• Clinical Research •

The prognostic value of lymphocyte-to-monocyte ratio in retinopathy of prematurity

Yu-Xiang Hu[1], Xiao-Xuan Xu[1], Yi Shao[1], Gao-Le Yuan[2], Feng Mei[1], Quan Zhou[1], Yi Cheng[1], Jun Wang[3], Xiao-Rong Wu[1]

[1]Department of Ophthalmology, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China
[2]Department of Pediatrics, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China
[3]Second Department of Respiratory Disease, Jiangxi Provincial People's Hospital, Nanchang 330006, Jiangxi Province, China
Co-first authors: Yu-Xiang Hu and Xiao-Xuan Xu
Correspondence to: Xiao-Rong Wu. Department of Ophthalmology, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China. wxr98021@126.com; Jun Wang. Second Department of Respiratory Disease, Jiangxi Provincial People's Hospital, Nanchang 330006, Jiangxi Province, China. wangjun5087@163.com
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Abstract

• AIM: To evaluate the associations between development of retinopathy of prematurity (ROP) and serum lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR).

• METHODS: A retrospective cohort study was performed, involving infants who were screened for ROP from January 2015 to December 2015. Preterm newborns of ≤32 gestational weeks with ROP were enrolled as the observation group, and non-ROP infants were enrolled as the control group, whose complete blood cell were measured within the first 24h of life. The levels of NLR, LMR and PLR were determined in all groups. The data obtained were analyzed using univariate and multivariate logistic regression analysis.

• RESULTS: In this study, 40 cases of ROP were enrolled and 40 cases of non-ROP as controls. The LMR levels were significantly higher (*P*<0.001) in ROP group (3.96±1.16) compared to non-ROP group (2.85±0.79). The NLR levels were significantly lower (*P*=0.035) in ROP group {median [interquartile range (IQR)], 0.88 (0.67-1.46)} compared to non-ROP group [median (IQR), 1.20 (0.85-1.89)]. The median PLR values were 61.99 (IQR, 50.23-75.98) in ROP group and 69.24 (IQR, 55.52-88.12) in non-ROP group (*P*=0.104). Logistic regression analysis suggested that LMR was an independent risk factor for ROP (OR: 0.275; 95% CI: 0.134-0.564; *P*=0.001).

• CONCLUSION: The findings demonstrate that higher LMR is independently and significantly associated with the development of ROP, and the LMR may be invoked as a predictive tool for identifying risk for ROP.

• KEYWORDS: neutrophil-to-lymphocyte ratio; monocyte-to-lymphocyte ratio; platelet-to-lymphocyte ratio; retinopathy of prematurity

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INTRODUCTION

Retinopathy of prematurity (ROP) is a bilateral eye disease with abnormal retinal capillary development in premature infants. ROP is characterized by retinal ischemia, and neovascularization and proliferative retinopathy, which are the main contributing factors that limit the development of retinal vessels in premature infants[1]. ROP is a leading cause of childhood blindness, accounting for about 6% to 8% of cases[2]. The mechanisms of the pathogenesis of ROP have not been fully elucidated, but many studies suggest that retinal neovascularization and fibrosis play a leading role in the occurrence and development of ROP[3-4]. The development of ROP has been correlated to several factors, including angiogenic factors, cytokines and oxidative and neuroprotective growth factors[1]. In recent years, inflammation has also been reported to be involved in ROP[5-7].

Ratios of white blood cells (WBC) have been proposed as indicators for general inflammatory responses[8]. The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have been proposed as potential markers of inflammation for predicting survival of patients in various diseases, including cancer, renal disease[9-12]. Ocular disorders, such as age-related macular degeneration[13], diabetic retinopathy (DR)[14], have been reported to correlate with these WBC

ratios, however the relationship between ROP and the NLR, LMR and PLR are not known. Therefore, the objective of this study was to evaluate the prognostic potential of LMR in patients with ROP. A retrospective cohort study was performed to assess the prognostic role of NLR, LMR and PLR on the clinical outcomes of patients with ROP.

SUBJECTS AND METHODS

Study Population Clinical data was collected from premature infants who underwent ROP screening in the First Affiliated Hospital of Nanchang University from January 2015 to December 2015. Infants without any other retinal disease and who gestational age less than 32wk or birth weight less than 2000 g were included in the study. Infants born with blood culture-proven sepsis, necrotizing enterocolitis and hematologic diseases, received a blood product transfusion or postnatal steroid therapy before the ROP screening were excluded. This study was approved by the medical Ethics Committee of the First Affiliated Hospital of Nanchang and adhered to the Declaration of Helsinki. Parents were informed of the study and provided written informed consent allowing their children to take part in this study.

Methods Fundus exams were performed on all infants according to the screening guidelines for ROP in China (2014). Initial screenings occured at 32wk postmenstrual age, or four to six weeks after birth. All exams were performed under mydriatic conditions by using two drops of tropicamide 0.5% and phenylephrine 2.5% before the examination began. Ophthalmological examinations were performed by an experienced ophthalmologist using a binocular indirect ophthalmoscope combined with sclera depressor and/or the RetCam III wide-angle digital retinal imaging system after topical anesthesia with proxymetacaine hydrochloride 0.5% eye drops. The ROP status of each infant was classified according to the international classification of ROP, including stage, zone, extent of disease, and presence or absence of plus disease[15]. Each infant was classified according to the maximum stage of ROP observed in either eye. Among the screened premature infants, 40 infants without ROP were randomly selected as the control group, and 40 infants with ROP were selected as the ROP group. Patients with threshold ROP, defined as 5 contiguous or 8 interrupted clock hours of stage 3 ROP with plus disease in zone I or II, or prethreshold type 1 ROP, defined as any ROP with plus disease or stage 3 without plus disease in zone I, and stage 2 or 3 with plus disease in zone II, were classified as severe ROP, who should be received treatment within 72h[16]. The other ROP infants were classified as non-severe ROP group. Other variables associated with ROP, such as birth weight, gestational age, sex, type of birth, and multiple pregnancies were also recorded. Patients with hypoxic-ischemic encephalopathy (HIE), premature rupture of membranes (PROM), respiratory distress syndrome (RDS), asphyxia neonatorum, and neonatal pneumonia were noted as have additional potential risk factors. Whole blood samples were collected within the first 24h of life, due to the potential need for blood transfusion later or the possibility of development of infection with or without sepsis. All blood samples were evaluated within the first 24h after birth. Peripheral venous blood (1 mL) was collected in tubes containing dipotassium ethylene diamine tetraacetate (EDTA-2K). Complete blood counts were evaluated by an automated hematology analyzer (Sysmex XE-2100, Kobe, Japan).

Statistical Analysis LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. Likewise, NLR and PLR were determined by dividing the absolute neutrophil count or the absolute platelet count by the absolute lymphocyte count, respectively. Continuous variables were presented as mean with standard deviation for normally distributed data or as medians and interquartile ranges (IQRs) for non-normally distributed data, and compared between ROP and non-ROP groups using one-way ANOVA test or Mann-Whitney nonparametric *U* test. Dichotomous variables were presented as absolute counts and percentage, and compared between groups by Chi-square statistical test. Univariate analysis was conducted to assess other potential risk factors for the presence of ROP, such as the NLR, LMR, PLR, HIE, PROM, RDS, asphyxia neonatorum and neonatal pneumonia. Logistic regression was used to estimate the significant independent risk factors associated with the presence of ROP. Exact P values <0.05 were considered statistically significant. The adjusted odds ratio (OR) and 95% confidence interval (CI) for each possible risk factor were calculated. Receiver operating characteristic (ROC) curve was plotted to determine the optimal cutoff value for LMR. All statistical analyses were performed using SPSS 22.0 (SPSS for Windows, version 22.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

In this study, 80 preterm infants who met the inclusion criteria were enrolled. Their birth weight ranged from 650 to 1900 g, and gestational age ranged from 25 to 32wk. Of the 80 infants, 40 presented some form of ROP. The distribution of stages of ROP was as follows: 18 (45%) developed stage 1 ROP; 10 (25%), stage 2; and 12 (30%), stage 3; 15 patients (37.5%) had plus disease. The basic characteristics of premature infants in ROP group and non-ROP group are presented in Table 1. The mean birth weight was 1210±190 g (range, 650-1570 g) and 1393±260 g (range, 900-1900 g), respectively, and mean gestational age in ROP group and non-ROP group was 28.88±1.18wk (range, 25-31wk) and 29.70±1.18wk (range, 28-32wk), respectively. Birth weight and gestational age were significantly different between both groups (P=0.001, 0.003, respectively). However, there were no statistically significant differences in terms of gender, type of birth, multiple pregnancy,

Table 1 Baseline clinical features and laboratory measurements of study subjects *n* (%)

Variables	ROP group (*n*=40)	Non-ROP group (*n*=40)	[a]*P*
Sex (M)	25 (62.5)	23 (57.5)	0.648
GA (wk)	28.88±1.18	29.70±1.18	0.003[a]
Birth weight (g)	1210±190	1393±260	0.002[a]
Type of birth: C/S	19 (47.5)	22 (55)	0.502
Multiple pregnancy	7 (17.5)	9 (22.5)	0.576
WBC count ($\times10^9$/L)	9.71 (7.73-13.25)	9.97 (7.60-13.61)	0.844
Platelet count ($\times10^9$/L)	264.53±95.72	261.91±80.57	0.896
Neutrophil count ($\times10^9$/L)	4.08 (2.69-5.36)	3.77 (2.98-6.15)	0.501
Lymphocyte count ($\times10^9$/L)	4.39 (3.27-5.13)	3.91 (2.63-5.01)	0.194
Monocyte count ($\times10^9$/L)	1.18 (0.75-1.43)	1.25 (0.91-1.96)	0.111
NLR	0.88 (0.67-1.46)	1.20 (0.85-1.89)	0.035[a]
PLR	61.99 (50.23-75.98)	69.24 (55.52-88.12)	0.104
LMR	3.96±1.16	2.85±0.79	<0.001[a]
HIE	13 (32.5)	15 (37.5)	0.639
PROM	9 (22.5)	10 (25.0)	0.793
RDS	35 (87.5)	29 (72.5)	0.094
Asphyxia neonatorum	28 (70.0)	21 (47.5)	0.108
Neonatal pneumonia	29 (72.5)	23 (57.5)	0.160

GA: Gestational age; C/S: Caesarean section; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; HIE: Hypoxic-ischemic encephalopathy; PROM: Premature rupture of membranes; RDS: Respiratory distress syndrome. [a]*P*<0.05, statistically significant.

Table 2 Comparison of NLR and LMR values among groups

Variables	Non-ROP group (*n*=40)	Non-severe ROP group (*n*=26)	Severe ROP group (*n*=14)	[a]*P*
NLR	1.20 (0.85-1.89)	0.84 (0.69-1.62)	0.95 (0.64-1.32)	0.065
LMR	2.85±0.79	3.63±1.00	4.56±1.23	<0.001[a]

NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; ROP: Retinopathy of prematurity. [a]*P*<0.05, statistically significant.

WBC count, platelet count, neutrophil count, lymphocyte count, monocyte count, HIE, PROM, RDS, asphyxia neonatorum and neonatal pneumonia (*P*>0.05).

The NLR values were significantly lower in patients with ROP compared to patients without ROP [median (IQR) 0.88 (0.67-1.46) *vs* 1.20 (0.85-1.89); *P*=0.035]. Also, the LMR levels were significantly higher (*P*<0.001) in the ROP group (3.96±1.16) compared to the non-ROP group (2.85±0.79). The median PLR values were 61.99 (IQR, 50.23-75.98) in the ROP group and 69.24 (IQR, 55.52-88.12) in the non-ROP group, but the difference between groups was not statistically significant (*P*=0.104). Among the infants without ROP, the infants with non-severe ROP, and the infants with severe ROP who need treatment, the NLR values were not significant (*P*=0.065), but the LMR values in severe ROP group (4.56±1.23) and non-severe ROP group (3.63±1.00) were, compared to those of non-ROP infants (2.85±0.79), significantly higher [*P*<0.001 (one-way ANOVA); Table 2, Figure 1].

Logistic regression analysis suggested that independent risk factors for ROP were LMR (OR: 0.275; 95% CI: 0.134-0.564; *P*=0.001) and gestational age (Table 3). Although, birth weight between groups did not achieve statistical significance, *P* values approached significance (*P*=0.073) and may reach statistical significance with a larger sample size. Figure 2 shows that as an independent risk factor for ROP, the optimal cut-off value of LMR was 3.21, with 77.5% sensitivity and 70.0% specificity and an area under the ROC curve for LMR was 0.785 (95% CI: 0.683-0.887).

Table 3 Logistic regression analysis showing independent predictors of retinopathy

Variables	OR	95% CI	[a]*P*
GA (wk)	1.884	1.049-3.384	0.034[a]
Birth weight (g)	15.640	0.774-315.857	0.073
LMR	0.275	0.134-0.564	0.001[a]
NLR	1.683	0.678-4.180	0.262

OR: Odds ratio; 95% CI: 95% confidence interal; GA: Gestational age; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio. [a]*P*<0.05, statistically significant.

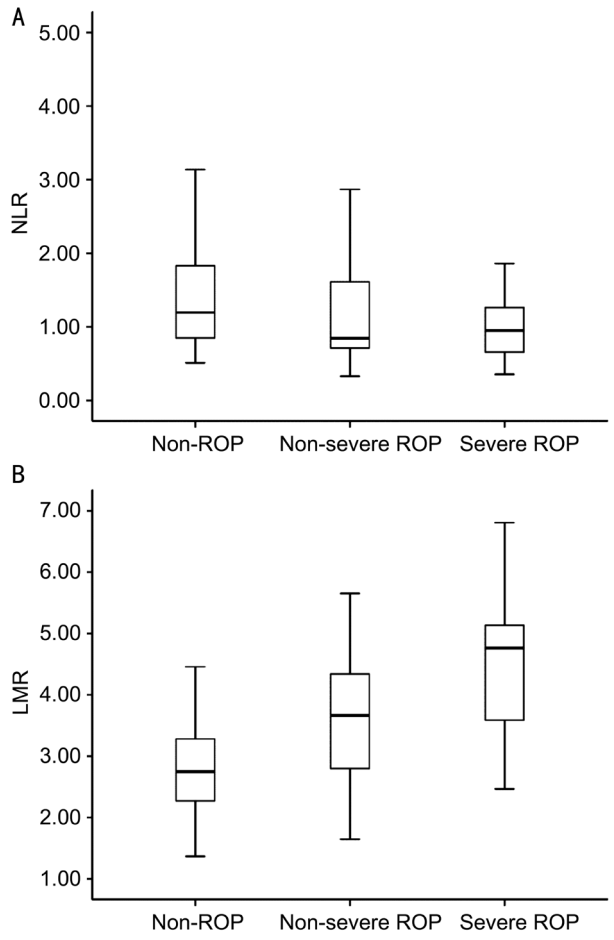

Figure 1 The boxplots showing the NLR and LMR levels in non-ROP, non-severe ROP, and severe ROP groups A: Comparison of the NLR levels among the three groups (P=0.065); B: Comparison of the LMR levels among the three groups (P<0.001).

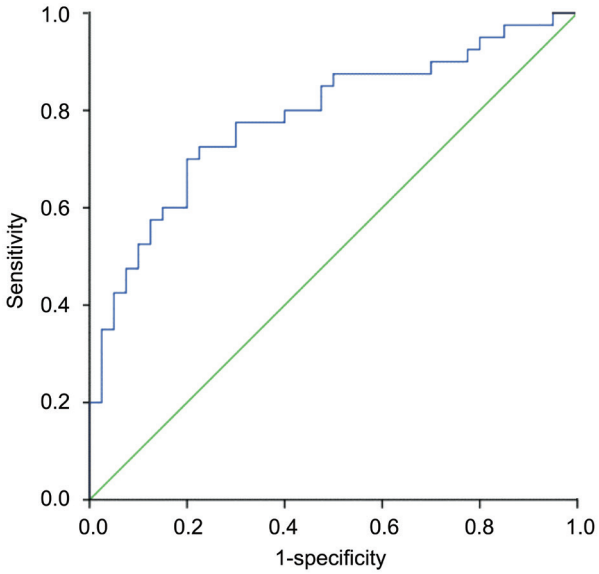

Figure 2 ROC curve analyses for LMR as a predictor of ROP.

DISCUSSION

It is known that the maternal systemic inflammatory responses and severe neonatal inflammatory reactions play a significant role in ROP pathogenesis[1,4]. Sood *et al*[7] have suggested that fetal inflammatory responses are an important factor in the cause of preterm birth. Woo *et al*[17] also reported that inflammatory mediators are significantly associated with the pathogenesis of ROP. Systemic inflammatory responses can directly or indirectly affect the formation of retinal neovascularization and increase the risk of ROP, independent of gestational age or severity of early systemic illness[5]. These findings suggest an interaction between inflammatory responses and the pathogenesis of ROP.

In recent years, several novel inflammatory prognostic indicators derived from peripheral blood, such as the NLR, LMR, and PLR, have been widely investigated for their predictive prognostic value in tumors[11,18-19]. The use of NLR, which quantitates neutrophilia (an indicator of inflammation) and lymphopenia (an indicator of physiologic stress), is a valuable prognostic gage for evaluating patients with systemic inflammation[20]. NLR also reflects the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses. Guthrie *et al*[21] suggest that the NLR may be more indicative of inflammation than total leukocyte count. In this study, the prognostic impact of the NLR on ROP was demonstrated on univariate analysis, but the significance of the association was lost with multivariate analysis (Tables 1, 3), which is similar to what has been reported by Kurtul *et al*[22]. However, the lymphocyte count alone turned out not to be an independent risk factor for ROP, which differs from the report of Kurtul *et al*[22]. One possible reason for this discrepancy is the case that the sample sizes in this study were slightly smaller. Additionally, subject heterogeneity may also account for this discrepancy.

Monocytes, an important component of peripheral blood, are considered an indicator of systemic inflammation, as monocytes are mobilization to migrate from the bone marrow to the peripheral blood[23]. LMR, as a novel inflammatory biomarker, reflects the balance between a favorable prognostic outcome involving lymphocytes and an unfavorable one, involving monocytes[24]. The prognostic value of LMR has been established in numerous tumor studies[24-26] and in retinal disease, such as DR[14], but has not been described in ROP. To the best of our knowledge, this is the first study to evaluate the association between LMR and ROP. In the present study, severe ROP patients are clearly inclined to get higher LMR compared to patients with non-severe ROP or without ROP, suggesting that there is an association between the LMR and ROP progression. Therefore, we hypothesized that the LMR of peripheral blood within 24h after birth is closely related to the occurrence and development of ROP and can be used as a reliable independent index for predicting ROP. Besides, the ROC curve was created to determine the cut-off value of LMR for the prediction of ROP, and figure out that the ideal value was 3.21. It suggests that the risk of ROP was higher in preterm infants with LMR over 3.21, but the significance needs to be verified by a large sample.

PLR is another indicator of systemic inflammation that has been validated as a prognostic predictor in some tumors[27-28]. Recent studies have shown that platelets play an important role in angiogenesis, fibrin formation and deposition, platelet parameters, and changes in premature birth-related diseases, such as sepsis and RDS[29-30]. This is the first study that has specifically investigated the significance of PLR in ROP. However, PLR is not found to be associated with the development of ROP in this study, which may be due to the amount of the patient cohort. The mechanisms underlying the association between the PLR and ROP should be investigated in future studies.

The major limitation of this study is the small number of patients. Additionally, as a retrospective observational study, patients were not treated by the same doctor and it was difficult to ensure the consistency of the clinicopathological data. Finally, all patients enrolled in this study were Chinese which provides little data to understand the influence of ethnic diversity. Further investigations including more patients are needed to investigate the possible role of serum LMR and NLR levels in ROP disease progression. Moreover, to better understand the prognostic role of the LMR and NLR, additional investigations should be conducted in these ratios, such as the differences based on gestational age, the dynamic changes in ROP progression, the relationships with different treatments and so on.

In conclusion, the current study revealed that higher LMR, measured within a critical window of 24h of birth, is independently associated with ROP. Early detection of abnormal LMR levels may be helpful for predicting the development of ROP in premature neonates. Additionally, NLR and PLR are uncorrelated with the development of ROP in premature infants. However, these findings should be validated in large-scale prospective studies.

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