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.

| Met | thods |
|---|---|
| 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/m² (some studies applied BMI <23 kg/m² for Asian | 850 citations identified I (PubMed, n=332; Embal 671 citations screened 2 additional citations identified from relevant review articles |
| 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. | 19 articles assessed for 10 articles included in n Figure 1. Literature |

Contact

Jane Ha

Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114 Email: jaha@mgh.harvard.edu; Twitter: @JaneHaMD; Phone: 978 429 1831

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

Jane Ha, MD¹; Sun Young Yim, MD²; Raffi Karagozian, MD³ ¹Massachusetts General Hospital, Boston, MA, USA, ²Korea University College of Medicine, Seoul, South Korea; ³Division of Gastroenterology and Hepatology, Tufts Medical Center, Boston, MA, USA



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).

| Author (Year) du | Follow-up uration (years) | RR (95% CI) | Events, Lean NAFLD | Events, Non-lean NAFLD | % Weight |
|--|------------------------------|--------------------|-----------------------|------------------------------|-------------|
| (A) All-cause | mortality | | | | |
| Ahmed (2022) | 6.4 | 1.60 (1.28, 1.99) | 74/414 | 495/4420 | 11.79 |
| Younes (2022) | 7.7 | 0.61 (0.25, 1.52) | 5/195 | 48/1144 | 8.47 |
| Feldman (2021) | 8.4 | 2.20 (1.12, 4.31) | 9/39 | 27/257 | 9.78 |
| Semmler (2021) | 7.5 | 1.03 (0.66, 1.60) | 21/294 | 137/1968 | 10.98 |
| Golabi (2020) | 22.4 | 0.69 (0.60, 0.79) | 178/797 | 761/2344 | 11.97 |
| Hirose (2020) | 19.5 | 0.63 (0.28, 1.43) | 8/102 | 15/121 | 8.99 |
| Zou (2020) | 15 | 2.31 (2.13, 2.51) | 175/229 | 1481/4482 | 12.05 |
| Chang (2019) | 5.2 | 0.91 (0.79, 1.05) | 305/39847 | 433/51545 | 11.96 |
| Hagstrom (2018) | 19.9 | 1.20 (0.93, 1.55) | 47/123 | 167/523 | 11.70 |
| Leung (2017) | 4.1 | 0.25 (0.01, 4.36) | 0/72 | 6/235 | 2.30 |
| Overall (I-square | ed = 97.7%, p = 0.000) | 1.09 (0.67, 1.77) | 822/42112 | 3570/67039 | 100.00 |
| (B) Liver dise | ease-specific mortality | | | | |
| Ahmed (2022) | 6.4 | 0.27 (0.04, 1.99) | 1/414 | 39/4420 | 8.35 |
| Younes (2022) | 7.7 | 1.17 (0.26, 5.31) | 2/195 | 10/1144 | 13.22 |
| Feldman (2021) | 8.4 | 2.40 (0.80, 7.15) | 4/39 | 11/257 | 21.47 |
| Semmler (2021) | 7.5 | 2.79 (0.99, 7.86) | 5/294 | 12/1968 | 23.10 |
| Hagstrom (2018) | 19.9 | 2.36 (1.12, 4.99) | 10/123 | 18/523 | 33.88 |
| Overall (I-square | ed = 29.4%, p = 0.226) | 1.88 (1.02, 3.45) | 22/1065 | 90/8312 | 100.00 |
| (C) CVD-spe | ecific mortality | | | | |
| Ahmed (2022) | 6.4 | 1.39 (0.83, 2.32) | 16/414 | 123/4420 | 15.78 |
| Younes (2022) | 7.7 | 2.93 (0.27, 32.19) | 1/195 | 2/1144 | 3.87 |
| Feldman (2021) | 8.4 | 1.10 (0.14, 8.88) | 1/39 | 6/257 | 4.77 |
| Semmler (2021) | 7.5 | 0.35 (0.09, 1.45) | 2/294 | 38/1968 | 7.97 |
| Golabi (2020) | 22.4 | 0.70 (0.51, 0.97) | 43/767 | 187/2344 | 17.31 |
| Zou (2020) | 15 | 2.80 (2.05, 3.80) | 39/229 | 273/4482 | 17.40 |
| Chang (2019) | 5.2 | 0.82 (0.58, 1.16) | 52/39847 | 82/51545 | 17.13 |
| Hagstrom (2018) | 19.9 | 1.08 (0.65, 1.80) | 16/123 | 63/523 | 15.77 |
| Overall (I-square | ed = 86.2%, p = 0.000) | 1.12 (0.66, 1.90) | 170/41908 | 774/66683 | 100.00 |
| NOTE: Weights are from random effects analysis | | | | | |

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| NOTE: Weights are from random effects analysis | | | | | |

Higher risk in lean NAFL

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

Results

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.

Table 1. S

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| Results |
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| ubgroup analyses of mortality between lean and non-lean NAFLD groups. | | | | | |
|---|-------------------|-------------------|--|--|--------------------|
| | Number studies | of RR (95% CI) | Number of events/total (lean NAFLD) | Number of events/total (non-lean NAFLD) | l ² (%) |
| mortality | | | | | |
| agnosis | | | | | |
| oroven only | 5 | 1.04 (0.63-1.70) | 822/42,112 | 3,570/67,039 | 55.6 |
| nd | 5 | 1.19 (0.61-2.33) | 753/41,581 | 3,307/64,759 | 98.9 |
| sign | | | | | |
| tive | 2 | 0.56 (0.24-1.34) | 5/267 | 54/1,379 | 0.0 |
| ective | 8 | 1.20 (0.72-1.99) | 817/41,845 | 3,516/65,660 | 98.1 |
| ion | | | | | |
| countries | 3 | 0.90 (0.78-1.04) | 313/40,021 | 454/51,901 | 0.0 |
| countries | 7 | 1.25 (0.69-2.26) | 509/2,091 | 3,116/15,138 | 98.1 |
| ated mortality | | | | | |
| agnosis | | | | | |
| oroven only | 3 | 2.15 (1.21-3.80) | 16/357 | 39/1,924 | 0.0 |
| ind | 2 | 1.00 (0.08-12.20) | 6/708 | 51/6,388 | 80.3 |
| sign | | | | | |
| tive | 1 | 1.17 (0.26-5.31) | 2/195 | 10/1,144 | NA |
| ective | 4 | 1.96 (0.95-4.04) | 20/870 | 80/7,168 | 42.0 |
| ion | | | | | |
| countries | 0 | NA | NA | NA | NA |
| 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 liverrelated 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.