"A Prospective Observational Study To Determine Association Of Platelet To Lymphocyte Ratio With Duration Of Hospital Stay Post Peptic Ulcer Perforation Repair"

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Abstract

Background : *the study was aimed to estimate the association of platelet to lymphocyte ratio with duration of hospital stay post-peptic ulcer perforation repair and determine the utility of platelet to lymphocyte ratio as a biomarker in predicting duration of hospital stay post peptic ulcer perforation repair. There are very few studies done on the subject.*

Methods : *This is a prospective observational study conducted between 2021 to 2022 at S.M.S. Medical college, Rajasthan. Preoperative blood samples were collected from 75 patients presenting with peptic perforation to calculate the platelet to lymphocyte ratio. Patients were categorised into two groups based on their hospital stay (<1 week vs. >1 week). The cut off value of platelet to lymphocyte ratio for prolonged was determined by plotting ROC (receiver operating characteristic) curve.*

Results : *The mean age of the patients was 52.6 with predominance in males (Hospital stay of more than 1 week was observed in 40 (53.3%) patients out of total 75. The duodenal ulcer perforations (82.7%) were more prevalent than the gastric ulcer perforations (17.3%). A positive association of higher leucocyte counts (p=.04), lower lymphocyte counts (p=.01) and higher platelet to lymphocyte ratio (p=.009) was observed in the group with hospital stay of >1 week.*

Conclusion : *Preoperative platelet to lymphocyte ratio predicts the postoperative hospital stay in peptic ulcer perforations and positively associated with prolonged hospital stay. There is a need of further studies to support the study findings.*

I. INTRODUCTION

Peptic ulcer disease is a common health problem with a lifetime risk of development ranging from 5% to 10% and incidence of 0.1 -0.3% per year.[1] Systematic review of epidemiological studies of PUD reported a pooled annual incidence of 0.10% to 0.19% and an overall prevalence of 0.12% to 1.50%.[2]With availability of better medical treatment, an incidence rate of peptic ulcer disease decreased over the years but mortality due to complications are still high and includes haemorrhage, perforation, and obstruction. Perforation has the highest mortality rate 15% among complications.[2]

Early diagnosis and appropriate management have significant effects on morbidity and mortality. Diagnosis tools include thorough clinical examination, blood investigations and radiology. Clinical presentation as abdominal pain and tenderness may be present in only two third of the patients.[3,4,5] First diagnostic investigation is radiograph of abdomen and chest to detect the presence of free abdominal air(present in 30-85% cases). A CT scan with contrast may improve diagnostic sensitivity and specificity can be used at higher centers.[6]

Blood investigations are although nonspecific can be used as a strong predictor of morbidity and mortality. Most important being hypoalbuminemia, others are leukocytosis and metabolic acidosis.[7,8,9]

In unstable patients rapid resuscitation targeted at restoring physiological parameters as mean arterial pressure >65 mmhg, a urine output 0.5 ml/kg/hr and lactate normalisation. As surgical intervention most peptic perforations can be accessed through upper midline incision and closed primarily and buttressed with a well vascularised omentum. A graham patch repair can be performed with healthy omentum for perforations with size >1 cm or with fibrotic edges that cannot be brought together without tension. Laparoscopic intervention is advised in stable patients with less pain and parenteral narcotic use without suture line complications postoperatively but hospital stay varies widely.[9]

In patients with perforated peptic ulcer with significant pneumoperitoneum or extra luminal contrast extravasation or signs of peritonitis surgical intervention is recommended as early as possible as mortality

increases with every hour of delay Buck et al.40 shown that from admission to surgery with every hour of delay was associated with an adjusted decreased probability of survival compared with the previous hour.[10]

There are multiple clinical predictors and prognostic scoring systems proposed as perforation is associated with high morbidity and mortality rates. These scoring systems are complex and difficult to calculate so there is minimum bedside utility.[11,12,13]

Laboratory markers have been investigated as a tool for prediction of prognosis of different diseases. Many biomarkers have been introduced to assess the severity of underlying inflammatory conditions, immune response, and coagulation status of patients.[14-18]

Platelet to lymphocyte ratio (P/LR) has been studied in various chronic inflammatory conditions and proved a significant predictor of prognosis. Neutrophil to lymphocyte ratio (N/LR) is also identified as an important biomarker in various medical conditions.

There are different studies suggesting N/LR and P/LR as important and reliable predictors in various medical conditions such as acute coronary syndrome, brain infarct, cerebral haemorrhage.19-25 In Percutaneous revascularization interventions preprocedural P/LR can predict prognosis.[19,20,21] P/LR found to be high in different conditions and predictor of bad prognosis such as mesenteric ischemia, peptic ulcer perforation and trauma. In mesenteric ischemia, a high P/LR predicts a bad prognosis with a high 30 day mortality rate.[22-25]

There are very few studies done focused on association of P/LR with peptic ulcer perforation repair. This study was aimed at investigating the association between the P/LR and the duration of hospital stays post peptic perforation repair as an outcome. It was hypothesised that high levels of P/LR is positively associated with prolonged duration of hospital stay.

II.   MATERIALS AND METHODS

This is a prospective observational cohort study for surgically treated cases of peptic ulcer perforation at Sawai Mansingh Medical college during January, 2022 to December, 2022. The inclusion criteria were all patients with age of >18 years old and were surgically treated with complete preoperative laboratory records.

Exclusion criteria included patients aged below 18 years, peptic perforation was due to non peptic ulcer cause, such as tumours, trauma, or iatrogenic, and relevant if preoperative laboratory records were not available.

Data were collected for the patients operated for peptic ulcer perforation from the general surgery department. Specifically, we collected data on age, gender, preoperative blood investigations (haemoglobin level, platelet count, leukocyte count, absolute neutrophil count, lymphocyte count, N/LR, P/LR, and mean platelet volume), operative reports (localization of perforation), and clinical outcomes (hospital length of stay and mortality). We calculated the P/LR and N/LR for all the patients.

The oral intake was gradually increased and advanced slowly as tolerated. Patients received an IV antibiotic regimen usually cefuroxime plus metronidazole along with IV ranitidine or proton pump inhibitor, and in case of duodenal perforation where H. pylori infection is considered, triple therapy was added as soon as the patient recovered for 4-6 weeks.

Patients were categorised into 2 groups based on the duration of hospital stay post peptic ulcer perforation repair (<1week vs. >one week). The approval for the study was taken from the institutional review board and Ethical committee

Sample of 75 was calculated at 95% confidence and 80% power to predict prolonged hospital length of stay on the basis of 11 independent variables including Platelet to lymphocyte ratio in postoperative perforation repair cases (as per seed article : Platelet to Lymphocyte Ratio Associated with prolonged length of hospital stay Post Peptic Ulcer Perforation Repair: An Observational Descriptive Analysis).

Statistical Analysis : Data were presented as proportions, medians (minimum–maximum range), or mean (±standard deviation; SD) as appropriate. Study variables were analysed and compared according to duration of hospital stay (≤ 1week versus >1 week). Differences between categorical variables were analyzed using the chi-square test, whereas Student's t test was performed to compare continuous variables, whenever applicable. The receiver operating characteristic (ROC) curve was plotted to determine the cutoff value for P/LR for predicting the prolonged hospitalisation (>1 week). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio and accuracy of the lymphocyte count, N/LR, and P/LR in predicting the prolonged hospitalisation were determined. A two-tailed p value < 0.05 was considered significant.

OUTCOME VARIABLES
1.   Age
2.   Gender
3.   Localization
Stomach
Duodenum

Laboratory Results
4. Haemoglobin level (g/dL)
5. Leukocyte count ($\times 10^3$/mcL)
6. Platelet count ($\times 10^3$/mcL)
7. Absolute neutrophil count ($\times 10^3$/mcL)
8. Lymphocyte count ($\times 10^3$/mcL)
9. Neutrophil to lymphocyte ratio
10. Platelet to lymphocyte ratio
11. Mean platelet volume

III. OBSERVATIONS AND RESULTS

A total number of 75 cases were studied based on the inclusion and exclusion criteria, who were admitted at the S.M.S. medical college and hospital during the period from the approval of the ethical committee to completion of the sample size.

MORTALITY RATE

OUTCOME	CASES	%
DEATH	9	12
DISCHARGED	66	88
TOTAL	75	100

Table 1.

Out of 75 subjects 66 (88%) discharged and 9 (12%) died during the hospital stay. There was no mortality occurred during the follow up 30 days after the surgery. The p value for age distribution between the two groups was 0.09.

LOCALISATION OF PERFORATION

SITE	CASES	%
Stomach	13	17.3
Duodenum	62	82.7
Total	75	100

Table 2.

It was observed that the duodenum was involved in 82.7% followed by antrum (12.0%) and pylorus (5.3%). The p value for perforation site distribution between the groups was 0.1.

Demographics, laboratory results and outcome of surgically treated perforated peptic ulcer patients (N= 75)

Age	52.62 ± 16.30
Gender	
Females	8
Males	67
Localization	
Stomach	13
Duodenum	62
Laboratory results	
Haemoglobin (g/dl)	12.16 ± 2.53

Leucocyte count (x10³/mcL)	12.33 ± 3.51
Platelet count (x10³/mcL)	253.51 ± 108.11
Neutrophil count (x10³/mcL)	9.5 ± 6.44
Lymphocyte count (x10³/mcL)	1.15 ± 0.37
Neutrophil to lymphocyte ratio	12.17 ± 15.13
Platelet to lymphocyte ratio	324.79 ± 45.72
Mean platelet volume	9.83 ± 1.77
Length of hospital stay	8.4 ± 3.68
Outcome	
discharged	66
Death	9

Table 3.

Characteristics of survivor and deceased

Variables	Survivors (n=66)	Deceased (n=9)
1. Age	49.6 ± 16.02	58.11 ± 17.33
2. Gender		
Females	6	2
Males	60	7
3. Localization		
Stomach	13	0
Duodenum	62	9
Laboratory results		
4. Haemoglobin (g/dl)	12.34 ± 2.48	10.8 ± 2.63
5. Leucocyte count (x10³/mcL)	11.83 ± 7.24	15.97 ± 7.5
6. Platelet count (x10³/mcL)	239.88 ± 106	353.46 ± 63.25
7. Neutrophil count (x10³/mcL)	9.05 ± 6.31	12.83 ±6.
8. Lymphocyte count (x10³/mcL)	1.2 ± 8.4	0.73 ± 0.29
9. Neutrophil to lymphocyte ratio	10.91 ± 14.86	21.36 ± 14.70
10. Platelet to lymphocyte ratio	291.23 ± 290.93	570 ± 250.48
11. Mean platelet volume	9.96 ± 1.69	8.84 ± 2.12

Table 4.

Table 5. Comparison of variables according to the hospital stay

VARIABLE	< 1 week n=35		> 1 week n=40		p value
Age (years)	51.8 ± 17.38		49.6 ± 15.44		0.28[T]
	min 18	max 80	min 19	max 89	
Gender					
Male	30	85.7%	37	92.5%	0.34[x]
Female	5	14.3%	3	7.5%	
Localization					
Stomach	7	80%	6	85%	0.1[x]
Duodenum	28	20%	34	15%	
Lab reports					
Haemoglobin (g/dl)	12.34 ±2.38		12.0 ± 2.67		0.7*
	Min 7.3	Max 18.1	Min 7.2	Max 16.4	
Leucocyte count (x10³/mcl)	10.78 ± 5.41		13.69 ± 8.53		0.04*
	Min 4.32	Max 29.33	Min 4.25	Max 35.64	
Platelet count (x10³/mcl)	222.91 ± 100		280.3 ± 108.87		0.01*
	Min 59.4	405	Min 56	Max 457.6	
Lymphocyte count (x10³/mcl)	1.35 ± 0.73		0.97 ± 0.54		0.01*
	Min 0.19	2.9	Min 0.14	Max 2.44	
Neutrophil count	8.24 ± 5.0		10.63 ± 7.37		0.04*
	Min 2.5	Max 24.53	Min 2.7	Max 30.14	
Neutrophil to lymphocyte ratio	8.6 ± 8.0		15.28 ± 18.92		0.05*
	Min 0.88	36.46	Min 2.05	Max 103.93	
Platelet to lymphocyte ratio	227.20 ± 175.65		409.02 ± 356		0.009*
	Min 37.12	Max 923.91	Min 58.11	Max 2090.5	
Mean platelet volume (fl)	9.8 ± 1.88		9.85 ± 1.69		0.6[x]
	Min 5.4	12.6	Min 6.2	Max 12.6	
Outcome					
Alive	33	94.2%	33	82.5%	0.09[x]
Dead	2	5.7%	7	17.5%	

*Test used for p value : t test ([T]); Chi square test ([x]); Mann-Whitney U test (*)*

The values described in table 5 are represented as mean ± standard deviation, percentage (%) or as absolute values. As shown in the table a total eleven variables were studied i.e. age, gender, localisation, preoperative haemoglobin, leucocyte count, platelet count, lymphocyte count, neutrophil count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV).

There were a total of 40 patients out of 75 who stayed for more than 1 week in the hospital and 9 out of 75 died. In this group the observations were suggestive that there is a significant association of platelet count (p value 0.01), neutrophil count (p = 0.04), lymphocyte count (p value 0.01), and PLR (p= 0.009) with duration of hospital stay. The mean with standard deviation for platelet to lymphocyte ratio (PLR) was found to be 409.02±356 and for neutrophil to lymphocyte ratio (NLR) it was 15.28 ± 18.92; there was no positive association found of other variables with the duration of hospital stay longer than one week.

Area under curve and Receiver Operating Characteristic Curve:

Area Under the Curve P/LR : duration of hospital stay					
Variable	Area under curve	Confidence Interval		Standard error	p value
		Lower Bound	Upper Bound		
P/LR	0.744	0.586	.902	0.801	0.009

Table 6. Area under curve (AUC) for P/LR with duration of hospital stay Area under curve found to be 0.744 for P/LR: duration of hospital stay with standard error of 0.801 and p value of 0.009.
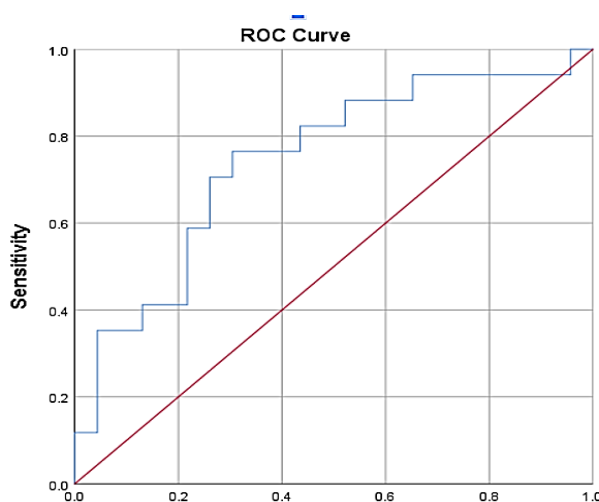
Fig 1. ROC curve for P/LR score

The area under the curve (AUC) used for discriminatory power of the study and calculated; it was 0.744 for P/LR and a p value of 0.009. In our study the cut off value of P/LR was found to be 293 with sensitivity of 76.2% and specificity of 73.4%. So the platelet to lymphocyte ratio P/LR can be used as a predictor of morbidity or severity.

IV. DISCUSSION

Peptic ulcer related perforation is a well-known surgical emergency and has high mortality and morbidity. The current study was focused on the objective to investigate if platelet to lymphocyte ratio (PLR) can be used as an important biomarker in predicting mortality and morbidity and to establish if there is any association between the PLR and duration of hospital stay (important indicator of disease course and worse outcome).[9,26]

Platelet to lymphocyte ratio has been studied as a biomarker for the predictability and severity of several chronic conditions, infections and sepsis. The association between the higher P/LR and severity in chronic diseases or postoperative complications is not well understood.

Initially it was reported in the prognostication of neoplastic diseases, such as breast cancer and hepatocellular carcinoma. Different studies over the years concluded that elevated P/LR is positively associated with increased systemic inflammation contributing to the prognosis of many disorders.[17,27] There is increasing evidence that deregulated cellular immunity is common in sepsis including pro- inflammatory or anti-inflammatory responses during different stages.[17,28] It may be due to excessive inflammatory response and altered immune response and thus resulting in the imbalance between body's response to inflammation and immunity mediators. Platelets contribute to the inflammatory process; chemokine produced by platelets such as PF-4

(platelet factor 4) and connective tissue activating peptide III can affect the inflammation. Lymphocytes are responsible for the immune response; low lymphocyte count may lead to altered immunity.

The study revealed that P/LR has a significant role in patients with prolonged hospital stay. The majority of the cases had perforation in the duodenum (82.7%) followed by the antrum (12%) and pylorus (5.3%) part. This is consistent with the study done by O. Aydin and F. Pehlivanli.[29]

Gender distribution: Peptic perforation was found to be more common in males as 89.3% cases were males and 10.7 % were females. In the group with hospital stay >week there were 92.5% males and 7.5% were females compared to the group with hospital stay <week having 85.7% males and 14.5% females; which suggests that there is higher incidence of peptic perforation in males with prolonged hospital stay. The same observations were made by P. Sivaram et al.[11]

Age distribution: It was observed that there was more prevalence with advancement of age; most cases were above the age of 60 years (26 cases) followed by 4th decade and 5th decade. There were only 10 cases with age < 30 years. Although the mean age in the group with hospital stay of more than one week was 49.6±15.44 years with minimum age of 19 and maximum age of 89 in comparison to the group having hospital stay less than one week with mean age of 51.8±17.38 years and minimum age of 18 and maximum age of 80 years. The p value for the age distribution between the two groups was 0.28. A same result was reported regarding age by Sivaram et al[11]. as age more than 50 years was associated with longer hospital stay.[11]

Duration of hospital stay: The average duration of hospital stay among the patients was 8.4 days and the majority of the patients stayed for more than one week. The average duration in the group with hospital duration more than one week was 10.85 days and maximum stay was for a duration of 21 days compared to the group with hospital stay less than one week having average hospital stay 5.82 and minimum hospital stay of 4 days and maximum hospital stay of 7 days. The reported duration of stay in patients of peptic perforations is between 7 to 11 days.[11]

The duration of hospital stay is associated with the disease course and the outcome in the form of morbidity and mortality. The longer duration is associated with higher chances of worse outcomes; it also has an impact on the cost and time spent by patients in hospital.[9, 26] so the duration of hospital stay was studied with P/LR as a predictor for the earlier.

The study suggests that there is a significant correlation between preoperative high P/LR, high leucocyte count, low lymphocyte count and high neutrophil count. There were no significant differences found between study groups in relation to age, sex, haemoglobin, mean platelet volume and neutrophil to lymphocyte ratio. These findings were consistent with the study done by O. Aydin and F. Pehlivanli.[29]

Complications and mortality: There were 7 deaths (17%) among the group with hospital stay more than one week and two deaths in the group of hospital stay with less than one week. The average age of all cases who died in the group with hospital stay >week was 52.90 and 4 out of 7 cases were above sixty years of age. The mean N/LR of the dead patients was 613±439. Most of them died of complications; pneumonitis followed by sepsis. The characteristics of the survivors and deceased are compared in table 6 it was observed that the mean age was higher in deceased with lower haemoglobin, higher leucocyte count, increased neutrophil counts, decreased lymphocyte count and significant increase in the platelet to lymphocyte ratio (mean P/LR was 570±250.48) The advanced age, comorbidity, malnutrition and altered immune response may have contributed to the mortality. O.Aydin et al.[29] reported 17% mortality in their study though the sample size was small.

The comparison of variables is done between the deceased and survivors in the table 7 a total 9 patients died in both groups and 66 survived and were discharged. In the deceased the mean age was 58.11 ± 17.33 years and in the survivor group it was 49.6 ± 16.02 years. The duodenum was involved in 100% deceased patients and 82.66% in the survivor group, may be due to higher incidence of duodenal perforations. The mean haemoglobin in the survivors was 12.34 ± 2.48 g/dl and 10.8 ± 2.63 g/dl in the deceased patients. There was higher leucocytosis observed in the deceased patients (15.97±7.5 x 10^3m/cL) in comparison to survivors (11.83 ± 7.24 x10^3 m/cL). The platelet counts were increased in the deceased group (353.56 ± 63.25 x10^3 m/cL), it was 239.88±106x10^3m/cL in the survivor group. The neutrophil counts were 9.05 ± 6.31 x10^3m/cL and 12.83 ±6.8 x10^3m/cL in the survivor and deceased patients respectively. The lymphocyte counts were significantly low in the deceased 0.73 ± 0.29 x10^3m/cL and higher in survivors 1.2±8.4 x10^3m/cL. The N/LRs were 10.91±14.86 and 21.36±14.70. The P/LRs were 570±250.48x10^3m/cL and 291.23±290.93x10^3m/cL respectively in the deceased and survivors. So the higher leukocyte counts, low lymphocyte counts, higher platelet counts and higher P/LR were significant in the deceased. Which is also observed by Y. shen, Xinmei Huang et al.[22](2019).The area under the curve (AUC) used for discriminatory power of the study and calculated; it was 0.744 for P/LR and a p value of 0.009. In our study the cut off value of P/LR was found to be 293 with sensitivity of 76.2% and specificity of 73.4%. So the platelet to

lymphocyte ratio P/LR can be used as a predictor of morbidity or severity. As there are very few studies available with small sample size related to the association of P/LR in surgical patients specifically post peptic perforation; we suggest further studies to be conducted for better conclusions.

V. CONCLUSION

There are different biomarkers available for critically ill patients presenting with different medical and surgical conditions. Most of them are complex to use and have very little bedside clinical value for prognostication. Platelet to lymphocyte ratio has been studied in the patients with chronic medical conditions. A very few studies with small sample sizes are available for surgical patients specifically for post peptic perforation repair. In this study preoperative platelet to lymphocyte ratio was found to be a significant biomarker in predicting the morbidity in the form of prolonged hospital stay post peptic perforation repair. Thus it should be further investigated so a predictive model can be developed to use platelet to lymphocyte ratio as a tool for better management of peptic perforation.

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