Sex Differences in Veterans Admitted to the Hospital for Chronic Obstructive Pulmonary Disease Exacerbation

Brett C. Bade^{1,2}, Eric C. DeRycke^{3,4}, Christine Ramsey⁴, Melissa Skanderson⁴, Kristina Crothers^{5*}, Sally Haskell^{4,6}, Bevanne Bean-Mayberry^{7,8}, Cynthia Brandt^{3,9}, Lori A. Bastian^{4,6}, and Kathleen M. Akgün^{1,2,4}

¹Section of Pulmonary, Critical Care, and Sleep Medicine, ³VA Connecticut Healthcare System, ⁴Pain Research, Informatics, Multimorbidities, and Education Center, Department of Veterans Affairs, and ⁹Veterans Aging Cohort Study Coordinating Center, Veterans Administration Connecticut Health Care System, West Haven, Connecticut; ²Section of Pulmonary, Critical Care, and Sleep Medicine, and ⁶Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; ⁵Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington; ⁷Veterans Administration Center for Study of Healthcare Innovation, Implementation and Policy, Veterans Administration Greater Los Angeles Healthcare System, Los Angeles, California; and ⁸Division of General Internal Medicine, UCLA David Geffen School of Medicine, Los Angeles, California

Abstract

Rationale: As chronic obstructive pulmonary disease (COPD) prevalence in women has outpaced that in men, COPD-related hospitalization and mortality are now higher in women. Presentation, evaluation, and treatment of COPD differ between women and men. Despite higher smoking rates in Veterans, little work has characterized differences in Veterans with COPD by sex.

Objectives: To determine risk factors for 30-day readmission among Veterans hospitalized for COPD exacerbations and how they differed by sex.

Methods: We performed a retrospective observational analysis of Veterans receiving primary care in Veterans Health Affairs facilities. We included Veterans Administration–based hospitalizations for Veterans with a COPD exacerbation (identified by *International Classification of Disease, Ninth Revision* codes) who survived to discharge between fiscal years 2012 and 2015. Primary outcome was 30-day readmission. Predictors ascertained before hospitalization included smoking status (current, former, never), pulmonary function testing, pulmonary medication prescriptions, and medical and psychiatric comorbidities (identified by *International Classification of Disease, ninth revision* codes). We created combined and sex-stratified multivariate logistic regression models to identify associations with 30-day readmission.

Results: Our sample included 48,888 Veterans (4% women). Compared with men, women Veterans were younger, more likely to be nonwhite, and differed in smoking status. Women were more likely to have asthma, drug use, and several psychiatric comorbidities. Before hospitalization, women were less likely to have pulmonary function testing (76% vs. 78%; $P = 0.01$) or be treated with antimuscarinic (43% vs. 48%) or combined long-acting bronchodilator/inhaled corticosteroid (61% vs. 64%) inhalers. Women were more likely to receive nicotine-replacement therapy (all $P < 0.01$). Women had shorter length of stay (median days, 2 vs. 3; $P = 0.04$) and lower 30-day readmission rate (20% vs. 22%; $P = 0.01$). In adjusted models including both sexes, age, antimuscarinic use, comorbidities, and diagnosis of drug or alcohol use were associated with readmission; there was no association with sex and readmission risk. In models stratified by sex, associations were similar between women and men.

Conclusions: This study suggests differences between women and men hospitalized for COPD regarding presentation, evaluation, and management. Readmission is strongly influenced by comorbidities, suggesting individualized and comprehensive case management may reduce readmission risk for women and men with COPD.

Keywords: chronic obstructive pulmonary disease; gender; sex; readmission; exacerbation

(Received in original form September 16, 2018; accepted in final form February 27, 2019)

*K.C. is an Associate Editor for *AnnalsATS*. Her participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

Supported in part by National Institutes of Health/National Heart, Lung, and Blood Institute U01HL142103 (K.C.). Views expressed in this manuscript are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. Government.

Author Contributions: B.C.B.: study design, data analysis, data interpretation, and drafting/revising the work. E.C.D. and C.R.: study design, data acquisition, data analysis, data interpretation, and revising the work. M.S. and C.B.: study design, data acquisition, data interpretation, and revising the work. K.C., S.H., B.B.-M., and L.A.B.: study design, data interpretation, and revising the work. K.M.A.: study design, data acquisition, data analysis, data interpretation, and drafting/revising the work. All authors approve of this final version of the work and agree to be accountable for its accuracy and integrity.

Correspondence and requests for reprints should be addressed to Brett C. Bade, M.D., Yale University School of Medicine, P.O. Box 208057, 300 Cedar Street, TAC-441 South, New Haven, CT 06520-8057. E-mail: brett.bade@yale.edu.

Ann Am Thorac Soc Vol 16, No 6, pp 707–714, Jun 2019

Copyright © 2019 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201809-615OC

Internet address: www.atsjournals.org

Although previously considered a disease of older men, more women than men are now struggling with and dying from chronic obstructive pulmonary disease (COPD) in the United States (1–3). In 2011, the estimated age-adjusted prevalence of COPD was 7.3% in women compared with 5.7% in men (1). Furthermore, whereas COPD mortality in men has declined over the past several decades, COPD mortality in women has increased by 107% between 1980 and 2014 (1, 4), and women account for more COPD hospitalizations and in-hospital deaths than men (5). As disease burden in women has risen, sex differences in the pathophysiology, presentation, diagnosis, and treatment of COPD have been recognized (3, 6). Women who smoke have accelerated loss of lung function compared with men, and nonsmokers who develop COPD are predominately women (2, 7, 8). Compared with men, women with COPD are also younger (6), have more self-reported dyspnea (9, 10), and more frequently develop chronic bronchitis rather than an emphysema phenotype (11, 12). Despite more symptoms, higher disease prevalence, and rising mortality, women smokers with similar symptoms are less likely to be diagnosed with COPD than men, even when spirometry shows fixed obstruction (13, 14). To ensure equitable delivery of high-quality and guideline-concordant COPD care, a better understanding of sex differences in the recognition and treatment of COPD is needed.

Because tobacco smoke is the biggest risk factor for COPD (15) and Veterans have a higher smoking prevalence than non-Veterans (16), sex differences may be more significant in this population. Prior work has reported that women Veterans admitted for COPD exacerbation were less likely to have inhalers prescribed before hospitalization and more likely to have inappropriate inhaler combinations (e.g., inhaled corticosteroid [ICS] use without long-acting bronchodilators) (17). However, information about smoking status or pulmonary function testing (PFT) was not included. In the current study, we examined if prehospitalization PFT evaluation, outpatient COPD inhaler prescription, comorbidities, and hospital outcomes of Veterans admitted for COPD exacerbation differed by sex. We hypothesized that associations between comorbidities and 30-day readmission would differ by sex for

Veterans surviving a COPD hospitalization. We also hypothesized that associations would be attenuated after adjusting for smoking status, PFT acquisition before hospitalization, and concurrent asthma diagnosis. Identifying sex differences in COPD treatment and predictors of readmission could help in outlining strategies to reduce readmissions and optimize the quality of care for women and men Veterans hospitalized for COPD exacerbation.

Part of this manuscript has been previously presented in the form of a poster presentation at the American Thoracic Society International Conference in 2018 (18).

Methods

Patients

We performed a retrospective observational analysis of women and men Veterans receiving primary care in Veterans Health Affairs facilities. We included Veterans who were admitted for a COPD exacerbation between fiscal year 2012–2015 and survived to discharge. Patients hospitalized for COPD were identified by *International Classification of Disease, Ninth Revision* (ICD-9) codes, using the principal ICD-9 codes for COPD and emphysema (491.2, 492.8, 493.2, and 496.xx) at discharge (19). Demographic data (including race and age at time of hospitalization) and clinical data from the electronic medical record (EMR) on eligible Veterans were linked to Veterans Health Affairs administrative and clinical data within the Corporate Data Warehouse. These databases provide a record of inpatient and outpatient health care encounters and coded diagnostic conditions based on ICD codes.

Primary Outcomes

Our primary outcome was 30-day readmission rate. We used Veterans Administration (VA) inpatient EMR data to identify hospital readmission within 30 days of the sentinel hospital discharge date.

Predictors

Our primary predictors of interest were sex and smoking status. Sex was identified from EMR, and smoking status was determined using EMR Health Factors smoking data from clinical reminders (20). Veterans were categorized as never, former, or current

smokers using a keyword algorithm (e.g., current smoker, never smoker, tobacco counseling).

Covariates

Covariates included demographics at hospitalization (age and self-reported race), PFTs, inhaler medications, and comorbidities. We identified PFTs using Common Procedure Terminology codes from PFT referral any time before hospitalization. Medications prescribed within 1 year before the index hospitalization were determined from VA Pharmacy data. We included prescriptions for pulmonary inhaler medications by drug classes (i.e., β -agonists, antimuscarinics [e.g., ipratropium, tiotropium], ICS, and combined long-acting β -agonists [LABA] and ICS) and nicotine-replacement therapies (NRT). Comorbidities were identified based on either one inpatient or two outpatient ICD-9 codes for the condition (21). This approach had been used in previous studies of Veterans Health Affairs patients to improve the validity of diagnoses derived from the administrative data (22). Medical and mental health conditions were classified using Clinical Classifications Software for ICD-9 codes from the Agency for Healthcare Research and Quality (23). We determined if patients had the following conditions *a priori* based on their frequent comorbidity with COPD and within the Veteran population: asthma, hypertension, diabetes, congestive heart failure (CHF), anxiety disorders (i.e., anxiety disorder not otherwise specified, panic disorder, generalized anxiety disorder, agoraphobia with and without panic, other anxiety states), major depressive disorder, post-traumatic stress disorder (PTSD), bipolar disorder, alcohol use disorder, and drug use disorder.

Hospitalization Characteristics

Length of stay, need for intensive care unit (ICU) admission, and need for mechanical ventilation (invasive or noninvasive) were included in the analysis. ICU admission was determined using bed section codes 12 and 13. Invasive and noninvasive ventilation were determined by common procedural terminology (94,660) and ICD-9 codes (9390, 9670, 9671, and 9672).

Statistical Analysis

We compared sample characteristics by sex using chi-square tests for categorical

variables and Student's *t* tests for continuous variables. To examine the association between sex and 30-day readmission, we used multivariable logistic regression models that were adjusted for age, smoking status, race, antimuscarinic or NRT prescription before hospitalization, PFT acquisition before hospitalization, mental health comorbidities, and medical comorbidities. Next, we examined potential differences by sex in factors associated with 30-day readmission, and we used two separate sex-stratified regression models. We used multiple imputation, using SAS MI procedure, to account for missing data from race/ethnicity ($n = 3,057$; 6.3%) and smoking variables ($n = 540$; 1.1%) (24). The imputation model included age, sex, smoking status, race/ethnicity, receipt of antimuscarinic inhalers before admissions, receipt of NRT before admissions, completed PFT before admissions, diabetes, asthma, major depression, PTSD, anxiety disorder, CHF, alcohol use disorder, drug use disorder, and readmission in 30 days. Ten datasets were imputed and PROC MIANALYZE procedure in SAS was used to combine odds ratio estimates. We conducted a sensitivity analysis comparing the results of a complete case analysis with the imputed result and found no substantial differences. We chose to report results of multivariable model using imputed data (25). All statistical analyses were performed using SAS 9.4 (SAS Institute). Statistical significance was defined as *P* less than 0.05.

Results

Of the 48,888 Veterans hospitalized for a COPD exacerbation, 1,833 (4%) were women. Compared with men, women were younger (mean age, 62 ± 11 vs. 69 ± 10 yr) and more likely to be nonwhite (Table 1). Smoking status varied by sex, and women were more frequently either current smokers (71% vs. 62%) or never-smokers (13% vs. 10%). Women were more likely to have a concurrent diagnosis of asthma (39% vs. 17%), anxiety (40% vs. 24%), PTSD (25% vs. 17%), major depression (27% vs. 13%), bipolar disorder (19% vs. 8%), and drug use disorder (15% vs. 12%). Women were less likely to have a concurrent diagnosis of hypertension (72% vs. 85%), diabetes (36%

vs. 42%), CHF (27% vs. 42%), and alcohol use disorder (15% vs. 21%).

Inhaler treatment and NRT also varied by sex (Table 2). Before hospitalization, women were more likely to receive NRT (24% vs. 15%; $P < 0.01$). Women Veterans were less likely to receive antimuscarinic (43% vs. 48%; $P < 0.01$) or combined LABA/ICS (61% vs. 64%; $P = 0.04$) inhalers. There were no differences in β -agonist or ICS inhaler use. Women were less likely to undergo PFTs before hospitalization (76% vs. 78%; $P = 0.01$) (Table 2).

ICU admission rate and need for mechanical ventilation (invasive or noninvasive) were similar between women and men (Table 3). Median length of stay was shorter in women (2 [interquartile range, 1–4] vs. 3 d [1–5]; $P = 0.04$). Nearly all Veterans were discharged home (97% in women and 96% in men; $P = 0.10$). Thirty-day readmission rate was lower in women compared with men (20% vs. 22%; $P = 0.01$); median time to readmission was not statistically different (2 vs. 3 d; $P = 0.09$).

To identify predictors of readmission at 30 days, we performed multivariable logistic regression in overall and sex-stratified models. In the overall model (Figure 1),

older age, white race, inhaler prescription, and multiple comorbidities were associated with increased risk of 30-day readmission. Veterans prescribed antimuscarinics before hospitalization were more likely to be readmitted compared with those who were not (odds ratio, 1.13; 95% confidence interval, 1.08–1.18). CHF, diagnosis of alcohol use, diagnosis of drug use, and anxiety were the most significant comorbidities associated with readmission. Smoking status, prior PFTs, and sex were not associated with readmission risk.

In the models stratified by sex, older age, CHF, anxiety, and the presence of drug use were associated with readmission at 30 days in both women and men. White race, diabetes, diagnosis of major depressive disorder, alcohol use disorder, and prescription of an antimuscarinic inhaler were only significant in men.

Discussion

We found sex differences in the demographics, health behaviors, comorbidities, evaluation, and treatment of Veterans hospitalized for a COPD exacerbation. We also identified several risk factors for readmission within 30 days of

Table 1. Demographics and comorbidities of veterans admitted for COPD exacerbation

	Women ($n = 1,833$)	Men ($n = 47,055$)
Age, mean (SD)	62 (11)	69 (10)
Race, %		
White	72	75
Black	19	14
Hispanic	2	3
Asian/Pacific Islander	1	1
Native American	1	<1
Unknown/decline	6	6
Smoking status, %		
Current	71	62
Former	16	28
Never	13	10
Comorbidities, %		
Medical		
Asthma	39	17
Hypertension	76	85
Diabetes	36	42
Congestive heart failure	27	42
Psychiatric		
Anxiety	40	24
Post-traumatic stress disorder	25	17
Major depression	27	13
Bipolar disorder	19	8
Drug use/dependence	15	12
Alcohol use/dependence	15	21

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; SD = standard deviation. Data adapted from Reference 18.

Table 2. Pharmacy data and pulmonary function test before hospitalization

	Women (n = 1,833)	Men (n = 47,055)	P Value
β-Agonist (albuterol, salmeterol), %	74	73	0.46
Antimuscarinic (ipratropium, tiotropium), %	43	48	<0.01
ICS, %	25	26	0.75
Combination LABA/ICS	61	64	0.04
Nicotine-replacement therapy, %	24	15	<0.01
Pulmonary function tests, %	76	78	0.01

Definition of abbreviations: ICS = inhaled corticosteroid; LABA = long-acting β-agonists.

The bold typeface values indicate their statistical significance (i.e., $P < 0.05$). Data adapted from Reference 18.

hospital discharge that differed by sex. This study extends the literature by 1) confirming that sex differences in COPD presentation, evaluation, and treatment identified among Veterans are similar to those identified previously in non-Veterans; 2) including PFT evaluation and smoking status to the existing literature on sex differences in Veterans with COPD; and 3) reporting predictors of readmission in Veterans admitted to the hospital with COPD.

Our study has three main findings. First, compared with men, women Veterans with COPD have a unique presentation that is similar to non-Veteran women. In our cohort, women Veterans admitted to the hospital with COPD were younger and had different smoking status compared with men. Prior studies in non-Veteran women with COPD have reported earlier age of onset (6, 12, 26, 27), lower smoking cessation rates (28), and higher rates of never-smokers (27, 28). Because women's lung function may be more susceptible to tobacco smoke (6, 7) and women Veterans in our cohort were more likely to be current smokers, our findings support that smoking cessation must remain a primary focus of

COPD management for women. Because women in this cohort were already prescribed higher rates of NRT, perhaps future efforts should identify additional barriers to smoking cessation.

Because of smoking and occupational/combat-related exposures, disease prevalence, and sex distribution, the VA population is unique, and the results of our study may be better understood by comparison with other VA studies. Overall, women comprise 7.5% of the veteran population based on the Women's Health Evaluation Initiative Sourcebook, whereas only 4% of patients in our study were women (29). Although the proportion of women included in this study was small relative to the entire Veteran population, this value is very similar to prior work evaluating COPD-related hospitalizations spanning 2008–2011 (17). In addition, comorbidity burden was substantially higher in the hospitalized COPD population. The Musculoskeletal Disease VA cohort includes more than 4 million veterans with chronic musculoskeletal conditions and is comprised of approximately 6% women (30, 31).

Comparing medical and psychiatric disease prevalence from the Musculoskeletal Disease cohort with the COPD cohort, the COPD cohort had a substantially higher proportion of patients who currently smoke cigarettes and higher proportions of the comorbidities of interest in both sexes. Rates of depression in men and women were similar in both cohorts. Because our cohort is defined by a COPD-related hospitalization, we would expect "sicker" patients with more comorbidities than other VA cohorts.

In this cohort of veterans admitted to the hospital with COPD, women Veterans had higher rates of asthma, psychiatric diagnoses (i.e., anxiety and depression), and diagnosis of drug use disorders. A recent study on Veterans with COPD reported differences in comorbidities similar to our findings, with women having higher rates of depression and asthma and men having higher rates of hypertension, diabetes, heart disease, and heart failure (17). Other studies in non-Veterans have reported distinct comorbidities in women with COPD. For example, ischemic heart disease was less common but osteoporosis and depression were more common in women compared with men (3, 27, 32). Combining results from our study and others, it seems likely that both Veteran and non-Veteran women with COPD are more burdened by psychiatric disorders (i.e., anxiety, depression, bipolar disorder, and PTSD), whereas men are more burdened by cardiovascular disease. Undertreated psychiatric disorders in women may contribute to difficulty with achieving smoking cessation.

The second finding in this study is that women Veterans admitted to the hospital with COPD are evaluated and treated differently than men Veterans before hospitalization. Women Veterans were slightly less likely to receive PFTs before hospitalization. Delayed acquisition of PFTs may suggest delayed recognition of COPD in women, although the sex differences observed in our study of hospitalized patients with COPD are likely of limited clinical significance (PFT acquisition in 76% in women vs. 78% in men). COPD is underdiagnosed in both women and men in other studies (13, 33); however, women are less likely to undergo spirometry (9) or to be diagnosed with COPD than men (14). Because prior work has shown that obtaining spirometry reduces the underdiagnosis of COPD in women (13),

Table 3. Hospital-specific variables and outcomes

	Women (n = 1,833)	Men (n = 47,055)	P Value
Duration of in-patient stay, d	2 (1–4)	3 (1–5)	0.04
ICU admission, %	10	10	0.94
Mechanical ventilation, %			
Noninvasive mechanical ventilation	7	7	0.27
Invasive mechanical ventilation	1	2	0.16
Readmission, 30 d, %	20	22	0.01
Time to readmission, median (IQR)	2 (0–14)	3 (0–15)	0.09
Disposition home after hospitalization, %	96.8	95.6	0.10

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range.

The bold typeface values indicate their statistical significance (i.e., $P < 0.05$). Data adapted from Reference 18.

Figure 1. Forest plot of multivariable models for 30-day readmission for Veterans admitted for chronic obstructive pulmonary disease (overall and sex-stratified). Overall model reports readmission risk with sex as the predictor of interest; separate models stratified by sex were run to compare how factors associated with readmission varied by sex. Models also adjusted for sex (overall model only), age, race, and asthma. CI = confidence interval; NRT = nicotine-replacement therapy; PFT = pulmonary function test; PTSD = post-traumatic stress disorder.

clinicians should be encouraged to obtain spirometry early if chronic cough, dyspnea, or sputum production are noted in either sex.

Regarding inhaler use, women Veterans in this study were less likely to receive antimuscarinic or combined LABA/ICS inhalers before hospitalization. Although inhaler treatment for COPD seems equally effective for women and men (34, 35), overall patterns of inhaler treatment by sex in COPD are unclear. Whereas prior work showed that women Veterans were less likely to be prescribed inhalers before a COPD-related hospitalization (17), others have shown that women with airflow obstruction were more likely than men to receive inhaler prescriptions (10). Complicating matters, Sundh and colleagues (36) have recently shown significant changes in inhaler prescriptions for COPD between 2005 and 2014. Specifically, “triple therapy” (i.e., combined LABA, long-acting muscarinic antagonist, and ICS) has become more common in COPD treatment, especially in women and patients with more symptoms.

The combination of lower-than-expected antimuscarinic inhaler use in women hospitalized with COPD in this study and higher-than-expected use of ICSs

in our prior study is noteworthy (17). Because long-term treatment with ICS in COPD carries an increased risk of pneumonia and potentially osteoporosis, COPD guidelines recommend avoiding ICS therapy excepting patients with persistent symptoms or frequent exacerbations (15). By contrast, ICSs are a mainstay of asthma therapy. The combination of increased ICS inhaler use with lower antimuscarinic inhaler use in women Veterans may be related to higher rates of asthma, misdiagnosis of COPD as asthma, or higher symptom burden. In the non-Veteran population, sex differences in asthma rates have been reported. Wheaton and colleagues (37) published higher self-reported rates of asthma and asthma-COPD overlap syndrome in non-Veteran women compared with men, and women with mild COPD have shown higher airway hyperresponsiveness (38). In patients presenting to the emergency room with COPD exacerbation, Cydulka and colleagues (39) also found higher mixed asthma/COPD in women with less frequent anticholinergic use. To better address inhaler treatment differences by sex, individual drug prescription (rather than drug classes) and rates of asthma,

bronchodilator-responsiveness on PFTs, and combined asthma/COPD overlap need to be clarified.

Nicotine replacement was more likely to be prescribed to women Veterans before their COPD hospitalization. In the literature, sex differences in tobacco cessation rates and therapeutic efficacy are also unclear. Some literature reports that women quit smoking less frequently than men and suggest that women obtain less benefit from NRT (2, 28, 40). By contrast, the Centers for Disease Control and Prevention’s 2002 Women and Smoking report showed that women’s smoking cessation rates were similar (or higher) than men’s (41). In addition, randomized controlled trials of bupropion (42) and varenicline (43) as well as a metaanalysis of NRT (44) have not shown clear differences in outcomes for women and men. Comorbid psychiatric diagnoses may further relate to women’s higher smoking rates and/or difficulty with smoking cessation. The contribution of psychiatric diagnoses and ongoing smoking despite more NRT use may suggest that future approaches to smoking cessation in women should prioritize tobacco cessation counseling and treatment of any comorbid psychiatric diagnoses.

The third finding of this study is that in unadjusted analyses, women Veterans had better hospitalization-associated outcomes, including lower 30-day readmission rate and shorter length of stay. Need for ICU-level care or mechanical ventilation did not differ by sex. Short-term readmission among women and men was strongly influenced by comorbidities. The multivariable logistic regression model showed that older age and comorbid CHF, anxiety disorder, or drug use were associated with readmission at 30 days. Although race, antimuscarinic use before hospitalization, diabetes, depression, and diagnosis of alcohol use disorder were also associated with readmission, these factors were only associated with 30-day readmission in men Veterans. Several recent studies have shown findings similar to our own. In a large retrospective study in the United States, Goto and colleagues (45) reported slightly lower 30-day readmission in women (18.6% for women and 20.1% for men), but women were more likely to be readmitted with a diagnosis of asthma. In a large, nationwide, and retrospective database analysis, Jacobs and colleagues (46) also recently showed that risk of 30-day readmission after a COPD exacerbation was lower in women and was influenced by patient comorbidities. In a Canadian cohort, Gonzalez and colleagues (47) found men had increased risk of death and rehospitalization after an admission for COPD.

There are several points worth noting in our findings on readmission rate and risk factors for readmission. First, although readmission rate at 30 days was slightly lower in women (20% vs. 22%), sex was not a risk factor for readmission in the adjusted models. These findings may suggest that comorbidities that differ by sex are the driving factors for 30-day readmission in patients who survive a hospitalization for COPD. Importantly, recent work by Rinne and colleagues (in Veterans) (17) and Jacobs and colleagues (in non-Veterans) (46) also had lower 30-day readmission rates in women admitted with COPD. Although Rinne's cohort did not reach statistical significance, there is a trend toward decreased rate of 30-day readmission for women after a COPD exacerbation. Second, it is noteworthy that diagnosis of drug use disorder increased readmission risk for women and men, whereas diagnosis of alcohol use disorder only predicted readmission in men. Because women in our cohort had higher rates of drug use disorder, it seems likely that diagnosis of drug and alcohol use

disorders may convey differential risk for short-term readmission rates by sex. Finally, it is unexpected that antimuscarinic inhaler use was a risk factor for 30-day readmission in men Veterans. Because long-acting antimuscarinic use is associated with improvements in lung function, quality of life, exacerbation rates, and time to hospitalization (48), it is unlikely that appropriate inhaler therapy increased risk of readmission for COPD. Rather, it is possible that patients with higher severity of illness were more likely to be treated with an antimuscarinic and at increased risk for hospitalization.

The main strength of this study is size of the cohort, which is one of the largest available cohorts of women Veterans hospitalized with a COPD exacerbation. Despite considerable evidence of sex differences in COPD in non-Veterans, very little has been published in the Veteran population. A second strength is the nationwide VA medical system and EMR. With the use of a single healthcare system and EMR, the potential for missing patients or hospitalizations may be lower. To better understand the sex differences in COPD, future work in this cohort will evaluate outcomes in age-stratified analyses that include COPD severity, clarify the prevalence of asthma in this cohort, and determine the effect of comorbid disease (especially psychiatric disorders). Because comorbid diseases play a role in both women's smoking patterns and readmission rates in both women and men, future work to reduce readmission rates in patients with COPD should focus on identifying and treating comorbidities, particularly CHF and substance use disorders.

This study has several limitations. Methodologically, the study is retrospective, allowing us to recognize differences between women and men but limiting our ability to predict COPD development or outcomes (i.e., hospitalizations). It is also possible that there is a sex bias in the coding of COPD exacerbations. Both issues require prospective studies for better understanding. Second, spirometry values, socioeconomic status, and symptom burden were not available. Lack of these data prevents us from spirometrically confirming asthma, stratifying readmission by disease severity, or evaluating the role of socioeconomic status or symptom severity. Third, the unadjusted analyses may be influenced by age; because women Veterans in our cohort were younger, it is possible

that between-group differences may be smaller if adjusted for age. Finally, Veterans were identified after a hospitalization for COPD, which may indicate a higher disease severity than other patients and limits our ability to generalize these results to all Veterans (and non-Veterans) with COPD.

This study confirms that sex differences exist in the presentation, evaluation, and management of COPD in the Veteran population. Our hypothesis that associations between comorbidities and readmission rate would differ by sex was confirmed. Women Veterans with COPD have a unique phenotype compared with men, including a younger presentation, higher smoking rates, and unique comorbidities. Although our knowledge of sex differences with COPD is growing, the published literature is discrepant in many areas and more work on this topic is needed. The results from this study may help ensure equitable treatment of COPD for both women and men. Primary care and pulmonary physicians alike must have a high index of suspicion to prevent delayed diagnosis and inappropriate treatment, and a distinct approach to COPD management in women must be considered. Specifically, if considering COPD, PFTs with bronchodilator testing should be obtained early in the course of the disease. Smoking cessation must also be prioritized and discussed at every visit. Finally, concomitant CHF, depression, anxiety, PTSD, and drug and alcohol use disorders should be screened for and treated. Future investigations will evaluate the influence of COPD severity and pulmonary specialist involvement on clinical outcomes, the contribution of comorbid disease (especially asthma and psychiatric disease) on readmission rates, unique approaches to smoking cessation between women and men, and potentially decision-aids for primary and specialty care providers managing women with COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: This work was completed as an operational quality improvement project at Veterans Administration (VA) Connecticut and VA Greater Los Angeles for the Department of Veterans Affairs through a specific request from VA Women's Health Services within the Office of Patient Care Services. It was also approved by the local institutional review board at VA Connecticut and determined to be operations work.

References

- 1 Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance: United States, 1999–2011. *Chest* 2013;144:284–305.
- 2 Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, *et al.* Gender and chronic obstructive pulmonary disease: why it matters. *Am J Respir Crit Care Med* 2007;176:1179–1184.
- 3 Jenkins CR, Chapman KR, Donohue JF, Roche N, Tsigianni I, Han MK. Improving the management of COPD in women. *Chest* 2017;151:686–696.
- 4 Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Shirude S, Naghavi M, *et al.* Trends and patterns of differences in chronic respiratory disease mortality among US counties, 1980–2014. *JAMA* 2017;318:1136–1149.
- 5 Goel K, Bailey M, Borgstrom M, Parthasarathy S, Natt B, Berry C, *et al.* Trends in COPD hospitalization and in-hospital deaths in the United States by sex: 2005–2014. *Ann Am Thorac Soc* 2018;16:391–393.
- 6 Sørheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010;65:480–485.
- 7 Gan WQ, Man SF, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Res* 2006;7:52.
- 8 Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997;10:822–827.
- 9 Watson L, Vestbo J, Postma DS, Decramer M, Rennard S, Kiri VA, *et al.* Gender differences in the management and experience of chronic obstructive pulmonary disease. *Respir Med* 2004;98:1207–1213.
- 10 Dales RE, Mehdizadeh A, Aaron SD, Vandemheen KL, Clinch J. Sex differences in the clinical presentation and management of airflow obstruction. *Eur Respir J* 2006;28:319–322.
- 11 Dransfield MT, Washko GR, Foreman MG, Estepar RS, Reilly J, Bailey WC. Gender differences in the severity of CT emphysema in COPD. *Chest* 2007;132:464–470.
- 12 Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, *et al.*; National Emphysema Treatment Trial Research Group. Sex differences in severe pulmonary emphysema. *Am J Respir Crit Care Med* 2007;176:243–252.
- 13 Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. *Chest* 2001;119:1691–1695.
- 14 Ancochea J, Miravittles M, García-Río F, Muñoz L, Sánchez G, Sobradillo V, *et al.* Underdiagnosis of chronic obstructive pulmonary disease in women: quantification of the problem, determinants and proposed actions. *Arch Bronconeumol* 2013;49:223–229.
- 15 Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017;195:557–582.
- 16 Volkman JE, DeRycke EC, Driscoll MA, Becker WC, Brandt CA, Mattocks KM, *et al.* Smoking status and pain intensity among OEF/OIF/OND Veterans. *Pain Med* 2015;16:1690–1696.
- 17 Rinne ST, Elwy AR, Liu CF, Wiener RS, Thayer L, Gerity A, *et al.* Implementation of guideline-based therapy for chronic obstructive pulmonary disease: differences between men and women veterans. *Chron Respir Dis* 2017;14:385–391.
- 18 Bade B, DeRycke E, Skanderson M, Crothers KA, Bastian L, Akgun KM. Gender differences in veterans admitted to the hospital for COPD exacerbation [abstract]. *Am J Respir Crit Care Med* 2018;197:A2771.
- 19 Cooke CR, Joo MJ, Anderson SM, Lee TA, Udris EM, Johnson E, *et al.* The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv Res* 2011;11:37.
- 20 McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, *et al.* Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res* 2011;13:1233–1239.
- 21 Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, *et al.* Development and verification of a “virtual” cohort using the National VA Health Information System. *Med Care* 2006;44(Suppl 2):S25–S30.
- 22 Haskell SG, Mattocks K, Goulet JL, Krebs EE, Skanderson M, Leslie D, *et al.* The burden of illness in the first year home: do male and female VA users differ in health conditions and healthcare utilization. *Womens Health Issues* 2011;21:92–97.
- 23 Elixhauser ASC, Palmer L. 2008 [accessed 2014 Aug 1]. Available from: <http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp>.
- 24 Little RJRD. Statistical analysis with missing data, 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2014.
- 25 Hausmann LRM, Brandt CA, Carroll CM, Fenton BT, Ibrahim SA, Becker WC, *et al.* Racial and ethnic differences in total knee arthroplasty in the Veterans Affairs Health Care System, 2001–2013. *Arthritis Care Res (Hoboken)* 2017;69:1171–1178.
- 26 Foreman MG, Zhang L, Murphy J, Hansel NN, Make B, Hokanson JE, *et al.*; COPDGen Investigators. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGen Study. *Am J Respir Crit Care Med* 2011;184:414–420.
- 27 Papaioannou AI, Bania E, Alexopoulos EC, Mitsiki E, Malli F, Gourgoulanis KI. Sex discrepancies in COPD patients and burden of the disease in females: a nationwide study in Greece (Greek Obstructive Lung Disease Epidemiology and health eNomics: GOLDEN study). *Int J Chron Obstruct Pulmon Dis* 2014;9:203–213.
- 28 Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: an update. *Transl Res* 2013;162:208–218.
- 29 Women's Health Evaluation Initiative. [accessed 2018 Dec 18]. Available from: https://www.womenshealth.va.gov/WOMENSHEALTH/docs/WHSourcebook_Vol-IV_508c.pdf.
- 30 Goulet JL, Kerns RD, Bair M, Becker WC, Brennan P, Burgess DJ, *et al.* The musculoskeletal diagnosis cohort: examining pain and pain care among veterans. *Pain* 2016;157:1696–1703.
- 31 Higgins DM, Fenton BT, Driscoll MA, Heapy AA, Kerns RD, Bair MJ, *et al.* Gender differences in demographic and clinical correlates among Veterans with musculoskeletal disorders. *Womens Health Issues* 2017;27:463–470.
- 32 Almagro P, López García F, Cabrera FJ, Montero L, Morchón D, Díez J, *et al.*; Grupo Epoc De La Sociedad Española De Medicina Interna. Comorbidity and gender-related differences in patients hospitalized for COPD. The ECCO study. *Respir Med* 2010;104:253–259.
- 33 Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax* 2008;63:402–407.
- 34 Tashkin D, Celli B, Kesten S, Lystig T, Decramer M. Effect of tiotropium in men and women with COPD: results of the 4-year UPLIFT trial. *Respir Med* 2010;104:1495–1504.
- 35 Vestbo J, Soriano JB, Anderson JA, Calverley P, Pauwels R, Jones P; TRISTAN Study Group. Gender does not influence the response to the combination of salmeterol and fluticasone propionate in COPD. *Respir Med* 2004;98:1045–1050.
- 36 Sundh J, Åberg J, Hasselgren M, Montgomery S, Stållberg B, Lisspers K, *et al.* Factors influencing pharmacological treatment in COPD: a comparison of 2005 and 2014. *Eur Clin Respir J* 2017;4:1409060.
- 37 Wheaton AG, Pleasants RA, Croft JB, Ohar JA, Heidari K, Mannino DM, *et al.* Gender and asthma-chronic obstructive pulmonary disease overlap syndrome. *J Asthma* 2016;53:720–731.
- 38 Kanner RE, Connett JE, Altose MD, Buist AS, Lee WW, Tashkin DP, *et al.* Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med* 1994;150:956–961.
- 39 Cydulka RK, Rowe BH, Clark S, Emerman CL, Rimm AR, Camargo CA Jr. Gender differences in emergency department patients with chronic obstructive pulmonary disease exacerbation. *Acad Emerg Med* 2005;12:1173–1179.
- 40 Camp PG, Goring SM. Gender and the diagnosis, management, and surveillance of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007;4:686–691.
- 41 Women and smoking: a report of the Surgeon General. Executive summary. *MMWR Recomm Rep* 2002;51:i–iv, 1–13.

- 42 Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001;357:1571–1575.
- 43 Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, *et al.*; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47–55.
- 44 Munafò M, Bradburn M, Bowes L, David S. Are there sex differences in transdermal nicotine replacement therapy patch efficacy? A meta-analysis. *Nicotine Tob Res* 2004;6:769–776.
- 45 Goto T, Faridi MK, Gibo K, Camargo CA Jr, Hasegawa K. Sex and racial/ethnic differences in the reason for 30-day readmission after COPD hospitalization. *Respir Med* 2017;131:6–10.
- 46 Jacobs DM, Noyes K, Zhao J, Gibson W, Murphy TF, Sethi S, *et al.* Early hospital readmissions after an acute exacerbation of chronic obstructive pulmonary disease in the Nationwide Readmissions Database. *Ann Am Thorac Soc* 2018;15:837–845.
- 47 Gonzalez AV, Suissa S, Ernst P. Gender differences in survival following hospitalisation for COPD. *Thorax* 2011;66:38–42.
- 48 Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, *et al.*; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.