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STUDY OF HAEMATOLOGICAL AND INFLAMMATORY PARAMETERS IN SEPSIS PATIENTS

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Aim: The aim of the present study was to assess haematological and inflammatory parameters in sepsis patients.
Methods: The study was conducted at Medical intensive care unit at Dr. DY Patil medical college and hospital, DY Patil Vidyapeeth, Pimpri, Pune from October 2020 – September 2022 and 100 cases were included in the present study. Approval was taken from institutional ethics committee before commencing the study. Informed and written consent was taken from all the patients.
Results: Among the study population, 68.00% of them were male, 32.00% of them were female. On study population, 44.00% of them diagnosed with DIC. On study population, 61.00% of them were Survivors, 39.00% of them were non-survivors. The mean platelet on admission was 117624 ± 89241.13, it was 105860 ± 85661.89 at 24 hours, it was 98990 ± 83391.29 at 48 hours. The mean D Dimer at Admission was 4073.37 ± 4361.13, it was 3956.39 ± 2432.91 at 24 hours, it was 5284.33 ± 8445.54 at 48 hours. The mean Fibrinogen at Admission was 2.07 ± 0.85, it was 1.76 ± 0.86 at 24 hours, it was 1.47 ± 0.95 at 48 hours. Among the study population, the mean ESR was 86.75 ± 97.97, the mean CRP was 73.7 ± 72.45, the mean Lactate was 28.95 ± 25.06, the mean Pro Calcitonin was 6.62 ± 3.4.
Conclusion: In uncontrolled cases of sepsis, acute organ dysfunction and shock may develop. Because of this rapid progression, it is of utmost importance that patients should be diagnosed and treated in a requisite time frame. The current literature and changing guidelines demonstrate that the bedside physical examination along with laboratory testing (haematologic and inflammatory biomarkers) are the most effective combination of parameters that clinicians can rely upon to accurately predict or diagnose sepsis in a critically ill patient.
Keywords: Sepsis, Haematological, Inflammatory, CRP, PCT, Fibrinogen

INTRODUCTION

Sepsis remains an important cause of hospitalization and mortality worldwide among patients admitted in intensive care units.1 In a 5 year prospective study conducted by Sharmila Chatterjee et al. it was found that ICU mortality was 56 % in patients admitted with sepsis.2 Sepsis can be defined as a life threatening organ malfunction caused by the dysregulated host response to an infection.3 It is based on three cardinal symptoms-altered mental status, fast respiratory rate (> 22 breaths / minute) and low blood pressure (≤ 100 mm Hg systolic). There are three levels of severity within sepsis which are identified as sepsis, severe sepsis, and septic shock which depends upon increasing organ system involvement and coinciding mortality rates.4 Early diagnosis and treatment is very important as mentioned in a study by Kumar et al. stating that mortality increases by 8 percent each hour if treatment is delayed.5 Organ dysfunction or failure was assessed with the help of SOFA (Sepsis related Organ Failure Assessment) score which was developed by Vincent et al.6 SOFA was designed to describe the sequence of complications in a critically ill patient and thus, helped to evaluate morbidity in sepsis. Positive blood or body fluid culture requires 24 to 48 hours to develop and many at times it can be falsely negative. Hence, there is an urgent need for biomarkers-inflammatory and haematological for early diagnosis of sepsis.

Whenever body is affected by harmful stimulus like infection and trauma, we can see release of pro inflammatory cytokines like interleukin 6, interleukin 1, TNFα and gamma interferon.7 These cytokines trigger the liver to release acute phase proteins such as CRP and fibrinogen. Fibrinogen is elevated in initial stages of sepsis. ESR determines the rate at which RBC by virtue of its rouleaux formation settles down when placed in a vertical tube for an hour and indirectly measures the amount of fibrinogen, hence, increased levels of fibrinogen can increase ESR, which generally increases within 24 to 48 hours. Acute inflammation due to infectious diseases, tissue trauma, ischemia or tumour can lead to high ESR.8 Endothelial dysfunction plays a key role in the pathogenesis of sepsis and is responsible for haematological changes which occur during sepsis. The endothelial injury generally occurs after entry of bacterial endotoxins or due to the effect of pro inflammatory cytokines and thus, can further lead to micro vascular coagulopathy and acute organ damage.9 The most common laboratory finding includes anaemia with fall in haematocrit (HCT) values, low RBC count or low haemoglobin concentration, thereby decreasing oxygen carrying capacity. Neutrophilic leucocytosis is also commonly observed. Neutropenia is more prevalent in paediatric age group with severe sepsis.10

The aim of the present study was to assess haematological and inflammatory parameters in sepsis patients.

MATERIALS AND METHODS

The study was conducted at Medical intensive care unit at Dr. DY Patil medical college and hospital, DY Patil Vidyapeeth, Pimpri, Pune from October 2020 – September 2022 and 100 cases were included in the present study. Approval was taken from institutional ethics committee before commencing the study. Informed and written consent was taken from all the patients.

Inclusion criteria: -

- All patients admitted in medical ICU satisfying q-SOFA score
- All patients of sepsis including diabetes mellitus
- All hematological malignancies and solid organ malignancies
- Immuno-compromised patients

Exclusion criteria: -

- Pregnancy.
- Chronic liver cell failure classified as Child-Pugh class C.
- Chronic renal failure on regular dialysis
- Patients receiving anticoagulation therapy

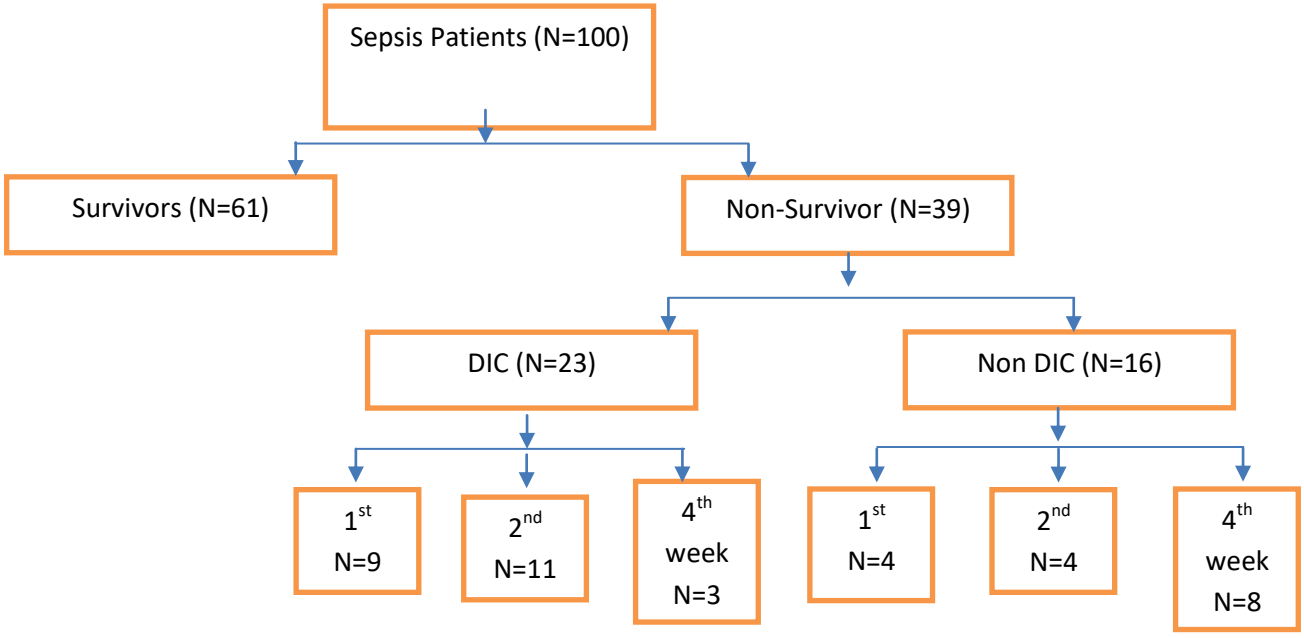
Each patient admitted in medical ICU was explained about the study in detail. Detailed clinical history of illness, physical examination and radiological examination was done. All the investigations enlisted in the subsequent page was carried out. Special investigations like FIBRINOGEN level by automated coagulation analyzer CA600 series and FIBRIN DEGRADATION PRODUCT – D DIMER level by automated enhanced immunoassay was carried out. The values obtained from the above investigations was calculated with DIC scores (ISTH, SIC) and SOFA score.

Glasgow Coma score (GCS), hemodynamics and systemic examination. Routine laboratory investigations were done together with special laboratory investigations (Quantitative Fibrinogen and Ddimer assays) on day of admission and repeated every 48 h till discharge. Length of ICU stay, the need of mechanical ventilation, need of vasopressor or inotropic support, need of renal replacement therapy (haemodialysis) and final outcome were evaluated. DIC and SOFA scores were evaluated on day of admission and serially every 48 h until discharge. All patients were followed up clinically and laboratory for a total of 28 days. Patients were classified as survivors and non-survivor and 28-days mortality were studied.

Statistical methods

All obtained data was analyzed statistically by SPSS (Statistical Package for Social Science) program. Statistical significance was analyzed using analysis of variance (ANOVA). All values was expressed as ranges and means ±SD (Standard Deviation) for numerical data or numbers and percentages for categorical data. Prevalence rate was determined from the number of identified cases at the time of the study divided by all patients examined. P value 60.05 was considered statistically significant. Chi square was used as a test of significance for the qualitative data. The relationship between the studied parameters was assayed by Pearson's correlation coefficient. The cut-off points were used as <0.3 for weak correlation, 0.3–0.7 for moderate correlation, and >0.7 for strong correlation.

Flowchart showing the outline of results



RESULTS

Table 1: Patient characteristics

Sex	**Frequency**	**Percentages**
Female	32	32.00%
Male	68	68.00%
DIC		
NO	66	66.00%
YES	44	44.00%
Outcome		
SURVIVORS	61	61.00%
NON-SURVIVORS	39	39.00%
Death		
DEATH DUE TO DIC	23	59%
DEATH DUE TO OTHER CAUSES (NON DIC)	16	41%

Among the study population, 68.00% of them were male, 32.00% of them were female. On study population, 44.00% of them diagnosed with DIC. On study population, 61.00% of them were Survivors, 39.00% of them were non-survivors. On study population, 59% of them were died with death due to DIC.

Table 2: Haematological parameters on admission, 24 hours and 48 hours in study population

Parameter	**Mean ± SD**	**Median**	**Minimum**	**Maximum**
HB ON ADMISSION	17.89 ± 90.28	8.60	4.30	911.50
HB AFTER 24 HOURS	8.42 ± 1.83	8.10	4.34	12.60
HB AFTER 48 HOURS	7.82 ± 1.86	7.35	4.30	12.80
TLC ON ADMISSION	25185.2± 17345.47	22000.00	13400.00	176000.00
TLC AFTER 24 HOURS	24382.8± 8143.38	22780.00	12200.00	48700.00
TLC AFTER 48 HOURS	23374.7± 9883.13	22000.00	10000.00	65000.00
PLATELETS ON ADMISSION	117624± 89241.13	88000.00	12000.00	430500.00
PLATELETS AFTER 24 HOURS	105860± 85661.89	74500.00	6500.00	412000.00
PLATELETS AFTER 48 HOURS	98990± 83391.29	73450.00	8000.00	371000.00
D Dimer At Admission	4073.37± 4361.13	3370.00	343.00	40000.00
D Dimer After 24 Hours	3956.39± 2432.91	3450.00	454.00	10000.00
D Dimer After 48 Hours	5284.33± 8445.54	3462.00	325.00	70000.00
FIBRINOGEN ON ADMISSION	2.07 ± 0.85	1.90	0.90	3.50
FIBRINOGEN AFTER 24 HOURS	1.76 ± 0.86	1.50	0.20	3.30
FIBRINOGEN AFTER 48 HOURS	1.47 ± 0.95	1.10	0.30	3.20

Among the study population, the mean Hb on Admission was 17.89 ± 90.28, it was 8.42 ± 1.83 at 24 hours, it was 7.82 ± 1.86 at 48 hours. The mean TLC on Admission was 25185.2 ± 17345.47, It was 24382.8 ± 8143.38 at 24 hours, it was 23374.7 ± 9883.13 at 48 hours. The mean platelet on admission was 117624 ± 89241.13, it was 105860 ± 85661.89 at 24 hours, it was 98990 ± 83391.29 at 48 hours. The mean D Dimer at Admission was 4073.37 ± 4361.13, it was 3956.39 ± 2432.91 at 24 hours, it was 5284.33 ± 8445.54 at 48 hours. The mean Fibrinogen at Admission was 2.07 ± 0.85, it was 1.76 ± 0.86 at 24 hours, it was 1.47 ± 0.95 at 48 hours.

Table 3: Inflammatory markers in study population

Parameter	**Mean ± SD**	**Median**	**Minimum**	**Maximum**
ESR	86.75 ± 97.97	66.50	28.00	990.00
CRP	73.7 ± 72.45	42.00	2.70	380.00
LACTATE	28.95 ± 25.06	24.00	3.00	218.00
PRO CALCITONIN	6.62 ± 3.4	7.00	0.50	14.00

Among the study population, the mean ESR was 86.75 ± 97.97, the mean Crp was 73.7 ± 72.45, the mean Lactate was 28.95 ± 25.06, the mean Pro Calcitonin was 6.62 ± 3.4.

Table 4: Comparison of d dimer, fibrinogen between survivors and non survivors

Parameter	**OUTCOME (Mean± SD)**		**P value**
	Survivors (N=61)	**Non-survivors (N=39)**	
D DIMER AT ADMISSION	3771.33 ± 5261.7	4545.79 ± 2336.9	0.389
D DIMER AFTER 24 HOURS	3479.26 ± 2230.73	4702.67 ± 2574.21	0.013
D DIMER AFTER 48 HOURS	4728.48 ± 6461.05	6153.74 ± 10892.24	0.413
FIBRINOGEN ON ADMISSION	2.14 ± 0.85	1.96 ± 0.84	0.296
FIBRINOGEN AFTER 24 HOURS	1.85 ± 0.81	1.62 ± 0.93	0.191
FIBRINOGEN AFTER 48 HOURS	1.43 ± 0.97	1.54 ± 0.92	0.550

On study population, the difference in mean of D DIMER AT ADMISSION, D DIMER AFTER 48 HOURS, FIBRINOGEN ON ADMISSION, FIBRINOGEN AFTER 24 HOURS, FIBRINOGEN AFTER 48 HOURS between outcome was not statistically significant. (p value >0.05). On study population, the difference in mean of D DIMER AT 24 HOURS between outcomes was statistically significant. (p value <0.05)

Table 5: Comparison of haemotological parameters and inflammatory markers between survivors and non survivors

Haemotological parameters	**OUTCOME (Mean± SD)**		**P value**
	Survivors (N=61)	**Non-survivors (N=39)**	
HB ON ADMISSION	9.36 ± 1.93	31.24 ± 144.67	0.239
HB AFTER 24 HOURS	8.83 ± 1.93	7.79 ± 1.45	0.005
HB AFTER 48 HOURS	8.11 ± 1.93	7.37 ± 1.68	0.051
PLATELETS ON ADMISSION	111785.25 ± 71323.07	126756.41 ± 112142.17	0.416
PLATELETS AFTER 24 HOURS	101659.02 ±	112430.77 ±	0.542

	73145.71	102940.96	
PLATELETS AFTER 48 HOURS	96883.61 ± 85628.2	102284.62 ± 80758.13	0.754

Inflammatory markers	**OUTCOME (Mean± SD)**		**P value**
	Survivors (N=61)	**Non-survivors (N=39)**	
ESR	97.38 ± 123.11	70.13 ± 24.65	0.176
CRP	81.56 ± 82.14	61.4 ± 52.59	0.176

On study population, the difference in mean of HB AT ADMISSION, HB AFTER 48 HOURS, Platelet ON ADMISSION, Platelet AFTER 24 HOURS, Platelet AFTER 48 HOURS between outcome was not statistically significant. (p value >0.05). On study population, the difference in mean of HB AT 24 HOURS between outcomes was statistically significant. (p value <0.05). On study population, the difference in mean of ESR, CRP between outcomes was not statistically significant. (p value >0.05).

DISCUSSION

Early assessment of critically ill patients and accurate prediction of prognosis in the intensive care unit are important to allow appropriate treatment decisions by medical attendants.11 In general, the earlier an accurate diagnosis is made and appropriate treatment started, the greater the chance of survival, fewer complications, better quality of life, and lower health care costs.12,13

Balwinder Singh et al. (2010) conducted a population-based, retrospective cohort study evaluating consecutively admitted adult (18 years old) critically ill patients with DIC. The incidence rate of DIC per 100,000 person-years decreased from 26.2 in 2004 to 18.6 in 2010, it was discovered. With the exception of the age group of 18 to 39 years, the incidence rate of DIC increased with age in both men and women, but was consistently higher in men.14 According to a 2016 study by J. Y. Park et al., the incidence of DIC was 27.9% on Day 1 and 30.1% on Day 3, respectively. Particularly in patients with non-pneumonia sepsis, day 3 DIC scores were more reliable than day 1 DIC scores at predicting hospital mortality (P 0.001). Despite their more severe illness and higher mortality rate, patients with pneumonia sepsis had a lower incidence of DIC on day 1 compared to those with other sources of sepsis.15

To determine whether elevated D-dimer levels could predict mortality in patients, Litao Zhang, et al., 2020 conducted a study. The best D-dimer cutoff value for predicting in-hospital mortality was discovered to be 2.0 g/mL, with a sensitivity of 92.3% and a specificity of 83.3%. When compared to patients with D-dimer levels 2.0 g/mL, patients with D-dimer levels 2.0 g/mL had a higher incidence of mortality.16 Our study found that 59% of DIC patients died as a result of their condition, with 56% passing away in the first week, 68% in the second week, and 19% in the fourth. A similar study conducted by José P. Cidade et al.,2022, conducted a study to describe the D-dimer admission profile in severe ICU COVID19 patients and its predictive role in outcomes and mortality. Depending on their dimer scores, the participants were split into three groups. A 23.7% overall in-hospital mortality rate was found by the study. At day 28, the Kaplan-Meier survival curves for the three groups did not differ from one another. The results of univariate Cox regression performed considering d-dimer serum level at ICU admission or

maximum d-dimer serum level registered also did not show any significant hazard ratios when analyzed individually.17

Muller et al.18 in 2007 conducted a study in patients with community acquired pneumonia, where he projected that PCT concentration helped to distinguish bacterial from viral pneumonia. In 2007 Kofoed et al.19 concluded that combined use of three or six pro inflammatory markers was more successful in accurately identifying patients with bacterial infection. Similar multi marker approach was used by Shapiro et al.20 in 2009 in diagnosing severe sepsis. A study done by Young et al.21 investigated the potentiality of PCT as a marker to diagnose septic shock in patients with acute pyelonephritis occurring secondary to ureteral calculi. It concluded that high PCT and low platelet count are high risk factors of septic shock in such cases. In a study done by Heffner AC et al. in division of critical care medicine, it was observed that more than 50 % of the patients with severe sepsis have negative culture results. Hence, culture and sensitivity offer a limited prospectus in management of severe sepsis.22

However, the best approach in early identification of sepsis would be selection of combination of markers like haematological, pro inflammatory and anti-inflammatory markers.

CONCLUSION

Sepsis is the leading cause of death in hospitalized patients in ICU settings. Patients with sepsis often present with nonspecific symptoms of inflammation which rapidly progress to a more severe condition if not treated. In uncontrolled cases of sepsis, acute organ dysfunction and shock may develop. Because of this rapid progression, it is of utmost importance that patients should be diagnosed and treated in a requisite time frame. The current literature and changing guidelines demonstrate that the bedside physical examination along with laboratory testing (haematologic and inflammatory biomarkers) are the most effective combination of parameters that clinicians can rely upon to accurately predict or diagnose sepsis in a critically ill patient.

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