Total cortisol level as a predictor of severity and outcome in community-acquired pneumonia

Sahar Farghly[a], Yousef Ahmed[a], Reham El-Morshedy[a], Randa A. El Zohne[b], Doaa M. Abd El-Kareem[b]

Departments of [a]Chest Diseases, [b]Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Reham ELmorshedy, MD, Lecturer of Chest Diseases Assuit University, Assiut, 71511, Egypt.Tel.: 01149009033; e-mail: reham1715@gmail.com

Received: 6 June 2019
Accepted: 12 September 2019
Published: 31 January 2020

The Egyptian Journal of Chest Diseases and Tuberculosis 2020, 69:142–147

Background
Several biomarkers have been checked and verified for use in improving risk rating and management resolutions in cases of community-acquired pneumonia (CAP) alongside the well-established severity scores.
Objective
Our objective was to evaluate the veracity of the serum total cortisol level as a biomarker for assessing the severity of CAP.
Patients and methods
Our research was a descriptive and prospective study of patients who have been diagnosed with CAP. All were admitted in the Chest Department of Assiut University Hospital between October 2017 and January 2019. The CAP severity was assessed for all enrolled patients by application of the pneumonia severity index (PSI). Serum total cortisol level was measured once in the morning (between 7 a.m. and 8 a.m.) within the first 24 h after admission. All of the patients were followed up until being discharged. The outcome variable was the intrahospital mortality.
Results
This research enrolled 94 patients with CAP; of them, 62 (56%) patients survived, whereas the health of 32 (44%) patients deteriorated and they died. The nonsurvivors had significantly higher cortisol level in the serum compared with the survivors (34.15±9.78 vs. 24.90±8.89; P=0.04). Of the study population, 37 (39.4%) patients had normal cortisol level, whereas 57 (60.6%) had high cortisol level. It was noticed that patients with high cortisol level had a significantly higher PSI (140.75±48.31 vs. 103.56±43.57), and 87.2% of them had PSI class V. The serum cortisol level had a positive significant correlation with PSI points (r=0.45, P=0.01). In terms of the diagnostic performance of serum cortisol, it was noticed that serum cortisol at cutoff point more than 43 μg/dl had 80% sensitivity and 91% specificity to predict the intrahospital mortality in patients with CAP.
Conclusion
The serum cortisol could be considered as a promising biomarker that is able to predict the severity and outcome of CAP. However, we recommend further larger studies with different aspects to investigate the accuracy of serum cortisol in assessing the severity of CAP and its potential effect on the treatment plan.

Keywords:
community-acquired pneumonia, serum cortisol, outcome

Egypt J Chest Dis Tuberc 69:142–147

2090-9950

Introduction

Community-acquired pneumonia (CAP) is a major cause of death. Risk factors include aging and associated medical conditions. CAP diagnosis is suggested through the clinical manifestations (e.g. cough, fever, AND pleuritic chest pain) and confirmed by the pulmonary imaging (chest radiography and or ultrasound) [1]. Early identification of patients with CAP at risk of poor outcome is critical for defining the site of care and may affect hospital resource consumption and prognosis. Severity scores, such as the pneumonia severity index (PSI) and CURB-65 (confusion, urea, respiratory rate, blood pressure, and age) scores, have been developed and well verified. These scores can help in the decision-making process of hospitalization and ICU referral [2,3]. In addition, biomarkers were found to improve risk rating and management resolutions in CAP. Several biomarkers have been checked and verified for use in CAP. Conventional biomarkers such as the number of white blood cell and erythrocyte sedimentation rate have become less dependent because of less sensitivity and specificity compared with the more favorable C-reactive protein and procalcitonin, which are currently widely used.

Other inflammatory mediators including cortisol in the serum were found to be high in response to the infection [4]. The objective of our research was to evaluate the veracity of the serum total cortisol level as a biomarker for assessing the severity of CAP.

Patients and methods

This is a descriptive and prospective research of 94 patients aged 18 years or over who have been diagnosed with CAP. All were admitted at the Chest Department of Assiut University Hospital between October 2017 and January 2019. CAP was known as a new pulmonary infiltration on chest radiography and symptoms corresponding to pneumonia such as coughing, breathlessness, high body temperature and/or chest pain that did not occur in the hospital. The exclusion criteria included patients under the age of 18 years as well as patients who had previously used corticosteroids (equivalent to 10 mg prednisone or more per day for≥2 weeks); medications that suppress the immunity; tuberculosis; human immunodeficiency virus infection; malignant neoplasm; hypoproteinemia; nosocomial pneumonia; pregnant women; and women taking oral contraceptives. Basic clinical information was obtained, and a bedside assessment was performed for each patient. The laboratory data and the chest radiographic findings were also collected. The CAP severity was assessed for all enrolled patients using pneumonia severity index [5]. All of the patients were followed up until being discharged. The outcome variable was the intrahospital mortality. Prior approval was obtained for the protocol of this study from the Local Ethics Committee, and informed permission was taken from all patients or those responsible for them. Serum total cortisol was measured in the morning (between 7 a.m. and 8 a.m.) within the first 24 h after admission. Overall, 3 ml of venous blood samples was obtained from all subjects and was centrifuged at 1600*g* for 10 min at room temperature, and the serum was collected and stored at 20°C until use. Quantitative determination of serum cortisol was measured by chemilunescent enzyme labeled immunoassay using ADVIA Centaur XPT (Siemens, Tarrytown, New York, USA). Serum cortisol kit was Siemens Ref. 10994929. Lot 72157317. Normal cortisol reference was 4.3–22.4 μg/dl.

Statistics

SPSS (version 20; IBM Corp., Armonk, New York, USA) was used for analyzing the collected data, and different statistical measures were calculated from this data. χ^2-Test was used to compare the nominal data of different groups in the study, whereas Student *t*-test was used to compare mean of two different groups. Pearson's correlation was used to determine the correlation between serum cortisol with PSI. Diagnostic performance of serum cortisol in prediction the outcome in patients with CAP was determined by receiver operating characteristic curve (ROC) curve. Level of confidence was kept at 95%, and *P* value was significant if less than 0.05.

Results

The characterized data of the included patients are summarized in (Table 1). This study enrolled 94 patients with CAP; of them, 62 (56%) patients survived, whereas the health of 32 (44%) patients deteriorated and they died. The interesting results that can be drawn from this table are as follows: (a) both survivors and nonsurvivors had significant difference regarding age and sex distribution; (b) most survivors was males, whereas most nonsurvivors was females; (c) the nonsurvivors had significantly lower frequency of unilobar pneumonia and significantly higher frequency of multilobar pneumonia in comparison with survivors; (d) referral to the ICU was much higher among nonsurvivors; (e) the nonsurvivors had significantly higher cortisol level in comparison with survivors; (f) mean PSI was significantly higher in nonsurvivors compared with survivors and most of the nonsurvivors had PSI class V; and (g) hospital stay was significantly prolonged in case of nonsurvivors. Distribution of serum cortisol based on PSI class is shown in (Table 2 and Figure 1). Of the study population, 37 (39.4%) patients had normal cortisol level in the serum, whereas 57 (60.6%) had high cortisol level. It was noticed that patients with higher cortisol level had significantly higher PSI (140.75±48.31 vs. 103.56±43.57) and 87.2% of them had PSI class V. Figure 2 shows that the serum cortisol level had positive significant correlation with PSI points (r=0.45, P=0.01). The diagnostic performance of serum cortisol in predicting deaths in patients with CAP is illustrated in (Table 3 and Figure 3). It was noticed that serum cortisol at cutoff point more than 43 μg/dl had 80% sensitivity and 91% specificity for the prediction of intrahospital mortality in patients with CAP.

Discussion

Based on the expected response of the adrenal gland in stressful conditions such as infection, the past few years

Table 1 Characterized data of enrolled patients

Items	Patients enrolled in the study (*n*=94)		*P* value
	Nonsurvivors [32 (44%)]	Survivors [62 (56%)]	
Age (years)	64.12±12.02	45.37±14.78	**0.03**
Sex			
Male	14 (43.8)	46 (74.2)	**0.04**
Female	18 (56.2)	16 (25.8)	
Current smoking	8 (25)	22 (35.5)	0.74
Coexisting illness	12 (37.5)	16 (25.8)	0.11
Antibiotics pretreatment	4 (12.5)	2 (3.2)	0.09
Radiological findings			
Unilobar pneumonia	8 (25)	29 (46.8)	**0.04**
Multilobar pneumonia	16 (50)	19 (30.6)	**0.01**
Interstitial pneumonia	3 (9.3)	9 (14.5)	0.98
Pleural effusion	6 (18.7)	9 (14.5)	0.45
White blood cell ($\times10^9$/l)	15.18±9.11	13.61±6.97	0.36
Positive sputum culture	27 (84.3)	56 (90.3)	0.56
Positive blood culture	6 (18.7)	2 (3.2)	0.06
PaO_2	44.46±7.49	44.45±8.20	0.99
Referral to ICU	20 (62.5)	22 (35.5)	**0.04**
Mechanical ventilation	16 (50)	19 (30.6)	0.15
Serum cortisol (μg/dl)	34.15±9.78	24.90±8.89	**0.04**
PSI points	134.68±40.04	114.06±45.10	**0.01**
PSI class			
II	0	2 (3.2)	**0.01**
III	0	7 (11.3)	
IV	7 (21.9)	20 (32.3)	
V	25 (88.1)	33 (53.2)	
LOH stay (days)	15.53±8.01	12.41±5.53	**0.02**

Data was expressed in form of frequency (percentage), mean±SD. LOH stay, length of hospital stay; PaO_2, partial pressure of arterial oxygen; PSI, pneumonia severity index. $P<0.05$, significant.

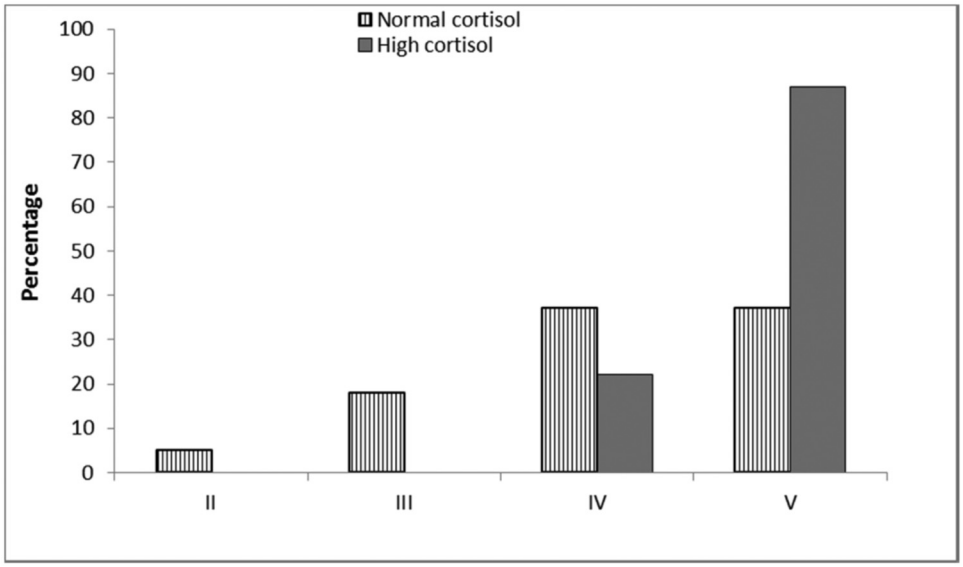
Table 2 Distribution of serum cortisol levels based on pneumonia severity index class

Items	Normal serum cortisol (*n*=37)	High serum cortisol (*n*=57)	*P* value
PSI points	103.56±43.57	140.75±48.31	**0.03**
PSI class			
II	2 (5.4)	0	**0.02**
III	7 (18.9)	0	
IV	14 (37.8)	13 (22.8)	
V	14 (37.8)	44 (87.2)	

Data was expressed in form of frequency (percentage), mean±SD. PSI, pneumonia severity index. $P<0.05$, significant.

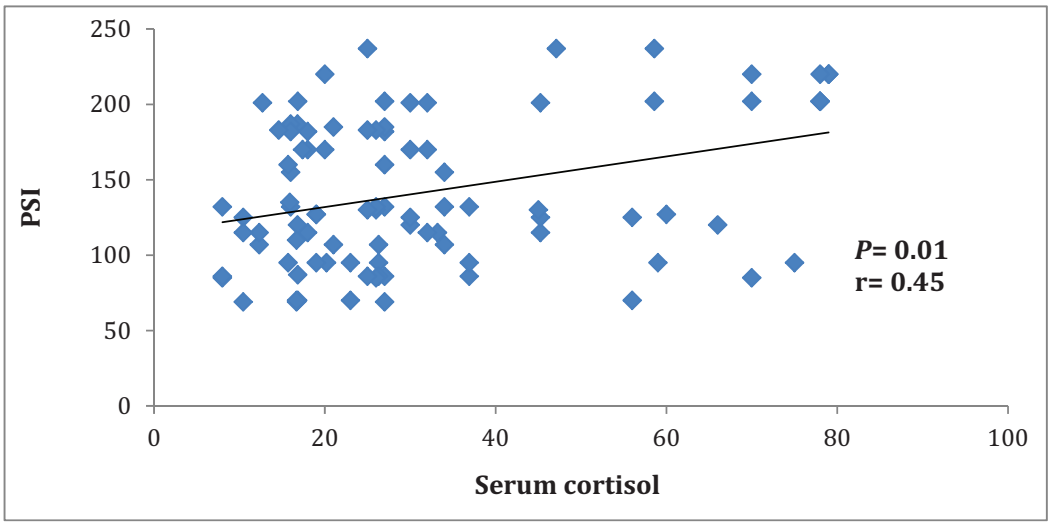
have seen some studies on the possibility of using the measurement of serum cortisol level as a potential biomarker that was associated with severity and deaths in CAP, thus helping to identify patients with high risk for a complex course [6–12]. In circulation, cortisol can be found in free biologically active form (<10%), but the majority is bound to globulin and albumin (>90%) [13]. In this prospective study, we planned to estimate the serum total cortisol level to evaluate its validity as a biomarker for assessing the severity of CAP. To our knowledge, no previous study has been conducted at Assiut University Hospital to estimate the serum cortisol level and valuing its use in patients with CAP. Our choice to measure total serum cortisol instead of free cortisol was based on conclusion that free cortisol was no better than total cortisol as a predictor of severity of CAP as concluded by Christ-Crain *et al.* [6]. In addition, free cortisol measurement is difficult, costly, and not widely obtainable [14]. In this study, we found that the nonsurvivors among patients with CAP had significantly higher serum cortisol level in comparison with survivors. This is in line with some previous studies in this area that revealed the role of cortisol in predicting deaths among these patients [15–17]. We also showed that patients with high cortisol levels in the blood have significantly higher PSI scores compared with those who have a normal

Figure 1



Distribution of serum cortisol levels based on pneumonia severity index class.

Figure 2



Correlation of serum cortisol with pneumonia severity index points.

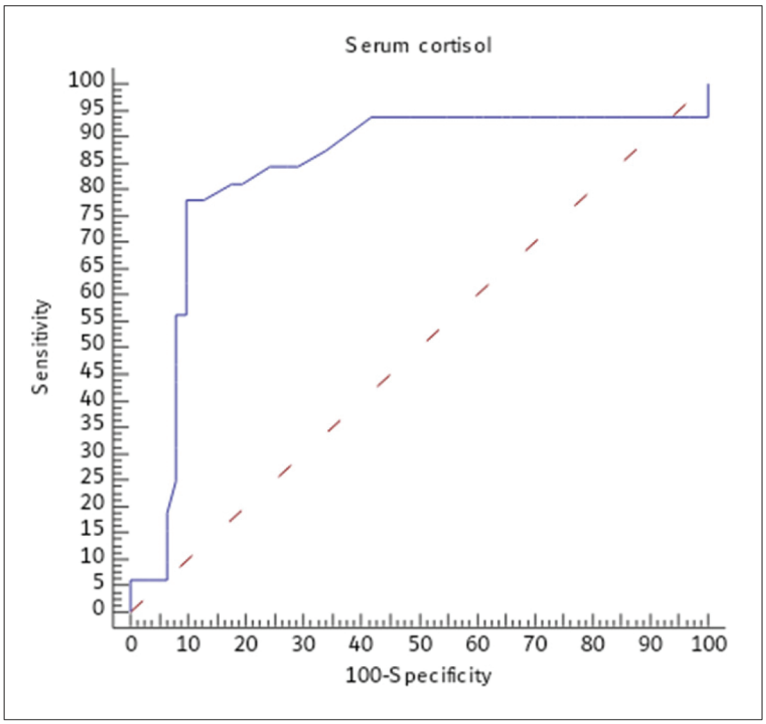
Table 3 Diagnostic performance of serum cortisol in prediction of mortality in patients with community-acquired pneumonia

Indices	Value
Sensitivity (%)	80
Specificity (%)	91
Positive predictive value (%)	81
Negative predictive value (%)	89
Area under the curve	0.81
Cutoff point	>43 μg/dl
P value	0.01

P<0.05, significant.

cortisol level. The serum total cortisol level was significantly positively correlated with this score. This finding is supported by Christ-Crain *et al.* [6], Gotoh *et al.* [7], Fouda and Elatar [9], Mueller *et al.* [10], and Khalil *et al.* [12]. Furthermore, in this study, we were able to identify that serum total cortisol level at cutoff point more than 43 μg/dl had high sensitivity and specificity for predicting the intrahospital mortality in patients with CAP, which could distinguish our results from the results of the aforementioned studies, which did not touch the cutoff point. What we can consider to be a constraint in this study is the measurement of serum total cortisol level only once at admission. It may be better to perform a serial measurement of the serum cortisol during the course of the disease and determine any change in its level and

Figure 3



ROC curve of serum cortisol in prediction of mortality in patients with community-acquired pneumonia.

its relation to the outcome of the disease, as experienced by Remmelts *et al*. [18]; this may be more accurate and on the contrary may help modify the treatment.

Conclusion

The serum cortisol could be considered as a promising biomarker that is able to predict the severity and outcome of CAP.

Recommendation

We recommend further studies that should be larger and have different aspects to investigate the accuracy of serum cortisol in assessing the severity of CAP and its potential effect on the treatment plan.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Watkins RR, Lemonovich TL. Diagnosis and management of community-acquired pneumonia in adults. Am Fam Physician 2011; 83:1299–1306.

2 Loke YK, Kwok CS, Niruban A, Myint PK. Value of severity scales in predicting mortality from community-acquired pneumonia: systematic review and meta-analysis. Thorax 2010; 65:884–890.

3 Chalmers JD, Singanayagam A, Akram AR, Mandal P, Short PM, Choudhury G, *et al.* Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia.Systematic review and meta-analysis. Thorax 2010; 65:878–883.

4 Shaddock EJ. How and when to use common biomarkers in community-acquired pneumonia. Pneumonia (Nathan) 2016; 28:17.

5 Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336:243–250.

6 Christ-Crain M, Stolz D, Jutla S, Couppis O, Muller C, Bingisser R, *et al.* Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med 2007; 176:913–920.

7 Gotoh S, Nishimura N, Takahashi O, Shiratsuka H, Horinouchi H, Ono H, *et al.* Adrenal function in patients with community-acquired pneumonia. Eur Respir J 2008; 31:1268–1273.

8 Kolditz M, Halank M, Schulte-Hubbert B, Höffken G. Adrenal function is related to prognosis in moderate community-acquired pneumonia. Eur Respir J 2010; 36:615–621.

9 Fouda OM, Elatar SL. The association of serum total cortisol and pneumonia severity index. Saudi Med J 2010; 31:887–890.

10 Mueller C, Blum CA, Trummler M, Stolz D, Bingisser R, Mueller C, *et al.* Association of adrenal function and disease severity in community acquired pneumonia. PLoS One 2014; 9:e99518.

11 Salluh JIF, Shinotsuka CR, Soares M, Bozza FA, Lapa e Silva JR, Tura BR, *et al.* Cortisol levels and adrenal response in severe community-acquired pneumonia: a systematic review of the literature. J Crit Care 2010; 25:541.e1–8.

12 Khalil MM, Maher MM, Abd Al-Kader MA, Kamal ES. The association between the serum total cortisol as an adrenal response biomarker and severe community-acquired pneumonia. Egypt J Bronchol 2019; 13:100–104.

13 Stewart PM. Williams textbook of endocrinology. 11th edition. Philadelphia, PA: Saunders; 2008. pp. 445–503.

14 Dubey A, Boujoukos AJ. Measurements of serum free cortisol in critically ill patients. Crit Care 2005; 9:E2.

15 Omelyanenko O, Makarevich A, Amelchenko E, Rybina T. Prognostic value of cortisol and adrenocorticotropic hormone (ACTH) in severe community-acquired pneumonia (SCAP) patients. Eur Respir J 2011; 38:1473.

16 Kolditz M, Höffken G, Martus P, Rohde G, Schütte H, Bals R, *et al.* Serum cortisol predicts death and critical disease independently of CRB-65 score in community-acquired pneumonia: a prospective observational cohort study. BMC Infect Dis 2012; 12:90.

17 Lu H, Zeng N, Chen Q, Wu Y, Cai S, Li G, *et al.* Clinical prognostic significance of serum high mobility group box-1 protein in patients with community-acquired pneumonia. J Int Med Res 2019; 47:1232–1240.

18 Remmelts HH, Meijvis SC, Kovaleva A, Biesma DH, Rijkers GT, Heijligenberg R. Changes in serum cortisol levels during community-acquired pneumonia: the influence of dexamethasone. Respir Med 2012; 106:905–908.