ORIGINAL ARTICLE

National trends and outcomes of genetically inherited non-alcoholic chronic liver disease in the USA: estimates from the National Inpatient Sample (NIS) database

Eric M. Sieloff [1,*], Brian Rutledge [2], Cuyler Huffman[3], Duncan Vos[3] and Thomas Melgar[4]

[1]Department of Internal Medicine, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI, USA; [2]Department of Internal Medicine, Division of Gastroenterology, Wayne State University School of Medicine, Detroit, MI, USA; [3]Department of Biostatistics, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI, USA; [4]Department of Pediatrics, Adolescent and Internal Medicine, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, MI, USA

*Corresponding author. 1000 Oakland Dr, Kalamazoo, MI 49008, USA. Tel: +1-832-287-1643; Email: Martin.sieloff@med.wmich.edu

Abstract

Background: Medical literature on the prevalence of genetic liver disease is lacking. In this study, we investigated the in-hospital healthcare and economic burden from genetic causes of non-alcoholic chronic liver disease (NACLD) and non-alcoholic liver cirrhosis (NALC) in the USA.
Methods: Data were abstracted from the National Inpatient Sample database between 2002 and 2014 using ICD9 codes for patients discharged with NACLD and NALC secondary to genetic diseases including alpha-1 antitrypsin deficiency (A1ATd), cystic fibrosis (CF), Wilson disease (WD), hereditary hemochromatosis (HHC), glycogen storage disease, and disorders of aromatic amino-acid metabolism (DAAAM).
Results: Throughout the study period, there were 19,332 discharges for NACLD associated with the six genetic diseases including 14,368 for NALC. There were $1.09 billion in hospital charges, 790 in-hospital deaths, and 955 liver transplants performed. Overall, A1ATd was associated with 8,983 (62.52%) hospitalizations for NALC followed by WD, CF, and HHC. The highest in-hospital mortality was seen with HHC. The greatest frequency of liver transplants was seen with DAAAM.
Conclusion: The number of hospitalizations for genetic liver diseases continues to increase. With increased funding and directed research efforts, we can aim to improve medical treatments and the quality of life for patients at risk for liver deterioration.

Key words: liver cirrhosis; inherited metabolic disease; epidemiology

Introduction

Chronic liver disease, including liver cirrhosis, is a significant and increasingly recognized cause of morbidity and mortality, impacting >4.5 million Americans [1]. The age-adjusted mortality from hepatocellular carcinoma, a primary liver cancer that can develop secondary to cirrhosis, is increasing annually in the USA by 2.1% [2]. Using the National Inpatient Sample (NIS) database, recent literature has determined the in-hospital healthcare and economic burden of liver cirrhosis to be associated with 570,700 hospitalizations, >$7.3 billion in charges, and an in-hospital mortality rate of 3.3%–6.6% in the year 2014 alone [3]. Historically, the most common cause of cirrhosis was alcohol consumption and viral hepatitis, yet non-alcoholic fatty liver disease (NAFLD) has become an increasingly prevalent cause due to the ongoing obesity epidemic in the USA with recent estimates of NAFLD affecting 80–100 million Americans [3, 4].

Less common, but significant, causes of chronic liver disease and liver cirrhosis are those from genetic diseases that influence liver metabolism. Affected individuals are born with certain genetic traits predisposing them to liver damage. In 2014, Scorza et al. [5] published a literature review of genetic diseases that cause cirrhosis including alpha-1 antitrypsin deficiency (A1ATd), Wilson disease (WD), hereditary hemochromatosis (HHC), cystic fibrosis (CF), glycogen storage diseases (GSDs), and tyrosinemia. For many of these diseases, rigorous monitoring, alcohol avoidance, and lifestyle choices are essential to prevent and slow the development and progression of liver cirrhosis. Unfortunately, many affected individuals develop liver disease and cirrhosis, and may inevitably require a liver transplant for curative and therapeutic purposes [6].

Current medical literature is lacking epidemiological studies investigating the healthcare and economic burden of chronic liver disease and liver cirrhosis due to genetic causes in the USA. We utilized the NIS healthcare database to establish estimates of the in-hospital prevalence of genetic forms of non-alcoholic chronic liver disease (NACLD) and non-alcoholic liver cirrhosis (NALC) for which patient characteristics, associated mortality, and liver-transplant occurrences were investigated.

Methods

The NIS database was utilized to collect data from the years 2002–2014. The NIS database is a large publicly available all-payer inpatient care database compiled by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (AHRQ HCUP), based primarily on diagnosis and procedure codes. Hospital-discharge data, collected from State Inpatient Databases, are assembled from a 20% stratified sample of American hospitals and used to develop weighted estimates to represent discharges at a national level.

Inclusion criteria

Descriptive analysis was used to assess hospital discharges and the economic burden of genetic liver diseases including alpha-1 antitrypsin deficiency (A1ATd), CF, WD, hereditary hemochromatosis (HHC), GSD, and disorders of aromatic amino-acid metabolism (DAAAM, which include tyrosinemia), identified by ICD9 codes 273.4, 277.03, 275.1, 275.01, 271.0, and 270.2, respectively. Liver disease was classified as NACLD including NALC. The ICD9 codes used for NACLD were chronic hepatitis, unspecified (ICD9 571.40), chronic persistent hepatitis (ICD9 571.41), other chronic hepatitis (ICD9 571.49), cirrhosis of the liver without mention of alcohol (ICD9 571.5), biliary cirrhosis (ICD9 571.6), other chronic non-alcoholic liver disease (ICD9 571.8), and unspecified chronic liver disease without mention of alcohol (ICD9 571.9), whereas the ICD9 code 571.5 alone was used for NALC. Discharges for alcoholic cirrhosis (ICD9 571.2) were excluded. Liver-transplant occurrences were further investigated using the ICD9 diagnosis code V42.7 and ICD9 procedure codes 50.51 and 50.59.

Clinical variables

Categorical patient characteristics are reported as weighted frequencies (percent, %; 95% confidence interval [CI]), and continuous patient characteristics are reported as median values and interquartile range (IQR). Covariates were analysed for all patients including patient age at admission, gender, racial ethnicity, insurance payer, income by quartile per zip code, and hospital regional geography. We investigated annual in-hospital charges, patient mortality, and the occurrence of liver transplants. Annual hospital charges in dollars were adjusted to 2020 US dollars using conversion factors from the Bureau of Labor Statistics [7]. Only weighted frequencies were reported to represent national hospital discharges, in accordance with the NIS sampling methodology. Per the data-use agreement with the HCUP, frequencies of <11 cannot be reported. SAS Studio 9.4 was utilized for analysis (SAS Institute, Inc., NC). Data collected from the NIS database contains publicly available de-identified patient information and therefore review and approval of the Institutional Review Board at Western Michigan University were not required.

Results

Between 2002 and 2014, there were 192,270 discharges for patients with genetic diseases that may lead to liver disease (A1ATd, CF, WD, HHC, GSD, and DAAAM). Of those, 19,332 (10.05%) discharges were for NACLD and 14,368 (7.47%) were for NALC. Over time, the annual number of discharges for patients with NACLD or NALC increased (Table 1 and Figure 1). Cirrhosis is an advanced form of chronic liver disease and our data suggest that 74.32% of the documented discharges for genetic NACLD were specifically for NALC between 2002 and 2014. Of all the genetic diseases investigated as causes of NACLD, A1ATd was most common, followed by CF. Discharges of genetic NALC were most frequently associated with A1ATd, followed by WD (Table 2 and Figure 1). Genetic diseases were associated with 0.45% (95% CI, 0.41%–0.48%) of all discharges for NALC between 2002 and 2014. Total discharges for both NACLD and NALC along with the gender distribution, patient characteristics, and liver-transplant occurrence with respect to individual genetic disease are shown in Table 2, which shows a small predominance of male patients for all genetic NALC, with A1ATd being associated with the majority (65.97%, 630/955) of liver transplants.

The number of annual discharges, in-hospital charges, and in-hospital deaths for genetic NACLD and NALC consistently increased over time, along with the number of annual liver transplants performed (Table 1). With regard to genetic NALC, there were $1.09 billion in hospital charges that accrued from 2002 to 2014. The frequency of annual hospitalizations for genetic NALC relative to liver transplants spiked between 2005 and 2008, reaching 35 hospitalizations per transplant, but then stabilized to ~15 hospitalizations per transplant between 2008 and 2014. The frequency of annual hospitalizations relative to in-

Table 1. Annual data for non-alcoholic genetic liver disease

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Non-alcoholic chronic liver disease													
Discharges, N	142	331	396	1,312	1,171	1,319	1,277	1,553	1,820	2,502	2,330	2,380	2,800
Rate per 100,000[a]	0.4	0.9	1.1	3.5	3.1	3.5	3.3	4.1	4.9	6.8	6.4	6.7	7.9
(95% CI, %)	(0.2, 0.3)	(0.5, 1.3)	(0.7, 1.4)	(2.5, 4.5)	(2.3, 3.8)	(2.5, 4.4)	(2.5, 4.2)	(3.1, 5.1)	(3.8, 6)	(5.4, 8.2)	(5.5, 7.3)	(5.9, 7.5)	(6.8, 9)
Median age at admission in years (IQR)	30.9 (18.5, 46.4)	23.8 (15.1, 31.8)	33.6 (18.1, 55.4)	39.0 (15.8, 55.9)	50.9 (23.1, 61.8)	47.8 (22.8, 60.2)	44.2 (23.9, 57.1)	48.0 (25.7, 60.6)	42.8 (23.3, 57.5)	51.0 (32.9, 60.2)	53.5 (34.1, 63.7)	52.8 (34.2, 62.5)	52.6 (30.8, 61.4)
Hospitalization costs, adjusted to 2020 dollars in millions	9.29	35.70	31.61	83.63	59.99	77.42	105.44	110.30	143.30	200.80	186.10	194.58	283.27
In-hospital deaths, N	–	–	19	64	48	38	34	91	80	124	121	106	146
Percentage			4.60%	4.87%	4.03%	2.84%	2.60%	5.85%	4.38%	4.93%	5.15%	4.41%	5.18%
(95% CI, %)			(0.00, 9.96)	(2.45, 7.29)	(1.59, 6.46)	(0.92, 4.76)	(0.67, 4.52)	(2.90, 8.79)	(1.19, 2.07)	(3.08, 6.77)	(3.18, 7.12)	(2.43, 6.39)	(3.29, 7.07)
Non-alcoholic liver cirrhosis													
Discharges, N	92	240	302	997	955	1,020	963	1,186	1,339	1,814	1,715	1,770	1,975
Rate per 100,000[a]	0.3	0.6	0.8	2.6	2.5	2.7	2.5	3.1	3.6	4.9	4.7	5.0	5.6
(95% CI, %)	(0.1, 0.4)	(0.4, 0.9)	(0.5, 1.1)	(1.9, 3.3)	(1.8, 3.2)	(2.0, 3.3)	(1.9, 3.1)	(2.3, 4.0)	(2.8, 4.4)	(3.8, 6.0)	(4.0, 5.4)	(4.3, 5.6)	(4.7, 6.5)
Median age at admission in years (IQR)	36.0 (20.9, 48.9)	25.9 (17.2, 33.7)	44.7 (22.6, 56.6)	46.8 (20.8, 57.7)	54.1 (30.1, 63.2)	50.4 (37.6, 61.2)	48.6 (32.0, 60.1)	52.0 (41.0, 62.4)	48.6 (32.4, 60.9)	53.9 (41.4, 63.1)	56.5 (41.9, 65.4)	56.4 (43.2, 64.2)	55.3 (42.3, 63.5)
Hospitalization costs, adjusted to 2020 dollars in millions	6.84	30.34	29.21	59.79	49.22	49.22	74.31	81.61	96.83	137.40	132.27	147.37	194.28
In-hospital deaths, N	–	–	18	60	48	38	25	82	70	115	105	96	126
Percentage			6.03%	5.93%	4.94%	3.67%	2.50%	6.88%	5.23%	6.34%	6.12%	5.42%	6.44%
(95% CI, %)			(0.00, 12.9)	(2.77, 9.08)	(1.99, 7.89)	(1.11, 6.23)	(0.39, 4.61)	(3.18, 10.6)	(2.41, 8.03)	(3.84, 8.78)	(3.58, 8.66)	(2.93, 7.81)	(3.92, 8.73)
Liver transplants, N	–	30	32	54	33	30	99	62	91	109	135	115	165
Percentage		12.31%	10.62%	5.38%	3.42%	2.91%	10.2%	5.19%	6.80%	6.01%	7.87%	6.50%	8.43%
(95% CI, %)		(1.69, 22.8)	(3.03, 18.2)	(1.90, 8.87)	(0.67, 6.18)	(0.66, 5.16)	(4.27, 16.1)	(2.74, 7.65)	(3.39, 10.2)	(3.39, 8.62)	(4.72, 11.0)	(3.93, 9.06)	(5.58, 11.1)

IQR, interquartile range; CI, confidence interval.
aRelative to all annual NIS discharges.
–indicates that the number recorded within the NIS database is <11 and thus cannot be reported as per the license-user agreement.
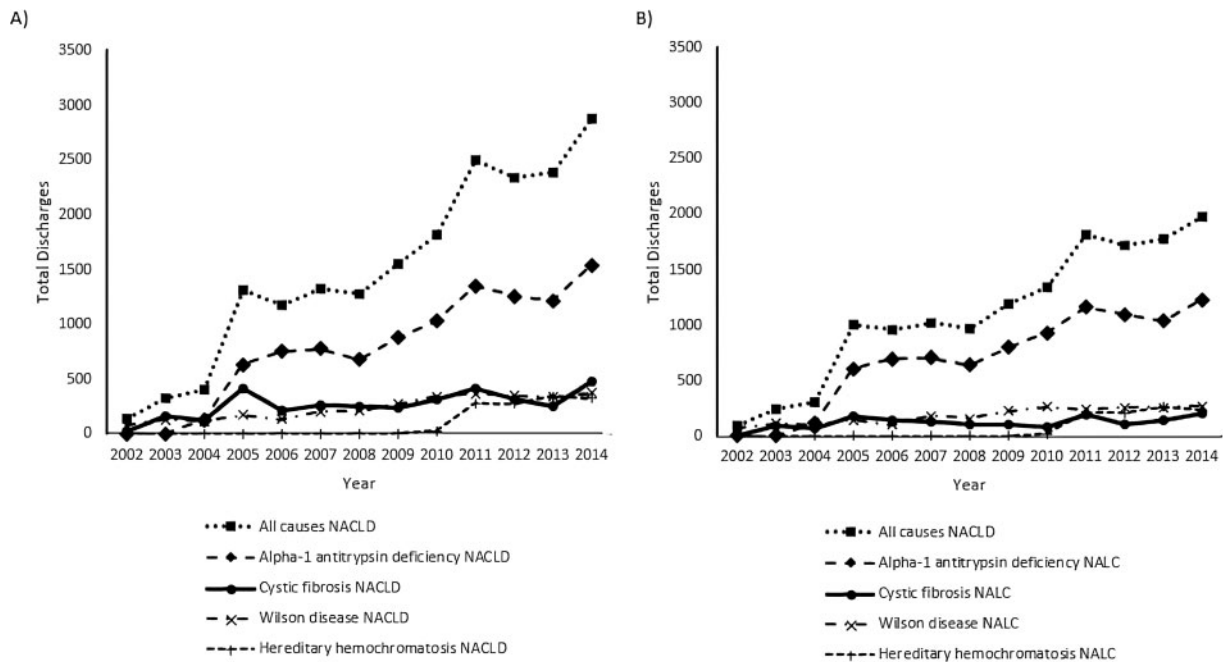
Figure 1. Annually increasing hospitalizations for genetic liver disease. (A) Non-alcoholic chronic liver disease (NACLD); (B) non-alcoholic liver cirrhosis (NALC).

hospital deaths associated with NALC followed a similar pattern (Figure 2). The greatest number of liver transplants was performed for A1ATd (7.01%, 630/8,987), followed by WD, HHC, and CF (Table 2); however, the greatest percentage of hospitalizations for NALC associated with a liver transplant was 16.15% (21/130) of hospitalizations for patients with DAAAM.

Alpha-1 antitrypsin deficiency was the most common cause of hospitalizations for genetic NALC with 8,983 cases (62.52%), whereas DAAAM had the fewest hospitalizations (130 cases, 0.90%) over the 12-year study period. Of all the 61,260 A1ATd discharges between 2002 and 2014, 10,243 (16.72%) were for NACLD and 8,983 (14.66%) were for NALC. The annual number of discharges for NACLD and NALC associated with A1ATd increased substantially from 2002 to 2014 (Table 3). Interestingly, the percentage of in-hospital deaths for patients with A1ATd NALC peaked in 2011 at 7.08% (Table 3). The consistently increasing numbers of annual discharges for both NACLD and NALC for WD, CF, and HHC are shown in Table 4.

Discussion

Literature reporting the epidemiological trends of the in-hospital prevalence of NACLD and NALC secondary to genetic diseases is lacking. This study provides one of the first large database analyses for NACLD and NALC associated with genetic diseases to date, for which there were nearly 20,000 hospitalizations for NACLD and 15,000 for NALC between 2002 and 2014. There was a significant increase in hospitalizations throughout the study period for both NACLD and NALC, which is likely due to the improved accuracy, availability, and access to testing as reported specifically for A1ATd, WD, and HHC, along with an increased awareness of genetic diseases by healthcare providers [8–12]. New information on hospitalized patient characteristics, healthcare expenditures, and geographical distribution has been provided for each genetic liver disease. There was a predominance of male patients admitted for all genetic causes of NALC, as having previously been reported in medical literature

for A1ATd, CF, and HHC, though WD has previously been documented as having an equal gender distribution [13–17]. Overall, patient age at hospitalization increased over the 12 years, suggesting that either treatments are improving or that there is an increased awareness and recognition of each disease with treatments being started at a younger age and earlier in the disease course. Annual hospitalization charges also increased substantially through the study period by over 25-fold for NALC, which may largely be due to increased recognition of these genetic diseases or the costs of treatments and liver transplants. Genetic NALC was observed primarily in Caucasian individuals, likely in part as it is the dominant ethnicity in the USA. However, GSDs and DAAAM showed an increased prevalence of hospitalizations associated with non-Caucasian patients, as GSDs have been shown to more commonly affect individuals from Indian, Native American, and Hispanic ethnicities [18]. Disorders of aromatic amino-acid metabolism (mainly targeting tyrosinemia, the one DAAAM disorder with associated liver disease) is more common in areas of Quebec, Canada, with a prevalence of 54 per 100,000 in certain regions and a carrier rate of 1/20, while, in the USA, it is rare, with a prevalence of $<1/100,000$ [19]. Hospitalizations for genetic NALC were overrepresented in the southern USA, which covers highly populated states including Texas, Georgia, Florida, and North Carolina. Though the total number of hospitalizations for genetic NALC was significant, they compose only a small portion of the total number of liver-cirrhosis hospitalizations as previously reported by Desai *et al.* [2].

Alpha-1 antitrypsin deficiency was associated with the greatest number of hospitalizations of all the genetic liver diseases over the 12-year study period for both NACLD and NALC. Recent literature has reported that the prevalence of severe A1ATd of the homozygous PiZZ genotype is ~1 in every 3,500 births for which the onset of liver involvement occurs anytime between the first and sixth decades [5, 20]. It is expected that pulmonary disease in the form of chronic obstructive pulmonary disease (COPD) secondary to A1ATd is even more common

Table 2. Total data from 2002 to 2014 per cause of genetic disease

Genetic disease	All combined genetic causes[d]	Alpha-1 antitrypsin deficiency	Cystic fibrosis	Wilson disease	Hereditary hemochromatosis	Glycogen storage diseases	DAAAM
All discharges, N	192,270	61,260	61,078	19,206	6,229	31,643	13,482
Rate per 100,000[a]	39.9	12.7	12.6	4.0	1.3	6.6	2.8;
(95% CI, %)	(36.2, 43.6)	(12.1, 13.2)	(9.5, 15.8)	(3.8, 4.2)	(1.2, 1.4)	(6.0, 7.1)	(2.6, 3.0)
NACLD discharges, N	19,332	10,243	3,550	3,063	1,230	1,099	212
Percentage of specific genetic disease	10.1%	16.7%	5.81%	15.9%	19.7%	3.47%	1.57%
(95% CI, %)	(9.40, 10.7)	(15.6, 17.8)	(5.15, 6.47)	(14.5, 17.4)	(17.4, 22.0)	(2.77, 4.18)	(0.97, 2.18)
NALC discharges, N	14,368	8,983	1,532	2,375	923	462	130
Percentage of all genetic NALC discharges[e]	7.47%[e]	62.52%	10.66%	16.53%	6.42%	3.21%	0.90%
(95% CI, %)	(6.83, 8.08)	(59.86, 65.18)	(8.46, 12.86)	(14.60, 18.46)	(5.53, 7.51)	(2.41, 4.02)	(0.39, 1.40)
Median age on admission in years	52.7	56.5	17.9	43.9	60.4	37.9	3.9
(IQR)[b]	(36.7, 62.2)	(46.8, 64.8)	(13.5, 25.0)	(31.6, 55.1)	(53.8, 67.6)	(19.6, 53.3)	(0.59, 23.2)
Male gender, N	8,032	5,057	793	1,228	618	274	76
Percentage[b]	55.9%	56.3%	51.8%	51.7%	67.0%	59.3%	58.3%
Race (percentage)[b]							
Caucasian	71.88	76.93	67.17	59.54	78.50	49.35	41.79
Other	28.13	23.07	32.83	40.46	21.50	50.65	58.21
Insurance (%)[b]							
Medicare	38.24	44.26	13.45	28.63	52.38	28.44	26.56
Medicaid	16.23	12.02	32.52	21.15	9.97	23.98	40.19
Private	38.72	38.23	48.96	38.43	29.29	34.29	30.06
Other	6.81	5.48	5.07	11.78	8.37	13.29	–
Income (%)[b]							
1st quartile	25.35	25.46	20.99	28.24	23.18	29.29	20.60
2nd quartile	27.10	28.69	23.29	23.62	25.26	32.30	20.32
3rd quartile	26.29	25.15	29.99	27.90	27.80	22.65	27.27
4th quartile	21.27	20.70	25.73	20.23	23.76	15.75	31.80
Geography (%)[b]							
Northeast	15.65	11.90	25.76	18.43	21.58	23.39	35.52
Midwest	26.87	32.01	14.04	20.87	18.21	19.26	–
South	40.61	41.43	43.02	39.11	42.07	35.18	–
West	16.88	14.67	17.18	21.59	18.14	22.17	44.27
Hospitalization costs adjusted to 2020 dollars in millions[b]	1,097.70	626.36	150.23	202.5	73.91	40.56	10.48
Total in-hospital deaths, N	790	518	63	107	74	28	0
Percentage[c]	5.50%	5.78%	4.12%	4.50%	8.02%	6.06%	(0%)
(95% CI, %)[b]	(4.69, 6.32)	(4.73, 6.82)	(1.91, 6.32)	(2.74, 6.25)	(4.29, 11.35)	(2.10, 10.36)	
Liver transplants performed, N	955	630	26	222	34	22	21
Percentage[c]	6.65%	7.01%	1.70%	9.34%	3.68%	4.76%	16.15%
(95% CI, %)[b]	(5.70, 7.61)	(5.76, 8.20)	(0.43, 3.34)	(6.63, 12.09)	(1.01, 6.46)	(0.94, 9.26)	(6.35, 31.13)

NACLD, non-alcoholic chronic liver disease; NALC, non-alcoholic liver cirrhosis; DAAAM, disorders of aromatic amino-acid metabolism; IQR, interquartile range; CI, confidence interval.

aRelative to all NIS discharges.

bNALC discharges.

cPercentage of disease-specific discharges for NALC.

dFigures reported for all combined genetic causes may differ from the row sum of the individual disease due to some patients being affected by more than one genetic disease.

ePercentage of all genetic-disease discharges.

–indicates that the number recorded within the NIS database is <11 and thus cannot be reported as per the license-user agreement.
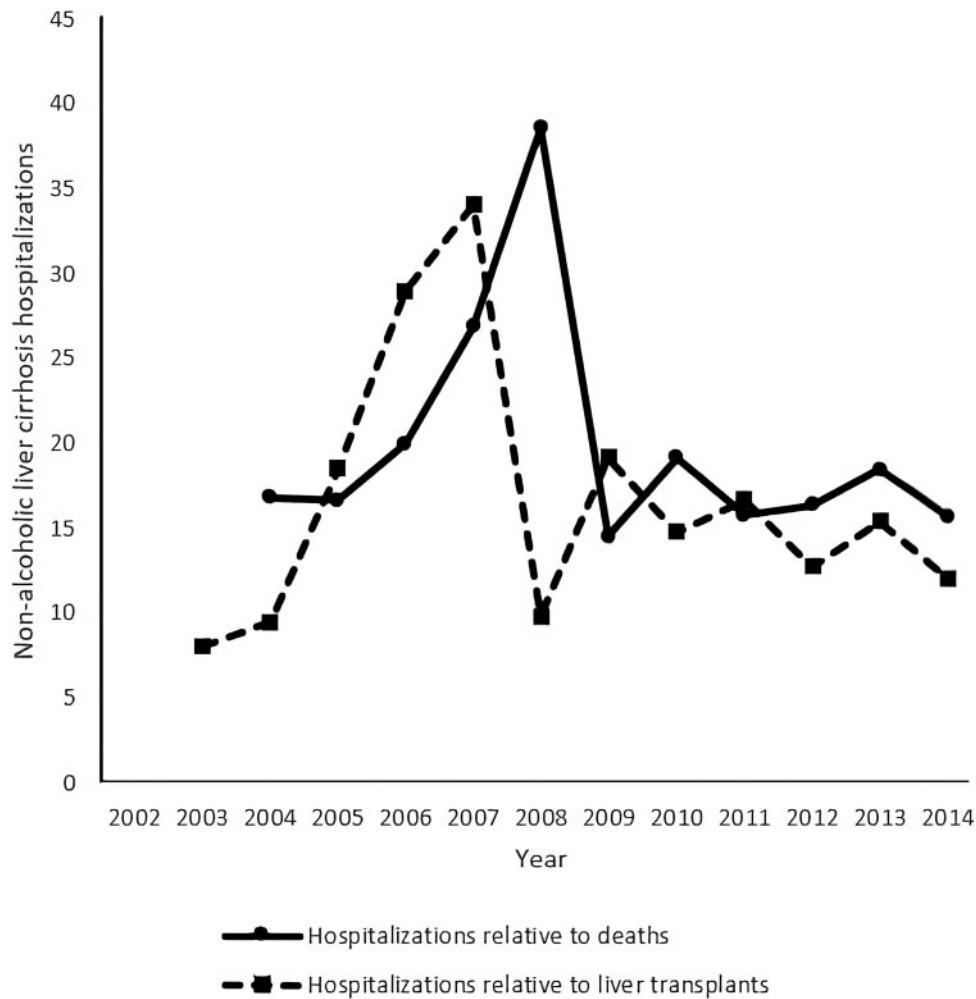
Figure 2. Hospitalizations relative to in-hospital deaths and liver transplants performed for genetic non-alcoholic liver cirrhosis. The frequency of annual hospitalizations relative to in-hospital deaths peaked at 40 in 2008 and leveled off thereafter at 20. The frequency of annual hospitalizations relative to liver transplants performed peaked at 35 in 2007 and leveled off thereafter at 15.

than presentations of liver disease, with estimates suggesting that ≤5% of all COPD cases involve underlying A1ATd [21]. Even though A1ATd is reported as the second most prevalent genetic liver disorder behind HHC by Scorza *et al.* [5], it was responsible for the greatest number of hospitalizations for genetic liver disease between 2002 and 2014. Hereditary hemochromatosis has a variable penetrance, an insidious onset later in life, and can be associated with protective factors including the female gender until reaching menopause—and, further, it can be effectively treated with a phlebotomy regimen to prevent further liver deterioration [22, 23]. Additionally, ICD9 codes for HHC were not adopted until 2010, likely contributing to its overall low prevalence in this study as compared to A1ATd, for which the ICD9 code was adopted in 2004; nevertheless, annual trends seen after the incorporation of these codes remain significant [24]. Of the genetic liver diseases studied here, A1ATd had the greatest percentage of NACLD hospitalizations designated as NALC (87.70%), suggesting that this disorder is largely associated with cirrhosis of the liver instead of other hepatic pathologies. Conversely, CF had the lowest percentage of NACLD designated as NALC (43.15%), as other common etiologies of NACLD have been established for CF patients including biliary cirrhosis [25]. Unfortunately, there are currently no medical therapies for A1ATd liver disease and thus the avoidance of

both alcohol and high-risk lifestyles is emphasized to prevent any additional toxic and viral hepatopathies. At the present time, the only curative treatment for A1ATd liver disease is a liver transplant, for which the annual occurrence increased throughout the study duration [6].

The fewest number of hospitalizations for genetic NALC was from DAAAM, which also had the youngest hospitalized patients and the greatest frequency of liver transplants performed for genetic liver disease between 2002 and 2014. For this study, DAAAM was mainly targeted towards tyrosinemia, which is the only DAAAM disease associated with liver disease. The ICD9 diagnosis code of 270.2 for DAAAM includes tyrosinemia, along with other diseases including alkoptonuria, albinism, disorders of tryptophan metabolism, indicanuria, Waardenberg syndrome, Woolf syndrome, ochronosis, and kynureninase deficiency—all of which had no published case reports involving liver disease as of 2014. Tyrosinemia is associated with a deficiency in the enzyme fumarylacetoacetate hydrolase that causes an accumulation of succinylacetone following the consumption of tyrosine-containing foods, which can result in neurological deterioration, renal damage, and either acute liver failure or progressive liver disease in the form of cirrhosis, particularly with type 1 tyrosinemia [26]. Dietary restrictions of tyrosine and phenylalanine (for which tyrosine is a metabolic

Table 3. Annual data for alpha-1 antitrypsin deficiency liver disease

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
NACLD discharges, N	–	–	125	629	750	775	678	879	1,030	1,354	1,250	1,215	1,540
Rate per 100,000[a]			0.3	1.7	2.0	2.0	1.8	2.3	2.8	3.7	3.4	3.4	4.4
(95% CI, %)			(0.2, 0.5)	(1.2, 2.2)	(1.4, 2.5)	(1.5, 2.5)	(1.3, 2.3)	(1.7, 2.9)	(2.1, 3.5)	(2.8, 4.5)	(2.8, 4.0)	(2.9, 4.0)	(3.5, 5.2)
NALC discharges, N Rate per 100,000[a]	0	0	111	606	691	698	635	799	932	1,158	1,095	1,035	1,230
(95% CI, %)	0.0	0.0	0.3	1.6	1.8	1.8	1.7	2.1	2.5	3.1	3.0	2.9	3.5
			(0.1, 4.0)	(1.1, 2.1)	(1.3, 2.4)	(1.3, 2.3)	(1.2, 2.2)	(1.5, 2.7)	(1.8, 3.2)	(2.4, 3.9)	(2.4, 3.6)	(2.4, 3.4)	(2.8, 3.2)
Median age at admission in years (IQR)[b]	–	–	56.3	54.9	56.6	54.4	52.9	56.2	53.6	56.4	58.7	58.3	58.4
			(48.1, 60.6)	(46.4, 61.0)	(44.0, 64.2)	(48.1, 63.3)	(41.2, 62.9)	(47.2, 66.4)	(41.3, 63.5)	(46.9, 64.5)	(47.2, 67.7)	(49.9, 65.8)	(50.3, 65.0)
Hospitalization costs adjusted to 2020 dollars in millions[b]	–	–	10.32	23.16	25.50	31.33	46.45	54.33	67.06	86.40	77.87	82.92	108.00
In-hospital deaths, N	0	0	–	31	33	24	20	66	40	82	75	60	80
% of NALC discharges	0.0%	0.0%		5.15%	4.77%	3.38%	3.06%	8.24%	4.29%	7.08%	6.85%	5.80%	6.50%
(95% CI, %)[b]				(1.51, 8.79)	(1.55, 7.99)	(0.52, 6.24)	(0.17, 5.94)	(3.66, 12.8)	(1.30, 7.20)	(3.62, 10.7)	(3.64, 10.1)	(2.41, 9.19)	(3.63, 9.38)
Liver transplants, N % of NALC discharges	0	0	19	25	24	19	71	53	57	87	100	75	100
	0.0%	0.0%	16.4%	4.08%	3.39%	2.85%	11.2%	6.52%	6.12%	7.51%	9.13%	7.25%	8.13%
(95% CI, %)[b]			(0.71, 32.1)	(0.00, 9.17)	(0.03, 6.75)	(0.14, 5.57)	(4.42, 17.9)	(2.89, 10.2)	(2.19, 10.0)	(4.32, 10.6)	(4.72, 13.5)	(3.73, 10.8)	(4.85, 11.4)

NACLD, non-alcoholic chronic liver disease; NALC, non-alcoholic liver cirrhosis; IQR, interquartile range; CI: confidence interval.
[a]Relative to all annual NIS discharges.
[b]NALC discharges.
–indicates that the number recorded within the NIS database is <11 and thus cannot be reported as per the license-user agreement.

Table 4. Annual data for liver disease from cystic fibrosis, Wilson disease, and hereditary hemochromatosis

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Cystic fibrosis													
NACLD discharges, N	19	161	122	415	217	257	245	241	318	420	315	350	475
Rate per 100,000[a]	0.1	0.4	0.3	1.1	0.6	0.7	0.6	0.6	0.8	1.1	0.9	1.0	1.3
(95% CI, %)	(0.0, 0.1)	(0.2, 0.7)	(0.1, 0.5)	(0.4, 1.8)	(0.3, 0.9)	(0.1, 1.2)	(0.2, 1.1)	(0.3, 1.0)	(0.3, 1.4)	(0.6, 1.7)	(0.6, 1.2)	(0.6, 1.3)	(0.9, 1.7)
NALC discharges, N	–	86	70	185	138	128	108	102	84	191	100	140	200
Rate per 100,000[a]		0.2	0.2	0.5	0.4	0.3	0.3	0.3	0.2	0.5	0.3	0.4	0.6
(95% CI, %)		(0.1, 0.4)	(0.1, 0.3)	(0.2, 0.8)	(0.2, 0.6)	(0.1, 0.6)	(0.0, 0.5)	(0.1, 0.5)	(0.1, 0.4)	(0.2, 0.8)	(0.1, 0.4)	(0.2, 0.6)	(0.3, 0.8)
Median age at admission in years (IQR)[b]	–	19.5 (12.2, 24.3)	22.2 (11.8, 23.5)	15.5 (13.4, 19.4)	17.1 (13.0, 23.7)	15.8 (12.1, 29.1)	21.7 (9.5, 32.3)	26.6 (16.9, 35.1)	15.7 (13.3, 24.3)	18.8 (13.2, 26.1)	20.5 (16.0, 24.0)	18.5 (14.3, 22.0)	16.5 (11.8, 21.7)
Hospitalization costs, adjusted to 2020 dollars in millions[b]	0.170	12.99	6.92	11.60	10.08	9.04	8.76	8.92	11.02	18.61	9.08	21.63	24.29
Wilson disease													
NACLD discharges, N	79	124	113	170	135	200	209	272	340	367	351	335	375
Rate per 100,000[a]	0.2	0.3	0.3	0.4	0.4	0.5	0.5	0.7	0.9	1.0	1.0	0.9	1.1
(95% CI, %)	(0.1, 0.3)	(0.2, 0.5)	(0.2, 0.4)	(0.2, 0.7)	(0.2, 0.5)	(0.3, 0.8)	(0.4, 0.7)	(0.4, 1.0)	(0.6, 1.2)	(0.7, 1.3)	(0.7, 1.2)	(0.7, 1.2)	(0.8, 1.3)
NALC discharges, N	60	116	100	147	104	182	160	228	264	239	256	255	270
Rate per 100,000[a]	0.2	0.3	0.3	0.4	0.3	0.5	0.4	0.6	0.7	0.6	0.7	0.7	0.8
(95% CI, %)	(0.0, 0.3)	(0.1, 0.5)	(0.1, 0.4)	(0.1, 0.6)	(0.1, 0.4)	(0.2, 0.7)	(0.3, 0.6)	(0.4, 0.9)	(0.5, 1.0)	(0.4, 0.9)	(0.5, 0.9)	(0.5, 0.9)	(0.5, 1.0)
Median age at admission in years (IQR)[b]	33.4 (24.1, 46.2)	32.2 (26.2, 36.3)	45.5 (34.2, 54.3)	39.1 (19.8, 46.8)	44.0 (36.3, 53.7)	44.9 (27.9, 51.0)	50.3 (37.2, 58.9)	40.2 (23.9, 48.7)	40.2 (23.9, 48.7)	48.2 (34.7, 54.0)	44.2 (34.3, 56.3)	47.0 (33.8, 58.8)	46.0 (31.4, 58.2)
Hospitalization costs, adjusted to 2020 dollars in millions[b]	5.94	13.34	9.17	22.52	12.26	8.46	11.39	14.07	16.24	14.09	26.91	18.28	35.58
Hereditary hemochromatosis													
NACLD discharges, N	–	–	–	–	–	–	–	–	25	276	271	341	321
Rate per 100,000[a]	–	–	–	–	–	–	–	–	0.1	0.7	0.7	1.0	0.9
(95% CI, %)	–	–	–	–	–	–	–	–	(0.0, 0.1)	(0.5, 1.0)	(0.5, 1.0)	(0.7, 1.2)	(0.7, 1.1)
NALC discharges, N	–	–	–	–	–	–	–	–	20	213	206	265	235
Rate per 100,000[a]	–	–	–	–	–	–	–	–	0.1	0.6	0.6	0.7	0.7
(95% CI, %)	–	–	–	–	–	–	–	–	(0.0, 0.1)	(0.4, 0.8)	(0.4, 0.8)	(0.5, 1.0)	(0.5, 0.9)
Median age at admission in years (IQR)[b]	–	–	–	–	–	–	–	–	64.1 (57.0, 67.1)	59.1 (52.4, 67.2)	60.6 (56.3, 65.5)	61.5 (53.6, 68.8)	58.5 (51.9, 67.6)
Hospitalization costs, adjusted to 2020 dollars in millions[b]	–	–	–	–	–	–	–	–	14.90	13.58	15.85	19.25	18.78

NACLD, non-alcoholic chronic liver disease; NALC, non-alcoholic liver cirrhosis; IQR: interquartile range; CI, confidence interval.
aRelative to all annual NIS discharges.
bNALC discharges.
–indicates that the number recorded within the NIS database is <11 and thus cannot be reported as per the license-user agreement.

product) do not alter the progression of liver damage but treatments of 2-(2-nitro-4-trifluoromethylmenzoyl)-1,3 cyclohexanedione (NTBC) have been found to reverse acute liver failure within days [27]. We found that 16.15% of hospitalizations for DAAAM NALC were associated with a liver transplant, the highest frequency of all the genetic liver diseases. Unfortunately, this disease is associated with one of the highest incidences of hepatocellular carcinoma at a rate of 15%–37% [19]. Literature suggests that cirrhosis, liver failure, and hepatocellular carcinoma can develop at ages as young as 1 year old and that liver transplants are often performed by 2 years old, explaining the relatively young age of hospitalized patients and the high percentage of liver transplants performed for tyrosinemia as compared to the other genetic diseases investigated here [19, 26]. With regard to the in-hospital mortality reported as zero for NALC from DAAAM, we believe that, because tyrosinemia is an exceedingly rare disease likely seen by only a handful of physicians in the USA, the true number of deaths is below the level of detection using the NIS methodology that samples only 20% of American hospitals to establish national estimates.

The genetic disease associated with the second fewest hospitalizations for NALC were GSDs, with only 462 over the 12-year study period. GSDs are uncommon, with an overall incidence estimated to be 1 in 43,000 births [28]. There are three GSDs associated with liver cirrhosis, including GSD type III (Cori disease), GSD type IV (Andersen disease), and GSD type IX [28]. Liver cirrhosis from GSD type I (von Gierke disease) is uncommon, with patients more often presenting with liver steatosis, hepatomegaly, and hepatic adenomas with associated hypoglycemia and hyperlipidemia [29]. With GSD IV being exceedingly rare, composing only 0.3% of all GSDs, and being associated with a rapidly progressing cirrhosis leading to death by age 3–5 years, this would be expected to compose only a small minority of our cohort [30]. With our results showing a median age of 37.9 years at admission, this population is likely represented primarily by individuals with the diagnosis of GSD III or GSD IX, which comprise 24% and 25% of all GSDs, respectively [28]. Patients with either of these two GSD types are known to live a near-normal lifespan into their late 60s [31, 32].

CF was the genetic liver disease associated with the second youngest hospitalized patients for NALC, at a median age of 18 years, and the fewest liver transplants performed for all genetic NALC. Patients with CF often have shorter life expectancies due to respiratory complications resulting in a median lifespan of ~40 years of age [33]. As treatments to mitigate CF-related respiratory disease have improved, patients' life expectancies have increased, leading to a growing prevalence of non-pulmonary CF complications including chronic liver disease [34]. With regard to causes of CF mortality, liver disease is second to pulmonary complications and causes 2.5% of all deaths [25]. The median age in our cohort for CF patients hospitalized with liver cirrhosis was 18 years, in agreement with results presented by Scott-Jupp *et al.* [35], who demonstrated that CF patients who develop liver cirrhosis often do so between 10 and 20 years old, with a peak incidence at the age of 18 years. Liver injury in CF can often be from biliary cirrhosis secondary to biliary obstruction, as cholangiocyte and CFTR-related abnormalities result in highly viscous bile, for which treatment can include ursodeoxycholic acid or, more definitively, a liver transplant [25, 36, 37]. Further, only 1.70% of NALC hospitalizations for CF were associated with a liver transplant—the lowest frequency of all the genetic liver diseases studied here. Hospitalizations for CF are most often for pulmonary complications, even in the presence of liver cirrhosis, which is likely a

large reason for this low frequency. Fewer liver transplants may be performed in CF patients due to poor outcomes stemming from malnourishment and diminished pulmonary reserve, as worse post-operative outcomes have been seen relative to other causes of liver disease—including when considering combined liver and lung transplants [38].

The genetic liver disease that was associated with the oldest age at hospitalization for NALC was hereditary hemochromatosis (HHC), with patients hospitalized at a median age of 60 years. Annually, there were up to 265 hospitalizations for this cause of NALC and 75% of all patients hospitalized for NACLD from HHC were designated as having NALC. A study published by Beaton *et al.* [39] demonstrated that the average age for cirrhosis diagnosis in HHC patients is ~57 years, with the 20-year survival rate thereafter being ~56%. Shortly after a diagnosis of HHC, a phlebotomy regimen is initiated to control serum iron levels and prevent further progression of cirrhosis, allowing many patients to achieve average life expectancies [40].

We hope that this information, showing a consistently increasing prevalence of patients hospitalized for genetic NACLD and NALC, can be used to advocate for increased funding for genetic liver diseases to further develop treatments with the goal of minimizing hospitalizations and liver transplants. Future research could explore how hospitalization trends for genetic liver diseases in patients consuming alcohol differ and, further, how the occurrences of complications of decompensated liver disease (ascites, portal hypertension, variceal bleeding, etc.) differ between patients with genetic liver disease who consume alcohol compared with those who do not. As more years of ICD10 data become available, longitudinal trends for additional rare forms of genetic liver disease (citrin deficiency, Neimann–Pick disease, etc.) could be investigated. Nevertheless, the data presented here provide valid estimates of relative trends, patient characteristics, and in-hospital data to effectively illustrate the healthcare and economic burden of genetic causes of NACLD and NALC within the USA.

Limitations

The NIS database is one of the largest national healthcare databases utilizing diagnosis and procedure codes, enabling analyses on patients with rare diseases, and is often used to report trends and associations in healthcare [41]. However, the NIS has several inherent biases due to data being discharge-specific (rather than patient-specific) and because of its reliance upon documented diagnostic and procedural codes. For this analysis, the designations NACLD and NALC were used with the intention of investigating trends in hospitalizations and patient characteristics for liver damage solely from the targeted genetic disorders discussed here; using specific inclusion criteria, we have managed to exclude liver damage from alcohol and a subgroup analysis yielded that there were too few cases of concomitant viral hepatitis B or C to be reported per the NIS user agreement (<11 weighted occurrences by any subgroup category). Though the NACLD and NALC designations are used to target genetic causes of liver damage, we cannot exclude additional concomitant hepatopathies including NAFLD (or, more recently, termed metabolic associated fatty liver disease) secondary to metabolic syndrome.

The diagnosis code of alcoholic cirrhosis of the liver (ICD9 571.2) was not included as physicians diagnose genetic causes of cirrhosis by initiating extensive testing, often in the absence of apparent toxic liver damage. In cases of liver cirrhosis in the setting of excessive alcohol intake, our experience is that

further investigation into the cause of liver damage is often overlooked even though the etiology could be multifactorial. This establishes a paradigm that suggests that many patients with alcoholic cirrhosis may have additional underlying genetic disorders contributing to their liver damage that remain undiagnosed.

With regard to organ transplants, the NIS database has previously been used to analyse specific trends and associations, for which we utilized the codes for liver transplant as used by Ali *et al.* [42–46]. Due to the sampling methodology utilized by the NIS database, it does not yield the exact results of specific organ-transplant registries such as the Organ Procurement and Transplantation Network registry. However, the NIS contains useful details including patient information collected from diagnostic and procedure codes that cannot be found in individual organ registries [43].

Conclusion

There were a significant number of hospitalizations, in-hospital deaths, and liver transplants performed for NACLD and NALC due to genetic causes between 2002 and 2014 in the USA. Though these figures are small relative to hospitalizations for cirrhosis from hepatitis C, alcoholic liver disease, and NAFLD, they demonstrate the burden of liver deterioration in many patients with genetic disorders. With increased funding and directed efforts in medical research, we can aim to improve the treatment modalities for each of these genetic diseases and help affected patients to have an increased quality of life with the goal of avoiding hospitalizations and transplants for liver disease.

Authors' contributions

Funding

Acknowledgements

Conflicts of interest

None declared.

References

1. US Department of Health and Human Services, and Centers for Disease Control and Prevention. *Summary Health Statistics: National Health Interview Survey*, 2018. National Center for Health Statistics. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-4.pdf (20 October 2020, date last accessed).

2. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. *BMJ* 2018;**362**:k2817.

3. Desai AP, Mohan P, Nokes B *et al.* Increasing economic burden in hospitalized patients with cirrhosis: analysis of a national database. *Clin Transl Gastroenterol* 2019;**10**:e00062.

4. Perumpail BJ, Khan MA, Yoo ER *et al.* Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. *World J Gastroenterol* 2017;**23**:8263–76.

5. Scorza M, Elce A, Zarrilli F *et al.* Genetic diseases that predispose to early liver cirrhosis. *Int J Hepatol* 2014;**2014**:1–11.

6. Zhang KY, Tung BY, Kowdley KV. Liver transplantation for metabolic liver diseases. *Clin Liver Dis* 2007;**11**:265–81.

7. Bureau of Labor Statistics. CPI Inflation Calculator. www.data.bls.gov/cgi-bin/cpicalc.pl (31 March 2020, date last accessed).

8. Campos MA, Wanner A, Zhang G *et al.* Trends in the diagnosis of symptomatic patients with alpha1-antitrypsin deficiency between 1968 and 2003. *Chest* 2005;**128**:1179–86.

9. Soriano JB, Lucas SJ, Jones R *et al.* Trends of testing for and diagnosis of α(1)-antitrypsin deficiency in the UK: more testing is needed. *Eur Respir J* 2018;**52**:1800360.

10. Majumdar R, Al Jumah M, Al Rajeh S *et al.* A novel deletion mutation within the carboxyl terminus of the copper-transporting ATPase gene causes Wilson disease. *J Neurol Sci* 2000;**179**:140–3.

11. Riordan SM, Williams R. The Wilson's disease gene and phenotypic diversity. *J Hepatol* 2001;**34**:165–71.

12. Liang Q, Lichy JH. Molecular testing for hereditary hemochromatosis. *Expert Rev Mol Diagn* 2002;**2**:49–59.

13. Rakela J, Goldschmiedt M, Ludwig J. Late manifestation of chronic liver disease in adults with alpha-1-antitrypsin deficiency. *Digest Dis Sci* 1987;**32**:1358–62.

14. Bowlus CL, Willner I, Zern MA *et al.* Factors associated with advanced liver disease in adults with alpha1-antitrypsin deficiency. *Clin Gastroenterol Hepatol* 2005;**3**:390–6.

15. Colombo C, Battezzati PM, Crosignani A *et al.* Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. *Hepatology* 2002;**36**:1374–82.

16. Moirand R, Adams PC, Bicheler V *et al.* Clinical features of genetic hemochromatosis in women compared with men. *Ann Intern Med* 1997;**127**:105–10.

17. Litwin T, Gromadzka G, Członkowska A. Gender differences in Wilson's disease. *J Neurol Sci* 2012;**312**:31–5.

18. Chen MA, Weinstein DA. Glycogen storage diseases: diagnosis, treatment and outcome. *Transl Sci Rare Dis* 2016;**1**:45–72.

19. Russo PA, Mitchell GA, Tanguay RM. Tyrosinemia: a review. *Pediatr Dev Pathol* 2001;**4**:212–21.

20. Fairbanks KD, Tavill AS. Liver disease in alpha 1-antitrypsin deficiency: a review. *Am J Gastroenterol* 2008;**103**:2136–41.

21. Lieberman J, Winter B, Sastre A. Alpha 1-antitrypsin pi-types in 965 COPD patients. *Chest* 1986;**89**:370–3.

22. Palmer WC, Zaver HB, Ghoz HM. How I approach patients with elevated serum ferritin. *Am J Gastroenterol* 2020;**115**:1353–5.

23. Lam M, Torbenson M, Yeh MW *et al.* HFE mutations in alpha-1-antitrypsin deficiency: an examination of cirrhotic explants. *Mod Pathol* 2010;**23**:637–43.

24. Conversion Table of New ICD-9-CM Codes, October 2013. www.cdc.gov/nchs/data/icd/ICD-9-CM_FY14_CNVTBL_Final.pdf (2 April 2020, date last accessed).

25. Colombo C. Liver disease in cystic fibrosis. *Curr Opin Pulm Med* 2007;**13**:529–36.

26. Chinsky JM, Singh R, Ficicioglu C *et al*. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. *Genet Med* 2017;**19**:1380.

27. Paradis K. Tyrosinemia: the Quebec experience. *Clin Invest Med* 1996;**19**:311–6.

28. Ozen H. Glycogen storage diseases: new perspectives. *World J Gastroenterol* 2007;**13**:2541–53.

29. Kishnani PS, Austin SL, Abdenur JE *et al*. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med* 2014;**16**:e1.

30. L'Hermine-Coulomb A, Beuzen F, Bouvier R *et al*. Fetal type IV glycogen storage disease: clinical, enzymatic, and genetic data of a pure muscular form with variable and early antenatal manifestations in the same family. *Am J Med Genet A* 2005;**139A**:118–22.

31. Kishnani PS, Austin SL, Arn P *et al*. Glycogen storage disease type III diagnosis and management guidelines. *Genet Med* 2010;**12**:446–63.

32. Kishnani PS, Goldstein J, Austin SL *et al*. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2019;**21**:772–89.

33. Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med* 2006;**173**:475–82.

34. Leeuwen L, Fitzgerald DA, Gaskin KJ. Liver disease in cystic fibrosis. *Paediatr Respir Rev* 2014;**15**:69–74.

35. Scott-Jupp R, Lama M, Tanner MS. Prevalence of liver disease in cystic fibrosis. *Arch Dis Child* 1991;**66**:698–701.

36. Lindblad A, Hultcrantz R, Strandvik B. Bile-duct destruction and collagen deposition: a prominent ultrastructural feature of the liver in cystic fibrosis. *Hepatology* 1992;**16**:372–81.

37. Lindblad A, Glaumann H, Strandvik B. A two-year prospective study of the effect of ursodeoxycholic acid on urinary bile acid excretion and liver morphology in cystic fibrosis-associated liver disease. *Hepatology* 1998;**27**:166–74.

38. Mendizabal M, Reddy KR, Cassuto J *et al*. Liver transplantation in patients with cystic fibrosis: analysis of United Network for Organ Sharing data. *Liver Transpl* 2011;**17**:243–50.

39. Beaton MD, Adams PC. Prognostic factors and survival in patients with hereditary hemochromatosis and cirrhosis. *Can J Gastroenterol* 2006;**20**:257–60.

40. Brandhagen DJ, Fairbanks VF, Baldus W. Recognition and management of hereditary hemochromatosis. *Am Fam Physician* 2002;**65**:853–60.

41. Quan H, Li B, Saunders LD *et al*. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res* 2008;**43**:1424–41.

42. Ali M, Ananthakrishnan AN, Ahmad S *et al*. Clostridium difficile infection in hospitalized liver transplant patients: a nationwide analysis. *Liver Transpl* 2012;**18**:972–8.

43. Massie AB, Kuricka LM, Segev DL. Big data in organ transplantation: registries and administrative claims. *Am J Transplant* 2014;**14**:1723–30.

44. Scarborough JE, Pietrobon R, Marroquin CE *et al*. Temporal trends in early clinical outcomes and health care resource utilization for liver transplantation in the United States. *J Gastrointest Surg* 2007;**11**:82–8.

45. Pant C, Anderson MP, O'Connor JA *et al*. Association of Clostridium difficile infection with outcomes of hospitalized solid organ transplant recipients: results from the 2009 Nationwide Inpatient Sample database. *Transpl Infect Dis* 2012;**14**:540–7.

46. Friedman AL, Cheung K, Roman SA *et al*. Early clinical and economic outcomes of patients undergoing living donor nephrectomy in the United States. *Arch Surg* 2010;**145**:356–62.