

The role of lymphocyte-monocyte ratio on ankylosing spondylitis diagnosis and sacroiliac arthritis staging

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Abstract

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disorder involving the sacroiliac joints, lumbar spine, thoracic spine and even cervical spine, and could lead to disability due to the failure of timely treatment. Therefore, early diagnosis is essential for AS treatment. The lymphocyte-monocyte ratio (LMR) is a systemic inflammatory and immunological indicator for prediction of disease development and progression. However, its role in AS remains unclear. The aim of this study was to investigate the role of LMR in AS diagnosis, disease activity classification and sacroiliac arthritis staging.

Methods: Seventy-eight AS patients and 78 sex-age-matched healthy controls (HCs) were enrolled in this study. The diagnosis of AS was performed according to the New York criteria, whereas the staging of sacroiliac arthritis of AS patients was determined by X-ray examination. Comparison between AS patients and HCs and between patients with high and low stages on LMR levels and other laboratory indicators were carried out.

Results: A higher level of NLR, RDW, PLR, MPV, ESR, CRP and lower level of RBC, Hb, Hct, LMR, ALT, AST, TBIL and A/G were noted in the AS patients compared to HCs. A positive correlation was observed between LMR and RBC, Hb, Hct and A/G, while negative correlation was found between LMR and NLR, PLR, AST, TBIL ($P < 0.05$). The ROC curve showed that the area under the curve of LMR was 0.803 (95% CI = 0.734-0.872), with a sensitivity and specificity of 62.8% and 87.2%, and the AUC (95% CI) for ESR, CRP and LMR in the combined diagnosis of ankylosing spondylitis were 0.975 (0.948-1.000), with the sensitivity and specificity of 94.9% and 97.4%. Levels of WBC and NLR were higher in high X-ray stage patients, whereas levels of LMR were lower ($P < 0.05$) and statistical differences were observed of LMR values among different stages ($P < 0.05$).

Conclusions: Our study suggested that LMR is an important inflammatory marker that can be used to diagnose AS and identify disease activity and X-ray stage of sacroiliac arthritis in AS patients.

Background

Ankylosing spondylitis (AS), an immune-mediated chronic inflammatory rheumatic disease with unknown etiology, mainly affects the axial bone and articular structures, but also other parts, such as peripheral arthritis, enthesitis and finger arthritis with extraarticular manifestations like uveitis (Xu, Wang, & Zheng, 2018). The prevalence of AS is about 0.2–0.3%, occurs mostly in males aged 20–30 years. Without effective treatment, severe disability could be presented in nearly one third of the patients (Arévalo et al., 2018). Until now, the pathophysiology of AS has not been fully understood. Risk factors resulted from heredity, immunity and inflammation are considered as the most important factors in the pathogenesis of AS. In current clinical practice, HLA-B27 is considered as the diagnosis maker for AS due to its 90%-95% high prevalence in AS and its direct role in the onset of AS (Stolwijk, Onna, Boonen, & Tubergen, 2015). Besides HLA-B27, imaging modalities are usually employed in the diagnosis of AS (Bradbury, Hollis, Gautier, Shankaranarayana, & Brown, 2018). However, the radioactive property, relative high expense and

limited use in specific patients (such as pregnant women) of imaging facility. Therefore, specific and sensitive biochemical markers for auxiliary diagnosis, treatment guidance and prognosis monitoring of AS are urgently needed.

Traditional inflammatory markers, including ESR and CRP[1], have been verified to be related to the disease activity of AS. ESR × duration of disease and CRP × duration of disease were demonstrated had a good correlation with poor physical activity of AS patients [2]. In recent years, some new inflammatory markers, such as Neutrophil-to-lymphocyte ratio (NLR) and RDW, have also been found to be associated with the disease activity of AS. In AS patients, NLR had a good correlation with ESR and CRP, and increased NLR was found in patients with high disease activity[3], whereas difference levels of NLR were found in the patients with different treatment, such as anti-TNF-alpha therapy, and non-steroidal anti-inflammatory drugs[4]. Moreover, there was a significant difference in RDW between patients with BASDAI index > 4 and < 4. RDW was positively correlated with BASDAI index, ESR and CRP levels[3]. Based on the finding, routine blood test indexes could be potential resource for novel and effective marker exploration for AS.

Lymphocyte-monocyte ratio (LMR), similar to RDW and NLR, is also a common blood routine indicator. It has been of great interest in a wide range of fields such as inflammation, immunology and carcinoma for a long period of time. Recent data from several studies suggested that LMR was associated with diagnostic, pretreatment and prognostic statue of diseases. A genome-wide association study has confirmed that mutations in ITGA4 and HLA-DRB1 genes could affect LMR levels and has been widely recognized as susceptible genes for autoimmune diseases, such as rheumatoid arthritis (RA)[5], suggesting its possible employment in AS diagnosis and prognosis evaluation.

To date, few studies have investigated the association between LMR and AS. Therefore, the aim of this essay was to explore the diagnostic value of LMR in AS and its role in reflecting disease activity and X-ray staging of sacroiliac arthritis .

Methods

Patients with AS

A total of 78 patients with AS [51 females and 27 males; mean age 41.0 (29– 52) years] were enrolled in this retrospective study. These patients were attending the Department of Endocrinology, Taizhou Hospital (Zhejiang, China). All patients fulfilled the AS criteria prescribed by the New York criteria[6],1984. All patients were treated by nonsteroidal anti-inflammatory drugs only. Patients combined with autoimmune diseases such as SS, SLE, RA and psoriasis, malignant diseases, end-stage kidney diseases, liver diseases, acute myocardial infarction, hypertension, diabetes, cerebrovascular diseases were excluded.

Sacroiliac arthritis X-ray staging of the AS Patients

The stage of sacroiliac arthritis was assessed using X-ray and staged from I to IV. Stage I with suspicious sacroiliac arthritis; Stage II with vague margin of sacroiliac joint, slightly sclerotic and minimally invasive lesions, and unchanged joint space; Stage III with moderate or progressive sacroiliac arthritis, accompanied by one or more following changes: sclerosis of proximal articular area, narrowing/widening of joint space, bone destruction or partial ankylosis; and Stage IV with complete joint fusion or ankylosis with or without sclerosis.

Healthy Controls

Healthy controls (HCs) included 55 males and 23 females with a mean age of 40 (30–53) years. These subjects were selected from the Physical Examination Center of Taizhou Hospital (Zhejiang, China) who underwent a physical examination, with features of sex and age match with AS patients. All subjects were healthy without any disease and the absence of drugs that affect bone metabolism, such as hormone replacement therapy.

Biological detection and Imaging system

Fasting blood samples were obtained from all included subjects, whereas X-ray were acquired simultaneously from AS patients. Blood routine test was detected by Mindray BC6800-plus (China) automatic blood analyzer, ESR was detected by ALifax Tes1(Italy) automatic blood analyzer, CRP was detected by Immage 800 (Beckman coulter, USA). ALT, AST, TBIL and Alb/Globin (A/G) were detected by AU5800 (Beckman coulter, USA) automatic biochemical analyzer. X-ray was taken by Digital X-ray imaging system (DR)(Philips, Holland).

Statistical analyses

All statistical analyses were carried out by SPSS version 19.0 (SPSS Inc., Chicago, IL), all graphs were drawn by GraphPad Prism 8. Quantitative and qualitative data were respectively expressed as median (range) or number (percentage). Comparison of between group quantitative and qualitative data was performed using Kruskal-Wallis test and the chi-square test. Receiver operating characteristic (roc) curve analysis with calculation of area under curve (AUC) and 95% confidential interval (CI) was used to determine the role of LMR in the diagnosis of AS. Moreover, optimal cut-off value was calculated Youden's index by for specificity and sensitivity. The correlations between LMR and other indicators was performed by Spearman correlation analysis. $P < 0.05$ was considered to have statistical significance.

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Results

Baseline characteristics of the included subjects

Seventy-eight AS patients [51 male, 27 female; mean age (range): 41 (29–52) years] and 78 healthy controls [55 male and 23 female with a mean age (range) of 40(30–53) years] were included in this study. The blood-routine test indexes, ESR and the serum levels of hs-CRP in both groups were assayed, and compared between AS and HCs. A higher level of NLR, RDW, PLR, MPV, ESR, CRP and lower level of RBC, Hb, Hct, LMR, ALT, AST, TBIL and A/G in the AS group were noted as compared to the healthy controls($P<0.05$), which showed significant differences. (Table 1)

Table 1. Comparison of baseline characteristics in the AS patients and healthy controls

Characteristics	AS (n1=78)	Healthy controls (HCs) (n2=78)	P-value
Age	41 (29-52)	40 (30-53)	0.783
Sex (Male, %)	51 (65.4%)	55 (70.5%)	0.607
WBC	6.6 (5.5-8.6)	6.0 (5.2-7.0)	0.004
LMR	3.62 (2.67-5.05)	5.82 (4.69-6.97)	0.000
NLR	2.63 (1.71-3.55)	1.67 (1.38-2.11)	0.000
RBC	4.24 (3.69-4.80)	5.05 (4.70-5.34)	0.000
Hb	116 (101-38)	150 (140-159)	0.000
Hct	0.361 (0.313-0.410)	0.456 (0.420-0.479)	0.000
RDW	13.4 (12.5-14.3)	12.5 (12.2-12.8)	0.000
PLR	152.2 (123.2-201.4)	124.6 (102.8-154.6)	0.000
MPV	10.2 (9.6-10.7)	9.5 (8.5-10.5)	0.002
ESR	37 (20-75)	6 (3-9)	0.000
CRP	32.1 (14.1-76.0)	2.9 (1.5-4.9)	0.000
ALT	16.5 (10.0-25.3)	20.5 (16.0-31.3)	0.003
AST	18.5 (15.0-25.5)	22.0 (22.0-26.3)	0.001
A/G	1.4 (1.2-1.6)	1.8 (1.7-2.0)	0.000
TBIL	9.34 (6.35-14.23)	15.85 (13.08-19.52)	0.000

WBC:White blood cells; LMR: Lymphocyte-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; RBC:Red blood cells; Hb:Hemoglobin; Hct:Hematocrit; RDW:Red cell distribution width; PLR:Platelet to lymphocyte ratio; MPV:Mean platelet volume; ESR:Erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate Aminotransferase; A/G: Albumin/globulin ratio; TBIL:Total bilirubin.

Correlation between LMR and other laboratory parameters in AS patients

We further analyzed the correlation between LMR and other laboratory parameters in AS patients. Positive correlations were observed between LMR and RBC ($r = 0.372$, $p = 0.001$), Hb($r = 0.339$, $p = 0.002$), Hct ($r = 0.341$, $p = 0.002$) and A/G ($r = 0.278$, $p = 0.042$), whereas negative correlations were observed between LMR and NLR($r = -0.736$, $p = 0.000$), PLR ($r = -0.430$, $p = 0.000$), AST ($r = -0.383$, $p = 0.004$) and TBIL ($r = -0.277$, $p = 0.042$). (Figure 1).

ROC Curve

The ROC curve explored the efficiency of clinical indicators in the diagnosis of AS. Indicators with AUC beyond 0.600 were shown in Tab.2. The AUC (95%CI) for LMR were 0.803(0.734-0.872) ,which were next to ESR and CRP[0.937(0.895-0.978), 0.899(0.845-0.954)].Based on the optimal cutoff values (LMR=4.26) calculated from the ROC curves, a sensitivity of 62.8% and a specificity of 87.2% was obtained. The AUC (95%CI) for ESR, CRP and LMR in the combined diagnosis of ankylosing spondylitis were 0.975(0.948-1.000),with the sensitivity and specificity of 94.9% and 97.4%(Fig.2).

Table 2. Comparison of areas under the ROC curve of clinical indicators for diagnosis of AS

	AUC	P
ESR	0.937(0.895-0.978)	0.000
CRP	0.899(0.845-0.954)	0.000
LMR	0.803(0.734-0.872)	0.000
RDW	0.773(0.696-0.849)	0.000
NLR	0.718(0.634-0.801)	0.000
PLR	0.687(0.602-0.772)	0.000
A/G	0.648(0.548-0.747)	0.002
MPV	0.639(0.550-0.729)	0.003
ESR+CRP+LMR	0.975(0.948-1.000)	0.000

Characteristics comparison between low X-ray stage group and high X-ray stage group

A total of 43 and 35 patients were respectively included in the low X-ray stage group (stage I-II) and high X-ray stage group (stage III-IV). The comparison results showed that levels of WBC [7.7(6.0-9.5) vs.4.9(6.2-7.5)] and NLR [3.00(1.85-5.60) vs.2.38(1.62-3.10)] were higher, and levels of LMR was lower [3.00(1.83-5.00) vs.4.17(2.74-5.40)] in high X-ray stage group compared to that in low X-ray stage group.

Table 3. Characteristics comparison between low X-ray stage group and high X-ray stage group

	Low X-ray stage (n1=43)	High X-ray stage (n2=35)	P-value
WBC (10⁹/L)	4.9 (6.2-7.5)	7.7 (6.0-9.5)	0.007
CRP (g/L)	31.0 (12.8-69.8)	34.5 (14.7-80.9)	0.786
ESR (mm/h)	40 (18-83)	35 (20-74)	0.637
TBIL	9.00 (6.10-13.25)	9.80 (6.40-14.85)	0.271
NLR	2.38 (1.62-3.10)	3.00 (1.85-5.60)	0.046
PLR	153.1 (128.1-201.1)	164.0 (112.4-217.5)	0.964
LMR	4.17(2.74-5.40)	3.00 (1.83-5.00)	0.047
RBC (10 ¹² /L)	4.31 (3.74-4.85)	4.14 (3.53-4.67)	0.149
Hb (g/L)	117.0 (103.0-140.0)	115.0 (94.0-133.0)	0.250
Hct	0.366 (0.326-0.414)	0.360 (0.309-0.401)	0.291
ALT (U/L)	16.0 (8.0-27.0)	17.0 (11.0-21.0)	0.889
AST (U/L)	17.0 (13.0-22.5)	19.0 (15.5-32.5)	0.152
A/G	1.4 (1.2-1.6)	1.3 (1.1-1.5)	0.507

WBC:White blood cells; LMR: Lymphocyte-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; RBC:Red blood cells; Hb:Hemoglobin; Hct:Hematocrit; RDW:Red cell distribution width; PLR:Platelet to lymphocyte ratio; MPV:Mean platelet volume; ESR:Erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate Aminotransferase; A/G: Albumin/globulin ratio; TBIL:Total bilirubin.

LMR in different X-ray stages of the AS Patients

Further staging of the AS patients by X-ray allocated 17, 27, 30 and 4 patients into the I to IV stages, respectively. Statistical differences were observed in LMR values of patients among different stages ($P<0.05$). The results showed that the higher the stage, the lower the LMR(Figure.3).

Discussion

In previous studies, the recently developed inflammatory and immunological indicators such as NLR and Platelet-to-lymphocyte ratio (PLR) have been verified as the diagnostic maker for disease activity and severity evaluation in many kinds of disorders. Peng et al. indicated that the combination use of NLR, PLR and CEA could be good diagnostic biomarkers for colorectal cancer, and positive correlations were found between the TNM stage and NLR or PLR[8]. In addition, Zhao et al. also observed that NLR was correlated with knee recurrence after arthroscopic surgery combined with local radiotherapy [9].

In recent years, another indicator LMR was attracted much attention on the diagnosis and prognosis of many diseases such as cancers or some immunological diseases. Rajwa et al. found that urothelial bladder cancer patients treated with radical cystectomy with lower LMR values had a greater chance to develop postoperative in-hospital complications[10]. Du et al. showed that the LMR was an inflammatory marker that is effective in disease activity evaluation in patients with RA and RA differentiation from other arthritis[11].

The present study revealed that decreased levels of LMR in AS patients compared to healthy controls, especially in high X-ray stages. Furthermore, the correlations between LMR and other AS related indicators showed that LMR was positively correlated with RBC, Hb, Hct and A/G, and negatively correlated with NLR, PLR, AST and TBIL.

As known to all, anemia is a common phenomenon in the process of chronic inflammation and is also found in AS patients, and the mechanisms were attributed to the inhibitory effects by cytokines (such as TNF- α on EPO) secretion. TNF- α could block the effects of EPO on CD34(+) hematopoietic stem/progenitor cells[12]. The increasing of hemoglobin level was observed in AS patients with significant improvement of physical function and fatigue [13]. In other words, hemoglobin level could reflect the activity and severity of AS, with the trend of decreased Hb level, decreased disease severity.

As a major component in serum protein, serum albumin was used to reveal long-standing malnutrition and was also associated with systemic inflammation[14]. Globulin is the carrier of sex hormones, and together with most pro-inflammatory proteins (including complement components, immunoglobulin, CRP, interleukin, TNF), were considered with the ability to reflect the inflammatory state[15]. A/G was based on serum albumin level and globulin level, could reflect immunonutritional status and systemic inflammatory reaction with more accuracy than with single albumin and globulin indexes. A higher A/G means good malnutrition status and low hormone environment. Besides, Lin et al also showed that a low A/G was found to be significantly correlated with high total bilirubin levels but a low hemoglobin level [16]. These results were consistent with the results obtained here.

Lymphocytes play an important role in immunology, although different subsets of T cells were associated with poor prognosis of tumors[17, 18], high absolute lymphocyte count was proved to be associated with good prognosis in patients with gastric cancer [19]. It was reported that the increase number of monocytes was associated with poor prognosis in various types of tumors[20, 21].

Monocytes could differentiate into tumor associated macrophages (TAM) through tumor microenvironment[22]. TAM could promote tumor angiogenesis and tumor growth by secreting TNF- α [23]. Therefore, LMR may be associated with good prognosis of AS due to the higher of LMR could result in lower inhibitory effects of TNF- α on EPO secretion, and higher hemoglobin level and A/G ratio. In contrast, lower NLR, PLR, total bilirubin levels and direct bilirubin were also observed, which supporting the results of this study.

Liver toxic effects could be resulted from systemic rheumatic diseases themselves and therapeutic drugs. Hepatic involvement was a severe kind of extra-articular manifestations in various rheumatic diseases. Hepatotoxicity is commonly observed in non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modified anti-rheumatic drugs (DMARD) as immunosuppressants[24]. In our study, we only included the AS patient were treated by NSAIDs, therefore negative correlation between LMR and AST was reasonable.

For the correlations we observed between AS and LMR, we further discussed the diagnostic value of LMR for AS prediction. The ROC curve analysis showed that LMR had high diagnostic value in the incidence of AS, next to ESR and CRP. The combined diagnostic AUC of LMR, ESR and CRP for ankylosing spondylitis was 0.975, with the sensitivity and specificity of 94.9% and 97.4%. According to the X-ray stages, AS patients were divided into low X-ray stage and high X-ray stage, and the levels of WBC and NLR were higher in high X-ray stage group, while the levels of LMR was lower. From these observation, it can be inferred that LMR was associated to the X-ray stage of sacroiliac arthritis in AS patients.

To discuss the relationship of LMR and X-ray staging of AS was rare in previous publications. In our research, we classified the AS patients from Stage I to IV according to X-ray imaging to discuss the associations between LMR and the severity of sacroiliac arthritis. The value of LMR was decreased with the increase of X-ray staging, indicating its role of LMR in AS severity judgement.

The main limitations of our study was its retrospective and single-center property. Therefore, a multi-center prospective study is needed in the future for further verification of our results obtained here. Secondly, we could not get scoring criteria related to AS activity such as BASDAI for the lacking or incomplete clinical data of AS patients. Thirdly, the sample size was relatively small because of the low prevalence and we only included AS patient treated by NSAIDs in present study.

Conclusion

In conclusions, we demonstrated here that LMR is an important inflammatory marker that can be used to identify disease activity and X-ray stage of sacroiliac arthritis in AS patients.

Abbreviations

AS: Ankylosing spondylitis; LMR: Lymphocyte-monocyte ratio; HCs: Healthy controls; NLR: Neutrophil lymphocyte ratio; RDW: Red blood cell distribution width; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RBC: Red blood cell; Hb: Hemoglobin; Hct: Hematocrit; LMR: Lymphocyte-monocyte ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; A/G: Albumin/globulin; AUC: Area under curve; CI: confidential interval; TAM: Tumor associated macrophages; EPO: Erythropoietin; NSAIDs: Non-steroidal anti-inflammatory drugs; DMARD: disease-modified anti-rheumatic drugs.

Declarations

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- Ethics approval and consent to participate: Medical ethics committee of Taizhou Hospital of Zhejiang Province.
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- Authors' contributions: JW, GL conceived, designed and coordinated the study, participated in acquisition and interpretation of data, and drafted the manuscript. X J participated in acquisition of data. Y Y participated in blood and urine determination levels and the interpretation of data. All authors have read and approved the manuscript in the "Authors' contributions" section.
- Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

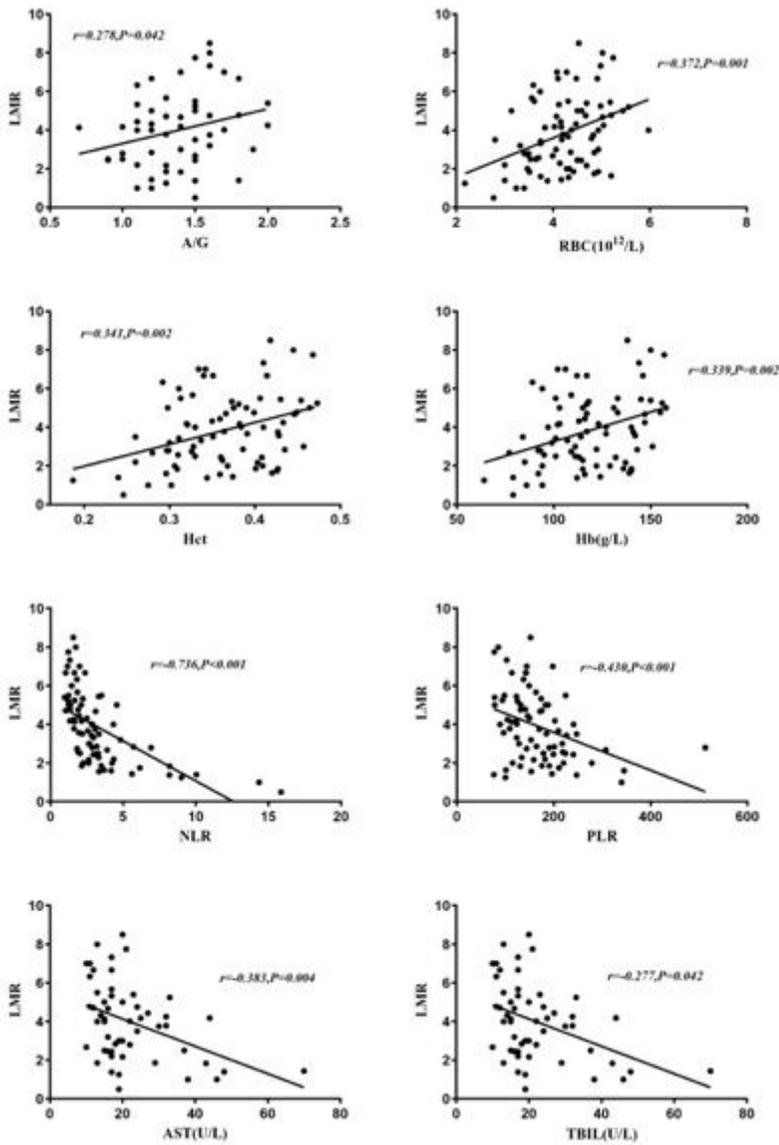


Figure 1

Spearman correlations analyses between LMR and different laboratory parameters including A/G, RBC, Hct, Hb, NLR, PLR, AST and TBIL

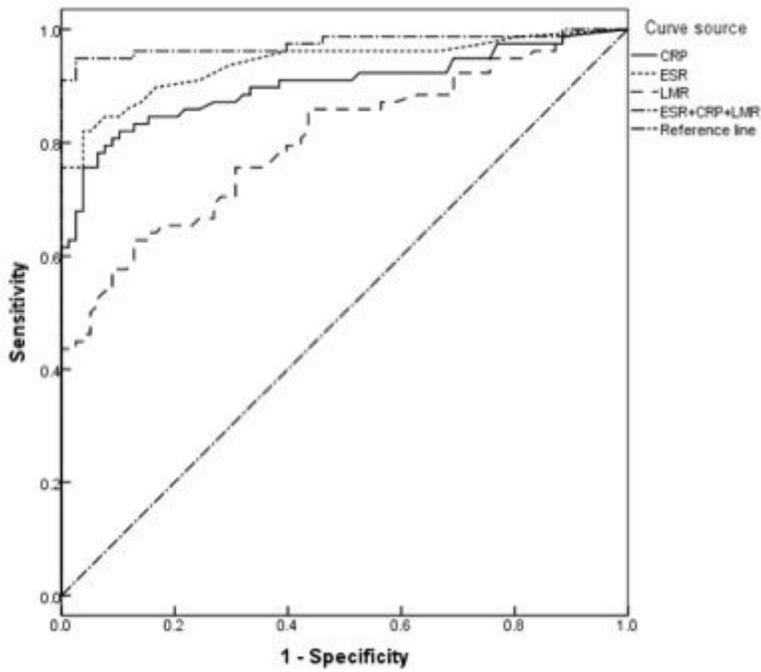


Figure 2

Receiver operating characteristic (roc) curve analysis of CRP, ESR and LMR in the diagnosis of AS.

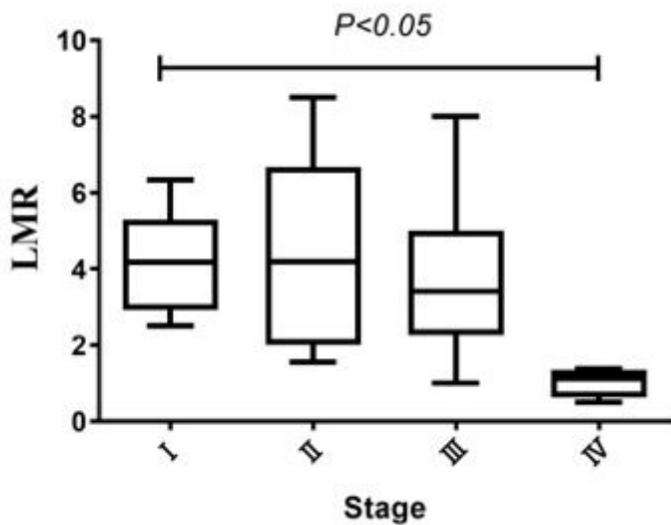


Figure 3

LMR value in the AS Patients with different X-ray stages. Significant difference was found between patients with different Stages.