

## Original Article

# Study of Clinical course and Prognostic factors affecting the course of Septicemia

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## ABSTRACT

**INTRODUCTION:** Sepsis is the combination of a known or suspected infection with accompanying systemic inflammatory response. This study evaluates clinical features, prognostic factors and their effect on outcome of septicemia.

**MATERIAL AND METHODS:** In this prospective, observational study, 50 patients of septicemia were studied from October 2016 to September 2018.

**RESULTS:** Diagnostic accuracy of procalcitonin and lactate was 62% and 44%. Sensitivity and specificity of APACHE II score in predicting outcome was 42.9% and 81.8% respectively, while that of MODS score was 71.4% and 90.9%. Diagnostic accuracy of APACHE II and MODS score was 60% and 80%.

**CONCLUSION:** Pneumonia was the most common source of infection. Most patients had raised Procalcitonin (> 2 ng/ml), Lactate (>2 mmol/l), APACHE II (>25) and MODS score (>15). Diagnostic accuracy of procalcitonin and lactate was comparable to APACHE II and MODS scores. Procalcitonin and lactate are good biological diagnostic markers for sepsis.

**Keywords:** Procalcitonin, Lactate, APACHE-II, MODS

## INTRODUCTION

Sepsis, severe sepsis and septic shock are terms used to describe the body's systemic responses to infection. Severe sepsis is sepsis with acute dysfunction of one or more organ systems and septic shock is a subset of severe sepsis. Underlying illness, increased age, and multisystem organ failure are major risk factors for mortality from sepsis.<sup>(1,2)</sup> The prognosis of the patient with severe sepsis is related to the number of dysfunctional organs. The transition to serious illness may occur during the critical "golden hours", when definitive recognition and treatment provide maximal benefit in terms of outcome.<sup>(3)</sup>

The incidence and associated mortality and morbidity rates of severe sepsis are commonly underestimated. This is a function of number of factors. Many multicenter observational cohort studies has been carried out across the world to find out prognostic factors for evaluation of mortality in septicemic patients with various ICU scoring systems (APACHE II, SAPS III, SOFA, MPM) which will aid in early detection of sepsis and to prepare strategies for management of such patients. Important methods for reducing mortality identified by recent studies include aggressive fluid resuscitation, Early goal directed therapy (EGDT), early administration of antibiotics and the administration of activated protein C to eligible patients with recently introduced PIRO grading system for assessment of Predisposition, severity of infection, physiologic Response, and Organ failure (PIRO).<sup>(4)</sup>

Despite appropriate antibiotics, source control and organ support, the mortality rate in patients with severe sepsis remains at 18% to 50% and that of septic shock ranges from 30% to 87%.<sup>(5)</sup>

## MATERIAL AND METHODS

This prospective observational study was done over a period of two years, from October 2016 to September 2018 in the Department of Medicine, Wanless Hospital, Miraj. It is a 450-bedded tertiary care centre with multiple super-specialty units, 24 hours emergency facilities with well equipped Intensive Care Units, Laboratories, Radiological Services, Operation Theatres, Blood Bank, Pharmacy store. 50 Patients admitted in ICU of Wanless Hospital and fulfilling the eligibility criteria were studied after taking written, informed consent.

The sample size was calculated using following formulae:

$$n = \frac{(Z\alpha/2)^2 * p(1-p)}{E^2}$$

n- Sample size

Z $\alpha/2$  – Z value at 5% error (1.96)

P - Prevalence of septicemia (taken as 28%)<sup>(6)</sup>

E – Allowable error (taken as 15%)

$$n = \frac{(1.96)^2 * 0.28 * 0.72}{(0.15)^2}$$

(0.15)<sup>2</sup>

n- 35 (approx.)

So, by rounding off, we took 50 subjects.

Consecutive type of non-probability sampling was followed for the selection of study subjects.

### Inclusion Criteria

1. Presence or suspicion of infection, coupled with evidence of systemic response to the infection manifested by a systemic inflammatory response of the following:
  - A. Alteration of body temperature : either <36<sup>0</sup>C or > 38<sup>0</sup>C
  - B. Increased heart rate - > 90/min
  - C. Increased respiratory rate (> 24/min); or evidence of hypoventilation (PaCO<sub>2</sub> <32 mmHg)
  - D. Changes in WBC count < 4000/cu.mm or > 12000/cu.mm or increased number of immature polymorphonuclear leucocytes.
2. Along with above mentioned criteria presence of one or more of the following:
  - I. Arterial hypotension that responds to intravenous fluid administration.
  - II. Systolic blood pressure <90 mmHg or mean blood pressure <70 mmHg.
  - III. Acute oliguria – Urine output <0.5 ml/kg/hr for at least 1 hour despite adequate fluid resuscitation
  - IV. PaO<sub>2</sub>/FiO<sub>2</sub> = <250 or if the lung is the only dysfunctional organ then <200
  - V. Platelet count < 80000/ cu.mm or < 50% of highest value recorded over previous 3 days
  - VI. Unexplained metabolic acidosis- pH < 7.30 or Base deficit >5 mEq/L and plasma lactate levels >1 mmol/L

**Exclusion Criteria:** Patients suffering from Chronic kidney disease, chronic liver diseases i.e. Cirrhosis etc and patients less than 12 years of age were excluded from this study.

After selection of cases, detailed history, clinical examination and then relevant investigations were carried out as required, which included CBC, Blood Sugar Levels, Serum Electrolytes, RFT, LFT, ABG, Sr. Lactate, Sr. Acetone, PT, INR, APTT, Procalcitonin levels (B.R.A.H.M.S. PCT-Q kit), C-reactive protein, Blood Cultures,

Urine Analysis, Urine and other cultures, Bronchoalveolar lavage, and Imaging studies such as Chest Xray, USG, CT scan, MRI.

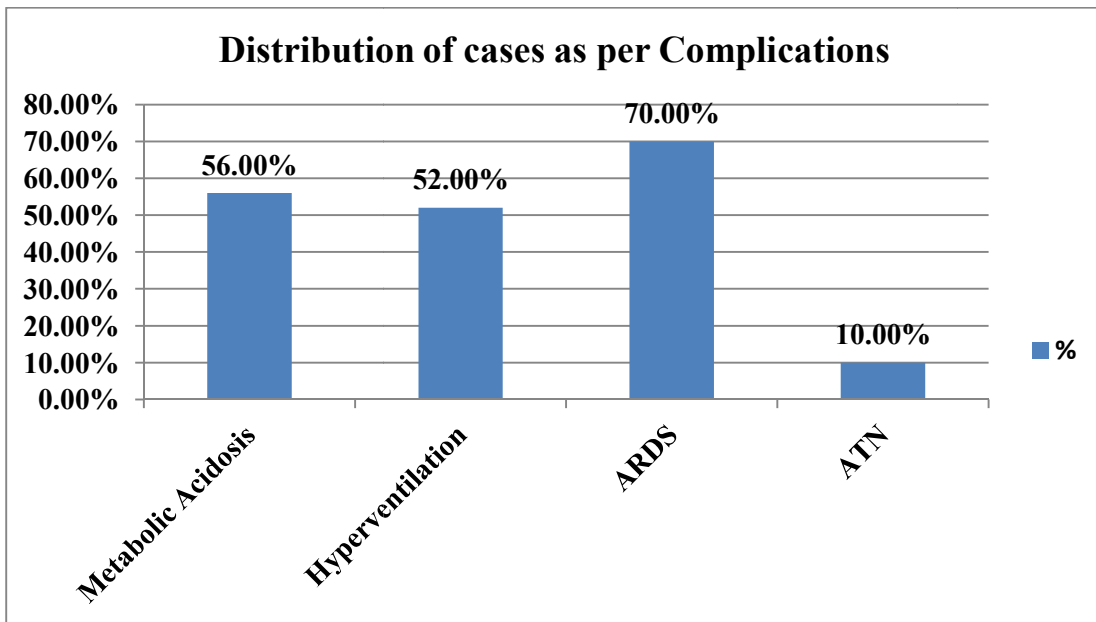
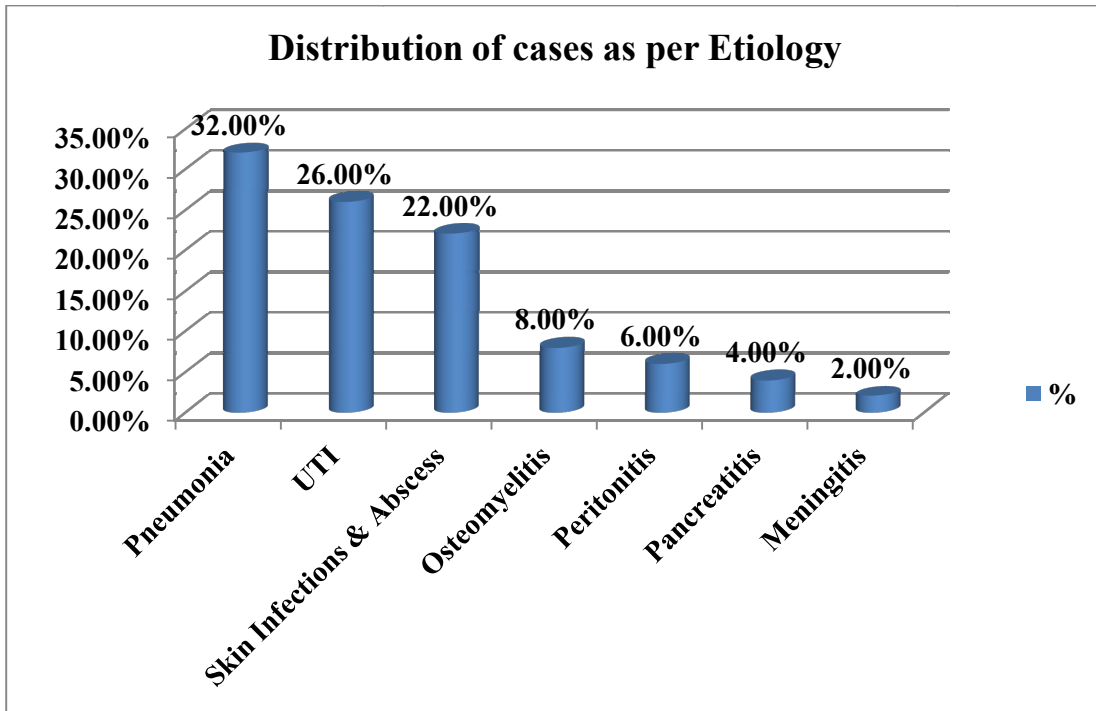
APACHE II and MODS scores were calculated for every patient. All the patients were treated with appropriate antibiotics, either according to suspicion of infection site or documented culture sensitivity. All patients were monitored on day 1, 3, 5, 10 and 15. Tables and charts were formed which included various clinical and biochemical parameters, e.g. Heart rate, fever, temperature, Respiratory rate, Blood pressure, GCS, Lactate, Procalcitonin. Values of Various parameters were correlated with each other and their significance with outcome of disease was evaluated statistically. The quantitative data was represented as the mean  $\pm$  SD. Categorical and nominal data was expressed in percentage. The t-test was used for analysing quantitative data, or else non-parametric data was analyzed by Mann Whitney test and categorical data was analyzed by using chi-square test. The significance threshold of p-value was set at  $< 0.05$ . All analysis was carried out by using SPSS software version 21.

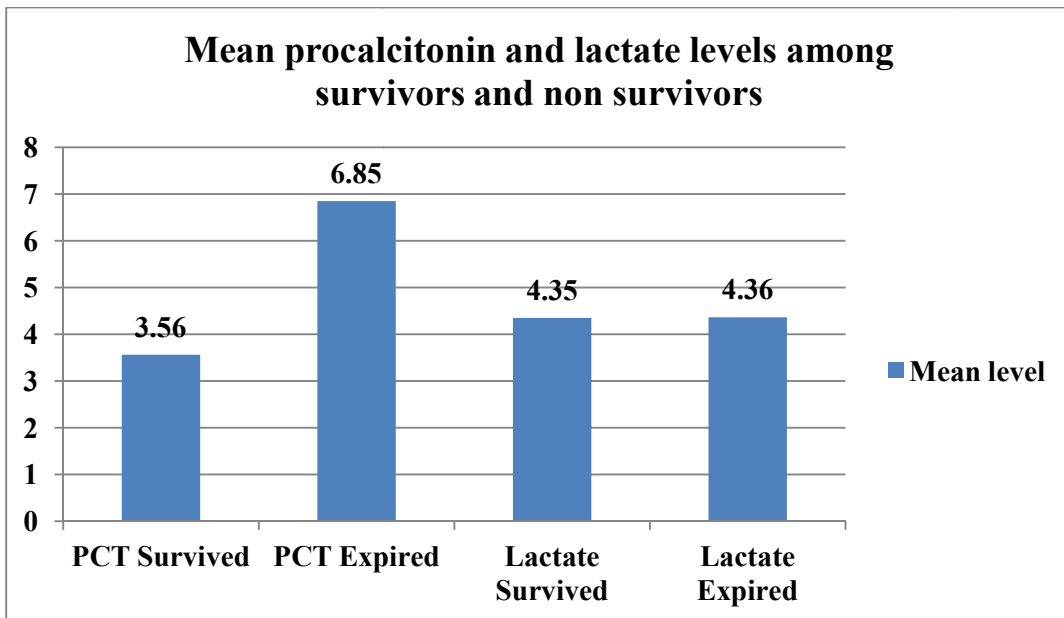
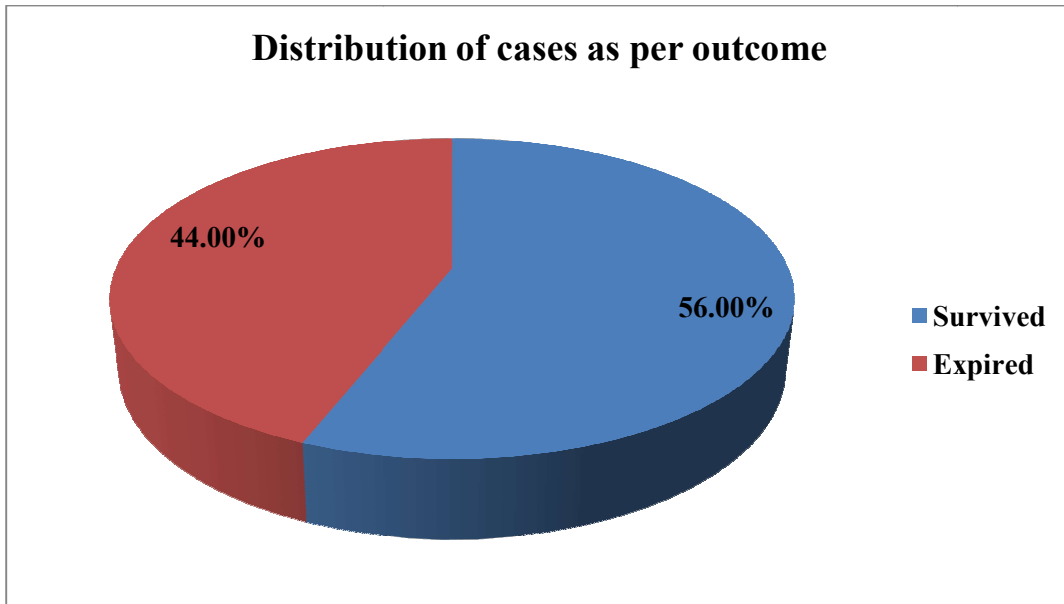
## RESULTS

Mean age of the study cases was 54.47 years with 54% cases being over 50 years of age. Male predominance was seen with 76% males to 24% females. Pneumonia was the most common etiology for sepsis (32%), followed by UTI (26%) and skin infections and abscesses (22%). 98% cases had temperature of 98.6<sup>0</sup> F or more while 41 (84%) patients had temperature  $>101^0$ F. Heart rate above 120 beats per minute was seen in 54%. Respiratory rate above 24 per minute was seen in 84% cases. GCS Score between range of 5-10 and below 5 was seen in 14% and 10% cases respectively. Prevalence of hypotension was 56%. CVP over 10 cm of H<sub>2</sub>O was noted in 44% cases while in 20% cases it was between the range of 5-10 cm of H<sub>2</sub>O. Prevalence of Oliguria was 60%. Raised Procalcitonin levels ( $>2$  ng/ml) was seen in 58% cases of sepsis. Raised APACHE score ( $> 25$ ) was seen in 68% cases. Raised MODS score ( $> 15$ ) was seen in 56% cases. Most commonly observed complication was ARDS (70%) followed by metabolic acidosis (56), hyperventilation (52%) and acute tubular necrosis (10%).

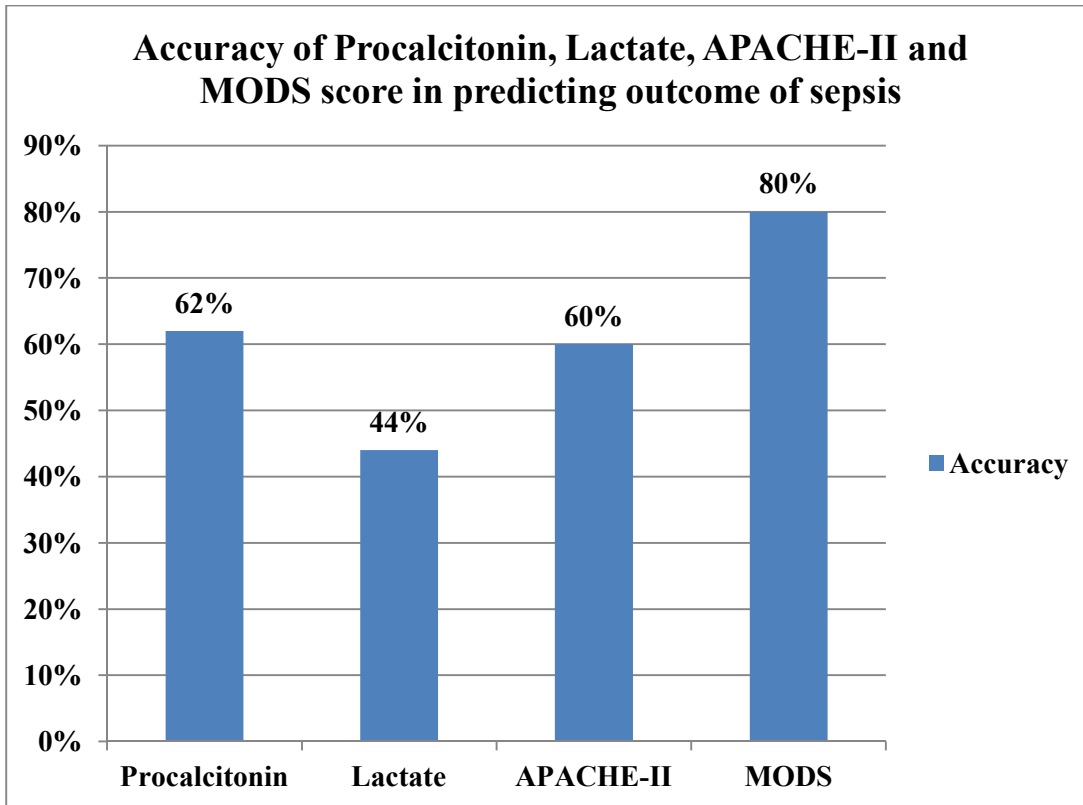
The mortality rate in the present study was 44%. Mean Procalcitonin (6.85 ng/ml vs 3.56 ng/ml) was significantly higher among expired cases as compared to survivors ( $p < 0.01$ ) while no difference was observed between lactate levels (4.36 vs 4.35 mmol/l;  $p=0.98$ ). Sensitivity and specificity of procalcitonin in predicting outcome of sepsis was 53.6% and 72.7% respectively with overall accuracy of 62%. Specificity of lactate in predicting outcome of sepsis was 100% with overall accuracy of 44%. Sensitivity and specificity of APACHE II score in predicting outcome of sepsis was 42.9% and 81.8% respectively, with overall accuracy of 60%. Sensitivity and specificity of MODS in predicting outcome of sepsis was 71.4% and 90.9% respectively, with overall accuracy of 80%.

The limitation of this study was that it included a small sample size and the prognostic value of other scoring systems such as SOFA, qSOFA, MPM II, were not assessed.





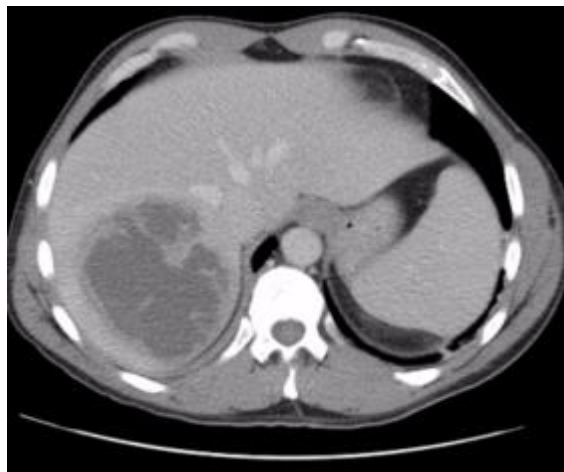
	Sensitivity	Specificity	PPV	NPV	Accuracy
<b>Procalcitonin</b>	53.6%	72.7%	71.4%	52.2%	62.0%
<b>Lactate</b>	N.A.	100%	N.A.	44%	44%
<b>APACHE-II</b>	42%	81.8%	75%	52.9%	60%
<b>MODS</b>	71.4%	90.9%	90.9%	71.4%	80%



**X RAY of ARDS**



**X RAY of Bronchopneumonia**



**CT of Liver Abscess**

## **DISCUSSION**

In this study we have observed the clinical course of sepsis and prognostic factors affecting outcome of disease using APACHE II, Multiple Organ Dysfunction Score (MODS) and Biochemical markers like serum lactate and procalcitonin levels. Mean age of the study cases was 54.47 years with 54% cases being over 50 years of age. Male predominance was seen with 76% males to 24% females.

Study in India in 2010 by S Todi et al had shown that sepsis is common in elderly age group (>50 years; 61%) and in males (57.71%).<sup>(7)</sup> Dash et al<sup>(8)</sup> in a similar study observed the mean age of cases were 38.15 years with male and female ratio as 1.63:1. Anand A et al found that the maximum number of patients with

sepsis were in the age group of 60-69 years. The mean age was  $67.52 \pm 6.65$  years with male:female ratio of 1.68.<sup>(9)</sup> Thus the age and gender distribution in our study was consistent with the findings of previous studies.

Pneumonia was the most common observed etiology for sepsis (32%) followed by UTI (26%) and skin infection and abscesses (22%). Osteomyelitis was seen in 8%, peritonitis in 6%, pancreatitis in 4%, and meningitis in 2%. Vincent JL et al<sup>(10)</sup> in the study of sepsis in European intensive care units found that the lung was the most common site of infection (68%), followed by the abdomen (22%), blood (20%) and urinary tract (14%). Study by S Todi et al<sup>(7)</sup> stated that the lung was predominant source of sepsis (57.45%). In the study by Paary et al<sup>(11)</sup> most common source of infection was from the respiratory tract (37.2%) followed by urinary tract (10.3%) and intra-abdominal (9.5%) infections. Maira M. Rosolem et al<sup>(12)</sup> in their study of critically ill patients with cancer and sepsis, found that out of 563 patients, 91% had sepsis. The most frequent sites of infection were lung, abdomen and urinary tract. Patients with pneumonia and abdominal infections had worse outcomes.

On Examination, total of 49 out of 50 cases had temperature of  $98.6^{\circ}\text{F}$  or more while 41 (84%) patients had temperature  $>101^{\circ}\text{F}$ . Heart rate  $> 120$  beats/min and respiratory rate  $>24$ /min was seen in 54% and 84% cases respectively. GCS Score between range of 5-10 and below 5 was seen in 14% and 10% cases respectively. Hypotension was noted in 56% and CVP  $> 10$  cm of water was noted in 44% of cases while in 20% cases it was between the range of 5-10 cm of water. Oliguria was seen in 60% patients.

Dash et al<sup>(8)</sup> in his study of clinical profile and outcome of organ dysfunction in sepsis observed that out of 100 cases of sepsis, fever was the most common clinical presentation (100%). Hypotension was present in 37% of the patients. Arun VG et al<sup>(13)</sup> in their study found that fever (71%) was the most common symptom, followed by cough. Only 30% of the patients were found to be febrile at the time of presentation. 38% of patients had shock at the time of presentation. Widodo D<sup>(14)</sup> in his study of patients with sepsis found that body temperature was  $>38^{\circ}\text{C}$  in 73.8% of subjects and  $<36^{\circ}\text{C}$  in 4.8%. Heart rate of  $>90$ /minute was seen in 100% of patients. Respiratory rate  $>20$  per minute was seen in 95.2%. Mean Arterial Pressure of  $<70$  mmHg was seen in 19% of subjects. GCS  $<15$  was seen in 71.4% of subjects.

We observed ARDS in 70% patients throughout the course of disease. The incidence of hyperventilation and metabolic acidosis in our study was 52% and 56% respectively. ARDS is quite common in patients with bacteremia or sepsis. Study by Fein AM et al had reported rates ranging from 18 to 38%.<sup>(15)</sup> Study by Mikkelsen ME et al<sup>(16)</sup> showed that the incidence of ARDS was 6.2% (48 out of 778 patients) in patients presenting to the emergency department with severe sepsis. Greg S. Martin et al<sup>(17)</sup> found in their US study, that the organs that failed most frequently in patients with sepsis were the lungs (18% of patients) and the kidneys (15% of patients). Widodo<sup>(18)</sup> found that metabolic acidosis ( $\text{HCO}_3 < 22$  mEq/L) was present in 69% of subjects, which was higher than that seen in our study.

In present study, mortality rate in cases of sepsis was observed as 44% which was comparable to 55.3% and 57.6% of previous two Indian studies: <sup>(7,18)</sup> Paary et al<sup>(11)</sup> also observed total mortality rate among patients with sepsis/ septic shock as 51.6%. In another similar study, Dash et al<sup>(8)</sup> observed mortality rate as 38% among sepsis cases. Thus, when we compared our mortality rates was similar to a German study (48.4%).<sup>(19)</sup> However, lower mortality rates have been reported from Australia and France, which were 26.5% and 35% respectively.<sup>(20,21)</sup> Raised Procalcitonin levels ( $> 2$  ng/ml) was seen in 58% cases of sepsis. Mean PCT levels (6.85 vs 3.56 ng/ ml) were significantly higher among expired cases as compared to survivors ( $p < 0.01$ ).



Sensitivity and specificity of procalcitonin in predicting outcome of sepsis was 72.7% and 53.6% respectively with overall accuracy of 62% in our study.

Indian studies by Rajesh V.I. et al from Hyderabad (2009) studied procalcitonin levels and CRP with SOFA scores and found that procalcitonin correlates significantly with severity scores and it is an independent predictor of mortality in sepsis and Multi Organ Dysfunction compared to CRP.<sup>(22)</sup> Esra Keçe et al<sup>(23)</sup> observed that procalcitonin had a sensitivity of 63.64% and specificity of 76.56% for differential diagnosis of sepsis. Jain S et al<sup>(24)</sup> studied procalcitonin as a prognostic marker for sepsis, but used higher cut off values of 7 ng/ml. They found that PCT levels <7 ng/ml showed higher cumulative survival than those with level  $\geq$  7 ng/ml. Procalcitonin levels  $\geq$  7 ng/ml predicted mortality with a hazard ratio of 2.6.

Raised lactate levels (>2 mmol/lit) was seen in 100% cases of sepsis in our study. Mean lactate (4.36 vs 4.35 mmol/lit) was not significantly higher (p value of 0.98) among expired as compared to non expired. Specificity of lactate in predicting outcome of sepsis was 100% with overall accuracy of 44%. Robert Robello Filho et al in his study to determine the mortality prediction rate of blood lactate levels (cut off > 2.5 mmol/lit) found that blood lactate levels had a sensitivity, specificity and negative predictive value of 67.4%, 61.7% and 94.2% respectively.<sup>(25)</sup> Ar-aishah Dadeh et al in their study of serum lactate levels as prognostic predictor of septic shock in emergency department patients with SIRS found that a lactate level greater than 36 mg/dl was associated with increased 28 day hospital mortality. Lactate level was also statistically significant to the progression to septic shock (p=0.013) with 50% sensitivity and 73.2% specificity.<sup>(26)</sup> Arvind Anand et al in his study of serum lactate as prognostic marker in Indian elderly with septicemia found that initial high serum lactate level was associated with increased mortality independent of etiology of sepsis.<sup>(27)</sup>

Raised APACHE score (>25) was seen in 68% cases of sepsis in our study. Sensitivity and specificity of APACHE II score in predicting outcome of sepsis was 42.9% and 81.8% with overall accuracy of 60%. Liu B et al<sup>(28)</sup> in their study too found APACHE II score to be independent predictor of 28-day mortality in septic patients. Hosseini M et al<sup>(29)</sup> observed similar results with diagnostic accuracy of APACHE II as 73% in predicting mortality among sepsis cases.

Raised MODS score (>15) was seen in 56% cases of sepsis. Sensitivity and specificity of MODS in predicting outcome of sepsis was 71.4% and 90.9% with overall accuracy of 80.0%. Jacobs S et al<sup>(30)</sup> in their study observed that difference between the maximum and initial Multiple Organ Dysfunction scores (delta score) was significantly greater in non-survivors than in survivors (5.6 +/- 4.7 vs. 2.8 +/- 3.0) (p< 0.05). The study concluded that Organ Dysfunction scores mirrored organ dysfunction and could accurately describe the outcome groups. Bota DP et al<sup>(31)</sup> observed similar results with diagnostic accuracy of MODS as 69.4% in predicting mortality among sepsis cases.

## CONCLUSION

Pathophysiology of sepsis is complex and multifactorial. In severe cases sepsis can lead to septic shock, widespread organ failure and death. Pneumonia was the most common source of infection in our study, and respiratory system was the commonest organ dysfunction seen. Mortality was highest among patients with multi-organ dysfunction. Most of the patients had raised Procalcitonin levels (> 2 ng/ml), Lactate levels (>2 mmol/l), APACHE II score (>25) and MODS score (> 15). Overall diagnostic accuracy of procalcitonin and lactate was comparable to APACHE II and MODS scores. Our results thus showed that Procalcitonin and lactate represent good biological diagnostic markers for sepsis and they should be included in diagnostic

guidelines for sepsis and in clinical practice in intensive care units. They can be considered as significant and sensitive predictors of sepsis syndrome and thus can guide for further management strategies.

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