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Disease spectrum of alcoholic liver disease in Beijing 302 Hospital from 2002 to 2013

A large tertiary referral hospital experience from 7422 patients

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Abstract

Alcohol consumption in China has substantially increased over the last 3 decades and the number of patients with alcoholic liver disease (ALD) is rising at an alarming rate. However, accurate and representative data on time trends in its hospitalization rates are not available. The aim of this study is to assess the current status and burden of ALD in China by analyzing the data from a large tertiary referral hospital, Beijing 302 Hospital.

Data were retrospectively recorded from patients diagnosed as ALD in Beijing 302 Hospital from 2002 to 2013. The disease spectrum and biochemical parameters of each patient were collected.

The patients with ALD accounted for 3.93% (7422) of all patients (188,902) with liver diseases between 2002 and 2013. The number of patients hospitalized with ALD increased from 110 in 2002 to 1672 in 2013. The ratio of patients hospitalized with ALD to all patients hospitalized with liver diseases was rising almost continuously and increased from 1.68% in 2002 to 4.59% in 2013. Most patients with ALD were male. Age distribution of ALD hospitalization showed that the highest rate was in 40- to 49-year-old group in subjects. Notably, the annual proportion of severe alcoholic hepatitis (SAH) increased 2.43 times from 2002 to 2013. We found the highest levels of mean corpuscular volume, the aspartate aminotransferase/alanine aminotransferase ratio, total bilirubin, international normalized ratio, and alkaline phosphatase in SAH patients, while serum levels of hemoglobin, albumin, and cholinesterase were significantly decreased in SAH group. Among these ALD, the SAH patient population has the worst prognosis. Alcoholic cirrhosis (ALC) is the most common ALD, and annual admissions for ALC increased significantly during the analyzed period.

The number of hospitalized patients with ALD and the annual hospitalization rate of ALD were increasing continuously in Beijing 302 Hospital from 2002 to 2013. More attention should be paid to develop population-based effective strategy to control ALD.

Abbreviations: AFL = alcoholic fatty liver, AH = alcoholic hepatitis, ALB = albumin, ALC = alcoholic cirrhosis, ALD = alcoholic liver disease, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHE = cholinesterase, GGT = gamma-glutamyl transferase, HBV = hepatitis B virus, HGB = hemoglobin, INR = international normalized ratio, MAH = mild alcoholic hepatitis, MDF = Maddrey's discriminant function, MCV = mean corpuscular volume, PLT = platelet, SAH = severe alcoholic hepatitis, TBIL = total bilirubin.

Keywords: alcoholic hepatitis, alcoholic liver disease, epidemiology

1. Introduction

Recent years, excessive alcohol consumption has significantly increased in China,[1] which can result in the associated health problems in Chinese people. It is reported that China had become the second country of heavy drinking in 2013, only next to the UK in the world.[2] Excessive drinking is associated with both short- and long-term liver injury.[3] Previous study showed that the prevalence of alcoholic liver disease (ALD) in north-eastern China has increased during the recent decade.[2] Recently, ALD has become the second most common cause of end-stage liver disease after viral hepatitis in China.[4] There is growing awareness that the incidence of ALD seems to be increasing.[5] ALD ranges from simple steatosis to cirrhosis. Usually, the histological stages of ALD can be divided into 3 parts: fatty liver or simple steatosis, alcoholic hepatitis (AH), and chronic hepatitis with hepatic fibrosis or cirrhosis.[6,7] A subpopulation of ALD patients may progress to severe alcoholic hepatitis (SAH). The spectrum of AH varies from mild liver damage to severe, life-threatening liver damage.[6] However, data about the last 10 years hospitalization rate of different stages of ALD remain largely unknown.

In order to provide the information of ALD hospitalization rates and prognosis, we retrospectively analyzed the hospitalized patients diagnosed with ALD in Beijing 302 Hospital admitted from 2002 to 2013.

2. Patients and methods

2.1. Patient selection

Beijing 302 Hospital has 1200 beds and is the largest hepatology tertiary referral hospital in China, where over 95% patients are

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hepatopathy. We performed a retrospective analysis of medical records and selected 7422 patients diagnosed with ALD admitted to Beijing 302 Hospital from January 2002 to December 2013. The clinical diagnosis criteria of ALD[6,7] included: a history of excess alcohol consumption over 5 years, ≥40 g/d for men and ≥20 g/d for women; the presence of clinical, biochemical, and/or detectable morphology abnormalities suggesting liver injury; negative serology for hepatitis B surface antigen and hepatitis C antibody (anti-HCV); and the absence of other causes of chronic liver disease.

The clinical classification criteria of ALD[7] were alcoholic fatty liver (AFL): detection of fatty liver using imaging techniques, negative of obesity, and slightly or no elevation in liver function test parameters; AH: the presence of one or more of the following: elevated levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), and no evidence of cirrhosis; alcoholic cirrhosis (ALC): cirrhosis confirmed by laboratory findings, radiographic evidence, or histology; and SAH: SAH in this study was defined as a Maddrey's discriminant function (MDF) ≥32.[5,8] MDF was calculated as follows: $4.6 \times$ [patient prothrombin time (PT) (s) − matched control PT (s)] + patient serum TBIL (mg/dL).

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Beijing 302 Hospital. Written informed consent was obtained from the patients or their relatives.

2.2. Data collection

Data were retrieved from hospital discharge record. The data of these patients on admission were collected. After active treatment, it was considered as improvement if the symptoms, physical findings, or complications ameliorated, and/or abnormal liver function or coagulation function became better. The symptoms and physical findings included fatigue, anorexia, nausea, vomiting, jaundice, losing body weight, shifting dullness, edema of lower extremity, etc. The laboratory index related to liver function or coagulation function contained albumin (ALB), TBIL, ALT, AST, ALP, GGT, total bile acid (TBA), cholinesterase (CHE), PT, prothrombin activity, international normalized ratio (INR), etc. Abdominal imaging was performed with ultrasound, computed tomography, and/or magnetic resonance imaging. In-hospital mortality was recorded.

2.3. Statistical analysis

Continuous variables normally distributed were expressed as mean ± standard deviation. The 1-way analysis of variance and Least-significant Difference tests were used to compare parametric continuous variables. When they were not normally distributed, median ± interquartile range was presented. Multiple comparisons were made between different groups with the Kruskal–Wallis H test. Comparison between various individuals was performed using the Mann–Whitney *U* test. Categorical variables were expressed as frequency with percentage. The categorical variables were analyzed by $R \times C$ chi-squared test or Kruskal–Wallis H test. Data were analyzed by SPSS version 16.0 for Windows (SPSS, Chicago, IL). Tests were 2-sided and a probability (*P*) value of <0.05 was considered statistically significant.

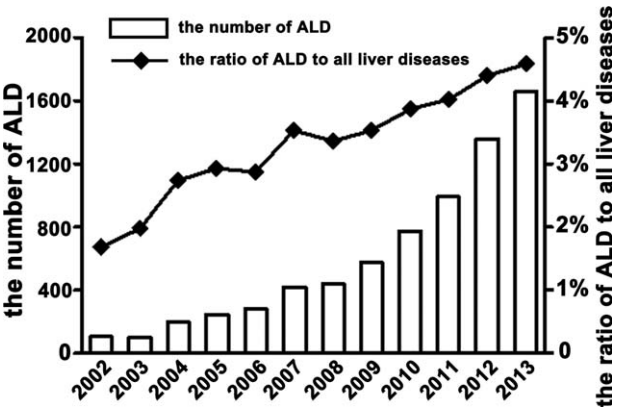

Figure 1. Change of alcoholic liver disease.

3. Results

3.1. Variation tendency of ALD

From 2002 to 2013, there were total 188,902 patients with different liver diseases admitted to Beijing 302 Hospital in China, including hepatitis B virus (HBV) and HCV, ALD, autoimmune liver diseases (such as autoimmune hepatitis, primary biliary cirrhosis), drug-induced liver injury, nonalcoholic fatty liver disease, and associated cirrhosis and hepatocellular carcinoma; 3.93% (7422) of episodes corresponding to ALD patients. The number of patients hospitalized with ALD increased from 110 in 2002 to 1672 in 2013. The rate of inpatient admission for ALD was rising almost continuously and increased from 1.7% in 2002 to 4.6% in 2013 (Fig. 1).

3.2. Percentage of different stages of ALD

The percentage of patients with different stages of ALD to all patients with ALD was expressed in Fig. 2 and Table 1. Between 2002 and 2013, ALC was present in 81.18% (6025) of all admissions, mild alcoholic hepatitis (MAH) in 9.51% (706), SAH in 5.51% (409), and AFL in 3.80% (282). ALC was the leading cause of inpatient hospitalization among different stages of ALD and increased significantly during the analyzed period. In addition, the annual proportion of SAH increased 2.43 times from 2002 to 2013 (Fig. 3).

3.3. Biochemical characteristics of the patients with ALD

The biochemical data were compared among the AFL, MAH, SAH, and ALC groups (Table 2). White blood cell, mean corpuscular volume (MCV), AST, the AST/ALT ratio, TBIL, INR, and ALP were the highest in SAH group. Serum levels of hemoglobin (HGB), ALT, ALB, GGT, and CHE in the SAH group were significantly lower than other different stages of ALD.

3.4. Gender distribution of the patients with ALD

The most patients with AFL, MAH, SAH, and ALC were male, accounting for 98.87%, 97.17%, 97.48%, and 98.23%, respectively.

3.5. Age distribution of the patients with ALD

Figure 4 shows that the patient population became older from patients with AFL to those with ALC. The ALC patient

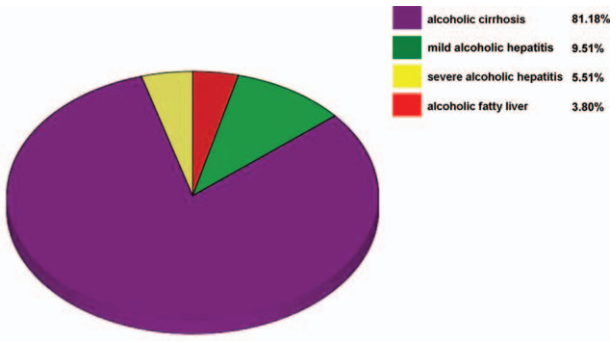

Figure 2. Percentages of different stages of alcoholic liver disease.

population has the highest proportion of older patients. Interestingly, the susceptible age was 40 to 49 years old for the patients with different stages of ALD.

3.6. Prognosis of the patients with ALD

Inpatient mortality rate among hospitalized patients with ALD was shown in Table 1. The SAH patient population has the worst prognosis, and the mortality rate of SAH was 8.56%, which was significantly higher than that of AFL (0%), MAH (0%), and ALC (1.36%). Our results revealed that the main complication for ALD-related cirrhosis (including ALC group and SAH with cirrhosis) was ascites (59.6%). The mortality rate of ALD-related cirrhosis with ascites was 3.83%, which was higher than that of those without ascites (1.73%) ($P=0.041$).

4. Discussion

Our center treats patients from all over China (exclude Hong Kong, Macao, and Taiwan). Therefore, this large study may well represent the current status of different stages of ALD in China. The spectrum of liver diseases in our country is changing gradually. A substantial decline in the number of newly HBV-infected patients was attributable to the establishment of the Expanded Program on Immunization in 1992.[9] However, the number of patients with ALD is rising at an alarming rate in China. During the last 3 decades, excessive alcohol consumption has significantly increased in China,[1] which can result in the associated health problems in Chinese people. In this study, our data show that the burden of hospitalized liver cirrhosis in China has been substantial. We observed an increasing trend in hospitalizations for ALD between 2002 and 2013. Most patients with ALD were male. Age distribution of ALD hospitalization showed that the highest rate was in 40- to 49-year-old group in subjects. Notably, the annual proportion of SAH increased 2.43 times from 2002 to 2013. We found the highest levels of MCV, the AST/ALT ratio, TBIL, INR, and ALP in SAH patients. By contrast, serum levels of HGB, ALB, and CHE were significantly decreased in SAH group. The SAH patient population has the worst prognosis. ALC is the most common ALD, and annual admissions for ALC increased significantly during the analyzed period.

Alcohol consumption in China has significantly increased over the last 3 decades.[4] Excessively drinking is becoming increasingly severe among the Chinese, especially in north-eastern China.[10] Unfortunately, nation-wide large-scale epidemiological ALD surveys have not been conducted in China. This is the first study examining the epidemiology of different stages of hospitalized ALD in China. Therefore, we are unable to directly compare our findings with those of a similar study. The drinking population and the incidence of ALD presented an uptrend according to the regional epidemiological investigation. At the beginning of this century, in some local areas of China, the percentage of drinking population have significantly increased along with the continuing growth of economy and the point prevalence of ALD in adults has been reported to range from 2.3% to 8.55%.[2,11] In England, in 2002/2003, admission rates for ALD were 27.3/100,000 and 13.5/100,000 in men and women, respectively.[12] Similarly, there were 7422 hospitalized ALD patients in Beijing 302 Hospital, with the ratio to all liver diseases rising from 1.7% in 2002 to 4.6% in 2013. The increase in hospitalizations for ALD between 2002 and 2013 likely reflects changes in drinking patterns, although there might be a risk of bias from changes in diagnostic methods.

There is a clear dose relationship between the amount of alcohol and the likelihood of developing ALD.[7] It is reported that 90% to 95% of heavy drinkers suffer from AFL, and 20% to 40% of them develop AH and 8% to 20% eventually progress to ALC.[13] In China, among heavy drinkers with a history of more than 5 years of alcohol consumption, it has been reported that the incidences of AFL, AH, and ALC were no <50%, 10%, and 10%, respectively.[11] In 2010 alone, the number of ALC deaths accounts for 47.9% of total number of deaths from all cirrhosis, and 46.9% of all cirrhosis disability-adjusted life years were related to ALC.[14] The results in our study also showed that the ALC is the predominant hospitalized ALD stage in China.

In addition, the annual proportion of SAH increased by more than 200% during the observed period. The spontaneous death rates of SAH were reported up to 30% at 1 month without effective treatment.[15] Patients with SAH have the worst prognosis. The disease is a clinical syndrome with jaundice and liver failure and generally occurs after chronic excessive alcohol consumption.[3,15] The major signs of SAH include markedly elevated jaundice and concomitant coagulopathy.[16] In agreement with the previous reports in patients with liver disease,[17–20] high levels of MCV, the AST/ALT ratio, TBIL, and

Table 1

Inpatient admission and mortality rate of different stages of ALD during the study period.

Alcoholic liver disease	Number of cases	Total hospitalized patients with ALD, %	Deaths during hospitalization	Mortality rate, %
AFL	282	3.80	0	0
MAH	706	9.51	0	0
SAH	409	5.51	35	8.56
ALC	6025	81.18	82	1.36
Total	7422	100	117	1.58

AFL = alcoholic fatty liver, ALC = alcoholic cirrhosis, ALD = alcoholic liver disease, MAH = mild alcoholic hepatitis, SAH = severe alcoholic hepatitis.

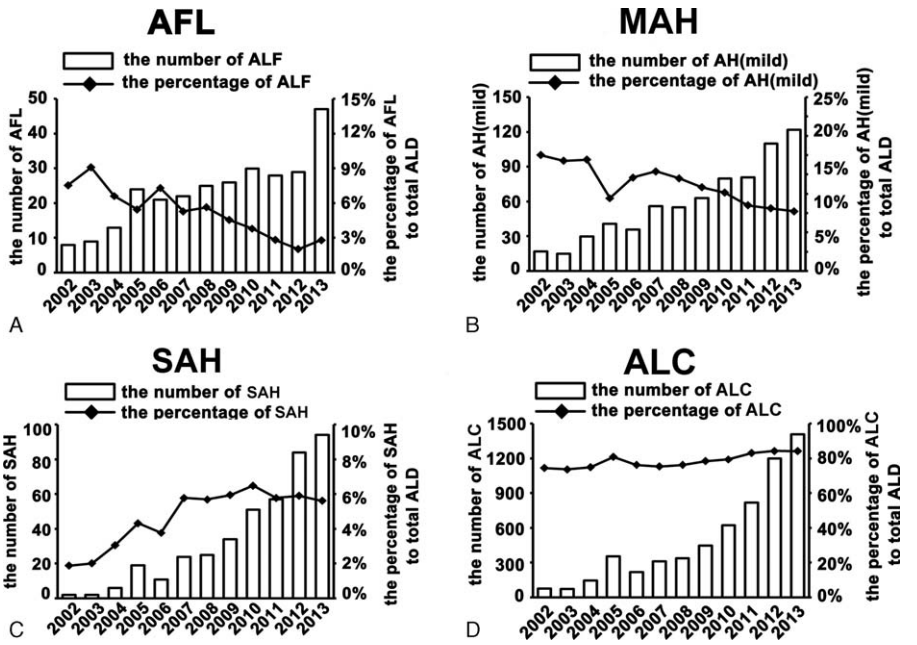

Figure 3. Trend of different stages of alcoholic liver disease.

INR were observed in SAH. Therefore, it would be important and necessary to do more studies on the prognosis of Chinese patients with SAH.

In China, women are often prevented or discouraged from consuming alcoholic beverages because of traditional culture. They commonly are less likely to take part in social events and have little chance of alcohol abuse. In keeping with previous studies,[2,21,22] our data also show Chinese patients with ALD had a lower proportion of female compared with western countries.

In this study, we have observed that the rate of ALD hospitalization is the highest in individuals with ages from 40 to 49 years old. In western country, the prevalence of ALD is usually the highest among people ages 18 to 34 years old. By contrast, young people are often prevented or discouraged from consuming alcoholic beverages in China because of traditional culture. Generally speaking, young people are considered not to be forced to drink too much even though they attend social banquets. Due to rich life experience and stable income, middle-aged Chinese people tend to be more active in attending social events and drinking alcoholic beverages. The risk of developing cirrhosis increases with an alcohol consumption of more than 60 to 80 g/d for 10 years in men. Our study showed that the patient population became older from patients with AFL to those with ALC in China.

There are some limitations that deserve further discussion. First of all, liver biopsy was not routinely performed during the time of

Table 2

Biochemical characteristics in hospitalized patients with ALD.

Variables	AFL group	MAH group	SAH group	ALC group
WBC, $\times 10^9$	$6.08 \pm 1.99^{*,\dagger}$	$5.66 \pm 2.1^{*,\dagger}$	$7.6 \pm 6.99^{\dagger,\ddagger,\S}$	$4.38 \pm 2.9^{*,\ddagger,\S}$
HGB, g/L	$154 \pm 16.75^{*,\dagger,\S}$	$146 \pm 30^{*,\dagger,\ddagger}$	$91 \pm 32^{\dagger,\ddagger,\S}$	$113 \pm 32^{*,\ddagger,\S}$
PLT, $\times 10^9$	$192.5 \pm 61^{*,\dagger}$	$184 \pm 96^{*,\dagger}$	$58 \pm 52^{\dagger,\ddagger,\S}$	$82 \pm 78^{*,\ddagger,\S}$
MCV	$91.05 \pm 6^{*,\dagger}$	$91.8 \pm 7.8^{*,\dagger}$	$103.3 \pm 12.5^{\dagger,\ddagger,\S}$	$94.2 \pm 10.38^{*,\ddagger,\S}$
ALT, U/L	$49 \pm 66^{*,\dagger,\S}$	$77 \pm 117^{*,\dagger,\ddagger}$	$33 \pm 31.5^{\dagger,\ddagger,\S}$	$43 \pm 46^{*,\ddagger,\S}$
AST, U/L	$31.5 \pm 23.3^{*,\dagger,\S}$	$52 \pm 51^{*,\dagger,\ddagger}$	$71 \pm 60.5^{\dagger,\ddagger,\S}$	$61 \pm 63^{*,\ddagger,\S}$
AST/ALT	$0.62 \pm 0.51^{*,\dagger}$	$0.66 \pm 0.72^{*,\dagger}$	$2.08 \pm 1.23^{\dagger,\ddagger,\S}$	$1.44 \pm 0.96^{*,\ddagger,\S}$
TBIL, μmol/L	$13 \pm 9.4^{*,\dagger,\S}$	$20.25 \pm 57.2^{*,\dagger,\ddagger}$	$246.5 \pm 202.7^{\dagger,\ddagger,\S}$	$27.9 \pm 33.85^{*,\ddagger,\S}$
ALB, g/L	$43 \pm 4^{*,\dagger}$	$41 \pm 8^{*,\dagger}$	$28 \pm 8^{\dagger,\ddagger,\S}$	$32 \pm 10^{*,\ddagger,\S}$
INR	$0.98 \pm 0.09^{*,\dagger}$	$0.98 \pm 0.1^{*,\dagger}$	$2 \pm 0.65^{\dagger,\ddagger,\S}$	$1.23 \pm 0.34^{*,\ddagger,\S}$
ALP, U/L	$80 \pm 39.5^{*,\dagger,\S}$	$92 \pm 71^{*,\dagger,\ddagger}$	$131.5 \pm 81.5^{\dagger,\ddagger,\S}$	$113 \pm 78^{*,\ddagger,\S}$
GGT, U/L	$64.5 \pm 133^{*,\dagger,\S}$	$77 \pm 171^{*,\dagger,\ddagger}$	$51 \pm 110.25^{\dagger,\ddagger,\S}$	$88 \pm 164^{*,\ddagger,\S}$
CHE, U/L	$8405 \pm 1912^{*,\dagger,\S}$	$7310 \pm 3052^{*,\dagger,\ddagger}$	$1963 \pm 1383.5^{\dagger,\ddagger,\S}$	$3402.5 \pm 3086^{*,\ddagger,\S}$

Data presented as median ± interquartile range.

AFL = alcoholic fatty liver, ALB = albumin, ALC = alcoholic cirrhosis, ALD = alcoholic liver disease, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHE = cholinesterase, GGT = gamma-glutamyl transferase, HGB = hemoglobin, INR = international normalized ratio, MAH = mild alcoholic hepatitis, MCV = mean corpuscular volume, PLT = platelet, SAH = severe alcoholic hepatitis, TBIL = total bilirubin, WBC = white blood cell.

* $P < 0.05$ compared with SAH group.

† $P < 0.05$ compared with ALC group.

‡ $P < 0.05$ compared with AFL group.

§ $P < 0.05$ compared with MAH group.

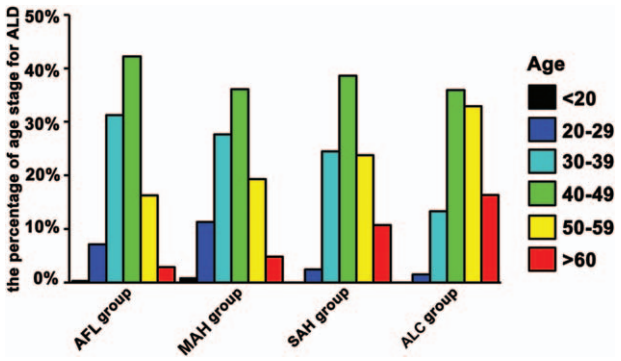

Figure 4. Age distribution for patients with different stages of alcoholic liver disease.

the study. Second, because the study was confined to hospitalized patients, the lack of effective follow-up led to a loss of long-term outcome of these patients after discharge. Despite these limitations, the sample size of hospitalized patients over the preceding decade still is an important advantage in our study.

In conclusion, during the last decade, there has been a gradual increase in the number of hospitalized patients with ALD and the annual hospitalization rate with of ALD among hospitalized patients with liver diseases. China has been making significant efforts to control primarily viral hepatitis (predominantly HBV). However, we need to develop population-based effective strategy to decrease the incidence of ALD and to reduce the economic burden of patients partly by educating people for adjusting their drinking patterns.

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