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Meta-Analysis

Liver transplant for hepatocellular carcinoma in metabolic dysfunction-associated steatotic liver disease versus other etiologies: A meta-analysis

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ABSTRACT

Background & Aims: Liver transplantation for hepatocellular carcinoma (HCC) in metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly being diagnosed and predicted to rise further. We compared outcomes of transplantation for MASLD-related HCC versus other etiologies (OE).
Methods: Databases were searched to identify studies comparing outcomes after transplantation MASLD-related HCC with OE-related HCC. Study data were pooled using random-effects modelling. Survival outcomes were analyzed using hazard ratio (HR) for overall survival (OS) and odds ratio (OR) for 1-,3-, and 5-years OS and disease-free survival (DFS).
Results: Ten retrospective comparative studies were identified including a total number of 51′761 patients (MASLD-related HCC=6′793, OE-related HCC=44′968). There were no significant differences in time-to-even survival (HR:0.93, $CI_{95\,\%}$ 0.81–1.07,p = 0.29), 1-year (87.6% vs 88 %;OR:1.15; $CI_{95\,\%}$0.73–1.79,p = 0.55), 3-year (77.2% vs 76 %;OR:1.36;$CI_{95\,\%}$0.96–1.94,p = 0.08), or 5-year (67.7% vs 66.3 %;OR:1.08; $CI_{95\,\%}$0.77–1.53,p = 0.65) OS rates between the groups. DFS was comparable at 1-year (87.9% vs. 87 %; OR:1.07,p = 0.62), 3-years (77.6% vs. 73.6 %;OR:1.66,p = 0.13) and 5-year (68% vs. 65.6 %;OR:1.37,p = 0.39).
Conclusion: This meta-analysis of the best available evidence (Level 2a) demonstrated that liver transplantation for MASLD-related and OE-related HCC has comparable survival outcomes. Given the global rise in MASLD-related HCC as indication for transplantation, larger studies from other continents, including Europe and Asia, are needed to confirm our findings.

1. Introduction

Obesity and overweight affect over one-third-of the world's population [1,2]. The prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) has increased by 10 % from 2005 to 20,10[2]. This condition was previously known as nonalcoholic fatty liver disease (NAFLD) and in 2020 it was renamed into MAFLD [3]. Three years later, the term metabolic dysfunction-associated steatotic liver disease (MASLD) was proposed, and it is diagnosed based on five cardiovascular risk factors [4]. Moreover, an additional condition, termed metabolic and alcohol related/associated liver disease (MetALD), was proposed to describe patients with MASLD who consume greater amounts of alcohol per week [4]. Even in countries like South Korea with historical low percentage of obesity, the rates of this condition and its associated risks with cardiovascular diseases are alarmingly increasing [5].

Metabolic dysfunction-associated steatohepatitis (MASH), a dangerous inflammatory complication of MASLD and previously

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known as non-alcoholic steatohepatitis (NASH), can deteriorate into end-stage liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in up to 20 % of patients [6]. Nowadays, MASLD and MASH are considered the second most common indication for liver transplantation (LT) in the US, and the related development of HCC represents the fastest growing indication for LT [2,6]. These evolving scenarios are concerning and represent a major challenge for the transplant community, because MASLD recipients have additional comorbidities, including diabetes, obesity, hypertension, kidney dysfunction and are at higher risk for significantly complications after LT [7]. There is also some evidence that MASH patients have a higher incidence of advanced HCC (beyond Milan criteria) and faster tumor progression, compared to other etiologies (OE) of liver disease [8]. Some studies have reported a clear disadvantage of MASH patients during transplant evaluation and a limited access to lifesaving transplantation due to the higher medical comorbidities [9].

Posttransplant outcomes after LT for HCC in MASLD versus OE have never been evaluated by a meta-analysis. The aim of this study was therefore to conduct a comprehensive systematic literature review and meta-analysis of available studies comparing oncological outcomes after transplantation for MASLD-related HCC versus OE.

2. Material and methods

2.1. Study design

The eligibility criteria, methodology, and investigated outcome parameters of this study were described first, in a protocol, registered at the International Prospective Register of Systematic Reviews (registration number PROSPERO: CRD42023416824). The methodology used in the present study respected the standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

2.2. Eligibility criteria and participants

Included publications were studies evaluating the outcomes after LT for HCC in MASLD compared with OE in adults (≥18 years old). Case reports with less than ten cases were excluded. Non comparative studies and conference abstracts were excluded. Pediatric cases were excluded.

2.3. Intervention and comparison of interest

LT for HCC in MASLD was considered as the intervention of interest, which was compared to LT for HCC in OE.

2.4. Outcome measures

- Overall survival (OS) which was reported as a time-to-event outcome parameter in order to resolve uncertainties associated with varying follow-up periods among the included studies
- One-, 3, and 5-years survival which were reported as dichotomous outcome parameters in order to report the proportion of patients who survived at the end of a specific follow- up period
- One-, 3, and 5-years disease-free survival (DFS)

2.5. Literature search strategy

A comprehensive search strategy was conducted based on thesaurus headings, search operators and limits in MEDLINE, EMBASE, WEB OF SCIENCE, and conducted by two independent authors (A.P., F.M.). The final literature search was performed on September 16th 2024. The search algorithm included the following terms: "nonalcoholic fatty liver disease" OR "NAFLD" OR "nonalcoholic steatohepatitis" OR "NASH" OR "metabolic associated fatty liver disease" OR "MAFLD" AND "liver transplant" OR "liver transplantation" OR "transplantation" AND "hepatocellular carcinoma" OR "HCC". No limits were set for the publication year and the language was limited to English.

2.6. Study selection

Titles and abstracts were assessed by two independent reviewers (A.P., F.M.). The full texts of relevant articles were collected and evaluated based on the eligibility criteria of this study. Discrepancies were resolved supported by consensus with a third independent senior author (A.S.). Complete consensus was reached for each collected study. In addition, the reference lists of included studies were searched to reduce the risk of missing potentially relevant studies.

2.7. Data extraction and management

An electronic data extraction spreadsheet according to the Cochrane's recommendations for intervention reviews was created and was pilot tested in randomly selected articles and adjusted accordingly. The following information was extracted from each of the included studies (A.P., S.H, S.H.) to ensure data homogeneity and to rule out any subjective influence:

- General study-related data (first author, publication year, country of origin of the corresponding author, journal, study design, procedure performed, and sample size in each group)
- Baseline demographics and clinical information of the study population (recipient age, recipient gender, recipient laboratory Model of end-stage liver disease (MELD) at time of transplantation, recipient BMI, and tumor characteristics)
- Post-transplant outcome data, OS and disease-free survival (DFS) at one, three and five years.
- Disagreements between the investigators were resolved following iteration, discussion, and consultation with a third and independent author (A.S.). Complete concordance for all variables was achieved.

2.8. Risk of bias assessment

Three investigators (A.P., F.M., S.H.) reviewed the publications, assessed the quality and extracted the data independently assessing the risk of bias by using the Newcastle–Ottawa Scale (NOS) based on selection (four items), comparability (one item) and outcome (three items) [11]. A nine-star rating system (ranging from 0 to 9) in NOS was used for assessing the quality of observational studies; a study with seven or more stars was regarded as good quality. Conversely, a study with three or more stars but fewer than six was regarded as being of fair quality, whereas two or fewer stars indicated poor quality. Disagreements were resolved by discussion and consensus between the three investigators. If no agreement could be reached, a fourth independent senior author was consulted (A.S.). Ultimately, complete concordance was achieved.

2.9. Summary measures, synthesis, and statistical analysis

For time-to-event outcome variables (OS) the natural logarithm of hazard ratios (HRs) was computed. Then, the natural logarithms of upper and lower confidence limits given for HRs were computed in order to obtain standard errors from confidence intervals (CIs). Finally, the generic inverse variance method was utilized to construct HRs meta-analytical models on the natural logarithm scale. For dichotomous outcome variables odds ratios (OR) were determined as the summary measure. For the adverse

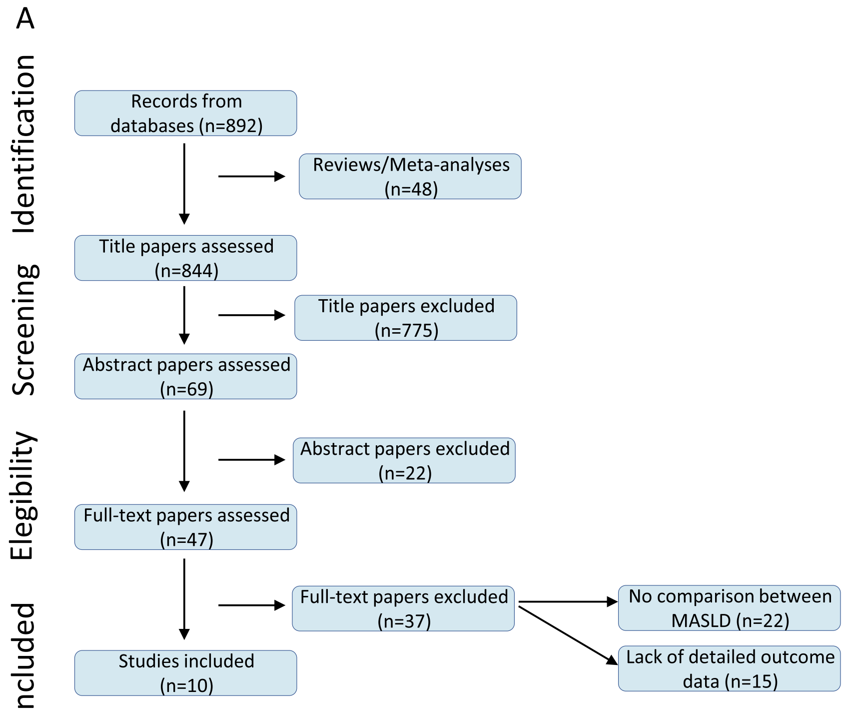

Fig. 1. Overview of search strategy and PRISMA.

dichotomous outcome variables (HCC recurrence), the OR of <1 would favor MASLD-related HCC over OE-related HCC. For non-adverse dichotomous outcome variables (survival and DFS), the OR of >1 would favor MASLD-related HCC over OE-related HCC. For outcomes reported as percentages only, the absolute number was extrapolated. For continuous parameters, a mean difference (MD) was calculated between the two groups. When mean values were not available for continuous outcomes, data on median and interquartile range were extracted and subsequently converted to mean and standard deviation (SD) using the established equation described by Hozo et al. [12].

One reviewer (A.P.) entered the extracted data into the Review Manager 5.4 software for data synthesis [13]. This data set was subsequently checked by two independent reviewers (S.H., S.H.) and statistical analysis was performed. Random-effects modelling was used for analysis as recommended by Kalkum et al. [14]. The results were reported in a forest plot with 95 % confidence intervals (CIs) for each outcome parameter.

Heterogeneity among the studies was assessed using the Cochran Q test ($\chi 2$). Data inconsistency was quantified by calculating I^2 and interpreted based on the following guidelines: 0–25 %: might not be important; 26–75 %: may represent moderate heterogeneity; >75–100 % may represent considerable heterogeneity. Sensitivity analyses were conducted to explore potential sources of heterogeneity and assess the robustness of the results. Finally, the effect of each study was evaluated based on the overall effect size and the study heterogeneity. For this purpose, the analysis was repeated following the exclusion of one study at a time (leave-one-out sensitivity analysis).

3. Results

3.1. Literature search and data collection

The literature search resulted in 892 articles; 48 were review and/or meta-analyses and were excluded. Of the remaining 844 articles, 775 were excluded based on the title. After assessing the abstract of 69 articles, 22 were excluded and 47 were reviewed for full text. Ultimately, 15 articles were included for systematic review as retrospective comparative studies (Fig. 1). However, five articles were excluded from the meta-analysis as they did not report relevant outcomes with enough details. Therefore, ten articles were included in the pooled results [15-24].

Overall, there were 51′761 patients, who received LT either for MASLD ($n = 6'793$) or OE ($n = 44{,}968$). Eight studies were conducted in North America, single center ($n = 3$) [15,17,21] or multicenter ($n = 2$) [18,22] retrospective databases or utilizing the United Network for Organ Sharing (UNOS) or SRTR dataset ($n = 3$) [19,20,23]. One study was conducted in the UK with a multicenter dataset [16] and one study from Italy utilized the Italian liver transplant registry database (Table 1). The baseline characteristics of the study population are summarized in Table 2. Seven studies [15-19,22,23] reported recipient age, which was significantly higher in MASLD ($p < 0.0001$), and recipient gender demonstrating that the majority were male (67 %; 2660/3968 and 78.3 %; 20′300/25′914) in MASLD and OE groups, respectively ($p = 0.0003$). Four studies [16,18,22,23] reported a significantly higher recipient BMI in the MASLD group ($p < 0.0001$). Six studies [16-19,22,23] reported the lab MELD score, and it was found that MASLD patients had a higher mean lab MELD at LT (13.2 vs 11.7, $p = 0.02$). Three studies [16,19,22] reported details on pre-transplant diabetes, which was found to be more frequent in MASLD group ($p = 0.0001$) (**Supplementary Table 2**).

Five studies [17,18,20,22,23] found that less recipients were within Milan criteria for MASLD (67.8 %; 1′868/2′752) compared OE (72.3 %; 18′000/24′890) and this reached statistical significance ($p = 0.02$). Seven studies [15-18,20,22,23] reported pre-transplant levels of alpha-feto protein (AFP), which was significantly lower in MASLD recipients ($p < 0.0001$) (Table 1). In addition, six studies [17-19,22-24] reported the number of patients who underwent pre-LT locoregional treatment. There was a trend towards more pre-LT locoregional treatments in MASLD (51.8 %) versus OE (46 %), however it did not reach statistical significance ($p = 0.06$) (**Supplementary Table 2**).

Table 1
Characteristics of the included retrospective comparative studies.

First Author	Year	Center	N of centers	Country	MASLD-HCC Group (n)	OE-HCC group (n)	OE
Reddy	2012	University of Pittsburgh Medical Center, Pittsburgh, PA	1	USA	20	83	ALD/HCV
Than	2017	University Hospitals Birmingham NHS Trust, Birmingham Birmingham Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham	2	UK	21	80	HCV
Sadler	2017	University Health Network and Department of Surgery, University of Toronto, Ontario University of California San Francisco, San Francisco, CA	2	Canada/USA	60	869	HBV/HCV/ALD/AD/Other
Younossi	2019	*Multicentric collaboration*	15	Multicenter (SRTR)	1631	13,851	HBV/HCV/ALD
Weinfurtner	2020	University of California San Francisco, San Francisco, CA	1	USA	32	393	HBV/HCV/ALD/AD
Holzner	2021	Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, New York, NY	1	USA	51	584	HBV/HCV/ALD
Lamm	2022	Thomas Jefferson University Hospital, Jefferson University Hospitals, Philadelphia, PA	1	USA	1175	1175	HBV/HCV/ALD/Other
Verna	2022	*Multicentric collaboration*	23	USA	538	4443	NA*
Rajendran	2023	*Multicentric collaboration*	6	Multicenter (UNOS and Toronto)	2071	18,601	HBV/HCV/ALD/AD/Other
Vitale	2024	*Italian Liver Transplant Registry*	21	Multicenter (ILTR)	1194	4889	HBV/HCV/ALD/AD/Other

AD: autoimmune disease (included autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis); ALD: alcoholic liver disease; HBV: hepatits B virus; HCV: hepatitis C virus; ILTR: Italian Liver Transplant Registry; NA: not available.

* in this study the detailed etiologies were not reported. SRTR: Scientific Registry of Transplant Recipients; UNOS: United Network for Organ Sharing; USA: United States of America; UK: United Kingdom.

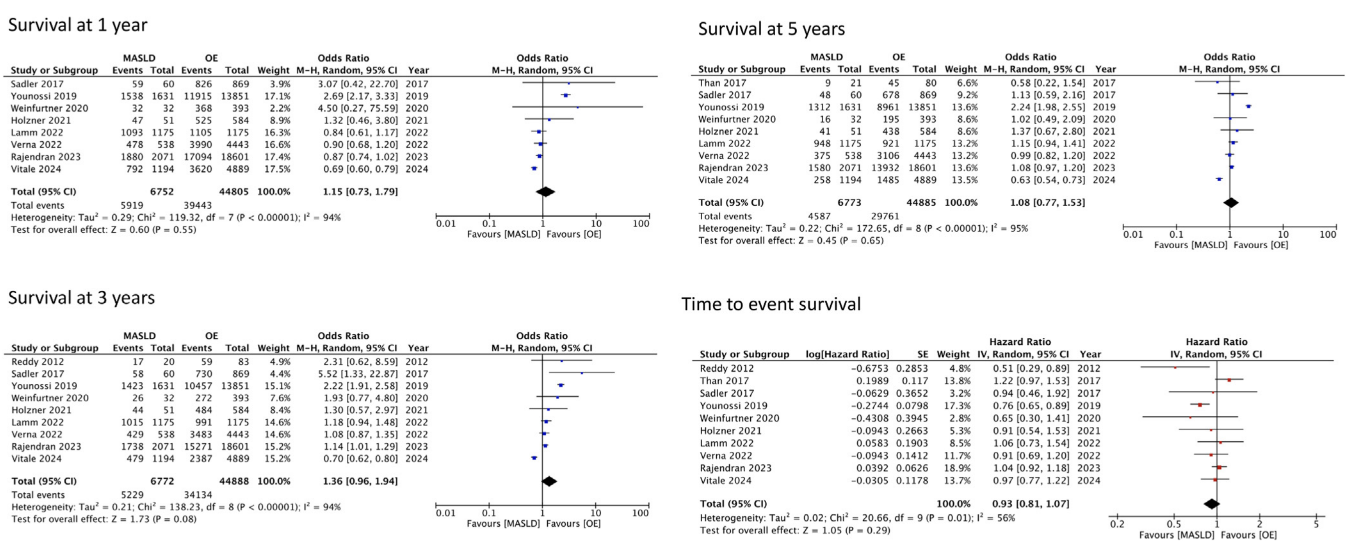

Fig. 2. Meta-Analysis on recipient overall survival post-transplant for MASLD vs OE related HCC.

3.2. Risk of bias assessment

Overall, one study had a total NOS score of 7 points, whereas eight studies had a score of 8 points. Only one study had an overall NOS score of 9 points. The risk of bias assessment following NOS is presented in **supplementary Table 1**.

3.3. Survival outcomes after liver transplantation

Posttransplant outcomes are summarized in Fig. 2, Fig. 3**, Supplementary Table 3**.

3.4. Patient survival

Survival outcomes are summarized in Fig. 2.

Overall survival (time-to-event). Ten studies (51′761 patients) were included in the analysis of OS. The time-to event analysis demonstrated that there was no significant difference in OS between the MASLD and OE groups (HR 0.93, 95 % CI 0.81–1.07, $p = 0.29$). Moderate heterogeneity detected among the included studies (I^2:56 %, $p = 0.01$).

1-year survival. Eight studies (51′557 patients) were included in the analysis of 1-year survival. The rates of 1-year survival in the

Table 2
Baseline characteristics of the nine included studies.

First author	Recipient age (y), Mean (SD)* or Median (IQR)		Recipient male, n (%)		Recipient BMI (kg/m^2), Median (IQR)		Recipient lab MELD points, Median (IQR)		Recipient pre-LT AFP (ng/mL), Median (IQR)		Milan in, n (%)	
	MASLD HCC	OE HCC	MASLD HCC	OE HCC	MASLD HCC	OE HCC	MASLD HCC	OE HCC	MASLD HCC	OE HCC	MASLD HCC	OE HCC
Reddy	65 (57.0–70.0)	58 (53.0–67.0)	27 (51.9)	135 (83.3)	31.3 (27.6–33.9)	28.7 (25.9–32.0)	NA	NA	11.0 (6.0–16.9)	16.5 (6–106)	NA	NA
Than	58.9 (5.5)	54.0 (7.2)	18 (86.0)	69 (86.0)	NA	NA	10 (8.0–15.0)	8 (7.0–11.0)	5 (3–8)	11 (5–39)	NA	NA
Sadler	63.1 (60.5–67.6)	58.8 (54.1–62.8)	37 (61.7)	708 (81.5)	NA	NA	11 (8.0–14.0)	10 (8.0–14.0)	6 (3–16.9)	9 (4–37.1)	44 (74.6)	686 (79.0)
Younossi	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Weinfurtner	NA	NA	NA	NA	NA	NA	NA	NA	6 (4–29)	8 (4–24)	16 (50.0)	165 (42.1)
Holzner	65 (63.5–67.3)	60 (55–65)	36 (70.6)	468 (80.1)	NA	NA	15 (11.0–21.0)	13 (9.0–18.0)	4.6 (3.2–10)	8.8 (4.7–28.6)	48 (94.1)	541 (93.3)
Lamm	64 (60.0–68.0)	64 (60.0–67.0)	797 (67.8)	797 (67.8)	31.8 (28.2–35.5)	27.7 (24.6–31.6)	12 (9.0–16.0)	12 (9.0–16.0)	NA	NA	NA	NA
Verna	63.4 (58.0–67.3)	57.9 (53.0–62.5)	365 (67.8)	3517 (79.2)	30.5 (26.9–33.9)	27.4 (24.6–31.0)	15 (11.0 - 21.6)	13 (9.3 – 19.0)	7.2 (4.7–25.1)	20.3 (7.5–97.0)	348 (64.8)	3253 (73.5)
Rajendran	64.0 (59.0–67.0)	60.0 (55.0–64.0)	1380 (66.7)	14,612 (78.2)	31.8 (28.0 – 35.5)	27.8 (24.7–31.5)	14.0 (10.0 – 20.0)	12.0 (9.0–17.0)	5.0 (3.0 – 10.0)	9.0 (4.0–27.0)	1412 (96.6)	13,355 (95.9)
Vitale	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

* Data in *italics are expressed as mean (SD)*AFP: alpha-feto protein; BMI: Body mass index; HCC: Hepatocellular carcinoma; MELD: Model End-stage Liver Disease; NASH: Non-alcoholic steatohepatitis; NA: not available; OE: other etiologies.

MASLD and OE groups were 87.6 % and 88 %, respectively. There was no statistically significant difference in 1-year survival between two groups (OR:1.15; CI$_{95\ \%}$0.73–1.79,$p = 0.55$). Considerable between-study heterogeneity was detected (I^2:94 %, $p < 0.00001$).

3-year survival. Nine studies (51′660 patients) were included in the analysis of 3-year survival. The rates of 3-year survival in the MASLD and OE groups were 77.2 % and 76 %, respectively. There was no statistically significant difference in 3-year survival rates between two groups (OR:1.36; CI$_{95\ \%}$0.96–1.94, $p = 0.08$). Considerable between-study heterogeneity was detected (I^2:94 %, $p < 0.00001$).

5-year survival. Nine studies (51′658 patients) were included in the analysis of 5-year survival. The rates of 5-year survival in the MASLD and OE groups were 67.7 % and 66.3 %, respectively. There was no statistically significant difference in 5-year survival rates between two groups (OR:1.08; CI$_{95\ \%}$0.77–1.53, $p = 0.65$). Considerable between-study heterogeneity was detected (I^2:95 %, $p < 0.00001$).

Notably, none of the studies included in this meta-analysis reported the graft survival, therefore for survival outcome solely the recipient survival was analyzed.

3.5. Disease-free survival

DFS outcomes are summarized in Fig. 3.

1-year DFS. Three studies (6′335 patients) were included in the analysis of 1-year DFS. The rates of 1-year DFS in the MASLD and OE groups were 87.9 % and 87 %, respectively. There was no statistically significant difference in 1-year DFS rate between two groups (OR 1.07; CI$_{95\ \%}$0.83–1.37, $p = 0.62$). Low between-study heterogeneity was detected (I^2:0 %, $p = 0.44$).

3-year DFS. Three studies (6′335 patients) were included in the analysis of 3-year DFS. The rates of 3-year DFS in the MASLD and OE groups were 77.6 % and 73.6 %, respectively. There was no statistically significant difference in 3-year survival rates between two groups (OR 1.66; CI$_{95\ \%}$0.86–3.21, $p = 0.13$). Moderate between-study heterogeneity was detected (I^2:71 %, $p = 0.03$).

5-year DFS. Three studies (6′335 patients) were included in the analysis of 5-year DFS. The rates of 5-year DFS in the MASLD and OE groups were 68 % and 65.6 %, respectively. There was no statistically significant difference in 5-year survival rates between two groups (OR 1.37; CI$_{95\ \%}$0.67–2.79, $p = 0.39$). Considerable between-study heterogeneity was detected (I^2:79 %, $p = 0.009$).

3.6. Sensitivity analysis

The direction of the described pooled effects size remained largely unchanged during the leave-one-out sensitivity analysis for most outcomes, in particular survival rates (**Supplementary Table 4, 5, 6**). An individual removal of Younossi ($p = 0.02$) and Vitale ($p = 0.01$) resulted in statistically significant for 1-year and 3-year OS, respectively. An individual removal of Verna ($p = 0.004$) turned results statistically significant for 3-year DFS.

4. Discussion

This is the first meta-analysis comparing outcomes of LT for HCC in MASLD versus other indications for transplantation. The recipient OS rates at 1-, 3- and 5-year were similar between MASLD and OE-related HCC. Similarly, the DFS rates at 1-, 3- and 5-year were comparable between the two groups. Furthermore, our study evaluated the pooled HRs, which is the gold standard in a time-dependent survival analysis and showed no differences in time-to-event survival between MASLD and OE-related HCC.

A trend towards a more frequent sedentary lifestyle together with excess calories intake have led to a sharp increase in obe-

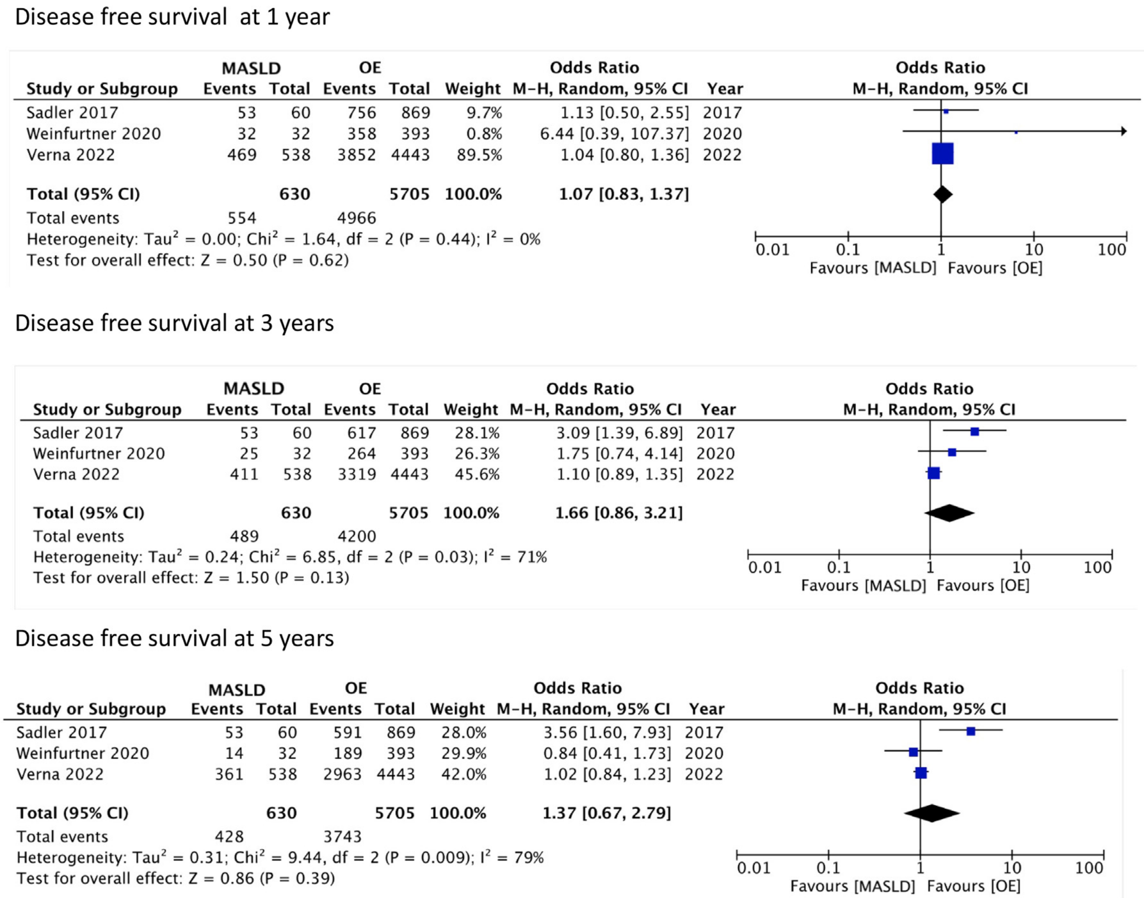

Fig. 3. Meta-Analysis on recipient disease free survival post-transplant for MASLD vs OE related HCC.

sity rates worldwide [1,2]. The global epidemic of obesity is affecting both developed and developing countries. Obesity is a strong independent risk factor for the development of both hepatic and extra-hepatic disease, which include MASLD and HCC [25]. Surprisingly, MASLD seems to affect one-third-of the adult population and is increasing even in countries where, historically, there has been low obesity rates, such as South Korea [5] and Japan [26], and it is predicted to become a significant healthcare burden in Asia [27]. These results are alarming, as it has been shown that the hepatic microenvironment of patients affected by MASLD promotes carcinogenesis [28]. In this regard, a meta-analysis from the US evaluated 1’599’453 patients and showed that individuals with obesity had a 2-fold increased risk of HCC-related mortality [29]. The incidence of HCC and overall death cases is markedly increased even in the Asian population [27]. As overweight and obesity become a global problem, there is mounting evidence that number of LT for end stage liver disease related to MASLD will continue to rise accordingly. Two recent studies from the US analyzing UNOS database highlighted that MASLD surpassed HCV as the leading cause for waitlist registrations and cases of MASLD-related HCC increased over time [30,31]. Another study showed that, in 2017, MASLD-related HCC represented 18 % of all HCC listings, which was an 8.5-fold increase from 2002, and the trend still is growing steadily at approximately 1.9 percentage points per year over the past 4 years [20]. A recent report analyzed the Scientific Registry of Transplant Recipients between 2013 and 2022 showing that, in candidates without HCC, MASLD increased from 19 % to 27 %. However, among the HCC cohort, MASLD increased from 10 % to 31 % and the rapid increase in the proportion of MASLD-related HCC continued during the most recent study years with 20 % in 2018, 28 % in 2020, and 31 % in 2022 [32]. The results of these studies underline the trend that MASLD-related HCC will likely increase further in the near future. Moreover, MASLD-related HCC tends to be diagnosed at later stages compared to OE, perhaps due to less established surveillance practices [33,34]. In addition, some studies have highlighted that patients affected by MASLD-related HCC are less likely to be offered liver resection or LT [35]. Nevertheless, in our study we did not find any significant differences in survival outcomes or DFS for MASLD-HCC versus OE. Our results highlight that positive outcomes are possible for this population and these patients should be considered for LT when indicated. Notably, one study reported that there was a significantly greater proportion of post-transplantation deaths from cardiovascular complications in the MASLD HCC group compared to OE, whereas the latter had higher proportions of deaths attributed to liver-related causes [23].

These trajectories pose unique challenges for transplant physicians. As demonstrated by our study, MASLD-related HCC recipients tend to be older, have higher BMI and diabetes which are conditions intimately linked with cardiovascular risk, metabolic syndrome, and increased comorbidities. These findings are in line with other studies which showed that MASLD patients have higher incidence of other medical conditions [9,35,36]. Of note, one study demonstrated that coronary artery disease is linked to significantly impaired survival after LT, especially when associated with MASLD [36]. Another study demonstrated that MASLD candidates are more often declined for LT given the higher rates of medical comorbidities. However, outcomes of those who undergo LT appear to be similar [9]. Our results are in line with this report and appear to be of great relevance given the increasing number of waitlist candidates affected by MASLD. However, the cause of death in both populations were not homogeneously reported in the studies. This poses significant challenges to understand the real impact of HCC recurrence on survival of patients, especially when comparing differences between etiologies.

Interestingly, the MASLD cohort had lower levels of pre-transplant AFP compared to OE. Some studies have demonstrated similar results [19,34,37]. Benhammous et al. evaluated the OS and HCC recurrence rates between NAFLD and viral (HBV/HCV) associated HCC. They showed that NAFLD-HCC cases were less likely to exhibit elevated serum AFP and, after HCC treatments, NAFLD-HCC patients had longer OS but not recurrence-free survival rates [37]. Another study, although with a limited number of patients, illustrated that, in patients undergoing LT, on explant pathology NAFLD-HCC had less vascular invasion and less likely to be poorly differentiated compared to HCV-HCC [38]. Overall, these results seem to support the evidence that, in patients undergoing LT, HCC burden in MASLD might be attenuated compared to OE, in particular viral etiologies. In our study, MASLD patients were less likely within Milan criteria compared to OE, however this did not translate into worse OS and DFS. The reasons behind these findings are still uncertain, however it could be possible that the tumor biology might to be more favorable in MASLD patients. The pathogenesis of HCC in this population has peculiar features with intricate interaction between liver microenvironment, chronic inflammation and increased carcinogenesis triggered by obesity and metabolic syndrome which are still under investigation [28]. Our results warrant the need for further research to better understand the biological tumoral behavior in this cohort of patients.

This meta-analysis has several limitations, which have to be acknowledged when interpreting the results. First, ten retrospective studies were identified without any randomized controlled trials. Although it would be challenging to conduct a randomized controlled trial on this topic, retrospective studies have inherently selection bias, thus limiting the robustness of our results. At the same time, patients with MASLD may have undergone a selection process that discards the most severe comorbidities, and this might represent a selection bias leading towards same post-transplant survival as other indications which we were not able to discern in our study. Moreover, when evaluating post-transplant outcomes, only one study [23] illustrated meticulously the causes of death, therefore a formal analysis was not feasible. Second, the pre-transplant HCC characteristics and post-transplant outcomes were not homogenously reported by all studies. For instance, we were not able to assess the DFS for all the included studies as only three reported this outcome. In addition, a subgroup analysis with different tumor criteria and their relationship with survival outcomes was not possible due to a relevant underreporting seen in almost every study. Third, the I^2, which is a measure of heterogeneity, was greater than 90 % in the OS analysis, which could be partially explained by the rather large sample size of the included patients. Although this has been previously well-recognized [39], the increased heterogeneity warrants careful interpretation of our results. Next, eight out of ten studies were based in North America (US and Canada) with only one study based in the UK and one based in Italy. Reports from Asia and other continents are lacking. In light of this, the results might not be widely generalizable to other countries, particularly those where healthcare system, allocation policies and population demographics differ considerably from North America, Italy and the UK. Lastly, in 2020 and 2023 the change to new nomenclatures in MAFLD/MASLD have been published [3,4]. In this regard, some of the reports included in this study used the former nomenclature of NAFLD/NASH or cryptogenic cirrhosis without differentiation between steatotic liver disease, MASLD or MetALD. Consequently, some patients with MetALD/cryptogenic cirrhosis could have been classified as NAFLD/MASLD or vice versa, leading to selection bias which we were not able to quantify in this study.

This meta-analysis based on ten retrospective cohort studies, provides the highest available evidence, and shows similar survival outcomes after LT for MASLD-related HCC compared to OE-related HCC. These results appear relevant given the increasing number of waitlist candidates diagnosed with MASLD-related HCC which are expected to rise further in the next future. Nevertheless, larger study from other continents, such as Europe and Asia, are needed to confirm our findings.

Author contributions

Study concept: AP, FM, AS; Study design: AP, FM, AS; Data curation, investigation and collection: AP, FM, SH, SH, AS; Data analysis and interpretation: AP, FM, SH, SH, AS; Project administration and resources: AP, FM, AS; Resources, validation and visualization: AP, FM, AS; Writing – original draft: AP, FM, AS; Writing – review & editing: all authors revised and approved the manuscript

Ethical approval

Considering the design of our study, ethical approval was not required. This article does not contain original data of human participants.

Informed consent

No patient data were collected for our study, thus informed consent was not required.

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None to declare.

Data sharing

Template data collection forms, data extracted from included studies, data used for all analyses, analytic code are confidential but can be shared upon reasonable request to corresponding author.

Conflict of interest

Nothing to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.09.025.

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