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Serum Albumin and Platelet counts: As a predictor of severity in Community-Acquired Pneumonia

Dr.S.Indhu[1], Dr.K.V.V.Vijaya Kumar M.D[2], Dr.B.M.S.Patrudu M.D[3], Dr.V.Suryakumari M.D[4],Dr.K.Preethi M.D[5],Dr.MohanRaj[6]
(Department of Pulmonary medicine, Andhra Medical College, Andhra Pradesh, India)[1,2,3,4,5,6]

Abstract
Aim: *To predict the severity ofCommunity Acquired Pneumoniausing hypoalbuminemia andthrombocytopenia.*
Materials and Methods:*A prospective study was conducted on 90 patients with CAP, hospitalized in Government Hospital for Chest and Communicable Disease, Visakhapatnam, from June 2019 to January 2020. The primary outcomes measured were requirement of ICU admission, duration of hospital stay, and 30-day mortality in CAP patients.*
Results: *Among the 90 patients hospitalized, 87.8% patients had hypoalbuminemia (Serum Albumin < 3.5g/dl) and 8.9% had thrombocytopenia (Platelet counts < $100\times10^3/mm^3$) within 24 hours of admission.36.7% of patients required ICU admission, the 30-day mortality rate was 14.4%, and the median duration of stay in hospital was 7days.On ROC analysis,serum albumin of $\leq$ 3.1g/dl has (92.3% sensitivity ,49.35% specificity)in prediction of 30-day mortalityand ICU admission (72.73% sensitivity and 52.63% specificity) respectively and the AUC was found to be 0.737 (p-value 0.0026) and 0.644(p-value 0.0192) respectively.*
The platelet counts of $\leq161\times10^3$ cells/mm^3has 84.62% sensitivity and 88.31% specificityinprediction of 30-day mortality, 48.5% sensitivity and 93 % specificity in prediction of ICU admission with the AUC of 0.882(p value-<0.0001) and 0.728(p value-0.0001) respectively.
Conclusion*:The presence of hypoalbuminemia and thrombocytopenia within 24 hours of hospitalizationleads topoor outcome in CAP. Platelet count of $\leq161\times10^3$ cells/mm^3 is considered as an independent 30-day mortality predictor.*
Keywords:*Community-acquired pneumonia, hypoalbuminemia, thrombocytopenia, 30-day mortality.*

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I. Introduction:

Pneumonia is characterizedby inflammation and consolidation of lung parenchyma due to an infectious agent. Clinical features of pneumonia includefever with chills and rigors, productive cough,dyspnea or tachypnea (respiratory rate> 20 breaths per minute), pleuritic chest pain, new opacity on chest radiograph[1].

CAP accounts for approximately 3.5 million deaths each year globally and is the highest cause of mortality among infectious disease[1]. Inappropriate outpatient treatment or delay in ICU admission has been shown to increase the mortality rate[2].

According to the Global Burden of Disease Study, LRTI was the second most cause of death[3]. Studies showed that in CAP, outpatient mortality is less than 1%[4], inpatients mortality rate ranges from 4% to 18%5 and among ICU admissions, the mortality rate is more than 50%[6]

To improve the outcome of CAP, several scoring systems such as PSI (Pneumonia severity index), CURB 65 score (confusion, blood urea > 7mmol/L, Respiratory Rate >30/ min, systolic BP < 90mmHg or diastolic

BP < 60mmHg, age> 65), SMART-COP (low systolic BP, multi-lobar infiltrates, low albumin, high respiratory rate, tachycardia, confusion, poor oxygenation, and low arterial pH) were used.

Although these scores help in identifying high-risk CAP patients, they have limitations in the prediction of ICU admission and mortality[7]. Further, age and complications are givenmore importance in both PSI and CURB 65, this leads to underestimation ofdisease severity in young patients and falsely refers thatonly elderly patients to have severe disease[8].

Many biochemical markers such as CRP, procalcitonin, D-dimer, TNF-α and IL-6 are considered as prognostic variables in CAP patients[9]. Hypoalbuminemia is associated with morbidity and mortality in several disease processes. The exact protective role of albumin is not known. However, few experiments show that serum albumin plays a major role as antioxidant, improvesvasoreactivity in endotoxemia, and reduces ischemic-reperfusion injury and anti-inflammatory effects[10].

Malnutrition, liver dysfunction, and infections lead to hypoalbuminemia. Presence of hypoalbuminemia increases the occurrence of complications such as bacteremia, septic shock, empyema, acute cardiac events, and nosocomial infections[11].

Secondly, platelets play major role in innate, adaptive immunity, and coagulation cascade. Since platelets produce antimicrobial peptides, its action is similar to leukocyte response to bacteria. Thrombocytopenia in CAP is associated with poor outcome and as it leads to DIC andsepsis. Thrombocytopenia (<100000 cells/µl) was included in minor criteria for defining severe community-acquired pneumonia by IDSA/ATS[11].

Materials and methods: A prospective study was conducted on 90 patients hospitalized with CAP in Government Hospital for Chest and Communicable Disease, Visakhapatnam, from June 2019 to January 2020.

Inclusion criteria:

1. Age ≥ 18 years.

2. ≥ 2 clinical signs and symptoms (fever> 38°C, cough with expectoration, dyspnea, pleuritic chest pain or crackles on auscultation)

3. Presence of radiological infiltrates.

Exclusion criteria:

1. Patients who were on immunosuppressive drug, HIV
2. Age < 18 years.

II. Methodology:

All patients admitted with CAP who were fulfilling the inclusion criteria were taken into study.
Demographic data, detailed clinical history, Co-morbidity disease were recorded.
Physical examination, radiological findings, and laboratory values such as Complete Blood Count, Renal and Liver function test, platelet counts, serum albumin, serum LDH, random blood sugar, Sputum for gram staining, and culture were collected within 24hrs of admission. The study was undertaken after getting clearance from the institutional ethics committee.

Statistical analysis:

Data were analysed in both Microsoft excel ver2013 and SPSS. Quantitative variables were described in mean and standard deviation, and qualitative variable in frequency and percentages. Median and interquartile ranges were used for non-normal distribution values. Tests of significance used were Chi-Square test and Fisher's exact test. ROC curves with AUC were calculated. A p-value ≤ 0.05 was considered statistically significant.

Results: Total of 90 patients hospitalized with CAP were evaluated. Themean age of the study group was 51.49± 16.63 years, with 64.4% were male, and 35.6% were female, and 30% of patients belong to age≥ 65 years. 83.3% of CAP patients had comorbidities, mainly COPD (60%), alcoholism (28.9%), DM (23.3%), and among those10% of patients had multiple comorbidities. **(Table 1,2,3).**

Table 1: Gender distribution

Gender	frequency	percentage
Male	**58**	**64.4%**
Female	**32**	**35.6%**
total	**90**	**100%**

Table 2:Age distribution

age (years)	frequency	percentage
< 65 years	63	70%
≥ 65 years	27	30%
total	90	100%

Table 3:Comorbidities

comorbidities	frequency	percentage
COPD	54	60%
Diabetes Mellitus	21	23.3%
CKD	8	8.9%
CVA	1	1.1%
hypertension	9	10%

alcoholism	26	28.9%
malignancy	3	3.33%

The predominant symptom being Cough with expectoration (94.4%) and sign being hypotension (95.5%)(**Table 4,5**).85% of the patient's sputum specimen had no isolates for causative agent.

Table 4: Symptoms

symptoms	frequency	percentage
fever	76	84.40%
Cough with expectoration	85	94.40%
Chest pain	68	75.60%
dyspnea	77	85.60%

Table 5:Physical examination findings

Examination findings	frequency	percentage
Confusion	12	13.30%
Respiratory rate≥ 30	49	54.40%
Systolic BP< 90mmHg or Diastolic BP ≤ 60 mmHg	86	95.5%

87.8% of patients had hypoalbuminemia (Serum Albumin < 3.5g/dl) and 8.9% had thrombocytopenia (Platelet counts < $100\times10^3/mm^3$) within 24 hours of admission.36.7% of patients required ICU admission ,30-day mortality rate was 14.4%, and the median duration of hospital stay was 7days (**table 6,7**). Presence of hypoalbuminemia and thrombocytopenia increases with increase in CURB 65 score **(table 8**). Among ICU admissions, 87.8% had hypoalbuminemia, and 21% hadthrombocytopenia. In patients with 30-day mortality, 92.3% had hypoalbuminemia, and 46% had thrombocytopenia **(Table 9).**

Table 6: laboratory findings

Parameters	Frequency	Percentage
BUN > 19mg/dl	4	4.44%
Platelet counts< $100\times10^3/mm^3$	8	8.90%
Albumin < 3.5g/dl	79	87.80%

Table 7: Patients outcomes

Outcomes	Frequency	Percentage
ICU admission	33	36.70%
30-day mortality rate	13	14.40%
Duration of hospital stay(days) median:7 days		

Table 8: Distribution of Thrombocytopenia and Hypoalbuminemia among different risk class of CURB 65

Subgroups	N (%)	Thrombocytopenia N (%)	hypoalbuminemia N (%)
CURB 65 SCORE			
0-1	49(54.4%)	3(6.1%)	43(87.8%)
2	35(38.9%)	4(11.4%)	31(88.6%)
3-5	6(6.7%)	1(16.7%)	5(83.3%)

Table 9: Thrombocytopenia and hypoalbuminemia among ICU admissions and death CAP patients.

Parameter	HypoalbuminemiaN(%)	ThrombocytopeniaN(%)
30- day mortality(13)	12(92.3%)	6(46%)
ICU admissions(33)	29(87.8%)	7(21%)

On ROC analysis,serum albumin of≤ 3.1g/dl predicts 30-day mortality with sensitivity of 92.3% and specificity of 49.35%) with AUC of 0.737(95% CI: 0.633 to 0.824) (p-value 0.0026**) (figure1)** and the cut-off for prediction of ICU admission was found to be ≤ 3.1g/dl with sensitivity of 72.73% and specificity of 52.63% and AUC of 0.644(95% CI: 0.536 to 0.742) (p-value 0.0192) **(figure2)**

Figure 1: The receiver operating curve (ROC) was constructed from serum albumin measurement to predict 30-day mortality in CAP patients

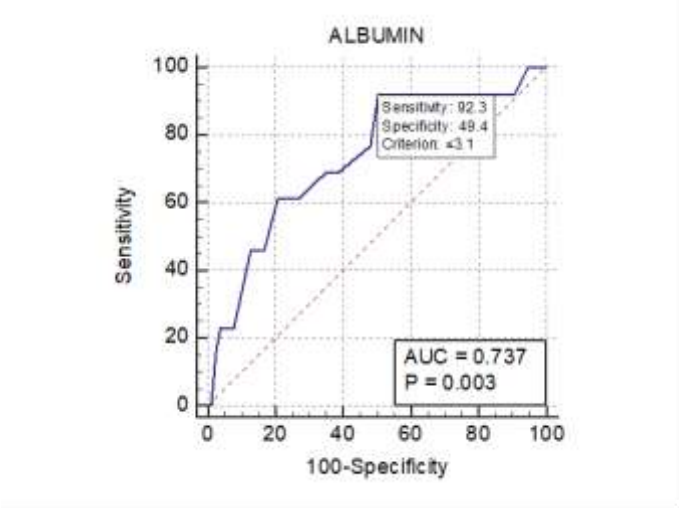


Figure 2: The ROC was constructed from albumin measurement to predict ICU admission in CAP patients.

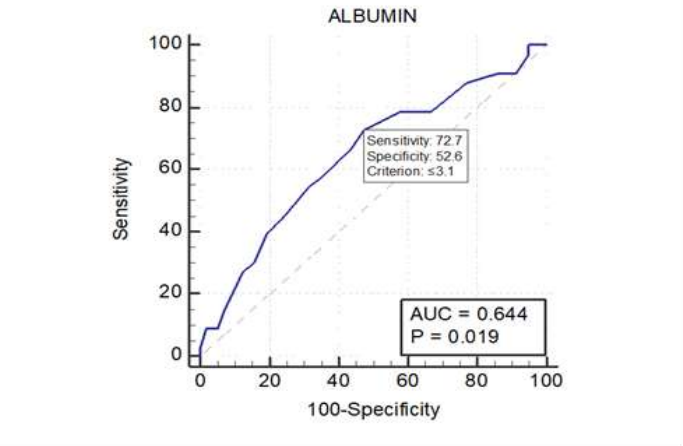


Figure 3: The ROC constructed from platelet counts measurement as a predictor of 30-day mortality in CAP patients:

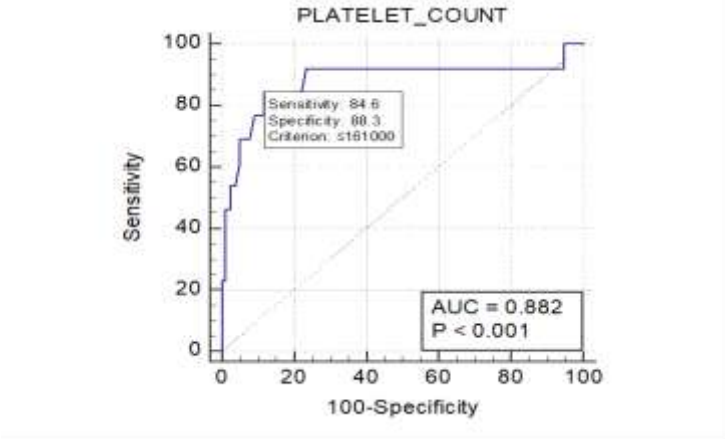
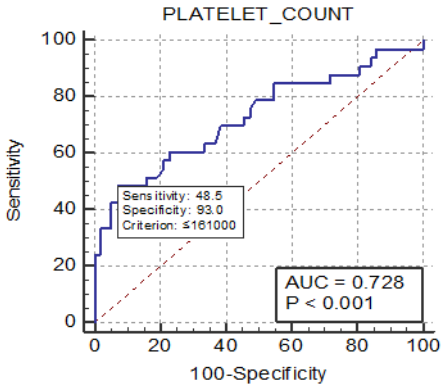


Figure 4: The ROC constructed from platelet counts measurement as a predictor of ICU admission in CAP patients:



The cut-off of platelet count in prediction of 30-day mortality was found to be $\leq 161\times10^3$ cells/mm^3 (sensitivity -84.62%,specificity-88.31%) with AUC of 0.882(95% CI: 0.796 to 0.940) (p-value<0.0001). **(figure3)** and the cut-off for prediction of ICU admission was found to be$\leq 161\times10^3$ cells/mm^3(sensitivity -48.5%,specificity-93%) with AUC of 0.728(95% CI: 0.624 to 0.817) (p-value 0.0001). **(figure 4)**

III. Discussion:

Community-acquired pneumonia is associated with high mortality as it leads to acute respiratory failure, circulatory failure, and worsening of pre-existing comorbidity. There is no single clinical predictor to evaluate the course of CAP.

Assessing the severity of community-acquired pneumonia and site of care decisions are very important for a better clinical outcome and optimal use of resources.

In the current study,90 patients hospitalized with CAP were evaluated, the mean age for overall patients was 51.49± 16.63 years, with 64.4% were male, and 35.6% were female, and 30% patients belong to age≥ 65 years. 83.3% of CAP patients had comorbidities, mainly COPD (60%), and 10% of patients had multiple comorbidities

Shehata SM et al. studies showed that the mean age of their study population was 59.17±14.04 years, with 62.8% being males and 37.2% were females.44% belong to the age≥ 65years, and 56% of patients had comorbidities[12] and concluded that hypoalbuminemia< 3.5g/dl,as an independent risk factor for mortality in CAP. **Irfan et al.**, studiesshowed that low serum albumin <2.2 g/l and elevated liver function tests were associated with increased mortality[13].

During acute infection, the endotoxins, cytokines, and IL-6 act on hepatocytes and inhibit the production of albumin. Also, there is increased albumin catabolism, and its redistribution to the extravascular compartment leads to decreased albumin level in the intravascular compartment. Cytokines produced during acute inflammation shift amino acids to increase the production of acute-phase protein, leading to decreased albumin level[14].

In present study, 87.80% of CAP patients had hypoalbuminemia (S. Albumin < 3.5g/dl) within 24hrs of hospitalization and the study. The median s.albumin value was 3.01g/dl. Among the CAP patients who had 30-day mortality,92.3% of patients had hypoalbuminemia, and among the patient who required ICU admission, 87.8% of patient had hypoalbuminemia at the time of admission. On ROC analysis,serum albumin of ≤ 3.1g/dl predicts of 30-day mortality with(92.3% sensitivity ,49.35% specificity)and ICU admission (72.73% sensitivity and 52.63% specificity) respectively and the AUC was found to be 0.737 (p-value 0.0026) and 0.644(p-value 0.0192) respectively

Although 30-day mortality increased with the increase in hypoalbuminemia, their association did not reach a statistically significant value. On univariate analysis of risk factors associated with 30-day mortality in CAP, hypoalbuminemia <3.5g/dl had OR of (1.791) with 95% CI (0.210-15.306) p-value of 1.00.

Viasus et al. studies showed hypoalbuminemiais associated with prolonged time for clinical stabilization, increased duration of hospital stay, requirement of mechanical ventilation and ICU admission, and increased 30-day mortality(p-value<0.001), and concluded that albumin <3g/dl as the best operating cut-off to predict30-day mortality. These results are in concordance with the results of present study[15].

Platelets play a major role in coagulation and host defense. Similar to leucocytes, platelets engulf microorganisms into phagosome-like vacuoles and helps in the clearance of pathogen and thereby limiting the

infection. Patients with thrombocytopenia have an increased chance of significant bleeding, acute renal injury and prolonged ICU stay[16].

Brogly et al. studies observed that 25% of ICU admitted CAP patents had thrombocytopenia of $<150\times10^9$/L and there is a significant increase in ICU mortality rates as the platelet counts decreases. This study showed that thrombocytopenia $\leq50\times10^3$cell/mm^3 was an independent mortality predictor [17].

In the current study,8.90%patient had thrombocytopenia (platelet counts$<100\times10^3$/mm^3), thrombocytopenia increases with increase in CURB -65 score, among the CAP patients who had 30-day mortality,46% of patients had thrombocytopeniaand among the patient who required ICU admission, 21% patient had thrombocytopenia.

On univariate analysis of risk factors for 30-day mortality in CAP, thrombocytopenia (platelet counts$<100\times10^3$/mm^3) is found to be significantly associated with 30-day mortality with OR of (32.142) with 95% CI (5.432-190.205) p value of 0.001.

On ROC analysis, platelet counts of $\leq161\times10^3$ cells/mm^3 predicts 30-day mortality with(84.62% sensitivity and 88.31% specificity) and ICU admission (48.5% sensitivity and 93 % specificity) respectively.The AUC was found to be 0.882(p-value <0.0001) and 0.728(p-value 0.0001) respectively.

This cut-off is higher than the cut-off predicted by **Brogly et al.** studies, this is probably because of the high prevalence of thrombocytopenia in their studies (25%), whereas present study had only 8.9% of patients with thrombocytopenia and also due to relatively less sample size.

Limitations:

Sample size of the study was relatively small, therefore multicentric studies are needed to validate the results.

This study was conducted in the tertiary care centre, thereby limiting the generalizability of the results.

IV. Conclusion:

CAP-specific scores such as CURB-65, PSI are traditionally being used as a guide for a clinician to predict the outcomes in community-acquired pneumonia. Hypoalbuminemia and thrombocytopenia are not the variables in both the scoring system. Several other quantitative score systems, such as SMART-COP and A-DROP, have been developed recently. PSI score has limited clinical utilityas it has 20 variables and on contrarily, CURB-65 is relatively a simpler score. Further, age and complications are given more importance in both PSI and CURB 65, this leads to underestimation of disease severity in young patients and falsely refers that only elderly patients to have severe disease.

The presence hypoalbuminemia and thrombocytopenia within 24 hours of hospitalization leads to poor outcome in CAP. Platelet count of $\leq161\times10^3$ cells/mm^3 is considered as an independent 30-day mortality predictor.

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