Mortality in patients with lean NAFLD: a systematic review and meta-analysis

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Introduction

- While obesity is a major contributing factor to NAFLD, approximately 40% of patients with NAFLD are nonobese and 20% are lean.
- With recent efforts to characterize lean NAFLD, studies have shown that patients with lean NAFLD have more favorable metabolic profiles, less degree of fibrosis, and less NAFLD activity compared to non-lean NAFLD.
- Current management of NAFLD is largely focused on modification of lifestyle-related risk factors and weight loss, which is less feasible for lean patients, however, is considered the cornerstone in the improvement of disease severity.
- We aimed to assess the comparative risk of mortality in patients with lean versus non-lean NAFLD.

Methods

- We systematically searched PubMed (Medline), Embase, and Cochrane Library from inception to May 2022 for cohort studies comparing clinical outcomes of lean and non-lean patients with NAFLD.
- Lean NAFLD was defined as NAFLD in patients with body mass index (BMI) <25 kg/m^2 (some studies applied BMI <23 kg/m^2 for Asian and Pacific Islanders).
- The risks of all-cause mortality, liver-related mortality, and cardiovascular mortality in patients with lean NAFLD compared to those with non-lean NAFLD were estimated as pooled relative risks (RRs) using the DerSimonian and Laird random-effects method.

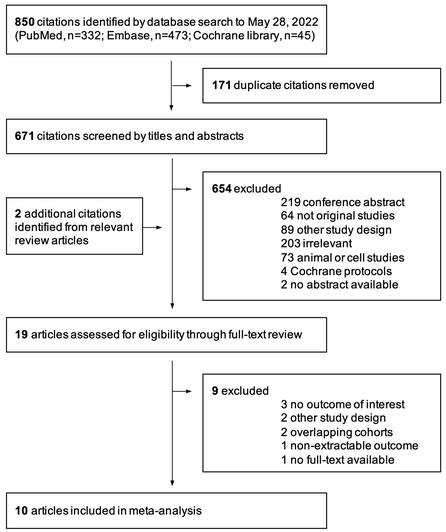

Figure 1. Literature selection

Results

Ten cohort studies involving 109,151 NAFLD patients were included. Patients with lean NAFLD had comparable risks for all-cause mortality (RR, 1.09; 95% confidence interval [CI], 0.66-1.90), cardiovascular mortality (RR, 1.12; 95% CI, 0.66-1.90). However, the risk of liver-related mortality was higher in patients with lean than non-lean NAFLD patients (RR, 1.88; 95% CI, 1.02-3.45).

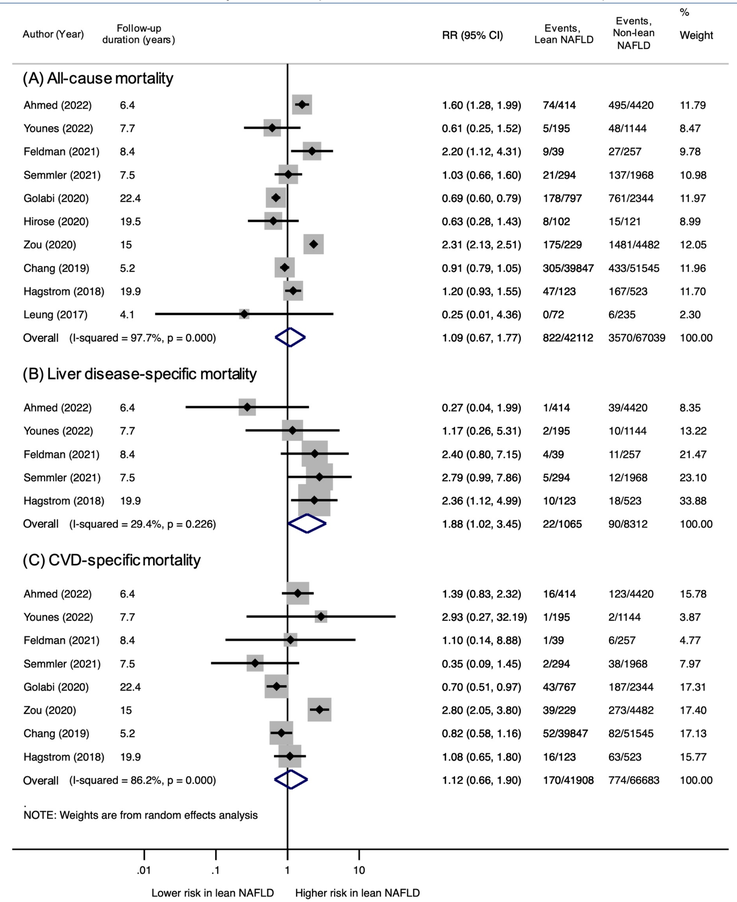

Figure 2. Comparative risk of all-cause mortality, liver disease-specific mortality, and cardiovascular-specific mortality in lean versus non-lean NAFLD patients

Results

Table 1. Subgroup analyses of mortality between lean and non-lean NAFLD groups.

	Number of studies	RR (95% CI)	Number of events/total (lean NAFLD)	Number of events/total (non-lean NAFLD)	I^2 (%)
All-cause mortality					
NAFLD diagnosis					
Biopsy-proven only	5	1.04 (0.63-1.70)	822/42,112	3,570/67,039	55.6
Ultrasound	5	1.19 (0.61-2.33)	753/41,581	3,307/64,759	98.9
Study design					
Prospective	2	0.56 (0.24-1.34)	5/267	54/1,379	0.0
Retrospective	8	1.20 (0.72-1.99)	817/41,845	3,516/65,660	98.1
Study region					
Eastern countries	3	0.90 (0.78-1.04)	313/40,021	454/51,901	0.0
Western countries	7	1.25 (0.69-2.26)	509/2,091	3,116/15,138	98.1
Liver- related mortality					
NAFLD diagnosis					
Biopsy-proven only	3	2.15 (1.21-3.80)	16/357	39/1,924	0.0
Ultrasound	2	1.00 (0.08-12.20)	6/708	51/6,388	80.3
Study design					
Prospective	1	1.17 (0.26-5.31)	2/195	10/1,144	NA
Retrospective	4	1.96 (0.95-4.04)	20/870	80/7,168	42.0
Study region					
Eastern countries	0	NA	NA	NA	NA
Western countries	5	1.88 (1.02-3.45)	22/1,065	90/8,312	29.4

Discussion

- A causal relationship between low BMI and higher liver-related mortality needs to be confirmed from further prospective studies.
- A higher frequency of *PNPLA3* rs738409 GG genotype in lean NAFLD patients, which is associated with higher liver-related mortality and differences in microbiome and body composition could be possible explanations for these findings.
- Limitations of this study include the observational design of the included studies, significant heterogeneity in the primary analysis, and possible potential confounders that were not evaluated including metabolic and histologic profiles, the severity of NAFLD, and genotypes.

Conclusion

This study highlights a higher risk of liver-related mortality in patients with lean NAFLD than those with non-lean NAFLD. This finding indicates that further understanding of the pathophysiology, risk factors of adverse outcomes, and genetic and ethnic variabilities of lean NAFLD phenotype is warranted for individualized treatment strategies in lean NAFLD patients.

Contact

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References

1. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology. 2020;5(8):739-752.
2. Sookoian S, Pirola CJ. Systematic review with meta-analysis: the significance of histological disease severity in lean patients with nonalcoholic fatty liver disease. Alimentary pharmacology & therapeutics. 2018;47(1):16-25.
3. Wijarnpreecha K, Scribani M, Raymond P, et al. PNPLA3 Gene Polymorphism and Liver- and Extrahepatic Cancer–Related Mortality in the United States. Clinical Gastroenterology and Hepatology. 2021;19(5):1064-1066.
4. Stender S, Kozlitina J, Nordestgaard BG, Tybjærg-Hansen A, Hobbs HH, Cohen JC. Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci. Nature Genetics. 2017;49(6):842-847.