Lymphocyte Count and Serum PCT Levels Improve the Sensitivity of CURB-65 in Prediction of 30-day Mortality of Patients with Community-acquired Pneumonia

Jin Zhang

Second Affiliated Hospital of Anhui Medical University <https://orcid.org/0000-0002-5568-4193>

Rui Tao

Second Affiliated Hospital of Anhui Medical University

Pengcheng Liu

Second Affiliated Hospital of Anhui Medical University

Dahai Zhao (✉ zhaodahai@ahmu.edu.cn)

<https://orcid.org/0000-0003-1500-5608>

Jiegou Xu

Anhui Medical University

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Abstract

Background Community-acquired pneumonia (CAP) is an infectious disease with high morbidity and mortality worldwide. The CURB-65 score and other blood biomarkers were used to evaluate prognosis of hospitalized patients with CAP. The aim of our study is to evaluate the prognostic values of other blood biomarkers and the CURB-65 score in hospitalized patients with community-acquired pneumonia (CAP).

Methods A retrospective study of clinical data of in-hospitalized adult CAP patients who fulfilled the CAP criteria and were admitted to the Second Affiliated Hospital of Anhui medical university between January 2015 and December 2018 was conducted. The CURB-65 score was calculated, and other biomarkers including blood lymphocyte count and serum PCT (a propeptide of calcitonin) level were collected at enrolment. Logistic regression analysis was performed to develop combined models to predict 30-day mortality in overall hospitalized and/or the ICU admission of CAP patients. Then, receiver operating characteristics curve (ROC) analysis was conducted to measure and compare the prognostic values of the CURB-65 score and biomarkers in the combined models.

Results The ROC curve analysis using logistic regression of the new combined models showed that the CURB-65 score combined with lymphocyte count and serum PCT level (designated as CURB-65LP) improved the predictive value and was sensitive diagnostic model in predicting the 30-day mortality of CAP patients.

Conclusion Serum level of lymphocytes or PCT alone is a strong prognostic factor for evaluation of 30-day mortality of CAP patients. Incorporation of both factors improves the sensitivity of the CURB-65 scoring system in the prediction of the 30-day mortality. This new CURB-65LP scoring system is simple, but more accurate for evaluating the severity of CAP with higher sensitivity and specificity than the current CURB-65 scoring system.

Background

Community-acquired pneumonia (CAP) is a common infectious disease with high morbidity and mortality worldwide [1–3]. The rates of adult patients hospitalized due to CAP are increasing by 22%–42%. In addition, approximately 5% of CAP patients require admission to an intensive care unit (ICU). In these severe cases, mortality rises to 35% [4].

Multiple biomarkers and several established models have been used to assess the severity of CAP to improve management of CAP patients [5–7], and among these models, the CURB–65 score is recommended in the guidelines for the diagnosis and treatment of adult CAP in Europe, America and China. The CURB–65 scoring system was created by the British thoracic society in 2003 and requires only five parameters (including confusion, urea >7 mmol/L, respiratory rate $\geq$ 30/min, low systolic < 90 mmHg or diastolic $\leq$ 60 mmHg blood pressure, age $\geq$ 65 years) with 1 point for each item and a total maximum score of 5 points. The higher the score, the more serious the disease [8]. The CURB–65 score is

convenient and simple, and often used in clinical practice. However, it does not include an immune background of CAP patients and other biomarkers, its clinical value is limited [9]. Therefore, a simple and more reliable scoring system is needed.

Lymphocytes are an important cellular component of the immune system and are produced by lymphoid organs. Lymphopenia is considered to be a total lymphocyte count fewer than 1000 mm^3 by the definition proposed in Hematology, 9th ed [10], and usually associated with immune deficiency [11].

PCT is a propeptide of calcitonin without hormone activity. The dynamic changes in its serum levels are closely related to bacterial infection and severity. The serum level of PCT in normal subjects is less than 0.046 ng/ml , and begin to increase after endotoxin injection and reach at the peak 24 hours later [12]. The role of PCT in infectious diseases such as sepsis has been described by Assicot et al.[13]. Thus, it can be used as a prognostic indicator for infectious diseases [7,14].

In the present study, we evaluated the prognostic values of lymphocyte count, serum PCT level and other biomarkers alone or in combination with the CURB-65 scoring in patients with CAP, and aimed to build a new model that can more accurately assess the prognosis of CAP.

Methods

CAP patients and Study design

Adult patients (age, ≥ 18 years) were included in our study. THE CRITERIA FOR INCLUSION AND EXCLUSION OF PATIENTS ARE BASED ON THE GUIDELINES FOR THE MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN IMMUNOCOMPETENT PATIENTS[15].

The CAP patients admitted to the Second Affiliated Hospital of Anhui Medical University from January 2015 to December 2018 were sub-grouped into the survivor and non-survival groups after 30-day tracking; as well as the ICU admission and non-ICU admission groups. A prospective observational analysis was performed the tracked patients.

Data collection

Patient age, sex, comorbidity, clinical features, and biochemical parameters such as albumin, aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), white blood cell (WBC), neutrophil count, lymphocyte count, mononuclear cell count, eosinophil count, basophil count, platelet (PLT), C-reactive protein (CRP), and procalcitonin (PCT) were recorded. CURB-65, CURB-65 plus lymphocyte count (CURB-65L), CURB-65 plus PCT level (CURB-65P) and CURB-65LP were calculated.

Statistical analysis

Differences in the demographic clinical characteristics between patient cohorts or sub-groups were calculated using the medians with interquartile ranges. Categorical variables are presented as numbers and percentages. Data from the vital signs and laboratory results were assessed by t-tests or one-way analysis of variance (One-Way ANOVA). Variables yielding a P value <0.05 on t-tests were further included in the logistic regression analysis. Potential confounding variables were selected by assessing the association between those variables shown in Table 1 with 30-day mortality and ICU admission. Variables with significant differences were tested by a binary logistic analysis together with the CURB-65 score and are presented with an odds ratio (OR) and a 95% confidence interval (CI). The association between lymphocyte and PCT (procalcitonin) levels and the risk of 30-day mortality and ICU admission were evaluated by logistic regression analysis [11]. The ability of lymphocyte counts and procalcitonin (PCT) levels to differentiate survivors from non-survivors and ICU admission from non-ICU were assessed by using area under the receiver operating characteristic curve analysis (AUC). All analysis were performed with IBM SPSS Statistics 24.0.

Results

Characteristics of the study cohort

During the study period, 201 adult patients were admitted to The Second Affiliated Hospital of Anhui Medical University. The baseline characteristics of these patients were shown in Table S1. The median age of these patients was 66 (51–77) years old, and 64.7% were male. The top three main complications were chronic heart failure (31.0%), chronic obstructive pulmonary disease (COPD) (25.4%) and diabetes mellitus (19.4%). The overall 30-day mortality rate was 12.9%, and the proportion of ICU admission was 27.9%. The mean length of hospitalization was 12 (7–18) days for all patients.

Differences in the parameters of the CURB-65 scoring system

As expected, among the 5 parameters in the CURB-65 scoring system, the median age, respiratory rate and mental confusion are 69 (62–75) years old, 25 (22–28) /min. and 38.5% in the non-survival group, significantly higher than those in the CAP survivors [61 (58–64) years old, $p = 0.047$; 21 (19–22) /min, $p = 0.003$; and 12.0%, $p < 0.001$]. No significant differences in systolic blood pressure and BUN levels were observed (p values were 0.353 and 0.713, respectively) between the two groups (Table 1).

Also, heart rate and mental confusion in the ICU admission patients were significantly different from those in the non-ICU group [106 (84–131) /min vs 97 (84–107) /min, $p = 0.010$; 30.3% vs 9.6%, $p = 0.001$]. However, no significant differences were noted in respiratory rate ($p = 0.052$), systolic blood pressure ($p = 0.107$) or BUN level ($p = 0.253$) between the two groups (Table S1).

PCT level and lymphocyte count as good predictors for 30-day mortality and ICU admission

Biomarkers in the blood including lymphocyte count, serum PCT level, serum albumin level and activity of LDH were analysed. As shown in the Table 2, PCT levels in the non-survival and in the ICU admission groups were 6.31(4.67–8.41) and 4.25(3.23–6.25) ng/mL, significantly higher than 1.87(0.63–3.36) and 1.56(0.39–3.11) ng/mL in the survival and in the non-ICU admission groups ($p < 0.001$ both), while lymphocyte counts in the non-survival and in the ICU admission groups were significantly lower than those in the survival and in the non-ICU admission groups [0.4(0.3–0.5) and 0.7(0.4–1.0) versus 1.1(1.0–1.2) and 1.1(0.6–1.4) per litre, $p < 0.001$ both]. Similarly, serum albumin level and activity of LDH in the non-survival and in the ICU admission were significant different from those in the survival and in the non-ICU admission groups (Table 2). These results suggested that these biomarkers were potential predictors for 30-day mortality and ICU admission.

For prediction of 30-day mortality and ICU admission, these biomarkers alone were analysed on the basis of the ROC curves. As shown in the Table 3, PCT level or lymphocyte count alone had better performance, with the sensitivity and specificity of 81% and 90%, 71% and 77%, respectively, in the prediction of 30-day mortality; and 94% and 60%, 65% and 68%, respectively, in the prediction of ICU admission.

Score performance of new models

For more sensitive and accurate prediction of 30-day mortality and ICU admission, new models incorporating lymphocyte count ($< 0.70 \times 10^3/\mu\text{l}$), or PCT level ($> 3.4 \text{ ng/ml}$), or both in the CURB–65 scoring system were built based on the ROC curves, designates as CURB–65L, CURB–65P and CURB–65LP.

The AUCs of the ROC curves for 30-day mortality are shown in Table 3. The area under the curve for 30-day mortality was 0.73 (0.63–0.83) for CURB–65, 0.79 (0.70–0.87) for CURB–65L, 0.80 (0.73–0.89) for CURB–65P, and 0.84 (0.77–0.91) for CURB–65LP. Similarly, as shown in Table 4, the area under the curve for ICU admission was 0.76 (0.69–0.83) for CURB–65, 0.78 (0.71–0.84) for CURB–65L, 0.83 (0.77–0.88) for CURB–65P, and 0.83 (0.78–0.89) for CURB–65LP.

Incorporation of lymphocyte count, or PCT level or both also increased the sensitivity and specificity of the CURB–65 scoring system. As shown in Table 4 and Fig 1, a CURB–65 score ≥ 2 points presented with sensitivity at 65% and specificity at 73% for predicting 30-day mortality, while a CURB–65L score ≥ 3 points, CURB–65P score ≥ 3 points and CURB–65LP score ≥ 4 points presented sensitivity at 65%, 62% and 81%, and specificity at 98%, 85% and 68%, respectively, for predicting 30-day mortality. Similarly, a CURB–65 score ≥ 2 points presented with sensitivity at 91% and specificity at 54% for predicting ICU admission, while a CURB–65L score ≥ 3 points, CURB–65P score ≥ 3 points and CURB–65LP score ≥ 4

points revealed sensitivity at 83%, 82% and 79%, and specificity at 66% 71% and 77% for predicting ICU admission.

These results indicate that both CURB-65L, CURB-65P and CURB-65LP models were more sensitive than CURB-65 scoring, with the highest sensitivity in the CURB-65LP model, in predicting 30-day mortality.

Discussion

In this study, the 30-day mortality rate of CAP patients was 12.9%, higher than that reported previously [16]. This may be ascribed to better economic conditions, better medical conditions and strong health awareness in developed countries where previous study was conducted [17]. In addition, our hospital is a third-grade hospital in Anhui Province that frequently admits older patients; thus, the patients are generally in a worse condition than those admitted to community hospitals. A hospitalization delay often happens, also contributing to the poor prognosis.

The higher mortality in this study is associated not only with the above factors, but also with the exclusion criteria used in this study. Advanced age, a history of COPD and cerebrovascular disease, and ventilator use are independent risk factors for 30-day mortality. The correlation between sex and mortality was consistent with the meta-analysis of Fine et al. [18].

Early identification of CAP patients at risk of death is an important step in the diagnosis and treatment process [19]. Current accepted CAP scoring systems include CURB-65 and PSI. PSI has high sensitivity and specificity, but it needs to be combined with 20 clinical parameters (including age, sex, nursing staff, tumour, etc.) and thus is complex and extremely inconvenient to apply in the clinic. The CURB-65 is more convenient and simpler, and often used in clinical practice. However, blood pressure and heart rate are easily affected by the environment, leading to interference with the assessment of the severity of CAP [20]. Our study indicate that the CURB-65 scoring system is an independent predictor of CAP patients' 30-day mortality, but the AUC was only 0.73 (0.63–0.83) and the area under the curve was lower than that from Chalmers et al. [21], suggesting that the CURB-65 scoring system has a limited predictive value for 30-day mortality. Among biomarkers analysed in this study, lymphocyte counts were lower in the non-survivors and ICU admissions than in the survivors and non-ICU patients. In the research by Marrie et al [22], a lymphocyte count $< 1000 \text{ cell/mm}^3$ is associated with early but not late mortality. The most important difference is that patients with lymphocyte counts $< 1000 \text{ cells/mm}^3$ and those with critical illnesses are excluded in their study. In addition, a hospital mortality is analysed in their study, but not 30-day mortality as analysed in this study. The value of PCT in predicting 30-day mortality was superior to that of CRP, which is consistent with a report by Kruger et al [23]. LDH and albumin are also independently associated with 30-day mortality in CAP patients [24,25].

In the present study, we established new models, in which lymphocyte count and PCT alone improve the predictive efficacy of the CURB-65 scoring system. The addition of both PCT and lymphocyte count to form the CURB-65LP scoring system can further improve the predictive value, especially in the prediction

of 30-day mortality. The area under the ROC curve of the CURB–65LP scoring system was 0.84 (0.77–0.91), much higher than that of CURB–65 (0.73 (0.63–0.83)). The new model can more comprehensively reflect the severity of a CAP patient's condition from multiple aspects such as autoimmune status and degree of inflammatory response, Lymphopenia could be a cause or a consequence of CAP. Impaired production or increased apoptosis of lymphocytes leads to critical illness [26]. However, the mechanisms still needs further study.

Although our new models show higher predictive value than the CURB–65 scoring, limitations exist in our study. First, it was a single-centre secondary analysis and the sample size was relatively small; thus, multi-centre prospective studies are needed to validate the clinical value of lymphocyte counts and PCT. Second, the criteria for admission to the ICU vary widely in different hospitals. Third, we did not explore the influence of antibiotic treatment on these serum biomarkers because of insufficient data.

PREVIOUS STUDIES HAVE SHOWED THAT LYMPHOCYTE COUNTS PLAY AN IMPORTANT ROLE IN LUNG INFECTIONS. IT IS GENERALLY BELIEVED THAT ELEVATED LYMPHOCYTE COUNTS ARE ASSOCIATED WITH VIRAL INFECTIONS, WHICH MAY BE RELATED TO THE INNATE IMMUNE RESPONSE MECHANISMS OF HUMAN INFLAMMATION. AS CAN BE SEEN IN OUR STUDY, SOME OF THE PATIENTS WITH BACTERIAL INFECTION, THE LYMPHOCYTE COUNT IS DECREASED, ACCOMPANIED BY AN INCREASE IN PROCALCITONIN LEVEL, AND PROCALCITONIN IS AN INDICATOR OF BACTERIAL INFECTION, WHICH MAY FURTHER EXPLAIN THAT IF THE ABOVE-MENTIONED SERUM INDEX CHANGES IN PNEUMONIA PATIENTS, THE VIRUS INFECTION CAN BE BASICALLY RULED OUT, WHICH CAN BRING REFERENCE SIGNIFICANCE TO CLINICAL DIAGNOSIS AND TREATMENT[27]. More research is needed to the prognosis of lymphocyte counts and PCT levels in identifying bacterial and viral infections.

In conclusion, the CURB–65 scoring system and serum biomarkers alone have limited predictive value for 30-day mortality. Incorporation of lymphocyte count and PCT can significantly improve the prognostic value of the CURB–65 scoring system.

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Abbreviations

CAP, community-acquired pneumonia; PCT, a propeptide of calcitonin; CRP, C-reactive protein; LDH, lactate dehydrogenase; COPD, chronic obstructive pulmonary disease; ICVD, ischemic cerebrovascular disease; AST, aspartate transaminase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; WBC, white blood cells; One-Way ANOVA, one-way analysis of variance; OR, odds ratio; CI, 95% confidence interval; AUC, area under the receiver operating characteristic curve analysis;

Declarations

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Author information

Affiliations

¹ Department of Respiratory Medicine, The Second Hospital of Anhui Medical University, Hefei, Anhui 230601, P. R. China.

² Department of Immunology, Anhui Medical University College of Basic Medical Sciences, Meishan Road 81, Hefei 230032, Anhui, China.

Contributions

Jin Zhang and Dahai Zhao were for the study design; Jin Zhang for conduction of the study, statistical analysis and manuscript preparation; Rui Tao and Pengcheng Liu for clinical data collection; and Jiegou Xu for interpretation of clinical data and manuscript revision.

All authors have read and approved the final manuscript.

Corresponding author

Correspondence to zhaodahai@ahmu.edu.cn or xujiegou@ahmu.edu.cn.

Ethics declaration

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (approval number is PJ-YX2019–036), and written informed consent was received from all of the participants or their relatives after explaining the objectives and details of the study to them.

Consent for publication

Not applicable.

Competing of interests

All the authors declare that they have no competing interests.

Tables

Table 1.Differences in the parameters of the CURB-65 scoring system

Variables	Index	BUN(mmol/l)	Respiratory rate(bpm)	SBP(mmHg)	Age(range)
Non-survivors	Mental confusion(%)	15.6(11.4-19.7)	25(22-28)	119(106-132)	69 (62-75)
Survivors	10(38.5)	14.1(10.2-18.0)	21(19-22)	124(120-127)	61(58-64)
<i>P</i> value	21(12.0)	0.713	0.003	0.353	0.047
ICU admission	<0.001	18.6(8.9-25.9)	23(19-26)	123(98-139)	66(52-79)
non-ICU	17(30.3)	12.6(4.6-13.4)	20(19-20)	123(106-143)	64(49-75)
<i>P</i> value	14(9.6)	0.253	0.052	0.107	0.418

Abbreviations: BUN, blood urea nitrogen; SBP, systolic blood pressure;

Table 2. Serum biomarkers levels comparison in 30-day mortality and ICU admission

	Variables	Serum biomarkers			
		Albumin(g/L)	Lymphocyte count($\times 10^9$ /L)	PCT(ng/ml)	LDH(u/L)
30-day mortality	Non-survivors	26.5(24.6-28.4)	0.4(0.3-0.5)	1.87(0.63-3.36)	424(275-573)
	Survivors	30.7(29.8-31.7)	1.1(1.0-1.2)	6.31(4.67-8.41)	302(261-337)
	<i>P</i> value	0.043	<0.001	<0.001	0.024
ICU admission	ICU admission	27.4(23.0-32.0)	0.7(0.4-1.0)	4.25(3.23-6.25)	395(252-422)
	non-ICU	31.2(26.0-35.5)	1.1(0.6-1.4)	1.56(0.39-3.11)	278(184-278)
	<i>P</i> value	<0.001	<0.001	<0.001	0.02

Abbreviations: LDH lactate dehydrogenase , PCT a propeptide of calcitonin ;

Variables did not conform to the normal distribution and were described by the median (25th percentile, 75th percentile). The T test was used for comparisons between the two groups.

Table 3. Performance of serum biomarkers and CURB-65 score for predicting 30-day mortality and ICU admission

	serum biomarkers	AUC(95%CI)	Cut-off value	Sensitivity(%)	Specificity(%)
30-day mortality	LDH(u/L)	0.61(0.50, 0.73)	344	38	83
	Albumin(g/L)	0.71(0.63, 0.81)	32	43	96
	PCT (ng/ml)	0.86(0.77, 0.94)	4.60	81	90
	CURB-65	0.73(0.63, 0.84)	2	65	74
	Lymphocyte count('10 ³ /μL)	0.76(0.66, 0.85)	0.66	71	77
ICU admission	LDH(u/L)	0.73(0.65, 0.81)	261	71	70
	Albumin(g/L)	0.67(0.59, 0.75)	33	43	88
	PCT (ng/ml)	0.81(0.75, 0.87)	1.85	94	60
	CURB-65	0.76(0.69, 0.83)	2	91	54
	Lymphocyte count('10 ³ /μL)	0.68(0.61, 0.76)	0.72	65	68

Abbreviations: LDH lactate dehydrogenase , PCT a propeptide of calcitonin ;

Table 4. Performance of CURB-65, CURB-65L, CURB-65P and CURB-65LP score for predicting 30-day mortality and ICU admission

	serum biomarkers	AUC(95%CI)	Cut-off value	Sensitivity(%)	Specificity(%)
30-day mortality	CURB-65	0.73 (0.63-0.83)	≥2	65	73
	CURB-65L	0.79 (0.70-0.87)	≥3	65	98
	CURB-65P	0.80(0.73-0.89)	≥3	62	85
	CURB-65LP	0.84(0.77-0.91)	≥4	81	68
ICU admission	CURB-65	0.76(0.69-0.83)	≥2	91	54
	CURB-65L	0.78(0.71-0.84)	≥3	83	66
	CURB-65P	0.83 (0.77-0.88)	≥3	82	71
	CURB-65LP	0.83(0.78-0.89)	≥4	79	77

Abbreviations: CURB-65L, incorporation of CURB-65 score and lymphocyte counts; CURB-65P, incorporation of CURB-65 score and PCT; CURB-65LP, incorporation of CURB-65 score, lymphocyte counts and PCT;

Figures

Figure 1

AUROC analysis of CURB-65, CURB-65L, CURB-65P and CURB-65LP score for predicting 30-day mortality and ICU admission A: AUROC analysis of CURB-65, CURB-65L, CURB-65P and CURB-65LP score for predicting 30-day mortality B: AUROC analysis of CURB-65, CURB-65L, CURB-65P and CURB-65LP score for predicting ICU admission

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