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ORIGINAL RESEARCH

Outcomes of Adult Patients Hospitalized with Community-Acquired Pneumonia with Liver Disease or Cirrhosis

Bibodh Jung Karki[1], MD; Sravan K. Ponnekanti[1], MD; Vidyulata Salunkhe[1], MD, MPH; Nishita Tripathi[1], MD; Mahder A. Tella[1], MPH; Stephen P. 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

*bibodhjung.karki@louisville.edu

Abstract

Introduction: Liver disease and cirrhosis are common causes of mortality worldwide. Community-acquired pneumonia is recognized as a significant cause of morbidity and mortality in this population of adults. There is a lack of data regarding outcomes or prognosis in patients with liver dysfunction who develop CAP. The objective of this study was to evaluate the clinical characteristics, incidence, and outcomes of hospitalized patients with CAP and liver disease.

Methods: This was a secondary analysis of the University of Louisville Pneumonia Study, which was a prospective population-based cohort study of adults hospitalized with community-acquired pneumonia. All patients were divided into three groups: 1) patients without liver disease, 2) patients with liver disease, and 3) patients with cirrhosis. Short and long-term outcomes were analyzed.

Results: Among 9201 patients, 8566 patients did not have liver disease, 515 patients had liver disease, and 120 patients had cirrhosis. The median age of patients with liver disease or cirrhosis was approximately 10 years younger than the median age of overall population, and a higher proportion was admitted directly to the ICU. Compared to patients without liver disease, we found no significant difference in time to clinical stability for patients with liver diseases (aHR: 1.01, 95% CI: 0.92 – 1.12; p=0.790), or cirrhosis (aHR: 0.85, 95% CI: 0.69 – 1.05; p=0.127). There were also no differences in median length of stay (LOS) between any two groups. Patients with cirrhosis had 35% higher risk of death at any time compared to patients with no liver disease (aHR: 1.35, 95% CI: 1.00-1.82; p=0.049), but did not have significantly increased risk compared to patients with liver disease (aHR: 1.37, 95% CI: 0.97 – 1.93, p=0.070).

Conclusions: In this study of hospitalized adults with CAP, patients with cirrhosis had a significantly higher risk of death compared to patients without liver disease.

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Introduction

Community-acquired pneumonia (CAP) is the leading cause of death among infectious diseases in adults with the majority of the deaths occurring in hospitalized patients. [1,2] Clinical outcomes in patients with CAP are associated with various independent risk factors, including the severity of clinical presentation, age of the patient, the presence of comorbidities, and specific pathogens. [3] Among the comorbidities, chronic liver disease is one of the risk factors for CAP. [4] Cirrhosis is a major cause of immunodeficiency; the coexistence of this disease in the pneumococcal pneumonia patient increases the mortality significantly, even with the appropriate intensive care support and antibiotic treatment. [5-7]

Patients with abnormal liver function tests are significantly more likely to die from an infectious disease or to stay in the hospital for a prolonged period. [8] The intrapulmonary cellular defense and killing of bacteria is decreased in liver disease, as evidenced by animal studies in pneumococcal pneumonia, and cirrhosis was evaluated to identify defects in pulmonary defenses in cirrhotic hosts. [9]

Although various studies have shown that clinical outcomes of infections, such as LOS and mortality, may be different in patients with or without liver diseases, to our knowledge no study has specifically evaluated CAP in this setting. As a result, outcomes of hospitalized CAP patients with liver disease are unknown. The objective of this study was to assess the outcomes of patients hospitalized for CAP who also had liver disease in Louisville, Kentucky.

Methods

Study Design and Study Population

This was a secondary analysis of data from the University of Louisville Pneumonia Study, a prospective population-based cohort study of all hospitalized adults with CAP who were residents in the city of Louisville, Kentucky, from June 1, 2014 to May 31, 2016 and from October 1, 2016 to March 31, 2017 [10]. The study was approved by the Institutional Review Board (IRB) at the University of Louisville Human Subjects Research Protection Office (IRB 11.0613), and by the research offices at each participating hospital. All hospitalized patients ≥18 years of age in Louisville underwent screening for participation in the study. Those who were enrolled were consented.

Inclusion Criteria

The diagnosis of CAP required three criteria: (1) presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a board-certified radiologist's reading; (2) at least one of the following features: (i) new or increased cough, (ii) fever >37.8°C (100 F) or hypothermia <35.6°C (96 F), (iii) changes in WBC (leukocytosis >11,000 cells/mm^3, left shift > 10% band forms/ml, or leukopenia < 4,000 cells/mm^3; and (3) no alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2.

A patient was considered to have liver disease if it was stated in the electronic medical record of the patient including the notes for the emergency room, history and physical, progress, consultations and discharge summary. If a patient was found to have liver disease, then a history of cirrhosis was also sought. All patients were divided into three groups: 1) patients without liver disease, 2) patients with liver disease, and 3) patients with cirrhosis. (**Figure 1**)

Study Variables

Demographic variables were age, sex, race, and nursing home residency. Risk factors for CAP recorded were alcohol intake, chronic obstructive pulmonary disease, diabetes mellitus, smoking status, neoplastic disease, prior hospitalization, coronary artery disease, essential hypertension, hyperlipidemia, prior myocardial infarction, and intravenous drug use. Vitals signs and laboratory values were recorded. Severity of illness determinants for CAP included ventilatory support, vasopressors, intensive care, pneumonia severity index risk class IV or V, and altered mental status.

Outcomes

Time to clinical stability was defined as being clinically stable the day that the following four criteria were met: a) improved cough and shortness of breath, b) lack of fever for at least 8 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 7 days of hospitalization to determine the day when clinical stability was reached. Patients who were not clinically stable by day 7 were censored at day 8. Length of stay (LOS) 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 in an effort to capture LOS data related only to bacterial CAP. Mortality was defined as death by any cause during hospitalization within 1 year.

Statistical Analysis

Descriptive statistics were performed. Categorical data was summarized as frequency and percent, and continuous data was summarized as median and interquartile range (IQR). Chi-squared tests of independence were performed to test for differences in baseline descriptive statistics for categorical data, and Kruskal-Wallis Rank Sum tests were performed to test for differences for continuous data. Clinical outcomes were assessed via stratified Cox proportional hazards regression adjusting for age, sex, race, and pneumonia severity risk class, with adjusted hazard ratios (aHR) reported.

Results

There were 9,201 unique patients during the study period and included in the analysis: 8,566 patients without liver disease, 515 patients with liver disease, and 120 patients with cirrhosis. (**Figure 1**) Patient characteristics, risk factors, laboratory values and severity of CAP are shown in **Table 1.** Among the three groups, patient with liver disease or cirrhosis were younger, male, and not a resident of a nursing home compared to those without liver disease. (**Table 1**) Among the cirrhosis group, 32% were alcoholic.

Table 1. Patient characteristics, risk factors, laboratory values and severity of CAP are shown.

Demographics	**LD-**	**LD+**	**Cirrhosis**	**P-value**
Total N	8566	515	120	
Age (median [IQR])	69 [57, 80]	59 [51, 67]	60 [55, 69]	<0.001
Sex: Male (%)	3888 (45)	306 (59)	71 (59)	<0.001
Race: Black (%)	1632 (19)	112 (22)	15 (12)	0.057
Nursing Home Resident (%)	1080 (13)	34 (7)	8 (7)	<0.001
Risk Factors				
Total N	8566	515	120	
Alcoholic (%)	413 (5)	78 (15)	38 (32)	<0.001
COPD (%)	3970 (46)	246 (48)	68 (57)	0.068
Diabetes (%)	2780 (32)	154 (30)	52 (43)	0.018
Neoplastic disease (%)	1132 (13)	90 (17)	22 (18)	0.007
Current Smoker (%)	2551 (30)	263 (51)	55 (46)	<0.001
Hospitalized in the Prior 90 Days (%)	2122 (25)	142 (28)	52 (43)	<0.001
Chronic Dialysis in the Prior 30 Days (%)	320 (4)	32 (6)	3 (2)	0.013
Coronary artery disease (%)	2597 (30)	131 (25)	35 (29)	0.062
Essential arterial hypertension (%)	6008 (70)	330 (64)	73 (61)	0.002
Hyperlipidemia (%)	3869 (45)	168 (33)	39 (32)	<0.001
Prior myocardial infarction (%)	1103 (13)	57 (11)	21 (18)	0.151
IV Drug Use (%)	90 (1)	50 (10)	8 (7)	<0.001
Labs				
Total N	8566	515	120	
INR (International Normalized Ratio) (median [IQR])	1 [1, 1]	1 [1, 1]	1 [1, 2]	<0.001
Serum sodium (mEq/L) (median [IQR])	137 [134, 140]	136 [133, 140]	135 [132, 138]	<0.001
Serum creatinine (mg/dL) (median [IQR])	1 [1, 1]	1 [1, 2]	1 [1, 2]	0.656
Albumin (g/dL) (median [IQR])	4 [3, 4]	3 [3, 4]	3 [2, 4]	<0.001
Aspartate transaminase (AST) (units/L) (median [IQR])	26 [20, 38]	39 [25, 69]	43 [28, 70]	<0.001
Alanine transferase (ALT) (units/L) (median [IQR])	24 [16, 35]	33 [19, 56]	29 [20, 47]	<0.001
Bilirubin (mg/dL) (median [IQR])	1 [0, 1]	1 [0, 1]	1 [1, 2]	<0.001
Severity				
Total N	8566	515	120	
Ventilatory Support (%)	1088 (13)	79 (15)	22 (18)	0.043
Vasopressors (%)	231 (3)	26 (5)	10 (8)	<0.001
Direct Admission to the ICU (%)	1386 (16)	119 (23)	32 (27)	<0.001
PSI (median [IQR])	100 [73, 128]	117 [88, 146]	124 [97, 154]	<0.001
PSI IV, V (%)	5031 (59)	367 (71)	101 (84)	<0.001
Hypotension (%)	4849 (57)	250 (49)	71 (59)	0.001

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; PSI, pneumonia severity index

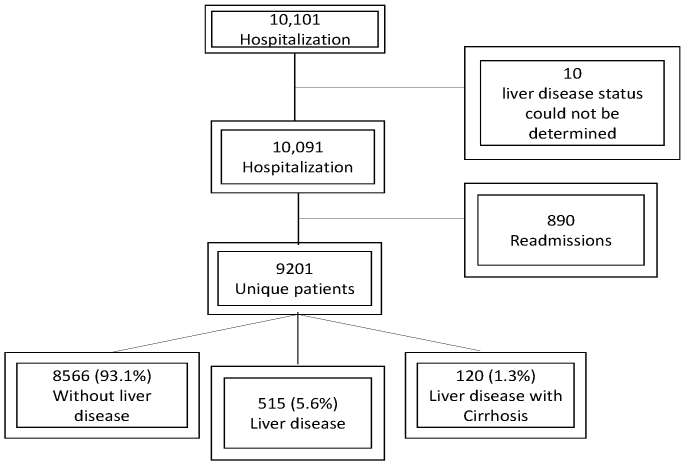

Figure 1. Flow chart for the three groups of the study population are shown.

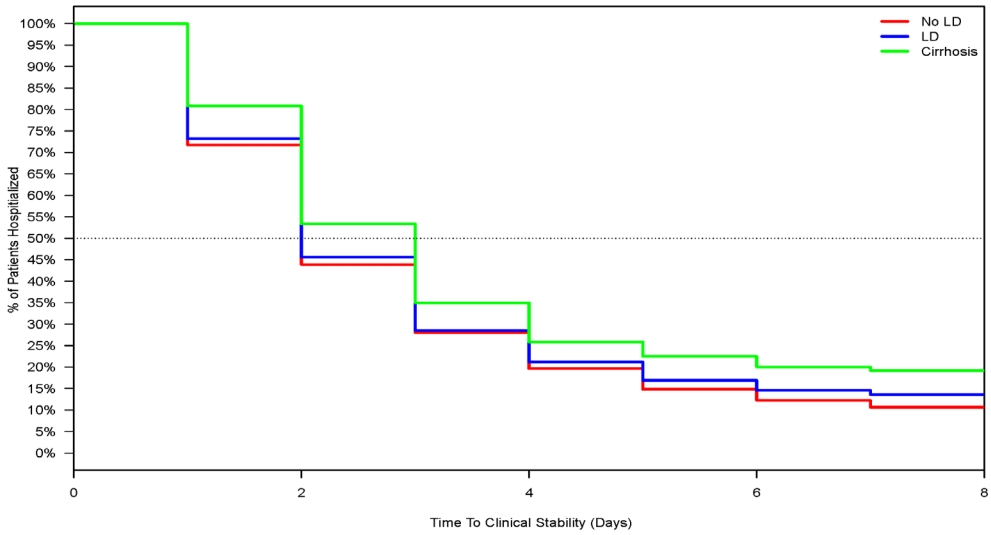

Figure 2. Kaplan-Meier curves for time to clinical stability for study population are shown.

Time to Clinical Stability

The median time to clinical stability for patients without liver disease was 2 days (IQR: 1-4 days), for patients with liver disease it was also 2 days (IQR: 1-4), and for patients with liver disease and cirrhosis it was 3 days (IQR: 2-5). Compared to patients without liver disease, we found no significant difference in time to clinical stability for patients with liver disease (aHR: 1.01, 95% CI: 0.92 – 1.12; p=0.790), or cirrhosis (aHR: 0.85, 95% CI: 0.69 – 1.05; p=0.127). There was also no difference between patients with liver disease with or without cirrhosis (aHR: 0.84, 95% CI: 0.67 – 1.05, p=0.130). (**Figure 2**)

Length of Stay

The median LOS for patients without liver disease was 5 days (IQR: 3-8 days), for patients with liver disease it was 5 days (IQR: 3-10 days), and for patients with liver disease and cirrhosis it was 6 days (IQR: 3-11 days). There were no differences in median LOS between any two groups. (**Table 2**)

Mortality

All-cause 30-day mortality for patients without liver disease was 11% (n=962), for patients with liver diseases it was 12% (n=59) and for patients with cirrhosis it was 22% (n=25). All-cause 1-year mortality for patients without liver dis-

Table 2. The length of stay for patients with CAP without liver disease, with liver disease and with cirrhosis

Comparison Groups	Adjusted Hazard Ratio	CI	*P*-Value
No LD vs LD	0.97	0.88 – 1.08	0.626
LD vs Cirrhosis	0.90	0.71 – 1.13	0.361
No LD vs Cirrhosis	0.87	0.71 – 1.08	0.216

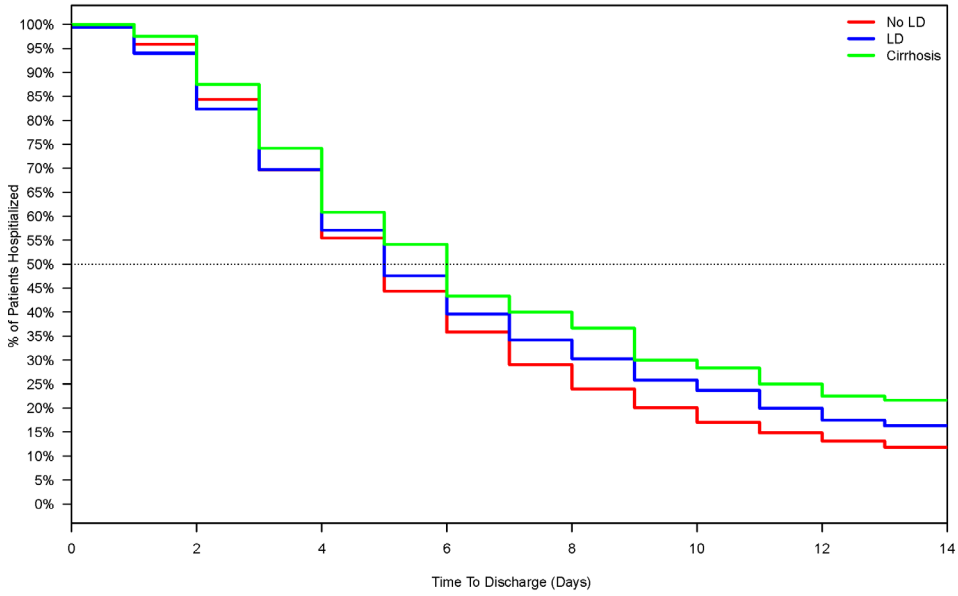

Figure 3. Kaplan Meier curves for Length of stay for study population are shown.

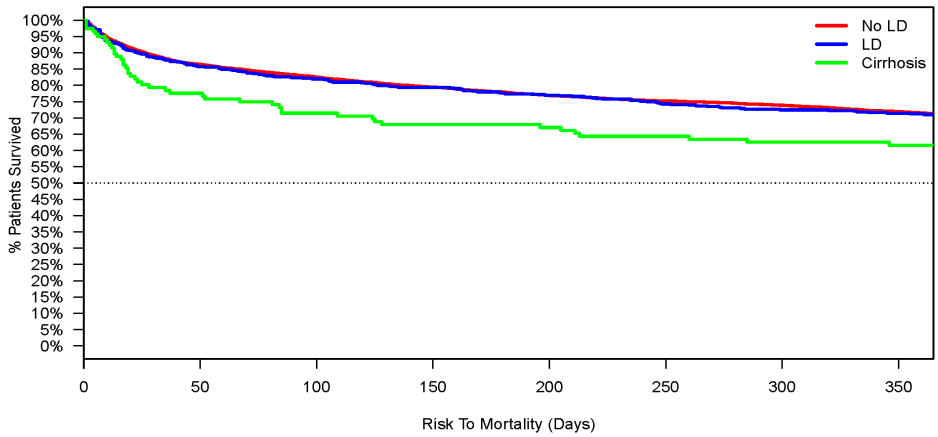

Figure 4. Survival curves for study population are shown.

ease was 30% (n=2405), for patients with liver diseases it was 29% (n=145) and for patients cirrhosis it was 40% (n=45). The absolute increased risk of death with cirrhosis compared to patients with no liver disease was 10%, but if adjusted it was 35% (aHR: 1.35, 95% CI: 1.01 – 1.82; p=0.049). Patients with cirrhosis did not have significantly increased risk compared to patients with liver disease (aHR: 1.37, 95% CI: 0.97 – 1.93, p=0.070). (**Figure 4**)

Discussion

In this study of hospitalized adults with CAP, patients with cirrhosis had a statistically significantly higher risk of death compared to patients without liver disease. Despite the mortality of patients without liver disease being nearly equal to those with liver disease, there was not a statistical difference of proportion between those with liver disease and those with cirrhosis. Regarding time to clinical stability and LOS there was no significant difference between any two groups.

One important implication of the study is that patients with cirrhosis had a higher mortality rate than those without liver disease despite being nearly a decade younger (median age 69 years vs 60 years). This implies patients with cirrhosis need more intense treatment than the patients with or without liver disease.

Cirrhosis is an immunocompromising state. The mechanism of increased pneumonia in such patients has been studied. The worse outcome in such patients with CAP could be explained by the reduced immune system clearance of pathogens at various levels, including impaired bacterial clearance by macrophages, complement deficiencies, altered neutrophilic killing, and increased level of procytokines. [7] Neutrophil-mediated killing of the type 3 pneumococcal strain affects the lungs. Levels of complement C3 and lysozyme were also decreased. Pneumolysin, a pore forming toxin of Streptococcus pneumoniae, has been observed to cause damage in the initial immune response that is already decreased with liver dysfunction. Hepatic signal transducer and activator of transcription 3 (Hepatic STAT3), a protein related in the host defense, is also decreased in liver disease and this predisposes to sepsis in patients with CAP. [11]

Our study supported the previous research by Zachary et al [7] who performed a retrospective cohort study of hospitalized patients with CAP at several Departments of Veterans Affairs (VA) hospitals and found that cirrhosis was associated with a significantly increased odds of 90-day mortality (OR 1.79, 95% CI, 1.57-2.04). Most of their patients were men and included patients greater than 65 years of age. Another study by Hung et al [12] described high 30-day mortality (HR 2.05, 95% CI, 2.05-4.25, p<0.001) and 90-day mortality (HR 2.57, 95% CI, 1.93-3.42, p<0.001) among patients with pneumonia and cirrhosis.

Our study is not without limitations. Except for cirrhosis, the present study did not distinguish among the different types of liver diseases, which may have varying outcomes associated with each. Our study also did not categorize cirrhosis to its four different stages preventing any difference in outcomes from being calculated, but the number with each category would have been quite small for statistical analysis.

One strength of our study was that the sample size allowed the population to be divided into three relevant groups. Other studies of outcomes in patients with CAP only compared patients without liver disease to patients with cirrhosis. No study included patients with liver disease without cirrhosis. In addition, we were able to define the number of unique patients hospitalized with CAP using patients' social security number and date of birth.
Our study has moderate generalizability to the US population because it includes a large sample size of an entire city. Moreover, many of the population characteristics within Louisville are similar to that of the US population.

In conclusion, the presence of cirrhosis in a patient hospitalized with CAP can increase the mortality, but does not significantly affect the time to clinical stability or LOS. Future research regarding outcomes in patients hospitalized with CAP with particular liver disease is warranted.

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