

Appendix 1

Search strategy for Embase database search

1. exp nonalcoholic fatty liver/
2. ((NASH or NAFL or NAFLD) and (fatty or liver)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. "non?alcoholic fatty liver".mp.
4. "non?alcoholic steato?hepatitis".mp.
5. 1 or 2 or 3 or 4
6. exp biological marker/
7. biomarker*.mp.
8. exp blood examination/
9. ((blood or h?ematolog*) adj2 test*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. exp liver function test/
11. "liver function test*".mp.
12. exp alanine aminotransferase/
13. exp aspartate aminotransferase/
14. exp gamma glutamyltransferase/
15. ("alanine transaminase" or "aspartate aminotransferase" or "gamma?glutamyltransferase" or "ALT" or "AST" or "GGT").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
16. ("enhanced liver function" or ELF or hepascore or "BARD score" or NFS or fibrometer or fibrotest or FIB?4 or "fibrosis?4" or APRI or "aspartate aminotransferase?to?platelet ratio" or FLI or "fatty liver index" or HSI or "hepatic steatosis index" or steatotest or "lipid accumulation product" or LAP or ION or "index of NASH" or "NAFLD-LFS").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

17. exp elastography/
18. (fibrosan or "transient elastograph*" or "elasticity imaging techniques").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
19. (ultrasonograph* or ultrasound).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
20. (prognos* and (marker* or test* or scor* or factor*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
21. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp all cause mortality/ or exp mortality/
23. (mortalit* or death*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24. 22 or 23
25. 5 and 21 and 24
26. 25 not (HCC or "hepato?cellular carcinoma").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
27. limit 26 to (human and english language)

Study search excluded studies and reasons for exclusion

(Abeles et al., 2019)	No mortality data
(Acharya et al., 2020)	Inadequate definition of NAFLD
(Alvarez et al., 2020)	No quantifiable biomarker
(Angulo et al., 2015)	Invasive biomarker
(Angulo, 2010)	Review article
(Arshad et al., 2018)	No mortality data
(Barré et al., 2020)	Inadequate definition of NAFLD
(Beale et al., 2008)	No mortality data

(Bellentani et al., 2008)	Review article
(Bush and Torres, 2018)	Editorial only
(Buzzetti et al., 2019)	Invasive biomarker
(Chen et al., 2020)	Inadequate definition of NAFLD
(Cheung et al., 2014)	Inadequate definition of NAFLD
(Chinnadurai et al., 2019)	No quantifiable biomarker
(Crocì et al., 2019)	No quantifiable biomarker
(Fracanzani et al., 2016)	No mortality data
(Gentili et al., 2016)	No mortality data
(Goessling et al., 2008)	Inadequate definition of NAFLD
(Golabi et al., 2019a)	No quantifiable biomarker
(Golabi et al., 2019b)	No quantifiable biomarker
(Golabi et al., 2018a)	No quantifiable biomarker
(Hagström et al., 2020)	Inadequate definition of NAFLD
(Hagström et al., 2017)	Invasive biomarker
(Hui et al., 2003)	No mortality data
(Keskin et al., 2017)	Inadequate definition of NAFLD
(Kumar et al., 2019)	Abstract only
(Lazo et al., 2015)	Inadequate definition of NAFLD
(Lee et al., 2020)	No quantifiable biomarker
(Lindenmeyer et al., 2020)	Inadequate definition of NAFLD
(Lioudaki et al., 2011)	Review article
(Long et al., 2016)	No mortality data
(Mandal et al., 2018)	No mortality data
(Mangla et al., 2019)	Inadequate definition of NAFLD
(Ozturk et al., 2020)	No mortality data
(Paik et al., 2019)	No quantifiable biomarker
(Pavlidis et al., 2016)	Inadequate definition of NAFLD
(Peleg et al., 2019)	Inadequate definition of NAFLD

(Perera et al., 2016)	No quantifiable biomarker
(Pisto et al., 2014)	Inadequate definition of NAFLD
(Ravaioli and Anstee, 2019)	Editorial only
(Roh et al., 2020)	No mortality data
(Sato et al., 2017)	Inadequate definition of NAFLD
(Sebastiani et al., 2015)	No mortality data
(Sesti et al., 2014)	No mortality data
(Simon et al., 2017)	No mortality data
(Song et al., 2020)	No mortality data
(Stepanova et al., 2010)	No quantifiable biomarker
(Stepanova et al., 2013)	No quantifiable biomarker
(Takahashi et al., 2018)	Inadequate definition of NAFLD
(Trembling et al., 2020)	Inadequate definition of NAFLD
(Unalp-Arida and Ruhl, 2016)	Inadequate definition of NAFLD
(Unalp-Arida and Ruhl, 2017)	Inadequate definition of NAFLD
(Unalp-Arida and Ruhl, 2020)	Inadequate definition of NAFLD
(Valva et al., 2018)	No mortality data
(van den Berg et al., 2019)	No mortality data
(Vatsalya et al., 2020)	Inadequate definition of NAFLD
(Viglino et al., 2018)	Inadequate definition of NAFLD
(Vilar-Gomez and Chalasani, 2018)	No mortality data
(Viveiros et al., 2018)	Inadequate definition of NAFLD
(Williams et al., 2016a)	Inadequate definition of NAFLD
(Williams et al., 2016b)	Inadequate definition of NAFLD, no mortality data
(Xia et al., 2020)	No quantifiable biomarker
(Yamada et al., 2016)	Abstract only
(Yoo et al., 2020)	No quantifiable biomarker
(Yoshihisa et al., 2018)	Inadequate definition of NAFLD
(Younossi et al., 2013)	No quantifiable biomarker

(Yun et al., 2009)	Inadequate definition of NAFLD
(Zelle et al., 2010)	Inadequate definition of NAFLD
(Zhu et al., 2020)	No mortality data

Table S1: Characteristics of studies reporting individual biomarkers and imaging-based modalities as prognostic factors for mortality in Non-alcoholic fatty liver disease

First author and year of publication, Country Setting	Study design Time period Length of follow-up (FU)	Number of participants NAFLD diagnosis (Dx) criteria Subgroups studied	Population demographics (age, sex, ethnicity, comorbidities)	Prognostic biomarker(s)	Outcomes reported	Main results	Main conclusions
(Hagström et al., 2016) Sweden Secondary care	Retrospective cohort study 1979 – 2009 Median FU 15.6 years (range 0.5-34.2)	222 participants Dx by liver biopsy 89 participants with high ferretin 133 participants with low ferretin	Mean 50.6 years Male 60% Female 40% HTN 29.3% DM 17.6% Mean BMI 27.9 Smoking 37.8%	Serum ferretin ≤ 350 $\mu\text{g/L}$ in males or ≤ 150 in females vs > 350 in males or > 150 in females	All-cause mortality	Incidence of deaths Multivariable adjusted Poisson regression for HR and 95% CI for mortality High ferretin HR 1.1 (1.01-1.21)	Serum ferretin is a prognostic marker for all-cause mortality in NAFLD.
(Ito et al., 2019) Japan Secondary care	Retrospective cohort study 1999-2014 Mean FU 7 years (IQR 4.4-	246 participants Dx by liver biopsy 196	Mean 55 years Male 52% Female 48% HTN 41.6% DM 45.1%	FIB-4 (< 2.76 vs ≥ 2.76) NFS (< -1.455 vs ≥ -1.455) Bilirubin (< 1.2 vs	All-cause mortality, 3-, 5-, 10- year mortality, incidence of	Cumulative incidence rates of mortality, Hazard ratio and 95% CI (univariate analysis) Bilirubin $\geq 1.2\text{mg/dL}$ HR	The progression of liver fibrosis was associated with mortality, hepatocarcinoge

	10)	participants biopsy fibrosis stage 0-2, 50 patients fibrosis stage 3-4	BMI 26.2 NASH 63.4%	≥1.2mg/dL)	HCC, cirrhosis- related complications, malignancies, and CVD	6.362 (1.393-29.052)	nesis, LC-related complications, and extrahepatic malignancies. Non-invasive liver fibrosis markers were useful for predicting the occurrence of liver-related diseases.
(Kim et al., 2017) USA Community care	Retrospective cohort study 1988 – 1994 Median FU 18.8 years	10960 participants Dx by USS hepatic steatosis 4015 NAFLD participants 4991 Vitamin D deficiency participants 5969 No Vitamin D deficiency participants	**Mean 43.3 years Male 45.1% Female 54.9% HTN 22.8% DM 5.4% Smoking 51.2%	Vitamin D ≥20mg/dL (reference) vs <20mg/dL	All-cause mortality, Cardiovascular , malignancy, cerebrovascula r, lung disease, kidney disease, diabetes, alzheimer's disease mortality	Incidence of deaths, Cox proportional hazards regression with limited adjustment (age, sex and race) Vitamin D <20 and diabetes HR 3.64 (1.51 – 8.82) Vitamin D <20 and alzheimer's HR 4.8 (1.53 – 15.1)	Vit D deficiency significantly related to DM and Alzhimers related mortality in NAFLD when adjusting for limited factors. This association was not observed in non- NAFLD participants.
(Kim et al., 2020) USA Community	Retrospective cohort study 1988-1994 Median FU 23	10144 participants Dx USS hepatic	**Mean 42.4 years Male 48.4% Female 51.6%	TSH 0.4-2.5 mIU/L (reference) vs ≥ 2.5 vs 2.4-4.5 vs >4.5	All-cause mortality, cardiovascular mortality,	Multivariate Cox proportional hazards regression analysis for HR and 95% CI	Low TSH is a prognostic factor for all-cause and cardiovascular

care	years	steatosis 8287 participants with normal thyroid function 1857 participants with low thyroid function 3439 participants with NAFLD			cancer-related mortality	NAFLD and TSH \geq 2.5 and ACM HR 1.24 (1.02- 1.50) NAFLD and TSH \geq 2.5 and CVM HR 1.62 (1.11- 2.34)	mortality in NAFLD population but not in non- NAFLD population.
(Kogiso et al., 2020) Japan Secondary care	Retrospective cohort study 1990 – 2008 Median FU 7.1 years	365 participants Dx by liver biopsy	Mean 54 years Male 50.7% Female 49.3% HTN 52.9% DM 52.3%	FIB4 <2.67 vs \geq 2.67 Albumin GGT Platelets <11.5 vs \geq 11.5 \times 104/ μ L HbA1C	All-cause mortality, liver-related deaths and non-liver related deaths	Incidence of deaths, cox regression univariate models and Kaplan Meier Curves to generate HR and 95% CI Platelets <11.5 \times 104/ μ L and ACM HR 0.909 (0.861-0.960), sensitivity 61.4% specificity 8.8%	Low platelet count was prognostic for all-cause and liver-related death. Low albumin, high GGT, and high HbA1c were associated with all-cause and liver related death.
(Munteanu et al., 2018) France	Prospective cohort study 1997-2012	7082 participants Dx liver	*Mean 56.7 years Male 57.4%	FibroTest Apolipoprotein A1	All-cause mortality, Liver-related	Incidence of deaths, univariate Kaplan- Meier curves, AUROC	FibroTest has prognostic value in NAFLD

Secondary care	Median FU 6 years (range 0.1-19.3 years)	biopsy or USS fatty liver NAFLD participants 2079 Other causes of CLD 6003	Female 42.9% Ethnicity – 6% Asian, 76% Caucasian, 18% African DM 35.8%	Haptoglobin SteatoTest-2 NashTest-2	mortality, CV mortality, extrahepatic malignancy mortality	and 95% CI FibroTest ACM AUROC 0.507 (0.443-0.571) FibroTest LRM AUROC 0.941 (0.905-0.978) FibroTest CVM AUROC 0.584 (0.478-0.6921) NashTest2 ACM AUC 0.492 (0.468-0.613) SteatoTest2 ACM AUC 0.535 (0.435-0.635) NashTest2 LRM AUC 0.942 (0.884-0.999) SteatoTest2 AUC 0.727 (0.579-0.875) Multivariate Cox analysis ApoA1 CVM Exp(B) 3.366 (1.357-8.531) R ² 0.058 Hapto CVM Exp(B) 0.566 (0.203-1.278) R ² 0.01 ApoA1 ACM Exp(B) 2.659 (1.733-4.078) R ² 0.065 Hapto ACM Exp(B) 0.465 (0.278-0.776) R ² 0.029	patients' overall survival and cardiovascular death. Low ApoA1 and high haptoglobin were independently associated with overall death and cardiovascular death. NashTest and Steatotest had a predictive value for liver-related deaths in univariate analysis, but not multi-valriate, and showed a negative (and opposite) association with all-cause mortality.
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(Paik et al., 2019) USA Community care	Retrospective cohort study 2009 – 2010 Median FU 19.2 years (IQR 15.5-21 years)	11555 participants Dx by USS hepatic steatosis 4040 participants with NAFLD 7514 participants without NAFLD	* Mean 46.2 years Male 50.5% Female 49.4% Ethnicity – Caucasian 74%, African 9%, Hispanic 8% CVD 5.6% HTN 39.4% DM 30.7%	HbA1C %, <5.7% vs ≥ 5.7 (reference)	All cause mortality, cardiovascular mortality	Multivariable adjusted HR and 95% CI HbA1C and ACM in NAFLD <5.7% HR 0.58 (0.48-0.71) HbA1C and CVM HR 0.48 (0.34-0.66)	HbA1C is predictive of all-cause and cardiovascular mortality in NAFLD and also in non-NAFLD. Smoking status, physical activity, and BP were also associated with all-cause mortality in NAFLD.
(Shili-Masmoudi et al., 2020) China and France Secondary care	Prospective cohort study 2004-2017 Median FU 27 months (IQR 25-38 months)	2245 participants Dx by USS hepatic steatosis	Mean 59.4 years Male 53.2% Female 46.8% HTN 59.5% DM 61.2% Mean BMI 28.3 Obesity 31.1%	Liver Stiffness Measurement (≤12 vs >12 kPa)	All-cause mortality, cardiovascular and liver-related complications	Incidence of deaths at 1-, 3-, and 5- years using death log rank test, and HR and 95% CI using multivariable backward stepwise Cox model LSM >12 kPa (≤12 as reference) HR 2.85 (1.65 – 4.92)	LSM is a very good predictor of overall survival. It also was very good at predicting liver events.
(Tsou and Wu, 2019) USA Community care	Retrospective cohort study 1979 – 2011 Median FU 18.8 years	2404 participants Dx USS moderate – severe steatosis	Mean age 43.8 Male 49.2% Female 50.7% HTN 45.1% DM 27.5% Mean BMI	Serum Vitamin E levels in μmol/L Lipid-corrected Vitamin E (Vitamin E in μmol/L /	All-cause mortality	multivariate Cox proportional hazards regression models (with different covariates combinations) to	Both serum vitamin E and lipid-corrected vitamin E were negatively associated with

		906 non-diabetics 836 pre-diabetics 662 diabetics	30.1 Smoking 25.6%	plasma total cholesterol in mmol/L)		estimate the hazard ratios of serum vitamin E and lipid-corrected Vitamin E. In the model that adjusts for FIB-4 there is no significant difference in HR for mortality in the 3 NAFLD subgroups, however when adjusting for smoking, age, and gender only there is a negative association with mortality in both VitE and VitE:C in non-diabetics.	all-cause mortality only in non-diabetic, and not in pre-diabetic or diabetic individuals when adjusting for gender, age, and smoking but not when FIB-4 or HbA1C are included.
(Wijarnpreecha et al., 2020) USA Community care	Retrospective cohort study 1991 – 2015 Mean FU 20.06 years (SD 5.36 years)	4814 participants Dx USS steatosis 311 Participants with NAFLD and PNPLA3 GG genotype 886 Participants with NAFLD	** Mean 42 years Male 49.3% Female 51.7% HTN 19.1% DM 3.4% Mean BMI 26.8	PNPLA3 I148M (rs738409) genotypes CC vs CG vs GG vs G allele carrier	All-cause mortality Cardiovascular mortality	Multivariable adjusted Cox proportional hazards regression analysis to generate HR and 95% CI (CC genotype used as reference) NAFLD G allele carrier and ACM HR 1.22 (0.99-1.49) NAFLD G allele carrier and CVM HR 1.22 (0.85-	The homozygous PNPLA3 I148M (rs738409) GG genotype showed an increase in overall mortality in the general population and NAFLD

		and PNPLA3 CC genotype 755 Participants with NAFLD and PNPLA3 CG Genotype 2441 4814 participants from general population and different PNPLA3 genotypes				1.74) NAFLD CG and ACM HR 1.18 (0.94-1.47) NAFLD CG and CVM HR 1.28 (0.85-1.92) NAFLD GG and ACM HR 1.45 (1.01-2.08) NAFLD GG and CVM HR 0.89 (0.55-1.42)	
(Younossi et al., 2004) USA Community and Secondary care	Retrospective cohort study 1979 – 1987 Mean FU 10 years	132 participants Dx by liver biopsy 44 NAFLD with DM 88 NAFLD without DM	Mean 53.1 years Male 48% Female 52% DM 32.9% Mean BMI 29.5	Prothrombin time (1s increase), Albumin (1g/dL increase), bilirubin (1mg/dL increase) in NAFLD with vs. without (reference) DM	All-cause mortality	Univariate Cox proportional hazards analysis was used to produce Risk Ratios and 95% CI PT RR 1.78 (1.04-3.04) Alb RR 0.23 (0.065-0.83) Bil RR 3 (1.31-6.87)	NAFLD patients with DM have higher mortality than without, bilirubin, prothrombin time and albumin serve as prognostic markers for all-cause mortality.

DM: Diabetes Mellitus

PT: Prothrombin Time

Alb: Albumin

Bil: Bilirubin

BMI: Body Mass Index

Table S2: characteristics of studies reporting value for mortality of non-invasive scoring systems

First author and year of publication, Country Setting	Study design Time period Length of follow-up (FU)	Number of participants NAFLD diagnosis (Dx) criteria Subgroups studied	Population demographics (age, sex, ethnicity, comorbidities)	Prognostic biomarker(s)	Outcomes reported	Main results	Main conclusions
(Angulo et al., 2013) USA, UK, Australia, Thailand, Italy, Iceland Secondary care	Retrospective cohort study 2002 – 2011 Median FU 104.8 months (range 3-17 months)	320 participants Dx by liver biopsy	Mean 52 years Male 43% Female 57% Ethnicity – Hispanic 0.6%, Caucasian 92%, Asian 16%, African 6%, other 4% HTN 47.5% DM 36.2% Mean BMI 33	FIB-4 <1.30 (reference) vs 1.30 – 2.67 vs >2.67 NFS <-1.455 (reference) vs -1.455 – 0.676 vs >0.676 APRI <0.5 (reference) vs 0.5-1.5 vs >1.5 BARD 0-1 (reference) vs 2-3 vs 4	All-cause mortality or transplant Liver-related events	Incidence of deaths, multivariable adjusted hazards regression. NFS > 0.676 HR 9.8 (2.7 – 35.3) APRI >1.5 HR 3.1 (1.1 – 8.4) FIB-4 >2.67 HR 6.9 (2.3-20.4) BARD 4 HR 1.6 (0.5-4.9)	Non-invasive scoring systems can predict the risk of mortality in NAFLD, with NFS seeming the most accurate.
(Bertot et al., 2018) Australia Secondary care	Prospective cohort study 2006 – 2015 Median FU 51 months (range	284 participants Dx by liver biopsy or USS hepatic	*Mean 54 years Male 47% Female 53% Ethnicity –	FIB-4 <1.30 vs >1.30 NFS <-1.455 vs >1.455 APRI <0.5	All-cause mortality / transplant Liver-related mortality /	Incidence of deaths, Harrell's concordance statistics (C index)	Non-invasive scores can predict mortality but are less accurate at predicting mortality and liver

	6.1 – 146 months)	steatosis 151 participants NAFLD with DM 133 participants NAFLD without DM	Caucasian 94%, Asian 12%, other 4% CVD 20% HTN 50% Mean BMI 36 Obesity 71%	vs >0.5 Hepascore <0.55 vs >0.55	transplant, liver-related events.		related events in diabetics vs non diabetics
(Chang et al., 2019) South Korea Secondary care	Retrospective cohort study 2002 – 2015 3,145,541 person-years of follow-up	437,828 participants Dx USS hepatic steatosis 91,392 participants with NAFLD 297,417 participants without NAFLD	*Mean 41.2 years Male 76.7% Female 23.3% HTN 24.4% DM 7.8% Mean BMI 26 Obesity 61.7% Smoking 2.4%	FIB-4 <1.30 vs 1.30-2.67 vs >2.67 APRI <0.5 vs 0.5-1.5 vs >1.5	Liver-related mortality	Incidence of deaths, multivariable adjusted cox proportional hazards regression for HR and 95% CI, using no NAFLD as a reference group FIB-4 <1.30 HR 0.57 (0.26-1.26) FIB-4 1.30-2.67 HR 1.27 (0.54-2.97) FIB-4 >2.67 HR 27.06 (11.2-65.31) APRI <0.5 HR 0.67 (0.31-1.27) APRI 0.5-1.5 HR 5.51 (2.44-12.46) APRI >1.5 HR 114.91 (38.2-345.61)	Non-invasive NAFLD fibrosis scores predict mortality in NAFLD vs. non-NAFLD patients.
(Golabi et al., 2018b)	Retrospective cohort study	2515 participants	Mean 48.7 years	NFS ≤0.676 vs > 0.676	All-cause mortality	Incidence of deaths, Multivariable adjusted	NFS is a predictor of

USA Community care	1988 – 1994 Mean FU 208 months (SD 59.5 months)	Dx USS moderate – severe hepatic steatosis	Male 48% Female 52% Ethnicity – Caucasian 35.7%, African 21.7%, Hispanic 38.8% CVD 4.3%, HTN 37.7%, DM 20.6%, Mean BMI 30.6, Smoking 21.1%			Cox proportional hazard model to identify independent potential predictors of mortality. NFS ≤0.676 HR 0.917 (0.768 – 1.096) NFS >0.676 HR 1.372 (1.073 – 1.755) Best threshold for NFS = 0.8, HR 1.411 (1.085 – 1.834)	mortality. HR for presence of comorbidities (HTN, DM, CHF, smoking) were higher than NFS.
(Golabi et al., 2019a) USA Community care	Retrospective cohort study 1988 – 1994 Median FU 17.7 years	1262 NAFLD participants Dx USS hepatic steatosis 667 participants with NAFLD and ASCVD score ≥ 7.5% 594 participants with NAFLD and ASCVD score <7.5%	*Mean 56.3 years Male 47.9% Female 52.1% Ethnicity – Caucasian – 39.3%, African 17.1%, Hispanic 37.1% HTN 24.6% DM 23.2% Mean BMI 30.1	ASCVD Score ≥ 7.5% vs <7.5% (reference)	All-cause mortality Cardiovascular mortality	Incidence of deaths, Multivariable adjusted Cox proportional hazards models for HR and 95% CI ASCVD score ≥7.5% and ACM HR 1.49 (1.09 – 2.02) ASCVD score <7.5% and CVM HR 2.02 (1.12 – 3.65)	ASCVD risk score is predictive of all-cause and cardiovascular mortality in NAFLD. Risk factors of CKD, smoking, and diabetes and NFS score are also predictive of mortality.
(Hagström et al., 2019)	Retrospective cohort study	646 participants	Mean 50 years Male 62%	FIB-4 <1.30 (reference) vs	All-cause mortality	Incidence of deaths, multivariable adjusted	NFS and FIB-4 best predicted overall

Sweden Secondary care	Mean follow-up 19.9 years (IQR 8.7)	Dx by liver biopsy	Female 38% HTN 30% DM 14% BMI 28 NASH 66%	1.30 – 2.67 vs >2.67 NFS <-1.455 (reference) vs -1.455 – 0.676 vs >0.676 APRI <0.5 (reference) vs 0.5-1.5 vs >1.5 BARD 0-1 (reference) vs 2-3 vs 4	Severe liver disease	hazards regression. NFS > 0.676 ACM HR 4.93 (2.63-9.26) APRI >1.5 ACM HR 1.71 (1.02 – 2.85) FIB-4 >2.67 ACM HR 3.48 (2.28-5.31) BARD 4 ACM HR 3.85 (2.18-6.79)	mortality and severe liver disease compared to BARD and APRI
(Ito et al., 2019) Japan Secondary care	Retrospective cohort study 1999-2014 Mean FU 7 years (IQR 4.4-10)	246 participants Dx by liver biopsy 196 participants biopsy fibrosis stage 0-2, 50 patients fibrosis stage 3-4	Mean 55 years Male 52% Female 48% HTN 41.6% DM 45.1% BMI 26.2 NASH 63.4%	FIB-4 (<2.76 vs ≥2.76) NFS (< -1.455 vs ≥ -1.455) Bilirubin (<1.2 vs ≥1.2mg/dL)	All-cause mortality, 3-, 5-, 10- year mortality, incidence of HCC, cirrhosis-related complications, malignancies, and CVD	Cumulative incidence rates of mortality, Hazard ratio and 95% CI (univariate analysis) Bilirubin ≥1.2mg/dL HR 6.362 (1.393-29.052)	The progression of liver fibrosis was associated with mortality, hepatocarcinogenesis, LC-related complications, and extrahepatic malignancies. Non-invasive liver fibrosis markers were useful for predicting the occurrence of liver-related diseases.
(Kim et al.,	Retrospective	11154	* Mean 46.2	NFS <-1.455	All-cause	Incidence of deaths for	Non-invasive

<p>2013) USA Community care</p>	<p>cohort study 1988-1994 Median FU 14.5 years (range 0.03 – 18.1 years)</p>	<p>participants Dx USS hepatic steatosis 4079 participants with NAFLD 7071 participants without NAFLD</p>	<p>years Male 50.9% Female 49.1% Ethnicity – Caucasian 75%, African 9%, Hispanic 7%, other 9% CVD 7.1% HTN 32.4% DM 9.5% Mean BMI 29.3 Smoking 55.2%</p>	<p>(reference) vs - 1.455 – 0.676 vs > 0.676 FIB-4 <1.30 (reference) vs 1.30-2.67 vs >2.67 APRI <0.5 (reference) vs 0.5-1.5 vs >1.5</p>	<p>mortality, Cause specific mortality (CVD, Liver, malignancy, diabetes)</p>	<p>NFS, multivariable adjusted Cox proportional hazards regression analysis NFS -1.455 – 0.676 and ACM HR 1.26 (0.98- 1.64) NFS >0.676 and ACM HR 1.69 (1.09-2.63) NFS -1.455 – 0.676 and CVM HR 2.16 (1.41- 3.29) NFS >0.676 and CVM HR 3.46 (1.91-6.25) NFS -1.455 – 0.676 and LRM HR 1.02 (0.54- 1.95) NFS > 0.676 and LRM HR 1.03 (0.38-2.77) FIB-4 1.30-2.67 and ACM HR 1.46 (1.16- 1.82) FIB-4 >2.67 and ACM HR 1.66 (0.98-2.82) FIB-4 1.30-2.67 and CVM HR 1.75 (1.26- 2.43) FIB-4 >2.67 and CVM HR 2.68 (1.44-4.99) FIB-4 1.30-2.67 and</p>	<p>fibrosis markers are prognostic for mortality in NAFLD. NFS, APRI, and FIB-4 are predictive of all- cause and cardiovascular mortality but not liver-related mortality.</p>
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						<p>LRM HR 0.68 (0.11-4.05)</p> <p>FIB-4 >2.67 and LRM HR 1.32 (0.12-14.8)</p> <p>APRI 0.5-1.5 and ACM HR 1.32 (0.78-2.23)</p> <p>APRI >1.5 and ACM 1.85 (1.02-3.37)</p> <p>APRI 0.5-1.5 and CVM HR 0.97 (0.40-2.34)</p> <p>APRI >1.5 and CVM HR 2.53 (1.33-4.83)</p> <p>APRI 0.5-1.5 and LRM HR 6.08 (0.77-48.21)</p> <p>APRI >1.5 and LRM HR 3.01 (0.20-45.62)</p>	
(Kogiso et al., 2020) Japan Secondary care	Retrospective cohort study 1990 – 2008 Median FU 7.1 years	365 participants Dx by liver biopsy	Mean 54 years Male 50.7% Female 49.3% HTN 52.9% DM 52.3%	FIB-4 <2.67 vs ≥2.67 Albumin GGT Platelets <11.5 vs ≥11.5 × 104/μL HbA1C	All-cause mortality, liver-related deaths and non-liver related deaths	<p>Incidence of deaths, cox regression univariate models and Kaplan Meier Curves to generate HR and 95% CI</p> <p>Platelets <11.5 × 104/μL and ACM HR 0.909 (0.861-0.960), sensitivity 61.4% specificity 8.8%</p>	Low platelet count was prognostic for all-cause and liver-related death. Low albumin, high AST, high GGT, and high HbA1c were associated with all-cause and liver related death.
(Le et al.,	Retrospective	4680	Mean 52.6	NFS <-1.455 vs -	All cause	Incidence of deaths,	RI is a good

2019) USA Community care	cohort study 1999-2016	participants Dx USFLI ≥30 1279 participants with NAFLD and renal impairment (RI) 3401 participants with NAFLD without RI	years Male 56.3% Female 43.7% Ethnicity – Caucasian 74.8%, African 6.3%, Hispanic 16.5%, other 2.5% CVD 13.3% HTN 52.3% DM 24.4% Mean BMI 34.3 Renal impairment – none 77.9%, mild 15.8%, moderate 3.9%, severe 2.4% Obesity 71.9% Smoking 45%	1.455 – 0.676 vs >0.676 No RI (eGFR 60 - >90 or ACR <3 mg/mmol) vs Mild RI (eGFR 45-59 or ACR 3- 30 mg/mmol) vs Moderate RI (eGFR 30-44 and ACR <3 OR eGFR 45-59 and ACR 3-30 OR eGFR 60 - >90 and ACR >30) vs Severe RI (eGFR 0-29 and ACR <3 OR eGFR 0-44 and ACR 3-30 OR eGFR 0 - >59 and ACR >30)	mortality, cardiovascular mortality	Cox regression and multivariable adjustment for HR and 95% CI (no RI and 'low' NFS score were used for reference) NFS -1.455 – 0.676 and ACM HR 1.53 (0.98- 2.39) NFS >0.676 and ACM HR 2.06 (1.22-3.46) NFS -1.455 – 0.676 and CVM HR 1.74 (0.47- 6.48) NFS >0.676 and CVM HR 1.56 (0.37-6.65) Mild RI and CVM HR 2.01 (0.92-4.38) Moderate RI and CVM HR 3.04 (1.02-9.08) Severe RI and CVM HR 6.78 (2.23-20.6) Mild RI and ACM HR 2.33 (1.68-3.22) Moderate RI and ACM HR 3.65 (2.51-5.30) Severe RI and ACM HR 4.4 (2.88-6.72)	prognostic factor for mortality in NAFLD both for all-cause mortality and for cardiovascular mortality. NFS is a prognostic factor for all- cause mortality but not for cardiovascular mortality.
(Munteanu et al., 2018)	Prospective cohort study	7082 participants	*Mean 56.7 years	FibroTest Apolipoprotein	All-cause mortality,	Incidence of deaths, univariate Kaplan-	FibroTest has prognostic value

France Secondary care	1997-2012 Median FU 6 years (range 0.1-19.3 years)	Dx liver biopsy or USS fatty liver NAFLD participants 2079 Other causes of CLD 6003	Male 57.4% Female 42.9% Ethnicity – 6% Asian, 76% Caucasian, 18% African DM 35.8%	A1 Haptoglobin SteatoTest-2 NashTest-2	Liver-related mortality, CV mortality, extrahepatic malignancy mortality	Meier curves, AUROC and 95% CI FibroTest ACM AUROC 0.507 (0.443-0.571) FibroTest LRM AUROC 0.941 (0.905-0.978) FibroTest CVM AUROC 0.584 (0.478-0.6921) NashTest2 ACM AUC 0.492 (0.468-0.613) SteatoTest2 ACM AUC 0.535 (0.435-0.635) NashTest2 LRM AUC 0.942 (0.884-0.999) SteatoTest2 AUC 0.727 (0.579-0.875) Multivariate Cox analysis ApoA1 CVM Exp(B) 3.366 (1.357- 8.531) R ² 0.058 Hapto CVM Exp(B) 0.566 (0.203-1.278) R ² 0.01 ApoA1 ACM Exp(B) 2.659 (1.733-4.078) R ² 0.065 Hapto ACM Exp(B) 0.465 (0.278-0.776) R ² 0.029	in NAFLD patients' overall survival and cardiovascular death. Low ApoA1 and high haptoglobin were independently associated with overall death and cardiovascular death. NashTest and Steatotest had a predictive value for liver- related deaths in univariate analysis, but not multi-valriate, and showed a negative (and opposite) association with all-cause mortality.
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(Nseir et al., 2019) Israel Secondary care	Retrospective cohort study 2013-2017 FU 30 days	561 participants Dx USS presence of fatty liver 200 participants with NAFLD + CAP, 361 participants with CAP without NAFLD	*Mean 64.3 years Male 61% Female 39% CVD 11% DM 32% Mean BMI 29.4 Smoking 35.5%	NFS <-1.455 vs >0.676	30-day all-cause mortality	Incidence of deaths, Odds ratio for mortality and 95% CI (Multivariate Cox regression analysis) NFS <-1.455) OR 1.38 (1.12-1.51) NFS >0.676 OR 1.52 (1.25-1.70)	Presence of NAFLD in patients with CAP was associated with 30-day all-cause mortality. Association was more prominent in patients with advanced hepatic fibrosis.
(Peleg et al., 2018) Israel Secondary care	Prospective cohort study 2005 – 2012 Mean FU 11.23 months (IQR 60-144)	153 participants Dx by liver biopsy 121 participants biopsy fibrosis stage 0-2 and 32 participants stage 3-4	Mean 49.5 years Male 55.5% Female 44.4% HTN 41% DM 63% Mean BMI 29.5 NASH 17.6%	FIB-4 (≤ 2.76 vs > 2.76) NFS (≤ 0.676 vs > 0.676) APRI (≤ 1.5 vs. > 1.5)	All-cause mortality, diagnosis of malignancies, liver events (varices, ascites, hepatic encephalopathy, TIPS)	Incidence of mortality, Hazard Ratio and 95% CI (multivariate analysis adjusted for gender, age, hypertension and type 2 DM and with the 'low' scores as a reference) FIB-4 > 2.76 HR 10.52 (2.92-37.07) APRI > 1.5 HR 2.85 (0.89-9.09) NFS > 0.676 HR 1.58 (1.23-1.88)	Non-invasive scores may reliably predict prognosis, including all-cause mortality, when compared to liver biopsy.
(Tada et al.,	Retrospective	4073	Mean 61 years	FIB-4 <1.30	Liver, cancer,	Incidence of deaths	FIB-4 and NFS

<p>2017) Japan Secondary care</p>	<p>cohort study 2006 – 2015 Median FU 7.1 years (IQR 4.8-9.2 years)</p>	<p>participants Dx by USS hepatic steatosis</p>	<p>Male 54.1% Female 45.9% DM 30.8% Mean BMI 25 Smoking 26%</p>	<p>(reference) vs ≥ 1.30 NFS <-1.455 (reference) vs -1.455 – 0.676 vs > 0.676</p>	<p>cerebro/cardiovascular, benign disease mortality.</p>	<p>(total and cause-specific), 3, 5, 10 year cumulative mortality, multivariate Fine and Gray proportional hazards modelling. NFS <-1.455 – 0.676 and cancer HR 2.16 (1.35-3.46) NFS >0.676 and cancer HR 4.81 (2.32-9.98) NFS -1.455 – 0.676 and CCVM HR 2.27 (1.14-4.98) NFS >0.676 and CCVM HR 8.48 (3.56-20.22) FIB-4 ≥ 1.30 and cancer HR 1.75 (1.13-2.74) FIB-4 ≥ 1.30 and CCVM HR 1.96 (1.06-3.63)</p>	<p>can prognosticate mortality from malignancy, cerebro-cardiovascular and benign disease causes.</p>
<p>(Treeprasertsuk et al., 2013) USA Community care</p>	<p>Retrospective cohort study 1980 – 2009 Mean FU 12 years (SD 3.9years)</p>	<p>302 participants Dx by liver biopsy or hepatic steatosis on imaging</p>	<p>Mean 47 years Male 43.7% Female 56.3% Caucasian 95% HTN 41.4% DM 15.9% Mean BMI 33.6 Obesity 73.2%</p>	<p>NFS <-1.5 vs -1.5 – 0.66 vs ≥ 0.676</p>	<p>All-cause mortality, cardiac or liver-related complications</p>	<p>Incidence of deaths, multivariable adjusted (3 models with different variables) logistic regression analysis to generate odds ratio and 95% CI and AUROC Baseline high NFS (Model 3) OR 2.6 (1.7-</p>	<p>Higher NFS at baseline was significantly predictive of death. The annual NFS change in patients who died was significantly</p>

						3.9) Baseline NFS cutoff -0.9 AUR 0.7, sensitivity 62% and specificity 76% for mortality	higher than those in patients who survived (0.14 vs 0.07, P = 0.03).
(Xun et al., 2014) China Secondary care	Retrospective cohort study 1996-2011 Median FU 6.6 years (IQR 4-9 years)	180 participants Dx USS	Mean 39 years Male 53.3% Female 46.7% CVD 1.1% HTN 11.1% DM 9.4% Mean BMI 26.3	NFS <-1.455 vs ≥- 1.455 FIB-4, APRI (no cutoffs reported)	All-cause mortality	Incidence of deaths, multivariate Cox model analysis to generate HRs and 95% CI (NFS <- 1.455 reference), AUCROC and sensitivity and specificity calculations. NFS HR 2.743 (1.67-4.5) AUC 0.828 (0.728- 0.928) specificity 88.3% sensitivity 96.9% with cutoff -1.836 FIB-4 AUC 0.806 (0.679 - 0.914) APRI AUC 0.732 (0.604- 0.859)	NFS is a predictor of all- cause mortality

CHF- Congestive Heart Failure

CKD- Chronic Kidney Disease

HTN- Hypertension

DM- Diabetes Mellitus

USS- Ultrasound Scan

CVD- Cardiovascular Disease

BMI- Body Mass Index

Table S3: Scoring system and outcomes for studies included in the meta-analysis

Author name, year of publication	Prognostic biomarker and cutoffs used	Outcomes reported	Main results reported in HR (CI)	Main conclusions
(Angulo et al., 2013)	FIB4 <1.30 (reference*) vs 1.30 – 2.67 vs >2.67 NFS <-1.455 (reference) vs -1.455 – 0.676 vs >0.676 APRI <0.5 (reference) vs 0.5-1.5 vs >1.5 BARD 0-1 (reference) vs 2-3 vs 4	All-cause mortality or transplant Liver-related events	NFS > 0.676 HR 9.8 (2.7 – 35.3) APRI >1.5 HR 3.1 (1.1 – 8.4) FIB4 >2.67 HR 6.9 (2.3-20.4) BARD 4 HR 1.6 (0.5-4.9)	Non-invasive scoring systems can predict the risk of mortality in NAFLD, with NFS seeming the most accurate.
(Hagström et al., 2019)	FIB4 <1.30 (reference) vs 1.30 – 2.67 vs >2.67 NFS <-1.455 (reference) vs -1.455 – 0.676 vs >0.676 APRI <0.5 (reference) vs 0.5-1.5 vs >1.5 BARD 0-1 (reference) vs 2-3 vs 4	All-cause mortality Severe liver disease	NFS > 0.676 HR 4.93 (2.63-9.26) APRI >1.5 HR 1.71 (1.02 – 2.85) FIB4 >2.67 HR 3.48 (2.28-5.31) BARD 4 HR 3.85 (2.18-6.79)	NFS and FIB-4 best predicted overall mortality and severe liver disease compared to BARD and APRI
(Kim et al.,	NFS <-1.455 (reference) vs -1.455 – 0.676 vs >	All-cause mortality,	NFS >0.676 and ACM** HR 1.69	Non-invasive fibrosis markers are prognostic

2013)	0.676 FIB4 <1.30 (reference) vs 1.30-2.67 vs >2.67 APRI <0.5 (reference) vs 0.5-1.5 vs >1.5	Cause specific mortality (CVD, Liver, malignancy, diabetes)	(1.09-2.63) NFS >0.676 and CVM** HR 3.46 (1.91-6.25) FIB4 >2.67 and ACM HR 1.66 (0.98-2.82) FIB4 >2.67 and CVM HR 2.68 (1.44-4.99) APRI >1.5 and ACM 1.85 (1.02-3.37) APRI >1.5 and CVM HR 2.53 (1.33-4.83)	for mortality in NAFLD. NFS, APRI, and FIB-4 are predictive of all-cause and cardiovascular mortality but not liver- related mortality.
(Le et al., 2019)	NFS <-1.455 vs -1.455 – 0.676 vs >0.676	All cause mortality, cardiovascular mortality	NFS >0.676 and ACM HR 2.06 (1.22-3.46) NFS >0.676 and CVM HR 1.56 (0.37-6.65)	NFS is a prognostic factor for all-cause mortality but not for cardiovascular mortality.

*Reference category used when calculating the hazards ratio

** ACM: All-cause mortality; CVM : Cardiovascular-related mortality

Table S4: Risk of bias (Quality in prognostic studies) for studies included in meta-analysis

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement
Le et al., 2019	Low	Low	Moderate	Low
Kim et al., 2013	Low	Moderate	Moderate	Low
Hagstrom et al., 2019	Low	Low	Low	Low
Angulo et al., 2013	Low	Low	Moderate	Low

Figure S1 (A) – BARD High vs. Low and all-cause mortality, (B) – BARD Intermediate vs. Low and all-cause mortality.

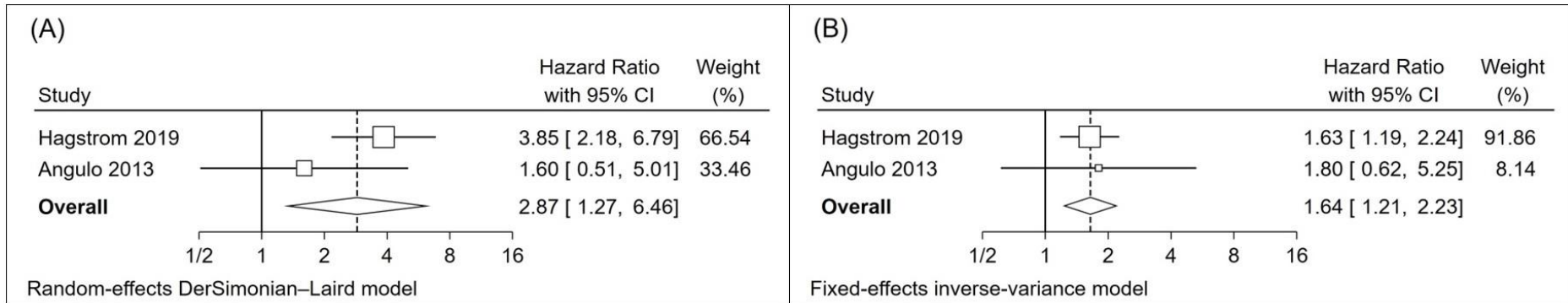
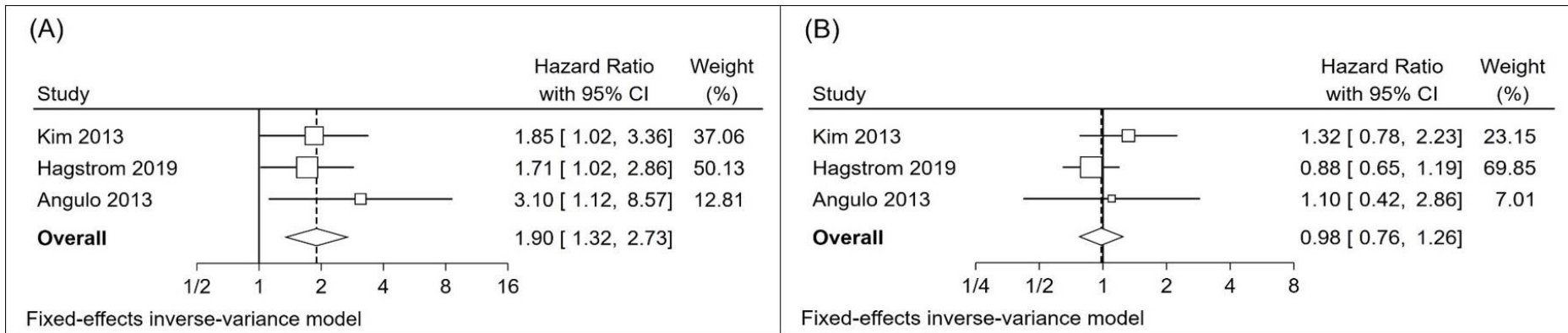


Figure S2 (A) – APRI High vs. Low and all-cause mortality, (B) – APRI Intermediate vs. Low and all-cause mortality.



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