Using artificial intelligence to identify patient characteristics associated with rapid fibrosis progression in NASH: a retrospective cohort study

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Aims

- To identify clinical phenotypic features associated with rapid fibrosis progression in nonalcoholic steatohepatitis (NASH).

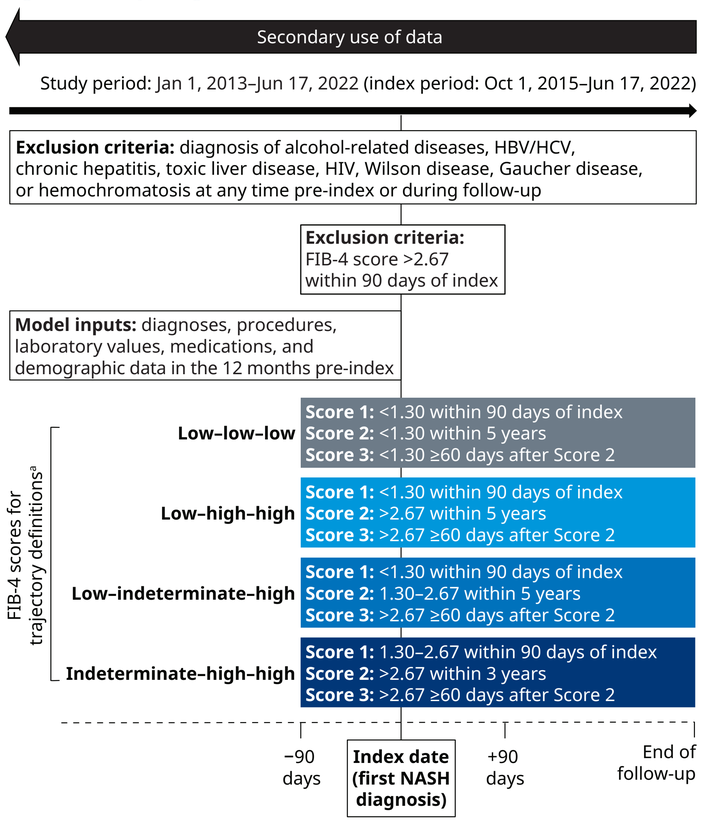
Introduction

- Fibrosis progression in NASH (also termed metabolic dysfunction-associated steatohepatitis [MASH]) is associated with an increased risk of liver-related morbidity,[1] in addition to overall and disease-specific mortality.[2]
- However, efforts to identify patient subgroups at risk of rapid fibrosis progression are complicated by the disease's multifactorial nature,[3] and the absence of a standard method for defining rapid progression.
- Furthermore, fibrosis progression is difficult to monitor because of the infrequent use of liver biopsy in clinical practice.[4] Instead, clinical guidelines recommend the use of noninvasive biomarkers such as Fibrosis-4 (FIB-4) score, which has been studied for its association with the extent of fibrosis and the prediction of liver-related outcomes.[5]
- A better understanding of patient characteristics associated with rapid fibrosis progression could enable identification of patients requiring more regular monitoring and suggest new approaches for management.
- We used artificial intelligence (AI) phenotyping to identify and characterize patients with rapid fibrosis progression (based on FIB-4 score trajectories) in NASH.

Methods

- This retrospective cohort study used the OM1 Real-World Data Cloud, a multisource dataset derived from US electronic medical records and claims data from over 300 million people.
- Inclusion criteria were a diagnosis of NASH (index date), based on International Classification of Diseases 10th Revision (ICD-10), MEDCIN or Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) diagnosis codes, between October 1, 2015 and June 17, 2022, plus:
  - at least one FIB-4 score within 90 days of first NASH diagnosis, and
  - two or more subsequent FIB-4 scores with at least 60 days between them (**Figure 1**).

Figure 1: Study design and cohort definitions



[a]A FIB-4 score at baseline (score 1) and at least two FIB-4 scores during follow-up were required for inclusion.
FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NASH, nonalcoholic steatohepatitis.

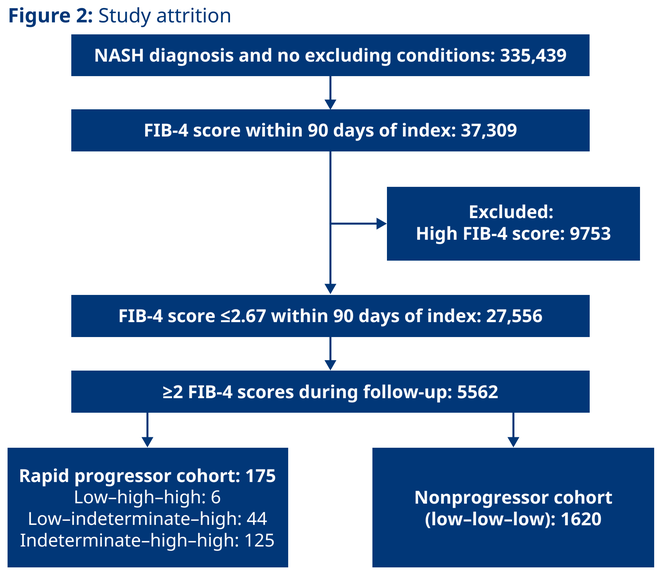
- Patients were also required to meet the inclusion criteria for the rapid progressor or nonprogressor cohorts defined in **Figure 1**.
  - Cohort definitions were informed by FIB-4 score thresholds corresponding to low, indeterminate, and high fibrotic states.[6]
  - There is no standard definition for rapid fibrosis progression, so this was defined based on FIB-4 score trajectories over time (low–high–high, low–indeterminate–high, and indeterminate–high–high), and time to progression depending on baseline FIB-4 score.
  - The nonprogressor cohort (low–low–low) served as the comparator group.
- The AI-based PhenOM™ platform (OM1 Inc., Boston, MA, USA) was calibrated to isolate phenotypic features associated with rapid fibrosis progression.
  - Inputs included diagnoses, procedures, laboratory values, medications, and demographic data in the 12 months pre-index.
  - The calibration process relied first on the PhenOM™ platform's AI-based generation of groupings of thematically related information elements (e.g. grouping a set of diagnoses, procedures, and medications together), which fully covered each patient's health record. Then, these groupings were iteratively refined and evaluated for strength of association with rapid fibrosis progression, as well as clinical plausibility.
  - Phenotypic signals were given descriptive thematic labels after their isolation, and were not constructed or amended based on these labels. While multiple signals may have similar descriptive labels, individual data elements can only appear within a single signal.
- Outcomes were the proportions of phenotypic signals in each cohort, and the degree of difference in proportions between cohorts.
  - Absolute differences were calculated by subtracting proportions in the nonprogressor cohort from proportions in the rapid progressor cohort, and were expressed using the alpha metric.
  - Relative differences were calculated by dividing the greater proportions by the lesser (regardless of cohort), and were expressed using the beta metric.
- Phenotypic signals underwent directional significance testing, comprising bootstrapped resampling of the rapid progressor and nonprogressor cohorts in each instance, and subsequent calculation of signal 'directionality' (i.e. overrepresentation in the rapid progressor cohort or in the nonprogressor cohort).
  - Signals passing this testing showed the same directionality at least 95% of the time, indicating stable performance in distinguishing rapid progressor and nonprogressor cohorts.

Results

Cohort characteristics

- Of approximately 500,000 individuals with a NASH diagnosis in the dataset, 335,439 had no excluding conditions (**Figure 2**).
  - Of those with a FIB-4 score at index and at least two scores during follow-up, 175 and 1620 patients met the inclusion criteria for the rapid progressor and nonprogressor cohorts, respectively.
  - Given the low number of patients in each rapid progressor cohort, the overall cohort was considered in subsequent analyses.

Figure 2: Study attrition



FIB-4, Fibrosis-4; NASH, nonalcoholic steatohepatitis.

- Compared with the nonprogressor cohort, patients with rapid progression were older on average (63.5–67.3 years vs 54.6 years), and a slightly greater proportion were women (63.3–66.7% vs 62.3%) (**Table 1**).
  - Age was a relatively strong factor in initial results distinguishing the cohorts (and is a FIB-4 input), so age filtering (for patients >40 years old) was applied for subsequent analyses.

Phenotypic signals based on absolute proportion differences

- One of the top signal themes for rapid fibrosis progression based on absolute differences was history of anemia and thrombocytopenia diagnoses, including general anemia, iron deficiency anemia, and general thrombocytopenia (**Figure 3**).
  - These features were observed in association with procedures relating to the diagnosis and management of these conditions, such as blood smears.

Table 1: Cohort characteristics

Characteristic	Rapid progressors: Low–high–high (n=6)	Rapid progressors: Low–indeterminate–high (n=44)	Rapid progressors: Indeterminate–high–high (n=125)	Nonprogressors: Low–low–low (n=1620)
Women, n (%)	4 (66.7)	28 (63.3)	82 (65.6)	1010 (62.3)
Age, mean (SD), years	66.3 (7.2)	63.5 (9.4)	67.3 (9.1)	54.6 (9.1)
US region, n (%)				
Northeast	2 (33.3)	5 (11.4)	18 (14.4)	294 (18.1)
Midwest	1 (16.7)	6 (13.6)	8 (6.4)	166 (10.2)
South	3 (50.0)	17 (38.6)	59 (47.2)	763 (47.1)
West	0 (0.0)	16 (36.4)	40 (32.0)	389 (24.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)

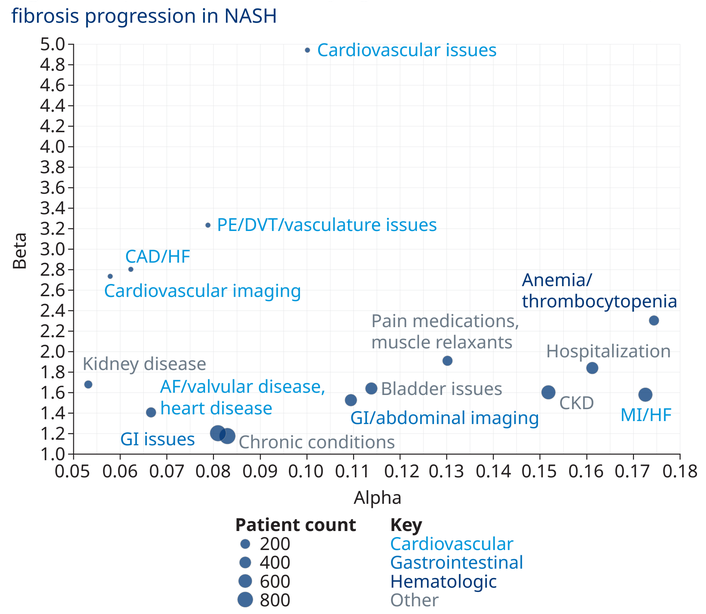
SD, standard deviation.

- Another signal theme emerged around history of heart failure and related procedures (**Figure 3**).
  - These included prothrombin time, electrocardiogram, emergency room visits, partial thromboplastin time, and troponin. In some patients, these were combined with procedures related to infection and sepsis.
- Patients with a history of hospitalization (including initial and subsequent hospital care) were also at elevated risk for rapid fibrosis progression (**Figure 3**).
  - Kidney issues emerged as a primary feature in combination with hospitalization, including acute kidney failure, chronic kidney disease, and hypokalemia.

Phenotypic signals based on relative proportion differences

- The major signal theme based on relative proportion differences was cardiovascular (CV) issues, including a collection of CV diagnoses (**Figure 3**).
  - This signal cluster included atrial fibrillation, dilated cardiomyopathy, coronary artery disease, myocardial infarction, and congestive heart failure.
- Other major signals included pulmonary embolism and deep vein thrombosis (**Figure 3**).
  - These CV issues were similarly reflected in the absolute proportion difference of the myocardial infarction and heart failure signal.

Figure 3: Top-level summary of key signal themes associated with rapid fibrosis progression in NASH



Key signal theme labels represent signal clusters of individual elements. Higher values indicate greater absolute (alpha) and relative (beta) differences between the proportions of rapid progressors and nonprogressors with each signal. For example, a signal present in 40% of the rapid progressor cohort and 10% of the nonprogressor cohort would have an alpha value of 0.3 and a beta value of 4.0; in this study, the absolute difference between cohorts for CV issues was small (0.10), but the relative difference was large (~5.0).
AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DVT, deep vein thrombosis; GI, gastrointestinal; HF, heart failure; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; PE, pulmonary embolism.

Clinical validation

- To assess the clinical validity of the signals in **Figure 3**, a medical expert manually recategorized a subset based on clinical logic; for example, a cardiac signal could contain subsignals related to structural issues (e.g. valve stenosis) and arrythmias (e.g. ventricular tachycardia).
  - These clinically informed signals maintained good signal strength overall, and reinforced confidence in the AI-generated signal themes, although some signals did not distinguish between cohorts as strongly.

Strengths and limitations

- The signals that emerged were generally thematically coherent, comprising information related to several aspects of patient history.
- The use of relative metrics reduced the risk of missing potentially relevant signals that might otherwise be missed by absolute metrics alone.
- The use of FIB-4 scores to define progression was based on evidence of FIB-4's prognostic potential;[7] however, additional data may be required to test the association between changes in FIB-4 scores and fibrosis stages (based on biopsy).
- The requirement for at least three FIB-4 scores meant that many patients with a NASH diagnosis were excluded from the analysis; in some instances, a lack of data limited our ability to test signal robustness.

Conclusions

- This proof-of-concept study demonstrates the ability of AI to create phenotypic representations based on detailed real-world data from all organ systems, to perform subsequent risk stratification, and to define progression phenotypes using these noninvasive biomarkers.
- The emergence of CV issues in both absolute and relative signal dimensions demonstrates the potential importance of using these features to distinguish patients with rapid fibrosis progression from others.
- This approach could support new methods to proactively identify patients who are more likely to experience rapid fibrosis progression and may, therefore, require closer monitoring and improved management.

[1]Novo Nordisk Inc., Plainsboro, NJ, USA; [2]Novo Nordisk A/S, Søborg, Denmark; [3]OM1 Inc., Boston, MA, USA.
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Disclosures:
SOG is an employee of Novo Nordisk Inc. and a shareholder of Novo Nordisk A/S. KKM is an employee and shareholder of Novo Nordisk A/S. DS, JB, JZ, GC, and CB are employees of OM1 Inc.; OM1 Inc. received consulting fees from Novo Nordisk Inc. and Novo Nordisk A/S to perform this analysis. BS is an employee of Novo Nordisk Inc. HN is an employee of Novo Nordisk A/S.

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(**1**) Taylor RS et al. Gastroenterology 2020;158(6):1611–25; (**2**) Ekstedt M et al. Hepatology 2015;61(5):1547–54; (**3**) Dufour J et al. Gut 2022;71(10):2123–34; (**4**) Rinella ME et al. Therap Adv Gastroenterol 2016;9(1):4–12; (**5**) Rinella ME et al. Hepatology 2023;77(5):1797–835; (**6**) Shah AG et al. Clin Gastroenterol Hepatol 2009;7(10):1104–12; (**7**) Lee J et al. Liver Int 2021;41(2):261–70.