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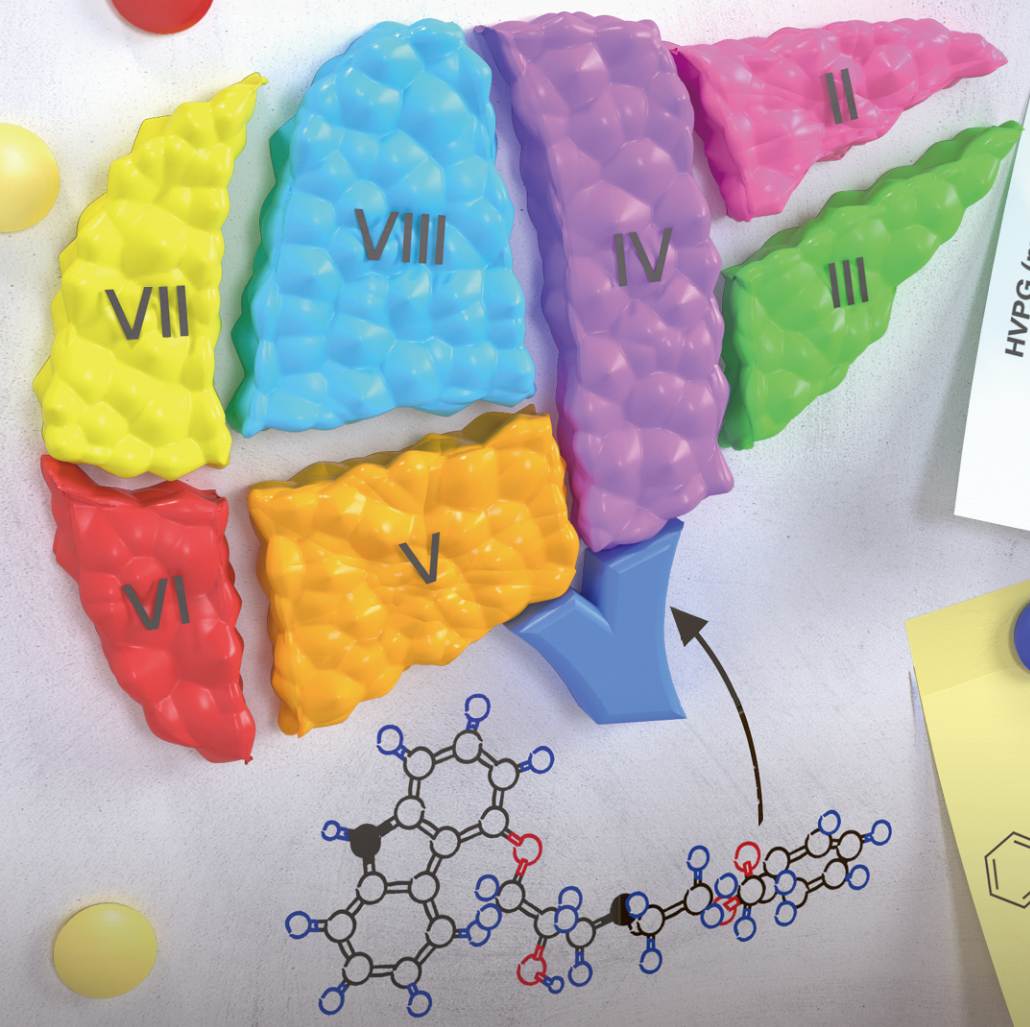

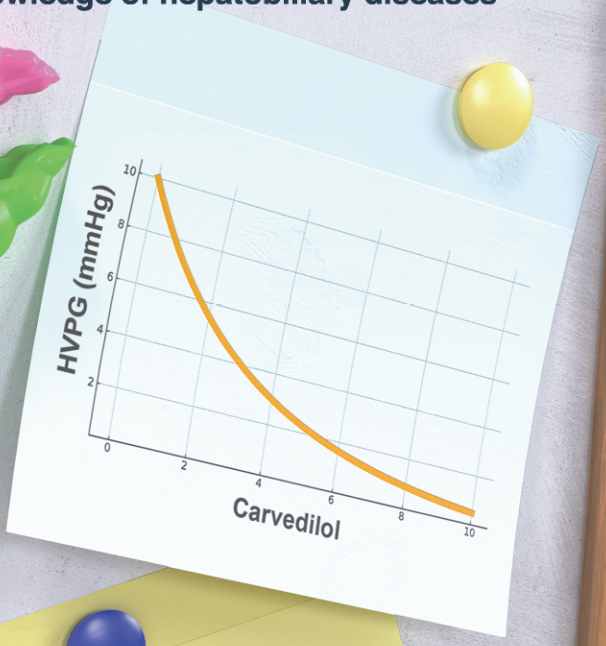

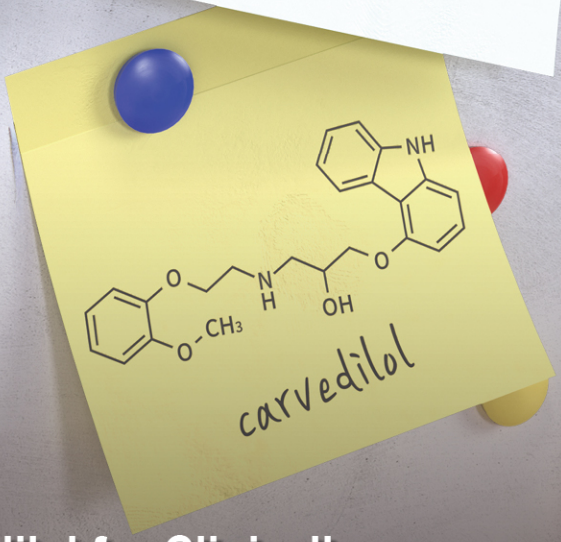

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

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Review

Long-term outcomes and risk modifiers of metabolic dysfunction-associated steatotic liver disease between lean and non-lean populations

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One-third of adults across the globe exhibit metabolic dysfunction-associated steatotic liver disease (MASLD)—formerly known as nonalcoholic fatty liver disease (NAFLD). To date, MASLD is the fastest-growing etiology of chronic liver disease and hepatocellular carcinoma (HCC). Besides the population with obesity, MASLD can also be found in lean populations, accounting for 13% of the global population, especially Asians. Notably, individuals with lean MASLD face equal or higher overall mortality rates compared to their non-lean counterparts. Risk modifiers encompass advanced age, hepatic fibrosis, and type 2 diabetes mellitus (T2DM). Moreover, the population with lean MASLD is associated with an increased risk of HCC, while their non-lean counterparts are more prone to cardiovascular outcomes and T2DM. Existing evidence indicates a similar risk of liver-related events and extrahepatic cancer between the two groups. However, MASLD-related genetic variants, such as *PNPLA3* and *TM6SF2*, did not significantly affect mortality between the two populations. Still, underreporting alcohol consumption and regional representation limits the study's comprehensiveness. Longitudinal studies and mechanistic explorations are needed to understand differences in lean versus non-lean MASLD populations. This review highlights the need for awareness and tailored interventions in managing MASLD, considering lean individuals' unique risks. **(Clin Mol Hepatol 2025;31:74-89)**

Keywords: NAFLD; Nonobese; SLD; Liver disease; Mortality; MASLD

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD)—formerly known as nonalcoholic fatty liver disease (NAFLD)—affects approximately one-third of adults worldwide and is considered the fastest-growing etiology of chronic liver disease and hepatocellular carcinoma (HCC) globally.[1-5] MASLD elevates the risk of various conditions, not only HCC but also cardiovascular disease (CVD) and extrahepatic cancers.[6-9] Despite being one of the most prevalent chronic liver diseases, MASLD remains underrecognized by the general public, policymakers, and the global health community.[10-12] Although MASLD is strongly associated with components of metabolic syndrome, especially obesity,[13] MASLD also manifests in individuals who are not obese as defined by body mass index (BMI).[6,14,15] Importantly, not all obese individuals develop MASLD; MASLD also can be found in lean populations.[15] In this review, we attempt to address this distinctive aspect of MASLD, exploring its epidemiology, potential underlying mechanisms, and disparities in long-term outcomes between lean and non-lean individuals with MASLD. Although emerging studies increasingly use the definition of MASLD over NAFLD, most currently available literature regarding lean MASLD still use the diagnostic criteria for NAFLD. Since studies were conducted before the nomenclature change from NAFLD to MASLD, there is considerable overlap in the data pertaining to both entities.[16-18] Several studies from Sweden, Hong Kong, and the United States have identified a similarity between NAFLD and MASLD, as approximately 95–99% of patients with NAFLD present with cardiometabolic risk factors, thereby fulfilling the criteria for MASLD.[16,17,19,20] Therefore, we proceed with our review article by incorporating the term MASLD.

Definition of MASLD in lean population

Individuals are typically classified as lean if their BMI falls below 25 kg/m^2 in Western populations and below 23 kg/m^2 in Asians.[21,22] Although BMI serves as a convenient tool for the classification of obesity, it has limitations as it does not account for fat distribution and metabolic status; lean individuals with high visceral adiposity and metabolic dysfunction can exist.[23] Alternative methods such as waist circumference, waist/hip ratio, and sagittal abdominal diameter have been explored in research to assess body fat distribution.[24] Therefore, a more comprehensive obesity index rather than BMI alone could be needed to determine the actual "lean" MASLD.[25,26]

EPIDEMIOLOGY

Previous systematic review and meta-analysis comprising nearly 540,000 individuals in 2023 revealed that MASLD in lean individuals accounts for 13.1% of the global population, while a slightly higher percentage of 15% was observed in the Asian population.[27] The higher lean MASLD in Asians could be due to higher visceral adiposity under the same BMI as other ethnicities.[23] Conversely, another meta-analysis involving 101,028 individuals found that the prevalence of MASLD was 70.0% in the overweight population and 75.3% in the obese population.[28] The sex differences between males and females vary significantly from study to study, with lean MASLD being higher in males in some studies,[29-31] higher in females in others,[32,33] or showing no differences.[34,35] A previous prospective observational study revealed that almost one-third of individuals diagnosed with MASLD tested positive for ethyl glucuronide, a marker indicative of alcohol consumption.[36] Recently, MetALD was defined, denoting that both metabolic factors and alcohol consumption play a role among individuals with MetALD.[37] Before the new nomenclature, individuals with MetALD would have been combined into either MASLD or alcohol-related liver disease, depriving them of due attention to the other significant driver in their advancing liver disease.[37] Until now, the epidemiology of MetALD in lean individuals remains unclear. Future studies are required.

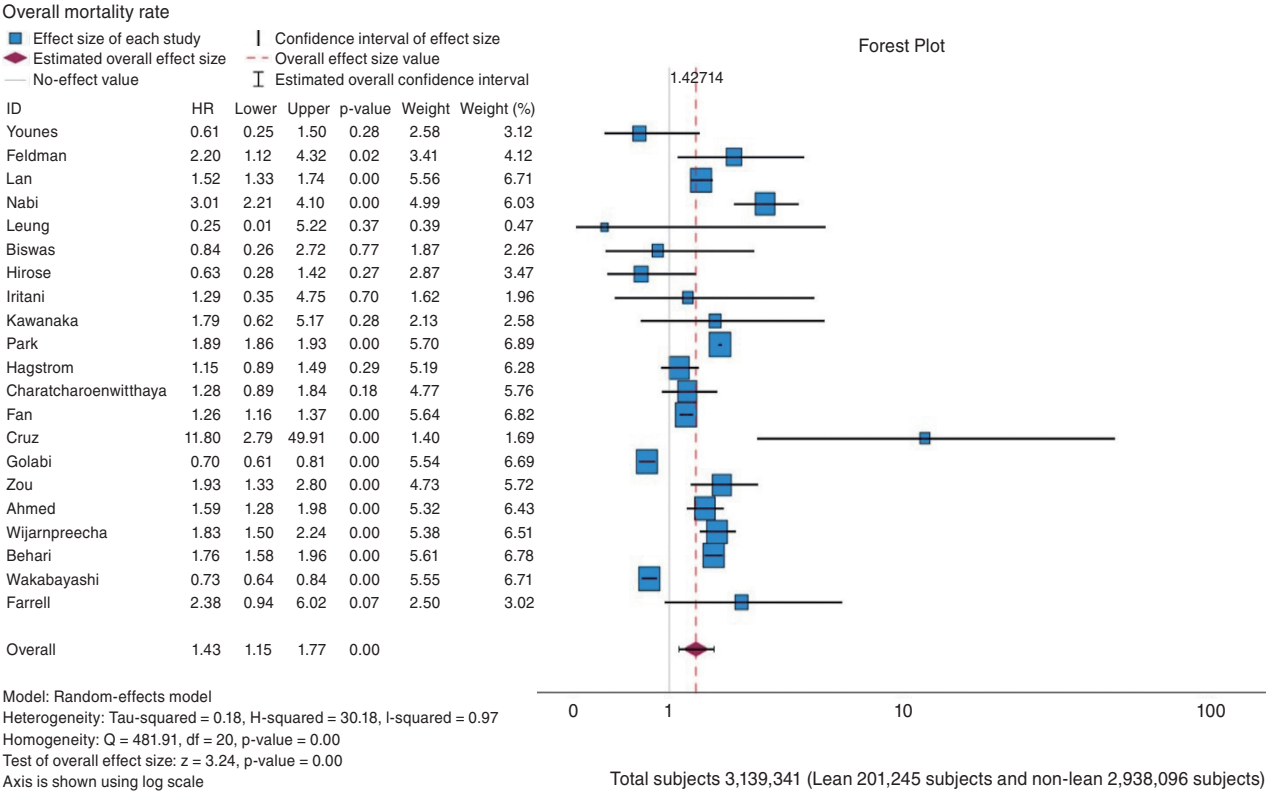
Abbreviations:

BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; FLI, fatty liver index; HCC, hepatocellular carcinoma; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; SNPs, single nucleotide polymorphisms; T2DM, type 2 diabetes mellitus

LONG-TERM OUTCOMES IN LEAN MASLD

Overall and cause-specific mortality of lean MASLD compared to non-lean MASLD

Whether individuals with lean MASLD experience higher mortality rates than those with non-lean MASLD has remained controversial for decades. Accumulated evidence indicates that individuals with lean MASLD exhibit equal or higher overall mortality rates than their non-lean counterparts. The mortality rates of the population with lean MASLD compared to the population with non-lean MASLD are summarized in Supplementary Table 1. Regarding MASLD diagnostic methods, studies that employed histology-based diagnosis indicated no difference in overall mortality between the two populations.[33,38-46] In contrast, studies using non-invasive test-based[30,47-53] or imaging-based[54-56] diagnosis showed higher overall mortality in the lean MASLD population compared to their non-lean counterparts. In other words, half of the longitudinal studies have noted that individuals with lean MASLD had higher overall mortality rates than those with non-lean MASLD.[30,45,46,48,50,52-56] With the most extended median follow-up of 22.4 years, Golabi et al.[55] highlight a higher risk of mortality in lean individuals compared to non-lean individuals in the United States. Meanwhile, Nabi et al.[48] prospectively observed this trend with 3.6 years of median follow-up in the French population. Of note, both studies have the advantage of inclusively enrolling various ethnic populations, compared to other indigenous-based studies, thus better representing a long-term clinical course of MASLD in the general population.[48,55] Furthermore, in recent years, besides the imaging-based approach and the gold-standard liver biopsy, the implementation of well-validated score-based tools for MASLD diagnosis, such as fatty liver index (FLI),[30,47-50,52] liver accumulation product,[51] and liver fat score,[57,58] has enabled clinicians and researchers worldwide to carry out retrospective studies utilizing their own or other countries' national databases. This includes the largest sample size of 2.24 million lean and non-lean individuals with MASLD in South Korea,[50] followed by 150,296 patients with MASLD in the United Kingdom. Notably, most



ID	HR	Lower	Upper	p-value	Weight	Weight (%)
Younes	0.61	0.25	1.50	0.28	2.58	3.12
Feldman	2.20	1.12	4.32	0.02	3.41	4.12
Lan	1.52	1.33	1.74	0.00	5.56	6.71
Nabi	3.01	2.21	4.10	0.00	4.99	6.03
Leung	0.25	0.01	5.22	0.37	0.39	0.47
Biswas	0.84	0.26	2.72	0.77	1.87	2.26
Hirose	0.63	0.28	1.42	0.27	2.87	3.47
Iritani	1.29	0.35	4.75	0.70	1.62	1.96
Kawanaka	1.79	0.62	5.17	0.28	2.13	2.58
Park	1.89	1.86	1.93	0.00	5.70	6.89
Hagstrom	1.15	0.89	1.49	0.29	5.19	6.28
Charatcharoenwitthaya	1.28	0.89	1.84	0.18	4.77	5.76
Fan	1.26	1.16	1.37	0.00	5.64	6.82
Cruz	11.80	2.79	49.91	0.00	1.40	1.69
Golabi	0.70	0.61	0.81	0.00	5.54	6.69
Zou	1.93	1.33	2.80	0.00	4.73	5.72
Ahmed	1.59	1.28	1.98	0.00	5.32	6.43
Wijarnpreecha	1.83	1.50	2.24	0.00	5.38	6.51
Behari	1.76	1.58	1.96	0.00	5.61	6.78
Wakabayashi	0.73	0.64	0.84	0.00	5.55	6.71
Farrell	2.38	0.94	6.02	0.07	2.50	3.02
Overall	1.43	1.15	1.77	0.00		

Figure 1. Forest plots of the overall mortality rate in lean MASLD compared to non-lean MASLD. MASLD, metabolic dysfunction-associated steatotic liver disease.

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studies using scored-based diagnosis for MASLD collectively contribute to statistical evidence favoring increased mortality rates in lean individuals.[30,47-50,52]

However, nearly half of the studies have shown that the mortality rates of the two groups were not significantly different.[33,38-44,47,51] One study by Wakabayashi et al.[49] opposes these trends. Dissimilar to other studies that used FLI for participant recruitment (showing increased mortality rates in lean individuals)[47-50,52] or were conducted within the same ethnicity (observing equal mortality rates between lean and non-lean),[33,42,43] this retrospective study had a relatively short median follow-up duration of 4.2 years.[49] It is reasonable to consider whether the median follow-up duration determines the disparity in mortality risk between individuals with lean and non-lean MASLD. Notably, the median follow-up years of the included studies with increased mortality rates in lean individuals is 8.9 years (interquartile range [IQR] 4.8–13.7),[45,46,48,50,52-56] while for other studies with equal mortality rates between the two populations, it is 6.7 years (IQR 4.5–11.3).[33,38-44,47,51] Together, this pattern corroborates the postulation by Eslam et al.[59] that lean individuals are less likely to be afflicted by adverse outcomes during the early clinical course. However, with long-term follow-up, lean individuals progressively exhibit an increase in complications and overall mortality relative to their non-lean counterparts.[59] Therefore, to effectively prevent the long-term outcomes of MASLD in lean individuals, particularly mortality, comprehensive follow-ups with treatments are required from the early years after diagnosis.

When we combined all literature to perform an updated meta-analysis of overall mortality between individuals with lean MASLD and non-lean MASLD, the results favored higher mortality rates among individuals with lean MASLD, with a pooled hazard ratio (HR) of 1.43 (95% confidence interval [CI] 1.15–1.77, Fig. 1).[30,33,38-56] The detailed methodology and article selection process are shown in Supplementary Material 1 and Supplementary Figure 1. Keywords used for meta-analysis are listed in Supplementary Material 2.

Some of the studies above have further investigated cause-specific mortality, subdividing them into 1) liver-related mortality,[39,41,44,46,49,54] 2) CVD-related mortality,[30,39,44,46,49,55] and 3) cancer-related mortality[30,39,46,55] (Supplementary Table 1). So far, there have been only two reports, by Wijarnpreecha et al.[46] and Wakabayashi et al.[49], that comprehensively note all three major causes of mortality in individuals with MASLD. Meanwhile, the others focused on the specific causes, especially liver-related and cancer-related mortalities. Most studies point out that the lean population tends to have a higher risk of both liver-related[39,44,49,54] and cancer-related mortalities[30,39,55] compared with its non-lean counterpart. In terms of CVD-related mortality, the existing evidence is inconclusive as to whether the lean or non-lean population is more inclined to afflict CVD-related mortality.[30,39,44,46,49,55] It is still uncertain which major cause contributes to the disparities in mortality rates between individuals with lean and non-lean MASLD.

Line Summary: Disparities in overall mortality were noted, with non-lean MASLD populations showing a survival advantage over their lean counterparts after long-term follow-ups.

Risk modifiers for mortality between lean MASLD and non-lean MASLD

Given that the pathogenesis of MASLD in both lean and non-lean individuals is intertwined with genetic, cardiovascular, and sociodemographic risk factors, unraveling the disparities in disease progression and long-term outcomes between the two groups is highly complicated.[6] As previous systematic reviews with meta-analysis initially pointed out, the prevalence of MASH and hepatic fibrosis was lower in lean MASLD compared with non-lean MASLD.[1] Although individuals with lean MASLD and non-lean MASLD shared altered metabolic and cardiovascular profiles,[60,61] waist circumference, BMI, and HOMA index were risk factors for disease progression, particularly in individuals with lean MASLD.[2] It is essential to investigate how these differences affect long-term outcomes in both groups. To date, available evidence shows that an increase in age,[30,33,38,41,42,44] advanced hepatic fibrosis,[30,38,42-44,48] and type 2 diabetes mellitus (T2DM)[30,38,42,50] are the most explored and shared risk modifiers associated with higher overall mortality rates in both lean and non-lean individuals with MASLD. Moreover, the effect of aging on increasing risk of overall mortality from MASLD was collectively observed in studies employing histology-based diagnosis.[33,41,42,44] Aside from these risk modifiers, other cardiovascular risks, including hypertension,[44,54] increased waist circumference,[55] and reduced muscle strength,[51] were also

related to higher overall mortality rates, particularly in the population with lean MASLD. In contrast, individuals with non-lean MASLD who exhibited metabolic abnormalities (dyslipidemia, dysglycemia, or both) had higher mortality compared to those without metabolic abnormalities; however, this trend was not observed in individuals with lean MASLD.[52]

Next, the role of sociodemographic factors, such as biological sex, race and ethnicity, education level, and history of HCC, in modifying overall mortality rates in the population with lean MASLD is still debatable.[30,38,41-43] Among these, a history of HCC may be an essential risk modifier for predicting overall survival likelihood in the lean population.[43] HCC is one of the leading causes of death in MASLD.[2,5,9] Unlike other HCC etiologies, apart from hepatitis B virus, MASLD can progress to HCC without cirrhosis and is one of the most prevalent causes of HCC in the absence of cirrhosis.[2,62] Moreover, the possibility of recurrent HCC in patients with MASLD was equal between those with and without cirrhosis.[63] However, the mechanistic pathway between a history of HCC and overall mortality in only lean patients but not the entire MASLD population remains unknown.

MASLD-related single nucleotide polymorphisms (SNPs) have been found in gene-encoding enzymes governing lipid metabolism.[6,64,65] The effect of gene variants and risk of steatohepatitis and fibrosis may be influenced by moderators such as age, sex, BMI, and diabetes.[66] Existing literature indicates that the genetic risk of well-identified MASLD-specific SNPs, including the missense variant *PNPLA3* (rs738409: GG),[38,43] the missense variant *TM6SF2* (rs58542926: CC),[43] and the splice-donor variant *HSD17B13* (rs6834314: AT/TT),[43] might not significantly affect overall mortality in individuals with lean MASLD compared with non-lean MASLD. Accumulated evidence suggests that the roles of *PNPLA3* and *TM6SF2* in the pathogenesis of MASLD might not differ between lean and non-lean status, while studies on *HSD17B13* in this context are scant.[6] New reports on *PNPLA3* and *TM6SF2* indicate that other genetic modifiers likely drive discrepancies in overall mortality between the two populations.[38,43] Recently identified variants associated with MASLD in lean individuals, such as *GCKR* (rs780093: CT/TT and rs780094: CT/TT), *TBC1D1* (rs2279028: AG/GG), *HFE* (rs1800562: GA/AA), *SLC17A3* (rs9348697: CT/TT), and *FTO* (rs1421085: CC, rs3751812: TT, rs8050136: AA, and rs9939609: AA), still lack information on how they relate to not only overall mortality but also other long-term outcomes.[6] These variants are worth exploring as they could lead to novel therapeutic developments.

In contrast to overall mortality, the understanding of risk factors associated with mortality attributed to CVD and cancer remains incomplete. Initially, Zou et al.[30] observed that increasing age, male sex, and advanced hepatic fibrosis were associated with mortality from both CVD and cancer. In addition to CVD-related and cancer-related mortality, risk factors associated with liver-related mortality, such as age and advanced hepatic fibrosis, seem reasonable but still need to be confirmed with more evidence.

Line Summary: Although many risk factors associated with mortality from MASLD, particularly increasing age, have been identified, performing a meta-analysis was not feasible due to the limited number of studies and high heterogeneity.

Cardiovascular outcomes and risk modifiers of cardiovascular events in lean MASLD

Individuals with MASLD experience mortality from CVD, liver complications, or cancer rather than healthy individuals.[67] Nevertheless, the disparity in acquiring those morbidities between the lean and non-lean populations could shed light on how to prevent disease progression and its long-term complications. Individuals with lean MASLD tend to experience cardiovascular outcomes equal to or less than those with non-lean MASLD. This trend was consistently observed in studies with histology-based[33,38-43,46,68] and imaging-based[31,54,56,69-76] diagnoses, while an inconclusive trend was noted in studies employing score-based diagnosis.[48,49,52,57,58] Supplementary Table 2 outlines the cardiovascular outcomes in individuals with lean MASLD compared to those with non-lean MASLD.

According to the included literature, cardiovascular outcomes encompass 1) the development of CVD risk factors—including T2DM, hypertension, dyslipidemia, chronic kidney disease, dysglycemia, and hyperuricemia, as well as 2) CVD events, including coronary artery disease, peripheral arterial disease, and stroke. In terms of cardiovascular outcomes, our meta-analysis showed that individuals with lean MASLD exhibit a lower risk of T2DM (pooled HR

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0.71, 95% CI 0.57–0.89, Fig. 2A) and overall cardiovascular outcomes, including development of CVD risk factors and CVD events (pooled HR 0.84, 95% CI 0.71–0.99, Fig. 2B) than those with non-lean MASLD. Supplementary Figure 2A–D illustrated forest plots of the risk of hypertension (Supplementary Fig. 2A), dyslipidemia (Supplementary Fig. 2B), chronic kidney disease (Supplementary Fig. 2C), and coronary artery disease (Supplementary Fig. 2D), respectively. Currently, there is no sufficient literature to investigate the association between lean MASLD and each CVD risk factor or CVD event.

Advanced age[54,68] and smoking[54] were considered risk modifiers for the development of CVD risk factors in the total population with MASLD. Moreover, Lan et al.[54] observed that individuals with lean MASLD who had hypertension, rather than those without, had an increased risk of developing other CVD risk factors. In addition, according to the hypothesis proposed by Eslam et al.[59], given that an obese phenotype of MASLD is considered a sign of poorer metabolic adaptation, while an obesity-resistant or lean pheno-

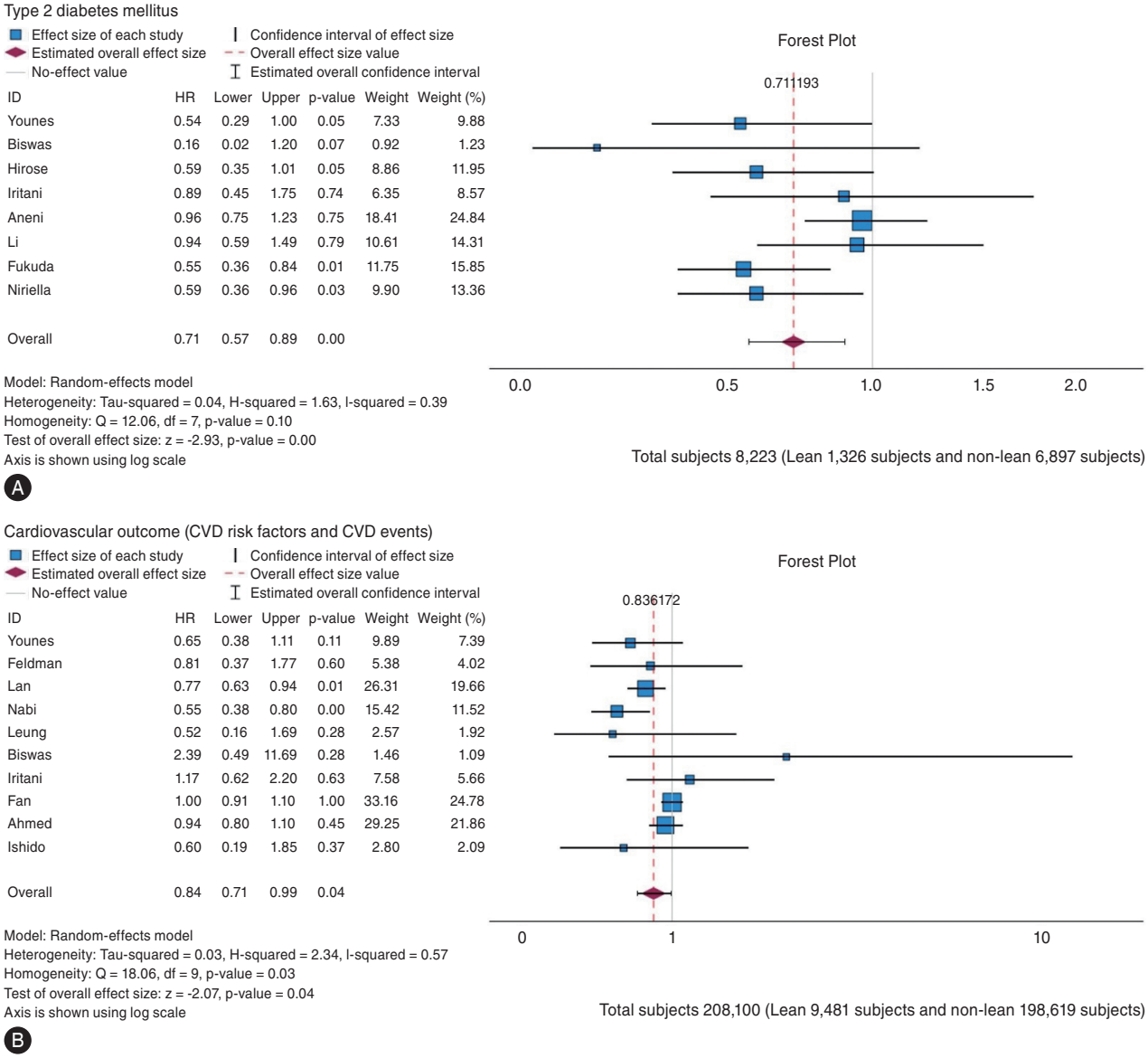

Figure 2. Forest plots of the cardiovascular outcome and liver-related outcomes in lean MASLD compared to non-lean MASLD. (A) Type 2 diabetes mellitus. (B) Cardiovascular outcome. (C) Hepatocellular carcinoma. (D) Liver-related events. MASLD, metabolic dysfunction-associated steatotic liver disease; CVD, cardiovascular disease.

type is a consequence of better metabolic adaptation, the detection of hepatic fibrosis in lean individuals with MASLD thus indicates severe metabolic maladaptation. It is not surprising that lean individuals with MASLD and hepatic fibrosis tend to develop CVD risk factors more frequently than those with non-lean MASLD, with or without hepatic fibrosis, during follow-ups.[57]

In terms of CVD events, Kawanaka et al.[33] and Wakabayashi et al.[49] reported that, in the Japanese population, lean MASLD patients with advanced age (over 60 years) had an increased risk for CVD events, similar to non-lean MASLD patients with advanced age. This finding suggests that advanced-aged patients with MASLD, regardless of lean or non-lean phenotypes, require close monitoring for CVD events. Wakabayashi et al.[49] also noted that other risk modifiers for CVD events included T2DM, hypertension, and dyslipidemia in lean MASLD. In parallel with the evidence confirming that smoking can induce CVD events in a dose-dependent manner,[77] lean individuals who are current smokers tend to have a higher risk of CVD events than those without.[49] Regarding the development of T2DM, advanced hepatic fibrosis[76] and increased abdominal obesity[71,75] were risk modifiers in the lean population. Notably, female sex was associated with an increased T2DM risk for both lean and non-lean individuals with MASLD.[73]

Line Summary: Overall, lean populations with MASLD tend to develop cardiovascular outcomes, particularly type 2 diabetes mellitus, less frequently than their non-lean counterparts. Similar to overall mortality, increasing age imposes a risk for cardiovascular outcomes in individuals with MASLD.

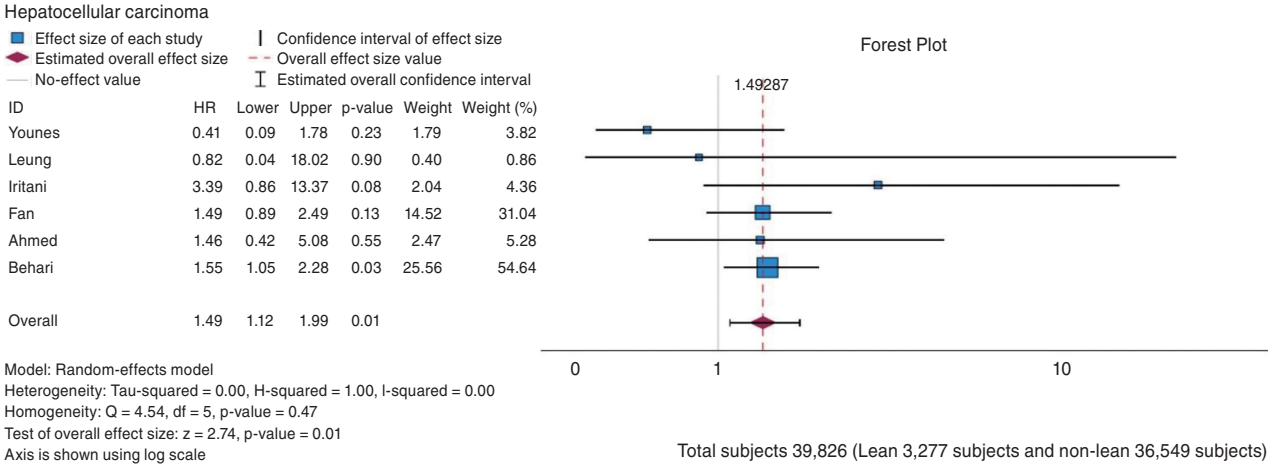

Figure 2. Continued.

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Liver-related outcomes and risk modifiers of liver-related outcomes in lean MASLD

Meanwhile, liver-related outcomes include HCC and liver-related events—such as cirrhosis, liver fibrosis, liver decompensation, and portal hypertension. Supplementary Table 3 summarizes the liver-related outcomes in patients with lean MASLD compared to those with non-lean MASLD. In terms of MASLD diagnosis methods, studies employing histology-based[33,38-41,43,44,46] and imaging-based[56,74,78] diagnoses showed no differences in liver-related outcomes, whereas studies using non-invasive test-based diagnosis[48,49,52,53,57] suggested a higher risk of liver complications. Regarding meta-analysis, as shown in Figure 2C, the population with lean MASLD exhibited an increased risk of HCC (pooled HR 1.49, 95% CI 1.12–1.99) compared to those with non-lean MASLD. Although a lower BMI characterizes individuals with lean MASLD, it does not necessarily indicate better metabolic health. For liver-related events, our meta-analysis showed that compared to individuals with non-lean MASLD, the risk of liver-related events (pooled HR 1.97, 95% CI 0.96–4.03) did not significantly differ in those with lean MASLD (Fig. 2D). When we divided by each liver-related event, liver fibrosis, liver decompensation, and cirrhosis did not significantly differ between individuals with lean MASLD and non-lean MASLD (Supplementary Fig. 3A–C). Consistent with the development of CVD risk factors, insufficient evidence exists to determine the association between lean MASLD and liver-related events. In the near future, more extensive cohort studies are required to investigate this issue further.

Advanced age was observed as a risk factor for liver-related events in individuals with MASLD, especially in the lean population.[33,41,42,49] This finding is especially concerning for the aging population in many parts of the world, including the rise in the prevalence of MASLD.[79,80] Additionally, prior research reported that apart from evidence of advanced hepatic fibrosis,[42] higher hepatic steatosis,[42] and a sign of hepatocyte injury like an increased ratio of aspartate aminotransferase by alanine aminotransferase,[49] CVD-risk factors, including T2DM[42,49] and dyslipidemia,[49] were also associated with an increased risk of liver-related events in both lean MASLD and non-lean MASLD. In addition, male sex and smoking were considered risk modifiers for the development of liver-related events.[49] Some studies also found that the development of hepatic fibrosis was associated with a higher fat-mass to fat-free mass ratio in individuals with MASLD, regardless of lean or non-lean status.[78] Regarding genetic risk, a recent report noted that *PNPLA3* (rs738409: GG), *TM6SF2* (rs58542926: CC), and *HSD17B13* (rs6834314: AT/TT) might not have a significant effect on advanced fibrosis in individuals with lean MASLD after adjustment by multivariate analysis.[43] Additionally, Vilar-Gomez et al.[66] found that another variant of *HSD17B13* (rs72613567: AT/AA) may act as a protective factor against steatohepatitis and fibrosis, particularly in non-lean MASLD female patients with at least class 2 obesity or T2DM. This variant warrants further study in the lean MASLD population in the future.

Line Summary: Lean populations with MASLD are inclined to develop HCC more frequently than non-lean populations with MASLD, while the risk for liver-related events is not significantly different between the two groups.

Extrahepatic cancer-related outcomes and risk modifiers of extrahepatic cancer-related outcomes in lean MASLD

Similar to other metabolic diseases,[81-84] there is sufficient evidence regarding the association between MASLD and increased risk of extrahepatic cancer.[85,86] This risk represents an approximately 1.2-fold increase in individuals with MASLD compared to those without it.[87,88] Moreover, extrahepatic cancers in MASLD are over 8-fold more frequent than HCC and not associated with liver fibrosis stage.[86] Liu et al.[89] note that the longer patients have MASLD, especially from a young age, the higher their risk of developing cancer later in life is. However, there is a lack of comprehensive analysis of cancer risk discrepancies and their modifiers between the lean and non-lean populations.

The extrahepatic cancer risks in individuals with lean MASLD compared to those with non-lean MASLD are summarized in Supplementary Table 4. The risk of any cancers—including hepatic and extrahepatic—is slightly increased in individuals with lean MASLD compared to their counterparts with a pooled HR of 1.2 (95% CI 1.1–1.3) (Fig. 3A). While the increased risk of developing HCC in individuals with lean MASLD has been highlighted earlier, the incidence of extrahepatic cancers appears to be comparable between individuals with lean and non-lean MASLD, re-

gardless of the diagnostic methods used, whether histology-[33,38-41,43,46] or non-invasive test-based.[48,50,52,53] Although a recent study pointed out that individuals with lean MASLD have higher incidence rates of extrahepatic cancer than those with non-lean MASLD,[50] our meta-analysis indicated that there was no significant difference in the risks of extrahepatic cancers (pooled HR 1.14, 95% CI 1.00–1.29, I^2=56%; *P*=0.05) between individuals with lean MASLD and those with non-lean MASLD (Fig. 3B). However, after performing sensitivity analysis by removing one study at a time, we found that lean MASLD had a statistically significant higher risk of extrahepatic cancer after removing the study by Fan et al.[52] with the pooled HR of 1.24 (1.21–1.26), I^2=0%, *P*-value<0.001. This is likely secondary to the heterogeneity of the study by Fan et al.[52] compared with all included studies. No statistical significance was seen after removing other studies from the pooled analysis. Several studies reported that individuals with lean MASLD, compared to their non-lean counterparts, tend to have a higher risk of obesity-related cancers.[46,53,54] However, due to differences in the definitions of obesity-related cancer across studies[46,53,54] and the lack of available HR,[53] a meta-analysis regarding this topic was not able to be performed at this time.

However, whether MASLD directly contributes to the development of extrahepatic cancer remains unknown. Regardless of BMI-defined obesity between lean and non-lean individuals, insulin resistance is often found in MASLD, contributing to metabolic dysfunction and playing a pivotal role in the pathogenesis of cancer later in life.[90,91]

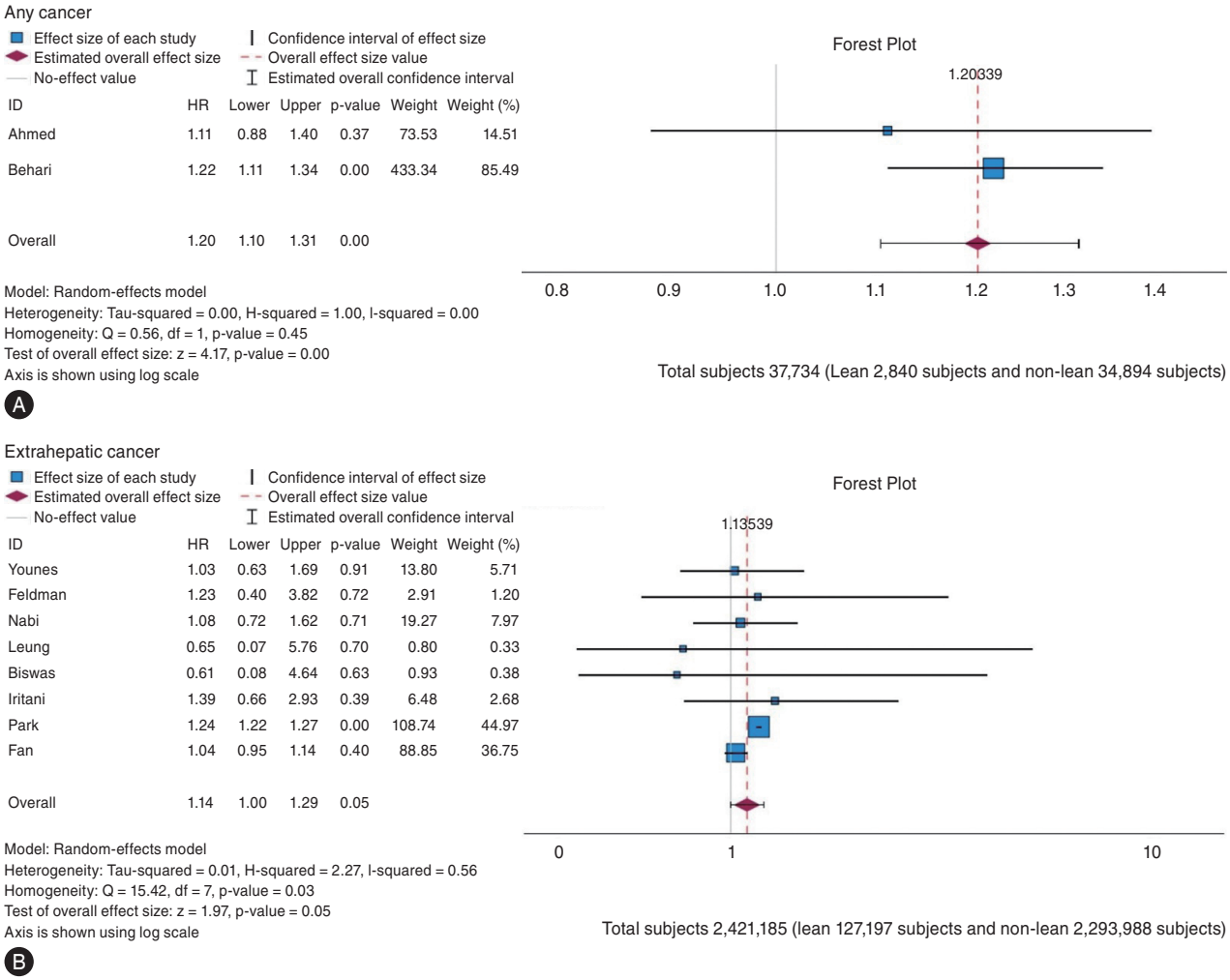

Figure 3. Forest plots of extrahepatic cancer-related outcomes in lean MASLD compared to non-lean MASLD. (A) Any cancer. (B) Extrahepatic cancer. MASLD, metabolic dysfunction-associated steatotic liver disease.

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Another question remains to be answered: whether extrahepatic cancer is equally caused by insulin resistance[92] in both lean and non-lean populations. Similar to a risk modifier of mortality, cardiovascular outcomes, and liver-related events, some reports observed that old age was a risk factor for developing extrahepatic cancers, obesity-related cancers, and digestive system cancers in the lean population with MASLD.[33,54] Additionally, hypertension was found to be associated with digestive system and obesity-related cancers.[54] However, little is known about the risk modifiers for extrahepatic cancer in MASLD in both lean and non-lean populations.

Line Summary: Individuals with MASLD, whether lean or non-lean, share a similar risk of extrahepatic cancer, which is associated with increasing age.

In addition, to assess whether combining overweight and obese patients as non-lean individuals or separating them affected the robustness of our meta-analysis, sensitivity analysis was performed. The corresponding forest plots of the outcomes of interest in individuals with lean MASLD compared to those with overweight MASLD, as well as individuals with lean MASLD compared to those with obesity MASLD, including 1) overall mortality rate, 2) cardiovascular outcomes, 3) HCC, liver decompensation, and cirrhosis, 4) extrahepatic cancer and any cancer risk, are illustrated in Supplementary Figures 4 and 5, respectively.

LIMITATIONS OF CURRENT STUDY AND FUTURE RESEARCH PERSPECTIVES

Although our review article highlights disparities in outcomes between populations with lean and non-lean MASLD, there were a few studies comparing clinical outcomes between populations with lean and non-lean MASLD. Multiple studies have highlighted a similarity between NAFLD and MASLD, with about 95–99% of individuals with NAFLD exhibiting cardiometabolic risk factors that meet the criteria for MASLD.[16,17,19,20] In addition, overall mortality rates do not show a significant difference between MASLD and NAFLD.[16] A recent review article reported that the natural histories of NAFLD and MASLD are identical, exhibiting no differences in liver-related outcomes, suggesting that they may be used interchangeably.[93] While NAFLD and MASLD share similar characteristics such as clinical profiles, non-invasive biomarker levels, and mortality outcomes,[16-18] no study has yet specifically compared these parameters and outcomes in populations between non-lean and non-lean MASLD populations because some lean NAFLD certainly may not be lean MASLD. This limitation could affect the interpretation of comparative findings when transitioning from the NAFLD classification to the new MASLD classification. Regarding MASLD diagnosis methods, our findings showed some inconsistent trends in disease outcomes among histology-, imaging-, and non-invasive test-based methods. Although liver biopsy has the highest accuracy in diagnosing MASLD, it is challenging to generalize limited populations with liver biopsy. The overall trends and meta-analysis results of disease outcomes were somewhat influenced by the heterogeneity of the various diagnostic methods, limiting our findings' generalizability. Despite these limitations, the accumulated evidence with systematic review and meta-analysis highlights that the population with lean MASLD experiences a higher risk of overall mortality, as well as both hepatic and extrahepatic cancer, compared to their non-lean counterparts. In contrast, the population with non-lean MASLD faces a higher risk of overall cardiovascular outcomes and T2DM than the population with lean MASLD. Furthermore, in terms of risk modifiers, an increasing age imposes a risk of morbidities and mortality in both lean and non-lean individuals with MASLD, indicating the need for awareness of complication monitoring in older adults with MASLD. However, as prior research has explored risk modifiers in overall MASLD patients or only in the lean population, determining which modifier preferentially influences each long-term outcome of MASLD in the lean population compared to the non-lean population requires further longitudinal studies with mechanistic exploration. Recently, some in vivo models of lean MASLD have been established, including, but not limited to, leucine-rich tetratricopeptide repeat-containing protein (*LRPPRC*)-knockout mice as well as dietary-induced lean-MASLD mice, such as those on choline-deficient, methionine-deficient, and high-fat-high-fructose diets.[94,95] These mimicking models can potentially elucidate the disparity of some modifiers between lean and non-lean MASLD in humans. In terms of the gut microbiota, the gut microbial profiles, dominated by *Proteobacteria*, of individuals with MASLD differ from those of a healthy population, indicating that gut dysbiosis is involved in the pathogenesis of

MASLD.[96,97] Furthermore, lean and non-lean populations with MASLD exhibit different dysbiotic profiles, suggesting that the characteristics of gut microbes are crucial in determining MASLD phenotype.[98,99] This was also confirmed by fecal transplantation from healthy individuals to patients with MASLD, as after the treatment, the lean individuals showed more attenuated steatotic livers than their non-lean counterparts.[99] However, there is limited evidence for whether differences in gut microbiota between lean and non-lean populations determine long-term outcomes in both groups. Exploring how gut dysbiosis in terms of both microbes *per se* and their metabolites differently drives MASLD in lean and non-lean populations could be pivotal to filling gaps in our understanding of MASLD phenotypes. Underreporting of alcohol consumption is a considerable issue, potentially resulting in the misclassification of patients with steatotic liver disease as MASLD when they should be classified as alcohol-related liver disease or MetALD.[100-105] Given that both diseases have different outcomes compared to MASLD, the CVD and cancer effects observed in this study could be more or less attributed to alcohol, as it is associated with various CVDs.[106-109] In addition, numerous factors beyond BMI, exemplified by body fat percentage, that could impact the differences were not thoroughly examined, particularly in the elderly, who often have a discordance between BMI and body fat.[110-112] Lastly, the small representation of certain regions, such as the Eastern Mediterranean and Africa, necessitates more evidence.

CONCLUSION

This review article reveals significant disparities between populations with lean and non-lean MASLD. Notably, lean individuals with MASLD face higher risks of overall mortality, HCC, and overall cancer-related outcomes compared to their non-lean counterparts. Individuals with non-lean MASLD, in contrast, are at greater risk for cardiovascular outcomes and T2DM. Additionally, increasing age consistently emerges as a significant risk modifier for morbidities and mortality in both populations. Future longitudinal studies and solid mechanistic explorations are essential to delineate how risk modifiers influence long-term outcomes in lean versus non-lean MASLD populations. This could lead to development of targeted therapeutic strategies and ultimately improve patient care for MASLD.

Authors' contributions

Conceptualization: Donghee Kim, Karn Wijarnpreecha, Pojsakorn Danpanichkul, Aijaz Ahmed. Data collection and literature review: Pojsakorn Danpanichkul, Kanokphong Suparan, Vitchapong Prasitsumrit, Karn Wijarnpreecha. Data analysis: Vitchapong Prasitsumrit. Writing, original draft: Pojsakorn Danpanichkul, Kanokphong Suparan, Vitchapong Prasitsumrit, Donghee Kim. Writing, review, and editing: Donghee Kim, Karn Wijarnpreecha, Aijaz Ahmed, Pojsakorn Danpanichkul. All authors have read and approved the final version of the manuscript for submission.

Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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