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Geriatric Medicine

Procalcitonin as a Marker of Sepsis in Hospitalised Elderly

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Abstract **Original Research Article**

Sepsis is systemic inflammatory response to acute infection; it is very common in elderly and is one of the leading causes of mortality. Due to immunosenescence and other ageing changes, atypical and subtle presentations are common and there will be diagnostic difficulties. There is a need `for means to diagnose sepsis early so that appropriate treatment can be initiated. The aim of the study was to determine the significance of procalcitonin as a biomarker in the early diagnosis and prognosis of sepsis in elderly patients and to compare it with conventional markers of sepsis. This cross sectional and observational study was done in the patients admitted to Geriatric medical ward and Geriatric intensive care unit (GICU) of Rajiv Gandhi Government general Hospital, Chennai. Ethical committee clearance for conducting the study was obtained and the study period was 6 months. The sample size was 75. Those who are above 60years, fulfilling the criteria for sepsis (Signs of systemic response to infection+ Evidence of atleast one organ dysfunction as per definition) and patients willing to and consenting to participate in the study. The patients with h/o trauma, pancreatitis and unwilling to participate were excluded. After admission, routine blood investigations including inflammatory markers like TLC, ESR, CRP were done. Severity scoring done using APACHE and SOFA scoring systems. Serum procalcitonin level was also measured using chemiluminiscence technique. Results were statistically analysed. Procalcitonin was found to be an excellent indicator of sepsis. In this study procalcitonin predicts mortality (P<0.001) and severity of sepsis (P<0.001) and was better when compared with usual markers of sepsis like WBC count (P=0.057), ESR(P=0.09) and CRP(P=0.714) Increased procalcitonin level at admission is a better predictor of organ dysfunction and mortality in elderly patients and its prognostic value in elderly patients is much better when compared to other markers of sepsis including CRP.

Keywords: Procalcitonin, biomarker, sepsis, elderly.

INTRODUCTION

Sepsis is a systemic inflammatory response secondary to an acute infection. The incidence of sepsis and mortality due to it has increased, particularly in older adults above 60yrs of age and is one of the leading causes of mortality in them. More than 50% of the population with severe sepsis is over 65 yrs old. Since there is a worldwide increase in aging population, the incidence of sepsis is also expected to rise.

Due to decline in immune function observed generally in elderly patients results in atypical and mostly subtle (e.g.mild fever or even apyrexia) clinical presentation of sepsis and bacteremia, Atypical symptoms and presentation in elderly can lead to difficulty in clinically diagnosing sepsis, leading to a delay in diagnosis and initiation of therapy resulting in higher mortality.

The early detection of patients with sepsis with poor prognosis or with an increased risk of mortality is very important in order to prevent subsequent organ dysfunction, which further increases the degree of complications and thereby mortality. Hence there is an obvious need for biomarkers of inflammation to detect bacterial infections in patients with sepsis.

Parameters other than infection may influence the conventional markers of inflammation and they may be slowly released during the progression of an infection. Bacteriological reports will not be available before 24 to 48 hours. Moreover positive reports may be due to contamination and negative reports will not exclude sepsis. Procalcitonin tends to increase earlier upon infection with a very rapid decline in serum level when the infection is controlled. Moreover the production of procalcitonin, unlike other biomarkers including C-reactive protein (CRP), seems not to be significantly weakened by non-steroidal and steroidal

anti-inflammatory drugs. Estimation of serum procalcitonin level may be helpful in diagnosing and treating sepsis at the earliest.

Procalcitonin levels tend to increase with organ dysfunction and increase in severity of sepsis, Furthermore, administration of procalcitonin to septic animals had shown to increase their mortality risk, thereby indicating a relationship between increased serum procalcitonin and death. The serum procalcitonin levels may aid in earlier identification and better stratification of septic patients with increased risk of death:

However the relation of serum procalcitonin level with the prognosis of sepsis is unclear. In addition to that the usefulness of bio markers such as procalcitonin in elderly population has not been studied adequately, as most of the previous studies included either adult or paediatric population, necessiating the need for further studies in elderly population

Aim and objectives

- To estimate the significance of procalcitonin as a biomarker in the diagnosis of sepsis in elderly patients.
- To estimate the role of procalcitonin in the prognosis of sepsis in elderly and to compare it with conventional markers of sepsis

METHODOLOGY

This cross sectional and observational study was done in the patients admitted to Geriatric medical ward and Geriatric intensive care unit (GICU) of Rajiv Gandhi Government general Hospital, Chennai. Ethical committee clearance for conducting the study was obtained and the study period was 6 months. The sample size was 75.

Inclusion criteria

- Those who are above 60years ,
- fulfilling the criteria for sepsis [11](Signs of systemic response to infection+ Evidence of atleast one organ dysfunction as per definition) and
- patients willing to and consenting to participate in the study

The patients with h/o trauma, pancreatitis and unwilling to participate were excluded. History including demographic characteristics (age and sex), co-morbidities and physical examination findings were recorded. Blood sample were drawn from patients within 24 hrs following admission for basic laboratory investigations including basic biochemistry, complete blood count, coagulation profile and other relevant investigations for sepsis inluding CRP and Procalcitonin, Microbiological cultures from the suspected sources of infection were also done on admission. Scoring for severity of illness like APACHE II and SOFA scoring were done on admission.

Measurement of Procalcitonin

After admission, by sterile technique 5 ml of venous blood was drawn. After keeping at room temperature for 2 hours, it was centrifuged for 10 minutes at 3000 rpm, and supernatant stored at -70 degree Celsius until analysis. Serum Procalcitonin was measured by chemiluminiscence technique, using fully automated analyzer. A cut off of >2 ng/dl was considered as cut off of severe bacterial infection, sepsis and multiorgan failure.

RESULTS

Age and Gender

Out of 75 participants, 38 were in the age group 61- 70 years, 20 were in 71-80 age group and 17 were above 80. The age ranged from 61 years to 101 years. The mean age group was 73 years. The maximum number of patients was in the age group of 60 to 69. There were 42 males and 33 female participants constituting 56% and 44 % of the study population respectively.

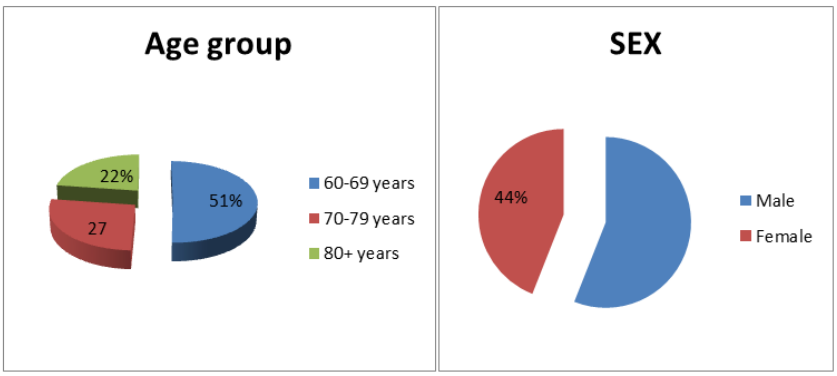

Fig-1

Severity of Sepsis

Out of the 75 subjects in our study, 36(48%) had severe sepsis and 39(52%) were with septic shock. Out of 38 in the age group of 60-69yrs, 15 had severe sepsis and 23 septic shock ;between 70-79 years of age, there were 20subjects, among them 9(45%)were with severe sepsis and 11(55%) with septic shock . Above 80 years of age, there were 17subjects, among them 12(71%) were with severe sepsis and 5(29%) were with septic shock.

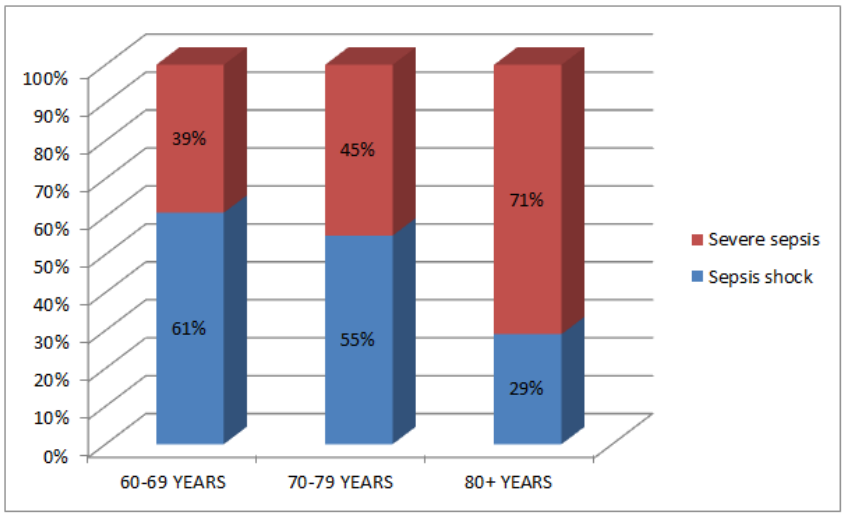

Fig-2

Influence of various factors on outcome

In our study the overall mortality due to sepsis was 48% and the mortality increased with increasing age. It was 29%, 70% and 65% among patients in the 61-70, 71-80 and >80 years of age group respectively. There is a statistically significant co-relation between increasing age and mortality (P Value-0.004). Maximum mortality is seen in patients above 70yrs of age. The gender association with mortality was not statistically significant.

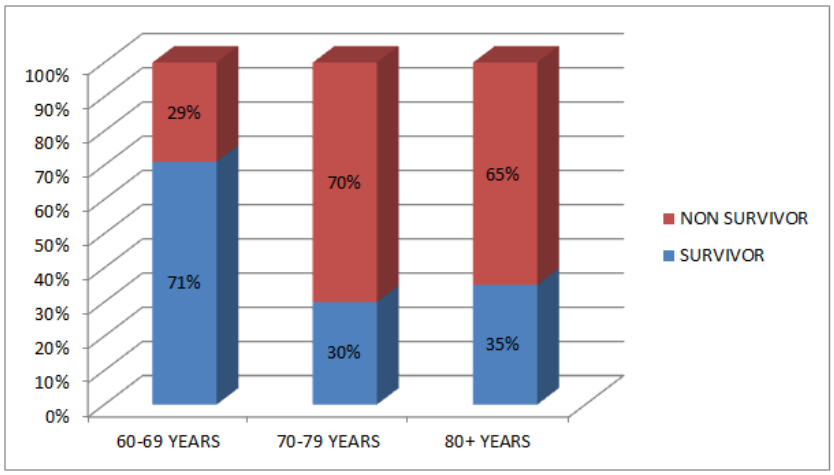

Fig-3

Among the 75 patients in our population only 20% of the subjects showed positive blood culture. Blood culture was negative in the remaining 80% of the population. There was no statistically significant relationship between blood culture positivity and mortality in our study. Gram Negative Septicemia was most common; Acinetobacter species was the most common organism causing bacteremia and sepsis followed by Pseudomonas and Klebsiella species.

In our study, Respiratory tract was the most common source of infection leading to sepsis in elderly. Pseudomonas followed by Acinetobacter species were the most common organisms isolated from respiratory specimens. Urosepsis was the second most common source of infection. E.coli was the most common organism isolated from urine samples. In our study there is no statistically significant relation between culture positivity and mortality and patients with culture positivity was seen in 66.7% of non-survivors and 48.7% of survivors.

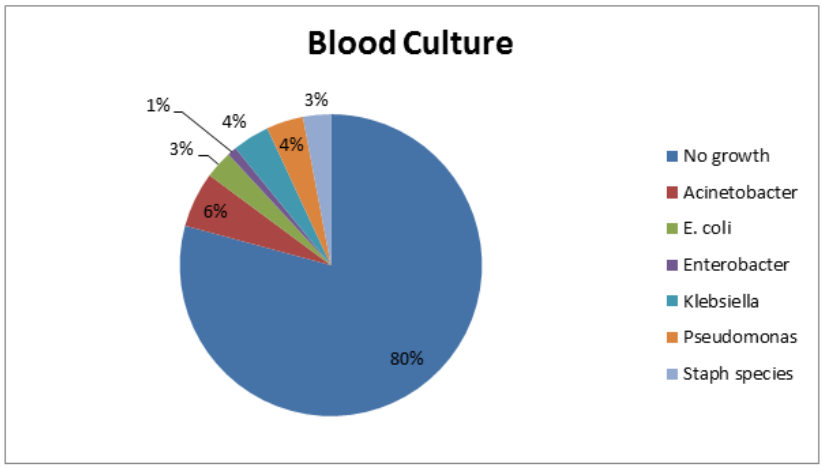

Fig-4

The percentage of renal failure increased with the severity of sepsis. In our study 41.7% of patients with severe sepsis and 76.9 % with septic shock presented with acute renal failure. Among the patients with sepsis, those who have got acute kidney injury had higher mortality rate, which was statistically significant (P value-0.011).

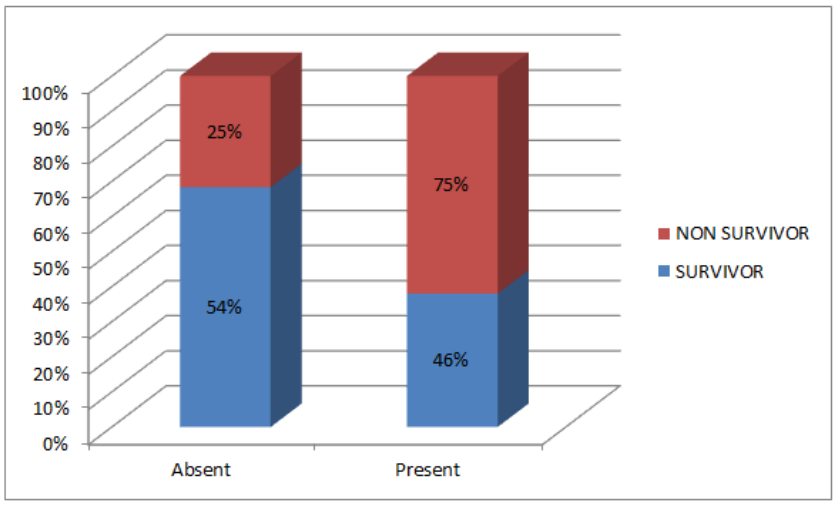

Fig-5

Among the clinical parameters, low Mean Arterial Pressure had better correlation with negative outcome of patients with sepsis. Similarly, among the lab parameters besides urea and creatinine, higher prothombin time and INR was associated with higher mortality whereas total WBC count, ESR and CRP had no predictive value for the outcome.

Baseline APACHE II and SOFA Scores were significantly higher in non-survivors. The APACHE score ranged from 11-27 in survivors compared to 25-34 in non- survivors. SOFA score ranged from2-8 in survivors compared to 7-16 in non- survivors. Higher scores were associated with mortality in statistically significant manner (P value <0.001).

Procalcitonin and outcome

In this study, Procalcitonin- a marker of sepsis was found to be elevated above 2 ng/ ml in all subjects i.e 100% of sepsis patients. There is a significant rise in serum procalcitonin based on the severity of sepsis, patients with septic shock showing a higher level of procalcitonin compared to those with severe sepsis. When viewing the outcome with reference to procalcitonin level, it was observed that the value was between 2-10 ng in 90% of survivors against 10% of non- survivors. The value of 10-30 ng was observed in about 67 % of non survivors compared to 33% of survivors. A value of > 30 ng was observed exclusively in 9 persons of non survivors group. This was found to be statistically significant (P value-0.001).

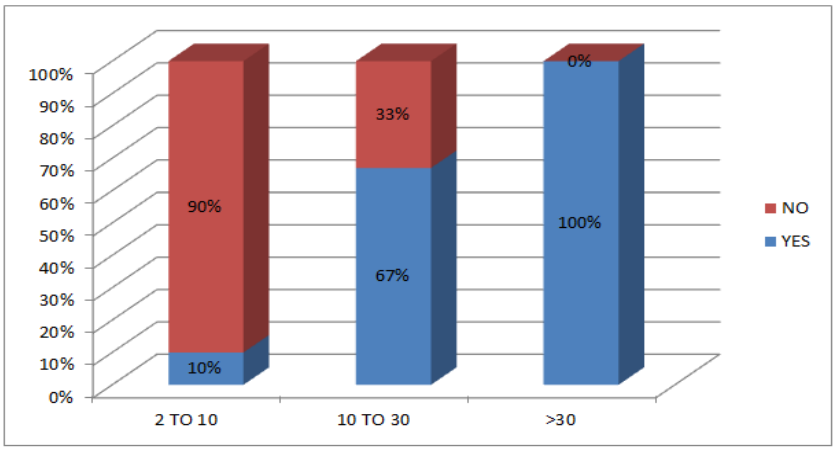

Fig-6

Table-1: Comparison of various factors in Survivors and Non-survivors

Outcome-Death		N	Mean	Std. Deviation	Std. Error Mean	t value	p value
Age	no	39	69.18	7.99	1.28	3.259**	0.002
	yes	36	76.36	10.97	1.83		
Temp	no	39	100.67	1.42	0.23	1.256	0.212
	yes	36	101.08	1.41	0.24		
MAP	no	39	79.31	7.76	1.24	5.771**	p<0.001
	yes	36	69.67	6.60	1.10		
TC	no	39	17.14	3.94	0.63	1.937	0.057
	yes	36	18.92	4.01	0.67		
Platelets	no	39	1.95	1.13	0.18	1.812	0.074
	yes	36	1.55	0.69	0.12		
Urea	no	39	56.46	20.87	3.34	4.352**	p<0.001
	yes	36	94.75	50.49	8.42		
Creatinine	no	39	2.03	0.73	0.12	4.533**	p<0.001
	yes	36	3.03	1.14	0.19		
PT	no	39	13.67	2.51	0.40	4.926**	p<0.001
	yes	36	17.22	3.66	0.61		
RBS	no	39	171.08	59.63	9.55	1.923	0.058
	yes	36	212.67	120.04	20.01		
pH	no	39	7.34	0.09	0.01	1.822	0.072
	yes	36	7.31	0.03	0.01		
HCO3	no	39	23.41	4.02	0.64	1.819	0.073
	yes	36	21.67	4.27	0.71		
Albumin	no	39	3.05	0.30	0.05	0.918	0.361
	yes	36	2.98	0.37	0.06		
CRP	no	39	18.38	10.40	1.67	0.368	0.714
	yes	36	19.25	9.95	1.66		
ESR	no	39	23.59	15.65	2.51	1.718	0.09
	yes	36	31.42	23.33	3.89		
Procalcitonin	no	39	8.87	3.89	0.62	7.872**	p<0.001
	yes	36	23.66	11.02	1.84		
APACHE	no	39	16.62	4.18	0.67	15.678**	p<0.001
	yes	36	29.33	2.60	0.43		
SOFA	no	39	4.23	1.69	0.27	14.253**	p<0.001
	yes	36	11.58	2.70	0.45		
Duration of Hospital Stay	no	39	12.62	4.59	0.74	9.071**	p<0.001
	yes	36	5.00	2.15	0.36		
Duration of ICU stay	no	39	4.46	1.23	0.20	4.263**	p<0.001
	yes	36	3.33	1.04	0.17		

DISCUSSION

In spite of the advances in medical science and antibiotic therapy sepsis proves to be a major cause of morbidity and mortality in elderly. There are only few studies based on the usefulness of procalcitonin in elderly with sepsis. Our study evaluated the significance of procalcitonin as a biomarker of sepsis in hospitalised elderly and compared it with other conventional markers of sepsis.

In our study the mortality due to sepsis was 48 % which was consistent with the previous studies including a study by Jain *et al*. [1-3]. In our study, respiratory tract was the most common source of sepsis followed by urinary tract which may be partly due to presence of risk factors like diabetes [4]. Culture positivity is seen in 57.3 % of patients which is consistent with previous reports [9], but lower values have also been reported [3, 10]. Blood culture positivity was seen in 20% of the patients. The most common microorganism isolated being Acinetobactor followed by Pseudomonas and Klebsiella, majority of them being gram negative. Culture positivity did not predict prognosis or mortality in our study. This is similar to the findings in previous studies which did not establish relation between culture positivity and mortality [5, 7].

Our study showed significant increase in serum procalcitonin in elderly patients with sepsis, proving its utility as a marker of sepsis, which is consistent with the previous study by Chivate *et al*. [12,13]. In our study serum procalcitonin on admission was markedly elevated in non-survivors, showing correlation between serum procalcitonin and mortality. This is comparable with the previous studies by Meng et al and Clec'h *et al*. [6, 13, 14] ,whereas some studies didn't find procalcitonin to predict mortality [15,16]. The variation may be due to the fact that our study was conducted in an exclusively medical setup excluding surgical and trauma cases which are believed to show spurious rise in procalcitonin level, also majority of the organisms isolated in our study were gram negative. A gram negative septicemia is believed to have significant correlation with serum procalcitonin levels [17,18]. Several studies have shown the significance of procalcitonin in predicting prognosis in sepsis patients [15, 19, 20]. In our study serum procalcitonin level tends to rise with severity of sepsis and organ dysfunction which is consistent with the findings reported by Giamarellos-Baorboulis *et al*. [21].

All the variables were compared including the regular markers of sepsis, sepsis prognostic scoring systems and biomarkers like CRP and Procalcitonin.

Both the survivors and non-survivors were similar in most of the characteristics except that the survivors were mostly of young old age group. With increasing age mortality also had raised significantly. APACHE II is a mortality predictor score commonly used to assess the baseline risk groups being compared in clinical trials. APACHE scoring will not help in the management of patients, but it is a useful tool for risk stratification. The APACHE II score provides an estimate of ICU mortality based on a number of laboratory values and patient signs taking both acute and chronic disease into account. The SOFA (Sequential Organ Failure Assessment) score is a mortality prediction score that is based on the degree of dysfunction of 6 organ systems. It is a scoring system that assesses the performance of several organ systems in the body (neurologic, blood, liver, kidney and Blood Pressure / Hemodynamics) and assigns a score based on the data obtained in each category. Higher the score, higher is the likely mortality. SOFA score has been recommended for assessment of patients with sepsis by the new 2016 Sepsis Definitions Consensus Statement.

In this study, the baseline severity of illness scores like APACHE II and SOFA Scores were significantly higher in non-survivors. In short both these scores are excellent prognostic indicators but do not help in diagnosis. Procalcitonin is significantly raised in non-survivors when compared to survivors whereas other markers of sepsis like Total Leukocyte Count, ESR and CRP didn't show any significant correlation between survivors and non-survivors.

In summary, Procalcitonin serves as good diagnostic and prognostic indicator in sepsis in elderly. Though the mortality predictors and few other clinical markers like age, MAP, and raised renal parameters correlate with increased mortality, they do not contribute for the confirmation of sepsis as well as procalcitonin.

CONCLUSIONS

- Procalcitonin test, as a biomarker of sepsis has greater value in detecting patients with sepsis.
- Its of greater significance also in elderly population with sepsis but test results should always be interpreted in conjunction with clinical findings.
- Increased procalcitonin level at admission is a better predictor of organ dysfunction and mortality in elderly patients and its prognostic value in elderly patients is much better when compared to other markers of sepsis including CRP.
- Further randomised control study on procalcitonin and non-procalcitonin monitored patients is needed to conclude if outcome and cost benefits increase with procalcitonin use.

Limitations

- Single Centre Study and short study period
- Small sample size of 75 patients with no control.
- Pre-existing organ dysfunction could not be ruled out without doubt and few patients were exposed to antibiotics before admission which could have

influenced the procalcitonin levels and other parameters.

- A serum level of Procalcitonin was measured only on admission and was not repeated in regular intervals.

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