Epidemiology of Chronic Liver Diseases

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Abbreviations

AIH	Autoimmune hepatitis
ALD	Alcoholic liver disease
AUD	Alcohol use disorder
CCA	Cholangiocarcinoma
CLD	Chronic liver disease
DAA	Direct-acting antivirals against HCV
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
OLT	Orthotopic liver transplantation
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
SDI	Social development index
SVR	Sustained virological response
WHO	World Health Organization

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Knowing statistics of chronic liver disease (CLD) and liver cancer is of utmost importance as formation of cirrhosis or primary liver cancer due to the big four diseases is preventable in a majority of cases. Orthotopic liver transplantation (OLT) is the second most common solid organ transplantation worldwide. However, only 10% of people in need for an organ transplantation get one. In Europe, 429 patients died on the waiting list in 2017 with 1631 being active on the waiting list at the end of 2017 and 99 patients needed to be removed from the transplantation list for being unfit for transplantation [1, 2] In the United States, 13% mortality on the waiting list was reported for 2014–2017. One has to acknowledge that in the United States, 20% of patients on the waiting had to be removed for being too sick. However, details on their further fate are missing [3]. Etiology of CLD varies geographically. In 2015, 325 million people were chronically infected with hepatitis B (HBV) including coinfection with hepatitis D (HDV) or C (HCV), thus viral hepatitis being the major cause of CLD and hepatocellular carcinoma (HCC) in the world [4]. Since chronic hepatitis C has become curable in most cases due to the advent of novel antiviral drugs and hepatitis B is controlled under antiviral therapy, the risk of cirrhosis and hepatocellular carcinoma should significantly decrease in the future. As a consequence, not only morbidity and mortality due to HBV and HCV will decrease but also the need for liver transplantation. These trends will differ between high-, middle-, and low-income countries. Of further importance will be the global prevention of vertical transmission of hepatitis B by universal neonatal vaccination against HBV. Prevalences of different liver diseases differ widely depending on the geographical region with viral hepatitis C and B being the major cause of CLD and OLT in southern and eastern Europe, hepatitis B being the major cause of liver disease in Asia, and alcoholic liver disease (ALD) dominating in Northern and Central Europe [5]. However, noncommunicable diseases account for 70% of deaths globally as shown recently [6]. As obesity and other components of the metabolic syndrome are increasing on a global scale, it is not surprising that noncommunicable liver diseases like nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are of increasing importance in addition to ALD. However, the majority of deaths in NAFLD and NASH patients occur from comorbidities rather than liver disease itself, namely cardio- and cerebrovascular diseases. The prevalence of NAFLD is estimated at 25.2% globally, and 5% of those NAFLD patients are estimated to progress to cirrhosis over a 20-year time frame. Numbers for OLT, HCC, or death due to NASH are rising and are assumed to become the number one cause of OLT in Europe in the not too far-distant future [7–10]. One has to acknowledge that the prevalence of NAFLD varies significantly worldwide. Prevalence is highest in South America and the Middle East and lowest in Africa [11]. Factors like gender, age, and ethnicity are associated with a modulation of risk of progression from NAFLD to NASH and cirrhosis. Harmful consumption of

alcohol leading to alcoholic steatohepatitis (ASH) and consecutively to cirrhosis accounts for 3.3 million deaths annually which accounts for 5.9% of all deaths annually [12]. It is unclear, however, which amount of annual deaths due to alcohol consumption can be attributed to ALD. Lastly, HCC has become the solid cancer with the highest increase in incidence globally. HCC incidence and mortality are still on the rise and account for significant mortality and morbidity. It is the second most common cause of death related to cancer, only being surpassed by lung cancer. HCC is the second-leading cause of cancer-related deaths in men and the sixth most common cause of cancer-related death in women [13]. Overall incidence is estimated at 16 cases per 100,000 people [14, 15]. In this chapter, we examine global trends in the etiology of CLD, especially in the context of OLT, analyze global and regional differences, and outline challenges and perspectives.

1.1 Introduction

Assessing accurate epidemiologic data of CLD is sometimes difficult as precise data are scarce for many regions with a high prevalence of CLD especially in Africa. The WHO has seen an increase in data quality recently, though. Furthermore, one has to take into account that mortality data are often biased and deaths due to liver disease are often underestimated when based on ICD-10 coding. When assessing global disease burden of CLD, there are two relevant entities – cirrhosis and primary liver cancer of which more than 75% is HCC. Looking at recent data, cirrhosis accounts for 1.3 million deaths annually and primary liver cancer accounts for approximately 819400 deaths per year. In total, they make up for 3.5% of all deaths every year with ischemic heart disease and stroke being the biggest killers and adding up to a combined 15 million deaths in 2017. Deaths due to acute liver disease are not included in the aforementioned numbers and will be discussed in a different chapter. Deaths caused by chronic liver disease have seen an increase of 0.5% since 2000. These numbers have to be taken cautiously, as these are estimated numbers. In 2017, there were 803000 incident cases of primary liver cancer, marking an increase of 71% since 1990 with 471000 incident cases at that time. Cirrhosis is currently the 13th- and liver cancer the 19th-leading cause of death. Different etiologies drive formation of cirrhosis and primary liver cancer to varying degrees. So far, HBV has been the major driver for the development of HCC globally, with HCV and alcohol taking the runner up spots. Both HCC and cirrhosis due to hepatitis C most probably will decline at least in regions where HCV DAAs have become available, diagnosis rates of HCV infection increase, and new infections are reduced and controlled according to the ambitious 2016 WHO target for an elimination of HCV by 2030. The burden due to HBV infection might also decrease significantly which will depend on effective global HBV vaccination programs and effective strategies to prevent vertical mother-to-child transmission in particular in low-income countries with high HBV prevalence. Alcohol use disorder (AUD), obesity, and

metabolic syndrome are on the rise and so will be CLD and HCC due to AUD and NAFLD/NASH in particular in high- and middle-income countries [16, 17].

- HBV infection, HCV infection, and alcoholic liver disease (ALD) are the three most common causes of CLD and HCC with NAFLD/NASH being on the rise and getting close in many regions. All four entities are preventable in the majority of cases. This is of utmost importance since CLD and primary liver cancer account for two million deaths annually, equaling 3.5% of global mortality, with numbers still rising and numbers of OLT missing current needs by far.

1.2 Epidemiology of Chronic Liver Disease

Chronic HBV and HCV infections combined affect more than 320 million people globally. To put this into context, there are more people dying from HBV or HCV than from HIV or malaria, equaling the numbers of death from tuberculosis, making HBV and HCV infection a relevant and at the same time a preventable global disease burden since potent vaccines exist against HBV and since HCV infection has become a curable disease due to the advent of HCV DAA therapies. Deaths from HIV, malaria, or tuberculosis are declining, while those due to viral hepatitis are still on the rise. HBV and HCV add up to 96% of global mortality due to viral hepatitis, which is around 1.3 million every year, mainly due to cirrhosis and its complications or HCC. For the latter, it is estimated that by reducing HBV and HCV burden significantly, 1 in 20 of all cancer-related deaths is preventable [4]. European burden of CLD ranges between 500 and 1100 cases per 100000. The majority of which is caused by alcohol consumption and hepatitis C. Northern and Western Europe show a predominance of alcohol as etiological cause, whereas in Southern and Eastern Europe, CLD and HCC occur mostly due to viral hepatitis, especially hepatitis C. Primary liver cancer has a modeled prevalence between <2 and 12 cases per 100000 in Europe. WHO estimates death from CLD and primary liver cancer between 10 and 36 deaths per 100000 population all over Europe, mostly occurring due to alcohol and HCC [18]. Indications for OLT in the Western world have been led by HCV-induced liver disease for many years, which is currently being replaced by alcohol, NAFLD, and HCC. In Asia, HCC and HBV remain leading indications for OLT. In the United States, HCV infection has been the leading cause for OLT, but NAFLD/NASH is going to be the major indication soon. Years of life lost due to CLD are working years of life lost in two thirds of cases. In comparison, only one third of years of life lost are working years of life in ischemic heart disease, lung cancer, or stroke. It is estimated that around one third of working years of life lost is associated with alcohol consumption [18, 19].

1.2.1 Hepatitis B and Hepatitis D

In 2015, 3.5% of the world's population were chronically infected with HBV, equaling 257 million people, as measured by HBsAg seroprevalence for longer than

6 months [4]. Route of infection differs between regions. Vertical transmission is of minor importance in high–income, so-called developed countries, whereas both horizontal and vertical transmissions play a significant role in middle and low-income, so-called developing countries, especially in Africa [20–25]. Chronic hepatitis B patients may suffer from coinfection with hepatitis D virus (HDV). While some sources estimate numbers of HBV/HDV-coinfected patients at 12.5–15 million, other estimates range as high as 20 million [26]. Reliable mortality data of HBV/HDV-coinfected people are missing so far. Of the 36.7 million people infected with HIV, 2.7 million are coinfected with HBV of which 71% live in Sub-Saharan Africa. Sixty-eight percent of people with chronic HBV infection live in the Western Pacific area and Africa. In the Western Pacific area and Africa, there were approximately 0.8 million deaths per year from HBV cirrhosis and HBV-related HCC (0.45 million from cirrhosis and 0.35 million from HCC) [4]. These numbers are put into perspective, when keeping in mind that in total about two million people die every year from CLD and primary liver cancer. Mortality is above average in subgroups of men, infected people over the age of 30 and people living with HBV infection in developing countries. Data from some areas are scarce or available only for specific subgroups, for example, HIV-infected people, pregnant women, or blood donors, especially in Africa. Even though Africa and the Western Pacific area account for the majority of HBV infections on a global scale, there also is a wide heterogeneity among different countries within one continent and even among different regions within one country. In Africa, prevalence might be as low as 0.48% in the Seychelles or 2.89% in Algeria, while on the contrary, prevalence is as high as 22.38% in Southern Soudan. In the Western Pacific region, prevalence is as high as 22.7% in Kiribati or 18.83% on the Solomon Islands and as low as 0.37% in Australia. South East Asian countries display a narrower range of prevalence. The whole region accounts for about 61 million cases of HBV infection, but data are inconsistent for this region. Interestingly, prevalence is strikingly different between tribal and non-tribal populations in India being 11.85% and 3.1%, respectively [27–29]. Prevalence in Europe ranges between 0.5% and 8.0% with a higher prevalence in Southern and Eastern Europe and overall a total prevalence of approximately 4.7 million people infected in the whole of Europe. Most European countries have seen a decrease in recent years, but prevalence in Poland and Russia might be even increasing due to remaining high rates of new infections through certain risk groups. Time will tell, if such increasing numbers present a real trend or are just a statistical phenomenon owing to weaknesses in data assessment, for example [18]. Overall prevalence is estimated at 3.01% in the Eastern Mediterranean region [28]. The minority of infections occurs in North and South America, probably owing to effective vaccination programs, provision of clean injection materials for people who inject drugs (PWID), and improved screening programs for blood and blood products. America, Europe, and the Eastern Mediterranean region account for the least of HBV infections, making HBV mainly a public health concern in Africa, the Western Pacific, and Southeast Asia [27–29]. Global coverage with three HBV vaccination doses has been 84% of every infant in 2015 [4]. WHO aims to increase vaccination rate to 90% in 2030. HBV prevalence in children decreased from 4.7% prevaccination to

1.3% recently and from 4.3% to 3.5%, respectively, in the general population providing proof of concept for WHOs ambitious goal in the combat to defeat HBV infection as a public health thread by 2030. High vaccination rates are a main part of this strategy [4]. About 90% of children being infected at birth develop chronic HBV infection emphasizing the importance of timely perinatal vaccination and adequate antiviral therapy of HBV positive pregnant women to prevent vertical transmission. In contrast, only 5% of people infected after the age of 5 years develop chronic hepatitis B [20].

1.2.2 Hepatitis C

Fifty to eighty-five percent of patients infected with HCV develop a chronic infection. In 2015, the global prevalence of chronic HCV infection was 1% equaling 71 million people, and 1.75 million people got newly infected in 2015, mainly due to unsafe health procedures and injection drug use [4]. China, Pakistan, Russia, India, Egypt, and the United States together account for 51% of global HCV infections. Six major HCV genotypes may be distinguished. Globally, genotype distribution is as follows: 1 (44%), 3 (25%), 4 (15%), and others (16%) with significant regional differences. Genotype 1 is the most prevalent in Russia (54.9%), the United States (72.5%), and China (58.2%). Seventy-nine percent of those infected in Pakistan and 64.1% of those infected in India are infected with HCV genotype 3. In Egypt, genotype 4 accounts for 90% of HCV infections. Genotype 5 is found in South Africa in 35.7% of cases and genotype 6 is predominant in Southeast Asia, for example, accounting for 95.6% of cases in Laos [30]. With pan-genotypic DAA being widely available pretreatment, genotyping is becoming less important. Availability of highly effective pangenotypic HCV DAA therapies, effective screening programs, and prevention of new infections might therefore facilitate WHO's ambitious HCV elimination goal by 2030, meaning diagnosing 90%, treating 80%, and reducing mortality by 65%. HIV or HBV coinfection, alcohol abuse, obesity, insulin resistance, and most important inflammation and fibrosis at baseline seem to be independent predictors of a progressive disease course with progression of fibrosis, cirrhosis decompensation, and development of HCC. A total of 400000 people die from HCV infection per year, mainly from cirrhosis and its complications including HCC [4]. HCV infection still is the leading cause of HCC development in Western countries. Prevalence in Europe is estimated at 1.8% with over 13 million individuals being infected. HCV prevalence varies throughout Europe significantly. Prevalence is estimated as low as <0.1% in Belgium or the Netherlands and at 5.9% in Italy [18]. In the United States, 2–four million people have been infected by HCV. Especially, high-risk groups like prisoners or PWIDs are prone to having chronic HCV infection and present hard to reach subgroups on the path to HCV elimination. They also are at highest risk for de novo HCV transmission. Egypt has set up a massive screening and treatment program to combat HCV infection and serves as an example on how to implement strategies to reach the goal of HCV elimination set by WHO. As early as of 2019, approximately 30 million people were screened of which 1.2

million were seropositive and 75% of those were viremic and received treatment [31]. Simplification of HCV treatment is another important approach to combat the HCV epidemic and reaching the WHO elimination goal by 2030. The SMART-C study has shown that HCV DAA therapy indeed might be simplified with easy to handle patients not having to show up at their practitioners as frequent as it is now still practiced [32].

1.2.3 Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Global prevalence of NAFLD is estimated at about 25.2%. Prevalence of NASH is estimated between 3% and 5%. In high-risk populations, the prevalence is significantly higher. NAFLD can be found in diabetics in up to 59% of patients and that number increases further in morbidly obese patients undergoing bariatric surgery [11, 33, 34]. Overall, there has been a continuous increase in recent years from 1988–1991 to 2011–2012, which is tightly linked to the increasing obesity epidemic, especially in western countries. In 1975, 100 million people were categorized as obese, whereas this number increased to an overwhelming 671 million in 2016 with a female predominance (390 million women and 281 million men) with another 1.3 billion adults being overweight, which translates to 13% and 39% of the total global population, respectively [35]. The number of patients with diabetes increased from 100 million in 1980 to 422 million in 2014 [36]. However, in some regions, correlation to common risk factors for NAFLD and NASH as diabetes, obesity, sedentary lifestyle, or high caloric intake is not as strong as commonly seen, suggesting that environmental, hereditary, or further, yet unknown, factors contribute to the development of NAFLD and NASH. Five to ten percent of all NAFLD is so-called lean NAFLD, meaning patients with normal BMI but features of NAFLD or NASH with its pathogenesis still not fully understood and being a diagnostic challenge. Some studies suggest that prevalence of lean NAFLD might be as high as 25–30% in some rural areas in Asia requiring further investigation. Lean NAFLD can arise from a variety of conditions, ranging from starvation over parenteral nutrition to endocrine, metabolic and hereditary disorders, or selected drugs. Even if classical features of metabolic syndrome like disturbances of glucose and lipid metabolism or visceral adipose tissue are present, rare entities of lean NAFLD have to be kept in mind [8, 37]. Recognizing the entity of lean NAFLD is of clinical significance, as, for example, median survival time between lean and obese individuals with NAFLD was significantly lower in the lean patients (18.1 vs. 26.6 years) [38]. It is estimated that in the United States, the prevalence of NAFLD and NASH rises about 21% and 63%, respectively, until 2030 with an increase in mortality of 178% (78300 deaths per year of CLD or HCC in NASH patients) [39]. Incidence of HCC in NAFLD is 0.44/1000 person years, which is 15- to 35-fold lower than the HCC risk in hepatitis B without cirrhosis. In NASH, the incidence rate rises to 5.29/1000 person years and 5-year HCC risk in NASH cirrhosis has been described at roughly 11% in a Japanese cohort [11, 40]. There is a regional variation between different

WHO regions. The Middle East and South America have the highest prevalence of NAFLD with 31.8% and 30.4%, respectively. The lowest prevalence is found in Africa with 13.5%. Europe has a prevalence of 23.7%, Asia of 27.4%, and North America of 24.1% [11]. Mortality of fatty liver disease patients is dominated by cardiovascular morbidity. Mortality from NAFLD is around 0.77 per 1000 person years and 11.77 per 1000 person years for NASH. To put these findings in context, one has to know that all-cause mortality is 15.44 per 1000 person years for NAFLD and 25.56 per 1000 person years for NASH patients [8, 37]. As fibrosis progression in NAFLD and NASH is usually slow, it is estimated that around 5% of patients progress to cirrhosis within 20 years and half of them decompensate with and another half of them dying from a liver-related cause, leaving the majority of NAFLD patients dying from other, non-liver-related diseases [9]. Nonetheless, NASH is estimated to become the major OLT indication in Western-developed countries as HCV infections decline owing to the sheer number of people affected. Prevalence of NAFLD in general and fibrosis in NAFLD appear to be associated with older age and female sex. The differentiation of NASH from ASH is often challenging as objective criteria are missing in clinical practice, emphasizing the importance of a concise patient history to dissect one from the other. The relative risk of liver disease increases from 3.16 in normal weight men solely consuming too much alcohol to 7.01 in overweight men with alcohol abuse and 18.9 in obese drinkers, providing clinical relevance for precise and accurate evaluation [41–43].

- Evaluate every patient with CLD for features of a second concomitant CLD. There might be features of NAFLD and NASH in AIH patients under immunosuppressive therapy, for example, especially when glucocorticoids are used and serological markers of AIH are present which makes it difficult sometimes to differentiate between AIH and NASH. Secondly, ASH and NASH might be sometimes hard to discriminate and both diseases can be present at the same time and overlap.

1.2.4 Alcohol Use Disorder (AUD) and Alcoholic Liver Disease (ALD)

A total of 2.4 billion people worldwide consumed alcohol regularly in 2016 and 75 million were diagnosed with AUD. Mean daily consumption of alcohol globally was 0.73 standard drinks for women and 1.7 standard drinks for men. In general, alcohol consumption is higher in countries with a higher SDI. In these countries, 72% of women and 83% of men consume alcohol regularly. In contrast, alcohol consumption is lowest in low to middle SDI countries, where 8.9% of women and 20% of men consume alcohol on a regular basis. Alcohol consumption is highest in Europe, with Eastern Europe and Russia leading, Australia and North America. Europe remains number one in per capita alcohol consumption, even though it decreased recently from 12.3 to 9.8 L of pure alcohol per year (2005–2016). In Europe, Australia, and North America, around one third of liver-related mortality in CLD is linked to

alcoholic liver disease. In this context, it has to be taken into account that a relevant portion of liver-related disease and death are coded as cryptogenic or unknown. It is estimated that in reality, deaths being attributed to alcohol-associated CLD are more closely settled in the range of 60–80%. While social drinking has been associated with no major impact on mortality for a long time and even protective effects have been attributed to low-dose alcohol consumption, it is known by now that every level of alcohol consumption has harmful potential with a dose-dependent effect. ALD has to be taken into account when alcohol consumption above 30 g daily in men and 20 g daily in women is present. Alcohol is the seventh-leading risk factor for morbidity and mortality and linked to 60 health-related outcomes. Globally, 2.8 million deaths were related to alcohol in 2016, accounting for 6.8% of male deaths and 2.2% of female deaths. In those aged 15–49 years, alcohol was the leading cause of death with 12.2% of male deaths and 3.8% of female deaths being attributed to alcohol. Major causes of death in this subgroup were tuberculosis, self-harm, and road injuries. Liver disease accounted for a minority of alcohol-related deaths. Over 50% of worldwide deaths related to cirrhosis can be linked to alcohol consumption, either as the sole cause or as a contributing factor. Alcohol consumption presents a major public health threat with average per capita consumption having increased from 5.5 L pure alcohol in 2005 to 6.4 L in 2016 and being estimated to rise to 7.0 L in 2025 globally. From 2010 to 2016, consumption increased 30% in South East Asia and decreased 12% in Europe. Alcohol consumption in Europe remains the highest in the world, though, with 9.8 L pure alcohol per capita. One has to keep in mind that there possibly is a synergistic effect of alcohol consumption and features of the metabolic syndrome [43–48].

- Every patient presenting with CLD or HCC should be evaluated for alcohol consumption and AUD, as alcohol consumption presents a significant comorbidity and potentiates risk of decompensation or death in patients with CLD or HCC of other etiologies.

1.2.5 Hepatocellular Carcinoma (HCC)

HCC makes up at least 75% of primary liver cancer (cholangiocarcinoma, CCA, 10–15%) [49, 50]. The incidence is highest in Asia with 75% of global cases occurring on this continent and with more than 50% of global HCC burden being located in China. The most common cause is HBV infection, followed by HCV infection. Whereas HBV infection is the major cause of HCC in Asia and Africa, HCV has been the leading cause in the United States so far [51]. In contrast to other neoplasms, mortality and incidence of HCC are increasing, making HCC the second-leading cause of cancer-related mortality only second to lung cancer while being the second-leading cause of cancer-related deaths in men and the sixth cause of cancer-related death in women [13, 16]. The United States saw an increase in HCC incidence of 3.1% per year from 2008 to 2012 [52]. Global incidence was about 803,000 in 2017. In 2005, there were 709000 incident cases of HCC. Between 1990 and 2015, global incidence of HCC increased about 75%. In 2015, according to the global burden of disease study,

43.3% of HCC cases were due to HBV infection, 18.7% due to HCV infection, 14.7% due to alcohol, and 23.3% due to other entities [53]. A change is expected with the prevalence and incidence of NASH increasing. On a global scale, HCC presents a rising transplant indication. Men are commonly affected more often than women, and older age is an additional risk factor for HCC development. Eighty to ninety percent of HCC patients have underlying cirrhosis with cirrhosis by itself being a major risk factor for occurrence of HCC. Risk of HCC is increased 5- to 100-fold in HBV infection and 15- to 20-fold in HCV infection. Alcohol consumption over 80 grams daily for at least 10 years places individuals at five-fold increased risk of HCC development, but alcohol acts also synergistically with other HCC causing factors [54–56]. Ten-year HCC risk was 53% in HBV-infected individuals who consumed large quantities of alcohol being superior to alcohol consumption (25%) or HBV-infection (40%) alone. [57] Obesity and diabetes mellitus present an additional combined risk factor for HCC development and are estimated to at least contribute to 25% of HCC cases [58]. For people without cirrhosis, it is important to acknowledge that especially patients with HBV and NAFLD appear to be at risk for developing HCC without underlying cirrhosis with HBV posing the people at higher risk than NAFLD. Prognosis is highly dependent on HCC stage with overall median survival of less than 1 year. Survival rate in HCC is the second worst survival rate in all cancers only being surpassed by pancreatic cancer, probably due to late diagnosis in both HCC and pancreatic cancer [59, 60]. Decrease of HCC incidence, morbidity, and mortality will be highly dependent on efficacy of public health measures to reduce burden of CLD, like lowering HBV burden by increasing vaccination rates or achieving cure in HCV-infected individuals.

1.2.6 Miscellaneous (Autoimmune, Genetic, and Other Rare Liver Diseases)

Numerous additional conditions may lead to CLD, HCC, and eventually to death or transplantation. Several of them are classified as rare diseases such as autoimmune liver disease, genetic liver diseases, vascular liver diseases, and others. Looking at global statistics, even though each disease on its own classifies as rare liver disease, rare and pediatric liver diseases as a whole accounted for 15.9% of all ELTR-registered liver transplantations between 1968 and 2017 [18]. Pediatric diseases will be discussed in a separate chapter of this book. Data on miscellaneous rare CLD in the context of OLT excluding pediatric CLD are scarce. Prevalence of AIH is estimated at 16–17 cases per 100,000 inhabitants in Europe and at 23.9 cases per 100000 people globally with a female predominance. AIH seems to occur at lower rates in Asia with the cost of being detected at later disease stages [61, 62]. Prevalence of primary biliary cholangitis (PBC) ranges from 1.91 to 40.2 per 100000 people with lower rates in Asia and the highest rates in Iceland and Olmsted County, Minnesota, USA [63–65]. Incidence of primary sclerosing cholangitis (PSC) is estimated at the range between 0 and 1.3 per 100000 people each year. Prevalence ranges between 0 and 16.2 per 100000 population [66]. It is associated with inflammatory bowel disease (IBD) in 65% of cases. Ulcerative colitis makes up 75% of IBD in these patients

[67]. There is a predominance of young to middle-aged men, and both PSC and IBD are more common in industrialized countries. Wilson disease is estimated to occur in 1 in 30000–40000 people, whereas 1 in 90 carry mutations of the Wilson disease-associated gene [68]. Early diagnosis and treatment is essential in Wilson disease in order to stop progression to cirrhosis with consecutive increased morbidity and mortality. Hemochromatosis has been considered rare but 10% of all people carry mutations of the HFE gene, homozygous mutations of the HFE gene, mainly C282Y, being detected at a frequency of around 0.5% [69–72]. Hemochromatosis is among the most frequent genetic diseases. From a public health perspective, there is no rational for a population-based intervention to reduce burden of rare and pediatric liver diseases although they make up 15.9% of all liver transplantations. The health burden by HBV, HCV infection, ALD, and NAFLD/NASH is by far higher.

Key Points

- CLD and primary liver cancer, mainly HCC, present a major burden of disease on a global scale.
- Years of life lost due to CLD and primary liver cancer are working years of life lost in a majority of cases.
- While HCV DAAs become globally available, end-stage liver disease or HCC due to HCV infection will become a minor indication for OLT in the not too far-distant future in several parts of the world.
- Global HBV prevalence is still high. However, effective HBV vaccination programs and widespread use of HBV medications should control HBV infection in the future and prevent progression of chronic disease. OLT indications for liver cirrhosis or HCC due to HBV infection will further decline.
- ALD and, in particular, NAFLD/NASH will increase in the future and will represent the major indications for OLT in the near future.
- Patients with rare autoimmune, hereditary, and metabolic disorders or pediatric chronic liver diseases present a rather small entity in the context of liver transplantation, and they will stay stable. However, early diagnosis of these liver diseases is important since early therapies prevent progression and thus end-stage liver disease, HCC, and need for OLT.

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Further Readings

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