Peer Review File

Article information: https://dx.doi.org/10.21037/tgh-23-62

Reviewer A:

Comment 1:

I would include the spelled out version of FIB-4 and APRI. Further, given the context of your study, I would also briefly include the NAFLD Fibrosis Score, since this calculation incorporates diabetes. I would also urge you to consider including the citation (PMID 34294656) to accompany your line "The inconsistent results of NITs..."

Reply 1:

We have included your suggestions regarding spelling out acronyms as well as including the citation. We have reviewed entire manuscript for accuracy.

Changes in text:

Changes are noted in line 6, 41, 46-49.

Comment 2:

Why were these 1,524 patients (110 in your sample) receiving VCTE? Given the sensitivity and specificity of the FIB-4 scores it appears a good many had a FIB-4 < 1.3, were they part of another study? Was the NFS elevated? Were they seen in a liver clinic for NAFLD where the VCTE was available?

Reply 2:

Patients suspected to have NAFLD (MASLD) underwent VCTE. It is noted that many patients did have a FIB-4 that was low and that was because these patients were all comers. Any physician (including non-hepatology providers) can order VCTE. We did not calculate NFS in this study. VCTE was completed in a hepatology clinic, read by the hepatologist.

Changes in text:

Changes noted in line 68.

Comment 3:

What did you use to identify co-morbid conditions? Were these ICD-9/10 codes? Did you use an ICD-9/10 administrative coding algorithm like Elixhauser?

Reply 3:

The 110 patients were identified from a database of patients who underwent FibroScan. The charts of each individual patient were reviewed. Co-morbid conditions were manually extracted from the chart.

Changes in text:

Changes noted in line 72-73.

Comment 4:

What time period was the FIB-4 score inputs and other covariates collected? At the time of the VCTE?

Reply 4:
Data for FIB-4 and other lab values were collected within 1 year of the date of VCTE.
Changes in the text:
Changes noted in lines 79-80.

Comment 5:
I would consider including the F0-1 and F2-4 fibrosis designation sentences in your outcome. It appears that you are using FIB-4 (+ diabetes) to accurately predict F2-4 fibrosis, defined as LSM > 9.7 kPa. How did you categorize LSM 8.3 - 9.7?
Reply 5:
Thank you for your comment. The values have been corrected in the text as written below.
Changes in the text:
Changes noted in lines 83-85. It reads: “Values of LSM ranging from 1.5 kilopascals (kPa) to 8.2 kPa were categorized as F0-F1, 8.3-9.7 F2, 9.8-13.6 F3 and 13.6 and above F4.”

Comment 6:
In the results, it would be nice to see the distribution of FIB-4 scores in your sample (mean, median, IQR, % FIB-4 > 1.3). I would include this (means if normal distribution of scores, median [IQR] if not normally distributed) in your Table 1, and compare by the outcome (using t-test if means, Mann Whitney U if medians). Since you categorize the outcome based on the LSM, the LSM rows are a little less useful.
Reply 6:
Changes have been made in Table 1 to show characteristics of FIB-4 in this population.
Changes in the text:
Changes have been incorporated based on the above comment and are located at the end of Table 1.

Comment 7:
While I am impressed by the improvement in FIB-4 ROC by adding diabetes and modifying the "positive" threshold, did you all look at the approximately 10 (of your 33 patients) with a FIB-4<1.3 and an F2-4 LSM finding? Were the FIB-4s low because of lower aminotransferases (as suggested in the discussion)? Were they young?
Reply 7:
We do suspect that FIB-4 scores were low in this population of patients due to low or normal aminotransferases. This could be for a myriad of reasons such as mentioned in the manuscript regarding potential normal aminotransferases in patients with diabetes who are at risk of progression of fibrosis. Mean age in the F2-F4 group was higher with a mean of 59 years of age. Additionally, another factor to consider is the limitations of VCTE and the possible overestimation of fibrosis. Regardless it is prudent to err on the side of caution in patients with suspected fibrosis based on VCTE.
Changes in text:
No changes were made.

Comment 8:
I think the reader would benefit from a Table that has FIB-4 performance for the overall cohort, then the stratification by diabetes. I think you could combine Tables 2 and 3.
Reply 8:
The AUC for the overall cohort is 0.74, as noted in Figure 2. We elected to keep Table 2 and 3 to clarify the different characteristics in the group with diabetes and group without diabetes.
Changes in text:
No changes were made.

Comment 9:
This is well written. I would consider writing a sentence or two on why you think FIB-4 with varying thresholds and diabetes stratification would be superior to NFS (which includes diabetes).
Reply 9:
We have included your suggestion in the discussion.
Changes in text:
Changes noted in lines 180-182.

Reviewer B:
Comment 10:
I suggest to consider all patients with NAFLD and not just Hispanics. Increasing the cohort size may increase the statistic power and reliability the analysis and conclusions of the paper and may allow to include a training and validation set.
Reply 10:
We aimed to study this population first but expanding the cohort size in the future is a great suggestion and direction for future studies.
Changes in text:
No changes were made.

Comment 11:
The number of enrolled patients is quite low also considering the uneven distribution of significant fibrosis (33% F2/F4) and the risk of spectrum bias. Increasing the enrolled patients may allow to have a training and validation cohort.
Reply 11:
In the future, we will certainly consider increasing the population size.
Changes in text:
No changes were made.

Comment 12:

It is intuitive that lowering the FIB-4 threshold increases sensitivity (from 69% to 83%) thus however reducing the sensitivity (from 67 to 50%) at the price of a greater number of false positive patients needing a second NIT before to be referred to Liver clinics.

Reply 12:

While it is intuitive that the specificity and specificity changes bases on the threshold, the novel factor was by including diabetes status since we know those patients are at higher risk for fibrosis progression. Patients with diabetes would likely benefit from a lower FIB-4 threshold to predict significant fibrosis. Referral to hepatology in this higher risk population may be warranted.

Changes in text:

No changes were made.

Comment 13:

How many patients have a metabolic syndrome?

Reply 13:

Thank you for your comment. I have added the results from Table 1 below.

Diabetes, n	53 (48%)	28 (36%)	25 (76%)	<.001
Essential Hypertension	51 (46%)	32 (42%)	19 (58%)	0.146
Dyslipidemia	53 (48%)	38 (49%)	15 (45%)	0.835

Changes in text:

No changes were made.

Comment 14:

Please add and discuss in the introduction the paper "Accuracy of FIB-4 to Detect Elevated Liver Stiffness Measurements in Patients with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study in Referral Centers"

Reply 14:

We have incorporated the paper into the introduction section.

Changes in text:

Changes noted in lines 53-55.

Comment 15:

I suggest to use the TE cut off of >8 KPa to identify patients with significant fibrosis

Reply 15:

We have updated the paper to reflect F2-F4 fibrosis as 8.3 kPa and higher.

Changes in text:

Changes noted in lines 83-85.

Comment 16:

The study did not provide information on the age range or comorbidities of the patients, which could potentially influence the diagnostic performance of FIB-4.

We recommended that the authors take this limitation into account in the discussion.

Reply 16:

Mean ages were provided for the cohort as well as co-morbid conditions including diabetes, hypertension and dysplipidemia. They are included below.

Outcome	Variable	Total (n=110)	F0-F1 (n=77)	F2-F4 (n=33)	p
	Age	53.2 ± 13.5	51.0 ± 13.8	59.3 ± 11.4	0.005
	Diabetes, n	53 (48%)	28 (36%)	25 (76%)	<.001
	Essential Hypertension	51 (46%)	32 (42%)	19 (58%)	0.146
	Dyslipidemia	53 (48%)	38 (49%)	15 (45%)	0.835

Changes in text:

No changes were made.