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RESEARCH ARTICLE

The Role of Serum Procalcitonin Levels in Predicting Ascitic Fluid Infection in Ascitic Patients Admitted to Zagazig University Hospital in 2014.

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Abstract

Background: It is difficult to diagnose spontaneous bacterial peritonitis (SBP) early in ascitic patients. The aim of the study was to measure serum procalcitonin (PCT) levels
to obtain an early diagnostic indication of SBP in ascitic patients.
Methods: A total of 62 patients (mean age: 54.4 ± 10.7, 77.4% were males) hospitalized due to cirrhosis (n=57) or non-cirrhosis related (n=5) ascites were included in this study. Spontaneous bacterial peritonitis (SBP, 19.4%), culture-negative SBP (35.5%), bacterascites (6.5%), sterile ascites (30.6%) and non-cirrhotic ascites (8.1%) groups were compared in terms of procalcitonin levels in predicting ascites infection. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic performance of procalcitonin levels.
Results: Culture positivity was determined in 25.8% of overall population. Serum procalcitonin levels were determined to be significantly higher in patients with positive bacterial culture in ascitic fluid compared to patients without culture positivity (median (min-max): 3.35 (0.05–6.4) vs. 0.2 (0.05-1.9), p=0.000). Using ROC analysis, a serum procalcitonin level of >1.9 ng/mL (area under curve (AUC): 0.791, sensitivity: 75%, specificity: 100%, positive predictive value 100% and negative predictive value 92%) were determined to accurately help the diagnosis of bacterial peritonitis.
Conclusion: According to our findings, determination of serum procalcitonin levels seems to provide accurate and rapid diagnosis of ascitic fluid infection.

Introduction:-

More than 50% of patients develop ascites within 10 years of the diagnosis of cirrhosis. Spontaneous Bacterial Peritonitis (SBP) is a frequent and severe complication in such patients with liver disease and ascites (1). The 1-year probability of development of the first episode of SBP in end-stage liver disease patients with ascites is about 10% (2).Of patients with cirrhosis who have SBP, 70% are Child-Pugh class C. In these patients, the development of SBP is associated with a poor long term prognosis (3).

Clinical presentation of SBP is highly variable and nonspecific. A significant proportion (approximately 10%-30%) of patients with SBP may be even completely asymptomatic (4). Common symptoms and signs that are reported to have some association with SBP include fever, diarrhea, gastro intestinal bleeding, abdominal pain/tenderness, hepatic encephalopathy etc (5).To date, it remains a challenge for clinicians to arrive at an early diagnosis of SBP in cirrhotic patients with ascites because the early symptoms and signs are not obvious (6). Biomarkers with high sensitivity and specificity for the diagnosis of SBP are lacking.

The diagnosis of SBP was based on ascitic fluidpolymorphonuclear (PMN) leukocyte counts >250/mm3 and positive bacterial cultures without any evidence of an external or intra-abdominal source of infection or malignancy according to all of the available guidelines (7). However, on the one hand, despite the use of sensitive pathogen culture methods, ascites culture has been negative in as many as 60% of patients with clinical manifestations suggestive of SBP and with increased ascites neutrophil leukocyte counts (8).

On the other hand, performing an ascitic fluid culture is time consuming and is not always an available option in an emergency. Therefore, the discovery of easy to use, rapid and reliable diagnostic biomarkers for SBP was needed. Levels of procalcitonin (PCT), a propeptide of calcitonin with a long half-life of 25–30 h that is produced by peripheral blood mononuclear cells, significantly increases during the systemic response of an organism to an infection and has been hailed as a novel inflammatory biomarker for bacterial infections (9).

Serum PCT measurements have been reported to be superior to C-reactive protein in discriminating infectious from other inflammatory diseases, such as acute pancreatitis, cardiogenic shock and acute transplant rejection (10). Meanwhile, serum PCT can be rapidly and easily detected as early diagnostic biomarker for sepsis (9).However, the utility of PCT as a marker for the early diagnosis of SBP has been reported limitedly, with conflicting results (11).

Methods:-

Study population:-

A total of 89 patients hospitalized due to ascites with data on diagnostic abdominal paracentesis for ascitic fluid analysis and concomitant evaluation of serum procalcitonin levels were included in this study which was conducted in the Department of Internal Medicine in ZagazigUniversity Hospital betweenAugust 1st, 2014and December 25th, 2014.

In this cross sectional study for determination of the value role of serum procalcitonin levels in predicting ascites infection in cirrhotic and non-cirrhotic patients, 27 patients were excluded because of antibiotic use prior to admission. A total of 62 patients (mean age: 54.4 ± 10.7, 77.4% were males) hospitalized due to cirrhosis (n=57) or non-cirrhosis related (n=5) ascites were included in this study.

Inclusion Criteria:-

Adult hospitalized patients with ascites (cirrhotic and non-cirrhotic).

Exclusion Criteria:-

Patients diagnosed with clinical infection other than ascitic fluid infection and Patients who received antibiotics ten days prior to hospital admission were excluded.

The studied cases were subjected to the following:

Clinical evaluation:-

Full assessment of history was performed, with a special focus on recent onset of fever, abdominal pain, nausea, vomiting, and diarrhea, symptoms suggestive of hepatic encephalopathy, symptoms suggestive of associated infection anywhere in the body, especially urinary tract infection, previous episodes of ascitic fluid infection and history of prophylaxis, history of iatrogenic procedures (intravenous catheters — urinary catheters), lack of response to diuretics, history of diagnostic or therapeutic paracentesis, and history of gastrointestinal bleeding.

Thorough clinical examination was carried out, with a special focus on signs of hepatic decompensation in the form of signs of encephalopathy, signs of hypoalbuminemia (white nails, muscle wasting, bilateral lower limb edema, and ascites), and abdominal tenderness.

Imaging studies:-

Abdominal ultrasonography examination was performed, with a special focus on the liver and spleen in terms of size and echogenicity and excluding the presence of hepatocellular carcinoma. Portal vein diameter and the presence of ascites.

Laboratory investigations:-
A blood sample was drawn for routine laboratory investigations (CBC, liver function tests, kidney function tests, ESR & CRP) as well as serum procalcitonin level. Serum levels of PCT were measured by an electrochemiluminescence immunoassay 'ECLIA' technique using Elecsys BRAHMS PCT immunoassay analyzers acting via the Sandwich principle. The analyzer automatically calculates the analyte concentration of each sample in ng/mL with the measuring range of 0.02-100 ng/mL.

Diagnostic abdominal paracentesis was done for all study participants. Total 15 - 20 cc ascitic fluid was collected from each patient. The ascitic fluid was analyzed for total proteins, total and differential leukocyte counts, glucose and lactate dehydrogenase (LDH). Ascitic fluid culture was done. 8 to 10 ml of ascitic fluid was inoculated in oxoid signal blood culture bottles (for aerobic and anaerobic culture) at the bed side using aseptic technique. While 3 cc samples was directly cultured on two blood agar plates (for aerobic and anaerobic bacteria), chocolate agar plate following centrifugation and incubated at 37°C. Direct culture plates were monitored daily for 48 hours for any growth. Blood culture bottles were incubated for 05 days at 37°C and monitored daily for any signs of positive culture (turbidity, gas production). Bottles showing any signs of positivity were sub-cultured on blood agar, chocolate agar and MacConkey's agar (12).

Classification of patients according to ascitic fluid infection:-
The presence of ascitic fluid infection was determined based on polymorphonuclear leukocyte (PMNL) counts and the culture positivity in ascitic fluids (AF). Accordingly patients were classified into four groups with respect to ascitic fluid infection including SBP (PMNL >250/mm3 in AF with a positive bacterial culture), culture-negative SBP (PMNL >250/mm3 in AF but the culture is negative), bacterascites (PMNL <250/mm3 in AF with a positive bacterial culture) and sterile ascites (PMNL <250/mm3 in AF and the culture is negative) (13). Additionally patients with non-cirrhotic ascites composed the fifth group. All of the cirrhotic patients were evaluated for the presence of hepatocellular carcinoma with ultrasonography and serum levels for AFP.

SBP, culture-negative SBP, bacterascites, sterile and non-cirrhotic ascites groups were compared in terms of procalcitonin levels to determine the value role of procalcitonin levels in predicting ascitic fluid infection. Cut-off values for procalcitonin levels (ng/mL) ruling out the diagnosis of bacteremia were calculated in each group. Receiver operating characteristics (ROC) curves were plotted for procalcitonin levels to evaluate their abilities to identify ascitic fluid infection in study population.

Statistical analysis:-
Mann-Whitney U test was used for comparison of quantitative variables with non-normal. ROC curves and decision plots were used to choose significant parameters and determine optimum cut-off values by maximizing sensitivity and specificity. Data are expressed as n (%), mean ± standard error of mean (SEM), median (minimum-maximum) or area under the curve (AUC, 95% confidence interval (CI)), where appropriate. $p<0.05$ was considered statistically significant.

Results:-

Patient demographics and classification according to classification of ascites Of 62 patients (age: 54.4 ± 10.7, 77.4% were males) hospitalized with ascites, cirrhosis was the underlying reason in 57 (91.9%) patients including SBP (19.4%), culture-negative SBP (35.5%), bacterascites (6.5%) and sterile ascites (30.6%), while the non-cirrhotic ascites was in 5 (8.1%) patients.

Table (1): Classification of patients according to culture positivity and PMN count of the ascitic fluid:

Groups	No.	%
Non-cirrhotic ascites	5	8.1%
SBP	12	19.4%
Bacterascites	4	6.5%
Culture negative SBP	22	35.5%
Sterile ascites	19	30.6%

Table (2): Comparison between various groups of patients regarding demographic characteristics.

		Non-cirrhotic ascites		SBP		Bacterascites		Culture negative SBP		Sterile ascites		Chi Square Test	
		No.	%	No.	%	No.	%	No.	%	No.	%	X^2	P-value
Gender	Female	2	40%	4	33.3%	1	25%	6	27.3%	1	5.3%	5.211	0.266
	Male	3	60%	8	66.7%	3	75%	16	72.7%	18	94.7%		
Age	Mean ± SD	42.60 ± 19.53		57.92 ± 10.23		50.75 ± 2.22		55.32 ± 9.62		54.89 ± 8.84		2.172	0.084*
	Range	18 – 60		44 – 81		49 – 54		39 – 71		35 – 73			

*: Independent t-test

Table (3): Comparison between various groups of patients regarding comorbid conditions.

		Non-cirrhotic ascites		SBP		Bacterascites		Culture negative SBP		Sterile ascites		Chi Square Test	
		No.	%	No.	%	No.	%	No.	%	No.	%	X^2	P-value
HE	Negative	5	100%	5	41.7%	4	100%	21	95.5%	16	84.2%	18.164	0.001
	Positive	0	0%	7	58.3%	0	0%	1	4.5%	3	15.8%		
GIB	Negative	5	100%	7	58.3%	3	75%	18	81.8%	16	84.2%	4.879	0.300
	Positive	0	0%	5	41.7%	1	25%	4	18.2%	3	15.8%		

HE: hepatic encephalopathy **GIB:** gastrointestinal bleeding

Table (4): Comparison between various groups of patients regarding laboratory data.

		Non-cirrhotic ascites	SBP	Bacterascites	Culture negative SBP	Sterile ascites	One Way ANOVA Test	
							t	P-value
RBCs	Mean ± SD	4.92 ± 0.82	3.54 ± 0.83	3.70 ± 0.82	3.66 ± 0.48	3.62 ± 0.74	4.141	0.005
	Range	4.3 – 6.3	2.4 – 4.6	2.9 – 4.5	2.7 – 4.7	2.2 – 5.1		
WBCs	Mean ± SD	5.18 ± 3.48	6.84 ± 4.22	5.30 ± 2.15	5.47 ± 2.80	7.37 ± 4.79	0.868	0.489
	Range	3.1 – 11.3	0.7 – 14.2	3 – 8.1	2 – 12.2	1.6 – 23.5		
Platelets	Mean ± SD	276.40 ± 168.06	80.17 ± 31.06	89.50 ± 16.42	112.27 ± 75.65	125.84 ± 101.92	4.847	0.002
	Range	105 – 455	39 – 129	67 – 104	31 – 324	53 – 504		
Serum total	Mean ±	0.71 ± 0.59	1.82 ±	2.03 ±	1.84 ± 2.29	2.76 ± 2.93	0.970	0.431

bilirubin	SD		1.58	1.22				
	Range	0.11 – 1.64	0.65 – 6.36	1.33 – 3.85	0.39 – 11.61	0.3 – 10.4		
INR	Mean ± SD	1.19 ± 0.12	1.61 ± 0.25	1.41 ± 0.12	1.45 ± 0.28	1.32 ± 0.23	3.780	0.009
	Range	1.06 – 1.37	1.27 – 2.03	1.29 – 1.56	1.01 – 1.84	1.03 – 1.9		
Serum albumin	Mean ± SD	2.40 ± 1.03	2.22 ± 0.31	2.93 ± 0.52	2.23 ± 0.43	2.29 ± 0.70	1.382	0.252
	Range	1.25 – 3.6	1.72 – 2.7	2.17 – 3.34	1.63 – 2.94	1.31 – 3.82		
Serum creatinine	Mean ± SD	2.09 ± 2.32	1.90 ± 1.08	1.02 ± 0.36	1.90 ± 0.86	4.39 ± 11.56	0.517	0.724
	Range	0.72 – 6.23	0.7 – 3.63	0.84 – 1.55	0.72 – 4.39	0.65 – 51		
Blood urea nitrogen	Mean ± SD	37.34 ± 25.20	66.33 ± 40.57	11.92 ± 8.45	46.43 ± 21.41	27.73 ± 20.61	5.651	0.001
	Range	13.3 – 79.7	8 – 120	7.7 – 24.59	8.15 – 92.07	1.34 – 74.1		

Table (5): Comparison between various groups of patients regarding serum AFP levels.

		Non-cirrhotic ascites	**SBP**	**Bacterascites**	**Culture negative SBP**	**Sterile ascites**	**Chi Square Test**	
		No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**X^2**	**P-value**
serum alpha fetoprotin	Mean ± SD	5.58 ± 3.62	15.49 ± 23.41	4.55 ± 1.22	9.36 ± 15.78	13.11 ± 17.59	0.590	0.671*
	Range	2 – 11.5	2 – 68	3.2 – 6	0.2 – 77.4	1.05 – 77		

*: One Way ANOVA Test

Table (6): Comparison between various groups of patients regarding parameters of ascitic fluid analysis.

		Non-cirrhotic ascites	**SBP**	**Bacterascites**	**Culture negative SBP**	**Sterile ascites**	**One Way ANOVA Test**	
							t	**P-value**
Ascetic Fluid Glucose	Mean ± SD	220.40 ± 175.14	115.42 ± 28.04	195.00 ± 39.83	137.68 ± 39.38	211.16 ± 138.27	2.925	0.029
	Range	94 – 503	80 – 190	160 – 247	80 – 210	91 – 583		
Ascetic Fluid	Mean ± SD	3812.00 ± 2076.13	964.50 ± 482.66	1025.50 ± 258.02	1818.18 ± 959.44	1266.05 ± 381.97	11.477	0.000

Total protein	Range	820 – 6000	260 – 2200	810 – 1400	760 – 4200	600 – 1900		
Ascetic Fluid LDH	Mean ± SD	141.26 ± 58.88	113.88 ± 40.27	125.75 ± 15.33	126.00 ± 33.75	119.58 ± 53.48	0.412	0.799
	Range	88 – 230	74 – 215	108 – 145	76 – 220	68 – 230		
Ascetic Fluid TLC (WBCs)	Mean ± SD	350.00 ± 327.41	651.83 ± 96.44	295.00 ± 119.58	725.91 ± 137.52	312.11 ± 124.75	26.271	0.000
	Range	40 – 740	540 – 850	160 – 410	510 – 950	80 – 490		

Table (7): Comparison between various groups of patients regarding inflammatory markers.

		Non-cirrhotic ascites	**SBP**	**Bacterascites**	**Culture negative SBP**	**Sterile ascites**	**One Way ANOVA Test**	
							t	**P-value**
ESR 1st hour	Mean ± SD	89.00 ± 29.27	34.08 ± 17.94	48.75 ± 6.29	44.27 ± 37.90	59.11 ± 44.06	2.549	0.049
	Range	42 – 120	12 – 68	40 – 55	6 – 140	12 – 140		
CRP	Mean ± SD	19.40 ± 8.82	12.79 ± 4.92	16.75 ± 7.41	5.40 ± 6.25	8.91 ± 7.07	6.958	0.000
	Range	8 – 30	7 – 22	10 – 25	1.2 – 27	2.4 – 24		
Serum Procalcitonin	Mean ± SD	0.50 ± 0.74	4.01 ± 1.06	0.05 ± 0.00	0.86 ± 0.60	0.19 ± 0.26	75.625	0.000*
	Range	0.05 – 1.8	2.6 – 6.4	0.05 – 0.05	0.05 – 1.9	0.05 – 1.1		

*: One Way ANOVA Test

Discussion:-

Cirrhosis holds the first rank among the etiologic factors of ascites followed by malignancy, heart failure, tuberculosis, pancreatic disease, or other miscellaneous causes. The development of ascites in cirrhosis indicates a poor prognosis with mortality of approximately 40% at 1 year and 50% at 2 years with increased risk for other complications of liver disease, including refractory ascites, SBP, hyponatremia, or hepatorenal syndrome (HRS) (14).

In our study patients were classified into five groups with respect to ascitic fluid infection including SBP, culture-negative SBP,bacterascites, sterile ascites, and non-cirrhotic ascites.

The five groups showed no statistically significant differences regarding to age or sex.
There was a highly significant difference between the 5 groups regarding hepatic encephalopathy. Recurrent admissions in patients with end-stage liver disease, particularly due to ascites and encephalopathy are frequent (15). Procalcitonin might be a useful tool to apply in these cases.

A highly significant correlation between serum procalcitonin and hepatic encephalopathy was observed.AsadiGharabaghi M et al., (16) reported, in a study that included 33 patients suspected to have SBP based

on clinical symptoms and signs, that patients with hepatic encephalopathy had increased levels of PCT even in the absence of SBP.

There was a significant difference between the five groups regarding RBC count and platelet count as well as a highly significant difference regarding serum levels of BUN. Furthermore, a highly significant correlation between serum procalcitonin and BUN was observed.

The incidence of renal failure and sepsis-related mortality is higher in the cirrhotic population than in non-cirrhotic patients (17). The prevalence of SBP depends on severity of liver dysfunction, being higher in advanced liver disease (18). Fever, high serum bilirubin, AF total protein level of < 1 g/dl and deranged renal functions are important predictors for development of SBP (19).

Renal elimination is thought to be one of the major pathways for the elimination of PCT (20). Previous studies showed that the urine levels of PCT were significantly reduced in patients with severe renal dysfunction. Despite decreased renal elimination, the plasma clearance rate correlated only weakly with renal dysfunction, and clinical decisions based on PCT may not be influenced (21).

On the other hand, there were no statistically significant differences between patients with positive cultures and patients with negative cultures regarding RBC count, WBC count or platelet count. This comes in accordance with the study done by Zhao-HuaCai et al, (22) who reported that WBC, and WBC/PLT ratios were not significantly different between ascites culture-positive and culture-negative patients.

Regarding to liver function tests, INR levels showed a significant difference between patients with positive ascitic fluid culture and patients with negative ascitic fluid culture. Furthermore, a highly significant correlation between serum procalcitonin and INR was observed. This comes in accordance with the study done by Kavita Paul et al, (23) who reported that INR was significantly higher in patients with SBP compared with those without SBP.

The five groups showed no statistically significant differences regarding to serum AFP levels.
Regarding to ascitic fluid analysis, ascitic fluid total protein levels showed a highly significant difference between patients with positive ascitic fluid culture and patients with negative ascitic fluid culture.

Two prospective studies comprising 127 patients (13 with SBP) (24) and 110 patients (28 with SBP) (18) confirmed low AF protein concentration as an independent predictor of SBP. Thus low AF protein helps us to identify cirrhotic patients at high risk for SBP.

The study of Terg et al, (25) and AvikMajumdar et al, (26) fail to replicate an association of SBP with low total AF protein concentration in three large cohorts of hospitalized patients with decompensated cirrhosis. Large prospective studies are needed to clarify the prognostic significance of low AF protein on the occurrence of SBP.

The 5 groups showed significant differences regarding ascitic fluid glucose levels while showing extremely significant differences regarding ascitic fluid PMN level. A significant correlation between serum procalcitonin and ascitic fluid glucose levels was noticed. A highly significant correlation between serum procalcitonin and ascitic fluid PMN was observed.

Highly significant differences between the 5 groups were observed regarding to ESR, CRP and serum procalcitonin levels. CRP levels showed a highly significant difference between patients with positive ascitic fluid culture and patients with negative ascitic fluid culture.

However, Giulia Pieri et al., (27) found that basal CRP level is generally higher in patients with cirrhosis than without cirrhosis. During bacterial infections CRP level rises, but in patients with cirrhosis the more severe the underlying liver dysfunction, the lower CRP increases. For this reason, CRP has a weak predictive power for infection and prognosis in patients with decompensated/advanced cirrhosis and in the intensive care setting. Therefore, it is advisable to clinically act on even moderate CRP increases in patients with advanced liver cirrhosis, and initiate empirical antibiotic therapy.

Regarding to serum procalcitonin measurement, procalcitonin levels showed an extremely significant difference between patients with positive ascitic fluid culture and patients with negative ascitic fluid culture (P value 0.000).

This comes in accordance with the study done by YesimCekin et al, (28) who reported that procalcitonin was significantly increased in serum of patients with cirrhosis related ascites but most markedly in culture-positive SBP with a high sensitivity and specificity for a cut off value of 0.61. Additionally, procalcitonin was better than CRP in predicting ascitic fluid infection in cirrhotic patients ($p< 0.004$).

Similarly, in a past study by Viallon et al, (29), serum levels of procalcitonin was reported to be one of the best markers for the diagnosis of SBP, with a cut-off value of 0.75 ng/ml, sensitivity of 95 % and specificity of 98%.

It does not come in accordance with the study done by Zhao-HuaCai et al, (22) who reported that serum PCT levels were not significantly different between ascites culture-positive and culture-negative patients.

Spahr et al (30) found that, in SBP, the measurement of PCT is not an accurate diagnostic test, possibly because of the absence of systemic inflammatory response syndrome in this condition. In addition, the diagnostic value of CRP is limited by the wide overlap between values.

Naglaa A. El-Gendy et al (31) found that CRP, and PCT serum and ascitic fluid levels are not accurate markers for the diagnosis of SBP, whereas an ascitic fluid polymorph leukocyte count higher than 200/mm3 is a rapid, sensitive, and specific test for the diagnosis of SBP.

Connert et al (32) demonstrated that serum PCT levels above 0.58 ng/mL is a valid marker of bacterial infection in decompensated cirrhotic patients with a sensitivity of 92% and specificity of 78%. Patients who present with such levels of serum PCT were associated with 50% mortality in the first two months. Interestingly, serum levels of C-reactive protein failed to discriminate the presence or absence of an associated bacterial infection.

Roc curve was plotted to show the diagnostic level of serum procalcitonin in infected ascitic patients. The cut off point for diagnosis was >1.9. The sensitivity was 75 % and specificity was 100% with positive predictive values of 100% and negative predictive values of 92%.

Table (8): Roc curve, sensitivity, specificity, PPV, NPV and cut off point for diagnosis of ascitic fluid infection.

Cut off point	AUC	Sensitivity	Specificity	**+PV**	**-PV**
>1.9 *	0.791	75.00	100.00	100.0	92.0

**Cut off point >1.9*

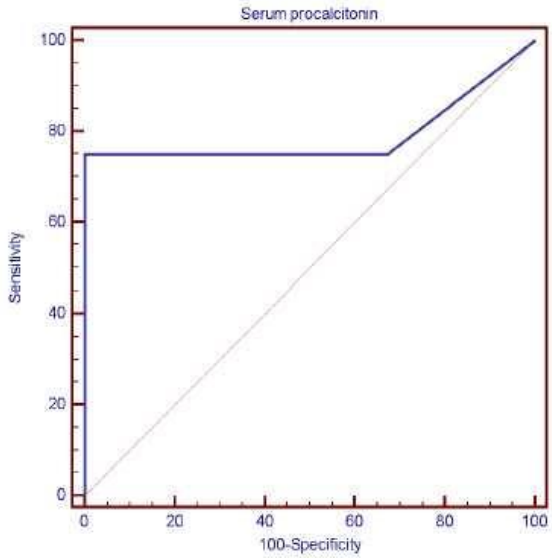

Figure (1): ROC curve of Procalcitonin

Conclusion:-

In conclusion, our study supports the usefulness of serum procalcitonin to aid clinicians by rapid and accurate diagnosis of SBP.

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