University of Louisville Journal of Respiratory Infections

ORIGINAL RESEARCH

Comparing Outcomes for Community-Acquired Pneumonia Between Females and Males: Results from the University of Louisville Pneumonia Study

Pavani Nathala[1], MD; Simrat Sarai[1], MD; Vidyulata Salunkhe[1], MD MPH; Mahder Tella[1], MPH; Stephen Furmanek[1], MPH; Forest W. Arnold[1], DO MSc*

[1]Division of Infectious Diseases, Department of Medicine, School of Medicine, University of Louisville, Louisville, KY, USA

*p0nath01@louisville.edu

Recommended Citation: Nathala P, Sarai S, Salunkhe V, Tella M, Furmanek S, Arnold FW. Comparing outcomes for community-acquired pneumonia between females and males: Results from the University of Louisvilile Pneumonia Study. Univ Louisville J Respir Infect **2022**; 6(1):Article 19. doi: 10.55504/2473-2869.1148.

Abstract

Introduction: Male sex is currently considered to be a risk factor for worsened community-acquired pneumonia (CAP) outcomes compared to female sex; hence, female sex equates to a lower score on the Pneumonia Severity Index. There is no recent update on sex-based outcomes of patients with CAP. The objective of this study was to compare the outcomes of CAP between females and males.

Methods: This was a secondary analysis of the University of Louisville Pneumonia Study database. It was a prospective population-based cohort study of all hospitalized adults with CAP who were residents of Jefferson County in the city of Louisville, Kentucky. The study included data from June 1, 2014, to May 31, 2016, and data from October 1, 2016, to May 31, 2017. The study population was divided into two groups: females and males.

Results: Female patients had a 13% lower mortality at one year compared to males (aHR 1.13 [95% CI 1.05–1.23], *P*=0.002). There was no significant difference in mortality between the two groups during hospitalization or at 30-day or six-month follow-up. The median time to discharge for both female and male patients hospitalized with CAP was five days (interquartile range [IQR] 3, 9 days). The median time to clinical stability for both female and male patients hospitalized with CAP was two days (IQR 1, 4 days).

Conclusion: This study shows that female patients had significantly lower one-year mortality compared to males. There was no significant difference between females and males in time to clinical stability or length of stay. Further investigation is needed to examine whether risk factors associated with female and male sex predict outcomes among hospitalized patients due to CAP.

Introduction

Community-acquired pneumonia (CAP) is the ninth leading cause of death in the United States and is the most common cause of death due to an infectious disease.[1] Mortality in CAP patients is associated with several risk factors, such as intensive care unit (ICU) admission, advanced age, and the presence of other comorbidities, as well as sex. The U.S. Public Health Service's Task Force on Women's Health Issues also reported that there are not enough data on women's health needs.[2] In 2013, the age-adjusted death rate due to pneumonia in females was 13.0% *versus* 17.5% for males.[3] Sex is a significant epidemiological factor for several diseases. However, the role of sex in the development and outcome of various infections, including CAP, has not been extensively studied.[4]

The existing literature suggests that females have better outcomes than males when hospitalized with CAP, although the opposite has also been reported.[1] In an effort to assess the need for hospitalization in CAP patients, the Pneumonia Severity Index (PSI) was introduced in 1997 as an accurate prognostic model.[5] Epidemiology does change over time, so physicians need to be aware of the most current evidence on the relationship between sex and the severity of CAP. A new study evaluating the relationship between sex and the outcomes of patients with CAP is warranted. The objective of this study was to compare outcomes between females and males with CAP.

Methods

Study design and study population

This was a secondary analysis of the University of Louisville Pneumonia Study database, a prospective population-based cohort study of all hospitalized adults with CAP who were residents of the city of Louisville, Jefferson County, Kentucky. The study included data from June 1, 2014, to May 31, 2016, and data from October 1, 2016, to May 31, 2017. The study was approved by the Institutional Review Board of the University of Louisville (IRB number 11.0613).

Inclusion Criteria

A diagnosis of CAP required the presence of three criteria: 1) new pulmonary infiltrate on imaging (computed tomography [CT] scan or chest X-ray) or worsening of a previously stable infiltrate within 48 hours of admission; 2) at least one of the following signs or symptoms of CAP: new or increased cough (subjective), fever >37.8 °C (100.0 °F), hypothermia <35.6 °C (96.0 °F), changes in white blood cell count (leukocytosis >11,000 cells/mm^3, left shift >10% band forms/mm^3, or leukopenia <4,000 cells/mm^3); and 3) having a preliminary diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours. The study population was divided into two groups: females and males. The variables collected from the medical records were categorized as the following: demographics, social/medical history, and comorbidities, including congestive heart failure, diabetes, cerebrovascular disease, human immunodeficiency virus (HIV), liver disease, alcoholism, chronic obstructive pulmonary disease (COPD), neoplastic disease, and renal disease. The following variables were collected: height, weight, temperature, heart rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, and FiO_2 at the time of O_2 saturation measurement. The following laboratory values during first 24 hours of hospitalization were collected: pH, $PaCO_2$, PaO_2, serum bicarbonate, blood urea nitrogen, serum glucose, hematocrit, and serum sodium. Severity was described based on ventilator support—either invasive or non-invasive needed—vasopressors, altered mental status, Pneumonia Severity Index (PSI), and CURB-65 criteria on admission.[5, 6] Microorganism data were collected from the medical record if they were ordered during routine testing. Microorganisms were reported if they were positive in blood cultures, respiratory samples, or urinary antigen testing. Respiratory samples included 1) cultures of sputum, tracheal aspirate, or bronchoalveolar lavage; and 2) nasopharyngeal and oropharyngeal swabs for viral polymerase chain reaction (PCR) testing, atypical pathogens PCR, or rapid influenza diagnostic tests. Urinary antigen tests included *S. pneumoniae* and Legionella urinary antigen tests. Positive growth was reported for each patient, not for each sample collected.

Study outcomes

The study outcomes were time to clinical stability, length of stay (LOS), and mortality. A patient was defined as clinically stable on the day that the following four criteria were met: a) improved cough and shortness of breath, b) lack of fever for at least eight 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 seven days of hospitalization to determine the day on which clinical stability was reached. Length of stay was 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 14 days so as to capture LOS related only to bacterial CAP. Mortality was defined as death by any cause and classified as in-hospital, 6-month, and 1-year. All-cause mortality was evaluated for patients by conducting death certificate review through the Kentucky Department for Public Health Office of Vital Statistics.

Statistical analysis

Categorical data were summarized as frequencies and percentages, and continuous data were summarized as means and standard deviations (SDs). Chi-squared tests of independence were performed to test baseline descriptive statistics between groups for categorical data, and t-tests were performed to test between groups for continuous data. Time-to-event data were analyzed using stratified Cox proportional hazards regression or log-rank tests when assumptions for proportional hazards were not met. Clinical outcomes were adjusted for sex, age, race, smoking status, and Pneumonia Severity Index risk class. Kaplan–Meier curves were produced, and differences in risk of clinical outcome were reported as adjusted hazard ratios (aHR) where appropriate.

Results

A total of 10,101 hospitalized patients were included in the analysis and divided into two groups: 4,673 males and 5,428 females. Patient characteristics are compared in **Table 1**. The median age was 68 years for both groups. The female group had a higher proportion of patients with COPD (50%) compared to males (46%). Among females, 65% were either current smokers or had a history of smoking compared to 75% of males. Fewer females had HIV infection (1%) or neoplastic disease (12%) than males (2% and 16%, respectively). A significantly lower proportion of females had renal disease, and females had lower median blood urea nitrogen compared to males at time of admission.

Table 1. Characteristics of female and male patients with community-acquired pneumonia.

	Females (*n*=5,428)	Males (*n*=4,673)	*P*
Demographics			
Age, mean±SD	67.1±16.7	65.9±16.5	<0.001
Black or African American, *n* (%)	1,104 (20)	842 (18)	0.003
Medical and social history, *n* (%)			
Congestive heart failure	1,631 (30)	1,355 (29)	0.257
COPD	2,713 (50)	2,148 (46)	<0.001
Diabetes mellitus	1,740 (32)	1,567 (34)	0.12
HIV infection	71 (1)	90 (2)	0.017
Neoplastic disease	645 (12)	751 (16)	<0.001
Renal disease	1,403 (26)	1,461 (31)	<0.001
Renal failure	376 (7)	430 (9)	<0.001
Cerebrovascular disease	728 (13)	609 (13)	0.595
Suspicion of aspiration	533 (10)	653 (14)	<0.001
Altered mental status	961 (18)	890 (19)	0.087
Pneumococcal vaccination	430 (9)	450 (11)	0.117
Influenza vaccination	444 (9)	525 (13)	0.008
Current smoker/history of smoking	3,527 (65)	3,477 (75)	<0.001
Vital signs, mean±SD			
Heart rate (beats/minute)	106±22	106±23	0.842
Respiratory rate (breaths/minute)	24.1±7.1	24.5±7.0	0.012
Systolic blood pressure (mm Hg)	119±27	117±26	<0.001
Diastolic blood pressure (mm Hg)	58±17	60±17	<0.001
Temperature (℃)	37.38±0.93	37.43±0.97	0.014
PaO_2 (mm Hg)	92±62	89±62	0.223
Laboratory findings, mean±SD			
Blood urea nitrogen (mg/dL)	22.7±16.9	25.7±18.5	<0.001
Serum glucose (mg/dL)	171±94	172±91	0.906
Serum sodium (mEq/L)	137.2±5.4	136.9±5.5	0.009
Hematocrit (%)	34.9±6.0	36.2±6.7	<0.001
O_2 saturation of hemoglobin (%)	93±5	93±5	0.211
Severity of disease, *n* (%)			
Direct admission to the ICU	841 (16)	892 (19)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SD, standard deviation.

Following routine testing, blood cultures were most commonly obtained—in 9,121 (90%) patients—followed by respiratory samples in 5,589 (55%) patients and urine samples in 2,132 (21%) patients. Microorganisms were isolated among 849 patients out of the 10,101 CAP patients; 421 among females and 428 among males. The most common pathogens were methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and methicillin-sensitive *S. aureus* (MSSA) as shown in **Table 2**. Females had less severe pneumonia than males as measured by the distribution of severity scores (**Table 3**).

Outcomes

A total of 505 (10%) females died within 30 days as compared to 542 (13%) males. Mortality at one year occurred in 1,277 (27%) women and in 1,320 (33%) men. Males had a 13% higher risk of death at one year compared to females (aHR 1.13 [95% CI 1.05–1.23], *P*=0.002; **Figure 1**). The 30-day and 1-year mortality rates, as well as the 30-day expected mortality rates, for each sex group in each severity category are listed in **Table 3**. The CURB-65 over-predicted mortality for females and under-predicted mortality for males except for CURB-65 score 4, which was vice versa. The PSI did not consistently predict mortality for each risk class based on sex, but whichever sex group had a lower 30-day mortality rate for a given risk class also had a lower 1-year mortality rate; the only exception was risk class III, in which females had a higher 30-day mortality and a lower 1-year mortality rate.

The median LOS for female and male patients hospitalized with CAP was five days (interquartile range [IQR] 3, 9 days). We found no significant differences in time

Table 2. Microorganisms isolated during routine testing among female and male patients with community-acquired pneumonia.

Organism isolated	Female	Male	Total
MRSA	77	96	173
Streptococcus pneumoniae	74	78	152
Pseudomonas aeruginosa	61	63	124
Haemophilus influenzae	46	41	87
MSSA	39	36	75
Klebsiella pneumoniae	14	17	31
Escherichia coli	13	17	30
Moraxella catarrhalis	13	12	25
Rhinovirus/enterovirus	11	9	20
Enterobacter spp.	9	10	19
Aspergillus spp.	13	5	18
Acinetobacter spp.	8	9	17
Influenza	10	1	11
Serratia spp.	5	6	11
Non-COVID-19 coronavirus	4	5	9
Nontuberculous mycobacteria	3	6	9
Proteus spp.	2	6	8
Mycoplasma pneumoniae	2	4	6
Metapneumovirus	3	1	4
Parainfluenza virus	2	2	4
Citrobacter spp.	2	1	3
Adenovirus	2	0	2
Legionella spp.	2	0	2
Pasteurella multocida	1	1	2
Respiratory syncytial virus	1	1	2
Actinomyces spp.	1	0	1
Chlamydia pneumoniae	0	1	1
Nocardia spp.	1	0	1

Abbreviations: COVID-19, coronavirus disease-2019; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 3. Pneumonia Severity Index and CURB-65 scores among females and males with community-acquired pneumonia.

	Female, *n* (%)	Mortality (%)			Male, *n* (%)	Mortality (%)			*P*
		30obs	1obs	30exp		30obs	1obs	30exp	
PSI risk class									<0.001
I	326 (6)	0.7	4.5	0.9	255 (5)	1.3	5.0	0.9	
II	1,123 (21)	1.0	6.8	0.8	458 (10)	0.2	7.3	0.8	
III	1,018 (19)	4.9	17.4	4.1	822 (18)	3.0	14.8	4.1	
IV	1,893 (35)	9.1	32.7	9.7	1,707 (37)	10.4	33.9	9.7	
V	1,068 (20)	31.8	56.6	30.1	1,431 (31)	28.9	56.2	30.1	
CURB-65 score									0.001
0	608 (11)	1.5	9.8	1.8	574 (12)	2.3	13.5	1.8	
1	1,334 (25)	4.1	15.8	4.8	992 (21)	5.6	20.3	4.8	
2	1,558 (29)	7.1	24.0	8.5	1,316 (28)	10.1	31.2	8.5	
3	1,307 (24)	15.2	37.3	16.9	1,200 (26)	18.8	42.7	16.9	
4	521 (10)	29.0	55.8	28.4	502 (11)	27.9	55.7	28.4	
5	95 (2)	48.2	67.9	50.0	87 (2)	52.1	72.5	50.0	

Abbreviations: 30obs, 30-day observed; 1obs, 1-year observed; 30exp, 30-day expected; PSI, Pneumonia Severity Index.

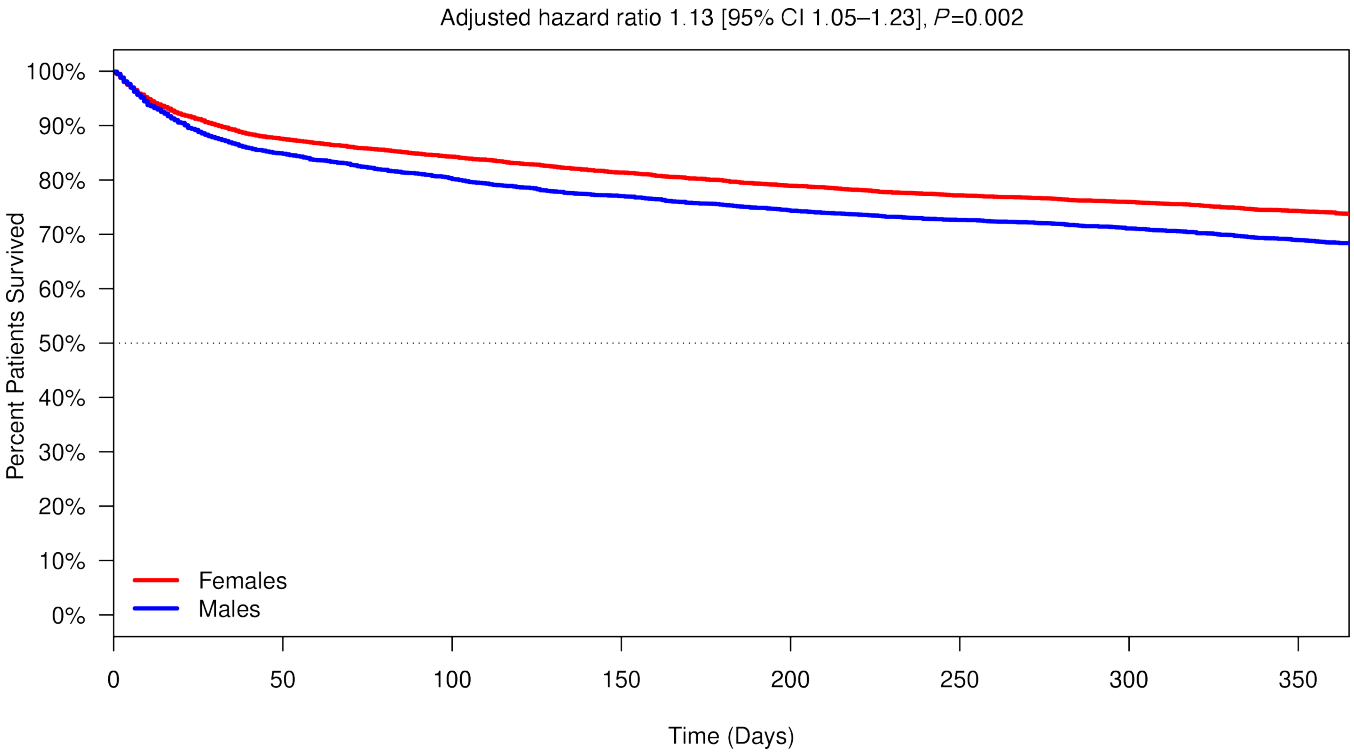

Figure 1. Survival curve for the study population of females and males with community-acquired pneumonia over one year.

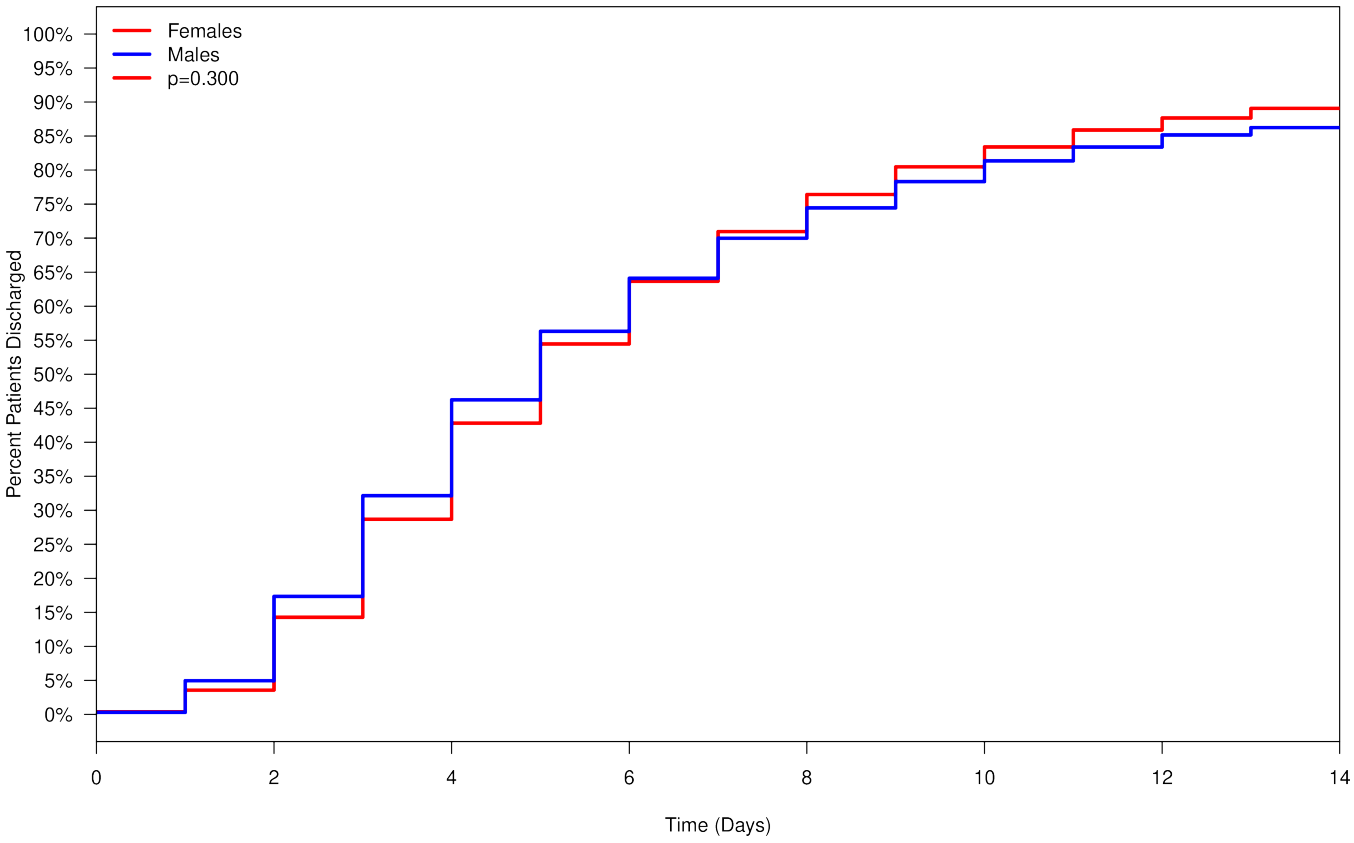

Figure 2. Cumulative incidence curve for length of stay in females and males with community-acquired pneumonia.

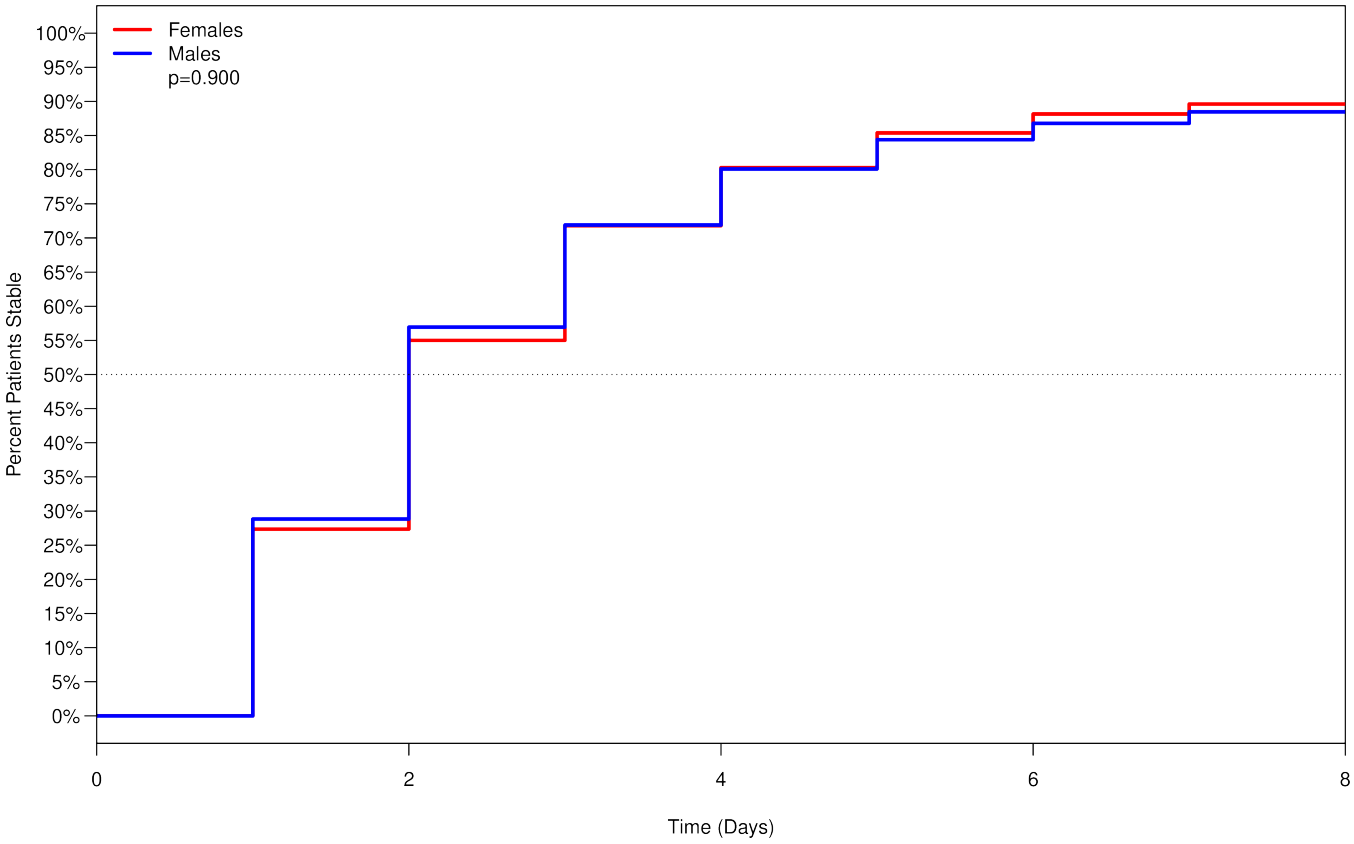

Figure 3. Cumulative incidence curve for time to clinical stability in females and males with community-acquired pneumonia.

to discharge (χ^2=1.13, P=0.294; **Figure 2**). The median time to clinical stability for female and male patients hospitalized with CAP was two days (IQR 1, 4 days). We found no significant differences in time to clinical stability between sexes (χ^2=0.02, P=0.888; **Figure 3**).

Discussion

This study showed that all-cause 1-year mortality in females hospitalized with CAP was lower than in males. While more females were hospitalized than males, they were less likely to receive intensive care support. Females had fewer comorbidities and less severe CAP, but early outcomes were not significantly different when adjusted. It is not clear why females did not demonstrate lower mortality until one year, but it may be due to males having slightly more comorbidities, which could exacerbate their pneumonia, or a manifestation of a longer expected life span.

A nationwide study of 623,718 elderly patients hospitalized with CAP showed that males were more likely to be hospitalized with CAP, receive ICU care or life support, or die than females.[7] Overall, mortality was higher in males than in females (11.6% *vs.* 9.8%, P<0.001), and males had greater odds of mortality than females (odss ratio [OR] 1.15 [95% CI 1.13–1.17]). Similar to the present study, this study also reported *S. pneumoniae*, *H. influenzae*, and Staphylococcus spp. as the most common etiologies of CAP. It also showed that males were more frequently treated in the ICU with or without mechanical ventilation (24% *vs.* 21%, P<0.001) as compared to females.

The smaller proportion of females with a PSI risk class of IV or V may be due to the fact that the PSI gives 10 additional points to males. The observed 30-day mortalities were similar but not equivalent between the sexes for each risk class. The 1-year mortality data observed in this study should prompt the re-evaluation of the PSI and CURB-65 scores.

Another large multicenter cohort study of 2,183 older adults reported higher risk of death in males compared to females over 1-year (HR 1.35 [95% CI 1.11–1.65], P=0.003).[8] The median length of hospital stay was similar for males and females (5 days each, P=0.84). In addition, no differences were seen in ICU utilization during hospital stay between males and females. Similarly, males had a higher prevalence of cardiac disease and neoplastic disease. In contrast to the present study,

this study had a higher prevalence of smoking among males.

While our study correlates with the findings of many studies of the literature [7-12], not all studies found females to have better outcomes than males. An international study of 6,718 patients reported that females had worse outcomes for CAP than males.[13] The adjusted risk ratio 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. Females also took longer to reach clinical stability, had longer lengths of stay, and had higher 28-day mortality than males. As the epidemiology and risk factors of CAP in males and females are changing over time, further research is needed to assess the severity of CAP.

The scope of our study is limited as the data were collected exclusively from patients in Jefferson County; therefore, generalizability is limited when applied to the general population. The strengths of our study include the prospective methodology and larger sample size, which mitigated confounding factors, such as age, race, PSI, and smoking status. Another strength was measuring mortality for an entire year.

In conclusion, the present study showed that female patients with CAP have significantly lower 1-year all-cause mortality than males. Length of hospital stay and clinical stability were similar for females and males. Further investigation is needed to determine whether risk factors associated with male and female sex predict outcomes among hospitalized patients due to CAP.

Acknowledgements: The authors acknowledge the efforts of University of Louisville Pneumonia Study Group and Jessica Petrey, MSLS, Clinical Librarian, Kornhauser Library, University of Louisville, Louisville, Kentucky.

Received: June 18, 2020

Accepted: August 10, 2022

Published: August 11, 2022

Funding Source: The author(s) received no specific funding for this work.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

References

1. Kochanek KD, Xu J, Arias E. Mortality in the United States, 2019. Data Brief: National Center for Health Statistics, **2019**. Report No.: 395.

2. McMurray RJ, Clarke OW, Barrasso JA. Gender disparities in clinical decision making. JAMA **1991**; 266(4):559-62. PMID: 1843800.

3. Trends in pneumonia and infuenza morbidity and mortality. Chicago, IL: American Lung Association, **2015** November.

4. van Lunzen J, Altfeld M. Sex differences in infectious diseases-common but neglected. J Infect Dis **2014**; 209 Suppl 3:S79-80. doi: 10.1093/infdis/jiu159. PMID: 24966193.

5. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med **1997**; 336(4):243-50. doi: 10.1056/nejm199701233360402. PMID: 8995086.

6. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax **2003**; 58(5):377-82. doi: 10.1136/thorax.58.5.377. PMID: 12728155.

7. Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R, Linde-Zwirble WT. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med **2002**; 165(6):766-72. doi: 10.1164/ajrccm.165.6.2103038. PMID: 11897642.

8. Reade MC, Yende S, D'Angelo G, et al. Differences in immune response may explain lower survival among older men with pneumonia. Crit Care Med **2009**; 37(5):1655-62. doi: 10.1097/CCM.0b013e31819da853. PMID: 19325487.

9. Marshall DC, Goodson RJ, Xu Y, et al. Trends in mortality from pneumonia in the Europe union: A temporal analysis of the European detailed mortality database between 2001 and 2014. Respir Res **2018**; 19(1):81. doi: 10.1186/s12931-018-0781-4. PMID: 29728122.

10. Holter JC, Ueland T, Jenum PA, et al. Risk factors for long-term mortality after hospitalization for community-acquired pneumonia: A 5-year prospective follow-up study. PLoS One **2016**; 11(2):e0148741. doi: 10.1371/journal.pone.0148741. PMID: 26849359.

11. Thomsen RW, Riis A, Norgaard M, et al. Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. J Intern Med **2006**; 259(4):410-7. doi: 10.1111/j.1365-2796.2006.01629.x. PMID: 16594909.

12. Barbagelata E, Cilloniz C, Dominedo C, Torres A, Nicolini A, Solidoro P. Gender differences in community-acquired pneumonia. Minerva Med **2020**; 111(2):153-65. doi: 10.23736/s0026-4806.20.06448-4. PMID: 32166931.

13. Arnold FW, Wiemken TL, Peyrani P, Mirsaeidi M, Ramirez JA. Outcomes in females hospitalised with community-acquired pneumonia are worse than in males. Eur Respir J **2013**; 41(5):1135-40. doi: 10.1183/09031936.00046212. PMID: 22835618.