Arch Clin Infect Dis. 2019 April; 14(2):e63893. doi: 10.5812/archcid.63893.

Published online 2019 April 24. **Research Article**

Relationship Between the Serum Level of C-Reactive Protein and Severity and Outcomes of Community-acquired Pneumonia

Farhad Malek [1], Ali Gohari [1,*], Majid Mirmohammadkhani [2] and Farnaz Ardiani [3]

[1] Department of Internal Medicine, Semnan University of Medical Sciences, Semnan, Iran
[2] Social Determinants of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran
[3] Semnan University of Medical Sciences, Semnan, Iran

[*] *Corresponding author*: Assistant Professor, Infectious Diseases Specialist, Department of Internal Medicine, Kosar Hospital, University of Medical Sciences, Semnan, Iran. Tel: +98-2333437844, Email: aligohari@semums.ac.ir

Received 2017 November 09; **Revised** 2018 January 26; **Accepted** 2019 February 17.

Abstract

Background: Evaluation of severity, complications, and risk of death due to community-acquired pneumonia (CAP) plays a major role in making decisions about treatment. Biomarkers are one of the tools used to diagnose the disease.
Objectives: The current study aimed at evaluating the relationship between C-reactive protein (CRP) serum level and outcomes of CAP in affected patients.
Methods: CRP serum level was measured on the 1st and 3rd days of admission in 73 patients. Chest X-ray was taken and CURB-65 (confusion, blood urea > 42.8 mg/dL, respiratory rate > 30/minute, blood pressure < 90/60 mmHg, age > 65 years) criteria was also applied. The patients were followed up for 30 days and evaluated for admission to intensive care unit (ICU), need for mechanical ventilation, inotropic support, incidence of pleural effusion, empyema, lung abscess, and death.
Results: CRP level on the 3rd day of admission had a significant and direct relationship with the incidence of complications and death in patients. There were no significant relationship between CURB-65 score and mean CRP level on admission. There was a significant relationship between mean CRP level on 3rd day and CURB-65 score. Clinical status had a significant relationship with mean CRP levels on the 1st and 3rd days of admission. Considering a cutoff point of 25 for CRP level on the 3rd day of admission, there was a significant difference between two groups in terms of mortality rate and CURB-65 scores.
Conclusions: The results of the current study showed that elevated CRP level on the 3rd day of admission could be a sign of increased risk of complications and severity of the disease as well as death. It can be used as a factor for the prognosis of complications and outcomes.

Keywords: Community-Acquired Pneumonia, C-Reactive Protein, Complications

1. Background

Pneumonia is defined as an infection of the lung parenchyma, which is classified into two groups of community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP). HCAP includes two subgroups: hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (1).

CAP is going to be a public health problem worldwide. The annual expenditures spent to deal with CAP in the United States are about US $9 - 10 billion. Its annual incidence among the adult population is 0.3% - 0.5%. The incidence of this disease is higher among people at the two ends of the age spectrum. CAP accounts for 5% - 15% of all deaths in hospitalized patients. In the United States, pneumonia is among the top 10 leading causes of death among all age groups and the 6th leading cause of death among people aged 65 years and above. It is also the most common cause of mortality due to infectious diseases (1-7).

In the United States, 4 million newly infected CAP cases are identified annually of which 80% are treated by outpatient services, while 20% need hospitalization (1). More than 36% of all hospitalized patients are admitted to the intensive care unit (ICU), and despite many advances made in antimicrobial therapy, mortality rate of CAP is above 30% (8-12).

Streptococcus pneumoniae is the most common bacterial cause of CAP, which covers about 35% of known microorganisms (13). The general risk factors for CAP play a major role in the selection of therapeutic regimen. CAP risk factors include alcoholism, asthma, immunosuppression, living in a nursing home, and being 70 years and older (as compared with 60 - 69 year age group) (1).

Some criteria objectively determine the risk of unfavorable outcomes, especially severe disease and death; the use of such criteria can help to minimize the frequency of unnecessary hospitalizations and detect the patients who are in need of hospital care services (1, 9, 14-16).

During the 1990s, there were some advances in the application of risk factor criteria, including CURB-65 (confusion, blood urea > 42.8 mg/dL, respiratory rate > 30/minute, blood pressure < 90/60 mmHg, age > 65 years) as well as its simplified version, i e, CRB-65 (16, 17). Both of these measures are valid (18, 19), though they have some limitations. They can predict the probability of death; however, they cannot determine the inflammatory response, which is now considered as a key aspect in the prognosis of CAP (20).

Since 2004, CURB-65 is used to identify patients at high risk of death. It prioritizes patients for invasive examinations, treatment, and receiving care services in the ICUs (16).

Previous studies showed that inflammatory markers may play a major role in the prognosis of severe CAP (21). Various cytokines are released into the bloodstream as a result of infection. C-reactive protein (CRP) and cytokines are the markers often associated with pneumonia (17, 20-29). A few studies showed that an elevated CRP level is almost non-specific and does not directly correlate with the severity of the disease (28, 30). Measurement of serum CRP level is recommended as a marker, which indicates the treatment failure in CAP (31). CRP level less than 10 mg/L in patients with pneumonia is atypical and can be used to rule out the diagnosis. CRP $\geq$ 100 mg/L confirms the diagnosis of pneumonia. It is also associated with 30-day mortality and may increase the need for mechanical ventilation or vasopressor support, all of which are associated with severe pneumonia (17, 21).

Most patients hospitalized due to CAP have a satisfactorily response to treatment, but treatment failure occurs in approximately 10% - 15% of cases, and nearly 6% of patients may develop a rapidly progressive and life-threatening pneumonia. It was shown that deaths due to CAP mainly occur in patients with treatment failure with a mortality rate of > 40% (32-34). It is recently shown that severe systemic inflammatory response in patients with sepsis or severe CAP is associated with poor prognosis and deleterious outcomes (35, 36). Previous studies on some biomarkers such as CRP and procalcitonin (PCT) had promising initial results (29, 37).

If CRP serum level does not reduce by 50% or more within four days after the admission, it is indicative of a complication such as empyema (21, 25). It was shown that elevated CRP independently predicts death in critically ill patients (21), although it was not assessed for CAP (21).

Evaluation of the patients in terms of severity of the disease, complications, and death plays an important role in making decisions about treatment plan. Given the high prevalence of the disease and the high costs of health care, it is of great importance to make a detailed clinical and therapeutic decision for the patients. A review of literature showed that some studies reported controversial results and the majority of them often focused only on one aspect of biomarkers in patients with CAP. Hence, the current study, owing to the important role of age, gender, body mass index (BMI), underlying disease, and tobacco and alcohol consumption, aimed at investigating the relationship between CRP and severity of the disease, complications, and mortality rate in patients with CAP.

2. Objectives

Since to the best of authors' knowledge, no similar study was conducted in Iran thus far, the results of the current study can help to adopt a better treatment approach for such patients

3. Methods

In a cross sectional study, eligible patients with CAP hospitalized in Kosar Hospital in Semnan, Iran were enrolled in the study. Inclusion criteria were: new infiltrates on chest radiograph with at least two clinical signs of CAP (fever higher than 38°C, productive cough, bloody sputum, chest pain, shortness of breath, and crackles on auscultation of the lungs). patients with a history of hospitalization within the past 15 days, taking immunosuppressive drugs and/or steroids more than 15 mg per day, leukopenia less than 1000/mm^3, and neutropenia less than 500/mm^3 (except for cases attributed to CAP) were excluded from the study. Considering P = 0.05, d = 0.05, and α = 0.05, the sample size was 73.

Demographic characteristics including age, gender, BMI, tobacco and alcohol consumption, underlying diseases, vital signs, and positive cases identified in clinical examination were registered in patient's records on admission. The CRP levels measured on the 1st and the 3rd days of admission (if the patient was available) were also recorded. CURB-65 scale was used to measure the severity of the disease. The emergence of any complication along with its time was recorded in the patient's datasheet. The patients were followed up for 30 days, starting from admission day (in one case on the day 15 and in another case on the day 30 of admission). During follow-ups, the following items were evaluated: admission to the ICU, need for mechanical ventilation or inotropic support, incidence of pleural effusions, empyema, lung abscess, and death.

T test and ANOVA were used for quantitative comparison and Chi-square test for qualitative comparison. $P < 0.05$ was considered as the significance level in all the tests. Statistical analysis was performed with SPSS version 16. All data were collected after obtaining informed consent from patients; data kept confidential.

4. Results

The current study aimed at determining the relationship between CRP and severity and outcomes (complications and death) of CAP in the affected patients. A total of 73 patients were enrolled in the study of which 39 were above 70 years old. The mean age of the patients was 69.64 $\pm$ 25.62 years; 45 subjects were male and 28 female. BMI of 51 subjects was < 26 kg/m^2, while it was $\geq$ 26 kg/m^2 in the rest 22 subjects. The presence of comorbidities including chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, and diabetes were also studied. Of all, 16 patients (21.9%) were smoker and 57 (78.1%) non-smoker. The following complications occurred in 15 patients: admission to the ICU, need for mechanical ventilation, empyema, and severe sepsis. Of all patients with complications, four patients died and 11 survived.

Mean days of hospitalization was 9.75 days. In 36 patients the duration of hospital stay was less than five days, while in 37 patients it was more than five days. Of all the studied patients, 63 had a stable condition and 10 had an unstable condition. The mean CURB-65 score of the patients was 1.56 $\pm$ 1.04. Moreover, 41 patients (56.2%) got a score of 1 or lower and 32 (43.8%) got a score of 2 or higher. Tables 1 and 2 present the frequency of complications and disease outcomes.

Table 1. Patients' Health Status, 15 Days After Admission[a]

	Positive	Negative
Admission to ICU	14 (19.2)	59 (80.8)
Mechanical ventilation	9 (12.3)	64 (87.7)
Pulmonary edema	3 (4.1)	70 (95.9)
Empyema	0 (0)	73 (100)
Abscess	0 (0)	73 (100)
Severe sepsis	2 (2.7)	71 (97.3)

[a] Values are expressed as frequency (%).

Based on the results of statistical analysis, there was no significant difference between the CRP levels measured on the 1st and 3rd days of admission (P = 0.127). There was a significant difference between the patients with a hospital stay of five days or less and the ones with a hospital stay of more than five days in terms of the mean CRP levels on the 1st and 3rd days of admission (P = 0.28 and P = 0.015, respectively).

Table 2. Patients' Health Status, 30 Days After Admission[a]

	Positive	Negative
Death	2 (2.7)	71 (97.3)
Admission to ICU	3 (4.1)	69 (93.2)
Mechanical ventilation	3 (4.1)	69 (93.2)
Pulmonary edema	1 (1.4)	70 (95.9)
Empyema	0 (0)	71 (97.3)
Abscess	0 (0)	71 (97.3)
Severe sepsis	0 (0)	71 (97.3)

[a] Values are expressed as frequency (%).

Based on the results of unadjusted regression analysis, there was no significant difference between patients who died and survived in terms of the mean CRP level on admission (P = 0.068); however, the mean CRP levels on the 3rd day were significantly different between the two groups (P = 0.016). There was no significant difference between patients with complications and the ones without complications in terms of the mean CRP levels on the 1st and 3rd days of admission (P = 0.058). The mean CRP levels on the day 3 were significantly different between the two groups (P = 0.005).

There were significant differences between the patients with stable clinical conditions and the ones with unstable clinical conditions in terms of the mean CRP levels on the 1st and 3rd days of admission (P = 0.016 and P = 0.004, respectively).

According to the results of adjusted regression analysis, based on the CRUB-65 criteria, there was no significant difference between the patients with different BMIs in terms of the mean CRP level on the day 1 after admission (P = 0.449), but there was no significant difference between the two groups in terms of the mean CRP level on the day 3 after admission (P = 0.049).

There was no significant difference between the patients with and without comorbidities in terms of the mean CRP levels on the 1st and 3rd days of admission (in patients with and without COPD: P = 0.550 and P = 0.068, respectively; in patients with and without asthma: P = 0.630 and P = 0.053, respectively; in patients with and without cardiovascular disease: P = 0.608 and P = 0.087, respectively; in smokers and non-smokers: P = 0.660 and P = 0.078, respectively). In other words, based on CRUB-65 criteria, the parameters of underlying disease, cardiovascular disease, and smoking had no mutual relationship with CRP, and increasing or decreasing their values could not be used for the prognosis of the other parameters.

Considering a cutoff point of 25 for CRP, the patients were divided into two groups and chi-square test was used to compare the frequency and percentage of mortality, complications, and disease severity between the two groups. There was no significant difference between the two groups of patients with a CRP level of less than and more than 25 on admission in terms of mortality (P = 0.091); however, considering CRP level on the 3rd day of admission, there was a significant difference between the two groups in terms of mortality (P = 0.004).

There were significant differences between the two groups of patients with a CRP level of less than and more than 25 on the 1st and 3rd days of admission in terms of the incidence of complications (P = 0.005, and P = 0.0001, respectively). Moreover, there were significant differences between the two groups of patients with a CRP level of less than and more than 25 on the 1st and 3rd days of admission in terms of disease outcomes (P = 0.017, and P = 0.0001, respectively).

There was no significant difference between the two groups of patients with a CRP level of less than and more than 25 on admission in terms of CURB-65 score (P = 0.091); however, considering CRP level on the 3rd day of admission, there was a significant difference between the two groups in terms of CURB-65 score (P = 0.004).

5. Discussion

In the current study, the results of unadjusted regression analysis showed a significant difference in terms of the CRP levels on the 3rd day between the two groups of patients who died or survived and in patients with and without complications (P = 0.016 and P = 0.005, respectively).

There were significant differences between the two groups of patients with CRP levels on 3rd day with a cutoff point of 25 in terms of mortality and disease severity (P = 0.004 and P = 0.021, respectively).

Several studies investigated the role of CRP in the prognosis of CAP and almost all reported similar results. In a study by Hoenthal U in Finland, CRP level was assessed in CAP, with a particular focus on the severity of illness (the pneumonia severity index). Results showed a positive correlation between high levels of CRP and the severity of the disease. A higher CRP levels on admission was associated with ICU stay. A significant difference was seen on the 1st day CRP level of patients in term of tobacco and alcohol consumption and history of antibiotic use (28).

In the current study, elevated level of CRP on admission was associated with higher complications as well as disease outcomes and clinical condition, but 1st and 3rd days CRP levels were not associated with smoking.

In a study by Menendez et al. (20), the role of biomarkers was investigated in the prognosis of death in patients with CAP. The 30-day mortality was 7.9% and 31 patients died during hospitalization. In their study, the patients who died were older, had more neurological disorders, and higher initial severity. The 1st day CPR level in the patients who died was higher than that of the survived ones. In the current study, 1st day CPR level had no significant relationship with the age and mortality rate, but higher levels of CRP on admission and presence of comorbidities increased mortality rate and ICU stay. Also, the results of regression analysis based on the CURB-65 criteria showed a significant difference in the 3rd day CRP levels with a cutoff point of 25, although the difference in the 1st day CRP level was not significant.

In another study in Spain, the relationship of systemic inflammatory response of cytokines, CRP, and PCT was investigated with treatment failure. Treatment failure occurred in 84 patients (18%) and 38 patients experienced early treatment failure. The mean interleukin-6, PCT, and CRP levels on the 1st and 3rd days and the mean IL-8 levels on the 1st day of admission were significantly higher in patients with treatment failure. Results of logistic regression showed that the CPR levels cutoff point of 21.9 mg/dL on admission was independently effective in treatment failure (odds ratio (OR): 2.6). In the study, elevated levels of CRP on admission independently predicted early and late treatment failure (29). In the current study, higher 3rd day CRP level was associated with incidence of complications. Also, the results of regression analysis showed that 3rd day CRP level at the cutoff point of 25 had a significant relationship with the incidence of complications and the exacerbation of conditions in the future days, and can be a prognostic factor, especially for death.

In a prospective cohort study, different patterns of CRP ratio in response to antibiotic therapy were evaluated in patients with severe CAP who admitted to ICU. CRP ratio was calculated on the basis of the CRP level measured on admission. In patients who survived, CRP level decreased from the 1st day to the 7th day (P = 0.01) (26). In the present study, the elevated CRP level on the 1st day and its high level until the 3rd day were associated with increased incidence of complications and outcomes.

In the study by Chalmers, the role of CRP level on admission and 4 days after admission was investigated in the prognosis of CAP severity. Overall, 20.7% of the patients were discharged within the first 24 hours of admission of which 13.5% were in need of mechanical ventilation and/or inotropic support. Complicated pneumonia was observed in 7.3% of the patients and 30-day mortality rate was 9.6%. CRP < 100 mg/L was independently associated with reduced risk of 30-day mortality (OR = 0.18; P =

0.03). In addition, it was associated with a reduction in the need for mechanical ventilation or inotropic support (OR = 0.21; P = 0.002). CRP < 100 mg/L was associated with reduced risk of pneumonia complications (OR = 0.05; P = 0.003). Their study also showed that if CRP level did not reduce within 1st four days of admission by 50% or more, it was independently associated with increased risk of 30-day mortality (OR = 24.5; P = 0.0001) (21). In the current study, mortality rate was lower than that of the latter study; however, the incidence of complications was higher. Considering a cutoff point of 25 mg/dL for CRP, no significant changes was observed in mortality rate (P = 0.091); however, the incidence of complications and patient outcomes were significantly different (P = 0.005 and P = 0.017, respectively).

The study by Gareth Walters HSL investigated the role of CRP level on admission in the prognosis of bacterial pneumonia complications. According to the findings of his study, the frequency of lung abscess, pulmonary effusion, empyema, admission to ICU, and 30-day mortality were 0%, 9.6%, 5.2%, 7.6%, and 12.2%, respectively. CRP $\geq$ 300 mg/L on admission was associated with increased risk of admission to ICU (P = 0.006; OR = 6.5), but it did not increase the risk of effusion, empyema, or death. CRP $\geq$ 100 mg/L on admission was not associated with a higher incidence of complications. Failure to reduce CRP level by 50% within four days or more after admission increased the mean length of hospital stay from 10 to 13 days, increased the risk of effusion (P = 0.03; OR = 5.83), and increased the OR of death (P = 0.02; OR = 4.82) (38). In the current study, the incidence of complication was 20.5%, ICU admission 19.2%, need for mechanical ventilation 12.3%, pulmonary edema 4.1%, and severe sepsis 2.7%. The incidence of complications was associated with the CRP level on the 3rd day of admission (P = 0.005). Elevated CRP level on admission was associated with increased risk of ICU stay and elevated CRP level on the 1st and 3rd days were associated with prolonged hospital stay (P = 0.028 and P = 0.015, respectively).

The study by Makarevich was conducted on patients with severe CAP and CURB-65 risk classes III to V who were admitted to the ICU. Severity of CAP was associated with elevated CRP level (P < 0.05). As observed, the patients who died had a higher level of CRP in comparison with the survived ones (241 mg/mL vs. 11 mg/mL; P < 0.05) (39). In the current study, there was no correlation between elevated CRP level on admission and death (P = 0.072) that might be due to differences in sample size and study method. However, considering a cutoff point of 25, the mean CRP levels were significantly different between patients with CURB-65 score $\leq$ 2 and > 2 and; thus, it can have a prognostic value for mortality and morbidity (P = 0.004).

The results of the current study showed no significant changes in CRP level of patients who developed complications or death. In addition, the controversy between the results can be attributed to applied research methods and sample size differences.

5.1. Limitations of the Study

Small sample size was one of the important limitations of the current study.

5.2. Recommendations

It is recommended to perform further studies with larger sample sizes using both qualitative and quantitative methods to measure CRP and cytokines levels, especially CRP, during the hospital stay (up to 30 days).

5.3. Conclusions

The results of the current study showed that elevated CRP level on the 3rd day of admission could be a sign of increased risk of complications, severity of the disease, and death. It can be used as a prognostic factor for CAP complications and outcomes.

Acknowledgments

The present paper was extracted from an MD thesis by Farnaz Ardiani (ethical code: IR.SEMUMS.REC.1397.263). The authors would like to express their gratitude to those who helped them to conduct the research.

Footnotes

Authors' Contribution: Farhad Malek and Ali Gohari: study conduction, data collection, preparation of the first draft of the manuscript; Majid Mirmohammadkhani: data analysis; Farhad Malek, Ali Gohari, and Majid Mirmohammadkhani: editing the manuscript critically for the important intellectual contents. All authors read and signed the final version of the manuscript.

Conflict of Interests: The authors declared no conflict of interests.

Ethical Considerations: The study protocol was approved by the Ethics Committee of Semnan University of Medical Sciences (ethical code: IR.SEMUMS.REC.1397.263).

Funding/Support: The study was financially supported by the vice-chancellor of research and technology, Semnan University of Medical Sciences.

Patient Consent: All data were collected from patients after obtaining informed consent; data kept confidential.

References

1. Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. *Harrison's principles of internal medicine*. 18th ed. New York: McGraw-Hill; 2012.
2. Hoyert DL, Heron MP, Murphy SL, Kung HC. Deaths: Final data for 2003. *Nat Vit Stat Rep*. 2006;**54**:30–8. doi: 10.1037/e518032006-001.
3. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F, Epivac Study Group . Epidemiology of community-acquired pneumonia in older adults: A population-based study. *Respir Med*. 2009;**103**(2):309–16. doi: 10.1016/j.rmed.2008.08.006. [PubMed: 18804355].
4. Hansen V, Oren E, Dennis LK, Brown HE. Infectious disease mortality trends in the United States, 1980-2014. *JAMA*. 2016;**316**(20):2149–51. doi: 10.1001/jama.2016.12423. [PubMed: 27893119].
5. Hifumi T, Jinbo I, Okada I, Kiriu N, Kato H, Koido Y, et al. The impact of age on outcomes of elderly ED patients ventilated due to community acquired pneumonia. *Am J Emerg Med*. 2015;**33**(2):277–81. doi: 10.1016/j.ajem.2014.10.046. [PubMed: 25541226].
6. Gibson GJ, Loddenkemper R, Lundback B, Sibille Y. Respiratory health and disease in Europe: The new European lung white book. *Eur Respir J*. 2013;**42**(3):559–63. doi: 10.1183/09031936.00105513. [PubMed: 24000245].
7. Kothe H, Bauer T, Marre R, Suttorp N, Welte T, Dalhoff K. Outcome of community-acquired pneumonia: Influence of age, residence status and antimicrobial treatment. *Eur Respirat J*. 2008;**32**(1):139–46. doi: 10.1183/09031936.00092507.
8. Restrepo MI, Mortensen EM, Velez JA, Frei C, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest*. 2008;**133**(3):610–7. doi: 10.1378/chest.07-1456. [PubMed: 17989157].
9. España PP, Capelastegui A, Quintana JM, Bilbao A, Diez R, Pascual S, et al. Validation and comparison of SCAP as a predictive score for identifying low-risk patients in community-acquired pneumonia. *J Infect*. 2010;**60**(2):106–13. doi: 10.1016/j.jinf.2009.11.013.
10. Benisi R, Bayat-Makoo Z, Mobaiyen H. Prognostic factors and outcome of patients hospitalized with community acquired Pneumonia. *J Analyt Res Clin Med*. 2018;**6**(2):86–92. doi: 10.15171/jarcm.2018.013.
11. Wunderink RG, Laterre PF, Francois B, Perrotin D, Artigas A, Vidal LO, et al. Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: A randomized trial. *Am J Respir Crit Care Med*. 2011;**183**(11):1561–8. doi: 10.1164/rccm.201007-1167OC. [PubMed: 21297074].
12. Shan J, Chen HL, Zhu JH. Diagnostic accuracy of clinical pulmonary infection score for ventilator-associated pneumonia: A meta-analysis. *Respirat Care*. 2011;**56**(8):1087–94. doi: 10.4187/respcare.01097.
13. Müller NL, Franquet T, Lee KS, Silva CI. *Imaging of pulmonary infections*. Lippincott Williams & Wilkins; 2007.
14. Charles PG, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, et al. SMART-COP: A tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis*. 2008;**47**(3):375–84. doi: 10.1086/589754. [PubMed: 18558884].
15. Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP, et al. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax*. 2006;**61**(5):419–24. doi: 10.1136/thx.2005.051326. [PubMed: 16449258]. [PubMed Central: PMC2111174].
16. Singanayagam A, Chalmers JD, Hill AT. Severity assessment in community-acquired pneumonia: A review. *Qjm*. 2009;**102**(6):379–88. doi: 10.1093/qjmed/hcp027.
17. Bennett JE, Dolin R, Blaser MJ. *Mandell, Douglas, and Bennett's Principles and practice of infectious diseases*. Churchill Livingstone; 2010.
18. Frei CR, Bell AM, Traugott KA, Jaso TC, Daniels KR, Mortensen EM, et al. A clinical pathway for community-acquired pneumonia: An observational cohort study. *BMC Infect Dis*. 2011;**11**(1). doi: 10.1186/1471-2334-11-188.
19. Leroy O, Mikolajczyk D, Devos P, Chiche A, Grunderbeeck NV, Boussekey N, et al. Validation of a prediction rule for prognosis of severe community-acquired pneumonia. *Open Respir Med J*. 2008;**2**:67–71. doi: 10.2174/1874306400802010067. [PubMed: 19365534]. [PubMed Central: PMC2606649].
20. Menendez R, Martinez R, Reyes S, Mensa J, Filella X, Marcos MA, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. *Thorax*. 2009;**64**(7):587–91. doi: 10.1136/thx.2008.105312. [PubMed: 19131448].
21. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med*. 2008;**121**(3):219–25. doi: 10.1016/j.amjmed.2007.10.033. [PubMed: 18328306].
22. Christ-Crain M, Muller B. Biomarkers in respiratory tract infections: Diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J*. 2007;**30**(3):556–73. doi: 10.1183/09031936.00166106. [PubMed: 17766633].
23. Torres A, Ramirez P, Montull B, Menéndez R. Biomarkers and community-acquired pneumonia: Tailoring management with biological data. *Seminar Respirat Crit Care Med*. 2012;**33**(3):266–71. doi: 10.1055/s-0032-1315638.
24. Akram AR, Chalmers JD, Taylor JK, Rutherford J, Singanayagam A, Hill AT. An evaluation of clinical stability criteria to predict hospital course in community-acquired pneumonia. *Clin Microbiol Infect*. 2013;**19**(12):1174–80. doi: 10.1111/1469-0691.12173. [PubMed: 23438068].
25. Eisenhut M. A persistently elevated C-reactive protein level in pneumonia may indicate empyema. *Crit Care*. 2008;**12**(1):409. author reply 409. doi: 10.1186/cc6204. [PubMed: 18341702]. [PubMed Central: PMC2374620].
26. Coelho LM, Salluh JIF, Soares M, Bozza FA, Verdeal JCR, Castro-Faria-Neto HC, et al. Patterns of C-reactive protein RATIO response in severe community-acquired pneumonia: A cohort study. *Crit Care*. 2012;**16**(2):R53. doi: 10.1186/cc11291.
27. Espana PP, Capelastegui A, Bilbao A, Diez R, Izquierdo F, Lopez de Goicoetxea MJ, et al. Utility of two biomarkers for directing care among patients with non-severe community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis*. 2012;**31**(12):3397–405. doi: 10.1007/s10096-012-1708-5. [PubMed: 23010902].
28. Hohenthal U, Hurme S, Helenius H, Heiro M, Meurman O, Nikoskelainen J, et al. Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. *Clin Microbiol Infect*. 2009;**15**(11):1026–32. doi: 10.1111/j.1469-0691.2009.02856.x. [PubMed: 19548923].
29. Menendez R, Cavalcanti M, Reyes S, Mensa J, Martinez R, Marcos MA, et al. Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax*. 2008;**63**(5):447–52. doi: 10.1136/thx.2007.086785. [PubMed: 18245147].
30. Coelho L, Povoa P, Almeida E, Fernandes A, Mealha R, Moreira P, et al. Usefulness of C-reactive protein in monitoring the severe community-acquired pneumonia clinical course. *Crit Care*. 2007;**11**(4):R92. doi: 10.1186/cc6105. [PubMed: 17723153]. [PubMed Central: PMC2206486].
31. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: Update 2009. *Thorax*. 2009;**64 Suppl 3**:iii1–55. doi: 10.1136/thx.2009.121434. [PubMed: 19783532].
32. Ott SR, Hauptmeier BM, Ernen C, Lepper PM, Nuesch E, Pletz MW, et al. Treatment failure in pneumonia: Impact of antibiotic treatment and cost analysis. *Eur Respirat J*. 2011;**39**(3):611–8. doi: 10.1183/09031936.00098411.
33. Chen X. Causes and management of initial treatment failure in patients with community-acquired pneumonia. *Commun Acquir Infect*. 2014;**1**(2):65. doi: 10.4103/2225-6482.147665.
34. Vukadinovic D, Samardzic N, Jankovic S, Tomic-Smiljanic M, Pavlovic R, Stefanovic S. Factors associated with early treatment failure in

adult hospitalized patients with community-acquired pneumonia. *Vojnosanitetski pregled*. 2017;**74**(9):803–13. doi: 10.2298/vsp160211085v.
35. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. *Nat Rev Dis Primers*. 2016;**2**:16045. doi: 10.1038/nrdp.2016.45. [PubMed: 28117397]. [PubMed Central: PMC5538252].
36. Moldoveanu B, Otmishi P, Jani P, Walker J, Sarmiento X, Guardiola J, et al. Inflammatory mechanisms in the lung. *J Inflamm Res*. 2009;**2**:1–11. doi: 10.2147/JIR.S4385. [PubMed: 22096348]. [PubMed Central: PMC3218724].
37. Le Bel J, Hausfater P, Chenevier-Gobeaux C, Blanc FX, Benjoar M, Ficko C, et al. Diagnostic accuracy of C-reactive protein and procalcitonin in suspected community-acquired pneumonia adults visiting emergency department and having a systematic thoracic CT scan. *Crit Care*. 2015;**19**(1). doi: 10.1186/s13054-015-1083-6.
38. Walters G, Liu HS, Gemza M, Rauf F. Does the serum C-reactive protein (CRP) predict adverse outcomes in patients admitted with community acquired pneumonia? *Eur Respirat J*. 2011;**64**(3):1–55.
39. Makarevich A, Omelyanenko O, Amelchenko E, Rybina T. C-reactive protein (CRP) utility in severe community-acquired pneumonia (SCAP) prognosis. *Eur Respirat J*. 2011;**38**:1470.