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Original Research Article

Evaluation of the diagnostic utility of leucocyte in comparison to other biomarkers in the management of patients with pulmonary tuberculosis

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ABSTRACT

Background: Pulmonary tuberculosis (PTB) is an infectious and debilitating disease that affects millions of people each year. Simple, reliable and cost effective biomarkers are vital to fore-stall the morbidity and mortality that is hallmark of the infection especially in resource poor economy.
Methods: This comparative study enlisted 140 subjects: 80 had PTB and 60 do not. Blood of 8mls was collected; 3mls in K_2-EDTA for FBC testing with XE-2100 Sysmex and ESR by Westergreen method. The remainder was used for serum CRP assay by ELISA. The radiological extent was determined from Chest X ray report and disease severity using modified Bandim TB scoring was extracted from the case note. The aim of the study is to investigate the relationship and diagnostic utility between leucocyte with CRP, ESR, radiological extent of disease and disease severity in PTB.
Results: Mean Lymphocyte count was lower while TWBC, Neutrophil and Monocyte counts were higher in subjects compared to control ($p<0.05$). Median CRP, ESR, NLR, NMR and MLR were higher in subjects compared to control ($p<0.05$), NLR and MLR showed strong positive significant correlation with ESR, disease severity, and radiological extend of disease. NMR ($p= 0.00$) had a negative correlation with ESR ($p<0.05$) and inverse correlation with disease severity and radiological extent.
Conclusions: This study found NLR, MLR and NMR as a readily, easily available and inexpensive indices that are as efficient and comparable to known biomarkers in PTB infection, therefore could serve as valuable predictive biomarker in areas of high disease burden with weak economy.

Keywords: Monocyte lymphocyte ratio, Neutrophil lymphocyte ratio, Neutrophil monocyte ratio, Predictive biomarkers, Pulmonary tuberculosis

INTRODUCTION

Pulmonary Tuberculosis (PTB) is a highly prevalent chronic infectious disease caused by Mycobacterium tuberculosis, an aerobic intracellular binding bacillus with preference for lungs and other sites of high oxygen levels but can readily disseminate to any part of the body.[1] PTB is prevalent globally, India, Indonesia, China and Nigeria having the highest case number among all the countries in the world.[2,3] It affects millions of people

each year and is ranked the second leading cause of death from infectious disease worldwide, after the Human immunodeficiency virus.[4]

Nigeria was rated the third highest PTB-burden country in the world and number one in Africa by WHO in 2014.[3] High prevalence had been reported across all the geo-political zones in Nigeria. Prevalence of 9.2% [5] and 6.9% [6] were reported in Lagos and Ibadan South -West respectively while Nwachukwu et al, 2016 reported a prevalence of 12.3% in Anambra South-East and Kooffreh et al, 2016, 24.8% in Calabar, South-South.[7,8] Sani et al reported 25.5% in Minna and Suleja, North-Central.[9] Aliyu et al, from Northern parts of Nigeria recorded 23.0% prevalence.[10]

Fatality rate is given as 12% from the study of Odusanya et al carried out in Lagos.[5] The age barrack that is mostly affected is 11-40 years, 81.6% of recorded infection was found in this age bracket.[9] Since this age group forms the productive work force, economy of countries with high prevalence will be negatively affected. Monocytes/macrophages are the target cells for mycobacterial proliferation whereas lymphocytes provide resistance to the spread encouraging clearance. So it is reasonable to suggest that monocyte/lymphocyte (M/L) ratio can be used as a prognostic tool in TB. M/L ratio has erstwhile been reported as a prognostic marker in various invasive malignances including colon cancer, non-Hodgkin lymphoma, multiple myeloma and TB.[11] This axiom also applies to Neutrophil Lymphocyte Ratio (NLR), which of recent had attracted attention as a new inflammatory marker.[12]

It had been reported by several authors as a convenient, readily calculable laboratory marker valuable in systemic inflammationand a predictive biomarker of PTB.[2,13-15] However, Jeon and colleague showed that NMLR is superior in discriminating TB from non-TB infectious lung diseases than NLR.[15] Although several biomarkers are available in accessing activity and in monitoring PTB, they are quite expensive and are not readily in countries with high PTB burden as posited by Yoom et al who also noted that delay in diagnosis could have a negative effect on patient morbidity and mortality.[13] In the present, neutrophil and lymphocyte have been considered inflammatory cells releasing chemokines and cytokines. Their counts and indices are readily obtained by simple automation systems accurately in few seconds. With this advantage, this study attempts to explore the possible use of NLR, MLR, and NMR for accessing disease activity and inflammation in active PTB and also to determine whether these indices compares favourably with already known biomarkers (ESR and CRP level), radiological extent of the disease and disease severity class.

METHODS

This study was carried out at 2 hospitals in Nnewi and Onitsha, Anambra State. These sites are two of the major sites that utilize GeneXpert for PTB diagnosis in the state. Being referral centres, they cater for a number of patients, including new cases, reoccurrence and rifampicin resistant cases.

Study design/Study protocol

In this cross sectional study, purposeful sampling was used in enlisting subjects. The first stage which was the diagnosis stage carried out with the aid of a physician. The diagnosis was based on having positive GenXpert and Ziehl-Neelson (ZN) tests consequent to PTB suspicion. The radiological extent based on chest X-Ray by a radiologist and disease severity class by the attending physician using modified Bandim TB scoring was also noted. Those who gave consent were enlisted to which 3mls of blood was collected into EDTA tube for full blood count using Sysmex XE-2100 Hematology Analyzer (Sysmex Corp., Kobe, Japan) so also the controls.[16]

Study population

The study population was 80 TB patients and 60 apparently healthy controls who were between the ages of 18 and 65 yrs without any other underlining conditions. This was made possible by the collaborative efforts of physician who also made the initial diagnosis of PTB based on clinical, laboratory and radiological findings as stated in the study protocol.

Statistical analysis

The data obtained was analyzed using SPSS version 20. Descriptive and inferential statistics of the independent and outcome variables were obtained. The significance of differences in median values of CRP, ESR, NLR, MLR and NMR between TB and control was tested using the Mann Whitney test while age and WBC indices were tested using student's t-test. Spearman's correlation test was done between two continuous variables while Bar chart was used to depict the correlation analysis between the severity class and radiological extent of disease with NLR, MLR, NMR and CRP and ESR. Statistical significance was set at $p<0.05$.

RESULTS

The mean age of the TB patients was 41.76±10.81 years and that of the control 39±7.48 years. The subjects were aged matched (p=0.156). The mean TWBC was TB 9.635±2.739x10^9/l and control 5.180±1.152x10^9/l (t=-11.736, p=0.00), neutrophil count (6.644±9.29 x10^9/l verses 5.322±5.48 x10^9/l (t=-9.678, p=0.000) and Monocyte count (5.29±x10^9/l verses 3.03±0.97 x10^9/l, t=-6.176, p=0.000), were all significantly raised in TB compared to control except lymphocyte count (2.647±1.056x10^9/l verses 4.232±0.529 x10^9/l, t=10.541, p=0.00) which was significantly lowered while eosinophil count (2.000±0.83 verses 1.760±0.69, t=1.676,

p=0.096) even though raised was not significant (Table 1). In Table 2, the median ESR was 57.50 and 5.50, CRP 16.25 and 4.80, NLR was 2.40 and 1.29, MLR 0.16 and 0.07 and NMR 18.00 and 15.00 for test and control respectively, all were significantly higher than the control (p<0.01).

Table 1: Mean values of absolute leucocyte counts.

Parameters	TB(n=80)	Control (n=60)	t-test	p-value
Age (years)	41.76±10.81	39±7.48	-4.539	0.156
WBC ($x10^9$/l)	9635.71±2739.30	5180.00±1152.41	-11.736	0.000*
NEUT($x10^9$/l)	66.44±9.29	53.22±5.48	-9.678	0.000*
LYMP($x10^9$/l)	26.47±10.56	42.32±5.29	10.541	0.000*
MONO($x10^9$/l)	5.29±2.68	3.03±0.97	-6.176	0.000*
EOSIN($x10^9$/l)	2.00±0.83	1.76±0.69	1.676	0.096

Key: WBC- white blood cell count, NEUT-Neutrophil, LYMP- Lymphocyte, MONO-Monocyte, EOSIN- Eosinophil, * p≤0.05 is significant

Table 2: Median levels of ESR, NLR, MLR, MPV, CRP and NMR.

Parameter	Control	TB	Mann-Whitney U	p-value
ESR (mm/hr)	5.50	57.50	0.02	0.000*
NLR	1.29	2.40	404.50	0.000*
MLR	0.07	0.16	598.00	0.000*
CRP (mg/L)	4.80	16.25	0.02	0.000*
NMR	15.00	18.00	1105.00	0.001*

Key: ESR- Erythrocyte sedimentation rate. NLR-Neutrophil lymphocyte ratio, MLR- Monocyte lymphocyte ratio, CRP- C-reactive protein, NMR- Neutrophil monocyte ratio *p<0.05 is significant

Table 3: Spearman's correlation between ESR and CRP with NLR, MLR and NMR.

Parameters	ESR		CRP	
	r	p-value	r	p-value
NLR (n=80)	0.481	0.001*	0.541	0.001*
MLR (n=80)	0.495	0.001*	0.635	0.001*
NMR (n=80)	-0.253	0.036*	-0.281	0.019*

Key: n= number of subjects r= denotes the degree of correlation NLR-Neutrophil lymphocyte ratio, MLR- Monocyte lymphocyte ratio, NMR- Neutrophil monocyte ratio *p<0.05 is statistically significant

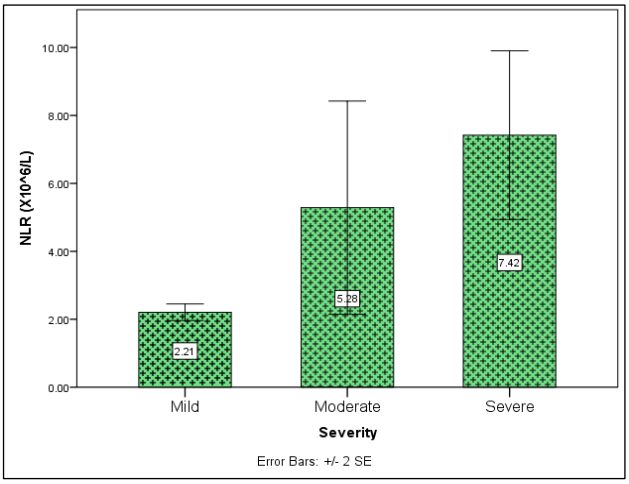

Figure 1: The relationship between NLR and severity of disease.

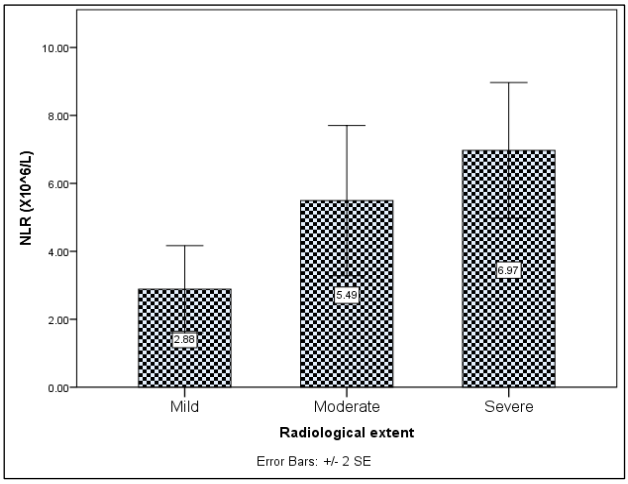

Figure 2: The relationship between NLR with radiological extent of disease.

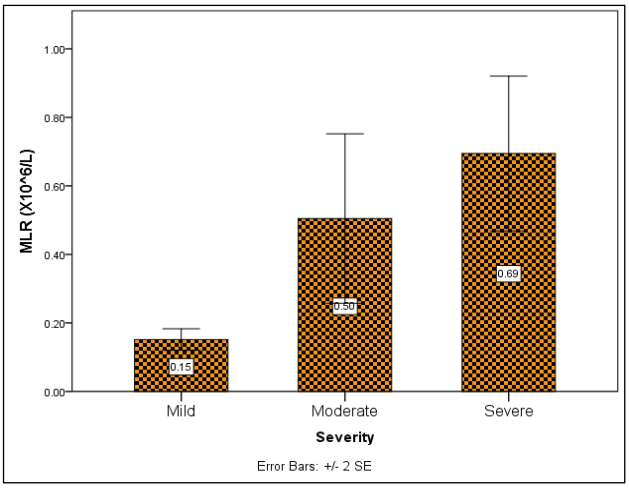

Figure 3: The relationship between MLR with severity of disease.

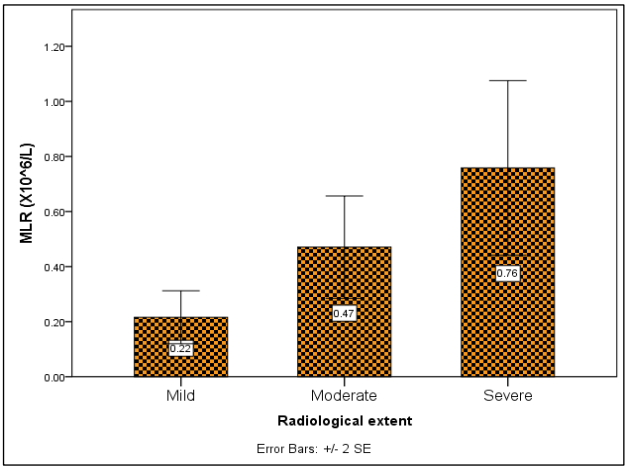

Figure 4: The relationship between MLR with radiological extent of disease

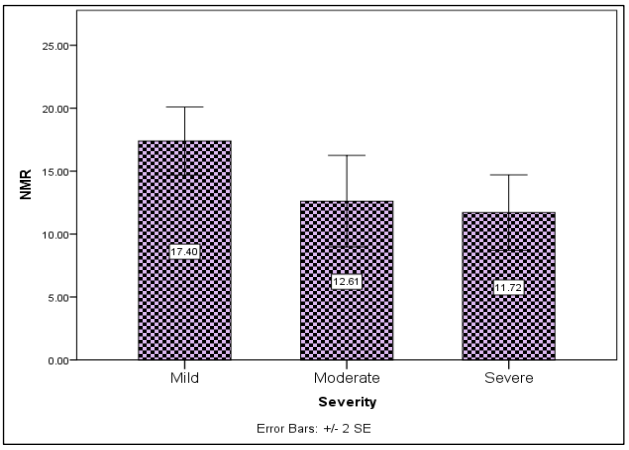

Figure 5: The relationship between NMR and severity of disease.

Table 3 was Spearman's correlation between ESR and CRP with NLR, MLR and NMR of TB and control, while CRP and ESR had positive correlation with NLR (r=0.541, p=0.01 and r=0.481, p=0.001 respectively) and MLR (r=0.631, p=0.01 and r=0.495, p=0.001 respectively) NMR had a negative one (r=-0.21, p=0.019 and r=-0.253, p=0.036 respectively).

Figure 1 and Figure 2 are bar charts of the relationship between NLR and disease severity and radiological extent of disease. (Results of disease severity and radiological extent of disease not shown) NLR correlates positively with disease severity (r=0.600, p=0.00), and radiological extent of disease (r=0.650, p=0.00).

In Figure 3 the same relationship was tested between MLR and disease severity, and a positive relationship was seen (r=0.504, p=0.00).

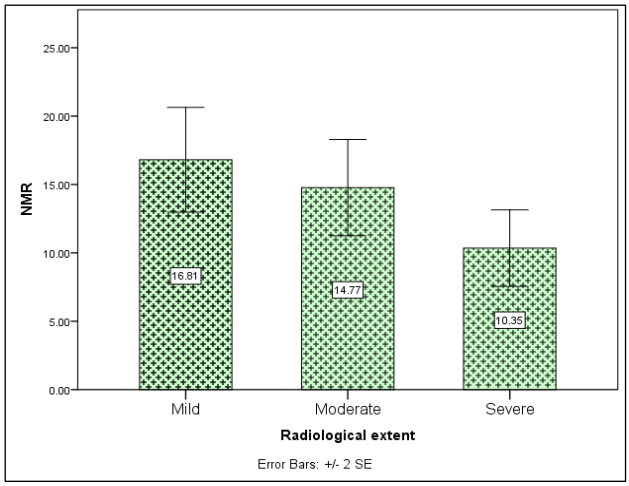

Figure 6: The relationship between the NMR and radiological extent of disease.

The same positive correlation was seen in Figure 4 between MLR and radiological extent of the disease (r=0.573, p=0.00). Figure 5 and 6 shows that NMR correlates positively with the disease Severity and radiological extent of disease respectively.

DISCUSSION

PTB is an infectious disease affecting up to one third of the world population. With continued rise in global population there is corresponding rise in number of new cases.

A rapid, simple, readily available and less cost biomarkers may be very cardinal in achieving positive treatment outcomes especially in high disease burdened country in the face of limited health resource where some biomarkers may not be readily available routinely and where available, are not affordable by the vulnerable population. In this study, authors set out to investigate possible relationship and diagnostic utility of leucocyte derived indices- NLR, MLR, and NMR with CRP, ESR, radiological extent of disease and disease severity in active PTB.

This study observed in the first instance changes in leucocyte counts with rise in TWBC, neutrophil, and monocyte counts and corresponding decrease in lymphocyte count in PTB when compared with the control. The physiological immune responses of circulating leukocytes to various stressors have been reportedly to be characterized by an increased neutrophil count and corresponding decreased lymphocyte count. Zahorec et al observed an increase in TWBC and neutrophils in the critically ill and Guadagnino et al, in PTB specifically.[17,18] Low lymphocyte count as suggested by Sumaira et al, was due to accumulation of lymphocytes at the site of infection which consequently depletes the peripheral blood count while increase in monocyte and neutrophil count may be associated with their role in granuloma formation (a characteristics of PTB) or in their role in initiation of T-cell response or even in amplification of macrophage anti-mycobacterial activity and its peptides secretion that kills the Mycobacterium.[11,19,20] Mononuclear cells (monocytes/macrophages) are professional phagocytes that are highly skilled in defence against many pathogens including PTB.[19] Also values of NLR, MLR, NMR, ESR, and CRP were significantly increased in PTB when compared with the control. With the alteration in the leucocyte counts, it is natural that the ratio derived from these cells becomes altered too. This explains the result pattern seen in our study population when compared with control. NLR and MLR of recent had attracted attention as a new inflammatory marker.[11,12] They had severally been reported as a predictive biomarker of PTB progression by various authors.[2,11,13,15] MLR is considered an important criterion to determine the immune efficiency of an individual during infectious conditions.[20] This statement is also true for NLR as posited by Kamilia et al, who in his work found it valuable in determining immunocompetency and predicting disease activity.[12] A cutoff value of 2.9 was seen among their study population. Therefore NLR of <2.9 was considered immunocompetent and >2.9 immunocompromised in chronic illness.[12] Authors therefore extrapolate and consider our study population having mean NLR value of 2.40 as immunocompetent, though the population in the work of Kamiliai et al had comorbidity with diabetic mellitus. Fortunately, these leucocyte indices are convenient, readily calculable laboratory marker that had been found to be valuable in systemic inflammation.[13-15] Iqbal et al, found a high MLR as an indicator of the effectiveness of anti-TB treatment having observed that the ratio normalizes following treatment.[21] The work of Sumaira et al, 2014 collaborated this finding.[11] Auhtors therefore suggest that MLR could serve as a useful tool as early indicator of both blood stream infection and drug resistance. Naranbhai et al, strengthened this argument that MLR has predictive role and can help in early detection and prompt treatment.[24] Studies by La Manna et al and Wang et al also suggest that the MLR can also be used as a marker to predict the risk of developing active TB.[22.23] NLR was equally found a useful laboratory marker in discriminating patients with PTB from patients with bacterial Community Acquired Pneumonia (CAP) especially in an intermediate TB-burden country. NLR value of <7 was an optimal cut-off value to discriminate patients with pulmonary TB from patients with bacterial CAP.[13] Jeon and colleagues comparing the usefulness of NLR with NMLR in discriminating TB from non-TB infectious lung diseases found NMLR superior to NLR.[15] MLR similar as significantly higher in our study population than control. This is consistent with the work by Guadagnino et al, that reported lower lymphocyte and higher monocyte count in PTB compared with control.[18] this explained the raised MLR in our study population. The third key finding in this present study is in diagnostic ability of the studied parameters in relation to known biomarkers. Authors observed that the diagnostic ability of NLR, MLR and NMR correlated positively with CRP, ESR, disease severity and radiographic picture of the lungs. The involvement of neutrophils in pulmonary destruction during TB disease has been suggested by several authors.[25-27] They observed an association between elevation in concentrations of neutrophil-derived metalloproteinase 8 with sever lung damage (evidence through radiograph) and disease severity. Since NLR and NMR are derived from neutrophil population this correlation holds. It was also observed that NLR has a positive significant correlation with disease severity and radiological extent of the disease just like the CRP and ESR. This agrees with the work by Yongmei et al, where NLR was seen to be a marker of PTB disease severity and was associated with tendency for retreatment of the disease.[28] In the same way, this work agrees with a work by Alexander et al, who showed that high neutrophil levels and low lymphocyte levels are associated with severity of PTB disease.[29] This is further explained by the fact that quantitative parameters of antigen-specific Th1 response play a minor role in determining TB severity, while general shifts in granulocytic and lymphocytic lineages represent an important factor of TB pathogenesis.[2,11]

Whole lymphocyte population was a significant negative correlate of severe TB, especially, clinical TB severity. Mechanisms underlying this association are not fully clear. One possibility is that unspecific lymphocytes are not directly involved in the protection, and an association between their high per cent/number and low TB severity is due to a bystander effect, i.e., to a concomitant decrease in pathological cell populations, such as neutrophils. However, in this study, lymphocyte and neutrophil populations associated with diverse TB manifestations. Another possibility to consider is a direct involvement of non-specific lymphocytes in host protection.

Although the mechanisms for this effect are unclear, this possibility cannot be ruled out. Of note, in line with a recent hypothesis suggesting that acquired immunity against infectious diseases can in part be mediated by pathogen non-specific responses.[30]

It was also observed in this study that MLR correlated positively with disease severity and radiological extent of the disease and the correlation was statistically significant. This is in agreement with the work done by Sumaira et al, where it was established that MLR ratio can be considered as an independent prognostic marker and predictor of anti-tuberculosis treatment and also a predictor of severity of disease.[11] This is further explained by the fact that lymphopenia was seen in more than 50% of the subjects at time of diagnosis. Lymphopenia is considered to be due to accumulation of lymphocytes at the site of infection leading to decreased number in peripheral blood. Another recent study by Naranbhai et al on 3 to 4 months old children suspected of having TB showed that MLR has a predictive role in PTB, thus helps in early detection and prompt treatment of the disease.[24]

CONCLUSION

This study found NLR, MLR and NMR as a readily, easily available and inexpensive indices in are as efficient and comparable to known biomarkers in PTB infection, therefore could serve as valuable predictive biomarker in areas of high disease burden with weak economy.

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