in Platelet count, PCT, MPV between DR-TB, DS-TB and Healthy control using one way Anova with p-value of 0.01 (Table 4).

Table 1: Comparison of Platelet indices between DR-TB and Healthy Control (Unpaired t-test)

PARAMETERS	DR-TB Mean ± SD	Healthy control Mean ± SD	P-VALUE
PLATELET COUNTS(10^9/L)	293.47± 116.90	197.73±104.23	0.01*
PCT(%)	2.78± 0.95	1.72±0.54	0.01*
MPV(FL)	10.04± 2.06	12.10±2.87	0.02*
PDW (%)	16.21±0.61	16.50±3.10	0.62

Table 2: Comparison of Platelet indices between DR-TB and DS-TB (Unpaired t-test)

PARAMETERS	DR-TB Mean ± SD	Healthy control Mean ± SD	P-VALUE
PLATELET COUNTS(10^9/L)	293.47± 116.90	197.73±104.23	0.01*
PCT(%)	2.78± 0.95	1.72±0.54	0.01*
MPV(FL)	10.04± 2.06	12.10±2.87	0.02*
PDW (%)	16.21±0.61	16.50±3.10	0.62

Table 3: Comparison of Platelet indices between DS-TB and Healthy control (Unpaired t-test)

PARAMETERS	DR-TB Mean ± SD	DS-TB Mean ± SD	P-VALUE
PLATELET COUNTS(10^9/L)	293.47± 116.90	282.43±147.58	0.75
PCT (%)	2.78± 0.95	2.22± 1.22	0.05*
MPV(FL)	10.04± 2.06	9.02 ± 1.30	0.03*
PDW (%)	16.21±0.61	16.15± 0.71	0.73

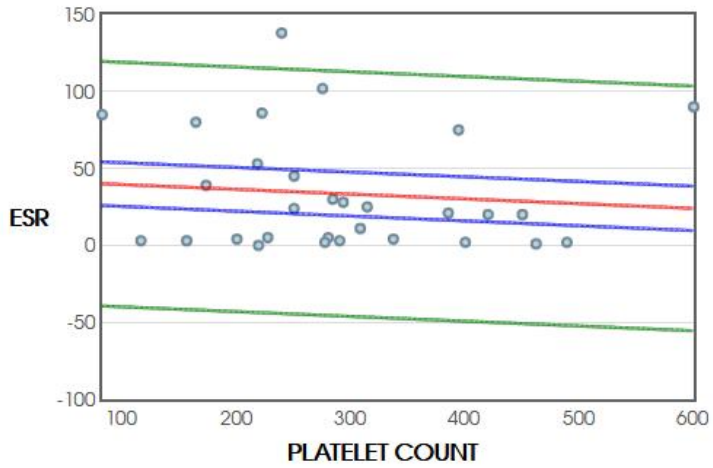
Table 4: Comprison of Platelet count, PCT, MPV between DR-TB, DS-TB and Healthy control using one way Anova with p-value of 0.01

PARAMETERS	DR-TB Mean ± SD	DS-TB Mean± SD	Healthy control Mean ± SD	F-value	P-value
PLATELET COUNTS(10^9/L)	293.47±116.90	282.43±147.58	197.73±104.23	5.33	0.01*
PCT(%)	2.78± 0.95	2.22± 1.22	1.72±0.54	9.43	0.01*
MPV(FL)	10.04± 2.06	9.02 ± 1.30	12.10±2.87	15.63	0.01*
PDW (%)	16.21±0.61	16.15± 0.71	16.50±3.10	0.30	0.74

3.2 Correlation between Platelet Indices and Erythrocyte Sedimentation Rate

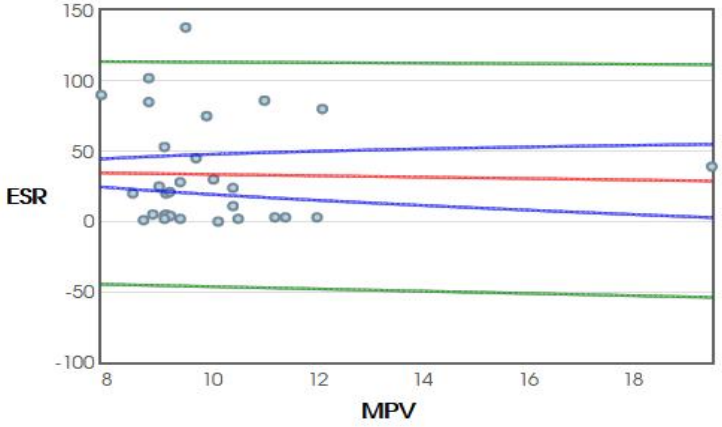
Among the DR-TB Patients group, Platelet counts, PCT, MPV and PDW show negative correlation with ESR. These Platelet indices decrease with increase in ESR, which shows Statistical significant association at P-value <0.05 (FIGURE 1-3). Among DS-TB Patients, Platelet counts and PCT show positive correlation with ESR (FIGURE 4). MPV and PDW show strong significant negative correlation when correlate with ESR at P-value <0.05 (FIGURE 5-6).

Regression, Correlation coefficient Graph are shown in the figure 1, 2, 3 below Respectively among DR-TB patients.



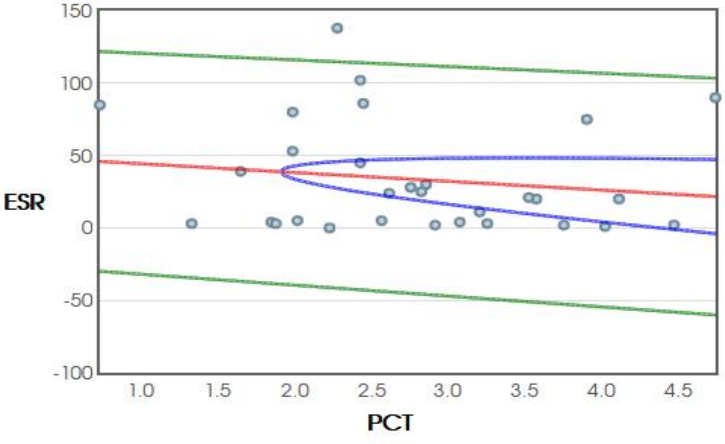
r = -0.10; R^2 = 0.009; t = -0.51; P-value = 0.61

Figure 1: The Regression and correlation between platelet count and Erythrocyte sedimentation rate(ESR) in DR-TB Patients



r = -0.03; R^2 = 0.001; t = -0.143; P-value = 0.89

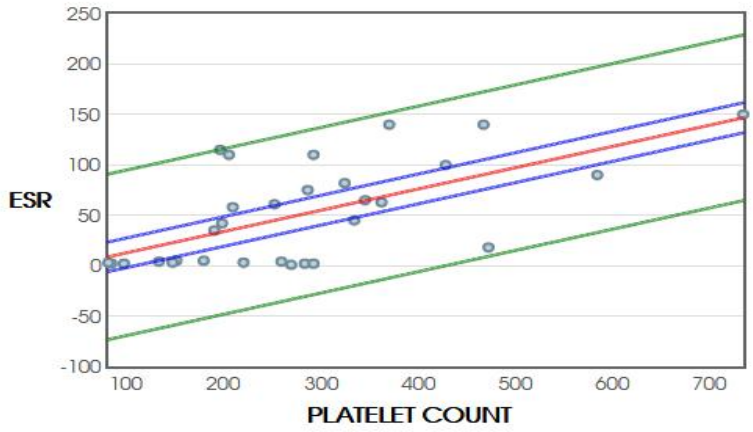
Figure 2: The Regression and correlation between Mean Platelet Volume and Erythrocyte sedimentation rate(ESR) in DR-TB Patients



r = -0.152; R^2 = 0.023; t = -0.82; P-value = 0.42

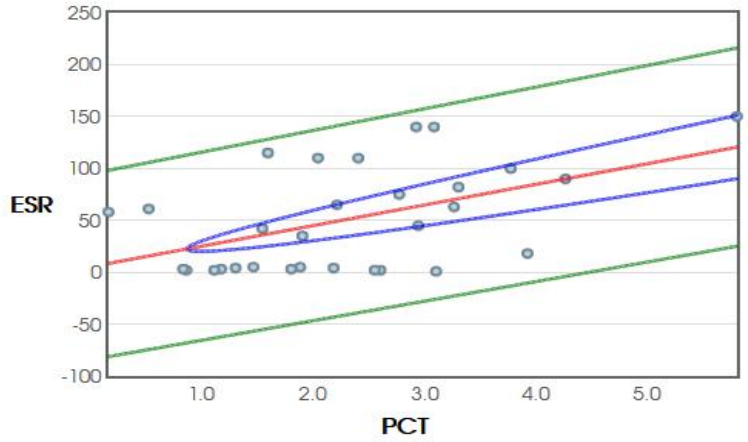
Figure 3: The Regression and correlation between plateletcrit and Erythrocyte sedimentation rate(ESR) in DR-TB Patients

Regression, Correlation coefficient Graph are shown in the figure 4,5,6 below Respectively among DS-TB patients.



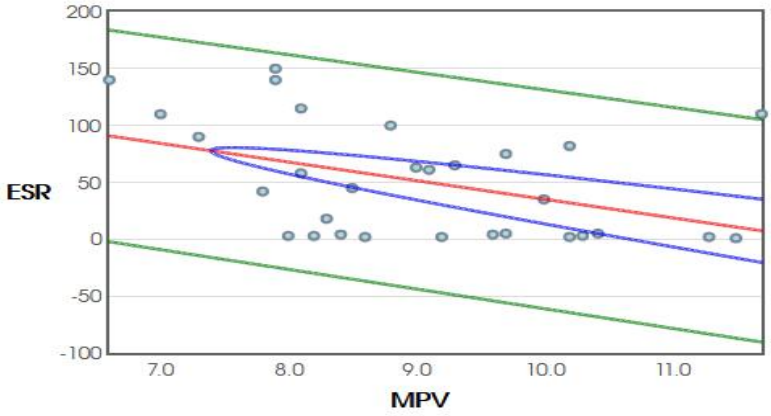
r = 0.63; R^2 = 0.390; t = 4.26; P-value = 0.01

Figure 4: The Regression and correlation between Platelet count and Erythrocyte sedimentation rate(ESR) in DS-TB Patients



r = 0.49; R^2 = 0.239; t = 2.96; P-value = 0.01

Figure 5: The Regression and correlation between Plateletcrit and Erythrocyte sedimentation rate(ESR) in DS-TB Patients



r = -0.427; R^2 = 0.182; t = -2.497; P-value = 0.02

Figure 6: The Regression and correlation between Mean platelet volume and Erythrocyte sedimentation rate(ESR) in DS-TB Patients

3.3 Sensitivity and Specificity Values of Platelet Indices when Compared with ESR

The ESR levels of cut-off point ⩾ 20 /Platelet count, ESR/ PCT and ESR/MPV for diagnosis of Drug resistance tuberculosis: Sensitivity = 36%, 47%, 47% Specificity = 47%, 55%, 55% diagnostic accuracy = 43 %, 50%, 50% Positive Predictive Value = 29%, 64%, 64%, Negative Predictive` Value= 56%, 38%, 38% (Table 5). Among DS-TB patients, ESR levels of cut-off point ⩾ 20 /Platelet count, ESR/ PCT and ESR/MPV for diagnosis of Drug susceptibility tuberculosis had Sensitivity = 77%, 68%, 72% Specificity = 53%, 63%, 58% diagnostic accuracy = 63%, 67%, 67% Positive Predictive Value = 56%, 83%, 72%, Negative Predictive` Value= 75%, 42%, 58% (Table 6).

Table 5: Sensitivity, Specificity, Accuracy, Positive Predictive Value, Negative Predictive Value for DR-TB

	SENSITIVITY	SPECIFICITY	ACCURACY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
ESR/PLT COUNT	36%	47%	43%	29%	56%
ESR/MPV	47%	55%	50%	64%	38%
ESR/ PCT	47%	55%	50%	64%	38%

Table 6: Sensitivity, Specificity, Accuracy, Positive Predictive Value, Negative Predictive Value for DS-TB

	SENSITIVITY	SPECIFICITY	ACCURACY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
ESR/PLT COUNT	77%	53%	63%	56%	75%
ESR/MPV	68%	63%	67%	83%	42%
ESR/PCT	72%	58%	67%	72%	58%

4. Discussion

In certain inflammatory diseases, such as lung inflammation caused by different pathogens such as inflammatory bowel diseases, ankylosing spondylitis, ulcerative colitis, rheumatoid arthritis, and atherosclerosis, platelet indices have been evaluated as an important diagnostic marker (Takeyama et al., 2015), but it has not been accurately investigated in drug resistant pathogens such as Mycobacterium tuberculosis. This sought the role of different platelet indices in drug resistant TB.

In this study, there was significance decrease in MPV among DR-TB patients when compare to healthy controls. Also, there was significance increase in PCT and Platelet count among DR-TB when compare to healthy controls; and no significant change in PDW among these patients. Similarly, there was significance increase in PCT and MPV among DR-TB when compare to DS-TB patients; and no significant change in Platelet count and PDW among these patients. This is similar to studies in Benin, Nigeria by Awodu et al., (2007) and in saudi by Al-omar et al., (2009). Thrombocytosis is either inherited, unregulated production of platelets or due to the reaction in response of cytokines. The abnormal platelets count is an indication of inflammation (Tozkoparan et al., 2007; Unsal et al., 2005; Mirsaeidi et al., 2010). The severity and mortality of bacterial infection is related to variation in platelets count (Mirsaeidi et al., 2010).

Acute phase reactant and severity of tuberculosis is also associated with increased number of platelet count (Tozkoparan et al., 2007; unsal et al.,2005). The MPV is a marker used to determine platelet function and also reflects the size of platelets. The intensity of inflammation is associated with the size of platelet in the circulation

(Gasparyan et al., 2011). In some chronic inflammatory disorders, the MPV is been used as an inflammatory marker of disease activity and to monitor the anti-inflammatory treatment response (Kisacik et al., 2008). The MPV is found to be significantly lower while the neutrophil percentage and the serum leukocyte count were higher than those during the stable period in acute exacerbation of the chronic obstructive pulmonary disease, in which there is also increase in the intensity of inflammation (Kapsoritakis et al., 2001). It has been suggested that the MPV could 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 the cases of TB, the lower MPV can be explained by the fact that excess production of proinflammatory cytokines affect megakaryopoiesis and acute-phase reactants which decrease the size of platelets, therefore smaller platelets are released from the bone marrow (Purnak et al., 2013). Contradictory to this study, it was found that the MPV in TB patients is higher than Healthy subjects but the difference was not significant (Lee et al., 2016). Tozkoparan et al., (2007) found that patients with active TB their MPV was significantly higher than in control patients with inactive TB and non-specific pneumonia and decreased with anti-TB treatment.

In this study, there was significance increase between ESR and DR-TB when compared to healthy controls, and insignificance change of ESR among DR-TB and DS-TB. This is consistent with the previous findings (Ibeneme et al., 2009; Ajayi et al., 2005). ESR is often raised in inflammatory conditions and infections. Increase in ESR could be attributed to increased production of acute phase proteins often observed in chronic infections and release of proteins by the causative organism (M. tuberculosis) into the circulation. Raised plasma viscosity has been reported to cause sluggish flow in microcirculation resulting in insufficient tissue perfusion (Doedhare, 2001). This increase in ESR implies that there is increased rheology of blood in pulmonary tuberculosis. So, an elevated ESR may assist as an indicator to the progression of disease that has previously been known and predominantly correct in case of pulmonary tuberculosis (Ursavas et al., 2010). In pulmonary tuberculosis ESR was regarded as test of activity. One of the prognostic tool and as an indicator of severity of disease was elevated ESR to different level (Hungund et al., 2012) In patients with increased sputum positivity elevated ESR level was observed. In tuberculosis patients elevated ESR was also reported by different scientists in earlier studies. These findings were in agreement with previous studies by (Hungund et al., 2012).

In this present study, ESR was found to be insignificantly correlated with Platelet indices among DR-TB. But among DS-TB, ESR was found to be significantly correlated with Platelet counts, PCT, MPV and PDW. ESR was positively correlated with Platelet count and PCT and negatively correlated with PDW. This means increase in ESR leads to increase in Platelet counts and PCT and decrease in MCV and PDW. This similar to study carried out by Ursavas et al., (2010), which said increase in ESR which is suggestive of infection and inflammation causes thrombocytosis in TB patients. This could be as a result of effect of anti-tubercular drugs among the patients.

In this present study, the sensitivity of DR-TD for platelet count, MPV and PCT were 36% , 47%, and 47% respectively. Also, the specificity of the platelet indices was 47%, 55% and 55% respectively. The sensitivity of DS-TB for platelet count, MPV and PCT were 77%, 68%, 72%. Also the specificity of Platelet count, MPV and PCT were 53%, 63%, 58% respectively. With the best of our knowledge, there have been rare journals on sensitivity and specificity of platelet count, MPV and PCT in diagnosis of DR-TB using ESR as predictive value. The only similar study related MPV to CRP and ESR (Gunluogu et al., 2014). But couldn’t do their sensitivity and specificity infer, from our study the sensitivity and specificity for PLT, PCT and MPV is low. Platelet count, MPV and PCT were found to be less sensitive and specific for the diagnosis of MDR-TB. However, Platelet count, MPV and PCT were found to be more sensitive and specific for diagnosis among DST-TB. This could be as a result of effect of anti-tubercular drugs among the patients. This study had several limitations. The only inclusion criteria for this study were patient with MDR-TB without

including their HIV status. C-reactive protein could not be use in this present study.

5. Conclusion

MPV was significantly reduced among DR-TB and DS-TB; Platelet count and PCT were significantly increased and there no significant change in PDW among DR-TB and DS-TB. The evaluation of the platelet indices among the DR-TB could be used as a marker during the course of diagnosis, prognosis and treatment of patients. Among DS-TB, the platelet indices could be used as a diagnostic marker for DS-TB patients.

6. Recommendation

Future research should include MDR-TB patient who are positive for HIV and also increase the sample size to confirm the findings of this present study. Future research should make use of C-reactive protein as the predictive biomarker.

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