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CLINICAL STUDY OF DYNAMIC CHANGES OF ACUTE PHASE REACTANTS IN SEPSIS

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ABSTRACT

Aim: - The aim of this original research is to evaluate APR levels in sepsis, evaluate procalcitonin's significance, analyze the predictive role of CRP and Procalcitonin, and examine the correlation of serum albumin levels with treatment outcomes.

Method: - The prospective observational study was conducted at a health care urban teaching hospital in Gujarat, India, between May 2019 and October 2020. The research included 105 ICU patients diagnosed with sepsis, meeting specific inclusion criteria such as age above 18 years and fulfilling the qSOFA score parameters. Patients with chronic inflammatory conditions, advanced malignancy, or who did not provide consent were excluded.

Result: - This study investigated biomarker trends and clinical outcomes in sepsis patients. The analysis included 105 ICU patients with sepsis. Results showed significant trends in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, while white blood cell (WBC) count and ferritin levels remained stable. Albumin levels were statistically significant. The distribution of scores revealed different levels of severity. Outcomes presented a discharge rate of 71.4% and a fatal outcome rate of 28.6%. This study provides valuable insights into biomarker dynamics and their correlation with sepsis outcomes.

Conclusion: - Acute Phase Reactants (APRs) provide valuable insights into sepsis. CRP is a strong predictor of prognosis, while procalcitonin indicates poor outcomes. Serum Albumin is useful for short-term outcome prediction. CRP and procalcitonin guide antibiotic treatments in sepsis.

KEYWORDS: *Sepsis, biochemical abnormalities, infections.*

INTRODUCTION

Sepsis is a complex medical condition characterized by a combination of physiological, pathological, and biochemical abnormalities, triggered by an infection. It is currently defined as a serious dysfunction of organs resulting from an imbalanced response by the body to an infection. This condition poses a significant healthcare challenge and is associated with substantial healthcare expenses. While it is challenging to determine the precise incidence of sepsis, reliable statistical analyses indicate that it is one of the primary reasons of mortality and life-threatening illness worldwide. Additionally, individuals who survive sepsis often experience long-term psychological, physical, and cognitive impairments. [1,2]

Infections are a significant global burden, contributing to illness and death in numerous cases. In current years, there has been increasing interest towards utilizing acute-phase reactants (APRs) for infection management. These markers, present in the bloodstream, indicate the presence of inflammation and wound. Acute-phase reactants encompass a diverse range of plasma proteins that undergo fluctuations, either increasing or decreasing, in response to inflammatory triggers like infections, trauma, severe arthritis, autoimmune diseases of the system, and tumours. [3,4]

The classification of the acute phase response is determined by the magnitude of change in the concentration of Acute Phase Proteins (APP). A significant increase of 10-100 times in APP concentration is categorized as a major elevation. A moderate elevation is considered when there is a 2-10 fold increase in APP concentration. On the other hand, a minor elevation is defined as a less than 2-fold increase in APP concentration.[5] During a major acute phase response, the elevated Acute Phase Proteins (APPs) primarily consist of C-reactive protein (CRP) and serum amyloid A protein (SAA). In a moderate acute phase response, α1-acid glycoprotein (AGP) is the main APP that shows an increase in concentration. In a minor acute phase response, the APPs that experience elevation include fibrinogen, haptoglobin (Hp), and ceruloplasmin (Cp).

In the presence of an infection, the liver plays a crucial role in synthesizing a significant quantity of APPs. There are eight proteins that are classified as "positive" acute phase reactants (APRs) as they are overexpressed during the acute phase response. These proteins include haptoglobin (Hp), serum amyloid A (SA), fibrinogen, ceruloplasmin (Cp), α-1 antitrypsin (AAT), lactoferrin (Lf), and C-reactive protein (CRP). Also, there are several "negative" APRs whose expression levels decrease during the acute phase response. These include albumin, transferrin, and transthyretin.[6]

The acute phase response is triggered by various cytokines, with those that function as positive and negative growth factors, as well as cytokines with proinflammatory or anti-inflammatory properties. Positive and negative growth factor cytokines implicated in this response contain Interleukin (IL)-2, IL-3, IL-4, IL-7, IL-10, IL-11, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Proinflammatory cytokines included in the acute phase response comprise tumor necrosis factor (TNF)-α/β, IL-1α/β, IL-6, IFN-α/γ, IL-8, and macrophage inhibitory protein-1. Conversely, anti-inflammatory cytokines that play a role in this response include IL-1 receptor antagonists, soluble IL-1 receptors, IL-1 binding protein, and TNF-α binding protein.[7,8]

The purpose of this research is to examine the dynamic changes of acute phase reactants in sepsis. The objectives include studying the correlation between reactant levels at the start of sepsis treatment, analyzing the trend of reactant levels with treatment, assessing the significance of Procalcitonin as a reactant, determining the correlation between elevated Procalcitonin levels and outcome, and evaluating the role of CRP and Procalcitonin in predicting sepsis patient outcomes. Additionally, the study aims to examine the correlation of serum albumin level with short-term outcome in sepsis.

METHODOLOGY

The prospective observational research was performed at the general medicine department of a tertiary care urban teaching hospital in Gujarat, India. The study period was between May 2019 to October 2020. The study population consisted of patients admitted to the ICU and diagnosed with

sepsis, with a total of 105 individuals involved in the research. Individuals were enrolled based on specific inclusion criteria, including being above 18 years of age, fulfilling the qSOFA score parameters in the ICU, and providing consent to participate in the study. Patients with chronic inflammatory conditions, advanced malignancy, or who did not provide consent were excluded from the study.

Statistical analysis

Data collection was performed by accessing hospital electronic medical records, including patient demographics, comorbidities, vital signs, and laboratory results. The collected data were analyzed using IBM SPSS software, and descriptive statistics, ANOVA, ROC curve, and correlation tests were applied for data analysis. The study adhered to ethical guidelines, obtaining clearance from the Institutional Ethics Committee and ensuring patient confidentiality and informed consent.

RESULTS:-

In a prospective study on 105 sepsis patients in the ICU, the correlation between acute-phase reactant levels at treatment initiation and their trend during treatment was investigated.

Table 1: Gender Distribution of research individuals [N=105]

Sex	**Number [%]**
Man	66 (62.9)
Woman	39 (37.1)
Age [in year]	**Number [%]**
18-30	5 (4.8)
31-40	11 (10.5)
41-50	26 (24.8)
51-60	20 (19)
>60	43 (41)
Mean ± SD	56.1 ± 15.3

Table 1 presents age distribution among participants, with the highest proportion in the >60 years group (41%) followed by the 41-50 years group (24.8%). The mean age was 56.1 years, with a standard deviation of 15.3. In terms of gender, 62.9% of participants were male, indicating a higher prevalence of sepsis in males compared to females (male-to-female ratio of 1:0.6).

Table-2: Comparison of acute phase reactants within each treatment days based on time.

	Day	**0**	**2**	**3**	**7**	**10**	**F value**	**p value**
WBC count	**Mean**	12753.5	13025.5	13769.5	13205	12054	1.43	0.239
	SD	8700.7	5449.9	4638.5	5138.5	7176.1		
ESR	**Mean**	55.9	45.3	36.4	30.4	25.1	98.8	**0.001**
	SD	30.2	22.8	18.4	16.6	16.9		
CRP	**Mean**	88.1	111.6	72.6	57.4	38.5	5	**0.02**
	SD	75.7	281.4	51	55.1	56.8		
FERRITIN	**Mean**	666.8	607.7	719.9	518.3	484.2	2.37	0.12
	SD	621.1	455.4	1600.9	370.1	368.1		
PROCALCITONIN	**Mean**	4.4	0.5	3.4	0.3	21.5	1.53	0.22
	SD	41	1.5	33.2	1	154.5		
APC	**Mean**	236.7	219.9	228.9	231.5	218.8	0.81	**0.008**
	SD	114	96.5	135.6	86.3	108.3		
Albumin	**Mean**	2.7	2.5	2.5	2.5	2.5	9	**0.001**
	SD	0.36	0.31	0.35	0.35	0.34		

The study examined biomarker levels in patients at different time points. WBC count showed no significant difference, while ESR and CRP levels decreased significantly. Ferritin and procalcitonin levels varied without significance. APC levels had minimal variation but were statistically significant. Albumin levels remained relatively constant with significance. These findings shed light on the dynamics of biomarkers during the study period.

Table-3: Distribution of qSOFA Score among study participants [N=105]

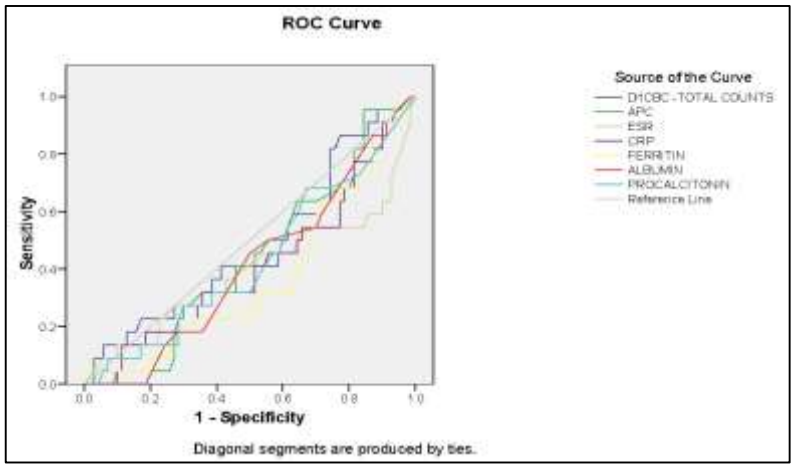
Score	Number	%
1	26	24.8
2	49	46.7
3	30	28.6

In this study, scores were categorized into three levels: 1, 2, and 3. Results showed that 24.8% of participants scored 1, 46.7% scored 2, and 28.6% scored 3.

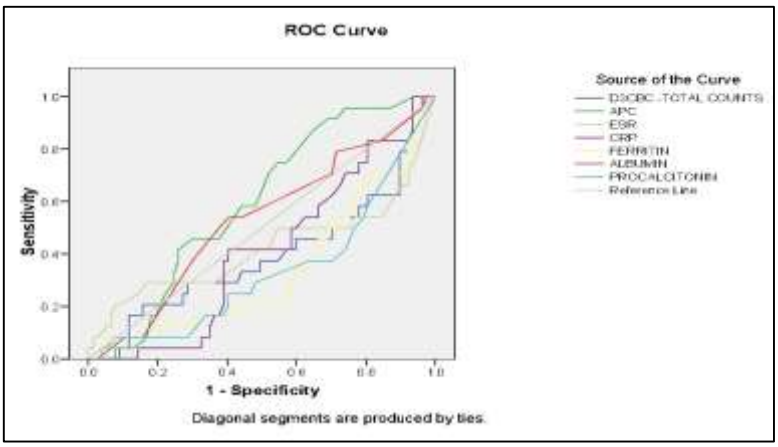
Table -4: Outcome of treatment [N=105]

Outcome	Number	%
Discharge	75	71.4
Death	30	28.6

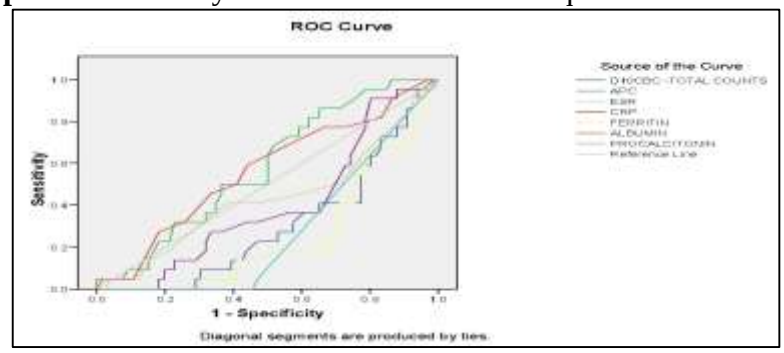
The study outcomes were divided into two categories: Discharge and Death. Among all participants, 71.4% were discharged, while 28.6% experienced a fatal outcome.



Graph-1: ROC analysis of different APR with qSOFA score at day-0



Graph-2: ROC analysis of different APR with qSOFA score at day-3



Graph-3: ROC analysis of different APR with qSOFA score at day-7

Table-5: ROC and AUC of acute phase reactants Vs qSOFA score on day-0, 1, 3, 7 and 10

	Day-0		Day-1		Day-3		Day-7		Day- 10	
APR	**AUC**	**P value**	**AUC**	**P value**	**AUC**	**P value**	**AUC**	**P value**	**AUC**	**P value**
Total WBC count	0.48	0.78	0.51	0.85	0.4	0.12	0.31	**0.005**	0.3	**0.006**
APC	0.44	0.4	0.62	0.08	0.6	0.15	0.4	0.12	0.58	0.25
ESR	0.39	0.13	0.41	0.12	0.42	0.26	0.43	0.32	0.43	0.34
CRP	0.41	0.21	0.42	0.38	0.41	0.17	0.33	**0.01**	0.4	0.17
Albumin	0.41	0.22	0.37	0.06	0.34	**0.02**	0.34	**0.02**	0.25	**0.001**
Ferritin	0.37	0.06	0.44	0.4	0.53	0.66	0.59	0.19	0.57	0.36
Procalcitonin	0.43	0.32	0.34	**0.02**	0.33	**0.02**	0.38	0.08	0.28	**0.002**

The AUC values for Total WBC count ranged from 0.30 to 0.51, p-values that range from 0.005 to 0.78. APC had AUC values ranging from 0.40 to 0.62, p-values that range from 0.08 to 0.40. ESR exhibited AUC values ranging from 0.39 to 0.43, p-values that range from 0.12 to 0.34. CRP had AUC values ranging from 0.33 to 0.42, p-values that range from 0.01 to 0.38. Albumin showed AUC values ranging from 0.25 to 0.41, p-values that range from 0.02 to 0.22. Ferritin and Procalcitonin displayed AUC values ranging from 0.37 to 0.59 and 0.28 to 0.43, correspondingly, with p-values varying across different time points. (Graph-1, 2 and 3)

Table-6: Analysis of day wise average correlation between acute phase reactants vs outcome

Parameters (Mean values)	Day 0		Day 2		Day 3		Day 7		Day 10	
	Death	Discharge	Death	Discharge	Death	Discharge	Death	Discharge	Death	Discharge
TC	13127.70	11622.29	14479.00	12444.11	15656.30	13014.76	15185.70	12412.67	16721.30	10187.92
APC	259.60	227.55	246.43	209.32	239.57	224.65	261.83	219.39	201.90	225.56
CRP	101.46	83.63	175.47	86.62	85.95	67.56	92.34	43.24	76.21	26.08
Ferritin	587.62	561.57	652.52	7526.26	647.19	542.59	569.76	463.45	630.74	394.66
Albumin	2.90	2.65	2.60	2.48	2.57	2.51	2.41	2.59	2.30	2.58
PCT	15.07	0.40	0.74	0.47	0.36	4.95	0.45	0.20	1.86	20.49

** Parameters are taken as mean values*

Analysis of day wise average correlation in table 6 revealed important findings: increasing WBC count correlated with poor prognosis and death, decreasing count with favorable response and discharge. In nonsurvivors, APC values showed a biphasic pattern, indicating higher mortality. Higher CRP values at sepsis treatment start linked to poor prognosis and death; lower values correlated with favorable prognosis and discharge. Ferritin trend lacked significance due to extreme values. Higher PCT values on day 0 indicated poor prognosis, lower values in survivors. Albumin levels varied between survivors and nonsurvivors, declining in the deceased group but stabilizing in survivors. These insights shed light on biomarker trends and clinical outcomes in sepsis.

DISCUSSION

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from an uncontrolled response to infection. Septic shock is a severe form of sepsis with higher mortality risk. Diagnostic criteria include increased SOFA score and the need for vasopressors to maintain blood pressure. A serum lactate level above 2 mmol/L is also indicative of septic shock. The quickSOFA score can help identify patients at risk for adverse outcomes in various healthcare settings based on clinical criteria such as respiratory rate, mental state, and blood pressure.[1]

This study included 105 sepsis individuals admitted to the ICU of a health care center in Gujarat. It aimed to examine the relationship between acute phase reactant levels at the start of sepsis treatment and their patterns during treatment. Patients were enrolled based on specific criteria. The study spanned from May 2019 to October 2020.

The present study revealed that participants over the age of 60 had the highest representation, followed by those aged 41 to 50. In a research perform by Martin et al. that age is an independent predictor of mortality in sepsis patients. As a result, ICU physicians may hesitate to admit elderly patients, even if clinical criteria suggest it. [9] The occurrence of sepsis rises with advancing age, particularly affecting individuals aged 80 years and above, and is accompanied by alarmingly high mortality rates. [10-12]

The current research found men to women ratio of 1:0.6, indicating a higher incidence of sepsis in men. This is consistent with previous research presentation that males have a higher rate of bacteremic infections compared to females, as noted by McGowan et al. [13] Gender disparities in the progression of septic complications and multiple organ failure in trauma victims are shown by epidemiological investigations.
Table 2 presents mean values, standard deviations, F values, and p values for laboratory parameters measured on different days (Day 0, 2, 3, 7, and 10) in the study, indicating the significance of observed differences.

In the present study, the mean WBC count exhibited a slight increase from Day 0 to Day 3, followed by a decrease on Day 7 and Day 10. However, the lack of statistical significance (F value = 1.43, p = 0.239) suggests that these changes are not clinically significant. This aligns with previous research by Seigel et al., which highlighted that WBC count alone may not be reliable for assessing infection. Normal WBC counts are often observed in septic individuals, and leukocytosis may occur as a delayed response. Therefore, relying solely on WBC count for infection assessment may lead to inaccuracies. [14]

The mean ESR values show a progressive decrease from Day 0 to Day 10, indicating a decreasing inflammatory response. The significant F value of 98.8 (p = 0.001) suggests that the observed differences in ESR values are statistically significant. These findings indicate that the study intervention may have influenced the inflammatory process, resulting in reduced ESR values. Markanday A. et al [4] found that Procalcitonin has higher specificity than CRP and ESR. ESR is

influenced by various factors and less reliable than plasma viscosity. Elevated ESR indicates inflammatory disorders, tuberculosis, myocardial infarction, or anemia. Low ESR can be seen in specific conditions. ESR is useful for diagnosing and monitoring polymyalgia rheumatica or temporal arteritis. Combined ESR and CRP help assess acute pelvic inflammatory disease severity. Raised ESR is a marker for coronary heart disease. [15] The mean CRP levels fluctuate during the study, but the significance is marginal, suggesting factors other than the intervention may influence these changes. In a study by Vanderschueren S. et al [16], CRP > 500 mg/l in 130 individuals (median age: 62). Bacterial infections: 88% cases, 36% fatal outcomes (61% with active malignancies). Extreme CRP elevation indicates bacterial infections, surpassing ESR as a sensitive marker. Ferritin levels fluctuate without clear trend. Non-significant differences observed ($F = 2.37$, $p = 0.12$). Study intervention may not impact ferritin levels significantly. In a study by Cristina Rosário et al.[17], it was found that Elevated ferritin levels were associated with septic shock and poor prognosis. Ferritin sequesters iron and inhibits microbial iron scavenging. It rises during malignancy and infection to limit iron availability. Proinflammatory cytokines upregulate ferritin production, but some organisms like Pseudomonas can decrease ferritin levels using siderophores to import iron. [18]

In the present study the mean procalcitonin levels show varying values throughout the study period. The F value of 1.53 with a p value of 0.22 suggests that the differences observed are not statistically significant. This indicates that procalcitonin levels may not be significantly influenced by the study intervention. Arora S. et al [19] conducted a meta-analysis to pool data from various studies on PCT levels in sepsis survivors and non-survivors, reaching a similar conclusion.

In the present study the mean APC levels remain relatively stable over the study period. However, the significant F value of 0.81 with a p value of 0.008 indicates that the observed differences in APC levels are statistically significant. This suggests that the study intervention may have an impact on APC levels. Fanny VardonBounes et al. [20] found that thrombocytopenia was linked to sepsis, organ failure, and poor prognosis in ICU patients. Platelet counts can increase in response to infections, inflammation, bleeding, and tumors. This reactive thrombocytosis is a normal response. Clonal thrombocytosis, on the other hand, is an abnormality in platelet production. Platelet volume indices like MPV and PDW indicate platelet function and activation. Elevated MPV is linked to inflammatory conditions and cardiovascular risk factors. [21]

In the present study the mean albumin levels show no significant changes throughout the study period. The significant F value of 9 with a p value of 0.001 suggests that the observed differences in albumin levels are statistically significant. This indicates that the study intervention may have an effect on albumin levels. In a study by Mirsaeidi et al., hypoalbuminemia was associated with a threefold higher short-term mortality rate. Albumin, as an acute phase reactant, can be influenced by various factors, including inflammation. [22]

Overall, the study suggests that the intervention influenced inflammatory markers like ESR and APC, while other parameters showed no significant changes. These findings highlight the importance of further investigation and interpretation for clinical implications.

The study population showed variations in scores, with the majority (46.7%) scoring a 2, followed by 28.6% scoring a 3 and 24.8% scoring a 1. This highlights different characteristics or outcomes among participants in the study.

The study results showed that total WBC count had moderate to good predictive accuracy on days 7 and 10, while APC, ESR, and other APRs had fair to moderate predictive accuracy without significant associations. Albumin demonstrated significant associations on days 3, 7, and 10,

indicating its potential as a predictive marker. Further study is wanted to understand the clinical implications of these results.

CONCLUSION

Sepsis is a complex condition induced by infection, and Acute Phase Reactants (APRs) have been instrumental in understanding and treating it. Monitoring changes in APR levels can predict ICU mortality and prolonged stay in sepsis patients. CRP is a strong predictor of prognosis, while procalcitonin indicates poor outcomes. Serum Albumin, as a negative APR, is useful for short-term outcome prediction. Other APRs analyzed were not reliable in predicting sepsis outcomes. CRP and procalcitonin are specific and reliable indicators, guiding antibiotic treatments.

REFERENCE

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801 –10.
2. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. Jama. 2010 Oct 27;304(16):1787–94.
3. Dowton SB, Colten HR. Acute phase reactants in inflammation and infection. Semin Hematol 1988; 25:84–90.
4. Markanday A. Acute Phase Reactants in Infections: Evidence Based Review and a Guide for Clinicians. Open Forum Infect Dis. 2015 Jul 3;2(3): ofv098.
5. Ceron JJ, Eckersall PD and Martynez-Subiela S: Acute phase proteins in dogs and cats: Current knowledge and future perspectives. Vet Clin Pathol 2005;34: 85-99.
6. Góez-Laguna J, Salguero FJ, Pallaré FJ, Rodríuez-Góez IM, Barranco I. Acute phase proteins as biomarkers in animal health and welfare. In: Acute Phase Proteins as Early Non-Specific Biomarkers of Human and Veterinary Diseases. Veas F (ed). InTech, 2011;259-298.
7. Koj A. Termination of acute-phase response: Role of some cytokines and antiinflammatory drugs. Gen Pharmacol 198; 31:9-18.
8. Khalil RH, Al-humadi N. Types of acute phase reactants and their importance in vaccination (Review). Biomedical reports 2020; 12:143-152.
9. Martin-Loeches I, Guia MC. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicentre cohort study. Ann Intensive Care. 2019; 9: 26.
10. Danai PA, Sinha S, Moss M, Haber MJ, Martin GS. Seasonal variation in the epidemiology of sepsis. Crit Care Med. 2007 Feb;35(2):410–5.
11. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303–1310.
12. Martin GS, Mannino DM, Eaton S, Moss M. The Epidemiology of Sepsis in the United States from 1979 through 2000. N Engl J Med. 2003 Apr 17;348(16):1546–54.
13. Angele MK, Pratschke S. Gender differences in sepsis. Virulence. 2014 Jan 1; 5(1): 12–19.
14. Seigel TA, Cocchi MN, Salciccioli J, et al. Inadequacy of temperature and white blood cell count in predicting bacteremia in patients with suspected infection. J Emerg Med 2012;42:254-9.
15. Yayan J; Erythrocyte sedimentation rate as a marker for coronary heart disease. Vasc Health Risk Manag. 20128:219-23.
16. Vanderschueren S, Deeren D, Bobbaers H. Extremely elevated C-reactive protein. Eur J Intern Med. 2006 Oct;17(6):430-3.
17. Cristina Rosário et al. The Hyperferritinemic Syndrome: macrophage activation syndrome, Still’s disease, septic shock and catastrophic antiphospholipid syndrome [Available from: https://bmcmedicine. biomedcentral.com/articles/10.1186/1741-7015-11-185]

18. Gulhar R, Ashraf MA. Physiology, Acute Phase Reactants. StatPearls Publishing; 2021 Jan.
19. Arora S, Singh P, Singh PM, Trikha A. Procalcitonin Levels in Survivors and Non-survivors of Sepsis: Systematic Review and Meta-Analysis. Shock 2015 Mar;43(3):212-21.
20. Fanny Vardon-Bounes et al. Platelets Are Critical Key Players in Sepsis [Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6679237/]
21. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Current Pharmaceutical Design. 2011;17(1):47–58.
22. Mirsaeidi M, Omar HR, Sweiss N. Hypoalbuminemia is related to inflammation rather than malnutrition in sarcoidosis. Eur J Intern Med. 2018 Jul;53:e14-e16.