



## ORIGINAL ARTICLE - HEPATOLOGY (CLINICAL)

# Patients with type 2 diabetes and elevated fibrosis-4 are under-referred to hepatology and have unrecognized hepatic decompensation

Winston Dunn,\*  Xing Song,<sup>†</sup>  Devin Koestler,<sup>‡</sup> Kristine Grdinovac,\* Eyad Al-hihi,\* John Chen,<sup>†</sup> Ryan Taylor,\* Jessica Wilson\* and Steven A. Weinman\*

\*Department of Internal Medicine, <sup>†</sup>Center for Medical Informatics and Enterprise Analytics, <sup>‡</sup>Department of Biostatistics and Data Science, University of Kansas Medical Center, Kansas City, Kansas, USA

## Key words

clinical hepatology, epidemiology hepatology, fatty liver, hepatocellular carcinoma, NAFLD, Screening.

Accepted for publication 22 May 2022.

## Correspondence

Winston Dunn, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA.  
Email: wdunn2@kumc.edu

**Declaration of conflict of interest:** Winston Dunn report speaking and consultation fees from Gilead. Ryan Taylor reports speaking and consultation fees from Gilead, Intercept, Abbvie, and Salix. The rest of the authors do not have conflict of interest.

**Author contribution:** Winston Dunn: planning and conducting the study, drafting the manuscript, approved the final draft. Xing Song: collecting data, approved the final draft submitted. Maren Lowrance: collecting data, approved the final draft submitted. Devin Koestler: Devin Koestler: interpreting data, approved the final draft submitted. Kristine Grdinovac: planning of the study, approved the final draft submitted. Eyad Al-hihi: planning of the study, approved the final draft submitted. G. John Chen: planning of the study, approved the final draft submitted.

## Abstract

**Background and Aim:** The American Association for the Study of Liver Diseases recommends a high index of suspicion for nonalcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes (T2D) and an elevated fibrosis-4 index (FIB-4). We investigated the referral pattern of patients with T2D and FIB4 > 3.25 to the hepatology clinic and evaluated the clinical benefits to the patient.

**Methods:** We included patients aged 18–80 years with T2D and a FIB4 score >3.25 who had visited the internal medicine, family medicine, endocrinology clinic from 01/01/2014–5/31/2019. The first time point of high-risk FIB-4 was identified as the baseline for time-to-event analysis. The patients were classified based on whether they had visited the hepatology clinic (referred vs not referred).

**Results:** Of the 2174 patients, 290 (13.3%) were referred to the hepatology clinic, and 1884 (86.7%) were not referred. In multivariate analyses, the referred patients had a lower overall mortality risk (Hazard Ratio: 0.57; 95% CI: 0.38–87). Notably, the referred patients had the same rate of biochemical decompensation, as measured by progression to MELD  $\geq$  14, but a substantially higher rate of diagnosis in cirrhosis (27, 19–38) and cirrhosis complications, including ascites (2.9, 2.0–4.1), hepatic encephalopathy (99, 13–742), and liver cancer (14, 5–38).

**Conclusions:** We found that patients with T2D and high-risk FIB4 are associated with better overall survival after referral to a hepatology clinic. We speculate that the survival difference is due to the increased recognition of cirrhosis and cirrhosis complications in the referred populations.

Ryan Taylor: planning of the study, approved the final draft submitted. Jessica Wilson: collecting data, approved the final draft submitted. Steven Weinman: planning of the study, drafting the manuscript, approved the final draft submitted.

**Ethical approval:** This study is approved by the University of Kansas Medical Center Human Research Protection Program, STUDY00145459. We received a waiver for patient consent given the retrospective nature of this study.

**Financial support:** Gilead NASH Models of Care RFP Program.

## Introduction

NAFLD is a common condition affecting 26% of the US general population. However, only 2% of the population has a more aggressive histological phenotype, Nonalcoholic steatohepatitis (NASH), or evidence of liver fibrosis.<sup>1,2</sup> The American Association for the Study of Liver Diseases does not recommend routine screening of the general population for NASH,<sup>3</sup> citing

“uncertainties surrounding diagnostic tests and treatment options.”<sup>4</sup> However, it does recommend referral to a hepatologist when there is a high index of suspicion for NASH and advanced fibrosis such as in patients with type 2 diabetes (T2D)<sup>5–7</sup> and those with an elevated fibrosis-4 (FIB-4) index.<sup>8,9</sup> These aids are under-utilized by physicians, resulting in many patients at high risk for fibrosis and are not referred to a hepatology clinic (9). Confusion regarding best defining the population at risk is a major

problem preventing the appropriate use of hepatology referral in the primary care setting.

There is an unmet need to determine the circumstances for which hepatology referral results in a clinical benefit to the patient. We investigated the referral pattern of patients with T2D and FIB4 > 3.25 to the hepatology clinic. We hypothesized that this group of patients might have a survival benefit from a hepatology referral. We further explored the mechanism, including increased diagnosis and management of cirrhosis and complications.

## Methods

This study used a retrospective cohort design to observe the liver-related outcomes in patients with a diagnosis of T2D and a FIB-4 score > 3.25 and compared the outcomes between patients who were referred to a hepatology clinic (the referred group) and those who were not (the not referred group). Healthcare Enterprise Repository for Ontological Narration (HERON) was used to identify the cohort and follow-up for liver-related outcomes.

**Patient population.** Eligible patients were adults 18–80 years of age with a diagnosis of (T2D) and a FIB4 score > 3.25 (high risk) and have visited internal medicine, family medicine, endocrinology clinic from 01/01/2014 to 5/31/2019. The FIB-4 score was calculated from age, AST, ALT, and platelet on the same day and was not automatically generated from the electronic medical record system. The first time point of having a diagnosis of T2D and a high-risk FIB-4 was identified as the baseline for patient characterization and time-to-event analysis.

The primary analysis focused on patients without viral hepatitis and decompensated cirrhosis. Patients who had liver transplantation, developed Child–Pugh Class B or C (CP-B/C) cirrhosis, hepatocellular carcinoma, or died before or within 30 days of baseline were excluded. To minimize bias related to health care access, we excluded patients who had less than 4 visits to the health system.

Sensitivity analysis tested the general hypothesis that patients with T2D and FIB-4 have improved survival with referral to the hepatology clinic. No exclusion criteria were applied.

**Variables.** The main exposure variable of interest was whether a patient was referred to and co-managed at the hepatology clinic or not referred, depending on whether a patient had at least 1 appointment at the hepatology clinic. The CP score for each patient was calculated monthly. The CP score was the sum of the laboratory component if the laboratory data were available in the given month and the diagnosis component if a diagnosis of ascites or hepatic encephalopathy was made. If the laboratory data were not available or if a diagnosis was not received, a score of 1 was given for the component. Because it was not possible to distinguish the severity of ascites and hepatic encephalopathy, the CP score component for ascites and hepatic encephalopathy ranged from 1 to 2. All the baseline measures were defined as the first available data at or after baseline.

**Outcomes.** The primary outcome was overall survival. Death was verified using the Social Security Administration's Death

Master File through HERON. We compared patients who were referred to the hepatology clinic *versus* those who were not referred.

Other secondary endpoints included the progression of MELD to  $\geq 14$ , diagnosis of cirrhosis based on ICD-9571, ICD-10 K74.60, diagnosis of ascites based on ICD-9789.5, ICD-10 R18, diagnosis of hepatic encephalopathy based on ICD-9572.2, ICD-10 K72.90 diagnosis of liver cancer based on ICD-9155.0, ICD-10 C22.0, and progression to CP-B/C cirrhosis. The purpose of the secondary endpoints was to explain the primary endpoints. Hepatology referral may occur after some of the secondary endpoints.

**Analysis.** The first time point of having a diagnosis of T2D and having a high-risk FIB-4 was identified as the baseline. All time-to-event analyses used this baseline as the reference to avoid lag-time bias. Kaplan-Meier survival curves were constructed for all events. The Cox proportional hazards model was used for univariate and multivariate analyses. Multivariable analysis was adjusted for age, gender, race/ethnicity, baseline FIB-4, BMI, MELD, and CP score (either 5 or 6) in overall survival. We compared patients who were referred to the hepatology clinic *versus* those who were not referred.

Exclusion criteria were applied to restrict the study population to likely NASH cirrhosis and compensated cirrhosis at baseline. In order to assess the generalizability of T2D and FIB-4, the sensitivity analysis included patients aged  $\geq 18$  years at the time of having T2D and high-risk FIB-4 and having visited the internal medicine, family medicine, endocrinology, or hepatology clinic at the University of Kansas Medical Center from 01/01/2014 to 5/31/2019. No further exclusion criteria were applied.

## Results

This study included 2174 patients. Of 1021, 1565, and 1078 overlapping patients seen in the endocrinology, internal medicine, and family medicine clinics, 17.2%, 12.3%, and 11.8%, respectively, were referred to and co-managed by hepatology. The characteristics of the 290 referred patients and 1884 not referred patients are outlined in Table 1. Of note, referred patients were younger, more often White and less often Black, had lower platelet counts, higher AST, ALT, and bilirubin levels, a lower creatinine level, and a high CP score but a lower MELD score driven by a lower creatinine level.

Among the referred patients, the median follow-up was 4.96 years (IQR: 2.36–8.08), and 33 patients died. Among the not referred patients, the median follow-up was 3.56 years (IQR: 1.60–6.80), and 372 patients died. Figure 1 shows that the referred patients have a lower risk of death than the not referred (HR: 0.66; 95% CI: 0.46–0.95). The association remained statistically significant in a multivariable analysis adjusting for age, gender, race/ethnicity, baseline BMI, FIB-4, MELD, and CP score (HR: 0.57; 95% CI: 0.38–87). The age-adjusted mortality rate was 17 (10–25) per 1000 person-years for referred patients and 33 (25–42) per 1000 person-years for not referred patients.

The natural history of disease progression is very similar in the referred and not referred patients. The referred patients had a similar rate of biochemical decompensation regarding the progression to MELD  $\geq 14$  (HR: 0.88; 95% CI: 0.81–1.3; Fig. 1b). However,

**Table 1** Baseline patient demographics of the referred and not referred patients

	Referred (n = 290)	Not referred (n = 1884)	P
Age	59.5 (10.5)	64.3 (10.4)	< 0.0001
Gender: male	160 (54.1%)	1001 (52.1%)	0.53
Race and ethnicity			0.0002
White	213 (72.0%)	1205 (62.7%)	
Black	40 (13.5%)	484 (25.2%)	
Hispanic	27 (9.1%)	137 (7.13%)	
Others	16 (5.4%)	95 (5.0%)	
BMI	34.4 (7.8)	32.7 (8.3)	0.0004
CP score at baseline			< 0.0001
5	174 (58.8%)	1369 (71.3%)	
6	122 (41.2%)	552 (28.7%)	
Baseline laboratory parameter			
Platelets	132 (62)	148 (62)	< 0.0001
ALT	55 (57)	41 (52)	< 0.0001
AST	73 (67)	63 (60)	0.004
Albumin	3.8 (0.5)	3.8 (0.5)	0.3
Bilirubin	0.91 (0.77)	0.65 (0.48)	< 0.0001
INR	1.2 (1.2)	1.3 (1.3)	0.30
Cr	1.2 (1.0)	1.6 (1.5)	< 0.0001
MELD	10.4 (4.6)	11.8 (6.3)	0.0002
FIB4	5.1 (3.6)	4.9 (6.5)	0.46

Continuous variables expressed as mean (standard deviation). Categorical variables expressed as n (%).

cirrhosis was more likely diagnosed in referred patients (HR: 27; 95% CI: 19–38; Fig. 1c). Cirrhosis complications that required clinician recognition and testing were also more readily diagnosed in the referred patients, such as ascites (HR: 2.9; 95% CI: 2.0–4.1; Fig. 1d), hepatic encephalopathy (HR: 99; 95% CI: 13–742; Fig. 2), and liver cancer (HR: 14; 95% CI: 5–38; Fig. 2b). Because of the different diagnosis rates in ascites and hepatic encephalopathy, the referred patients were more likely to receive a diagnosis of CP-B/C cirrhosis (HR: 1.5; 95% CI: 1.2–1.9; Fig. 2c).

In the sensitivity analysis, we included all the patients aged  $\geq 18$  years with T2D and high-risk FIB-4  $> 3.25$  at baseline. Of the 4502 patients seen in the endocrinology, internal medicine, and family medicine clinics, 1368 (30.4%) were referred to and managed by the hepatology clinic. The referral rate was high mainly because 903 referred patients who had liver transplantation, developed Child–Pugh Class B or C (CP-B/C) cirrhosis, hepatocellular carcinoma, or died before or within 30 days of baseline were not excluded. Figure 2d shows that the referred patients had a lower risk of death than the not referred patients (HR: 0.69; 95% CI: 0.60–0.80). In multivariable analysis, the association remained statistically significant (HR: 0.81; 95% CI: 0.67–0.99).

Figure 3 shows the timing of onset of high-risk FIB-4 and T2D in relation to hepatology referral, diagnosis of cirrhosis, and diagnosis of CP-B/C cirrhosis or liver cancer diagnosis. Figure 3a shows that referral to hepatology parallels the diagnosis of cirrhosis. Among the 188 referred patients diagnosed with cirrhosis, 95 (50.5%) were referred before a diagnosis of cirrhosis. The median time from hepatology referral to cirrhosis diagnosis was 1.5 days

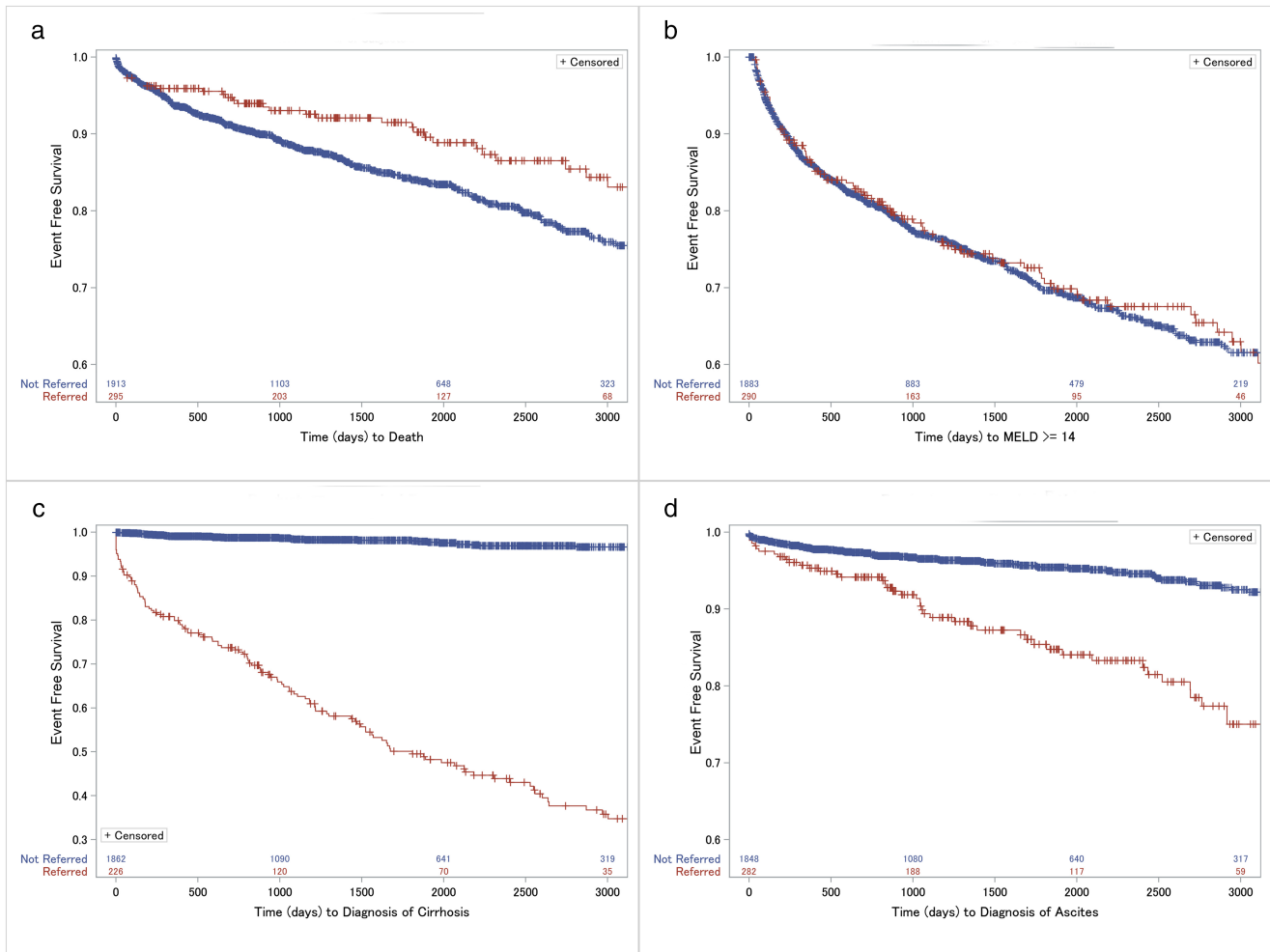
(IQR: –27 to 96.5). Figure 3b shows that half of the patients already had a diagnosis of CP-B/C cirrhosis or liver cancer upon referral to hepatology. The remaining one-quarter of the patients would have a diagnosis within 1 year. Among the 99 patients diagnosed with CP-B/C cirrhosis or liver cancer, 49 (49.5%) were referred before diagnosis. The median time from referral to a diagnosis of CP-B/C cirrhosis or liver cancer was –4 days (IQR: –861 to 369). Of note, according to the exclusion criteria, Figure 3 has excluded patients diagnosed with CP-B/C cirrhosis and liver cancer within 30 days or before the onset of high-risk FIB-4 and T2D.

## Discussion

The current study demonstrated that less than a fifth of the patients with T2D and high-risk FIB4 were referred to the hepatology clinic for co-management. These patients were at a very high risk of death, and hepatology referral was associated with improved survival. The referred and not referred patients were very similar because they have the same rate of biochemical decompensation, as measured by MELD progression to 14. However, cirrhosis and cirrhosis-related complications were readily diagnosed in the referred patients, likely accounting for the variability in outcome. We speculate that the early diagnosis of cirrhosis and recognition of cirrhosis-related complications contributes to improved survival in the referred patients. CP-B/C cirrhosis and liver cancer often occur at the onset of high-risk FIB-4 and T2D, while most of the referrals to hepatology occurred after progression to CP-B/C cirrhosis or HCC.

Our study had several strengths and limitations. We used the same time scale to measure the time to event in the referred and not referred patients based on the first time the patient had T2D and high-risk FIB-4. This approach eliminates lag-time bias.<sup>10</sup> We used a primary analysis that focused on patients with NASH and compensated cirrhosis and applied elaborate exclusion criteria to exclude other diseases and patients with decompensation or liver cancer before baseline. We also performed a sensitivity analysis that attended to the generalizability of the study and removed all exclusion criteria and demonstrated the benefit of patients with T2D and high FIB-4 being referred to the hepatology clinic. The most important limitation was the observational nature of this study, which was not sufficient to demonstrate causality. We are only able to make speculations about the mechanism of improved survival. We do not have data on death causes and cannot distinguish liver-related mortality from other causes.

Our study is the only study that demonstrated that patients with T2D and high FIB-4 might have survival benefits with referral to hepatology. Many studies have associated elevated FIB-4 scores with liver-related mortality.<sup>11</sup> Meta-analysis has compared the FIB-4 against other diagnostics tests for diagnosing fibrosis.<sup>12</sup> FIB-4 has also been associated with liver disease progressions and outcomes,<sup>13,14</sup> including the risk of developing HCC.<sup>15</sup> The current study confirms that those with T2D and high FIB-4 are at risk of death. Our study is the first to demonstrate that referral to hepatology is associated with improved survival. This is significant because AASLD has not recommended routine screening of the general population for NASH,<sup>3</sup> citing “uncertainties surrounding diagnostic tests and treatment options.”<sup>4</sup> Before recommending a policy change regarding referral, we must first



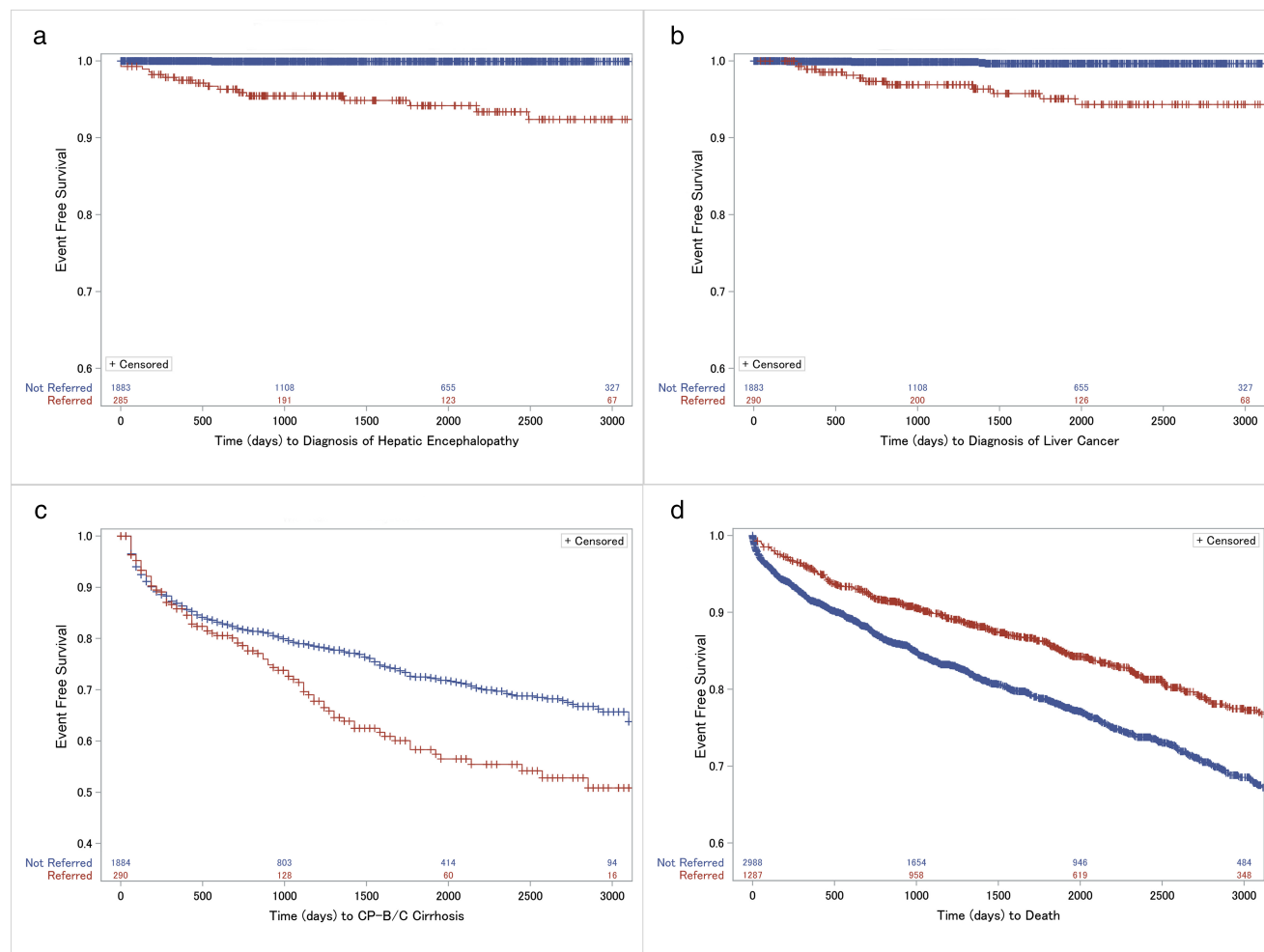
**Figure 1** (a–d) Comparison of overall survival, progression of MELD to  $\geq 14$ , diagnosis of cirrhosis, and diagnoses of ascites between referred and not referred patients. (a) Patients referred to the hepatology clinic have improved overall survival compared with patients not referred to the hepatology clinic. (b) The referred and not referred patients were very similar under objective measurement because they have similar rates of MELD progression to  $\geq 14$ . (c) The referred patients were more likely to be diagnosed with cirrhosis. (d) The referred patients were more likely to be diagnosed with ascites. All the figures use the first time point when a patient develops T2D and have FIB-4 > 3.25 as the baseline. (a–d) —, Not referred; —, Referred.

understand the hepatology consultation factors that potentially improve survival. Our data speculate that improved diagnosis of cirrhosis and cirrhosis complications, namely the HCC, leads to improved survival.

In our study, the incidence of HCC in T2D and a high FIB-4 index among the referred cohort was extremely high at 25.3 cases per 1000 person-years, while the incidence was contrastingly low in the not referred cohort at 1.3 cases per 1000 person-years. We suspect that HCC was underdiagnosed because the mortality and decompensation event rates were very comparable in both groups. We suspect that some patients died from other etiologies, and HCC was never diagnosed, while others presented with HCC at a late stage. As noted in our not referred cohort, most of the HCC presented at a late stage. The incidence of HCC has been rapidly rising in the United States over the last 20 years (10). This trend is thought to mirror the obesity epidemic and the rise in the prevalence of NAFLD (12). A preexisting diagnosis of cirrhosis

is found in more than 80% of individuals diagnosed with HCC (3). In cost-effectiveness analysis, screening for HCC in compensated cirrhosis was suggested to be cost-effective, with the incidence exceeding 1.5%/year.<sup>16</sup> An 18-million real-world European cohort with NAFLD, T2D, and high-risk FIB4 were independent risk factors for HCC. The incidence of HCC occurred at a rate of 0.76 per 1000 person-years. T2D increased the risk by 2.3 fold, while high-risk FIB4 increased the risk by 25.2 fold, compounding the rate to 4.4 per 1000 person-years.<sup>17</sup> There is a more pressing need for HCC for screening in the FIB-4 T2D cohort because a delayed diagnosis is often associated with a poor outcome. Patients with higher FIB4 may be less tolerant of transcatheter arterial chemoembolization.<sup>18</sup> A meta-analysis of 8 studies and 3320 HCC patients showed that a high FIB 4 score is associated with poor overall survival and recurrence survival. Contributing factors include a late diagnosis and more advanced diseases.<sup>15</sup>



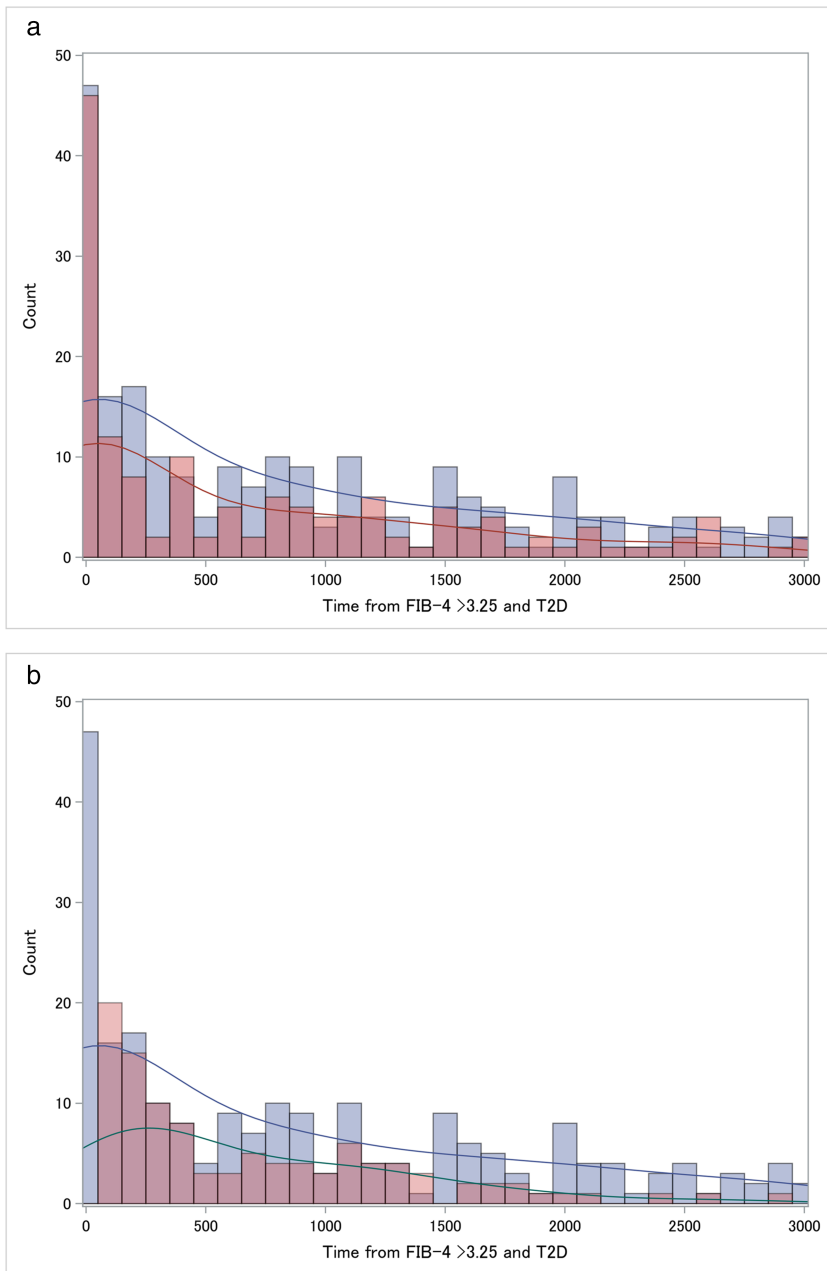


**Figure 2** (a–d) Comparison of diagnosis of hepatic encephalopathy, diagnosis of liver cancer, development of CP-B/C cirrhosis, and sensitivity analysis between referred and not referred patients. (a) The referred patients were more likely diagnosed with hepatic encephalopathy. (b) The referred patients were more likely to be diagnosed with liver cancer. (c) The referred patients were moderately more likely to progress to CP-B/C cirrhosis. (d) After sensitivity analysis without applying exclusion criteria, the referred patients demonstrated improved overall survival compared with not referred patients. (a–d) —, Not referred; —, Referred.

We considered whether the NAFLD fibrosis score (NFS) or FIB-4 was a better clinical aid for referral to the hepatology clinic and whether a higher or lower cut-off should be used. In the diabetes clinic setting, both NFS and FIB-4 had high negative predictive values.<sup>19</sup> The NFS is problematic in the diabetes clinic setting because it results in referral for over 50% of the patients,<sup>20</sup> while a high-risk FIB-4 would only promote referral for 13%.<sup>21</sup> Regarding the lower *versus* higher cut-off, according to real-world data in Germany, applying the FIB-4 score across 507 patients with fatty liver in 13 clinics resulted in 10% of patients above the higher cut-off of 3.25 and 26% above the lower cut-off of 1.3.<sup>22</sup> U.S. Members of the Global NASH Council recommended using a FIB-4 score  $\geq 1.3$  for PCP and diabetologists.<sup>23</sup> A letter to the editor outlined the counter-argument—the FIB-4 cut-off of 1.3 identified F2 patients in the setting of enrolment for the NASH clinical trial. However, in the setting of a primary care referral pathway, a

higher cut-off of 3.25 targeting F-3/4 would be more appropriate.<sup>24</sup> In our patient cohort from the endocrinology, internal medicine, and family medicine clinics, less than 10% of patients with a FIB-4  $> 3.25$  and T2D were referred to the hepatology clinic at this time. A recent survey has suggested that only 5.7% of endocrinologists have been using a non-invasive algorithm to assess liver fibrosis to facilitate referral.<sup>25</sup> Therefore, it is prudent to focus the referral effort on the highest risk cohort.

In conclusion, We found that patients with T2D and high-risk FIB-4 are associated with better overall survival after referral to a hepatology clinic. We speculate that the survival difference is due to the increased recognition of cirrhosis and cirrhosis complications in the referred populations. While early referral of this group of high-risk patients to hepatology is potentially life-saving, the referral has been underutilized and often occurs late in the disease.



**Figure 3** (a) Referral to hepatology parallels the diagnosis of cirrhosis. Among the 188 referred patients diagnosed with cirrhosis, 95 (50.5%) were referred before a diagnosis of cirrhosis. The median time from hepatology referral to cirrhosis diagnosis was 1.5 days (IQR:  $-27$  to  $96.5$ ). (b) Half of the patients already had a diagnosis of CP-B/C cirrhosis or liver cancer upon referral to hepatology. The remaining one-quarter of the patients would have a diagnosis within 1 year. Among the 99 patients diagnosed with CP-B/C cirrhosis or liver cancer, 49 (49.5%) were referred before diagnosis. The median time from referral to a diagnosis of CP-B/C cirrhosis or liver cancer was  $-4$  days (IQR:  $-861$  to  $369$ ). (a) ■, Referral; ■, Diagnosis of Cirrhosis; (b) ■, Referral; ■, Diagnosis of CP B/C or Liver Cancer.

**Data availability statement.** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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