E-ISSN: 2616-3470
P-ISSN: 2616-3462

www.surgeryscience.com
2021; 5(2): 318-324
Received: 03-02-2021
Accepted: 05-03-2021

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Haematological markers as a predicting tool for gallstone induced severe acute pancreatitis

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DOI: https://doi.org/10.33545/surgery.2021.v5.i2f.715

Abstract
Severe acute pancreatitis (SAP) has high morbidity and mortality. Gallstones being the most common cause, warrants study into the haematological markers for swift and easy prediction of gallstone induced SAP. Patients of gallstone induced acute pancreatitis were included in this study. Blood investigations of all patients were sent within one hour of arrival. Computed Tomography (CT) was done after 72 hours of onset of pain. Values of all haematological markers, BISAP and MCTSI were then calculated. 70 patients were included in this study. Area under the ROC curve and cut offs based on these curves for predicting SAP were calculated for NLR, PLR, LMR, RDW, Blood sugar, BISAP (≥3) and MCTSI (>6). Their sensitivity and specificity were then calculated. All tested variables except blood sugar could predict SAP. PLR turned out to the best predictive factor among all. We suggest a combination of NLR and PLR for detecting maximum cases.

Keywords: gallstone induced acute pancreatitis, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, lymphocyte to monocyte ratio, red cell distribution width

1. Introduction
Acute Pancreatitis (AP) is a sudden inflammation of the pancreas which can occur due to various causes, of which gallstones and alcohol are the most common ones [1]. The clinical presentation of this disease varies a lot. Most have a mild course, however 15-20% of these patients will develop severe acute pancreatitis (SAP) [2]. Various scoring systems like Ranson, APACHE-II, Bedside Index for Severity in Acute Pancreatitis (BISAP) and Modified computed tomography severity index (MCTSI) are in use around the world, for predicting as to which patients will have a severe attack of acute pancreatitis. C-reactive protein (CRP), procalcitonin, interleukin-6, and interleukin-8 have also been used for prediction of SAP but with only limited efficiency as these tests are expensive and not adequate for this purpose[3]. BISAP was given by Wu *et al.* in 2008 in order to calculate the risk of mortality in patients of acute pancreatitis [4]. The MCTSI is a modification in the CT severity index introduced by Balthazar *et al.* in 1994 [5]. The problem with scoring systems is that these are cumbersome as they have multiple variables and also take time to calculate. What is required is a parameter to predict the severity of pancreatitis quickly and easily.
Various haematological markers have been in use for prediction of severity of several inflammatory conditions including acute pancreatitis. Neutrophil to lymphocyte ratio (NLR) is rapid and easy to obtain marker for severity prediction in AP. An increase in neutrophil count indicates an acute inflammatory response, whereas a low lymphocyte count is suggestive of deteriorating general health and physiological stress [6, 7]. Hence, NLR provides an added advantage over either of the two parameters alone. Raised serum cortisol and catecholamines in inflammation may play a major role in bringing out these changes in haematological parameters of these patients. Cortisol causes increase in absolute neutrophil count and has an inverse effect on the lymphocyte count [8]. Similarly, catecholamines may lead to increased leukocyte count and decrease in total lymphocytes [9]. Acute inflammation also causes rise in the platelet count. Hence, in some diseases platelet to lymphocyte ratio (PLR) is considered to be a better marker of severity [10-12] and has been applied to AP as well. Red cell distribution width (RDW) has been in use as a prognostic marker for patients admitted to the intensive care units [13]. A continually low lymphocyte to monocyte ratio (LMR) can help us foresee the upcoming SAP on

admission[14]. Elevated blood glucose level has also shown some promise in the same[15]. SIRS progressing to MODS is the main cause of high morbidity and mortality in patients with SAP. As NLR, PLR, RDW and LMR envisage serious inflammatory conditions, therefore they can predict bad prognosis in AP. A complete hemogram is easily attainable in emergency setting and is the sole investigation required for calculating the values of these markers.

If these markers can predict severity in AP, they will go a long way in the management of these patients. An easy and quick prediction of patients at higher risk of severe disease, will place these patients under more aggressive resuscitative measures and stringent monitoring which will invariably yield better outcomes. Gallstones are the single most common cause of AP[1] and are very common in North India [16], where this study has been undertaken. So, gallstone induced acute pancreatitis (GIAP) is also seen very frequently in our institute. As the relation of these markers with GIAP alone has been seldom studied, this study was done to find the association between NLR, PLR, RDW, LMR and initial blood sugar levels; and severity of GIAP.

2. Materials and Methods

This prospective observational cohort study was conducted in the Department of Surgery IGMC Shimla between May 2016 to May 2017. Patients who presented with AP in the emergency department with presence of gallstones on ultrasound abdomen were included in the study. Diagnosis of AP was defined as characteristic abdominal pain, a threefold or greater rise in the serum levels of the pancreatic enzymes' amylase or lipase, and/ or characteristic findings of pancreatic inflammation on contrast enhanced CT. Pregnant females, patients below 18 years of age and patients with advanced cardiac, pulmonary, renal and liver diseases were excluded from the study. Patients were included after a written informed consent was obtained from all of them. Total of 70 patients were enrolled in this study. All of them were monitored during their hospital stay for the purpose of this study.

2.1 Data Collection

Peripheral blood samples of all patients were collected within 1 hour of arrival to the emergency department. Routine blood investigations and chest X-ray were ordered for all patients. Samples were collected, transported and processed following standard procedure in the hospital laboratory. All blood counts were obtained. NLR was calculated as a ratio of absolute neutrophil count to absolute lymphocyte count. Similarly, PLR and LMR were calculated as a ratio of absolute platelet count to absolute lymphocyte count and absolute lymphocyte count to absolute monocyte count, respectively. These ratios were recorded for each patient. RDW and blood sugar levels were obtained for all patients. BISAP score was calculated for each patient within 24 hours of admission to the hospital. CT scan was performed in all patients after 72 hours of the onset of pain and MCTSI was recorded.

2.2 Outcome of interest

Primary outcome of SAP was defined as per the revised Atlanta classification, that is presence of persistent organ failure (POF), which in turn was defined by modified Marshall score of ≥2 for more than 48 hours. Mild acute pancreatitis was defined as lack of organ failure and local/systemic complications. Moderate acute pancreatitis was presence of transient organ failure (organ failure less than 48 hours) and/or local or systemic complications [17]. All patients were divided into two groups based on this. One included the mild and moderate acute pancreatitis and the other severe acute pancreatitis. The NLR, PLR, RDW, LMR, Blood sugar, BISAP and MCTSI were compared to the occurrence of SAP and their ability to predict its occurrence was calculated.

2.3 Statistical analysis

NLR, PLR, LMR, Blood sugar and RDW were considered as continuous variables being exhibited as mean and standard deviation. The remaining variables, BISAP and MCTSI were treated as categorical variables and were portrayed by frequency. Cut off's for NLR PLR, LMR, RDW and blood sugar for prediction of SAP, were calculated by selecting the optimum sensitivity and specificity as per the receiver-operating characteristic (ROC) curves. BISAP score of ≥3 and MCTSI of >6 was considered as predictor of SAP. Data was recorded in a 2 X 2 contingency table for each variable. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were computed for each variable. Chi-square test was used to test the null hypothesis for categorical variables and student's t-test was used for continuous variables. Area under the curve (AUC) in the ROC curves was calculated for assessing the predictive capability of NLR, PLR, LMR, RDW, Blood sugar, BISAP and MCTSI. A p-value of <0.05 was deemed statistically significant. All data was analysed using Epi info version 7.2.3.1 software.

3. Results

A total of 70 patients of GIAP were included in the study. The disease was most common in the fifth decade of life. Females were affected three times more as compared to male patients. 9 patients (12.9%) had diabetes mellitus and 12 patients (17.1%) were known cases of hypertension. In accordance with the revised Atlanta classification, 16 patients (22.86%) were recorded to have developed SAP and 54 were in the not severe (mild and moderate) category. Mean WBC count in the severe group was 13.3 (±5.35) x 10^3 /dL and in the other group was 12.5(±4.89) x 10^3 /dL. However, the difference was not significant (p-value 0.577).

Mean NLR, PLR, LMR, RDW and blood sugar for severe group were 9.45 (±5.06), 263 (±121), 3.43 (±2.41), 12.6 (±2.30) and 168 (±88.3); and for not severe group were 5.03 (±2.94), 131 (±116), 5.13 (±2.58), 11.1 (±2.92) and 142 (±71.9), respectively. The difference for NLR (p-value <0.001), PLR (P value <0.001) and LMR (p-value 0.022) was significant, whereas for RDW (p-value 0.057) and blood sugar (p-value 0.230) was not (Table 1, Fig. 1).

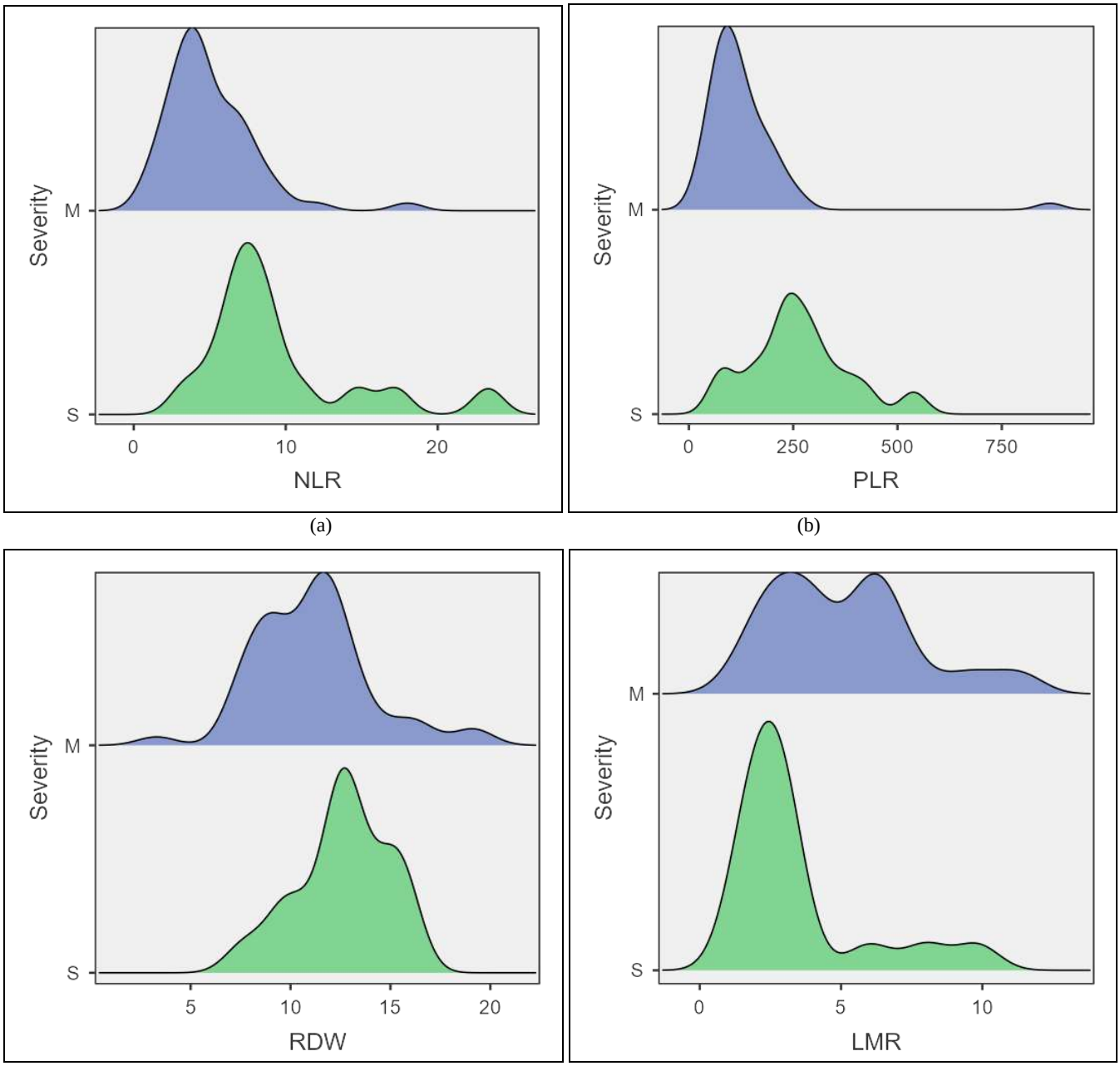
Table 1: Demographics, inflammatory markers and scoring systems in patients of gallstone induced acute pancreatitis.

Variables	Overall (N=70)	SAP (N=16)	MAP (N=54)	p-value
Age	53.2±15.7	57.3±15.9	51.9±15.6	0.239*
Sex (Female)	52(74.3%)	14(87.5%)	38(70.4%)	0.169#
Diabetes mellitus	9 (12.9%)	3 (18.8%)	6 (11.1%)	0.423#
Hypertension	12(17.1%)	4 (25%)	8 (14.8%)	0.342#
WBC (x 10^3/dL)	12.7±4.97	13.3±5.35	12.5±4.89	0.577*

NLR	6.04±3.96	9.45±5.06	5.03±2.94	<0.001*
PLR	161±129	263±121	131±116	<0.001*
LMR	4.74±2.62	3.43±2.41	5.13±2.58	0.022*
RDW (%)	11.4±2.85	12.6±2.30	11.1±2.92	0.057*
Blood Sugar (mg/dL)	147±76	168±88.3	142±71.9	0.230*
BISAP (≥3)	15(21.4%)	9(56.25%)	6 (11.1%)	<0.001#
MCTSI (>6)	13(18.6%)	8 (50%)	5 (9.3%)	<0.001#

Continuous variables are presented as mean±SD.
*Student's t-test #Chi-square test

SAP- severe acute pancreatitis; MAP- mild and moderate acute pancreatitis; WBC- white blood cell count; NLR- neutrophil to lymphocyte ratio; PLR- platelet to lymphocyte ratio; LMR- lymphocyte to monocyte ratio; RDW- red cell distribution width; BISAP- bedside index of severity in acute pancreatitis; MCTSI- modified computed tomography severity index.



(NLR- neutrophil to lymphocyte ratio; PLR- platelet to lymphocyte ratio; RDW- red cell distribution width; LMR- lymphocyte to monocyte ratio)

Fig 1: Density histogram of, (a) NLR (b) PLR (c) RDW (d) LMR, in severe (S) and not severe (M) acute pancreatitis.

AUC for NLR, PLR, LMR, RDW and Blood sugar levels on the ROC curves plotted was 0.828, 0.852, 0.729, 0.702 and 0.610, respectively. Based on these, appropriate cut offs for each variable were determined for prediction of severe disease (Fig. 2).

Keeping the cut off of >7.0 for NLR, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for prediction of SAP were 75%, 79.63%, 52.17% and 91.49%. For PLR (cut off >215) these values were 75%, 92.59%, 75% and 92.59%. Similarly, for RDW (cut off >12.2) these were 75%, 74.07%, 46.15% and 90.91%, respectively. Blood sugar levels of more than 138 mg/dL were kept as determinants of severe disease with sensitivity, specificity, PPV and NPV of 56.25%, 68.52%, 34.62% and 84.09%. As LMR values tend to fall in severe disease, the cap of this ratio for prediction was determined to be <3.4. Sensitivity, specificity, PPV and NPV with this cap was 81.25%, 70.37%, 44.83% and 92.68%. All these results except for blood sugar levels were highly significant. With the p-values of NLR, PLR, LMR and RDW being <0.001. P-value for blood sugar levels was 0.072 which was not significant.

BISAP (≥3) and MCTSI (>6) scores recorded sensitivity 56.25% and 50%; specificity 88.89% and 90.74%; PPV 60% and 61.54%; and NPV 87.27% and 85.96%, respectively, for prediction of SAP. Results for both these scores were significant with their p-values being <0.001. AUC for them were 0.714 and 0.665, respectively (Table 2).

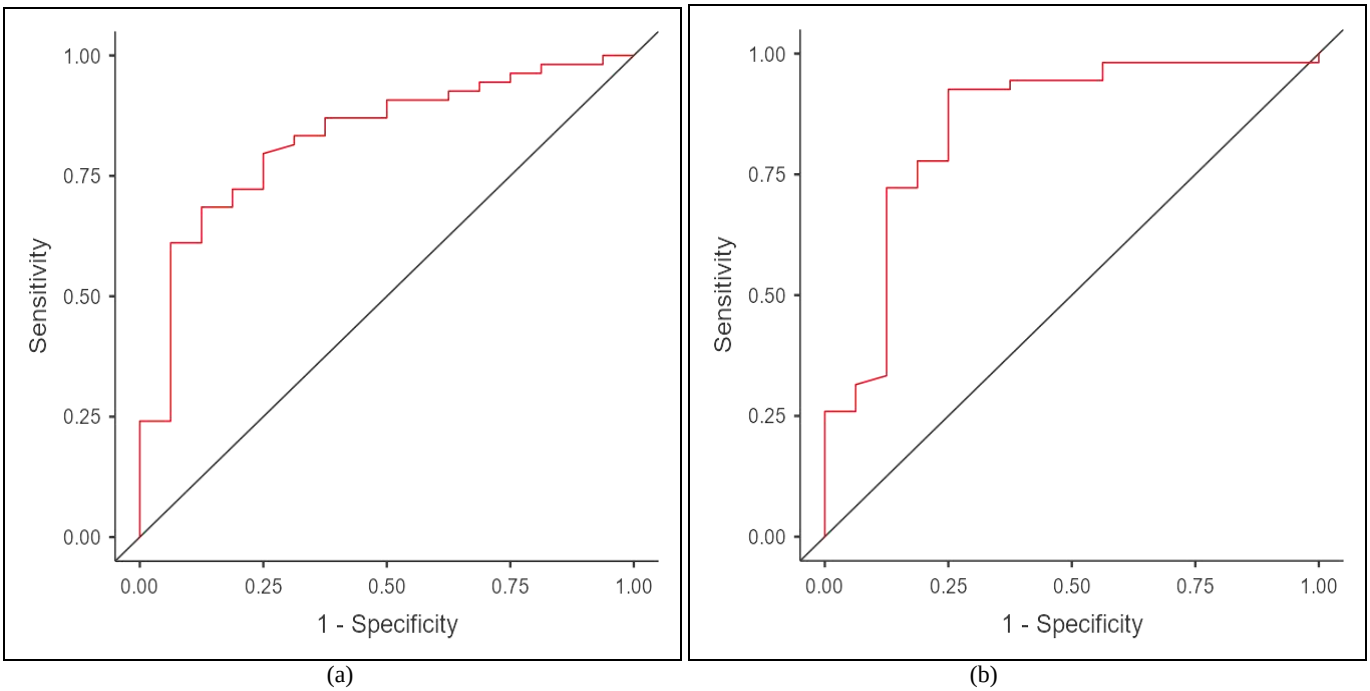
A combination of NLR and PLR (either NLR>7 or PLR >215) showed promise with sensitivity 87.5%, specificity 74.07%. PPV 50% and NPV 95.24% (p-value <0.001).

Table 2: Predictive values of inflammatory markers and scoring systems for prediction of SAP

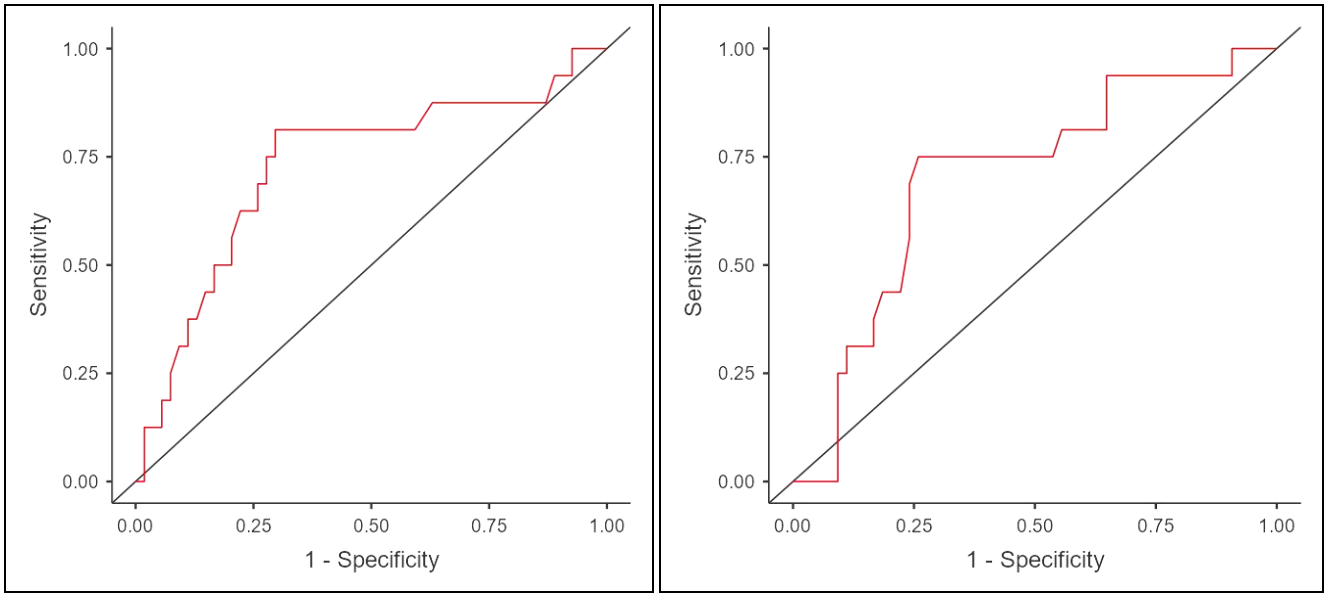
Variable	AUC	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)	p-value[#]
NLR	0.828	>7.0	75	79.63	52.17	91.49	<0.001
PLR	0.852	>215	75	92.59	75	92.59	<0.001
LMR	0.729	<3.4	81.25	70.37	44.83	92.68	<0.001
RDW	0.702	>12.2 (%)	75	74.07	46.15	90.91	<0.001
Blood sugar	0.61	>138 (mg/dL)	56.25	68.52	34.62	84.09	0.072
BISAP	0.714	≥3	56.25	88.89	60	87.27	<0.001
MCTSI	0.665	>6	50	90.74	61.54	85.96	<0.001
NLR and PLR		NLR>7 or PLR >215	87.5	74.07	50	95.24	<0.001

[#]Chi-square test

SAP- severe acute pancreatitis; AUC- are under the ROC curve; Sens- sensitivity; Spec- specificity; PPV- positive predictive value; NPV- negative predictive value; NLR- neutrophil to lymphocyte ratio; PLR- platelet to lymphocyte ratio; LMR- lymphocyte to monocyte ratio; RDW- red cell distribution width; BISAP- bedside index of severity in acute pancreatitis; MCTSI- modified computed tomography severity index



(a) (b)



(c) (d)

(NLR- neutrophil to lymphocyte ratio; PLR- platelet to lymphocyte ratio; LMR- lymphocyte to monocyte ratio; RDW- red cell distribution width)

Fig 2: Receiver operating characteristic (ROC) curves of, (a) NLR (b) PLR (c) LMR (d) RDW, for prediction of severe acute pancreatitis

4. Discussion

Since the advent of Ranson criteria in 1977 [18], various complex scoring systems have been used for the prediction of SAP. Few among these include APACHE II, Glasgow score, Japanese severity score and BISAP. Most of these scoring systems are cumbersome and some even take around 48 hours to be calculated. In contrast to these, the various haematological parameters are easy to obtain and calculate. The NLR, PLR, RDW, LMR and Blood sugar levels have been evaluated in this study, to try and find a simple alternative to the above-mentioned complex scoring systems.

In our study, on analyses of the AUC in the ROC curves plotted for each variable, both NLR and PLR were excellent in the prediction of SAP. LMR and RDW were acceptable for this prediction however, blood sugar levels did not perform well. These were compared to the standard scoring systems BISAP and MCTSI. Among all these parameters PLR was the best for this purpose, even surpassing BISAP and MCTSI. PLR was closely followed by NLR, which itself outperformed other variables.

As with any inflammatory process, AP is associated with rise and fall of various types of blood cells. Platelets and neutrophils get activated and are involved in the defense response of the patient's body. But this reaction is too much and in turn ends up damaging the pancreas itself by massive cell transmigration and discharge of destructive defense molecules. This inflammatory response also damages other organs of the body leading to organ failure [19]. The magnitude of lymphopenia is associated with the degree of severity of disease. Prognosis of various diseases including AP has been described by reduced lymphocyte count. Damage to the pancreas and distant organs caused by the recruitment of inflammatory cells is further aggravated by the several inflammatory mediators released by monocytes [20]. Thus, AP witnesses a rise in neutrophils, platelets and monocytes, whereas total lymphocyte count falls. So, there is a rise in the NLR and PLR, while LMR shows a declining trend.

Initially being used for other diseases, NLR was first employed in AP by Azab *et al.* [21]. ICU admission and prolonged hospitalization were found to be related to the NLR of the patients. Predictive ability of NLR measured in the first 48 hours for developing severe form of this disease was further corroborated by Suppiah *et al.* [3]. However, this study had its limitations which included a small sample size and most of the cases were mild acute pancreatitis. Cho *et al.* [19] investigated the predictive value of NLR and PLR for predicting persistent organ failure (POF) in GIAP. They determined cutoffs of 7.8 and 229.1 for NLR and PLR, respectively and concluded that these two variables were independent predictive factors for POF. Kokulu *et al.* [22] also concluded that a strong association exists between NLR, severity and systemic complications of AP. This study was limited by being a single center study and low number of cases of severe pancreatitis. All these above-mentioned studies are in agreement with the results in the present study.

The relation between RDW and mortality in AP has been established by Yao and Lv [23]. The exact process leading to this relationship is not clear. It may be due to disturbance in the homeostasis of red blood cells. There is impaired production of RBC's along with anomalous survival of these cells [24]. This is in agreement with our study as SAP is invariably associated with higher mortality.

Various inflammation markers were evaluated by Li Y *et al.* [20]. This study demonstrated that both NLR and RDW were good markers for overall survival in patients of AP, NLR being the best overall. G. Liu *et al.* [25] also worked on inflammation-based markers and concluded NLR, LMR and RDW were similar to BISAP for prediction of POF. These studies are similar to our study in some aspects and provided similar results.

In our study blood sugar levels could not correlate well with SAP like the other variables. Lankisch *et al.* [15] also reported that blood glucose did not correlate with organ failure however could detect pancreatic necrosis.

This study was conducted in the Himalayan state of Himachal Pradesh in North India. The peculiar aspect of this study was that it studied the relationships of various inflammatory markers with only GIAP. Gallstones are prevalent in north India, occurring in at least 7.4% of adults. These are about 2-4-fold more common in North Indians as compared to the South [16]. Therefore, it becomes imperative to study gallstone as a cause of AP individually. Such study has not been done in our state and will aid a lot in the management of these patients which are

frequent in our institute.

On comparison of the AUC's, PLR and NLR were better than BISAP and MCTSI. While the other parameters (except for blood sugar) performed rather similarly with minor differences. As seen in the previous studies, more importance has always been focused on NLR in acute pancreatitis. This study shifts the focus to PLR which is better than all other parameters. A combination of both NLR and PLR appears to be better with great sensitivity and acceptable specificity. If either one is raised, we can expect the patient to develop severe disease. Thus, these markers have a long way to go, and need larger studies to unearth their true potential.

This study had its limitations. First, this study was performed in a single tertiary institute with a predilection towards more severe cases presenting most of the time. Second, number of patients included in this study was small. Studies with higher sample size are required to yield better results. Third, the values of these markers were not followed up to see how they behave with improvement or deterioration of the disease. This study however, had its strengths too. To the best of our knowledge a study with all NLR, PLR, LMR and RDW in GIAP has not been done before. This is the first study in our state for predicting the severity of pancreatitis using such parameters. We calculated these values using blood samples drawn within first hour of arrival to the emergency department. This provided values which were not muddled by intravenous fluids and injectables. This is also the first study to use a combination of both NLR and PLR in GIAP only. This improved the sensitivity of detection of patients who would develop SAP.

5. Conclusion

To conclude, the relationship between NLR, PLR, LMR and RDW, and gallstone induced SAP is significant. All these variables have turned out to be good individual predictive factors for the disease under study. In previous studies done in this aspect, the focus mostly remained on NLR among various factors. However, in this study PLR turned out to the best predictive factor among all the tested haematological markers. We also suggest the use of a combination of both NLR and PLR for detection of as many cases of SAP as possible. Studies with greater sample size are required to further confirm the differences between these markers and use of their combinations as suggested. Such swift and high sensitivity markers would greatly help in assessing severity and deciding appropriate line of management in a resource limited environment resulting in better care.

Acknowledgment

We are thankful to all our patients who consented to participate in this study. We are also grateful to our institute 'Indira Gandhi Medical College, Shimla" for providing us a platform to carry out these studies.

Disclosure: The authors declare no conflict of interest.

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