Progression in Liver Fibrosis as Assessed by the FIB-4 Index in Patients with Type 2 Diabetes (T2DM)

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Introduction

- The prevalence of type 2 diabetes (T2DM) and diabetes-associated health burden is increasing world-wide. Diabetic patients are at high risk of developing cirrhosis and liver outcomes, in most cases due to non-alcoholic liver disease (NAFLD). However, liver disease remains a neglected hepatic complication of diabetes.
- Data on the prevalence of advanced hepatic fibrosis and the main predictors of the progression of liver fibrosis in patients with T2DM are scarce.
- Numerous non-invasive panels have been developed to stage liver disease. These include a combination of clinical and routine laboratory parameters as well as specialized tests such as biomarkers of fibrosis and elastographic imaging.
- The FIB-4 index was developed as a non-invasive composite panel to stage liver disease in subjects with HIV-hepatitis C virus co-infection. It relies on the following parameters: age, aspartate- and alanine aminotransferase levels and platelet count. It is a simple and inexpensive lab assessments that can be done routinely in patients with T2DM at the primary care or specialist level.
- The FIB-4 index has also been validated in patients with HCV infection and has shown to be superior to seven other non-invasive markers of fibrosis in patients with NAFLD.
- At a cut-off of <1.45, the negative predictive value of FIB-4 to exclude advanced fibrosis was 90% with a sensitivity of 70%.
- A cut-off of >3.25 had a positive predictive value of 65% and a specificity of 97%.
- More recently, FIB-4 values ≥2.67 were reported to be associated with a 16-fold increase in adverse clinical outcomes in a NAFLD population.
- A FIB-4 range ≥1.45 - <2.67 is suggested to be an indeterminate area.

Aim

The aim of the present study was to evaluate liver fibrosis using the FIB-4 score and the changes of this composite index over a 4-year period in a large group of patients with T2DM using a proprietary clinical database from LabCorp™.

Methods

- Patients with T2DM (ICD-10 E11 diagnostic code) whose baseline assessments included those required for the FIB-4 index (age, AST, ALT and platelet count) that were obtained during the 2012 calendar year and who also had a follow-up assessment in 2016 were analysed.
- The subset was defined as all patients whose comorbidities include Type2DM and who had blood samples in 2012 and 2016 with data sufficient to calculate FIB-4; where >1 sample for a year was available the earliest in 2012 and the latest in 2016 was used.

FIB-4 formula: age (years) X AST (U/L) / [(Platelet count (10^9/L) X ALT (U/L)]$^{1/2}$

Results: Baseline Data

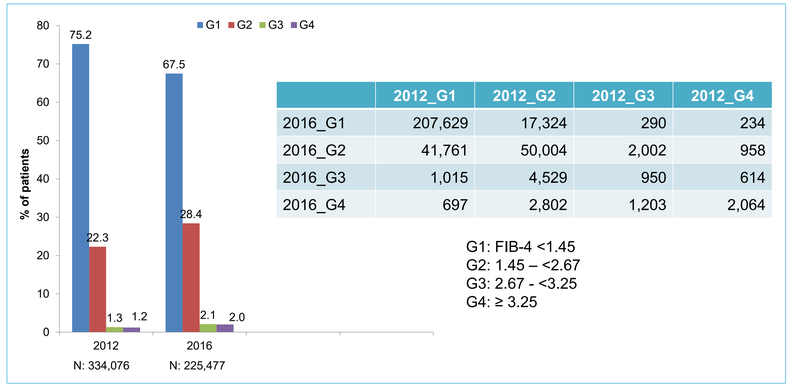
- The study sample included a total of 334,076 subjects.
- The median (IQR) FIB-4 score was 1.08 (0.80, 1.45).
- A total of 75.2%, 22.3%, 1.3% and 1.2 % of subjects had a FIB-4 <1.45 (G1), ≥1.45 - <2.67 (G2), ≥2.67 - <3.25 (G3) and ≥3.25 (G4) (Table 1).
- As expected, subjects without a signal of advanced fibrosis (FIB-4 <1.45) were younger and had lower ALT and AST levels.
- Platelet counts were lower in G4 vs G3 vs G2 vs G1.
- Mean plasma HbA1C and triglycerides (TG) were similar among groups.

Table 1. Patient Characteristics by FIB-4 Category at Baseline

	<1.45 (G1)	1.45 – <2.67 (G2)	2.67 - <3.25 (G3)	≥ 3.25 (G4)	Overall
N (M %)	251,102 (44%)	74,659 (58%)	4,445 (62%)	3,870 (59%)	334,076 (48%)
Age*	57.2 (10.8)	66.3 (7.3)	67.0 (7.4)	65.2 (7.99)	59.5 (10.8)
ALT*	25.3 (15.0)	28.3 (21.2)	38.4 (33.9)	54.2 (52.24)	26.5 (18.1)
AST*	21.1 (8.3)	28.5 (14.8)	42.3 (27.3)	66.0 (59.01)	23.6 (13.6)
Platelet counts*	272.9 (62.1)	200.5 (40.6)	158.5 (39.5)	131.7 (46.1)	253.5 (67.2)
HbA1C *	7.0 (1.65)	6.7 (1.3)	6.9 (1.47)	7.0 (1.6)	6.9 (1.59)
TG	161.3 (143.5)	150.4 (124.1)	154.9 (114.3)	160.1 (156.7)	158.7 (139.3)

*Mean (SD). M: males, TG: Triglycerides

Figure 1. Proportion of Patients by FIB-4 Range at Baseline and Follow-Up



	2012_G1	2012_G2	2012_G3	2012_G4
2016_G1	207,629	17,324	290	234
2016_G2	41,761	50,004	2,002	958
2016_G3	1,015	4,529	950	614
2016_G4	697	2,802	1,203	2,064

G1: FIB-4 <1.45
G2: 1.45 – <2.67
G3: 2.67 - <3.25
G4: ≥ 3.25

Results: Fibrosis Progression

- Among the G1 patients, 83% remained in the same category, 17% progressed to the indeterminate area (G2) and 0.7% had a FIB-4 ≥ 2.67 after the 4-year period.
- A total of 10% and 27% of patients initially in G2 and G3, respectively, progressed to a category associated with a higher risk of liver outcomes, while 23%, 7% and 6% of patients in G2, G3 and G4, respectively, regressed to G1 during this period.

Summary

- The present study shows that only 75% of the patients had a FIB-4 suggesting absence of advanced liver fibrosis
- Approximately 1 out of 3 patients progressed in a 4-year period
- A total of 50% of subjects at risk of liver outcomes had ALT and AST levels within reference ranges.
- **Limitations** of this study include a lack of detailed clinical information, absence of causal descriptions, potential treatment bias, potential bias due to the lack of follow-up data and systemic sampling errors.
- **Advantages** of the LabCorp™ database as a source include the very large numbers of available patients.

Conclusions

- Proactive screening of patients with T2DM using an inexpensive and non-invasive method may help reduce the number of patients with undiagnosed advanced liver fibrosis by potentially identifying and managing those at risk at an earlier stage.
- FIB-4 index, an inexpensive method based on simple routine parameters, may help identify patients at risk of these adverse liver outcomes.
- FIB-4 levels may also support strategies to monitor the development of liver complications and responses to therapeutic interventions which will be necessary to mitigate the NASH disease burden in patients with T2DM.

References

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