

The role of inflammatory markers derived from complete blood count results in the diagnosis of intrahepatic cholestasis of pregnancy

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ABSTRACT

Objective: This study aimed to investigate complete blood count (CBC) markers, particularly those indicating systemic inflammation, in healthy subjects and those with mild and severe intrahepatic cholestasis of pregnancy (ICP).

Material and Method: Seventy-nine subjects with ICP and 100 healthy age-matched women who were matched based on their scheduled singleton deliveries (on the same day) were included. ICP was defined as the increase in serum bile acid levels ≥ 10 $\mu\text{mol/L}$ coupled with pruritus which could not be explained by other conditions. Patients with ICP were further categorized to mild and severe ICP according to bile acid levels, as follows: Mild ICP (< 40 $\mu\text{mol/L}$, $n=55$) and severe ICP (≥ 40 $\mu\text{mol/L}$, $n=24$). Venous blood samples were drawn upon admission to analyze bile acid concentration, liver enzymes and CBC.

Results: Mean platelet volume (MPV) was similar in subjects with mild and severe ICP whose values were higher than that of controls ($p < 0.001$). The red cell distribution width (RDW) of subjects with severe ICP was lower compared to controls, although no significant difference existed between the mild and severe ICP groups. Platelet to lymphocyte ratio (PLR) was higher in subjects with mild and severe ICP compared to controls, but it was similar in mild and severe ICP. There were no significant differences in neutrophil to lymphocyte ratio (NLR) between the groups. Correlation analysis revealed that bile acid, bilirubin, AST and ALT levels were correlated positively with MPV and PLR, and negatively with RDW value. MPV was also positively correlated with the length of stay in ICU (intensive care unit). ROC (Receiver Operating Characteristic) curve analysis showed that MPV and PLR could discriminate subjects with ICP from controls with a high sensitivity but relatively low specificity. However, neither NLR nor PLR were sensitive for discriminating severe ICP from mild ICP.

Conclusions: Some CBC derived parameters associated with inflammatory state, such as MPV and PLR, appear to have value for ICP diagnosis. However, MPV, NLR, PLR, RDW, and leukocyte count cannot be used for the discrimination of mild and severe ICP.

Keywords: Markers, cholestasis, pregnancy

INTRODUCTION

Cholestasis is historically defined as a limitation in bile flow owing to impaired secretion by hepatocytes or to obstruction of bile flow through intra- or extra-hepatic bile ducts (1). Clinical presentation of a patient with cholestasis may vary due to the retained bile component. Cholestasis of pregnancy is an intrahepatic disorder specific to pregnancy which typically presents in the third trimester and resolves rapidly following delivery (2, 3). The etiology of intrahepatic cholestasis of pregnancy (ICP) is not well understood; however, several genetic, environmental, and hormonal factors are believed to contribute to the development of ICP (4).

Although ICP resolves following delivery, accumulating data has shown that it can also be associated with spontaneous and iatrogenic preterm labor, meconium-stained amniotic fluid, fetal hypoxia, and stillbirth (5, 6). Increase of bile acids in fetal and placental circulation is considered to play a role in development of adverse fetal outcomes (7). Previous data indicate that subjects with severe ICP, characterized with a higher increase in bile acids, more frequently encounter fetal complications compared to subjects with mild ICP (8).

A recent study has shown that systemic inflammation could be associated with the etiology of ICP. Leukocyte count, platelet to lymphocyte ratio (PLR), and mean platelet volume (MPV), which are components of a simple complete blood count (CBC) test were found to be increased in subjects with ICP compared to controls (9). However, there is still paucity in evidence concerning the role of inflammation in subjects with ICP.

In this study, we aimed to investigate CBC markers that have been associated with systemic inflammation in healthy subjects and patients with mild and severe ICP, and to assess whether these parameters could be used for diagnostic purposes.

MATERIAL AND METHOD

The study was approved by University of Health Sciences Kanuni Sultan Süleyman Training and Researches Hospital Clinical Research Ethics Committee (Date:10.12.2020, Decision No: KAEK/2020.12.210). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present cross-sectional study was conducted at the Kanuni Sultan Suleyman Training and Research Hospital Department of Gastroenterology and Rumeli Hospital Department of Obstetric and Gynecology, Istanbul, Turkey between 02.03.2021 and 15.07.2021. All subjects provided written informed consent before enrollment. Seventy-nine subjects with ICP and 100 healthy age-matched women who were matched based on their scheduled date of singleton delivery (same dates as the patient group) were selected for the study. ICP was defined as an increase of ≥ 10 $\mu\text{mol/L}$ in serum bile acid levels in the presence of pruritus which could not be explained by any other clinical condition. Patients with any acute or chronic inflammatory disease (rheumatoid arthritis or inflammatory bowel disease) and those with conditions which may lead to increase in liver enzymes and bile acids (Wilson's disease, cholecystitis, primary sclerosing cholangitis, primary biliary cirrhosis, alpha-1-antitrypsin deficiency, symptomatic cholelithiasis, cytomegalovirus, Epstein-Barr virus infection, autoimmune hepatitis, or acute fatty liver of pregnancy) and those with HELLP syndrome were excluded. All patients with ICP received ursodeoxycholic acid (UDCA) treatment. Patients' demographic and clinical characteristics (including self-reported itching frequency) were also recorded.

Patients with ICP were further categorized into mild and severe ICP according to bile acid levels, as per the following definitions: mild ICP (< 40 $\mu\text{mol/L}$, $n=55$) and severe ICP (≥ 40 $\mu\text{mol/L}$, $n=24$). Venous blood samples were acquired to measure bile acid concentration, liver

enzymes (GEN-S; Beckman-Coulter, Brea, CA, USA) and complete blood count (Cell-Dyn 3700; Abbott, USA). Patients were started on UDCA treatment after diagnosis, and therefore, follow-up blood samples were also withdrawn to assess bile acid concentration and liver enzymes. The samples were centrifuged at $2000 \times g$ for 10 min within 5–10 min of blood sampling, and analyses were conducted immediately. Serum total bile acid concentration was measured via spectrophotometry using an enzymatic method on a Cobas C501 Analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

The primary outcome measure of this study was to investigate the difference in CBC derived parameters indicating acute inflammation, including leukocyte count, neutrophil to lymphocyte ratio (NLR), red blood cell distribution width (RDW), and PLR between patients with and without ICP and between patients with and without severe ICP.

Statistical Analysis

Analyses were performed with SPSS v25 (SPSS Inc., Chicago, IL, USA) and significance was defined as a p value of < 0.05 . Histogram and Q-Q plots were used to determine quantitative variable distribution features. Data concerning continuous variables are given as mean \pm standard deviation or median (1st quartile-3rd quartile) (according to normality of distribution); whereas categorical variables were depicted with frequency (percentage) values. Normally distributed variables were analyzed with the independent samples t -test or one-way analysis of variance (ANOVA) depending on group count. Non-normally distributed variables were analyzed with the Mann-Whitney U test or Kruskal Wallis test depending on group count. Categorical variables were analyzed with the chi-square tests or Fisher's exact tests. Pairwise corrections employed the Bonferroni correction. Repeated measurements were analyzed with the Wilcoxon signed ranks test. Pearson, Spearman or point-biserial correlation coefficients were calculated to evaluate relationships between markers and other variables. Prediction performance of the markers were assessed by using Receiver Operating Characteristic (ROC) curve analysis.

RESULTS

A total of 79 patients with ICP (mean age 29.79 ± 5.84 years) and 100 controls were enrolled in this study. Of the subjects with ICP, 55 were classified as mild ICP (mean age 29.82 ± 5.73 years) and 24 were classified as severe ICP (mean age 28.71 ± 6.01 years). Patients with ICP had greater gestational age ($p < 0.001$), higher bile acid concentration before ($p < 0.001$) and after UDCA treatment ($p = 0.038$). Additionally, these patients had

higher aspartate transaminase (AST, $p < 0.001$) and alanine transaminase (ALT, $p < 0.001$) levels and higher total ($p < 0.001$) and direct bilirubin levels ($p < 0.001$) compared to control subjects. Subjects with severe ICP more frequently experienced severe itching compared to those with mild ICP. Although AST, ALT, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels were similar in mild and severe ICP, direct bilirubin was significantly higher in those with severe ICP compared to the mild ICP group [0.41 (0.29-0.64) mg/dl vs. 0.20 (0.12-0.40) mg/dl, $p < 0.001$].

Comparison of CBC parameters between the groups is presented in **Table 1** and **2**. Platelet count of subjects with ICP was higher than that of controls ($p < 0.001$); however, there were no significant differences in platelet count between the severe and mild ICP groups. The leukocyte count of subjects with severe ICP was lower than that of the controls, but values were similar in controls and subjects with mild ICP. Mean platelet volume (MPV) was similar in subjects with mild and severe ICP and was higher than that of controls ($p < 0.001$). Red cell distribution width (RDW) of subjects with severe ICP was lower than the RDW of the controls, while the mild and severe ICP groups were similar in this respect. Platelet to lymphocyte ratio (PLR) was higher in subjects with ICP compared to controls, but the mild and severe ICP groups had similar values. There were no significant differences in neutrophil to lymphocyte ratio (NLR) between the groups. Newborns who were

born to mothers with ICP had longer intensive care unit (ICU) stay and lower birth weights compared to newborns born to healthy mothers.

Correlation analysis revealed that MPV and PLR were positively, and RDW was negatively correlated with bile acid concentration, bilirubin, and AST and ALT levels. MPV was also positively correlated with the length of stay in ICU (**Table 3**). ROC curve analysis revealed that MPV (cut-off: 9.7) and PLR (cut-off: 107.2) could discriminate subjects with ICP from controls with high sensitivity but relatively low specificity (**Table 4, Figure 1**). However, neither NLR nor PLR were sensitive for the discrimination of severe ICP from mild ICP (**Table 5, Figure 2**).

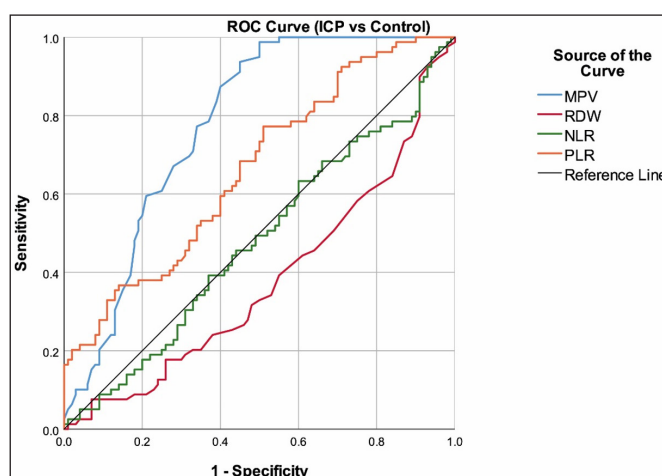


Figure 1. Receiver operating characteristic (ROC) curves of study variables to discriminate ICP patients from controls

	Groups			P
	Control (n=100)	Mild ICP (n=55)	Severe ICP (n=24)	
Age	29.18±5.30	29.82±5.73	28.71±6.01	0.670
Gestational week	27.5 (23-30) ^a	33 (31-35) ^b	32.5 (31-34) ^b	<0.001
Number of pregnancy	-	2 (1-3)	2.5 (1-4)	0.921
Pregnancy				0.661
Singleton	-	50 (90.91%)	23 (95.83%)	
Twin	-	5 (9.09%)	1 (4.17%)	
Bile acid				
Initial	5 (4-7) ^a	17 (12-25) ^b	60.5 (47.5-84.5) ^c	<0.001
After UDCA	-	3 (3-4)	4 (3-4)	0.038
p (within groups)	N/A	<0.001	<0.001	
Itching				0.003
None	-	2 (3.64%)	0 (0.00%)	
Mild	-	9 (16.36%)	0 (0.00%)	
Moderate	-	18 (32.73%)	2 (8.33%)	
Severe	-	26 (47.27%)	22 (91.67%)	
Pruritus regression with UDCA	-	39 (70.91%)	15 (62.50%)	0.634
Intrauterine / Neonatal death	0 (0.00%)	2 (3.64%)	0 (0.00%)	0.102
Birth week	38 (37-39) ^a	37 (37-38) ^b	37 (36-37.5) ^b	<0.001
Type of birth				0.108
Natural	-	26 (47.27%)	6 (25.00%)	
Cesarean	-	29 (52.73%)	18 (75.00%)	
Birth weight	3214.7±464.61 ^a	2810.51±554.20 ^b	2776.30±590.88 ^b	<0.001
Length of stay in ICU	1 (1.00%) ^a	11 (20.00%) ^b	6 (25.00%) ^b	<0.001

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. a,b: Same letters denote the lack of statistically significant difference between groups. Abbreviations: N/A: Not applicable, ICU: Intensive care unit, UDCA: Ursodeoxycholic acid

Table 2. Summary of patient laboratory measurements with regard to groups

ALT (IU/mL)				
Initial	12 (9-14) ^a	62 (40-117) ^b	147.5 (69-243.5) ^b	<0.001
After UDCA	-	43 (24-65)	49 (33.5-107.5)	0.129
p (within groups)	N/A	<0.001	0.001	
AST (IU/mL)				
Initial	14 (12.45-18) ^a	48 (35-70) ^b	77 (45-139.5) ^b	<0.001
After UDCA	-	31.5 (22.5-40.5)	34 (22-58)	0.339
p (within groups)	N/A	<0.001	0.001	
Total bilirubin (mg/dL)	0.24 (0.15-0.30) ^a	0.40 (0.29-0.70) ^b	0.64 (0.41-0.78) ^b	<0.001
Direct bilirubin (mg/dL)	0.13 (0.11-0.18) ^a	0.20 (0.12-0.40) ^b	0.41 (0.29-0.64) ^c	<0.001
ALP (IU/L)	-	195.84±60.01	222.63±74.89	0.095
GGT (IU/L)	-	15 (11-26)	18.5 (11-27)	0.725
LDH (IU/L)	-	222.94±46.65	223.79±43.66	0.940
Hemoglobin (g/dL)	11.35±1.59	11.56±1.36	11.56±1.14	0.638
Platelet (×10 ³ /mm ³)	210.82±67.27 ^a	243.82±67.95 ^b	270.96±76.23 ^b	<0.001
WBC (×10 ³ /mm ³)	10.73±2.89 ^a	10.15±2.54 ^{ab}	9.07±1.62 ^b	0.001
Neutrophil (×10 ³ /mm ³)	7.93±2.64 ^a	7.45±2.24 ^{ab}	6.51±1.63 ^b	0.006
Lymphocyte (×10 ³ /mm ³)	1.95±0.55	1.83±0.54	1.89±0.43	0.380
MPV (µm ³)	9.39±1.78 ^a	11.07±1.13 ^b	11.05±1.06 ^b	<0.001
RDW (%)	13.65 (13.05-15.2) ^a	13.2 (12.8-14.6) ^{ab}	13.05 (12.6-13.5) ^b	0.005
Neutrophil lymphocyte ratio	3.92 (3.01-5.15)	4 (3.06-5.14)	3.43 (2.59-4.34)	0.202
Platelet lymphocyte ratio	109.8 (83.68-143.9) ^a	126.25(107.39-173.9) ^b	124.4(108.23- 212.14) ^b	0.001

Table 3. Correlations between MPV, RDW, NLR, PLR and other variables

		MPV	RDW	NLR	PLR
Age	r	0.016	-0.065	0.049	-0.040
	p	0.832	0.385	0.517	0.596
Gestational week	r	0.370	-0.101	-0.071	0.134
	p	<0.001	0.179	0.347	0.075
Number of pregnancy	r	-0.074	-0.005	-0.012	0.141
	p	0.517	0.962	0.919	0.216
Bile acid	r	0.409	-0.230	-0.074	0.223
	p	<0.001	0.002	0.323	0.003
Itching	r	0.113	-0.158	-0.007	0.063
	p	0.321	0.165	0.954	0.580
ALT (IU/mL)	r	0.461	-0.223	-0.094	0.264
	p	<0.001	0.003	0.209	<0.001
AST (IU/mL)	r	0.442	-0.165	-0.091	0.278
	p	<0.001	0.028	0.225	<0.001
Total bilirubin (mg/dL)	r	0.185	-0.146	-0.057	0.164
	p	0.013	0.051	0.448	0.029
Direct bilirubin (mg/dL)	r	0.101	-0.191	-0.035	0.180
	p	0.178	0.011	0.644	0.016
ALP (IU/L)	r	-0.086	-0.002	0.022	0.188
	p	0.451	0.987	0.847	0.097
GGT (IU/L)	r	-0.067	-0.008	-0.201	-0.029
	p	0.563	0.944	0.080	0.800
LDH (IU/L)	r	0.093	-0.109	-0.053	-0.030
	p	0.419	0.346	0.647	0.793
Duration of stay in ICU	r	0.265	-0.061	0.034	0.052
	p	<0.001	0.415	0.655	0.491

r: Correlation coefficient, Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase LDH: Lactate Dehydrogenase, ICP: Intrahepatic cholestasis of pregnancy, ICU: Intensive care unit, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, RDW: Red Cell Distribution Width

Table 4. Performance of markers to discriminate patients with ICP from healthy controls

	MPV	RDW	NLR	PLR
Cut-off	≥ 9.7	≥ 13.5	≥ 3.5	≥ 107.2
Sensitivity	93.67%	39.24%	63.29%	77.22%
Specificity	55.00%	45.00%	40.00%	49.00%
Accuracy	72.07%	42.46%	50.28%	61.45%
PPV	62.18%	36.05%	45.45%	54.46%
NPV	91.67%	48.39%	57.97%	73.13%
AUC (95.0% CI)	0.777 (0.709-0.845)	0.378 (0.295-0.460)	0.479 (0.393-0.565)	0.662 (0.583-0.741)
p	<0.001	N/A	N/A	<0.001

Abbreviations: PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, MPV: Mean platelet volume, RDW: Red Cell Distribution Width, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, N/A: Not applicable (p values are not calculated due to AUC is below 0.5)

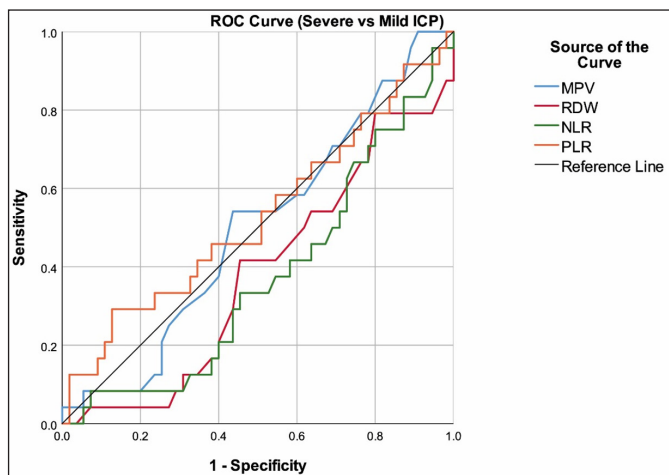


Figure 2. Receiver operating characteristic (ROC) curves of study variables to discriminate mild ICP patients from severe.

Table 5. Performance of markers to discriminate mild and severe ICP

	MPV	RDW	NLR	PLR
Cut-off	≥ 11.2	≥ 13.4	≥ 3.75	≥ 140
Sensitivity	54.17%	41.67%	41.67%	45.83%
Specificity	56.36%	54.55%	41.82%	61.82%
Accuracy	55.70%	50.63%	41.77%	56.96%
PPV	35.14%	28.57%	23.81%	34.38%
NPV	73.81%	68.18%	62.16%	72.34%
AUC (95.0% CI)	0.500 (0.365-0.635)	0.381 (0.250-0.512)	0.373 (0.242-0.504)	0.528 (0.383-0.673)
p	0.996	N/A	N/A	0.693

Abbreviations: PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, MPV: Mean platelet volume, RDW: Red Cell Distribution Width, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, N/A: Not applicable (p values are not calculated due to AUC is below 0.5)

DISCUSSION

This study demonstrates that patients with ICP had higher MPV, platelet count and PLR, but similar NLR compared to controls. Subjects with mild and severe ICP were similar with respect to the great majority of variables analyzed. In addition, bile acids, AST, ALT and bilirubin levels were correlated with RDW (inversely) and MPV and PLR (positively). MPV and PLR appear to be sensitive for the discrimination of patients with ICP from healthy subjects; however, CBC derived parameters could not discriminate patients in terms of ICP severity.

Intrahepatic cholestasis of pregnancy is recognized by elevation in bile acid concentrations and transaminase levels in addition to unexplained pruritus, particularly after the 30th gestational week (4,10). ICP spontaneously resolves rapidly following delivery. However, ICP has been shown to be related to fetal adverse outcomes, including preterm labor, fetal distress, low birthweight, intrauterine fetal death, and perinatal mortality correlating with the severity of cholestasis (11). Although the exact mechanism underlying ICP has not been clearly understood yet, multiple factors including nutritional deficiency, hormonal changes, environmental and genetic variations have been reported to take part in development of ICP (12-14).

Recent data have shown that inflammation and inflammatory processes may also contribute to ICP (15-18). During the course of cholestasis, inflammation-induced lipopolysaccharides are cleared by the hepatocytes and Kupfer cells produce increased amounts of proinflammatory cytokines (19). In addition, bile acids can directly activate signaling pathways in hepatocytes that stimulate production of proinflammatory mediators (20). Recently, the study of Biberoglu et al. (15) has reported that serum IL-6 level was upregulated in subjects with ICP, although no significant difference was observed between subjects with mild and severe ICP (15). Accumulated data has

revealed that simple and readily available CBC derived parameters, including MPV, NLR, PLR, RDW, and leukocyte count, can be used to determine the presence of an inflammatory state particularly in patients with cardiovascular disorders. Since the prenatal complications and fetal adverse events increase with the severity of cholestasis in ICP, estimating the severity of ICP and discriminating mild ICP from severe ICP is critical to prevent prenatal events. For this purpose, Abide et al. studied CBC derived parameters in subjects with ICP and found that PLR, MPV and leukocyte count was increased and RDW was decreased in subjects with ICP. MPV was also significantly higher in subjects with ICP compared to those with mild ICP. The authors concluded that MPV could be utilized to discriminate severe ICP from mild ICP (9). However, the role of CBC markers, particularly those believed to indicate inflammation such as leukocyte count, NLR, PLR, and MPV is still a matter of debate.

Our findings demonstrate that MPV and PLR are higher in subjects with ICP, and that these markers are correlated with the bile acid concentration, AST, ALT and bilirubin levels. Moreover, MPV and PLR have high sensitivity for discriminating subjects with ICP from controls. However, none of the CBC derived parameters including leukocyte count, NLR, PLR, and MPV demonstrate neither sensitivity nor specificity for discriminating mild ICP from severe ICP, which conflicts with the study by Abide et al.; however, our inclusion/exclusion criteria and the fact that we matched patients and controls with respect to expected delivery date are some of the important advantages of our study. With this background in mind, we consider that MPV and PLR can be utilized for discrimination of ICP from healthy controls. However, further research with larger study population is required to address the role of MPV and PLR in the evaluation of ICP severity.

There are some limitations to be mentioned. The cross-sectional design of the study limits further evaluation of perinatal outcomes. Second, lack of other simple markers of inflammation including C-reactive protein and IL-6 levels is an important limitation concerning the assessment of inflammation in ICP. Further prospectively designed studies with larger sample sizes that provide more detailed monitoring of perinatal complications may improve the knowledge concerning the role of inflammatory markers in the severity of ICP.

CONCLUSION

Some inflammation-related CBC derived parameters, such as MPV and PLR, can be utilized to address the presence of ICP with high sensitivity but low specificity. However, there appears to be no role for MPV, NLR,

PLR, RDW, and leukocyte count in the discrimination of mild and severe ICP. Further prospective studies with larger sample size may provide additional information regarding the usefulness of these markers in ICP.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date:10.12.2020, Decision No: KA EK/2020.12.210).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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