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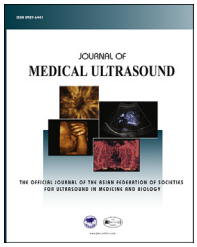

REVIEW ARTICLE

# Alcoholic Liver Disease in the Asian—Pacific Region with High Prevalence of Chronic Viral Hepatitis

CME Credits

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**Abstract** The hospitalized cases and mortality from alcoholic liver disease (ALD) are increasing in Taiwan and worldwide. Meanwhile, the Asia—Pacific region also has a high prevalence of hepatitis B virus (HBV) and hepatocellular carcinoma (HCC). The Taiwanese have the highest percentage of aldehyde dehydrogenase 2 (ALDH2) deficiency and the lowest amount of alcohol consumption. Based on the histological changes, ALD is clinically classified as steatosis, alcoholic hepatitis, alcoholic fibrosis, alcoholic cirrhosis, and alcoholic hepatitis on cirrhosis. Patients with overt alcoholic hepatitis often develop marked hepatomegaly, audible hepatic arterial bruit, mild leukocytosis, and mild fever. Patients having alcoholic cirrhosis had much more serious complications and mortality. It is clinically important to identify hepatic fibrosis and cirrhosis earlier for early management. Active assessments for esophageal varices and ascites may help the diagnosis of cirrhosis. Sonography is helpful for exanimating features of cirrhosis including portal hypertension, ascites, increased hepatic portal flow, and collaterals. Synergistic damage of viral hepatitis on ALD patients lead to rapid progression to cirrhosis and HCC. Distinct from the Western population, 30% of Taiwanese alcoholics had concomitant chronic HBV regardless of the different histologic categories. Patient groups with combined alcoholics and HBV had fewer platelet counts and much more cirrhosis with Ishak Stage 5—6 fibrosis. The annual incidences of HCC were significantly higher in alcoholic cirrhotic patients having concomitant HBV infection than those with only HBV infection or alcoholism alone. Antiviral nucleotide and nucleoside analogs therapy reduces the prevalence of HCC to a similar level to those ALD patients without active HBV.


Conflicts of interest: All authors have no conflicts of interest to declare.

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## Increase in alcoholic liver disease in Asian—Pacific region which has a high prevalence of hepatitis B virus

The cost of alcohol in the Asia—Pacific region is declining as a result of the improved economic status. The affordability of alcohol brings increased market sales and the price paid is the rising hospitalized cases and mortality from the alcoholic liver disease (ALD) not only in Taiwan but also worldwide [1,2]. In China, alcohol consumption per capita alcohol consumption dramatically increased from 2.5 L in 1978 to 6.7 L in 2010 [3]. Psychological conditions such as anxiety and depression result in further increased risk for alcohol abuse [4,5]. Meanwhile, the Asian—Pacific region also has a high prevalence of hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) [6,7]. Ethanol abuse is common among patients with HBV. The synergistic damage of alcohol abuse and HBV infection can exacerbate hepatic injury.

Genetics of the Asian population plays an important role in susceptibility to alcoholic liver disease. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) is responsible for ethanol metabolism [8]. ALDH2 deficiency results in reduced ability of aldehyde clearance; and aldehyde accumulation leads to Asian alcohol facial flushing syndrome, ALD, and cancer [9]. The region of high ALDH2 variant prevalence in Southern-East Asia almost completely overlays the HBV-endemic areas, and it is hypothesized that ALDH2 deficiency may be an evolutionary adaptation to HBV infection [10]. It is interesting that in the Asian—Pacific region, the Taiwanese have the highest percentage of ALDH2 deficiency and the lowest amount of alcohol consumption. However, the Koreans have the lowest percentage of ALDH2 deficiency and the highest amount of alcohol consumption (Table 1) [11—16]. The relatively lower ethanol consumption among the Taiwanese can be explained by the discomfort caused by excess aldehyde accumulation secondary to ALDH2 deficiency. Taiwanese patients with ALDH2 polymorphisms tend to drink less and they are found to have lower prevalence of HCC [17]. In Japanese patients of alcoholic cirrhosis, patients with HCC have much more prevalence of ALDH2*2 genotypes than those of non-HCC patients (23.9% vs 7.5%, $p = 0.017$) despite lower daily ethanol consumption (125 g vs 132 g, $p = 0.005$) [18]. Among patients with combined HBV infection and ALD, Taiwanese patients have a higher prevalence of cirrhosis (49% vs 31%) and HCC (12% vs 5%) than the Italians [19,20]. The difference may be in part explained by the high prevalence of ALDH2 deficiency in Taiwan.

**Table 1** ALDH2 variant carrier rate is inversely correlated with per capita alcohol consumption in the Asian—Pacific region.

| | HBV carrier rate (%) | ALDH2 variant carrier rate (%) | Per capita alcohol consumption (L) |
|---|---|---|---|
| Taiwan | 13.7 | 45—47 | 3.0 |
| China | 5.5 | 35 | 6.7 |
| Japan | 1.0 | 27—30 | 7.2 |
| Korea | 4.4 | 20—21 | 12.3 |

ALDH2 = aldehyde dehydrogenase 2; HBV = hepatitis B virus.

## Clinical features: Binge drinking induces overt alcoholic hepatitis

The pathogenesis of ALD includes increasing oxidative stress and lipid peroxidation, impaired regeneration, and increasing gut-derived endotoxin [21,22]. Steatosis, apoptosis, necrosis, and fibrosis are the major histological changes of a hepatic injury [21]. Based on the histological changes, ALD is clinically classified as steatosis, alcoholic hepatitis, alcoholic fibrosis, alcoholic cirrhosis, and alcoholic hepatitis on cirrhosis [23]. Severe alcoholic hepatitis with jaundice and decompensated liver function has recently being classified as overt alcoholic hepatitis (OAH); whereas mild and moderate degrees of alcoholic hepatitis are categorized as subclinical alcoholic steatohepatitis [24].

In animal models, mice fed with a small dosage of alcohol for 10 days followed by a single dose of binge alcohol can induce elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and hepatic injury, which are similar to those of alcoholic hepatitis [25], whereas mice with 4—6 weeks of chronic feeding induce only mild AST and ALT changes and steatosis [26]. Thus, a single binge drinking in a chronic alcoholic may induce severe alcoholic hepatitis.

Eighteen percent of the alcoholic patients with simple steatosis can progress to fibrosis or cirrhosis in 10 years; heavy drinking of $>$ 320 g of ethanol per week increases the risk of cirrhosis to 30—40% [27]. Up to 3% of patients having alcoholic cirrhosis may develop HCC [28].

The conventional laboratory results have only a limited role in the definite diagnosis of ALD. ALD should be considered at the presence of high gamma-glutamyl transferase (GGT), AST/ALT ratio, and mean corpuscular volume (MCV) [29]. Conventional sonographic features are similar among the different histologic groups including hepatomegaly and bright echogenicity due to fatty liver or fibrosis (Figure 1). Some patients with alcoholic cirrhosis may develop coarse echo and ascites. Most heavy drinking patients do not develop splenomegaly. Liver histology remains to be important for the assessment of fibrosis staging and diagnosis of alcoholic hepatitis [30].

## Early diagnosis of OAH

OAH is a clinical concern because of the high mortality. Most patients having OAH do not have liver histology to confirm the clinical diagnosis due to decompensated function, coagulopathy, and ascites. Patients with OAH often develop marked hepatomegaly, audible hepatic arterial bruit, mild leukocytosis, and mild fever. The audible hepatic arterial bruit is caused by severe portal hypertension with compensatory increased hepatic arterial inflow; and the sonographic feature of the dilated hepatic artery may be presented as pseudoparallel channel sign [31,32] (Figure 2).

Several prognostic scores based on the laboratory data from the 1$^{st}$ day of admission are frequently employed to