ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2024 July 27; 16(7): 973-1069

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
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EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

PUBLICATION DATE
July 27, 2024

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PUBLISHING PARTNER
Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

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ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

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World Journal of Hepatology

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World J Hepatol 2024 July 27; 16(7): 1029-1038

DOI: 10.4254/wjh.v16.i7.1029

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Trends of autoimmune liver disease inpatient hospitalization and mortality from 2011 to 2017: A United States nationwide analysis

Ali Wakil, Yasameen Muzahim, Mina Awadallah, Vikash Kumar, Natale Mazzaferro, Patricia Greenberg, Nikolaos Pyrsopoulos

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D, Grade D

Novelty: Grade C, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade C

P-Reviewer: Sholkamy A

Received: April 6, 2024

Revised: May 23, 2024

Accepted: June 25, 2024

Published online: July 27, 2024

Processing time: 110 Days and 15.7 Hours

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Abstract

BACKGROUND

Autoimmune liver diseases (AiLD) encompass a variety of disorders that target either the liver cells (autoimmune hepatitis, AIH) or the bile ducts [(primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC)]. These conditions can progress to chronic liver disease (CLD), which is characterized by fibrosis, cirrhosis, and hepatocellular carcinoma. Recent studies have indicated a rise in hospitalizations and associated costs for CLD in the US, but information regarding inpatient admissions specifically for AiLD remains limited.

AIM

To examine the trends and mortality of inpatient hospitalization of AiLD from 2011 to 2017.

METHODS

This study is a retrospective analysis utilizing the National Inpatient Sample (NIS) databases. All subjects admitted between 2011 and 2017 with a diagnosis of AiLD (AIH, PBC, PSC) were identified using the International Classification of Diseases (ICD-9) and ICD-10 codes. primary AiLD admission was defined if the first admission code was one of the AiLD codes. secondary AiLD admission was defined as having the AiLD diagnosis anywhere in the admission diagnosis (25

diagnoses). Subjects aged 21 years and older were included. The national estimates of hospitalization were derived using sample weights provided by NIS. χ^2 tests for categorical data were used. The primary trend characteristics were in-hospital mortality, hospital charges, and length of stay.

RESULTS

From 2011 to 2017, hospitalization rates witnessed a significant decline, dropping from 83263 admissions to 74850 admissions ($P < 0.05$). The patients hospitalized were predominantly elderly (median 53% for age > 65), mostly female (median 59%) ($P < 0.05$), and primarily Caucasians (median 68%) ($P < 0.05$). Medicare was the major insurance (median 56%), followed by private payer (median 27%) ($P < 0.05$). The South was the top geographical distribution for these admissions (median 33%) ($P < 0.05$), with most admissions taking place in big teaching institutions (median 63%) ($P < 0.05$). Total charges for admissions rose from 66031 in 2011 to 78987 in 2017 ($P < 0.05$), while the inpatient mortality rate had a median of 4.9% ($P < 0.05$), rising from 4.67% in 2011 to 5.43% in 2017. The median length of stay remained relatively stable, changing from 6.94 days (SD = 0.07) in 2011 to 6.51 days (SD = 0.06) in 2017 ($P < 0.05$). Acute renal failure emerged as the most common risk factor associated with an increased death rate, affecting nearly 68% of patients ($P < 0.05$).

CONCLUSION

AiLD-inpatient hospitalization showed a decrease in overall trends over the studied years, however there is a significant increase in financial burden on healthcare with increasing in-hospital costs along with increase in mortality of hospitalized patient with AiLD.

Key Words: Autoimmune hepatitis; Autoimmune liver disease; Epidemiology; Cost-Effective care; Admissions trend; Mortality rate

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Core Tip: This study revealed a notable decline in the number of hospitalizations due to autoimmune liver disease (AiLD) across the United States, alongside an overall increase in the associated costs and financial burden. The findings offer valuable data for future prospective research, which could lead to more proactive screening efforts in outpatient settings to identify patients with AiLD earlier.

Citation: Wakil A, Muzahim Y, Awadallah M, Kumar V, Mazzaferro N, Greenberg P, Pyrsopoulos N. Trends of autoimmune liver disease inpatient hospitalization and mortality from 2011 to 2017: A United States nationwide analysis. *World J Hepatol* 2024; 16(7): 1029-1038

URL: https://www.wjgnet.com/1948-5182/full/v16/i7/1029.htm

DOI: https://dx.doi.org/10.4254/wjh.v16.i7.1029

INTRODUCTION

Autoimmune liver diseases (AiLDs) are chronic inflammatory hepatobiliary disorders characterized by an autoimmune-based pathogenesis. These diseases are subdivided into three clinical types: Primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH)[1-4].

Although the three types of AiLDs share a common autoimmune pathogenesis, their clinical presentations can be distinguished. AIH is characterized by an infiltration of plasma cells and cytotoxic T cells around the portal tracts, which causes progressive destruction of the hepatocytes. In contrast, PSC affects the large intra- and extrahepatic bile ducts, resulting in obliteration of the biliary tree and biliary cirrhosis, eventually leading to portal hypertension. In PBC, the small bile ducts are damaged, causing further destruction of the portal tract and biliary cirrhosis. Patients occasionally present with mixed features suggestive of an overlap syndrome between AIH and PBC or PSC[5-8].

Genetic predispositions, environmental factors, and defects in immune regulation trigger the onset and continuation of AiLDs. Previous studies have shown that AiLDs have a lower prevalence compared to other liver diseases such as viral hepatitis, Metabolic dysfunction- associated steatotic liver disease, and alcoholic liver disease. Genetic, cultural, social, racial, environmental and other differences across various geographic regions may influence the manifestation of AiLDs [9-12].

Early literature indicates that AiLDs are a common reason for liver transplantation (LT) worldwide. Like other liver diseases with different etiologies, such as decompensated cirrhosis, liver failure, or hepatocellular carcinoma (HCC), AiLDs may necessitate LT. Over the past few years, the number of patients requiring LT for conditions like AIH and PSC has remained stable[13-16].

Recently published data have shown an increase in hospitalizations and financial burdens due to chronic liver diseases (CLD) in the United States from 2012 to 2016. Results indicated a 20.8% increase in the number of advanced liver disease-associated admissions, accompanied by a 26.2% increase in the total estimated admission financial burden, contributing

$18.8 billion to the economic burden[17-19]. To date, information about inpatient admission rates for AiLD is limited. The aim of our study was to provide more insight into AiLD-related hospital admissions and the financial burden on the healthcare system in the United States. Data were obtained using the National Inpatient Sample (NIS) database from 2011 to 2017.

MATERIALS AND METHODS

This study is a retrospective analysis using the NIS databases. All subjects admitted between 2011 and 2017 with a diagnosis of AiLD, including AIH, PBC and PSC were identified using International Classification of Diseases (ICD-9 and ICD-10) codes. A primary AiLD admission was defined if the first admission code was one of the AiLD codes. A secondary AiLD admission was defined as having the AiLD diagnosis listed anywhere in the admission diagnoses (25 diagnoses). Only subjects aged 21 years and older were included. National estimates of hospitalization were derived using sample weights provided by the NIS. χ^2 tests were used for categorical data. The primary trend characteristics analyzed were in-hospital mortality, hospital charges, and length of stay.

Data source

Maintained by the Agency for Healthcare Research and Quality, The NIS is part of the Healthcare Cost and Utilization Project (HCUP), and contains the largest de-identified publicly available all-payer inpatient care database in the United States. All states participate in the HCUP which covers roughly 97% of the United States population and allows the NIS to approximate a 20% stratified sample of discharges from United States community hospitals, as of 2012. The study was initiated in early 2020 and utilizes data from the years 2011-2017. The study period includes the transition from ICD, Ninth Revision, Clinical Modification (ICD-9-CM) to the ICD, Tenth Revision, Clinical Modification (ICD-10-CM)/ Procedure Coding System. All NIS data are in compliance with the Health Insurance Portability and Privacy Act. There are extensive explanations of the NIS database, methods of data collection, training of personnel and descriptions of collected data and outcomes available on the Agency for Healthcare Research and Quality HCUP-NIS website. Methods of data extraction from the NIS database have been described extensively in previous studies. There are no patient identifiers in the HCUP-NIS database thus no Institutional Review Board approval was necessary for this study.

Statistical analysis

Patients included in the study were those with any ICD-9-CM or ICD-10-CM codes documenting a diagnosis of AiLD (including AIH, PBC, and PSC. Patients excluded from the study were those less than 18 years old. To identify patients with AiLD, we considered the following ICD-9-CM codes: 576.1, 571.6, 571.42 and ICD-10-CM codes: K83.01, K74.3, K75.4. Patients were categorized into those with a primary *vs* secondary diagnosis of AiLD. Those considered as having a primary diagnosis of AiLD were cases with AIH/PBC/PSC codes listed as the first diagnosis.

Demographics, socioeconomic status factors (insurance coverage and median household income), mortality, and total hospital charges per visit were first stratified by year and reported as weighted percentages with 95% confidence interval or weighted means with 95% confidence intervals. An admissions rate for each year was calculated by dividing the total number of admissions for any diagnosis of AiLD by the total number of admissions for each respective year. A subset analysis of deceased patients with a diagnosis of AiLD was performed and stratified by year. To observe differences of financial burden by demographics in deceased patients diagnosed with AiLD, a subset analysis of hospital charges was reported and stratified by hospital admission year. Bivariate analyses were performed using Pearson's χ^2 tests for categorical variables and *t*-tests for continuous variables. Tests for trend were performed using two-sided Cochran-Armitage Trend tests for categorical variables and simple linear regression for continuous variables. Frequencies of major mortality risks associated with AiLD including sepsis, GI hemorrhage and acute renal failure (ARF) were also calculated and stratified by year. Two-sided *P*-values < 0.05 were considered statistically significant, and all analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, United States).

RESULTS

Overall, AiLD-related hospital admissions decreased from 83263 (0.23% of total admissions in 2011) to 74850 (0.21% of total admissions in 2017; $P < 0.0001$). This includes all AiLD-related admissions, whether AiLD was the primary or secondary diagnosis. Additionally, the admission rate also decreased when the primary diagnosis was AiLD, with 13432 admissions in 2011 and 10100 admissions in 2017; $P < 0.0001$, as illustrated in Table 1 and Figure 1.

Data on demographic outcomes, as detailed in Table 2, revealed that the median age of patients admitted with AiLD was 53.4 years. The majority of patient were 65 years and older ($P < 0.0001$). The predominant race was White (69.39%-67.54%; overall $P < 0.0001$). The predominant gender among AiLD admissions was female (60.08%-60.56%; overall $P = 0.0079$). The primary healthcare payer was Medicare (56.3%-56.47%; overall $P < 0.0001$). Most AiLD-related hospital admissions were reported in the southern region of the United States (33.9%-34.2%; overall $P = 0.0006$). Most reported admissions with AiLD were from teaching hospitals (56.38%-77.54%; $P < 0.0001$). The most common discharge outcome was routine (58.53%-55.34%; overall $P < 0.0001$). The median length of stay remained similar, from 6.94 days in 2011 to 6.51 days in 2017 (overall $P < 0.0001$). Total hospital admission cost increased from $66031 in 2011 to $78987 in 2017 ($P < 0.0001$), as shown in Table 3.

Table 1 Weighted hospital admissions with autoimmune liver diseases diagnosis years 2011-2017, mean ± SD

	2011	2012	2013	2014	2015	2016	2017	*P* value	*P* value
Primary AiLD diagnosis	13432	12650	12960	12595	12040	10505	10100		< 0.0001
Total AiLD admissions	83263	81430	84080	90350	88515	72585	74850		
Total admissions	36962415	36484846	35597792	35358818	35769942	35675421	35798453		
Total AiLD admission rate (%)	0.23	0.22	0.24	0.26	0.25	0.20	0.21		
Age group (%)									
< 25	2.47	2.62	2.65	2.68	2.37	2.81	2.55	0.65	< 0.0001
25-44	11.7	11.53	11.98	12.53	12.12	13.52	12.73	< 0.0001	
45-64	32.53	31.9	31.3	30.28	30.31	33.18	32.22	0.96	
65/65+	53.3	53.95	54.07	54.5	55.21	50.49	52.5	0.0008	
Reported death (%)	4.67	4.23	4.6	4.39	4.9	5.56	5.43	< 0.0001	< 0.0001
Type of insurance/payment (%)									< 0.0001
Medicare	56.3	57.5	57.1	57.73	57.75	54.81	56.47	0.15	
Medicaid	9.21	9.04	9.08	10.21	10.44	11.81	11.32	< 0.0001	
Private insurance	28.25	26.98	27.03	27.1	27.06	28.66	27.3	0.97	
Self-Pay	3.35	3.61	3.69	2.62	2.51	2.31	2.43	< 0.0001	
No charge	0.59	0.39	0.56	0.26	0.19	0.22	0.27	< 0.0001	
Other	2.3	2.48	2.54	2.08	2.05	2.19	2.2	0.01	
Median household income based on zip code (%)									< 0.0001
0-25th percentile	25.08	25.43	24.48	24.74	25.97	25.76	25.22	0.03	
26th to 50th percentile (median)	24.85	24.48	25.22	27.06	24.32	24.79	25.67	0.1	
51st to 75th percentile	26.61	24.88	26.44	23.72	25.18	25.28	24.7	0.001	
76th to 100th percentile	23.47	25.21	23.86	24.48	24.53	24.17	24.41	0.48	
Sex (%)									0.0079
Male	39.92	41.08	40.86	40.97	41.17	40.34	39.44	0.25	
Female	60.08	58.92	59.14	59.03	58.83	59.66	60.56	0.25	
Hospital bedsize (%)									< 0.0001
Small	10.19	11.76	11.7	15.72	14.57	14.69	15.54	< 0.0001	
Medium	22.22	24.11	23.85	26.05	26.48	25.37	25.16	< 0.0001	
Large	67.59	64.12	64.45	58.23	58.95	59.94	59.3	< 0.0001	
Hospital region									0.0006
Northeast	21.29	22.1	21.5	21.17	20.82	20.16	20.62	0.0007	
Midwest	22.65	22.79	22.52	22.93	23.53	23.58	23.2	0.17	
South	33.9	32.42	33.31	32.82	33.16	34.04	34.2	0.26	

West	22.16	22.69	22.67	23.08	22.49	22.22	21.98	0.49	
Race (%)									< 0.0001
White	69.39	69.82	68.82	69.7	69.04	68.22	67.54	0.35	
Black	10.43	9.84	10.58	10.44	10.9	11.63	11.87	< 0.0001	
Hispanic	13.15	11.67	12.2	11.52	11.59	11.91	12.51	0.56	
Asian or Pacific Islander	3.7	4.24	4.67	4.66	4.66	4.14	4.07	0.03	
Native American	0.6	0.72	0.67	0.67	0.74	0.86	0.77	0.006	
Other	2.72	3.72	3.06	3.01	3.07	3.24	3.24	0.17	
Hospital location (%)									< 0.0001
Rural	8.55	7.91	7.44	5.95	5.68	5.85	5.35	< 0.0001	
Urban nonteaching	35.08	31.78	31.58	20.82	21.41	19.12	17.11	< 0.0001	
Urban teaching	56.38	60.31	60.98	73.23	72.91	75.03	77.54	< 0.0001	
Discharge (%)									< 0.0001
Routine	58.53	59.21	57.87	57.56	57.08	56.17	55.37	< 0.0001	
Transfer to short-term hospital	4.86	4.64	4.82	4.62	4.67	4.8	4.51	0.54	
Transfer other[1]	15.52	15.69	15.43	16.19	15.63	14.89	15.2	0.15	
Home health care	15.88	15.76	16.76	16.65	17.19	17.97	18.67	< 0.0001	
Against medical advice	0.47	0.42	0.49	0.53	0.53	0.58	0.79	< 0.0001	
Died	4.67	4.23	4.6	4.39	4.9	5.56	5.43	< 0.0001	
Total charges	66031 ± 959.67	64643 ± 917.22	67530± 873.54	70390 ± 846.90	73081 ± 935.86	75856 ± 1162.0	78987 ± 1120.29	< 0.0001	< 0.0001
Length of stay	6.94 ± 0.07	6.72 ± 0.07	6.65 ± 0.06	6.76 ± 0.06	6.70 ± 0.06	6.56 ± 0.06	6.51 ± 0.06	< 0.0001	< 0.0001

[1]Includes skilled nursing facility, intermediate care facility, another type of facility.
AiLD: Autoimmune liver diseases.

Table 2 Weighted mortality-related risk factors among deceased hospitalized patients diagnosed with autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, 2011-2017

	2011	2012	2013	2014	2015	2016	2017	*P* value
n	83263	81430	84080	90350	88515	72585	74850	
Risk factors								
Sepsis (%)	13.08	11.17	10.65	10.49	26.65	71.94	73.93	< 0.0001
Gastrointestinal hemorrhage (%)	10.94	9.17	9.24	10.24	10.14	12.71	11.81	0.07
Acute renal failure (%)	61.94	63.1	65.47	67.54	68.34	68.71	68.82	< 0.0001

Table 3 Weighted hospital admissions resulting in mortality with autoimmune liver diseases diagnosis years 2011-2017, mean ± SD

	2011	2012	2013	2014	2015
Total mean charges ($)	66031 ± 959.67	64643 ± 917.22	67530 ± 873.54	70390 ± 846.90	73081 ± 935.86
Age group					
< 25	66380	58196	70023	64827	70241
25-44	67980	59435	64813	63039	77106
45-64	71465	70030	70951	72934	78617
65/65+	62294	62889	66035	70965	69282
Type of insurance/payment					
Medicare	63976	62771	65338	69634	69826
Medicaid	89300	74468	78293	73732	85970
Private insurance	63474	66434	69955	70758	74432
Self-Pay	59502	58456	62497	67545	76839
No charge	42195	46303	71761	55820	56524
Other	67153	64584	60546	75497	77006
Sex					
Male	73209	72125	74568	77969	80807
Female	61244	59435	62677	65143	67712
Race					
White	61321	60626	62750	66755	67207
Black	81958	66471	74005	73835	85676
Hispanic	84390	78300	87317	84775	86062
Asian or Pacific Islander	105588	110862	89349	102233	103801
Native American	57071	50091	60905	55484	62996
Other	71681	74580	86077	85352	97951
Linear regression was used to assess trend in charges over years within each demographic group					

[1]Two-Sided Cochran-Armitage Trend Tests were performed for all categorical variables to test trend. Simple Linear Regression was performed for all continuous variables to test trend.

The median inpatient mortality increased from 2011 to 2017 (4.67%-5.43%; $P < 0.0001$; Figure 2), as detailed in Table 2. The most significant risk factor associated with AiLD mortality was the incidence of ARF, which rose from 61.94% in 2011 to 68.82% in 2017 ($P < 0.0001$). The second most common risk factor related to AiLD inpatient hospital death was found to be sepsis, which increased significantly from 13.08% in 2011 to 73.93% in 2017; $P < 0.0001$, as detailed in Table 2.

DISCUSSION

AiLDs are chronic inflammatory hepatobiliary disorders that present as complex conditions, thought to arise from the interplay of genetic susceptibility and nonspecific environmental triggers[20,21]. Although AiLDs are considered rare across the spectrum of liver diseases, with a prevalence of less than 50 *per* 100000 population, studies continue to show their high morbidity and mortality[22,23].

Generally, epidemiological studies offer current insights into the presentation, clinical course, and financial burden that AiLDs impose on the healthcare system, along with their outcomes and impact on patients' quality of life[24]. However, population-based epidemiological data for AiLDs are relatively scarce. Many international epidemiological studies have shown both heterogeneous results and inconsistent trends in the incidence and prevalence of AiLDs[25].

In our retrospective study, we aimed to analyze the epidemiology, economic burden, and mortality rate of AiLDs in the United States. We queried the NIS database from 2011 to 2017. The primary outcomes included the rate of hospitalization, hospital costs, and inpatient mortality, while also examining contributing risk factors and demographic patterns

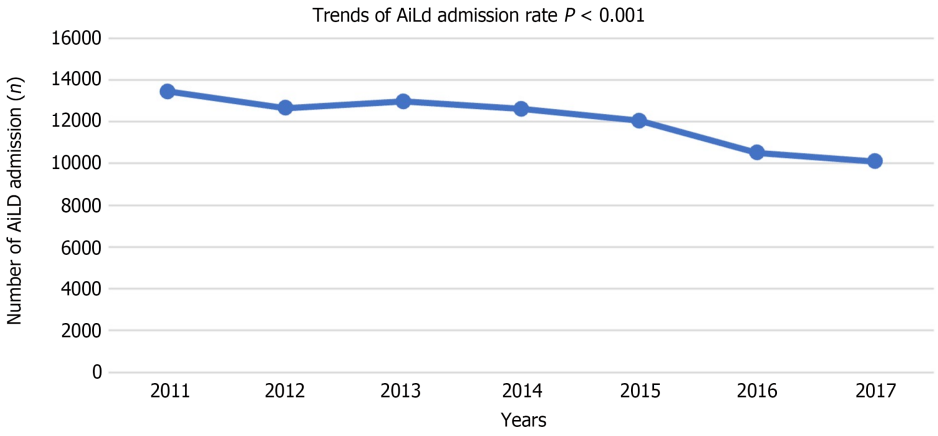

Figure 1 Trends of autoimmune liver diseases number of hospital admissions from 2011 to 2017. AiLD: Autoimmune liver diseases.

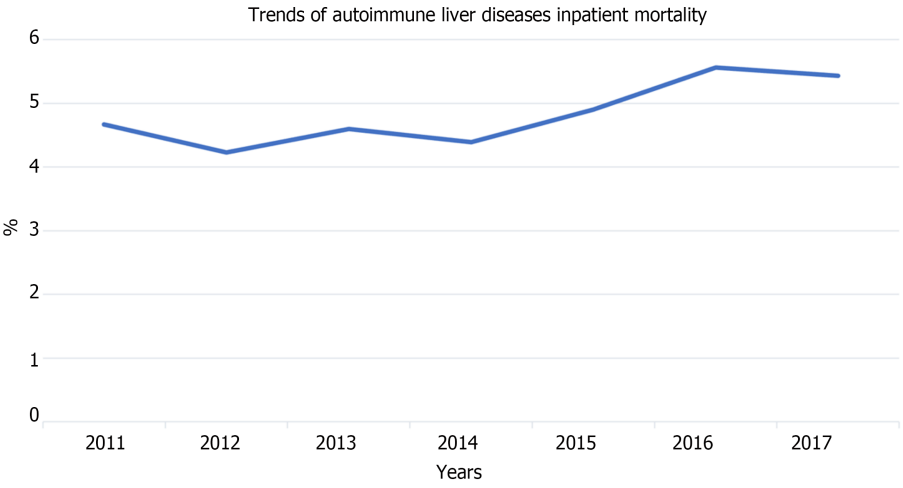

Figure 2 Trends of autoimmune liver diseases inpatient mortality from 2011 to 2017.

in the hospitalized AiLDs population.

Our data analyzed all AiLDs-associated hospital stay from 2011 to 2017 using the NIS database. There were about 36.9 million total admissions in 2011, approximately 83263 (0.23%) were due to AiLDs. This number decreased to 74850 (0.21%) out of 35.8 million admissions in 2017 ($P < 0.001$), as shown in Table 3. Furthermore, the number of admissions with a primary diagnosis of AiLDs declined from 13432 (0.04%) in 2011 to 10100 (0.03% in 2017; $P < 0.001$). This downward trend in hospitalizations over the years may correlate with significant advancements in diagnostic methods and pharmacotherapy for AiLDs, which have positively impacted the adequacy of symptom control, early recognition of extra-hepatic manifestations, and surveillance for complications[26].

Additionally, we found that each admission related to AiLDs incurred an average cost of $66031 in 2011 and $78987 in 2017 ($P < 0.0001$), with the average in-hospital length of stay decreasing from 6.94 days in 2011 to 6.51 days in 2017 per admission (overall $P < 0.0001$) (Table 1). Approximately 56% of these patients had Medicare as the primary expected payer. The rising cost per admission significantly escalates the burden on the healthcare system and the public payer, which is funded by tax income[17].

Literature discussed that LT is a standard therapeutic approach for the treatment of end-stage acute and CLD including AiLDs patients with end-stage liver disease, hepatic malignancies, intractable symptoms, acute liver failure in AiLDs patients who are unresponsive to conventional therapy. These data suggest that the transplant percentage and transplant rate are decreasing for HCC, while increasing for autoimmune conditions, among which ALD, metabolic dysfunction-associated steatohepatitis, and viral hepatitis with ALD display the fastest rate. AiLDs account for approximately 10.45 % of LT procedures performed in the United States with current five- and ten-year survival rates post-transplant in autoimmune disease are excellent, at 88% and 78%, respectively[27-29].

Our study showed that most AiLDs hospitalized individuals were female 60.08%-60.56%, and the hospital admissions are predominantly made by patients with age of 65 and older. Studies reported that the mechanisms behind the sex differences observed in AiLDs, specifically the female predominance in AIH and PBC. Statistics show a more severe disease progression in male PBC patients. There is a male predominance among PSC patients, accompanied by a reduced risk of ulcerative colitis. Additionally, there is a higher incidence of cholangiocarcinoma in female patients. However, the underlying etiology of these trends remains largely unclear. Future research can be more dedicated on understanding the

effects of sex-related genes and intestinal microbiota underlying AiLD immune dysregulation, as well as the role of sex hormones in immune cells, and eventually predict clinical course, complications, prognosis, and quality of life in AiLDs patients[10].

We also observed that the mortality of hospitalized patients with AiLDs was 4.67% in 2011, which has increased to 5.43% in 2017 (Table 3). We also examined some of the major inpatient mortality-related risk factors among AiLDs. ARF was the most common mortality-risk factor in these patients approaching around 61.94% in 2011 and 68.82% in 2017. A possible explanation of these results is that more than 35% of hospitlizated AiLD patient have decompensated cirrhosis [30] which in itself has association with high incidence of ARF. Literature explained that ARF in CLD encompass three main categories; first one is volume-responsive pre-renal failure, volume unresponsive prerenal failure with tubular dysfunction and acute tubular necrosis, and last is hepatorenal syndrome type 1, with prevalence rates of 68%, 33%, and 25% respectively[31,32]. Sepsis was also noted as mortality-risk 13.08% in 2011 and was significantly increased to 73.93% in 2017 (Table 2). This is likely a result of implementing the conversion of ICD-9 to ICD-10 in 2015. The explicit use of ICD-9 and ICD-10 codes for sepsis are inconsistent and unreliable, and it likely led to an overestimate of prevalence rate of sepsis in this study.

Our retrospective data is one of the few studies focusing on trends in inpatient admissions, mortality rates, and complications while also observing demographic patterns; however, our data were interpreted within the context of certain limitations. The NIS data were reported per hospitalization, without providing a detailed study of each individual patient or follow-up data after hospital discharge. Given the nature of the database analysis, a longitudinal analysis is not possible, and therefore, causality cannot be established. Additionally, there may be repeated hospitalizations of patients with AiLDs within this study cohort. Since the main objective of this study was to characterize the overall clinical and economic burden of AiLD hospitalizations in the United States, these results still provide critical data to address this significant public health concern.

CONCLUSION

Analysis of trends in AiLDs-related hospitalizations from 2011 to 2017 revealed a decrease in both the overall admission rate and the length of stay. However, there was a significant increase in both mortality and healthcare utilization costs in the United States. The impact of our study results can be considered a turning point to guide healthcare strategies towards more efficient allocation of health resources. Additionally, these strategies can address the imminent financial burden across the diverse clinical spectrum in the AiLDs population, especially given the ongoing increase in morbidity and mortality.

FOOTNOTES

Author contributions: Wakil A, Muzahim Y, Awadallah M, Kumar V conducted research conceptualization, manuscript writing, analyzed the data and drew conclusion; Mazzaferro N, Greenberg P conducted research methodology, statistical analysis, data analysis; Pyrsopoulos N conducted research supervision and proofreading.

Institutional review board statement: This study was done using the National Inpatient Sample database which does not require approval from the institutional review board, thus no institutional review board approval was needed for this study.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data using National Inpatient Sample database which contains no identifying patient information and does not require informed consent to use the data.

Conflict-of-interest statement: All authors have no conflict of interest.

Data sharing statement: Statistical code, and dataset available from the corresponding author at pyrsopni@njms.rutgers.edu. Participants gave informed consent for data sharing.

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S-Editor: Liu H

L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Kaplan MM**. Primary biliary cirrhosis. *N Engl J Med* 1996; **335**: 1570-1580 [PMID: 8900092 DOI: 10.1056/NEJM199611213352107]
2 **Krawitt EL**. Autoimmune hepatitis. *N Engl J Med* 1996; **334**: 897-903 [PMID: 8596574 DOI: 10.1056/NEJM199604043341406]
3 **Lee YM**, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med* 1995; **332**: 924-933 [PMID: 7877651 DOI: 10.1056/NEJM199504063321406]
4 **Trivedi PJ**, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. *Gut* 2021; **70**: 1989-2003 [PMID: 34266966 DOI: 10.1136/gutjnl-2020-322362]
5 **Czaja AJ**, Manns MP. Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. *Gastroenterology* 2010; **139**: 58-72.e4 [PMID: 20451521 DOI: 10.1053/j.gastro.2010.04.053]
6 **Bogdanos DP**, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: virtuous intentions, malign consequences. *Liver* 2001; **21**: 225-232 [PMID: 11454184 DOI: 10.1034/j.1600-0676.2001.021004225.x]
7 **Enrique CA**, Julio G, Misael U, Aldo T. Does HLA-DR7 differentiate the overlap syndrome of auto-immune hepatitis-primary biliary cirrhosis (AIH-PBC) from those with auto-immune hepatitis type 1? *Ann Hepatol* 2011; **10**: 28-32 [DOI: 10.1016/S1665-2681(19)31583-2]
8 **Manns MP**, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM; American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; **51**: 2193-2213 [PMID: 20513004 DOI: 10.1002/hep.23584]
9 **Czaja AJ**. Frequency and nature of the variant syndromes of autoimmune liver disease. *Hepatology* 1998; **28**: 360-365 [PMID: 9695997 DOI: 10.1002/hep.510280210]
10 **Invernizzi F**, Cilla M, Trapani S, Guarino M, Cossiga V, Gambato M, Morelli MC, Morisco F, Burra P, Floreani A; Special Interest Group Gender in Hepatology of the Italian Association for the Study of the Liver (AISF). Gender and Autoimmune Liver Diseases: Relevant Aspects in Clinical Practice. *J Pers Med* 2022; **12** [PMID: 35743710 DOI: 10.3390/jpm12060925]
11 **Krawitt EL**. Autoimmune hepatitis. *N Engl J Med* 2006; **354**: 54-66 [PMID: 16394302 DOI: 10.1056/NEJMra050408]
12 **Invernizzi P**. Geoepidemiology of autoimmune liver diseases. *J Autoimmun* 2010; **34**: J300-J306 [PMID: 20036105 DOI: 10.1016/j.jaut.2009.12.002]
13 **Fernández MIC**, Hernández DR, Cabrera Eugenio DE, Palanca W, Guridi ZD, González Fabián L. Diagnosis and Treatment of Autoimmune Liver Diseases in a Tertiary Referral Center in Cuba. *Curr Ther Res Clin Exp* 2017; **85**: 8-14 [PMID: 29158853 DOI: 10.1016/j.curtheres.2017.04.002]
14 **Carbone M**, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. *J Hepatol* 2014; **60**: 210-223 [PMID: 24084655 DOI: 10.1016/j.jhep.2013.09.020]
15 **Montano-Loza AJ**, Bhanji RA, Wasilenko S, Mason AL. Systematic review: recurrent autoimmune liver diseases after liver transplantation. *Aliment Pharmacol Ther* 2017; **45**: 485-500 [PMID: 27957759 DOI: 10.1111/apt.13894]
16 **Ilyas JA**, O'Mahony CA, Vierling JM. Liver transplantation in autoimmune liver diseases. *Best Pract Res Clin Gastroenterol* 2011; **25**: 765-782 [PMID: 22117641 DOI: 10.1016/j.bpg.2011.09.008]
17 **Hirode G**, Saab S, Wong RJ. Trends in the Burden of Chronic Liver Disease Among Hospitalized US Adults. *JAMA Netw Open* 2020; **3**: e201997 [PMID: 32239220 DOI: 10.1001/jamanetworkopen.2020.1997]
18 **Asrani SK**, Kouznetsova M, Ogola G, Taylor T, Masica A, Pope B, Trotter J, Kamath P, Kanwal F. Increasing Health Care Burden of Chronic Liver Disease Compared With Other Chronic Diseases, 2004-2013. *Gastroenterology* 2018; **155**: 719-729.e4 [PMID: 29802851 DOI: 10.1053/j.gastro.2018.05.032]
19 **Asrani SK**, Hall L, Hagan M, Sharma S, Yeramaneni S, Trotter J, Talwalkar J, Kanwal F. Trends in Chronic Liver Disease-Related Hospitalizations: A Population-Based Study. *Am J Gastroenterol* 2019; **114**: 98-106 [PMID: 30333543 DOI: 10.1038/s41395-018-0365-4]
20 **Corrigan M**, Hirschfield GM, Oo YH, Adams DH. Autoimmune hepatitis: an approach to disease understanding and management. *Br Med Bull* 2015; **114**: 181-191 [PMID: 25995334 DOI: 10.1093/bmb/ldv021]
21 **Hirschfield GM**, Gershwin ME. The immunobiology and pathophysiology of primary biliary cirrhosis. *Annu Rev Pathol* 2013; **8**: 303-330 [PMID: 23347352 DOI: 10.1146/annurev-pathol-020712-164014]
22 **Hirschfield GM**, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. *Lancet* 2013; **382**: 1587-1599 [PMID: 23810223 DOI: 10.1016/S0140-6736(13)60096-3]
23 **Dyson JK**, Webb G, Hirschfield GM, Lohse A, Beuers U, Lindor K, Jones DE. Unmet clinical need in autoimmune liver diseases. *J Hepatol* 2015; **62**: 208-218 [PMID: 25234946 DOI: 10.1016/j.jhep.2014.09.010]
24 **Hahn JW**, Yang HR, Moon JS, Chang JY, Lee K, Kim GA, Rahmati M, Koyanagi A, Smith L, Kim MS, López Sánchez GF, Elena D, Shin JY, Shin JI, Kwon R, Kim S, Kim HJ, Lee H, Ko JS, Yon DK. Global incidence and prevalence of autoimmune hepatitis, 1970-2022: a systematic review and meta-analysis. *EClinicalMedicine* 2023; **65**: 102280 [PMID: 37876996 DOI: 10.1016/j.eclinm.2023.102280]
25 **Lamba M**, Ngu JH, Stedman CAM. Trends in Incidence of Autoimmune Liver Diseases and Increasing Incidence of Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2021; **19**: 573-579.e1 [PMID: 32526342 DOI: 10.1016/j.cgh.2020.05.061]
26 **Trivedi PJ**, Hirschfield GM. Treatment of autoimmune liver disease: current and future therapeutic options. *Ther Adv Chronic Dis* 2013; **4**: 119-141 [PMID: 23634279 DOI: 10.1177/2040622313478646]
27 **Tanaka T**, Sugawara Y, Kokudo N. Liver transplantation and autoimmune hepatitis. *Intractable Rare Dis Res* 2015; **4**: 33-38 [PMID: 25674386 DOI: 10.5582/irdr.2014.01034]
28 **Kelly C**, Zen Y, Heneghan MA. Post-Transplant Immunosuppression in Autoimmune Liver Disease. *J Clin Exp Hepatol* 2023; **13**: 350-359 [PMID: 36950491 DOI: 10.1016/j.jceh.2022.07.002]
29 **Keeling SS**, McDonald MF, Anand A, Goff CR, Christmann CR, Barrett SC, Kueht M, Goss JA, Cholankeril G, Rana A. Do Patients with Autoimmune Conditions Have Less Access to Liver Transplantation despite Superior Outcomes? *J Pers Med* 2022; **12** [PMID: 35887656 DOI: 10.3390/jpm12071159]

30 **Tunio NA**, Mansoor E, Sheriff MZ, Cooper GS, Sclair SN, Cohen SM. Epidemiology of Autoimmune Hepatitis (AIH) in the United States Between 2014 and 2019: A Population-based National Study. *J Clin Gastroenterol* 2021; **55**: 903-910 [PMID: 33074948 DOI: 10.1097/MCG.0000000000001449]

31 **Slack A**, Yeoman A, Wendon J. Renal dysfunction in chronic liver disease. *Crit Care* 2010; **14**: 214 [PMID: 20236458 DOI: 10.1186/cc8855]

32 **Garcia-Tsao G**, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology* 2008; **48**: 2064-2077 [PMID: 19003880 DOI: 10.1002/hep.22605]

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