Hepatic, Extra-hepatic Outcomes and Causes of Mortality in NAFLD – An Umbrella Overview of Systematic Review of Meta-Analysis

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Background: **Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally. While the prevalence, impact, and causes of mortality have been described in various meta-analyses, a systematic all-encompassing umbrella review has yet to be conducted to consolidate the evidence on outcomes associated with NAFLD.** ***Methods:*** **Search was conducted on Medline and Embase for meta-analysis investigating associated complications and causes of mortality in NAFLD patients. Summary estimates were presented with original units, sample size, and I^2 for heterogeneity. The Assessment of Multiple Systematic Reviews 2 was employed for article selection.** ***Results:*** **25 meta-analyses were included in the present review. NAFLD increased the risks of systemic complications, including cardiovascular diseases, systemic malignancies, diabetes, and chronic kidney disease. Regarding hepatic outcomes, the incidence of hepatocellular carcinoma in NAFLD was 2.39 per 100 person years (CI: 1.40 to 4.08). Individuals with NAFLD were also found to have an increased likelihood of cholangiocarcinoma (OR: 1.88, CI: 1.25 to 2.83) and gallstone disease (OR: 1.55, CI: 1.31 to 1.82) compared to individuals without NAFLD. NAFLD was associated with a higher risk of fatal and non-fatal CVD events (HR: 1.45, CI: 1.31 to 1.61) compared to individuals without NAFLD. Coronary heart disease and subclinical and clinical coronary heart disease were also significantly elevated in NAFLD individuals compared to individuals without NAFLD. Additionally, NAFLD was associated with an increased risk of all-cause mortality (HR: 1.34, CI: 1.17 to 1.54) and cardiovascular (HR: 1.30, CI: 1.08 to 1.56) but not cancer–related mortality.** ***Conclusion:*** **The study summarizes high-level evidence from published meta-analyses to provide a much-needed update on the outcomes in patients with NAFLD. The significant systemic burden associated with NAFLD and impending fatty liver epidemic requires prompt action from multidisciplinary providers, policy providers, and stakeholders to reduce the burden of NAFLD.** **(J Clin Exp Hepatol 2023;13:656–665)**

NAFLD

Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease affecting 25–33% of the global population.[1,2] Accompanying a growing metabolic disease epidemic, the prevalence of NAFLD has been rising consistently; in addition, it is closely associated with the presence of obesity and

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Abbreviations: AMSTAR-2: Assessment of Multiple Systematic Reviews 2; BMI: Body mass index; CHD: Coronary heart disease; CI: Confidence interval; CKD: Chronic kidney disease; CVD: Cardiovascular disease; GI: Gastrointestinal; HCC: Hepatocellular carcinoma; HR: Hazard ratio; IR: Incidence rate; LT: Liver transplant; MD: Mean difference; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; OR: Odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RR: Risk ratio; VLDLs: Very-low-density lipoproteins; WMD: Weighted mean difference
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diabetes.[3,4] While there are multiple factors involved in the causation of NAFLD, the pathophysiology of NAFLD involves the inability of the liver to handle lipids and excrete very-low-density lipoproteins (VLDLs), causing hepatocellular injury and hepatic fibrosis as the disease progresses.[5–10] Furthermore, links between NAFLD and multiple hepatic and extrahepatic complications have been established.[11–15] The presence of NAFLD has been associated with an increased risk in cardiovascular disease (CVD), stroke, hepatocellular carcinoma (HCC), and chronic kidney disease (CKD) along with other systemic diseases. NAFLD is also currently the fastest growing cause of HCC with up to 40% of patients presenting without cirrhosis.[16,17] Similarly, NAFLD has become a major contributor of indications for liver transplantation and is associated with an increase in CVD-related events post-liver transplant (LT) compared to patients without the disease.[18,19]

However, despite the significant burden of NAFLD, the global awareness of NAFLD remains considerably low. A recent study conducted on the global preparedness of NAFLD found that policies and strategies for the prevention and management of NAFLD have been persistently lacking.[20–22] The significant burden and rising interest of NAFLD have, in turn, given rise to a myriad of meta-analyses summarizing the prevalence and associated end organ complications of NAFLD compared to non-NAFLD patients. Meta-analysis remains the highest order of clinical evidence providing pooled events based on the existing literature, but the certainty of evidence remains unclear, in part due to risk of bias, scheme design defects, publication bias, or inconsistencies in overlapping meta-analyses.[23] This presents a major challenge in the literature interpretation, and to date, there has yet to be a systematic effort to summarize and critically appraise the evidence. Umbrella reviews not only provide a means for a prompt review of broad and high-quality evidence regarding the topic of discussion but also allows for a better recognition of the uncertainties, biases, and knowledge gaps.[24] Given the notable burden of NAFLD, an umbrella review could aid in improving the interpretability of established evidence in a reliable manner, thereby potentially guiding developments in clinical management and improving global awareness of NAFLD. Thus, we sought to conduct an updated umbrella systematic review of existing meta-analyses on the associated complications and causes of mortality of NAFLD.

METHODS

Search Strategy

This umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[25,26] A comprehensive search was conducted on Medline and Embase electronic databases with assistance from a medical librarian for meta-analyses on the prevalence and outcomes of NAFLD. The search was conducted from inception on March 1, 2022 and used search terms including "NAFLD," "meta-analysis," and "systematic review." The full search strategy can be found in supplementary material 1. All references were imported into Endnote X9 for the removal of duplicates. To ensure a comprehensive search, the bibliographies of the included articles were also screened.

Eligibility Criteria and Data Extraction

Four authors (JX, CHN, KEC, and CF) independently conducted the screening of abstracts and evaluation of full text for inclusion. Discrepancies were then resolved through consensus and consultation with a senior author (MDM). The eligibility criteria for this umbrella review are (i) meta-analyses of articles with observational study designs (e.g., cohort study, case–control study, or cross-sectional study), (ii) articles that investigated the associated complications of NAFLD, and/or (iii) investigated the causes of mortality in NAFLD patients with relation to non-NAFLD individuals. Review articles without quantitative analysis and studies, including animal trials or *in vitro* investigations, were excluded. In this umbrella review, only English articles were included. The focus of this review was primarily on the adult population, and pediatric studies were excluded. Four authors (JX, CHN, KEC, and CF) independently extracted data from each included meta-analysis which includes author, publication year, journal name, number of studies included, study population, and outcome(s) of interest investigated.

The unit of measurement along with the effect sizes, including risk ratio (RR), odds ratio (OR), hazard ratio (HR), mean difference (MD), weighted mean difference (WMD), incidence rate (IR), 95% confidence intervals (95% CI), and heterogeneity measures (I2 values) were extracted. There was no conversion of units between effect sizes to maintain the nature of the unit of analysis. When there are overlapping meta-analyses published on similar outcomes of interest, the higher quality study will be preferred as an inclusion over later studies. The quality of the study can be judged by the unit of analysis or a higher score in the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2). HR is preferred to account for longitudinal risk[27], whereas OR offers ease of interpretation, however, can exaggerate the size of effect compared to RR and does not account for longitudinal risk.[28] Random effects model was also preferred over the fixed effect model since it better accounts for between-study heterogeneity that often prevalent in observational studies.[29] Discrepancies between the data extracted were resolved by a fifth investigator (MDM).

Results Synthesis and Quality Assessment

For each eligible meta-analysis, the summary effect size and the corresponding 95% CI were extracted. Re-analysis,

including but not limited to pooling of the effect size, was not performed to prevent the overlapping of primary articles and maintain the original nature of the analysis. Similarly, the unit of analysis within the articles did not undergo the conversion of events, and the summary effect sizes were presented as RR, OR, HR, MD, WMD, IR, and corresponding 95% CI. The corresponding effect sizes were extracted and were summarized in a forest plot. Statistical heterogeneity was assessed via I2 values, where an I2 value of ≥40% was considered heterogeneous.[30,31] The methodological quality of the included meta-analyses was evaluated using the AMSTAR-2 checklist, a popular instrument for assessing systematic reviews of randomized and non-randomized studies.[32] The AMSTAR-2 checklist consists of 16 items which assess the quality of meta-analyses, including seven critical domains, which are registration of protocol before commencement of study, adequacy of the literature search, sufficient explanation provided for exclusion of studies, risk of bias of individual studies, suitability of statistical methodology used, consideration for risk of bias in interpretation of results, and evaluation of publication bias.[32] AMSTAR-2 then rates the quality of meta-analyses as high, moderate, low, and critically low based on the presence of non-critical or critical weakness.[32]

RESULTS

Summary of Included Articles

From the initial search strategy, 2734 references were retrieved with 2483 remaining after duplicate removal. After the screening of title and abstract, 91 full texts were

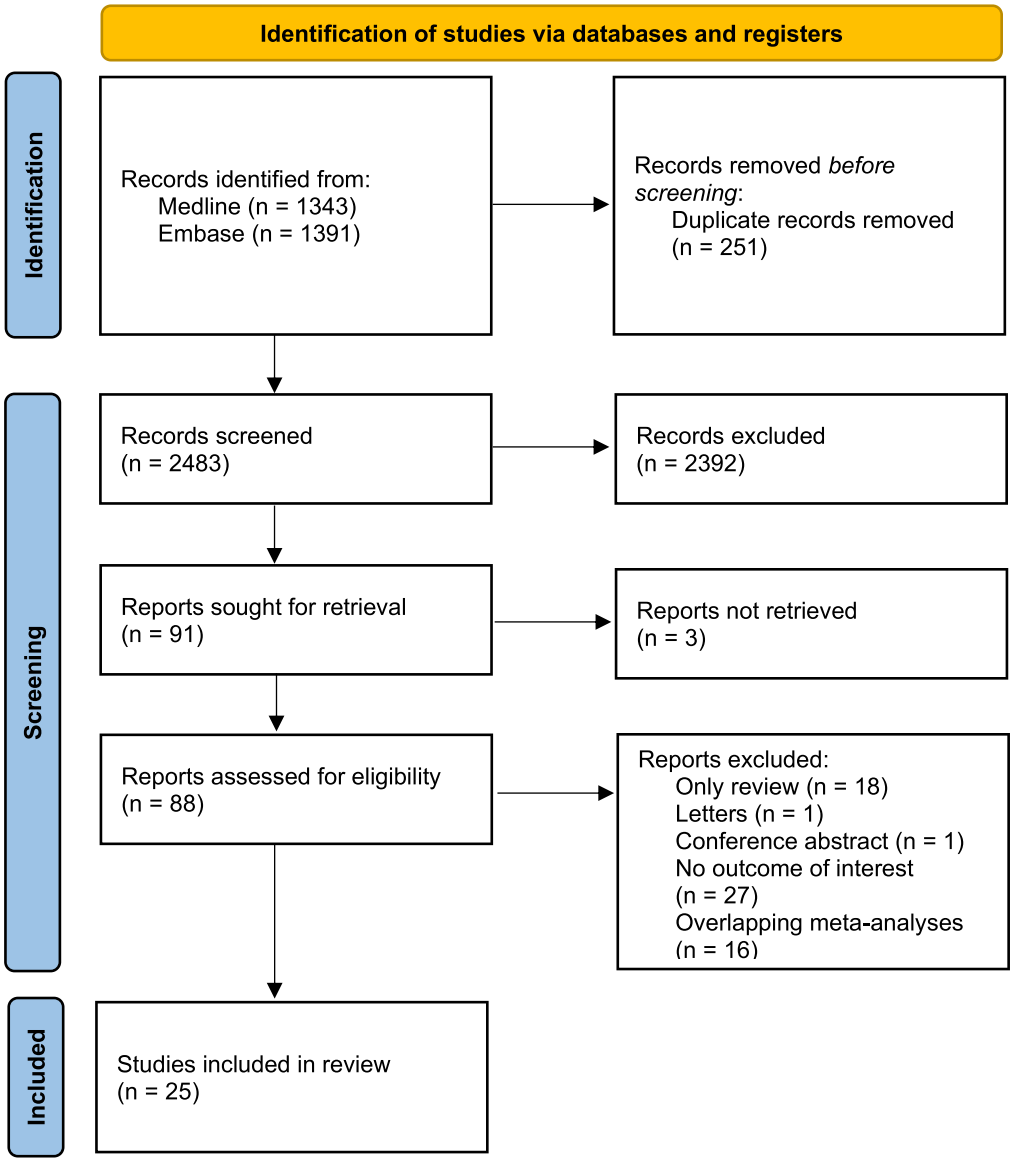

Figure 1 PRISMA flow diagram.

reviewed (Figure 1). A total of 25 meta-analyses were then included in this umbrella review (supplementary material 2). There were 25 meta-analyses reported that data on the complications of NAFLD with 3 studies utilizing MD,[14,33,34] 13 studies utilizing OR,[15,35–46] 2 studies utilizing WMD,[45,47] 6 studies using HR,[48–53] and 1 study each utilizing RR[54] and IR[55] as units of measurement. A summary of the included studies can be found in supplementary material 2. The majority of the included meta-analyses were found to have low or moderate risk of bias (supplementary material 3), and the original risk of bias assessment presented in the included articles can be found in supplementary material 4.

Complications of NAFLD

Hepatic Complications

There were three included studies reporting hepatic complications associated with NAFLD. The IR of hepatocellular carcinoma in NAFLD was 2.39 per 100 person years (CI: 1.40 to 4.08, n = 470,404, I^2 = 93.0%) as reported in a study by Orci *et al.*[55] According to a study done by Carrao *et al.*, individuals with NAFLD are also associated with increased cholangiocarcinoma (n = 68,694, OR: 1.88, CI: 1.25 to 2.83, I^2 = 79.7%) compared to individuals without NAFLD.[36] NAFLD was also associated with an increase in gallstone disease (n = 79,629, OR: 1.55, CI: 1.31 to 1.82, I^2 = 64.0%) in comparison with patients without NAFLD according to a study done by Jaruvongvanich *et al.* (Figure 2).[35]

Cardiovascular Disease (CVD)

Nine of the included articles assessed cardiovascular-related complications in NAFLD. In an analysis of 5,790,329 individuals by Mantovani *et al.*, NAFLD was associated with a higher risk of fatal and non-fatal CVD events (HR: 1.45, CI: 1.31 to 1.61, I^2 = 86.2%) compared to non-NAFLD individuals.[48] There was a 40% increase in non-fatal CVD events in NAFLD compared to non-NAFLD individuals (n = 5,240,595, HR: 1.40, CI: 1.20 to 1.64, I^2 = 87.7%).[48] Coronary heart disease (CHD) and subclinical and clinical CHD were significantly elevated in NAFLD individuals (Figure 3) compared to individuals without NAFLD as reported by Toh *et al.*[38] In a study by Mantovani *et al.*, NAFLD was associated with an increased risk of new onset heart failure compared to individuals without NALFD (n = 11,242,231, OR: 1.50, CI: 1.34 to 1.67, I^2 = 94.8%).[46] An analysis of 23,793 individuals found that there was a significant increase in carotid atherosclerosis (OR: 3.20, CI: 2.37 to 4.32, I^2 = 87.8%) and stroke events (n = 83,043, OR: 1.88, CI: 1.23 to 2.88, I^2 = 45.3%), particularly for ischemic stroke (n = 82,146, OR: 2.05, CI: 1.05 to 1.98, I^2 = 57.3%) in individuals with NAFLD compared to those without in a study done by Tang *et al.*[15] In comparison with individuals without NAFLD, individuals with NAFLD were also associated with an increase in atrial fibrillation, prolong QT Interval, premature ventricular contractions, and heart blocks as reported by Cai *et al.*[54] and Gong *et al.*[37] (Figure 3). In a study by Ciardullo *et al.*, elevated risk for hypertension was similarly observed in NAFLD individuals (n = 390,348, HR: 1.66, CI: 1.38 to 2.01, I^2 = 90.9%) than in individuals without NAFLD.[49]

Systemic Malignancies

NAFLD was associated with the highest risk of thyroid cancers (n = 64,732, HR: 2.63, CI: 1.27 to 5.45, I^2 = 0.0%) compared to individuals without NAFLD among all the systemic malignancy related to NAFLD. Significantly, GI-related cancers, including esophageal, pancreatic, stomach, and colorectal, were significantly elevated in individuals with NAFLD compared to individuals without NAFLD (Figure 5). Compared to individuals without NAFLD, NAFLD was also associated with an increase in colorectal adenomas (n = 14,244, HR: 1.40, CI: 1.20 to 1.63, I^2 = 30.0%). Other cancers including but not limited to lung, urinary system, breast, gynecological, and prostate were also significantly elevated in individuals with NAFLD than in individuals without NAFLD (Figure 4). Result estimates of systemic malignancies associated with NAFLD were reported in one study by Mantovani *et al.*[50]

Other Complications and Associated Measurements

Eight studies reported other complications while three studies presented other clinical and biometric measurements. The presence of NAFLD was associated with an increased risk of diabetes than in individuals without NAFLD in an analysis of 501022 patients (HR: 2.19, CI: 1.93 to 2.48, I^2 = 91.2%) by Mantovani *et al.*[51] Similarly, NAFLD significantly increases the risk of chronic kidney disease (n = 1,215,872, HR: 1.43, CI: 1.33 to 1.54, I^2 = 60.7%) compared to individuals without NAFLD as reported by Mantovani *et al.*[53] NAFLD was also related with

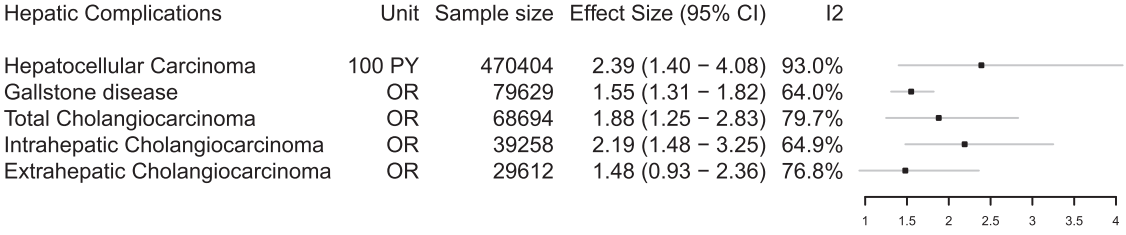

Figure 2 Forest plot of hepatic complications. Legend: 100PY, 100 person years; OR, odds ratio; 95% CI, 95% confidence interval.

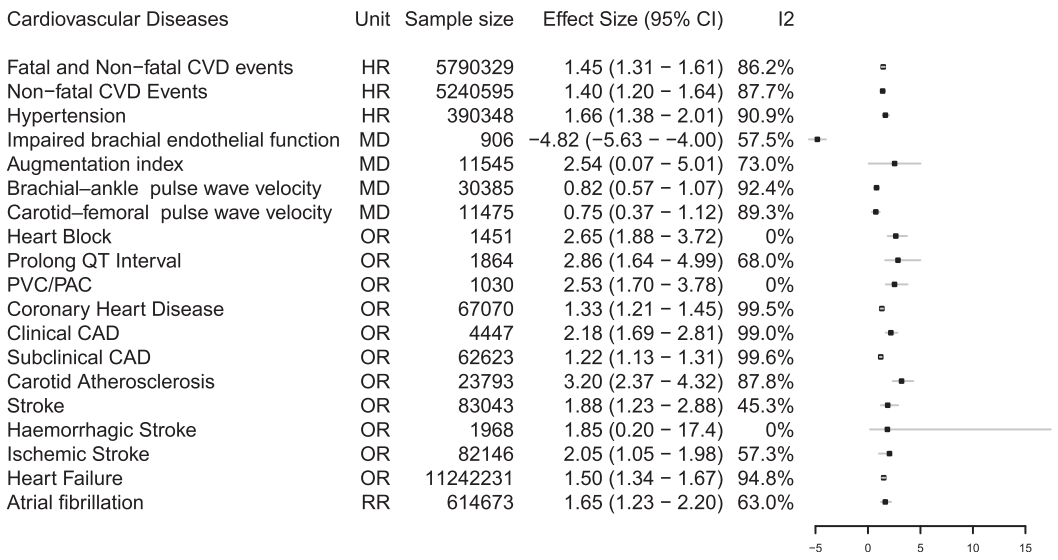

Figure 3 Forest plot of cardiovascular diseases. Legend: CVD, cardiovascular; PVC/PAC, premature ventricular contractions/premature atrial contractions; CAD, coronary artery disease; HR, hazard ratio; MD, mean difference; OR, odds ratio; RR, risk ratio; 95% CI, 95% confidence interval.

an increased risk of frailty associated with osteoporosis (n = 10,492, OR: 1.43, CI: 1.00 to 2.06, I^2 = 55.1%) compared to non-NAFLD in a study by Mantovani *et al.*[45] Other associated risk of NAFLD and clinical measurements are summarized in Figure 5.

Cause of Mortality

Causes of mortality in NAFLD patients were reported in two included studies. The presence of NAFLD was associated with an increased risk of all-cause mortality (HR: 1.34, CI: 1.17 to 1.54, I^2 = 80.0%) but not in cancer–related mortality (n = 465,112, HR 1.05, CI: 0.89 to 1.25, I^2 = 35.3%) in comparison with the absence of NAFLD in a study by Liu *et al.*[52] As reported by Mantovani *et al.*, NAFLD was also associated with an increased risk of CVD-related mortality (n = 414,333, HR, 1.30, CI: 1.08 to 1.56, I^2 = 86.1%, Figure 6).[48]

DISCUSSION

Given the rapidly rising rates of NAFLD, the current umbrella review provides a comprehensive update of the literature on the associated outcomes and causes of mortality in NAFLD based on the highest quality evidence from existing meta-analyses. The prevalence of NAFLD will only continue to increase in parallel with the metabolic disease epidemic given the lack of effective pharmacological treatment for the disease.[3,4] In turn, consolidating the evidence with an umbrella review provides informative results on the whole hosts of systemic complications associated with NAFLD which raises public awareness of the significant burden of the disease. This serves to underscore the urgent need for effective measures and multidisciplinary care models to address the incoming NAFLD crisis.

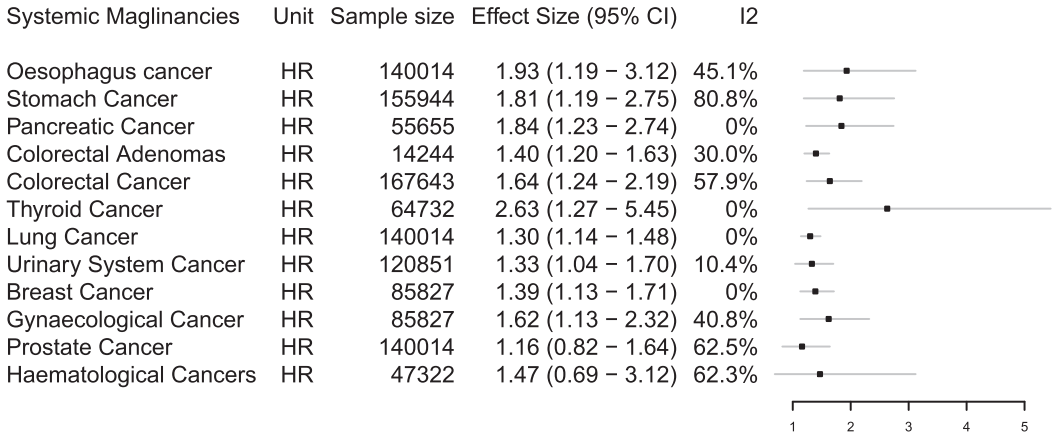

Figure 4 Forest plot of systemic malignancies. Legend: HR, hazard ratio; 95% CI, 95% confidence interval.

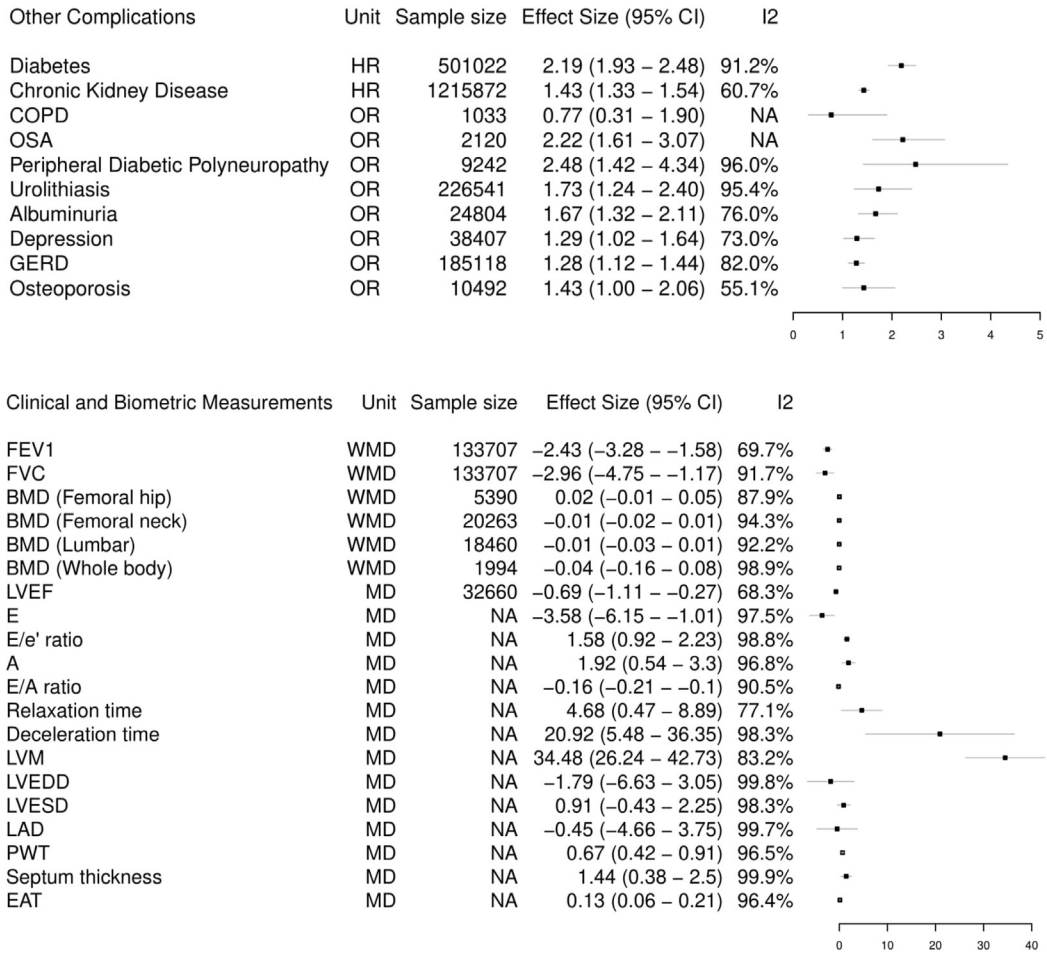

Figure 5 Forest plot of other complications associated with NAFLD and forest plot of other clinical and biometric measurements. Legend: COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; BMD, bone mineral density; LVEF, left ventricle ejection fraction; E, peak E wave; A, peak A wave; LVM, left ventricular mass; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LAD, left atrial diameter; PWT, posterior wall; EAT, epicardial adipose thickness; HR, hazard ratio; 95% CI, 95% confidence interval; OR, odds ratio; WMD, weighted mean difference; MD, mean difference.

Importantly, NAFLD was associated with a host of extrahepatic and hepatic complications particularly that of CVD.[12,14,15] The link between NAFLD and CVD is well established in the existing literature given that NAFLD is closely related to many traditional CVD risk factors including but not limited to metabolic syndrome, hypertension, and dyslipidemia.[56–59] The increase in systemic malignancies in NAFLD may also be the result of alterations in metabolic and stress-response mechanisms caused by NAFLD or the accompanying by-product of metabolic dysregulation, obesity, and/or hormonal derangements.[60–63] The existing literature also suggest that NAFLD facilitates a microenvironment suitable for carcinogenesis due to insulin resistance and chronic inflammation.[62,64,65]

Furthermore, NAFLD was associated with significant hepatic complications, including hepatocellular carcinoma, cholangiocarcinoma, and gallstone diseases as illustrated in the present review. It is widely recognized that NAFLD contributes significantly to increased risk for HCC due to the accumulation of lipids in hepatocytes

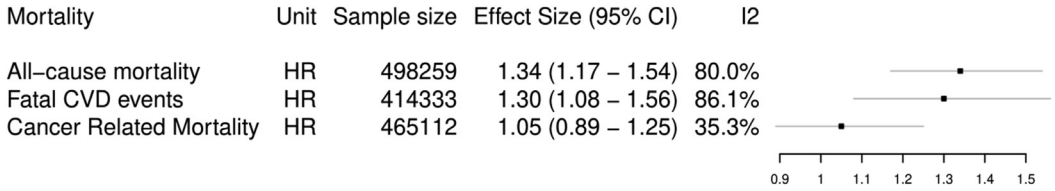

Figure 6 Cause of mortality in patients with NAFLD. Legend: CVD, cardiovascular; HR, hazard ratio; 95% CI, 95% confidence interval.

which drives carcinogenesis through oxidative DNA damage.[6,55,66] While screening and surveillance for HCC in patients with non-alcoholic steatohepatitis (NASH) is recommended by the American Association for the Study of Liver Diseases, it has only been recommended in the context of cirrhosis.[67] However, a recent meta-analysis by Tan and Ng *et al.* found that up to a third of HCC in NAFLD occur in non-cirrhotic patients.[16] However, while there is an increased risk of HCC in NAFLD, the absolute risk may be not be sufficiently high enough to justify routine screening given the significant prevalence of NAFLD, and low-cost screening methods are required to identify patients at risk for HCC evaluation. In addition, NAFLD was also found to be associated with an increased risk of cholangiocarcinoma, especially hepatic cholangiocarcinoma. This might be attributed to NAFLD-induced systemic inflammation, resulting in hyperinsulinemia and increased insulin-like growth factor-1 which stimulates cell proliferation in cholangiocarcinoma.[36] Lastly, the pathogenesis of increased gallstone disease in patients with NAFLD could be related to the multiple common risk factors shared, such as increased age, BMI, diabetes, and hypertension.[35,68]

With the rapidly growing prevalence and global burden of NAFLD evident in its wide hosts of associated extrahepatic disease, there is an urgent need to refocus public health efforts to target the development of multidisciplinary care models. Studies have positioned the establishment of a multilevel intervention involving stakeholders ranging from researchers, healthcare providers to policymakers, and funders as a vital need to address the NAFLD epidemic.[20] Additionally, the awareness of the disease remains low in the community with recent reviews highlighting that relevant knowledge of NAFLD is generally poor in non-hepatologists, and efforts should also gear toward increasing cognizance and awareness surrounding fatty liver among general practitioners, patients, and relatives of patients.[20,69]

Strengths and Limitations

This umbrella review systematically and comprehensively presented evidence on the associated complications and causes of mortality in patients with NAFLD through consolidated information from various meta-analyses. The current review encompasses a thorough evaluation of clinically relevant information on NAFLD based on various meta-analyses, which were assessed for methodological quality and robustness of evidence. However, there are several limitations. We were limited to the studies that have been thoroughly examined in previous meta-analyses and complications that have yet to be examined may have been excluded in the selection process. There was additionally moderate to high statistical heterogeneity in most of the outcomes presented by the included meta-analyses. Furthermore, there could be a potential overlap in included studies across the various meta-analyses reviewed. There is also currently a lack of published literature evaluating potential differences in various outcome measures based on region or demographic factors, which can be a focus for future studies. Lastly, the diagnosis of NAFLD may be limited by the primary articles where ICD-9/10 coding may also be employed for large-scale population-based analysis.

In this umbrella review, data from published meta-analyses were assessed to evaluate and update the complications and causes of mortality in patients with NAFLD. In particular, NAFLD was associated with significant hepatic complications, cardiovascular diseases, systemic malignancies, and metabolic complications. A multi-faceted intervention should be adopted to tackle the disease burden of NAFLD.

DATA AVAILABILITY

All articles in this manuscript are available from Medline and Embase.

REGISTRATION AND PROTOCOL

Study was not registered.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

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Provision of study materials or patients: Nicholas Syn, Zhen Yu Wong, Michael Tseng, Nicholas Chew, Daniel Q Huang, Yock Young Dan, Vincent Wai-Sun Wong, Mohammad Shadab Siddiqui, Arun J. Sanyal, Rohit Loomba, Mazen Noureddin, Mark D. Muthiah.

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Manuscript **writing:** All authors.

Final approval of manuscript: All authors.

CONFLICTS OF INTEREST

Arun J. Sanyal: Dr Sanyal is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana,

Indalo, Durect, and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen, and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland, and Norvatis. He receives royalties from Elsevier and UptoDate.

Mazen Noureddin: Dr Noureddin MN has been on the advisory board/consultant for 89BIO, Altimmune, Gilead, cohBar, Cytodyn, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Madrgial, NorthSea, Prespecturm, Terns, Siemens, and Roche diagnostic; MN has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking, and Zydus; MN is a shareholder or has stocks in Anaetos, Chrownwell, Ciema, Rivus Pharma, and Viking.

Vincent Wong: Dr Wong has served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, ProSciento, Sagimet Biosciences, and TARGET PharmaSolutions; and a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, and Novo Nordisk. He has received a research grant from Gilead Sciences and is a cofounder of Illuminatio Medical Technology Limited.

Rohit Loomba: Dr. Loomba consults and received grants from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Galmed, Gilead, Intercept, Janssen, Madrigal, NGM, and Pfizer. He consults for Anylam/Regeneron, Amgen, Arrowhead, CohBar, Glympse, Inipharm, Ionis, Metacrine, Novartis, Novo Nordisk, Sagimet, 89 Bio, and Viking. He received grants from Allergan, Boehringer Ingelheim, Galectin, Genfit, Inventiva, Merck, and Siemens.

All other authors have no conflicts of interests.

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All authors have made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures, and tables, has not been previously published, and the manuscript is not under consideration elsewhere.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.11.006.