Review Article

Cardiovascular disease in patients with metabolic dysfunction-associated steatohepatitis compared with metabolic dysfunction-associated steatotic liver disease and other liver diseases: A systematic review

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ABSTRACT

The burden of cardiovascular disease (CVD) in patients with metabolic dysfunction-associated steatohepatitis (MASH) is poorly characterized, particularly *vs* other liver diseases including metabolic dysfunction-associated steatotic liver disease (MASLD). To identify available evidence, Embase, MEDLINE, and Cochrane database searches (main search: 2011–September 6, 2021; additional *ad hoc* search [MEDLINE only]: September 7, 2021–February 15, 2023), plus manual searches (2019–September 2021), were performed. Studies reporting CVD outcomes (angina, coronary artery disease [CAD], heart failure, myocardial infarction, peripheral artery disease, stroke, venous thromboembolic disease, and CV mortality) in adults with histologically confirmed MASH and MASLD or other liver diseases were identified, with studies of MASLD without confirmed MASH excluded. Of 8732 studies, 21 were included. An increased incidence or prevalence of CVD in patients with MASH *vs* other conditions was reported in 12 studies; odds ratios (OR), where reported, ranged from 3.12 (95 % CI: 1.33–5.32) to 4.12 (95 % CI: 1.91–8.90). The risk of CAD was increased in people with MASH in 6 of 7 studies, while the risk of stroke was increased in 6 of 6 studies, and heart failure in 2 of 4 studies. Three of 6 studies provided evidence of increased CVD-related mortality in patients with MASH *vs* those without. In conclusion, this literature review suggests that CVD is prevalent in patients with MASH and may contribute to increased mortality. Accordingly, cardiovascular risk factors should be aggressively managed in this population. Whether the CVD burden in patients with MASH is a direct consequence of MASH itself requires further study.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), now known as metabolic dysfunction-associated steatotic liver disease (MASLD) [1], is a leading cause of liver disease globally, affecting approximately 1/4 of the adult population [2]. The prevalence of MASLD has increased dramatically in recent decades and this trend is predicted to continue [3]. In the USA, MASLD cases are forecasted to increase to >100 million by 2030 [4].

MASLD encompasses a spectrum of liver diseases ranging from isolated steatosis in the presence of cardiometabolic risk factors to the progressive, severe subtype of non-alcoholic steatohepatitis (NASH), now known as metabolic dysfunction-associated steatohepatitis (MASH) [2]. Up to 20 % of patients with MASLD have MASH, and these patients may progress to advanced fibrosis, cirrhosis, and/or hepatocellular carcinoma [2]. MASH is associated with a reduction in health-related quality of life and imposes a substantial healthcare burden [2,5]. MASH has also been linked to increased risk of cardiovascular (CV) disease (CVD), and CVD is the leading cause of morbidity and mortality in patients with MASLD/MASH [6,7]. However, many aspects of the burden of CVD among patients with MASH remain poorly characterized.

Although several literature reviews and meta-analyses have investigated the burden of CVD in patients with NAFLD/MASLD, there is a

lack of such studies specifically focusing on patient populations with MASH. This systematic literature review was conducted to identify the available evidence and gain a better understanding of the epidemiological burden of CVD in patients with MASH.

2. Materials and methods

2.1. Data sources and searches

To identify relevant studies, searches of the electronic databases Embase (Elsevier), MEDLINE (PubMed), and The Cochrane Library (Wiley) were conducted on September 6, 2021, through the Ovid platform. A further *ad hoc* search of MEDLINE was performed to identify studies published between September 7, 2021, and February 15, 2023. Other key resources, including conference proceedings, reference lists of included publications and relevant reviews, and selected websites (Supplementary Table SI) were searched manually to identify studies not captured in the electronic database searches. A broad approach was used for the electronic database search strategy (Supplementary Table SII). As this review was conducted prior to the MASLD/MASH nomenclature update [1], NAFLD/NASH terms were included in the search strategy, and therefore these terms have been retained when reporting the methods and results of the current review.

2.2. Study selection

Studies were required to have included adults with histological confirmation of NASH and report CVD outcomes (Table I).

Outcomes of focus included angina, coronary artery disease (CAD), heart failure, myocardial infarction, peripheral artery disease, stroke, venous thromboembolic disease, and CV mortality. A total of 2 independent analysts used a bespoke database to remove duplicates and screened abstracts using the pre-defined eligibility criteria. An independent expert resolved any discrepancies. Full-text publications were obtained for abstracts included after the first-pass screening, and these were further screened by 2 independent analysts using the eligibility criteria. The final studies for inclusion were verified by the project lead and any disputes regarding eligibility were resolved by an independent expert.

2.3. Data extraction and quality assessment

A data extraction template in Microsoft® Excel was used to collect data on the design, patient characteristics, and outcomes of the included studies. Data extraction was conducted by a single analyst and reviewed and quality checked by the project lead. The reported methodological quality of the included studies was assessed using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies [8]. Given our focus on the burden of CVD in patients with NASH, the resulting studies were further selected to include data on the incidence and/or prevalence of CVD in patients with NASH. Furthermore, to place the reported prevalence/incidence in context, selection of studies was restricted to only those that reported on a comparator arm. This was done following a literature review that revealed several analyses characterizing the CVD burden in NAFLD, but a lack of such studies specifically focusing on patient populations with NASH.

3. Results

3.1. Search results

The main electronic database search identified 8732 studies and the *ad hoc* search identified 12 additional studies (Fig. 1).

After removing duplicates, the remaining 6944 citations were screened using titles and abstracts. Of these, 653 studies had a full assessment of eligibility based on full-text publications.

After excluding 591 publications, 62 were eligible for inclusion. A further 12 publications were added based on searching of conference abstracts ($n = 5$) and additional manual searches ($n = 7$). A total of 73 unique studies underwent a complete systematic synthesis, with 52 studies excluded based on the lack of a clearly defined NASH population ($n = 23$), lack of a comparator ($n = 17$) or because the outcome was a proxy for CVD rather than CVD itself, or the focus was on the economic and humanistic burden of NASH rather than clinical outcomes ($n = 12$). Among the 21 remaining eligible studies, 15 provided CVD incidence/prevalence information [9–23], 4 provided CVD-related mortality information [24–27], and 2 provided both [28,29] (Fig. 1). Most studies included were assessed as being of moderate to strong quality (Supplementary Table SIII).

3.2. Relative epidemiological burden of CVD in patients with NASH

A total of 17 studies reported data on the relative epidemiological burden of CVD in patients with NASH *vs* a comparator population (summarized in Table II), with 12 studies reporting an increased incidence or prevalence of CVD in patients with NASH *vs* those without.

Table I
Eligibility criteria for studies included in this review.

Criteria	Include	Exclude
Population	Adult patients with NASH reporting CVD outcomes	Patients with any other disease
Intervention/ Comparator	Population with NAFLD or other liver disease etiologies as comparator	Other interventions
Outcomes	Outcomes evaluated included: angina, CAD, HF, MI, PAD, stroke, venous thromboembolic disease, and CV mortality, reported alone or in combination	Other outcomes
Study design/setting	• Population-based studies (observational studies) • Non-interventional/observational/non-randomized/retrospective/chart-review studies. Any studies reporting original epidemiological, cost, and/or resource use, QoL/HSUV data • SLR and meta-analyses (for reference checking only)	• Interventional clinical trials • Animal/*in-vitro* studies • Editorials • Case reports/case series • Narrative reviews
Language of publication	English language publications	Studies published in languages other than English
Date of publication	• Full publications: 2011–present • Conference abstracts: 2019–present	Prior to 2011
Countries	No restrictions	–

CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HSUV, health state utility value; HF, heart failure; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease;
NASH, non-alcoholic steatohepatitis; PAD, peripheral artery disease; QoL, quality of life; SLR, systematic literature review.
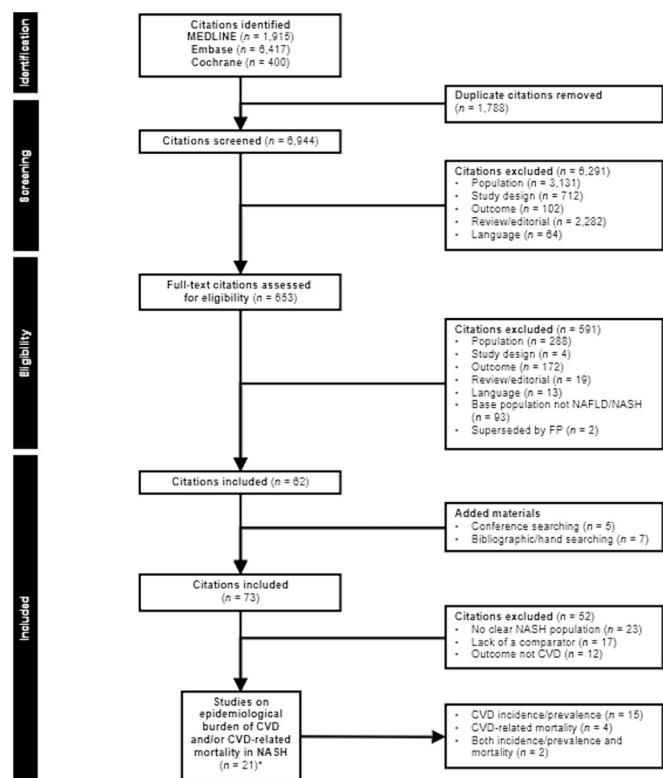
Fig. 1. PRISMA flow diagram.
*A total of 2 citations reported data from the same study.
CVD, cardiovascular disease; FP, full publication; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2.1. Incidence and prevalence

3.2.1.1. Studies comparing patients with NASH vs patients with NAFLD.
Among 5 studies comparing patients with NASH and NAFLD, only 1 noted an increased risk in patients with NASH. A cross-sectional analysis of registry data from patients with or without biopsy-confirmed NAFLD ($N = 500$) found that the 10-year risk of atherosclerotic CVD (calculated from age, sex, race, systolic blood pressure, use of antihypertensives, levels of total and high-density lipoprotein cholesterol, smoking status, and history of diabetes) was significantly increased for patients with NASH *vs* those with no NAFLD (odds ratio [OR] 4.07; 95 % confidence interval [CI]: 1.40–11.88), whereas this was not the case for patients with NAFLD but no NASH *vs* non-NAFLD (OR 1.46; 95 % CI: 0.55–3.88) [16]. The prevalence of hypertension, diabetes, metabolic syndrome, and dyslipidemia were all elevated in patients with NASH compared with those with NAFLD [16]. However, it should be noted that this analysis did not report estimated or observed CV event rates in the NASH and NAFLD groups [16].

The 4 remaining studies found no significant difference in between-group risk of CV events; however, trends for increases in patients with NASH *vs* comparators were observed. For instance, over a mean follow-up of 2.6 years, CV events occurred in 5.2 % of patients with biopsy-proven NASH *vs* 2.7 % of patients with NAFLD but without NASH in a Spanish registry study, but the difference did not reach statistical significance [9]. Similarly, a single-center chart review of patients with biopsy-confirmed NAFLD found a numerically but not statistically significant difference in the prevalence of a combined CVD endpoint between patients with NASH (58.1 % of 219 patients) and non-NASH fatty liver (41.9 % of 158 patients). Prevalence rates of the individual conditions were also similar between the 2 groups (Table II) [11]. In a prospective study of patients with chronic obstructive pulmonary

disease, including those with NASH ($n = 41$), simple liver steatosis ($n = 46$), or liver fibrosis ($n = 68$ [$n = 9$ NASH with liver fibrosis]), NASH or steatosis were not associated with an increased rate of CV events. Nevertheless, after 5 years of follow-up, the rate of CV events was significantly higher in patients with liver fibrosis *vs* without, and this risk remained after adjustment for confounders [21]. Among patients with complicated obesity who underwent first-time laparoscopic bariatric surgery, the baseline prevalence of CAD and congestive heart failure was not significantly different in patients with no liver disease or simple steatosis ($n = 141$), mild NASH ($n = 151$), and advanced NASH ($n = 48$); at 30 days post-surgery, rates of CV events were similar in all groups [22].

3.2.1.2. Studies comparing patients with NASH vs cirrhosis due to other etiologies.
Of 12 studies evaluating patients for liver transplantation who had either NASH or other liver disease etiologies, 10 reported that NASH was associated with a higher prevalence of CAD (*e.g.* 3-vessel disease)/ CVD.

In a prospective study, rates of obstructive and non-obstructive CAD were highest in those with biopsy-proven NASH cirrhosis ($n = 53$) *vs* hepatitis C virus (HCV; $n = 109$) or alcoholic cirrhosis ($n = 45$) [18]. Patients with NASH cirrhosis were more likely to have single-vessel CAD (15.1 %) and 3-vessel disease (9.4 %) *vs* those with HCV or alcoholic cirrhosis, and NASH was an independent predictor of significant CAD (OR 3.12; 95 % CI: 1.332–5.321) [18]. A database study reported a higher prevalence of CAD in pre-transplant patients with NASH *vs* hepatitis B or C, alcoholic cirrhosis, or biliary cirrhosis (7.4 % *vs* 1.7–2.9 %), and a higher prevalence of hypertension (34 % *vs* 12–20 %) and diabetes (50 % *vs* 11–20 %) [12]. Among patients undergoing liver transplant for NASH, HCV, or alcoholic cirrhosis, a higher baseline prevalence of both obstructive and non-obstructive CAD was observed with NASH than the other 2 etiologies [17]. In another study of patients who underwent liver transplant for NASH ($n = 115$) or alcohol-induced cirrhosis ($n = 127$), the pre-transplant prevalence of CAD was higher in the NASH group, with no significant between-group differences in rates of myocardial infarction, congestive heart failure, atrial fibrillation, or stroke 1-year post-transplant [20]. Patients with NASH were more likely than those with alcoholic cirrhosis to experience a CV event (26 %) within 1 year of transplant, after adjustment for confounders (OR 4.12; 95 % CI: 1.91–8.90). However, there was no difference between the 2 groups in the incidence of myocardial infarction, stable ventricular or supraventricular tachycardia, new-onset heart failure, or stroke [20].

In patients undergoing a primary or secondary liver transplant owing to underlying NASH ($n = 5057$), HCV ($n = 14,820$), alcohol-induced liver disease ($n = 6998$), or other causes ($n = 21,485$), the pre-transplant prevalence of CVD was significantly higher in the NASH *vs* all non-NASH groups. The prevalence of angina and cerebrovascular disease was also higher in the NASH group [29]. A single-center, retrospective database analysis revealed a higher prevalence of CVD (as well as higher body mass index and rates of type 2 diabetes [T2D], hypertension, and metabolic syndrome) in the pre-transplant medical history of patients with NASH than those without [19]. Similarly, among liver transplant recipients with NASH ($n = 7100$), HCV ($n = 20,901$), alcoholic liver disease (ALD) ($n = 7962$), or HCC ($n = 5326$), the baseline prevalence of cardiac disease was significantly higher in patients with NASH *vs* those without (BMI and diabetes prevalence were also significantly higher) [23]. A further study of liver transplant recipients aged ≥ 65 years with ($n = 207$) or without ($n = 816$) NASH reported higher rates of diabetes, hypertension, and hyperlipidemia, and a greater relative baseline prevalence of CVD, in those patients with NASH *vs* those without. However, at 12 months post-transplant, no significant between-group differences were noted in rates of atrial fibrillation, myocardial infarction, heart failure, or stroke [14].

A cohort study found a significantly higher baseline prevalence of CVD in patients with ($n = 74$) *vs* without ($n = 881$) NASH [10], while

Table II

Summary of epidemiological studies reporting on the burden of CVD in patients with NASH.

Author, year (country)	Database	Study design	Population	Comparator/ subpopulation (cirrhosis/fibrosis *etc.*) and comorbidities	Sample size, *n*	CV/cerebrovascular events (%)	Limitations
Studies comparing patients with NASH *vs* patients with NAFLD							
Ampuero, 2018 [9] (Spain)	HEPAmet Spanish Registry	Prospective cohort study using registry analysis Mean follow-up: 2.6 years	Patients with biopsy-proven NAFLD (NASH/fibrosis defined according to Steatosis, Activity, and Fibrosis score) Obesity: 56.7 % HTN: 46.3 % T2D: 31.7 % Hypertriglyceridemia: 38.8 % Dyslipidemia: 32.4 %	NASH	265	CVD: 5.2 (*P* = 0.4 *vs* NAFLD)	Data available from abstract only; data on comorbidities only reported for the overall population and not for the individual subpopulations
				NAFLD	303	CVD: 2.7	
Domanski, 2012 [11] (USA)	Brooke Army Medical Center within the Gastro-enterology and Hepatology clinic	Retrospective chart review	Biopsy-confirmed NAFLD (including NASH and non-NASH fatty liver)	NASH Obesity: 72.1 % DM: 47.5 % (*P* < 0.01 *vs* non-NASH fatty liver)	219	CVD: 6.8[a] HF: 1.8 MI: 3.2 Unstable angina: 3.2 Stroke: 1.4 Revascularization: 4.6	Low number of patients identified with CVD, increasing the potential for a type 2 error
				Non-NASH fatty liver Obesity: 67.7 % DM: 22.8 %	158	CVD: 6.3 HF: 1.9 MI: 1.3 Unstable angina: 1.3 Stroke: 1.3 Revascularization: 2.5	
Park 2021 [16] (Republic of Korea)	Boramae NAFLD registry (NCT 02206841)	Retrospective cross-sectional analysis	Biopsy-confirmed NAFLD (NASH: 45.7 %, NAFL: 54.3 %) Liver biopsy performed if ≥2 risk factors were present (central obesity, triglycerides ≥150 mg/dL, HDL-C <40 mg/dL [male]/<50 mg/dL [female], presence of HTN or insulin resistance, or clinically suspected NASH or liver fibrosis)	NASH Mean BMI: 27.6 ± 3.6 kg/m^2 Obesity: 41.2 % HTN: 42.4 % DM: 46.8 %	182	10-year risk of atherosclerotic CVD: OR [95 % CI] 4.07 [1.40–11.88]; *P* = 0.014 *vs* non-NAFLD group	CV event rates not reported; the instrument used to estimate CVD risk may underestimate this in the NAFLD and non-NAFLD subpopulations
				NAFL Mean BMI: 27.0 ± 3.1 kg/m^2 Obesity: 48.5 % HTN: 41.6 % DM: 43.6 % (All *P* < 0.05 *vs* NASH)	216	10-year risk of atherosclerotic CVD: OR [95 % CI] 1.46 [0.55–3.88];	
				Non-NAFLD Mean BMI: 24.3 ± 3.3 kg/m^2 Obesity: 10.4 % HTN: 16.0 % DM: 9.6 % (All *P* < 0.05 *vs* NASH)	102	10-year risk of atherosclerotic CVD: OR [95 % CI] 1 [reference]	
Viglino, 2018 [21] (France)	Grenoble Alps University Hospital	Prospective longitudinal cohort study 5-year follow-up	Patients with COPD (liver damage evaluated using the Fibromax® algorithm that combines 3 tests: FibroTest, SteatoTest, and NashTest) BMI: 26 kg/m^2 T2D: 74 %	NASH	41	During 5 years of follow-up: CV event: 31.7 (*P* = 0.48 *vs* no NASH) Arrhythmia: 4.9 (*P* = 0.32 *vs* no NASH) MI: 2.4 (*P* = 0.37 *vs* no NASH) Stroke: 2.4 (*P* = 1 *vs* no NASH) PAD: 26.8 (*P* = 0.22 *vs* no NASH) VTD: 0 (*P* = 1 *vs* no NASH)	Small and specific study sample that might not reflect the overall NASH population; data on BMI and T2D only reported for the overall population and not for individual subpopulations; study design may be limited by potential selection bias of including only patients with COPD; no information provided on how the 'fibrosis' cohort differed from the 'NASH' cohort
				Moderate-to-severe steatosis	46	During 5 years of follow-up: CV event: 30.4 Arrhythmia: 13.0 MI: 0 Stroke: 0 PAD: 21.7 VTD: 0	
				Fibrosis	68	During 5 years of follow-up: CV event: 33.8 (*P* = 0.08 *vs* no fibrosis) Arrhythmia: 11.8	

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Table II (*continued*)

Author, year (country)	Database	Study design	Population	Comparator/ subpopulation (cirrhosis/fibrosis *etc.*) and comorbidities	Sample size, *n*	CV/cerebrovascular events (%)	Limitations
				No liver disease	28	MI: 1.5 Stroke: 1.5 PAD: 23.5 VTD: 0 During 5 years of follow-up: CV event: 14.3 Arrhythmia: 7.1 MI: 0 Stroke: 0 PAD: 14.3 VTD: 3.6	
Weingarten 2011 [22] (USA)	EMR	Retrospective analysis	Patients with medically complicated obesity who underwent first-time laparoscopic bariatric surgery with intraoperative liver biopsies (biopsy-proven NASH)	No liver disease or simple steatosis DM: 31.2 % HTN: 54.6 %	141	CV event within 30 postoperative days: 2.1 Baseline CAD: 9.9 Severe dysrhythmia event within 30 days: 0.7 Baseline CHF: 2.1 MI event within 30 days: 0	Short follow-up period of 30 days; study design may be limited by potential selection bias as 'healthier' people are usually selected for bariatric surgery, thus the baseline prevalence of CVD is lower than expected for this population
				Mild NASH DM: 28.5 % HTN: 57.0 %	151	CV event within 30 postoperative days: 2.6 Baseline CAD: 7.9 Severe dysrhythmia event within 30 days: 1.3 Baseline CHF: 1.3 MI event within 30 days: 0.7	
				Advanced NASH DM: 58.3 % (*P* < 0.0007 *vs* mild or no NASH) HTN: 64.6 %	48	CV event within 30 postoperative days: 2.1 Baseline CAD: 6.3 (*P* = 0.8 *vs* mild or no NASH) Severe dysrhythmia event within 30 days: 0 Baseline CHF: 0 (*P* = 0.7 *vs* mild or no NASH) MI event within 30 days: 0	
Studies comparing patients with NASH *vs* cirrhosis due to other etiologies							
Danford, 2019 [10] (USA)	EMR from Beth Israel Deaconess Medical Center	Retrospective cohort study	NASH (on listing for LT) (documented as recorded by the transplant hepatologist at the initial evaluation)	NASH Obesity: 63.5 % (*P* = NS *vs* non-NASH) DM: 51.4 % (*P* < 0.001 *vs* non-NASH) HTN: 46.0 % (*P* = 0.01 *vs* non-NASH)	74	Baseline[d]: 23 % (*P* = 0.002 *vs* no NASH)	Baseline prevalence of reported without adjustment for the presence of other parameters; study design may be limited by potential selection bias of including only patients undergoing LT
				Non-NASH Obesity: 58.5 % DM: 23.4 % HTN: 30.8 %	881	Baseline[d]: 11 %	
Gologorsky 2013 [12] (USA)	OPTN	Retrospective multicenter analysis	LT recipients	NASH DM: 49.6 % HTN: 33.8 %	605	CAD: 7.4 PVD: 1.0	Study design may be limited by a potential selection bias of including only patients undergoing LT
				HCV DM: 19.7 % HTN: 19.9 %	6000	CAD: 2.7 PVD: 1.0	
				HBV DM: 17.5 % HTN: 19.1 %	653	CAD: 2.3 PVD: 1.5	
				Alcoholic cirrhosis DM: 18.8 % HTN: 20.4 %	3168	CAD: 2.9 PVD: 1.3	

Table II (*continued*)

Author, year (country)	Database	Study design	Population	Comparator/ subpopulation (cirrhosis/fibrosis *etc.*) and comorbidities	Sample size, *n*	CV/cerebrovascular events (%)	Limitations
				Biliary cirrhosis DM: 10.6 % HTN: 12.3 %	1541	CAD: 1.7 PVD: 0.5	
Herndon, 2020 [13] (USA)	University of Alabama	Retrospective chart review	Patients at high risk for CAD with a coronary evaluation as part of workup for LT	Non-NASH cirrhosis BMI: 29.66 kg/m^2 DM: 33.85 %	65 transplanted	90 days post-transplant: Arrhythmia: 14.29 MI: 3.17 Stroke: 4.76	Data available from abstract only; study design may be limited by potential selection bias of including only patients undergoing LT
				NASH cirrhosis BMI: 32.65 kg/m^2 DM: 63.46 %	52 transplanted	90 days post-transplant: Arrhythmia: 9.80 ($P = 0.5$ *vs* non-NASH cirrhosis) MI: 3.92 ($P = 0.8$ *vs* non-NASH cirrhosis) Stroke: 5.88 ($P = 0.8$ *vs* non-NASH cirrhosis)	
Kwong, 2020 [14] (USA)	REALT consortium; EMR	Retrospective multicenter cohort study	LT recipients aged ≥65 years with or without NASH (NASH was considered the primary etiology if the clinical suspicion for the primary cause of chronic liver disease was NASH or if there was a dual diagnosis of HCC and NASH)	Non-NASH[b] DM without chronic complications: 25.4 % HTN: 54.0 % Hyperlipidemia: 23.8 %	816	Baseline CAD: 20.6 Within 12 months of LT: AF: 13.8 HF: 6.2 MI: 2.9 Stroke: 5.0	Study design may be limited by a potential selection bias of including only patients undergoing LT
				NASH DM without chronic complications: 58.5 % HTN: 66.3 % Hyperlipidemia: 46.3 %	207	Baseline CAD: 36.7 ($P < 0.001$ *vs* no NASH) Within 12 months of LT (all $P = NS$ *vs* no NASH): AF: 13.7 HF: 6.9 MI: 2.5 Stroke: 7.8	
Park 2011 [15] (USA)	Transplant Institute at Hawaii Medical Center	Retrospective cohort study	Patients with and without NASH referred for LT Patients divided into NASH and non-NASH groups based on etiology of their end-stage liver disease	NASH Obesity: 53.4 % ($P < 0.001$ *vs* other chronic liver disease) DM: 69.0 % ($P < 0.001$ *vs* other chronic liver disease) HTN: 55.2 % ($P < 0.001$ *vs* other chronic liver disease)	71 (including 11 patients with initial diagnoses of 'cryptogenic cirrhosis')	Baseline cardiac disease: 22.4 ($P < 0.001$ *vs* other chronic liver disease)	Study design may be limited by potential selection bias of including only patients undergoing LT
				Other chronic liver disease Obesity: 8.0 % DM: 19.9 % HTN: 24.6 %	472	Baseline cardiac disease: 4.9	
Patel, 2018 [18] (USA)	Virginia Common-wealth University	Prospective study (follow-up period not stated)	Patients undergoing elective coronary angiography as part of LT evaluation (patients with cryptogenic cirrhosis: diagnosis of NASH suspected if they had a prior liver biopsy showing steatosis or components of metabolic syndrome in the presence of a negative serological workup for chronic liver disease)	Biopsy-proven NASH cirrhosis Mean BMI: 32.7 ± 6.7 kg/m^2 DM: 69.8 % HTN: 62.3 % Obesity: 67.9 % Dyslipidemia: 43.4 %	53	At time of LT evaluation: CAD: 52.8 % ($P = 0.004$ for difference between groups) Non-obstructive CAD: 22.6 % ($P = 0.02$ for difference between groups) Obstructive CAD: 30.2 % ($P = 0.06$ for difference between groups) Single-vessel CAD: 15.1 % ($P = 0.02$ for difference between groups) 3-vessel CAD: 9.4 % ($P = 0.001$ for difference between groups) Independent predictor of significant CAD: OR [95 % CI]	Study design may be limited by a potential selection bias of including only patients undergoing LT

Table II (*continued*)

Author, year (country)	Database	Study design	Population	Comparator/subpopulation (cirrhosis/fibrosis etc.) and comorbidities	Sample size, n	CV/cerebrovascular events (%)	Limitations
				HCV Mean BMI: 29.4 ± 5.9 kg/m² DM: 19.3 % HTN: 37.6 % Obesity: 42.2 % Dyslipidemia: 18.3 %	109	3.121 [1.332–5.321]; $P = 0.005$ At time of LT evaluation: CAD: 39.4 % Non-obstructive CAD: 20.2 % Obstructive CAD: 19.3 % Single-vessel CAD: 4.6 % 3-vessel CAD: 0.9 %	
At time of LT evaluation: CAD: 20.0 % Non-obstructive CAD: 8.9 % Obstructive CAD: 11.1 % Single-vessel CAD: 6.6 % 3-vessel CAD: 0 %				Alcoholic cirrhosis Mean BMI: 28.7 ± 9.5 kg/m² DM: 24.4 % HTN: 33.3 % Obesity: 31.1 % Dyslipidemia: 24.4 %	45		
Patel, 2019 [17] (USA)	NA (primary data collection)	Prospective study Median follow-up (range): 4.5 years (0–11 years)	Patients undergoing LT for NASH, HCV, or alcoholic cirrhosis	HCV	Overall 495	Baseline CAD – obstructive: 8.4, non-obstructive: 19.8	Data available from poster only; study design may be limited by potential selection bias of including only patients undergoing LT
				Alcoholic cirrhosis	Not stated	Baseline CAD – obstructive: 5.1, non-obstructive: 21.5	
				NASH	Not stated	Baseline CAD – obstructive: 12.8, non-obstructive: 25.6	
Piazza, 2016 [28] (USA)	Medical records	Retrospective cohort study	LT recipients with NASH or alcoholic cirrhosis (liver biopsy or explant histology results and/or if other causes of liver disease could be excluded, as well as the presence of metabolic syndrome. Alcohol use of <10 g/day was considered consistent with diagnosis of NASH-related liver disease)	LT recipients with alcoholic cirrhosis Median BMI: 29 ± 5 kg/m² DM: 26 % HTN: 35 %	65	CVD 1-year: 6.1, CVD 3-year: 13.8 Baseline CAD: 12 Baseline AF: 3 Baseline arrhythmia: 0 Baseline CHF: 3 Baseline MI: 1 Baseline stroke: 1	Small sample size; study design may be limited by potential selection bias of including only patients undergoing LT
				LT recipients with NASH Median BMI: 34 ± 7 kg/m² DM: 58 % HTN: 54 %	78	CVD 1-year: 7.7 ($P = 0.5$ *vs* alcoholic cirrhosis), CVD 3-year: 14.1 ($P = 0.9$ *vs* alcoholic cirrhosis) Baseline CAD: 15 Baseline AF: 4 Baseline arrhythmia: 5 Baseline CHF: 3 Baseline MI: 0 Baseline stroke: 3	
van den Berg, 2018 [19] (The Netherlands)	Medical records	Retrospective cohort study	LT recipients with or without NASH (NASH defined as: [1] exclusion of other liver disease; [2] histological evidence of NASH based on liver biopsy before LT or on explant histology after LT; or [3] pre-cirrhotic imaging demonstrating hepatic steatosis)	LT recipients with NASH Median (IQR) BMI: 31.5 (28.6–36.4) kg/m² ($P < 0.01$ *vs* no NASH) T2D: 73.5 % ($P < 0.01$ *vs* no NASH) HTN: 60.6 % ($P < 0.01$ *vs* no NASH) METS: 83.3 % ($P < 0.01$ *vs* no NASH)	34	Baseline CVD^c: 29.4 ($P < 0.01$ *vs* no NASH)	Small sample size; study design may be limited by potential selection bias of including only patients undergoing LT

Table II (*continued*)

Author, year (country)	Database	Study design	Population	Comparator/ subpopulation (cirrhosis/fibrosis *etc.*) and comorbidities	Sample size, *n*	CV/cerebrovascular events (%)	Limitations
				LT recipients without NASH Median (IQR) BMI: 25.3 (23.4–28.1) kg/m² T2D: 20.0 % HTN: 30.0 % METS: 37.8 %	135	Baseline CVD[c]: 11.1	
VanWagner, 2012 [20] (USA)	Two Chicago medical centers	Retrospective review	Patients undergoing LT for NASH or alcoholic cirrhosis (NASH: biopsy-proven or explant histology demonstrating a diagnosis of NASH cirrhosis)	NASH cirrhosis Mean BMI: 32.1 ± 7.4 kg/m² DM or fasting glucose >110 mg/dL: 51 % BP >130/85 mmHg or anti-HTN treatment: 53 % Hypertriglyceridemia (>150 mg/dL): 25 %	115	Any CV event within 1 year of transplant: 26 (OR [95 % CI] 4.12 [1.91–8.90]; *P* < 0.001 *vs* alcoholic cirrhosis) Baseline CAD: 20 (*P* = 0.05 *vs* alcoholic cirrhosis) Baseline AF: 6 (*P* = NS *vs* alcoholic cirrhosis) New-onset AF within 1 year of transplant: 10 (*P* = NS *vs* alcoholic cirrhosis) Baseline HF: 7 (*P* = NS *vs* alcoholic cirrhosis) Acute HF within 1 year of transplant: 3 Baseline MI: 6 (*P* = NS *vs* alcoholic cirrhosis) Non-STEMI within 1 year of transplant: 2 (*P* = NS *vs* alcoholic cirrhosis) STEMI MI within 1 year of transplant: 1 Stable ventricular tachycardia within 1 year of transplant: 2 (*P* = NS *vs* alcoholic cirrhosis) Supraventricular tachycardia within 1 year of transplant: 2 (*P* = NS *vs* alcoholic cirrhosis) Baseline stroke: 8 (*P* = NS *vs* alcoholic cirrhosis) Stroke within 1 year of transplant: 5 (*P* = NS *vs* alcoholic cirrhosis)	Study design may be limited by potential selection bias of including only patients undergoing LT
				Alcoholic cirrhosis Mean BMI: 28.3 ± 6.6 kg/m² DM or fasting glucose >110 mg/dL: 52 % BP >130/85 mmHg or anti-HTN treatment: 38 % Hypertriglyceridemia (>150 mg/dL): 6 %	127	Any CV event within 1 year of transplant: 8 Baseline CAD: 9 Baseline AF: 4 New-onset AF within 1 year of transplant: 8 Baseline HF: 6 Acute HF within 1 year of transplant: 8 Baseline MI: 2 Non-STEMI within 1 year of transplant: 2 STEMI MI within 1 year of transplant: 1 Stable ventricular tachycardia within 1 year of transplant: 0 Supraventricular tachycardia within 1 year of transplant: 1 Baseline stroke: 2	

Table II (*continued*)

Author, year (country)	Database	Study design	Population	Comparator/subpopulation (cirrhosis/fibrosis *etc.*) and comorbidities	Sample size, *n*	CV/cerebrovascular events (%)	Limitations
VanWagner, 2015 [29] (USA)	OPTN database	Retrospective database study	LT recipients Primary or secondary indication for LT	NASH Mean BMI: 32.0 ± 5.8 kg/m^2 Obesity: 64.0 % (*P* < 0.001 *vs* all other groups) HTN: 35.7 % (*P* < 0.001 *vs* all other groups) DM: 57.1 %	5057	Stroke within 1 year of transplant: 6 Baseline CVD: 37.7 (*P* < 0.001 *vs* all other groups) Baseline angina: 7.0 (*P* < 0.001 *vs* all other groups) Baseline cerebrovascular disease: 1.2 (*P* ≤ 0.04 *vs* all other groups) Baseline PVD: 1.8 (*P* < 0.001 *vs* HCV)	Study design may be limited by potential selection bias of including only patients undergoing LT
				HCV Mean BMI: 28.3 ± 5.3 kg/m^2 Obesity: 33.6 % HTN: 18.6 % DM: 22.8 %	14,820	Baseline CVD: 19.8 Baseline angina: 3.0 Baseline cerebrovascular disease: 0.5 Baseline PVD: 0.9	
				Alcohol-induced Mean BMI: 28.0 ± 5.4 kg/m^2 Obesity: 32.2 % HTN: 20.9 % DM: 22.5 %	6998	Baseline CVD: 22.8 Baseline angina: 3.2 Baseline cerebrovascular disease: 0.7 Baseline PVD: 1.3	
				Other (drug-induced, autoimmune, other viral hepatitis, cholestatic, metabolic) Mean BMI: 27.3 ± 5.4 kg/m^2 Obesity: 26.5 % HTN: 15.6 DM: 20.5 %	21,485	Baseline CVD: 17.0 Baseline angina: 2.7 Baseline cerebrovascular disease: 0.6 Baseline PVD: 0.8	
Wong, 2014 [23] (USA)	United Network for Organ Sharing registry/OTPN	Retrospective analysis	LT recipients with NASH, HCV, or ALD	HCV BMI: 28.3 ± 5.3 kg/m^2 (*P* = 0.02 *vs* HCV and ALD) DM: 13.6 % (*P* < 0.001 *vs* HCV and ALD)	20,901	Baseline CVD: 2.6	Study design may be limited by potential selection bias of including only patients undergoing LT
				NASH BMI: 30.5 ± 6.1 kg/m^2 DM: 35.3 %	7100	Baseline CVD: 6.3 (*P* < 0.001 *vs* other groups)	
				ALD BMI: 28.0 ± 5.4 kg/m^2 DM: 12.6 %	7962	Baseline CVD: 4.0	
				HCC BMI: 28.2 ± 5.2 kg/m^2 DM: 24.0 %	5326	Baseline CVD: 3.2	

Obesity was defined as BMI ≥30 kg/m^2, except for Ampuero, 2018 [9] and Patel, 2018 [18] (both not specified), Danford, 2019 [10] (BMI >30 kg/m^2), and Park, 2021 [16] (central obesity according to waist circumference ≥90 cm for males and ≥80 cm for females).

AF, atrial fibrillation; ALD, alcoholic liver disease; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes; EMR, electronic medical record; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; —HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; LT, liver transplant; METS, metabolic syndrome; MI, myocardial infarction; NA, not available; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NS, non-significant; OR, odds ratio; OTPN, Organ Procurement Transplantation Network; PAD, peripheral arterial disease; PVD, peripheral vascular disease; REALT, Re-Evaluating Age Limits in Transplantation; STEMI, ST-segment elevation myocardial infarction; T2D, type 2 diabetes; VTD, venous thromboembolic disease.

[a] CHF, unstable angina, MI, stroke, and revascularization.
[b] Patients with viral hepatitis, alcohol-related liver disease, autoimmune or cholestatic liver disease, or another/unspecified etiology.
[c] Confirmed MI, CAD, angina pectoris, CHF, AF, stroke, or transient ischemic attack.
[d] Presence of CAD, CHF, arrhythmia, peripheral arterial disease, or cerebrovascular disease.

another single-center cohort study observed that the baseline prevalence of cardiac disease was significantly higher in patients with NASH (*n* = 71) *vs* those with other chronic liver diseases (*n* = 472), as were rates of obesity, diabetes, and hypertension [15].

In contrast, no statistical difference in the prevalence of CV events in patients with NASH *vs* without was observed in a chart review of liver transplant recipients with NASH (*n* = 78) or alcoholic cirrhosis (*n* = 65) [28]. At the time of pre-transplant evaluation, the prevalence of CV and

cerebrovascular diseases was highest for CAD and ≤5 % in both groups for atrial fibrillation, arrhythmia, congestive heart failure, myocardial infarction, and stroke. There were no between-group differences in the frequency of post-transplant CV events at 1 and 3 years [28]. Regarding individual outcomes of interest, a chart review of patients at high risk for CAD found no significant difference between patients with NASH (*n* = 52) and non-NASH cirrhosis (*n* = 65) at 90 days post-liver transplant for myocardial infarction, arrhythmia, or stroke [13].

3.2.2. CVD mortality

A total of 6 retrospective studies reported data on the risk of CVD mortality in patients with NASH *vs* a comparator (Table III).

3.2.2.1. Studies comparing mortality in patients with NASH vs patients with NAFLD.
Findings from a single cohort study suggested that CVD-related mortality was not increased in patients with NASH *vs* those with NAFLD. Among patients with biopsy-proven NAFLD followed for approximately 12 years, cardiac-related deaths occurred in 15 of 171 patients with NASH (8.8 %) compared with 18 of 118 patients without NASH (15.3 %); both groups had non-significant differences in rates of obesity, T2D, and hyperlipidemia [27].

3.2.2.2. Studies comparing mortality in patients with NASH vs cirrhosis due to other etiologies.
Data on CVD-related mortality were equivocal from 2 studies comparing patients with NASH *vs* those with cirrhosis due to other etiologies. Among patients with NASH (*n* = 6344), HCV (*n* = 17,037), or ALD (*n* = 9279), NASH was associated with an increased risk of 1-year mortality compared with the HCV (hazard ratio [HR] 1.30) and ALD (HR 1.34) groups; the proportions of patients with obesity and diabetes in the NASH group were higher than those observed in the HCV and ALD groups [25]. In contrast, a single-center chart review found no increase in CVD-related mortality in liver transplant recipients with NASH *vs* those with alcoholic cirrhosis at 3-year follow-up, despite the former group having a significantly higher body mass index, and significantly higher rates of diabetes and hypertension [28].

Two of 3 studies in liver transplant recipients comparing populations with NASH *vs* those with cirrhosis due to other etiologies suggested an increase in CVD-related mortality in the former group. Over a mean 1.62 years of post-transplant follow-up, patients with NASH (*n* = 5057) were more likely to die from CVD than patients without NASH (*n* = 43,303; HCV, alcohol-induced, and other causes) (HR 1.42) [29]. A single-center chart review found that patients with NASH (*n* = 129) had significantly higher baseline rates of CAD and cerebrovascular disease, and higher comorbidity rates compared with patients without NASH (*n* = 775) [24]. Deaths due to a cardiac event occurred in 19 % of patients with NASH compared with 7 % of those without NASH, with 75 % of these deaths occurring within 4 months of transplantation [24]. In both studies, rates of obesity, hypertension, and diabetes were markedly greater in patients with NASH than their non-NASH counterparts [24,29].

Conversely, a US cohort study of primary liver transplant recipients (NASH, *n* = 3170; non-NASH HCV+, *n* = 3012; non-NASH HCV−, *n* = 3159) found that although the prevalence of obesity and diabetes was significantly higher in the NASH *vs* non-NASH groups at the time of transplant, the risk of CVD-related mortality was significantly lower (adjusted HR 0.65) [26]. A significantly lower risk of CV-related death was observed in patients with NASH *vs* patients without NASH but with HCV (adjusted HR 0.49), but not *vs* those without both NASH and HCV [26].

4. Discussion

This systematic review adds to the existing literature by documenting that CVD is highly prevalent in patients with MASH, who have an elevated CVD risk compared with patients with other advanced liver disease etiologies. Comparisons between these disease states are challenging based on published studies owing to the varying prevalence of CV risk factors in patients classified as having other conditions and the heterogeneity of disease severity assessments. Several of the identified studies reporting no significant difference in CVD risk between MASH and a comparator group were conducted in populations that have a similarly high CVD risk profile to MASH, notably patients who have had bariatric surgery. It is likely that cardiometabolic risk factors play a greater role in the development of CVD than MASH, which could explain the similar risks of CV events found in many of these studies, especially those comparing populations with MASH *vs* MASLD.

Although we believe this systematic literature analysis is unique in focusing on patients with a histological diagnosis of MASH, our findings are in line with similar recent meta-analyses evaluating the risk of CV adverse events in patients with or without MASLD. MASLD was associated with an increased risk of myocardial infarction, ischemic stroke, atrial fibrillation, and heart failure compared with no MASLD in a systematic review and meta-analysis of 20 studies, with the strength of these associations moderated by age and male sex [30]. A second meta-analysis of 11 longitudinal cohort studies with data on >11 million middle-aged individuals followed over a median of 10 years found that MASLD was associated with a 1.5-fold higher long-term risk of new-onset heart failure, compared with no MASLD, regardless of the presence of diabetes, hypertension, and other common CV risk factors [31]. However, these studies did not specifically report on populations with MASH. It remains unclear whether MASLD with or without biopsy-proven MASH has a true association with CVD, and further research is required.

Many patients included in the identified studies had other CV risk factors in addition to MASH. In particular, MASH was often comorbid with T2D, which is commonly the case as the 2 conditions share several risk factors, notably insulin resistance and obesity [32], and the presence of both increases the risk of CV events [33]. The relationship between T2D and MASLD is thought to be bidirectional, in that T2D promotes the progression of MASLD to MASH and cirrhosis, and increases all-cause and liver-related mortality, while MASLD leads to insulin resistance and poor glycemic control [32]. Other comorbidities, such as overweight/obesity and lipid imbalances, also likely mediate the relationship between MASH and CVD risk, and indeed MASH is considered as the liver manifestation of the metabolic syndrome [2,34]. At present, published data are insufficient to permit definitive conclusions to be drawn on whether the increased CVD risk in patients with MASH compared with their counterparts without MASH is driven by MASH itself and/or its associated comorbidities, and if the presence of MASH on a background of certain comorbidities may have an incremental or synergistic effect on CVD risk.

It was unclear from the studies included in our literature review whether co-existence of MASH and CVD led to increased CVD-related mortality *vs* the co-existence of CVD with other liver etiologies, because patients in these studies did not necessarily have confirmed CVD; rather, they were included as they did not have advanced heart disease as a condition of receiving a liver transplant. Nevertheless, CVD is a major cause of death in patients with more advanced liver disease [6,7], including patients with MASH, particularly among those with metabolic comorbidities, and these patients are likely to benefit from aggressive CV risk factor modification both pre- and post-liver transplant. For example, statin use may be beneficial, because it reduces CVD risk and appears to be well tolerated in this patient population [35,36]. However, statins should only be used with caution in patients with decompensated cirrhosis. Further studies of liver and mortality outcomes with statins in patients with compensated cirrhosis are ongoing [37]. We can hypothesize that treatments that positively affect cardiometabolic risk in other at-risk populations, *e.g.* glucagon-like peptide-1 receptor agonist therapy or sodium-glucose cotransporter-2 inhibitors for people with T2D, may be effective in reducing CVD risk in patients with MASH, but this requires careful prospective evaluation. Large

Table III
CVD-related mortality in patients with NASH.

Author, year (country)	Database	Study design	Population	Comparator/ subpopulation (cirrhosis/ fibrosis *etc.*) and comorbidities	Sample size, *n*	CVD mortality, % (unless otherwise stated)	Limitations
Studies comparing patients with NASH *vs* patients with NAFLD							
Stepanova, 2013 [27] (USA)	Forces Institute of Pathology databases	Retrospective cohort	Biopsy-proven NAFLD with and without NASH	NASH Obesity: 43.9 % T2D: 28.1 % Hyperlipidemia: 27.2 %	171	Over ~12 months of follow-up: 8.8 ($P = 0.09$ *vs* no NASH)	Data not available for various major CVD risk factors and confounders (*e. g.* smoking status, hypertension, visceral obesity and insulin resistance), which may have contributed to the high mortality rates observed
				Non-NASH Obesity: 49.2 % T2D: 22.9 % Hyperlipidemia: 37.5 %	118	Over ~12 months of follow-up: 15.3	
Studies comparing patients with NASH *vs* cirrhosis due to other etiologies							
Kennedy, 2012 [24] (USA)	Internal transplant database	Retrospective chart review	LT patients with a diagnosis of NASH or without NASH (NASH defined as no other forms of liver disease and pre-transplant biopsy consistent with NASH or pre-cirrhotic imaging demonstrating hepatic steatosis or met criteria for the NASH phenotype)	NASH Obesity: 68 % DM: 59 % HTN: 75 % Hypercholesterolemia: 22 %	129	19 Post 4 months LT: 8.5	Overall number of mortality events was low, which significantly raises the possibility of a type 2 error. Furthermore, the identification of pre-transplant risk factors that may specifically predict a cardiac or sepsis-related cause of death was limited by the low number of events
				Non-NASH Obesity: 28 % DM: 17 % HTN: 41 % Hypercholesterolemia: 12 %	775	7 Post 4 months LT: 4.2	
Nagai, 2019 [25] (USA)	OPTN registry	Retrospective registry analysis	LT patients with NASH, HCV, or ALD (diagnoses of cirrhosis: cryptogenic [idiopathic] or cirrhosis; etiology unknown were not considered NASH)	HCV BMI ≥30 kg/m^2: 34.6 % DM: 25.0 %	17,037	7.0 (deaths within 1 year of LT)	OPTN registry lacks detailed clinical information, *e.g.* on diabetes control and pretransplant history of CVD, which could affect post-transplant outcomes; follow-up times differ among eras. An endpoint of 1-year patient and liver graft survival was chosen to minimize bias secondary to different follow-up times
				ALD BMI ≥30 kg/m^2: 34.7 % DM: 21.4 %	9279	9.6 (deaths within 1 year of LT)	
				NASH BMI ≥30 kg/m^2: 61.7 % DM: 59.3 %	6344	11.5 (deaths within 1 year of LT; $P < 0.001$ *vs* HCV and ALD) Mortality rate: 1 *vs* 3 *vs* 5 year: 1.4 *vs* 1.8 *vs* 2.8 Multivariate analyses: NASH *vs* HCV: HR [95 % CI] 1.30 [1.04–1.61]; $P = 0.02$ NASH *vs* ALD: HR [95 % CI] 1.34 [1.06–1.69]; $P = 0.01$	
Piazza, 2016 [28] (USA)	Medical records	Retrospective cohort study	LT patients with NASH or alcoholic cirrhosis (NASH diagnosed by liver biopsy or explant histology results and/or if other causes of liver disease could be excluded, as well as the presence of metabolic syndrome. Alcohol use of <10 g/day was considered consistent with diagnosis of NASH-related liver disease)	Alcoholic cirrhosis Median BMI: 29 ± 5 kg/m^2 DM: 26 % HTN: 35 %	65	8 deaths occurred with 2 due to CV events	Study design may be limited by potential selection bias of including only patients undergoing LT
				NASH Median BMI: 34 ± 7 kg/m^2 ($P < 0.0001$ *vs* alcoholic cirrhosis) DM: 58 % ($P = 0.0002$ *vs* alcoholic cirrhosis) HTN: 54 % ($P = 0.03$ *vs* alcoholic cirrhosis)	78	10 deaths occurred with 1 due to CV events	
Satapathy, 2017 [26] (USA)	UNOS STAR dataset	Retrospective cohort study	LT patients with and without NASH (NASH patients were identified using the primary diagnosis numeric code for NASH in the dataset. Cryptogenic cirrhosis with BMI ≥30 was included in the NASH group)	NASH BMI ≥30 kg/m^2: 72.05 % ($P < 0.0001$ *vs* non-NASH groups) DM: 49.72 % ($P < 0.0001$ *vs* non-NASH groups)	3170	NASH *vs* non-NASH group for CV-related death: aHR [95 % CI] 0.648 [0.531–0.791]; $P < 0.0001$	Prevalence of NASH during the first 2 years may be underestimated; study combined NASH diagnoses with cryptogenic cirrhosis
				Non-NASH HCV+ BMI ≥30 kg/m^2: 35.09 % DM: 20.92 %	3012	NASH *vs* non-NASH HCV+: aHR [95 % CI] 0.491 [0.396–0.609]; $P < 0001$	
				Non-NASH HCV− BMI ≥30 kg/m^2: 28.30 % DM: 21.59 %	3159	NASH *vs* non-NASH HCV−: aHR [95 % CI] 0.892 [0.711–1.121]; $P = 0.3276$	

Table III (*continued*)

Author, year (country)	Database	Study design	Population	Comparator/ subpopulation (cirrhosis/ fibrosis *etc.*) and comorbidities	Sample size, *n*	CVD mortality, % (unless otherwise stated)	Limitations
VanWagner, 2015 [29] (USA)	OPTN database	Retrospective database	LT patients with and without NASH (NASH defined as a diagnosis of cryptogenic cirrhosis with ≥1 component of the metabolic syndrome)	NASH cirrhosis Obesity (BMI ≥30 kg/m²): 64.0 % HTN: 35.7 % DM: 57.1 %	5057	4.5 NASH patients more likely to die from CVD-related death *vs* non-NASH patients over mean 1.62 years of follow-up HR [95 % CI] 1.42 [1.23–1.63]; *P* < 0.001	
				Non-NASH (included HCV, alcohol-induced, other) Obesity (BMI ≥30 kg/m²): 29.8 % HTN: 8.1 % DM: 21.6 %	43,303	3.4	

ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes; HCV, hepatitis C virus; (a)HR, (adjusted) hazard ratio; HTN, hypertension; LT, liver transplant; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OPTN, Organ Procurement Transplantation Network; STAR, Standard Transplant Analysis and Research; T2D, type 2 diabetes; UNOS, United Network for Organ Sharing.

studies of the safety and efficacy of such treatments in MASH are ongoing [38,39].

A key strength of this systematic review is that it focused exclusively on reports from biopsy-proven MASH cohorts. This review also has several limitations, notable among which is the fact that most studies did not adjust for the presence of CV risk factors, meaning firm conclusions cannot be made regarding whether increased CVD and mortality risks are driven by MASH itself or a higher prevalence of cardiometabolic risk factors in this population. Some of the epidemiological studies included had very small patient populations and thus their findings could be subject to selection bias or chance. Additionally, causality between MASH and CVD could not be assessed in the identified studies because most were retrospective in design. Furthermore, the prevalence of cardiometabolic risk factors known to significantly impact the occurrence of CVD was vastly lower in the comparator arm in most of the studies, therefore any noted differences in the prevalence of CVD could be driven exclusively by the excess prevalence of cardiometabolic risk factors. A total of 12 studies were conducted in patients who were listed for, or had received, a liver transplant, 1 study enrolled patients who had undergone bariatric surgery, and another enrolled patients with chronic obstructive pulmonary disease; these specialized populations may not be representative of the general population with MASH and the presence of confounding clinical factors that may influence CV-related mortality in this group should be noted. Interpretation of the transplant literature is complicated by fact that patients have extensive cardiac evaluation prior to transplant and only those with a relatively manageable cardiac status are allowed to proceed to transplant, therefore this represents a selection bias where it is likely that patients with only low-to-moderate heart disease were included. None of the studies considered possible time trends in the incidence, prevalence, or mortality associated with comorbid CVD. Finally, although studies involving biopsy-confirmed MASH were included, no staging of MASH was documented, nor were patients classified by presence or absence of cirrhosis and/or hepatic decompensation.

Because it is difficult to pinpoint which patients have MASH in most cohorts, it is important that future research characterizes types of heart disease in patients with MASLD, stratified according to fibrosis severity (as currently defined by the Fibrosis-4 Index for Liver Fibrosis or elastography). This may reveal whether there are differences in the prevalence of atherosclerotic CVD, heart failure with preserved ejection fraction, or atrial fibrillation across different stages of the disease.

Recently, the new nomenclature for NAFLD/NASH was proposed by EASL-AASLD-APASL in a multi-society Delphi consensus statement [1].

With a focus on positive metabolic criteria, MASLD encompasses patients who have hepatic steatosis diagnosed histologically or by imaging and have ≥1 of 5 cardiometabolic risk factors such as T2D and obesity. Persons with MASLD and steatohepatitis are designated as having MASH [1]. As previously noted, the new MASLD/MASH criteria were not included as search terms in the current literature review; however, it is likely that most of the patient populations in the included studies would retrospectively fulfil these criteria. In the current review, we have generally assumed that both old and new terms are used interchangeably but retained NAFLD/NASH when reporting the results, given all included studies were conducted prior to the nomenclature updates [1].

In conclusion, CVD is prevalent in patients with MASH, particularly those with more severe liver disease, and is likely to contribute to mortality. Accordingly, CV risk factors should be carefully and proactively managed in this population. Whether the CVD burden in patients with MASH is a direct consequence of MASH itself, or a reflection of the underlying cardiometabolic abnormalities that lead both to CVD and MASH, remains to be resolved in future studies.

Ethical statement

All authors ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association and the manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

CRediT authorship contribution statement

Arun J. Sanyal: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mansoor Husain:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Crystel Diab:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kamal Kant Mangla:** Conceptualization; Investigation; Methodology; Project administration; Roles/Writing - original draft; Writing - review & editing. **Ahsan Shoeb:** Writing – review & editing, Writing – original draft,

Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ildiko Lingvay:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Elliot B. Tapper:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.ahjo.2024.100386.

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