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ORIGINAL ARTICLE

Role of Systemic Immune Inflammatory Index to Predict Intrahepatic Cholestasis of Pregnancy

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SUMMARY

Background: **The goal was to investigate the change of systemic immune inflammation index (SII) in high-risk pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP).**
Methods: **Between May 2018 and April 2020, we retrospectively enrolled 218 pregnant women who were followed in our hospital from the first trimester to delivery. We looked at the sociodemographics, laboratory data, SII values, Apgar ratings, and newborn birth weights of pregnant women with ICP. We also compared SII values in the first (SII 1), second (SII 2), and third trimesters (SII 3) between ICP and the control group.**
Results: **In the ICP group, the neutrophil level increased in the second trimester and decreased in the third trimester. The SII 2 was significantly higher in the severe ICP group, and when the SII values of the subgroups were examined, the SII 2 was significantly higher in the severe ICP group. The SII 2 showed a significant cutoff value for ICP with 92% sensitivity and 96% specificity. Again, a positive but weak correlation was found between SII 2 and SII 3 and FBA. When the neonatal outcomes were evaluated between the groups, gestational age at birth, birth weight and Apgar scores at 1 and 5 minutes were significantly lower in the ICP group.**
Conclusions: **The relationship between SII and ICP was investigated for the first time in the literature and a significant cutoff value was found with the SII of the 2nd day. This showed that inflammation occupies an important place in the pathophysiology of cholestasis.**
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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic disease characterized by pruritus, elevated liver enzymes, and an increase in serum bile acids, usually beginning in the third trimester of pregnancy. Although ICP is the most frequent liver illness during pregnancy, its incidence has been reported in the literature to be as high as 4% [1,2]. Diagnosis and follow-up of the disease is important due to maternal morbidity and especially fetal morbidity and mortality. The disease is more common, especially in the winter months, in women with a family history of biliary disease, in hepatitis C seropositivity, in multiple pregnancies, and in women

over 35 years of age [3-5]. ICP is distinguished from other diseases by pruritus in specific areas accompanied by elevated serum fasting bile acids (FBA). Diagnosis is made with FBA levels of 10 mol/L or higher, with values above 40 mol/L considered severe ICP [2]. It is believed that inflammatory cells are activated in cholestasis in pregnant women and that these cells are taken to the liver, and then secreted pro-inflammatory cytokines cause cholestasis [6-8].

The monocyte-lymphocyte ratio (MLR), thrombocyte-neutrophil ratio (TNR), and neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (TLR) are all efficient predictors of systemic inflammation and immunological status. The Systemic Immune Inflammation measure (SII) is a new measure that is calculated using peripheral thrombocyte, neutrophil, and lymphocyte counts (thrombocytes neutrophils/lymphocytes). It is used to forecast disorders such as coronary heart disease, type 2 diabetes, arthritis, and ulcerative colitis, and it can also be used as a marker for ovarian, colon, and breast cancer [9,10]. Despite previous study revealing aberrant changes in cell differential numbers during cholestasis, it is unclear how these novel systemic immune-inflammatory markers will be used in differential diagnosis and outcome prediction.

We investigated changes in systemic immune-inflammatory markers and SII levels by trimester and studied their clinical implications, building on earlier research that stresses the role of inflammatory blood parameters in cholestasis.

MATERIALS AND METHODS

Study Population and Data Collection

This retrospective cross-sectional study was done between May 2018 and April 2020, and it included 218 pregnant women who were tracked at our hospital from their first trimester until delivery. The study protocol received institutional review board approval. The authors have acknowledged that they followed the World Medical Association's Declaration of Helsinki on the Ethical Conduct of Human Subjects.

This group included 108 people with cholestasis and 110 healthy people between 18 - 45 age. During the study period, the patients were chosen at random from a pool of 16,650 deliveries at our hospital. ICP criteria were recognized for FBA levels with particular pruritus of the hands and feet. FBA levels of 10 mol/L or higher were considered diagnostic. Based on FBA levels, patients were separated into two subgroups: severe ICP (FBA > 40 mol/L) and mild ICP (FBA > 10 mol/L but less than 40 mol/L [2]. After diagnosis, all patients were started on ursodeoxycholic acid for treatment. Dosage was adjusted according to liver enzymes and the patient's complaints. Patients describing pruritus with fasting bile acid values above 10 μmol/L are delivered at 36 - 38 weeks depending on the patient's clinic [11]. The study's exclusion criteria encompassed the presence of coexisting chronic systemic diseases, hepatitis infection, acute fatty liver, placental abruption, multiple pregnancies, HELLP (hemolysis, elevated liver enzymes, and low thrombocyte count) syndrome, diabetes mellitus, as well as pregnancy complications such as gestational hypertension, fetal growth restriction, premature rupture of membranes, chorioamnionitis, and the presence of fetuses with congenital or chromosomal abnormalities.

Age, gravidity, parity, delivery types, fetus gender, body mass index (BMI), the number of live-born infants, birth weight, gestational week at delivery, gestational age at diagnosis, maternal serum fasting bile acid values, Apgar scores at the first and fifth minutes, and hospitalizations both before and after delivery were all recorded for each patient. The gestational age was calculated using the beginning day of the last menstrual period and then confirmed using ultrasonography throughout the first trimester. The dataset for the study was created using data from venous blood samples taken from pregnant women during each trimester as part of regular clinical practice. Complete blood count (CBC) measured in all trimesters was included in the study. The Mindray BC-6000 Automated Haematology Analyser is used to measure leukocytes, thrombocyte, monocytes, and neutrophils. The Mindray BC-6000 performs its analysis using SF Cube cell analysis technology, which was installed by Mindray Bio-Medical Electronic Corporation's service technicians during installation. Using three levels of E-Check (Level 1, 2, and 3) as quality control, the device is powered down and powered up each day before sample analysis, with attention paid to background levels. The Mindray BC-6000s were calibrated and verified using the supporting calibrators. The analysis methods were stable over time.

Definitions

The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and thrombocyte-to-lymphocyte ratio (TLR) were calculated using the ratios of absolute neutrophil (N) count to absolute lymphocyte (L) count, absolute monocyte count to absolute lymphocyte count, and absolute thrombocyte (T) count to absolute lymphocyte count, respectively. By dividing the absolute monocyte count by the absolute lymphocyte count, the monocyte-to-lymphocyte ratio (MLR) was calculated from the differential blood count. The SII was calculated as T x N/L, where T, N, and L represented the counts of peripheral thrombocytes, neutrophils, and lymphocytes, respectively [12]. SII 1 was defined as SII in first trimester; SII 2 was defined as SII at time of diagnosis; SII 3 was defined as SII at time of delivery. In the first, second, and third trimesters, TLR, MLR, NLR, and SII (neutrophil x thrombocyte/lymphocyte) levels were evaluated between the study and control groups.

Statistical analysis

The SPSS 23.0 program (IBM Corp., Armonk, NY, USA) was used for the analysis. Because the variables

did not follow a normal distribution, the Kolmogorov-Smirnov test was used to determine their normality. Due to the non-normal distribution of the data, nonparametric tests were chosen for the analysis. The chi-squared test was used to compare categorical variables, while the Kruskal-Wallis and Mann-Whitney U tests were used to analyze numerical variables. SII's diagnostic value was assessed using Receiver Operating Characteristic (ROC) analysis. Spearman's correlation analysis was used for nonparametric variables. A $p < 0.05$ significance level was judged statistically significant.

RESULTS

The mean maternal age was 29.2 ± 5.1 in the ICP group ($p < 0.001$). The mean gravidity was 2.1 ± 1.3 and the mean parity was 0.8 ± 1.0 in the ICP group ($p = 0.002$, $p < 0.001$, respectively). The number of live-born children in the ICP group was 0.9 ± 0.9 ($p < 0.001$). The mean BMI was 31 ± 4.3 and number of live-born children was 0.9 ± 0.9 in the ICP group ($p < 0.001$, $p < 0.001$, respectively). In the ICP group, 55.6% (n = 60) of births were by cesarean and 58.3% (n = 63) of the fetuses were male. When neonatal outcomes were evaluated between groups; gestational ages at birth, birth weights, and Apgar scores at 1 and 5 minutes were all significantly lower in the ICP group. Prepartum and postpartum length of hospital stay were significantly more common in the ICP group ($p < 0.001$, $p < 0.001$, respectively, Table 1).

While thrombocyte and monocyte counts grew in the ICP group as the trimester proceeded, WBC, hemoglobin (Hb), monocyte, and lymphocyte counts fell in the second trimester before increasing again in the third trimester. In the ICP group, neutrophil levels increased in the second trimester and declined in the third trimester. Hb count was statistically substantially greater in the control group than in the ICP group in the second trimester ($p = 0.004$). There were no significant variations between groups in terms of TLR, NLR, MLR, and SII levels in the trimesters (Table 2).

When the association between 2nd-trimester SII and variables such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), FBA, SII 1, and SII 3 was investigated, a positive but weak correlation between the length of SII 3 and FBA was discovered (Table 3). The severe ICP category included 43 patients, while the mild ICP subgroup included 65 patients. When the SII scores for the subgroups were analyzed, the SII 2 was considerably higher in the severe ICP group ($p = 0.002$, Table 4).

ROC analysis of the SII value was performed between groups according to trimester. The diagnostic significance of SII between the cholestasis was observed in the second trimester. Diagnostic significance of SII in ICP was observed also in the 3rd trimester, but the area under the curve (AUC) was close to 0.5 and was not associated with a specific cutoff value. Optimal cutoff values for the prediction of the ICP were 0.036 and 0.418 for SII 2 and SII 3, respectively. SII 2 gave a significant cutoff value in ICP with 92% sensitivity and 96% specificity (Table 5 and Figure 1).

DISCUSSION

Many studies in the literature have looked into inflammation, which has been proposed as the underlying etiology of ICP. In this study, we investigated the clinical importance of systemic immunological inflammatory index and SII levels in ICP according to trimesters and obtained important findings. The SII 2 was significantly higher in the severe ICP group. SII 2 gave a significant cutoff value in ICP with 92% sensitivity and 96% specificity. Again, a positive but weak correlation was found between SII 2 and SII 3 and FBA.

Although the most common comorbidities in ICP patients are obesity, overweight, and pre-eclampsia, it is known that pathologies of the placenta are not uncommon in these patients [13]. The BMI of the ICP group was greater than that of the control group in our study. In addition, the fact that the prenatal and postnatal hospital stay is longer than the control group and the prenatal and postnatal hospitalization rate is high in the cholestasis group suggests that patients with cholestasis need more hospitalization in terms of liver function tests and close follow-up in the prenatal and postnatal period. Negative neonatal outcomes in ICP have been reported quite frequently in the literature [14]. According to Pek et al. study, poor newborn outcomes were considerably higher in the ICP group [2]. In our study, newborn outcomes were compared between groups, and the ICP group had significantly lower gestational ages at birth, birth weights, and Apgar scores at 1 and 5 minutes. The existence of negative neonatal outcomes suggests that it is difficult for the fetus to remain in an environment insulated by the placenta against adverse inflammatory conditions such as cholestasis.

It is known that bile acids and other toxic compounds accumulate intrahepatically in cholestasis and lead to the progression of liver pathology [6]. Neutrophils and lymphocytes play a crucial part in this inflammation [7], and studies demonstrate that NLR, TLR, and WBC levels are significantly greater in the ICP group, as are WBC and NLR levels at the time of diagnosis [15]. In our study, there were no significant differences between the groups with regard to TLR, NLR, MLR, and SII values in the trimesters. WBC, hemoglobin (Hb), monocyte, and lymphocyte counts fell in the second trimester before increasing again in the third trimester. Silva et al. found neutrophil count and NLR to be low in cholestasis. In another study, NLR was found to be significantly higher in pregnancy-related cholestasis [1,16]. Although the ICP group's thrombocyte and monocyte counts increased as the trimester progressed, neutrophil levels climbed in the second trimester and fell in the third trimester in our study. The reason that we obtained differ-

Table 1. Sociodemographic characteristics of the groups.

	ICP (n = 108)	Control group (n = 110)	p *
Age (year)	29.2 ± 5.1	27.9 ± 5.6	0.06
Gravidity (n)	2.1 ± 1.3	2.5 ± 1.3	0.002
Parity (n)	0.8 ± 1.0	1.3 ± 1.1	< 0.001
Number of live-born children	0.9 ± 0.9	1.3 ± 1.1	< 0.001
BMI (kg/m^2)	31 ± 4.3	25.3 ± 3.4	< 0.001
Birth weight (gram)	3,101 ± 336	3,347 ± 432	< 0.001
Gestational age at delivery (week)	37.4 ± 1.5	39.2 ± 1	< 0.001
Delivery method			< 0.001
Vaginal	48 (44.4%)	89 (80.9%)	
CS	60 (55.6%)	21 (19.1%)	
Gender of fetus			0.34
Male	63 (58.3%)	71 (64.5%)	
Female	45 (41.7%)	39 (35.5%)	
1-minute Apgar score	8.8 ± 0.4	9.4 ± 1.1	< 0.001
5-minutes Apgar score	9.8 ± 0.3	9.8 ± 0.5	0.551
NICU stay	7 (6.4%)	4 (3.6%)	0.33
Prepartum length of hospital stay (day)	1.5 ± 0.5	0.06 ± 0.2	< 0.001
Postpartum length of hospital stay (day)	1.0 ± 0.1	1.2 ± 0.8	< 0.001

*** - The Mann-Whitney U test was performed. Results were considered statistically significant at a 95% confidence interval with significance level p < 0.05. Values are reported as mean ± standard deviation, categorical variables are presented as number (percentage).**
ICP - intrahepatic cholestasis; h - hour, BMI - body mass index, NICU - neonatal intensive care unit, CS - cesarean section.

Table 2. Evaluation of SII values by trimesters for cholestasis and control groups.

	1st Trimester			2nd Trimester			3rd Trimester		
	ICP Mean ± SD	Control Mean ± SD	p *	ICP Mean ± SD	Control Mean ± SD	p *	ICP Mean ± SD	Control Mean ± SD	p *
Hb (g/dL)	12.6 ± 1	12.6 ± 1.08	0.8	10.8 ± 0.6	11.4 ± 0.9	0.004	11.4 ± 1.3	11.7 ± 1.3	0.1
WBC (10^3 µL)	8,764 ± 2,285	8,394 ± 2 219	0.4	1,902 ± 4,097	5,094 ± 5,280	0.1	10,651 ± 2,896	11,338 ± 2,665	0.2
Thrombo-cyte (10^3/µL)	265.1 ± 60	268.8 ± 75	0.6	45,217 ± 100,501	36,772 ± 90,902	0.5	31,268 ± 79,729	38,947 ± 93,554	0.4
Neutrophile (10^3/µL)	6,163.3 ± 2,112	5,915 ± 1,842	0.6	8,144 ± 1,475	7,486 ± 2,142	0.3	8,018 ± 2,611	8,498 ± 2,440	0.2
Monocyte (10^3/µL)	410.0 ± 189	456 ± 594	0.2	384 ± 70	449 ± 156	0.4	516 ± 176	572 ± 192	0.09
Lymphocyte (10^3/µL)	1,892.2 ± 441	1,847 ± 540	0.4	1,610 ± 329	1,728 ± 530	0.7	1,942 ± 700	2,077 ± 614	0.09
TLR	0.15 ± 0	0.15 ± 0.1	0.4	35 ± 77	23 ± 59	0.6	19.7 ± 52	18.7 ± 45	0.2
NLR	3.47 ± 1.7	0.4 ± 1.2	0.6	5.35 ± 1.9	4.5 ± 1.4	0.4	4.4 ± 1.9	4.4 ± 2.1	0.9
MLR	0.2 ± 0	0.4 ± 3.7	0.1	0.2 ± 0	0.2 ± 0	0.6	0.2 ± 0.1	0.2 ± 0.1	0.6
SII (10^9/L)	945.33 ± 582	0.04 ± 0.1	0.8	347,821 ± 774,741	160,528 ± 432,783	0.6	135,534 ± 341,735	153,061 ± 381,100	0.4

*** - Mann-Whitney U test was performed, and the results were accepted with a 95% confidence interval, with statistical significance set at p < 0.05. Values are presented as mean ± standard deviation. SII - Systemic Immune Inflammation Index, SII 1 - SII in first trimester, SII 2 - SII at time of diagnosis, SII 3 - SII at time of delivery. FBA, ICP - intrahepatic cholestasis, NLR - Neutrophil-to-Lymphocyte Ratio, TLR - Thrombo-cyte-to-Lymphocyte Ratio, MLR - Monocyte-to-Lymphocyte Ratio, WBC - White Blood Cells, Hb - Hemoglobin.**

Table 3. The correlations between SII 2 values and other variables.

Variables	SII 2	
	r	p *
SII 1	-0.116	0.088
SII 3	0.217	0.001
ALT	0.051	0.6
AST	0.082	0.39
FBA	0.366	< 0.001

*** - Spearmen's correlation coefficient. Results were considered statistically significant at a 95% confidence interval with a $p < 0.05$.**
SII - Systemic Immune Inflammation Index, SII 1 - SII in first trimester, SII 2 - SII at time of diagnosis, SII 3 - SII at time of delivery, ALT - alanine aminotransferase, AST - aspartate aminotransferase, FBA - fasting bile acids.

Table 4. SII comparison between severe and mild ICP.

	Mild ICP (n = 65)	Severe ICP (n = 43)	p *
SII 1	845.6 ± 285.4	840.3 ± 257.2	0.9
SII 2	714,283 ± 223,940	841,938 ± 203,853	0.002
SII 3	388,156 ± 339,104	407,890 ± 363,355	0.843

*** - Mann-Whitney U test was performed, and the results were accepted with a 95% confidence interval, with statistical significance set at $p < 0.05$. Values are presented as mean ± standard deviation.**
SII - Systemic Immune Inflammation Index, SII 1 - SII in first trimester, SII 2 - SII at time of diagnosis, SII 3 - SII at time of delivery, ICP - intrahepatic cholestasis of pregnancy.

Table 5. Receiver operating characteristics curves for SII values between groups.

	Cutoff value	AUC	Sensitivity (%)	Specificity (%)	95% CI	p *
SII 1	0.527	0.982	44	47	0.963 - 1	0.169
SII 2	0.036	0.617	92	96	0.542 - 0.692	< 0.001
SII 3	0.418	0.446	58	58	0.370 - 0.522	0.003

*** - ROC analyses were performed, and the results were accepted with a 95% confidence interval, with statistical significance set at $p < 0.05$.**
AUC - area under the curve, CI - confidence intervals, SII - Systemic Immune Inflammation Index, SII 1 - SII in first trimester, SII 2 - SII at time of diagnosis, SII 3 - SII at time of delivery.

ent results than the literature could be attributed to differences in the study population.

In the study by Ipek et al. the relationship between SIRI, a similar index, and cholestasis was investigated and negative significant differences were found between SIRI 2 and SIRI 3, ICP, and the control [2]. In our study, it was found that SII 2 was significantly higher in the severe ICP group. Moreover, SII 2 gave a significant cutoff value for ICP with 92% sensitivity and 96% specificity. When comparing the ICP group with the control group, the SII value in any trimester was not found to be significant, while a positive but weak correlation was found between SII 2, SII 3, and FBA. This shows that SII is very important for cholestasis, which has an inflammatory etiology, especially in the 2nd trimester. We attribute the lack of correlation with SII 1 to the fact that cholestasis is a process that starts in the 2nd trimester.

Limitations

There are some limitations to our study. Since we start treatment for all patients diagnosed with cholestasis, we do not have a no-treatment group. The study was unable to cover all patients in the region under investigation due to its retrospective methodology and the lack of fol-

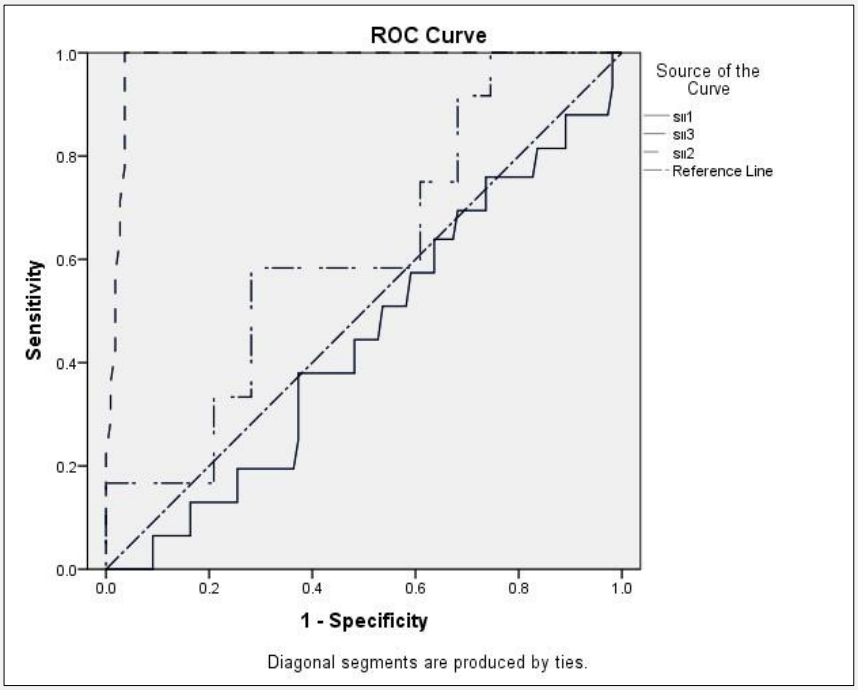

Figure 1. Comparison of the cholestasis group, 2nd trimester SII value ROC analysis curve.

low-up data. The incorporation of data from the hospital's electronic database, as well as systematic randomization in patient selection, improves the study's power.

CONCLUSION

The relationship between SII and ICP has been examined for the first time in the literature, and a significant cutoff value with 92% sensitivity and 96% specificity was obtained in the 2nd trimester SII. This suggests that inflammation is essential and should be considered in SII, and that it may be used in the future in conjunction with other clinical and laboratory data for the diagnosis and prediction of ICP. The use of prognostic inflammatory markers at the time of diagnosis could assist in determining follow-up frequency and the need for hospitalization. Nonetheless, more research is required to have a better understanding of these findings and their therapeutic implications.

Availability of Data and Materials:
The datasets of the current study are available upon reasonable request.

Source of Funds:
The study did not receive any funding.

Informed Consent:
Informed consent was obtained from all individuals included in this study.

Declaration of Interest:
The authors declare no conflicts of interest.

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