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Original Research Article

Diagnostic accuracy of neutrophil to lymphocyte ratio in comparison with liver function tests for the diagnosis of intrahepatic cholestasis of pregnancy

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ABSTRACT

Background: In this study, we aimed to find diagnostic accuracy of neutrophil to lymphocyte ratio in comparison with liver function tests for the diagnosis of intrahepatic cholestasis of pregnancy and adverse fetal-maternal outcomes.
Methods: NLR and aminotransferase (AST/ALT) levels in the blood samples of pregnant women with complaint of pruritus. 90 women with elevated transaminase were taken as cases and same number of women with normal aminotransferase levels taken as control. All were examined in this prospective case-control study.
Results: Not only was the mean NLR elevated in the pregnant women with cholestasis when compared to the controls, but it also predicted the severity of the cholestasis. The correlation between transaminase levels and NLR was significant.
Conclusions: Although TBA is still the diagnostic standard, NLR can be used as an initial screening tool due to its high specificity.

Keywords: Intrahepatic cholestasis of pregnancy, Neutrophil to lymphocyte ratio

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is also known as obstetric cholestasis, is the most common liver disease unique to pregnancy. It is a reversible type of hormonally influenced cholestasis and frequently develops in late pregnancy in individuals who are genetically predisposed. It is characterized by pruritus without rash and an elevation in serum bile acid concentrations in 90% cases. Typically develops in late second and/or third trimester. Along with bile acids, serum transaminases are also raised in 58-60% of cases of pruritus in pregnancy without rash due to liver dysfunction.[1-3] IHCP can lead to complications for both mother and fetus, such as fetal distress, meconium stained liquor, sudden fetal demise, perinatal mortality, and preterm labor.[4]

The etiology of IHCP is still not fully understood. It is considered as a multifactorial disease. Genetic, endocrinology, nutritional, and environmental factors are likely to be important in the pathogenesis of the disease. The association between inflammation and cholestatic liver disease has been previously described. It has been reported that elevated bile acid levels trigger an inflammatory response, causing hepatocellular injury.[5] Systemic inflammation can be measured by using a variety of biochemical and hematological markers. Although novel disease-specific biomarkers have been identified, most of them, including the measurement of total bile acid (TBA) concentration, are time consuming, expensive and not available at various hospitals. Recent evidence indicates that measuring the ratio of blood cell subtypes, such as the neutrophil-to-lymphocyte ratio (NLR) might have prognostic significance for diseases related to chronic

low-grade inflammation.[6] In addition, because it is readily available and easily calculated, this method might be a promising alternative diagnostic tool for diseases associated with chronic low-grade inflammation, such as IHCP, However, little is known and has been published about NLR and its relationship with IHCP; therefore, the present study was conducted to evaluate the efficacy and diagnostic accuracy of NLR and its correlation between transaminase levels and adverse fetal-maternal outcomes.

METHODS

This prospective case-control study was conducted at the department of obstetrics and gynaecology, Safdarjung Hospital New Delhi on 90 pregnant women with IHCP. They were recruited for the study between May 2019 and May 2021.

Inclusion criteria

Inclusion criteria for the study group included itching without rash specially at palms and soles and elevated aminotransferase levels in the blood sample. Women with complaint of pruritus with deranged LFT were taken as cases.

Exclusion criteria

Exclusion criteria consist of women with surgical obstructive jaundice, pruritus due to preexisting skin disease, viral hepatitis, chronic liver disease, cardiovascular illness, pregnancy specific causes of elevated liver enzymes such as preeclampsia, HELLP and acute fatty liver of pregnancy, on drugs that effect LFT, patients with signs and symptoms of active infection, patients with multiple gestation, with chronic inflammatory diseases or in active labour. The control group consisted of 90 women with complaint of pruritus with normal LFT.

Blood samples were obtained for LFT and complete blood count. NLR was calculated as the ratio of absolute neutrophil count to absolute lymphocyte. Transaminase more than normal upper limit of pregnancy were considered as diagnostic of IHCP. The following clinical and demographic data were obtained: maternal age, obstetric history, period of gestation at diagnosis and delivery, mode of delivery, and presence of maternal and neonatal complications.

The statistical analyses were conducted using the Statistical Package. The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. The data were summarized as mean standard deviation and median (minimum-maximum). Proportions were compared with Fisher's exact test or the chi-square test where appropriate. For parametric variables, one-way ANOVA was used for comparing three independent groups, and post hoc comparisons were performed with SJH test. The Mann-Whitney U test was used for nonparametric variables in two independent groups. Spearman's rank correlation was used to assess the relationship between quantitative variables.

RESULTS

The demographic and obstetric data of the IHCP and control groups are shown in Table 1. The cases with IHCP were aged between 18-33 years, with a mean age of 25.25 years. They were diagnosed to be having IHCP between POGs of 28-39 weeks, with the mean POG of 34.5 weeks. Out of a total of 90 cases, 37 were primigravidas while 53 were multiparous women.

Table 1: Demographical parameters in cases and controls.

Parameters	Group		P value
	Case (n=90)	Control (n=90)	
Age (years)	25.23±4.39	24.66±2.29	0.923
POG at diagnosis (weeks)	34.50±2.71	-	
POG at delivery (weeks)	37.57±1.22	37.62±1.24	
Gravida			
G1	37 (41.1%)	33 (36.7%)	0.541
≥G2	53 (58.9%)	57 (63.3%)	
Parity			
P0	43 (47.8%)	44 (48.9%)	0.945
P1	36 (40.0%)	34 (37.8%)	
≥P2	11 (12.2%)	12 (13.3%)	

The mean POG at delivery was 37.5 weeks. There was no difference between demographic and obstetric data between two groups are shown in Table 1.

Table 2: NLR and transaminase levels in case and control.

	Case	Control	P value
NLR	3.57±0.51	3.05±0.42	<0.001
NLR category			
≤3.3	31 (34.4%)	69 (76.7%)	<0.001
>3.3	59 (65.6%)	21 (23.3%)	
ALT (U/l)	128.39±42.90	30.97±3.68	<0.001
AST (U/l)	114.77±39.45	30.08±3.65	<0.001

The IHCP group had significantly higher levels of NLR (range 2.6-4.7) with a mean3.58±0.51. There was direct correlation between transaminase and NLR levels. ALT (range 78-240 U/l) with a mean of 129.13±42.55 U/l and AST (range 76-244 U/l) with a mean of 115.37±39.25U/l (p value <0.0001) are shown in Table 2.

The ROC curve analysis was also performed to assess the predictive value of NLR in IHCP. The area under curve

was 0.785 (Figure 1) the best cut off value in predicting IHCP was 3.3, above which the sensitivity of 74%, specificity 73%, PPV 73.6%, NPV 74.2% are shown in Table 3.

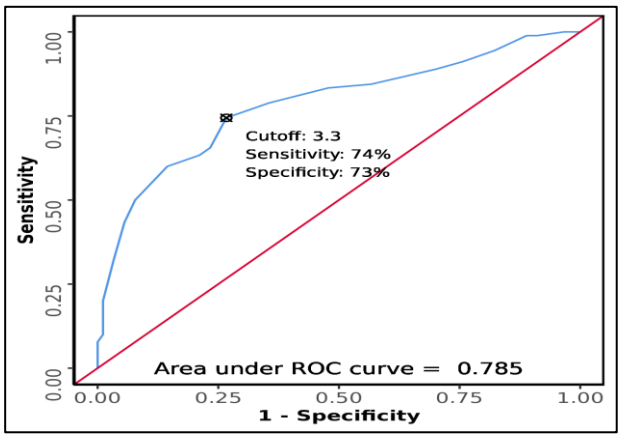

Figure 1: ROC curve analysis showing diagnostic performance of NLR in predicting IHCP in cases and controls (n=180).

Table 3: Diagnostic accuracy to NLR in IHCP.

Parameters	Value (95% CI)
Cutoff (p value)	≥3.3 (<0.001)
AUROC	0.785 (0.718-0.853)
Sensitivity	74.4% (64-83)
Specificity	73.3% (63-82)
Positive predictive value	73.6% (63-82)
Negative predictive value	74.2% (64-83)
Diagnostic accuracy	73.9% (67-80)
Positive likelihood ratio	2.79 (1.94-4.01)
Negative likelihood ratio	0.35 (0.24-0.51)
Diagnostic odds ratio	8.01 (4.12-15.58)

Various maternal and fetal outcomes were compared between cases and controls. All adverse fetal-maternal adverse outcomes in cases of IHCP were correlated with levels of transaminase and NLR.

A significantly higher number of cases of IHCP underwent Induction of labour, compared to controls (out of 90 cases, 73.3% were induced)

The adverse maternal outcomes were found to occur significantly more in IHCP patients than controls such as PPH but no difference found in APH, ICU admission, and maternal mortality.

No significant association was found between transaminase, NLR levels and the occurrence of adverse maternal outcomes. Except number of cesarean deliveries were higher in cases as compared to control. This may be because of higher number of inductions, meconium-stained liquor and fetal distress. There was a significantly higher number of babies born with meconium stained liquor amongst the IHCP cases (28 cases, i.e. 31.5%) than the controls (8, i.e. 8.9%) with a p value 0.012, non-reassuring FHS, IUD, babies' 5 minute APGAR<7, NICU admission and RDS. No significant difference was found in the occurrence of preterm delivery.

Significant associations were found between transaminase, NLR levels and the occurrence of adverse maternal outcomes shown in Table 4.

Table 4: Comparison of NLR and transaminase with maternal outcomes in cases of IHCP.

Parameters	NLR<3.3	NLR>3.3	P value
Induction of labour	20 (30.3%)	46 (69.7%)	0.170
Normal vaginal delivery	29 (40.27%)	43 (59.72%)	0.226
Instrumental Delivery	0 (0.0%)	5 (100%)	0.226
LSCS	2 (15.38%)	11 (84.6%)	0.226
Antepartum haemorrhage	1 (33.3%)	2 (66.7%)	1.000
Postpartum hemorrhage	2 (16.66%)	10 (83.33%)	0.615

An ALT value of 143 U/l and NLR value of 3.3 at the time of diagnosis could be used as a predictor of adverse fetal outcomes shown in Table 5.

Table 5: Comparison of NLR and transaminase with fetal outcomes in cases of IHCP.

Parameters(n)	NLR<3.3	NLR>3.3	P value
Preterm delivery (7)	3 (42.9%)	4 (57.1%)	0.688
Non-reassuring FHS	2 (10%)	18 (90%)	0.009
MSL	4 (14.3%)	24 (85.7%)	0.007
IUD	0 (0.0%)	3 (100%)	0.549
APGAR<7	0 (0.0%)	10 (100%)	0.014
NICU	1 (8.34%)	11 (91.67%)	0.052

DISCUSSION

In the prospective case and control study we calculated diagnostic accuracy of NLR in IHCP women and correlated it with transaminase levels and adverse fetal-maternal outcomes. Not only was the mean NLR elevated in the cases than controls, but it also predicted the severity of cholestasis. The correlation between transaminase levels and NLR was significant. Our study found significant higher level of NLR in cases group as compared with control (Table 5, Figure 1). Our result were keeping with studies done by Kirbas et al, Zekai Tahir women's health education and research hospital, Turkey, Abid et al, Silva et al, who all founded raised NLR in cases of IHCP. Study by Kirbas et al shows the best cutoff value of 2.93.the ratio above this value had sensitivity 91%

sensitivity, 84%, specificity, 83% positive predictive value, and 91% negative predictive value for the diagnosis of ICP.[5,6]

Diagnostic value of NLR was calculated with the help of ROC cure and we calculated cutoff of 3.3 for diagnosis of IHCP with the sensitivity of 74%, specificity of 73%, PPV 73.6% and NPV 74.2%. Our results were keeping with the study done by Kirbas et.[5]

This study has some limitations. A bigger cohort of patients would have helped to increase the sensitivity of the study. Our results suggest that NLR is a viable diagnostic marker for IHCP but, the availability of bile acid testing in our hospital would have helped to compare and correlate the sensitivity of NLR and bile acids as a predictor of adverse outcomes. NLR is an indirect marker, hence it cannot be used as a diagnostic marker of IHCP but it can support the diagnosis of IHCP with the correlation with transaminase levels as a screening marker. It's a non-specific marker raising levels seen with other obstetrical complications such as preeclampsia, preterm labour, preterm rupture of membrane and diabetes.

CONCLUSION

IHCP is an inflammatory process, in the search of a cost-effective, readily available laboratory test; we decided to conduct the current study.

NLR is an indirect and non-specific marker, can use as initial screening tool for the diagnosis of IHCP with a cutoff 3.3 due to high sensitivity and specificity.

Hence, NLR can be used as a surrogate marker for the diagnosis of IHCP where LFT is not available. Although TBA is still the diagnostic standard, NLR can be used as an initial screening tool due to its high sensitivity.

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