

Original Research Article

A prospective study of preoperative neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and sonological findings in predicting severe cholecystitis

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ABSTRACT

Background: The aims and objectives of the study was to assess the utility of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and ultrasound findings to predict severe cholecystitis and to identify an NLR, PLR cut off value that discriminates between simple and severe cholecystitis.

Methods: A prospective observational time bound study was conducted with sample size of 100 patients from December 2019 to January 2021. Severe cholecystitis was defined as cholecystitis complicated by secondary changes like haemorrhage, gangrene, emphysema, abscess, perforation, carcinoma. NLR, PLR values were calculated from absolute neutrophil count and absolute lymphocyte count. All patients underwent ultrasound abdomen by the same radiologist and findings were grouped into three categories, luminal, mural and pericholecystic changes. Intraoperative findings, Histopathological examinations were also taken into account. Data was analysed using Statistical package for social sciences (SPSS) Software Version 22. Receiver operating characteristic curve analysis was employed to identify optimal NLR, PLR cut off values and to predict combined accuracy of NLR, PLR and Ultrasound findings to predict severe cholecystitis.

Results: In our study, 23% patients had severe cholecystitis. The mean age of patients was 46 years. 65% were females. Presence of calculi and presence of multiple calculi was higher in patients with severe cholecystitis (p value 0.25) calculated using Chi square test. Ultrasound findings of luminal, mural and pericholecystic changes were also found to be higher in severe cholecystitis (p<0.001). Mann whitney test showed mean NLR, PLR higher in severe cholecystitis. A Cut off NLR of 3.75 had a sensitivity of 100%, specificity of 77.92%. Length of hospital stay in patients with severe cholecystitis was longer.

Conclusions: NLR of 3.75 is a cut off value to predict severe cholecystitis and prolonged length of hospital stay. Combined Predictive Accuracy of NLR, PLR, Ultrasound findings was 91%. Ultrasonography is a reliable, specific diagnostic tool.

Keywords: Cholecystitis, Laparoscopic cholecystectomy, Prognosis, Severity, Ultrasonography, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio, Predict, Cut off value

INTRODUCTION

Cholecystitis can be defined as a histological finding of inflammatory infiltrate on examination of the gallbladder wall. Severe cholecystitis was defined as cholecystitis

complicated by secondary changes, including hemorrhage, gangrene, mucocele, empyema, or perforation, and/or when the pathological examination indicated xanthogranulomatous cholecystitis; the representative forms of severe cholecystitis were

gangrenous cholecystitis and gallbladder perforation. All other pathological findings were categorized as simple cholecystitis. Cholecystitis is seen in about 10% of adult population in Asian countries and 4% in India. Cholecystitis accounts for most of the hospital admissions related to gastrointestinal diseases. Delayed management can lead to increased morbidity, due to progression to severe cholecystitis, such as gangrenous change, abscess formation, and gallbladder perforation. Unfortunately, patients with severe cholecystitis are challenging to accurately diagnose, both clinically and radiologically, as the clinical manifestations are uncommon, and imaging studies are often equivocal. However, marked contrasts in the morbidity and mortality rates have been observed between patients with simple cholecystitis and severe cholecystitis. Prompt detection and proper management of patients at risk of severe cholecystitis is essential in preventing associated complications. To predict the prognosis of inflammatory conditions, several inflammation-based scores have been suggested, including the Modified Glasgow Prognostic Score and Prognostic Nutritional Index.¹ However, NLR, PLR has received great interest, since it is simple to calculate, and involves no additional cost, as it uses results from a standard complete blood count test. The inflammation-triggered release of arachidonic acid metabolites and platelet-activating factors results in neutrophilia, and cortisol-induced stress results in relative lymphopenia. Thereby representing the underlying inflammatory process.

Sonography is the initial imaging modality of choice for the evaluation of cholecystitis. It is non invasive, relatively cheap and easily available. Sonographic findings were grouped into three categories i.e., Luminal changes, Mural changes and Pericholecystic changes.²

Luminal changes included sludge, intraluminal membranes, sloughed off mucosa, strands of fibrinous exudate.

Mural changes constituted majorly of wall thickening which is postulated to occur due to a host of factors in relation to the gall bladder such as chronic infection, acute on chronic infection, perforation, abscess, mucocele to name a few.

Pericholecystic changes such fluid, usually has a characteristic triangular appearance as it conforms to the confines of the peritoneal spaces in presence of pathology.

This is a prospective study to predict severe cholecystitis to arrive at a diagnosis early such that prompt treatment can be exercised.

Aims and objectives

The aims and objectives of this study are: to assess the utility of NLR, PLR and ultrasound findings in predicting

severe cholecystitis and to identify an NLR, PLR cut off value that discriminates between simple and severe cholecystitis.

METHODS

The study was conducted between December 2019 to June 2021 at Kempegowda Institute of Medical Sciences Hospital (Bangalore, India) after obtaining approval from the Hospital's Ethical Committee. This prospective observational time bound study conducted from December 2019 to June 2021, included 100 patients admitted for cholecystitis above 18 years of age. Those patients unfit to undergo surgery on medical grounds were excluded. Written informed consent for participation in the study was obtained. After admission to the ward, a detailed clinical history was taken and clinical examination was performed on all patients. The patients were then subjected to undergo routine blood investigations and ultrasonography of abdomen and pelvis, which was performed by the same Radiologist on all patients, the findings of which were grouped into three categories, Luminal, Mural and Pericholecystic changes. Intraoperative and histopathological findings were recorded. NLR, PLR values were calculated from absolute neutrophil count and absolute lymphocyte count. Data was organized and tabulated onto a unique master chart and subjected to statistical analysis using Statistical package for social sciences (SPSS) software version 22. Receiver operating characteristic curve analysis was employed to identify optimal NLR, PLR Cut off values and to predict combined accuracy of NLR, PLR and ultrasound findings to predict severe cholecystitis.

RESULTS

A prospective observational time bound study was conducted with sample size of 100 admitted patients from December 2019 to January 2021, satisfying the inclusion criteria, at Kempegowda Institute of Medical Sciences, Bengaluru.

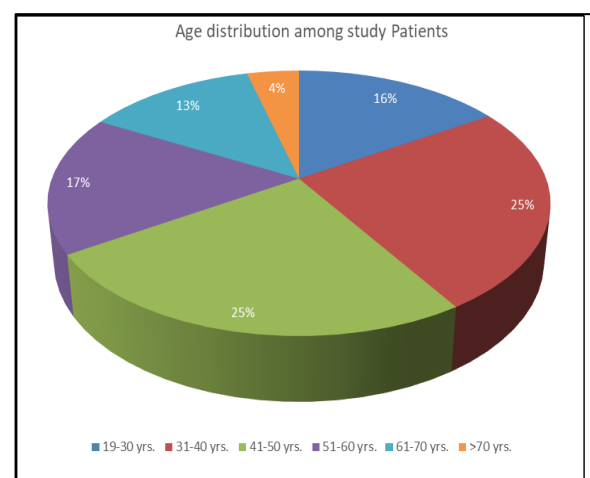


Figure 1: Age distribution.

Gender distribution

Figure 1 shows the age distribution of the study subjects, mean age of patients was 45.69 years. Majority of patients were in the age group of 31 to 50 years. Female predominance of 65% was seen as shown in Figure 2.

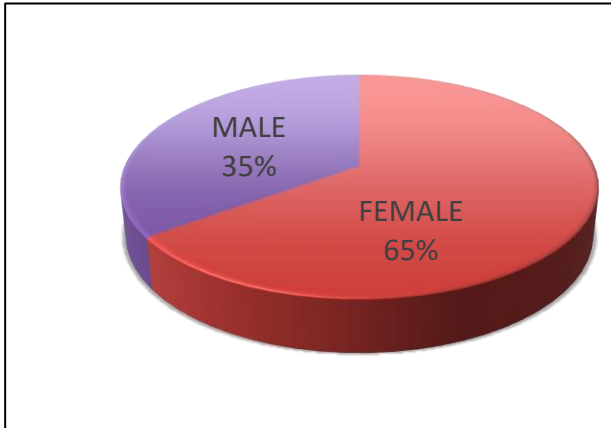


Figure 2: Gender distribution.

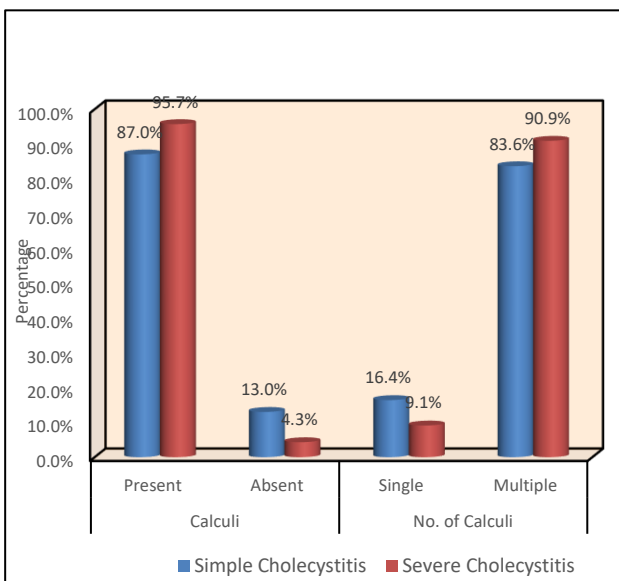


Figure 3: Distribution of calculus characteristics between simple and severe cholecystitis.

Table 1 shows the distribution of calculus characteristics between simple and severe cholecystitis. 95.7% of patients with severe cholecystitis had presence of calculi while 90.9% of severe cholecystitis patients had multiple calculi.

66 out of 100 patients showed histopathological impression of chronic calculous cholecystitis. 11 were chronic acalculous cholecystitis. 8 were acute calculous cholecystitis. 6 were xanthogranulomatous cholecystitis. 3 patients had a perforated gall bladder. 2 patients had chronic calculous cholecystitis with inflammatory polyp. Acute on chronic calculous cholecystitis, chronic

acalculous cholecystitis with inflammatory polyp, chronic calculous cholecystitis with cholesterosis and moderately differentiated adenocarcinoma was seen in 1 patient each as represented in Figure 3.

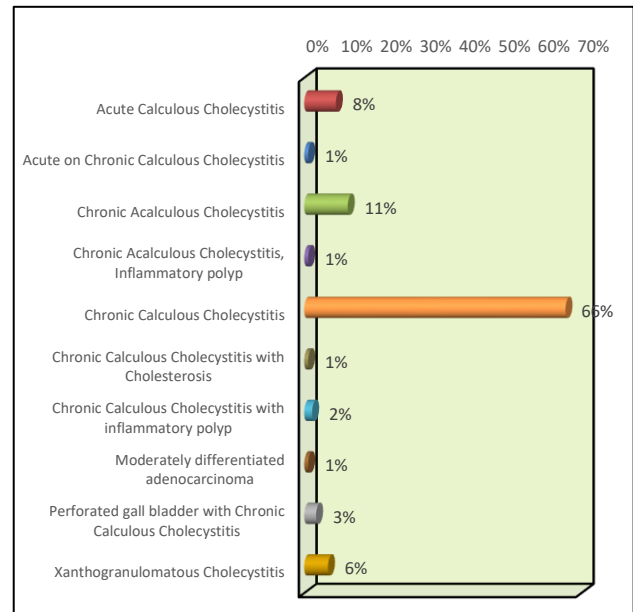


Figure 4: Distribution of histopathological findings among study subjects.

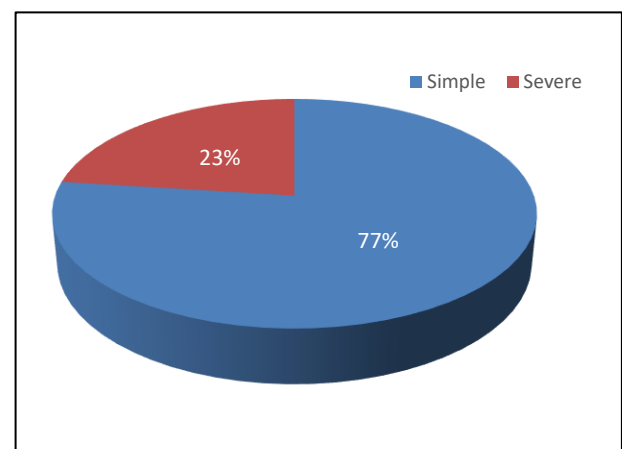


Figure 5: Distribution of study patients based on type of cholecystitis.

Among the 100 patients, 77% had simple cholecystitis while 23% had severe cholecystitis as shown in Figure 4.

80% patients had sonological impression as Chronic calculous cholecystitis. Chronic cholecystitis was seen in 9% patients. 4% patients were acute calculous cholecystitis. 3% had a perforated gall bladder. 2% were acute on chronic cholecystitis and gall bladder polyps respectively represented in Figure 5. Table 2 shows the Mann Whitey Test which was employed and it was found that the Mean NLR value in Severe cholecystitis cases was significantly higher (6.82 ± 3.31) as compared to

simple cholecystitis cases (2.80 ± 1.64) and this difference was statistically significant at $p < 0.001$.

Table 3 represents a Chi Square Test to compare the proportion, revealed that the presence of calculi and presence of multiple calculi are seen to be relatively higher in severe cholecystitis cases at 95.7% and 90.9% respectively however a significant difference was not found between the two groups. Luminal changes of polyp and sludge were noted in severe cholecystitis cases at 13% and 17.4% respectively but luminal changes were nil in all simple cholecystitis patients and this was found to be statistically significant at $p < 0.001$. Mural changes of gall bladder wall thickening was also found to be higher in severe cholecystitis cases as compared to simple cholecystitis cases and this was found to be statistically significant at $p < 0.001$. Wall thickness of 4 mm was predominantly seen in severe cholecystitis cases.

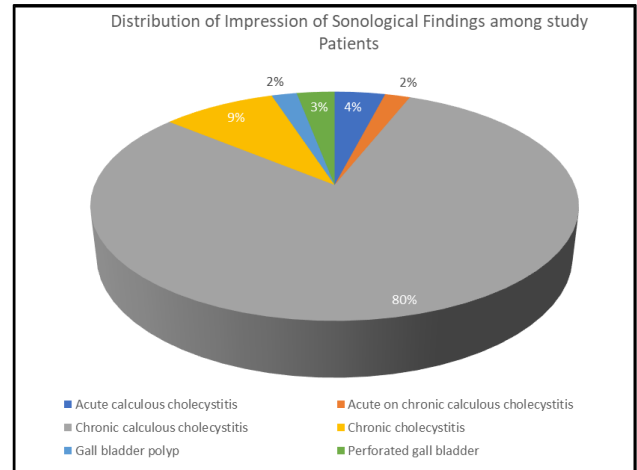


Figure 6: Distribution of impression of the sonological findings.

Table 1: Comparison of mean NLR and PLR values based on the type of cholecystitis using Mann Whitney test.

Parameters	Cholecystitis	N	Mean	SD	Mean Diff	P value
NLR	Simple	77	2.80	1.64	-4.03	<0.001*
	Severe	23	6.82	3.31		
PLR	Simple	77	112.93	39.97	-61.48	<0.001*
	Severe	23	174.41	72.88		

* - Statistically Significant

Table 2: Comparison of sonological findings based on the type of cholecystitis using chi square test.

Variables	Category	Simple		Severe		χ^2 Value	P value
		N	%	N	%		
Calculi	Present	67	87.0%	22	95.7%	1.350	0.25
	Absent	10	13.0%	1	4.3%		
No. of calculi	Single	11	16.4%	2	9.1%	0.713	0.40
	Multiple	56	83.6%	20	90.9%		
Luminal changes	Polyp present	0	0.0%	3	13.0%	25.199	<0.001*
	Sludge present	0	0.0%	4	17.4%		
	Nil	77	100.0%	16	69.6%		
Mural changes	WT 2 mm	2	2.6%	2	8.7%	31.142	<0.001*
	WT 4 mm	1	1.3%	8	34.8%		
	WT 6 mm	0	0.0%	1	4.3%		
	Adherent soft calculi to posterior wall of gall bladder	1	1.3%	0	0.0%		
	Nil	73	94.8%	12	52.2%		
Pericholecystic changes	Fluid Present	1	1.3%	9	39.1%	28.164	<0.001*
	Nil	76	98.7%	14	60.9%		

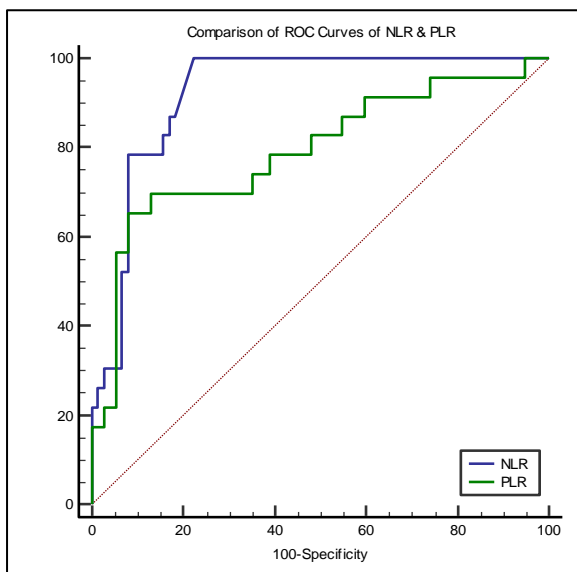
Table 3: Comparison of mean length of stay based on the type of cholecystitis using Mann Whitney Test.

Parameter	Type of cholecystitis	N	Mean	SD	Mean Diff	P value
Length of stay	Simple	77	4.92	1.01	-3.17	<0.001*
	Severe	23	8.09	1.31		

Table 4: ROC curve analysis for NLR and PLR Parameters for determining the cut-off between simple and severe cholecystitis.

Variable	AUC	Std. Error	95% Conf. Interval		P value	Cut off	Sn (%)	Sp (%)
			Lower	Upper				
NLR	0.92	0.03	0.85	0.97	<0.001*	3.75	100.0	77.92
PLR	0.79	0.06	0.70	0.87	<0.001*	154.73	65.22	92.21

Pericholecystic fluid was present in 39.1% of severe cholecystitis cases which was also found to be higher than simple cholecystitis cases and was statistically significant at $p<0.001$.

**Figure 7: Comparison of ROC curves of NLR, PLR.**

It was also observed that 91% of our patients had distended gall bladder and 9% had contracted gall bladder.

Table 4 shows the length of hospital stay was also found to be longer, as shown in the Mann Whitney Test, in cases of severe cholecystitis than simple cholecystitis with a mean of 8.09 at standard deviation of 1.31 at $p<0.001$ it was statistically significant.

Mann Whitey Test was employed and it was found that the Mean NLR value in Severe cholecystitis cases was significantly higher (6.82 ± 3.31) as compared to simple cholecystitis cases (2.80 ± 1.64) and this difference was statistically significant at $p<0.001$.

The mean PLR value in severe cholecystitis cases was significantly higher (174.41 ± 72.88) as compared to simple cholecystitis cases (112.93 ± 39.97) and this difference was statistically significant at $p<0.001$.

Table 5 represents a receiving operating characteristic curve analysis for NLR, PLR to determine a cut off value which was plotted and the following were observed.

AUC for NLR was found to be 0.92. Hence, NLR has a diagnostic ability ranging between 0.85 to 0.97 at 95% confidence interval and it was statistically significant at $p<0.001$. A Cut off value of NLR was for this study was obtained at 3.75, implying thereof that if NLR is equal to or more than 3.75, the case is severe cholecystitis. The sensitivity of which was 100% and specificity was 77.92%.

The AUC for PLR was found to be 0.79. Hence, PLR has a diagnostic ability ranging between 0.70 to 0.87 at 95% confidence interval and it was statistically significant at p value <0.001 . A Cut off value of PLR was for this study was obtained at 154.73 implying thereof that if PLR is equal to or more than 154.73, the case is severe cholecystitis. The sensitivity of which was 65.22% and specificity was 92.21%. This has been represented Figure 6.

Since both NLR, PLR have a diagnostic ability. Determination of accuracy becomes necessary. The AUC for NLR and PLR was 0.92 and 0.79 with a difference of 0.13. This difference is statistically significant at $p<0.001$. Therefore, NLR is a more reliable diagnostic tool as compared to PLR.

DISCUSSION

Cholecystectomy is one of the commonest causes for admission to hospital with an associated mortality of 0.45 to 6% depending on severity of gall bladder disease.

The purpose of this study is to predict severity of cholecystitis preoperatively such that it aids in prompt detection, early and efficient management of complications, both local and systemic.

In a developing country like India, a simple, cost effective, non-invasive yet accurate method of prediction becomes the need of the hour. This method may also be utilised by our healthcare workers in the rural set up and can manage such patients effectively.

NLR, PLR is easy to calculate from routine blood investigations and ultrasonography is a simple, accurate, non-invasive, cost-effective diagnostic tool.

Several studies including ours has shown that detection of severe cholecystitis has relied mainly on imaging studies such as the Abdominal ultrasonography and that NLR has the potential to accurately differentiate between simple and severe cholecystitis.

Prioritizing patients with high NLR for surgery would reduce postoperative morbidity and length of hospital stay.

Amongst the 100 subjects in our study, the cut off NLR was obtained at 3.75 with a sensitivity and specificity of 100% and 77.92% respectively. In the study conducted by Sang et al, Hareen et al, and Micić et al, they demonstrated a preoperative NLR of 3.0, 3.0 and 4.18 respectively.^{1,3,4}

The mean age of our study subjects was found to be 45.69 years (ranging from 19 – 75 years) and comprised a majority of women forming 65% which was consistent with the study conducted by Hareen et al, Dixit et al, Lee, and Surekha.^{3,5,6,7}

In the study conducted by Wilson et al and Bree et al presence of calculi was higher in patients of severe cholecystitis and our study showed similar findings, calculi was visualised in 89% of patients, out of which 85% (76 patients) had multiple calculi.^{8,9}

80% of our patients had sonological impression as Chronic calculous cholecystitis. Chronic cholecystitis was seen in 9% patients. 4% patients were acute calculous cholecystitis. 3% had a perforated gall bladder. 2% were acute on chronic cholecystitis and gall bladder polyps respectively.

91% of our patients had gall bladders that were distended and 9% had contracted gall bladder which was consistent with the study by Wang et al and Sood et al.^{10,11}

92% of the patients underwent laparoscopic cholecystectomy. 7% were converted to open procedure. the various reasons for conversion included common bile duct injury, cystic artery injury, perforated gall bladder, gangrenous gall bladder and one patient turned out to have moderately differentiated adenocarcinoma.

Among the 100 patients, 77% had simple cholecystitis while 23% had severe cholecystitis.^{1,3}

Several studies have found a higher mean NLR to be associated with severe cholecystitis patients. In our study a Mann Whitey Test was employed and it was found that the Mean NLR value in Severe cholecystitis cases was significantly higher (6.82 ± 3.31) as compared to simple

cholecystitis cases (2.80 ± 1.64) and this difference was statistically significant at $p < 0.001$.^{1,3,4,12}

The mean PLR value in severe cholecystitis cases was also significantly higher (174.41 ± 72.88) as compared to simple cholecystitis cases (112.93 ± 39.97) and this difference was statistically significant at $p < 0.001$.^{1,3,5,13}

A Chi square test was conducted to compare the proportion revealed that the presence of calculi and presence of multiple calculi are seen to be relatively higher in severe cholecystitis cases at 95.7% and 90.9% respectively, however a significant difference was not found between the two groups.

Luminal changes of polyp and sludge were noted in severe cholecystitis cases at 13% and 17.4% respectively but luminal changes were nil in all simple cholecystitis patients and this was found to be statistically significant at $p < 0.001$ which was also found in the study conducted by Charalel.²

Mural changes of gall bladder wall thickening were also found to be higher in severe cholecystitis cases as compared to simple cholecystitis cases and this was found to be statistically significant at $p < 0.001$. Wall thickness of 4 mm was predominantly seen in severe cholecystitis cases.²

Pericholecystic fluid was present in 39.1% of severe cholecystitis cases which was also found to be higher than simple cholecystitis cases and was statistically significant at $p < 0.001$.²

Length of hospital stay was found to be longer, as shown in the Mann Whitney Test, in cases of severe cholecystitis than simple cholecystitis with a mean of 8.09 at standard deviation of 1.31 at $p < 0.001$ which was consistent with study conducted by Sang et al, Lee and Hareen et al.^{1,3,6}

The AUC for NLR was found to be 0.92. Hence, NLR has a diagnostic ability ranging between 0.85 to 0.97 at 95% confidence interval and it was statistically significant at $p < 0.001$. A Cut off value of NLR for this study was obtained at 3.75, implying thereof that if NLR is equal to or more than 3.75, the case is severe cholecystitis. The sensitivity and specificity of NLR obtained by Lee et al and Hareen et al was 70.5% and 70.0% respectively. Our study shows a sensitivity of 100% and specificity of 77.92%.^{1,3}

The AUC for PLR was found to be 0.79. Hence, PLR has a diagnostic ability ranging between 0.70 to 0.87 at 95% confidence interval and it was statistically significant at $p < 0.001$.^{1,3} A cut off value of PLR for this study was obtained at 154.73 implying thereof that if PLR is equal to or more than 154.73, the case is severe cholecystitis. The sensitivity of which was 65.22% and specificity was 92.21%.

Since both NLR, PLR have a diagnostic ability. Determination of accuracy becomes necessary. The AUC for NLR and PLR was 0.92 and 0.79 with a difference of 0.13. This difference is statistically significant at $p < 0.001$. Therefore, NLR is a more reliable diagnostic tool as compared to PLR.

Combined predictive accuracy using sensitivity and specificity was calculated statistically and ROC curve was plotted. Arriving at 91% with a range of 83.6 to 95.8.

Patient mortality rate is directly related to severe complications, such as gallbladder perforation, abscess formation, and peritonitis. Gall bladder perforation is the eventual result of severe cholecystitis, where inflammation can either be localized or spread throughout the whole abdominal cavity via the perforated gallbladder.¹

In both forms, inflammation is expected to result in elevated NLR, which validates our results. Patients with advanced inflammatory or malignant diseases usually present with elevated NLR as a manifestation of the systemic inflammatory response. Many investigators have attempted to identify the association between NLR and its underlying molecular basis, and have found that there is an elevation in the levels of pro-inflammatory cytokines (e.g., IL-1ra, IL-6, IL-7, IL-8, IL-12) in the plasma of patients with elevated NLR. These inflammatory cytokines are expected to perpetuate a tissue microenvironment favoring aggressive inflammation.¹

In this study, high NLR was found to be a predictor of severe cholecystitis as well as an independent risk factor for prolonged length of hospital stay as is demonstrated in the results. Therefore, prioritizing patients with high NLR for surgery would reduce postoperative morbidity and length of hospital stay.

We determined the cut-off value of severe cholecystitis as 3.75 based on our ROC curve analysis; which had an acceptable reliability in the analysis (100% sensitivity and a specificity of 77.92%). Therefore, we believe that an NLR cut-off value of 3.75 is suitable, and consistent with previous studies.^{3,13-16}

Sonography is the initial imaging modality of choice for the evaluation of cholecystitis. When diagnosis and treatment are delayed, it can progress to complicated cholecystitis (with gangrene, hemorrhage, emphysematous change, and/or perforation). Sonography is easy availability, carries with it no risk of radiation, low cost, and high accuracy making it a suitable tool for the assessment for severe cholecystitis.

CONCLUSION

Patients with advanced inflammatory or malignant diseases usually present with elevated NLR as a

manifestation of the systemic inflammatory response. The inflammation triggers an elevated NLR, which validates the results of our study. Among the 100 study subjects, 23% had severe cholecystitis. The cut-off NLR was found to be 3.75 which correlated with the ultrasonographic findings of luminal, mural and pericholecystic changes seen profoundly in severe cholecystitis. In a developing country like India, a simple, cost effective, non-invasive yet accurate method of prediction becomes the need of the hour. Preoperative NLR and Ultrasonographic findings may also be utilised by our healthcare workers in the rural set up (secondary health care centres) and can manage patients effectively by distinguishing them into simple and severe cholecystitis. This approach to determine the operative priority based on NLR and Ultrasound findings is expected to achieve a favourable outcome in terms of surgery by fulfilling the 'sickest first' principle and predicting prolonged length of hospital stay. Therefore, the association between preoperative NLR and Ultrasonography is validated in this study and is of immense use in predicting patients with severe cholecystitis and to prevent its dreaded complications. Ultrasonography is an initial imaging modality of choice for the evaluation of gall bladder pathologies. It is a reliable, specific diagnostic tool. In cases of delayed presentation or ambiguous diagnosis, cholecystitis may progress to complications such as gangrene, empyema, perforation etc. These dreaded, often life-threatening complications can be prevented, and prompt, effective detection can be made preoperatively by calculating NLR and correlating with an Abdominal Ultrasound. If necessary, ultrasound guided minimally invasive procedures like cholecystostomy may be performed on an emergency basis as well. This can buy precious time for the patient and doctor by facilitating transport to higher centre and thereby alleviating complications. Hence, preoperative determination of NLR and Abdominal Ultrasound is a simple, quick and effective method to predict severe cholecystitis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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