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Use of the LiverRisk Score for prediction of fibrosis and all-cause mortality risk in United States adults

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BACKGROUND

- Despite the growing morbidity and mortality of metabolic dysfunction-associated steatotic liver disease, efficient screening is lacking. (1)
- FIB-4, a non-invasive test (NIT) recommended for initial screening, has higher false negative rates in at-risk groups vs. in the general population, for identifying significant fibrosis (as measured by LSM from VCTE). (1-2)
- The LiverRisk Score (LRS), based on blood-tests and demographics (age, sex, AST, ALT, GGT, fasting glucose, total cholesterol, and platelet count) was developed for prediction of liver fibrosis and liver-related outcomes in the general population. (3)

OBJECTIVES

To evaluate:

1. Performance of LRS for prediction of LSM ≥ 8 kPa compared to FIB-4
2. Association of LRS-defined risk groups with mortality

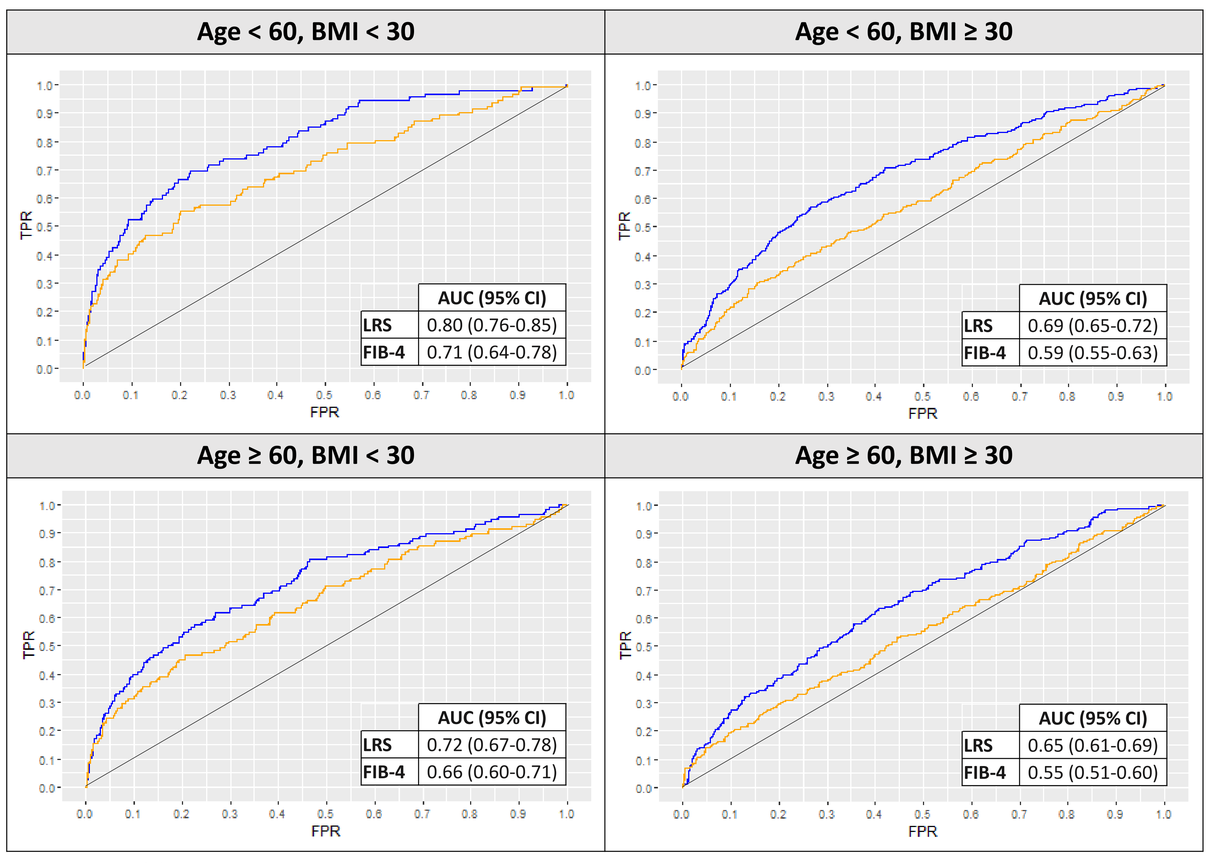
METHODS

- An observational analysis was conducted of data from the NHANES 2017-2020 cycle, including participants with complete information to calculate the LRS.
  - When missing, fasting plasma glucose was imputed based on non-fasting serum glucose and other inputs to the LRS, using a hot-deck, predictive mean matching approach.
  - In each of the two analyses, participants were further restricted to those with outcomes data (i.e., LSM by VCTE, and linkage to mortality outcomes [available for >99%]).
- Performance of LRS vs. FIB-4 for prediction of LSM ≥ 8 kPa was estimated as area under the curve (AUC) by survey-weighted logistic regression of LSM ≥ 8 kPa vs. the LRS or FIB-4, and reflected by receiver operating characteristic (ROC) curves.
  - Discrimination was further assessed in at-risk subgroups, varying by age </≥ 60 years,(2,3) and body mass index (BMI) </≥ 30 kg/m^2.(1,3)
- Association of LRS risk groups (6 to < 8, 8 to < 15, and ≥ 15) with all-cause mortality was evaluated in participants from NHANES III (1988-1994) and continuous NHANES cycles from 1999-2016, linked to National Death Index (NDI) data through 2019, with survey-weighted Cox proportional-hazards models adjusting for self-reported age, sex, and race/ethnicity.

RESULTS

- The unweighted study population included N=7,005 participants for prediction of LSM ≥ 8 kPa, and N=57,101 for prediction of all-cause mortality (median follow-up: 12.3 years).
- The LRS demonstrated superior discrimination of LSM ≥ 8 kPa in all adults, with AUC (95% CI) of 0.73 (0.71-0.75) vs. 0.63 (0.61-0.65) for FIB-4.
  - For fixed sensitivity at 90%, LRS had higher specificity vs. FIB-4 (33% vs. 17%).
- Superior discrimination was maintained in at-risk subgroups (**Figure 1**).
  - Although AUC for both LRS and FIB-4 was lower at ages ≥ 60 years and for BMI ≥ 30 kg/m^2, LRS remained superior to FIB-4 in these subgroups.

Figure 1. ROC curves for discrimination of LSM ≥ 8 kPa



Notes: FPR – false positive rate; TPR – true positive rate.

RESULTS (cont.)

- In unadjusted analyses, all-cause mortality was significantly elevated for LRS ≥ 6 vs. < 6 (**Figure 2**).
- In adjusted analyses, statistically significant association of LRS with all-cause mortality was maintained (**Table 1**).
  - Adjusted hazard ratios (95% CI) compared to LRS < 6 were estimated as 1.67 (1.57-1.78) for LRS 6 to < 8, 2.61 (2.33-2.92) for 8 to < 15, and 4.81 (3.69-6.27) for ≥ 15.

Figure 2. Unadjusted survival probability from all-cause mortality

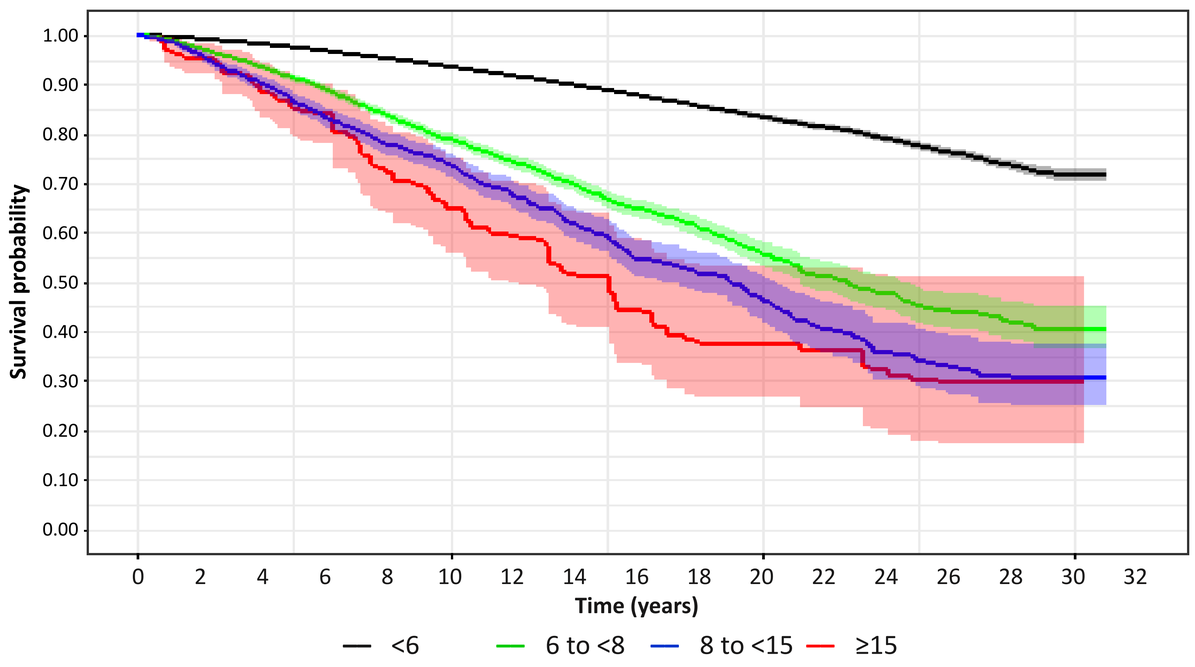


Table 1. Multivariable-adjusted hazard ratios (HRs) of all-cause mortality

Covariate	HR	95% CI Low	95% CI High	P value
Age				
<50		*Reference*		
50-59	3.86	3.49	4.28	<0.001
60+	16.60	15.28	18.02	<0.001
Sex				
Male		*Reference*		
Female	0.85	0.81	0.89	<0.001
Race / ethnicity				
White		*Reference*		
Black	1.13	1.06	1.20	<0.001
Hispanic	0.72	0.64	0.80	<0.001
LRS				
< 6		*Reference*		
6 to < 8	1.67	1.57	1.78	<0.001
8 to <15	2.61	2.33	2.92	<0.001
≥ 15	4.81	3.69	6.26	<0.001

DISCUSSION

- This analysis reports novel insights on use of the LRS in initial screening for chronic liver disease, characterizing accuracy of prediction of liver fibrosis (assessed by LSM from VCTE) in at-risk subgroups, and extending the range of follow-up in analysis of association with all-cause mortality (median [IQR] 12.3 [7.3-18.2] years in this analysis, vs. 12.1 [11.3-12.8] previously reported (3)).
- Certain limitations of the analysis should be noted, including:
  - Participants were excluded if missing necessary information for the analysis, which could introduce bias if information is not missing at random.
  - Incomplete measures of LSM (i.e., fasting <3 hours, <10 valid measures, IQR/median >30%) were excluded, and were more common for BMI ≥ 30 (9%) vs. BMI < 30 (5%).
  - Liver-related mortality could not be identified, as it is not distinguished in the classification of causes of death in NDI data linked to NHANES.

CONCLUSION

- **In US adults, the LRS demonstrated superior discrimination vs. FIB-4 for prediction of LSM ≥ 8kPa, and was maintained in at-risk subgroups distinguished by age ≥ 60 years and/or BMI ≥ 30 kg/m^2.**
- **Notably higher all-cause mortality risk was observed for LRS ≥ 6, emphasizing its clinical utility in screening for chronic liver disease.**

REFERENCES

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DISCLOSURES

DISCLOSURES – CONFLICT OF INTEREST:
MR has received consulting fees from Madrigal Pharmaceuticals, as well as Akero, 89 bio, CytoDyn, Boehringer Ingelheim, GSK, Eli Lilly, Novo Nordisk, Sagimet, and Histoindex.
MRC, YK, JJM, and SH are employed by and own stock/stock options in Madrigal Pharmaceuticals.
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