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Original Article

Prognostic value of five serum markers predicting in–hospital mortality among adults with community acquired pneumonia

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Abstract

Introduction: To evaluate the prognostic value of serum markers predicting in–hospital mortality among community acquired pneumonia patients

Methodology: Total 134 patients admitted in Sir Ganga Ram Hospital Lahore Pakistan during 2014–16 included. Serum markers recorded upon admission included blood urea nitrogen, albumin, creatinine, blood urea nitrogen/albumin ratio and blood urea nitrogen/creatinine ratio. Patients were observed for the incidence of mortality during hospitalization. Comparison between survivors and non–survivors for means by t test; odds ratios by contingency tables; and effectiveness of predictors by receiver operating characteristic curve analyses were assessed.

Results: Overall mean age was 50 ± 21 years; males 45.5%; and in–hospital mortality 9.7%. For in–hospital mortality, creatinine ≥ 2.8 mg/dL showed the highest odds (OR = 7.656, 95% CI = 2.281–25.692; $p = 0.001$); followed by CURB-65 score ≥ 4 (OR = 4.958, 95% CI = 0.418–58.784; $p = 0.266$); and blood urea nitrogen ≥ 24.7 mg/dL (OR = 3.364, 95% CI = 1.033–10.954; $p = 0.062$). Serum creatinine was a fair predictor of in–hospital mortality (AUC = 0.721) showed 53.0% sensitivity and 87.0% specificity at cut–off 2.8 mg/dL. Blood urea nitrogen (AUC = 0.691) and blood urea nitrogen/albumin ratio (AUC = 0.675) were poor predictors; whereas albumin (AUC = 0.424) and blood urea nitrogen/creatinine ratio (AUC = 0.403) failed to predict in–hospital mortality.

Conclusions: Among five serum markers, raised serum creatinine was a better predictor of in–hospital mortality in adults with community acquired pneumonia.

Key words: Biomarkers; creatinine; hospital mortality; pneumonia; prognosis.

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Introduction

Community acquired pneumonia (CAP) is one of the acute infections significantly associated with higher rate of mortality [1]. Each year 3.0 million people die from CAP worldwide [2]. Overall CAP related mortality rate is 11.0% in Pakistan [3]. Poor outcomes of CAP are associated with characteristics of patients, comorbid diseases and severity of infection [4]. CURB–65 (confusion, uremia, respiratory rate, blood pressure, age ≥ 65 years) score and Pneumonia Severity Index (PSI) are commonly used scales for assessing the severity of pneumonia, however these scales have certain limitations such as confusion assessment error, time consuming and expensive [5,6]. For these reasons, some studies evaluated the predictive role of various biomarkers for predicting mortality in pneumonia patients. Elevated serum creatinine level was reported as an independent predictor of in–hospital mortality in severe CAP patients [7]. Elevated serum phosphorus [8], low serum albumin [9] and low serum iron [10] were also associated with in–hospital mortality in pneumonia patients.

Available literature suggests various biomarkers can be used as predictors of mortality in pneumonia patients [7-10] however, it requires more research data. In addition, similar work was lacking from Pakistan. Therefore, the present study aimed to evaluate the prognostic value of serum markers including blood urea nitrogen (BUN), albumin, creatinine, BUN/albumin ratio, and BUN/creatinine ratio for predicting in–hospital mortality among adults with CAP.

Methodology

Ethical clearance

Institutional Ethical Review Board of Fatima Jinnah Medical University, Lahore, Pakistan approved the study vide letter No.1177 IERB dated 30th September 2014. Written informed consent was obtained from all volunteer patients.

Study design, settings and duration

This prospective observational study was conducted at Sir Ganga Ram Hospital Lahore Pakistan during the period of two years from November 2014 to December 2016.

Patient selection criteria

The inclusion criteria were adult male and female patients diagnosed with CAP, newly hospitalized and did not use antibiotics for the last 14 days. The exclusion criteria were patients with comorbid diseases such as chronic kidney disease, advanced liver disease or sepsis; or patients using immunosuppressive drugs.

Hospital admission criteria

CAP was diagnosed with a history of high-grade fever, pleuritic chest pain, cough, and dyspnea. Laboratory findings included infiltration on chest X–ray; leukocytosis, and sputum examination. The patients reported with confusion, dehydration, fever and suggestive chest X–ray were admitted in the ward; and the patients requiring ventilator support were moved to the intensive care unit (ICU).

Study tools

Upon hospital admission, a 3cc venous blood specimen was collected to estimate the levels of serum markers including BUN, albumin, creatinine, BUN/albumin ratio, and BUN/creatinine ratio. As per selection criteria, the patients were newly hospitalized and not taking any antibiotic at the time of specimen collection. Other demographic and clinical data were collected by interviewing the patients and noted from their admission files.

Predictors and outcomes

The blood specimen was collected by a phlebotomist; and the levels of serum markers estimated by the laboratory staff. Serum creatinine level was estimated using Jaffe reaction method [11] and serum albumin level using bromcresol green method [12]. The BUN level was calculated by multiplying the factor 0.47 with blood urea level. The BUN/albumin ratio and BUN/creatinine ratio were calculated. The levels of BUN, albumin, creatinine, BUN/albumin ratio and BUN/creatinine ratio estimated upon admission were used as independent predictors of in–hospital mortality. The incidence of mortality during hospital stay was the outcome of interest; therefore, the status of CAP patients with or without outcome was noted on discharge from hospital. The medical officer on duty was the independent assessor of the outcome.

CURB–65 score

The five parameters of CURB–65 score [13] collected upon admission utilized to calculate scores at the time of data analysis. The parameters included age ≥ 65 years; blood urea (≥ 20 mg/dL); respiratory rate (≥ 30 breaths per minute); low blood pressure (systolic blood pressure, SBP ≤ 90 mmHg, diastolic blood pressure, DBP ≤ 60 mmHg); and confusion (present). Each positive parameter had been assigned with one score, and none was given to the negative parameter. The interpretation of CURB–65 score is as follows: the patient who scores 0–1 should be treated as outpatient; who scores 2 require short hospital stay; who scores 3 require indoor treatment; and who scores 4–5 require intensive care.

Sample size and missing data

The study duration of two years from November 2014 to December 2016 spanned over three winter seasons. During the study period, total 134 patients were enrolled using non–probability purposive sampling technique. The prospective design and purposive enrollment enabled to obtain the required data from all patients and admission files. No amputation was required / performed.

Statistical analysis methods

Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis. The numerical variables were expressed using mean ± standard deviation; and categorical variables using number (percentage). The independent sample t test was used to compare the means of serum markers between non–survivors and survivors. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the effectiveness of predictors under investigation. Based on area under the curve (AUC), the markers were classified as follow: excellent (0.90 to 1.00); good (0.80 to 0.90); fair (0.70 to 0.80); poor (0.60 to 0.70); and fail (0.50 to 0.60). The Youden index was used to find the optimal cutoff points for the serum markers. The contingency tables (2×2) were constructed using the cut–off point of predictor under investigation e.g. serum creatinine < 2.8 and ≥ 2.8 mg/dL and the binary outcomes i.e. survivor and non–survivor. Odds ratios were calculated and Fisher's exact test was used to determine the significance of relationship between serum markers and in–hospital mortality. p–values ≤ 0.05 were considered significant.

Results

In this prospective observational study, the purposive enrollment of 134 adults with CAP enabled the investigators to gather all the requisite data. The amputation of data or adjustment of any variable was not performed. The incidence of in–hospital mortality was observed in 13 (9.7%) patients; and who remained alive till the day of discharge from hospital were 121 (90.3%).

The demographic and clinical characteristics of study population (n = 134) included mean age 50 ± 21 years; males 45.5%; mean family income 222 ± 162 USD per month; living in a crowded house (7–20 family members) 43.4% patients; living in a single room house 11.9% patients; no separate kitchen 22.4% patients; wooden stove use 16.4% patients; active cigarette smokers 29.1% patients; and passive smokers 38.1%. The most common co–illness was hypertension (10.6%), followed by chronic obstructive pulmonary disease (9.1%), and tuberculosis (6.1%). The frequency of patients with bronchial pneumonia was higher than of patients with lobar pneumonia (59.7% > 40.3%). Total 19.4% patients received treatment in the ICU and 80.6% patients in the ward.

Based on the incidence of in–hospital mortality, the study population was categorized into two groups i.e. non–survivor (n = 13) and survivor (n = 121). Using the independent sample t test, the comparison between non–survivors and survivors demonstrated significantly different means of age, systolic BP, BUN, creatinine, BUN/creatinine ratio and CURB–65 score, see Table 1.

The incidence of in–hospital mortality was almost similar in male and female patients (9.8% *vs*. 9.6%); and in patients with bronchial pneumonia and lobar pneumonia (10.0% *vs*. 9.25%). The mortality rate was markedly higher in ICU patients than of ward patients (23.1% *vs*. 6.5%). Additional analysis revealed that the incidence of mortality was gradually increased with increase in the CURB–65 score. A direct relationship

Figure 1. In–hospital mortality rate and CURB–65 score in adults with CAP.

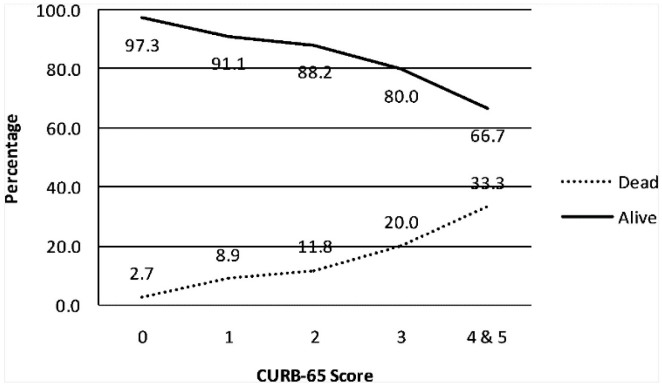
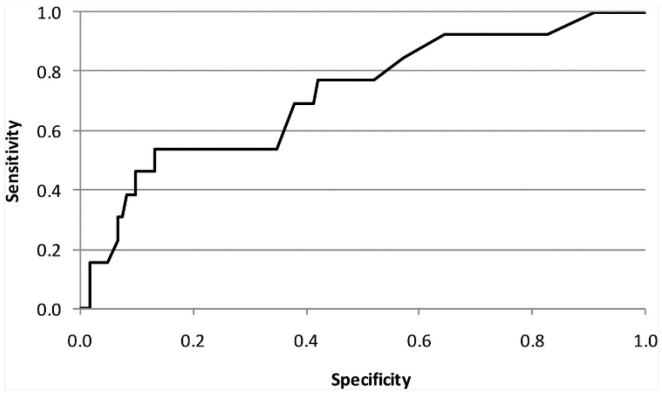


Figure 2. Elevated serum creatinine as a predictor of in–hospital mortality in adults with CAP.



Area Under the Curve				
Test Result Variable(s):	Creatinine			
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.721	0.076	0.009	0.571	0.870

The test result variable(s): Creatinine has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a] Under the nonparametric assumption; [b] Null hypothesis: true area = 0.5.

Table 1. Comparison of demographic, anthropometric and clinical parameters between non-survivors and survivors.

	Non-survivors (n = 13)	Survivors (n = 121)	*p*-value
Age (years)	61.1 ± 16.7	49.1 ± 20.7	0.046
Hospital Stay (days)	4.5 ± 2.8	4.9 ± 3.4	0.687
Body Mass Index (Kg/m^2)	23.0 ± 2.1	23.1 ± 5.5	0.865
Systolic Blood Pressure (mmHg)	135.4 ± 20.7	120.7 ± 20.8	0.017
Diastolic Blood Pressure (mmHg)	79.2 ± 11.2	74.4 ± 12.8	0.167
Blood Urea Nitrogen (mg/dL)	40.9 ± 26.5	24.4 ± 13.3	0.047
Serum Albumin level (g/dL)	3.3 ± 0.7	3.4 ± 0.7	0.540
Serum Creatinine level (mg/dL)	3.8 ± 3.1	1.9 ± 1.8	0.048
BUN over Albumin ratio	14.0 ± 11.9	7.5 ± 5.1	0.073
BUN over Creatinine ratio	12.1 ± 3.4	14.4 ± 6.1	0.049
CURB-65 Score	1.9 ± 1.1	1.2 ± 1.0	0.018

BUN: Blood Urea Nitrogen.

Table 2. The usefulness of various biomarkers at different cut-off points predicting in-hospital mortality in CAP patients.

	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		24.7	61	68	66	64
BUN (mg/dL)	0.691 (0.544-0.838)	27.5	53	72	65	61
		35.8	38	82	68	57
		3.0	62	32	48	46
Albumin (g/dL)	0.424 (0.263-0.586)	3.2	46	40	43	42
		3.3	30	52	39	43
		1.8	69	62	65	67
Creatinine (mg/dL)	0.721 (0.571-0.870)	2.8	53	87	80	65
		3.6	46	91	84	63
		6.9	61	62	62	61
B/A ratio	0.675 (0.513-0.836)	8.5	53	70	64	60
		9.8	46	75	65	58
		12.4	61	42	51	52
B/C ratio	0.403 (0.253-0.554)	13.2	46	49	47	48
		13.8	38	54	45	47

AUC: Area under the curve; BUN: Blood Urea Nitrogen; B/A: BUN/albumin; B/C: BUN/Creatinine; NPV: Negative Predictive Value; PPV: Positive Predictive Value.

between the score and in–hospital mortality was observed, see Figure 1.

The ROC curve analysis revealed serum creatinine as a fair predictor of in–hospital mortality (AUC = 0.721, 95% CI = 0.571–0.870, see Figure 2. However, BUN (AUC = 0.691) and BUN/albumin ratio (AUC = 0.675) were poor predictors; and albumin (AUC = 0.424) and BUN/creatinine ratio (AUC = 0.403) were failed to predict in–hospital mortality. Serum creatinine at Youden optimal cutoff point 2.8 mg/dl showed 53.0% sensitivity and 87.0% specificity for predicting in–hospital mortality. The usefulness of other serum markers at different cut–off points for predicting in–hospital mortality is illustrated in Table 2.

A contingency table (2×2) was constructed using the cut–off point of serum creatinine < 2.8 and ≥ 2.8 mg/dL, and the binary outcome i.e. non–survivor (n = 13) and survivor (n = 121). Serum creatinine (≥ 2.8 mg/dL) showed the highest odds (OR = 7.656, 95% CI = 2.281–25.692; p = 0.001); followed by CURB–65 score ≥ 4 (OR = 4.958, 95% CI = 0.418–58.784; p = 0.266); and BUN ≥ 24.7 mg/dL (OR = 3.364, 95% CI = 1.033–10.954; p = 0.062). The odds calculated for other serum markers are presented in Table 3.

Among five serum markers under investigation, serum creatinine with higher means (3.8 ± 3.1 *vs*. 1.9 ± 1.8, p–value = 0.048), area under the ROC curve (AUC = 0.721) and odds ratio (OR = 7.656, p–value = 0.001) in non–survivors vs. survivors was revealed as a better predictor of in–hospital mortality in adults with CAP.

Discussion

Several studies evaluated the prognostic value of a variety of serum markers such as creatinine, albumin, phosphorus, and iron for predicting short– and/or long–term mortality [7-10] that require more evidence. Therefore, the present study aimed to assess the role of five serum markers including BUN, albumin, creatinine, BUN/albumin ratio and BUN/creatinine ratio as predictor of in–hospital mortality among Pakistani adults with CAP; and found that raised serum creatinine (≥ 2.8 mg/dL) was a better predictor of in–hospital mortality among markers under investigation. Similar findings had also been reported by other

Table 3. Factors associated with the risk of in-hospital mortality in CAP patients.

	OR value	95% CI		p-value
		Lower	Upper	
Age ≥ 65 years	1.946	0.612	6.189	0.265
Body Mass Index < 18 Kg/m^2)	0.207	0.012	3.639	0.214
Systolic Blood Pressure < 90 mmHg	1.770	0.081	38.83	0.521
Diastolic Blood Pressure < 60 mmHg	0.439	0.241	7.966	0.599
Blood Urea Nitrogen ≥ 24.7 mg/dL	3.364	1.033	10.954	0.062
Serum Albumin level < 3.2 g/dL	2.194	0.693	6.950	0.173
Serum Creatinine level ≥ 2.8 mg/dL	7.656	2.281	25.692	0.001
BUN over Albumin ratio ≥ 6.9	2.608	0.804	8.456	0.137
BUN over Creatinine ratio ≥ 13.2	0.738	.234	2.364	0.771
CURB-65 Score ≥ 4	4.958	0.418	58.784	0.266

BUN: Blood Urea Nitrogen; OR: Odd ratio.

studies. Wang *et al.* reported that hypercreatininemia (> 2.9 mg/dL) was an independent predictor of in–hospital mortality in severe CAP patients [7]. Sloane *et al.* also reported that 20% rise in serum creatinine level above baseline was associated with 30–days mortality in CAP patients [14]. These findings show that hypercreatininemia has a prognostic value for predicting the in–hospital mortality among adults CAP patients.

The incidence of in–hospital mortality in CAP patients varies between studies ranging from 4.2% in China [15], 6.2% in Korea [16], 13.2% in England [17], 15.3% in Italy [18] to 23.0% in Ireland [19]. It was 9.7% in the present study, which is a little lower but comparable to the mortality rates 11.0% [20] and 13.89% [21] reported from Pakistan. Differently, a 3–times higher mortality rate 27.6% was also reported among Pakistani patients with CAP [22]. Likewise other studies [8,23,24], the present study validated that older adults, males and ICU admitted patients had higher incidence of in–hospital mortality. Noteworthy, several studies had reported either higher occurrence of lobar pneumonia [25,26] or higher incidence of in–hospital mortality in patients with lobar pneumonia [27] than of patients with bronchial pneumonia. Opposite to these results, both the occurrence of bronchial pneumonia and the incidence of in–hospital mortality in patients with bronchial pneumonia were higher than of patients with lobar pneumonia in our study.

In a study, Lee *et al.* compared the means of BUN, albumin and creatinine between survivor and non–survivor groups and found no significant difference for mean creatinine levels [28]. Similarly, Akpinar *et al.* reported no significant differences for mean creatinine, albumin, BUN and BUN/albumin ratio [29]. On the other hand, the present study revealed that mean creatinine levels of non–survivors were significantly higher than of survivors of CAP. In another study, Uematsu *et al.* reported that elevated BUN and low systolic BP had significantly higher risk of 30–days mortality in CAP patients [30]. Similarly, Liu *et al.* reported that elevated BUN, low systolic BP, and low albumin had greater risk of in–hospital mortality [31]. Rather than elevated BUN, low systolic BP and low albumin, the present study demonstrated that hypercreatininemia had higher odds and was revealed as a fair predictor for in–hospital mortality among adult patients with CAP.

CAP, with significant mortality and morbidity, is a major burden on the health system of Pakistan [32]. There are national guidelines for the management of CAP in adults, which recommend the utilization of CURB-65 and PSI for clinical decisions [6]. However, adherence to these guidelines is not optimal. Hypercreatininemia, revealed as a predictor of in–hospital mortality in the study, may be used independently or with existing pneumonia severity assessment scales to prevent or decrease the incidence of adverse events in adults hospitalized with CAP.

Conclusions

CAP patients of older age, gender male, or admitted in the ICU had higher incidence of in–hospital mortality. Among five serum markers, only raised serum creatinine was revealed as a better predictor of in–hospital mortality in adults with CAP.

Limitations

Limitations of the study include small size of sample, majority of the included patients from poor class, and none of the pneumonia severity assessment scales considered for clinical decision making.

Recommendations

Serum creatinine estimation upon hospital admission may be utilized to prevent or decrease the incidence of adverse events in adults hospitalized with CAP. Further studies with a large enough sample size representative of all socioeconomic classes are recommended.

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Authors' Contributions

MA: Conceived and designed the study, received funding, supervised the project, wrote the original draft; AND critically reviewed and revised the manuscript; AND approved the final version to be published; AND takes responsibility for the content and similarity index of the manuscript. NH: Collected data; AND critically reviewed and revised the manuscript; AND approved the final version to be published; AND takes responsibility for the content and similarity index of the manuscript. TR: Entered and analyzed the data; AND critically reviewed the manuscript; AND approved the final version to be published; AND takes responsibility for the content and similarity index of the manuscript. AB: Collected data; AND critically reviewed the manuscript; AND approved the final version to be published; AND takes responsibility for the content and similarity index of the manuscript. All authors have critically reviewed and

approved the final draft and are responsible for the content and similarity index of the manuscript.

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