



## DIAGNOSTIC VALUE OF HEMATOLOGICAL INFLAMMATORY MARKERS IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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### ABSTRACT

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| <b>Introduction</b>          | Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder associated with elevated bile acid levels, systemic inflammation, and increased maternal and fetal risks. Identifying accessible and cost-effective inflammatory biomarkers may improve clinical assessment of patients with ICP.                                                                                                                                                                                                                         |
| <b>Materials and methods</b> | The case-control study included 142 pregnant women: 71 diagnosed with ICP and 71 healthy controls. Hematological inflammatory markers were evaluated, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW), and emerging ratios such as platelet-to-monocyte ratio (PMR) and C-reactive protein-to-lymphocyte ratio (CLR). Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis. |
| <b>Results</b>               | NLR and PLR were significantly higher in the ICP group than in the control group ( $p < 0.0001$ ). ROC analysis demonstrated moderate discriminatory ability for NLR (AUC=0.707) and PLR (AUC=0.709). Other markers showed limited diagnostic value.                                                                                                                                                                                                                                                                      |
| <b>Conclusions</b>           | NLR and PLR provide additional information regarding systemic inflammation in patients with ICP and may serve as complementary tools in clinical evaluation. Further studies are required to confirm their prognostic and diagnostic relevance.                                                                                                                                                                                                                                                                           |
| <b>Keywords</b>              | Intrahepatic cholestasis of pregnancy, obstetric cholestasis, ICP, hematological inflammatory markers.                                                                                                                                                                                                                                                                                                                                                                                                                    |

### VALOAREA DIAGNOSTICĂ A MARKERILOR HEMATOLOGICI DE INFLEAMATIE ÎN COLESTAZA INTRAHEPATICĂ DE SARCINĂ

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Introducere</b>         | Colestaza intrahepatică de sarcină (CIS) este o afecțiune hepatică asociată cu creșterea concentrației acizilor biliari, inflamație sistemică și riscuri materne și fetale crescute. Identificarea unor biomarkeri inflamatori accesibili și rentabili ar putea îmbunătăți evaluarea clinică a pacientelor cu CIS.                                                                                                                                                                                                                                                                                                |
| <b>Materiale și metode</b> | Studiul de tip caz-control a inclus 142 de femei gravide: 71 diagnosticate cu CIS și 71 gravide sănătoase în lotul de control. Au fost evaluați markerii hematologici ai inflamației, inclusiv raportul neutrofile/limfocite (NLR), raportul trombocite/limfocite (PLR), volumul trombocitar mediu (MPV), amplitudinea distribuției eritrocitare (RDW), precum și indicatori emergenți, cum ar fi raportul trombocite/monocite (PMR) și raportul proteina C reactivă/limfocite (CLR). Performanța diagnostică a markerilor a fost evaluată prin analiza curbelor caracteristicii de operare a receptorului (ROC). |
| <b>Rezultate</b>           | Valorile NLR și PLR au fost semnificativ mai mari în grupul cu CIS comparativ cu lotul de control ( $p < 0,0001$ ). Analiza ROC a demonstrat o capacitate moderată de discriminare pentru NLR (AUC=0,707) și PLR (AUC=0,709). Ceilalți markeri au prezentat o valoare diagnostică limitată.                                                                                                                                                                                                                                                                                                                       |
| <b>Concluzii</b>           | NLR și PLR oferă informații suplimentare privind inflamația sistemică asociată colestazei intrahepatice de sarcină și pot servi drept instrumente complementare în evaluarea clinică a acestor paciente. Sunt necesare studii suplimentare pentru confirmarea relevanței lor diagnostice și prognostice.                                                                                                                                                                                                                                                                                                          |
| <b>Cuvinte-cheie</b>       | Colestaza intrahepatică de sarcină, colestaza gravidarum, CIS, markeri hematologici de inflamație.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

## INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a hepatic disorder affecting bile flow that typically presents during the second and third trimesters of pregnancy. It is characterized by elevated serum bile acid (BA) levels and intense pruritus, usually affecting the palms and soles (1, 2). The diagnosis of ICP is based on serum BA levels  $\geq 19 \mu\text{mol/L}$ , with levels  $\geq 40 \mu\text{mol/L}$  indicating moderate disease and  $\geq 100 \mu\text{mol/L}$  indicating severe intrahepatic cholestasis of pregnancy. This classification reflects the increased risk of adverse maternal and fetal outcomes, including preterm birth, fetal distress, and stillbirth, as BA levels rise (1-6). Although ICP symptoms and biochemical indicators generally resolve postpartum, the condition poses significant risks during pregnancy, particularly with respect to coagulation, fetal well-being, and the timing of delivery (7-9).

The pathophysiology of ICP remains incompletely understood, with evidence suggesting interactions among genetic, hormonal, and environmental factors (10-13). Genetic mutations affecting bile acid transport proteins, particularly in the ABCB4 and ABCB11 genes, have been associated with increased susceptibility to ICP, as these proteins play essential roles in bile acid transport and metabolism (11, 12, 14). Elevated estrogen and progesterone levels are also thought to exacerbate bile flow impairment, thereby increasing BA levels (7, 11). In addition, emerging evidence suggests that gut microbiota–bile acid–FXR signaling may influence bile acid homeostasis and inflammatory responses in ICP (11-15).

Given the potential inflammatory state in ICP, there is growing interest in hematological inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV), as potential indicators of disease severity and progression (16-21). These markers are already well established in cardiovascular, autoimmune, and inflammatory conditions and are inexpensive and widely available in clinical practice (22-29). Studies indicate that elevated NLR and PLR values correlate with systemic inflammation and predict adverse outcomes in hepatic disorders, suggesting their potential utility in ICP (23-25, 30-35). Recent studies have also introduced novel biomarkers as promising tools for diagnosis and prognosis. These include the platelet-to-monocyte ratio (PMR), neutrophil-to-monocyte ratio (NMR), monocyte-to-lymphocyte ratio (MLR), eosinophil-to-lymphocyte ratio (ELR), and C-reactive protein-to-lymphocyte ratio (CLR) (26, 36, 37).

Hematological markers are increasingly recognized for their role in pregnancy complications. The NLR, calculated by dividing the neutrophil count by the lymphocyte count, has shown promise as a predictor of inflammation severity. In cardiovascular settings, higher NLR values are associated with worse outcomes (38, 39). Similarly, PLR, a ratio of platelet to lymphocyte counts, has demonstrated diagnostic value in systemic inflammation and is associated with adverse outcomes when elevated. Higher PLR values may indicate increased platelet activation, which is pertinent to ICP given the role of platelets in coagulation (33, 34). MPV, a measure of platelet size, has also been associated with heightened inflammatory responses and could be an indicator of coagulation risks in ICP, particularly given the coagulation challenges posed by possible Vitamin K deficiency in this population (40-42), although MPV's diagnostic value varies substantially across clinical contexts (29, 43, 44). These findings led the authors to examine their relevance in ICP.

Although guidelines from the Royal College of Obstetricians and Gynaecologists currently focus on monitoring bile acid levels and liver function in ICP, recent studies suggest that adding hematological inflammatory markers to routine evaluations could enhance ICP management by identifying women at higher risk of complications, such as hemorrhage, and providing additional clinical information, especially in settings where bile acid testing may be delayed or

less accessible (1-4). Ongoing research emphasizes that, when combined with biochemical markers, hematological indices such as NLR, PLR, and MPV could improve risk stratification and provide a more comprehensive clinical assessment of ICP (16). Integrating these markers may enable earlier identification of at-risk patients, thereby improving maternal and fetal outcomes in ICP management.

The aim of this study was to evaluate the diagnostic performance of hematological inflammatory markers in women with intrahepatic cholestasis of pregnancy and to determine their potential utility as complementary diagnostic biomarkers.

## MATERIALS AND METHODS

### Study Design and Participants

Participants were selected based on predefined inclusion and exclusion criteria. The study group included pregnant women diagnosed with intrahepatic cholestasis of pregnancy. The control group consisted of pregnant women matched for age and gestational week, without ICP. Exclusion criteria included pre-existing liver disease, preeclampsia, HELLP syndrome, and any known hematological disorders.

### Sample Size Calculation

This study was designed as a case-control study aimed at evaluating the diagnostic performance of hematological inflammatory markers in intrahepatic cholestasis of pregnancy.

Data were collected between 2020 and 2023.

The sample size was calculated using Epi Info version 7.2.2.6 (StatCalc module, Sample Size and Power) for an analytical observational cohort study. The calculation was based on:

- a 95% confidence level;
- 80% statistical power;
- an expected 20% difference in the proportion of elevated inflammatory markers between the ICP and control groups, based on the literature (45, 46); and
- a 1:1 ratio between study groups.

The minimum required sample size was estimated at 44 participants per group. After accounting for a 10% non-response rate, this number increased to 48 participants per group.

To enhance statistical robustness, a total of 142 pregnant women were ultimately included and allocated to two groups according to predefined inclusion and exclusion criteria. The study group (L1) consisted of 71 women diagnosed with ICP, while the control group (L0) included 71 healthy pregnant women without ICP.

### Data Collection and Laboratory Assessments

Participants were evaluated using questionnaires, medical record analysis, and laboratory tests, which included inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW), platelet-to-monocyte ratio (PMR), neutrophil-to-monocyte ratio (NMR), monocyte-to-lymphocyte ratio (MLR), eosinophil-to-lymphocyte ratio (ELR), C-reactive protein (CRP), and the CRP-to-lymphocyte ratio (CLR).

### Calculation of Hematological Ratios

The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while the PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. Similarly, the PMR, MLR, NMR, ELR, and CLR were calculated by dividing the corresponding absolute blood cell counts. MPV and RDW values were automatically calculated using the Sysmex XN-1000 hematology analyzer.

### Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 21 and GraphPad software. The normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were presented as means and standard deviations ( $M \pm SD$ ) or medians and interquartile ranges (Me: Q1: Q3), depending on data distribution. Categorical variables were compared using the chi-square ( $\chi^2$ ) test with Yates' correction. A p-value  $< 0.05$  was considered statistically significant, and 95% confidence interval (CI) was calculated.

The study was designed to evaluate the diagnostic performance of hematological inflammatory markers by comparing their levels between the ICP and control groups and assessing their discriminatory ability using receiver operating characteristic (ROC) curve analysis, to determine sensitivity (Se), specificity (Sp), and optimal cut-off values. The Youden index ( $J = \text{sensitivity} + \text{specificity} - 1$ ) was applied to identify the optimal cut-off value for each hematological marker by maximizing the combined sensitivity and specificity derived from ROC curve analysis. Area under the ROC curve (AUC) values were categorized as follows:  $AUC > 0.9$  (excellent), 0.81-0.9 (very good), 0.71-0.8 (good), and 0.61-0.7 (satisfactory). To increase statistical robustness and improve the precision of ROC estimates, a larger sample size of 71 participants per group was ultimately included.

## RESULTS

The participants ranged in age from 18 to 43 years, with a mean age of  $29.5 \pm 6.3$  years in L1 and  $27.3 \pm 5.4$  years in L0 ( $p = 0.029$ ).

Hemoglobin levels were assessed (Me 117: 106; 123) in the ICP group (L1), compared to (Me 118 (108; 124)) in the control group (L0). The average red blood cell count was (Me 3.8: 3.5; 4.2) in the ICP group vs. (Me 3.9: 3.6; 4.1) in the control group. The median hematocrit was (Me 36: 32.4; 37.9) in L1 vs. (Me 36: 33.7; 37.9) in L0.

Considering the high prevalence of anemia during pregnancy worldwide and its potential health risks for the mother and child, we analyzed data in terms of the presence and degree of anemia in the participants.

Pregnant women from both groups were categorized as follows, based on the presence and degree of anemia:

- Mild anemia (hemoglobin levels 100-109 g/L): L1 – 15 women (21.1%; 95% CI: 9.4-31.4%) vs. L0 – 12 cases (16.9%; 95% CI: 8.2-25.4%),  $\chi^2$  0.183;  $p=0.6689$ .
- Moderate anemia (hemoglobin levels 70-99 g/L): L1 – 11 women (15.5%; 95% CI: 6.6-25.4%) vs. L0 – 10 cases (14.1%; 95% CI: 5.6-22.8%),  $\chi^2$  0.056;  $p=0.8131$ .
- Severe anemia (hemoglobin levels  $<70$  g/L) was not observed in either group.

The median platelet count was (Me 243: 209; 275) in L1 vs. (Me 230: 190; 278) in L0. The median neutrophil count was (Me 8.7: 6.9; 10.9) in L1 compared to (Me 8.0: 6.1; 10.5) in L0. The median lymphocyte count was (Me 1.7: 1.4; 2.1) in L1 vs. (Me 2: 1.7; 2.6) in L0.

The median NLR was (Me 5.1: 3.7; 7.2) in L1, compared to (Me 3.9: 3.0; 4.7) in L0. The median PLR was (Me 135.1: 110.5; 184.3) in L1 compared to (Me 104.4: 83.7; 132.9) in L0. The median MPV was (Me 11.8: 11.0; 12.6) fl in L1 and (Me 11.6: 10.9; 12.3) fl in L0. The median leukocyte count was (Me 11.8: 9.6; 14.5)  $\times 10^3/\mu\text{L}$  in L1 compared to (Me 9.3: 8.2; 11.4)  $\times 10^3/\mu\text{L}$  in L0.

Regarding the red cell distribution width indices, our findings revealed the following median values: RDW-SD: (Me 45.4: 41.4; 49.5) fl in L1 vs. (Me 48.8: 44.9; 53.1) fl in L0; RDW-CV: (Me 13.4: 12.8; 14.6) % in L1 vs. (Me 14.5: 13.6; 15.3) % in L0.

The median PMR was (Me 355.1: 285.9; 465.0) in L1, compared to (Me 305.4: 245.7; 391.1) in L0. The median NMR was (Me 11.1: 8.4; 13.5) in L1 compared to (Me 10.5: 8.6; 14.2) in L0. The median MLR was (Me 0.37: 0.30; 0.47) in L1 and (Me 0.4: 0.28; 0.52) in L0. The median ELR level was (Me 0.032: 0.024; 0.055) in L1 compared to (Me 0.036: 0.024; 0.057) in L0.

The median CRP level was (Me 4.1: 2.2; 8.2) mg/L in L1, compared to (Me 4.3: 1.8; 6.3) mg/L in L0. Elevated CRP levels were observed in 19 cases (26.8%; 95% CI: 16.9-34.7%) in L1 and 14 cases (19.7%; 95% CI: 11.0-31.2%) in L0, with no significant difference ( $\chi^2$  0.632;  $p=0.4268$ ). The median CLR was (Me 1.75: 0.68; 3.09) in L1, compared to (Me 2.8: 1.41; 7.22) in L0.

Additionally, we evaluated hematological inflammatory markers through ROC curve analysis and determined their sensitivity and specificity (Table 1, Figure 1).

**Table 1.** Sensitivity and specificity of the hematological inflammatory markers in the study participants.

|            | AUC ROC | 95% CI      | p       | Youden index | Associated criterion            | Se (%) | Sp (%) |
|------------|---------|-------------|---------|--------------|---------------------------------|--------|--------|
| NLR        | 0.707   | 0.624-0.780 | <0.0001 | 0.3803       | >4.56                           | 63.4   | 74.6   |
| PLR        | 0.709   | 0.627-0.782 | <0.0001 | 0.3099       | >104.4                          | 80.3   | 50.7   |
| MPV        | 0.529   | 0.444-0.613 | 0.5509  | 0.09859      | >11.9 fl                        | 47.9   | 61.9   |
| RDW-SD     | 0.648   | 0.564-0.727 | 0.0013  | 0.2394       | $\leq 45.4$ fl                  | 50.7   | 73.2   |
| RDW-CV     | 0.663   | 0.579-0.740 | 0.0005  | 0.3099       | $\leq 13.7\%$                   | 60.6   | 70.4   |
| CRP        | 0.534   | 0.448-0.618 | 0.4853  | 0.09859      | >6.1 mg/L                       | 36.6   | 73.2   |
| PMR        | 0.612   | 0.527-0.693 | 0.0176  | 0.1972       | >245.71                         | 94.37  | 25.35  |
| NMR        | 0.520   | 0.434-0.604 | 0.6874  | 0.1127       | $\leq 15.8$                     | 90.14  | 21.13  |
| MLR        | 0.551   | 0.466-0.635 | 0.2944  | 0.1549       | $\leq 0.5$                      | 87.32  | 28.17  |
| ELR        | 0.502   | 0.417-0.587 | 0.9655  | 0.05634      | $\leq 0.12$                     | 88.73  | 5.63   |
| CLR        | 0.624   | 0.538-0.703 | 0.0091  | 0.2394       | $\leq 4.39$                     | 87.32  | 36.62  |
| Leucocytes | 0.698   | 0.616-0.772 | <0.0001 | 0.3380       | >9.41 $\times 10^3/\mu\text{L}$ | 78.9   | 54.9   |

*Note:* NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, RDW-SD: red cell distribution width-standard deviation, RDW-CV: red cell distribution width-coefficient of variation, CRP: C-reactive protein, PMR: platelet-to-monocyte ratio, NMR: neutrophil-to-monocyte ratio, MLR: monocyte-to-lymphocyte ratio, ELR: eosinophil-to-lymphocyte ratio, CLR: CRP-to-lymphocyte ratio. ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval; Se: sensitivity; Sp: specificity; p: probability value; fl: femtoliters; mg/L: milligrams per liter;  $\mu\text{L}$ : microliter.

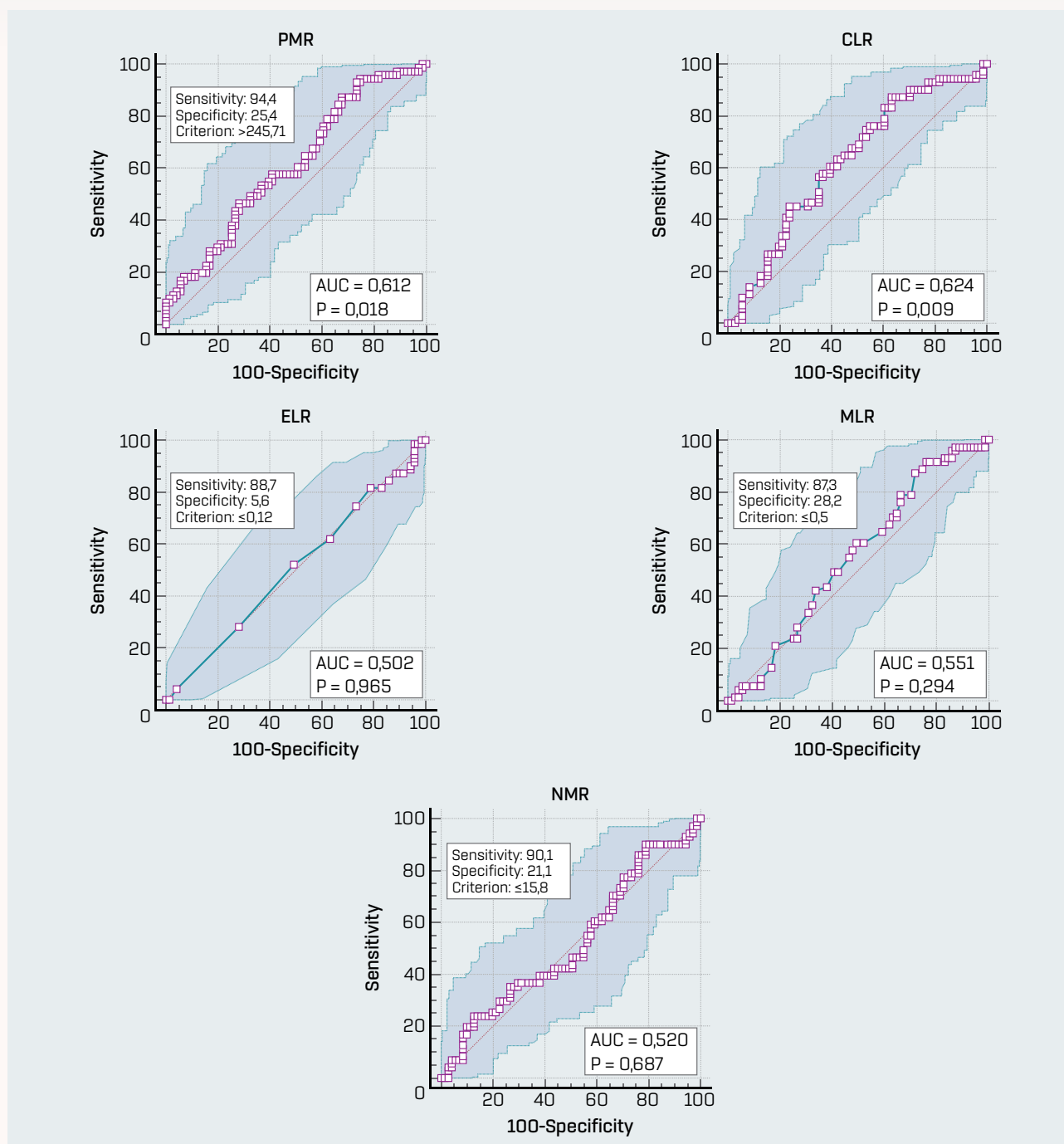


**Figure 1.** ROC curves of the hematological inflammatory markers in the study participants.

Hence, based on ROC analysis, the diagnostic value of NLR, PLR, RDW-SD, RDW-CV, PMR, CLR, and leukocyte levels for the diagnosis of ICP was considered satisfactory, with AUC values ranging from 0.61 to 0.70.

This study has several limitations that should be addressed in future research. The relatively small sample size may limit the generalizability of the findings, and the lack of long-term follow-up precludes an assessment of how inflammatory markers predict maternal and fetal outcomes beyond delivery. Larger, multicenter studies are needed to validate these findings and explore the role of novel markers such as CLR and PMR in ICP.

## DISCUSSION

### Principal Findings

The findings of this study highlight the potential role of hematological inflammatory markers, specifically the NLR and PLR, in the assessment and management of intrahepatic cholestasis of pregnancy. This study demonstrated that NLR and PLR are significantly elevated in pregnant women with ICP compared to healthy controls, and ROC analysis confirmed the satisfactory diagnostic performance of both markers. In contrast, other markers, including MPV, RDW, and newer ratios such as PMR and CLR, showed limited to moderate diagnostic utility. These low-cost, readily accessible markers proved useful for identifying ICP, with significantly higher levels observed in affected women.

### Results in the Context of What is Known

Previous studies have proposed NLR and PLR as useful inflammatory indicators in hepatic, cardiovascular, autoimmune, and obstetric conditions (22, 23, 24, 25, 33, 34, 35). The elevated NLR and PLR levels observed in the ICP group are consistent with previous research highlighting the inflammatory nature of ICP. A study by Zhao et al. demonstrated that elevated NLR and PLR levels are indicative of systemic inflammation, which has been implicated in various hepatic disorders (34). Similarly, Liu et al. found that these markers are significantly associated with hepatic dysfunction and may serve as indicators of disease severity in liver-related conditions (33). Our study corroborates these findings, showing that both NLR and PLR had satisfactory areas under the curve in ROC analyses, with values of 0.707 and 0.709, respectively, reflecting the systemic inflammatory response associated with ICP.

The growing interest in hematological inflammatory markers in obstetric practice extends beyond intrahepatic cholestasis of pregnancy. Recent evidence suggests that NLR, PLR, and other composite inflammatory indices may have potential value in identifying women at increased risk of several pregnancy-related complications. Yuce et al. reported that elevated NLR and PLR values were associated with spontaneous preterm birth, supporting the role of systemic inflammation in adverse obstetric outcomes (47). Similarly, a systematic review and meta-analysis by Qiang et al. demonstrated that PLR may serve as a predictive marker for preeclampsia, highlighting its potential utility in risk assessment during pregnancy (48). In addition, Cui et al. found that elevated NLR values were associated with liver and coagulation dysfunction in women with preeclampsia, suggesting that inflammatory cell ratios may reflect the underlying pathophysiological processes affecting both the hepatic and hematologic systems (49). More recently, Kapci et al. reported that the systemic immune-inflammation index (SII) showed prognostic value in the diagnosis of preeclampsia, further supporting the concept that readily available blood count-derived inflammatory markers may provide clinically relevant information in obstetric disorders characterized by systemic inflammatory activation (50). Collectively, these findings reinforce the rationale for investigating hematological inflammatory markers in ICP and support their potential role as adjunctive indicators of disease-related inflammatory status.

The relatively modest AUC values observed in this study may be explained by the physiological immunological adaptations that occur during pregnancy, including baseline leukocytosis and altered inflammatory responses, which can reduce the discriminatory performance of systemic inflammatory markers.

The increased inflammatory response observed in patients with ICP can be attributed to the pathophysiological mechanisms underlying the disease. Elevated bile acid levels, a hallmark of ICP, have been shown to activate inflammatory pathways, contributing to systemic inflammation and oxidative stress (39).

This inflammatory cascade may explain the significant elevation in NLR and PLR levels observed in the present study.

While NLR and PLR demonstrated diagnostic potential, other markers, such as mean platelet volume (MPV) and red cell distribution width (RDW), were less informative. Similar findings were reported by Budzianowski et al., who noted that MPV often has variable diagnostic value across different conditions, depending on the disease context (29). Additionally, although RDW values were slightly lower in patients with ICP, the difference was not statistically significant, suggesting that RDW has limited utility in the clinical assessment of ICP.

Novel markers such as the platelet-to-monocyte ratio (PMR) and C-reactive protein-to-lymphocyte ratio (CLR) have shown promise in other inflammatory conditions but were not as strongly associated with ICP in this study. A recent investigation by Rezaeian et al. highlighted the potential of these markers in inflammatory diseases such as COVID-19, suggesting their broader applicability across systemic inflammatory states (26). However, their role in ICP warrants further investigation, as their sensitivity and specificity were suboptimal in the current study.

The inclusion of hematological inflammatory markers, notably NLR and PLR, in the standard diagnostic and monitoring protocol for ICP may provide additional information to support clinical assessment. The Royal College of Obstetricians and Gynaecologists currently emphasizes bile acid levels as the primary diagnostic marker for ICP (1). However, incorporating NLR and PLR into this assessment could provide a more comprehensive picture of disease progression, especially in resource-limited settings where advanced biochemical testing may not be readily available.

The significant association between elevated inflammatory markers and the presence of ICP also raises concerns about the potential maternal and fetal complications associated with systemic inflammation. Inflammatory markers have been linked to an increased risk of adverse outcomes, such as preterm birth and postpartum hemorrhage, emphasizing the need for proactive management strategies in patients with ICP (7).

### Clinical Implications

The clinical utility of NLR and PLR lies in their accessibility, affordability, and potential to aid in the early diagnosis or risk stratification in ICP, particularly in settings where bile acid testing is delayed. Incorporating these markers into routine antenatal screening may assist clinicians in identifying women at higher risk of complications such as preterm birth or postpartum hemorrhage. Nevertheless, these markers should complement, rather than replace, standard diagnostic criteria.

### Research Implications

Further research is needed to evaluate the prognostic value of NLR and PLR across diverse populations and clinical settings. Longitudinal studies should assess whether these markers are associated with maternal or neonatal outcomes, disease progression, or response to treatment. Additionally, further research is needed to explore and validate novel markers such as PMR and CLR in the context of ICP.

### Strengths and Limitations

Strengths of this study include its design, clearly defined inclusion criteria, and the use of standardized hematologic analyses. However, its limitations include the relatively small sample size and single-center design, which

may limit the generalizability of the findings. The study also lacked long-term follow-up data to assess how these markers relate to clinical outcomes beyond delivery.

## CONCLUSIONS

This study highlights the potential of NLR and PLR as accessible and cost-effective markers of systemic inflammation in intrahepatic cholestasis of pregnancy. The integration of NLR and PLR values into clinical practice could complement traditional diagnostic tools and improve the management of this complex condition. However, further research is required to validate these findings, explore the role of additional markers, and improve both diagnostic accuracy and patient-specific risk stratification in ICP.

**CONFLICT OF INTEREST** The authors declare no conflict of interest.

**ETHICAL APPROVAL** This case-control study was approved by the Research Ethics Committee of Nicolae Testemițanu State University of Medicine and Pharmacy (No. 46, dated 28 February 2020), and written informed consent was obtained from all participants prior to enrollment. The study was registered under ISRCTN21187408 <https://www.isrctn.com/ISRCTN21187408>

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