

STUDY OF THE RELATIONSHIP OF ACUTE PHASE REACTANTS LEVEL WITH SEVERITY OF ILLNESS AND MORTALITY IN PATIENTS WITH SEPSIS AND ITS CORRELATION WITH APACHE IV SCORE

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

ABSTRACT-

Background- With sepsis as a major cause of concern in increasing ICU mortality, several prognostic scoring systems, including the Acute Physiology and Chronic Health Evaluation (APACHE) or the Mortality Probability Models (MPM) have been used so far to assess the acute clinical condition of seriously ill patients with sepsis, to predict prognosis and to assist physicians clinical decision.

Aim- To study the relationship of acute phase reactants level with severity of illness and mortality in patients with sepsis and its correlation with APACHE IV score

Study Design: Propective observational study.

Place and Duration of Study: This study was conducted at Department of General Medicine, Dr D Y Patil Medical College, Hospital and research centre, Pune from October 2020 to September 2022.

Methodology- This study conducted in a semi-urban teaching Hospital in Maharashtra, India. Study included patients admitted to ICCU of the study institute for sepsis (Sepsis is any suspected (or documented) infection and an acute increase in ≥ 2 sepsis-related organ failure assessment (SOFA) points.) and full filling the below mentioned inclusion and exclusion criteria. The collected data was analyzed with IBM, SPSS (IBM Corp., Statistics for Windows, version 24.0, Armonk, NY). Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were expressed as a percentage.

Results and Conclusion- Mean level of Acute phase reactants proteins like C reactive protein, ESR, lactate dehydrogenase level, D Dimer, Serum Procalcitonin, Serum lactate, Serum Ferritin, APACHE IV score was significantly higher in patients who died during the treatment as compared to patients who survived.

Key Words- Sepsis, Mortality, Acute phase reactants

INTRODUCTION-

Sepsis is a major concern in the care of critically ill patients. Despite the availability of potent antibiotics and intensive supportive care, mortality of septic patients admitted in ICU is more[1,2]Infections are a major cause of morbidity and mortality worldwide. There has been increasing focus on the use of acute-phase reactants (APRs) in the management of infections because the presence of these markers in the serum signifies inflammation and injury[3].

Important APRs include erythrocyte sedimentation rate (ESR), CRP, Procalcitonin (PCT), LDH, D-Dimer, Serum lactate, serum ferritin, Serum amyloid A (SAA) protein, fibrinogen, ferritin, alpha-1 antitrypsin, haptoglobin, alpha-1 acid glycoprotein, ceruloplasmin, and complement proteins C3 and C4[4]. The level of response may vary among different APRs. Erythrocyte sedimentation rate is a nonprotein APR that changes in response to plasma fibrinogen levels and plasma viscosity and hence is an “indirect” APR[5]. The ESR and CRP are currently the most commonly used acute-phase markers in clinical practice[6]. C-reactive protein has an important role in many parts of the inflammatory process[7]. It is involved in the innate immune response by attaching to microorganisms and damaged cellular components via phosphocholine. C-reactive protein is a useful marker of the acute phase reaction as it responds quickly to the inflammatory process, whether it is an infection, autoimmune disease or tissue necrosis[8].Procalcitonin (PCT), regarded as a biomarker specific for bacterial infections, is used in a variety of clinical settings including primary care, emergency department and intensive care[9]. PCT measurement aids in the diagnosis of sepsis and to guide and monitor antibiotic therapy. Procalcitonin is a sensitive marker for sepsis and can be used to guide treatment[10]. Other acute-phase markers like LDH, D Dimer, Serum lactate and Serum ferritin also used as marker to assess severity of infection. The use LDH as biomarkers in medicine lies in their ability to detect disease and support diagnostic and therapeutic decisions[11]. They have also a potential value as an important prognostic tool.

Several prognostic scoring systems, including the Acute Physiology and Chronic Health Evaluation (APACHE) or the Mortality Probability Models (MPM) , have been used so far to assess the acute clinical condition of seriously ill patients with sepsis, to predict prognosis and to assist physicians clinical decisions[12].

APACHE IV- It was designed in 2006 to assess the severity of illness as well as the prognosis in the ICU and has 17 physiological criteria, adding new variables such as mechanical ventilation,

thrombolysis, and impact of sedation on Glasgow Coma Scale, rescaled Glasgow Coma Scale, PaO₂ / FiO₂ ratio and disease-specific subgroups, to the existing APACHE III variables[13].

MATERIALS AND METHODS-

The present study was conducted with the aim to study the relationship of acute phase reactants level with severity of illness and mortality in patients with sepsis and its correlation with APACHE IV score.

TYPE OF STUDY: Prospective Observational study.

PLACE OF STUDY: Department of General Medicine, DrD.Y.Patil Medical College, Hospital And Research Centre, Pimpri, Pune.

ETHICAL COMMITTEE APPROVAL: The study was undertaken after approval from the institutional ethical committee

DURATION OF STUDY: 2 yrs (October 2020 – September 2022)

REFERENCE POPULATION: Study included patients admitted to ICCU of the study institute for sepsis (Sepsis is any suspected (or documented) infection and an acute increase in ≥ 2 sepsis-related organ failure assessment (SOFA) points.) and full filling the below mentioned inclusion and exclusion criteria.

SAMPLE SIZE: In research terms, a sample is a group of people, objects or items that are taken from a larger population for measurement. The sample should be representative of the population to ensure that we can generalize the findings from the research sample to the population as a whole. Considering prevalence of Sepsis as 49% at 95% CI with 10% margin error, sample size was calculated as 96-98. So, the minimum sample size required was taken as 100 patients.

METHODOLOGY OF STUDY:

- Total leucocyte count, Packed Cell Volume (PCV), serum creatinine, serum bilirubin, serum sodium/potassium/bicarbonate and arterial pH was done in each patient.
- The various acute phase reactants were also evaluated and their levels were compared with the severity of illness and mortality in patients with sepsis.
- APACHE IV score was also calculated and its correlation with compared with the severity of illness and mortality in patients with sepsis.

SELECTION CRITERIA:

Inclusion Criteria

- Age 18 or older
- Presumed or confirmed infection
- At least 2 positive Systemic inflammatory response syndrome (SIRS) criteria:
 - a) Temperature $>38^{\circ}\text{C}$ ($>100.4^{\circ}\text{F}$) or $<36^{\circ}\text{C}$ ($<96.8^{\circ}\text{F}$)
 - b) Heart rate >90 beats per minute
 - c) Respiratory rate >20 breaths per minute
 - d) WBC count $>12,000$ or $<4,000$ mm³ or $>10\%$ Immature Neutrophils
- At least one newly diagnosed organ dysfunction on admission or during patient's ED stay
 - a) Transient Hypotension (Systolic blood pressure <90 mm hg)
 - b) Hyperlactemia (Serum lactate > 2.0 mmol/L)
 - c) Unexplained Acidemia (Arterial pH <7.35 or Serum Bicarbonate <21 mmol/L)
 - d) Thrombocytopenia (Platelet count $<150,000/\mu\text{l}$)
 - e) Hyperbilirubinemia (Total Bilirubin >1.2 mg/dL or Direct Bilirubin >0.2 mg/dL)
 - f) Coagulation abnormalities (INR >1.10 or aPTT >30.4 without anticoagulant therapy.
 - g) Acute kidney injury (Creatinine >1.2 mg/dL or increase >0.5 mg/dL above baseline)
 - h) Hypoxemia (O₂ saturation $<90\%$)
 - i) New neurologic dysfunction (change from baseline mental status by GCS)
- Viral infections (including COVID-19)
- Diabetic Patients

Exclusion criteria

- Age <18 years
- Acute Pancreatitis
- Trauma
- Burns cases
- Connective tissue disorders

DATA ANALYSIS:

The collected data was analyzed with IBM, SPSS (IBM Corp., Statistics for Windows, version 24.0, Armonk, NY). Continuous variables were expressed as mean \pm standard deviation (SD)

and categorical variables were expressed as a percentage. To find the significant difference between the bivariate samples in independent groups, unpaired sample t-test was used and the Chi-square test was used to find the significance in categorical data. In all the above statistical tools, $P \leq 0.05$ will be considered statistically significant.

RESULTS AND DISCUSSION-

Table 1: Distribution of study subjects as per Acute phase reactants

Acute phase reactant	Mean	SD
C-REACTIVE PROTEIN	4.34	1.30
ESR	44.01	11.84
LACTATE DEHYDROGENASE	7.62	1.26
D-DIMER	3.25	2.38
SERUM PROCALCITONIN	1.72	0.93
SERUM LACTATE	3.52	1.08
SERUM FERRITIN	353.33	89.55

It was observed that mean level of C-reactive protein was 4.34 (± 1.30), mean ESR level was 44.01 (± 11.84), mean lactate dehydrogenase level was 7.62 (± 1.26), mean D-DIMER level was 3.25 (± 2.38), mean serum prolactin level was 1.72 (± 0.93), mean serum lactate level was 3.52 (± 1.08) and mean serum ferritin level was 353.33 (± 89.55).

Table 2: Distribution of study subjects as per Outcome

Outcome	Number	%
Survived	87	87
Death	13	13

Out of 100 study participants 87 (87%) were survived and 13 (13%) participants died during treatment.

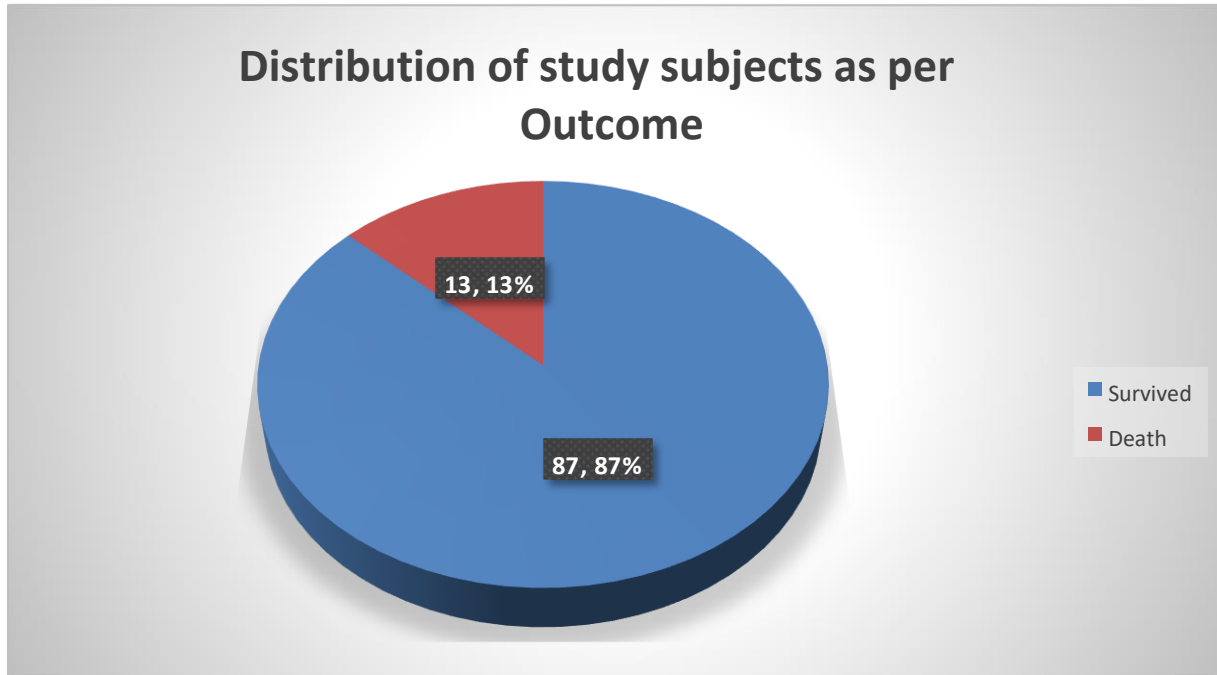


Table 3. Comparison APACHE IV score levels with outcome

	Survived	Death	P value
APACHE IV score	51.10 ± 26.24	74.13 ± 22.70	<0.001

Mean APACHE IV score in participants who survived and died was 51.10 ± 26.24 and 74.13 ± 22.70 respectively. Difference observed was statistically significant.

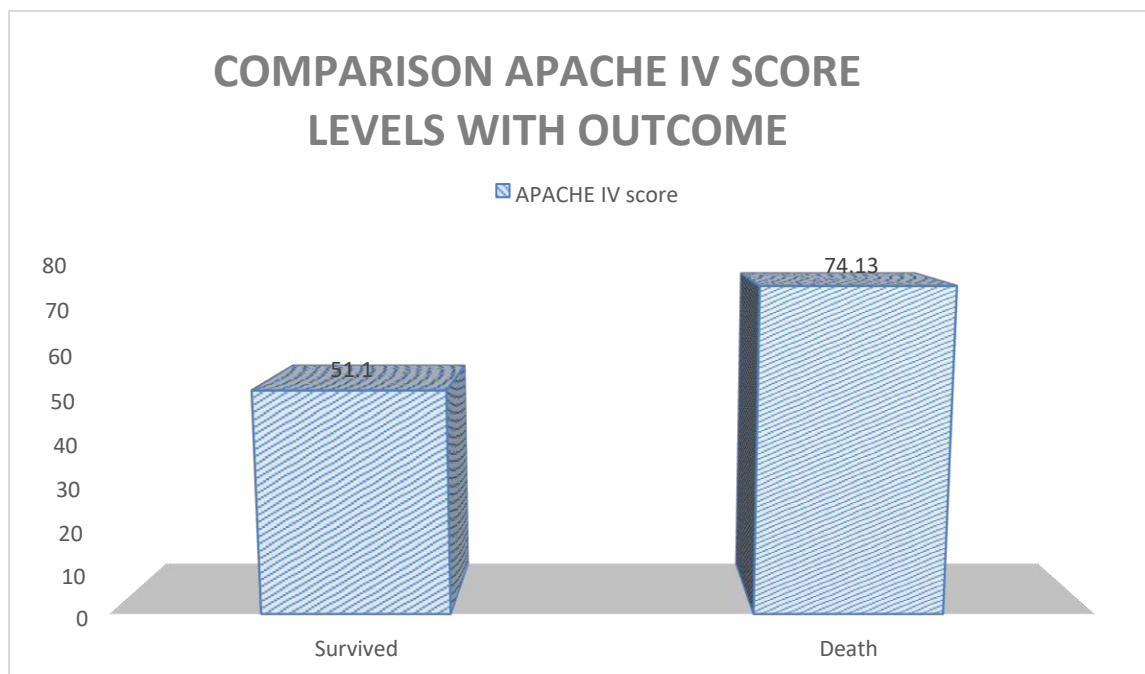


Table 4: Correlation of acute phase reactant with significance

Acute reactant	phase	R value	P value	Significance
C-REACTIVE PROTEIN		0.3127	0.001537	Significant
ESR		0.379	0.000101	Significant
LACTATE DEHYDROGENASE		0.3057	0.001982	Significant
D-DIMER		0.3227	0.001059	Significant
SERUM PROCALCITONIN		0.2602	0.008936	Significant
SERUM LACTATE		0.3054	0.002032	Significant
SERUM FERRITIN		0.2876	0.003715	Significant

Above table shows correlation of R Value & P value in acute phase reactants. R value & P value of C reactive protein was 0.3127 & 0.001537 respectively. R value & P value of ESR was 0.379 & 0.000101 respectively. R value & P value of lactate dehydrogenase was 0.3057 & 0.001982 respectively. R value & P value of D DIMER was 0.3227 & 0.001059 respectively. R value & P value of serum procalcitonin was 0.2602 & 0.008936 respectively. R value & P value of serum lactate was 0.3054 & 0.002032 respectively. R value & P value of serum ferritin was 0.2876 & 0.003715 respectively. Difference observed in R value & P value of C reactive protein, ESR, Lactate dehydrogenase, D DIMER, serum procalcitonin, serum lactate and serum ferritin was statistically significant.

OBSERVATIONS:

In the study of hundred cases admitted in Emergency and ICU diagnosed with sepsis.

Within 24 hours of admission, lab parameters such as Erythrocyte sedimentation rate, C-reactive protein, Serum Lactate dehydrogenase, D-Dimer, SerumProcalcitonin, Serum Lactate, Serum Ferritin were measured and APACHE IV score calculated and based on that severity of the illness and mortality was predicted[14].

The study showed an average increase in on admission inflammatory markers with APACHE IV score values to be statistically significant and may be a predictor for the observed ICU mortality[15].

CONCLUSION:

Acute phase reactants and APACHE IV in prediction of hospital mortality have fair discrimination and calibration and should be useful for benchmarking ICU performance.

INFORMED CONSENT- Purpose of the study and details of protocols were discussed with the patients (if possible) and their relatives and informed written consent was obtained.

DISCLAIMER- The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL- All authors hereby declare that the study was approved by the Institutional ethics subcommittee of Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pimpri (I.E.S.C./10/2020)

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