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Original Article A Systematic Review and Meta-Analysis of Liver Transplant Outcomes in Lean Versus Non-Lean Metabolic Dysfunction-Associated Steatotic Liver Disease Patients

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ABSTRACT

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent hepatic disease with metabolic dysfunction-associated steatohepatitis (MASH) as its severe necro-inflammatory subtype. At present, it is the second leading cause of liver transplant. A systematic literature review (SLR) was conducted to assess the effect of lean vs non-lean BMI on clinical outcomes after transplant in MASLD patients.

Methods: A systematic search of PubMed, Cochrane Library, and Google Scholar databases was executed. Review Manager 5.4.1 was used for statistical analyses. A random-effect model was used with the results reported as Odds Ratio (OR) and 95% confidence interval (CI). A narrative approach was used where it was not feasible to conduct a meta-analysis.

Results: Eleven observational studies were included in the SLR. Pooled results from three studies showed no significant difference in mortality between lean and non-lean patients at 1 year (OR= 0.78, p= 0.76), 2 years (OR= 0.83, p= 0.24), and 5 years (OR= 1.07, p= 0.51) post-transplant. There was also no significant relation of lean and non-lean BMI in graft survival, observed over 30 days (OR= 1.34, p= 0.27), 1 year (OR= 0.75, p= 0.25), 2 years (OR= 1.20, p= 0.45), and 5 years (OR= 1.07, p= 0.60) post-transplant. Qualitative analysis suggested morbid obesity is linked with higher waitlist dropout in MASH patients.

Conclusion: The qualitative analysis of eight studies indicates a trend towards poorer outcomes in the non-lean group. There is a need for further investigations to comprehensively examine the factors influencing the relationship between BMI and post-transplant outcomes.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent hepatic condition characterized by a build-up of macrovesicular steatosis in $\geq 5\%$ of hepatocytes, occurring without significant alcohol or drug consumption [1]. A recent review of 72 records described the overall prevalence of MASLD worldwide increased significantly over time, from 25.5% before 2006 to 37.8% in 2016 or later [2]. Given the prevalence estimate, MASLD

stands as the primary cause of chronic liver disease worldwide [3]. MASLD shares metabolic risk factors, including type 2 diabetes mellitus, obesity, and hypercholesterolemia, with metabolic syndrome [1]. Diagnosis involves identifying steatosis on ultrasound, often prompted by elevated liver transaminases [1]. Management of MASLD focuses on addressing modifiable risk factors such as blood pressure, body mass index (BMI), cholesterol, and blood sugar levels, with weight reduction being notably associated with decreased fibrosis among patients [4].

Metabolic dysfunction-associated steatohepatitis (MASH) is defined as a severe necro-inflammatory subtype of MASLD, which involves hepatic steatosis accompanied by inflammation and hepatocellular ballooning, which can progress to hepatocellular carcinoma (HCC) [5]. MASH frequently leads to complicated liver cirrhosis or failure, making liver transplantation the primary treatment option and a preventive measure against HCC [6]. MASH has an estimated global prevalence of 5.27% [6] and is currently the second leading indication for liver transplantation [7, 8].

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Although obesity can predispose individuals to various clinical comorbidities and post-operative complications, the impact of obesity on survival and transplantation outcomes in liver transplant patients remains uncertain. The American Society of Transplantation describes morbid obesity (BMI $\ge 40 \text{ kg/m2}$) as a potential contraindication for liver transplant due to the heightened risk of post-transplant complications. A previous study conducted by Barone et al. assessed post-transplant outcomes in obese patients [9], which observed that a BMI > 40 was linked to a greater risk of mortality, while a BMI \geq 30 led to significantly more posttransplant complications [9]. When comparing outcomes in MASH versus non-MASH patients, a meta-analysis by Wang et al. comparing post-transplant outcomes, survival, and mortality rates in liver transplant patients with and without MASH reported similar mortality rates at 1, 3, and 5 years between the two groups, with cardiovascular complications being more common in the MASH group [10]. Another study published in 2022 concluded no significant difference in post-transplant survival between the MASH and non-MASH groups. However, the MASH group exhibited higher sepsis-related mortality and better graft survival [11].

Given the current conflicting data and lack of consensus on the impact of obesity on liver transplant patients, our systematic literature review (SLR) and meta-analysis aim to compare post-transplant outcomes in lean and non-lean MASLD patients who underwent liver transplantation.

2. Methods

2.1. Data sources and search strategy

A SLR and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] was conducted. PubMed, Cochrane Library, and Google Scholar were searched from inception to April 22, 2023. To update the search for any potential new relevant publications, hand searching was performed on November 30, 2024, to identify any additional studies published since the last search date. The search strategy comprised both older and newer terminologies for the disease, including Non alcoholic fatty liver disease (NAFLD), Non-alcoholic fatty steatosis (NASH), MASH, and MAFLD. The search string used was: (NAFLD OR nonalcoholic fatty liver disease OR NASH OR MASLD OR MASH OR non-alcoholic Steatohepatitis OR non-alcoholic cirrhosis) AND (transplant* OR post-transplant*) AND (lean OR BMI OR obese). Additionally, we cross-referenced any identified SLRs to ensure comprehensive coverage.

2.2. Eligibility criteria

The eligibility criteria was formulated using the PECO framework: P (Patients): nonalcoholic fatty liver disease patients or nonalcoholic steatohepatitis patients who underwent transplantation; E (Exposure): BMI ≥ 25 kg/m² pre-transplantation; C (Control): BMI ≤ 25 kg/m² pre-transplantation; O (Outcome): mortality and graft survival/loss. Lean was defined as BMI ≤ 25 kg/m², and non-lean was defined as BMI ≥ 25 kg/m² [13].

2.3. Screening, data extraction, and quality assessment of studies

Two independent reviewers conducted electronic database searches. The retrieved studies were exported to EndNote Reference Library version 20.0.1 software for screening after deduplication. The screening was conducted in duplicate by two reviewers (FP and UH) at the title/abstract and full text stages. Any disagreements or conflicts were resolved through discussion or by a third reviewer (MKG), if needed. Two reviewers (FJ and DSD) independently extracted data and further assessed the risk of bias in the included studies. The variables extracted included study author names, year of publication, study duration, country of origin, total number of patients, BMI, male proportions, mean age, and outcomes reported.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies. NOS score of 1-5 was considered at high risk of bias, 6-7 indicated moderate risk, and scores greater than 7 were considered low risk of bias (**Table 1**).

2.4. Statistical analysis

All statistical analyses were performed using Review Manager (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). The extracted data were pooled using a random-effects model. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated to analyze the results. The chi-square test was used to assess any subgroup differences. Heterogeneity was evaluated using the Higgins et al. scale: $I^2 = 25-60\%$ (moderate), 50-90% (substantial), and 75-100% (considerable heterogeneity) [14]. A p-value < 0.05 was considered statistically significant. A qualitative synthesis was performed on studies that met the inclusion criteria but did not provide data suitable for quantitative analysis.

3. Results

The comprehensive search of electronic databases yielded a total of 1,361 records. After removing duplicates, 946 records underwent title and abstract screening. Out of these, 135 records underwent eligibility assessment based on full-text. Finally, 11 studies [15, 16, 17, 18, 19, 20, 21, 22, 23, 24] were selected for inclusion in the SLR, with evidence from eight studies [18, 19, 20, 21, 22, 23, 24, 25] synthesized qualitatively and three [15, 16, 17] feasible to be included in meta-analysis. The PRISMA flowchart illustrating the study selection process is shown in (**Figure 1**).



Figure 1: PRISMA flow diagram of systematic review process

Table 1: Quality assessment of included studies

		Selection (Maximum 4)		Comparability (Maximum 2)	Outcor			
Study	Representative of the Exposed Cohort	Selection of the Non- Exposed Cohort	Ascertainment of Exposure	Demonstratio That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow- Up Long Enough for Out- comes to Occur	Adequacy of Follow Up of Cohorts	Total Score
Malik et al.	1	1	1	1	2	1	1	1	9
Leonard et al.	1	1	1	1	2	1	1	1	9
Heuer et al.	1	1	1	1	2	1	1	1	9
Kenedy et al.	1	1	1	1	2	1	1	1	9
Conzen et al.	1	1	1	1	2	1	1	1	9
Kardashian et al.	1	1	1	1	2	1	1	1	9
Halder et al.	1	1	1	1	2	1	1	1	9
Eshraghian et al.	1	1	1	1	2	1	1	1	9
Satapathy et al.	1	1	1	1	2	1	1	1	9
Qazi-Arisar et al.	1	1	1	1	2	1	1	1	9

The selected studies, comprising 18,783 patients, were all observational studies. (**Table 2**) provides an overview of the baseline characteristics of the included articles [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25]. These studies were conducted in various geographical regions, including six in the USA, two in Iran, and one each in Europe, Canada, and Germany. The mean age of the patients was 50.8 years.

3.1. Publication Bias and Quality Assessment

Due to the limited number of articles available for quantitative analysis, it was impossible to assess publication bias. However, all the included studies demonstrated a low risk of bias, as assessed by the NOS, as shown in **(Table 1)**.

3.2. Quantitative Analysis

Only three studies [15, 16, 17] were feasible to be included in the meta-analysis. Eight studies [18, 19, 20, 21, 22, 23, 24, 25] could not be included in the quantitative analysis due to heterogeneity of analysis parameters, outcome endpoints, and different BMI cutoffs to classify lean and non-lean patients.

3.2.1. Patient Mortality

Three studies were included in the quantitative analysis to evaluate patient mortality based on pre-transplant BMI [15, 16, 17]. No significant difference was observed in mortality between lean and non-lean patients at 1 year (OR= 0.78 [CI 0.15, 4.01]; p= 0.76; I²= 81%), 2 years (OR= 0.83 [CI 0.62, 1.13]; p= 0.24; I²= 57%), and 5 years (OR= 1.07 [CI 0.87, 1.31]; p= 0.51; I²= 38%) post-transplant (Figure 2).

3.2.2. Graft Survival

Three studies were included in the quantitative analysis to assess graft survival based on pre-transplant BMI [15, 16, 17]. The results showed no statistically significant relationship of BMI with graft survival at 30 days (OR= 1.34 [CI 0.79, 2.26]; p= 0.27), 1 year

 $(OR= 0.75 [CI 0.46, 1.22]; p= 0.25; I^2= 24\%)$, 2 years $(OR= 1.20 [CI 0.75, 1.91]; p= 0.45; I^2= 76\%)$, and 5 years $(OR= 1.07 [CI 0.84, 1.35]; p= 0.60; I^2= 0\%)$ post-transplantation (**Figure 3**).

3.3. Qualitative Analysis

Eight studies were included in the qualitative analysis, which examined the impact of BMI on clinical outcomes [18, 19, 20, 21, 22, 23, 24, 25]. The studies provided varied outcomes assessing the association between BMI and post-transplant outcomes. Eshraghian et al. [25] found an increased risk of hepatic steatosis after liver transplant in patients with a higher BMI. Haldar et al. [19] observed that high BMI (>40 kg/m2) independently predicted death in patients transplanted for NASH without HCC. Kardashian et al. [20] reported that morbid obesity was significantly linked to waitlist dropout in MASH patients with and without ascites (hazard ratio (HR) = 1.27 [1.20, 1.36]). Heur et al. [22] observed that sustained obesity and features of the metabolic syndrome in patients were associated with worse 1-year mortality. Kennedy et al. [23] noted worse survival in the high-risk cohort (age >60 years, BMI >30 kg/m2, and the presence of both diabetes and hypertension). Meanwhile, Satapathy et al. [21] described lean NASH patients to have lower graft and patient loss at 10 years follow-up than their obese counterparts. A sub-analysis from Malik et al. [24] revealed that patients transplanted for NASH cirrhosis who died within the first year post-transplant were older (≥60 years), more obese (BMI ≥30 kg/m2), and had pre-transplant DM and HTN. Eshragian et al. [18] observed a higher BMI to be marginally associated with NASH occurrence in non-obese compared to those without NASH (P=0.05). BMI-related results in these studies were often available without complete raw data, and with variable follow-up durations and outcomes; therefore, they could not be added to the metaanalysis.

Table 2:	Characteristic	cs of Inc	luded Studies	
Lanc 2.	Characteristi	cs of me	iuuuu stuuies	

Study	Year	Study design	Duration	Country	Total patients (n)	BMI <25 kg/m ² (n)	$BMI \\ \ge 25 \\ kg/m^2 \\ (n)$	Male (%)	Mean Age (years)	Qualitative or Quantitative	Outcomes reported	Risk of Bias
Malik et al.	2008	Cohort	July 1997-June 2008	USA	98	N/A*	N/A*	44.9	59.8	Qualitative	Mortality	Low Risk
Leonard et al.	2008	Cohort	April 1990-June 1994	USA	1313	628	685	60.4	50.8	Quantitative	Patient mortality, Graft survival	Low Risk
Heuer et al.	2012	Cohort	Oct 2007-Jan 2011	Germany	40	4	36	60	N/A*	Qualitative	Mortality, Graft failure	Low Risk
Kenedy et al.	2012	Cohort	1999-2009	USA	129	N/A*	N/A*	47	57	Qualitative	Patient survival	Low Risk
Conzen et al.	2015	Cohort	Jan 2002-Dec 2012	USA	785	219	566	67.2	N/A*	Quantitative	Patient mortality, Graft survival	Low Risk
Kardashian et al.	2018	Cohort	March 2002-Dec 2013	USA	10001	N/A*	N/A*	66.3	N/A*	Qualitative	Waitlist dropout	Low Risk
Halder et al.	2019	Cohort	Jan 2002-Dec 2016	Europe	2741	N/A*	N/A*	71.1	N/A*	Qualitative	Patient survival	Low Risk
Eshraghian et al.	2020	Cohort	July 2012-Oct 2018	Iran	310	246	64	42	32.64	Qualitative	Prevalence	Low Risk
Eshraghian et al.	2020	Cohort	March 2010- March 2017	Iran	462	N/A*	N/A*	65.5	46.9	Qualitative	Graft rejection	Low Risk
Satapathy et al.	2020	Cohort	Jan 2002-June 2013	USA	2728	278	2450	54.3	57.9	Qualitative	Patient survival and Graft loss	Low Risk
Qazi-Arisar et al.	2022	Cohort	Nov 2012-May 2019	Canada	176	54	122	53.9	N/A*	Quantitative	Patient mortality, Graft survival	Low Risk

N/A*= Not Available

4. Discussion

The current SLR and meta-analysis evaluated the role of BMI in post-transplant outcomes in patients with MASLD who underwent liver transplantation. Our analysis included both quantitative and qualitative evidence synthesis. The quantitative analysis did not find a significant association between long-term mortality rates and graft survival when comparing lean and non-lean patients [15, 16, 17]. While the qualitative analysis of eight studies observed a trend towards poorer outcomes in the non-lean patients [18, 19, 20, 21, 22, 23, 24, 25], statistical association could not be assessed. These findings align with previous studies that have shown a relationship between obesity and poorer outcomes following liver transplantation. Evidence in the literature is mixed regarding any differences in outcomes between lean and non-lean patients. One of the initial studies conducted by Nair et al. served as the basis for the American Association for the Study of Liver guidelines in 2005, which contraindicated liver transplantation for morbidly obese individuals. Subsequent studies, such as those by Beckmann et al., further supported this association, showing worse survival and graft survival rates in patients with a pre-transplant BMI higher than 30 kg/m² [26, 27]. However, variations in study populations

and primary causes of transplantation introduced heterogeneity in the results.

Interestingly, when accounting for concomitant comorbidities, studies have not consistently established an independent link between obesity and liver transplantation outcomes. Wong et al. demonstrated that when diabetes was considered, the survival rates between obese and non-obese patients were similar [3]. Additionally, some studies reported improved survival rates in patients with moderately elevated BMI, highlighting the potential confounding effect of being underweight on post-transplant survival [28, 29].

To explain the heterogeneity observed in study results, further analysis is needed regarding the definition of BMI and its relationship to MASLD/MASH patients. The use of BMI as an estimate of body adiposity has limitations, as it does not account for variations in body composition. In MASLD/MASH patients, ascites or volume overload may lead to overestimating body weight [26, 30]. Moreover, racial disparities in BMI cutoffs, particularly in the Asian population, may contribute to discrepancies in outcomes among liver transplant patients [31].



Figure 2: Forest plot of Mortality in lean vs. non-lean patients.

Furthermore, post-transplant mortality in MASLD patients can result from various factors, including disease recurrence, allograft rejection, progression to MASH cirrhosis or HCC, and metabolic syndrome [17, 32]. Higher BMI is associated with an increased risk of cardiovascular incidents and metabolic symptoms, which may confound the association between high BMI and survival [33, 34].

Our study also did not find a statistically significant association between BMI and graft survival. However, graft survival is multifactorial and depends on factors such as compliance with immunosuppressive therapy [35]. Previous studies have reported conflicting results, with some suggesting that obesity significantly impacts graft survival while others have found no significant differences [15, 17, 29]. The inconsistency in results can be attributed to variations in the definition of obesity and the inclusion of fluid overload rather than true obesity in some studies.

It is worth mentioning that some studies have associated BMI with HCC, potentially due to pro-inflammatory cytokine production by adipose tissue [17, 36, 37, 38]. However, the mechanism underlying this association remains unclear.

4.1. Strengths and Limitations

Our study's strengths include searching multiple databases to ensure comprehensive coverage and the inclusion of several studies with larger sample sizes and longer follow-up periods. Furthermore, while previously published meta-analyses do not determine the transplant outcomes regarding BMI in MASLD patients or MASH patients, we specifically focused on both subgroups, which consist of a substantial number of liver transplant patients.

The findings of this review require cautious interpretation due to some limitations. Firstly, only three studies were included in the quantitative analysis due to a lack of studies reporting sufficient raw data and heterogeneity in BMI classifications, outcome endpoints, and their durations, limiting the feasibility of producing pooled estimates. Furthermore, the low number of studies and the limited sample size in the quantitative analysis may underestimate the important effects that could have emerged better in larger and uniform datasets, reduce the statistical power of the pooled estimates, and limit the generalizability of findings. This limitation stresses the urgent need for future research to adopt standardized BMI classifications and outcome definitions. Secondly, all included studies were observational, which may introduce potential selection, reporting, and confounding biases that are inherent to non-randomized study designs. Thirdly, normal weight and underweight patients were pooled as "lean" (BMI 25 kg/m²) and all overweight and obese patients grouped as "non-lean" (BMI \geq 25 kg/m²), potentially obscuring important differences within these groups. Lastly, the quantitative analysis focused primarily on mortality and graft survival, not extensively analyzing other important post-transplant outcomes such as length of hospital stay, complications, quality of life, or disease recurrence, which can be critical for understanding transplant success in these patients.

Future research requires focusing on a few critical areas, including conducting larger, multicenter, international studies to gather representative data on MASLD patients across various racial and geographical backgrounds. Investigating any pathophysiological mechanisms driving MASLD progression in lean versus non-lean patients, which can include metabolic and genetic factors that may potentially influence liver transplant outcomes, and moving beyond BMI-based classifications to include other analyses of body composition (e.g., muscle mass, fat distribution) and their effect on post-transplant outcomes should be considered. Prospective multicentric studies with standardized BMI classifications can be conducted for appropriate comparability across studies. Additionally, future analyses can stratify outcomes by the different categories of BMI and control for confounding comorbidities. A shared data registry with uniform definitions, follow-up durations, and outcomes can facilitate pooled analyses of a larger cohort of patient data across multiple centers. Although the quantitative analysis from three studies did not identify any relation of BMI

	BMI < 25 k	(a/m2	BMI > 25	ka/m2		Odds Ratio			Odds Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	Year		M-H. Random, 95% CI
1.2.1 1 year survival									
Leonard et al.	528	628	591	685	82.4%	0.84 [0.62, 1.14]	2008		
Qazi-Arisar et al.	22	29	72	82	17.6%	0.44 [0.15, 1.28]	2022		- _
Subtotal (95% CI)		657		767	100.0%	0.75 [0.46, 1.22]			
Total events	550		663						
Heterogeneity: Tau ² =	0.05; Chi ² =	1.31, df:	= 1 (P = 0.2	5); I ² = 24	1%				
Test for overall effect:	Z = 1.16 (P =	= 0.25)							
1.2.2 2 year survival									1
Leonard et al.	511	628	562	685	53.2%	0.96 [0.72, 1.26]	2008		• •
Conzen et al.	171	219	395	566	46.8%	1.54 [1.07, 2.23]	2014		
Subtotal (95% CI)		847		1251	100.0%	1.20 [0.75, 1.91]			-
Total events	682		957						
Heterogeneity: Tau ² =	0.09; Chi ² =	4.13, df:	= 1 (P = 0.0	4); I ² = 76	i%				
Test for overall effect:	Z = 0.75 (P =	= 0.45)							
1.2.3.5 year survival									
Leonard et al	467	628	499	685	95.3%	1 08 00 85 1 381	2008		_
Qazi-Arisar et al		29	17	82	4 7%	0.80 (0.26, 2.40)	2000		
Subtotal (95% CI)		657		767	100.0%	1.07 [0.84, 1.35]	LOLL		★
Total events	472		516						[
Heterogeneity: Tau ² =	0.00; Chi ² =	0.28, df:	= 1 (P = 0.6	0); $l^2 = 0.9$	6				
Test for overall effect:	Z = 0.52 (P =	= 0.60)							
								0.01	U.1 1 1U 1UU Eavoure IBMI > 25 ko/m21 Eavoure IBMI < 25 ko/m21
Test for subgroup diffe	erences: Chi	i ² = 2.11,	df = 2 (P =	0.35), I ² =	5.2%				ravours (omi 2 25 kg/m2) - ravours (omi 5 25 kg/m2)

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Figure 3: Forest plot of Graft Survival in lean vs. non-lean patients

with post-transplant outcomes, transplant centers can move beyond BMI when assessing the candidacy of MASLD patients for liver transplant. The clinical assessment and decision-making can incorporate additional clinical factors, including metabolic health, other comorbid conditions, and functional status [39].

5. Conclusions

In conclusion, the quantitative analysis did not demonstrate a significant impact of BMI on post-transplant outcomes in MASLD patients. However, the qualitative analysis indicated a trend towards an association between higher BMI and poor post-transplant outcomes, although statistical conclusions could not be definitively drawn. Our study is useful as it plays a pivotal role in presenting and summarizing all the available evidence, highlighting the existing dichotomy in the literature, and its potential causes. It also emphasizes the need for future investigations to consider key parameters that may influence the relationship of BMI with post-transplant outcomes.

Conflicts of Interest

None

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Institutional Review Board (IRB)

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Large-Language Model

None

Authors Contribution

Author contributions: MGSDS and MKG conceptualized the study design and objectives. MA, FP, DSD, UH, FJ, HA, and SI conducted the literature search, study screening, selection, and data extraction. MKG, OI, and MA designed the data extraction template, extracted data, and carried out data analysis. OI, MA, FP, DSD, UH, FJ, HA, and SI drafted the initial manuscript. MKG, SI, and MGSDS critically reviewed and revised the final manuscript. MGSDS is the guarantor, and the manuscript has been critically reviewed. All authors approve the final manuscript as submitted for publication.

Data Availability

All studies used in the research are available in various databases.

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