The role of lymphocyte-monocyte ratio on Chronic inflammatory demyelinating polyradiculoneuropathy diagnosis and disease activity

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Research Article

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Abstract

Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by significant clinical heterogeneity, and as such reliable biomarkers help to identify and measure disease activity. The purpose of this study was to investigate the role of lymphocyte/monocyte ratio (LMR) in CIDP diagnosis and disease activity classification.

Method: This retrospective study involved 36 patients with CIDP and 36 healthy controls (HC). The CIDP patients were grouped into 23 active CIDP patients and 13 with long-lasting remission. Hematological parameters, C-reactive protein (CRP) and erythrocyte sedimentation rate(ESR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) , and LMR were compared between the CIDP patients and HCs. Pearson or Spearman correlation analyses were used to evaluate the correlations between LMR and other indicators. Receiver operating characteristic (ROC) curves were used to determine the role of LMR in the diagnosis of CIDP.

Results: The CIDP patients showed lower LMR compared to HCs ($P<0.05$), and active disease patients showed lower LMR levels compared to the remission group ($P<0.05$). Positive correlations were observed between LMR and Hb (Hemoglobin), RBC (Red blood cells), and A/G (Albumin/globulin ratio), whereas LMR was negatively correlated with NLR, PLR, RDW (Red cell distribution width) ($P<0.05$). ROC curves showed that the area under the curve (AUC) for LMR in the diagnosis of CIDP was 0.807 (95% CI=0.705-0.908) with a sensitivity and specificity of 77.78 and 75%, and the AUC (95% CI) for the combination of ESR, A/G and LMR was 0.885 (0.809- 0.961) with a sensitivity and specificity of 80.56% and 77.48% respectively.

Conclusion: Our study suggests that LMR may be an important inflammatory marker for recognizing CIDP and assessing disease activity.

Background

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disease of the peripheral nerves,presenting as chronic progressive or relapsing disease.It is the most common chronic autoimmune peripheral neuropathy in humans.The prevalence of CIDP in the general population is 1.9-8.9 per 100,000[1, 2]. To date, the pathogenesis and etiology of CIDP are not completely understood. The pathological manifestations of CIDP were multifocal demyelination of myelinated nerve fibers, intimal edema, inflammatory cell infiltration, and coexistence of demyelination and myelin regeneration[3]. So far, accumulating evidence shows that the involvement of inflammatory markers is driving peripheral nerve demyelination in CIDP and affecting patients to varying degrees of severity[4].

Campared to some inflammatory markers commonly used , including white blood cell (WBC) count, neutrophil, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), quite a few new inflammatory markers, such as the neutrophil to lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been shown to be useful in several neurological diseases, including stroke[5], Alzheimer's

disease[6], Parkinson's disease[7], multiple sclerosis (MS)[8], Guillain Barré syndrome (GBS)[9]and primary Sjogren's syndrome (pSS)[10], dermatomyositis (DM) and polymyositis (PM)[11].

Besides NLR and PLR, LMR is usually studied as a indicator of inflammation and prognosisin malignancies,cardiovascular[12]and cerebrovascular disease[13],a variety of immune and inflammatory diseases[14, 15]. Recent data from several studies suggested that LMR was associated diagnosis, preconditioning, and prognostic status of disease[16-18].

However, to our knowledge, few studies have explored the relationship between LMR and CIDP.It is not clear whether NLR, PLR and LMR can be useful markers for assessing CIDP disease activity.Therefore, the purpose of this study was to investigate the diagnostic value of hematological parameters,especially LMR, in CIDP and their role in reflecting disease activity and monitoring longitudinal disease activity.

Materials And Methods

Patients with CIDP

A total of 36 patients with CIDP were enrolled in our study.The patients received were treated in the Department of Neurology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Zhejiang, China), from 2017 to 2020. Relevant clinical and laboratory data were collected from the electronic medical records system.

All patients were diagnosed according to the European Federation of Neurological Societies/Peripheral Nerve Society criteria. Clinical examinations and electrophysiological studies were performed on all patients prior to inclusion in the study. Muscle strength tests were performed and a five-grade scale motor score was given according to Medical Research Council (MRC). The disability degree was assessed by modified Rankin disability score (mRDS). All patients had been without methylprednisolone, plasma exchange, immunomodulatory or immunosuppressive treatment for at least 4 weeks before sampling. Patients were excluded if they had one of the following conditions:malignant diseases, nephropathy, liver diseases, hypertension, diabetes,cardiovascular and cerebrovascular diseases, cancer,immune system diseases,peripheral neuropathy other than CIDP,infection within 2 weeks before admission, hematological disease, or blood transfusion in the past 4 months.

The CIDP patients included 23 active CIDP patients and 13 with long-lasting remission. The disease was defined as 'active' if continuous neurological examinations recorded at least one grade of objective clinical deterioration on the Rankin disability score,or in 'remission' if there was no recurrence for at least 6 months after treatment suspension.

Healthy controls

The study included 36 healthy controls (HCs), 20 males and 16 females with a an average of 50 years. These subjects were selected from individuals who underwent a physical examination at the Physical Examination Center of Sir Run Run Shaw Hospital(Zhejiang, China). The HCs were matched for

age and gender with CIDP patients. All subjects were screened for infectious conditions and other inflammatory, and their laboratory tests were usually within the reference interval.

Blood-routine markers

Fasting blood samples were taken from all included subjects, flowing information was extracted from the medical records: age, gender and course of disease. Blood routine tests were performed by Heaten Meikang XS-900i(Japan) automatic blood analyzer, ESR was performed by ESR-30(China) automatic ESR Dynamic Analyzer, and CRP,Albumin (Alb), Total Protein (TP), and albumin/globulin (A/G) levels were performed by the AU680 (Beckman Coulter, Japan) automatic biochemical analyzer. This study was approved by Ethics Committee of the Sir Run Run Shaw Hospital, Zhejiang University School of Medicine and conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Since this study is based on the electronic database of medical records and has no impact on the future management of the patients, informed consent was waived.

Statistical analyses

Statistical analysis was performed by IBM SPSS Statistics 22 program, and all graphs were drawn by GraphPad Prism9. The Kolmogorov-Smirnov test was used to verify the normality of the distribution. Continuous variables conforming to normal distribution were expressed as the mean±standard deviation, and t-tests was used to compare groups. The median (P25-P75) was used for non-normal distributions, and the Mann Whitney U test and Kruskal Wallis tests were used for comparison between groups. Pearson correlation analysis or Spearman correlation analysis was used to evaluate the correlation between LMR and other indicators for normal distribution data and non-normal distribution data, respectively. Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) and 95% confidence interval (CI) to determine the role of LMR in CIDP diagnosis.The optimal cut-off point of Youden index was calculated according to the specificity and sensitivity.The **p**-value**≤0.05** was considered as statistically significant.

Results

Characteristics of the objects included

Of the 36 patients diagnosed with CIDP with a mean age of 51 years (45-61 years), including 21 males (58.3%). The mean age of the 36 HCs was 50 (43-58) years, and 20 (55%) were male. As a result of hematologic parameters analysis between CIDP and HCs, higher WBC, NLR, RDW, PLR, ESR, and CRP, and lower RBC, Hb, LMR, Alb, TP, and A/G levels were noted in the CIDP group compared to HC group, and the differences were statistically significant ($P < 0.05$) (Table 1).

Table 1 Demographic and hematologic parameters in CIDP patients and healthy controls

Characteristics	CIDP (n1=36)	HCs (n2 = 36)	P-value
Sex (Male, %)	21(58.3)	20(55)	0.812
WBC($\times 10^9$ /L)	7.61 ± 3.63	6.01 ± 1.35	0.016
RBC($\times 10^{12}$/L)	4.22 ± 0.83	5.12 ± 0.60	< 0.001
Hb(g/L)	121 (118–124)	145.13 (135.5–152)	< 0.001
RDW (%)	13.8 (12.7–14.6)	12.8 (12.4–13.3)	0.001
NLR	2.73 (2.03–3.87)	1.88 (1.38–2.40)	< 0.001
LMR	3.92±2.42	5.80±3.57	< 0.001
PLR	154.2 (123.5–195.1)	121.6 (111.8–153.7)	< 0.001
ESR (mm/h)	14.50(6–20)	5(3.25–6)	< 0.001
CRP (mg/L)	6.15 (1.15–15)	1.13(0.40–2.37)	< 0.001
Alb(g/L)	37.35±3.44	44.81±3.87	< 0.001
TP(g/L)	62.6(58.9–66.7)	69.9 (67.5–76.1)	< 0.001
A/G	1.43 (1.32–1.59)	1.76 (1.54–1.90)	< 0.001

Abbreviations: WBC, White blood cells; RBC, Red blood cells; Hb, Hemoglobin; RDW, Red cell distribution width; NLR, Neutrophil-to-lymphocyte ratio; LMR, Lymphocyte-monocyte ratio; PLR, Platelet to lymphocyte ratio; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; Alb, Albumin; TP, Total protein; A/G, Albumin/globulin ratio.

Correlation studies

We further analyzed the correlation between LMR and other hematologic parameters in CIDP patients. The results showed that LMR is positive correlated with Hb (r = 0.357, P = 0.033), RBC (r= 0.472, P =0.004), and A/G (r = 0.362, P =0.030), whereas LMR is negatively correlated with NLR (r = − 0.606, P < 0.001), PLR (r = − 0.459, P =0.0048), RDW (r =− 0.366, P = 0.028) (Fig. 1).

ROC curve

ROC curve was used to evaluate the effectiveness of clinical indicators in diagnosis of CIDP. Indicators with an AUC values greater than 0.60 are shown in Table 2. The AUC (95% CI) of LMR was 0.807 (0.705-0.908), and the optimal cut-off value was 4.41, with a sensitivity of 77.78% 62% and specificity of 75%.The AUC (95% CI) of ESR, A/G and LMR combined was 0.885(0.809- 0.961) ,and the sensitivity and specificity of 80.56 and 77.78%, respectively (Fig. 2).

Table 2 Comparison of areas under the ROC curve for clinical indicators of CIDP

	AUC	*P*
ESR	0.872(0.789 to 0.955)	*P*<0.001
LMR	0.807(0.705 -0.908)	P<0.001
A/G	0.797(0.697-0.897)	*P*<0.001
Hb	0.781(0.668 -0.892)	*P*<0.001
CRP	0.754(0.633- 0.874)	*P*<0.001
RDW	0.750(0.636-0.864)	*P*<0.001
NLR	0.691(0.569-0.811)	*P*=0.006
PLR	0.668(0.539-0.796)	*P*=0.014
ESR+LMR+A/G	0.885(0.809- 0.961)	P<0.001

Abbreviations: ESR, Erythrocyte sedimentation rate; A/G,Albumin/globulin ratio; LMR, Lymphocyte-monocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; RDW, Red cell distribution width; Hb, Hemoglobin; PLR, Platelet to lymphocyte ratio.

Comparison between different disease activity status of CIDP

A total of 36 CIDP patients were enrolled in this study, including 23 patients in the active stage and 13 patients in remission.Of the 23 patients with active CIDP:fifteen were newly diagnosed (3 months to 2 years, median 6 months), eight patients had prolonged disease(5 to 12 years),who had clinical deterioration within 3 months after drug withdrawal;five was relapsing remitting (RR) CIDP patients.Thirteen patients were in remission: all of them had a chronic progressive form,and the mean period was 5.5 years (2.5 to 10 years).

The results showed that the WBC(8.53±3.87 vs.5.96±2.53) and CRP (7.00 (3.9-2.0) vs. 2.5(0.25-15) levels in the active CIDP group were higher than those in the remission group. LMR(3.65±1.17 vs. 2.51±1.21) was low (Table 3).

Table 3 Comparison of CIDP patient in active phase and in remission

Characteristics	Activity CIDP (n1=23)	Remission CIDP (n2 = 13)	P-value
WBC(× 10^9 /L)	**8.53 ± 3.87**	**5.96 ± 2.53**	**0.022**
RBC(× 10^{12}/L)	4.39 ± 0.71	54.02 ± 0.85	0.15
Hb(g/L)	122 (118–127)	121(112.5–124.5)	0.41
RDW (%)	14.1 (13.4–14.8)	13.4 (12.5–14.1)	0.09
NLR	2.39 (1.82–3.15)	3.19 (2.57–4.84)	0.031
LMR	**3.65±1.17**	**2.51±1.21**	**0.009**
PLR	151.9 (119.58.–170.53)	194.83(138.08–215.50)	0.51
ESR (mm/h)	15(6–20)	14(4.5–20)	0.552
CRP (mg/L)	**7 (3.9–20)**	**2.5(0.25–15)**	**0.035**
Alb(g/L)	37.9±3.3	36.36±3.57	0.199
TP	64.42±6.17	62.33±5.86	0.248
A/G	1.46 ±3.30	1.29 ±0.43	0.108

Abbreviations: WBC, White blood cells; RBC, Red blood cells; Hb,Hemoglobin; RDW, Red cell distribution width; NLR, Neutrophil-to-lymphocyte ratio; LMR, Lymphocyte-monocyte ratio; PLR, Platelet to lymphocyte ratio; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; Alb Albumin; TP, Total protein; A/G Albumin/globulin ratio.

Discussion

CIDP is considered an acquired inflammatory disease of the peripheral nerves. About two-thirds of patients experienced relapse and one-third experienced progression (stable or stepwise)[19].Pathologic markers of CIDP are segmental demyelination and remyelination, as well as endoneural mononuclear infiltration[20].During the active stage of CIDP, peripheral nerve biopsy often reveals inflammatory infiltration of T cells and macrophage-mediated demyelination of the intima of the nerve, suggesting that T lymphocytes, macrophages, and their cytokines play a key role in the pathogenesis of the disease[21].

The blood-nerve barrier (BNB) is a dynamic andeffectiveinterface between the endoneurial microenvironment and the surrounding extracellular space or blood. Because BNB tightly seals the healthy peripheral nervous system (PNS) to prevent random migration of cells tothe PNS, the peripheral nerves are under constant immune monitoring by T, B cells and macrophages[22].Thoseautoimmune disorders of PNS including CIDP follows BNB impairment. The breakdown of the BNB has been considered an important role in disease pathogenesis[23].Local activation of cell-adhesion molecules, inflammatory cytokines, matrix metalloproteinases, or other inflammatory substances may disrupt the

barrier, leading to the development and further deterioration of peripheral neuropathy,and hematogenous leukocytes were actively involved in axonal degeneration, demyelination, or both, with resultant motor and sensory disturbances[24].Immune-mediated demyelination initially affects distal nerve endings/roots, but with upregulation of pro-inflammatory cytokines (e.g., interleukin, tumor necrosis factor, interferon) and complement, the blood-nerve barrier is disrupted and demyelination gradually extends to the nerve stem.Pro-inflammatory cytokines are mainly induced by lymphocytes, neutrophils, macrophages and monocytes[25, 26].

The inflammatory markers such as white cell counts (WBC), C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR), or there components have pivotal role in Neuroimmune disease development and progression. White blood cells, especially neutrophils are the primary response to systemic inflammation.CRPis mainly classed as one of the most sensitive acute phase reactants buta nonspecific indicator of inflammation.ESRcan be increased in infection, inflammation, trauma, tumor and other diseases.Albumin is made in the liver and acts as a nourishing cell.Decreased serum albumin level is also associated with increased systemic inflammatory load[27].Globulin is also useful in immune responses.

The albumin/globulin ratio (A/G) is a more accurate indicator of nutritional status and systemic inflammatory response than a single.The decrease of albumin or the increase of globulin are the main reasons for the low A/G,which often suggestive chronic inflammatory and immune diseases.Furthermore,low A/G was significantly correlated with low hemoglobin level[28, 29].

In our study, we assessed the diagnostic accuracy of hematologic parameters to determine the disease activity in CIDP patients, since biomarkers are available and universally monitored in clinical practice.

Monocytes are the largest white blood cells that play a crucial part in the defense system.Studies have shown that monocytes are significantly pluripotent in different inflammatory environments[30].Compared with other blood cells, monocytes contain more non-specific lipases and have stronger phagocytosis.When inflammation or other immune diseases occur in the body, the number of total monocytes can be changed[31]. Similarly,Lymphocyte have a sensitive immune response in inflammation.Therefore, the examination of monocyte and lymphocyte counts have become an important method for auxiliary diagnosis[4].Besides, Platelets are also a component of the immune system and play a directrolein regulating and inducing tissue damage and pathogen responses.They contain and release or re-produce a large number of immune molecules that directly affect the development and outcome of inflammatory diseases[32].Morerecently, PLR, NLR, and LMR values have been often used as prognostic indicators of systemic inflammation,immunological diseases and malignancies[33-37].

In previous studies, LMR has been widely used due to its of measurement,low price and strong practicability. In recent years, LMR has attracted extensiveattention in the diagnosis and/or prognosis of cancers,various immunological diseases,even cardiovascular and cerebrovascular diseases.Goto et al.had reported that LMR might be a useful prognostic indicator for breast cancer patients. Accordingly, low LMR was an independent risk factor for disease-free survival rate[38].Wang et al. suggested that LMR

may be an important inflammatory marker for the identification of axial spondyloarthritis(SpA) and assessment of disease activity and X-ray staging of sacroilitis[39].In short,LMR represents a balance between the lymphocyte and monocyte levels of the patient.Low LMR represents a decreased lymphocyte count and an increased monocyte count in the blood,leading to a weakened immune response and a strong inflammatory reaction.

The main findings of this study were as follows: (1)LMR was lowerin CIDP patients vs.HCssubjects, and the differences were significant. Active disease CIDP patients showed lower LMR levels compared to the remission group;(2) LMR was positively correlated with parameters ofHb, RBC, and A/G ($P<0.05$),andnegatively correlated withNLR, PLR, RDW;(3) ROC curve analysis showed that LMR had a high diagnostic value for CIDP witha sensitivity of 77.78% and a specificity of 75%.The sensitivity was strong in the combined diagnostic AUC of ESR, A/G, but the specificitywas weak.

To the best of our knowledge,our study is the first attempt to assess the role of LMR in CIDP patients. This comprehensive study demonstrated a significant association between LMR and CIDP. Furthermore, multivariate analysis showed that LMR was significantly reduced in patients with active CIDP, thoughweak sensitivity and specificity. It showed that LMR had been identified as a diagnostic marker of activity and severity in CIDP disease. Moreover, the LMR (based on ESR and A/G) was shown to be of prognostic value in predicting outcomes.

The simple correlation analysis showed positive associationswere found between LMR and Hb (Hemoglobin), RBC (Red blood cells), and A/G (Albumin/globulin ratio), whereas negative correlations were observed between LMR and NLR, PLR, RDW (Red cell distribution width) ($P<0.05$), indicating the correlation between LMR and systemic severity index.

Nevertheless, the thesis remains hypothetical and should be addressed in further studies. Firstly, this study was a retrospective, single-center research with a relatively small sample size.Therefore,we plan to include more CIDP patients in a multi-center randomized study for verification, so as to obtain more definite results. Secondly, LMR is a nonspecific marker of inflammation that is affected by inflammation, immune system diseases and other tumors in patients.Therefore, further prospective validation is needed to support the use of LMR in CIDP prognostic and predictive models.

Conclusions

Consequently, while the presence of inflammatory infiltrates on sural nerve biopsies implicate a cell-mediated immune response, more ubiquitous biomarkers are necessary for routine clinical use. Collectively, our work has indicated that LMR may be a promising inflammatory and dysmetabolic marker in CIDP. Furthermore, LMR might be an important inflammatory marker to identify CIDP and assess disease activity. However, prospective studies on large sample sizes are needed for further validation.

Abbreviations

CIDP:Chronic inflammatory demyelinating polyneuropathy; ROC: Receiver operating characteristic; WBC, White blood cells; RBC, Red blood cells; Hb,Hemoglobin; RDW, Red cell distribution width; NLR, Neutrophil-to-lymphocyte ratio; LMR, Lymphocyte-monocyte ratio; PLR, Platelet to lymphocyte ratio; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; Alb Albumin; TP, Total protein; A/G Albumin/globulin ratio.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committees in Sir Run Run Shaw Hospital with a waiver of informed consent (LQ15H090002),because this was the secondary use of the electronic database and has no impact on the future management of the patients.This study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

Conceived of or designed study: PX; Performed research: ZMH; Analyzed data: SJZ, BFG; Contributed new methods or models: YBW, SJZ; Wrote the paper: ZMH. All authors have read and approved the manuscript.

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Availability of data and materials

Patient data were protected and confidential.The datasets presented in this article are not readily available due to hospital policy. The datasets used and analysed during the current study available from the corresponding author on reasonable request.

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Figures

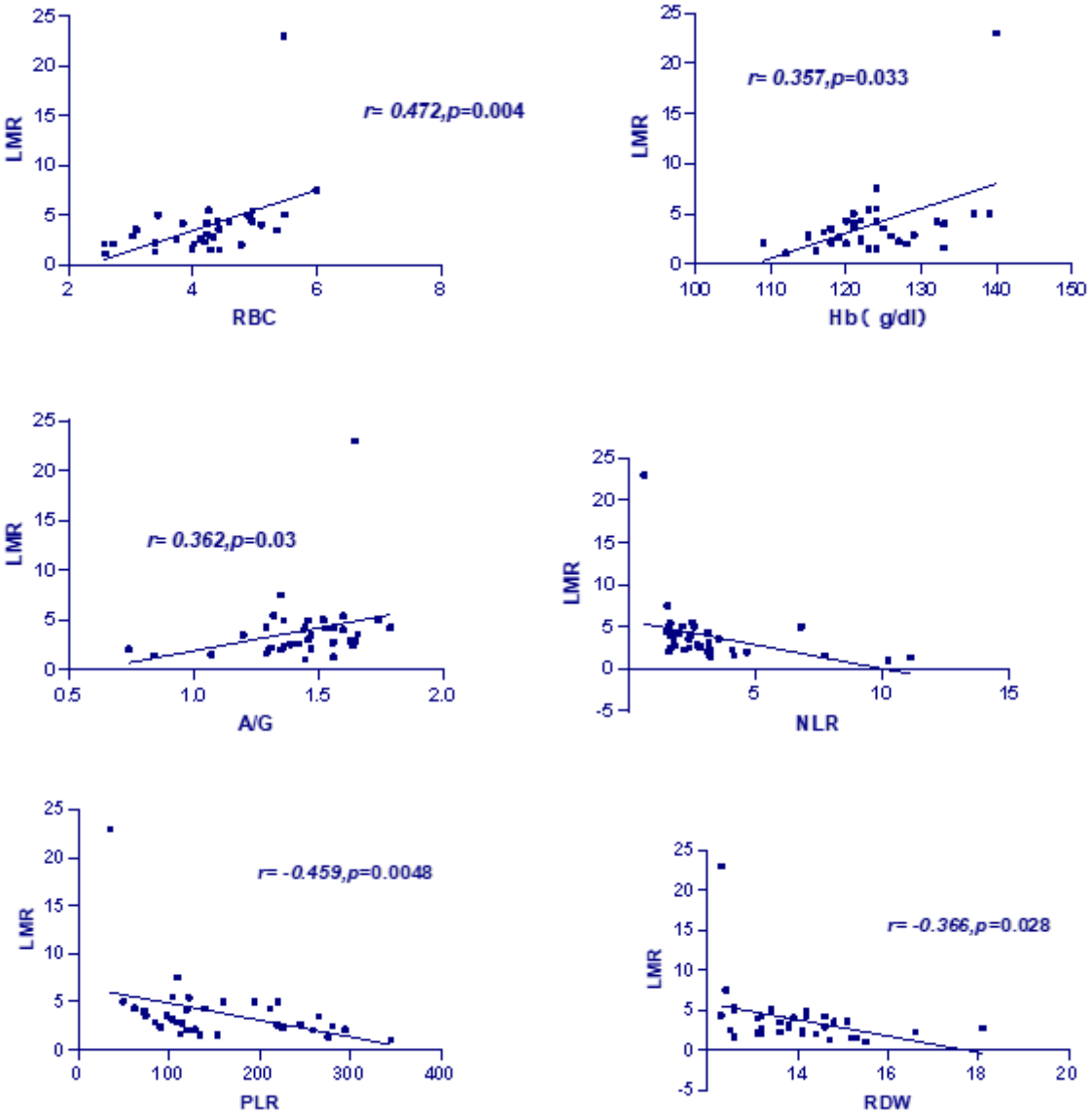

Figure 1

The correlation between LMR and Hb, RBC, A/G, NLR, PLR, RDW and other laboratory parameters was analyzed. Pearson correlation method was used for LMR and RBC, and Spearman correlation was used for other indicators.

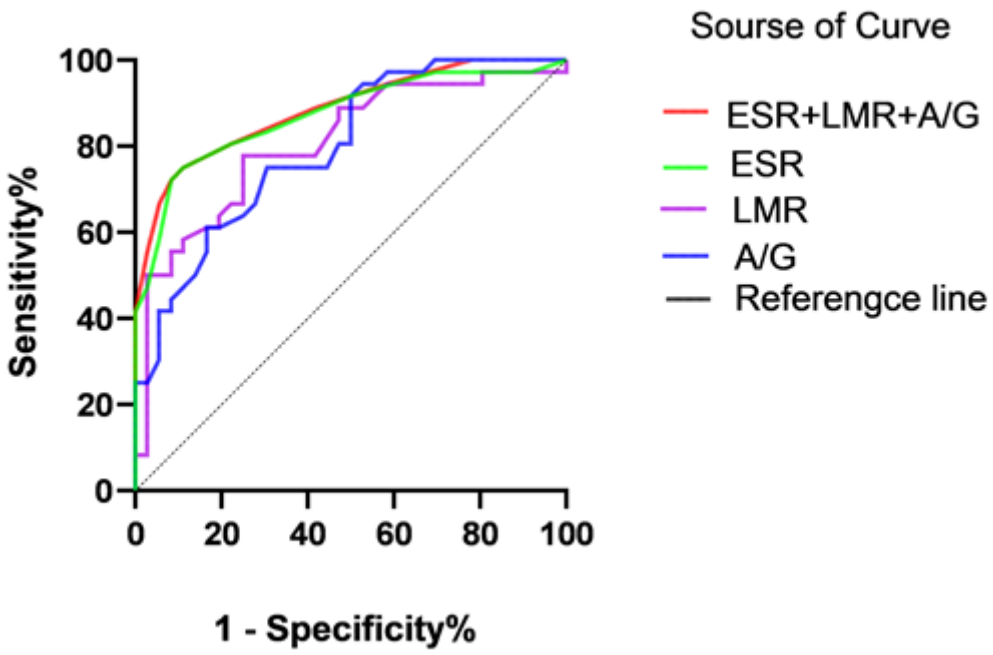

Figure 2

Receiver operating characteristic (ROC) curve analysis of ESR, A/G and LMR for CIDP diagnosis