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Impact of Cirrhosis on Pneumonia-Related Outcomes in Hospitalized Older Veterans

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Abstract

Background: Prior research has demonstrated high mortality rates in patients with cirrhosis who contract bacterial infections. The purpose of our study was to explore clinical outcomes such as 90-day mortality, rehospitalization, and ICU admission in older veterans with pneumonia and cirrhosis.

Method: We conducted a retrospective cohort study of hospitalized patients with community-acquired pneumonia at any Departments of Veterans Affairs (VA) hospital over a 10-year period. We included patients 65 years or older who consistently received VA care and who were diagnosed with community-acquired pneumonia. There were 103,997 patients who met the inclusion criteria, and 1,246 patients with cirrhosis. We used multilevel regression models to examine the association between cirrhosis and the outcomes of interest after controlling for potential confounders.

Results: Cirrhosis was associated with significantly increased odds of 90-day mortality (odds ratio 1.79, 95% confidence interval, 1.57–2.04). There were also significantly increased odds of rehospitalization within 90-days (1.30, 1.16–1.47). No significant association was found with ICU admission (1.00, 0.83–1.19).

Conclusion: We found an association between cirrhosis and 90-day mortality and rehospitalization in older patients with pneumonia. We suggest that physicians should carefully monitor patients with cirrhosis who develop pneumonia.

Keywords

Cirrhosis; Pneumonia; mortality; rehospitalization

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INTRODUCTION

Pneumonia, along with influenza, was the eighth leading cause of death in the United States in 2014, while cirrhosis and chronic cirrhosis were the twelfth leading cause¹. Prior studies have shown that cirrhosis depresses the immune system, making it more likely that a patient will develop a bacterial infection such as pneumonia². Prior research has demonstrated high mortality rates in patients with cirrhosis who contract bacterial infections, ranging from 7%–40%³. Arvaniti et al. found that infections in patients with cirrhosis increased mortality fourfold, and that mortality within 30 days of infection was 30%, whereas mortality within 1 year was 66%⁴. Most of the literature available, associating mortality with bacterial infections in cirrhotic patients, is related to spontaneous bacterial peritonitis (SBP) and sepsis, with only a few small reports associating cirrhosis with pneumonia. A larger report based on administrative data was published by Hung et al. showing an increased mortality in patient with cirrhosis and ascites who had pneumonia in Taiwan⁵.

Current estimates place the prevalence of cirrhosis at 0.27% of people in the United States⁶. Risk factors for developing cirrhosis include old age, hepatitis B and C, nonalcoholic fatty cirrhosis, male sex, and alcohol abuse^{6–8}. Additionally, the number of military veterans treated for cirrhosis steadily rose over the past two decades. Beste et al. reported the prevalence of cirrhosis in patients receiving care at the VA to be 1.1%, or 4 times higher than the overall prevalence among the general US population⁹.

The purpose of our study was to explore the association between cirrhosis and clinical outcomes in the US and in veterans > 65 years old hospitalized with community-acquired pneumonia. We hypothesized that patients with cirrhosis hospitalized with pneumonia would have an increased 90-day mortality compared to those who do not have cirrhosis.

METHODS

We conducted a retrospective cohort study using clinical and administrative databases of the Department of Veterans Affairs (VA) Health Care System. These databases contain clinical data from all of the national VA hospitals and outpatient clinics¹⁰. The Institutional Review Board of VA North Texas approved this study.

Inclusion Criteria

We included patients who met the following criteria:

- a. Hospitalization between October 1, 2001 – September 30, 2012.
- b. 65 years or older on the date of admission.
- c. Discharged with a diagnosis of community-acquired pneumonia defined as either a primary diagnosis of pneumonia (ICD-9 codes 480.0–483.99 or 485.0–487.0) or a secondary diagnosis of pneumonia with a primary diagnosis of respiratory failure (ICD-9 code 518.81) or sepsis (ICD-9 code 0.38xx).
- d. Had at least one dose of antimicrobial therapy within the first 48 hours of admission.

- e. Present at three or more VA outpatient clinic visits in the year preceding admission.
- f. Received at least 1 outpatient medication from a VA pharmacy within 90 days prior to admission, ensuring the patients were receiving medications from VA pharmacies.
- g. For patients who had multiple pneumonia-related hospitalizations during the study period, we included only their first hospitalization. We also excluded those with an acquired immune deficiency syndrome (AIDS)-defining illness.

Data Sources and Definitions

We controlled for race and ethnicity categories (White, Black, Hispanic, and Asian/American Indian/other/unknown), smoking cessation/tobacco use (ICD 9 codes 305.1 and V15.82, smoking cessation clinic use, and/or use of medications for the treatment of nicotine dependence such as Zyban, nicotine replacement, or varenicline), alcohol abuse (ICD-9 codes 291, 303, 305.0), and illicit drug use (ICD-9 codes 292, 304, 305, excluding 305.0-.1). We identified preexisting comorbidities utilizing the Charlson-Deyo comorbidity system¹¹ and used VA priority status as a marker for socioeconomic status¹². We defined cirrhosis using ICD-9 codes from the Charlson-Deyo Comorbidity Index for both cirrhosis (ICD-9: 571.2, 571.4, 571.5, 571.6) and hepatic failure (ICD-9: 572.2–572.8, 456.0–456.21). These ICD-9 codes have been previously validated in both VA¹³ and non-VA settings¹⁴. Priority status is defined as either (a) at least 50% disabled by a military service-connected condition (priority group 1), (b) up to 40% service-connected disability or special wartime cohorts such as Operation Enduring Freedom/Operation Iraqi Freedom (priority groups 2–6), or (c) higher income patients with no service-connected injuries (priority groups 7–8). Outpatient medications dispensed within 90-days of admission were grouped as previously described¹⁵. Severity of illness was defined as requiring admission to the intensive care unit (ICU), use of vasopressors, and/or receipt of invasive mechanical ventilation.

Outcomes

The primary outcome of this study were all-cause mortality within 90-days of admission. Our secondary outcomes were all-cause rehospitalization within 90-days, and ICU admission during the first 48 hours. Date of death was identified using the VA Vital Status file, which has an accuracy of approximately 98% in reporting mortality¹⁶.

Statistical Analysis

Bivariate statistics were used to test the association of socio-demographic and clinical characteristics with the primary outcomes. Categorical variables were analyzed using the chi-square test and continuous variables were analyzed using Student's t-test. We used generalized linear mixed effect regression models ("multi-level models") to examine the association of cirrhosis on the outcomes of interests with the admitting hospital as a random effect after controlling for potential confounders, including sociodemographics (age, race, gender, marital status, and priority status), physical comorbid conditions based on a Charlson comorbidity score, psychiatric comorbid conditions¹⁷, prior outpatient health care

utilization, severity of illness, and medications received within the 90-days prior to the admission (Tables 1 and 2).

To analyze time to event for 90-day mortality for patients with cirrhosis, we used Kaplan-Meier plots to display the survivor functions and log rank test to determine statistical significance.

All analyses were performed using STATA 15 (College Station, Texas). Statistical significance was set as a two-tailed p-value 0.05.

RESULTS

There was a total of 103,997 patients who met the inclusion criteria. Overall, the mean age of the patients was 77.8 (SD 7.4), 98.3% were male, 51.8% were married, 81.1% were white, and 6.4% were Hispanic. In this cohort, 24,103 (23.2%) died within 90 days. A total of 1,246 (1.2%) of patients in the cohort met the defined criteria for cirrhosis (Table 1). Mortality at 90-days was 34.5% in those with cirrhosis versus 23.0% in those without ($p < 0.0001$).

Table 1 shows the results of the univariate analysis for those patients with cirrhosis versus those with no cirrhosis. Patients with cirrhosis were significantly more likely to have diabetes, cancer, and abuse alcohol. Table 2 shows the results of the univariate analysis for medications received prior to admission.

Outcomes

In the univariate analysis, 90-day mortality for those with cirrhosis was 34.5%, compared to 23.0% for those with no cirrhosis ($p < 0.0001$). Of those with cirrhosis 31.4% were rehospitalized within 90-days, compared to 25.0% of those without cirrhosis ($p < 0.0001$). ICU admission was 23.3% for those with cirrhosis and 17.2% for those without cirrhosis ($p < 0.0001$).

Figure 1 is a Kaplan-Meier graph that demonstrates that there is significantly lower survival for patients with a history of cirrhosis (log rank test $p < 0.0001$).

After adjusting for potential confounders (Table 3) we found cirrhosis to be associated with a significantly higher mortality (OR 1.79, 95% CI, 1.57–2.04). Cirrhosis was also associated with a significantly higher rehospitalization rate (OR 1.30, 95% CI, 1.16–1.47) within 90-days. Cirrhosis was not associated with a higher risk of ICU admission in this population (OR 1.00, 95% CI, 0.83–1.19).

DISCUSSION

Our analysis showed that a history cirrhosis was associated with significantly increased mortality and rehospitalization within 90-days in older patients hospitalized with community-acquired pneumonia after adjusting for confounders. We did not find a significant association with ICU admission for those with cirrhosis.

One strength of our study was our ability to look at patients with less severe cirrhosis, something not seen in other studies. Our inclusion of patients with less severe cirrhosis, due to the use of ICD-9 codes and desire to define cirrhosis broadly, allowed us to increase the sample size of patients well beyond other studies. We believe our results suggest the need for clinicians to consider the mortality and rehospitalization risk for patients with cirrhosis when treating for pneumonia. While the recommended antibiotic treatment does not differ in patients with cirrhosis, delayed antibiotic treatment¹⁸ has been associated with an increased mortality.

The most common infections associated with cirrhosis are spontaneous bacterial peritonitis, urinary tract infections, and pneumonia¹⁹. While spontaneous bacterial peritonitis has been well studied, there is a lack of studies on the outcome of patients with cirrhosis who contract pneumonia. The incidence of pneumonia has been estimated to be between 13%–20% in cirrhotic patients^{20–22}. Our results support previous studies which found pneumonia associated mortality rates within 90-days as high as 51% in patients with cirrhosis^{23,24}. These studies had sample sizes <100 for pneumonia specifically, however, which suggested the need for a study with a much larger sample size.

The mechanism behind the increased bacterial infection rate in cirrhosis has been well studied. The organisms causing pneumonia in patients with cirrhosis are no different than for patients without cirrhosis, suggesting a similar pathogenesis²⁴. The increased mortality, however, may be due to a reduced immune system clearance of bacteria. There are multiple defects, including impairment of bacterial clearance by macrophages, complement system deficiencies, altered neutrophil phagocytosis, and increased levels of pro-inflammatory cytokines, all of which lead to an increased pneumonia incidence^{19,25}. In addition, in our study patients with cirrhosis were slightly less likely to receive guideline-concordant antibiotics, which has been demonstrated to be associated with increased mortality²⁶.

Our results supported previous research by Hung et al., who performed a retrospective cohort study using Taiwan's National Health Insurance Program and found a significant increase in both 30 (Hazard ratio [HR] 2.95, 95% CI, 2.05–4.25) and 90-day (HR 2.57, 95% CI 1.93–3.42) mortality for cirrhotic patients with ascites who developed pneumonia. Their cohort's 90-day mortality of 51.0% was larger than our finding of 34.5%, however, they looked at patients who had cirrhosis with ascites, whereas our cohort was healthier. Other differences were that our population was older, and we used more comorbidities in our model.

Viasus et al. looked at clinical features and outcomes in patients with severe cirrhosis with pneumonia in an observational analysis²³. Their findings of increased 30-day mortality in patients with cirrhosis (14.4% vs 7.4%) showed a significant association despite only having 90 patients from one institution with both cirrhosis and pneumonia. In addition, they found an association between mortality and ICU admission in patients with cirrhosis and pneumonia however they were unable to perform multivariable regression due to the small sample size. We were however, able to perform multivariable regression analysis and adjust for potential confounders in our analysis because of our larger sample size.

Our study had several limitations. The VA primarily treats men, limiting the generalizability of our results to women. Future studies should examine both females and different age groups. In addition, the study database was restricted to those > 65 years of age so we are unable to comment on how younger patients with cirrhosis would do. Additionally, we were unable to identify those who were receiving hospice care, which we felt could have affected the outcome of ICU admission. We believe our results could reflect patients with cirrhosis and pneumonia choosing hospice care instead of the ICU, but further studies need to be done to assess this relationship. When defining cirrhosis, we acknowledge that all cirrhosis is not the same, and we did not have Child-Pugh or MELD scores available to help further classify disease severity. We are also unable to identify the specific cause(s) of cirrhosis in these patients. In addition, we did not have all of the information needed to compute severity of illness such as the Acute Physiology and Chronic Health Evaluation (APACHE II, Pneumonia Severity Index (PSI), or similar scores. Also, we were unable to examine rehospitalizations that occur outside of the VA nor examine the specific causes of readmission. In addition, as with most retrospective studies of pneumonia we are unable to examine the impact of bacterial etiology on outcomes. Finally, we cannot assert causality between the exposure and the outcome, however, we believe that our findings are still important to consider when treating patients with pneumonia.

Patients with cirrhosis are at increased risk of developing bacterial infections due to immune system dysfunction. Treating pneumonia and cirrhosis presents a clinical challenge, and it is essential to treat patients promptly. Patient care continues beyond admission and initial treatment, as patients have a significantly increased mortality rate up to 90 days after their initial admission. Additionally, there is a significantly higher rate of readmission within 90 days for these patients. We conclude that patients admitted with community-acquired pneumonia, who have cirrhosis as a comorbidity, have a higher mortality and readmission risk. This association should be further studied to assess the effects of early admission to a higher level of care, such as step down or ICU, or other interventions that may impact patient outcomes in this cohort.

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Figure 1:
Survival curves demonstrating a statistically significant ($p < 0.0001$) increase in mortality in patients with a history of cirrhosis

Table 1:

Univariate Demographics and Clinical Characteristics by Study Group

Variables	No Cirrhosis N, % (N = 102,751)	Cirrhosis N, % (N = 1,246)	P value
Age, mean (standard deviation[SD])	77.9 (7.4)	73.8 (6.7)	< 0.0001
Men	100959 (98.3)	1232 (98.9)	0.1
Race			
White	83372 (81.1)	1000 (80.3)	0.3
Black	11590 (11.3)	151 (12.12)	
Other/unknown	7789 (7.6)	95 (7.1)	
Hispanic	6485 (6.3)	128 (10.3)	<0.001
Married	53174 (51.8)	570 (45.8)	< 0.0001
Smoker	43154 (42)	637 (51.1)	< 0.0001
Socioeconomic Proxy			
VA Priority group 1	21648 (21.1)	306 (24.6)	
VA Priority group 2–6	70738 (68.9)	838 (67.3)	
VA Priority group 7–8	10365 (10.1)	102 (8.2)	
ICU admission	17650 (17.2)	290 (23.3)	< 0.0001
Guideline concordant antibiotics	83015 (80.8)	946 (76.0)	< 0.0001
Nursing home residence	1710 (1.7)	25 (2.0)	0.3
Mechanical Ventilation	6875 (6.7)	147 (11.8)	< 0.0001
Vasopressor use	5264 (5.1)	123 (9.9)	< 0.0001
Comorbid conditions			
Myocardial Infarction	7750 (7.5)	82 (6.6)	0.2
Heart Failure	27139 (26.4)	374(30.0)	0.004
Peripheral vascular disease	17363 (16.9)	222 (17.8)	0.4
Cerebrovascular disease	19731 (19.2)	238 (19.1)	0.928
Chronic obstructive pulmonary disease	54049 (52.6)	654 (52.5)	0.936
Rheumatologic disease	3008 (2.9)	37 (3.0)	0.9
Peptic ulcer disease	3146 (3.1)	85 (6.8)	< 0.0001
Diabetes	35789 (34.8)	556 (44.6)	< 0.0001
Diabetes with complications	11336 (11.0)	204 (16.4)	< 0.0001
Hemiplegia	1558 (1.5)	18 (1.4)	0.8
Renal disease	17740 (17.3)	276 (22.2)	< 0.0001
Cancer	26112 (25.4)	385 (30.8)	< 0.0001
Metastatic cancer	4582 (4.5)	73 (5.9)	0.02
HIV Positive (No AIDS)	83 (0.1)	9 (0.7)	< 0.0001
Alcohol abuse	4709 (4.6)	312 (25.0)	< 0.0001
Illicit drug abuse	1504 (1.5)	56 (4.5)	< 0.0001
Depression	19163 (18.7)	291 (23.4)	< 0.0001
Anxiety	8681 (8.5)	104 (8.4)	0.9
Bipolar	2429 (2.4)	31 (2.5)	0.8

Variables	No Cirrhosis N, %	Cirrhosis N, %	P value
	(N = 102,751)	(N = 1,246)	
Schizophrenia	2869 (2.8)	21 (1.7)	0.02
PTSD	5228 (5.1)	81 (6.5)	0.02

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Table 2:

Prior Outpatient Medication Used by History of Cirrhosis

Medications Use (count [*])	No Cirrhosis N= 102,751 Mean (SD)	Cirrhosis N= 1,246 Mean (SD)	P-value
Statins, count	0.36 (0.48)	0.19 (0.40)	<0.0001
Anti-arrhythmics, count	0.03 (0.18)	0.02 (0.13)	0.002
Calcium channel blockers, count	0.26 (0.45)	0.22 (0.44)	0.005
Diuretics, count	0.78 (0.96)	0.96 (0.97)	<0.0001
Diabetic medications, count	0.14 (0.39)	0.15 (0.40)	0.49
Other Lipid lowering agents, count	0.47 (0.22)	0.03 (0.18)	0.02
Other anti-hypertensives, count	0.23 (0.46)	0.19 (0.42)	0.005
Antianginal medications, count	0.19 (0.46)	0.14 (0.41)	<0.0001
Bronchodilators, count	0.48 (0.77)	0.43 (0.72)	0.02
Beta Blockers, count	0.36 (0.50)	0.42 (0.52)	<0.0001
Prior outpatient antibiotics (n;%) [#]	27,132; 26.4%	348, 27.9%	0.23

* The number of medications in this class that the patient received within the last 90-days.

[#] Dichotomized by whether they received any prior antibiotics within the last 90-days.

Table 3:

Results of Multivariable Regression models

Outcome	Adjusted Odds Ratio	95% Confidence Interval
90-day mortality	1.79	1.57–2.04
Rehospitalization within 90 days	1.30	1.16–1.47
ICU admission	1.00	0.83–1.19