Clinical outcomes of male vs. female patients hospitalized with community-acquired pneumonia (CAP)

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ABSTRACT

Introduction: Biological differences between males and females may impact the predisposition, clinical course, and outcomes of infection. The X chromosome has several genes involved in immune responses. Since mammalian females have two X chromosomes, it is considered that females have a stronger immune response to infection. [1] There is a controversy regarding the influence of sex and the outcomes of hospitalized patients with CAP.

Objectives: The objective of this study was to compare in-hospital mortality in males and females hospitalized with CAP.

Methods: This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) international cohort study database. Log-binomial regression was used to evaluate the adjusted impact of sex on in-hospital mortality.

Results: A total of 4,724 males and 3,107 females were included in the analysis. After adjusting for the pneumonia severity index, need for ICU admission and history of COPD, females had a 15% increased risk of in-hospital mortality (P=0.044) and a 13% increases risk of 30 day mortality (P=0.0468) compared to males.

Conclusions: This study indicates that females are at increased risk for mortality during hospitalization for CAP. An exaggerated inflammatory response has been associated with poor outcomes in patients with CAP. We can speculate that a more robust response to infection in females may lead to an exaggerated inflammatory response and poor clinical outcomes.

INTRODUCTION

Pneumonia is the leading cause of death due to infectious diseases in the United States. Approximately 1 million people are hospitalized with pneumonia every year and over 50,000 die from the disease. [2] The percentage of women dying from pneumonia is 2.3%, whereas for men it is 2.1%. [3] This data suggests that there are sex differences in regards to pneumonia outcomes. However, there are conflicting results regarding the relationship between gender and mortality in community-acquired pneumonia (CAP). One study reported similar mortality for men and women. [3] However, two other studies found that females were 2.94 times more likely to be admitted than males P=0.0018 and that the male sex was significantly associated with long-term mortality. [4,5]

The objective of this study was to compare in-hospital mortality in males and females hospitalized with CAP.

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 from 130 hospitals in 30 countries, between 2001 and 2015. 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.

METHODS

Study groups: Males and females

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 Analyses

Baseline categorical explanatory variables were summarized as frequencies and percentages and differences between both groups of patients were analyzed using a chi-square test or Fisher's exact test when appropriate and warranted. Continuous variables were summarized as frequencies and interquartile range and differences between groups were analyzed by Wilcox-Mann-Whitney test. TCS and LOS were analyzed with the Kaplan-Meier method, and log-rank tests were applied to evaluate differences between both groups of patients. P-values ≤ 0.05 were considered statistically significant. All data were analyzed in R v.3.1.1 (R Foundation for Statistical Computing, Vienna, Austria)

RESULTS

- A total of 4,724 males and 3,107 females were included in the analysis. Forty percent of the population was female and the median age was 68 for males and 69 for females.
- Patients' characteristics of the study population are shown in Table 1.
- Unadjusted analysis of clinical outcomes for the study population is shown in Table 2.
- Kaplan-Meier curve for LOS is shown in Figure 1.
- After adjusting for the pneumonia severity index, need for ICU admission and history of COPD, females had a 13% increased risk of 30-day mortality (P=0.0468) (Table 3) and 15% increased risk of in-hospital mortality (P=0.044) (Table 4) when compared to males

Table 1. Patients' characteristics of the study population stratified by gender.

Variable	Males	Females	P-value
Demographics			
Age , Median (IQR)	68 (27)	69 (32)	0.002
Sex, n (%)	4724(60)	3107(40)	
Nursing home resident, n (%)	206 (4)	208 (7)	<0.001
Comorbid Conditions			
Congestive Heart Failure, n (%)	794 (17)	516 (17)	0.829
COPD, n (%)	1343 (28)	528 (17)	<0.001
Diabetes, n (%)	883 (20)	481 (16)	<0.001
Renal Disease, n (%)	540 (11)	239 (8)	<0.001
Liver Disease, n (%)	290 (6)	128 (4)	<0.001
Neoplastic Disease, n (%)	539 (11)	236 (8)	<0.001
Physical Exam			
Altered mental status on admission, n (%)	546 (12)	474 (16)	<0.001
Systolic blood pressure, Median (IQR)	125 (30)	122 (32)	0.011
Temperature (degrees Celsius), Median (IQR)	37.8 (1.6)	37.7 (1.6)	0.221
Lab/Radiography			
PaO2, Median (IQR)	61.1 (19)	63 (22)	0.007
Blood Urea Nitrogen, Median (IQR)	33 (33)	29.8 (30)	<0.001
Serum sodium, Median (IQR)	137 (6)	136 (6)	0.85
Hematocrit, Median (IQR)	39 (7.9)	37 (6.7)	<0.001
Severity of Disease			
ICU admission, n (%)	652 (21)	357 (17)	<0.001
Pneumonia Severity Index, Median (IQR)	103 (50)	92 (51)	<0.001

RESULTS (continued)

Table 2. Unadjusted analysis of clinical outcomes for study population.

	Male	Female	P-value
	N = 4724	N = 3107	
Time to Clinical Stability, Median (IQR)	4 (6)	5 (5)	<0.001
Length of Stay, Median (IQR)	7 (8)	8 (7)	0.05
In-hospital Mortality, n (%)	373 (8)	274 (9)	0.154
Died within 30 days, n (%)	696 (20)	504 (23)	0.008

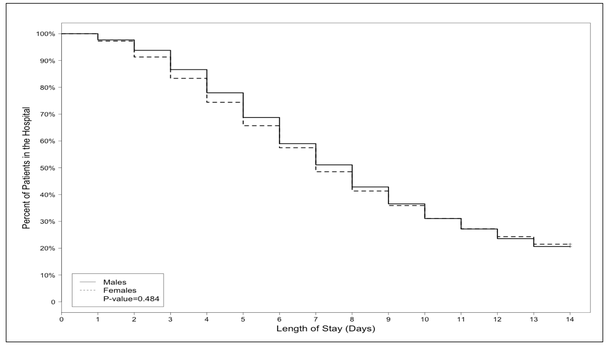

Figure 1. Kaplan-Meier curve for Length Of Stay

Table 3. The impact of sex on 30-day mortality after adjusting for ICU admission, history of COPD, and PSI score.

Variables	Relative Risk	Lower 95% CI	Upper 95% CI	P-value
Men	0.87	0.76	1.00	0.0468
ICU Admission	3.19	2.80	3.64	< 0.001
History of COPD	0.98	0.84	1.13	0.7745
PSI	1.01	1.01	1.01	< 0.001

Table 4. The impact of sex on in-hospital morality after adjusting for ICU admission, history of COPD, and PSI score.

Variables	Relative Risk	Lower 95% CI	Upper 95% CI	P-value
Intercept	0.02	0.01	0.02	< 0.001
Men	0.85	0.72	1.00	0.044
ICU Admission	3.08	2.63	3.61	< 0.001
History of COPD	1.05	0.88	1.25	0.622
PSI	1.012	1.010	1.014	< 0.001

CONCLUSIONS

This study indicates that females are at increased risk for mortality during hospitalization for CAP. The TCS was longer for female patients than male patients and the risk for in-hospital mortality was also higher for females than males. This difference has been hypothesized to originate from the X chromosome, which has several genes involved in immune response.[1] Since mammalian females have two X chromosomes, it is considered that females have a stronger immune response to infection.[1] However, several studies have shown that the X chromosome is also responsible for hyper-responsiveness of the immune system, which has been associated with poor outcomes in patients with CAP.[6] The mechanism is explained by cytokines and chemokines, which are released in order to attract neutrophils to the affected lung area to combat bacteria.[6] However, if there is an exaggerated response in females with an excess of cytokines, this can lead to harmful and damaging inflammation and consequently poor clinical outcomes.

A recent meta-analysis study showed that the use of corticosteroids in the treatment of CAP was significantly associated with 3% lower mortality, 5% reduction in need for mechanical ventilation, and a 1-day shorter hospital stay for hospitalized patients with CAP.[7]

Also, when calculating the PSI score, if the gender of the patients is female, 10 points is deducted. This may be an inappropriate estimation based on the results of this study. Updating the PSI criteria may improve the PSI prediction of clinical outcomes.

Better prediction of clinical outcomes may improve the management of patients with CAP.

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