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Ten-year trends and prediction model of 30-day inpatient mortality for alcoholic hepatitis in the United States

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Abstract

Background Alcoholic hepatitis (AH) results in significant morbidity, mortality and healthcare burden. We aimed to evaluate the temporal trends of AH hospitalizations in the last decade and to devise a mortality scoring system for risk stratification.

Methods National Inpatient Sample (NIS) databases from 2009-2019 were used to identify AH hospitalizations. Outcomes of interest included temporal trend analysis of length of stay (LOS), mean inpatient cost (MIC), mortality, and mortality predictors. A mortality scoring system was derived using multivariate Cox regression and validated using receiver operating characteristic curves.

Results There was an increase in total AH hospitalizations, from 67,070 in 2009 to 125,540 in 2019 (P=0.004). The inpatient mortality increased from 2.48% in 2009 to 3.78% in 2019 (P=0.008). The MIC was $31,189 in 2009 and $62,229 in 2019 (P<0.001). A trend for LOS was not significant. Ten variables were selected for incorporation into a risk score, including anemia, age >60 years, female sex, mechanical ventilation, vasopressor use, spontaneous bacterial peritonitis, hepatorenal syndrome, acute renal failure, coagulopathy (thrombocytopenia), and hepatic encephalopathy. The score has a maximum of eight points, and the cutoff for predicting mortality was set as 4 points. The area under the curve (AUC) of the derivation cohort was 0.8766 (95% confidence interval [CI] 0.865-0.888) and AUC 0.862 (95%CI 0.855-0.868) for a 30-day period.

Conclusions There has been an increase in AH hospitalizations and mortality in the last decade. The Tahira score provides an easy objective method to estimate inpatient 30-day mortality for AH hospitalizations.

Keywords Alcoholic hepatitis, healthcare costs, national inpatient sample, NIS, mortality predictors

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Conflict of Interest: None

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Introduction

Chronic alcohol use can result in acute liver inflammation, resulting in alcoholic hepatitis (AH). The mortality of AH varies depending upon the severity of the disease, with severe cases carrying mortality up to 30% at 30 days [1-3]. The prevalence of AH is not reported widely in the current literature. However, some studies estimate approximately 30% of chronic alcohol drinkers will develop AH [4,5]. One in 5 patients with AH will develop alcoholic cirrhosis annually, and these patients have a 70% risk of developing liver cirrhosis in their lifetime [4,5]. AH places a significant burden on the healthcare system in the United States (US), with healthcare expenditures on the inpatient AH population being comparable to those on chronic liver disease [1,6,7]. There are epidemiological data for the last decade regarding the incidence of AH in the US [1]. While the current literature on various chronic liver diseases is abundant, data on AH are limited. It was previously reported that a

rise in AH hospitalizations could be secondary to increased alcohol consumption, suggesting that AH will continue to be a significant healthcare problem in the US [8-10]. A contributing factor is a shift in drinking age towards the younger population [11]. There are limited therapeutic options for patients with severe AH, resulting in higher mortality in the last decade [1]. Given the insufficient data on AH hospitalizations in the current decade, we aimed to describe the demographic characteristics and magnitude of the AH burden on the US healthcare system through analyzing inpatient mortality, healthcare costs, and length of stay (LOS). We used the National Inpatient Sample (NIS) from 2009-2019 to report 10-year trends for hospitalized AH patients in the US and their associated mortality. Given the paucity of a specific mortality scoring system to predict AH-associated inpatient mortality, we also aimed to develop an objective severity score using a large national database.

Materials and methods

Design and data source

This was a retrospective study conducted using the NIS database to evaluate hospitalizations for AH in the US from January 1, 2009, to December 31, 2019 [12]. Inclusion criteria included patients with a primary diagnosis of AH. Patients were excluded if they were aged less than 21 years, or had a history of viral hepatitis infection or nonalcoholic liver disease. The NIS database was developed as a stratified probability sample to represent all nonfederal hospitals in the US. During the designated study period, NIS used the International Classification of Diseases (ICD) 9 (prior to September 2015) and 10 (after October 2015) coding systems. Detailed information on the design and sampling methods of NIS is available at https://www.hcup-us.ahrq.gov.

Outcome measures

The NIS database was analyzed for hospitalizations with a primary principal discharge diagnosis of AH, using ICD-9 code (571.1) and ICD-10 code (K701.0, K701.1), from 2009-2019. The outcomes of interest included demographic characteristics, mean LOS, mean inpatient cost (MIC), and mortality trends. In addition, we determined independent predictors that had a hazard ratio with a >10% increase and used them to develop a risk scoring system for 30-day inpatient mortality for AH hospitalizations. This was used to devise a mortality scoring system.

Statistical analysis

Analyses were performed using STATA version 16.0 software. Hierarchal multivariate linear and logistic regression models were built based on univariate analysis to adjust for confounding variables. Only variables associated with the outcome of interests on univariate regression analysis at P<0.2, or known potential confounders despite a P-value indicating no significance, were used in the multivariate regression. Our analysis had 0.05 as the threshold for statistical significance and all P-values were 2-sided. All outcomes were adjusted for patient- and hospital-level characteristics, including age, race, sex, insurance type, residential region, Elixhauser Comorbidity Index score, hospital teaching status, and hospital size confounders (such as LOS and inpatient hospital costs), as in prior studies [13-15]. Standard errors were reported as ±SE for continuous outcomes. Variables such as age, sex, acute renal failure and vasopressor use were included in a hierarchal multivariate Cox regression analysis. A score of one was assigned to these variables, and the mortality rate for aggregate scores was obtained. We also used the receiver operating characteristics (ROC) curve to assess the model's performance in terms of the area under the curve (AUC) [16]. The models' prediction performance was assessed using the validation cohort. Any difference between models was compared using a standard nonparametric test (Delong Test), with statistical significance when P<0.001 [17]. The regression models were also tested for over-dispersion using a Pearson goodness-of-fit test before our analysis, and these models were not over dispersed. Since the NIS contains de-identified patient data, as per guidelines it was deemed exempt from review by the institutional review board. Patient consent was also waived in view of the public availability of data. The NIS has been used previously for other mortality scoring systems [18].

Results

There was an increase in the total number of AH hospitalizations from 67,070 in 2009 to 125,540 in 2019 (P=0.04) (Fig. 1). The mean age ranged from 47.5±0.1 to 48.2±0.15 years, with a statistically significantly declining trend over the study period (P<0.001) (Table 1). Males had a higher proportion of AH hospitalizations; however, females showed an increasing rate of hospitalizations, from 29.1% in 2009 to 34.1% in 2019 (P<0.001). In addition, racial disparities were seen for AH hospitalizations, with Whites being the predominant race (Table 1).

The adjusted trend analysis revealed that the mean LOS for AH hospitalizations was 5.4±0.09 days in 2009 and 6.1±0.05 in 2019, nearing significance (P=0.07). Subgroup analysis revealed that the patients who were mechanically ventilated on admission (in the intensive care unit [ICU]) had a significant increase in LOS for AH hospitalizations, from 12.7±0.05 days in 2009 to 15.1±0.04 in 2019 (P<0.001). Non-ICU admissions had a non-significant rise in LOS, from 5.1±0.01 days in 2009 to 5.6±0.01 in 2019, (P=0.09) (Supplementary Fig. 1). The adjusted trend analysis revealed that the MIC for these hospitalizations was $31,189±1049 in 2009 and $62,229±1197 in 2019 (P<0.001). Subgroup analysis

revealed that ICU patients had a significant rise in MIC from $126,780±1957 in 2009 to $233,576±329 in 2019 (P<0.001). Non-ICU admissions also showed a significant rise in MIC, from $26,297±1008 in 2009 to $52,397±1487 in 2019, P<0.001 (Supplementary Fig. 2). For AH hospitalizations between 2009-2019, Medicaid was the largest insurer, with a significantly increasing trend (P=0.006). This was followed by private insurance, with a statistically significantly decreasing trend (P=0.006) (Table 1).

Adjusted trend analysis revealed a statistically significant trend toward rising inpatient mortality, from 2.48% in 2009 to 3.78% in 2019 (P=0.008) for AH hospitalizations (Table 2). Subgroup analysis revealed a significant rise in ICU and non-ICU admissions for AH hospitalizations, from 28.6% and 1.1% in 2009 to 30.5% and 2.3% in 2019, respectively (Supplementary Fig. 3). Independent predictors for 30-day all-cause mortality included anemia (adjusted hazard ratio [aHR] 1.45, 95% confidence interval [CI] 1.18-1.78; P<0.001], age >60 years (aHR 1.75, 95%CI 1.51-2.03; P<0.001), female sex (aHR 1.16, 95%CI 1.01-1.33; P<0.001), mechanical ventilation (aHR 2.8, 95%CI 2.4-3.3; P<0.001), vasopressor use (aHR 2.3, 95%CI 1.82-2.8; P<0.001), hepatorenal syndrome (aHR 1.73, 95%CI 1.45-2.04; P<0.001), spontaneous bacterial peritonitis (aHR 1.37, 95%CI 1.1-1.72; P<0.001), acute renal failure (aHR 4.9, 95%CI 4.1-6.1; P<0.001), and coagulopathy (aHR 1.76, 95%CI 1.51-2.1; P<0.001) (Fig. 2). These were used to develop the "Tahira" scoring system for inpatient 30-day inpatient mortality (Table 3). AH hospitalizations with a score of one had a 0.45% 30-day mortality rate, while hospitalizations with a score of ≥8 had a mortality rate of 99% (Table 3). The ROC curve evaluated the diagnostic efficiency of the Tahira score. A total of 25,108 patients were included in the derivation cohort (NIS January 1st 2019 to December 31st 2019). The AUC of the derivation cohort was 0.8766 (95%CI 0.865-0.888). The validation cohort contained a sample of 74,094 patients (NIS January 1st 2017 to December 31st 2018), AUC 0.862 (95%CI 0.855-0.868) (Fig. 3). Based on the calculated highest sensitivity and specificity values from the ROC curves, the determined cutoff values for predicting AH inpatient mortality at 30-day period using the Tahira scoring system were 4 points using the Liu index (sensitivity 78.38%, specificity 92.98%) for 30-day mortality (Table 4).

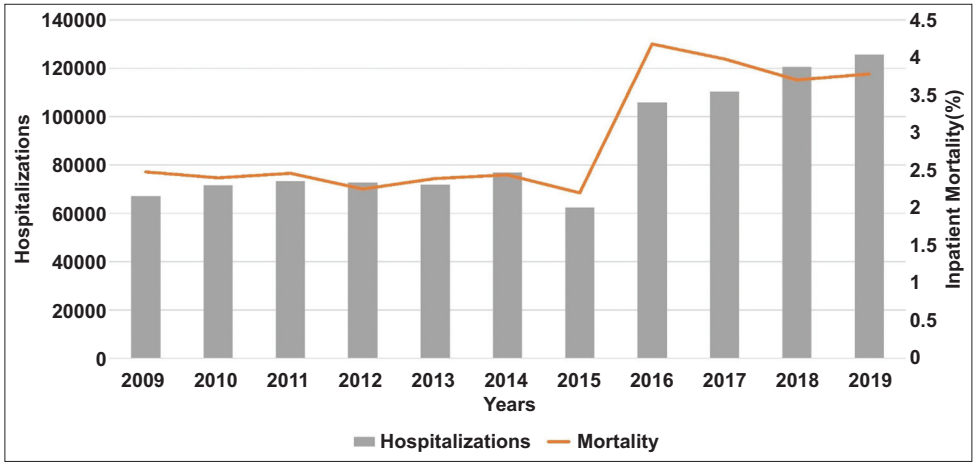

Figure 1 Trends for alcoholic hepatitis hospitalizations and inpatient mortality for the study period (2009-2019)

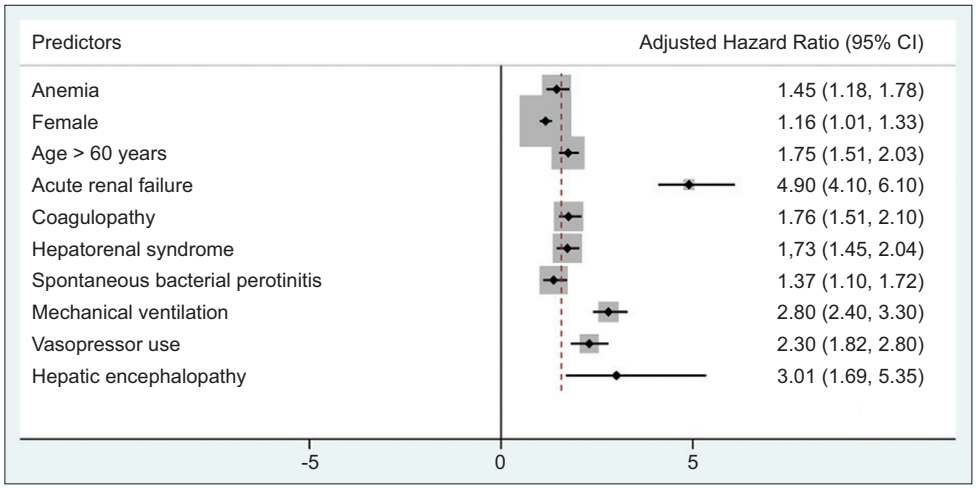

Figure 2 Forest plot showing independent predictors of 30-day all-cause inpatient mortality for alcoholic hepatitis in the United States
CI, confidence interval

Table 1 Biodemographic characteristics of hospitalizations for alcoholic hepatitis from 2009-2019 in the United States

Variables	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Hospitalizations*	67070	71492	73233	72790	71719	76910	62330	105824	110309	120534	125540
Mean age (years) ± SE	48.2 ± 0.15	48.1 ± 0.14	48 ± 0.17	48.1 ± 0.15	48 ± 0.17	48.1 ± 0.14	48 ± 0.1	47.7 ± 0.09	47.9 ± 0.1	47.8 ± 0.12	47.5 ± 0.1
Women (%)*	29.1	29.53	30.2	31	30.8	31.8	31.8	32.7	32.9	33.6	34.1
Racial distribution*											
White	73.26	71.9	71.89	72.5	71.8	72.5	71.7	72.1	71.1	70.5	71.1
Black	11.05	12.5	12.27	11.1	11.2	10.8	10.9	9.7	10.3	9.94	9.7
Hispanic	10	10.85	10.15	10.7	11.3	10.9	11.6	11.8	12.29	12.7	12.6
Asian	1.03	1.07	0.9	0.08	1.01	0.01	1.1	1.1	1.2	1.1	1.3
Native American	1.45	1.05	1.8	1.9	1.9	1.9	1.9	2.3	2.2	2.5	2.4
Others	3.17	2.5	2.92	2.76	2.6	2.7	2.7	2.9	2.8	3.1	2.8
Insurance type (%)*											
Medicare	18	17.6	18	18.9	18.8	20.1	18.02	17.1	17.2	17.2	16.4
Medicaid	20.2	23.7	22.5	24.1	24.6	39.9	38.5	39.9	40.1	40.2	41.4
Private	33.1	31.5	32.6	30.4	30.3	33.6	29.7	29.8	29.1	29.3	28.5
Uninsured	28.1	27.2	27.4	26.4	26.2	18.9	13.7	13	13.1	13.3	13.6

*Indicates statistical significance (P<0.05)

SE, standard error

Table 2 Hospitalization outcomes for alcoholic hepatitis in the United States from 2009-2019

Outcomes	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Inpatient mortality (%)*	2.48	2.4	2.46	2.25	2.39	2.44	2.2	4.18	3.98	3.7	3.78
ICU patients*	28.6	27.6	29.4	23.7	26.1	27.3	25.4	33.4	29.6	29.4	30.5
Non-ICU patients*	1.1	1.2	1.1	1.01	1.04	1.1	1.3	2.4	2.4	2.2	2.3
Mean length of stay (days) ± SE	5.4 ± 0.09	5.4 ± 0.07	5.1 ± 0.09	5.5 ± 0.1	5.3 ± 0.05	5.5 ± 0.04	5.4 ± 0.06	6.04 ± 0.06	6.1 ± 0.05	6.07 ± 0.06	6.1 ± 0.05
ICU patients*	12.7 ± 0.05	13.5 ± 0.04	11.7 ± 0.06	12.9 ± 0.01	12.2 ± 0.09	12.9 ± 0.03	12.9 ± 0.02	15.5 ± 0.08	15.5 ± 0.01	16.2 ± 0.03	15.1 ± 0.04
Non-ICU patients	5.1 ± 0.01	4.9 ± 0.04	4.8 ± 0.03	5.02 ± 0.05	4.9 ± 0.07	4.9 ± 0.04	5.03 ± 0.01	5.46 ± 0.06	5.52 ± 0.07	5.48 ± 0.09	5.60 ± 0.01
Mean total hospital cost ($) ± SE*	31189 ± 1049	32522 ± 1087	34189 ± 1194	37582 ± 722	39279 ± 720	41758 ± 807	42988 ± 780	52936 ± 951	57211 ± 1094	59238 ± 1128	62229 ± 1197
ICU patients*	126780 ± 1957	140990 ± 2228	126609 ± 1643	135893 ± 913	143053 ± 285	155988 ± 275	155978 ± 616	211028 ± 561	231016 ± 1054	238043 ± 913	233576 ± 329
Non-ICU patients*	26297 ± 1008	27314 ± 1031	29038 ± 1182	31647 ± 703	33326 ± 758	34751 ± 846	36677 ± 772	43326 ± 951	46620 ± 1074	48799 ± 1378	52397 ± 1487

*Indicates statistical significance (P<0.05)

SE, standard error; ICU, intensive care unit

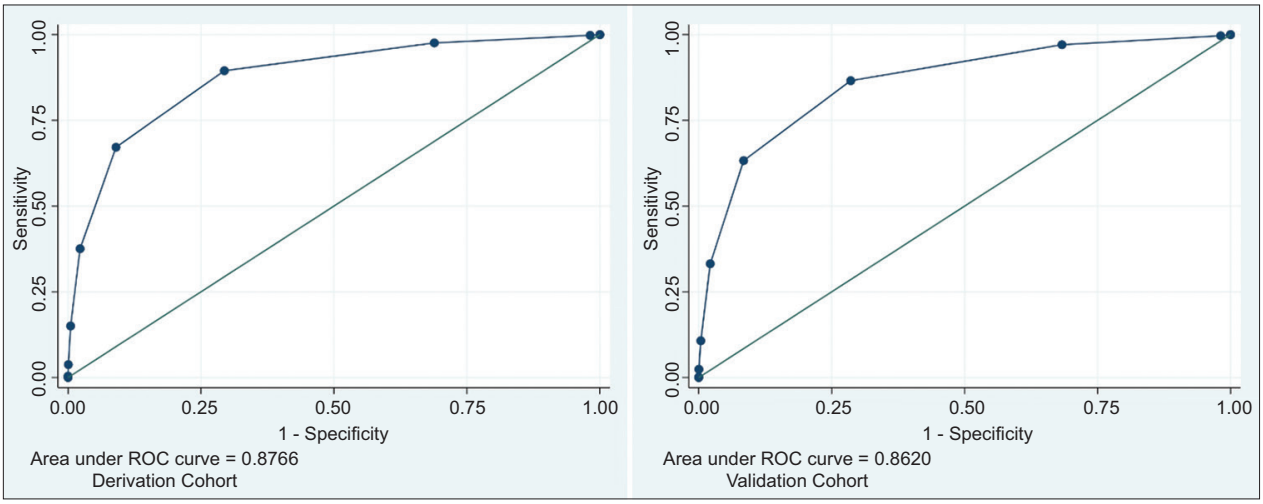

Figure 3 Receiver operating curve (ROC) for the Tahira score in derivation and validation cohorts to predict inpatient 30-day mortality outcomes

Table 3 Risk score system for 30-day inpatient mortality associated with hospitalizations for alcoholic hepatitis in the United States using the Tahira scoring system

Tahira score	Mortality rate per 1000 hospitalizations	30-day mortality rate (%)*
1	2.9	0.29%
2	8	8.01%
3	41	4.1%
4	147	14.7%
5	331	33.1%
6	512	51.1%
7	696	69.6%
≥8	990	99%

*Indicates statistical significance (P<0.001)

Table 4 Point-specific sensitivity and specificity of proposed risk score system for 30-day inpatient mortality associated with hospitalizations for alcoholic hepatitis in the United States

Score	30-day period (Cutoff point=4)	
	Sensitivity	Specificity
0	100%	0.00%
1	99.79%	1.81%
2	97.58%	31.12%
3	89.47%	70.60%
4	37.58%	90.98%
5	15.05%	97.73%
6	3.79%	99.52%
7	0.42%	99.94%
≥8	0.00%	100.00%

Discussion

In the present study, we report a rise in the total number of AH hospitalizations between 2009 and 2019 and an increase in inpatient mortality from 2.48% in 2009 to 3.78% in 2019 (P=0.008). In addition, the majority of AH hospitalizations were for White males, but females did show an upward trend over the last 10 years. There was a non-statistically significant trend for mean LOS. However, the trend for MIC was significant from a healthcare utilization standpoint for AH hospitalizations. In an inpatient setting, recognizing hepatitis secondary to alcohol abuse can control poor prognosis and reduce inpatient mortality [1-3]. The exact incidence and prevalence of AH are presently unknown in the US. Sandahl *et al* estimated an annual incidence for AH in Denmark of 46 per 100,000 for men and 34 per 100,000 for women in 2008 [19]. They also reported a 69% 5-year mortality rate in AH with cirrhosis, compared to 47% in those without cirrhosis [19]. Increasing levels of alcohol consumption and binge drinking are the most probable reasons for these previously reported trends [9,11]. While the exact incidence remains unknown, a prevalence of 20% has been reported previously in patients with a history of alcoholism [20].

It is estimated that approximately 10-35% of patients with alcoholism develop AH. The lifetime prevalence of severe alcohol use disorder in the US is estimated to be 13.9%, or about 41 million people, reflecting a prevalence of approximately 1.3-4.8% in the US population [3]. AH most often affects individuals in their fourth to sixth decade of life, with a mean age of 54 years [16]. In our study from 2009-2019, the mean age was 48.2-47.5 years, with a declining trend. This decreasing trend probably reflects the increased alcohol use among younger populations [9,11]. In addition, we noted a significant male predominance for AH during the study period and an increase in AH hospitalizations for females, from 29.1% in 2009 to 34.1% in 2019 (P<0.001).

This finding may be due to a rising prevalence of alcohol use in females [21]. Previous studies suggest that males are more likely to consume and abuse alcohol, supporting the sex-related differences observed in our study [22]. In recent years, females have had an increased rate of AH hospitalizations, as well as an upward trend in alcohol consumption, with binge rates rising from 2006-2018 [21]. From a racial perspective, significant disparities exist in AH hospitalizations. Whites were predominant in our study, followed by Hispanics, Blacks, and other races (Table 1). These results are consistent with prior studies and are supported by similar ethnic distributions of liver cirrhosis and alcohol use [1,23,24].

The exact cost of the healthcare burden for AH hospitalizations has not been reported previously. Chronic liver disease makes up a substantial part of annual healthcare costs and is estimated to account for approximately $18.8 billion [25]. Severe AH may require ICU-level care, further increasing inpatient costs, length of hospital stay and utilization of healthcare resources. There are limited studies estimating the inpatient costs for AH hospitalizations. The mean LOS was noted to be 5.4 days in 2008 and 6.1 days in 2019, and these results were not statistically significant. The MIC for AH hospitalizations was $31,189 in 2009 compared to $62,229 in 2019. This increase in hospitalization costs could be secondary to concurrent comorbid conditions in patients with chronic liver disease [25,26]. Further studies examining trends in comorbidities in the younger US population are needed to allow a definitive conclusion. Previous reports stated federal- (Medicare) or state- (Medicaid) supported health insurance programs were the primary payers. Our results were slightly different in more recent years. In 2009, private insurance was the primary payer for AH hospitalizations (33.1%), followed by Medicaid and uninsured patients (Table 1). However, the trend for primary payers shifted significantly over the last decade and in 2019 Medicaid was the primary payer for up to 41.4% of AH hospitalizations, followed by private insurance and Medicare (Table 1). These results could be explained by a slow but consistent growth in Medicaid enrollment in recent years [27].

AH is associated with a poor prognosis in severe cases, with a 30-day mortality of 30-50% in patients with a Maddrey's Discriminant Function (MDF) score of 30 or higher [28]. The MDF is a more practical model than the end-stage liver disease (MELD) scoring system for predicting short-term mortality in patients with AH [29]. No other scoring system exists regarding the effect of comorbidities in patients with AH. In this study, inpatient mortality for AH hospitalizations increased from 2.48% in 2009 to 3.78% in 2019 (Table 2). The exact reason for this increased mortality is unknown. However, it may have been due to the rapid rise in AH hospitalizations and the lack of significant advances in treatment for severe AH cases [28]. Subgroup analysis of AH hospitalizations revealed higher mortality in ICU patients than in non-ICU admissions (Supplementary Fig. 3). In our study, independent predictors for 30-day all-cause mortality included anemia, age ≥40 years, female sex, vasopressor use, mechanical ventilation, acute renal failure, spontaneous bacterial peritonitis, hepatorenal syndrome, coagulopathy, and hepatic encephalopathy. We attempted to determine individuals at the highest risk of 30-day all-cause inpatient mortality by developing a scoring system (Tahira score). We used independent risk factors for the scoring system and one point was given for each variable. We then calculated the risk of mortality for these patients based on the designated scores. The patients with a score of one had a mortality rate of 0.45%, while patients with a score ≥8 had a mortality rate of 99% (Table 3). We believe that this scoring system will help clinicians to identify and closely monitor individuals with the highest risk factors, thereby reducing overall inpatient mortality. Further comparison with MDF, MELD and Glasgow AH scores would also be beneficial [30].

This study had several strengths, including the sample size. The study population was obtained from one of the largest inpatient databases available in the US. The weighted counts in the NIS approximate up to 95% of the US population, allowing for generalizable results. Hierarchal regression models allowed for adjusting patient and hospital level confounders providing a more accurate and detailed analysis. The study also had several limitations. The database does not report subjective symptoms, the severity of disease, hospital course or the treatment aspects of AH. Furthermore, our study identified cohorts retrospectively and was not able to determine causality. The incidence of AH is challenging to estimate, as the diagnostic accuracy of administrative coding is less reliable. The study's retrospective nature does not allow for further validation of AH diagnoses based on the published consensus criteria for AH. Additionally, the study did not have randomization and blinding, which can impact result interpretation. Lastly, information was collected from billing data rather than individual patients. Therefore, patients admitted multiple times for the same diagnosis may have been included more than once in the study cohort. Despite these limitations, the large study cohort, unique methodology and analysis add valuable details to the current literature on AH.

In conclusion, because of increasing alcohol use among younger populations, gastroenterologists are likely to encounter growing numbers of AH hospitalizations. In the present study, AH hospitalizations continued to increase across the past decade. The mean age was approximately 47 years, with patients being predominately male and of the White race. There was a significant upward trend in mortality and MIC for AH hospitalizations; however, a change in LOS was not statistically significant. Independent predictors for 30-day all-cause mortality included iron deficiency or blood loss anemia, age ≥40 years, female sex, history of congestive heart failure, peripheral vascular disease, acute or chronic renal failure, coagulopathy (thrombocytopenia), and electrolyte disturbance (hyper- or hypokalemia, hypo- or hypernatremia, acidosis, or alkalosis). Future research using prospective multicenter studies would be beneficial to confirm these findings.

Summary Box

What is already known:

- Alcoholic hepatitis (AH) is a known complication of chronic alcohol abuse
- Mild AH is self-limiting; however, severe AH leads to significantly higher inpatient mortality rates, up to 30%
- AH with cirrhosis has a higher mortality rate than AH without cirrhosis

What the new findings are:

- In the last decade, AH hospitalizations and mortality have been increasing
- From 2009-2019, the length of inpatient stays did not change significantly; however, the cost of inpatient care has gone up substantially
- The Tahira score is a simple mortality scoring system to predict inpatient mortality for AH hospitalizations

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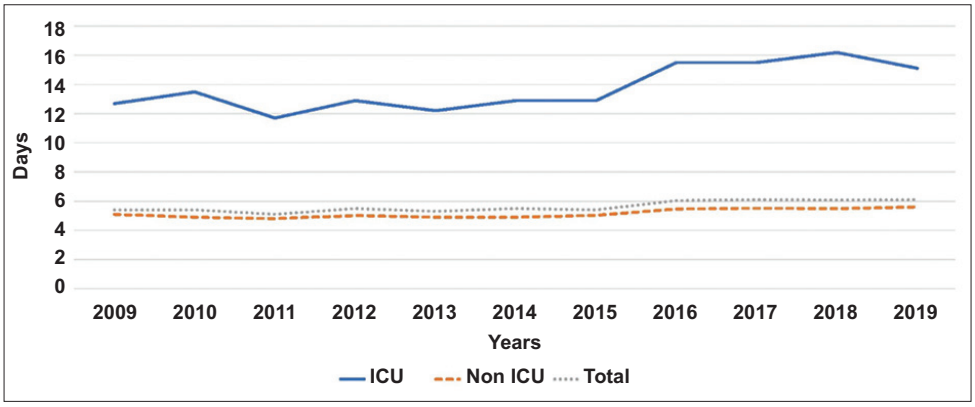
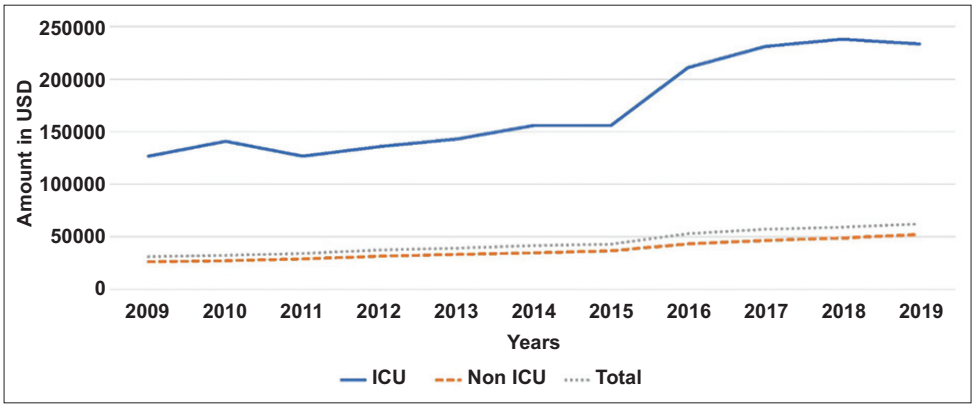
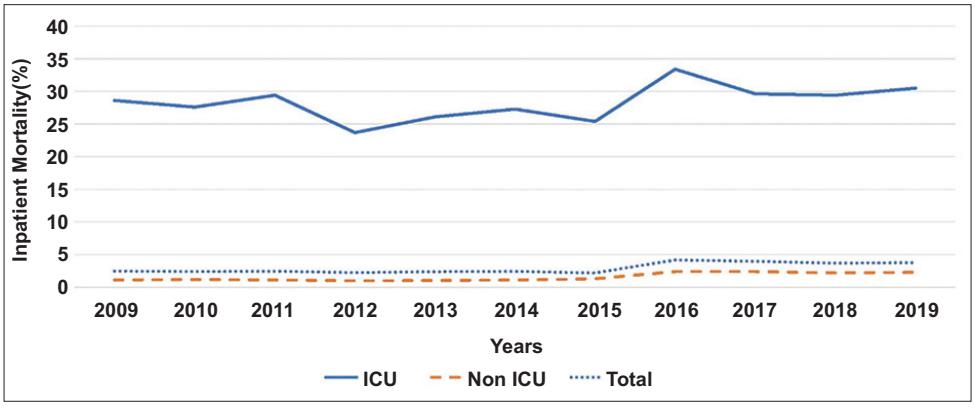
Supplementary material



Supplementary Figure 1 Trends for alcoholic hepatitis length of stay for the study period (2009-2019) for intensive care unit (ICU) and non-ICU hospitalizations



Supplementary Figure 2 Trends for mean inpatient cost associated with alcoholic hepatitis for the study period (2009-2019) for intensive care unit (ICU) and non-ICU hospitalizations



Supplementary Figure 3 Trends for mortality of alcoholic hepatitis for the study period (2009-2019) for intensive care unit (ICU) and non-ICU hospitalizations