Seminar

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Burden of liver diseases in the world

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Summary

Liver disease accounts for approximately 2 million deaths per year worldwide, 1 million due to complications of cirrhosis and 1 million due to viral hepatitis and hepatocellular carcinoma. Cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death; combined, they account for 3.5% of all deaths worldwide. Cirrhosis is within the top 20 causes of disability-adjusted life years and years of life lost, accounting for 1.6% and 2.1% of the worldwide burden. About 2 billion people consume alcohol worldwide and upwards of 75 million are diagnosed with alcohol-use disorders and are at risk of alcohol-associated liver disease. Approximately 2 billion adults are obese or overweight and over 400 million have diabetes; both of which are risk factors for non-alcoholic fatty liver disease and hepatocellular carcinoma. The global prevalence of viral hepatitis remains high, while drug-induced liver injury continues to increase as a major cause of acute hepatitis. Liver transplantation is the second most common solid organ transplantation, yet less than 10% of global transplantation needs are met at current rates. Though these numbers are sobering, they highlight an important opportunity to improve public health given that most causes of liver diseases are preventable.

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Introduction and global burden

Liver disease accounts for approximately 2 million deaths per year worldwide, 1 million due to complications of cirrhosis and 1 million due to viral hepatitis and hepatocellular carcinoma (HCC).[1] Accurate statistics are not always available because cause-specific mortality data are sparse for many regions where liver disease is highly prevalent, particularly in Africa. Moreover, approximately one-third of all countries worldwide do not have accurate mortality data. Even in developed countries clear separation of liver disease burden according to aetiology and stage of disease is not possible. The incidence and prevalence of chronic liver disease is not well-established even in the available population-based studies. Be that as it may, there are striking differences in liver disease burden based upon geographic region, race, gender, ethnicity and socioeconomic strata. Studies are further limited by referral bias (*e.g.* tertiary care centre), composition of population under study (inpatient *vs.* outpatient), incomplete ascertainment and lack of standardised definitions (*e.g.* alcoholic hepatitis *vs.* cirrhosis) and method of assessment (laboratory tests, biopsy, non-invasive markers, imaging, death certificates, or self-reported). In some studies, a large proportion of patients have cirrhosis on presentation, possibly biasing the estimate towards patients with advanced fibrosis.[2] Accurate mortality data is also hampered as official death records underestimate liver diseases and cirrhosis as the main cause of death.[3] With the aforementioned caveats, current data suggest that both acute and chronic liver diseases are prevalent worldwide, causing significant morbidity and mortality. Further, the global burden of both acute and chronic liver disease is expected to increase.[1,4,5]

Global mortality

Globally, cirrhosis currently causes 1.16 million deaths, and liver cancer 788,000 deaths, making them the 11th and 16th most common causes of death, respectively, each year (Table 1). Combined, they account for 3.5% of all deaths worldwide. This marks an increase from 2000, when liver-related mortality accounted for 3% of all deaths, with cirrhosis and liver cancer ranking as the 13th and 20th leading causes of death, respectively. The burden is likely higher if one accounts for deaths due to acute hepatitis (145,000) and alcohol-use disorders (AUDs) (129,000). These numbers suggest that approximately 2 million deaths worldwide may be attributed to liver disease. The highest percentage of regional deaths due to liver disease was seen in Latin America & Caribbean and Middle East & North Africa, whereas the absolute number of deaths was highest in South Asia and East Asia and Pacific. Egypt, Moldova and Mongolia have some of the highest cirrhosis mortality rates in the world.[6] Given the population burden, India accounts for one-fifth (18.3%) and China accounts for 11% of all cirrhosis deaths globally.[6] Mortality in Central Asian countries and the Russian federation is increasing. In Europe, mortality is increasing in the UK but decreasing in France and Italy. Globally more men than women develop cirrhosis, while in Moldova and Russia the

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Table 1. Global mortality related to liver disease and liver cancer, 2015.

	Cirrhosis and the liver				HCC
	Global rank	Deaths (000s)	% of total deaths	CDR (per 100,000 population)	Deaths (000s)
World	11	1,162	2.1	15.8	788
East Asia & Pacific	13	328	2.0	14.4	547
Europe & Central Asia	17	115	1.2	12.7	78
Latin America & Caribbean	9	98	2.7	15.6	33
Middle East & North Africa	8	77	3.5	18.2	24
North America	12	50	1.7	14.0	27
South Asia	10	314	2.5	18.0	38
Sub-Saharan Africa	16	179	1.9	17.9	42

This is likely an underestimate and does not account for deaths due to acute hepatitis. Data available from Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015. Geneva, World Health Organization; 2016. CDR, crude death rate; HCC, hepatocellular carcinoma.

Key point

The main causes of cirrhosis in Western and industrialised countries are alcohol and NAFLD, while viral hepatitis B is the primary cause in China and other Asian countries.

ratio is almost the same.[6] The causes of cirrhosis vary: in Western and industrialised countries alcohol and non-alcoholic fatty liver disease have overtaken viral hepatitis as the primary causes, whereas in China and other Asian countries hepatitis B continues to be a major cause.[7] In Mongolia, 99% of cases of cirrhosis are attributable to viral hepatitis B and C individually and 20% of patients have hepatitis B and C coinfection.[8] In the US, chronic liver disease and cirrhosis is the 12th leading cause of death; among patients aged 45–64 years it is the 4th leading cause of death.[3]

Global morbidity

Besides an increased risk of mortality, the economic impact is high and quality of life indices are low in patients with chronic liver disease.[9] Global and regional-level estimates of chronic liver disease-related disability-adjusted life years (DALYs) and years of life lost consistently show cirrhosis within the top 20 causes (Table 2). The largest burden is seen in South-East Asia.[10,11] Liver diseases can cause a variety of extrahepatic morbidities, which significantly contribute to mortality and reduced quality of life. In the US, patients with chronic liver disease are more likely to be unemployed (55% *vs.* 30%), have higher rates of disability related unemployment (30.5% *vs.* 6.6%) and have higher annual health care expenditures ($19,390 *vs.* $5,567) than those without chronic liver disease.[9] Indeed, inpatient healthcare utilisation is higher for patients with chronic liver disease and has increased over the last 2 decades; amongst gastrointestinal-related hospitalisation, chronic liver disease had the highest inpatient mortality.[12] Though these numbers are sobering, they highlight an important opportunity to improve public health given that most causes of liver diseases are preventable. The following sections outline the global burden by liver disease type.

Specific liver diseases

Alcohol-associated liver disease

Alcohol-associated liver disease (AALD), is a major cause of liver disease worldwide.[13] Further, alcohol use often exacerbates liver injury, as it coexists with other factors (*e.g.* viral hepatitis). According to the World Health Organization (WHO), about 2 billion people consume alcohol worldwide and upwards of 75 million are diagnosed with AUDs.[14] Worldwide annual consumption in 2010 was 6.2 litres of alcohol per person aged 15 years or older. In Belarus, Moldova and Lithuania, annual per capita alcohol consumption was above 15 litres. Age-standardised heavy drinking was highest in European countries. In addition, the highest percentage of 15–19 years old who drink heavily was seen in Germany, the Netherlands and France. In 2012, about 3.3 million deaths (5.9% of all global deaths) were attributable to alcohol consumption.[15] In 2012, 139 million DALYs, or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption. Alcohol is the leading global risk factor for death and DALYs among those less than 20 years old.[4] Globally, over 50% of mortality related to cirrhosis is attributable to

Table 2. Global morbidity related to chronic liver disease, 2015.

	DALYs (000s)	Rank	% DALYs	DALYs per 100,000 population	Rank	YLLs (000s)	% YLLs	YLLs per 100,000 population
Global	41,486	16	1.6	565	12	40,986	2.1	558
WHO African Region	7,242	18	1.2	732	17	7,195	1.3	727
WHO Region of the Americas	4,890	17	1.8	496	10	4,826	2.7	489
WHO South-East Asia Region	15,581	13	2.2	808	10	15,450	3.0	801
WHO European Region	3,608	>20	<1.3%	n/a	12	3,502	1.7	385
WHO Eastern Mediterranean Region	3,409	17	1.4	530	11	3,371	1.8	524
WHO Western Pacific Region	6,518	19	1.3	351	11	6,407	2.0	345

Data available from Global Health Estimates 2015: Disease burden by Cause, Age, Sex, by Country and by Region, 2000–2015. Geneva, World Health Organization; 2016. DALY, disability-adjusted life years; WHO, World Health Organization; YLL, years of life lost.

alcohol. In addition, between 4% and 25% of the global disease burden of specific cancers is attributable to alcohol.[16] A higher percentage of cirrhosis within a country or region is linked to higher rates of heavy alcohol consumption.[17] The global patterns of alcohol consumption, prevalence of abuse and dependence as well as mortality attributed to alcohol are described (Tables 3 and 4).[16] The global prevalence of AUDs is 4.1% and the prevalence of alcohol-use dependence is 3.0%. The highest prevalence of AUD is observed in Europe and the Western Pacific and correlates with higher alcohol consumption. Using National Health and Nutrition Examination Survey (NHANES) data in the US, the prevalence of AALD was 1–2.5% between 1988 and 2008.[18] However, AALD covers a disparate population that includes patients with steatosis, fibrosis, alcoholic hepatitis and cirrhosis. In a single-centre study of patients with AALD undergoing biopsy, 26% had cirrhosis, 7% had acute alcoholic hepatitis and 18% had fibrosis.[19] Cirrhosis rates are higher in enriched populations with higher alcohol consumption and are higher among patients with alcoholic hepatitis. Among patients with alcoholic hepatitis, approximately 3–12% progress to cirrhosis annually, though this rate is likely modified by baseline prevalence and ascertainment.[20] Progression to cirrhosis may be higher in patients with AALD compared to non-alcoholic fatty liver disease (NAFLD). Given the burgeoning problem of obesity in the developed world, it is likely that alcohol-related injury will increase.[21] Obesity may also potentiate the severity of all stages of AALD.[22] In AALD, mortality is higher in the presence of alcoholic hepatitis. Further, mortality with AALD may be higher than mortality with NAFL; liver-related deaths were 36% for AALD compared to 7% for NAFLD.[23]

Non-alcoholic fatty liver disease

NAFLD encompasses 2 distinct conditions i) NAFL which includes steatosis or steatosis with mild lobular inflammation and ii) non-alcoholic steatohepatitis (NASH) that includes varying degrees of fibrosis, cirrhosis and HCC.[24] Currently, the definitive diagnosis of NASH requires a liver biopsy. There has been a palpable increase in NAFLD across the world. The true incidence and prevalence globally are hard to characterise given variations in assessment and definitions.

Analogous to alcohol use and AALD, in NAFLD there is a high prevalence of co-existing risk factors such as obesity and diabetes.[25] A large part of the worldwide increase in NAFLD is driven by obesity; however patterns of increased prevalence do not always correlate with areas of higher caloric consumption, suggesting that other modifiers or factors may lead to progression among patients with NAFLD.[26] The prevalence of obesity has increased 6-fold over the last 4 decades[27] (Fig. 1). The number of obese adults increased from 100 million in 1975 (69 million women, 31 million men) to 671 million in 2016 (390 million women, 281 million men). Another 1.3 billion adults were overweight. Over the last 4 decades, though median BMI has plateaued in high income countries, it has accelerated in several parts of Asia. The increased rates among children are even more concerning. In a global analysis of 2,400 population-based studies on 129 million participants, the global age-standardised prevalence of obesity increased from 0.7% (1975) to 5.6% (2016) in girls, and from 0.9% (1975) to 7.8% (2016) in boys. In 2016, 50 million girls and 74 million boys worldwide were obese. An additional 213 million were overweight. The largest increase was noted in Polynesia, Micronesia and Latin America. (http://www.ncdrisc.org/index.html) The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million. From 1980 to 2014, global age-standardised diabetes prevalence increased from 4.3% to 9.0% in men, and from 5.0% to 7.9% in women.[28] The prevalence of NAFLD within a population varies between 8 and 45% depending on the definition utilised[29,30] (Fig. 2). The global prevalence of NAFLD was estimated to be 25.2%, with a prevalence above 30% in the Middle East and South America.[31] Among patients that underwent

Key point

Worldwide, over 50% of mortality related to cirrhosis is attributable to alcohol.

Table 3. Global burden of alcohol consumption.

	Liters per capita 2005	Liters per capita 2010	Prevalence of alcohol use disorders, 2010 (%)	Prevalence of alcohol dependence, 2010 (%)
Africa	6.2	6.0	3.3	1.4
Americas	9.2	8.4	6.0	3.4
South-East Asia	2.9	3.5	2.2	1.7
Europe	9.1	10.9	7.5	4.0
Eastern Mediterranean	0.7	0.7	0.3	0.2
Western Pacific	5.4	6.8	4.6	2.3
(WHO) Global	5.6	6.2	4.1	2.9

Data available from Global Status Report on Alcohol and Health 2014, Geneva, World Health Organization; 2014.

Table 4. Top 10 countries with high global burden of alcohol-related cirrhosis mortality, 2012.

	Liver cirrhosis, age-standardised death rates (15+), per 100,000 population, 2012	
	Male	Female
Country		
Republic of Moldova	98.5	71.9
Egypt	122.3	67.8
Turkmenistan	94.9	66.9
Sierra Leone	102.5	52.6
Uzbekistan	62.6	52.4
Uganda	67.8	50.1
Mongolia	78.8	47.6
Tajikistan	39.4	45.1
Kyrgyzstan	99.3	44.2
Kazakhstan	82.6	43.9

Data available from Global Status Report on Alcohol and Health 2014, Geneva, World Health Organization; 2014. WHO, World Health Organization.

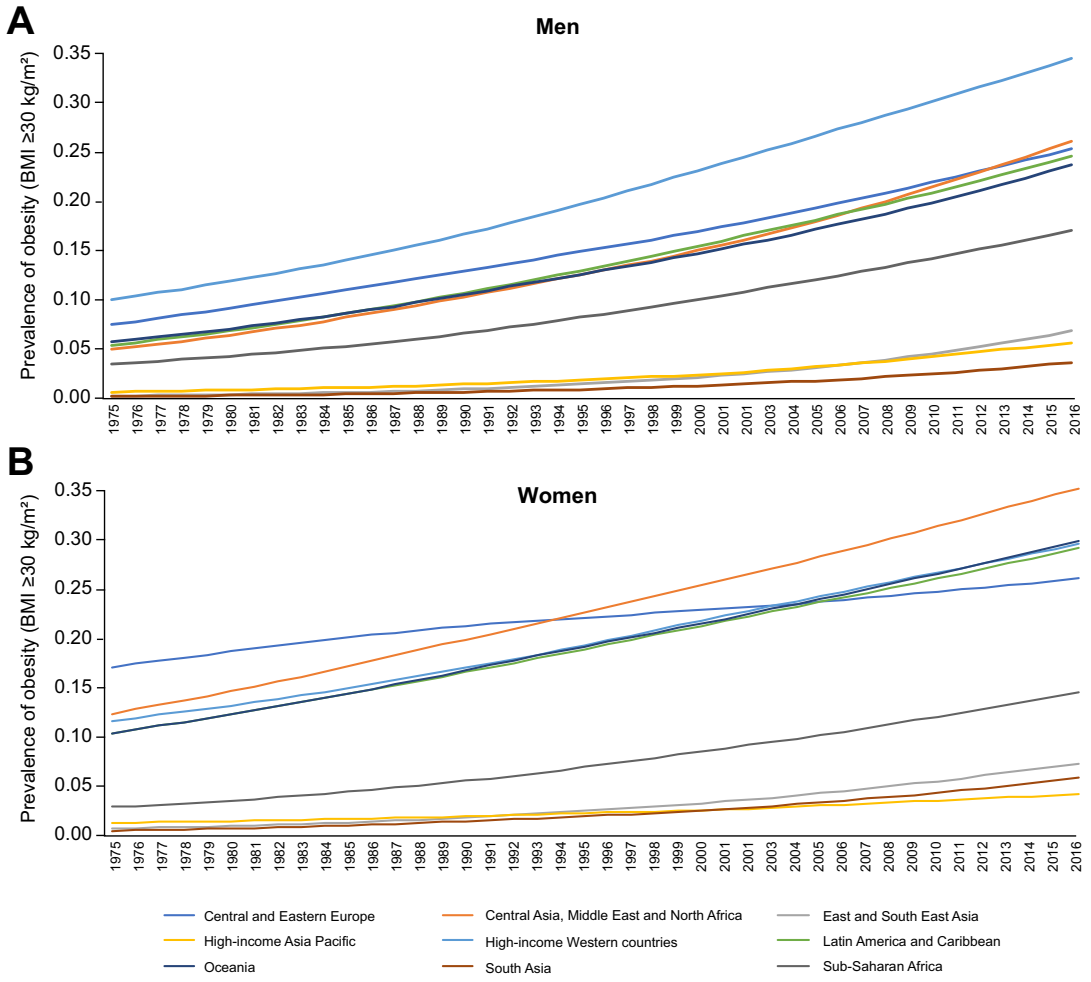

Fig. 1. Trends in obesity by region, 1976–2015. (A) Men and (B) women. Figures from data available through the NCD Risk Factor Collaboration (NCD-RisC).

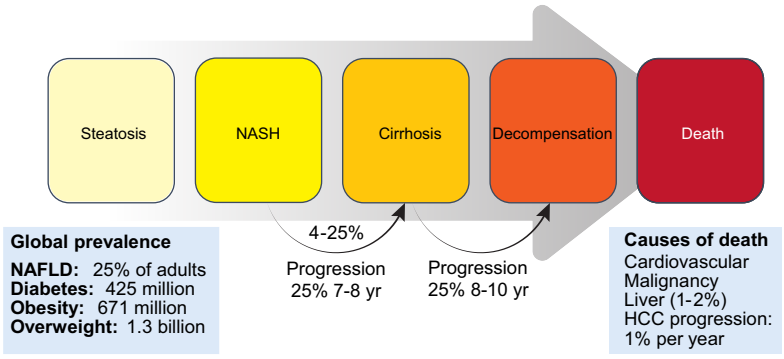

Fig. 2. Global burden and natural history of non-alcoholic fatty liver disease.

Key point

The global prevalence of NAFLD is estimated at 25.2%.

biopsy, the prevalence of NASH was 59%. The prevalence of NAFLD is higher in enriched populations, such as patients with diabetes (59%), those undergoing bariatric surgery,[32] patients with class III obesity and those of Hispanic ethnicity.[29,33] Genetic factors may also affect regional, racial and ethnic distribution of NAFLD.[34] In the US, using NHANES data, the prevalence of NAFLD is between 18 and 24%. The prevalence of NAFLD among lean patients is approximately 7%.[35] However, there may be regional variation, with a prevalence of NAFLD among lean individuals in Asian populations of around 20%.[36] It is estimated that the prevalence of NASH in the US general population is between 1% and 3%.[37] Using NHANES data, the prevalence of NAFLD is calculated to be 30 million.[38] However, in a recent analysis using steady state prevalence models, it was estimated that there are 64 million people in the US and 52 million people in 4 countries (Germany, France, Italy, and United Kingdom) with NAFLD.[39] In the US for example, 500,000 prevalent cases of NASH with cirrhosis are predicted annually. Another study further amplifies current estimates for the US. In multistate modelling, prevalent NAFLD cases are forecast to increase from 83 million (2015) to 101 million (2030), with NASH cases increasing from 1.5 million to 2.7 million.[40]

Fibrosis progression is slow among patients with NAFLD, occurring at a rate of 0.09 stage/year, suggesting that progression from a significant level of fibrosis (*e.g.* stage 2) to cirrhosis still takes 20 years. Fibrosis progression with NAFL is rare for steatosis alone. Fibrosis progression by 1 stage takes 14.3 years for patients with NAFL (95% CI 9.1–50.0 y) and 7.1 years for patients with NASH.[41] Only 5% of patients with NAFLD likely

progress to cirrhosis over 20 years or more. Of that proportion, only half develop complications of decompensated liver disease, with half of those dying from a liver-related cause or requiring a transplant.[26] The vast majority of patients with NAFLD die from non-liver-related causes, particularly cardiovascular events. Liver-related mortality may be higher in the subset of patients with NASH and in certain subsets with enhanced risk factors such as diabetes and chronic kidney disease. However, given the overall higher prevalence of NAFLD, it is anticipated that deaths due to NAFLD will likely supersede deaths related to hepatitis C. NAFLD as a risk factor for progression in other disease states is also understated. As an example, the threshold for qualifying alcohol use is >14 and >21 standard drinks per week for women and men, respectively. However, the impact of NAFLD as a cofactor for alcoholic liver disease or viral hepatitis is poorly understood. Hence the impact of NAFLD is likely higher. For example, there is a synergistic relation between alcohol consumption and obesity. Among alcoholics, the relative rate of liver disease for normal weight men was 3.16, but it was 7.01 and 18.9 for overweight and obese men, respectively.[42]

Viral hepatitis

Although viral hepatitis affects individuals in all geographic regions, those from low and middle-income countries are disproportionately affected.[43] In 2010, deaths from viral hepatitis accounted for 0.3 million deaths per year, an increase of 46% from 1990.[7] During 1990–2013, the absolute number of deaths attributable to viral hepatitis-related deaths (from acute infection, cirrhosis and cancer) increased by 63% and DALY by 34%.[44]

Viral hepatitis increased from the 10th leading cause (1990) to the 7th leading cause of mortality in 2013.[45] In 2015, viral hepatitis-related disease led to 1.34 million deaths,[45] similar to the number caused by tuberculosis (1.37 million) and higher than the number caused by HIV (1.06 million deaths) or malaria (0.44 million deaths).[43] Hepatitis B virus (HBV) (66%) and hepatitis C virus (HCV) (30%) accounted for 96% of mortality and were predominantly a burden in Asia and sub-Saharan Africa,[45] whereas hepatitis A virus (HAV) and hepatitis E virus (HEV) accounted for 0.8% (11,000 deaths) and 3.3% (44,000) deaths, respectively[43] (Fig. 3). Cirrhosis, and viral hepatitis, specifically B and C are independent risk factors for the development of HCC and cholangiocarcinoma (CCA) (discussed below).

Key point

Deaths from viral hepatitis-related disease (1.34 million deaths) are higher than the number caused by HIV (1.06 million deaths) or malaria (0.44 million deaths) and similar to the number caused by tuberculosis (1.37 million).

Hepatitis A

Approximately 1.5 million cases of clinically apparent HAV occur annually worldwide; the actual rate may be higher as the infection may be asymptomatic.[46] HAV Infection is closely linked to socioeconomic indices including poor sanitary conditions, low standards of hygiene and lack of availability of clean drinking water. As a result high income regions have very low endemicity but a higher proportion of susceptible adults.[47] Low income countries such as sub-Saharan Africa and South Asia including parts of India and Pakistan have high endemicity levels (with intra country differences) mostly from childhood infections and few susceptible adults.[47] By contrast middle-income regions in Asia, Middle East, Latin America and Eastern Europe have intermediate or low levels and a population that is susceptible to infection.[47] The clinical outcome of HAV is age-related: infection in young children is often asymptomatic while older age groups are at risk of more severe disease.[48,49] Following a massive

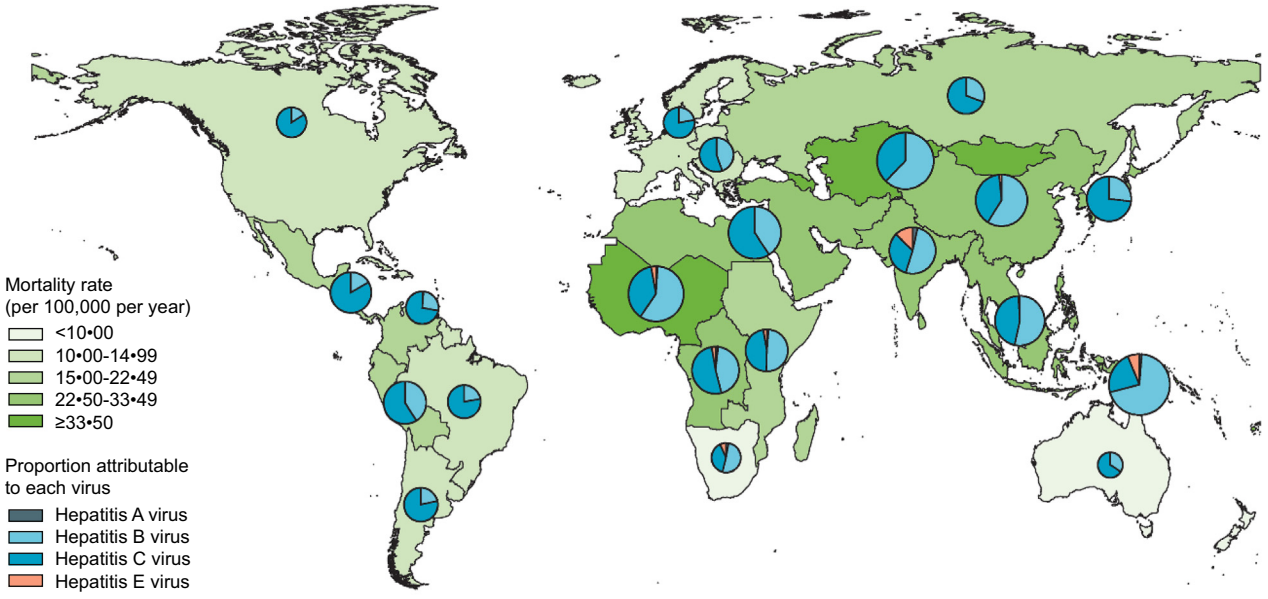

Fig. 3. Global burden of viral hepatitis-related mortality. Reprinted from[45] with permission from Elsevier.

outbreak of HAV in Shanghai, there were 47 deaths among >300,000 infected patients.[50] Outbreaks of hepatitis A have occurred in multiple states in the US among people who are homeless and people who use drugs (https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm). Several high-risk groups, such as men who have sex with men, travellers from non-endemic to HAV endemic countries, family members and close contacts of an individual with acute hepatitis A, patients with chronic liver disease, day care centre staff, users of i.v. drugs and food handlers benefit from testing and receipt of the HAV vaccine.[51]

Immunisation with HAV vaccine together with improvement in socioeconomic indices has reduced the incidence in high- and intermediate-income countries.

Hepatitis B

In 2015, an estimated 257 million people (3.5% of the world's population) were living with chronic HBV infection.[43] The Western Pacific and African regions account for 68% of those infected.[43] The burden of chronic HBV is highest in China (74 million), India (17 million) and Nigeria (15 million).[52] (Fig. 4) In the WHO European Region, approximately 15 million people are chronically infected with HBV. Approximately 56,000 deaths a year are attributed to hepatitis B related cirrhosis and liver cancer. The HEPAHEALTH project recently summarised the current epidemiological burden of liver disease in 35 European countries. The prevalence of chronic hepatitis B infection varies within and in between countries and ranges from less than 0.5% to 8%.[53]

The prevalence of HBV in countries in Western, Northern, Southern and Eastern Europe is less than 1%, 1.5%, 2% and 5% respectively, while Uzbekistan showed a prevalence of less than 8% in 2017. Although overall there was a decreasing trend in prevalence, countries including Russia and Poland showed a recent increase, partially attributed to increased access to injectable drugs.[53] About 2.7 million (interquartile range 1.8–3.9) of the 36.7 million living with HIV are also infected with HBV; 71% of them (1.96 million) live in sub-Saharan Africa.[43] In 2015, an estimated 0.9 million died from HBV: approximately 0.1 million die from acute HBV, 0.45 million from cirrhosis and its complications and 0.35 million from HCC.[43]

Mother to child transmission and person to person transmission are 2 major risk factors in the transmission of HBV worldwide. Other risk factors include needle stick injuries or re-use of needles and syringes, as well as sharing of razors, tooth brushes and chewing gums. Among adolescents and adults, major routes of infection are sexual transmission, particularly in Western countries, or the use of contaminated needles during i.v. drug use.[43]

The risk of developing chronic HBV infection is dependent upon the age of acquisition of infection. It is over 90% when acquired perinatally but decreases progressively with age to less than 5% when acquired in adulthood.[54] Increased coverage with HBV vaccination is expected to reduce the incidence of new infection and its complications. Globally, in 2015, the initial birth dose vaccination was low at 39%, but varied across regions. Birth dose HBV vaccination coverage is 70% in the American and the Western Pacific region but only 10% in the African region.[43] However, the global coverage in 2015 with 3 doses of HBV vaccination in infancy was 84%, which is expected to rise to

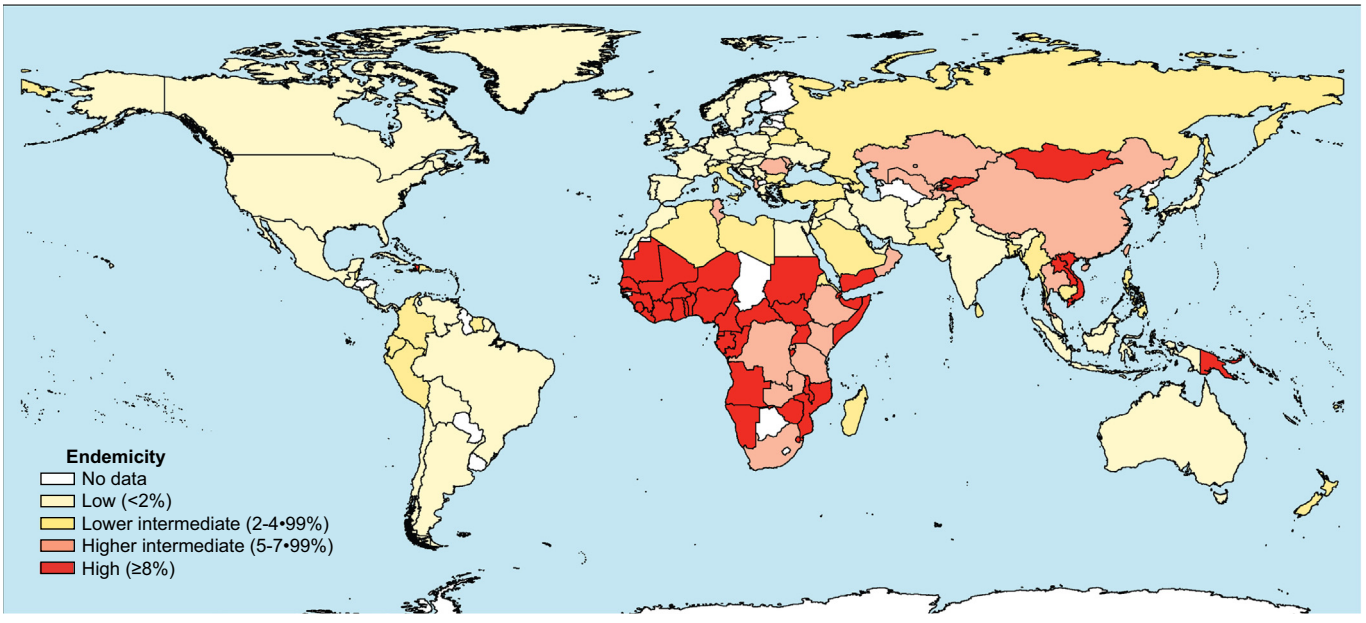

Fig. 4. Global burden of hepatitis B surface antigen endemicity. Reprinted from[52] with permission from Elsevier.

90% by 2030.[43] Increasing vaccination coverage has reduced HBV prevalence in children from 4.7% (pre-vaccination) to 1.3%.[43] In Taiwan, the seroprevalence of HBV declined from 9.8% to 0.6% among children under 15 years of age[55] and was associated with a 4-fold decline in HCC incidence.[55] Amongst adults, 0.5% (1.3 million) of HBV-infected individuals inject drugs.[56] Screening for infection in pregnant mothers, treating with antivirals when required and immunising the child soon after birth all help reduce the burden of HBV in countries where mother to child transmission is the main route of infection. Further, focussed assessment of high-risk population groups such as i.v. drug abusers and migrants from countries with high HBV prevalence, as well as promoting easier and wider access to screening, monitoring, care and treatment, including improved blood donation screening and health worker vaccination, should reduce the burden of liver disease.[54]

Survival rates on antiviral therapy are excellent, with 8-year survival similar to the general population.[57] Long-term treatment with oral antivirals reduces the risk of HCC, particularly in those with cirrhosis.[58] Another prospective recent study showed that discontinuation of effective long-term (>4 years) entecavir/tenofovir therapy in non-cirrhotic chronic hepatitis B e antigen negative patients led to increasing hepatitis B surface antigen loss rates exceeding 20% after the first year of follow-up.[59]

Hepatitis C

In 2015, the global prevalence of HCV infection was 1%, with 71 million people living with chronic HCV infection.[43] Of these, 5.6 million (8%) were injecting drugs and 2.3 million had HIV coinfection.[56] The most common genotype was genotype 1 (44%), followed by genotype 3 (25%), genotype 4 (15%), and others (16%).[60] Estimates of anti-hepatitis C antibody prevalence amongst people who inject drugs is almost 50 times higher than in the general population.[61] Genotype 1 is more common in high income and upper- middle-income countries (60% of all infections) whereas genotype 3 is common in lower middle-income countries (36% of all infections) and genotype 4 is common in lower income countries (45% of all infections).[60]

The highest burden is seen in 6 countries; China (genotype 1 58.2%), Pakistan (genotype 3 79%), India (genotype 3 64.1%), Egypt (genotype 4 90%), Russia (genotype 1 54.9%) and the US (genotype 1 72.5%), which together account for 51% of global HCV infections.[62] Genotype 5 is common in South Africa, accounting for 35.7% of all genotypes. Genotype 6 is common in South-East Asian countries like Laos (95.6%) and Cambodia (56%).[63]

The prevalence of HCV is 1.8% in Europe, accounting for over 13 million estimated cases. There is wide inter country variation, with prevalences ranging from 0.1% in Belgium, Ireland and the Netherlands to 5.9% in Italy.[64] Overall, Northern, Southern, Western and Eastern Europe have prevalences of <2.5%, <2%, <1.5%, and <3.5%, respectively.[53] The most common genotypes were genotype 1 and genotype 3 in i.v. drug users in Europe.[65] An estimated 1.75 million new individuals are infected annually, suggesting that the burden of HCV may continue to rise.[43] The eastern Mediterranean (2.3%) region followed by the European region (1.5%) had the highest rates of infection.[66] Modes of transmission in these regions were from unsafe health care practices and injection drug use, respectively. High rates of unsafe injection practices and re-use (5–14%) in South-East Asia and the eastern Mediterranean region likely contribute to transmission of HCV.[43] Approximately 400,000 people die each year from hepatitis C, mostly from cirrhosis and HCC.[66] Treatment and achievement of sustained virological response is associated with a considerable reduction in the risk of HCC, particularly in those without cirrhosis.[67]

Despite the availability of nucleic acid testing and excellent oral antivirals against hepatitis C, there are several barriers to timely diagnosis and access to treatment. Of the 71 million people living with HCV, only 14 million (20%) are diagnosed with the infection. In 2015 an estimated 950,000 patients were treated for HCV, with two-thirds receiving direct-acting antivirals.[68] An estimated 700,000 achieved sustained virologic response, accounting for only 1% of the total population with HCV being cured of the infection.[60] The eastern Mediterranean region, particularly Egypt, accounted for a large proportion of those started on treatment.[43]

Hepatitis D

Approximately 12.5–15 million people are infected worldwide.[69] Hepatitis delta virus (HDV) occurs in individuals with underlying or concomitant HBV. Two patterns of infection can occur: coinfection with HBV and HDV and superinfection with HDV in an HBV carrier.[70] Though 5% of HBV carriers are affected by HDV, there is wide geographic variation. In Mongolia, up to 60% of HBV-infected persons may also have HDV.[71] Although the prevalence is decreasing in America and Europe as a result of vaccination against HBV, a rise in Western Europe has been ascribed to migration from high HDV endemic countries such as Romania, Turkey, Central Asian Republics and North Africa.[72,73] No effective treatment for chronic HDV is approved.

Hepatitis E

An estimated 20 million infections with HEV occur worldwide; only 3.3 million become symptomatic.[74] In 2015, the WHO estimated that HEV caused approximately 44,000 deaths, accounting for 3.3% of mortality from viral hepatitis.[43]

Key point

HBV (66%) and HCV (30%) account for 96% of viral hepatitis-related mortality mainly from complications of cirrhosis and development of hepatocellular carcinoma predominantly from Asia and sub-Saharan Africa.

There are 8 HEV genotypes. Hepatitis E is endemic in Asia and Africa and is primarily caused by genotype 1 and 2. It is transmitted by faeco-oral contamination. Genotype 3 to 8 are found in animals. There has been increasing recognition of autochthonous HEV infection in Western countries, mainly associated with genotype 3 and 4 from ingestion of contaminated animal products (deer, boar, domestic pigs).[75–77] including a liver transplant recipient with chronic HEV infection.[77] Genotypes 5 & 6 are found exclusively in animals with no reports of human transmission.

Epidemics related to HEV have been described in India and Africa. Hepatitis E causes self-limiting acute hepatitis and only rarely leads to acute liver failure (ALF). Pregnant women in the last trimester are particularly at risk of ALF.[78] HEV may rarely be chronic in patients that are immunosuppressed, such as those following organ transplantation or individuals with HIV infection.[79] Reduction of immunosuppression and or treatment with ribavirin are effective in most cases although treatment failures are reported.[80] In some of these patients the disease can progress to cirrhosis.[79] Acute hepatitis E is a concern in patients with underlying chronic liver disease. It has been reported to precipitate acute-on-chronic liver failure (ACLF) not just in endemic countries but also recently in Europe.[81] A vaccine against HEV has only been licensed in China and is currently not available in other countries.[43]

Primary sclerosing cholangitis

Both primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) are common in industrialised countries; as a result, most epidemiological studies on PSC are from the West.[82,83] PSC with or without ulcerative colitis is less common in the Asia-Pacific and African region, though population-based epidemiological studies are lacking.[82] IBD is the strongest risk factor for PSC.[84] About 65% of all cases of PSC are associated with IBD; ulcerative colitis accounts for nearly 75% of the IBD cases.[83] PSC is often seen in young or middle age men with a history of IBD, though the male gender predominance may be questioned.[85,86] In addition, a significant burden is also seen in the paediatric population.[87] The incidence of PSC ranges from 0 to 1.3 per 100,000 people/year and the prevalence from 0 to 16.2 per 100,000 people.[82] Higher observed rates may be related to increased awareness, identification of subclinical disease, increased use of better cross-sectional imaging modalities such as contrast enhanced computed tomography, magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography. However, rates of asymptomatic disease are high. Forty-four percent of patients with PSC are asymptomatic[62]. In a 2016 Norwegian study of patients with IBD who underwent a MRCP screening test 20 years after their initial diagnosis, regardless of symptoms or laboratory abnormalities, 24 of 322 patients with IBD (7.5%) were found to have PSC-like lesions; only 7 of these (2.2%) were previously diagnosed with PSC. The detection rate with MRCP was 3 times higher than that based on symptoms.[88]

Cholangiocarcinoma

PSC is a risk factor for CCA, gall bladder and colorectal cancer and may contribute to premature mortality. Colorectal cancer risk is increased 10-fold and develops 20 years earlier in patients with PSC compared to controls with ulcerative colitis (median age 39 years *vs.* 59).[83] Patients identified in a population-based cohort had a longer survival time (21.3 years) compared to those identified from tertiary referral cohorts (13.2 years) (p <0.0001).[83] In a cohort of 604 Swedish patients with PSC, the incidence rate of hepatobiliary cancers was 1.5% per year, the prevalence was 13.3%, and 44% of deaths were due to cancer.[89] In a recent Dutch study of 590 patients, 32% and 8% of all deaths could be attributed to CCA and colorectal cancer, respectively.[83] CCA arises from the intra and or extrahepatic bile ducts and is the most common biliary malignancy and the second most common primary hepatobiliary malignancy (approximately 10–15% of all hepatobiliary cancers). It often occurs in later decades and there is a small male predominance. CCA is further classified based on anatomic location: intrahepatic (5–10%) that originates from the biliary tree within the liver, perihilar or Klatskin (60–70%), or distal (20–30%).[90] Whereas many cases of CCA occur *de novo*, there are several established risk factors. Many of these risk factors are pro-inflammatory and besides PSC also include hepatobiliary flukes, hepatolithiasis, congenital malformations of the biliary tree, HBV and HCV.[91] There is regional variation in risk factors; perihilar cancer may be associated with PSC in Western countries and hepatobiliary flukes or hepatolithiasis in Asian countries. Cirrhosis (odds ratio [OR] 22.9), viral infection (OR 5.0), alcohol (OR 2.8), diabetes mellitus (1.9), obesity (1.6), and smoking (1.31) are major risk factors associated with the presence of intrahepatic CCA.[92–95] Amongst Asian countries, liver fluke (both *Opistorchis viverrini* and *Clonorchis sinensis*) appear to portend a similar magnitude of risk as viral hepatitis.[96]

Compared to the general population, patients with PSC have a 4-fold increased risk of mortality, but specifically have a 398-fold increased risk of developing CCA.[83] The rate of CCA development is approximately 0.6% per year.[97]. However, CCA among paediatric patients with PSC is very uncommon.[98] The cumulative risk of developing CCA rises to an estimated 20% after 39 years of disease.[83] Twenty-seven percent of CCAs are diagnosed within the first year of diagnosis of PSC, particularly in younger individuals with nearly half of them at index presentation.[83] South-East

Asia and specifically Thailand have the highest incidence of CCA, which is the most common hepatobiliary malignancy in Thailand, with an incidence of up to 113 per 100,000 person-years among men. This is largely attributed to the endemic liver fluke.[99] In contrast, the age-standardised incidence rates are between 0.5 and 1.5 per 100,000 person-years in Western countries.[91] The incidence of CCA, particularly intrahepatic CCA, appears to be increasing in several countries. This may be reflective of improved detection, diagnostic imaging, migration patterns, increased burden of chronic liver disease and possibly environmental toxins and increased frequency of cholecystectomy procedures.[90,92,100] Alternatively, misclassification by ICD coding may play a role.[101] The second version of the ICD for Oncology may have resulted in classification of perihilar tumours as intrahepatic. Additionally, large databases and registries often combine intrahepatic CCA and HCC. Lastly, CCA is often diagnosed at a late stage, when distinguishing the subtype is challenging and may lead to misclassification.[102–104] Consequently, studies derived from registry data which suggest a global increase in intrahepatic CCA should be interpreted with caution.[105,105,106] However, several recent studies which may not be prone to these limitations suggest that the incidence of intrahepatic CCA is indeed increasing in the US (0.3–2.1 per 100,000 person-years over a 30 year period), France and Italy.[107,108]. In Thailand, France, and Italy, intrahepatic CCA rates have increased while HCC rates have declined.[109–111]

Primary biliary cholangitis

Population-based studies on primary biliary cholangitis (PBC) are scarce and often biased towards studies from Western countries. In a systematic review of 24 studies, PBC incidence rates ranged from 0.33 to 5.8 per 100,000 population/year and prevalence rates from 1.91 to 40.2 per 100,000 population.[84] One of the highest disease burdens is seen in Iceland, with an incidence of 3.4 and prevalence of 38.3 in a population of 317,630.[112] The highest prevalence of 40.2 per 100,000 population was found in Olmsted County, Minnesota, US.[113] The burden of disease is often manifested by poor quality of life, impaired health status and significant symptoms of fatigue, itching and depression.[41,114–116] PBC is a disease of perimenopausal women and one study suggests women in the age group 70–79 have the highest incidence (4.2 per 100,000) and prevalence (42.3 per 100,000).[117] Both incidence and prevalence increases over time.[82,117] Like PSC, PBC appears to be more common in Western populations although reports of PBC in Eastern countries are increasing.[82,117] More than 90% of PBC occurs in women. 78% of asymptomatic anti-mitochondrial antibody (AMA) positive individuals are women.[118] Despite the overwhelming female predominance, reproductive factors such as menarche, age at first pregnancy and number of pregnancies were not associated with PBC in a Dutch population-based study.[117] In a prospective study from France, the prevalence of AMA positive patients (without evidence of PBC) was 16.1 per 100,000 people.[118] Seventy-eight percent were females and 46% had an extrahepatic autoimmune disorder.[118] Only 1 in 6 patients with positive AMAs and normal alkaline phosphatase levels will develop PBC within 5 years.[118] In a meta-analysis consisting of 4,845 patients from North American and European cohorts, 10-year survival in patients with PBC was 77%. Levels of alkaline phosphatase and bilirubin were strongly associated with clinical outcome. Alkaline phosphatase levels (≤2 times upper limit of normal) and bilirubin levels ≤1.0 times the upper limit of normal were associated with 10-year survival of greater than 85%.[119] Male sex and age less than 50 years were predictors of poor response to ursodeoxycholic acid treatment.[120]

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a rare disease occurring in all races, ethnic groups and ages. Females are affected more commonly than males by a ratio of 4:1. Incidence studies are few and are mainly reported from Europe where the disease is more common and increasing. Recent estimates show a higher figure than those reported 1–2 decades ago and vary from 1.5 to 3 per 100,000 inhabitants.[121] The point prevalence of AIH was 17.3 cases per 100,000 population in a large Swedish cohort[122] and 18.3 cases per 100,000 in the Netherlands, with the peak incidence among women aged 40–60 years.[123] An increasing incidence was reported in Denmark where it rose from 1.37 in 1994 to 2.33 in 2012 per 100,000 population. The overall prevalence was estimated to be 23.9 per 100,000 population; 34.6 for women and 13.0 for men.[124] AIH is rare in Asia where the disease is detected at an advanced stage with higher mortality.[125]

Two subtypes (AIH-1 and AIH-2) are recognised with characteristic serologic and phenotypic characteristics.[121] AIH type 1 (AIH-1) is defined by the presence of antinuclear antibody and/or anti-smooth muscle antibody, whereas AIH type 2 (AIH-2) is characterised by the presence of anti-liver kidney microsomal type 1 antibody or anti-liver cytosol type 1 antibody. Further, AIH-1 commonly affects adolescents and young adults whereas AIH-2 affects children and adolescents. At presentation the disease is mild to moderate in AIH-1 and moderate to severe in AIH-2.[126]

AIH-1 is strongly associated with susceptibility genotypes HLA-DRB1*0301 and HLA-DRB1*0401 as confirmed by a recent AIH genome-wide association study on a Dutch and German population.[127] Cirrhosis is present in 28.3% of patients who underwent biopsy, while male gender and the presence of cirrhosis were risk factors for the

Key point

The increasing incidence of primary biliary cholangitis, primary sclerosing cholangitis and autoimmune hepatitis may be related to increased awareness and early detection.

development of HCC, which is otherwise rare in AIH.[124]

Wilson's disease

Wilson's disease is a rare autosomal recessive genetic disorder characterised by excess accumulation of copper in various body tissues, such as the liver, brain, and eyes. Wilson's disease is caused by mutations of the *ATP7B* gene, which plays an important role in the movement of copper from the hepatocytes to biliary canaliculi for eventual excretion. More than 600 different mutations of the *ATP7B* gene have been identified without clear genotype-phenotype correlates, although the disease appears at a younger age with increased severity in Egyptians[128] and Indians.[128] Wilson's disease is estimated to occur in approximately one in 30,000–40,000 people worldwide, with approximately 1 in 90 people carrying the disease mutation gene.[129] However, the burden may be higher based on recent data. In the UK, Coffey *et al.* estimated the frequency of individuals predicted to carry 2 mutant pathogenic *ATP7B* alleles to be 1:7,026. A discrepancy between the genetic prevalence and the number of clinically diagnosed cases of Wilson's disease may be related to reduced penetrance of *ATP7B* mutations and failure to diagnose patients with this treatable disorder.[130] Early diagnosis is the key to limit liver dysfunction and neurological damage.

Drug-induced liver injury

Liver injury is a common reason to withdraw drugs during development, preclinical studies and following marketing. From 1953 to 2013, drug-induced liver injury (DILI) was a leading cause of withdrawal (18%) followed by immune reactions (17%) and cardiotoxicity (14%).[131] The estimated incidence of DILI varies between 1 in 10,000 and 1 in 1,000,000 patients. Incidence is dependent on the definition used, frequency of testing, population characteristics, diseases prevalence, type of drugs ingested, sociocultural factors and reporting mechanisms. The reported incidence of DILI in 2 prospective population studies varied between 13.9 per 100,000 and 19 cases per 100,000 individuals.[132,133] These rates were 6 to 8 times higher than previous estimates; yet the real magnitude may be even higher as adverse drug reaction reporting is heavily dependent on spontaneous reporting. Population studies from France and Iceland demonstrated that the presence of drug-related jaundice leads to hospitalisation in a quarter of patients, with high risk of fatality (Table 5). In 2 population-based studies from the UK, DILI incidence ranged from 1.27 per 100,000 people to 2.4 per 100,000, mainly in the elderly and predominantly related to antibiotics.[134,135] The reported incidence in outpatient settings where liver injury is generally milder ranges from 1.4% in Switzerland to 6.6% in Sweden.[136,137] DILI constitutes 1.4% and 2.5% of gastrointestinal and hepatobiliary admissions respectively in India, predominantly from anti-tuberculosis and anti-epileptic drugs.[138]

Table 5. Characteristics of drug-induced liver injury from two population-based prospective studies from Europe.

Characteristics	France[132]	Iceland[133]
Year	1997–2000	2010–2011
Population	81,301	251,000
Mean age	55 yr	55 yr
Total cases	34	96
Out patients	82%	30%
Crude incidence	13.9/100,000	19.1/100,000
Urban/rural	79%/21%	–
Female:male ratio	–	54:40
Recovery	32/34	95/96
Death	2 (both from ALF)	1
Hospitalisation	17.6%	23%
Jaundice	10/34	27%
Implicated drugs	Antimicrobials (25%)	Antibiotics (22%)
	Psychotropics (22.55)	HDS (16%)
	Antilipidemic (12.5%)	Diclofenac (6%)
	NSAID (10%)	Azathioprine (4%)
		Infliximab (4%)
		Nirtrofurantoin (4%)

Permission Therapy in Liver diseases. HDS, herbal and dietary supplements; NSAID, non-steroidal anti-inflammatory drugs.

Although over a thousand drugs are speculated to cause liver injury, only 353 drugs have convincingly been linked to liver injury.[139] Many of these drugs were approved before 1999. Antimicrobials (27%) were the leading cause followed by central nervous system agents including anti-epileptic drugs (17%), cardiovascular drugs (15%) and anti-neoplastic agents (14%).[139] The advent of drugs that undergo minimal or no liver metabolism will likely result in a decreased incidence of DILI.[140] The type of drugs producing liver injury has varied over time. Epidemiologic studies before the turn of the century found chlorpromazine, isoniazid, amoxicillin and cimetidine as the top 4 drugs that cause DILI.[141] Presently, antimicrobial agents continue to be the leading cause of idiosyncratic DILI worldwide, with amoxicillin/clavulanic acid-induced DILI in the West[142] and combination anti-tuberculosis DILI in the East.[138] In the UK and the US, acetaminophen (paracetamol) is a top cause of intrinsic DILI. The "era effect" is highlighted by newer drugs causing DILI such as, infliximab, immune check point inhibitors and herbal and dietary supplements.[133] Herbals and complementary medicines are leading causes in the Far East with an estimated incidence of 12 per 100,000 in a recent study from South Korea.[143]

DILI due to amoxicillin/clavulanate occurs in 1 in 2,350 individuals.[133] It is unsurprising that DILI related to anti-tuberculosis treatments occurs in Eastern countries, considering that India and Nigeria have the highest burden of tuberculosis in the

world.[144] Herbal and alternative medicines are the most common cause of DILI in China and South Korea, where a large proportion of the population are exposed to these agents for various diseases.[143,145] Herbal and dietary supplements are an increasingly frequent cause of DILI globally, ranked second behind antimicrobials in the US drug-induced liver injury network (DILIN).[146] The herbal and dietary supplements that contribute to DILI in the US are mainly those used for body building (in men) and weight loss (in women), whereas in Asia it is from drugs used for a variety of diseases. Weight loss agents produce hepatocellular injury that can progress to liver failure, requiring liver transplantation, while body building agents produce mixed or cholestatic injury.[146,147] ALF related to DILI will be discussed in the section on ALF.DILI occurs across all age groups, but is distinctly uncommon in children. Despite receiving a higher dose of drugs based on body weight, children are less prone to develop DILI and constitute less than 10% of all cases in most registries. Older age is a risk factor for DILI for unclear reasons; polypharmacy leading to drug-drug interactions, together with multisystem involvement may be contributing factors. Women are disproportionately more at risk of DILI than men. Severe DILI requiring hospitalisation and leading to liver failure and death is more common in women across all populations.

Consequences of liver disease

Acute liver failure

The estimated incidence of ALF varies between 1.4 per million population in Spain[148] to 5.5 per million population in the US.[149] The causes vary geographically. Drugs are the most common cause in the West, while in large parts of the East viruses continue to remain the most important cause of ALF, followed by drugs.[150] While hepatitis E is the most common cause of ALF in India and Africa, hepatitis B remains the most common cause in China and Korea.[150] The type of drugs causing ALF vary between and within continents.[150] For example, acetaminophen induced ALF is still the most common cause in the US,[151] while its incidence is decreasing in the UK.[152] Paradoxically, acetaminophen is rarely a cause of ALF in Spain.[148] Although legislation on the quantities of acetaminophen sold may have played a role in the UK, widespread availability of the drug may not always be related to prevalence of ALF. Acetaminophen is easily available elsewhere in the world but is very rarely a cause of ALF in India.[153] Globally, antimicrobials are the most common cause of idiosyncratic DILI.[154,155] Anti-tuberculosis drugs are the prime cause in most parts of the world, including India and China. While combination anti-tuberculosis drugs cause ALF in the East, isoniazid used as monotherapy for primary prophylaxis is the second most common cause of idiosyncratic drug-induced ALF in the US, the most common being non-tuberculosis antimicrobials such as amoxicillin/clavulanic acid.[155] In China and Korea, ALF is more commonly caused by traditional medicines than antimicrobials or viruses and is associated with significant mortality.[143,156] Identifying the cause is important because outcome is cause dependent. Acetaminophen induced ALF has a good prognosis with transplant-free survival over 50% in adults,[151] and over 90% in children[157] while anti-tuberculosis drug-induced ALF has a mortality of 70%.[153] ALF from hepatitis A and E virus has a better prognosis[158] compared to those caused by hepatitis B virus or herpes simplex virus.[150] Liver transplantation has revolutionised the care of patients with ALF and survival after transplant is only slightly less than when carried out for end-stage liver disease.[150]

Compensated and decompensated cirrhosis

It is difficult to assess the global burden of compensated cirrhosis *vs.* decompensated cirrhosis. Compared to the general population, patients with compensated cirrhosis and decompensated cirrhosis have a 5-fold and 10-fold increased risk of mortality, respectively.[159] In a large systematic review, the median survival was 12 years for patients with compensated cirrhosis and 2 years for decompensated cirrhosis.[160] In an analysis of the UK General Practice Research Database, the overall survival for patients with compensated and decompensated cirrhosis was 87% *vs.* 75% (1 year) and 67% *vs.* 45% (5 years), respectively.[159]

Transition to decompensated cirrhosis

Most deaths among patients with cirrhosis occur due to the complications of cirrhosis, rather than the presence of comorbidities. Among patients with compensated cirrhosis, morbidity and mortality result from a transition to a decompensated state. Decompensation, defined by the development of at least one of variceal bleeding, ascites, jaundice or encephalopathy, occurs in 4–12% of patients per year.[161–164] Once again, the rate likely varies based on the study population and setting (inpatient *vs.* community). Annual rates of progression to a decompensated state range from 4% for viral hepatitis C, to 6–10% for alcoholic cirrhosis and 10% for viral hepatitis B.[165] In competing risks analyses, the most common decompensating event is ascites followed by bleeding and encephalopathy, with many patients presenting with more than one complication.[161,163]

Varices and ascites

In patients without varices, the rate of development is approximately 7–8% per year.[166,167]. In patients with evidence of varices, progression from small varices to medium or large varices occurs at a rate of 7–10% per year (5–12% at 1 year and 31% at 3 years). The annual risk of variceal bleeding is 5–15%.[166,167] In patients with

ascites, the 5-year probability of dilutional hyponatremia, refractory ascites and development of hepatorenal syndrome is 37.1%, 11.4%, and 11.4%, respectively.[168]

Hepatic encephalopathy

In a recent population-based study of Danish patients with alcoholic cirrhosis, 1-year survival was worst among patients with hepatic encephalopathy (36%), followed by those with ascites and variceal bleeding (51%), but was relatively better among patients with variceal bleeding regardless of their ascites status (80%).[169]

Infection and renal failure

Recently, the important role of infection and renal failure (regardless of aetiology) has been highlighted. The presence of any infection in patients with cirrhosis, compared with uninfected patients, leads to a 4-fold increase in mortality (OR 3.8). There is a high risk of early mortality (30% at 1 month), with poor survival among patients with spontaneous bacterial peritonitis (median mortality 44%).[170] Compared with patients without renal failure, renal dysfunction among those with cirrhosis is associated with an almost 8-fold increase in the risk of death (OR 7.6)[171]. The presence of either infection or renal failure is associated with a median 1-year survival of 37%[171]. This has led to the proposal of further stages in the natural history of cirrhosis, which is characterised by either the presence of refractory symptoms (namely, ascites), jaundice, encephalopathy or the presence of infection or renal failure in patients with cirrhosis.[161] A significant proportion of global liver-related morbidity and mortality is reflected in inpatient hospitalisations. However, there is global variation in inpatient utilisation and stage of disease at presentation. In a large national study from India, 99% of patients with cirrhosis presented with decompensation.[172] Data from the Nationwide Inpatient Sample in the US, years 2003–2011, show that overall mortality was 7% with two-thirds (66%) of deaths occurring in patients with a decompensating event, defined as variceal haemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and/or hepatorenal syndrome.[173] Mortality was higher in patients with variceal haemorrhage (OR 1.6), hepatic encephalopathy (OR 1.8), spontaneous bacterial peritonitis (OR 2.6) and hepatorenal syndrome (OR 9.1) compared with patients with no complications. Recent data suggests that though traditional complications of portal hypertension have remained stable, there has been a marked increase in renal failure and infection, which may signify presentation at a later stage of liver disease, at least in the US.[174]

Acute-on-chronic liver failure

Although a universally accepted clinical and epidemiologic definition for ACLF is lacking, ACLF is increasingly recognised as an important source of liver-related disease burden worldwide.[175] Alcohol abuse tends to be the most common cause worldwide, while chronic hepatitis B infection is a leading cause in China, with reactivation as a precipitating factor for ACLF.[176] Widespread immunisation with HBV vaccine has reduced the incidence of ACLF in China from 3.4 (2005) to 2.06 per 100,000 population (2014).[176] ACLF prevalence varies from 9.5% to 34% according to definitions, population under consideration and aetiology (Table 6).[177,178–182] There is greater awareness of the increasing burden, cost and high fatality associated with ACLF. In the US, hospitalisations for ACLF have increased several-fold in the last decade and are associated with a high mortality rate.[175] Results from the national inpatient sample database showed a doubling in the number of hospitalisations from cirrhosis from 371,000 in 2001 to 659,000 in 2011.[185] The prevalence of ACLF among hospitalisations increased from 1.5% (n = 5,400) to 5% (n = 32,300), with two-thirds developing sepsis. Further, while the costs for cirrhosis increased 2-fold, they increased 5-fold for ACLF.[185] The cost per hospitalisation for ACLF was 3.5-fold higher than that for cirrhosis ($53,570 *vs.* $15,193). Although the in-hospital fatality rates in ACLF have decreased from 65% to

Table 6. Comparison of acute-on-chronic liver failure characteristics across regions.

Country/ region	Author	Year	ACLF criteria	Prevalence	Population characteristics	28-day mortality from ACLF	Top 2 causes of liver disease	Top 2 precipitants
Europe	Moreau R *et al.*[183]	2013	EASL-CLIF	30.9%	1,343 patients	32.8%	Alcohol, HCV	No precipitant detected, bacterial infection, GI bleed
North America	Bajaj JS *et al.*[179]	2014	NACSELD	24%	507	23%	HCV, alcohol	Bacterial infection, UTI, SBP
Sweden	Sargenti K *et al.*[180]	2015	EASL-CLIF	24%	398	49%	Alcohol, viral	Bacterial infection, active alcoholism
China	Shi Y *et al.*[181]	2015	EASL-CLIF	40%	1,365	49.4% 28 day	HBV, alcohol	HBV, bacterial infections
China	Li H *et al.*[182]	2016	EASL-CLIF	33.7%	890	44%	HBV only	GI bleed, PVT
Korea	Kim T *et al.*[184]	2016	EASL-CLIF	18.6%	1,470	32%	Alcohol, HBV	Active alcoholism, GI Bleed
Korea	Kim T *et al.*[184]	2016	APASL-AARC	9.5%	1,470	6.1%	Alcohol, HBV	Active alcoholism, GI Bleed

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; APASL, Asia Pacific Association for the Study of Liver; CLIF, chronic liver failure; EASL, European Association for the Study of the Liver; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

50%, the economic burden continues to be high given the measures needed to support failing organs, together with expenses incurred following discharge to nursing facilities or hospice care.[185]

The number and type of organ failures contribute to mortality, particularly from respiratory and renal dysfunction.[185] In the NACSELD study, mortality increased proportionately from 27% with 1 organ failure to 77% in patients with 4 organ failures.[179] Two Chinese studies estimated mortality from 24% to 40% in ACLF grade I, 41% to 54% in ACLF grade 2 and 63% to 85%in ACLF grade 3.[182,186] Bacterial infection leading to sepsis is a leading cause of hospitalisation, decompensation and death in cirrhosis and ACLF.[179] The global presence of multidrug resistant organisms (34%) is concerning. The prevalence of multidrug resistant organisms in patient samples varies from 73% in some parts of Asia to 18% in Europe and America.[187]

Hepatocellular carcinoma

In 2015 there were 854,000 incident cases of liver cancer (primarily HCC) making it the 6th leading cause of cancer worldwide. It is more common in men (5th leading cancer among men compared to 8th among women) with 1 in 45 men (*vs.* 1 in 113 in women) developing it before age 79. Globally, 810,000 deaths due to liver cancer occurred worldwide making it the 4th most common cause of cancer deaths and 2nd leading malignant cause of absolute years of life lost in 2015. Among men it is the 2nd leading cause of cancer deaths worldwide and among women the 6th.[188] About 40% of HCC is due to hepatitis B, 40% due to hepatitis C, 11% due to alcohol and about 10% due to other causes; however the underlying aetiology is expected to change with an increasing prevalence of NASH cirrhosis. [189] According to data from The Surveillance, Epidemiology, and End Results (SEER) Program, 5 year survival for cancer from liver and intrahepatic ducts was only 18% (if localised 31%, with regional spread 11% and with distant metastasis 3%).[190] (accessed April 2018) Hepatobiliary cancer has the second worst survival rate among cancers, second only to pancreatic cancer (5-year survival 8%) and 5 times worse than colorectal cancer (5-year survival 65%). This is likely due to pancreatic and hepatobiliary malignancies being diagnosed at a late stage.Incidence and risk factors for HCC vary regionally (Table 7).[191] Sub-Saharan Africa and East Asia have the highest incidence rates (more than 20 per 100,000 individuals). Resource-poor countries carry the largest burden. Among countries with the lowest socioeconomic index, liver cancer was the 4th leading cause of cancer and the 1st in cancer mortality in 2015.[188] Among men, liver cancer was the most commonly diagnosed malignancy in 2015 in 11 countries (majority located in sub-Saharan Africa) and the most common cause of cancer deaths in 40 countries (most located in Africa, South-East Asia). Among women, liver cancer was the most common cancer diagnosed in Mongolia and the leading cause of cancer deaths in 5 countries in 2015.[188] Overall, 75% of all liver cancers occur in Asia, with Mongolia being the country with the highest incidence (78 cases per 100,000 persons).[192] Generally, Southern Europe has mid-incidence rates (10–20 per 100,000 individuals) while North America, South America and Northern Europe have lower

Table 7. Actual and predicted incidence of mortality attributed to hepatocellular carcinoma in 2012, 2025 and 2035 by WHO Region.

	Incidence				Mortality			
	Year	Male	Female	Both sexes	Year	Male	Female	Both sexes
Global	2012	554,369	228,082	782,451	2012	521,041	224,492	745,533
	2025	761,985	313,865	1,075,850	2025	720,308	310,128	1,030,436
	2035	944,112	397,232	1,341,344	2035	901,920	397,021	1,298,941
WHO Africa region	2012	24,791	14,032	38,823	2012	23,758	13,403	37,161
	2025	36,770	20,537	57,307	2025	35,193	19,617	54,810
	2035	50,684	28,186	78,870	2035	48,419	26,903	75,322
WHO Americas region	2012	40,288	22,872	63,160	2012	34,704	23,180	57,884
	2025	55,971	32,270	88,241	2025	49,671	33,271	82,942
	2035	68,576	40,408	108,984	2035	62,443	42,696	105,139
WHO East Mediterranean region	2012	19,844	9,523	29,367	2012	18,893	9,056	27,949
	2025	30,492	14,815	45,307	2025	29,025	14,173	43,198
	2035	43,696	20,956	64,652	2035	41,893	20,280	62,173
WHO Europe region	2012	47,155	23,421	70,576	2012	44,087	24,959	69,046
	2025	57,412	27,678	85,090	2025	54,003	29,543	83,546
	2035	65,052	31,588	96,640	2035	61,945	34,215	96,160
WHO South-East Asia region	2012	54,678	25,284	79,962	2012	52,351	24,395	76,746
	2025	79,293	36,646	115,939	2025	75,816	35,251	111,067
	2035	102,206	48,102	150,308	2035	98,203	46,100	144,303
WHO Western Pacific region	2012	367,572	132,934	500,506	2012	347,208	129,484	476,692
	2025	509,041	190,588	699,629	2025	486,225	187,170	673,395
	2035	614,204	241,766	855,970	2035	594,905	241,303	836,208

(source: Globocan 2012: Estimated Cancer Incidence, mortality and prevalence worldwide, 2012 http://globocan.iarc.fr/Default.aspx accessed April 2018). WHO, World Health Organization.

incidence levels (typically less than 5 per 100,000 individuals).[193] HCC can also differ between racial groups within a given country. For example, in the US the incidence of HCC among Asians was nearly twice the incidence found in Hispanics (11 *vs.* 6.8 per 100,000 person-years) and 4-fold higher than in Caucasians (11 *vs.* 2.6 per 100,000 person-years).[194] However, these observations can largely be explained by the prevalence of viral hepatitis in the populations. However, the increasing prevalence of NAFLD may alter these dynamics.[195] HBV and HCV are responsible for 60–85% of cases of HCC.[193,196] HBV may increase the risk of HCC by 5–100-fold. Similarly, HCV can increase the risk by 15–20-fold. Both of these chronic infections can lead to the development of cirrhosis, which is found in 80–90% of individuals with HCC and is an important risk factor for HCC regardless of the aetiology.[193] HBV is the driving factor for HCC in most Asian countries and Africa. Japan, Pakistan and Egypt are notable exceptions as HCV infections are more likely to be associated with HCC. HCV is a predominant aetiology in most European and American countries (with the exceptions of Peru, Greece and Russia where hepatitis B may be more commonly associated with HCC).[196] The country of birth also impacts on the age of HCC detection when immigrants move to lower incidence areas. For example, in the US, birth in Africa (except North Africa) and Oceania were the strongest predictors of very early onset HCC (age less than 40).[197] This may be related to movement from regions with a high prevalence of HBV. Virus-specific factors that can vary across the globe such as HBV genotype, mutations in precore, DNA levels and coinfection with HCV may also play a role.[196,198–202] Exposure to region-specific hepatotoxins also influences the global distribution of HCC. For example, Aflatoxin B_1 is endemic in many warm climates located between 40°N and 40°S of the equator.[203,204] Alone, aflatoxin may increase the risk of HCC, but when another factor such as HBV is present it exponentially increases the likelihood of malignancy.[205] Chronic aflatoxin exposure has been linked to up to one-quarter of all HCC cases worldwide.[206] Aristocholic acid, found in herbal remedies predominately in China and betel nut chewing, a practice employed in many parts of Asia, may play a role in the carcinogenesis of some cases of liver cancer.[207–209]

Key point

Cirrhosis and hepatocellular carcinoma cause 3.5% of all deaths worldwide.

Alcohol is an important hepatoxin found throughout the world. Per capita alcohol consumption mirrors the prevalence of alcohol-related cancers.[63] Consuming more than 80 grams of alcohol/day for 10 years increases the risk of HCC 5-fold.[210] Furthermore, heavy ingestion of alcohol can have a synergistic effect on the risk of HCC when other risk factors are present.[211,212] For example, the 10-year cumulative incidence of HCC among patients with HBV who consumed large quantities of alcohol was 53%, in contrast to the 10-year cumulative incidence of HCC among those who either consumed large amounts of alcohol (25%) or had HBV alone (40%).[213]

Among areas considered to have a low incidence of viral hepatitis, non-viral factors contribute to a larger pool of liver cancers, which in turn vary across populations. For example, in the US, one-quarter of individuals with HCC have alcoholic liver disease and 20–30% may have some features of metabolic syndrome or NAFLD.[214,215] However, in Europe where the prevalence of obesity is lower, only 16% of HCC cases were attributed to underlying obesity.[216] In stark contrast, viral hepatitis contributes to approximately 90% of cases of HCC in high incidence areas such as Vietnam or Egypt.[196] The evolving obesity and NAFLD epidemic will alter the epidemiologic landscape for HCC in the Western world. In the United Kingdom, there was a 10-fold increase in HCC cases associated with NAFLD between 2000 and 2010, accounting for more than one-third of all cases of liver cancer.[217] Over the past decade in the US, the number of patients with NAFLD-associated HCC who underwent a transplant increased by 4-fold while those with HCV increased by 2-fold, making NAFLD the most rapidly growing indication for transplant in patients with HCC in the US.[195]

In 2012, 5.6% of all incident cancers were attributable to the combined effect of diabetes mellitus and high BMI. About 25% of cases of liver cancer were attributable to these risk factors. Compared to a more common cancer, such as colorectal cancer, the combined impact of diabetes mellitus and high BMI on liver cancer incidence was 3-fold higher for men (23.3% *vs.* 8.6%) and women (27.3% *vs.* 9.7%).[218] The global epidemiology of HCC is evolving and future forecasts regarding the burden of liver cancer vary across regions. Largely due to aging and population growth, the absolute number of HCC cases increased from 709,000 in 2005 to 854,000 in 2015. Moreover, while the global incidence has remained stable or slightly decreased, the age adjusted incidence of HCC has increased over the 25 years in countries with both a high and a low socioeconomic index.[188] Indeed, between 1983–1987 and 2003–2007, the incidence has increased in India, Oceania, the Americas and most European countries.[192] Despite an overall decrease in cancer incidence, the incidence of liver cancer has increased sharply (2nd only to thyroid cancer) in men in the US in 2012. Moreover, mortality from liver cancer increased at the highest rate, compared to all other cancer sites, for both men and women.[219] This increase is largely due to prevalent cases of HCV, with a rising incidence of HCV cirrhosis and related HCC among the baby-boomer generation in the US.[67] In contrast, the incidence may be decreasing in parts of Asia, namely China (likely due to public health programmes aimed at reducing HBV transmission and aflatoxin exposure) and Japan (largely due to the diminishing rates of HCV

infection in the population).[192,220] HBV immunisation, treatment of chronic HBV and HCV and public health measures aimed at reducing aflatoxin exposure are poised to have a favourable impact on the burden of HCC.[221–226] However, access to these interventions and identification of individuals who would benefit from antiviral therapy remain key challenges.

Liver transplantation

Liver transplantation is the second most common solid organ transplantation after kidney transplantation worldwide.[227] However, less than 10% of global organ transplantation needs are met at current rates of transplantation.[227] In 2015, 126,670 solid organs were transplanted worldwide: 66.5% were kidney transplants and 22% were liver transplants.[227] Living donor transplantation constituted 42% of kidney transplants and 21% of liver transplants.[227] Although a steady increase in transplants was observed from 2011 to 2014, a sharp increase of 5.8% for all transplants and 6.1% for liver transplants was seen between 2014 and 2015.[227,228] There was a 28% increase in living donor liver transplantation in the US and a 5% increase in deceased donor liver transplantation (DDLT) in 2015 compared with 2014.[229] In 2015, the highest number of transplants were in the American region, particularly the US (n = 10,426), followed by the European region (n = 9,582).[228] In 2015, 7,694 liver transplants (3% living donor) were performed in the European Union, compared to 20,102 kidney transplants (21% living donor).[230] Deceased organ donation is common in Western countries, whereas living organ donation is common in Asian countries, with the exception of China.[231] Less than 6.5% of liver transplantations from the American region were from live donors;[227] by contrast more than 96% of liver transplantations in Japan were from living donors.[227,232]

There is tremendous heterogeneity in the practice of liver transplantation worldwide (Table 8). Organ donation is often reflective of socioeconomic, religious and cultural factors in performing countries.[231,240] Adoption of brain death law has increased the proportion of DDLT in several Asian countries, such as South Korea and India, where DDLT constitutes only 23.5%[241] and approximately 20%[235] of liver transplants, respectively. China has no brain death law and hence >95% of transplants are from donation after cardiac death, which in China is often equated with physical death.[240]

The overall global liver transplantation rate is 3.7 per million population (PMP).[227] Many countries in Asia have organ donation rates less than 1 PMP. Means to increase the deceased donor pool include donation after circulatory death, inclusion of expanded criteria for organ suitability, domino transplantation and changing the consent process from "opt-in" (*e.g.* UK and US) to "opt-out" (*e.g.* Spain and France).[242] Split liver grafts and donor exchange pairing also marginally increase the donor pool.[240] Paradoxically opt-out countries have lower rates of living donation.[242] Spain holds a privileged position worldwide, with 40 donors PMP (43.4 in 2016) and more than 100 transplant procedures PMP in 2015.[243] In addition to opt-out policy, factors that appear to have optimised organ donation include:[243] (i) measures for early identification and referral of potential organ donors, encouraging patients to consider organ donation as part of end-of-life care; (ii) fostering the use of expanded (older age donors) and non-standard risk donors (donors with localised malignancy); and (iii) developing the framework for the practice of donation after cardiac death. Investment in education, training and infrastructure have also contributed to Spain's success as a leader in organ donation.[243]

Despite measures taken to improve the donor pool, the number of transplants in Western countries has either plateaued or is increasing only gradually, compared to a sharp rise seen in middle-income countries such as Brazil and India.[235,238] Brazil performs the second highest number of transplants after the US, driven partly by a 6-fold increase in split liver transplantation.[238]

Indications also vary according to geography. In the West, HCV has been the leading indication for liver transplantation, although it is increasingly being replaced by alcoholic liver disease, NAFLD and HCC.[231] In Asia, hepatitis B and HCC remain a common indication for liver transplantation.[240] While Milan and UCSF criteria continue to guide transplantations for HCC, some countries such as India and China tend to go beyond these criteria.[235] Most countries use either model for end-stage liver disease (MELD) score or a variant, both for listing and recipient selection; the minimal listing criteria is usually an MELD score between 11 and 14. The median MELD score at which patients receive a transplant is 18–20 in most countries, but is much higher in the US and Germany.[229,231]

Outlook and projections

Liver disease accounts for a significant burden of disease and costs worldwide. Currently the major cause of acute liver disease is viral hepatitis, while alcohol and viral hepatitis are the main causes of chronic liver disease. These trends are changing and in the future DILI will be increasingly recognised as a cause of acute hepatitis. Vaccination and newer drugs will reduce the burden of viral related liver disease in developed countries; where access to health-related resources is limited, viral hepatitis will still be a burden. NAFLD and AALD will increasingly become the leading causes of chronic liver disease in the Western world.

Table 8. Worldwide comparison of liver transplantation practices.

	Germany[233]	UK[234]	India[235]	Ireland[236]	Australia and New Zealand[237]	Brazil[238]	Spain[239]	Japan[232]	USA[229]
Population	82 million	64 million	1.19 billion	4.59 million	27.7 million	202 million	47.8 million	127 million	318.9 million
Allocation/ prioritisation Committee	DSOT	NHSBT	Zonal Coordinating Committee State	ODTI	Transplant Society of Aus & NZ	National Transplantation System	Spanish National Transplant Organization	Japan Organ Transplant Network	UNOS
Funding/ insurance	Health insurance	NHS	Private >government	Health Service executive (funded by govt). No private provision	Federal and State funding	Brazilian Public Unified Health System	Public universal health care system	State National health insurance	Private insurance (53.9)/Medicare (27.7) Medicaid (13.3)
No of LT annually (2015)	846	882	~1,000	50–60	270	1,700	>1,000	450–500	7,127 (total) (6,768 DDLT)
LT centres	23	7	30 (most private funded hospitals)	1 (public funded hospital)	5 Australia 1 NZ	56	24	67	136 (27 paediatric only, 84 adult only, 25 both adult and children)
Allocation system	MELD	UKELD	–	MELD	MELD	MELD	MELD	Medical points system MELD	MELD
Approximate MELD listing score	>15–20	>49	No nationally agreed minimal listing criteria	No minimal MELD criteria	MELD >15	MELD >11	MELD 12		>14
Age limit	<70 yr	No limit	–	–	Mostly <65 yr	–	>65 yr additional compressive tests required	60 yr (no strict cut-off)	No cut-off
Living donation	<10%	–	80% LDLT, 20% DBD	DBD	DBD	<12%	<2%	>96%	5% (359)
Deceased donor PMP 2014	10.8	20.8	0.5	13.4	17 (Aus) 11 (NZ)	14.4	39.7	<1	26.6
1-year survival rate	75–80%	92% (5-yr 80%)	–	93% (5-yr 79%)	94%	>90%	>90%	>91%	>90% (5 yr 73.6%)
Common indications LT recipient characteristics	NAFLD, ALD	HCC (25%), ALD (23%), Viral hepatitis - HBV/HCV (12%)	ALD, Viral hepatitis, NAFLD, HCC	ALD 32%, HCC 27%, HCV 21%, NAFLD 15%, Autoimmune disease 17%	HCV (28%), Others (34%), HCC 14%, ALD 13%, NAFLD 6%, HBV 6%	Viral hepatitis 35%, AD 11%, NAFLD 10%, HCC 10%	ALD and HCV (60%), HCC 19%	Cholestatic liver disease, HCV/HBV, ALD	HCV (22.7%), ALD (21.0), Unknown (25.5), Cholestatic (8.8), Malignancy 18.7, ALF 3.3
Criteria for transplanting ALD	6-month abstinence	No minimum period of abstinence	No minimum	6-month abstinence	6-month abstinence			6-month abstinence	6-month abstinence

AD, acute decompensation; ALD, alcoholic liver disease; ALF, acute liver failure; Aus, Australia; DBD, donation after brain death; DDLT, deceased donor liver transplant; DCD, donation after circulatory death; DSOT, Deutsche Stiftung Organ Transplantation (German Organ Transplantation Foundation); HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NHSBT, National Health Service Blood and Transplant; NZ, New Zealand; ODTI, Organ Donation and Transplant Ireland; UKELD, United Kingdom model for end-stage liver disease; PMP, per million population; UNOS, United Network for Organ Sharing.
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The authors declare no conflicts of interest that pertain to this work.

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