Systemic inflammatory response and clinical outcomes in hospitalized patients with community-acquired pneumonia (CAP)

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ABSTRACT

Introduction: The normal immune response in a patient with CAP is to produce a local and systemic inflammatory response. Production of cytokines by alveolar macrophages produce elevated temperature and elevated white blood cell (WBC) count. Therefore, a normal temperature and WBC count may indicate that the patient's immune system is not able to produce enough cytokines. We hypothesize that patients hospitalized with CAP with this abnormal response may have worse outcomes than patients with a normal response.

Objective: The objective of this study was to compare clinical outcomes of hospitalized patients with CAP having normal temperature and WBC count versus patients with elevated temperature and WBC count.

Methods: This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. In-hospital and 30-day mortality were compared between patients with elevated WBC and temperature (Group 1) versus those with non-elevated WBC and temperature (Group 2). Chi-squared tests were used to compare mortality between groups.

Results: A total of 1570 patients were included in the analysis, 928 in Group 1 and 642 in Group 2. In-hospital and 30-day mortality were significantly higher in Group 2 versus Group 1. In-hospital mortality: 11% vs 6%, P<0.001; 30-day mortality: 17% vs 9%, P<0.001.

Conclusions: This study indicates that patients without an inflammatory response have worse outcomes. An elevated temperature and WBC count should be seen as an appropriate response to pneumonia. A lack of elevated temperature and WBC count is a marker of an immunocompromised underlying condition.

INTRODUCTION

The normal immune response in a patient with community-acquired pneumonia (CAP) is to produce a local and systemic inflammatory response. Production of cytokines by alveolar macrophages produce elevated temperature and elevated white blood cell (WBC) count. Several inflammatory biomarkers (pro-adrenomedulin, hsCRP, procalcitonin) and cytokines (IL-1β, IL-6, and IL-10) have been implicated in the inflammatory process in CAP[1]. Multiple studies have been done in patients with CAP using these biomarkers to assess long term mortality[2]. Procalcitonin and hsCRP can improve the diagnostic value of the clinical assessment[3].

However, these biomarkers are not measured routinely in day to day practice. This emphasizes the use of more commonly assessed variables in almost all patients hospitalized with CAP like white blood cell count (WBC) and temperature changes as a measure of inflammation. Interestingly, a normal temperature and WBC count may indicate that the patient's immune system is not able to produce enough cytokines.

Much less is known about the association between changes in WBC and temperature with time to clinical stability and length of stay in hospitalized CAP patients. We hypothesize that patients hospitalized with CAP with abnormal responses may have worse outcomes than patients with a normal response as depicted in Figure 1.

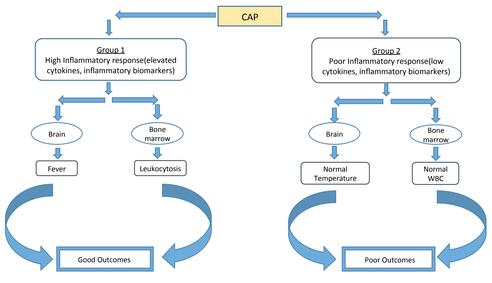

Figure 1: Correlation of Clinical outcomes in CAP with inflammatory response

OBJECTIVES

The objective of this study was to compare clinical outcomes of hospitalized patients with CAP having normal temperature and WBC count versus patients with elevated temperature and WBC count.

MATERIALS AND METHODS

Study design and Study population

This was a secondary analysis of patients enrolled in the Community-Acquired Pneumonia Organization (CAPO) international cohort study. Data was collected between 2001 and 2014. In each participating center, non-consecutive medical records of hospitalized patients with the diagnosis of CAP were reviewed. A sample of the data collection form is available at the study website (www.caposite.com). Validation of data quality was performed at the study center before the case was entered in to the CAPO database. Institutional Review Board approval was obtained by each participating center.

Study definitions

CAP: Diagnosis of CAP required the presence of criterion A, B, and C:

A. New pulmonary infiltrate on imaging (CT scan or chest x-ray) at the time of admission to the hospital.
B. Signs and Symptoms of CAP (at least one of the following)
    1. New or increased cough (per the patient)
    2. Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F).
    3. Changes in WBC (leukocytosis >11,000 cells/mm^3, left shift > 10% band forms/microliter, or leukopenia < 4,000 cells/mm^3
C. Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

Study Groups

Group 1: Patients with elevated WBC and temperature within 24 hours of admission
Group 2: Patients with normal WBC and temperature within 24 hours of admission

Study outcomes

Time to clinical stability (TCS): A patient was defined as clinically stable the day that the following four criteria were met: a) improved cough and shortness of breath, b) lack of fever for at least 8 hours, c) improving leukocytosis (decreased at least 10% from the previous day), and d) tolerating oral intake with adequate gastrointestinal absorption. Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached.

Length of stay (LOS): defined in days and calculated for each patient as the day of discharge minus the day of admission. Patients hospitalized for more than 14 days were censored at 15 days in an effort to capture LOS data related only to bacterial CAP.

In-hospital mortality: defined as death by any cause during hospitalization.

Day 30 morality: defined as death by any cause during the first 30 days after hospital admission

Statistical analysis

The statistical evaluation of our data utilized two primary methods. Evaluation of associations between categorical data was performed using Pearson's chi-square test. When appropriate, Fischer's exact test was used. To evaluate differences between two continuous variables the Mann-Whitney U-test was performed. All data were analyzed in R v.3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). For the purposes of our research a P-value of ≤ 0.05 was considered statistically significant

RESULTS

- A total of 1,570 patients were included in the analysis, 928 in Group 1 and 642 in Group 2.
- Patient characteristics are depicted in Table 1.
- The median TCS was 4 days (IQR 5 days) in Group 1 and 4 days (IQR 6 days) in Group 2 (P-value = 0.621).
- The median LOS was 7 days (IQR 7 days) in Group 1 and 8 days (IQR 8 days) in Group 2 (P-value = 0.026)
- The rates for in-hospital mortality are depicted in Figure 2.
- The rates for 30-day hospital mortality are depicted in Figure 3.

Table 1: Patient Characteristics

Variable	Group 1 n = 928	Group 2 n = 642	P-value
Demographics			
Age , Median (IQR)	64(33)	70(30)	<0.001
Sex, n (%)	549(59)	351(55)	0.078
Nursing home resident, n (%)	46(5)	37(6)	0.493
Comorbid Conditions			
Congestive Heart Failure, n (%)	128(14)	111(17)	0.063
COPD, n (%)	199(21)	150(23)	0.388
Diabetes, n (%)	156(17)	132(21)	0.063
HIV, n (%)	84(9)	70(11)	0.228
Renal Disease, n (%)	67(7)	76(12)	0.002
Liver Disease, n (%)	52(6)	47(2)	0.171
Neoplastic Disease, n (%)	88(9)	79(12)	0.08
CVA, n(%)	1(0)	6(1)	0.021
Cardiovascular Meds, n(%)	337(36)	272(42)	0.018
Antiplatelet Meds, n(%)	177(19)	141(2)	0.18
Acute Myocardial Infarction, n(%)	16(2)	11(2)	1
Cardio-pulmonary Edema, n(%)	29(3)	29(3)	0.172
Cardiac Arrhythmia, n(%)	48(5)	38(6)	0.573
Long-term Arrhythmia, n(%)	25(3)	11(2)	0.232
Pulmonary Embolism, n(%)	6(1)	6(1)	0.563
Physical Exam			
Altered mental status on admission, n (%)	118(13)	84(13)	0.878
Respiratory Rate, Median (IQR)	23(8)	22(8)	0.001
Systolic blood pressure, Median (IQR)	125(30)	125(30)	0.959
Temperature (degrees Celsius), Median (IQR)	100.9(1.6)	98.1(2)	<0.001
Lab/Radiography			
pH, Median (IQR)	7.5(0.1)	7.4(0.1)	<0.001
PaO2, Median (IQR)	62.2(20.3)	63(20)	0.787
Blood Urea Nitrogen, Median (IQR)	30(29)	33(34)	0.011
Serum sodium, Median (IQR)	136(6)	137(5.8)	<0.001
Serum glucose, Median (IQR)	120(49)	116(48.2)	0.007
Hematocrit, Median (IQR)	38(7.3)	36.9(8.3)	<0.001
Pleural effusion, n (%)	28(97)	21(91)	0.577
Severity of Disease			
ICU admission, n (%)	120(13)	89(14)	0.598
Pneumonia Severity Index, Median (IQR)	113(53)	121(57)	<0.001

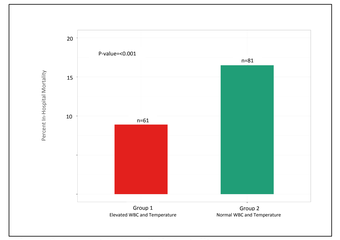

Figure 2: Percent In-Hospital Mortality

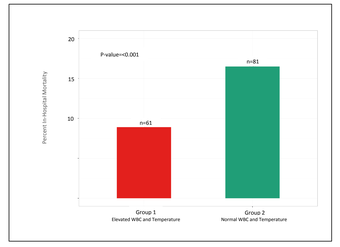

Figure 3: Percent 30-Day Mortality

CONCLUSIONS

- This study indicates that patients without an inflammatory response have worse outcomes.
- A lack of elevated temperature and WBC count is a marker of an immunocompromised underlying condition.
- An elevated temperature and WBC count should be seen as an appropriate response to pneumonia.
- A study performed by the Pneumonia Patient Outcomes Research Team reported that a lack of feeling feverish was associated with higher long-term mortality among patients with CAP compared with age-matched controls(4). Our findings are in concordance with this study.
- Clinicians while working up for CAP, in patients present without any fever or in those who cannot mount leukocytosis, need to evaluate them more intensely than CAP patients who either have a fever or leukocytosis.

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