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Review

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Epidemiology of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD)

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD) together represent the majority of individuals with steatotic liver disease (SLD). MASLD and ALD prevalence continues to rise globally, which is driven by several factors including an aging population, increasing prevalence of cardiometabolic risk factors such as obesity and diabetes mellitus, and the increasing trends in high-risk unhealthy alcohol use which surged during the COVID-19 pandemic. As a result, MASLD, as well as ALD-related cirrhosis and hepatocellular carcinoma, is also on the rise, becoming major etiologies contributing to end-stage liver disease among adults awaiting liver transplantation. Accurately understanding MASLD and ALD epidemiology is critical to guide healthcare resource planning and health policy. Accurate estimates of MASLD and ALD epidemiology are particularly important to understand in the context of recent updates in nomenclature terminology. This review provides an updated assessment of existing literature describing the epidemiology of MASLD and ALD.

Keywords: MASLD, ALD, epidemiology, cirrhosis, hepatocellular carcinoma

INTRODUCTION

Steatotic liver disease (SLD), which spans the spectrum from metabolic dysfunction-associated steatotic

liver disease (MASLD) to predominantly alcohol-related liver disease (ALD), is a leading cause of morbidity and mortality globally[1-5]. Globally, it presents an increasing healthcare and economic burden as the aging population with SLD progresses to more advanced stages of liver disease, such as cirrhosis and hepatocellular carcinoma (HCC)[2,3,6-10]. Furthermore, the increasing clinical burden of SLD, particularly MASLD, is due to the rising prevalence of metabolic comorbidities, such as obesity and diabetes mellitus, which are important cardiometabolic risk factors that not only increase the risk of MASLD, but are also associated with the increasing risk of disease progression among those who have already developed MASLD[4,5,8,11-13]. With respect to ALD, many epidemiological studies have shown the continued rise of high-risk alcohol use and the associated rise in alcohol-related comorbidities, including ALD[14-18]. High-risk and unhealthy alcohol use was exacerbated by the coronavirus disease 19 (COVID-19) pandemic, which led to a surge in unhealthy alcohol use across various populations. This led to detrimental health consequences, especially as it relates to ALD and ALD-related complications[19-25]. In the subsequent sections of this review, we will expand on the updated epidemiology of SLD, with a specific focus on MASLD and ALD.

DEFINITIONS

MASLD and the more advanced form of metabolic dysfunction-associated steatohepatitis (MASH) were previously referred to as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), respectively[1]. However, the terms NAFLD and NASH implied that these were exclusionary diagnoses that required ruling out other potential competing etiologies. There were also concerns raised that the terms were stigmatizing to patients, given the emphasis on "nonalcoholic" and "fatty". Furthermore, while it is generally accepted that the major risk factors of NAFLD/NASH development were cardiometabolic risk factors (e.g., obesity, diabetes or insulin resistance, hypertension, dyslipidemia), the terms NAFLD and NASH did not capture the important cardiometabolic factors that are believed to drive disease development[1]. Finally, it was noted that a major catalyst for the development of new unifying nomenclature was the introduction of yet another term, metabolic dysfunction-associated fatty liver disease (MAFLD). The definition of MAFLD required more restrictive metabolic criteria but was more liberal with the inclusion of alcohol use, and as a result, individuals meeting MAFLD criteria seemed to be a distinct subset from those with what was traditionally known as NAFLD[26-28]. There were concerns that wider adoption of MAFLD would derail the progress thus far on biomarker development as well as therapeutics for NAFLD/NASH.

A global Delphi process was coordinated over the course of 2-3 years, which incorporated 224 people representing 56 countries[1]. Representatives from patient organizations and individuals from the pharmaceutical industry were also surveyed to gather feedback. The result of this global effort was the development of new nomenclature to replace existing NAFLD/NASH terminology. Under this new nomenclature, SLD served as an umbrella term encompassing different terminologies and associated etiologies of SLD based on the purported main contributing risk factors. MASLD, which was previously referred to as NAFLD, now required the presence of 1 or more concurrent cardiometabolic risk factors. Another new terminology introduced was the term MetALD, which included individuals who drink alcohol in quantities greater than 20 g/day for females and greater than 30 g/day for males, but less than 50 g/day for females and less than 60 g/day for males. Individuals with SLD who drink alcohol in quantities > 50 g/day for females or > 60 g/day for males are categorized as ALD. The updated nomenclature also included other less common causes of SLD, such as drug-induced liver injury, Wilson disease, cryptogenic liver disease, etc.[29]. Although a wealth of epidemiology data predates the new nomenclature change and uses NAFLD/NASH terminology, we will categorically apply the updated nomenclature throughout this paper, even when referencing these older studies. We will also expand below on more recent studies that have compared epidemiology data between NAFLD/NASH and MASLD/MASH, highlighting the significant overlap in

terms of disease prevalence and outcomes.

EPIDEMIOLOGY OF MASLD

The prevalence of MASLD has been rising steadily, driven by an aging population and the increasing prevalence of cardiometabolic risk factors that are strongly associated with its development and progression. There have also been studies identifying potential genetic polymorphisms associated with increased risk of MASLD. The most well-studied polymorphism includes the patatin-like phospholipase domain-containing 3 (PNPLA3). Existing studies have reported on significant geography heterogeneity in the prevalence of PNPLA3 polymorphisms that are associated with disease risk[30]. A recent systematic review included a total of 92 studies, representing population-based studies published through 2022. The overall prevalence of MASLD was 30.1% (95%CI: 27.9-32.3) from 1990-2019[31]. During the study period, MASLD prevalence rose steadily from 25.3% in 1990-2006 to 38.0% in 2016-2019. Significant geographic variations in MASLD prevalence were observed across world regions. For example, MASLD prevalence was 44.4% (95%CI: 30.7-59.0) in Latin America, 36.5% (95%CI: 28.6-45.2) in the Middle East and North Africa, 33.8% (95%CI: 22.9-37.1) in South Asia, 33.1% (95%CI: 19.0-51.0) in Southeast Asian, 31.2% (95%CI: 25.9-37.1) in North America, 29.7% (95%CI 26.0-33.8) in East Asia, 28.0% (95%CI: 24.7-31.6) in Asia Pacific regions, and 25.1% (95%CI: 20.6-30.3) in Western Europe[31].

Diving a little deeper into geographic variations, among the Asia-Pacific regions, Li *et al.* observed significant variations from as high as 33.8% MASLD prevalence in South Asia to 28.0% MASLD prevalence in Oceania[32]. Studies with histologic liver biopsy data to assess the prevalence of MASH were limited, but among the data available, the authors also reported a MASH prevalence of 5.4% in South Asia, 5.3% in Southeast Asia, 4.8% in East Asia, and 4.5% in Oceania. A similar systematic review and meta-analyses reported similar prevalence estimates and additionally reported a pooled annual MASLD incidence rate of 50.9 cases per 1,000 person-years (95%CI: 44.8-57.4) in Asia[32]. Data specifically from China, one of the most populated countries in the world, also report prevalence estimates similar to the rest of the Asia-Pacific region. For example, a recent systematic review and meta-analysis observed that MASLD prevalence in China increased from 25.4% in 2008-2010 to 32.3% in 2015-2018[33]. Interestingly, even within China, significant differences in MASLD prevalence by geographical region were observed, from 19.3% in the Southwestern region to 33.8% in the Northwestern region[33]. In addition to differences in lifestyle, dietary, and environmental factors that may in part contribute to some of these observed differences, variations in socio-demographics likely also influence differences in MASLD prevalence. For example, in this same systematic review and meta-analyses of Chinese populations, the authors observed that the prevalence of MASLD was lowest in regions with a per capita gross domestic product (GDP) of 70,000-80,000 yuan (24.2%), and highest in regions with a GDP < 50,000 yuan (29.7%) and > 100,000 yuan (32.1%)[33].

Overall, there is a paucity of data from the Middle East and Africa regions. In the aforementioned systematic review, MASLD prevalence in this world region was 36.5% (95%CI: 28.6-45.2). Data for Africa are limited and population-based estimates are difficult to estimate due to inherent selection bias associated with existing studies, which often involve small cohorts, are conducted at a single center, or focus on high-risk populations. For example, one single-center study from South Africa included 111 patients with histologically confirmed MASLD, among whom 36% had MASH and 17% had advanced fibrosis[34]. However, the generalizability of these observations to the broader South African population is severely limited. Data from the Middle East region, while also limited, have reported some country-specific data on MASLD prevalence, including populations in Kuwait (33.3%) and Iran (33.9%)[35].

MASLD prevalence data from North America is predominantly from the United States (U.S.). In a recent study utilizing data from the National Health and Nutrition Examination Survey (NHANES) from 2017-2020, Kalligeros *et al.* observed age-adjusted prevalences of 32.5% (95%CI: 29.8-35.2) for MASLD and 2.6% (95%CI: 1.9-3.4) for MetALD among U.S. adults[36]. Data from Lee *et al.* utilized the same dataset and reported similar findings. Among 7,367 participants, the overall prevalence of SLD was 34.2% (95%CI: 31.9-36.5): MASLD 31.3% (95%CI: 29.2-33.4), MetALD 2% (95%CI: 1.6-2.9), and ALD 0.7% (95%CI: 0.5-0.9)[37]. In the aforementioned systematic review, MASLD prevalence was observed to be 44.4% (95%CI: 30.7-59.0) in Latin America[38]. Previous country-specific studies in Latin America have reported a range of heterogeneous estimates of MASLD prevalence ranging from 17% in Mexico to 35% in Brazil[39]. As with other world regions with limited data, the heterogeneity of prevalence estimates is likely affected by small cohorts, variations in how MASLD was identified, and selection bias that may be present in targeted studies of high-risk populations.

MASLD prevalence in patients with diabetes mellitus

Individuals with concurrent diabetes mellitus are at particularly high risk of developing MASLD. A recent systematic review aimed to evaluate the prevalence of MASLD among individuals with diabetes mellitus. Among a total of 123 studies included, the global pooled prevalence of MASLD among individuals with diabetes mellitus was 65.3% (95%CI: 62.4-68.2)[38]. The authors also observed that MASLD prevalence among individuals with diabetes mellitus had increased from 55.9% (95%CI: 42.4-68.5) in 1990-2004 to 68.8% (95%CI: 63.4-73.7) in 2016-2021. Among the subset of 12 studies that had available liver biopsy histology data, the global pooled prevalence of MASH, significant fibrosis, and advanced fibrosis was 66.4% (95%CI: 56.6-75.0), 40.8% (95%CI: 24.2-9.7), and 15.5% (7.0-31.0), respectively[38].

MASLD *vs.* NAFLD: similarities and differences

With the new nomenclature adoption, several studies have compared the epidemiology of NAFLD *vs.* MASLD. For example, Lee *et al.* utilized 2017-2020 U.S. data from NHANES and observed a 99% overlap in cases of NAFLD and MASLD[37]. Similarly, investigators from the TARGET-NASH study group also reported 99% concordance overall when comparing the updated MASLD/MASH nomenclature and definitions with their existing longitudinal cohort of NAFLD/NASH patients[40]. For example, concordance rates were 96.3% among their cohort of 1,541 NAFLD/MASLD patients, 99.7% among 2,210 NASH/MASH patients, and 99.8% among patients with cirrhosis due to NASH/MASH. Additional studies have also reported similar clinical characteristics, performance of non-invasive diagnostic tests, and long-term outcomes. Younossi *et al.* utilized data from the NHANES III-National Death Index linked dataset in the U.S. Among 6,429 patients identified with NAFLD, 99% also met the criteria for MASLD, with 95% meeting MASLD criteria based on body mass index only[41]. The investigators observed excellent concordance with a Cohen's kappa coefficient of 0.968 (95%CI: 0.962-0.973). The study also reported that the predictive accuracy of non-invasive tests such as fibrosis-4 score and enhanced liver fibrosis test were identical between patients with MASLD *vs.* NAFLD. On long-term follow-up with a median of 22.8 years, there were also no significant differences in mortality outcomes between individuals meeting NAFLD *vs.* MASLD criteria[41].

MASLD outcomes

With the increasing burden of MASLD globally, it is important to understand the risk of disease progression and long-term outcomes. In the aforementioned systematic review evaluating global prevalence of MASLD, the investigators observed mortality rates of 12.60 per 1,000 person-years (95%CI: 6.68-23.67) for all-cause mortality, 4.20 per 1,000 person-years (95%CI: 1.34-7.05) for cardiac-specific mortality, 2.83 per 1,000 person-years (95%CI: 0.78-4.88) for extrahepatic cancer-specific mortality, and 0.92 per 1,000 person-years (95%CI: 0.00-2.21) for liver-specific mortality[31]. Among individuals with MASLD and diabetes mellitus, the

pooled all-cause mortality was 16.79 per 1,000 person-years (95%CI: 10.64-26.40), 4.19 per 1,000 person-years (95%CI: 1.34-7.05) for cardiac-specific mortality, 6.10 per 1,000 person-years (95%CI: 0.78-4.88) for extrahepatic cancer-specific mortality, and 2.15 per 1,000 person-years (95%CI: 0.00-2.21) for liver-specific mortality[38].

Individuals with MASLD can progress to cirrhosis and HCC. A recent study utilizing a national database of Veterans in the U.S. evaluated nearly 1 million adults with non-cirrhotic MASLD. The investigators observed a 10-year risk of 3.70% and 0.69% for cirrhosis and HCC, respectively[42]. In a subsequent study, the authors also reported that Veterans with MASLD who also reported concurrent high-risk alcohol use or increased their alcohol use over time had a significantly greater risk of developing cirrhosis during follow-up[43]. While the risk of cirrhosis among patients with MASLD is lower than other etiologies, the large global population affected by MASLD, along with increasing trends of MASLD-related cirrhosis across regions, is concerning[44]. In addition to cirrhosis, MASLD/MASH-related HCC also contributes to a significant global disease burden. While the majority of patients with MASLD/MASH-related HCC progress to cirrhosis, existing studies report that up to 38% of these patients do not have underlying cirrhosis[45]. In a recent review by Huang *et al.* significant variations in the incidence of non-cirrhotic MASLD/MASH-related HCC were observed, including 0.08 to 0.6 per 1,000 person-years among two large U.S. cohort studies, 0.04% to 0.6% annual incidence among multiple cohort studies from Asian regions, and 0.22 per 1,000 person-years in Spain to 0.57 per 1,000 person-years in the United Kingdom from European cohort studies[46]. The risk of HCC among MASLD/MASH patients with cirrhosis was much higher, but also demonstrated significant heterogeneity, ranging from 0.9 per 100 person-years to 2.6% annual cumulative incidence among U.S. cohorts to 4.5 per 100 person-years among a cohort of patients with MASH cirrhosis in New Zealand[46].

Data in the U.S. have also demonstrated that the prevalence of MASLD/MASH-related end-stage liver disease and HCC has continued to rise. For example, Wong *et al.* utilized data from the United Network for Organ Sharing (UNOS) liver transplantation database in the U.S. and observed that MASH and ALD have rapidly become the leading etiologies of liver disease among adults awaiting liver transplantation[14]. Updated data through the end of 2022 focusing specifically on adults who received liver transplantation demonstrated that MASH accounted for 31% of adults with HCC, followed by chronic hepatitis C at 27%[47]. Among adults without HCC who received a liver transplant, the leading indication was ALD at 48%, followed by MASH at 27%[47].

EPIDEMIOLOGY OF ALD

Accurate estimates of ALD epidemiology have been difficult to obtain due to challenges in accurate assessments of alcohol use, heterogeneous definitions used to categorize ALD, and limited population level-based data across world regions. A systematic review and meta-analysis from Niu *et al.* incorporated a total of 372 studies to evaluate global ALD epidemiology[48]. The authors observed a global prevalence of 4.8%. Another similar systematic review and meta-analysis focused specifically on populations subjected to a universal testing process. A total of 35 studies involving 513,278 persons were evaluated. Overall, the prevalence of ALD was 3.5% (95%CI: 2.0-6.0)[49]. When evaluating ALD prevalence among different subpopulations, the authors observed an ALD prevalence of 2.6% (95%CI: 0.5-11.7) among primary care settings and 51.0% (95%CI: 11.1-89.3) in populations with alcohol use disorder. When evaluated prevalence of ALD cirrhosis, overall prevalence was 0.3% (95%CI: 0.2-0.4) in general populations, 1.7% (95%CI: 0.3-10.2) in primary care settings, and 12.9% (95%CI: 4.3-33.2) in populations with alcohol use disorder[49].

ALD prevalence has also been evaluated in the U.S. Using 2001-2016 NHANES data, Wong *et al.* reported that the prevalence of ALD remained stable from 4.3% in 2001-2002 to 4.7% in 2015-2016[16]. However,

patients with ALD and stage 2 or greater fibrosis increased from 0.6% (95%CI: 0.5-0.8) to 1.5% (95%CI: 1.3-1.8) ($P < .001$), and ALD with stage 3 or greater fibrosis increased from 0.1% (95%CI: 0.02-0.10) to 0.2% (95%CI: 0.2-0.4) ($P = .045$)[16]. Another study in the U.S. by Dang *et al.* utilized three large databases to comprehensively describe the epidemiology of ALD in the U.S.: NHANES, UNOS, and the National Inpatient Sample[17]. From 2001-2002 to 2015-2016, overall weighted ALD prevalence was observed to be stable from 8.8% to 8.1%, whereas the proportion of individuals with ALD and stage ≥ 3 fibrosis increased from 2.2% (95%CI: 0.4-4.0) to 6.6% (95%CI: 2.0-9.9; $P = 0.007$). Using the National Inpatient Sample, the number of hospitalizations among patients with ALD-related cirrhosis increased by 32.8%. From 2007 to 2017, the total number of adults with ALD listed for liver transplant increased by 63.4% and the proportion with concurrent HCC increased by 178%[17].

ALD outcomes

Even prior to the onset of the COVID-19 pandemic, existing studies have reported on the increasing trends in ALD-related mortality. Tapper *et al.* evaluated trends in cirrhosis mortality in the U.S. from 1999 to 2016 using data from the Vital Statistics Cooperative and the U.S. Centers for Disease Control and Prevention's WONDER database. Overall, cirrhosis deaths increased by 65%, and from 2009 to 2016, the annual increase in cirrhosis deaths was 3.4%[18]. The investigators observed that increases in cirrhosis-related deaths were most pronounced for adults aged 25-34 years (average annual percent increase of 10.5%), which seems to be driven primarily by ALD. Following the onset of the COVID-19 pandemic, high-risk and unhealthy alcohol use surged. Lee *et al.* evaluated the Nielsen National Consumer Panel, a longitudinal household cohort that collects retail and e-commerce purchase data[22]. The investigators observed that retail purchases of alcohol (wine, liquor, and beer, malt beverages, and cider) in U.S. increased by 34.4% from 2019 to 2020 ($7.10 to $9.55 billion dollars). Data from Pollard *et al.* utilized the RAND Corporation American Life Panel, which conducts surveys of nationally representative, probability sample cohort of adults[25]. The investigators observed that overall alcohol consumption increased by 14% from April 29-June 9, 2019, to May 28 to June 16, 2020. These data are particularly concerning given that modeling data demonstrated that a one-year increase in alcohol consumption during the COVID-19 pandemic is estimated to result in 8,000 [95%CI: 7,500-8,600] additional ALD-related deaths, 18,700 [95%CI: 17,600-19,900] cases of decompensated cirrhosis, 1,000 [95%CI: 1,000-1,100] cases of HCC, and 8.9 million disability-adjusted life-years between 2020 and 2040[23].

SEX-SPECIFIC DIFFERENCES IN MASLD AND ALD

Existing studies have reported on sex-specific differences in the prevalence of MASLD and MASH, with higher prevalence seen in men, which may be attributed to underlying differences in concurrent cardiometabolic risk factors, but may also reflect differences in MASLD risk related to sex-specific hormonal patterns. A recent literature review by Burza *et al.* identified several population-based studies, predominantly U.S. cohort, that provided sex-specific prevalence estimates of MASLD among adults[50]. Across different cohorts and time periods, MASLD prevalence among women ranged from 1.6% to 24%, while MASLD prevalence in men ranged from 4.3% to 42%[51-54]. More recently, Wong *et al.* utilized data from NHANES from 2011 to 2018, during which the prevalence of MASLD increased for both men and women[55]. However, the prevalence among men was consistently higher than among women. For example, MASLD prevalence in men increased from 38.7% in 2011-2012 to 42.1% in 2017-2018, whereas MASLD prevalence in women increased from 29.9% in 2011-2012 to 33.9% in 2017-2018[55]. In a more recent systematic review and meta-analyses evaluating global MASLD epidemiology, which included a total of 72 studies involving over 1 million individuals from across 17 countries, the worldwide prevalence of MASLD was 32.4%[56]. However, significant sex-specific differences were observed. The prevalence of MASLD was significantly higher in men *vs.* women (39.7% *vs.* 25.6%, $P < 0.001$). In addition, the incidence of MASLD was estimated to be 70.8 per 1,000 person-years for men and 29.6 per 1,000 person-years for women[56].

Similar trends in sex-specific differences are also observed when evaluating ALD epidemiology.

Using NHANES data from 2001 to 2016, Wong *et al.* evaluated the prevalence of alcohol-related fatty liver disease among the U.S. population[16]. Across the entire study period, while overall prevalence remained stable, men consistently had a higher prevalence of alcohol-related fatty liver compared to women. For example, in 2015-2016, the prevalence of alcohol-related fatty liver among men was 5.8% (95%CI: 3.5-6.3) and 3.7% (95%CI: 2.6-4.2) among women. Similarly, Dang *et al.* performed a comprehensive evaluation of three large U.S. databases to describe ALD epidemiology. Using an updated definition for ALD, the investigators observed that in 2015-2016, ALD prevalence in men was 9.0% (95%CI: 6.2-11.7) compared to 7.2% (95%CI: 5.9-8.5) among women[17]. However, when looking at hospitalization data for ALD-related cirrhosis, concerning trends were observed. From 2007 to 2014, ALD-related hospitalizations were higher among men than women; however, the increase in ALD cirrhosis-related hospitalizations over time was significantly higher among women. For example, from 2007 to 2014, ALD cirrhosis-related hospitalizations increased by 14.7% among men, but increased by 33.5% among women[17]. These observations are particularly concerning, especially in light of recent data showing a significant rise in alcohol-related deaths among women. Karaye *et al.* utilized data from the U.S. Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiology Research to evaluate alcohol-related death trends from 1999 to 2020[57]. While the mortality burden of alcohol-related deaths in men was almost 3 times higher than women, temporal trends showed concerning patterns. For example, from 2018 to 2020, the age-adjusted mortality rate of alcohol-related deaths increased by 12.5% among men and by 14.7% among women, suggesting a higher rate of increase in alcohol-related deaths among women[57]. The surge in high-risk and unhealthy alcohol use after the onset of the COVID-19 pandemic has further fueled the concerning rise of ALD among women. Recent data demonstrate that the surge in alcohol use in recent years has been changing the epidemiology of ALD, with a significantly greater increase in alcohol use disorder and ALD among women, which are likely attributed to multiple factors, including physiological differences between sexes in alcohol absorption, first-pass metabolism, and hormonal variations[58,59]. These concerning trends emphasize the importance of routine assessment of alcohol use to identify high-risk and unhealthy levels of alcohol use early with referral to appropriate resources.

CONCLUSION

MASLD and ALD, together presenting the majority of patients with SLD, are major causes of liver-related morbidity and mortality globally. Across all world regions, there has been a steady rise in the prevalence of both MASLD and ALD, attributed to an overall aging population with multiple cardiometabolic comorbidities and high levels of unhealthy alcohol use which surged during the COVID-19 pandemic. The continued rising burden of MASLD and ALD is a major public health concern and emphasizes the importance of timely identification of MASLD and ALD and implementing effective care cascade pathways to ensure patients are receiving guideline-concordant care, especially given novel therapeutics available now and more on the horizon.

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Authors' contributions

The author contributed solely to the article.

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