

Correlation between Serum C-Reactive Protein Levels and CURB-65 in Elderly Patients With Community-Acquired Pneumonia

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Abstract: Background: CURB-65 is an important clinical score for severity of community-acquired pneumonia (CAP). C-reactive protein (CRP) is an acute phase protein marker for bacterial infection or tissue inflammation. Serum CRP levels are well correlated with the severity of CAP. Objective: To investigate whether serum levels of CRP correlates with CURB-65 ranking in hospitalized patients with CAP. Methods: We studied 858 patients aged 18-90 years who were hospitalized with CAP during a period of two years in the departments of Internal Medicine at Ziv Medical Center in Safed, Israel. Five hundred patients who met the inclusion and exclusion criteria were included. CURB-65 and serum levels of CRP within 24 hours of admission were collected for each participant. The correlation between serum CRP levels and CURB-65 was analyzed by Spearman's rank correlation test presented by correlation coefficient (R). Results: The mean CRP levels and CURB-65 score were 114 ± 100 mg/dL, 1.4 ± 1.1 points, respectively. No significant correlation was found between CRP and CURB-65 for all study group ($r = -0.014$, $p = 0.768$). Nevertheless, we found a significant correlation between CRP levels and CURB-65 in 320 patients aged ≥ 65 years ($r = 0.126$, $p = 0.024$). Conclusions: In this study we found a significant correlation between CRP levels and CURB-65 among elderly patients aged ≥ 65 years but not among patients below the age 65 years. CRP measurements could be used as adjuvant biomarker to CURB-65 for disease severity assessment in elderly patients with CAP.

Key words: Community-acquired pneumonia, CURB-65, C-reactive protein, elderly.

1. Background

Pneumonia is the most frequent cause of infectious disease-related mortality among patients of all ages and the eighth leading cause of death in the United States [1]. Pneumonia in patients who have not been hospitalized or a resident of a long-term care facility for more than 14 days before the onset of symptoms is considered community acquired pneumonia (CAP) [2]. The overall rate of CAP in adults is approximately 5.16 to 6.11 cases per 1,000 persons per year, the rate of CAP increases with increasing age [3]. Many investigators have attempted to identify independent

risk factors for CAP especially in the elderly population. Studies have shown that subjects with cardiopulmonary disease, poor functional status, low weight, or recent weight loss have a greater risk of developing CAP [4, 5]. The classic triad of symptoms of pneumonia is fever, cough, and dyspnea. But clinical presentation of pneumonia in the elderly may be subtle, lacking the typical acute symptoms observed in younger adults [6, 7]. It appears that the manifestations of CAP are atypical in the elderly. Furthermore, it has been suggested that the local inflammatory response to infection of the lungs is decreased in the elderly, resulting in less cough and sputum production [8].

C-reactive protein (CRP) is an acute phase protein synthesized by hepatocytes. In response to infection or

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tissue inflammation, CRP production is rapidly stimulated by cytokines, particularly interleukin (IL)-6, IL-1 and tumor necrosis factor [9, 10]. CRP levels are usually lower in viral and superficial bacterial infections than in deep bacterial infections, studies have also shown that serum CRP levels are significantly raised and associated with severity and mortality in patients with bacterial pneumonia [11].

CURB-65 score which contains several parameters (confusion, blood urea nitrogen, respiratory rate, blood pressure, and age ≥ 65 years) is very useful tool for clinician making decision to manage patients with CAP [12]. Even though, There are cases of CAP with a low score of CURB-65 that deteriorate during hospitalization, indicating that sometimes CURB-65 does not reflect the severity of the disease and needs to be improved [13].

The relationship between CRP and CURB-65 in patients with CAP is not well established yet. The lack of classical manifestation of CAP in elderly patients makes the diagnosis quite a challenge. Moreover, the CURB-65 score does not include any inflammatory marker making it easy to underestimate the mortality risk in patients with CAP. Therefore, we aimed to investigate whether serum levels of CRP correlate with CURB-65 ranking.

2. Methods

2.1 Design and Study Population

A retrospective cohort study was conducted to examine the correlation between CRP and CURB-65 in adult patients with CAP. The study was conducted at Internal Medicine Department Ziv Medical Center in Safed, Israel, affiliated to Faculty of Medicine in the Galilee, Bar-Ilan University, Israel. The study period lasted from 2015 to 2016. The study was approved by local Helsinki Committee.

The study population was composed of patients with CAP that required admission in Internal Medicine Department. We included patients aged ≥ 18 years with CAP, and available CRP measurements within

24 hours of admission. We excluded patients aged below 18 years and over 90 years. Patients with: hospital-acquired pneumonia, severe structural lung diseases (interstitial lung disease, cystic fibrosis, recurrent aspiration pneumonia), asthma, empyema, medical conditions that could disrupt the measurements of CRP (arthritis, lupus, vasculitis and inflammatory bowel disease), HIV infection, malignancy, intravenous drug use, severe neutropenia ($< 0.5 \times 10^9 /L$), an active autoimmune disease, and pregnancy were excluded.

2.2 Clinical and Laboratory Measurements

The study data included: age, gender, body mass index (BMI), smoking and alcohol consumption, pregnancy, comorbid conditions and medications. We recorded the following clinical signs, and symptoms: headache, cough, expectoration, dyspnea, chest pain, mental confusion, diarrhea, fever, heart rate, respiratory rate and blood pressure. The laboratory data included complete blood count, serum electrolytes, serum creatinine, glucose, blood urea nitrogen, C-reactive protein (CRP) and arterial gases. Imaging data on the lungs such as: chest X-ray and or CT were obtained. CURB-65 was calculated for each participant.

2.3 Definitions

CAP was defined as present in cases with ≥ 3 of the following symptoms: cough, productive cough, dyspnea or pleuritic chest pain; ≥ 2 of the following: fever or hypothermia, hypotension, tachycardia or tachypnea; and ≥ 1 of the following: hypoxemia, pulmonary consolidation on physical examination or elevated total white blood cell count or leukopenia or elevated immature neutrophils, with onset ≥ 48 hours before hospital admission and the presence of new or progressive pulmonary infiltrate on chest imaging.

CURB-65 is a clinical prediction rule that has been validated for predicting mortality in CAP. It includes five variables: confusion (new disorientation to person, time, or place), urea (blood urea nitrogen > 20 mg/dL), respiratory rate (≥ 30 breaths/min), blood pressure

(systolic < 90 mm Hg or diastolic \leq 60 mm Hg), and age \geq 65 years. Each criterion is assigned 1 point. The investigators proposed that patients with a CURB-65 score of 0 or 1 (low mortality, 1.5%) can be treated as outpatients, those with a score of 2 (intermediate mortality, 9.2%) should be admitted to the hospital, and patients with a score \geq 3 (high mortality, 22.0%) should be considered for management in an intensive care unit [10].

BMI was defined as the weight in kilograms divided by height in meters squared (kg/m^2). Normal weight is considered when $\text{BMI} = 20\text{--}25 \text{ kg}/\text{m}^2$, overweight when $\text{BMI} = 25.1\text{--}29.9 \text{ kg}/\text{m}^2$, and obesity when $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$. Chronic kidney disease is defined as either kidney damage (micro- or macroalbuminuria) or decreased glomerular filtration rate (GFR) to < 60 mL/min per 1.73 m^2 for 3 months or more, regardless of cause. MDRD was used for calculation of GFR.

2.4 Statistical Analysis

All tests applied are two-tailed, and p value of 5% or less is considered statistically significant, our sample size is 500 patients with CAP. The data were analyzed using the SPSS version 23 (SPSS Inc., Chicago, IL, USA). The general descriptive characteristics were presented as means, standard deviations, medians, and percentages. The correlation between the CURB-65 score and CRP was analyzed by Spearman's rank correlation.

3. Results

During the study period, 838 medical files of patients that have been diagnosed with CAP and were hospitalized during the years 2015-2016 in the department of Internal Medicine at Ziv Medical Center in Safed, were studied. 338 patients did not met the inclusion and exclusion criteria and were excluded (most common cause: lack of CRP testing within 24 hours of admission, inflammatory diseases, uncertainty upon CAP diagnosis).

The mean (mean \pm SD) age of the 500 patients was 67 ± 19 years, with median of 72 years. Table 1 presents the baseline characteristics of the two study groups according to age 65 (CAP aged < 65 and CAP aged \geq 65 years). We did not find any significant differences between the two groups concerning gender, smoking, diabetes, and cardiovascular diseases. In contrast we found a significant difference in term of BMI, CRP, CRF, CURB-65.

Of 500 patients with CAP, The study group consisted of 500 patients with CAP, 144 patients (28.8%) had a CURB-65 score of 0; 111 patients (22.2%) scored 1; 154 patients (30.8%) scored 2; 72 patients (14.4%) scored 3; 18 patients (3.6%) scored 4 and only 1 patient (0.2%) scored 5. Because of the relatively small number of patients with CURB-65 scores of 4 and 5, both groups were combined in the data analysis.

To assess whether a combination of CRP with CURB-65 score could improve the prediction of CAP severity rather than relying solely on CURB-65, by that creating a more informed decision on hospitalization. For each CURB-65 score, the mean CRP levels were calculated. The average CRP level for CURB-65 score 0 was $120.7 \pm 108.6 \text{ mg}/\text{dL}$, for CURB-65 score 1 was $110.1 \pm 94.5 \text{ mg}/\text{dL}$, for CURB-65 score 2 was $103.6 \pm 100.5 \text{ mg}/\text{dL}$, for CURB-65 score 3 was $115.4 \pm 101.9 \text{ mg}/\text{dL}$ and for CURB-65 score 4+5 was $156.34 \pm 94.7 \text{ mg}/\text{dL}$ (Table 2).

In order to investigate whether serum levels of CRP correlate with CURB-65 ranking in hospitalized patients with CAP, we used Spearman's rank correlation test presented in correlation coefficient (R) which can take values from +1 to -1. A R of +1 indicates a perfect association of ranks, a R of zero indicates no association between ranks. A R of -1 indicates a perfect negative association of ranks. In our study we did not find any significant correlation between CURB-65 score and CRP levels in all study group ($R = -0.014$, p value = 0.768) (Table 2, Fig. 1).

Table 1 Baseline characteristics of the subjects with CAP according to their age more and younger than 65 years.

	CAP aged < 65 y (n = 178)	CAP aged ≥ 65 y (n = 322)	p value
Male Gender (%)	110 (61.8)	209 (64.9)	0.582
BMI (kg/m ²)	28.4 ± 3.2	26.2 ± 3.3	0.05
Smoking (%)	62 (34.8)	64 (19.8)	0.58
Diabetes (%)	50 (28.1)	113 (35.1)	0.491
Cardiovascular diseases (%)	28 (15.7)	63 (19.5)	0.3
Chronic renal failure (GFR ≤ 60) (%)	31 (17.4)	100 (31)	0.04
CURB-65 (points)	1.4 ± 1.2	2 ± 1.1	0.02
CRP (mg/dL)	123 ± 110	106 ± 94	0.06

Data are expressed as the mean ± standard deviation or number (%).

CAP: community acquired pneumonia. BMI: body mass index. GFR glomerular filtration rate. CRP: C-reactive protein.

Table 2 Correlation analysis between CURB-65 score and CRP of all patients with CAP.

	CURB-65	CRP (mg/L)
Correlation Coefficient (R)	1.000	-0.014
Sig. (2-tailed)	.	.758
N	500	500

Spearman's rank correlation. N: number of patients. Correlation is significant at the 0.05 level (2-tailed).

CRP: C-Reactive protein. CAP: community acquired pneumonia.

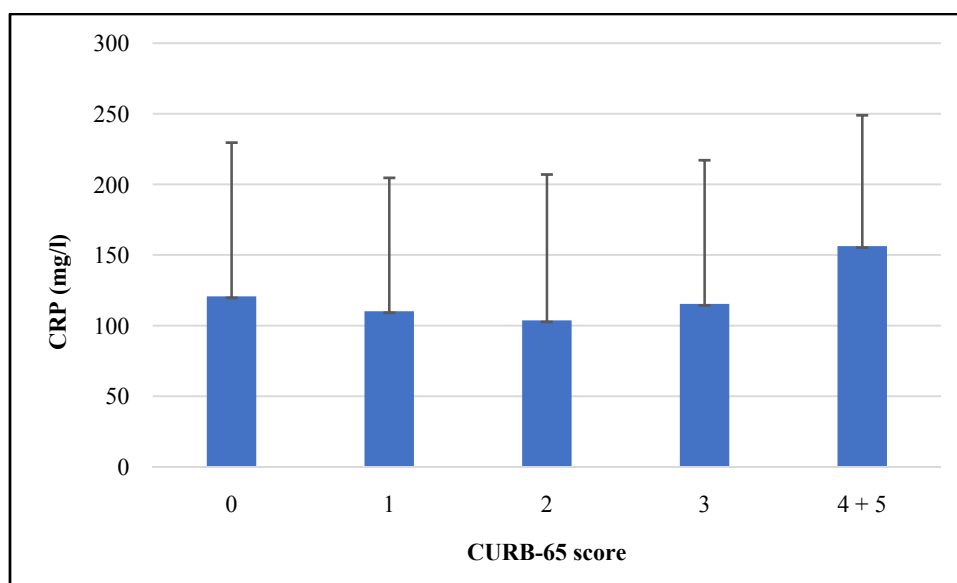


Fig. 1 Meanserum CRP levels (mg/L) of all study patient with community-acquired pneumonia who were classified into five subgroups according to CURB-65 score (0, 1, 2, 3 and 4+5).

The total number of the elderly group (aged ≥ 65years) was 322. The CURB-65 score (mean ± SD) of all the elderly patients was 2 ± 0.9. Seventeen patients (5.1%) had a CURB-65 score of 0; 71 patients (22%) with a score of 1; 145 patients (45%) with a score of 2; 70 patients (21.7%) with a score of 3; 18 patients (5.6%) with a score of 4; and 1 patient (0.3%) with a score of 5. Because of the relatively small

number of patients with CURB-65 scores 4 and 5, both groups were combined in the data analysis. Again the average CRP levels were classified by their CURB-65 score: score 0 was 68.8 ± 94.3 mg/dL, in CURB-65 score 1 was 100.1 ± 84.1 mg/dL, in CURB-65 score 2 was 104 ± 104 mg/dL, in CURB-65 score 3 was 115.3 ± 101.6 mg/dL, in CURB-65 score 4+5 was 156.3 ± 92.19 mg/dL (Fig. 2). In the elderly

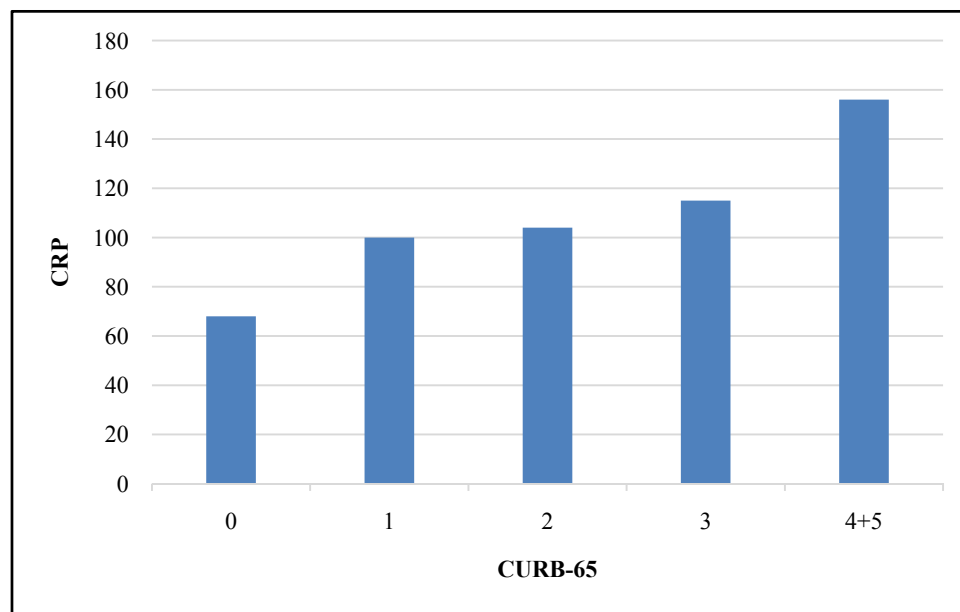


Fig. 2 Mean serum CRP levels (mg/L) in patients aged 65 and over with community-acquired pneumonia who were classified into five subgroups according to CURB-65 score (0, 1, 2, 3 and 4+5).

Table 3 The correlations between CURB-65 score with CRP in adults aged 65 and over.

	CURB-65	CRP (mg/L)
Correlation coefficient (<i>R</i>)	1.000	.126*
Sig. (2-tailed)	.	.024
<i>N</i>	322	322

Spearman's rank correlation. *N*: number of patients. *Correlation is significant at the 0.05 level (2-tailed). CRP: C-Reactive protein.

population (aged ≥ 65 years) as CURB-65 score increases, CRP scores consistently increases as well. These two variables were analyzed by Spearman's rank correlation, and the results showed there is a significant correlation between CURB-65 and CRP ($R = 0.126$, $p = 0.024$) (Table 3).

4. Conclusions

In the current study, we examined whether there is any correlation between CRP and CURB-65 in hospitalized patients with CAP. In a retrospective study, of 500 hospitalized patients aged 18-90 years with CAP, we found a significant correlation between CRP and CURB-65 among elderly patients aged ≥ 65 years but not among patients below the age 65 years.

Pneumonia is the most frequent cause of infectious disease-related mortality among patients of all ages

and the eighth leading cause of death in the United States. Clinical presentation of pneumonia in the elderly may be subtle, lacking the typical acute symptoms observed in younger adults. In the elderly, pneumonia is known to be lethal and atypical, it has been suggested that this is due to reduced local inflammatory response to infection of the lungs. In this study we showed that CRP could be as adjuvant to CURB-65 in assessment elderly patients with CAP.

Another finding of this study was that serum CRP levels which were not well correlated with CURB-65 among patients aged less than 65 years old. These results could be explained by the fact that younger population tend to experience the classical symptoms of typical pneumonia, where they usually experience a sharp increase in the acute phase reactant but at the same time have a moderate increase in CURB-65 criteria. For this reason, it may be that CRP levels are

relatively high in some patients with low CURB score even 0 in population aged less than 65.

Two previous studies with small number of patients with CAP showed that serum CRP is strong prognostic factor for evaluating severity of CAP in addition to the CURB-65, and improves the decision making of whether a patient with CAP should be admitted or not in intensive care unit [14, 15]. One study observed a statistically significant association between CURB-65 criteria and CRP levels [14]. Another study conducted between 2006 and 2008 in Switzerland among 925 patients with CAP, CURB-65 criteria compared with serum levels of CRP and procalcitonin (PCT), and it was reported that PCT is significantly a better predictive factor for bacteremia in patients with pneumonia than CRP and CURB-65 criteria [16]. In our study we showed a significant correlation between CRP levels and CURB-65 score in elderly patients with CAP, but not among patients younger than age 65 years.

Our retrospective study has several drawbacks, in retrospective studies sometimes it is difficult to collect data and out of 838 CAP patients' records that were examined, also, in some of the data we obtained large standard deviations that could weaken the results of the study. Another factor that is not considered in this study is the pathogen's type, whether it is bacterial or viral, this information is not simple to collect. We can rely on the fact that CRP levels are usually lower in viral and superficial bacterial infections than in deep bacterial infections. Co-morbidity like COPD and CHF was also unconsidered.

We suggest that the addition of CRP measurements to the CURB-65 score, especially in the elderly patients with CAP, can help to determine the severity of the disease and the decision making. Further studies are needed to assess the prognostic factor of CURB-65 with CRP in elderly patient with CAP.

Funding

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

The study was approved by local Helsinki Committee.

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