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Diagnostic Markers in Patients with Sepsis in Surgical and Trauma Intensive Care Units

Nashwa Sayed Hasan Abdel-Al*[1], Zeinab Hamed Sawan[2], Mona Abdel-Hamed Elharrisi [2], Amr Shaaban Elshafei [2]

[1] Intensive Care Department, Suez Canal Authority Hospital, Ismailia, Egypt.

[2] Anesthesia and Surgical Intensive Care Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding Author: Nashwa Sayed Hasan, Email: drnashwa2010@hotmail.com

ABSTRACT

Background: Sepsis is a significant cause of intensive care unit (ICU) admission and is associated with high morbidity and mortality rates. C-reactive protein (CRP) and serum albumin levels should diverge during sepsis. Using a ratio between CRP and albumin would provide a variable capable of merging the information provided by CRP and albumin into an index that correlates positively with infection. This study aimed to assess the C-reactive protein/albumin ratio as a diagnostic biomarker in monitoring patients with sepsis. **Patients and methods**: This study involved 181 patients who were admitted to the surgical and trauma intensive care unit due to documented or suspected infections and who met at least two criteria for admission related to these infections, as well as at least two criteria for systemic inflammatory response syndrome (SIRS) and the Quick Sequential Organ Failure Assessment (qSOFA) score. **Results**: The age of patients ranged from 20 to 80 years, with the mean age ±SD being 44±18.6 years, and the median was 37.5 years. About 24.8% of patients had a head infection, 35.4% of patients had a chest infection, 23.8% of patients had an abdominal infection, and 16% of patients had a skin infection. qSOFA Score: 39.7% of patients had a score of 1, 22.7% of patients had a score of 2, and 37.6% of patients had a score of 3. The CRP/albumin ratio had a significant negative correlation with systolic blood pressure ($p = 0.002$). It had a significant positive correlation with heart rate ($p < 0.001$), temperature ($p < 0.001$), lactate ($p < 0.001$), WBC ($p < 0.001$), and qSOFA Score ($p = 0.004$). There was a positive correlation between procalcitonin (PCT) and the CRP/albumin ratio ($p=0.003$). Procalcitonin had a significant negative correlation with systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p=0.002$). It also had a significant positive correlation with heart rate ($p<0.001$), temperature ($p=0.023$), lactate ($p<0.001$), WBCs ($p=0.018$), and qSOFA Score ($p<0.001$). **Conclusion**: The CRP/albumin ratio may be an efficient diagnostic biomarker in patients with sepsis.

Keywords: C-reactive protein/albumin ratio, Procalcitonin, Sepsis, Trauma

INTRODUCTION

Typical sepsis, exemplified by severe bacteremia and its consequences, begins when Toll-like receptors (TLRs), particularly TLR4, are stimulated by endotoxins such as lipopolysaccharide (LPS), which those bacteria produce as virulence factors **(1).** This process initiates a global, nonspecific innate inflammatory response that produces a cascade of first pro-inflammatory, followed by anti-inflammatory cytokines **(2).** The most prominent cytokines in the early phase, which are often taken as an estimate of severity if measured, are three cytokines most often defined as standard: interleukin (IL)- 1β, IL-6, and tumor necrosis factor alpha (TNF-α) **(3).**

PCT testing is often combined with C-reactive protein (CRP) to make a putative diagnosis of sepsis. In addition, CRP serves as a generalized marker of inflammation

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

and may be present as a result of such disparate factors as trauma or surgery (both put patients at risk for infection and possibly sepsis) or pre-existing acute or chronic infection **(4).** PCT may also rise as a result of other stimuli, but it is more specific for sepsis risk than CRP **(5)**. Serum albumin is a negative acute-phase protein; thus, the degree of hypoalbuminemia in critically ill patients correlates with the intensity of the inflammatory response triggered by infection **(6).** This study aimed to assess the C-reactive protein/albumin ratio as a diagnostic biomarker for monitoring patients with sepsis.

PATIENTS AND METHODS

This study was conducted as a cross-sectional clinical study at surgical and trauma intensive care units in Zagazig University Hospitals. The included patients' age range from 20 to 80 years old of both sexes (both male and female) admitted to intensive care units show clinical pictures suggesting sepsis and fulfill all criteria of sepsis. Official permission was obtained from the Faculty of Medicine and Zagazig University Hospitals. Approval was obtained from the ethical committee in the Faculty of Medicine (Institutional Review Board, IRB). All participants filled out a formal written consent form and were managed following Surviving Sepsis Campaign international guidelines for management of sepsis and septic shock.

Sample size calculation:

Assuming that the number of patients with sepsis attending surgical and trauma ICUs was 400 patients in 1 year, the positive predictive value of the CRP/albumin ratio in the diagnosis of sepsis is 31%, and the sample size is calculated to be 181 patients using www.openepi.com with a 95% confidence interval (CI).

Inclusion & exclusion criteria:

Patients were included if they had documented or suspected infection and met at least two of the study's systemic inflammatory response syndrome (SIRS) criteria: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >22 breaths/min or arterial partial pressure of carbon dioxide ($PaCO_2$) <32 mmHg; or white blood cell (WBC) count >12,000/mm³ or <4,000/mm³, or >10% immature neutrophils (band forms). Initial lactate levels >2 mmol/L were considered elevated. A quick Sequential Organ Failure Assessment (qSOFA) score ≥2 indicated increased risk of poor outcomes **(Table 1).** Cultures were obtained from the suspected infection site before antibiotics were started.

Table 1: Quick Sequential Organ Failure Assessment (qSOFA) score

qSOFA (QUICK SOFA)	Points
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mmHg	1

The exclusion criteria were patients with causes/diseases other than sepsis that may cause hypoalbuminemia, e.g., hepatic, renal, malnourished, hyponatremic, and acute heart failure patients, and patients with causes/diseases other than sepsis that may cause an increase

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

in CRP level, e.g., autoimmune and chronic inflammatory diseases (such as rheumatoid arthritis, lupus, and vasculitis), and inflammatory bowel diseases.

From each patient, the following data were collected upon admission:

1) Complete history taking, including: Age, Gender, Hospital diagnosis, Date of ICU admission, cause of admission, onset of suspected infection, initial PCT and C-reactive protein/albumin ratio levels.
2) Clinical examination: Level of consciousness by Glasgow Coma Scale (GCS), Head and neck examination. Cardiovascular examination. Chest examination. Abdominal examination.
3) Investigations: Complete blood count, Serum lactates, Arterial blood gases, serum PCT, serum albumin, and serum CRP, cultures from the site of suspected infection.
4) Medications: Diuretics, Proton pump inhibitors, Insulin.

Statistical Analysis:

The collected data were analyzed using SPSS (Inc., Chicago, IL, U.S.A.) version 26.0, Microsoft Excel 2016, and MedCalC program software version 19.1. Data were tested for normal distribution using Shapiro-Wilk's test. Descriptive statistics were done for numerical parametric data as mean ±SD (standard deviation) and range, and for nonparametric numerical data as median and interquartile range, while they were done for categorical data as number and percentage. Independent t-test and Mann-Whitney test were used to calculate the difference between quantitative variables in two groups. Paired t-test was used to compare two dependent groups of normally distributed variables. Chi-square test ($\chi 2$) and Fisher's exact test were used to calculate the difference between qualitative variables. Correlation (Spearman and/or Pearson) was used to identify relations between continuous data. Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of the parameter and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value. P-value was considered significant at <0.05.

RESULTS

The present study showed that the age of patients ranged from 20 to 80 years, with a mean age ±SD being 44±18.6 years, and the median was 37.5 years **(Figure 1).** About 57.5% of patients were females and 42.5% were males **(Figure 2).** About 38% of patients presented post-operatively, 33% with RTA, and 19% with head trauma **(Figure 3)**. About 24.8% of patients had head infection, 35.4% of patients had chest infection, 23.8% of patients had abdominal infection, and 16% of patients had skin infection **(Figure 4).** qSOFA Score: 39.7% of patients had a score of 1, 22.7% of patients had a score of 2, and 37.6% of patients had a score of 3 **(Figure 5).**

CRP/Albumin ratio had a significant negative correlation with systolic blood pressure (p= 0.002). It had a significant positive correlation with heart rate (p< 0.001), temperature (p< 0.001), lactate (p< 0.001), WBC (p< 0.001), and qSOFA Score (p= 0.004). There was a positive correlation between Procalcitonin and CRP/Albumin ratio (p=0.003) **(Table 2).** Procalcitonin had a significant negative correlation with systolic blood pressure (p<0.001) and diastolic

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

blood pressure (p= 0.002). It also had a significant positive correlation with heart rate (p< 0.001), temperature (p=0.023), lactate (p< 0.001), WBCs (p= 0.018), and qSOFA Score (p<0.001) (Table3). There was no correlation between the time of onset of sepsis from the day of admission and other variables in septic patients (p>0.05) (Table4). Validity of Procalcitonin, CRP, Albumin and CRP/Albumin ratio in diagnosing sepsis were shown in **(Figure 6,7,8,9).**

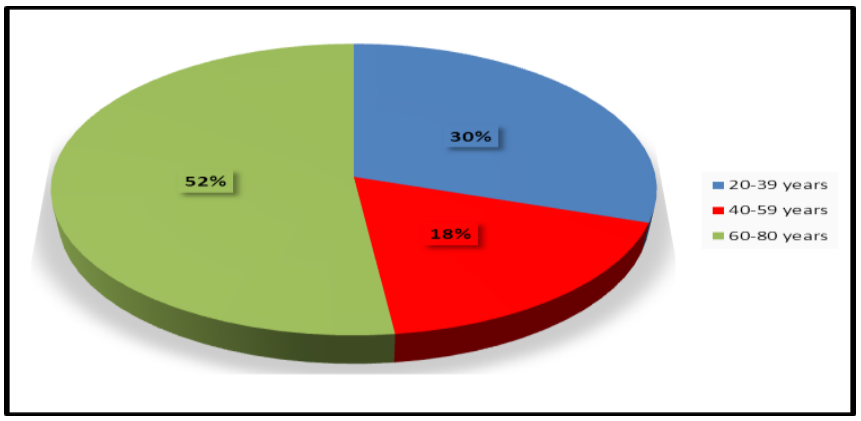

Figure (1): Age distribution in the study group.

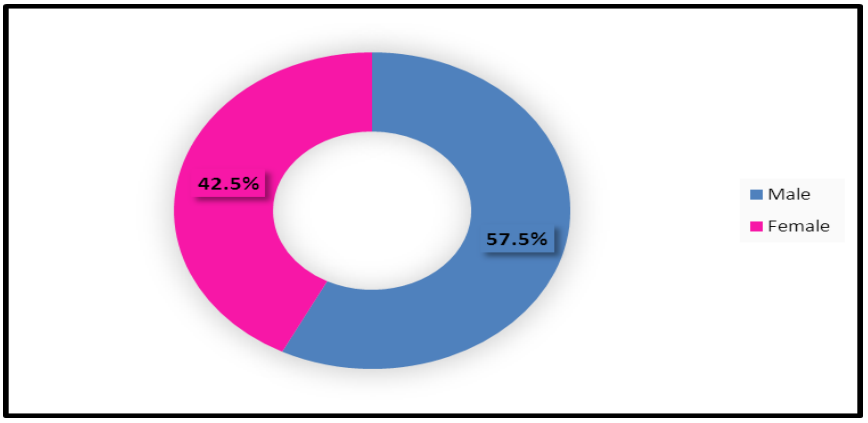

Figure (2): Gender distribution in the study group.

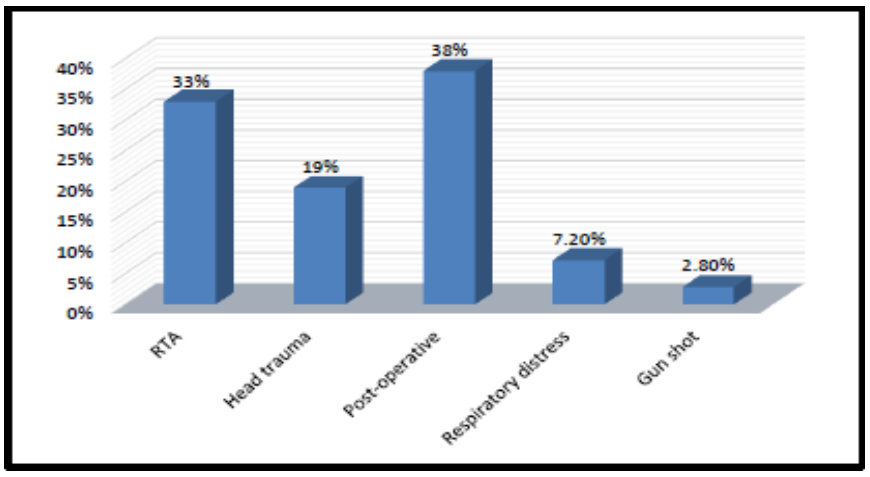

Figure (3): Cause of admission in the study group

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

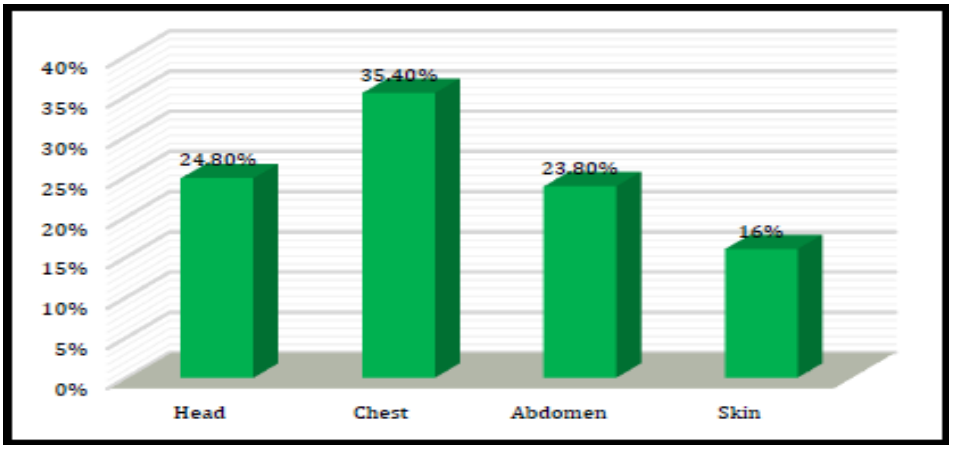

Figure (4): Site of sepsis in the study group

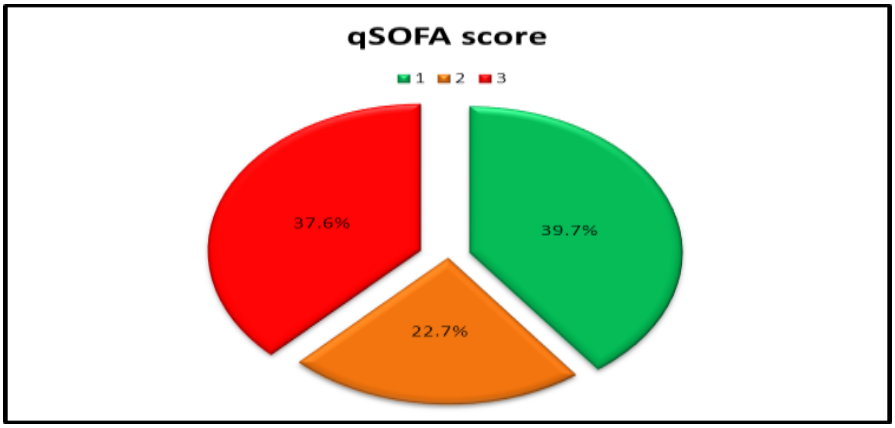

Figure (5): qSOFA Score in the study group.

Table (2): Correlation between CRP/Albumin ratio and other variables in sepsis patients

	CRP/Albumin ratio	
	r	P-value
Age (years)	0.091	0.324
Gender	-0.015	0.518
SBP	-.466	0.002
DBP	-.255	.112
HR	.265	<0.001
Temperature	.435	<0.001
WBCs	.633	<0.001
Lactate	.943	<0.001
Procalcitonin	.219	.003
qSOFA Score	0.443	0.004*

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

Table (3): Correlation between Procalcitonin and other variables in septic patients

	Procalcitonin	
	r	P-value
Age (years)	0.091	0.324
Gender	-0.252	0.116
SBP	-.542	<0.001
DBP	-.484	0.002
HR	.317	<0.001
Temperature	.169	.023
WBCs	.157	.018
Lactate	.272	<0.001
CRP/Albumin ratio	.219	.003
qSOFA Score	0.576	<0.001

Table (4): Correlation between Time of onset of sepsis from the day of admission and other variables in septic patients.

	Time of onset of sepsis	
	r	P-value
Age (years)	-0.037	0.823
Gender	0.069	0.671
SBP	0.138	0.397
DBP	0.11	0.498
HR	0.011	0.95
Temperature	0.21	0.193
WBCs	.295	.064
Lactate	-.126	.440
qSOFA Score	-.024	.883

** $p \leq 0.05$ is considered statistically significant, analysis done by Spearman correlation.*

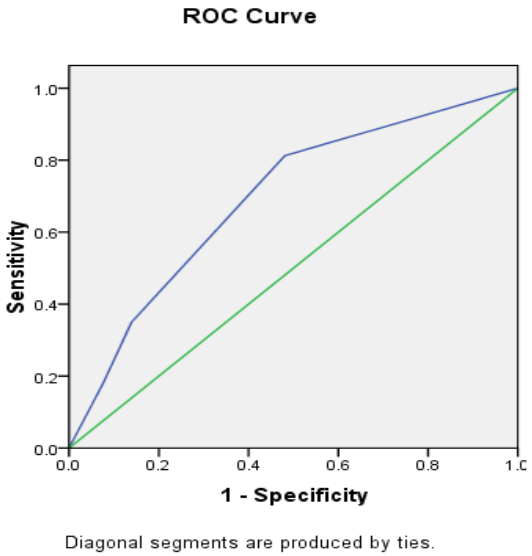

Figure 6: ROC curve showing the validity of Procalcitonin in diagnosing sepsis.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

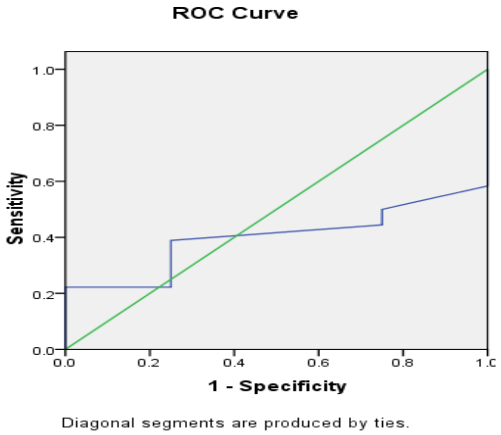

Figure 7: ROC curve showing the validity of CRP in diagnosing sepsis.

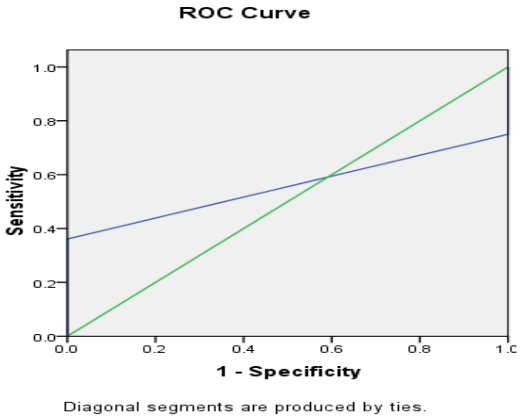

Figure 8: ROC curve showing the validity of albumin in diagnosing sepsis.

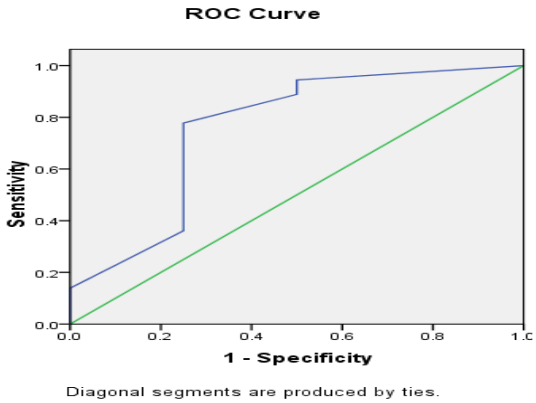

Figure 9: ROC curve showing the validity of CRP/Albumin ratio in diagnosing sepsis.

DISCUSSION

Sepsis is disproportionately increased in elderly adults, and age is an independent predictor of mortality. Compared with younger sepsis patients, elderly nonsurvivors of sepsis die earlier during hospitalization, and elderly survivors more frequently require skilled nursing or

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

rehabilitative care after hospitalization. These findings have implications for patient care and health care resource prioritization and provide insights for expanded scientific investigations and potential patient interventions **(5,6).**

The current study involved number of cases admitted to our surgical and trauma intensive care units is about 30 cases/month. In the study period of 6 months, 181 patients were examined; each patient was observed during the time of onset of sepsis, which ranged from 4 to 6 days from the day of admission. This study aimed to assess the C-reactive protein/albumin ratio as a diagnostic biomarker in monitoring patients with sepsis.

Our study is in agreement with **Angus et al. (7),** a study that determined that the incidence of severe sepsis increased more than 100-fold with age (0.2/1000 in children to 5.3/1000 in patients aged 60–64 years and 26.2/1000 in patients ≥85) and that mortality increased from 10% in children to 26% in patients 60–64 and 38% in those ≥85.

In our study, chest infection was the most prevalent cause. This is in agree with **Esper et al. (8)** study who revealed that respiratory tract infections, particularly pneumonia, are the most common site of infection, and associated with the highest mortality. Moreover, **Argiles et al.(9)** reported that albumin helps to maintain intravascular oncotic pressure, facilitate the transport of substances, and scavenge free radicals. Albumin is considered an indicator of malnutrition, and hypoalbuminemia is related to a systemic inflammatory response. It has been suggested that patients with sepsis with hypoalbuminemia have already had increased serum CRP concentrations and that hypoalbuminemia might be secondary to elevated CRP **(10).** It has been shown that malnutrition and low serum albumin concentrations are associated with poor prognosis in patients with sepsis and that improved nutritional status is related to better outcomes. Thus, it may reflect both the inflammatory and nutritional state in patients with sepsis **(11).**

Our results are in agreement with a previous study; **Özkan Devran et al.(12)** & Quispe et al. **(13)** reported that C-reactive protein (CRP) and albumin (ALB) are useful markers that can predict morbidity and mortality among critically ill patients. This is because CRP effectively reflects acute-phase inflammation **(14),** while ALB may reflect malnutrition among critically ill patients **(15).** Additionally**, Ranzani et al. (4)** revealed that the ratio of CRP to ALB (CRP/ALB) has also recently been used to predict the prognosis of patients with severe sepsis or septic shock.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 06, 2021

CONCLUSION

The CRP/Albumin Ratio may be an efficient diagnostic biomarker in patients with sepsis.

Further studies with a larger sample size and on a large geographical scale are needed to support our conclusion. Future studies should evaluate the efficacy of CRP /albumin ratio as a diagnostic biomarker in sepsis. Further clinical trials and studies are needed for evaluation of new diagnostic biomarkers of sepsis.

No conflict of interest.

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