Hepatitis C as a prognostic indicator among noncirrhotic patients hospitalized with alcoholic hepatitis

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PJ Thuluvath, E Ahn, GC Nguyen. Hepatitis C as a prognostic indicator among noncirrhotic patients hospitalized with alcoholic hepatitis. Can J Gastroenterol 2013;27(11):639-642.

OBJECTIVE: A nationwide analysis of alcoholic hepatitis (AH) admissions was conducted to determine the impact of hepatitis C virus (HCV) infection on short-term survival and hospital resource utilization.

METHODS: Using the Nationwide Inpatient Sample, noncirrhotic patients admitted with AH throughout the United States between 1998 and 2006 were identified with diagnostic codes from the *International Classification of Diseases, Ninth Revision*. The in-hospital mortality rate (primary end point) of AH patients with and without co-existent HCV infection was determined. Hospital resource utilization was assessed as a secondary end point through linear regression analysis.

RESULTS: From 1998 to 2006, there were 112,351 admissions for AH. In-hospital mortality was higher among patients with coexistent HCV infection (41.1% versus 3.2%; P=0.07). The adjusted odds of in-hospital mortality in the presence of HCV was 1.48 (95% CI 1.10 to 1.98). Noncirrhotic patients with AH and HCV also had longer length of stay (5.8 days versus 5.3 days; P<0.007) as well as greater hospital charges (US$25,990 versus US$21,030; P=0.0002).

CONCLUSIONS: Among noncirrhotic patients admitted with AH, HCV infection was associated with higher in-hospital mortality and resource utilization.

Key Words: *Alcoholic hepatitis; Hepatitis C; Mortality*

L'hépatite C comme indicateur pronostique chez les patients non cirrhotiques hospitalisés en raison d'une hépatite alcoolique

OBJECTIF : Les chercheurs ont mené une analyse nationale des hospitalisations attribuables à l'hépatite alcoolique (HA) pour déterminer les répercussions de l'infection par le virus de l'hépatite C (VHC) sur la survie à court terme et l'utilisation des ressources hospitalières.

MÉTHODOLOGIE : À l'aide de l'échantillon national de patients hospitalisés, les chercheurs ont déterminé qui étaient les patients non cirrhotiques hospitalisés en raison d'une HA aux États-Unis entre 1998 et 2006, selon les codes diagnostiques de la *Classification internationale des maladies, 9e révision*. Au moyen de l'analyse à régression logistique multiple, ils ont déterminé le taux de mortalité hospitalière (paramètre primaire) des patients atteints d'une HA accompagnée ou non d'une infection par le VHC. Ils ont également évalué les ressources hospitalières comme paramètre secondaire, au moyen de l'analyse à régression linéaire.

RÉSULTATS : De 1998 à 2006, on a recensé 112 351 hospitalisations en raison d'une HA. La mortalité hospitalière était plus élevée chez les patients présentant également une infection par le VHC (41,1 % par rapport à 3,2 %; P=0,07). Le risque relatif rajusté de mortalité hospitalière en présence de VHC s'élevait à 1,48 (95 % IC 1,10 à 1,98). Les patients non cirrhotiques ayant une HA conjuguée à un VHC étaient également hospitalisés plus longtemps (5,8 jours plutôt que 5,3 jours; P<0,007) et présentaient des frais hospitaliers plus élevés (25 990 $US par rapport à 21 030 $US; P=0,0002).

CONCLUSIONS : Chez les patients non cirrhotiques hospitalisés en raison d'une HA, l'infection par le VHC s'associe à une mortalité hospitalière plus élevée et à une plus grande utilisation des ressources.

Approximately 8.5% of Americans either abuse or are dependent on alcohol, with mortality secondary to alcoholism being the third most preventable cause of death in the United States (US) (1). Approximately 90% of alcoholics develop fatty liver and, of these, 20% develop alcoholic hepatitis (AH). The severity of AH may vary from mild abnormalities of liver disease to severe AH that typically present with jaundice, hepatomegaly, encephalopathy and liver failure. Approximately 50% of patients with mild alcoholic hepatitis will progress to cirrhosis. Severe AH is associated with a 30% mortality rate at 30 days (2,3). The prognosis of AH and management guidelines are largely dictated by disease severity characterized by various scoring systems including Maddrey's Discriminant Function, the Model for End-stage Liver Disease and the Lille score (4-7).

Hepatitis C virus (HCV) and alcohol abuse account for the majority of all cases of liver disease in the Western world, with the two conditions often coexisting among patients with chronic liver disease (8). The mechanism of liver injury from the interaction between alcohol and HCV appears to be multifactorial and involves increased oxidative stress, decreased immune clearance of HCV, increased HCV replication and an increased rate of hepatocyte apoptosis (9,10). In patients with HCV, alcohol has been shown to facilitate the progression of liver fibrosis and is associated with an increased incidence of hepatocellular carcinoma and cirrhosis. There is also evidence that alcohol impedes the responsiveness of interferon treatment for HCV (8). However, there is a paucity of data investigating the effect of HCV on AH. Given the evidence suggesting a synergistic effect of alcohol and HCV infection on liver disease, we postulated that HCV would be a risk factor for worse outcome in noncirrhotic patients admitted with AH (10). Given that the evidence suggests the complications of liver disease, rather than etiology, determine prognosis in patients with cirrhosis, our study investigated only noncirrhotic patients (11).

In the present study, using the Nationwide Inpatient Sample (NIS), the largest database of all-payer hospital discharges in the US, we conducted a nationwide analysis of hospitalized patients with noncirrhotic AH with and without HCV to assess the independent impact of concomitant HCV infection on in-hospital mortality and hospital resource utilization.

METHODS

Data source

All data were obtained from the NIS, the largest all-payer database of national hospital discharges in the US. It was developed as part of the Healthcare Cost and Utilization Project and sponsored by the Agency for Healthcare Research and Quality. The NIS approximates a 20% stratified sample of nonfederal acute-care hospitals throughout the US. This sample includes community hospitals and academic medical centres, but excludes long-term nonacute care facilities, short-term rehabilitation centres, psychiatric hospitals and chemical dependency treatment facilities. The NIS datasets were formed by selecting a 20%

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Received for publication June 16, 2013. Accepted June 24, 2013

TABLE 1
Demographic characteristics of all patients with noncirrhotic alcoholic hepatitis

	Noncirrhotic alcoholic hepatitis		
Demograpic variable	Without hepatitis C (n=105,453)	With hepatitis C (n=6898)	P
Age, years, mean ± SE	46.6±0.1	45.0±0.2	<0.0001
Female sex	32.5	32.5	0.9892
Charlson Index, mean ± SE	0.35±0.007	0.69±0.047	<0.0001
Health insurance			<0.0001
Private	36.6	21.3	
Medicare	14.6	14.8	
Medicaid	18.9	32.1	
Self-pay	23.5	24.4	
Other	6.4	7.4	
Median household income			<0.001
Below national average	43.9	49.4	
Above national average	56.1	50.6	
Geographical regions			<0.0006
Northeast	21.6	23.1	
Midwest	23.3	19.7	
South	35.9	32.3	
West	19.2	24.9	
Location			<0.0001
Rural	17.8	13.1	
Urban	82.2	86.9	
Hospital type			<0.0001
Nonteaching	60.3	46.6	
Teaching	39.7	53.4	
Hospital size			0.5508
Small or medium	42.6	41.5	
Large	57.4	58.5	

Data presented as % unless otherwise indicated

probability sample from each of 60 strata based on urban versus rural location, geographical region, ownership, teaching status and quantity of beds. Each record in the NIS represents a single hospital discharge and includes various clinical and nonclinical information such as demographic data (age, sex and ethnicity), admission type (emergent, urgent or elective), primary and secondary diagnoses (up to 15), expected payment source, length of stay (LOS), total hospital charges and hospital characteristics (region, bed size and teaching status).

Eligibility criteria

All hospital stays between 1998 and 2006 were surveyed to identify hospital admissions with AH using the *International Classification of Diseases, Ninth Revision – Clincal Modification* (ICD-9-CM) diagnostic codes (571.1). Subjects with cirrhosis (ICD 571.2, 571.5 and 571.6) were excluded.

Predictor and outcome variables

Hepatitis C status was identified by the presence of ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, 070.70 and 070.71. Other clinical predictors included protein-calorie malnutrition (260.0 to 263.9, 269.8, 799.4, 783.21 and 783.3) and hepatic encephalopathy (572.2). Hospital size was determined by the quantity of beds and defined as large if this bed number was in the top tertile for that state, or small/medium if it was not. Health insurance type was obtained from the hospital discharge abstract and 'self-pay' referred to individuals with no health insurance coverage. Case-mix adjustment was performed using the validated Deyo modification of the Charlson Index, which is a validated predictor of all-cause in-hospital mortality (12,13). The primary outcome was in-hospital mortality. Secondary outcomes were hospital resource utilization, including total LOS and hospital charges.

Statistical analysis

Data were analyzed using STATA 9.0 SE (StataCorp LP, USA). Analyses accounted for the stratified two-stage cluster design using Stata's SVY (survey data) commands while integrating individual discharge-level weights. Using two-way χ^2 analyses, comparisons of categorical variables between those with and without hepatitis C were made. Survey-based multiple logistic regression was used to determine the association between in-hospital mortality and HCV, while adjusting for demographic variables (age, sex, comorbidities and type of health insurance), and the presence of encephalopathy and protein-calorie malnutrition. Survey-based linear regression models were used to assess the association between hepatitis C and hospital utilization (LOS and total hospital charges). Given that these variables were non-normally distributed, logarithmic transformation was applied to the analyses of total charges and LOS.

Ethics considerations

The analysis of the NIS database used completely anonymous data with no compromise to patient confidentiality. An initial review by the Institutional Review Board of the Johns Hopkins Medical Institutions (Maryland, USA) exempted the study from further ethical review.

RESULTS

The demographic characteristics of noncirrhotic AH patients with and without coexistent HCV are outlined in Table 1. Between 1998 and 2006, there were 112,351 admissions for patients with noncirrhotic AH in the NIS, of which 105,453 were without concomitant HCV and 6898 (6.5%) with coexistent HCV infection. Compared with non-HCV inpatients, patients with HCV were younger, more likely to reside in urban centres, be admitted to large teaching hospitals, have a higher Charlson Index score and were less likely to have private insurance.

In-hospital mortality among patients with noncirrhotic AH

The crude in-hospital mortality rate was higher among patients with coexistent HCV relative to those admitted without HCV, but did not reach statistical significance (4.1% versus 3.2%; P=0.07). When adjusted for age, sex, comorbidity, encephalopathy, malnutrition and heath insurance, the adjusted odds of mortality in the presence of HCV among AH admissions was 1.48 (95% CI 1.10 to 1.98). The associations of the aforementioned variables in relation to in-hospital mortality are listed in Table 2. Age, comorbidity, encephalopathy and malnutrition were all associated with higher in-hospital mortality.

Impact of HCV on hospital resource utilization among inpatients with noncirrhotic AH

Patients with noncirrhotic AH had a longer LOS if they had coexistent HCV relative to those who did not (5.8 days versus 5.3 days; P<0.007). After multivariate adjustment, the presence of HCV increased the LOS (ratio of 1.10 [95% CI 1.05 to 1.16]). Association of other variables with LOS are shown in Table 3.

There were also higher hospital charges associated with inpatients with AH and HCV compared with inpatients without coexistent HCV (US$25,990 versus US$21,030; P=0.0002). After adjusting for demographic, clinical and hospital factors, the presence of HCV increased the average hospital charges in AH patients (ratio of 1.14 [95% CI 1.07 to 1.21]). Total hospital charges were also affected by age, sex, Charlson Index score, encephalopathy, malnutrition, geographical region, rural versus urban location and hospital type (Table 3).

DISCUSSION

Using nationwide hospital discharge data from 1998 to 2006, we found that the presence of HCV infection in noncirrhotic AH patients was associated with significantly higher in-hospital mortality and greater use of hospital resource allocation. Our study also found significantly higher in-hospital mortality with increasing age, higher Charlson Index score, encephalopathy, malnutrition and HCV. Many of these

TABLE 2
In-hospital mortality among patients with noncirrhotic alcoholic hepatitis (n=22,902)

Predictor	In-hospital mortality, adjusted OR (95% CI)
Hepatitis C	1.48 (1.10–1.98)
Age (per 10 years)	1.38 (1.28–1.50)
Female versus male sex	0.98 (0.83–1.16)
Charlson Index (per point)	1.15 (1.08–1.20)
Encephalopathy	9.16 (7.78–10.77)
Malnutrition	1.89 (1.50–2.36)
Health insurance	
Private	Reference
Medicare	0.85 (0.67–1.08)
Medicaid	1.00 (0.80–1.24)
Self-pay	1.00 (0.80–1.23)
Other	0.80 (0.55–1.15)

variables, including the Charlson Index, have been shown to be associated with worse prognosis in many other conditions (13-15). Hepatic encephalopathy usually indicates advanced liver failure and portends a poor prognosis; similarly, malnutrition has previously been shown to be associated with increased mortality in AH patients (16-18).

In our study, the crude in-hospital mortality rate was not significantly higher among AH patients with HCV, although there was a trend (P=0.07). Multiple logistic regression analyses, however, showed a significant association with HCV and increased in-hospital mortality in this heterogeneous population. We do not believe that our study was underpowered; however, there were many limiting factors including our inability to assess the severity of AH and the lack of longitudinal data. Nevertheless, our data are a broad indication of in-hospital mortality of all patients admitted to hospital with a clinical diagnosis of AH.

In our study, only 6.5% of patients admitted with AH had HCV. This is less than previously reported prevalence of HCV among alcoholics. Although initial studies may have overestimated HCV prevalence because of the use of first-generation immunoassays for anti-HCV, studies using second- and third-generation immunoassays have continued to show high rates of prevalence of HCV among alcoholics, ranging from 1.2% to 55% and 4.4% to 31.2%, respectively (9). The wide range of prevalences may be due to selection bias given that most of the studies were performed as inpatients or during detoxification. Interestingly, studies involving the general population or outpatients have shown relatively lower rates of HCV, ranging from 1.2% to 4.4% (9,19). The prevalence noted in our study is only applicable to individuals who were admitted with AH and cannot be generalized.

Singal et al (20) retrospectively identified 76 cases of AH (of which 29 were HCV positive) from 1993 to 2008 and compared the impact of HCV on severity of liver disease and six-month survival. They found that patients with AH and HCV were more likely to have worse liver disease and a worse six-month survival rate compared with those admitted with AH alone (69% versus 91%; P=0.015). Unlike this study, we could not obtain longitudinal information on the patients admitted with AH because of limitations in the NIS database. Moreover, our study included all patients with a clinical diagnosis of AH without stratifying them according to the severity of their disease; this could explain the lower than expected in-hospital mortality.

In a previous study using NIS data, Liangpunsakul (21) examined mortality in 56,809 patients admitted to hospital with a primary diagnosis of AH. In that study, the investigator reported that acute renal failure, coagulopathy and infection, including sepsis, urinary tract infection, pneumonia and spontaneous bacterial peritonitis, were independently associated with increased in-hospital mortality.

TABLE 3
Impact of hepatitis C on length of stay and hospital costs among inpatients with noncirrhotic alcoholic hepatitis

Predictor	Length of stay	Hospital charges*
Hepatitis C	1.10 (1.05–1.16)	1.14 (1.07–1.21)
Age (per 10 years)	1.06 (1.05–1.07)	1.06 (1.05–1.08)
Female sex	1.08 (1.06–1.11)	1.10 (1.07–1.13)
Charlson Index (per point)	1.03 (1.02–1.05)	1.07 (1.05–1.08)
Encephalopathy	1.97 (1.87–2.07)	2.17 (2.04–2.31)
Malnutrition	1.53 (1.46–1.60)	1.52 (1.44–1.61)
Health insurance		
Private	Reference	Reference
Medicare	1.06 (1.02–1.10)	1.01 (0.97–1.06)
Medicaid	1.05 (1.02–1.09)	1.00 (0.95–1.04)
Self-pay	0.97 (0.94–1.01)	1.00 (0.96–1.04)
Other	1.02 (0.97–1.08)	1.05 (0.97–1.13)
Median household income		
Below national average	Reference	Reference
Above national average	1.04 (1.01–1.07)	1.02 (0.98–1.06)
Geographical regions		
Northeast	Reference	Reference
Midwest	0.89 (0.85–0.94)	0.83 (0.76–0.91)
South	0.94 (0.90–0.98)	0.89 (0.82–0.97)
West	0.84 (0.81–0.88)	1.15 (1.05–1.26)
Location		
Rural	Reference	Reference
Urban	1.07 (1.03–1.11)	1.47 (1.38–1.56)
Hospital type		
Nonteaching	Reference	Reference
Teaching	1.03 (0.99–1.06)	1.12 (1.05–1.19)

*Data presented as the ratio of length of stay and hospital charges in individuals with hepatitis C versus those without hepatitis C (95% CI). *Converted to 2008 US dollars*

Consistent with our study, hepatic encephalopathy and older age were also found to be risk factors for in-hospital mortality. Although the author did not find an increased risk of in-hospital mortality with HCV, we argue that a direct comparison of mortality rates between AH patients with and without HCV may have yielded findings similar to our study.

There were few noted limitations to our study. The use of the ICD-9 coding system to identify patients with AH and HCV, while excluding cirrhosis, is likely a less sensitive measure than a comprehensive medical chart review or a prospective database. As noted earlier, we could not determine the severity of AH and, therefore, our AH group comprised a heterogeneous group of patients with varying severity of AH. Ideally, we would have liked to assess 30-day and six-month mortality; however, both of these were not possible with NIS data. Finally, while the Charlson Index is a commonly used indicator of comorbidity and was shown to be associated with in-hospital mortality in our study, residual confounding was inevitable. Despite its limitations, the NIS dataset enabled us to analyze a large sample size that was arguably a nationally and geographically representative population sample with varying severity of AH.

SUMMARY

Our study found HCV to be a risk factor for in-hospital mortality among noncirrhotic patients admitted with AH. We also demonstrated that HCV in noncirrhotic AH patients resulted in greater use of hospital resources including hospital charges and total LOS.

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