INVITED REVIEW

Epidemiological differences of common liver conditions between Asia and the West

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Abstract

Liver diseases form a heterogenous group of acute and chronic disorders of varying etiologies. Not only do they result in significant morbidity and mortality, but they also lead to a marked reduction in quality of life, together with a high socioeconomic burden globally. A better understanding of their global distribution is necessary to curb the massive health-care and socioeconomic burden that they entail. Notable differences and similarities have been described between common liver disease conditions occurring in Asia and the West (Europe and North America), giving rise to the need for an updated collective appraisal of this subject. In this review, the epidemiological differences of common liver conditions, specifically acute liver failure, drug-induced liver injury, acute-on-chronic liver failure, hepatocellular carcinoma, and non-alcoholic fatty liver disease, between Asia and the West are discussed.

Introduction

Liver diseases form a heterogenous group of acute and chronic disorders encompassing infectious, malignant, and inflammatory disease processes of varying etiologies. They confer a significant burden of disease, with liver cirrhosis alone contributing to 2% of all deaths globally in 2010. The Global Burden of Disease Study 2016 estimated that viral hepatitis, liver cancer, and liver cirrhosis caused 134,000, 830,000, and 1.3 million deaths, respectively, as observed using data pooled from 195 locations worldwide. The relative mortality rate for cirrhosis was found to be 27% higher compared to five different major cancers. In addition to the high mortality, there is also a high socioeconomic burden associated with liver diseases. In the United States, the annual cost of treating non-alcoholic fatty liver disease (NAFLD) was projected to be US$103 billion. Hepatitis B-related diseases were estimated to cost from 30 to 300% of the annual household income in China. Apart from the increased health-care utilization and cost, people with chronic liver disease were less likely to be employed and had worse self-reported general and mental health status.

Although the burden of chronic liver disease and its sequelae, that is, cirrhosis and hepatocellular carcinoma (HCC), is increasingly recognized, geographical variations in epidemiology have been scarcely reported. The recognition of regional differences in the etiology of acute and chronic liver failure, for instance, have a profound effect on the clinical management of these conditions from one population to another. Diagnostic assessment and treatment algorithms for various liver diseases will differ depending on the recognition of these varied epidemiologies.

In this review, we aim to discuss the epidemiological differences of common liver conditions between Asia and the West, specifically acute liver failure (ALF), drug-induced liver injury (DILI), acute-on-chronic liver failure (ACLF), HCC, and NAFLD. These liver conditions are well recognized globally, with certain epidemiological and clinical differences that will be highlighted in this review.

Acute liver failure

ALF is a rare condition that can be broadly defined as acute and severe liver dysfunction causing coagulopathy and hepatic encephalopathy in a patient with no pre-existing liver disorder. The specific definition of ALF is not standardized across studies, and there have been more than 40 variations of the definition found. In the United States, the incidence of ALF is 5.5 per million population, which yields an estimated 1600 new cases every year. ALF has a wide variety of causes that leads to significant heterogeneity in terms of outcome; for example, paracetamol-related ALF is associated with the highest rate of recovery and lowest rate of death compared to other etiologies.

The common causes of ALF in Asia and the West are shown in Table 1, while a comparison of the etiologies and outcomes between Asia and the West are outlined in Table 2. The predominant cause for ALF in the West is DILI, with paracetamol being the leading cause in the United States and the United Kingdom. In some European countries, viral hepatitis

Key words

acetaminophen toxicity, acute liver failure, acute-on-chronic liver failure, drug-induced liver injury, epidemiology, hepatocellular carcinoma, non-alcoholic fatty liver disease.

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remains a significant cause of ALF, with the most common etiology being hepatitis B. In Asia, viral hepatitis is the predominant cause of ALF, but recent data indicate that DILI is increasingly common in Asia, apart from Japan. Unlike the West, however, the most common drugs implicated are herbal and traditional medications in China, whereas antituberculosis therapy is the main culprit in India. The major virus responsible for ALF in East Asia is hepatitis B, whereas in India, it is hepatitis E, where it is also endemic.

Most studies in Asia and the West report similar rates of transplant-free survival of approximately 30–50%, with notable exceptions being one study in the United Kingdom and another in Taiwan, both with reported rates of above 60%.

### Drug-induced liver injury

The epidemiology of DILI is difficult to ascertain as it is often a diagnosis of exclusion, leading to an underestimation of the problem. Variations in biochemical patterns of liver injury and time to onset after drug exposure add to the challenge of recognizing DILI, thus contributing to underreporting. Reported incidence of DILI in the West varies from as low as 2.3–2.4 per 100 000 person-years in the United Kingdom and Sweden, to 14–19 per 100 000 person-years in France and Iceland. In contrast, the incidence of DILI in Asia appears to be higher based on a recent study from China with a reported annual incidence of 23.8 per 100 000 persons.

#### Paracetamol-induced hepatotoxicity

Paracetamol-induced hepatotoxicity rates in Western Caucasian patients have been reported to be 15–36%, however, studies from Asia have reported paracetamol-induced hepatotoxicity rates of only 2–7%. One possible explanation for this difference may relate to the quantity of paracetamol ingested during the overdose. The minimal amount of paracetamol reported to cause toxicity in adults is 7.5 g, and liver toxicity is typically associated with dosages of more than 10 g. Based on the published literature, patients with paracetamol-induced hepatotoxicity in Asia seem to have ingested lower doses of the drug compared to Caucasian patients (Table 4), but the reason for this is uncertain.

One explanation is that it could be due to differences in the rate of alcohol coingestion between Asia and the West. Chronic alcohol exposure is recognized to increase toxicity from paracetamol overdose by a two to threefold increase in hepatic content of cytochrome P4502E1, the major isoform responsible for the formation of the toxic metabolite from paracetamol. Regular and excessive alcohol consumption in Western patients with paracetamol overdose has been documented to be 25 and 20–40%, respectively. In contrast, the rate of alcohol coingestion was only 4.2–17% in Asian studies (Table 4).

Finally, variation in pharmacogenetics between Asians and Caucasians may explain the lower hepatotoxicity rates in the
A study examining the excretion of paracetamol metabolites demonstrated heterogeneity in the conversion of paracetamol cysteine conjugates (toxic paracetamol metabolites) to mercapturate via N-acetylation in healthy Chinese and Caucasian volunteers. Ethnic Chinese adults have been found to have relatively extensive glucuronidation but lower sulfation in paracetamol metabolism compared to Caucasians.

**Acute-on-chronic liver failure**

ACLF is a clinical syndrome characterized by severe hepatic dysfunction following an acute insult in patients with underlying chronic liver disease or cirrhosis. In contrast to acute decompensated cirrhosis, ACLF has a high short-term mortality, similar in prognosis to ALF. Currently, there is no single uniform definition for ACLF, and up to 13 different variations have been reported. The two most widely accepted definitions are given by the Asian Pacific Association for the Study of Liver (APASL) ACLF Research Consortium (AARC) and the European Association for the Study of Liver (EASL) Chronic Liver Failure Consortium (EASL-CLIF). While the AARC definition includes all patients with chronic liver disease, with or without cirrhosis, the EASL-CLIF definition restricts itself to patients with cirrhosis only. This fundamental difference poses a significant challenge in making a reliable comparison of ACLF epidemiology between Asia and the West. The most common etiology of chronic insult in ACLF in Asia and the West is alcohol and viral hepatitis, with hepatitis B being the predominant virus.

**Table 3** Summary of studies on drug-induced liver injury and the common causative agents

| Author  | Country   | n     | Study period     | Common causes                                                                 |
|---------|-----------|-------|------------------|-------------------------------------------------------------------------------|
| Friis*28 | Denmark   | 1100  | 1978–1987        | Halothane 25.5%, antimicrobials 15%, antiepileptic 9%                          |
| Sgro*25  | France    | 34    | 1997–2000        | Antimicrobial 25%, psychotrophic 22.5%, NSAIDs 10%                            |
| de Abajo23 | UK       | 128   | 1994–1999        | Amoxycillin-clavulanate 10.2%, paracetamol 9.4%, diclofenac 7.8%              |
| Andrade*29 | Spain    | 461   | 1994–2004        | Amoxycillin-clavulanate 12.8%, ebrotidine 5%, ATT 5%                          |
| Meier*30  | Switzerland | 88    | 1996–2000        | Heparin 37.5%, amoxycillin-clavulanate 10.2%, NSAIDs 5.7%                    |
| De Valle*24 | Sweden   | 77    | 1995–2005        | Diclofenac 18%, fluocoxacin 10.4%, azathioprine 6.5%                         |
| Björnsson*31 | Iceland | 96    | 2010–2011        | Amoxycillin-clavulanate 22%, diclofenac 6%, azathioprine 4%, infliximab 4%, nitrofurantoin 4% |
| Licata*32 | Italy     | 185   | 2000–2016        | NSAIDs 35.5%, antibiotics 23.4%, immunosuppressants 10.9%                    |
| Chalasani*33 | US       | 300   | 2004–2007        | Amoxycillin-clavulanate 7.7%, nitrofurantoin 4.3%, isoniazid 4.3%, trimethoprim-sulfamethoxazole 4.3% |
| Chalasani*34 | US       | 899   | 2004–2013        | Amoxycillin-clavulanate 10%, isoniazid 5.3%, nitrofurantoin 4.7%             |
| Devabhavi*35 | India   | 313   | 1997–2008        | ATT 58%, antiepileptics 11%, olanzapine 5.4%                                 |
| Rath*36   | India     | 82    | 2014–2015        | ATT 49%, antiepileptic 12%, CAM 10%                                         |
| Wai*37    | Singapore | 31    | 2004–2006        | Traditional Chinese medications 55%, traditional Malay medications 16%, ATT 6% |
| Sobhonsidisuk*38 | Thailand | 589   | 2009–2016        | Paracetamol 35%, ATT 34.6%, antivirals 3.7%                                  |
| Takikawa*39 | Japan    | 1676  | 1997–2006        | Antibiotic 14.3%, neuropsychiatric drugs 10.1%, dietary supplements 10%      |
| Aiso*40   | Japan     | 307   | 2010–2018        | Anti-inflammatory 11%, antimicrobial 11%, anticancer 10%                      |
| Suk*41    | South Korea | 371   | 2005–2007        | HM 27.5%, prescription medications 27.3%, health foods 13.7%               |
| Kwoon*42  | South Korea | 567   | 2007–2008        | ATT 19.8%, antiepileptics 9.7%, cephalosporins 9.5%                         |
| Zhu*43    | China     | 1985  | 2009–2014        | Chinese HM 28.4%, antibiotics 10%, ATT 5%                                    |
| Shen*27   | China     | 25 927| 2012–2014        | Traditional Chinese HM 26.8%, ATT 22%                                       |
| ATT, antituberculosis medication; CAM, complementary and alternative medicine; HM, herbal medications; NSAID, non-steroidal anti-inflammatory drugs.

**Table 4** Summary of studies that have examined hepatotoxicity rates in patients with paracetamol overdose

| Author            | Country   | Hepatotoxicity (%) | Survival (%) | Paracetamol dose |
|-------------------|-----------|--------------------|--------------|------------------|
| Schiedt, 1997*51  | USA       | 32                 | 93           | Median = 17.6 g 93% > 4 g |
| Hawton*52         | UK        | 31                 | NA           | 69% > 12.5 g     |
| Gyamal*53         | USA       | 16                 | 96           | NA               |
| James*54          | USA       | 15 (1.3% ALF)       | 100          | Mean = 18 g      |
| Ayonrinde*45      | Australia | 14                 | 100          | Median = 12 g    |
| Mohd Zain*47      | Malaysia  | 7.3                | 100          | 38% > 10 g       |
| Marzlufati*49     | Malaysia  | 7.5                | 100          | Median 10 g (54.3% > 10 g) |
| Chan*48           | China     | 6                  | 100          | Median 5 g 6.7% > 10 g |
| Schmidt*55        | Denmark   | No data on hepatotoxicity 0.9% (ALF) | 99.9         | Median 25 g      |

ALF, acute liver failure.
in Asia and hepatitis C in Europe and North America (Table 5).

The acute precipitating event for ACLF is also reported differently according to the EASL-CLIF definition and the AARC definition. While the EASL-CLIF criteria include both hepatic and nonhepatic insults, the AARC criteria accept only hepatic insults, thus making it difficult to make direct comparisons between the triggers for ACLF in Asia and the West.

Currently, the most common acute insult in Asia is alcohol (50.3%) followed by viral hepatitis (22.6%: hepatitis B; 13.2%, hepatitis E virus; 9.4%) and DILI (9.3%), and no attributable cause was found in 4.8% of cases. In Europe, 43.5% of ACLF cases have an unknown cause. Bacterial infections are the second most common trigger (32.6%) followed by alcohol (24.5%) and gastrointestinal hemorrhages (13.2%), with 13.5% of cases having more than one precipitating event.

The acute insult for ACLF varies depending on geography and population studied and includes both infectious and non-infectious causes. The predominant acute insults triggering ACLF were previously reported to be quite distinct between Asia and the West. Infectious etiology was thought to predominate in Asia, with hepatitis B reactivation still being an important cause in Asia. This is acknowledged by the AARC in their last consensus as being “a bit unexpected for the Asian countries” in relation to the rise of “westernization” of Asia.

The 28-day and 90-day mortality rate for ACLF in Asia was 40.5 and 49.2%, respectively, while it was 32.8 and 51.2% in Europe and the United States, respectively.

**Hepatocellular carcinoma**

Primary liver cancer is the sixth most common cancer in the world, accounting for 5.6% of total cancers worldwide, and is ranked second for cancer mortality, causing 9.6% of cancer deaths in 2012. The predominant histological type of primary liver neoplasms globally is HCC. Asia harbors two-thirds of the global HCC cases, with China having the highest incidence, with approximately 50% of new cases in 2012 occurring there. Table 6 highlights the major differences of HCC in Asia and the West.

**Table 5** Underlying chronic liver disease in patients with acute-on-chronic liver failure

| Region       | Reference | n   | Alcohol, (%) | Hep B, (%) | Hep C, (%) | Alcohol and Hep C, (%) | NASH, (%) | Others, (%) |
|--------------|-----------|-----|--------------|------------|------------|------------------------|-----------|-------------|
| Europe       | 60        | 303 | 60.3         | 0          | 13         | 9.3                    | 0         | 17.4        |
| North America| 62        | 507 | 15           | 0          | 25         | 27                     | 15.4      | 17.6        |
| Asia Pacific | 63        | 1402| 56.1         | 15.1       | 1.9        | 0                      | 6.1       | 20.8        |

Hep B, hepatitis B; hep c, hepatitis C; NASH, non-alcoholic steatohepatitis.

The high prevalence of HCV-associated HCC in Japan compared to the rest of East Asia is due to the mass utilization of used and unsterile hypodermic needles as part of a schistosomiasis eradication program in the 1950s. NAFLD is becoming an important risk factor as its incidence increases in relation to obesity and diabetes, worldwide. Data from the United States suggests that non-alcoholic steatohepatitis (NASH) could be responsible for 50% of HCC, while in Japan, it was reported to be 2%. A strong geographic correlation has been demonstrated between the prevalence of HBV and the incidence of HCC: countries with high HBV infection prevalence (>8%) have a very high incidence of HCC. Exposure to aflatoxins, a recognized risk factor in Southeast Asian and East Asian countries, contributes to between 4.6 and 28.2% of all HCC cases worldwide.

**Table 6** Differences in hepatocellular between Asia and the West

| Differences                        | East | West |
|------------------------------------|------|------|
| Incidence (age-standardized rates per 100 000 persons) | East Asia: men; 31.9, women; 10.2 | Europe: men; 9.3, women: 2.2 |
|                                    | Southeast Asia: men; 22.2, women: 7.2 | North America: men; 6.8, women: 2.7 |
| Decreasing incidence rate          | East Asia: younger | Europe: older age |
| Etiology                           | HBV infection | HCV infection |
| Age of diagnosis                   | Younger | Older |
| Mortality (age-standardized rates per 100 000 persons) | East Asia: men; 29.9, women; 9.6 | Europe: men; 6.1, women: 2.2 |
|                                    | Southeast Asia: men; 21.4, women; 8.8 | North America: men; 6.8, women: 2.3 |

HBV, hepatitis B virus; HCV, hepatitis C virus.
Nevertheless, there has been a global change in the trend of HCC over recent times; normally high-incidence countries in Asia are experiencing a decrease in new cases, while countries in North America and Northern Europe are reporting a rise in new cases.\textsuperscript{67-79} This has been attributed in part to the decreasing incidence of HBV due to national immunization programs and improved farming practices reducing the effect of aflatoxins in endemic countries, coupled with the unabated rise of metabolic syndrome and NAFLD in the developed world.

**Non-alcoholic fatty liver disease**

NAFLD is related to obesity and the metabolic syndrome and has been increasing in prevalence alongside the prevalence of obesity worldwide, particularly in Asia.\textsuperscript{80} A recent meta-analysis showed that the prevalence of NAFLD in Asia, estimated at 27\%, has now reached levels similar to that observed in the Western world.\textsuperscript{81}

In both Asian and Western populations, NAFLD increases with increasing age, particularly between the ages of 30 and 50 years old, and is higher in men compared with women. The prevalence of NAFLD catches up in women after the age of 50 years, presumably due to the loss of the protective effect of female hormones. The prevalence of NAFLD also increases with increasing number of components of the metabolic syndrome. Hence, the screening for NAFLD is now considered in at-risk groups, such as patients with diabetes mellitus and obesity, in both the Asian and Western guidelines.\textsuperscript{82,83}

Ethnic differences in the prevalence of significant hepatic steatosis has been reported in the West\textsuperscript{84} in a multiethnic population-based study on 2287 subject in the United States using magnetic resonance spectroscopy. African Americans had a significantly lower prevalence of hepatic steatosis despite an equally high prevalence of obesity and insulin resistance compared with the Hispanics. In a separate study, the prevalence of cryptogenic cirrhosis (now recognized to be caused by NASH) was the highest among the Hispanics and the lowest among the Chinese.\textsuperscript{82} The proportion of cryptogenic cirrhosis also mirrored the difference in the prevalence of NAFLD observed in the different ethnic groups, higher among the Malays and Indians at 21\% compared with 12\% among the Chinese.\textsuperscript{90} However, in a study on 198 healthy controls and 114 patients with biopsy-proven NAFLD, the PNPLA3 gene polymorphism appeared to be higher among the Chinese compared with the Malays and Indians, suggesting that there could be differences in susceptibility to the gene polymorphism among the different Asian ethnic groups.\textsuperscript{91}

NAFLD patients are at increased risk of mortality compared with the general population, with much of the mortality excess attributable to liver-related complications in patients with NASH and advanced fibrosis.\textsuperscript{92} While longitudinal studies with paired liver biopsies have mostly come from Western populations,\textsuperscript{93} data from Asian populations are beginning to emerge.\textsuperscript{94-96} In two Asian studies comprising mostly NASH patients, fibrosis progression was observed in more than half of the patients over a median interval of 6 years.\textsuperscript{94,96} Recent evidence points to fibrosis stage as the most important determinant of disease-specific mortality in NAFLD.\textsuperscript{97}

**Conclusion**

This review of common acute and chronic liver conditions has highlighted several notable differences in epidemiology between Asia and the West. We have intentionally not discussed less common conditions such as autoimmune liver diseases, which are relatively infrequent, from a global perspective. Etiological differences in ALF and variation in paracetamol-induced hepatotoxicity between Asia and the West have clear implications on the clinical management of these conditions. Marked variations in DILI epidemiology between Asia and the West warrants further investigation into the factors underpinning the differences. Similarly, etiological and differing diagnostic criteria for ACLF between Asia and the West will influence the way this condition is detected and treated. Clinical variation in HCC between Asia and the West, largely due to epidemiological differences relating to viral hepatitis and NAFLD, will influence the prevention and treatment of this deadly disease. Finally, NAFLD is rising globally in tandem with the obesity and diabetes epidemic, with Asia having caught up to the West in terms of prevalence and disease burden.

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