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Original Research Article.

Significance of Early Coagulation Parameters Screening in Predicting Severity of Acute Pancreatitis

Nidhi Sharma[1], Sandhya Gulati[2], Mohit Punjabi[3*], Gaurav Kumar Gupta[4], Rajesh Gulati[5]

[1]Assistant Professor, [2]Senior Professor, [3*]Resident,
Department of Pathology, SMS Medical College, Jaipur, Rajasthan, India.
[4]Associate Professor, Department of Gastroenterology, SMS Medical College, Jaipur, Rajasthan, India.
[5]Senior Physician, Government Hospital, Bassi, Jaipur, Rajasthan, India.

ABSTRACT

Purpose: Hemostasis pathways disturbances occur in acute pancreatitis (AP) due to crosslinkage between inflammation and coagulation. The study was done with the aim to find out the spectrum of early (72 hrs) alteration of coagulation profile {prothrombin time (PT), activated partial thromboplastin time (APTT), Fibrinogen level} and Platelet count in AP, to see the correlation, if any, with severity of AP.

Methods: 100 patients of AP fulfilling the inclusion and exclusion criteria were selected. Diagnosis of AP was based on history, clinical examination, serum amylase, lipase level, abdominal ultrasonography (USG) and Computed Tomography (CT). PT, APTT and serum fibrinogen level were processed in a fully automated coagulation analyser. Platelet count was analyzed in an automated hematology analyser.

Results: Age range was 06 – 81 years. Patients were graded into mild, moderate and severe AP by Mortele modified CTSI scoring. There was significant difference among the mean of PT { 22.2%, 35.5%, 40% of mild, moderate severe AP respectively}, while none in the mean of APTT, serum fibrinogen and platelet count in the three grades of AP. Severity index was positively correlated only with PT. A cut–off of 13.6 seconds for PT and 598 mg/dl for fibrinogen could discriminate mild AP from moderate plus severe cases with sensitivity of 85% and specificity of 67%.

Conclusion: This study correlates the coagulation parameters with severity of AP. We evaluated that PT can be used as marker of severity in patients with AP. Deranged coagulation parameters at admission are an indication for early referral.

Keywords: Acute Pancreatitis, Coagulation, Severity, PT, APTT, Fibrinogen.

***Correspondence to:**

Dr. Mohit Punjabi,
Resident,
Department of Pathology,
SMS Medical College, Jaipur, Rajasthan, India.

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INTRODUCTION

Acute pancreatitis (AP) is a potentially lethal disorder with no specific medical treatment. AP induces a strong inflammatory response which is independent of the initiating factor for acinar cell damage.[1] In turn, these mediators can influence hemostasis as the pathways of inflammation and coagulation are intimately linked. The contribution of disturbed haemostasis due to platelets (which constitute the primary hemostasis) and coagulation pathways (which constitute the secondary hemostasis) in prognosis of acute pancreatitis, although extensively studied, remains obscure.[2] Fibrinogen is an acute-phase reactant and is elevated in inflammatory conditions, tissue damage, infections, cancer and strokes.[3] Its role in the prognosis of acute pancreatitis needs to be studied. Hence, the present study was done with the aim to find out the spectrum of altered coagulation profile among patients with acute pancreatitis and to determine the platelet count, PT, APTT and fibrinogen level among patients with AP and see the correlation, if any, with severity.

MATERIALS & METHODS

It was a descriptive type of observational study of 100 patients, of AP carried out at a tertiary care institute from June 2018 till November 2019. Study population was determined by applying the inclusion (all cases of acute pancreatitis during the study period) and exclusion criteria (patients with known bleeding disorder/ malignant tumour/on oral anticoagulant drugs hemolysed samples/ patients who did not give consent/ late referral). Sample size was calculated at 95% confidence level, alpha error of 0.05, as 94 subjects, which were rounded of to 100 subjects.

The patients were divided into groups: mild AP (MAP, 09 patients), moderately severe AP (MSAP, 76 patients), and severe AP (SAP, 15 patients), according to the Mortele modified CTSI scoring for diagnosis and classification of acute pancreatitis. There were no significant differences in gender or age between the groups (P>0.05). This study was conducted in accordance with the declaration of Helsinki, and it obtained the approval from the Ethics Committee of the institute. Written informed consent was obtained from all participants.

Clinical History

The clinical data obtained from requisition form included the following details: name, age and sex of the patient, chief complaints, dietary history (including alcohol consumption), any medications, blood transfusion, family history). The patients were diagnosed as acute pancreatitis if they had two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) (2) serum lipase or amylase activities at least three times greater than the upper limit of normal (3) characteristic findings of acute pancreatitis on Contrast-Enhanced Computed Tomography (CECT) or transabdominal ultrasonography. On the 72 hours after admission, all subjects had body temperature, respiratory rate, blood pressure, and heart rate measured, and arterial blood gas analysis, serum electrolytes, liver and kidney function, routine blood and other tests performed.

Treatment: All patients were given standard care for AP.

For Coagulation Parameters: 2.7ml of venous sample was collected on the 72 hours after admission from each patient without applying pressure cuff in a BD vacutainer that contained buffered sodium citrate 0.109M, 3.2%. Sample was taken in a ratio of 9:1 (9 part blood to 1 part anticoagulant). The blood was then mixed with anticoagulant by inverting the container 4-6 times. Samples were then centrifuged at 2000 rpm for 10 minutes at room temperature. Platelet poor plasma was then separated out and transferred to three aliquots. One aliquot was used to perform the test in the fresh state. Out of the remaining two aliquots, one was stored at -20^{o}C while the other one was stored at -80^{o}C for future use, if any. None of the samples were thawed and refrozen. PT, APTT and fibrinogen level were processed in STA Compact (a fully automated coagulation analyser) which makes use of the electromechanical principle with a steel ball were performed on the fully automated stago analyzer using Neoplastine Cl Plus kit (for PT analysis) and Diagnostic kit Cephascreen (for APTT analysis).Diagnostic kit Liquid FIB manufactured by Diagnostica Stago was used for fibrinogen level analysis. Normal and abnormal controls were run first in the machine on a daily basis.

Platelet Count: 3 ml venous sample was taken from each patient in ethylene-diamine-tetra-acetic acid (EDTA) vial. The samples were run in automated hematology analyser (Sysmex XT4000i) for platelet count.

Data Management and Statistical Analysis

Qualitative data was expressed in percentage, proportion, graph, and tables and analysed by appropriate statistical test and Quantitative data was expressed in mean, standard deviation and analysed by appropriate statistical test. p value <0.05 will be taken as significant.

Table 1: Coagulation parameters alteration in relation to grade of acute pancreatitis

Parameter	Grade	Normal	Altered	Range	Mean±SD	Total Cases n (%)	'p' Value*
PT (In seconds)	**Mild AP**	7 (77.8%)	2 (22.2%)	12.1–21.8	14.78±2.99	9 (100%)	0.046
	Moderate AP	49 (64.5%)	27 (35.5%)	13.2–23.9	15.72±1.87	76 (100%)	
	Severe AP	9 (60%)	6 (40%)	12.7–32.5	17.50±5.77	15 (100%)	
APTT (In seconds)	**Mild AP**	5 (55.5%)	4 (44.5%)	27.2–56.7	37.99±10.04	9 (100%)	0.881
	Moderate AP	24 (31.6%)	52 (68.4%)	26.3–107.8	38.14±10.08	76 (100%)	
	Severe AP	4 (26.6%)	11 (73.4%)	28.1–47.5	30.19±6.13	15 (100%)	
Fibrinogen (Mg/dl)	**Mild AP**	1 (11.1%)	8 (88.9%)	382–881	624.11±153.00	9 (100%)	0.145
	Moderate AP	15 (19.7%)	61 (80.3%)	220–977	544.21±163.51	76 (100%)	
	Severe AP	3 (20%)	12 (80%)	388–679	502.87±100.13	15 (100%)	
Platelet count (x 10^6/dl)	**Mild AP**	7 (77.8%)	2 (22.2%)	77–266	186.89±66.42	9 (100%)	0.299
	Moderate AP	41 (53.9%)	35 (46.1%)	7–782	205.01±125.52	76 (100%)	
	Severe AP	10 (66.6%)	5 (33.4%)	43–584	262.67±148.25	15 (100%)	

Table 2: Correlation among coagulation parameters

		Severity index	Age	PT	APTT	Fibrinogen	Platelet count
Severity index	**'r' coeff.**	1	.069	.215*	–.024	–.088	.159
	p–value		.496	.031	.810	.385	.113
Age	**'r' coeff.**		1	.003	.030	.238*	–.006
	p–value			.978	.768	.017	.953
PT	**'r' coeff.**			1	.230*	–.052	–.016
	p–value				.022	.609	.877
APTT	**'r' coeff.**				1	.244*	–.056
	p–value					.015	.577
Fibrinogen	**'r' coeff.**					1	.017
	p–value						.864
Platelet count	**'r' coeff.**						1
	p–value						

Table 3: Comparison between Group A (mild) and Group B (moderate + severe cases) in terms of coagulation parameters

Variable	Group	N	Mean	Std. Deviation	P–value
Age (Years)	**A**	9	36.11	17.31	0.710
	B	91	38.12	15.24	
PT (Seconds)	**A**	9	14.778	2.99	0.229
	B	91	16.014	2.91	
APTT (Seconds)	**A**	9	37.989	10.04	0.982
	B	91	37.913	9.53	
Fibrinogen (Mg/dl)	**A**	9	624.11	153.00	0.113
	B	91	537.40	155.16	
Platelet (x 10^6/dl)	**A**	9	186.89	66.42	0.828#
	B	91	214.52	130.42	
Amylase (U/L)	**A**	9	761.44	605.81	0.430#
	B	91	746.57	886.09	
Lipase (U/L)	**A**	9	620.89	668.84	0.782#
	B	91	630.42	680.16	

Independent t–test, #Mann Whitney test

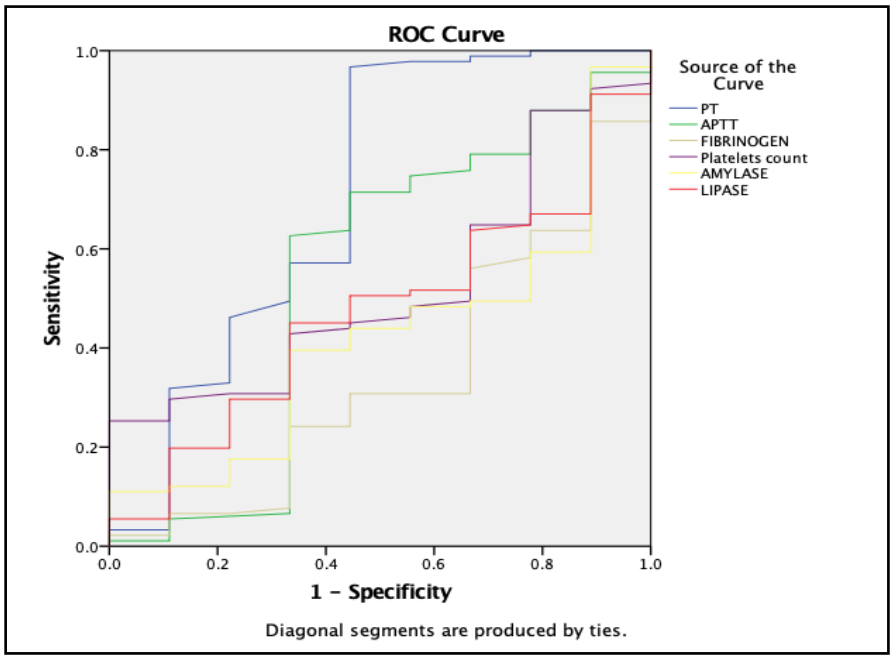

Figure 1: ROC curve of linear combination of PT, APTT, fibrinogen, platelet count, amylase and lipase as diagnostic test between group A and group B

OBSERVATION AND RESULTS

The present study included 100 consecutive patients of acute pancreatitis admitted in the gastroenterology ward during the study period. The age range was 06 – 81 years with a mean of 37.94 ± 15.35 years. Male patients were more in the present study making up 71% of total cases and female patients were 29%. Alcohol (45%) was found to be the most common cause of acute pancreatitis followed by gall stone (40%), idiopathic (11%) and traumatic (4%). Alcohol (63.4%) was found to be the most common cause of acute pancreatitis among the male patients, followed by gall stone (25.3%). In female patients gall stone (75.9%) was the most common cause of acute pancreatitis, followed by idiopathic (20.7%). Pain abdomen was the most common symptom present in all the (100%) patients followed by vomiting 55%, constipation 25%, abdominal distension 17% and fever in 12% of patients. Serum amylase was found to be increased in 91% of the patients. Serum lipase was found to be increased in 93% of the patients. In all the 100 cases USG findings was bulky/oedematous pancreas with ill-defined margins, with or without peripancreatic fluid collection, suggestive of acute pancreatitis. CT scan was done in all 100 cases of acute pancreatitis. Patients were graded into mild, moderate and severe pancreatitis by mortele modified CTSI scoring. Moderate grade formed the main bulk of cases comprising 76% of total cases, followed by severe grade 15% and mild grade 9%.

There was significant difference among the mean of PT in different categories of AP (table 1).No significant difference was found among the mean of APTT, serum fibrinogen and platelet count in three AP grades.

Severity index was positively (weak positive) correlated with PT with statistical significance. Severity index was positively (weak positive) correlated with platelet count but it was not statistically significant (table 2).

All patients were further classified into group A (Mild AP) and group B (moderate and severe AP) for statistical evaluation. When comparing there was no significant difference in the mean of any of the parameter (table 3).

ROC curve was plotted to see the prediction of moderate plus severe cases from mild cases using different coagulation parameters. Area under the curve was highest for PT (AUC=0.705) and lowest for Fibrinogen (AUC=0.342). None of the coagulation parameter was significant except PT (0.043) which had good discrimination (figure1).

Combined sensitivity and specificity of PT and serum fibrinogen was 85% and 67% respectively. That is, when a cut–off of 13.6 seconds for PT was taken and for fibrinogen a cut–off of 598 mg/dl was taken for discriminating mild cases of AP from moderate plus severe cases with combined net sensitivity of 85% and net specificity was 67%.

Table 4: Comparison of mean coagulation parameters in various studies

Studies	Mean PT (Seconds)	Mean APTT (Seconds)	Mean fibrinogen (mg/dl)	Mean platelet count (x 10^6/dl)
Badhal SS et al [4]	14.52	34.87	489.32	Not mentioned
Abdalla SE et al [5]	14.9	40.5	246.8	244.9
Rajkovic ST et al [6]	82.08	27.07	732.5	Not mentioned
Deng W et al [7]	18.19	31.23	Not mentioned	Not mentioned
Obied ASH et al [8]	31.06	57.33	Not mentioned	306.53
Radovanovic–Dinic B et al [9]	79.34	25.85	737	231.46
Mamun AA et al [10]	13.6	27.33	275.33	Not mentioned
Present study	15.90	37.92	545.20	212.03

DISCUSSION

The present study on coagulation profile in acute pancreatitis was done on 100 cases. Out of the total cases of acute pancreatitis, 35% cases had altered PT, 67% had altered APTT, 81% had altered fibrinogen and 42% cases had an altered platelet count. The mean in various studies is compared in Table 4.

Most patients were in early stage of the disease and did not have frank haemostatic disturbance This increased fibrinogen value in 81% of patients can be explained by the fact that fibrinogen is a acute phase reactant like CRP and high serum fibrinogen indicates a serious compensatory mechanism at work and can be increased with severe inflammation.[11]

Thrombocytopenia was noted in 33% of study group. Thrombocytopenia could be due to a) a part of ongoing DIC or b) manifestation of thrombotic microangiopathy.[12]

None of the coagulation parameter was significant except PT (0.043) which had good discrimination. A cut–off value of PT was 13.6 seconds, because the maximum sensitivity specificity product was achieved here. Patients with a value lower than 13.6 seconds had a mild form of AP (group A) and those with a values higher than or equal to the cut–off value had a moderate or severe form of AP (group B) with sensitivity of 55.6% and specificity of 96.7%.

Combined sensitivity and specificity of PT and serum fibrinogen was 85% and 67% respectively. That is, when a cut–off of 13.6 seconds for PT was taken and for fibrinogen a cut–off of 598 mg/dl was taken for discriminating mild cases of AP from moderate plus severe cases with combined net sensitivity of 85% and net specificity was 67%.

We evaluated that PT can be used as marker of severity in patients with acute pancreatitis. It is useful at primary level where general physician can do PT in patient with acute pancreatitis, if the value is 13.6 seconds or above, patients can be classified as moderate or severe acute pancreatitis and referred to higher centre at earliest.

The coagulation pathway along with the acute phase reactants play a significant role in the pathogenesis of acute pancreatitis which is reflected by the various coagulation parameters. This is a

unique study that tries to correlate the coagulation parameters with the severity of acute pancreatitis. The parameters that have been used in the study can be done even as routine tests and does not require costly equipments or expertise for evaluation. Deranged coagulation parameters at admission are an indication for early referral and hence serve as useful parameters. A cut–off value of PT was 13.6 seconds. Patients with a value lower than 13.6 seconds had a mild form of AP (group A) and those with a values higher than or equal to the cut–off value had a moderate or severe form of AP (group B) with sensitivity of 55.6% and specificity of 96.7%.

This study has paved the way for further studies on the relationship between coagulation parameters and severity and prognosis of acute pancreatitis.

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