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Non-invasive liver fibrosis scores and mortality in a cohort of World Trade Center rescue/recovery workers

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ABSTRACT

Objectives Higher liver fibrosis scores have been associated with all-cause and liver disease-related mortality. We investigated whether liver fibrosis scores were associated with all-cause, liver disease-related and non-liver disease-related mortality and liver cancer incidence in an occupational cohort.

Methods The study included 43 870 Combined World Trade Center Rescue/Recovery Worker Cohort members who had blood drawn between 11/9/2001-31/12/2020. Aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 score (FIB-4), and non-alcoholic fatty liver disease fibrosis score (NFS) were calculated and categorised as low, intermediate or high scores per established cut-offs. Deaths and liver cancers were identified via National Death Index records and state cancer registries. Cox proportional hazards regression models estimated HRs and 95% CIs for each outcome in those with intermediate and high versus low fibrosis scores.

Results By 31/12/2020, 1996 deaths, 81 liver disease-related deaths and 36 incident liver cancers occurred. Participants with intermediate or high APRI (HR=1.73, 95% CI 1.50 to 1.99 and HR=7.23, 95% CI 5.63 to 9.29), FIB-4 (HR=1.18, 95% CI 1.05 to 1.34 and HR=3.96, 95% CI 3.22 to 4.85) or NFS (HR=1.61, 95% CI 1.43 to 1.81 and HR=4.73, 95% CI 3.78 to 5.93) had increased risks of all-cause mortality vs those with low scores, controlling for potential confounders. Those with intermediate/high scores also had increased liver disease- and non-liver disease-related mortality. High APRI, FIB-4 and NFS, and intermediate APRI and NFS were associated with liver cancer.

Conclusions Intermediate and high liver fibrosis scores predicted all-cause, liver disease-related and non-liver disease-related mortality, and high scores predicted liver cancer, in this population. Liver fibrosis scores may identify those at greater risk for poor health outcomes, even in a healthy occupational cohort.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A non-invasive method of assessing liver fibrosis is via liver fibrosis scores calculated using blood biomarker measurements. Previous studies have found that higher scores are associated with mortality in general populations and adults with non-alcoholic fatty liver disease.

WHAT THIS STUDY ADDS

⇒ In an occupational cohort of rescue/recovery workers, intermediate and high liver fibrosis scores were associated with all-cause, liver disease-related and non-liver disease-related mortality when compared with low scores, and high scores were also associated with liver cancer. Elevated fibrosis scores were associated with mortality even among participants without diabetes and those who reported no alcohol use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Liver fibrosis scores calculated using measurements from routine blood tests can be used to identify individuals at greater risk for mortality and liver cancer, even in an occupational cohort that was healthy at baseline.

INTRODUCTION

While World Trade Center (WTC) rescue/recovery work has been associated with various chronic physical and mental health conditions,[1–3] WTC-exposed rescue/recovery workers were found to have lower than expected mortality rates when compared with general populations, likely because of healthy worker effects and improved access to healthcare via the WTC Health Program.[4–6] As this WTC-exposed cohort ages, we and other investigators have identified cohort subgroups that are at increased risk for mortality.[4 7]

Non-alcoholic fatty liver disease (NAFLD) has become increasingly common in recent years, among adults in the USA and worldwide, with prevalence estimates for most regions being around 30%–40%.[8] Studies conducted in general populations and among adults with NAFLD have shown that liver fibrosis severity predicts all-cause mortality and liver disease-specific mortality.[9 10] A

non-invasive, validated method of assessing liver fibrosis involves the calculation of fibrosis scores from blood biomarker measurements. These have been found to be useful in identifying advanced fibrosis and cirrhosis in multiple studies.[11] In longitudinal analyses, higher liver fibrosis scores were associated with all-cause mortality and some types of cause-specific mortality, including non-liver disease-related mortality.[10 12–15] There is also evidence that links liver fibrosis scores to non-fatal adverse health outcomes;[16–18] however, few studies have investigated the scores' utility in predicting liver cancer in general populations or in individuals without pre-existing liver disease.[14 19] To date, no study has investigated the scores' utility in predicting mortality or liver-related outcomes in an occupational cohort. For the present study, we selected three liver fibrosis scoring systems that used measurements of commonly assessed blood biomarkers: the aspartate aminotransferase to platelet ratio index (APRI), the fibrosis-4 score (FIB-4) and the NAFLD fibrosis score (NFS). Our objective was to determine whether these fibrosis scores were associated with all-cause mortality, liver disease-related and non-liver disease-related mortality, and/or liver cancer incidence over nearly 20 years of follow-up in a large cohort of rescue/recovery workers who responded to the WTC disaster.

METHODS

Study population

The source population for this study, the Combined WTC Rescue/Recovery Workers Cohort (n=69 100), hereafter referred to as the Combined Cohort, consists of individuals who participated in the WTC rescue, recovery and/or clean-up efforts anytime between September 11 2001 (9/11) and the end of July 2002.[20] Details on the Combined Cohort have been reported elsewhere.[4 20] This study was restricted to Combined Cohort members who received medical services through the WTC Health Program, specifically through the Fire Department of the City of New York (FDNY) Clinical Center of Excellence (CCE) or any General Responder Cohort (GRC) CCE (n=49 346). These individuals were firefighters, emergency medical service (EMS) providers, police officers, construction workers and other paid and volunteer WTC rescue/recovery/clean-up workers. We further restricted our analyses to members who were ≥18 years old on 9/11, had provided their race/ethnicity and had their blood drawn at least once at a post-9/11 routine medical monitoring examination before 31/12/2020 (n=44 468). We excluded individuals who had viral hepatitis, defined as testing positive for hepatitis B surface antigen or hepatitis C RNA on or before the blood draw date (n=598). The final study population included 43 870 rescue/recovery workers.

This study was approved by the Biomedical Research Alliance of New York Institutional Review Board (#22-08-614), and a waiver of informed consent was obtained. All research was conducted in accordance with the Declaration of Helsinki. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies when creating this report (STROBE checklist included in an online supplemental file).

Data sources

Demographic data (sex, race/ethnicity and date of birth) were obtained from the FDNY and GRC data centres for FDNY members and GRC members, respectively. All participants reported their smoking status (current, former or never smoker) and alcohol consumption during their medical monitoring visits. Individuals who reported drinking alcohol within the previous 12 months were considered alcohol users, and those who had not had an alcoholic drink in over 12 months were considered non-users. Only answers given at one's first post-9/11 monitoring examination with a concurrent blood draw were used in the analyses.

Measurements taken at participants' first post-9/11 monitoring examinations and concurrent blood draw, including body mass index (BMI), haemoglobin A1C, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin and platelet count, were used to calculate their baseline liver fibrosis scores. Diabetes status at baseline was ascertained using fasting blood glucose level (>125 mg/dL) or physician diagnosis of diabetes. Three liver fibrosis scores were calculated with the available data: the APRI, calculated using AST and platelet count measurements; the FIB-4, which includes AST, platelet count, ALT and age in years at time of blood draw; and the NFS, which includes all of the above measurements in addition to albumin, BMI and diabetes status (yes/no). The formulas used for calculating each score are shown in online supplemental table S1. Each score was categorised into low, intermediate or high score groups, per previously defined cut-points from other populations. The cut-points were as follows: ≤0.5, >0.5 to 1.5 and >1.5 for low, intermediate and high APRI, respectively; <1.3, 1.3 to 2.67 and >2.67 corresponded to low, intermediate and high FIB-4; and <–1.455, –1.455 to 0.676 and >0.676 defined low, intermediate and high NFS, respectively.[10 21–24] Higher scores corresponded to a greater probability of liver fibrosis.

Outcomes

Mortality data were obtained by linking participants' data (social security number, name, sex and date of birth) to National Death Index (NDI) records through 31/12/2020. Underlying and contributing cause of death information was available in the form of International Classification of Diseases, 10th revision (ICD-10) codes.[25] ICD-10 codes were then classified into the 28 major cause of death categories used by the National Institute for Occupational Safety and Health (NIOSH).[25 26] The primary mortality outcomes assessed in this study were all-cause mortality, liver disease-related mortality and

non-liver disease-related mortality. Liver disease-related mortality included liver cancer ICD-10 codes (C22.0–C22.9) and cirrhosis/other chronic liver disease ICD-10 codes (K70–K76).[10] Non-liver disease-related mortality was defined as all cases in which the cause of death was not one of the above liver disease ICD-10 codes. In secondary analyses, we examined associations between liver fibrosis scores and cardiovascular disease (CVD)-related mortality, using the following ICD-10 codes: I00–I02, I05–I09, I11, I13, I20–I25, I30–I38, I40, I42, I44–I51, I97 and R00.

For the liver cancer analyses, cancer case information was obtained by matching participants' data to state cancer registry data and/or from review of medical records by a trained clinician, as detailed in our previous studies.[20 27] States selected for linkage were those where the rescue/recovery workers resided, including Arizona, California, Connecticut, Florida, Massachusetts, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Texas, Virginia and Washington. First primary malignant tumours of the liver and intrahepatic bile duct (ICD-O-3 codes C220 and C221)[28] diagnosed between first post-9/11 monitoring examination and 31/12/2020 were considered as events.

Statistical analyses

Cohort demographics and other baseline characteristics were summarised as medians (IQR) or as counts with proportions, as appropriate. For each of the evaluated fibrosis scoring systems (APRI, FIB-4 and NFS), the counts and proportions of the study population that scored into the low, intermediate and high fibrosis risk groups were provided. We evaluated agreement between fibrosis scoring systems (APRI vs FIB-4, APRI vs NFS and FIB-4 vs NFS) using Cohen's *kappa* coefficient.[29] We also calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each scoring system pertaining to each outcome of interest, when considering a high fibrosis score to be a positive test result.

For the mortality analyses, follow-up time began at the first post-9/11 monitoring exam and ended on date of death or on 31/12/2020, whichever came earlier. In cause-specific mortality analyses (ie, liver disease-related mortality, non-liver disease-related mortality and CVD-related mortality), deaths from causes other than the outcome of interest were treated as censoring events at date of death. For the analyses in which liver cancer was the outcome, follow-up time ended on the date of diagnosis for liver cancer cases and either date of death or 31/12/2020 for all others, and all deaths were censoring events.

Kaplan-Meier curves of all-cause mortality were compared among the low, intermediate and high fibrosis score groups of each fibrosis scoring system using the log-rank test. Multivariable Cox proportional hazards regression models were used to estimate the HRs and 95% CIs for all-cause, liver disease- and non-liver disease-related mortality, CVD-related mortality and liver cancer in those with intermediate and high fibrosis scores compared with those with low fibrosis scores, controlling for sex, race/ethnicity, age, BMI, smoking status (ever/never) and alcohol use within the past 12 months (yes/no) at time of the first post-9/11 blood draw. The proportional hazards assumption for each of these models was assessed by the Schoenfeld residuals.[30]

To account for possible effect modification by age, alcohol use and diabetes status at baseline, we conducted several stratified analyses. For the age group analyses, the population was stratified into older (≥60 years at baseline, ~10% of the cohort) and younger adults. The above-described multivariable Cox proportional hazards regression models were repeated for each stratum of age (older/younger), alcohol use (yes/no), and diabetes status (yes/no). The stratification variable was not included in the corresponding stratified models. Bonferroni correction was used to obtain confidence intervals adjusted for multiple testing in these stratified analyses.

In sensitivity analyses, we restricted the population to cohort members whose first medical monitoring exam occurred by the end of 2011 (n=34 369) to minimise selection bias introduced by the expansion of WTC Health Program eligibility and benefits. We then repeated the primary all-cause mortality analysis, excluding the participants who later enrolled in the WTC Health Program because of poor health.

Slightly less than five per cent of the study population (n=2011) were not included in the multivariable analyses due to missing covariate data. For these participants, we were missing either smoking status, alcohol use status or BMI. All analyses were conducted in SAS V.9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Population characteristics and liver fibrosis scores at baseline

Baseline characteristics of the study population are shown in table 1. Participants were 44.1 (IQR=37.5–51.4) years old, on average, at the time of their first post-9/11 blood draw. The majority of participants were male (89.5%) and non-Hispanic white (67.1%) and most identified as never-smokers (61.8%) and as alcohol users (64.1%). The median BMI at baseline was 28.9 (IQR=26.3–32.0) kg/m^2; about 40% of participants were obese with BMI ≥30 kg/m^2. The proportions of individuals categorised as having an intermediate risk of liver fibrosis varied from 7.1% to 17.1%, depending on the scoring system used, while the proportions considered to be high risk ranged from 0.5% to 1.0% (table 2). Online supplemental tables S2A–S2C show that agreement on risk categories (low, intermediate, high) between APRI and NFS was weak (κ=0.17) and agreement of the FIB-4 with APRI and NFS categories was moderate (κ=0.39 and κ=0.48, respectively). The sensitivity, specificity, PPV and NPV of high APRI, FIB-4 and NFS for each outcome are listed in

Table 1 Population characteristics (total n=43 870)

Age, median (IQR)*	44.1 (37.5–51.4)
Sex, N (%)	
Male	39 271 (89.5)
Female	4599 (10.5)
Race, N (%)	
White	29 451 (67.1)
Black	3848 (8.8)
Hispanic	7513 (17.1)
Other	3058 (7.0)
BMI, median (IQR)**	28.9 (26.3–32.0)†
Smoking, N (%)*‡	
Never	27 096 (61.8)
Ever	15 754 (35.9)
Alcohol use, N (%)*§	
No	15 046 (34.3)
Yes	28 120 (64.1)
Diabetes, N (%)**	3483 (7.9)
Follow-up years, median (IQR)	15.0 (9.8–18.1)
Deceased by 31/12/2020, N (%)	1996 (4.6)
Liver disease-related death by 31/12/2020, N (%)	81 (0.2)
Liver cancer diagnosis by 31/12/2020, N (%)	36 (0.1)

*At time of first post-9/11 blood draw.
†N missing=717.
‡N missing=1020.
§N missing=704.
BMI, body mass index.

Table 2 Proportions of Combined Cohort members with low, intermediate and high liver fibrosis scores

APRI	**N**	**%**
Low (≤0.5)	40 539	92.4
Intermediate (>0.5–1.5)	3092	7.1
High (>1.5)	239	0.5
FIB-4 score	**N**	**%**
Low (<1.3)	37 707	86.0
Intermediate (1.3–2.67)	5718	13.0
High (>2.67)	445	1.0
NFS	**N***	**%**
Low (<−1.455)	35 204	80.3
Intermediate (-1.455–0.676)	7504	17.1
High (>0.676)	445	1.0

*N missing=717.
APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score.

online supplemental table S3. Overall, the tests had low sensitivity and high specificity when using high score as a proxy for positive screen. Sensitivities were best for the liver-related outcomes.

Liver fibrosis scores and all-cause mortality, cause-specific mortality and liver cancer incidence

By the end of 2020, there were 1996 deaths (4.6%) and 592 218.5 years of follow-up in the study population (table 1). The most frequent causes of death were cancer (n=675) and heart disease (n=409). Eighty-one deaths had liver disease listed as the underlying cause. Thirty-six participants were diagnosed with liver cancer during follow-up; of those, 24 died before the end of follow-up and, as such, were also included in the mortality analyses as liver disease-related deaths.

The median follow-up time was 15.0 years (IQR: 9.8–18.1 years). Kaplan-Meier survival curves showed that crude survival differed across risk categories; this was the case for each of the scoring systems assessed (figure 1A–C) (log-rank p<0.001 for all). Shown in table 3 are the adjusted HRs and 95% CIs for all-cause mortality in the intermediate and high fibrosis score groups compared with the low fibrosis score group. Overall, the risk of all-cause mortality increased at least fourfold among those categorised as having high fibrosis scores and was modestly elevated in the intermediate fibrosis score group. Participants with intermediate or high APRI scores both had significantly increased risks of all-cause mortality compared with those who had low APRI scores (HR=1.73, 95% CI 1.50 to 1.99 and HR=7.23, 95% CI 5.63 to 9.29, respectively). All-cause mortality was also increased in participants with intermediate and high FIB-4 scores (HRs vs low=1.18, 95% CI 1.05 to 1.34 and 3.96, 95% CI 3.22 to 4.85) and intermediate and high NFS (HRs vs low=1.61, 95% CI 1.43 to 1.81 and 4.73, 95% CI 3.78 to 5.93). Sensitivity analyses restricted to the subpopulation that had its first post-9/11 medical monitoring examination by the end of 2011 showed similar associations between fibrosis scores and all-cause mortality (online supplemental table S4).

Intermediate and high scores of all scoring systems (APRI, FIB-4 and NFS) were also all strongly associated with liver disease-specific mortality, compared with low scores, as shown in table 3. Participants with intermediate and high liver fibrosis scores also had an elevated risk of non-liver disease-specific mortality compared with those in the low-score group (table 3). Associations between fibrosis scores and CVD-related mortality varied depending on the scoring system used. Individuals with intermediate (HR=1.34, 95% CI 1.04 to 1.72) and high NFS (HR=3.26, 95% CI 2.03 to 5.23) had a significantly greater risk of CVD-related mortality than those in the low NFS group, but for APRI and FIB-4, the associations were less consistent; only intermediate APRI scores and high FIB-4 scores were associated with increased CVD mortality (data not shown).

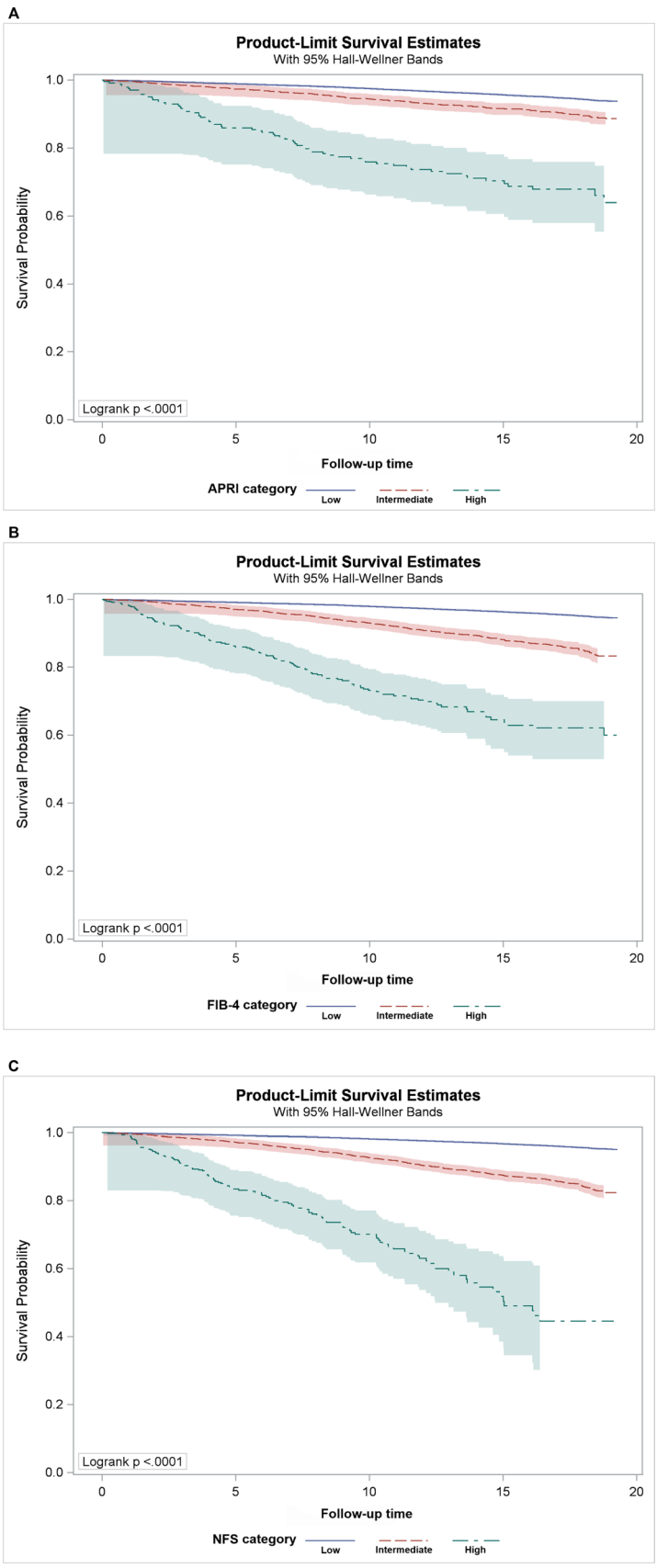

Figure 1 Kaplan-Meier survival curves of all-cause mortality over follow-up time (years) by liver fibrosis score category (low, intermediate or high) of different scoring systems in the Combined World Trade Center Rescue/Recovery Worker Cohort by 31/12/2020. (A) Aspartate aminotransferase to platelet ratio index (APRI). (B) Fibrosis-4 score (FIB-4). (C) Non-alcoholic fatty liver disease fibrosis score (NFS).

Table 3 Risk of mortality and liver cancer by liver fibrosis score category in Combined World Trade Center Rescue/Recovery Worker Cohort

	All-cause mortality HR (95% CI)*†	Liver disease mortality HR (95% CI)*†	Non-liver disease mortality HR (95% CI)*†	Liver cancer HR (95% CI)*†
APRI				
High	7.23 (5.63–9.29)	116.52 (69.30–195.93)	4.64 (3.39–6.35)	202.40 (89.36–458.45)
Intermediate	1.73 (1.50–1.99)	5.69 (3.19–10.14)	1.63 (1.41–1.89)	8.67 (3.47–21.67)
Low	ref	ref	ref	ref
FIB-4 score				
High	3.96 (3.22–4.85)	96.30 (54.04–171.60)	2.89 (2.29–3.64)	82.78 (34.03–201.38)
Intermediate	1.18 (1.05–1.34)	3.60 (1.84–7.03)	1.13 (1.00–1.28)	1.55 (0.46–5.26)
Low	ref	ref	ref	ref
NFS				
High	4.73 (3.78–5.93)	114.23 (52.57–248.21)	3.81 (3.00–4.85)	150.38 (47.01–481.00)
Intermediate	1.61 (1.43–1.81)	5.00 (2.71–9.23)	1.53 (1.36–1.73)	6.28 (2.37–16.68)
Low	ref	ref	ref	ref

*HRs adjusted for age, sex, race, BMI, ever smoking, and alcohol consumption.
†N=41,859 due to some missing covariate data.
NFS, nonalcoholic fatty liver disease fibrosis score.APRI, aspartate aminotransferase to platelet ratio index; BMI, body mass index; FIB-4, fibrosis-4.

When assessing liver cancer as the outcome, we observed that high fibrosis scores were strongly associated with liver cancer incidence (table 3). For two of the scoring systems (APRI and NFS), intermediate fibrosis scores were also associated with liver cancer incidence when compared with low scores.

Liver fibrosis scores and mortality by age group, alcohol use and diabetes status

Age-stratified analyses showed that the associations between liver fibrosis scores and mortality were stronger in younger participants than in those who were older (table 4). In both age strata (<60 years old and ≥60 years), those with high fibrosis scores had significantly greater mortality and those with intermediate APRI or NFS had modestly elevated mortality compared with the low score groups. Among participants ≥60 years of age at baseline, however, the HRs for mortality were attenuated.

When stratifying the population by alcohol use at baseline, we found that the HRs for mortality in the high and intermediate versus low fibrosis score groups were higher among alcohol users than in non-users. Even so, among individuals who did not use alcohol, those with high fibrosis scores or intermediate APRI or NFS had significantly elevated mortality compared with those with low scores.

Finally, analyses stratified by diabetes status at baseline showed that associations between liver fibrosis scores and mortality tended to be stronger among participants without diabetes than among diabetics. High fibrosis scores were significantly associated with mortality in both groups of participants, as was intermediate APRI score. Associations of intermediate NFS and FIB-4 scores with mortality in both strata were more modest; intermediate NFS was linked with greater mortality solely in nondiabetic individuals, while the association between intermediate FIB-4 score and mortality was only significant in diabetic individuals.

DISCUSSION

Over almost two decades of follow-up in the Combined Cohort of WTC-exposed rescue/recovery workers, we observed that intermediate and high liver fibrosis scores were predictive of all-cause, liver disease-specific and non-liver disease-specific mortality and, further, that high liver fibrosis scores consistently predicted liver cancer. Although agreement between the three liver fibrosis scoring systems assessed was only fair, scoring into the intermediate and high fibrosis risk categories at baseline was associated with increased mortality risk, regardless of the scoring system used.

In recent years, NAFLD prevalence has been increasing in the USA and worldwide.[8] Among populations with NAFLD, patients with greater liver fibrosis, assessed via either higher APRI or NFS or higher fibrosis stage (by pathology or imaging), had an elevated risk for mortality—including non-liver disease-related mortality.[9 13 15] These associations between liver fibrosis levels and mortality have also been observed in general populations; Unalp-Arida and Ruhl found that higher APRI, FIB-4 and NFS were associated with both liver disease-related and overall mortality in a sample of the US population.[10] Another study conducted in a general population showed that high APRI and FIB-4 scores predicted liver cancer mortality.[14] Some studies also linked higher liver fibrosis scores to CVD-related outcomes; high FIB-4 scores were associated with CVD morbidity and mortality in general populations,[10 16] and high scores (including APRI, FIB-4, NFS

Table 4 Risk of mortality by fibrosis score category in Combined World Trade Center Rescue/Recovery Worker Cohort members stratified by age, alcohol use, and diabetes status at baseline

	<60 years old at baseline	60+ years old at baseline
	HR (95% CI)*†‡	HR (95% CI)*†§
APRI		
High	7.64 (5.67–10.28)	3.61 (1.17–11.20)
Intermediate	1.74 (1.45–2.10)	1.69 (1.24–2.30)
Low	ref	ref
FIB-4 score		
High	7.25 (5.56–9.46)	1.60 (1.03–2.49)
Intermediate	1.15 (0.96–1.38)	1.06 (0.83–1.34)
Low	ref	ref
NFS		
High	7.01 (5.06–9.69)	2.94 (1.90–4.54)
Intermediate	1.70 (1.46–1.99)	1.33 (1.02–1.72)
Low	ref	ref
	No alcohol use	**Any alcohol use**
	HR (95% CI)†¶**	HR (95% CI)†¶††
APRI		
High	5.50 (3.34–9.05)	8.60 (6.06–12.21)
Intermediate	1.39 (1.05–1.84)	1.96 (1.61–2.38)
Low	ref	ref
FIB-4 score		
High	3.50 (2.34–5.23)	4.36 (3.26–5.83)
Intermediate	1.02 (0.81–1.27)	1.31 (1.10–1.57)
Low	ref	ref
NFS		
High	3.83 (2.54–5.79)	5.40 (3.88–7.51)
Intermediate	1.52 (1.23–1.87)	1.68 (1.40–2.00)
Low	ref	ref
	No diabetes	**Diabetes**
	HR (95% CI)†‡‡§§	HR (95% CI)†‡‡¶¶
APRI		
High	7.54 (5.37–10.60)	4.90 (2.86–8.39)
Intermediate	1.75 (1.46–2.09)	1.52 (1.07–2.15)
Low	ref	ref
FIB-4 score		
High	4.15 (3.16–5.45)	3.19 (2.03–5.01)
Intermediate	1.15 (0.98–1.35)	1.41 (1.06–1.87)
Low	ref	ref
NFS		
High	4.33 (2.78–6.73)	3.52 (2.19–5.65)
Intermediate	1.43 (1.22–1.67)	1.27 (0.89–1.81)
Low	ref	ref

*HRs adjusted for continuous age, sex, race, BMI, ever smoking, and alcohol consumption.
†Confidence intervals adjusted for multiple testing by Bonferroni correction.
‡N=38,450 due to some missing covariate data
§N=3,409 due to some missing covariate data.
¶HRs adjusted for age, sex, race, BMI, and ever smoking.
**N=14,593 due to some missing covariate data.
††N=27,266 due to some missing covariate data.
‡‡HRs adjusted for age, sex, race, BMI, ever smoking, and alcohol consumption.
§§N=38,586 due to some missing covariate data.
¶¶N=3,273 due to some missing covariate data.
APRI, aspartate aminotransferase to platelet ratio index; BMI, body mass index; CI, confidence interval; FIB-4, fibrosis-4; HR, hazard ratio; NFS, nonalcoholic fatty liver disease fibrosis score.

and others) were all associated with CVD-related and all-cause mortality in coronary artery disease patients.[12] These results are consistent with literature showing NAFLD to be associated with CVD events.[31 32] In our study population, intermediate and high NFS were both linked to an elevated risk of CVD-related mortality, as were intermediate APRI and high FIB-4 scores. High APRI and intermediate FIB-4 scores were not significantly associated with CVD-related mortality, possibly due to competing mortality events in these fibrosis score groups.

Our results indicate that liver fibrosis scores at baseline can define high-risk groups, even in a healthy worker cohort in which overall mortality rates remain low. Previous studies of mortality in WTC rescue/recovery workers found reduced rates when compared with US adults, likely as a result of the healthy worker effect, in which occupational cohorts tend to be healthier than the general population.[4 33–35] In the current study cohort, while the proportion of participants who reported smoking was low, the prevalence of obesity was similar to that of the US general population in recent years.[36] WTC rescue/recovery workers also have better access to healthcare than the US general population, however, because of both their employment benefits and the no-cost routine medical monitoring and treatment available to them via the WTC Health Program.[6] More recently, our studies have identified characteristics associated with greater mortality risk within subpopulations of WTC rescue/recovery workers.[4 7 37]

In this combined cohort, liver fibrosis scores were more successful at predicting mortality among participants who were young or middle-aged at baseline than among older (≥60 years) adults. The three scoring systems we used may be less effective at assessing liver fibrosis levels in older individuals. McPherson *et al* observed that the FIB-4 and NFS had lower specificity when used to detect advanced fibrosis in a population of NAFLD patients 65 years and older than when used in NAFLD patients under age 65.[38] In our full study population, we observed high specificity and NPV for all scoring systems and outcomes assessed, possibly reflecting the younger age distribution of our cohort at baseline. Further, the low PPVs and sensitivities we observed suggest that in a clinical setting, these scores, while strongly associated with liver disease mortality and liver cancer, are better at ruling out disease than identifying it.

Greater fibrosis scores were also stronger risk factors for mortality among individuals who reported drinking alcohol than among those who did not drink for 12 months before blood draw; however, high fibrosis scores were significantly associated with mortality in both groups. Our results indicate that high-level liver fibrosis is an independent risk factor for mortality even when accounting for alcohol use. Similarly, high fibrosis scores were associated with increased mortality risk, regardless of diabetes status. Intermediate scores tended to be modestly associated with increased mortality in both diabetic and non-diabetic participants. The fibrosis score-mortality associations appeared slightly attenuated in the diabetic group, possibly due to higher mortality rates in this group overall.

There are several limitations to this study. We did not perform validation analyses in the current study population, because liver imaging and liver biopsy results were not available. Another reason for the attenuated associations between fibrosis scores and mortality in older Combined Cohort members could be the presence of comorbid conditions in that group; in this study, we did not account for comorbidities in our analyses. There was also the possibility of misclassification or residual confounding caused by imperfect or unavailable covariate data; potential confounders were all assessed at a single time point, and some were self-reported. For example, we used a binary variable to represent alcohol use at time of blood draw. As such, misclassification of alcohol use status was possible. However, given the magnitude of the associations of high liver fibrosis scores with mortality and liver-related outcomes, it is unlikely that controlling for comorbidities or additional confounders would meaningfully change these results. Finally, for this study, we did not have longitudinal blood draw data for the majority of participants and therefore could not assess the effect of longitudinal changes in fibrosis scores on mortality or liver cancer.

The primary strength of this investigation is that it used data from 43 870 participants over a median of 15 years of follow-up. It was therefore well-powered to find associations between fibrosis scores and rare outcomes, such as liver cancer and liver disease-related mortality. Importantly, strong associations between high fibrosis scores and poor health outcomes were found even though, on average, the scores were calculated using measurements taken relatively early in the post-9/11 follow-up period, as they were from participants' first post-9/11 medical monitoring visit that included a blood draw. After restricting the analytic cohort to participants whose first monitoring visit date was before the end of 2011, the associations remained significant. This suggests that early assessment of liver fibrosis in a middle-aged cohort could prevent some premature deaths and/or liver cancer cases, if high-risk individuals are then targeted for treatment/intervention.

In conclusion, intermediate to high liver fibrosis scores were associated with mortality and adverse hepatic outcomes among rescue/recovery workers, particularly among those who were young to middle-aged at the time of assessment. Associations shown in other populations therefore hold true for a relatively healthy, occupational/environmentally exposed cohort. The associations between high fibrosis scores and mortality were significant even in those without the known risk factors of alcohol use and diabetes. Given that the scores can be calculated using measurements that are often readily available via existing laboratory work, liver fibrosis scoring is a non-invasive method of determining which patients could be at increased risk for mortality. Although high scores are strongly associated with mortality and

liver cancer regardless of the scoring system used, we would suggest using the APRI to detect high-risk individuals in this and other similar populations going forward because of its simplicity, as fewer measurements are required in its calculation.

Contributors Conceptualisation: RZO, DJP. Methodology: RZO, CBH, JC. Data curation: AS, NI, VG. Formal analysis: AS, DGG, NI. Writing – original draft preparation: AS, RZO, DJP. Writing – review and editing: RZO, NI, DGG, CBH, JC, CRD, VG, ACT, DJP. Supervision: RZO, ACT, DP. RZO is the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

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