Serum Leptin in Hospitalized Community-Acquired Pneumonia Children under the Age of Five Years

Heba Abouhussein 1, Shereen Mohamed 1,2*, Talal Dougman 1 and Rabab ElHawary 3

Abstract

Background: Community-acquired pneumonia (CAP) accounts for 19% of the world’s total deaths among all age groups yearly, with highest rates in children less than 5 years. This study is designed to evaluate the serum leptin level in hospitalized children under the age of 5 years with CAP.

Results: This prospective cross-sectional study included CAP children under the age of 5 years. Forty-one patients admitted to pediatric intensive care unit (PICU) and 41 patients admitted to general ward were enrolled. Patients with any other cause that may elevate serum leptin were excluded. Serum leptin was measured on the day of admission. The PICU patients had a significantly higher median serum leptin than that of the ward patients ($p < 0.001$). C-reactive protein (CRP) level was significantly higher in patients with elevated serum leptin than in patients with normal serum leptin ($p = 0.001$). There was a significant association between high serum leptin and positive sputum cultures ($p < 0.001$), particularly cultures growing more than one organism ($p < 0.001$). There was a positive, weak correlation between serum leptin and length of stay ($r = 0.30$, $p = 0.007$). Serum leptin showed good discrimination between PICU admissions and inpatient ward admissions (AUC = 0.777, $p < 0.001$); at a cut-off value of $> 29.6$ pg/ml, serum leptin had a sensitivity of 70.7% and a specificity of 87.8%.

Conclusion: We may conclude that CAP patients with a serum leptin level above 29.6 pg/ml should be considered for PICU admission.

Keywords: Serum leptin, Community-acquired pneumonia, Severity, Pediatric intensive care unit, Children

Background

Community-acquired pneumonia (CAP) is a common disease worldwide [1]. It accounts for 19% of the world’s total deaths among all age groups yearly; rates are greatest in children less than 5 years [2].

The national guidelines that were published in 2011, by the Infectious Diseases Society of America (IDSA) and the Pediatric Infectious Disease Society (PIDS) concerning the management of CAP in children, recommended that children with moderate to severe pneumonia should be considered for hospital admission [3].

It is crucial to assess the severity of pneumonia in the emergency department to make a wise decision of either sending the patient home or admitting him in the hospital. Merely few scoring systems for assessment of severity of pneumonia in children are available [4].

Pediatric intensive care units (PICUs) are burdened with high costs and scarcity of available beds [5]; hence, appropriate decisions of PICU admission are indispensable.

Leptin (satiety hormone) is an adipocyte-derived hormone. Its production is associated with total body fat mass. Leptin has a vital role in regulating energy homeostasis as well as innate and adaptive immunity. Blood and tissue leptin levels rise during bacterial infections, contributing to host defense against bacterial pneumonia [6].

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Methods

Objectives
The aim of the present study is to:

- Evaluate the serum leptin level in children with CAP
- Assess the correlation between serum leptin and pneumonia severity
- Assess the utility of serum leptin to aid in the early decision of PICU admission in CAP patients

Study design and setting
This prospective cross-sectional study was conducted at University Children’s Hospitals from September 2014 to June 2015.

Patients’ enrollment

Inclusion criteria
The study included 82 children under the age of 5 years with CAP who were admitted either in general pediatric ward or PICU. The decision to admit patients to PICU or inpatient ward was made by the emergency department physicians.

Exclusion criteria
- Patients with growth percentile more than 95 were excluded
- Also, patients with upper respiratory tract infections, other acute lower respiratory tract infections apart from pneumonia, or chronic lower respiratory tract infections as tuberculosis were excluded. Patients with chronic systemic illness, oropharyngeal abnormalities, and congenital heart diseases were excluded as well.

Classification of pneumonia severity
The severity of CAP was classified based on the national guidelines that were published by the IDSA and PIDS concerning the management of CAP in children [3]. “Criteria of the moderate CAP are respiratory distress in the form of tachypnea, dyspnea, retractions, grunting, nasal flaring, apnea, altered mental status, or hypoxemia (sustained oxygen saturation of less than 90%).

Criteria of severe CAP was pneumonia requiring invasive ventilation or non-invasive positive pressure ventilation, those having impending respiratory failure, or hypotension or requiring vasopressor support, those having sustained tachycardia and those having persistent pulse oximetry readings of <92% on more than 0.5 liters of oxygen, or having altered mental status, in these patients PICU admission was considered” [3].

The enrolled patients were divided into two equal groups:
- The PICU group of patients included 41 patients
- The ward inpatient group included 41 patients

Both study groups were subjected to the following:

1. History and clinical assessment
   (a) Full clinical history taking with particular emphasis on symptoms of pneumonia.
   Thorough clinical examination was carried out with detailed cardiac and chest examination.
   Level of consciousness was evaluated using the Glasgow Coma Scale (GCS).
   (b) Growth assessment
2. Body measurements (weight and length)
   (a) For infants less than 2 years of age or above who cannot stand without assistance:
      I Recumbent length was used to measure their length.
      II Digital infant scale was used to measure their weight.
   (b) For children above 2 years of age and can stand without assistance:
      I Standing height was used to measure their height.
      II Digital scale was used to measure their weight.
   (c) We determined the body mass index (BMI) as weight/height².
   (d) Body measurements were plotted against appropriate percentile for age and sex
   (e) In patients less than 24 months old, body weight to length percentile curves were used [7].
   (f) In patients older than 24 months old, BMI percentile curves were used.
3. Laboratory investigations
   (a) On the day of admission, basic blood tests were performed including complete blood picture (CBC), C-reactive protein (CRP), and arterial blood gasses (ABG), as well as renal and hepatic function tests. Sputum cultures were also done.
   (b) Simultaneously, serum leptin samples were withdrawn. Serum leptin was measured using enzyme-linked immunosorbent assay (ELISA). Reference range from zero to 0.036 pg/ml was considered normal values.

Secondary outcome included the length of hospital stay, need of mechanical ventilation (MV), duration of MV, and survival to discharge.

Statistical methods
Data were analyzed using the Statistical Package for Social Sciences software (SPSS), version 22.0 (SPSS Inc., Chicago, IL). Quantitative variables were summarized by
|                  | PICU group (n = 41) | Ward group (n = 41) | P value |
|------------------|---------------------|--------------------|---------|
| **Sex**          |                     |                    | 1.000^d|
| Male             | 27 (65.9%)          | 27 (65.9%)         |         |
| Female           | 14 (34.1%)          | 14 (34.1%)         |         |
| **Age (months)** | 12.0 (10.0–36.0)*^a| 12.0 (8.0–36.0)*^a| 0.922^d |
| **Growth percentiles** |                |                    |         |
| < 5th percentile | 1 (2.4%)            | 4 (9.8%)           | 0.274^d |
| 5th to less than 85th percentile | 29 (70.7%) | 32 (78.0%) |         |
| 85th to less than 95th percentile | 6 (14.6%) | 3 (7.3%) |         |
| 95th percentile  | 5 (12.2%)           | 2 (4.9%)           |         |
| **Tachypnea**    | 41 (100%)           | 41 (100%)          | 1.000^f |
| **Respiratory distress** |                |                    |         |
| RD I             | 0 (0.0%)            | 0 (0.0%)           | < 0.001*^c |
| RD II            | 10 (24.4%)          | 30 (73.2%)         |         |
| RD III           | 24 (58.5%)          | 11 (26.8%)         |         |
| RD IV            | 7 (17.1%)           | 0 (0.0%)           |         |
| **Cough**        | 39 (95.1%)          | 31 (75.6%)         | 0.012^c |
| **Fever**        | 31 (75.6%)          | 19 (46.3%)         | 0.007^c |
| **Wheeze**       | 29 (70.7%)          | 28 (68.3%)         | 0.809^f |
| **Crepitation**  | 29 (70.7%)          | 27 (65.9%)         | 0.635^f |
| **Tachycardia**  | 26 (63.4%)          | 8 (19.5%)          | < 0.001*^d |
| **Feeding intolerance** |          |                    |         |
| **GCS**          | 13.0 (12.0–14.0)*^a| 15.0 (15.0–15.0)*^a| < 0.001*^d |
| **Pneumonia severity** |            |                    |         |
| Moderate         | 15 (36.6%)          | 38 (92.7%)         | < 0.001*^c |
| Severe           | 26 (63.4%)          | 3 (7.3%)           |         |
| **Serum leptin (pg/ml)** | 235.2 (0–677.8)*^a| 0.0 (0.0–0.0)*^a| < 0.001^d |
| **CRP (mg/L)**   | 120.0 (46.0–189.0)*^a| 11.0 (5.0–19.0)*^a| 0.001^d |
| **Sputum culture positive** | |                    |         |
| No growth        | 12 (29.3%)          | 41 (100.0%)        | < 0.001*^a |
| Single organism  | 17 (41.5%)          | 0 (0.0%)           |         |
| More than one organism | 12 (29.3%) | 0 (0.0%) |         |
| **Organisms in sputum** |            |                    |         |
| Acinetobacter    | 6 (14.6%)           | 2 (4.9%)           | 0.264^f |
| Klebsiella       | 20 (48.8%)          | 4 (9.8%)           | < 0.001*^c |
| Pseudomonas      | 15 (36.6%)          | 8 (19.5%)          | 0.085^c |
| Needed mechanical ventilation | 26 (63.4%) | 0 (0.0%) | < 0.001*^c |
| **Duration of mechanical ventilation (days)** | 6.7 ± 1.9^b |                    |         |
| **Hospital stay (days)** | 15.0 (11.0–19.0)*^a| 10.0 (7.0–12.0)*^a| < 0.001*^e |
| **Mortality**    | 3 (7.3%)            | 0 (0.0%)           | 0.241^f |

*Median (IQR)
^Mean ± SD
^Pearson’s Chi square test for independence/Fisher’s exact test
^Mann-Whitney test
^Student’s t test
^Significant at p < 0.05
^Calculated from body weight to length percentile curves in patients less than 24 months old and from body mass index percentiles curves in those aged 24 months or older

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mean and standard deviation (SD) for normally distributed data and groups were compared using the Student t test. Variables that did not follow normal distribution were summarized by median and interquartile range (IQR), groups were compared using Mann-Whitney U test, and correlation between variables was assessed using Spearman rank order correlation. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic ability of serum leptin as regards pneumonia severity and PICU admission. The area under ROC curve (AUC) was graded as follows: 0.90–1 = excellent, 0.80–0.90 = good, 0.70–0.80 = fair, and 0.60–0.70 = poor. For all statistical tests, a p value of < 0.05 was defined as the level of significance.

Results

Characteristics of PICU and ward inpatient groups

Eighty-two children were enrolled in our study. The patients were categorized according to their admission into the PICU and ward inpatient groups; each group included 41 patients. There was no statistically significant difference between the two groups as regards age (p = 0.922), sex (p = 1.000), or growth percentiles (p = 0.274). A significantly higher percentage of PICU patients had severe respiratory distress (p < 0.001), cough (p = 0.012), fever (p = 0.007), and severe degree of pneumonia (p < 0.001) than the ward group. Moreover, median GCS was significantly lower in the PICU group (13 versus 15, p < 0.001). The median serum leptin level on admission was significantly higher in the PICU group than the ward group (235.2 versus 0, p < 0.001). The median CRP level showed similar difference between the two groups (120 versus 11, p = 0.001). Most patients in PICU groups had high leptin and CRP levels (70.7% and 95.1% of cases, respectively) compared to the ward group (14.6% and 61%, respectively). Sputum culture was positive in a significantly higher percentage of PICU group than the ward group (70.7% versus 29.3%, p < 0.001). The hospital stay was significantly longer in the PICU group (15 versus 10 days, p < 0.001). In this study, 31.7% of patients required MV; all of them belonged to PICU group (63.4% of PICU patients). None of the ward inpatients deceased while 7.3% of PICU patients deceased (Table 1 and Fig. 1).

Evaluation of serum leptin

Serum leptin level was above normal values in 35 patients (43.2% of all cases). Comparison between patients with normal leptin level and those with high levels revealed that high leptin level was significantly associated with the severity of respiratory distress (p < 0.001) and the severity of pneumonia (p = 0.009), positive sputum culture (p < 0.001), infection with a single or more than one organism (p < 0.001), and PICU admission (p < 0.001) as well as the need of MV (p = 0.008). In addition, the median CRP level and LOS were significantly longer in patients with high leptin level (p < 0.001) compared to those with normal level (Table 2).

Serum leptin level was significantly higher in patients with severe pneumonia (p = 0.016). However, when the severity of pneumonia was stratified according to the type of admission (Table 3), no significant difference was detected in median serum leptin level between moderate and severe pneumonia, neither in PICU group (p = 0.547) nor in the ward group (p = 0.652).

The correlation between the serum leptin level and CRP and LOS was studied (Table 4). There was a positive strong correlation with CRP when assessed in all patients ($r_s = 0.810, p < 0.001$). The correlation was still positive and significant, though moderate in the PICU ($r_s = 0.700, p < 0.001$) and ward ($r_s = 0.555, p < 0.001$) groups. Serum leptin correlated positively, significantly,
and weakly with the duration of hospital stay ($r_s = 0.295$, $p = 0.007$) when analyzed in the whole sample. When the analysis was repeated for PICU and ward groups separately, the correlation was weak and non-significant (PICU: $r_s = 0.003$, $p = 0.986$; ward group: $r_s = 0.171$, $p = 0.286$).

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the value of serum leptin on admission as an indicator of pneumonia severity and a predictor of PICU admission. As regards pneumonia severity, serum leptin had a fair discriminatory power (AUC = 0.646, 95% CI = 0.532–0.748, $p = 0.030$). At a

| Table 2 | Comparison between patients with normal and elevated leptin levels |
|---------|---------------------------------------------------------------|
|         | Normal leptin level (n = 47) | High leptin level (n = 35) | $P$ value |
| Sex     |                                |                              |           |
| Male    | 31 (66.0%)                     | 23 (65.7%)                   | 0.982c    |
| Female  | 16 (34.0%)                     | 12 (34.3%)                   |           |
| Age     | 12.0 (8.0–48.0)$^a$            | 12.0 (8.0–36.0)$^a$          | 0.922d    |
| Growth percentile$^b$ |                              |                              |           |
| < 5th percentile | 3 (6.4%)                     | 2 (5.7%)                    | 1.000f    |
| 5th to less than 85th percentile | 35 (74.5%)                   | 26 (74.3%)                  |           |
| 85th to less than 95th percentile | 5 (10.6%)                    | 4 (11.4%)                   |           |
| 95th percentile | 4 (8.5%)                     | 3 (8.6%)                    |           |
| Respiratory distress |                              |                              |           |
| RD I    | 0 (0.0%)                       | 0 (0.0%)                     | < 0.001c  |
| RD II   | 30 (63.8%)                     | 10 (28.6%)                   |           |
| RD III  | 17 (36.2%)                     | 18 (51.4%)                   |           |
| RD IV   | 0 (0.0%)                       | 7 (20.0%)                    |           |
| Pneumonia severity |                              |                              |           |
| Moderate | 36 (76.6%)                     | 17 (48.6%)                   | 0.009c    |
| Severe  | 11 (23.4%)                     | 18 (51.4%)                   |           |
| CRP (mg/L) | 10.0 (6.0–18.0)$^a$          | 149.0 (110.0–190.0)$^a$     | < 0.001d  |
| Sputum culture positive | 11 (23.4%)                     | 30 (85.7%)                   | < 0.001c  |
| Organisms in sputum |                              |                              |           |
| No growth | 44 (93.6%)                     | 9 (25.7%)                    | < 0.001c  |
| Single organism | 3 (6.4%)                    | 14 (40.0%)                   |           |
| More than one organism | 0 (0.0%)                     | 12 (34.3%)                   |           |
| Organisms in sputum |                              |                              |           |
| Acinetobacter  | 3 (6.4%)                     | 5 (14.3%)                    | 0.277f    |
| Klebsiella   | 4 (8.5%)                     | 20 (57.1%)                   | < 0.001c  |
| Pseudomonas  | 5 (10.6%)                     | 18 (51.4%)                   | < 0.001c  |
| Admission |                              |                              |           |
| Ward     | 35 (74.5%)                     | 6 (17.1%)                    | < 0.001c  |
| PICU     | 12 (25.5%)                     | 29 (82.9%)                   |           |
| Needed mechanical ventilation | 4 (8.5%)                     | 11 (31.4%)                   | 0.008c    |
| Duration of mechanical ventilation (days) | 7.3 ± 3.3$^b$                 | 6.5 ± 1.2$^b$               | 0.703a    |
| Hospital stay (days) | 11.0 (8.0–14.0)$^a$         | 15.0 (11.0–19.0)$^a$        | < 0.001d  |
| Mortality | 0 (0.0%)                       | 3 (8.6%)                     | 0.074e    |

*Median (IQR)
^Mean ± SD
{Pearson's Chi square test for independence/Fisher's exact test
#Mann-Whitney test
*Student's $t$ test
*Significant at $p < 0.05$
$^c$Calculated from body weight to length in patients less than 24 months old and from body mass index in those aged 24 months or older [7]
cut-off value > 117.6 pg/ml, serum leptin had a sensitivity of 62.1% and a specificity of 73.6% (Fig. 2). As regards the prediction of PICU admission, serum leptin showed good discriminatory power (AUC = 0.777, 95% CI = 0.672–0.861, *p* < 0.001); at a cut-off value of > 29.6 pg/ml, serum leptin had a sensitivity of 70.7% and a specificity of 87.8% (Fig. 3).

Discussion

Pneumonia is considered one of the leading infectious causes of pediatric morbidity and mortality. In 2010, 120 million cases of pneumonia were reported in children younger than 5 years, with 14 million of them proceeding to severe episodes. In 2011, a study estimated that 1.3 million cases of pneumonia deceased and 81% of deaths occurred in the first 2 years of life [8].

Investigating the association of serum leptin and pulmonary diseases in adults attracted a great interest in the past few years. A meta-analysis included ten articles that concluded a positive association between leptin and tumor necrosis factor (TNF-α) levels in COPD exacerbations in adults [9]. Moreover, other studies reported that asthma severity positively correlated with serum leptin [10, 11]. It was suggested that leptin presence is essential for an effective immune response against variable bacterial pulmonary infections [12]. Recently, research proved that leptin has a critical role in the immune system, and its deficiency results in increased severity of pulmonary infections [13]. Therefore, the present study evaluated serum leptin in CAP children.

We found that serum leptin was more elevated in severe cases of pneumonia than moderate cases. However, ROC curve analysis revealed that serum leptin fairly discriminated between moderate and severe pneumonia (AUC = 0.646).

Interestingly, in our study serum leptin showed good discriminatory ability between CAP cases admitted in PICU and those admitted in the general ward. This finding offers a good tool in the emergency department to aid in making a sound objective decision for the appropriate admission location of the patients. Up to the best of the authors’ knowledge, no previous research has studied this point.

In our study, we found a significant association between high serum leptin in the studied patients and sputum cultures growing more than one organism. This was in agreement with Mancuso et al. who reported increased leptin levels in serum, BAL fluid, and whole lung homogenates in response to intra-tracheal challenge with Klebsiella pneumonia in experimental murine models [14] Likewise, another study demonstrated up-regulation of pulmonary leptin levels in both humans and mice following bacterial- and viral-induced pneumonia [15].

On the other hand, Al Biltagi et al. found that low serum leptin level was associated with pneumonia in

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**Table 3** Comparison of serum leptin between different grades of pneumonia severity

|                      | Both study groups (n = 82) | Moderate pneumonia (n = 53) | Severe pneumonia (n = 29) | *P* value |
|----------------------|---------------------------|-----------------------------|---------------------------|----------|
| Serum leptin (pg/ml) | 0.0 (0.0–167.0)*a         | 205.0 (0.0–562.0)*a         | 0.016b                    |
| PICU (n = 41)        |                           | Moderate pneumonia (n = 15) | Severe pneumonia (n = 26) |          |
|                      | 283.4 (59.2–677.6)*a      | 233.1 (0.0–677.6)*a         | 0.547b                    |
| Ward (n = 41)        |                           | Moderate pneumonia (n = 38) | Severe pneumonia (n = 3)  |          |
|                      | 0.0 (0.0–0.0)*a           | 0.0 (0.0–205.0)*a           | 0.652b                    |

*Median (IQR)

**Table 4** Correlation between the serum leptin level, CRP, and length of hospital stay

| Serum leptin on admission | All patients (n = 82) | PICU patients (n = 41) | Ward patients (n = 41) |
|---------------------------|-----------------------|------------------------|------------------------|
| CRP                       |                      |                        |                        |
| *r*                       | 0.810                 | 0.700                  | 0.555                  |
| *p*                       | < 0.001*              | < 0.001*               | < 0.001*               |
| Length of hospital stay   |                      |                        |                        |
| *r*                       | 0.295                 | 0.171                  | −0.003                 |
| *p*                       | 0.007*                | 0.286                  | 0.986                  |

*r* Spearman rank order correlation

*Significant at *p* < 0.05
malnourished children [16]. This may be attributed to lower serum leptin in malnourished children than in healthy controls [17, 18]. Hence, malnourished patients were excluded from our study. Another study by Diez et al. reported the lack of significant differences in leptin levels between adult patients hospitalized for community-acquired pneumonia and healthy controls, after adjusting for BMI [19].

We did not find an association between high serum leptin level and mortality from CAP. This finding is in line with comparable studies which concluded that leptin lacks prognostic value for pneumonia lethality [19] and overall all-cause mortality rates in adult males [20].

We found a significantly elevated CRP level in patients with a high serum leptin level. Moreover, the correlation between serum leptin and CRP levels in the studied patients was positive, significant, and strong. Similarly, Somech et al. reported that leptin levels significantly correlated with CRP levels during acute infections in children [21]. Likewise, a research on chronic COPD in adults studied the complex relationship between adipokine metabolism and mild systemic inflammation in chronic COPD and reported the presence of significant correlation between circulating leptin and CRP levels [22].

The present study was subject to few limitations, including the limited number of patients and the non-inclusion of mild cases of CAP as these cases were sent on home treatment from the emergency department.

**Conclusion**

It can be concluded that cases of pneumonia with serum leptin above normal level are mostly in need of higher level of care after excluding other factors that may increase serum leptin. Serum leptin level above 29.6 pg/ml can fairly differentiate between patients who would be admitted to PICU and in the ward. This finding is a helpful tool in the emergency department to aid in the appropriate location of patients’ admission. However, serum leptin cannot predict CAP mortality.

**Abbreviations**

ABG: Arterial blood gases; AUC: Area under the curve; BMI: Body mass index; CAP: Community-acquired pneumonia (CAP); CBC: Complete blood picture; CRP: C-reactive protein; ELISA: Enzyme-linked immunosorbent assay; GCS: Glasgow Coma Scale; IDSA: Infectious Diseases Society of America; IQR: Interquartile range; MV: Mechanical ventilation; PICU: Pediatric intensive care unit; PIDS: Pediatric Infectious Disease Society; RD I: Respiratory distress grade one; RD II: Respiratory distress grade two; RD III: Respiratory distress grade three; RD IV: Respiratory distress grade four; ROC: Receiver operating characteristic; SD: Standard deviation

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**Authors’ contributions**

HA shared in the study design and approved the manuscript. SM shared in the study design and wrote the manuscript. TD did the patients enrollment and collection of data, RH did the laboratory work and shared in the study design. All authors revised and approved the manuscript and agree to publish it in the *Egyptian Pediatric Association Gazette* (EPAG).

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Ethics approval and consent to participate
The Research Ethics Committee of the Faculty of Medicine, Cairo University, approved the protocol (on 5 May 2014) (reference number I-111011). Written consent was obtained from the patients’ guardians.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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