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STUDY OF IMMATURE PLATELET FRACTION AS A PREDICTOR OF SEPSIS IN CRITICALLY ILL PATIENTS

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ABSTRACT

Background: Sepsis is a life-threatening medical emergency. The management of Sepsis in clinical practice would greatly benefit from new biomarkers. Platelets play an important role in the diagnosis and prognostication of sepsis in critically ill patients. This has prompted studies that have explored the possibility of using Immature Platelet Fraction(IPF) as a biomarker in sepsis. **Objective:** To determine whether Immature Platelet Fraction (IPF) can be used to predict sepsis and severity of sepsis in critically ill patients and to compare Immature Platelet Fraction (IPF) with existing biomarkers like C-reactive protein (CRP) in predicting sepsis. **Methods:** This is a cross sectional study of 150 patients categorized into sepsis and non-sepsis groups based on the SOFA score. The association of sepsis with gender, age, comorbidities, culture positivity, IPF and CRP were assessed. Result: Among 75 patients with sepsis, 68.2% had an IPF of more than 3.65 (68.2%) and remaining 24.2% had IPF value less than or equal to 3.65. The cut off value of IPF was found to be 6.10 for predicting mortality. **Conclusion:** IPF values were found to be higher in patients with sepsis. IPF could predict sepsis with a sensitivity of 80.0% and a specificity of 62.6% . This study indicated that CRP is a slightly better predictor of sepsis than IPF. Higher IPF values were found to have a higher mortality; thus, a better predictor of mortality than CRP in sepsis

KEYWORDS

Immature Platelet Fraction, Sepsis, Severity, Biomarker

INTRODUCTION:

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. A main factor affecting sepsis-related mortality is the diagnostic delay that hinders proper treatment. Early recognition of sepsis therefore improves patient's outcomes.

An ideal biomarker in sepsis would
Differentiate between infection and host response
Appear in the blood in measurable quantities even before the onset of clinical features
Be used across all populations in a variety of clinical settings
Be cost effective as well as specific and sensitive in predicting sepsis.

Various biomarkers like D-dimer, Procalcitonin and C-reactive protein (CRP) have shown promising results in this aspect. The Immature Platelet Fraction (IPF) is a modern expanded CBC parameter that measures young and more reactive platelets in the peripheral blood and has been found to be useful in the differentiation of various thrombocytopenic states. Platelets, being intrinsic in the pathogenesis of sepsis, are an ideal target for the diagnosis and prognostication of sepsis in critically ill patients. This has prompted studies that have explored the possibility of using immature platelet fraction as a biomarker in sepsis. However, little is known about the sensitivity and specificity of this biomarker in sepsis and hence this study. This study evaluates the performance of IPF as a biomarker of sepsis diagnosis and severity.

METHODS:

A cross sectional study was conducted among 147 patients who were admitted in the Medical ICU in a tertiary care hospital over a period of one and a half years. . Patients admitted to the medical ICUs of the institution were categorized into sepsis and non-sepsis groups based on the SOFA score measured at the time of admission to ICU. Patients with thrombocytopenic disorders, patients with infections causing thrombocytopenia like dengue, malaria, leptospirosis and patients with preexisting bone marrow disorders were not included. Patients having a SOFA score of less than 2 were placed in the control group and with a SOFA score more than 2 in the sepsis group. A detailed history was taken including other comorbidities and drug intake.IPF monitoring was done along with PT-INR, CRP, Neutrophil% and platelet count. Association of sepsis with sex, age, comorbidities, type of organism (bacteria, fungi), IPF, CRP and mortality were assessed.

Numerical variables were expressed as mean and standard deviation. Association of IPF and sepsis, IPF and mortality, CRP and mortality were assessed by frequency and percentages. To obtain the associations Chi-square test was applied.

Group Distribution:

Among 150 patients, 75 patients were in the sepsis group and 75 patients in the non sepsis group.

Table 1 Sex Distribution In Total Study Sample:

Groups	Number	Percentage
Sepsis	75	50
Controls	75	50
Total	150	100.0

82 patients were male and 68 were females in the total study sample.

Sex	Frequency	Percentage
Male	82	54.7
Female	68	45.3
Total	150	100.0

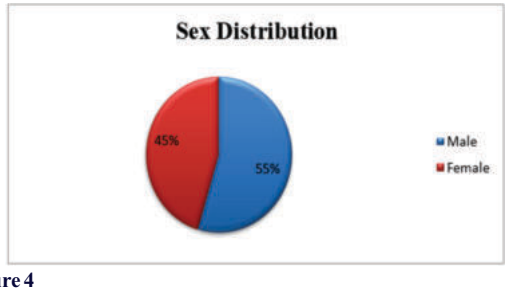


Figure 4

Gender Comparison:

In the Sepsis group 49.3% were male and 50.7% female. In the non-sepsis group 60% was male and 40% female. There is no statistically significant difference in the gender between 2 groups.

Table 3

Sex	Groups				χ^2 Value	p Value
	With Sepsis		Without Sepsis			
	n=75	%	n=75	%		
Male	37	49.3	45	60.0	1.722	0.189
Female	38	50.7	30	40.0		

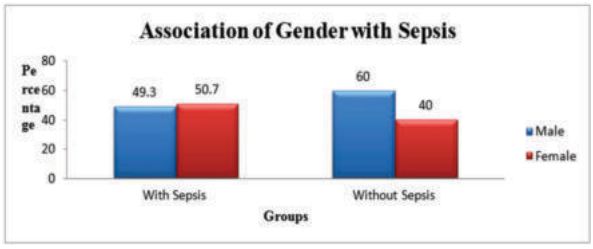


Figure 5

Age Distribution:
The mean age in patients with sepsis was 64.4 years and in patients not in sepsis was 47.4 years. The results were statistically significant with p value < 0.001. Mean age of the total sample was 55.91 ± 14.86.

Table 4

Groups		Age		p Value
	N	Mean	SD	
With Sepsis	75	64.4	12.9	<0.001
Without Sepsis	75	47.4	11.5	

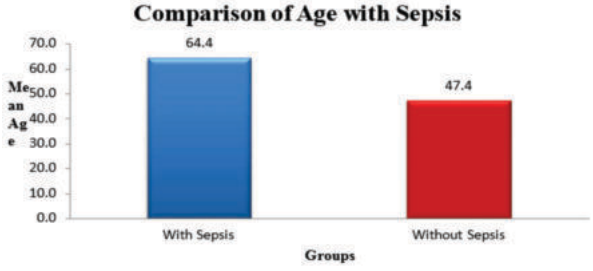


Figure 6

Distribution Of Comorbidities In The Study Population
In the 150 patients, the most common comorbidity found was Type 2 Diabetes Mellitus (75 patients, 50%) followed by Systemic Hypertension (61 patients, 40.7%).

Table 5

Comorbidities	Frequency	Percentage
T2DM	75	50.0
HTN	61	40.7
DLP	31	20.7
CKD	22	14.7
Thyroid disorder	16	10.7
COPD/BA	11	7.3
CVA	9	6.0
CAD	8	5.3

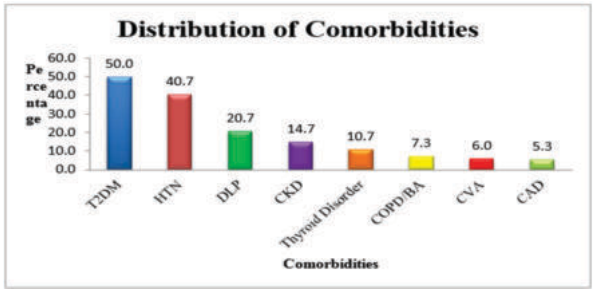


Figure 7

Distribution Of Comorbidities In Sepsis And Non Sepsis Groups
Comorbidities were analyzed in sepsis and non-sepsis patients and there were no statistically significant results.

Table 6 Distribution Of Focus Of Sepsis In The Study Population:

Comorbidities	Groups				χ2 Value	p Value
	With Sepsis		Without Sepsis			
	n=75	%	n=75	%		
T2DM	38	50.7	37	49.3	0.027	0.870
HTN	33	44.0	28	37.3	0.691	0.406
DLP	19	25.3	12	16.0	1.992	0.158
Thyroid Disorder	9	12.0	7	9.3	0.280	0.597
CAD	6	8.0	2	2.7	2.113	0.146
CKD	14	18.7	8	10.7	1.918	0.166
CVA	5	6.7	4	5.3	0.118	0.731
COPD/BA	6	8.0	5	6.7	0.098	0.754

In 75 patients with sepsis the most common focus of sepsis as indicated by culture positivity was urinary tract (28) followed by blood (27) and lung (25).

Table 7

Focus of Infection	Frequency	Percentage
Genito urinary system	28	18.7
Blood	27	18.0
Respiratory system	25	16.7
SSI	4	2.7
Others	2	1.3

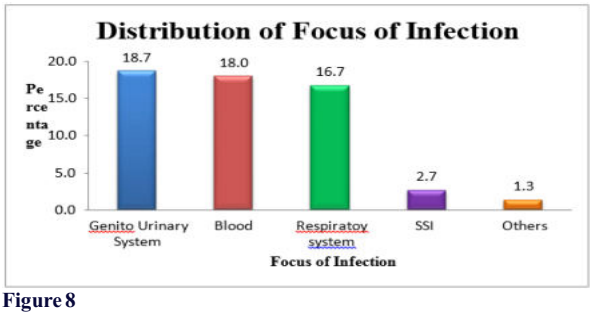


Figure 8

Incidence Of Bacterial Infection:
Among 75 patients with sepsis, most common type of organism causing sepsis was bacteria, 45(60%).

Table 8

Bacteria	Groups				2χ Value	p Value
	With Sepsis		Without Sepsis			
	n=75	%	n=75	%		
Present	45	60.0	2	2.7	57.292	<0.001
Absent	30	40.0	73	97.3		

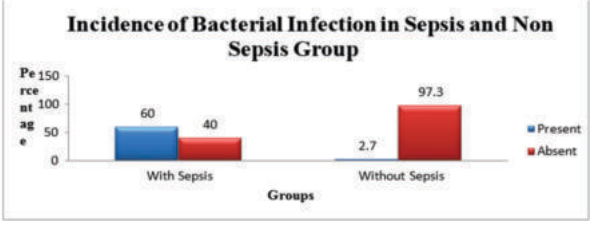


Figure 9

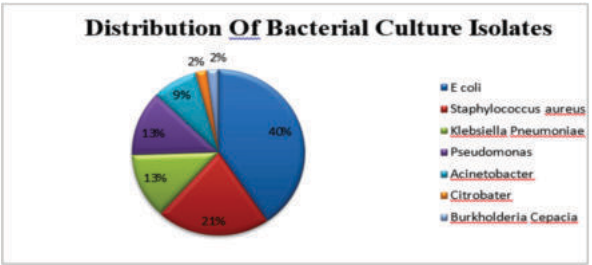


Figure 10

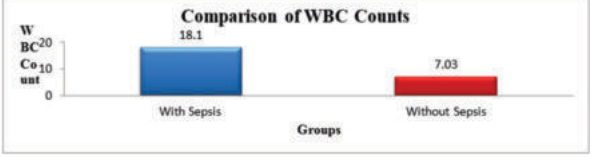


Figure 14

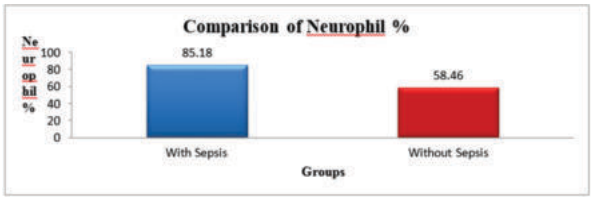


Figure 15

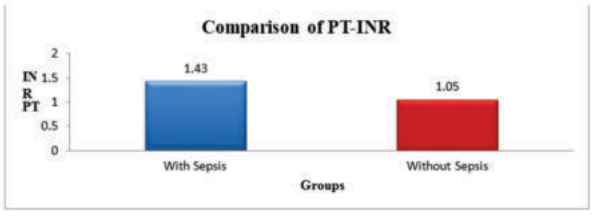


Figure 16

Association Of Ipf And Sepsis :
Among 75 patients with sepsis, 68.2% had IPF > 3.65 , and remaining 24.2% had IPF values ≤ 3.65. The results showed statistically significant association (p Value<0.001)

Table 11

IPF	Groups				2χ Value	p Value
	With Sepsis		Without Sepsis			
	n=75	%	n=75	%		
> 3.65	60	68.2	28	31.8	28.152	<0.001
≤ 3.65	15	24.2	47	75.8		

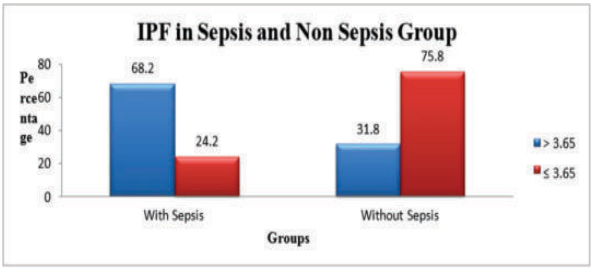
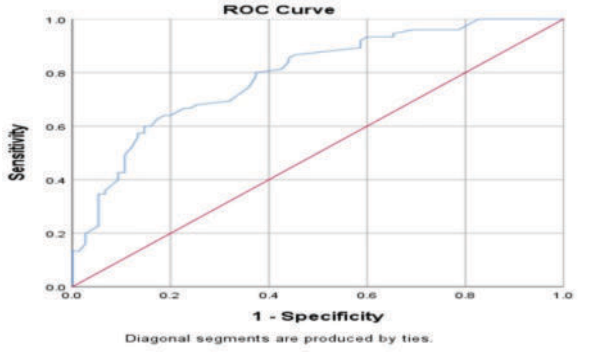


Figure 17

Roc Curve Of Ipf For The Prediction Of Sepsis:
The Area under the curve for IPF with Sepsis is 0.790. The cut off value of IPF was found to be 3.65 for predicting Sepsis with a sensitivity of 80.0% and a specificity of 62.6%, PPV is 68.2%, NPV is 75.8% and Accuracy 71.3%.



Association Of Ipf And Mortality:
62.5% of the patients with IPF>6.10 expired. The results showed statistically significant association (p Value<0.001)

Table 12

IPF	Mortality				2χ Value	p Value
	Expired		Alive			
	n	%	n	%		
> 6.10	30	62.5	18	37.5	67.472	<0.001
≤ 6.10	3	2.9	99	97.1		

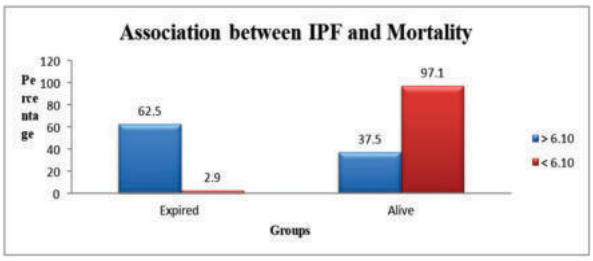


Figure 19

Roc Curve Of Ipf For The Prediction Of Mortality:
The Area under the curve for IPF with Mortality is 0.936. The cut off value of IPF was found to be 6.10 for predicting Mortality with the sensitivity of 90.1%, specificity of 84.6%, PPV is 62.5%, and NPV is 97% and Accuracy 86%.

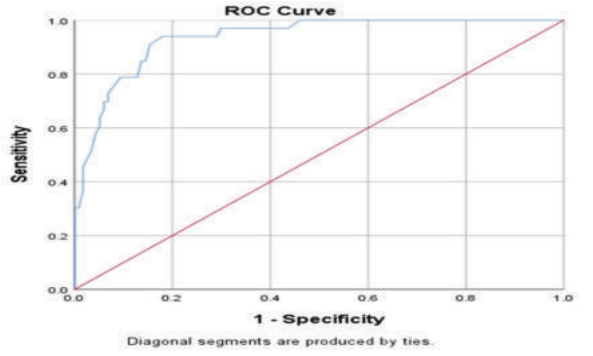


Figure 20

Association Of Crp And Sepsis:
Among the 75 patients with sepsis, 100% had CRP values of > 6.05 and in the nonsepsis group , only 5.3% had CRP values of >6.05. The results showed statistically significance (p Value<0.001).

Table 13

CRP	Groups				2χ Value	p Value
	With Sepsis		Without Sepsis			
	n=75	%	n=75	%		
> 6.05	75	100.0	4	5.3	134.81	<0.001
≤ 6.05	0	0.0	71	94.7		

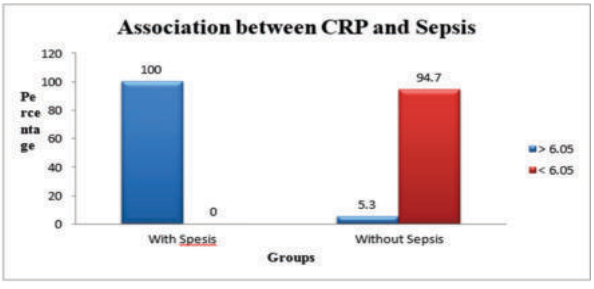


Figure 21

Roc Curve Of Crp For The Prediction Of Sepsis:
The Area under the curve for CRP with Sepsis is 0.999. The cut off value of CRP was found to be 6.05 for predicting Sepsis with the sensitivity of 100%, specificity of 94.6%, PPV is 95%, and NPV is 100% and Accuracy 97.3%.

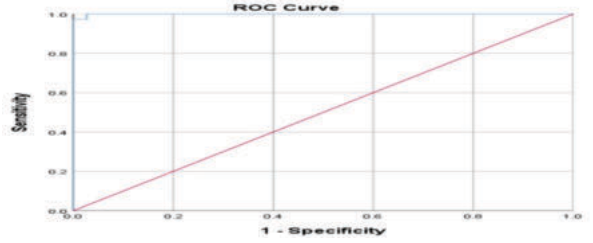


Figure 22

Association Of Crp And Mortality:
45% of the patients with CRP>19.50 expired. The results showed statistically significant association (p Value<0.001)

Table 14

CRP	Mortality				2 χ Value	p Value
	Expired		Alive			
	n=75	%	n=75	%		
> 19.50	27	45.0	33	55.0	30.828	<0.001

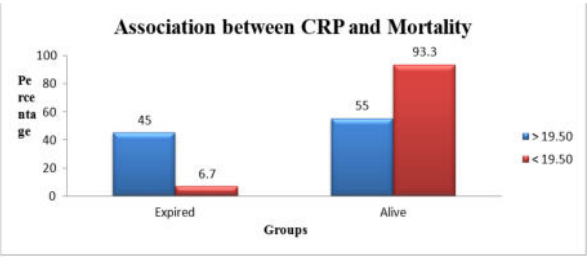
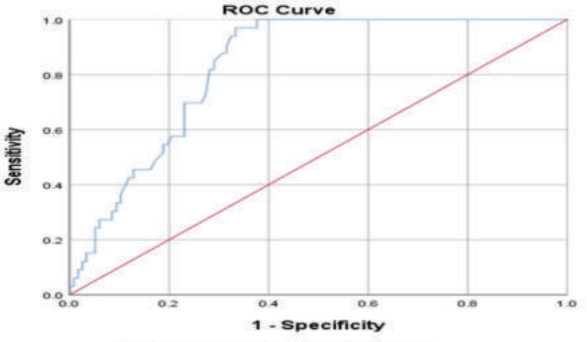
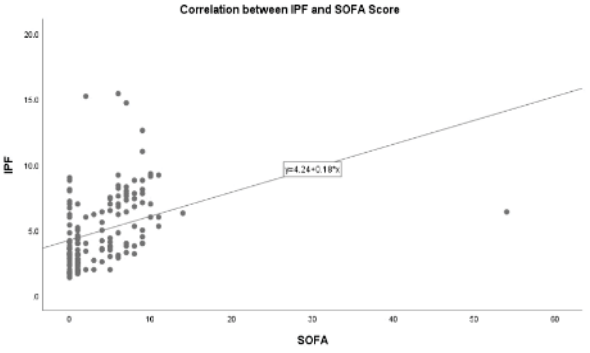


Figure 23

Roc Curve Of Crp For The Prediction Of Mortality:
The Area under the curve for CRP with Mortality is 0.829. The cut off value of CRP was found to be 19.50 for predicting Mortality with the sensitivity of 81.8%, specificity of 71.8%, PPV is 45%, and NPV is 93.3% and Accuracy 74%.





DISCUSSION :
Early recognition is a key goal of sepsis management protocols, since delayed antibiotic therapy increases morbidity and mortality rates of septic shock and generates significant higher costs to the health care system. For this reason, the search for new biomarkers capable of predicting early sepsis development, as well as the risk of sepsis complications, remains one of the most active areas of sepsis research. Platelets, being a cornerstone in the pathogenesis of sepsis, are an ideal target for diagnosis and prognostication of sepsis in critically ill patients. This has prompted studies that have explored the possibility of using immature platelet fraction (IPF) as a biomarker in sepsis. This study is aimed to find whether IPF can be used as a biomarker to predict sepsis and the severity of sepsis as well as comparing it to CRP values, a well-recognized biomarker. Our study is a cross sectional study, where we assessed IPF%, CRP and other sepsis related parameters, among the patients who presented to the medical ICU department of a tertiary care center. The study comprised of 150 patients, all of whom fulfilled the inclusion criteria. In our study, out of 150 patients, 75 were having sepsis (as determined by a SOFA score more than 2) and were taken into sepsis group and 75 in the non-sepsis group (controls). Out of the 150 patients, 54.7% were males and 45.3% were females. 75% patients were above 45 years of age (Mean age: 55.91 ± 14.86). 49.3% of the sepsis group was male and 50.7% females. In the control group, 60% were male and 40% female. In a recent study by De Blasi RA et al [(1)], 95 subjects were enrolled, of which 58.9% were males and 41.1% were females. A study done by Kansuke Koyama et al [(4)] had 205 patients with sepsis with 60.4% male and remaining female and the group was having a mean age of 68.35. In our study mean age of patients in sepsis group was 64 and in nonsepsis was 47. Results were statistically significant with p value < 0.001. However as in previous studies there was no statistically significant correlation between gender and sepsis. 48 This study analyzed the common comorbidities among the patients both in sepsis and control groups. Among 150 patients, the most common comorbidity found was Type 2 Diabetes Mellitus (75 patients, 50%) followed by Systemic Hypertension (61 patients, 40.7%).Among 75 patients with Type 2 Diabetes Mellitus, 38(50.7%) had sepsis.33 (44%) patients with associated hypertension had sepsis. Among 22 patients with CKD, 14 had sepsis and 8 had no sepsis. A recent study done by Van Vught LA et al [(5)] that evaluated 1,104 patients with sepsis found that 241 (21.8%) had a medical history of DM. Another study by Pandey NR et al [(6)] had 89 sepsis patients sample out of which 30 were hypertensive. Our study could not find any statistically significant correlation with any of the comorbidities and sepsis. Out of the 75 patients of the sepsis group in our study, the main source of infection was genitourinary system (18.7%) followed by blood (18%) and Lung (16.7%). A recent study done by Kansuke Koyama et al [(4)], in Tochigi, Japan in 205 sepsis patients however showed that 24.9% had Pulmonary infection, and 5% had urinary infection. In our study the most common type of organism causing sepsis was bacteria, 45patients, (60%) followed by fungi affecting 12 (16%) patients. Sepsis laboratory parameters like SOFA score, Platelet, WBC count, Neutrophil % , PT INR were analyzed in all 150 patients in our study. The mean SOFA score in sepsis group was 7.21 and in the control was 0.45. The results were statistically significant. In a study done by De Blasi et al [(1),] , mean SOFA score in non-sepsis group of 31 patients were 2.9 and sepsis group was 4.3. A cut off SOFA score of 4 was derived in predicting sepsis. Our study was in line with this. In another study by Enz Hubert RM et al [(2)] , mean SOFA score in a severe sepsis group of 12 patients was 10 and in a group of 11 patients with noncomplicated sepsis was 4. Patients with sepsis had lower platelet counts. The mean platelet count in sepsis cases was 2.21L per cubic mm and in controls were 2.55L per cubic mm in this study. The observation was similar to a study done by Guclu et al [(7)] in which a group of 88 patients with severe sepsis had a mean platelet count of 2.04L with a control group having 2.64L as the mean platelet count. 49 In our study, patients with sepsis were observed to have higher WBC counts. The mean WBC count in the sepsis group was found to be 18,100 per cubic mm and in the control group was 7030 per cubic mm. A recent study by Park SH et al [(3)] had similar results where mean WBC count was 5600 per cubic mm in 47 non-sepsis patients and 10400 per cubic mm in a severe sepsis group of 61 patients. Another study by Tanaka, H et al [(8)] had sepsis patients having very low WBC count which is different from our observation. Neutrophil percentage was seen to be high in sepsis patients in our study. The sepsis group had a Mean Neutrophil % of 85.18 and the control group with 58.46%.

The value was statistically significant with p < 0.001. This was in par with the study done by Park SH et al [(3)] in which Neutrophil% was 62.6 for the non-sepsis control group with 47 patients and 85.5% for sepsis group with 215 patients. Another study by Guclu et al [(7)] showed similar results where Neutrophil% increased based on the severity of Sepsis. C-reactive protein (CRP) is the most prominent existing bio marker of sepsis. Our study analyzed the correlation of CRP with sepsis in detail. The Area under the curve for CRP with Sepsis is 0.999. The cut off value of CRP was found to be 6.05 for predicting Sepsis with the sensitivity of 100%, specificity of 94.6%, PPV is 95%, and NPV is 100% and Accuracy 97.3%. Among 75 patients with sepsis, 100% had CRP > 6.05 and in the other 75 non sepsis patients 5.3% had CRP>6.05. The results showed statistically significant association (p Value6.10 expired. The Area under the curve for IPF with Mortality was 0.936. IPF was able to predict mortality with a sensitivity of 90.1%, specificity of 84.6%, PPV is 62.5%, and NPV is 97% and Accuracy 86%. A study by De Blasi et al [(1)] done in Berlin showed similar results in which, out of 64 patients IPF% was more sensitive but less specific in predicting mortality than in predicting sepsis (cutoff[4.7 %, sensitivity 88.9 %, IC95 %: 51.7–98.2; specificity 75.7

%, IC 95 %: 61.7–86.2). In our study, IPF was found to be more sensitive and specific in predicting mortality than in predicting sepsis. Our study also analyzed the correlation of CRP with mortality. The cut off value of CRP was found to be 19.50 for predicting mortality with the sensitivity of 81.8%, specificity of 71.8%, PPV is 45%, and NPV is 93.3% and Accuracy 74%.45% of the patients with CRP>19.50 expired. The results showed a statistically significant association p value<0.001. in a recent similar study by Ryoo, SM etal [(9)], the sensitivity, specificity, positive predictive value, and negative predictive value of CRP were 52.5%, 56.4%, 23.9%, and 82.0%, respectively in predicting mortality. In our study (as in Figure 21), IPF was found to be a better predictor of mortality as compared to CRP. The area under the curve for IPF with Mortality is 0.936 and area under the curve for CRP with Mortality is 0.829. As seen in figure 22, the study was able to find a statistically significant positive correlation for IPF as compared to CRP in patients with sepsis. (r=0.406, p-value <0.001) We were able to attain the objective of finding a relation with IPF and sepsis, IPF and mortality and also able to compare IPF as a bio marker with CRP with this study. Our study was in line with other studies in most of the analysis. One limitation of the study was that the patient's IPF, CRP and other parameters were collected during the admission to MICU and were not monitored regularly during hospitalization. Regular monitoring of these values along with correlation of the SOFA scores could have possibly given a better picture of the fluctuating dynamics of the sepsis process. Also, a group with more patients may have resulted in better data and analysis

CONCLUSION:

This study evaluated the performance of IPF as a biomarker of sepsis diagnosis and sepsis severity and also compared it with the commonly used biomarker CRP. The following conclusions were obtained

IPF values were found to be higher in patients with sepsis compared to patients without sepsis, so it may be possible to use IPF as a biomarker of sepsis.

Higher IPF values (more than 6.10) were seen to be a predictor of mortality in sepsis patients.

CRP was found to be a better predictor of sepsis than IPF.

IPF was found to be better than CRP in predicting mortality in sepsis patients

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