Liver fibrosis is associated with clinical and economic burden of cardiovascular disease amongst patients with non-alcoholic steatohepatitis: the unCoVer-NASH longitudinal cohort study

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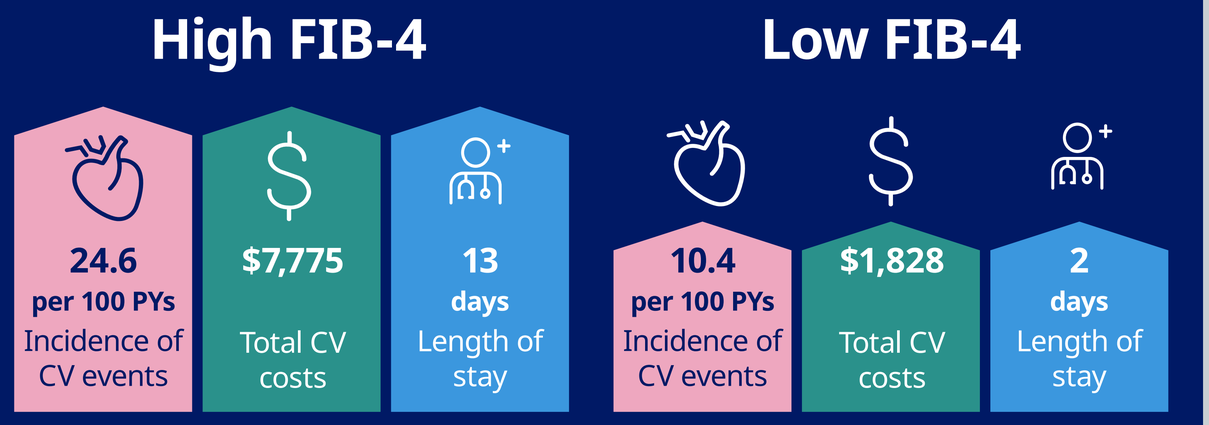
Higher FIB-4 is associated with higher clinical and economic burden of CV events in non-cirrhotic NASH



Aim

- Non-alcoholic steatohepatitis (NASH) has been linked to an increased risk of cardiovascular (CV) disease (CVD)[1]
- The clinical and economic burden of CVD in patients with NASH is incompletely understood
- This study addresses this knowledge gap in patients with NASH without cirrhosis stratified by Fibrosis-4 Index (FIB-4) using real-world US healthcare data (TriNetX)

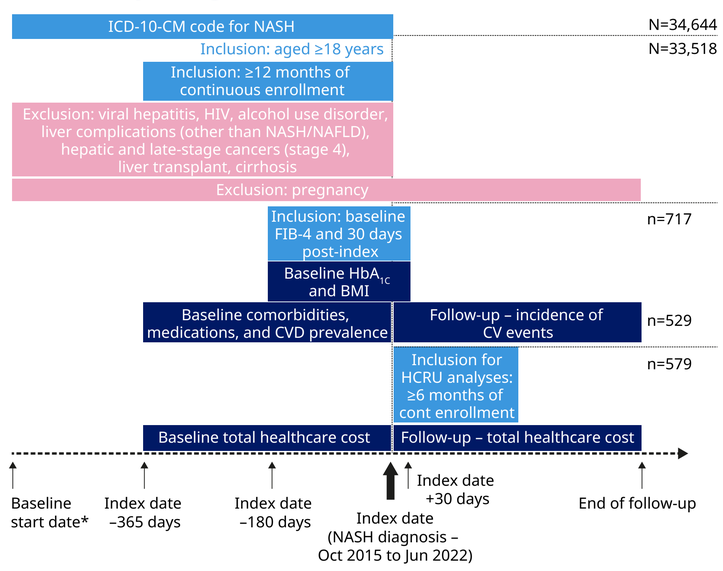
Methods

- Patients (aged ≥18 years) were identified using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for NASH from October 2015 to June 2022 (**Figure 1**)
- FIB-4 score categories were defined as low (<1.30), intermediate (1.30–2.67), and high (>2.67)

Results

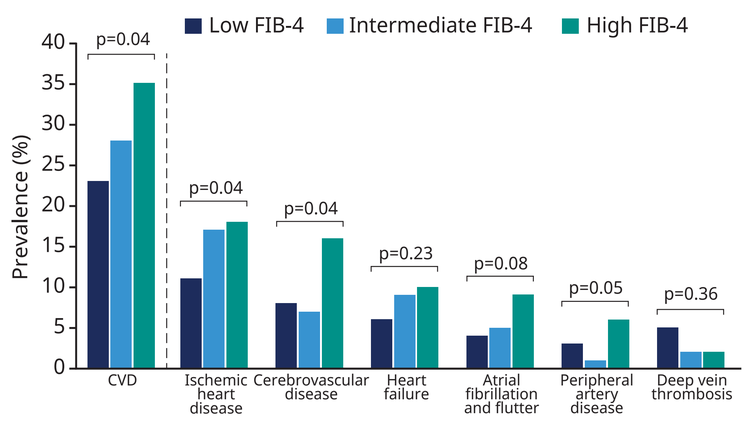
- Of 717 patients included, 102 had high, 201 had intermediate, and 414 had low FIB-4
  - Of these, 529 and 579 patients were included in the analysis of CV incidence and economic burden, respectively
- In the high, intermediate, and low FIB-4 groups, mean age was 60, 57, and 44 years, respectively, and most were female (71%, 54%, and 57%, respectively); 50%, 45%, and 36% of patients had type 2 diabetes, 38%, 45%, and 54% had obesity, 17%, 9%, and 6% had chronic kidney disease, and 54%, 59%, and 43% had hyperlipidemia, respectively
- The most prevalent CVD phenotypes in all FIB-4 groups are shown in **Figure 2**
- Incidence rate (per 100 person-years) and cumulative incidence of any CV event increased with FIB-4 score (**Table 1**, **Figure 3**)
- Risk of CV events was higher for high and intermediate vs low FIB-4 and remained significant for high vs low FIB-4 after adjustment for CV risk factors (**Table 1**)
  - Similar results were obtained for individual CV events (data not shown)
- Total healthcare and medical costs were higher for high vs low FIB-4 and CV-related resource utilization increased with FIB-4 score (**Table 1**)

Figure 1: Study design and cohort selection



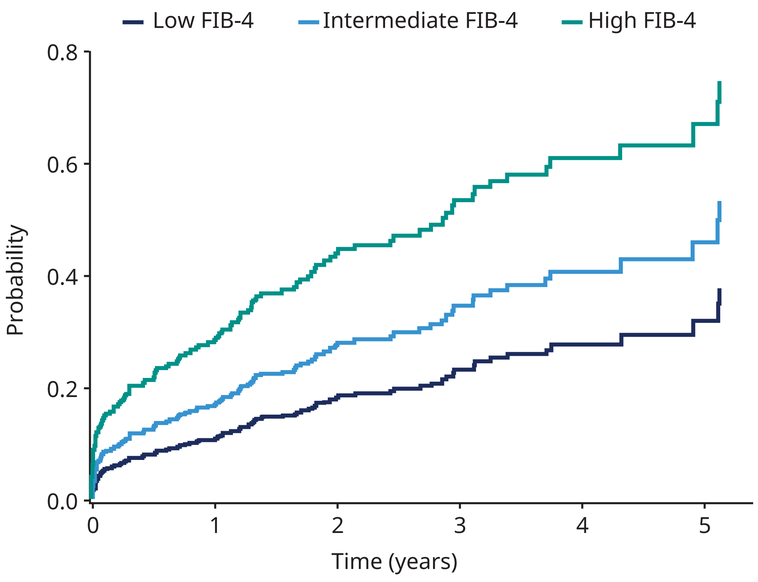
*Data start date is defined based on the earliest claim record (medical claim to record diagnosis) available for patients.
BMI, body mass index; cont, continuous; CV, cardiovascular; CVD, cardiovascular disease; FIB-4, Fibrosis-4 Index; HbA_{1c}, glycated hemoglobin; HCRU, healthcare resource utilization; HIV, human immunodeficiency virus; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Figure 2: Prevalence of CV events in FIB-4 groups



Statistical significance was tested using Fischer's exact text.
CV, cardiovascular; CVD, cardiovascular disease; FIB-4, Fibrosis-4 Index.

Figure 3: Cumulative incidence for any CV event by FIB-4 category



Cumulative incidence of any CV event (atrial fibrillation and flutter, angina pectoris, cardiac arrest, deep vein thrombosis, heart failure, ischemic heart disease, atherosclerosis, cerebrovascular disease, and peripheral artery disease) by FIB-4 risk category was estimated using Fine and Gray's regression after adjusting for competing risk due to death.
CV, cardiovascular; FIB-4, Fibrosis-4 Index.

Table 1: Incidence and CV-related healthcare cost and resource utilization at follow-up — **Key result**

Outcome	Low FIB-4	Intermediate FIB-4	High FIB-4
N, incidence analysis	318	145	66
IR of any CV event, per 100 PYs	10.4	17.2	24.6
HR (95% CI) vs low FIB-4	—	1.53 (1.01, 2.29)*	3.43 (2.21, 5.31)***
aHR† (95% CI) vs low FIB-4	—	0.87 (0.55, 1.37)	2.05 (1.23, 3.41)**
N, economic burden analysis	335	166	78
Total healthcare costs, $ PPPY	1,828 (6,721)	3,242 (11,212)	7,775 (24,116)
Estimate (95% CI) vs low FIB-4‡	—	1.40 (0.93, 2.10)	3.93 (2.32, 6.63)***
Medical costs, $ PPPY	1,661 (6,372)	3,081 (11,149)	7,228 (23,390)
Estimate (95% CI) vs low FIB-4‡	—	1.48 (0.95, 2.31)	4.08 (2.32, 7.16)***
Pharmacy costs, $ PPPY	167 (993)	161 (504)	547 (2,646)
Estimate (95% CI) vs low FIB-4‡	—	1.00 (0.64, 1.57)	3.05 (1.59, 5.86)**
Number of INP visits, PPPY	0.30 (0.85)	0.54 (1.48)	0.95 (2.08)
Estimate (95% CI) vs low FIB-4‡	—	1.38 (0.84, 2.25)	2.50 (1.38, 4.54)**
Number of OP visits, PPPY	8.55 (13.75)	12.88 (19.26)	9.71 (11.87)
Estimate (95% CI) vs low FIB-4‡	—	1.00 (0.76, 1.31)	0.89 (0.62, 1.27)
Number of ER visits, PPPY	0.22 (0.88)	0.16 (0.69)	0.20 (0.55)
Estimate (95% CI) vs low FIB-4‡	—	0.84 (0.39, 1.78)	1.65 (0.65, 4.16)
Length of stay, days	1.49 (5.41)	2.46 (7.75)	12.67 (50.94)
Estimate (95% CI) vs low FIB-4‡	—	1.26 (0.62, 2.55)	4.86 (2.03, 11.63)**

Data are mean (SD) unless stated otherwise. IR of any CV event (atrial fibrillation and flutter, angina pectoris, cardiac arrest, deep vein thrombosis, heart failure, ischemic heart disease, atherosclerosis, cerebrovascular disease, and peripheral artery disease) by FIB-4 risk category was calculated per 100 PYs. HRs were estimated using Cox proportional hazard model. Generalized linear models with log link were used to compare healthcare cost (using gamma distribution) and resource utilization and length of stay (using negative binomial distribution). Total healthcare cost included medical and pharmacy costs.
*p≤0.05; **p≤0.01; ***p≤0.0001. †HRs were adjusted for age, sex, and comorbidities (type 2 diabetes, hyperlipidemia, hypertension, chronic kidney disease, and obesity). ‡Estimates were adjusted for age, sex, race, comorbidities (type 2 diabetes, hyperlipidemia, hypertension, chronic kidney disease, and obesity), type of insurance, and number of distinct baseline CV-related inpatient events in the last 6 months.
aHR, adjusted hazard ratio; CI, confidence interval; CV, cardiovascular; ER, emergency room; FIB-4, Fibrosis-4 Index; HR, hazard ratio; INP, inpatient; IR, incidence rate; N, number of patients; OP, outpatient; PPPY, per person per year; PY, person-year; SD, standard deviation.

Conclusions

- Clinical and economic burden of CVD in patients with NASH without cirrhosis was higher in those with higher baseline FIB-4 score
- Patients with intermediate vs low FIB-4 had an increased incidence of any CV event(s); further research around risk in this group and how to manage these patients is needed
- These results indicate a direct relationship between CV-related burden and hepatic fibrosis

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Reference:

(1) Shroff H and VanWagner LB. Curr Hepatol Rep 2020;19:315–26.

Disclosures:

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