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Association of Platelet Indices to predict prognosis and severity of Acute Pancreatitis and its correlation with

established severity score of Acute Pancreatitis.

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Abstract

Acute pancreatitis is acute inflammation of the pancreas and a common cause of acute abdominal pain causing hospitalization. As regards the course of acute pancreatitis, it is clinically important to determine the severity of acute pancreatitis, since outcomes of mild acute pancreatitis is better than that of severe acute pancreatitis. Prediction of the course and prognosis of the disease is rather difficult. Several prognostic scoring systems and inflammatory markers have been studied with the purpose of determining the severity of acute pancreatitis and establishing the mortality risk accordingly. This study was performed to check the association of Platelet Indices to predict prognosis and severity of Acute Pancreatitis and its correlation with established severity score of acute pancreatitis. In this prospective observational study 50 adult patients of acute pancreatitis irrespective of sex ethnicity or etiology were included from department of medicine between june 2016 to December 2017. Platelet indices (platelet count, mean platelet volume, platelet distribution width and plateletcrit) and severity score of

pancreatitis (APACHE-II Score, RANSON acute Score, BISAP Score) were measured. Median APACHE -- II score in severe pancreatitis was 8.5 while in mild pancreatitis the median APACHE - II score was 3, median RANSON score in severe pancreatitis was 3 while in mild pancreatitis the median RANSON score was 2, median BISAP score in severe pancreatitis was 2.5 while in mild pancreatitis the median BISAP score was 2. We found that mean platelet count in severe pancreatitis group (440.9 thousand/ml) was higher as compared to mild pancreatitis group (342.4 thousand/ml), mean platelet distribution width in severe pancreatitis group (17.8%) was higher as compared to mild pancreatitis group (15.3%), mean plateletcrit in mild pancreatitis group (0.23%) was lower as compared to severe pancreatitis group (0.28), mean platelet volume in severe pancreatitis group (8.4fl) was higher as compared to mild pancreatitis group (8.3fl). In acute pancreatitis, increases in platelet count (p=0.001), platelet Distribution width (p<0.001) and plateletcrit (p=0.020) positively parallel with the increases in APACHE-II, RANSON Score, CRP and erythrocyte sedimentation rate but no statistically significant (p=0.769) relation between acute pancreatitis and mean platelet volume. BISAP score was also not has statistically significant correlation with platelet indices, Thus in this study we conclude that platelet indices (platelet count, platelet distribution width and plateletcrit) are important inflammatory prognostic biomarkers for assessing severity of acute pancreatitis. **Keywords:** Acute pancreatitis, APACHE-II Score, BISAP Score, Platelet indices, RANSON Score.

Introduction

Acute pancreatitis (AP) is a systemic inflammatory disease that can have various clinical courses. While majority of the acute pancreatitis cases heal without sequels, 10-20% of these can have a severe course, and out of them 30% can be fatal.^[1, 2] Mortality can be prevented with treatment given by diagnosing the highrisk patients in the early period^[3] According to revised Atlanta Criteria, AP is divided into three groups as mild, moderate and severe. There are no local/systemic complications or organ failure in mild AP, pancreatitis episode becomes milder or limits itself within a period less than 7 days. In AP with medium severity, transient organ failure lasting less than 48 hours or local complications (peripancreatic fluid collection. pancreatitic necrosis) or systemic complications (exacerbation of a previously existing disease) are observed. In severe AP however, organ failure lasts for more than 48 hours.^[4, 5] AP is an inflammatory disease with various clinical presentations and the process following the onset of inflammation is the same in almost all the patients, whatever the underlying cause is. In this context the most frequently used scoring systems include the Ranson criteria, Computed tomography severity index (CTSI), Acute Physiology and Chronic Health Evaluation II (APACHE-II) and Bedside index for severity in acute pancreatitis (BISAP) scoring systems. Together with this, all the scoring systems have their own pros and cons. Ranson criteria is the method that is used most frequently in practice to assess the severity of Acute pancreatitis. Together with this, its failure in providing the possibility of a clear assessment before the completion of the first 48 hours following admission and failure in determining the mortality risk are its most important disadvantages.^[6] The most important advantage of the APACHE-II scoring system is that it can be used to determine the severity of pancreatitis even on the day of application to the hospital. However, multitude and complexity of parameters in APACHE II system are the most important disadvantages.^[7] CTSI scoring system allows evaluation of pancreatic and peripancreatic local complications through the use of contrast tomography. However, it is rather insufficient as regards the systemic inflammatory response developing secondary to acute pancreatitis. The few studies (Mimidis et al^[8], Akbal et al^[9], Yavuz Beyazit et al^[10]) conducted for establishment the relation between the severity and prognosis of Acute pancreatitis and platelet indices {Mean platelet volume (MPV), platelet count, plateletcrit (PCT) and platelet distribution width (PDW)} on the prognosis of Acute pancreatitis but not well proved. Over the last several decades, a new paradigm of platelet function has evolved. Platelets, long forgotten hemostatic cells, were demonstrated to be versatile immune effector cells engaged in every compartment of the immune system. Platelets avidly interact with immune cells, endothelial cells, neutrophils, and monocytes in particular. Platelets were shown to propagate and modulate the inflammatory response of other immune cells in sterile inflammatory diseases, such as atherosclerosis and

metabolic diseases, acute lung injury, ischemia reperfusion, autoimmune diseases and acute pancreatitis. Platelets were recently shown to be involved in adaptive immunity and possibly link innate and adaptive responses together.^[11] Several of these scoring systems have been developed to assist the clinician in the assessment of the severity of AP. The most commonly used systems are the RANSON criteria, The Acute Physiology And Chronic Health Evaluation II(APACHE)^[12-17] and BISAP SCORE. The platelet indices offer valuable information about the morphology and maturity of platelets but they are under reported. So in this study, we aimed at determining if there is any correlation between the Ranson's criteria, BISAP, APACHE-II, CRP, and erythrocyte sedimentation rate parameters, of which the relation to the prognosis of Acute pancreatitis is known, with the Platelet count, MPV, PCT and PDW.

Material and methods

This prospective observational study was conducted between june2016 to December 2017 in department of general medicine, J.L.N. Medical College and Associated group of hospitals, Ajmer, Rajasthan. The subject for the study were selected from the patients attending medical outdoor and admitted in the various medical wards, 50adult patients of acute pancreatitis irrespective of sex ethnicity or etiology were included. After admission with written valid consent, clinical examination was carried out and relevant investigations were performed. All data was recorded as per the enclosed preformed and the severity of pancreatitis was assessed by APACHE, RANSON and BISAP scoring system.

Inclusion criteria

Patients of acute pancreatitis diagnosed on clinical, biochemical and radioimaging ground.

Exclusion criteria

Following patient were excluded from the study, Patients with hematologic diseases, Patients with body mass indices greater than 30, Patient those using drugs causing thrombocytopenia, Patients with advanced cardiac diseases and Patient with other cause of thrombocytopenia (viral fever, malaria, leukemia).

Statistical Analysis

Categorical data was expressed as proportion and analyzed using Chi square test. Quantitative data was expressed as mean and standard deviation and median and range was also depicted. Difference in mean was analyzed using student t test. Ordinal data was expressed as median and range and was analyzed using Mann Whitney test. Correlation between scores and platelet indices was determined using Spearmann correlation coefficient. A p value <0.05 was taken as statistically significant. All analysis was done using Epi Info statistical software.

Routine investigation

Blood Sugar, Serum Amylase, Lipase, ABG Analysis, Blood Urea, Serum Creatinine, Lft, Lipid Profile, Serum Electrolytes, Urine Complete ,X-ray chest ,FPA (if needed),CECT abdomen (if needed),MRI abdomen (if needed).

Special investigation : CBC (by coultior analysis) – Sample collected in EDTA vial, 20µl whole blood taken by auto analyzer by Sysmex Analyzer, ESR (byThe Westergren method), CRP, PLATELET INDICES (coultior analysis)

Mean platelet volume

It is the measurement of the average size of platelets in the blood.^[18-22]

Normal range of MPV is between 7.4 to 10.4 fL.^[18-22] MPV is calculated by dividing Plateletcrit by platelet count.^[23]

Platelet distribution width

PDW reflects the variability in the platelet size and it is therefore increased in presence of platelet anisocytosis, Normal PDW range is 9 to 14 fL. ^[22,23]

Plateletcrit

PCT is the volume occupied by platelets in the blood as a percentage and calculated according to the formula, PCT = platelet count \times MPV / 10,000,The normal range for PCT is 0.22–0.24%.

Results and Discussion

Acute pancreatitis (AP) is an inflammatory disease with various clinical presentations and classified under two headlines primarily as the biliary and non-biliary disease. The process following the onset of inflammation is the same in almost all the patients, whatever the underlying cause . Clinical diagnosis of AP is made based on the revised Prediction of the course and prognosis of the disease is rather difficult. For this reason, several prognostic scoring systems and biochemical markers have been studied to predict the prognosis of the disease and risks of mortality and morbidity. The most commonly used biochemical markers include the trypsinogen activation peptide, Procalcitonin, PMN-elastase, Phospholipase A2, TNF- α , IL-6 and IL-8 are not easily available and costly .Few studies reported that platelet count and platelet derivatives are used as biochemical markers. Platelets were known as non-immune blood cells originating from megakaryocytes. It was believed that platelets were involved only in primary hemostasis until the recent years. However, it has been shown in the studies of the recent years that platelets play a role as the proinflammatory cells in many inflammatory processes as well as their hemostatic functions. The present study was conducted on 50 patients who presented with acute pancreatitis to assess the role of platelet indices as a prognostic marker in severity of acute pancreatitis. After taking relevant history and written consent from the patient, these patients were subjected to complete clinical examination, routine investigation and special investigation like ABG and Platelet indices. Severity of AP is assessed by APACHE, RANSON and BISAP scores.

In our study the mean age of Severe pancreatitis group (71.5 years) was higher as compared to Mild Pancreatitis (50.2) and this difference was statistically significant(p<0.001). In this study minimum age of patient with AP was 23 and maximum is 84 years. We found more chances of severe AP with increasing age. In one another study (**GI Papachristou** *et. al.*²⁴) the mean age of Severe pancreatitis group (49.4 years) was higher as compared to Mild Pancreatitis (39.6).

In our study there were more female patients (76.5%) in Mild pancreatitis group as compared to Severe pancreatitis group (37.5%). Application of Chi square test revealed that Male gender is significantly associated with Severe Pancreatitis (<0.05). In one another study(**GI Papachristou** *et. al.*²⁴) there were more female patients (66.70%) in Mild pancreatitis group as compared to Severe pancreatitis group (40.40%).

Present study reveals that mean hemoglobin in Mild pancreatitis group (13.4 gm/dl) was higher as compared to Severe pancreatitis group (13.3 gm/dl) however, this difference was statistically not significant (p=0.844).

Present study shows that mean AST in Mild pancreatitis group (240.9 U/L) lower as compared to Severe pancreatitis (328.2 U/L) and this difference was statistically significant (p=0.003).

Present study reveals that mean ALT in Severe pancreatitis group (509.9 U/L) was higher as compared to Mild pancreatitis group (226.5 U/L) and application

of unpaired t test this difference was statistically significant (p<0.001). In this study we found that mean Indirect bilirubin in Severe pancreatitis group (1.23 mg/dl) was higher as compared to Mild pancreatitis group (0.86 mg/dl) and this difference was statistically significant (p=0.005). Present study shows that mean Total bilirubin in Mild pancreatitis group(1.5 mg/dl) was lower as compared to Severe pancreatitis group (2.1 mg/dl) and this difference was statistically significant (p=0.009).

In our study the mean Amylase level in Mild pancreatitis group (2953 U/L) was higher as compared to Severe pancreatitis group (2475 U/L) however, application of unpaired t test showed that this difference was statistically not significant (p=0.362). In one another study(**Y. I. Kibar** *et. al.*²⁵) The mean Amylase level in Mild pancreatitis group (1755 U/L) was higher as compared to Severe pancreatitis group (1720 U/L) however, application of unpaired t test showed that this difference was statistically not significant (p=0.142)

In our study the mean Lipase level in Severe pancreatitis group (1735 U/L) was higher as compared to Mild pancreatitis group (1664 U/L) however, application of unpaired t test revealed that this difference was statistically not significant (p=0.809). The elevation of serum lipase generally parallels the serum amylase level in AP. However, the serum lipase level often remains elevated longer, making it more useful to diagnose pancreatitis after symptoms have subsided. Lipase is considered more specific than amylase for pancreatic tissue injury. In one another study(**Y. I. Kibar** *et. al.***²⁵**) the mean Lipase level in Severe pancreatitis group (2809 U/L) was higher as compared to Mild pancreatitis group (2651 U/L) however, application of unpaired t test revealed that

this difference was statistically not significant (p=0.305). It is important to note that a correlation has not been found between the degree or trend of serum amylase and lipase elevation with the amount of structural damage of the pancreas or severity of AP.In our study the mean LDH in Severe pancreatitis group (571.9 U/L) was higher as compared to mild pancreatitis group (344.1 U/L) and this difference was statistically significant (p<0.001). Elevated LDH is observed in disease conditions such as tissue injury, necrosis, hypoxia, hemolysis or malignancies. LDH is clarified as a prognostic factor for severe type of AP, pancreatic necrosis, infection and mortality in AP. In one another study (J.-J. Lei et. al.²⁶) the mean LDH in Severe pancreatitis group (280-1 U/L) was higher as compared to mild pancreatitis group (230.7 U/L).

In our study the mean CRP level in Severe pancreatitis group (9.79 mg/L) was higher as compared to Mild pancreatitis group (2.70 mg/L) and this difference was statistically significant (p<0.001). C-reactive protein (CRP), is a commonly used marker for distinguishing between a mild and severe acute pancreatitis attack. Damage to the pancreas in acute pancreatitis and the intensity of the organism response (i.e., the acute-phase response) is accompanied by a substantial increase in the serum CRP level, which is the most significant reactant in this response, as a result of hepatocyte stimulation by cytokines. In one another study (**Y. I. Kibar** *et. al.*²⁵) the mean CRP level in Severe pancreatitis group (10.7 mg/L) was higher as compared to Mild pancreatitis group (6.18 mg/L).

In our study the mean ESR level in Severe pancreatitis group (64.5 mm in 1^{st} hour) was higher as compared to Mild pancreatitis group (41.7 mm in 1^{st} hour) and this difference was statistically significant (p<0.001). ESR is the well established inflammatory marker that's why

increase in inflammation with severity of AP. In one another study (**S. Pongprasobchai** *et. al.*²⁷) the mean ESR level in Severe pancreatitis group (77 mm in 1st hour) was higher as compared to Mild pancreatitis group (50 mm in 1st hour).

In our study the Mean APACHE –II score in Severe Pancreatitis was 8.25 with a range of 5 – 12, while in Mild pancreatitis the median APACHE – II score was 3.21 ranging from 0–8. Application of Mann Whitney Rank sum test revealed that this difference was statistically significant (P<0.001). In one another study(**J. H. Cho et. al.**²⁸) the Mean APACHE –II score in Severe Pancreatitis was 10.80 with a range of 5 – 12, while in Mild pancreatitis the median APACHE – II score was 6.50 ranging from 0–8.

In our study the mean RANSON score in Severe pancreatitis was 3.06 with a range of 1 - 4, while in Mild pancreatitis the mean RANSON score was 1.88 ranging from 0–4 and this difference was statistically significant (p<0.001). In one another study(**P. Huang** *et. al.*²⁹) the mean RANSON score in Severe pancreatitis was 4.76 with a range of 1–4, while in Mild pancreatitis the mean RANSON score was 3.07 ranging from 0–4.

In our study the Mean BISAP score in Severe pancreatitis was 2.09 with a range of 1–4, while in Mild pancreatitis the mean BISAP score was 1.4 ranging from 0–4 and this difference was statistically not significant (p=0.208). In one another study (**J. H. Cho** *et. al.*²⁸) the Mean BISAP score in Severe pancreatitis was 1.90 with a range of 1–4, while in Mild pancreatitis the mean BISAP score was 1 ranging from 0–4. BISAP score more or equal to 3 was associated with an increased risk of developing organ failure, persistent organ failure and pancreatic necrosis. Thus the BISAP score represents a simple way to identify patients at risk

of increased mortality and the development of intermediate markers of severity within 24 hrs of presentation.

In our study the mean Platelet count in Severe pancreatitis group (440.9 thousand/ml) was higher as compared to Mild pancreatitis group (342.4 thousand/ml) and difference was statistically significant (p=0.001). In one another study (**Y. Bilgic** *et. al.*³⁰) the mean Platelet count in Severe pancreatitis group (440 thousand/ml) was higher as compared to Mild pancreatitis group (334 thousand/ml).

In our study the mean Platelet Distribution Width (PDW) in Severe pancreatitis group (17.8%) was higher as compared to Mild pancreatitis group (15.3%) and difference was statistically significant (p<0.001). There is always a morphological change when platelet is activated in the environment of inflammation. Thus, PDW can be utilized as a sign of activated platelet releasing in some inflammatory diseases like AP. Studies have demonstrated that PDW level changes under specific conditions compared to healthy individuals. In one another study (**Y. Bilgic et. Al .**³⁰) the mean Platelet distribution width in Severe pancreatitis group (17.8%) was higher as compared to Mild pancreatitis group (14.9%).

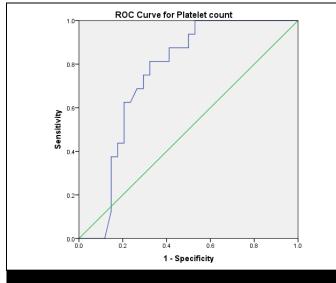
In our study the mean Plateletcrit (PCT) in Mild pancreatitis group (0.23%) was lower as compared to Severe pancreatitis group (0.28%) and this difference was statistically significant (p=0.020). In one another (**Y. Bilgic** *et. al.*³⁰) study the mean Plateletcrit in Mild pancreatitis group (0.23%) was lower as compared to Severe pancreatitis group (0.28%).

In our study the Mean Platelet Volume(MPV) in Severe pancreatitis group (8.4fl) was higher as compared to Mild pancreatitis group (8.3fl) however, application of unpaired t test showed that this difference was

statistically not significant (p=0.769). In one another study (**Y. Bilgic** *et. al.*³⁰) the mean Platelet volume in Severe pancreatitis group (7.8fl) was higher as compared to Mild pancreatitis group (8.1fl) however, application of unpaired t test showed that this difference was statistically not significant. In our study the Mean Duration of Hospital Stay (days) in Severe pancreatitis was 13 with a range of 6–40, while in Mild pancreatitis the mean Duration of Hospital Stay (days) was 5.7 ranging from 4–14 and This difference was statistically significant (p<0.001). In one another study (**J. H. Cho** *et. al.*²⁸) the Mean Duration of Hospital Stay (days) in Severe pancreatitis was 11.7, while in Mild pancreatitis the mean Duration of Hospital Stay (days) was 8.4.

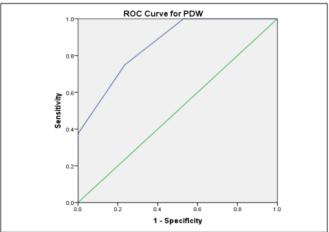
1. ROC curve for Platelet count in predicting severe pancreatitis

Area Under the Curve (95% Confidence	0.753 (0.619 - 0.886)
interval)	
P value	0.004 (S)
Optimal cutoff point	390*1000/dl
Sensitivity	81.3%
Specificity	68.6%



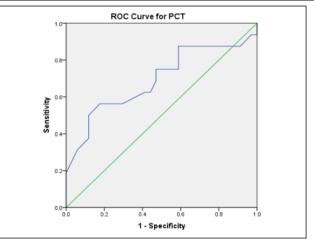
^{2.} ROC curve for PDW in predicting severe pancreatitis

Area Under the Curve (95% Confidence interval)	0.860 (0.758 -
	0.963)
P value	<0.001 (S)
Optimal cutoff point	16.5
Sensitivity	75%
Specificity	76.5%



3. ROC curve for PCT in predicting severe pancreatitis

Area Under the Curve (95% Confidence interval)	0.692 (0.519 - 0.866)
P value	0.030 (S)
Optimal cutoff point	0.295
Sensitivity	56.3%
Specificity	92.4%



4. ROC curve for MPV in predicting severe pancreatitis

Area Under the Curve (95% Confidence interval)	0.517 (0.318 - 0.717)
P value	0.843 (NS)
Optimal cutoff point	9.5
Sensitivity	43.8%
Specificity	79.4%

age

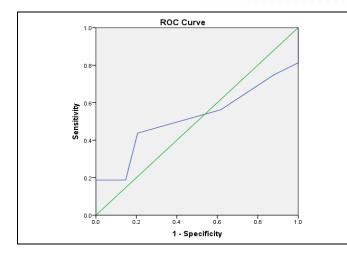


Table-1: The statistical correlation between platelet indices and prognostic scoring system in patients with mild pancreatitis

Platelet	APACHE	BISAP	Ranson	CRP	ESR
indices					
Platelet	0.018	-0.114	-0.034	-0.439*	-0.075
count					
PDW	-0.007	0.150	0.238	-0.290	-0.166
MPV	-0.092	-0.083	0.289	-0.125	0.079
PCT	-0.088	0.342*	-0.062	-0.175	-0.251

Table-2: The statistical correlation between platelet indices and prognostic scoring system in patients with severe pancreatitis

Platelet	APACHE	BISAP	Ranson	CRP	ESR
indices					
Platelet	-0.331	-0.103	0.534*	-0.193	-0.253
count					
PDW	0.198	-0.313	0.164	-0.239	-0.192
MPV	0.095	-0.130	0.254	-0.112	-0.423
РСТ	0.333	0.314	-0.352	0.194	0.201

Table-3: Association of APACHE score with other

indices

Other indices	APACHE <8	APACHE ≥8	P value
MPV (fl)	8.3 ±1.58	8.4 ± 2.53	0.796 (NS)
Plateletcrit (%)	0.23 ± 0.064	0.28 ± 0.079	0.020 (S)
PDW (%)	15.3 ± 1.73	17.8 ± 1.34	<0.001 (S)
ESR (mm)	41.7 ±16	64.5 ± 11.7	<0.001 (S)
CRP (mg/L)	2.70 ± 1.61	9.79 ± 5.07	<0.001 (S)
Platelet count	3.42 ± 1.09	4.41 ± 0.52	<0.001 (S)
(lakh/dl)			

Table-4: Association of RANSON score with other indices

Other indices	RANSON <3	RANSON ≥3	P value
MPV (fl)	7.78 ±1.67	8.96 ± 2.01	0.028 (NS)
Plateletcrit (%)	0.25 ± 0.07	0.24 ± 0.07	0.681 (NS)
PDW (%)	15.3 ± 1.81	17 ± 1.78	0.002 (S)
ESR (mm)	43.3 ±18.9	55.7 ± 15	0.015 (S)
CRP (mg/L)	3.67 ± 3.41	6.49 ± 5.30	0.028 (S)
Platelet count	3.47 ± 1.09	4.05 ± 0.93	0.050 (NS)
(lakh/dl)			

Table-5: Co	mparison	of	pancreatitis	patients	according
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to severity of disease

Parameters	Mild	Severe	P value
	Pancreatitis	Pancreatitis	
Age	50.2	71.5	< 0.001 (S)
Gender (Female/ Male)	71.5	6/10	0.018 (S)
Mean Hemoglobin	13.4	13.3	0.844 (NS)
(gm/dl)			
Mean AST(U/L)	240.9	328.2	0.003 (S)
Mean ALT (U/L)	226.5	509.9	< 0.001 (S)
Mean Total bilirubin	1.5	2.1	0.009 (S)
(mg/dl)			
Mean Indirect bilirubin	0.86	1.23	0.005 (S)
(mg/dl)			
Mean LDH(U/L)	344.1	571.9	< 0.001 (S)
Mean Amylase (U/L)	2953	2475	0.362 (NS)
Mean Lipase level (U/L)	1664	1735	0.809 (NS)
APACHE-II score	3.21	8.25	< 0.001 (S)
RANSON score	1.88	3.06	< 0.001 (S)
Mean BISAP score	1.40	2.09	0.208(NS)
Mean Platelet	342.4	440.9	0.001 (S)
count(*1000/ml)			
Mean Platelet	15.3	17.8	< 0.001 (S)
Distribution Width (%)			
Mean Plateletcrit (%)	0.23	0.28	0.020 (S)
Mean Platelet Volume	8.3	8.4	0.769 (NS)
(fl)			
Mean CRP level (mg/L)	2.70	9.79	< 0.001
Mean ESR (mm in 1 st	41.7	64.5	< 0.001 (S)
hour)			
Duration of Hospital	5.7	13	<0.001 (S)
Stay (days)			

Conclusion

This Prospective observational was conducted on platelet indices as prognostic biomarkers in acute pancreatitis and compared with classical prognostic scoring system (APACHE-II, , RANSON, BISAP). The

severity of acute pancreatitis was assessed by APACHE-II, RANSON and BISAP scoring system. In acute pancreatitis, increases in platelet count (p=0.001), Platelet Distribution Width (p<0.001) and Plateletcrit (p=0.020) are positively correlated with the increases in APACHE-II Score, RANSON Score, CRP and erythrocyte sedimentation rate but no statistically significant relation with the Mean Platelet Volume (p=0.769). BISAP score was not statistically significant correlated with platelet indices, Thus in this study we conclude that platelet indices(platelet count, Platelet Distribution Width and Plateletcrit) are important inflammatory prognostic biomarkers for assessing severity of AP. platelet indices are easily available, cost effective biomarker however, more large scale scientific and clinical research is needed before establishing the role of platelet indices as prognostic biomarkers in acute pancreatitis.

Abbreviation: MPV-Mean platelet volume, PDW-Platelet distribution width, PCT-Plateletcrit, AP-Acute pancreatitis.

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