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Outcomes in Females Hospitalized with Community-Acquired Pneumonia are Worse than Males

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ABSTRACT

Little recent information exists on sex-specific outcomes of patients with community-acquired pneumonia (CAP). The objective of this study was to determine if female gender is indeed associated with better clinical outcomes in hospitalized patients with CAP.

A secondary analysis was conducted of the Community-Acquired Pneumonia Organization regarding male and female patients with CAP from 80 hospitals in 17 countries from June 1, 2001 to August 2, 2011. Outcomes were time to clinical stability (TCS), length of stay (LOS), and in-hospital and 28-day mortality. Propensity-adjusted, multivariable regression models were used to predict the probability of occurrence of each of the study outcomes.

There were 6718 patients in this study; 40% female. The adjusted hazard ratio (aHR) for TCS was 0.91 (95%CI 0.85-0.97; p=0.005). The aHR for LOS was 0.94 (95%CI 0.88-1.01; p=0.089). The adjusted risk ratio (aRR) for in-hospital mortality was 1.04 (95%CI 0.86-1.24); p=0.717, and for 28-day mortality was 1.15 (95%CI 1.02-1.30); p=0.018.

This study demonstrates that epidemiology may be changing, and that females have worse outcomes for CAP than males. They are more likely to take longer to reach clinical stability, have longer hospital stays and 15% more likely to be dead

after 28 days. Current pneumonia scoring systems may need to be revised regarding female mortality risk.

Key Words:

Community-acquired pneumonia

Female gender

Length of stay

Mortality

Outcomes

Quality measures

Time to clinical stability

INTRODUCTION

Two decades ago, gender-dependent differences in outcome and quality of care were acknowledged by the American Medical Association's Council on Ethical and Judicial Affairs as requiring prudent investigation.[1] This was followed by an emphasis in research needs about respiratory health of women, but recent data is lacking.

Community-acquired pneumonia (CAP) is one of the most frequent infectious diseases and ranks as the fourth leading cause of death in the United States for females.[2] Studies with men and women combined have shown that mortality in CAP patients is associated with several independent risk factors, such as, intensive care unit admission, advanced age, pleural effusion, increased time to first antimicrobial dose, the presence of comorbidities (*e.g.*, anemia, chronic renal failure ,congestive heart failure) as well as gender.[3,4]

The first inquiry with gender and pneumonia started with HAP. One study found that male patients had a greater incidence of HAP, and increased intensive care unit length of stay (LOS) after trauma, but female patients who developed HAP demonstrated a higher mortality rate.[5] In another study, females died three-times more than males with ventilator-associated pneumonia[6], but not in other studies.[7,8]

Two large studies from 1997 Medicare and Medicaid data described information regarding CAP outcomes and gender. It was shown that in >140 000 elderly,

hospitalized CAP patients that males had a greater mortality than females (11.6% *vs.* 9.8%, p <0.001).[9] In another study, elderly males died more than females in the subsequent year after hospitalization for CAP, with the highest risk for death in the first month after discharge (44.8% *vs.* 36.9%, adjusted Kaplan-Meier p ≤0.001).[10]

Inquiries into gender outcomes and CAP started after the first HAP studies addressed gender. The cost of treating CAP patients is significant—$10 billion per year—with approximately 92% spent on hospital care.[11] Therefore, the decision to hospitalize patients for pneumonia is an important health economy issue. In an effort to improve the decisions about hospitalization, the pneumonia severity index (PSI) was introduced in 1997 as an accurate prognostic model of CAP to assess patients' risks.[12] The PSI was designed based on 21 study cohorts providing data (17 641 patients) that males die more than females, thus ten points are subtracted from the PSI of a female patient.[13] The difference in points attributed to each sex using the PSI was accurate for the time period in which it was published, however, epidemiology has the potential to change over time. A new study evaluating the relationship between gender and outcome of patients with CAP is warranted.

We evaluated a large, multicenter, international cohort study of subjects with CAP to reassess the relationship between gender and poor outcomes in hospitalized patients with CAP.

MATERIALS AND METHODS

Study design and study patients

This was an international, retrospective study of adult patients hospitalized with CAP. Data was collected from 80 hospitals in 17 countries, between June 1, 2001 and August 2, 2011. In each participating center medical records of hospitalized patients with the diagnosis of CAP were reviewed. Charts were selected among all patients diagnosed with CAP at each respective institution. Antimicrobial regimens were not dictated by randomization, nor were they recorded prospectively. Investigators completed a case report form that was transferred via a secure website to the Community-Acquired Pneumonia Organization (CAPO) study headquarters at the University of Louisville in Louisville, Kentucky. A sample of the data collection form is available at: www.caposite.com. Validation of data quality was performed at the study center before the case was entered in the CAPO database. The study was reviewed by the IRB and waived because this was a retrospective, observational study.

Records of all the patients enrolled in the study were reviewed for several factors. Demographic and comorbidity information included age, gender, world region, smoking status, nursing home residency status, and comorbidities including chronic obstructive pulmonary disease, congestive heart failure , coronary artery disease, hypertension, liver, renal or cerebrovascular diseases, diabetes mellitus, human immunodeficiency virus infection, and malignancy. Physical exam

findings noted on admission included altered mental state, and vital signs. Radiological findings reviewed were the number of involved lobes, and the presence of cavitation or pleural effusion. Laboratory values from admission day included the platelet count, leukocyte count, arterial blood gas analysis (pH, PaO_2, PaO_2/F_iO_2 ratio), serum sodium, serum creatinine, albumin, blood urea nitrogen (BUN) and hematocrit. The PSI[12] and CRB-65[14] were calculated, and microbiological information, when present, was also recorded.

Study variable definitions

CAP was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization associated with at least one of the following: 1) new or increased cough, 2) an abnormal temperature (<35.6ºC or >37.8ºC), 3) an abnormal serum leukocyte count (leukocytosis, left shift, or leukopenia defined by local laboratory values).

Hypotension was defined as a systolic blood pressure < 90 mmHg or diastolic blood pressure <60 mmHg. Alteration of gas exchange was defined as a PaO_2 <60 mmHg, a PaO_2/FiO_2 <300, or an oxygen saturation <90%. Five processes of care were measured. Each subject was evaluated for blood cultures within 24 hours of admission, antimicrobial administration within eight hours of admission, oxygenation status assessment and prior influenza and pneumococcal vaccine administration. CAPO regions are designated as the United States/Canada, Europe, South America, and Asia/Africa.

Time to clinical stability (TCS) was calculated as the number of days from the date of admission to the date that the patient met clinical stability criteria. TCS criteria was defined per the American Thoracic Society guidelines for CAP as all of the following: lack of fever for at least 8 hours, improving leukocytosis (decreased at least 10% from the previous day), tolerating oral intake, and improved clinical signs (*e.g.,* improved cough and shortness of breath).[15] Criteria for clinical stability were evaluated daily during the first seven days of hospitalization. Patients who reached clinical stability within seven days of admission were defined as clinically improved. Length of stay (LOS) was calculated as the number of days from the date of admission (designated as day 0) to the date of discharge. Mortality was defined as death by any cause during hospitalization while in the hospital (in-hospital mortality), and within 28 days (28-day mortality). TCS, LOS, in-hospital mortality and 28-day mortality were selected as outcomes.

Statistical Analyses

Baseline patient characteristics and clinical outcomes of females and males were compared using χ^2 or Fisher's Exact tests for categorical variables and Student's t-tests or Mann-Whitney U-tests for continuous variables. Gender differences in time to clinical stability and length of hospital stay were evaluated using Kaplan-Meier survival curves. Significant differences between the survival curves were analyzed using the log-rank test.

To examine the impact of gender on in-hospital and 28-day mortality, propensity score adjustment methodologies were utilized.[16] Using a logistic regression model, a propensity score was created that included all of the baseline patient characteristics included in Table 1 plus processes of care and need for intensive care. The propensity score was then used to adjust for differences in the study population using a Poisson regression model with robust error variance.[17] This methodology allowed us to obtain adjusted mortality (in-hospital mortality and 28-day mortality) risk ratios for those in each gender. The propensity score adjustment was also used to control for differences in the relationship between gender and time to clinical stability and length of hospital stay using Cox Proportional Hazards Regression models.

P values of ≤ 0.05 were considered statistically significant in all analyses. SAS v9.3 (SAS Inc., Cary, NC) and MedCalc v12.0 (Mariakerke, Belgium) were used for all analyses.

RESULTS

A total of 6718 patients were included in the study; 2665 women and 4053 men. The mean age was 64.7 years (standard deviation (SD) 19.1, range: 18-104) and 40% were female. Among the 25 variables collected, seven of them were worse for females (nursing home residence, cerebrovascular accident, mental status

changes, abnormal temperature, tachypnea, abnormal systolic blood pressure, and anemia), while five of them were worse for males (COPD, liver disease, renal disease, diabetes mellitus and abnormal BUN). (Table 1) Among the processes of care, females had blood cultures obtained less often and fewer females had received a pneumococcal vaccine prior to admission. (Table 1) The severity of disease was statistically similar using the CURB-65, but was worse for males when using the PSI. The mean PSI for females was 85.8 (SD 46.6), and for males was 94.7 (SD 45.7); p=<0.001. (Table 2) The mean PSI for females without 10 points removed from their score was 94.7 (SD 48.8). (eFigure) A pathogen was identified in 2204 patients. *Streptococcus pneumoniae* was the most common pathogen in each gender. The most common pathogens are in Table 3. Incidentally, among the 92 patients with Pseudomonas, only 11 were from a nursing home. The pneumonia unadjusted outcome results stratified by gender are in table 4 where each outcome was worse for females. The number of females varied in each region; US/Canada – 603 (30%), Europe – 1213 (42%), South America – 804 (46%), and Asia/Africa 45 (61%).

The analysis for TCS showed that females were less likely than males to reach clinical stability on any given day up to the seventh day after admission. There was a difference in the Kaplan Meier curves for each gender; p<0.001. (Figure 1) The adjusted hazard ratio (aHR) for TCS was 0.91 (95% CI 0.85-0.97; p=0.005). The unadjusted analysis for LOS showed that females were less likely than males to be discharged from the hospital on any given day up to the fourteenth day after

admission. A difference between the Kaplan Meier curves was detected; p=0.006. (Figure 2) But, the aHR for LOS was 0.94 (95%CI 0.88-1.01; p=0.089).

The proportion of patients who died while in the hospital was higher for females (10.8%) than for males (9.3%); p=0.041, but the adjusted risk ratio (aRR) for in-hospital mortality was not statistically significant; aRR 1.04 (95% CI 0.86-1.24); p=0.717. The proportion of patients who died within 28 days was 26.0% *vs.* 21.4%, respectively; p<0.001. The result for this outcome was statistically significant when adjusted. The aRR for 28-day mortality was 1.15 (95% CI 1.02-1.30); p=0.018.

DISCUSSION

This study shows that female gender was an independent predictor of clinical outcomes of CAP when examining hospitalized patients. Female patients were more likely to take longer to clinically improve when compared to male patients, and the 28-day mortality was higher for female patients with an absolute difference of approximately 5%. Adjusted outcomes were also worse for females, aside from LOS, which trended toward significance and similar in-hospital mortality. The differences we observed between male and female patients conflict with those previously observed in CAP.[9,10] We may be witnessing an epidemiological shift that has occurred over the last recent decades, though there

has been little attention given to how males and females with CAP are managed; in other words there is a question of difference between genders in processes of care.

Including processes of care in the present study was important because one or more of them could have been a significant factor to explain the differences in outcomes between the two genders. Obtaining blood cultures and having had a pneumococcal vaccine were performed in different proportions for each gender in the present study. These two processes of care, despite being quality measures per the National Hospital Quality Measures, have had conflicting literature in the last few years to support either one improving outcomes in patients with CAP. A recent study of over 11,000 patients did not find a more frequent hospitalization or a higher mortality among subjects who had been vaccinated prior to study entry.[18] Likewise, in a recent study regarding the effect of quality measures in CAP patients prior to antimicrobials, none were found to be significant, including obtaining blood cultures.[19] Professional society guidelines in the United States now no longer recommend obtaining blood cultures in every patient admitted with CAP. Regardless, the differences in outcomes found in the present study were performed after adjusted analysis, including adjustment for the processes of care.

An implication of the present study is that the concept that female patients have a lower risk than men with CAP may need revised. Because, female patients had worse outcomes in the present study, they may need to be hospitalized with a

lower PSI score, or the PSI score needs revised. A certain number of points may not need to be subtracted from females, or may even need added for females rather than the current procedure of having ten points subtracted from their score. Furthermore, other current pneumonia scoring systems, such as the CURB-65 may need to adjust for gender.[14] In clinical studies, with females represented more accurately, they would be distributed according to their real severity of disease, and hence there would be less alpha and beta errors.

Our study was limited by its retrospective nature, which means that there may have been selection bias. If all patients admitted for CAP were included, then that would have helped, but that was not the case. Furthermore, the patients that were enrolled were limited to the type of specialized patients seen by each principal investigator. The study was limited to the five processes of care that were reviewed. Another process of care, such as, whether to do a special procedure (*e.g.*, bronchoscopy, parapneumonic effusion drainage) or when to admit to an intensive care unit, were not available in the database and may have been significant. Although the proportion of comorbidities and severity of illness were controlled for statistically, it would have been ideal for these values to be equal between the sexes obviating the need for adjustment. A prospective trial or a case control study could be designed to equalize the severity of disease in each group. A prospective, randomized controlled study would also control for confounding factors.

Despite these limitations, this study demonstrates several unique strengths. It is an international study including patients from multiple continents. It highlights an area that needs to be studied further to ensure that females are being attributed an accurate severity of illness when cared for clinically. The exclusion criteria were minimal allowing the representation of patients to be close to what might be encountered in many areas of the world, thus increasing its generalizability. The present study includes nearly 7000 patients whose diagnoses of CAP were confirmed radiographically, as opposed to identification with diagnosis or billing codes.

In conclusion, this study shows that female patients have a higher risk of poor CAP outcomes than males during hospitalization worldwide. They have a longer time to clinical stability, and higher 28-day mortality than males. Further research is needed to verify our findings prospectively. If epidemiology has changed and females with CAP truly have worse outcomes compared to males, as the data in this study demonstrates, then future research to revise current pneumonia scoring systems regarding higher female mortality risk is needed.

Appendix

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Figure Legends

Figure 1

Kaplan Meier curve for time to clinical stability among 2665 females and 4053 males patients with community-acquired pneumonia.

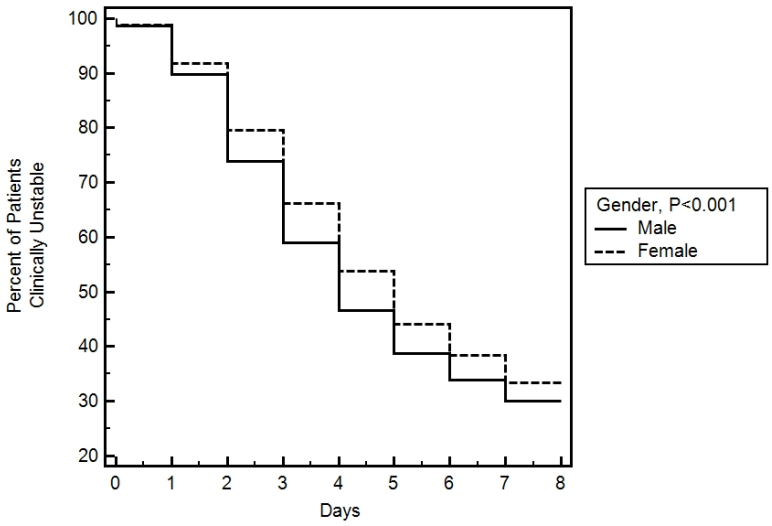

Figure 2

Kaplan Meier curve for length of stay among 2665 females and 4053 males patients with community-acquired pneumonia.

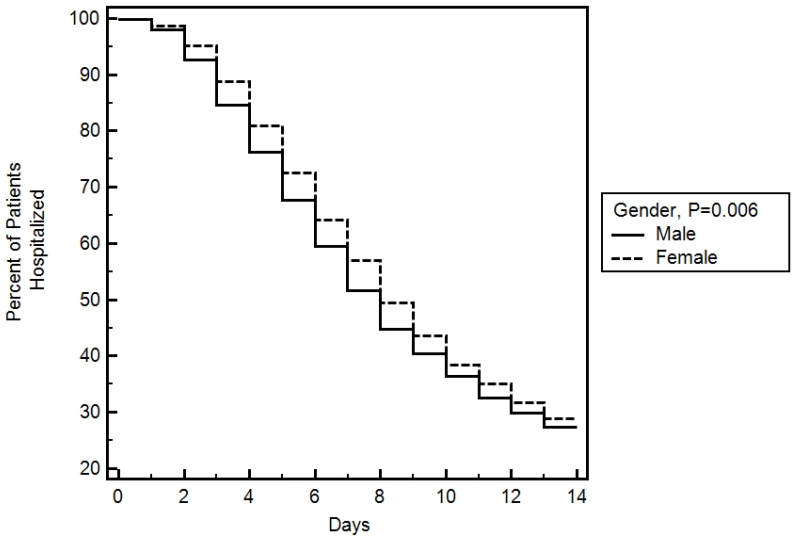
Percent of Patients Hospitalized
100
90
80
70
60
50
40
30
20
0
2
4
6
8
10
12
14
Days
Gender, P=0.006
Male
Female

Table 1

Demographic, clinical, laboratory and radiographical characteristics for 6718 patients with CAP.

Variable	Female	Male	p value
	n=2665	n=4053	
	No. (%)	No. (%)	
Demographics			
Age	64.8 (21)*	64.2 (18.2)*	0.2431
Nursing Home Resident	190 (7.1)	189 (4.7)	<0.001
Comorbidities			
COPD	469 (17.6)	1246 (30.7)	<0.001
Congestive Heart Failure	455 (17.1)	704 (17.4)	0.7529
Cerebrovascular Accident	427 (16)	533 (13.2)	0.0010
Liver Disease	106 (4)	266 (6.6)	<0.001
Renal Disease	211 (7.9)	475 (11.7)	<0.001
Diabetes Mellitus	402 (15.1)	785 (19.4)	<0.001
Clinical Signs and Laboratory Findings			
Altered Mental Status	464 (17.5)	534 (13.2)	<0.001
Heart Rate ≥125/min	364 (13.7)	483 (11.9)	0.0352
Respiratory Rate >30/min	572 (22.5)	741 (19.1)	0.0011
Systolic Blood Pressure <90mm Hg	188 (7.1)	206 (5.1)	0.0008
Temperature <35°C or ≥40°C	229 (8.6)	270 (6.7)	0.0031
PaO2 <60mm Hg	1263 (47.4)	1974 (48.7)	0.2922

Blood Urea Nitrogen ≥30 mg/dl	621 (24.8)	1193 (30.7)	<0.001
Glucose ≥250 mg/dl	157 (6.1)	258 (6.5)	0.4883
Sodium <130 mmol/liter	227 (8.5)	336 (8.3)	0.7418
Hematocrit <30%	293 (11)	350 (8.6)	0.0013
Radiological Findings			
Cavitary Lesion	5 (0.2)	19 (0.5)	0.0588
Multilobar Infiltrates	371 (13.9)	502 (12.4)	0.0671
Processes of Care			
Blood Cultures Obtained	1759 (66)	2928 (72)	<0.001
Antibiotics within 8 hours	1818 (78)	2813 (78)	0.5698
Oxygenation Assessed†	2616 (98)	3998 (99)	0.1177
Prior Pneumococcal Vaccine	400 (15)	740 (18)	<0.001
Prior Influenza Vaccine	381 (14)	663 (16)	0.0225

* Mean (Standard Deviation)

† Oxygenation missing data – 769 subjects

Table 2

The severity of disease for each gender among 6718 patients with community-acquired pneumonia.

Severity Measure	**Female**	**Male**	**p value**
	n=2665	n=4053	
	No. (%)	No. (%)	
CURB-65			
0	1831 (69)	2899 (72)	0.20
1	253 (10)	355 (9)	
2	301 (11)	415 (10)	
3	190 (7)	284 (7)	
4	69 (3)	80 (2)	
5	10 (0.4)	15 (0.4)	
Pneumonia Severity Index Risk Class			
I	308 (12)	433 (11)	<0.001
II	588 (22)	471 (12)	
III	493 (19)	807 (20)	
IV	836 (32)	1509 (37)	
V	414 (16)	805 (20)	
ICU Admission			
	280 (11)	489 (12)	0.0497

CURB-65 missing data – 16 subjects; PSI missing data – 54 subjects

Table 3

The most common pathogens identified in 2204 patients with community-acquired pneumonia who had a positive respiratory sample culture; 205 patients had coinfection.

Pathogen	**Female**	**Male**	**Total Positive Cultures**
	n = 836	n = 1368	
	No. (%)[a]	No. (%)[a]	No.
Streptococcus pneumoniae	356 (43)	514 (38)	870
Pandemic 2009 (H1N1) influenza A[b]	159 (19)	165 (12)	295
Staphylococcus aureus			239[c]
MRSA	27 (3)	84 (5)	111
MSSA	30 (4)	54 (4)	84
Atypical Pathogens			153
Chlamydia species[d]	8 (<1)	10 (<1)	18
Legionella spp.	25 (3)	65 (5)	90
Mycoplasma pneumoniae	21 (3)	24 (3)	45
Haemophilus influenzae	38 (5)	96 (7)	128
Pseudomonas aeruginosa	25 (3)	67 (5)	92
Klebsiella pneumoniae	15 (4)	47 (3)	62
Escherichia coli	17 (2)	27 (2)	44
Moraxella catarrhalis	18 (2)	26 (2)	44
Other[e]	739 (88)	1179 (86)	1918

a The proportion is relative to the number of patients; not the number of specimens. Also, 205 patients were coinfected, therefore the sum of proportions in each region is more than 100%.

b Among 274 cases, 295 (93%) were confirmed.

c Sensitivity information was not available for 44 subjects.

d All cases were *C. pneumoniae* except for one, which was *C. psittaci*.

e Other organisms isolated were: *Acinetobacter*, adenovirus, *Aspergillus* spp., Candida spp., coagulase negative *Staphylococcus*, *Cryptococcus neoformans*, *Enterobacter* Spp., *Enterococcus faecalis*, untyped or H3N1 influenza, metapneumovirus, mixed anaerobic bacteria, nontuberculous bacteria, *Paragonimus westermani*, parainfluenza virus 1 and 4, *Pneumocystis jiroveci*, *Proteus* spp., *Pseudomonas pseudomallei*, respiratory syncytial virus A and B, rhinovirus/enterovirus, *Salmonella* spp., *Serratia* spp., and *Streptococcus pyogenes*

Table 4

Clinical outcomes for 6718 patients with community-acquired pneumonia for each gender.

Outcome	Female	Male	p value
	n=2665	n=4053	
	No. (%)	No. (%)	
Length of Hospital Stay (days)	8.9 (SD 4.2)	8.5 (SD 4.4)	<0.001
Time to Clinical Stability (days)	5.1 (SD 2.5)	4.8 (SD 2.6)	<0.001
In-hospital Mortality	287 (10.8%)	375 (9.3%)	0.0413
28-Day Mortality	503 (26%)	666 (21.4%)	<0.001

SD, Standard Deviation