Mortality Risk Factor Stratification in a Retrospective Cohort of Hospitalized Patients with Community Acquired Pneumonia

Meredith Sloan[1*], Anna Owings[1], Sarah Glover[1], Julia Liu[2], George E Abraham[1], Brian Claggett[3], Michal Senitko[1]

[1]Department of Medicine, University of Mississippi Medical Center, Jackson, USA
[2]Department of Medicine, Morehouse School of Medicine, Atlanta, USA
[3]Department of Medicine, Harvard Medical School, Boston, USA

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***For Correspondence:** Meredith Sloan, Department of Medicine, University of Mississippi Medical Center, Jackson, USA

E-mail: mesloan@umc.edu

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ABSTRACT

A retrospective cohort was used to investigate the conditions that affected mortality in hospitalized Community-Acquired Pneumonia (CAP) patients. 1223 patients were identified based on diagnostic codes. T-tests, chi-squared tests, and logistic regression models were used to evaluate the data. There were 613 (50%) patients on proton pump inhibitors (PPIs) with a mortality rate of 26.3% vs. 13.4% in non-PPI users (P<0.001). Variables that increased the risk of death included: each decade of age, odds ratio (OR)=1.15 (95% confidence interval 1.07 to 1.23), congestive heart failure OR=2.06 (1.46 to 2.91), cancer OR=1.66 (1.20 to 2.23), cardiovascular disease OR=2.04 (1.19 to 3.49), and stroke OR=1.53 (1.05 to 2.23). Statin use was associated with improved mortality, OR=0.28 (0.13 to 0.59). Statin use may improve and PPIs may worsen mortality in CAP.

Keywords: Community acquired pneumonia; Mortality; Statins; Proton pump inhibitors; Inpatient

INTRODUCTION

Community Acquired Pneumonia (CAP) related admissions burden the U.S. health care system with more than 1.5 million unique adults annually and is associated with high mortality [1]. Statins and proton pump inhibitors are among the most prescribed medicines, and their prevalence has been increasing over the past decade [2]. A meta-analysis of thirteen studies suggested positive impact of statins on the CAP associated in-hospital mortality [3]. However, a prospective study in the intensive care unit setting comparing subjects receiving statins before and throughout hospitalization with those who did not receive statins, failed to show a reduction in length of stay or in-hospital mortality [4]. There is growing concern over potential adverse outcomes associated with long-term use of PPIs, including increases in community-acquired pneumonia risk and overall mortality [5-9]. A recent cohort study revealed an increased mortality and higher risk of infection associated with Proton Pump Inhibitor (PPI) use in patients infected with COVID-19 [10]. This raised the question of whether a similar association would be observed in patients with CAP without a concomitant COVID-19 infection. In this study we examined the association of underlying conditions and medication use on the mortality of patients hospitalized with community-acquired pneumonia in the pre-COVID-19 era.

MATERIALS AND METHODS

Data acquisition

The University of Mississippi Medical Center (UMMC) Research Data Warehouse continually captures de-identified electronic medical record (EMR) data from patients in six hospitals within the UMMC system: University Hospital, Batson Children's Hospital, Wiser Hospital for Women and Infants, and Conerly Critical Care Hospital in Jackson, MS; UMMC Grenada in Grenada, MS; and UMMC Holmes County in Lexington, MS. The UMMC Patient Cohort Explorer is a self-service online application that allows direct access to fully de-identified subsets of EMR data within this database [11]. In this retrospective observational study, we included all patients admitted from January 1 to December 31, 2019 with a diagnosis of community-acquired pneumonia based on ICD-10 diagnostic codes. A total of 1223 patients were hospitalized with community-acquired pneumonia. Co-morbidities were identified from ICD-10 diagnostic codes found on inpatient problem lists and medical histories. Medication use was identified as an administration of at least one dose of the medication of interest during hospitalization.

Statistical analysis

The primary outcome was mortality in patients hospitalized with community-acquired pneumonia. Other covariates used for analysis included patient demographics (age, sex, and race), comorbid conditions (cancer, hypertension, obesity, cardiovascular disease, Congestive Heart Failure (CHF), stroke, diabetes, asthma, and Gastroesophageal Reflux Disease (GERD), and the use of other medications (H2 blockers, anti-hypertensives, and statins)).

T-tests and chi-squared tests were used for comparisons of continuous variables and dichotomous variables between the groups of patients who died after being hospitalized with community-acquired pneumonia *vs.* those who survived. Logistic regression models were used to estimate the associations between baseline covariates and mortality. To construct the multivariable adjusted model, backwards stepwise selection was used with a P-value threshold for removal of 0.10. Potential modifications of the association between PPI use and mortality were evaluated by testing for interactions between covariates and PPI use within the multivariable model. For any covariates that produced a significant interaction (P<.05), we refitted the multivariable model separately for the

associated subgroups. All analyses were conducted using the STATA 14 statistical software package (College Station, TX).

RESULTS

Baseline patient information is shown in Table 1. Survivors were younger with less comorbidity. In univariate analysis, there were 613 (50.1%) patients on PPIs with a mortality rate of 26.3% (161/613) vs. 13.4% (82/610) in non-PPI users (P<0.001). Of the covariates analyzed, diabetes mellitus, asthma, obesity, GERD, hypertension, H2RA use, and race did not meet the P=0.10 threshold.

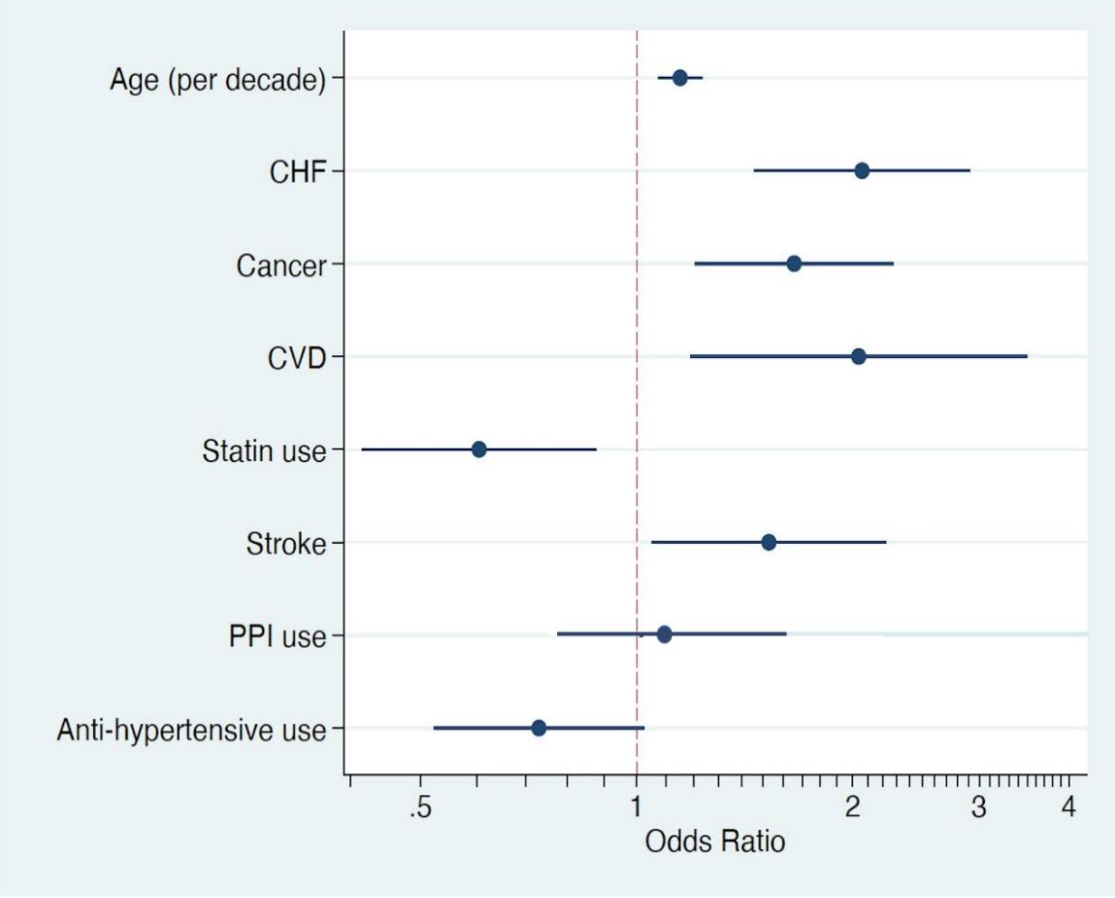
In the multivariate analysis including the patients in the univariate analysis, variables that increased the risk of death included: each additional decade of age (OR=1.15 (95% CI of 1.07 to 1.23)), congestive heart failure (OR=2.06 (1.46 to 2.91), cancer (OR=1.66 (CI 1.20 to 2.23)), cardiovascular disease (OR=2.04 (1.19 to 3.49)), and stroke (OR=1.53 (1.05 to 2.23)). PPI use (OR=1.10 (0.76 to 1.60)) and anti-hypertensive use (OR=0.73 (0.52 to 1.02)) effects were not significant. Statin use was associated with improved mortality (OR=0.28 (0.13 to 0.59)) in Figure 1, all cause in-hospital mortality in those with community-acquired pneumonia was 243/1223 (19.87%).

Table 1: Baseline demographics and medical information for the patients included in the study (N=1,223). The average age of the patients was 45.6 ± 27.9 years.

Characteristics	No. (%)
Sex	
Male	535 (43.74%)
Female	688 (56.26%)
Race	
Black	665 (54.37%)
White	485 (39.66%)
Asian	7 (0.58%)
Mississippi Choctaw	6 (0.49%)
American or Alaskan Native	5 (0.41%)
Hispanic	1 (0.08%)
Multiracial	9 (0.74%)
Other	28 (2.29%)
Unknown	14 (1.14%)
Comorbid conditions	
Cardiovascular disease	907 (74%)
Obstructive lung disease	528 (43%)
Hypertension	749 (61%)
Diabetes mellitus	314 (26%)
Cancer	314 (26%)
Congestive heart failure	305 (25%)
Gastroesophageal reflux	248 (20%)

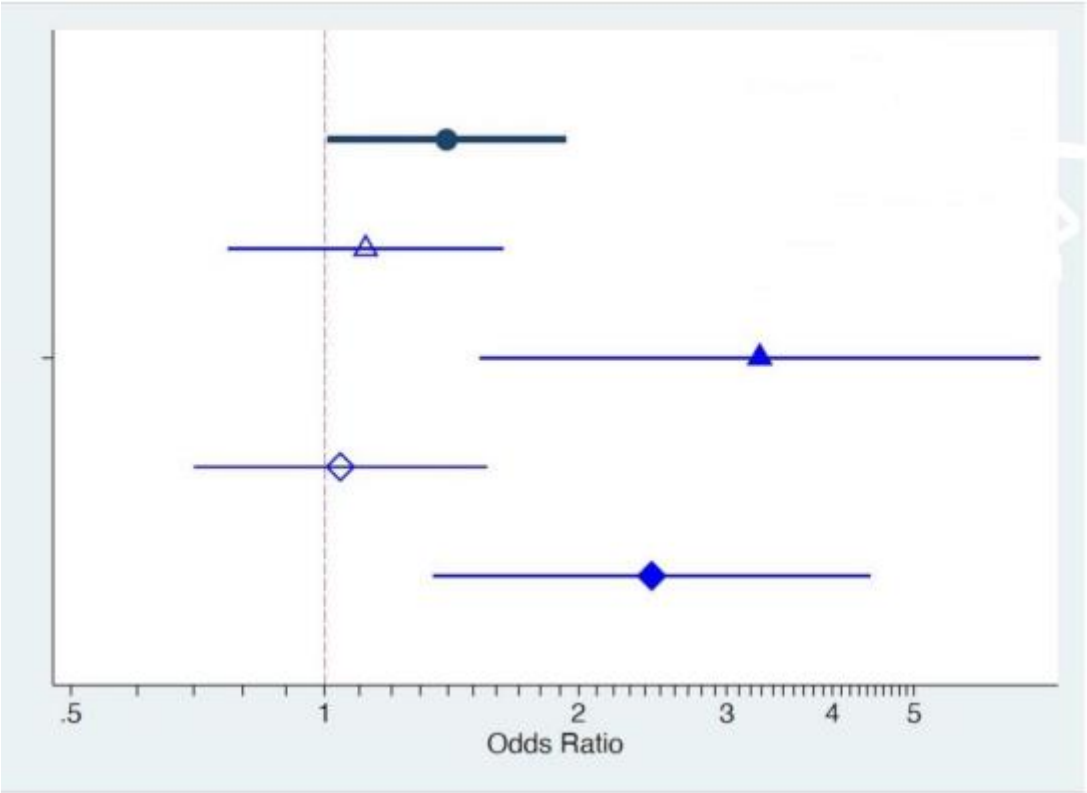
Stroke	196 (16%)
Obesity	134 (11%)
Medications	
Proton pump inhibitors	613 (50%)
Anti-hypertensives	551 (45%)
H2 receptor antagonists	276 (23%)
Statins	271 (22%)

Figure 1. Comparison of comorbidities and medication effect on mortality. This figure demonstrates multivariate analysis results for the effects of several comorbidities and medications on mortality from community-acquired pneumonia. The use of statins without PPIs was associated with significant lower mortality, (Created with STATA 14 statistical software package (College Station, TX)).



Multivariate analysis of covariate interactions with PPIs showed significant interactions with statin use and CHF. PPI use was not associated with a significant mortality risk when used without a statin (OR=1.12 (0.77, 1.63)). Concomitant statin use with a PPI had an increased risk of death (OR=3.28 (1.53, 7.05)). The benefit of statins was lost in patients with heart failure (OR=0.86 (0.53 to 1.39)). Patients with CHF who were administered PPIs demonstrated a trend towards worse outcomes (OR=2.48 (1.64 to 3.73) compared to those who were not given PPIs (P=0.036; OR=1.39 (9(0.70 to 2.75)) (Figure 2).

Figure 2. The effects of PPI use on mortality. This figure shows the multivariate analysis results in odds ratios for the effects of PPI use on mortality from community-acquired pneumonia (1) overall, (2) with and without statin use and (3) with and without Congestive Heart Failure (CHF). The protective effect of statins on overall mortality is diminished when combined with PPI use. (created with STATA 14 statistical software package (College Station, TX). **Note:** (●) Overall; (△) Without statin use; (▲) With statin use; (◇) Without CHF; (◆) With CHF



DISCUSSION

Our study evaluated the potential effects of comorbidities and medication use on in-hospital mortality in a large cohort of patients hospitalized with community-acquired pneumonia in Mississippi in 2019. We found that statin use during admission was associated with a reduction in overall mortality, consistent with prior observational studies. However, the use of PPIs together with statins during admission seemed to negate this benefit. Our study has several limitations. First, its retrospective nature and the de-identified patient data limited our ability to obtain additional data, such as the original indications for statin or PPI use. For example, the ICU patients may have received PPIs for stress ulcer prophylaxis during hospitalization, which could confound our results. The same is true for statin use. Although most patients are on long term statin therapy, there are several indications to start statin therapy in the hospital. Duration of treatment was not available in our data. We were unable to determine which patients were on long-term PPI medication and whether long-term use would further alter their risk. Additional prognostic information such as vital signs was not part of our data set. Our comorbidity data depended on the diagnoses listed in the records, but many patients may have had diagnoses of interest that were not listed; such missing data may have affected the significance of the risk of death for several of the analyzed variables. This cohort of patients also had a high number of comorbidities which may have contributed to the mortality noted and decreased the significance of the observed associations. Such retrospective data must be interpreted with caution but does provide hypotheses for future study. The etiology of the increased in-hospital mortality associated with

PPIs remains unclear. However, one study in cardiothoracic patients receiving long-term treatments with PPIs showed reduced oxidative burst as well as small decreases in the killing activity of neutrophils [12]. Moreover, pneumonia developed in significantly more patients who were receiving PPIs, which suggests that immunosuppression likely contributed to their increased mortality. Statins have also been shown to be immunomodulatory, with effects on T-cell proliferation, antigen presentation, leukocyte migration, and cytokine production [13]. These two drug types may have conflicting effects, which would explain the comparable odds ratios we found for the "PPI only" and "PPI plus statin" categories. These data suggest that when acid reducers are indicated in patients hospitalized for community-acquired pneumonia, clinicians should consider an alternative to PPI therapy. We also found a trend towards worsened outcomes in patients with comorbid CHF who were exposed to PPIs. There are concerns about increased cardiovascular risks and potential adverse effects of concurrent PPI use [14]. However, this remains controversial. For instance one observational study looking at PPI use in CHF patients actually demonstrated an improved mortality in the PPI group as compared to control and H2RA [15]. One proposed mechanism of the cardiovascular effects of PPIs is *via* impaired nitric oxide synthase activity, which can worsen platelet aggregation and increase the interactions between leukocytes and endothelial cells, subsequently leading to a major adverse cardiac event.

CONCLUSION

As the patients in our study had active infections, PPI use may have had an additive effect with their concurrent inflammatory state and contributed to the trend of poorer outcomes in CHF patients. In this multivariable analysis of hospitalized community-acquired pneumonia patients, each additional decade of age, congestive heart failure, cancer, cardiovascular disease, and stroke all increased the risk of death. Statin use, however, was associated with improved mortality. The benefit seen with statins was eliminated when statins and PPI were used concomitantly. These findings warrant confirmation with future prospective studies.

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CONFLICT OF INTEREST

MS is a scientific consultant for MedWave Inc. and Optellum Inc. GEA is a scientific consultant for AstraZeneca. MES, AHO, SCG, JJL have nothing to disclose.

AUTHOR CONTRIBUTIONS

Meredith Sloan, Anna Owings, Sarah Glover, Julia Liu, George Abraham, Brian Claggett and Michal Senitko are the guarantors of the entire manuscript as they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Meredith Sloan, Anna Owings, Sarah Glover, Julia Liu, George Abraham, Brian Claggett and Michal Senitko contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

ETHICS APPROVAL

The data warehouse from which the information for this study is derived has been de-identified and date-shifted so that it does not include any Protected Health Information (PHI). Pursuant to 45 CFR 46, use of this database does not meet the definition of human subjects' research and does not require IRB review.

CONTRIBUTION TO FIELD STATEMENT

Community Acquired Pneumonia (CAP) related admissions burden the U.S. health care system with more than 1.5 million unique adults annually and is associated with high mortality, making identifying risk factors of clinical importance. This paper evaluated the potential effects of comorbidities and medication use on in-hospital mortality in a large cohort of patients hospitalized with CAP in Mississippi in 2019. We found that statin use during admission was associated with a reduction in overall mortality, consistent with prior observational studies. However, the use of Proton Pump Inhibitors (PPIs) together with statins during admission seemed to negate this benefit. PPIs also worsened outcomes in patients with congestive heart failure. Other identified risks included each additional decade of age, congestive heart failure, cancer, cardiovascular disease, and stroke. Statin and PPI use are potentially modifiable risks that can be addressed in patients admitted for CAP and could affect outcomes.

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