Association of All-Cause and Cause-Specific Mortality with High-Risk NAFLD/NASH in US Adults, NHANES III (1988-1994) Linked to Mortality Data through 2019

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BACKGROUND

- Nonalcoholic fatty liver disease (NAFLD) refers to a condition in which excess fat is stored in the liver (hepatic steatosis) and is not attributable to other causes of chronic liver disease (CLD).[1]
  - The progressive form, nonalcoholic steatohepatitis (NASH), distinguished by presence of inflammation and hepatic injury, may lead to fibrosis and potentially cirrhosis, followed by complications including decompensation (i.e., liver failure) and hepatocellular carcinoma (HCC).[1]
- Beyond liver-related complications, cardiovascular (CV) disease is recognized to be a principal cause of death in NAFLD,[2-3] as highlighted in a recent scientific statement by the American Heart Association (AHA).[4]
- With the US Food and Drug Administration's approval of resmetirom (REZDIFFRA™),[5] and other treatments in development for NAFLD/NASH,[6] cost-effectiveness analysis (CEA) of such interventions is of growing interest.[7-9]
- Evidence characterizing the association of NAFLD/NASH with mortality is required for CEA, to inform/validate accurate modeling of the natural history of the condition.
  - Systematic review of clinical evidence suggests that all stages of fibrosis in NAFLD are associated with all-cause mortality, and that fibrosis stages ≥F2 are associated with liver-related mortality.[10]
  - However, understanding of the relative contribution of liver- vs. CV-related mortality to all-cause mortality in NAFLD / NASH remains less clear, particularly considering the non-linear, increasing association with age of primary CV-event risk in the general population.[11-12]
- Research characterizing variation of CV- vs. liver-related mortality risk in NAFLD by age and fibrosis stage may therefore assist in informing CEA.
- New nomenclature – metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) – has been proposed.[13] However, this study refers to NAFLD / NASH for consistency with / comparison to prior evidence.

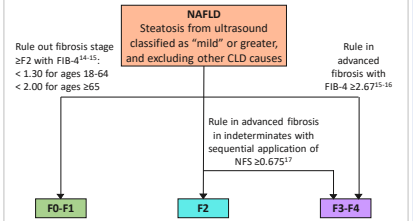
OBJECTIVES

- To estimate the association of NAFLD / NASH with all-cause and cause-specific (CV- and liver-related) mortality, and potential variation by fibrosis stages and age ranges.
- To calculate predicted probabilities of all-cause and cause-specific mortality, to inform CEA modeling.

METHODS

- An observational, longitudinal study was conducted using NHANES III (1988-1994), linked by the National Center for Health Statistics (NCHS) to National Death Index (NDI) mortality outcomes through 2019.
- A complete-case approach was used for the analysis – i.e., any participant with a missing value for an analytic variable required was excluded.
- NAFLD was identified as:
  - Presence of steatosis graded "mild" or greater from ultrasound
  - Absence of other causes of CLD, including excessive alcohol consumption (self-report of > 2/1 drinks per day, for men/women) and hepatitis B or C (by antigen test)
- Among NHANES participants identified as having NAFLD, fibrosis stages (F0-F1, F2, and F3-F4) were predicted as reflected in **Figure 1**.
  - NFS ≥0.675 has been shown to identify a high probability of F3-F4 without the need of a liver biopsy.[17]
- In the linked NDI data, the NCHS specifies ten cause-of-death categories, including (1) Diseases of the heart (2) Malignant neoplasms (3) Chronic lower respiratory diseases (4) Accidents (unintentional injuries) (5) Cerebrovascular diseases (6) Alzheimer's disease (7) Diabetes mellitus (8) Influenza and pneumonia (9) Nephritis, nephrotic syndrome, and nephrosis (10) All other causes.
  - This analysis defined CV-related mortality as those classified as causes #1, #5, or #9.
  - As liver-related mortality is not classified separately in the linked NDI data, the residual category (#10) is expected to include liver-related mortality, which is likely the leading cause of death in the presence of NAFLD and fibrosis[18-19] (although HCC may be captured in cancer-related mortality).
- Analyses included:
  - Unadjusted Kaplan-Meier analyses of all-cause, CV-related, and residual (likely liver-related) mortality.
  - Multivariable Cox proportional-hazards models, adjusting for NAFLD/fibrosis-stage exposures and age 18-64 vs. ≥65 years, allowing for estimation of mortality risk for use in CEA.

Figure 1: Algorithm for prediction of fibrosis stage in NAFLD

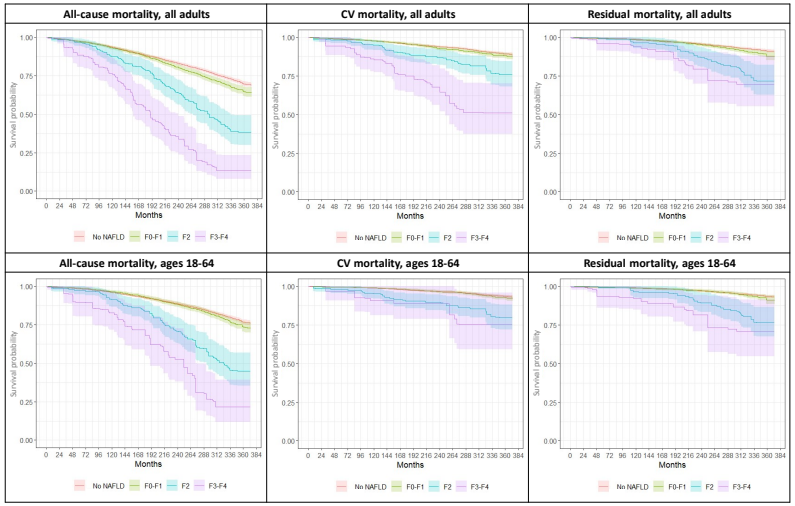


Abbreviations: FIB-4 – Fibrosis-4 index; NFS – NAFLD Fibrosis Score.
References: [14]McPherson et al. (2017); [15]Shah et al. (2009); [16]Cusi et al. (2022); [17]Kosick et al. (2021).

RESULTS

- In the N=12,499 unweighted study population, 8,882 were identified as "No NAFLD" (7,658 aged 18-64, 1,224 aged ≥65), 3,156 as stages F0-F1 (2,648, 508), 312 as stage F2 (264, 48), and 149 as stages F3-F4 (79, 70).
- Weighted prevalence was estimated at 27.4% for NAFLD (mean age 41.3 years, 51% female), consisting of 24.2% at stages F0-F1 (44.0 years, 51% female), 2.3% at stage F2 (55.8 years, 42% female), and 0.8% at stages F3-F4 (61.2 years, 45% female).
- Follow-up time to death or censoring was mean (SD) 24.7 (6.8) years and median (IQR) 27.1 (24.8, 28.8) years.
- Unadjusted Kaplan-Meier analyses (**Figure 2**), and log-rank tests of each exposure level vs. No NAFLD, reflected:
  - In adults of all ages, significantly increased mortality risk compared to No NAFLD in all fibrosis stages for all-cause mortality (P values for logrank test <0.001) and residual mortality (P values <0.05), and in F2-F4 for CV mortality (P value <s0.001).
  - In adults aged 18-64 years, significantly increased mortality risk compared to No NAFLD in F2-F4 for all-cause mortality (P values for logrank test <0.001), CV mortality (P values <0.05), and residual mortality (P values <0.01).

Figure 2: Kaplan-Meier estimates of survival from all-cause, CV, and residual mortality, by NAFLD-fibrosis group



- Estimated Cox models (**Table 1**), adjusting for NAFLD/fibrosis-stage exposures and age 18-64 vs. ≥65 years, reflected statistically significant association of:
  - All-cause and residual mortality in all fibrosis stages
  - CV mortality in fibrosis stages F2-F4
- In scenario analyses adjusting for diabetes status, associations were generally maintained.
- Predicted 10-year mortality probabilities (**Figure 3**) were estimated using results of the Cox models, relative to survival for a reference group (ages 18-64, No NAFLD), according to the following equation:[11-12]

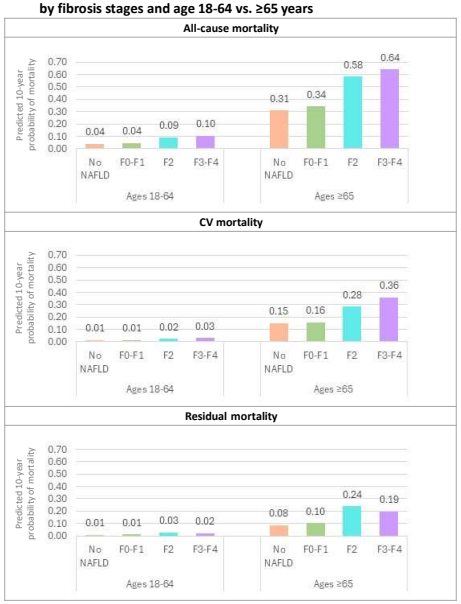
$$\hat{p} = 1 - S_0(t)^{\exp(\beta X)}$$

where: $\hat{p}$ is the predicted probability of the event over a period of duration t
$S_0(t)$ is the reference group's event-free survival proportion over the period t
β is the vector of coefficient estimates from the Cox model
X is the vector of risk-factor values for the predicted group

Table 1: Multivariable Cox proportional-hazards models of the association of NAFLD/fibrosis-stage groups with mortality

Characteristic	All-cause mortality			CV mortality			Residual mortality		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Exposure									
No NAFLD (n=8,882)	Reference			Reference			Reference		
F0-F1 (n=3,156)	1.13	1.03, 1.25	0.01	1.05	0.85, 1.30	0.7	1.21	1.01, 1.45	0.042
F2 (n=312)	2.36	1.89, 2.93	<0.001	2.03	1.45, 2.86	<0.001	3.07	1.98, 4.74	<0.001
F3-F4 (n=149)	2.76	2.13, 3.58	<0.001	2.71	1.80, 4.08	<0.001	2.45	1.39, 4.30	0.002
Age (years)									
18-64 (n=10,649)	Reference			Reference			Reference		
≥65 (n=1,850)	9.29	8.52, 10.10	<0.001	14.8	12.80, 17.00	<0.001	9.78	7.97, 12.0	<0.001
Reference 10-year survival:	96.1%			98.9%			99.1%		

Figure 3: Predicted 10-year probability of all-cause, CV, and residual mortality, by fibrosis stages and age 18-64 vs. ≥65 years



DISCUSSION

- Overall, a statistically significant association was observed in all fibrosis stages in NAFLD with all-cause mortality, and a significant association in stages F2-F4 with CV and residual (including liver-related) mortality, which are consistent with previous findings.[10,18-19]
- Strengths of this analysis include the length of follow-up (median >25 years), quality of the outcomes data (NCHS reports a 99.9% link rate of NHANES III to NDI), and NAFLD steatosis identified by ultrasound in NHANES III.
- Limitations of the analysis include:
  - Small sample sizes for fibrosis stages F2 (n=312) and F3-F4 (n=149) could limit the ability to differentiate risks between groups.
  - Competing risks including older age of the F3-F4 group, and correspondingly high CV risk, may have precluded observation of liver-related mortality.
  - To improve certainty, correlations of biopsy-based fibrosis stage with the NITs used in our study may be warranted, as FIB4 and NFS do not perfectly correspond with stage, although cutoffs used in this analysis have high reported specificity for ruling out ≥F2[14-15] and ruling in F3-F4.[15-17]
  - Analysis of "residual" cause mortality as a proxy for liver-related, which is not classified separately in the NHANES data linked to the NDI by the NCHS.

CONCLUSIONS

- In this analysis, NAFLD with all fibrosis stages was associated with statistically significantly increased risk of all-cause and "residual" (inclusive of liver-related) mortality, and stages F2-F4 with CV mortality.
- Cox models reported in this study allow for the prediction of 10-year mortality probabilities for US adults with NAFLD, by fibrosis stages (F0-F1, F2, F3-F4) and age range (18-64, ≥65), which can be used to inform CEA modeling.

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DISCLOSURES

JF and YK are employed by and own stock/stock options in Madrigal Pharmaceuticals.
MC has received advisory and consulting honoraria from Madrigal, Novo Nordisk, Cytodyn, Terns, Alnylam, AMR, Glympse, Northsea, Sagmimet, Genentech, and Merck; he has also received research grants from Pfizer and Madrigal, unrelated to this work.
JJW and TO received consulting fees from Madrigal Pharmaceuticals in the conduct of this analysis, and have received consulting fees from other biopharmaceutical manufacturers.
CMP has received consulting fees from Sensorum Health, Medicus Economics, Evidation Health, TTi Health Research & Economics, Canopy, Collective Acumen, ConcertAI, Flatiron Health, EQRx, Clue by Biowink, Omada Health, Outcomes4Me, Plinth, IQ Solutions, and Jazz Pharmaceuticals.