Epidemiology of Alcohol-Related Liver and Pancreatic Disease in the United States

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Background: The epidemiology of acute alcoholic pancreatitis (AP), chronic alcoholic pancreatitis (CP), acute alcoholic hepatitis (AH), and chronic alcoholic hepatitis with cirrhosis (CH) alone or in combination is not well described. To better understand alcohol-related liver and pancreas effects on and associations with different ethnic groups and sexes, we analyzed the trends of AP, CP, AH, CH, AP plus AH, or CP plus CH in the United States.

Methods: We examined discharge records from the Nationwide Inpatient Sample, the largest representative sample of US hospitals. Hospital discharges, case-fatality, and sex and race contributions were calculated from patients with discharge diagnoses of AP, CP, AH, CH, AP plus AH, or CP plus CH between 1988 and 2004.

Results: The distribution of overall hospital discharges per 100 000 persons between 1988 and 2004 was as follows: AP, 49.2; CP, 8.1; AH, 4.5; and CH, 13.7. Overall hospital discharges per 100 000 persons for AP plus AH were 1.8; and for CP plus CH, 0.32. There were higher male to female ratios for AH and CH, and less so for AP and CP. A markedly higher frequency of AP (63.5) and CP (11.3) was seen among blacks than among whites (AP, 29.6 and CP, 5.1), Hispanics (AP, 27.1 and CP, 3.7), Asians (AP, 12.8 and CP, 1.4), and American Indians (AP, 15.5 and CP, 2.3). This higher frequency remained stable between 1994 and 2004. Overall case fatality steadily decreased in all categories, but remains highest in CH (13.6%) with similar racial distributions.

Conclusions: In the United States, AP is the most common discharge diagnosis among alcohol-related liver or pancreas complications, while CH has the highest case fatality rate and male to female ratio. Blacks have the highest frequency of alcohol-related pancreatic disease.

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holic cirrhosis incidence and mortality.\textsuperscript{13} It is unclear why pancreatic and/or liver disease is acquired and what determines the tissue predilection in a given individual. Some studies suggest that the coexistence of alcohol-associated pancreatic and liver disease is relatively common,\textsuperscript{14,15} while others have noted infrequent involvement of the 2 organs simultaneously.\textsuperscript{16}

In the present study, we use US national data on hospital discharges to provide an up-to-date analysis of trends in alcoholic-related acute and chronic pancreatic and liver diseases. We also examine the number of hospital discharge diagnoses of combined AP and AH and combined CP and CH.

### METHODS

#### DATABASE

The Nationwide Inpatient Sample (NIS) is the largest all-payer inpatient database in the United States and includes a stratified random sample of hospitals that makes up approximately 85\% of all hospital discharges in the United States (www.hcup-us.ahrq.gov/nisoverview.jsp). The sample includes community and general hospitals and academic medical centers. It is the only national hospital database with information on all patients, regardless of payer, including persons covered by Medicare, Medicaid, private insurance, and the uninsured. Data from NIS are available from 1988 to 2004, allowing for analysis of trends over time. For each hospital discharge, data include over 100 clinical and nonclinical variables for each hospital stay, such as primary and secondary diagnoses (up to 15) and primary and secondary procedures (up to 15) using International Classification of Diseases, Ninth Revision (ICD-9) codes (www.cdc.gov/nchs/ict9.htm), patient demographics (sex, age, race, median income, and zip codes), length of stay, and discharge status.

#### PATIENT ELIGIBILITY

The study cohort included all hospital discharges in the NIS database with 1 of the following primary ICD-9 discharge diagnoses: acute pancreatitis (577.0), chronic pancreatitis (577.1), acute alcoholic hepatitis (571.1), or alcoholic liver cirrhosis (571.2). The cohort also included patients who were diagnosed as having combined alcoholic AP and AH or CP and CH. All patients were discharged between 1988 and 2004.

For the AP group, since there is no specific ICD-9 code for alcohol-related disease, those with a concurrent diagnosis of acute cholecystitis (575.0), other cholecystitis (575.1), cholecystitis unspecified (575.10), calculus of the gallbladder with acute cholecystitis without/with obstruction (574.00-574.01), calcui of the gallbladder with other cholecystitis without/with obstruction (574.10-574.11), calculus of the gallbladder without cholecystitis without/with obstruction (574.20-574.21), cholecystitis with/without obstruction (574.3-574.9), cholangitis (576.1), and those who underwent endoscopic retrograde cholangiopancreatography on the same admission (Current Procedural Terminology codes 5110, 5111, 5184, 5187, and 3213) were subtracted from the total to arrive at an estimated number of hospital discharges of acute AP.

#### CENSUS DATA

The estimated national population during the 1988-2004 period, along with sex- and race-specific population data were obtained from the US Census Bureau (www.census.gov). The US Census Bureau contained data for the following races: white, black, Hispanic, Asian American/Pacific Islander, American Indian/Alaska Native.

### HOSPITAL DISCHARGES AND CASE-FATALITY DATA

The number of hospital discharges of each disease alone or in combination per 100 000 US residents overall and per year were calculated for each racial and/or ethnic group and sex. The case-fatality data were obtained from the NIS and calculated as a percentage of all discharges.

### STATISTICAL ANALYSIS

Statistical analyses were performed by accounting for the survey design of the NIS database, using SAS 9.1 software (SAS Institute, Cary, North Carolina). To define the numbers of hospitalized patients with specific diagnoses in different groups of patients, we used an SAS PROC SURVEYFREQ statement that allowed calculation of the weighted frequency with the standard deviation (SD) using modified weights. We then calculated rates of hospital discharges and population-based case fatalities per 100 000 population using the US Census Bureau national population estimates.

### RESULTS

The total number of discharges reviewed in the NIS between 1988 and 2004 was 608,584,037. The total number of hospital discharges of AP (all causes) between 1988 and 2004 was 2,999,516. Hospital discharges with diagnoses of AP, CP, AH, CH, AP plus AH, or CP plus CH with 95\% confidence intervals (CIs) per 100,000 US persons per year for each year between 1988 and 2004 are shown in Figure 1A. From 1988 to 2004, the number of AP diagnoses per 100,000 persons has progressively increased, from 39.8 (95\% CI, 37.3-42.2) to 65.0 (95\% CI, 62.5-67.5), an increase of 63\%, while the other clinical entities did not increase as much. The number of CH diagnoses per 100,000 persons changed minimally, from 11.9 (95\% CI, 11.0-12.8) in 1988 to 18.1 (95\% CI, 16.8-19.4) in 2004, a 52\% rise. The rates per 100,000 persons of AH and CP diagnoses changed minimally, from 4.9 (95\% CI, 4.4-5.3) to 4.2 (95\% CI, 3.9-4.5) for AH and from 7.0 (95\% CI, 7.2-7.8) to 8.1 (95\% CI, 7.5-8.7) for CP (Figure 1A). The number of hospital discharge diagnoses of combined AP plus AH was much lower than that of each disease individually, but the number has nearly doubled between 1988 and 2004, from 1.4 (95\% CI, 1.2-1.6) to 2.4 (95\% CI, 2.2-2.6) cases per 100,000 persons (Figure 1B). The number of hospital discharge diagnoses per 100,000 persons of combined CP plus CH is also much lower than each disease individually: 0.11 (95\% CI, 0.07-0.14) in 1988 and 0.46 (95\% CI, 0.39-0.52) in 2004.

The hospital discharge diagnoses of the separate and combined alcohol-related acute and chronic pancreatic and liver complications were then analyzed in the context of different patient ethnic backgrounds (Table 1). Per 100,000 persons, a markedly higher overall frequency of AP (63.5 cases) and CP (11.3 cases) was seen in blacks (Table 1) than in whites (29.6 and 5.1 cases,
respectively), Hispanics (27.1 and 3.7), Asians (12.8 and 1.4), and American Indians (15.5 and 2.3). The high rate per 100,000 persons of hospital discharge diagnoses of AP among blacks has been relatively constant during the past 10 years (Figure 2A), but with a sharp rise occurring for unknown reasons between 1991 (19.2; 95% CI, 12.9-25.6) and 1993 (75.3; 95% CI, 65.6-85). Despite this high rate, the case fatality trend in blacks for all 4 diseases (AP, CP, AH, and CH) reflected that of the population overall (Figure 2B and Table 2). The disease with the highest overall case fatality rate was CH (13.6 per 100,000), while that with the lowest case fatality was CP (0.8 per 100,000) (Table 2).

Another prominent ethnicity-related disease association per 100,000 persons was noted for CH in Hispanics, 16.9 cases, compared with 11.1 cases among whites.

Table 1. Prevalence of Hospital Discharge Diagnoses of Alcohol-Related Pancreatic and Liver Disease, Alone and in Combination, by Ethnic Backgrounda

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>AP</th>
<th>CP</th>
<th>AH</th>
<th>CH</th>
<th>AP+AH</th>
<th>CP+CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>49.2 (47.5-50.9)</td>
<td>8.1 (7.7-8.6)</td>
<td>4.5 (4.2-4.7)</td>
<td>13.7 (13.0-14.3)</td>
<td>1.8 (1.7-1.9)</td>
<td>0.32 (0.29-0.34)</td>
</tr>
<tr>
<td>White</td>
<td>29.6 (28.2-30.9)</td>
<td>5.1 (4.7-5.5)</td>
<td>3.1 (2.9-3.3)</td>
<td>11.1 (10.5-11.8)</td>
<td>1.1 (0.9-1.12)</td>
<td>0.21 (0.19-0.23)</td>
</tr>
<tr>
<td>Black</td>
<td>63.5 (58.5-68.4)</td>
<td>11.3 (10.3-12.3)</td>
<td>4.4 (4.0-4.8)</td>
<td>9.9 (9.0-10.9)</td>
<td>2.8 (2.6-3.1)</td>
<td>0.57 (0.49-0.64)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>27.1 (24.8-29.5)</td>
<td>3.7 (3.2-4.2)</td>
<td>2.9 (2.5-3.2)</td>
<td>16.9 (14.9-18.9)</td>
<td>1.0 (0.9-1.1)</td>
<td>0.24 (0.20-0.28)</td>
</tr>
<tr>
<td>Asian</td>
<td>12.8 (11.2-14.5)</td>
<td>1.4 (1.2-1.7)</td>
<td>0.6 (0.48-0.73)</td>
<td>2.7 (2.3-3.1)</td>
<td>0.29 (0.22-0.37)</td>
<td>0.06 (0.03-0.09)</td>
</tr>
<tr>
<td>American Indian</td>
<td>15.5 (12.8-18.2)</td>
<td>2.3 (1.7-3.0)</td>
<td>2.9 (2.2-3.6)</td>
<td>9.9 (7.4-12.5)</td>
<td>0.82 (0.6-1.1)</td>
<td>0.07 (0.02-0.13)</td>
</tr>
</tbody>
</table>

Abbreviations: AH, acute alcoholic hepatitis; AP, acute alcoholic pancreatitis; CH, chronic alcoholic hepatitis; CI, confidence interval; CP, chronic alcoholic pancreatitis.

a All data are reported as averaged prevalence per 100,000 persons (95% CI) in the United States from 1988 to 2004. Ethnic background data were not available for 13 states.
9.9 among blacks, 2.7 in Asians, and 9.9 in American Indians (Table 1). For AH, the racial contribution was similar: 3.1 cases per 100,000 persons in whites, 4.4 in blacks, 2.9 in Hispanics, and 2.9 in American Indians (Table 1).

In general terms, Asians had the lowest hospital discharge diagnosis numbers for any of the 4 diseases studied (Table 1).

We also examined the overall case fatality rates associated with each disease. Case fatality steadily decreased in all 4 individual disease categories from 1988 to 2004 (2.5% to 1.3% in AP, 0.9% to 0.7% in CP, 7.8% to 5.6% in AH, and 17.4% to 11.5% in CH) (Figure 3). Case fatality remains highest overall in CH (13.6%) between 1988 and 2004 compared with 1.9% for AP, 0.8% for CP, and 6.6% for AH, with similar racial contributions (Table 2). The case fatality rate of combined AP plus AH also decreased (3.3% to 1.5%), as did the case fatality rate in CP plus CH (6.2% to 5.4%), which was much lower than in individuals with CH alone (Table 2).

Table 2. Case Fatality Rates of Alcohol-Related Pancreatic and Liver Disease, Alone and in Combination, by Ethnic Backgrounda

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>AP</th>
<th>CP</th>
<th>AH</th>
<th>CH</th>
<th>AP+AH</th>
<th>CP+CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.9</td>
<td>0.8</td>
<td>6.6</td>
<td>13.6</td>
<td>2.2</td>
<td>6.5</td>
</tr>
<tr>
<td>White</td>
<td>2.2</td>
<td>0.7</td>
<td>7.3</td>
<td>13.5</td>
<td>2.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Black</td>
<td>1.3</td>
<td>0.8</td>
<td>5.1</td>
<td>15.5</td>
<td>1.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.5</td>
<td>0.6</td>
<td>5.9</td>
<td>11.1</td>
<td>2.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Asian</td>
<td>1.8</td>
<td>2.4</td>
<td>4.0</td>
<td>15.1</td>
<td>2.2</td>
<td>4.1</td>
</tr>
<tr>
<td>American Indian</td>
<td>0.7</td>
<td>0</td>
<td>5.5</td>
<td>11.1</td>
<td>2.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AH, acute alcoholic hepatitis; AP, acute alcoholic pancreatitis; CH, chronic alcoholic hepatitis; CP, chronic alcoholic pancreatitis.

a All data are reported as percentages. Race data were not available for 13 states.
Sex associations were also examined. There were high male to female ratios for AH (1.83) and CH (2.64) and not as high for AP (1.23) and CP (1.02) ([Table 3](#)). The higher incidence for men in liver but not pancreatic disease carried through when the combined acute or chronic diseases were analyzed. For AP plus AH, the male to female ratio was 2.72, and in CP plus CH, the male to female ratio was 2.41 ([Table 3](#)). The male to female ratio remained relatively consistent between 1988 and 2004 for all 6 disease groups (data not shown).

**COMMENT**

Alcohol-related pancreas and liver diseases include AP, CP, AH, and CH. The NIS database allowed us to study the epidemiology of these 4 diseases in the racially diverse US population over the span of 17 years (1988-2004). Similar to previous reports in Europe and the United States, we found that the number of hospital discharge diagnoses of AP is rising steadily, followed by a slower increase in the number of alcoholic liver cirrhosis cases. On the contrary, the hospital discharge diagnoses of AH and CP changed minimally during that 17-year period. The case fatality rates of these 4 diseases have decreased from 1988 to 2004, as expected, owing to advances in medical and surgical care and in endoscopic and radiologic diagnostic techniques. The case fatality rate from alcoholic cirrhosis remains the highest.

**Table 3. Prevalence of Hospital Discharge Diagnoses of Alcohol-Related Pancreatic and Liver Disease, Alone and in Combination, by Sex**

<table>
<thead>
<tr>
<th>Disease</th>
<th>All Cases</th>
<th>Male to Female Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>49.2 (47.5-50.9)</td>
<td>1.23 (1.21-1.25)</td>
</tr>
<tr>
<td>CP</td>
<td>8.1 (7.7-8.6)</td>
<td>1.02 (0.99-1.05)</td>
</tr>
<tr>
<td>AH</td>
<td>4.5 (4.3-4.7)</td>
<td>1.83 (1.77-1.88)</td>
</tr>
<tr>
<td>CH</td>
<td>13.7 (13.0-14.3)</td>
<td>2.64 (2.58-2.69)</td>
</tr>
<tr>
<td>AP+AH</td>
<td>1.8 (1.7-1.9)</td>
<td>2.72 (2.66-2.83)</td>
</tr>
<tr>
<td>CP+CH</td>
<td>0.32 (0.29-0.34)</td>
<td>2.41 (2.19-2.64)</td>
</tr>
</tbody>
</table>

Abbreviations: AH, acute alcoholic hepatitis; AP, acute alcoholic pancreatitis; CH, chronic alcoholic hepatitis; CI, confidence interval; CP, chronic alcoholic pancreatitis.

Data are reported as hospital discharge diagnoses per 100,000 persons (95% CI) in the United States from 1988 to 2004.
The reason for the increase in the number of hospital discharge diagnoses of AP is unclear and does not appear to be related to a major shift in alcohol consumption. Per capita consumption of all alcoholic beverages increased between 1962 and the early 1980s, then decreased until 1998. Since 1998, per capita alcohol consumption has changed minimally (8.10 L/y in 1998 to 8.25 L/y in 2001). Hence, since there was a decrease in alcohol consumption until 1998, other factors likely contribute to the increase in AP prevalence. When 54 patients with alcohol-induced pancreatitis were compared with a control group of male patients with alcoholic cirrhosis, no difference was found in alcohol consumption between the 2 groups, but smoking was more common in the men with alcohol-induced pancreatitis.

However, the pattern of drinking may be a contributing factor. Binge drinking (≥5 drinks on 1 occasion in men, ≥4 drinks in women) is common among those 26 years or younger, and more so among men. Per capita binge drinking episodes have steadily increased between 1993 and 2001, particularly since 1995. In this regard, the amount of alcohol consumed during the 1 week prior to presentation of symptoms determines the severity of the first episode of AP. In a study of Japanese men, the high consumption of alcohol over a short period of time was found to be an independent risk factor for the severity of alcoholic CP. It is possible that the more alcohol consumed over a shorter time increases susceptibility to AP, but further studies addressing this issue are warranted. We are unable to determine from our cohort whether smoking, potential dietary factors, changes in body mass index, or other factors contributed to the observed increase in AP.

Few studies have examined the epidemiology of AP due to alcohol, possibly because of the lack of a specific diagnostic code for alcohol-induced AP. The latest ICD-10 coding system (www.cdc.gov/nchs/about/otheract/icd9/abticd10.htm) does include a new diagnostic code for alcohol-induced AP, but that system is currently not used in the United States. We specifically excluded AP cases associated with a concurrent diagnosis of cholelithiasis, cholangitis, or other biliary diseases and also cases with a concurrent procedure code of endoscopic retrograde cholangiopancreatography to primarily capture cases of alcohol-related AP. It is possible that we overestimated the number of alcohol-related AP cases because we were unable to exclude idiopathic AP (that does not have a designated ICD-9 code), which according to some estimates may be 80% more common than alcohol-related AP. Alternatively, diagnostic screening criteria (laboratory, clinical, and radiologic criteria) for pancreatitis are not standardized, and some mild cases of AP might not have been diagnosed in the hospital setting. This would result in underestimating the number of AP cases.

Another caveat is that the admission rate for AP might be higher than for CP, AH, and CH, since AP is nearly always an indication for hospital admission, and the other conditions are not. Hence, the high hospital admission and discharge rates for AP could be due, in part, to disease-dependent hospital admission bias. This should not necessarily influence sex, race, or trend data, but it could cause an underestimate of the incidence of AH, CP, and CH.

The differences among the number of hospital discharge diagnoses of alcohol-related AP and CP between races was striking, particularly in blacks, who had a much higher number of hospital diagnoses than the other ethnic groups. A significantly higher rate of alcoholic AP was also noted in blacks than in other groups in an analysis of the California Patient Discharge Data Set and for overall AP in an analysis of the 1988-2003 National Hospital Discharge Survey. The ethnic background differences are unlikely to be due to differences in alcohol consumption. In a study of 91 659 subjects, men consumed alcohol more frequently than women, and whites drank alcohol more frequently than blacks or Asians. Furthermore, the 1992 National Longitudinal Alcohol Epidemiologic Study did not find differences in drinking patterns among ethnic groups. Other likely relevant factors that might account for the increased susceptibility of blacks to alcohol-related pancreatitis are genetic and epigenetic parameters. Increases in aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT) levels occur more frequently in blacks and Hispanics than in whites, and the AST or GGT levels increased with the frequency of alcohol intake.

In contrast to alcohol-related pancreatic complications, the increased frequency of alcoholic liver cirrhosis in Hispanics compared with other races may be related, at least in part, to the extent of alcohol consumption. For example, heavy drinking was found to be highest in Hispanic men, followed by black men, and Hispanic men were more likely than white men to persist with heavy drinking habits. Even though Hispanics had the highest incidence of CH (16.9 cases per 100 000 persons) (Table 1), they had a relatively low incidence of AH (2.9 cases per 100 000 persons) (Table 1), which suggests that they may harbor a greater propensity for liver disease progression than those of other ethnic backgrounds.

The male to female ratio was highest for CH, followed by AH. The sex-specific differences in alcoholic AP and CP were less prominent. A review of 18 European studies with population-based information on the epidemiology of first-attack acute pancreatitis (of all causes) showed that gallstone AP was more common in women, while alcoholic AP was more common in middle-aged men, and the rate of idiopathic AP was similar in both sexes. The male to female ratio for alcoholic AP has varied between studies and ranges from nearly 3.5 for the year 2000 in the United States to 1.12 in heavy drinkers in Germany. The NIS does not provide alcohol consumption and/or duration data; therefore, we were unable to determine if sex differences or similarities in our report are due to alcohol consumption or other factors.

Aside from alcohol-induced liver disease, chronic infection with hepatitis C virus (HCV) is another major determinant of liver cirrhosis. At present, about 30% of US liver transplantations have an indication of alcoholic cirrhosis, while 30% to 40% are used to treat HCV cirrhosis. In our study, a subset analysis showed that the coexistence of alcohol-related AH and HCV or CH and HCV
(from 1992 to 2004) was too small (compared with the occurrence of AH or CH alone) to affect our conclusions (Figure 4). However, it is possible that we underrepresented the impact of chronic HCV infection because it is unknown what sample size in the NIS database was tested for the infection. Similarly, the coexistence of alcohol-related CH and chronic hepatitis B infection, including ethnic contribution, was also too small to affect our conclusions (data not shown).

The reported combined frequencies of association between pancreas and liver disease have varied between studies. Higher frequencies are reported in autopsy than in clinical data. A review of 1022 autopsies in which the cause of death was alcoholic liver disease found histologic evidence of pancreatitis (mild inflammation to moderate fibrosis) in 28% of cases.28 However, a prospective study has reported lower coexistence frequencies. Fourteen of 72 patients (19%) with known alcoholic cirrhosis had chronic pancreatitis diagnosed by endoscopic ultrasound or endoscopic pancreatogram criteria, but none of the 14 patients had clinical symptoms of pancreatic insufficiency.29 This suggests that the autopsy finding of a relatively high prevalence of comorbid conditions does not reflect clinically relevant disease. In the present study, the observed number of cases of combined acute or chronic pancreatic and liver disease (AP plus AH or CP plus CH) was significantly lower than the involvement of either organ alone (Table 1).

In conclusion, we defined the US epidemiologic trends of alcohol-related pancreatic and liver disease. The number of hospital discharge diagnoses of AP is increasing, and AP is the most common of the 4 alcohol-related complications. At the same time, the case fatality rates of AP, CP, AH, and CH are decreasing. The incidences of the combined conditions AP plus AH or CP plus CH are markedly lower than the incidences of any of the entities alone. Acute or chronic liver disease was more common in men than in women. A much higher number of hospital discharge diagnoses of acute and chronic pancreatitis was
found in blacks than in the other ethnic groups studied, and the highest number of hospital discharge diagnoses of CH was found in Hispanics. The reasons for these ethnic differences, whether genetic or environmental factors, remain to be defined.

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REFERENCES