RESEARCH LETTER

High Fibrosis-4 is Associated With Increased Risk of Cirrhosis Decompensation and Liver-Related Mortality in at-Risk Patients With Metabolic Dysfunction–Associated Steatotic Liver Disease

Metabolic dysfunction–associated steatotic liver disease (MASLD) is highly prevalent and a proportion of affected individuals (<5%–10%) progress to advanced fibrosis, with a risk of developing complications of cirrhosis over 10–20 years.[1] Identifying individuals at risk of future liver-related events and mortality is crucial to enable treatment to slow liver disease progression, and to refer people with advanced fibrosis for hepatology care. Clinical guidelines recommend use of the Fibrosis-4 (FIB4) score as the initial test to identify people with MASLD at low risk of advanced fibrosis (FIB4 <1.30) who can be managed in primary care. More recently, FIB4 has shown utility as a prognostic biomarker to stratify risk of future liver-related clinical outcomes in MASLD.[2] In a large population-based study of individuals with obesity or type 2 diabetes in general practice, the cumulative incidence of liver events at 10 years was 15%, 3%, and 1% in the baseline high (>2.67), indeterminate (1.30–2.67), and low (<1.30) risk FIB4 groups, respectively.[2]

Since the presence of advanced fibrosis/cirrhosis and diabetes mellitus are key factors associated with increased risk of liver-related mortality,[1,3,4] we examined whether a diagnosis of cirrhosis or presence of diabetes mellitus impacts on the prognostic utility of FIB4. In a retrospective population-based study during 2009–2018 in the state of Queensland, Australia, including all hospital admissions for any reason, MASLD was identified in 8006 patients. Thirty-seven point one percent of 486 patients with MASLD-related cirrhosis *with* diabetes mellitus and 29.3% of 620 patients with cirrhosis *without* diabetes progressed to decompensated cirrhosis within 10 years (median follow-up 4.6 years).[5] We obtained hospital admission, death registration and pathology data for this cohort of 8006 patients up to December 2022. Pathology data were used to calculate FIB4, and predefined risk thresholds for noninvasive assessment of liver fibrosis[6] were used to categorise results as low (FIB4 ≤1.30), indeterminate (1.30–2.67), and high (FIB4 ≥2.67) risk of advanced fibrosis. Among 857 patients with FIB4 results within 6 months of their first admission with MASLD (index admission), we examined the 10-year cumulative incidence of mortality (all-cause and cause-specific), and cirrhosis decompensation (identified by the first hospitalization with ascites, hepatic encephalopathy, or oesophageal variceal bleeding). Patients were followed from index admission until study endpoint (mortality or cirrhosis decompensation), liver transplant, or December 2022, whichever came first. Multivariable Cox regression analysis was used to assess differences in mortality and cirrhosis decompensation according to FIB4 (low, indeterminate, or high) and a diagnosis of cirrhosis and/or diabetes mellitus at index admission. See detailed study methods in Supplementary Material.

Patients (n = 857, mean age 61.3 years, 52.7% female) were followed for a median 7.8 years (interquartile range 5.8–10.0). Most patients (59.7%) had at least 1 comorbidity, 41.5% had diabetes, and 29.5% had cirrhosis at index admission (Table A1). During the follow-up period, 105 patients (12.3%) had cirrhosis decompensation, and 329 patients (38.4%) died. The most common causes of death were extrahepatic cancer (EHC) (23.1%), major adverse cardiovascular event (MACE) (20.7%), and liver disease (13.4%). The cumulative 10-year all-cause mortality was 46.2% (95% confidence interval [CI] 41.9–50.7), and varied significantly according to FIB4 at index admission, with the highest mortality among patients with high FIB4 (68.7%, 95% CI 61.6–75.7) (Figure). In unadjusted analysis, high FIB4 significantly increased the risk of all study endpoints (Table A2). In multivariable analysis, adjusting for age and sex (Model 1) slightly attenuated the associations between FIB4 and liver-related mortality, cirrhosis decompensation, and all-cause mortality, and mortality due to EHC or MACE were no longer significantly associated with FIB4. In Model 2, also adjusting for cirrhosis, diabetes, EHC, and MACE, high FIB4 significantly increased the risk of liver-related mortality, cirrhosis decompensation, and to a lesser extent all-cause mortality: adjusted hazard ratios (aHRs) for patients with high vs low FIB4 were aHR = 28.8 (95% CI 3.1–263.5), aHR = 7.6 (95% CI 3.7–15.6), and aHR = 1.7 (95% CI 1.2–2.4), respectively. High FIB4 was the key risk factor for liver-related mortality and cirrhosis decompensation independent of a diagnosis of cirrhosis. Patients with high FIB4 and diabetes had a 40-fold increase in liver-related mortality (aHR = 40.4, 97% CI 4.9–329.6) and an 11-fold increase in cirrhosis decompensation (aHR = 10.9, 95% CI 5.3–22.5) independent of cirrhosis (Model 3) compared to those with low/indeterminate FIB4 and no diabetes. Comorbidity (EHC, MACE, and diabetes), cirrhosis, high FIB4 and age were risk factors for all-cause mortality. See Table A2 for more details about unadjusted and multivariable analysis.

Our data show that in a hospital-based cohort of people with MASLD, FIB4 category at index admission provides prognostic information about future risk of overall mortality and high FIB4 score is associated with

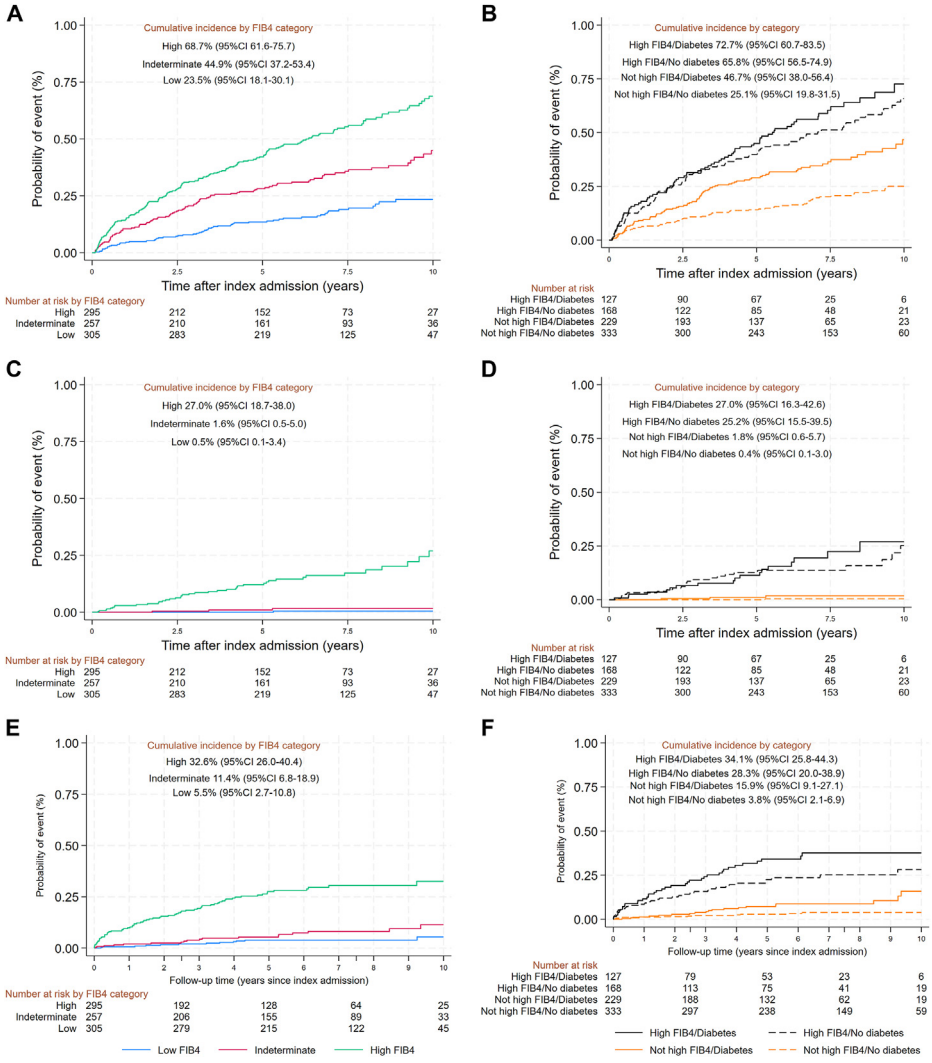

Figure. Cumulative 10-year incidence according to FIB4 categories (low, indeterminate, or high) and high FIB4 and/or diabetes at index admission for all-cause mortality (Panels A and B), liver-related mortality (C and D), and cirrhosis decompensation (E and F).

significantly increased risk of liver-related mortality and cirrhosis decompensation. These findings support earlier studies showing that FIB4 reliably stratifies the risk of liver-related events in people with MASLD[7,8] and confirm the association remains robust in a high-risk population and is independent of cirrhosis at baseline. In addition, diabetes further increases the risk of all-cause mortality and cirrhosis decompensation. In contrast to a recent primary care cohort of people at risk for MASLD,[2] FIB4 was not associated with MACE following adjustment for age and sex. Given the competing health priorities in our patients with MASLD, with a high prevalence of cardiovascular mortality and extrahepatic cancer,[9] identifying the subgroup at highest risk of adverse liver events across different clinical settings is a priority. Our data highlight the utility of FIB4 as a predictive marker for liver-related complications and mortality, independent of other prognostic factors, and advocate its use as part of the multidisciplinary approach to care of these patients.

ELIZABETH E. POWELL[1,2,3]
GUNTER HARTEL[3]
KATHARINE M. IRVINE[4]
JAMES O'BEIRNE[5]
VIKAS BHASKER[1,3]
PATRICIA C. VALERY[2,3]
[1]Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia
[2]Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia
[3]QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia
[4]Mater Research, Translational Research Institute, Brisbane, Queensland, Australia
[5]Sunshine Coast University Hospital, Sunshine Coast, Queensland, Australia

Correspondence:
Address correspondence to: Patricia C. Valery, MD, MPH, PhD, Cancer & Chronic Disease Research Group, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston, Queensland 4006, Australia. e-mail: Patricia.Valery@qimrberghofer.edu.au.

Supplementary Materials

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Abbreviations used in this paper: **aHR, adjusted hazard ratios; CI, confidence interval; EHC, extrahepatic cancer; FIB4, Fibrosis-4 score; MACE, major adverse cardiovascular event; MASLD, metabolic dysfunction–associated steatotic liver disease**

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