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A Pragmatic Clinical Prognostic Classification Suitable for Universal Application Stratifies Patients with NAFLD by Risk of Mortality and Both Hepatic and Extrahepatic Outcomes

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Introduction

- The current approach to risk stratify patients with NAFLD is based on histological assessment.
- In clinical practice, biopsies are infrequently performed, and there is a need to establish a pragmatic but accurate prognostic classification system.
- This study validated a prognostic system, derived from previously described profiles (Nature Reviews, 2016; 13:196-205), using widely available measures to predict incident outcomes in those with NAFLD.

Methods

- A retrospective-prospective analysis was performed in TARGET-NASH, a non-interventional real-world cohort study of NAFLD, as defined by imaging evidence of steatosis and conventional alcohol thresholds, assessed by AUDIT.
- FIB-4/LSM criteria: Low- (Class A), Intermediate- (Class B) and High (Class C). Class A was defined by having either a FIB-4 ≤1.3 or a liver stiffness measurement (LSM) ≤8 kPa by Fibroscan. Class B was defined by FIB-4 1.3-2.6 kPa or LSM 8.1-12.5 kPa. Class C was defined by FIB-4 >2.6 or LSM >12.5.
- Upstaging using clinical-lab criteria: Patients were upstaged to Class C if they had at least one of diabetes or hypertension and AST:ALT >1 or platelets <150,000/mm^3. If patients had at least one of diabetes or hypertension and AST:ALT ≤1 or platelets ≥150,000/mm^3, they were upstaged to Class B.
- Differences in the crude incidence rate of liver events (ascites/encephalopathy/variceal bleed), major adverse cardiac events (MACE), hepatocellular and extrahepatic cancers, and death were compared across risk strata using Cochran-Armitage test.
- The Kaplan-Meier method was used to estimate the overall survival and time to each event stratified by risk strata.

Results

- 2,523 patients with NAFLD (A: 554, B: 880, C: 1089) were included in the analysis (Table 1).
- The mean age (61.8 yrs.; SD:9.7) was highest in group C (Table 1).
- Median duration of follow up was 1005 days.
- There was a significant stepwise increase in the mortality and incidence rate of liver and cardiac events from class A to B to C (p< 0.0001 for trend) (Table 2).
- KM analyses suggested that the unadjusted probabilities in mortality and liver and cardiac events were different across strata (P<0.001) (Figure 1).
- Those meeting criteria for intermediate and high risk based on clinical criteria alone had outcomes similar to low and intermediate risk categories respectively as defined by FIB4/LSM.

Table 1. Baseline Characteristics by Risk Strata: TARGET-NASH Adults

	Risk Strata			
Summary	Class A (N=554)	Class B (N=880)	Class C (N=1089)	All (N=2523)
Age(years)[1]				
Median (n)	47.0 (554)	58.0 (880)	63.0 (1089)	59.0 (2523)
Sex, n (%)				
n	554	880	1089	2523
Female	308 (55.6%)	518 (58.9%)	676 (62.1%)	1502 (59.5%)
Male	246 (44.4%)	362 (41.1%)	413 (37.9%)	1021 (40.5%)
Race, n (%)				
n	554	880	1089	2523
White	391 (70.6%)	674 (76.6%)	935 (85.9%)	2000 (79.3%)
Black or African American	27 (4.9%)	65 (7.4%)	46 (4.2%)	138 (5.5%)
American Indian or Alaska Native	2 (0.4%)	2 (0.2%)	10 (0.9%)	14 (0.6%)
Asian	77 (13.9%)	71 (8.1%)	34 (3.1%)	182 (7.2%)
Other	29 (5.2%)	26 (3.0%)	35 (3.2%)	90 (3.6%)
Not Reported	28 (5.1%)	42 (4.8%)	29 (2.7%)	99 (3.9%)
BMI (kg/m^2)				
Median (n)	32.1 (554)	33.6 (880)	34.2 (1089)	33.6 (2523)
FIB-4				
Median (n)	0.8 (554)	1.4 (880)	3.6 (1089)	1.6 (2523)
Stiffness (kPa)				
Median (n)	5.5(63)	8.1(120)	14.3(134)	8.5(317)

[1]Age calculated based on year of consent minus birth year.
Class A = low risk; Class B = intermediate risk; Class C = high risk

Conclusions

- **This pragmatic prognostic classification of NAFLD is associated with increasing severity of clinical outcomes, is suitable for use across virtually all clinical settings, can be used to support clinical decisions, and provides a framework for design of outcome-trials.**
- **FIB-4 (and LSM) is more accurate than clinical criteria for the classification of the severity of liver disease in this NAFLD population.**

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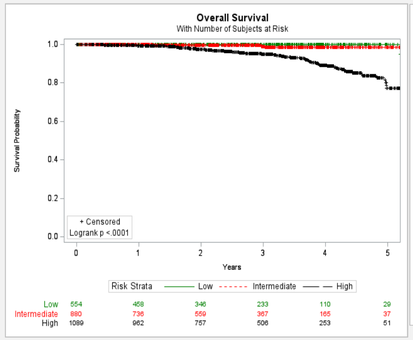
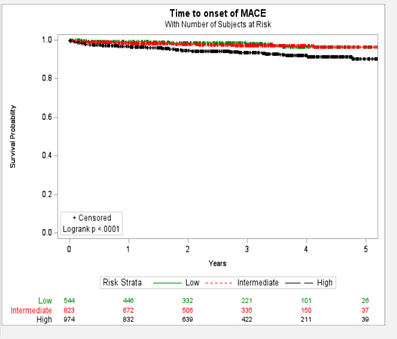
Table 2. Incidence Rate (per 100 person years) by Risk Classification at Baseline

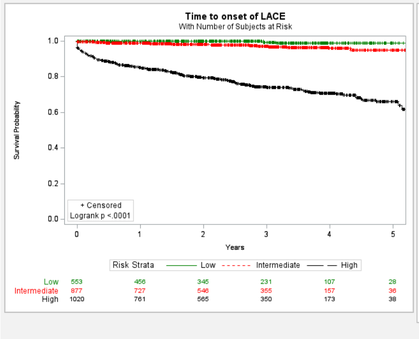
	Included using FIB-4 and/or LSM criteria			Upstaged using clinical-lab criteria	
	Class A (n=554)	Class B (n=536)	Class C (n=846)	Class B (n=344)	Class C (n=243)
Deaths	0.07	0.42	3.08	0.12	0.45
Liver events	0.21	1.32	9.50	0.46	2.68
MACE	0.69	1.11	1.96	0.46	2.23
HCC	0	0.07	1.08	0.12	0.15

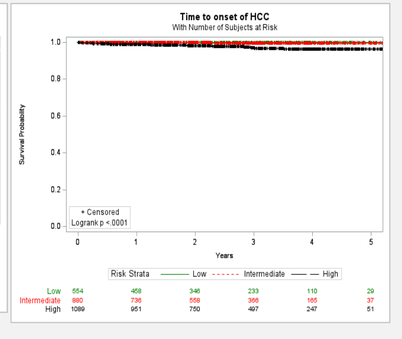
Class A = low risk; Class B = intermediate risk; Class C = high risk
If patients met the FIB-4/LSM criteria or FIB-4/LSM and clinical criteria, they were counted as included in the category based on FIB-4/LSM; if patients only met the clinical-lab criteria, they were counted as in the strata based on clinical-lab criteria.

Figure 1. Time to Event









MACE = major adverse cardiovascular events; LACE = liver-associated clinical events; HCC = hepatocellular carcinoma