

Chronic Liver Disease-Associated Hospitalizations Among Adults with Diabetes, National Inpatient Sample, 2001–2012

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ABSTRACT

Objective. Many people with diabetes have a variety of diabetes-related complications. Among the variety of conditions associated with diabetes, however, liver diseases are less well recognized. As such, we aimed to describe chronic liver disease (CLD)-associated hospitalization rates among U.S. adults with diabetes from 2001–2012.

Methods. We used a nationally representative database of hospitalizations, the National Inpatient Sample, to determine CLD-associated hospitalization rates among U.S. adults aged ≥ 18 years with and without diabetes, from 2001–2012. Hospitalizations listing an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for CLD on the discharge record were selected for analysis and were further classified by diabetes status based on concurrent presence of a diabetes ICD-9-CM code. We calculated average annual age-adjusted hospitalization rates and 95% confidence intervals (CIs), and conducted a test for trend.

Results. For 2001–2012, the total age-adjusted CLD-associated hospitalization rate among adults with diabetes (1,680.9 per 100,000 population; 95% CI 1,577.2, 1,784.6) was approximately four times the rate of adults without diabetes (424.2 per 100,000 population; 95% CI 413.4, 435.1). Total age-adjusted hospitalization rates of adults with and without diabetes increased 59% and 48%, respectively, from 2001–2002 to 2011–2012 ($p < 0.001$). Hepatitis C- and chronic hepatitis and cirrhosis-associated hospitalizations comprised the largest proportion of total CLD-associated hospitalizations among adults with and without diabetes.

Conclusion. Providers should be aware of the potential existence of CLD among adults with diabetes and counsel patients on preventive methods to avoid progressive liver damage.

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Approximately 11% of U.S. adults, or 25.6 million people, have diabetes mellitus. Diagnosed diabetes accounts for 73% of all cases of diabetes.¹ The number of Americans diagnosed with diabetes has more than tripled over the years, from approximately 6 million in 1980 to 21 million in 2011.² Type 2 diabetes, usually beginning with insulin resistance, comprises 90% to 95% of diagnosed diabetes cases among adults.¹ Insulin resistance and type 2 diabetes are associated with chronic liver disease (CLD), which has also increased in prevalence among U.S. adults, from 12% during 1988–1994 to 15% during 2005–2008.³ The spectrum of CLD associated with diabetes includes nonalcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, and viral hepatitis.^{3–15}

Despite the increasing prevalence of both type 2 diabetes and CLD and the wide spectrum of CLD associated with diabetes, few studies have explored CLD-associated hospitalizations among adults with diabetes. We used hospital discharge data from the 2001–2012 National Inpatient Sample (NIS) to estimate CLD-associated hospitalizations among adults aged ≥ 18 years with and without diabetes.¹⁶

METHODS

The NIS is a nationally representative sample of hospitals produced by the Healthcare Cost and Utilization Project in collaboration with participating states. The NIS is the largest all-payer inpatient dataset in the United States and includes a 20% sample of participating U.S. community hospitals, which approximates 20% of all U.S. community hospitals.¹⁷ Participating hospitals are short-term, nonfederal, general, and specialty hospitals sampled annually from up to 42 states.

Total CLD-associated hospitalizations were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes.¹⁸ Total CLD-associated hospitalizations were defined as hospitalizations with a discharge diagnosis containing one or more of 32 ICD-9-CM diagnostic codes for the following: alcoholic liver disease, chronic hepatitis and cirrhosis, viral hepatitis B, viral hepatitis C, unspecified viral hepatitis, malignancy of the liver and bile ducts, and sequelae of liver disease (e.g., portal hypertension) (Table 1). The NIS includes up to 15 discharge diagnoses prior to 2009 and up to 25 discharge diagnoses from 2009 onward. Hospitalizations with a CLD diagnosis listed as one of up to 15 discharge diagnoses were included.

To examine specific etiologies of CLD, we also created the following nine liver disease subcategories using ICD-9-CM codes (Table 1): viral hepatitis B, viral

hepatitis B and chronic hepatitis and cirrhosis, viral hepatitis B and malignancy of the liver or bile ducts, viral hepatitis C, viral hepatitis C and chronic hepatitis and cirrhosis, viral hepatitis C and malignancy of the liver or bile ducts, viral hepatitis B/hepatitis C coinfection, chronic hepatitis and cirrhosis, and malignancy of the liver or bile ducts. For each CLD subcategory, hospitalizations were included only if the discharge record did not also list an ICD-9-CM code for another liver disease subcategory. For example, the hepatitis C subcategory only includes hospitalizations with hepatitis C listed on the discharge record, but not hospitalizations with hepatitis C and another CLD subcategory, such as chronic hepatitis and cirrhosis.

Total CLD and subcategory hospitalizations were stratified by diabetes status. Diabetes was defined as one or more of 11 ICD-9-CM codes indicating diabetes status (Table 1). Hospitalizations with diabetes listed as one of up to 15 discharge diagnoses were included as hospitalizations among adults with diabetes. Hospitalizations without an ICD-9-CM code for diabetes, within the first 15 discharge diagnoses, were considered hospitalizations among people without diabetes.

Hospitalization rates were calculated by using the weighted number of hospitalizations and the population of people with and without diabetes for each two-year period. We used discharge weights that were developed by the Healthcare Cost and Utilization Project to allow for trend tests across the study period.^{16,17} Standard errors (SEs) for hospitalization estimates were calculated using SUDAAN[®] release 9 to account for the complex sampling design of the NIS.^{19,20} The unit of analysis for this study was a hospitalization.

Total CLD and subcategory-associated hospitalization rates among all adults and people with and without diabetes were examined overall and by age group (18–29, 30–49, 50–64, and ≥ 65 years of age), sex, and two-year intervals (2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012). Average annual age-adjusted hospitalization rates with 95% confidence intervals (CIs) for people aged ≥ 18 years were calculated and expressed as the weighted number of hospitalizations per 100,000 corresponding population. Average annual population estimates and SEs for adults with and without diabetes for two-year periods were derived from the National Health and Nutrition Examination Survey (NHANES).²¹ Age-adjusted rates were calculated using the direct method, with the 2000 projected U.S. population for people aged ≥ 18 years as the standard. SEs for unadjusted and age-adjusted hospitalization rates used to determine 95% CIs for adults with or without diabetes were calculated using the Delta method to account for both the estimated

Table 1. Case definitions for total chronic liver disease, diabetes mellitus, and chronic liver disease subcategories based on ICD-9-CM codes

ICD-9-CM code ^a	Case definition
Total chronic liver disease (defined as any of the following ICD-9-CM codes)	
571.0	Alcoholic fatty liver
571.2	Alcoholic cirrhosis of the liver
571.3	Alcoholic liver damage, unspecified
571.40	Chronic hepatitis, unspecified
571.41	Chronic persistent hepatitis
571.49	Other chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol
070.2x ^b	Viral hepatitis B with hepatic coma
070.3x ^b	Viral hepatitis B without hepatic coma
070.44	Chronic hepatitis C with hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.51 (2004: 070.70)	Unspecified viral hepatitis C without hepatitis coma
070.41 (2004: 070.71)	Unspecified viral hepatitis C with hepatic coma
070.49	Other specified viral hepatitis with hepatic coma
070.59	Other specified viral hepatitis without hepatitis coma
070.6	Unspecified viral hepatitis with hepatitis coma
070.9	Unspecified viral hepatitis without mention of hepatic coma
155.0	Primary liver cancer
155.1	Intrahepatic bile duct cancer
155.2	Liver cancer not specified as primary or secondary
572.2	Hepatitis coma
572.3	Portal hypertension
572.4	Hepatorenal syndrome
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without bleeding
572.1	Portal pyemia
572.8	Other sequelae of chronic liver disease
789.5x ^b (2007: 789.51, 789.59)	Ascites
Diabetes mellitus (defined as any of the following ICD-9-CM codes)	
250.0x ^b	Diabetes mellitus without mention of complication
250.1x ^b	Diabetes with ketoacidosis
250.2x ^b	Diabetes with hyperosmolarity
250.3x ^b	Diabetes with other coma
250.4x ^b	Diabetes with renal manifestations
250.5x ^b	Diabetes with ophthalmic manifestations
250.6x ^b	Diabetes with neurological manifestations
250.7x ^b	Diabetes with peripheral circulatory disorders
250.8x ^b	Diabetes with other specified manifestations
250.9x ^b	Diabetes with unspecified complication
648.0x ^b	Diabetes mellitus

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Table 1 (continued). Case definitions for total chronic liver disease, diabetes mellitus, and chronic liver disease subcategories based on ICD-9-CM codes

<i>Chronic liver disease subcategories^c</i>	<i>Column 1</i>	<i>Column 2</i>
Viral hepatitis B	070.2x, ^b 070.3x ^b	NA
Viral hepatitis B and chronic hepatitis and cirrhosis	070.2x, ^b 070.3x ^b	571.40, 571.41, 571.49, 571.5, 571.6, 571.8, 571.90
Viral hepatitis B and malignancy of the liver or bile ducts	070.2x, ^b 070.3x ^b	155.0, 155.1, 155.2
Viral hepatitis C	070.41 (2004: 070.71), 070.44, 070.51 (2004: 070.70), 070.54	NA
Viral hepatitis C and chronic hepatitis and cirrhosis	070.41 (2004: 070.71), 070.44, 070.51 (2004: 070.70), 070.54	571.40, 571.41, 571.49, 571.5, 571.6, 571.8, 571.90
Viral hepatitis C and malignancy of the liver or bile ducts	070.41 (2004: 070.71), 070.44, 070.51 (2004: 070.70), 070.54	155.0, 155.1, 155.2
Viral hepatitis B/C coinfection	070.2x, ^b 070.3x ^b	070.41 (2004: 070.71), 070.44, 070.51 (2004: 070.70), 070.54
Chronic hepatitis and cirrhosis	571.40, 571.41, 571.49, 571.5, 571.6, 571.8, 571.90	NA
Malignancy of the liver or bile ducts	155.0, 155.1, 155.2	NA

^aDepartment of Health and Human Services (US). International classification of diseases, ninth revision, clinical modification (CD-ROM). 6th ed. Washington: HHS, Public Health Service, and Health Care Financing Administration; 2008.

^bAn "x" denotes that all iterations of the ICD-9-CM fifth digit were included in the case definition. ICD-9-CM codes in parentheses were created in the fiscal year indicated and replaced the previous code in the case definition.

^cChronic liver disease subcategories were defined as having ≥ 1 of the ICD-9-CM codes from column 1 and ≥ 1 of the ICD-9-CM codes from column 2 unless otherwise indicated.

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification

NA = not applicable

number of hospitalizations and the estimated population.²² A weighted least-squares technique was used to assess the trend in age-adjusted hospitalization rates during the study period.^{23,24} We also calculated the percentage of change in age-adjusted hospitalization rates from 2001–2002 to 2011–2012. We considered $p < 0.05$ to be statistically significant. All analyses were performed using SAS[®] version 9.3 and SUDAAN.^{21,25}

RESULTS

Total CLD-associated hospitalizations, 2001–2012

From 2001 to 2012, a total of 78,431,704 (95% CI 77,522,452, 79,340,955) hospitalizations were recorded among people with diabetes and 321,576,834 (95% CI 318,156,849, 324,996,818) among people without diabetes. The majority of the hospitalizations were within large bed-size (65%) hospitals that were designated as private or government owned (55%). Hospitalizations occurred primarily in the South (38%) followed by the West (22%), Northeast (20%), and Midwest (20%) regions.

The overall age-adjusted total CLD-associated hos-

pitalization rate was approximately four times higher among adults with diabetes (1,680.9 per 100,000 population; 95% CI 1,577.2, 1,784.6) than among adults without diabetes (424.2 per 100,000 population; 95% CI 413.4, 435.1) (Table 2). Among adults with diabetes, age-adjusted rates were higher for men (1,946.5 per 100,000 population; 95% CI 1,781.0, 2,112.1) than for women (1,418.4 per 100,000 population; 95% CI 1,315.2, 1,521.5) (Table 3). Age-specific rates were highest among adults aged 50–64 years with diabetes (2,094.3 per 100,000 population; 95% CI 1,934.7, 2,253.8) compared with adults aged 18–29 years (822.4 per 100,000 population; 95% CI 650.4, 994.5), 30–49 years (1,687.6 per 100,000 population; 95% CI 1,512.9, 1,862.3), and ≥ 65 years (1,509.7 per 100,000 population; 95% CI 1,392.7, 1,626.6) with diabetes. Similar patterns were seen among adults without diabetes (Table 4).

Trends in total CLD-associated hospitalizations, 2001–2002 and 2011–2012

From 2001–2002 to 2011–2012, the overall age-adjusted total CLD-associated hospitalization rate increased for

Table 2. Age-adjusted chronic liver disease-associated hospitalization rates and trends among U.S. adults aged ≥18 years, by liver disease subcategory, diabetes status, and time period—National Inpatient Sample, 2001–2012^a

Disease	Time period	Adults with diabetes			Adults without diabetes		
		Rate (95% CI) ^b	Percent rate change ^c	P-value for trend ^d	Rate (95% CI) ^b	Percent rate change ^c	P-value for trend ^d
Total chronic liver disease ^e	Total	1,680.9 (1,577.2, 1,784.6)	+59.1	<0.001	424.2 (413.4, 435.1)	+47.9	<0.001
	2001–2002	1,249.0 (1,058.1, 1,439.9)			333.5 (317.9, 349.0)		
	2003–2004	1,552.3 (1,254.0, 1,850.7)			376.9 (352.0, 401.7)		
	2005–2006	1,545.4 (1,330.1, 1,760.6)			400.2 (371.1, 429.4)		
	2007–2008	1,663.3 (1,431.7, 1,894.9)			444.2 (420.4, 468.1)		
	2009–2010	2,003.6 (1,702.0, 2,305.2)			474.0 (447.6, 500.4)		
	2011–2012	1,987.6 (1,706.5, 2,268.7)			493.3 (457.2, 529.5)		
Hepatitis B only ^f	Total	42.5 (40.4, 44.5)	+26.4	<0.001	13.7 (13.6, 13.9)	+29.7	<0.001
	2001–2002	35.0 (30.3, 39.8)			11.2 (11.0, 11.4)		
	2003–2004	41.6 (34.9, 48.2)			13.0 (12.5, 13.5)		
	2005–2006	41.0 (36.3, 45.8)			12.8 (12.4, 13.3)		
	2007–2008	42.7 (38.5, 47.0)			15.1 (14.7, 15.5)		
	2009–2010	48.8 (43.1, 54.4)			15.3 (14.9, 15.6)		
	2011–2012	44.3 (39.4, 49.2)			14.5 (13.9, 15.1)		
Hepatitis B and chronic hepatitis and cirrhosis ^f	Total	8.8 (8.7, 9.0)	+12.0	<0.001	1.8 (1.8, 1.8)	−4.7	0.003
	2001–2002	8.2 (8.0, 8.4)			1.8 (1.8, 1.8)		
	2003–2004	10.3 (9.4, 11.2)			2.0 (1.9, 2.0)		
	2005–2006	7.3 (7.2, 7.5)			1.7 (1.6, 1.7)		
	2007–2008	8.6 (8.4, 8.7)			1.8 (1.8, 1.9)		
	2009–2010	9.8 (9.5, 10.0)			1.8 (1.7, 1.8)		
	2011–2012	9.2 (8.7, 9.6)			1.7 (1.6, 1.8)		
Hepatitis B and malignancy of liver or bile ducts ^f	Total	0.9 (0.8, 1.0)	+26.7	0.03	0.5 (0.5, 0.5)	+50.5	<0.001
	2001–2002	0.6 (0.5, 0.8)			0.3 (0.3, 0.4)		
	2003–2004	0.9 (0.7, 1.0)			0.5 (0.4, 0.5)		
	2005–2006	0.8 (0.6, 0.9)			0.4 (0.4, 0.4)		
	2007–2008	1.1 (1.0, 1.3)			0.6 (0.5, 0.7)		
	2009–2010	1.1 (1.0, 1.3)			0.6 (0.5, 0.7)		
	2011–2012	0.8 (0.7, 0.9)			0.5 (0.5, 0.5)		
Hepatitis C only ^f	Total	473.5 (443.2, 503.7)	+44.0	<0.001	114.5 (112.5, 116.6)	+67.7	<0.001
	2001–2002	342.9 (279.6, 406.2)			78.9 (76.9, 80.9)		
	2003–2004	496.7 (394.0, 599.4)			103.3 (98.4, 108.3)		
	2005–2006	477.6 (408.6, 546.7)			114.8 (109.4, 120.2)		
	2007–2008	468.4 (400.4, 536.3)			120.5 (115.4, 125.6)		
	2009–2010	536.3 (457.3, 615.4)			128.5 (123.7, 133.2)		
	2011–2012	494.0 (425.8, 562.2)			132.3 (124.4, 140.1)		
Hepatitis C and chronic hepatitis and cirrhosis ^f	Total	119.6 (113.5, 125.6)	+61.5	<0.001	22.1 (21.6, 22.6)	+71.4	<0.001
	2001–2002	84.7 (73.5, 95.9)			15.4 (15.0, 15.8)		
	2003–2004	116.9 (97.3, 136.6)			20.5 (19.5, 21.4)		
	2005–2006	110.5 (97.8, 123.2)			21.4 (20.1, 22.7)		
	2007–2008	116.9 (104.4, 129.4)			21.9 (20.9, 23.0)		
	2009–2010	141.9 (124.5, 159.3)			24.7 (23.4, 25.9)		
	2011–2012	136.8 (120.9, 152.7)			26.4 (24.3, 28.4)		
Hepatitis C and malignancy of liver or bile ducts ^f	Total	4.0 (3.9, 4.1)	+127.0	<0.001	1.5 (1.5, 1.5)	+123.5	<0.001
	2001–2002	2.1 (1.9, 2.2)			0.8 (0.8, 0.9)		
	2003–2004	3.9 (3.6, 4.2)			1.1 (1.0, 1.2)		
	2005–2006	3.3 (3.1, 3.4)			1.1 (1.1, 1.1)		
	2007–2008	4.3 (4.1, 4.4)			1.7 (1.6, 1.8)		
	2009–2010	5.3 (5.1, 5.4)			1.9 (1.9, 1.9)		
	2011–2012	4.7 (4.4, 5.0)			1.9 (1.8, 2.0)		

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Table 2 (continued). Age-adjusted chronic liver disease-associated hospitalization rates and trends among U.S. adults aged ≥18 years, by liver disease subcategory, diabetes status, and time period—National Inpatient Sample, 2001–2012^a

Disease	Time period	Adults with diabetes			Adults without diabetes		
		Rate (95% CI) ^b	Percent rate change ^c	P-value for trend ^d	Rate (95% CI) ^b	Percent rate change ^c	P-value for trend ^d
Hepatitis B and C coinfection ^f	Total	21.3 (20.5, 22.1)	−30.0	<0.001	6.1 (6.0, 6.1)	−17.3	<0.001
	2001–2002	23.0 (20.1, 25.9)			6.0 (5.8, 6.1)		
	2003–2004	27.8 (23.5, 32.2)			7.0 (6.8, 7.2)		
	2005–2006	22.4 (20.4, 24.4)			6.5 (6.4, 6.6)		
	2007–2008	18.6 (17.3, 19.9)			6.0 (5.8, 6.2)		
	2009–2010	20.7 (18.9, 22.4)			5.9 (5.8, 6.1)		
	2011–2012	16.1 (15.0, 17.2)			4.9 (4.8, 5.1)		
Chronic hepatitis and cirrhosis only ^f	Total	506.5 (477.1, 536.0)	+124.9	<0.001	78.3 (76.0, 80.6)	+67.6	<0.001
	2001–2002	315.4 (278.5, 352.2)			59.0 (55.7, 62.3)		
	2003–2004	395.8 (328.7, 462.8)			65.9 (61.0, 70.8)		
	2005–2006	428.3 (373.7, 482.9)			71.9 (65.2, 78.6)		
	2007–2008	502.2 (434.3, 570.2)			82.5 (78.0, 87.1)		
	2009–2010	654.2 (555.2, 753.1)			88.4 (83.0, 93.8)		
	2011–2012	709.2 (607.9, 810.4)			98.8 (91.1, 106.6)		
Malignancy of liver or bile ducts only ^f	Total	19.7 (19.0, 20.5)	+29.9	<0.001	9.0 (8.7, 9.2)	+12.2	<0.001
	2001–2002	17.6 (16.4, 18.8)			8.5 (8.1, 8.9)		
	2003–2004	16.5 (14.3, 18.7)			8.7 (8.3, 9.2)		
	2005–2006	17.9 (16.2, 19.7)			7.8 (7.0, 8.6)		
	2007–2008	20.8 (19.6, 22.0)			9.6 (9.3, 9.8)		
	2009–2010	21.4 (20.3, 22.4)			9.5 (8.9, 10.1)		
	2011–2012	22.9 (20.5, 25.3)			9.6 (8.8, 10.4)		

^aDetails on the National Inpatient Sample can be found in: Steiner C, Elixhauser A, Schnaier J. The Healthcare Cost and Utilization Project: an overview. *Eff Clin Pract* 2002;5:143-51.

^bAll rates are per 100,000 corresponding population.

^cPercentage rate change was calculated by comparing time period 2001–2002 with 2011–2012.

^dA weighted least-squares technique was used to assess the trend in age-adjusted hospitalization rates during the study period using two-year time periods.

^eTotal chronic liver disease includes diagnoses for hepatitis B, hepatitis C, chronic hepatitis and cirrhosis, malignancy of liver or bile ducts, unspecified viral hepatitis, sequelae of chronic liver disease, and alcoholic liver disease.

^fRepresents diagnoses with an International Classification of Diseases, Ninth Revision, Clinical Modification liver disease code only for the listed diagnosis (i.e., the row titled “hepatitis B only” does not represent people who also have other liver disease diagnoses such as diagnoses for both hepatitis B and chronic hepatitis and cirrhosis or malignancy of liver or bile ducts).

CI = confidence interval

adults with and without diabetes (59.1% and 47.9%, respectively, $p < 0.001$), although there was not a significant difference in the increase between people with and without diabetes (Table 2). Among adults with diabetes, there was a greater increase for males (64.6% increase from 1,412.0 per 100,000 population; 95% CI 1,143.7, 1,680.3, to 2,324.2 per 100,000 population; 95% CI 1,861.1, 2,787.4) than for females (55.4% increase from 1,082.9 per 100,000 population; 95% CI 872.1, 1,293.7, to 1,683.0 per 100,000 population; 95% CI 1,390.8, 1,975.2). The pattern was reversed in adults without diabetes, for whom the rate increased 42.9% among males (from 410.1 per 100,000 population;

95% CI 387.9, 432.3, to 586.0 per 100,000 population; 95% CI 536.7, 635.4) and 55.7% among females (from 264.4 per 100,000 population; 95% CI 252.1, 276.8, to 411.7 per 100,000 population; 95% CI 379.1, 444.2).

CLD subcategory-associated hospitalizations

The majority (59.1%) of all CLD-associated hospitalizations had one CLD diagnosis; 22.0% had two CLD diagnoses. For 2001–2012, adults with diabetes had approximately 2 to 6 times higher rates of liver disease-associated hospitalizations in each CLD subcategory. The greatest disparity was among adults with diabetes aged 18–49 years who had rates 2 to 12 times higher

than their counterparts without diabetes (Tables 2 and 4). Men with diabetes had higher hospitalization rates than women with diabetes, women without diabetes, and men without diabetes, in all CLD subcategories, with the exception of chronic hepatitis and cirrhosis only, for which women with diabetes had the highest hospitalization rates (Table 3).

Hepatitis C- and chronic hepatitis and cirrhosis-associated hospitalizations comprised the largest proportion of total CLD-associated hospitalizations among adults with and without diabetes. The rate of hepatitis C-associated hospitalizations among adults with diabetes was 473.5 per 100,000 population (95% CI 443.2, 503.7) compared with 114.5 per 100,000

population (95% CI 112.5, 116.6) among adults without diabetes. The rate of chronic hepatitis and cirrhosis only-associated hospitalizations was 506.5 per 100,000 population (95% CI 477.1, 536.0) among adults with diabetes and 78.3 per 100,000 population (95% CI 76.0, 80.6) among adults without diabetes (Table 2).

From 2001–2002 to 2011–2012, overall hospitalization rates increased in all CLD subcategories among adults with and without diabetes, with the exception of viral hepatitis B/hepatitis C coinfection, which decreased 30.0% ($p < 0.001$) among adults with diabetes and 17.3% among adults without diabetes, and hepatitis B/chronic hepatitis and cirrhosis coinfection, which decreased 4.7% among adults without diabetes

Table 3. Age-adjusted chronic liver disease-associated hospitalization rates and trends among U.S. adults aged ≥ 18 years, by liver disease subcategory, diabetes status, and sex—National Inpatient Sample, 2001–2012^a

Liver disease category	Sex	Adults with diabetes			Adults without diabetes		
		Rate (95% CI) ^b	Percent rate change ^c	P-value for trend ^d	Rate (95% CI) ^b	Percent rate change ^c	P-value for trend ^d
Total chronic liver disease ^e	Male	1,946.5 (1,781.0, 2,112.1)	+64.6	<0.001	510.2 (495.6, 524.8)	+42.9	<0.001
	Female	1,418.4 (1,315.2, 1,521.5)	+55.4	<0.001	346.6 (337.3, 356.0)	+55.7	<0.001
Hepatitis B only ^f	Male	52.2 (48.5, 55.8)	+34.6	0.002	15.5 (15.3, 15.7)	+25.1	<0.001
	Female	33.0 (31.3, 34.7)	+19.6	0.002	12.2 (12.0, 12.3)	+36.8	<0.001
Hepatitis B and chronic hepatitis and cirrhosis ^f	Male	12.0 (11.7, 12.3)	+14.6	<0.001	2.5 (2.5, 2.5)	−1.1	0.04
	Female	5.7 (5.7, 5.8)	+21.0	<0.001	1.1 (1.1, 1.1)	−9.5	<0.001
Hepatitis B and malignancy of liver or bile ducts ^f	Male	1.6 (1.5, 1.7)	+25.5	0.08	0.9 (0.8, 0.9)	+37.7	<0.001
	Female	0.2 (0.2, 0.3)	+119.2	0.005	0.2 (0.2, 0.2)	+123.3	<0.001
Hepatitis C only ^f	Male	580.0 (528.5, 631.5)	+56.4	0.002	139.9 (137.1, 142.7)	+67.3	<0.001
	Female	367.5 (339.3, 395.7)	+33.5	0.008	90.9 (89.2, 92.7)	+70.0	<0.001
Hepatitis C and chronic hepatitis and cirrhosis ^f	Male	138.7 (128.6, 148.8)	+88.5	<0.001	27.1 (26.4, 27.7)	+81.8	<0.001
	Female	100.2 (94.7, 105.7)	+36.8	<0.001	17.3 (16.9, 17.7)	+59.9	<0.001
Hepatitis C and malignancy of liver or bile ducts ^f	Male	6.4 (6.2, 6.5)	+129.0	<0.001	2.4 (2.4, 2.4)	+133.3	<0.001
	Female	1.7 (1.6, 1.8)	+164.1	<0.001	0.6 (0.6, 0.6)	+102.1	<0.001
Hepatitis B and C coinfection ^f	Male	28.2 (26.6, 29.9)	−20.8	<0.001	8.3 (8.2, 8.4)	−17.0	<0.001
	Female	14.4 (13.9, 14.9)	−39.2	<0.001	4.0 (4.0, 4.1)	−15.9	<0.001
Chronic hepatitis and cirrhosis only ^f	Male	443.8 (407.7, 479.8)	+156.3	<0.001	74.4 (71.9, 76.8)	+70.8	<0.001
	Female	566.0 (527.9, 604.1)	+100.5	<0.001	81.8 (79.4, 84.2)	+65.8	<0.001
Malignancy of liver or bile ducts only ^f	Male	26.0 (24.9, 27.1)	+9.2	0.02	11.4 (11.1, 11.8)	+12.0	<0.001
	Female	14.2 (13.6, 14.8)	+56.0	<0.001	7.0 (6.8, 7.2)	+12.8	<0.001

^aDetails on the National Inpatient Sample can be found in: Steiner C, Elixhauser A, Schnaier J. The Healthcare Cost and Utilization Project: an overview. *Eff Clin Pract* 2002;5:143-51.

^bRate per 100,000 corresponding population

^cPercentage rate change was calculated by comparing time period 2001–2002 with 2011–2012.

^dA weighted least-squares technique was used to assess the trend in age-adjusted hospitalization rates during the study period using two-year time periods.

^eTotal chronic liver disease includes diagnoses for hepatitis B, hepatitis C, chronic hepatitis and cirrhosis, malignancy of liver or bile ducts, unspecified viral hepatitis, sequelae of chronic liver disease, and alcoholic liver disease.

^fRepresents diagnoses with an International Classification of Diseases, Ninth Revision, Clinical Modification liver disease code only for the listed diagnosis (i.e., the row titled “hepatitis B only” does not represent people who also have other liver disease diagnoses, such as diagnoses for both hepatitis B and chronic hepatitis and cirrhosis or malignancy of liver or bile ducts)

CI = confidence interval

Table 4. Age-specific chronic liver disease-associated hospitalization rates among U.S. adults aged ≥18 years, by liver disease subcategory, diabetes status, and age group—National Inpatient Sample, 2001–2012^a

<i>Liver disease category</i>	<i>Age group (in years)</i>	<i>Adults with diabetes Rate (95% CI)^b</i>	<i>Adults without diabetes Rate (95% CI)^b</i>
Total chronic liver disease ^c	18–29	822.4 (650.4, 994.5)	80.1 (77.7, 82.5)
	30–49	1,687.6 (1,512.9, 1,862.3)	356.0 (346.2, 365.8)
	50–64	2,094.3 (1,934.7, 2,253.8)	738.2 (700.3, 776.2)
	≥65	1,509.7 (1,392.7, 1,626.6)	683.0 (642.5, 723.5)
Hepatitis B only ^d	18–29	31.1 (28.1, 34.1)	7.7 (7.6, 7.8)
	30–49	47.4 (43.8, 51.0)	15.6 (15.4, 15.8)
	50–64	43.8 (41.3, 46.3)	16.8 (16.2, 17.4)
	≥65	29.1 (27.6, 30.6)	14.0 (13.5, 14.6)
Hepatitis B and chronic hepatitis and cirrhosis ^d	18–29	NR ^e	0.2 (0.1, 0.2)
	30–49	8.5 (8.3, 8.7)	1.5 (1.5, 1.5)
	50–64	12.9 (12.5, 13.2)	3.2 (3.1, 3.2)
	≥65	9.6 (9.3, 9.8)	3.0 (3.0, 3.1)
Hepatitis B and malignancy of liver or bile ducts ^d	18–29	NR ^e	0.1 (0.1, 0.1)
	30–49	0.6 (0.4, 0.7)	0.4 (0.4, 0.4)
	50–64	1.6 (1.5, 1.8)	0.9 (0.8, 0.9)
	≥65	1.5 (1.4, 1.6)	0.8 (0.7, 0.9)
Hepatitis C only ^d	18–29	203.4 (167.9, 238.8)	33.1 (32.6, 33.5)
	30–49	570.2 (516.3, 624.1)	133.7 (131.3, 136.2)
	50–64	573.7 (535.6, 611.8)	211.6 (202.5, 220.6)
	≥65	143.6 (134.6, 152.7)	67.1 (63.8, 70.4)
Hepatitis C and chronic hepatitis and cirrhosis ^d	18–29	9.3 (9.0, 9.6)	0.7 (0.6, 0.7)
	30–49	122.3 (111.8, 132.9)	16.8 (16.5, 17.1)
	50–64	195.2 (182.7, 207.7)	54.9 (52.7, 57.1)
	≥65	64.6 (60.9, 68.2)	24.9 (23.8, 26.0)
Hepatitis C and malignancy of liver or bile ducts ^d	18–29	NR ^e	NR ^e
	30–49	2.0 (1.9, 2.1)	0.4 (0.4, 0.4)
	50–64	9.9 (9.8, 10.1)	4.1 (4.1, 4.2)
	≥65	5.3 (5.2, 5.3)	2.7 (2.7, 2.8)
Hepatitis B and C coinfection ^d	18–29	5.7 (4.6, 6.9)	1.1 (1.0, 1.1)
	30–49	28.2 (26.5, 29.8)	8.4 (8.3, 8.4)
	50–64	22.2 (21.4, 23.0)	10.9 (10.7, 11.1)
	≥65	3.8 (3.8, 3.9)	2.0 (2.0, 2.0)
Chronic hepatitis and cirrhosis only ^d	18–29	434.7 (346.6, 522.9)	16.8 (16.3, 17.2)
	30–49	457.8 (411.4, 504.1)	49.2 (47.9, 50.5)
	50–64	565.1 (521.9, 608.4)	108.7 (103.1, 114.4)
	≥65	625.9 (578.2, 673.5)	194.2 (182.9, 205.4)
Malignancy of liver or bile ducts only ^d	18–29	NR ^e	0.7 (0.7, 0.8)
	30–49	6.1 (5.9, 6.2)	2.3 (2.3, 2.4)
	50–64	24.1 (23.0, 25.2)	11.5 (11.2, 11.7)
	≥65	67.0 (63.0, 71.1)	32.8 (31.4, 34.2)

^aDetails on the National Inpatient Sample can be found in: Steiner C, Elixhauser A, Schnaier J. The Healthcare Cost and Utilization Project: an overview. *Eff Clin Pract* 2002;5:143-51.

^bRate per 100,000 corresponding population

^cTotal chronic liver disease includes diagnoses for hepatitis B, hepatitis C, chronic hepatitis and cirrhosis, malignancy of liver or bile ducts, unspecified viral hepatitis, sequelae of chronic liver disease, and alcoholic liver disease

^dRepresents diagnoses with an International Classification of Diseases, Ninth Revision, Clinical Modification liver disease code only for the listed diagnosis (i.e., the row titled "hepatitis B only" does not represent people who also have other liver disease diagnoses, such as diagnoses for both hepatitis B and chronic hepatitis and cirrhosis or malignancy of liver or bile ducts)

^eValue was not reported due to unstable estimates caused by no or too few hospitalizations.

CI = confidence interval

NR = not reported

(Table 2). The greatest increases in CLD subcategory-associated hospitalization rates among adults with diabetes were for chronic hepatitis and cirrhosis only (124.9%) and for hepatitis C and malignancy of the liver or bile ducts (127.0%); the greatest increases among adults without diabetes were for hepatitis C and chronic hepatitis and cirrhosis (71.4%) and hepatitis C and malignancy of the liver or bile ducts (123.5%) (Table 2). Increases in CLD subcategory-associated hospitalization rates varied by diabetes status and sex (Tables 2 and 3).

DISCUSSION

This study used a nationally representative sample of hospitals from the NIS to determine CLD-associated hospitalization rates among adults with diabetes. During 2001–2012, the overall age-adjusted total CLD-associated hospitalization rate was approximately four times higher among adults with diabetes than adults without diabetes, and increased 59.1% and 47.9% from 2001–2002 to 2007–2012 for adults with and without diabetes, respectively. Higher hospitalization rates among adults with diabetes persisted by CLD subcategory, for both men and women, and by age group.

In this study, chronic hepatitis and cirrhosis and hepatitis C-associated hospitalizations comprised the largest proportion of CLD-associated hospitalizations for adults with diabetes, with rates 4 to 6 times higher than those for adults without diabetes. The high rates of chronic hepatitis and cirrhosis, and hepatitis C-associated hospitalizations, are congruent with other studies.^{6,7,12,14,15} A potential explanation for higher rates of cirrhosis-associated hospitalizations, among adults with diabetes, could be the high prevalence of non-alcoholic fatty liver disease (NAFLD) in this population. NAFLD is a spectrum of liver disease ranging from fatty infiltration of the liver to inflammatory steatohepatitis. NAFLD is found in an estimated 40% to 70% of people with diabetes and in nearly all obese people with diabetes.^{4,26} The presence of NAFLD and nonalcoholic steatohepatitis increases the risk of cirrhosis and hepatocellular carcinoma.^{27,28}

Several studies have shown an association between hepatitis C and the development of diabetes.^{12,14,15,29–31} In a 2012 meta-analysis of 35 observational studies, Naing et al. reported adults with hepatitis C had increased risk for developing type 2 diabetes mellitus (odds ratio [OR] = 1.26, 95% CI 1.03, 1.54); the risk was highest among males and adults older than 40 years of age.¹² In an earlier meta-analysis, White et al. found increased odds of diabetes mellitus among hepatitis C-infected vs. non-hepatitis C-infected adults

in both retrospective (OR=1.68, 95% CI 1.15, 2.20) and prospective (OR=1.67, 95% CI 1.28, 2.06) studies.¹⁴ In addition, emerging evidence suggests that the hepatitis C virus might contribute to the development of diabetes.^{27,29} For example, hepatitis C-infected people who have undergone liver transplantation have a greater incidence of diabetes than patients receiving transplants for other liver diseases. Also, interferon treatment for hepatitis C improves glucose tolerance when hepatitis C is eradicated, suggesting a causal role for hepatitis C in the development of diabetes.²⁹

People with diabetes could also be at increased risk for hepatitis C infection because of frequent medical interventions. Thompson et al. identified 16 nonhospital health care-associated hepatitis C transmissions in the United States from 1998 to 2008. These outbreaks resulted in 275 people with incident hepatitis C infection. Reuse of syringes resulting in contamination of medication vials was considered responsible for transmission.³²

Although the association among hepatitis C, cirrhosis, and diabetes has been documented, the temporal relationship is not always clear, confounding the relationship between disease processes. Hepatitis C infection is associated with impaired glucose tolerance in 40% of patients.³³ Diabetes is a common complication of cirrhosis.⁷ In this analysis, we were unable to determine the temporal relationship between diabetes, and chronic hepatitis and cirrhosis, and hepatitis C diagnoses. As such, we were unable to determine whether or not diabetes predisposed people to these diseases or whether or not these diseases predisposed people to diabetes. Nonetheless, the rates of chronic hepatitis and cirrhosis and hepatitis C-associated hospitalizations among people with diabetes were high, which should alert providers to possible liver damage among these patients.

Epidemiologic evidence demonstrates a greater prevalence of hepatitis B among people with diabetes than among the general population.^{11,13,34} Previously reported results from an analysis of NHANES data among noninstitutionalized adults demonstrated a 60% higher prevalence of past hepatitis B infection among adults with diabetes diagnosis compared with no diabetes diagnosis.¹¹ Among adults without well-established risks for hepatitis B infection, those with diagnosed diabetes had approximately twice the risk for acute hepatitis B than those without diabetes.¹³ Our finding of increased hepatitis B-associated hospitalization rates among people with diabetes strengthens the findings of previous reports showing an association between the two diseases.

When compared with the association between

hepatitis C and diabetes, evidence for a causal role of hepatitis B in the development of diabetes is weak, and some studies have found no effect of hepatitis B on the development of diabetes mellitus.³⁵ However, as in hepatitis C infection, people with diabetes can acquire hepatitis B through lapses in infection control practices during medical procedures. For example, multiple hepatitis B outbreaks that were associated with shared use of blood glucose monitoring equipment have been documented.³²

Our analysis demonstrated a greater disparity in CLD-associated hospitalization rates among young adults (18–29 and 30–49 years of age) with and without diabetes. The proportionately greater rates of hospitalization for young adults persisted for each liver disease subcategory, and was consistent with studies assessing hepatitis B among people with diabetes.^{11,13} Although the cause of the disparity in total CLD-associated hospitalization rates among younger adults with diabetes compared with those without diabetes is unclear, it is possible that liver disease is not readily suspected nor diagnosed in older adults with diabetes who have multiple other comorbidities.¹³

CLD and most CLD subcategory-associated hospitalization rates increased during the study period. The trend toward increases in rates of hospitalizations associated with chronic hepatitis and cirrhosis, and with malignancies of the liver and bile ducts (those not associated with cirrhosis or hepatitis B or C), might be partially explained by increasing rates of obesity and the associated risk of NAFLD with obesity.³⁶ In a recent study examining changes in prevalence of CLD using NHANES data, rates of obesity, diabetes, and NAFLD increased during the two-decade study period.³ Increasing rates of NAFLD might lead to increases in cirrhosis and hepatocellular carcinoma.^{4,27–29} Increasing hepatitis B and hepatitis C and malignancy of the liver or bile duct-associated hospitalization rates may reflect progression of the disease states from chronic infection to malignancy. The reason for increasing chronic hepatitis B- and C-associated hospitalizations (those with no other CLD diagnosis) among people with diabetes is unclear. However, increasing hospitalization rates do not necessarily equate to increasing prevalence; rather, they may represent increasing utilization of resources or increasing morbidity.

Our findings suggest that clinicians should have a low index of suspicion for considering CLD in the diabetic population. Given the high rate of CLD-associated hospitalizations, adults with diabetes should receive counseling on measures to prevent progressive liver damage. Preventive measures include limiting alcohol

consumption and administering hepatitis B vaccine for people <60 years of age with diabetes with consideration of hepatitis B vaccination for adults aged ≥60 years.^{37,38} Although hepatitis A vaccination is recommended for people with CLD, a recommendation for hepatitis A vaccination based solely on the presence of diabetes without CLD does not currently exist.³⁹

Limitations

This study's results should be viewed in the context of its limitations. First, the unit of analysis was a hospitalization; adults who were hospitalized more than once for CLD or a subcategory of CLD during the study period would have had each hospitalization counted separately. Therefore, we could not account for hospital readmissions, which might have resulted in an overestimation of the CLD-associated hospitalization rate. Second, only the top 15 discharge diagnoses were used in our analysis, which may have caused an underestimation of the number of hospitalizations; however, 96% of hospitalizations in our study had ≤15 discharge diagnoses. Finally, major differences exist by race/ethnicity in the prevalence of diabetes mellitus and in other liver disease categories (e.g., hepatitis B).^{2,40} Because of the large amount of missing race/ethnicity data in the NIS and differences between race/ethnicity categories between the NIS and NHANES, we were not able to stratify CLD-associated hospitalizations by race/ethnicity.

CONCLUSION

Adults with diabetes have higher rates of CLD-associated hospitalizations for a wide spectrum of CLD than adults without diabetes. Health-care providers should be aware of the potential for CLD among adults with diabetes and ensure preventive measures to avoid progressive liver damage. Studies that examine mechanisms for the association between diabetes and CLD, as well as optimal management of people with diabetes and CLD, could benefit these patients.

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