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Research Article

T-HAD Score: A Novel Diagnostic Model for Advanced Fibrosis in Nonalcoholic Fatty Liver Disease (NAFLD)

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Background and Aims. The NAFLD disease spectrum includes simple steatosis, nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis. Progression from NASH, the forerunner of developing cirrhosis, portends a poor outcome as mortality is proportionately increased. This study sought to propose a new diagnostic model for advanced fibrosis in an Asian population cohort affected with NAFLD. *Methods*. Cross-sectional study conducted in the Department of Medical Gastroenterology, Medical College, Trivandrum. The study period was 2 years. After excluding secondary causes of hepatic steatosis, patients were subjected to vibration-controlled transient elastography or transient elastography (VCTE or TE) to assess hepatic fibrosis. Subjects were grouped into those with advanced fibrosis (TE > 10 Kpa) and those without (TE < 10 Kpa) based on the estimation of TE. A new scoring system was then developed. This was then validated in a cohort of 84 biopsy-proven patients.*Results*. 1617 NAFLD patients were included in the study. Independent predictors of advanced fibrosis in this cohort were hip circumference, triglycerides, aspartate aminotransferase (AST), and diabetes mellitus (duration more than 10 years). The coefficient of beta for these variables was calculated. T-HAD score was calculated using the following formula: (Hip circumference × 0.044 + AST × 0.028 + diabetes mellitus × 3.7) − (0.03 × triglycerides). The AUROC of the T-HAD score was 0.929. The T-HAD score had a sensitivity of 90% and a specificity of 77% at a cut off of >2 for advanced fibrosis. We validated this score in another cohort of liver biopsy with advanced fibrosis. In the validation cohort, the T-HAD score had an AUROC of 0.926 in diagnosing advanced fibrosis (sensitivity of 89% and specificity of 71% at a cut off of >2). *Conclusion*. The T-HAD score based on data from the Asian population is a new diagnostic model which is beneficial in estimating the risk of advanced fibrosis. It is a simple yet effective tool that could be in-cooperated into day-to-day practice in a resource-limited setting.

1. Introduction

The incidence of NAFLD has risen to such an extent that it has surpassed most other etiologies to become the commonest cause of chronic liver disease and liver transplantation. NAFLD is defined as the presence of steatosis in >5% of hepatocytes in the absence of excessive alcohol consumption (>20 g/day for females and >30 g/day for males) [1]. NAFLD has a wide and varied spectrum of clinical presentations. It could be subtle, asymptomatic simple steatosis which is often diagnosed incidentally to NASH which progresses to advanced fibrosis and often results in the end stage of cirrhosis and associated complications including hepatocellular carcinoma. NAFLD has several distinct associations which could be detected or missed in subjects if not carefully screened for. The pathogenesis of NAFLD is closely linked with the development of metabolic syndrome, obesity, diabetes mellitus, dyslipidemia, and insulin resistance [2]. The earliest form of the disease in the NAFLD spectrum includes simple steatosis which is followed by NASH. The major cause of mortality in NALFD patients is contributed by adverse cardiovascular outcomes. Added to the varied

cardiovascular risks depending on the patient's phenotypes, a vast majority succumb to liver-related mortality as well, owing to the relentless progression of the disease to cirrhosis.

The worldwide prevalence of NAFLD is around 25.4%. It is highest in the Middle East and lowest in incidence on the African continent. Subjects with a BMI of more than 30 have a higher prevalence of NAFLD (90%) when compared to those with a BMI <25 (25%) [3].

Histology is the gold standard in diagnosing NAFLD and differentiates simple steatosis from more dangerous counterparts like NASH, advanced fibrosis, and cirrhosis. There are numerous noninvasive techniques for assessing the degree of fibrosis in NAFLD. They include imaging and various scores which combine clinical and biochemical factors. Vibration-controlled transient elastography (VCTE) or better known as TE is presently considered the point of care in the management of NAFLD [4]. It is the best available and most validated noninvasive imaging for advanced fibrosis. The major drawback encountered with VCTE is the difficulty in obtaining values in obese patients with the M probe. For this reason, the XL probe was introduced. The specificity of the XL probe may be lower as it gives lower cut-off values than the M probe. A value of more than 9.9 Kpa could be taken as a reliable cut off to diagnose advanced fibrosis in NAFLD [5] (≥10).

Among the currently available noninvasive scoring system FIB-4, the NFS score (NAFLD fibrosis score), BARD score, enhanced liver fibrosis score, and European liver fibrosis score are the most accepted scores. Almost all of these scoring systems were based on data incorporated from European and Western settings. There are very few scoring systems based on data from the Asian population. The NAFIC score was developed by Sumida et al. based on a study of the Japanese population. This required type IV collagen and fasting insulin assessment which prove rather costly and less clinically feasible owing to its availability. Hence, we attempted to develop a score based on simple biochemical and clinical variables to diagnose advanced fibrosis in an Asian cohort of patients with NAFLD.

1.1. What Is the Need for a New Score?

(ii) Most of the biochemical scoring systems for NAFLD-advanced fibrosis are based on Western data which if applied in our settings could be biased

(iii) There are only a few scores based on the Asian population in determining fibrosis

2. Materials and Methods

This was a cross-sectional observational study conducted in the Department of Medical Gastroenterology, Government Medical College, Trivandrum, from July 2017 to June 2019.

(i) Inclusion criteria

(1) Those patients undergoing ultrasonography abdomen in the Department of Medical Gastroenterology, Medical College, Trivandrum, with fatty liver who were willing to give consent were taken up for the study

(ii) Exclusion criteria

(1) History was taken, and investigations were done to rule out secondary steatosis

(2) Those patients with decompensated cirrhosis were excluded

(3) Patients in whom a successful VCTE examination could not be done

History was taken, and investigations were done to rule out secondary steatosis. The following was done to rule out common secondary steatosis.

(i) Alcohol intake ≥ 2 standard drink (one standard drink is 12 g) in females and ≥3 standard drink in males were excluded

(ii) Those taking drugs which are likely to cause secondary steatosis were excluded, e.g., tamoxifen

(iii) Simplified autoimmune hepatitis score (pre biopsy score) ➔ to rule out autoimmune hepatitis

(iv) HBsAG and IgM/IgG HBc ➔ to rule out occult and overt HBV infection

(v) Anti-HCV ➔ to rule out HCV infection

(vi) Ceruloplasmin level, KF ring by slit lamb, and 24 hr urine copper (if ceruloplasmin is low) ➔ to rule out Wilson's disease

(vii) S. ferritin and trasferrin saturation ➔ to rule out hereditary haemochromatosis

VCTE using the Echosens Paris M probe was performed in all those patients who were willing to give consent during our study period. Transient elastography was done by a person who had done > 10000 transient elastography scans. All transient elastography were done by the same person to avoid interobserver variabilities. 10 measurements were taken using the M probe, and the mean values of the ten readings were taken as the final test result. All TE were done with the M probe, and the XL probe was not used in the study. Informed consent was obtained from all patients participating in our study. Based on the TE score obtained, we grouped patients into 2 groups—those with advanced fibrosis and those without. Advanced fibrosis was defined as F3 or more fibrosis with a VCTE value of ≥10 Kpa. Clinical, anthropometric, and biochemical variables were assessed on the same day as VCTE. Diabetes mellitus duration was obtained from the history. Waist circumference (WC) was measured midway between the lower rib and the iliac crest on the midaxillary line, and hip circumference at the level of the widest circumference over the great trochanters. We selected another cohort of patients who had undergone liver biopsy for NAFLD to validate our newly developed score.

The score was validated in a separate liver biopsy cohort because liver biopsy is the gold standard investigation to detect advanced fibrosis.

(i) Inclusion criteria

(1) Those patients undergoing liver biopsy at the Department of Medical Gastroenterology, Medical College, Trivandrum, with biopsy-proven NAFLD who were willing to give consent were taken up for the study

(ii) Exclusion criteria

(1) Inadequacy of biopsy

(2) Competing etiologies in biopsy

Indications of liver biopsy in the validation cohort were

(i) Transaminitis with other etiological workup negative

(ii) Advanced fibrosis (defined as transient elastography (TE) value > 10 Kpa)

(iii) Positive autoantibodies to distinguish between autoimmune hepatitis or epiphenomenon associated with NAFLD

(iv) High ferritin level to determine the extent of liver injury and iron accumulation

(v) Competing etiologies with NAFLD were suspected

A liver biopsy was taken using a 16G liver biopsy needle under ultrasound guidance. One core biopsy was taken with a length of 1-1.5 cm. At least 8 portal tracts were considered adequate biopsy specimen. All biopsies were analyzed by a single pathologist who had an experience of more than 15 years in liver histopathology to avoid interobserver variability.

All patients undergoing liver biopsy with biopsy-proven NAFLD without competing etiologies in liver biopsy were taken up for the study.

2.1. Statistical Analysis. Data was analyzed using SPSS version 16.0 statistical software (SPSS, Inc., Chicago, IL, USA). Statistically significant variables for diagnosing advanced fibrosis were derived using a chi-square test and an independent t-test. Statistically significant variables were analyzed using logistic regression. A new score for advanced fibrosis was derived by multiplying the coefficient of beta of significant variables and adding the sum of their products. The sum of the variables was plotted to generate an AUROC curve. The score was then validated in a cohort of patients who had undergone liver biopsy for NAFLD.

2.2. Ethical Consideration. Ethical clearance was obtained from the Institutional Ethical Committee (HEC.NO.05/25/2019/MCT). Written informed consent was obtained from all the study subjects in English and the local language (Malayalam). All expenses were met by investigators. Confidentiality was maintained.

3. Results

A total of 1617 patients were taken up for the study after excluding those with secondary steatosis (470 patients were having competing etiologies) and patients in whom TE value could not be obtained (we were not able to obtain TE in 86 patients) (Figure 1).

The mean age group of our study population was 43.36 years. The sex distribution in our population was as follows: 693 (42.9%) were females and 924 (57.1%) were males. The baseline characteristics of the patient cohort and validation cohort are elaborated in Table 1.

Quantitative variables diagnosing advanced fibrosis in NAFLD were analyzed using an independent t-test. Hip circumference, AST level, alanine aminotransferase (ALT) level, age, and triglycerides were statistically significant in diagnosing advanced fibrosis in NAFLD (Table 2).

A chi-square test showed that hypertension and diabetes mellitus (duration of more than 10 years) significantly predicted advanced fibrosis (Table 3).

The significant variables obtained by univariate analysis were subjected to logistic regression to determine the independent predictors of advanced fibrosis. Age was a potential confounder as TE values tend to increase proportionately with age. Regression analysis suggested that AST, triglycerides, diabetes mellitus (duration more than 10 years), and hip circumference were independent predictors of advanced fibrosis (Table 4).

3.1. Derivation of New Score. The new score was derived by multiplying the coefficient of beta of significant variables and adding the sum of multiplication products. The equation for the new score is as follows:

$$(H * 0.044 + A * 0.028 + D * 3.7) - 0.03 * T. \quad (1)$$

T-HAD score (T for triglycerides, H for hip circumference, A for AST, and D for diabetes mellitus (duration more than 10 years)).

The AUROC curve for the new score was plotted and was 0.929. It succeeded FIB-4 (fibrosis-4) and BARD score (body mass index AST/ALT ratio and diabetes mellitus score) in the prediction of advanced fibrosis (BARD had an AUROC of 0.586 and 0.819 for FIB-4) (Figure 2).

A cut off of >2 had a sensitivity of 90% and a specificity of 77% in diagnosing advanced fibrosis. The negative predictive value is 97.92%, and the positive predictive value is 39%. When males and females were separately analyzed, the new score has an AUROC of 0.908 for female patients. For males, AUROC was 0.96.

The T-HAD score in short had demonstrated excellent performance in diagnosing advanced fibrosis with a better predictive outcome for males.

3.2. Validation of New Score/T-HAD Score. The sample size for the validation cohort was calculated by the formula 4 PQ/D^2/prevalence.

P is the sensitivity, Q is the 1-P, and D is the 20% of P.

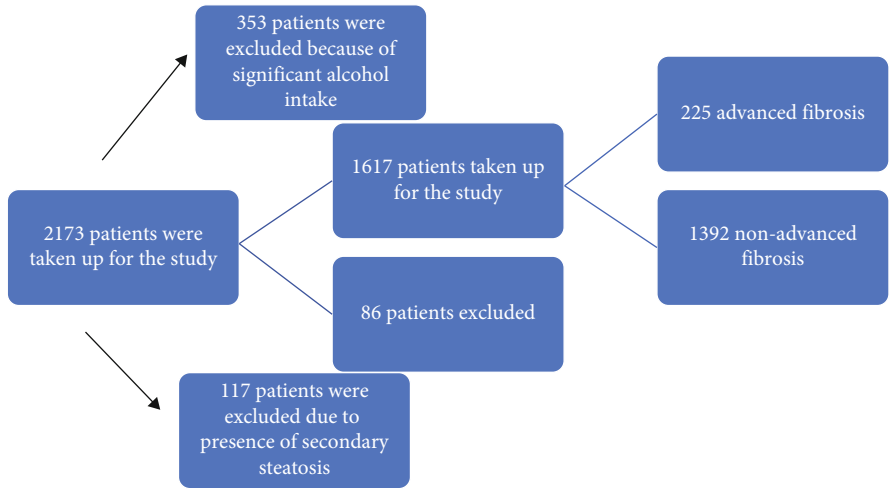

Figure 1: Consort diagram of test cohort.

Table 1: Baseline characteristics of test cohort and validation cohort.

	Test cohort (advanced fibrosis based on VCTE) Mean	Validation cohort (advanced fibrosis based on liver biopsy) Mean
Transient elastography	7.3014660	8.971
Sample size	1617	84
% of patients with advanced fibrosis	13.9	21.42
Height	159.35	162.02
Weight	66.57	74.60
Body mass index	26.29	29.1
Hip circumference	95.38	90.33
Aspartate aminotransferase	35.75	69.39
Alanine aminotransferase	43.86	111.38
Age	43.36	43.93
High-density lipoprotein	50.34	40.04
Triglycerides	130.74	129.37

Abbreviations: VCTE = vibration-controlled transient elastography.

The sample size was calculated to be 79. For validation, we included 103 patients. 12 were excluded due to competing etiologies, and 7 were excluded because of the inadequacy of the liver biopsy. After excluding 19 patients, 84 patients were taken up for the study (Figure 3).

The new score had an AUROC of 0.926 in diagnosing advanced fibrosis in the validation cohort (liver biopsy patients) (Figure 4). At a cut off of >2, the validation cohort had a sensitivity of 89% and a specificity of 71% in diagnosing advanced fibrosis.

4. Discussion

Our study had a reasonably large sample size in comparison with other studies where the population of NAFLD patients studied was less than 1000. Our study included 1617 patients. A similar study done by Angulo et al. had 733 patients studied, and the NAFLD fibrosis score/NFS score was arrived [6], Harrison et al.'s [7] study, where the BARD score was developed, included 827 patients, 541 in the study by Shah et al. (FIB-4 score) [8], 192 patients in the study by Guha et al. (enhanced liver fibrosis score/ELF score) [9], and 619 by Sumida et al. (NAFIC score) [10]. Except for the NAFIC scores, most scores were based on data from Europe and the West. Scoring systems established previously included parameters like hyaluronic acid in the ELF and type IV collagen in NAFIC, which were costly and not widely available in resource-limited countries. There are no studies to date, from the Indian population, examining the risk of the development of advanced fibrosis. The mean BMI of the study population was 26.29. In the Asian Indian phenotype, obesity is defined as a BMI > 25.

Our study had a lesser proportion of old-age patients, but it was not a selection bias. In the inclusion criteria, we mentioned that all patients with fatty liver who were willing to take part in the study during the study period were included in the study. AST values were higher in the test cohort compared to the validation cohort, as one of the indications for liver biopsy in the validation cohort was elevated transaminase. In the test cohort, a biopsy was not done to prove advanced fibrosis; instead, a fibroscan was used as an indicator of advanced fibrosis. But that shortcoming was overcome by doing a liver biopsy in the validation cohort.

Our study population had an almost equal proportion of males and females (924 to 693). In Harrison et al.'s study, 51% were females [7]. In Angulo et al.'s study, 53% were males [6]. In our study, 13.9% had advanced fibrosis. In Angulo et al.'s NFS study, 199 out of 480 patients were having advanced fibrosis [6]. Among the study variables, hip circumference, AST, ALT, age, hypertension, diabetes mellitus for more than ten years, and triglycerides were

Table 2: Independent t-test for advanced fibrosis and significant variables.

	Sig. (2-tailed)	Mean difference	Std. error difference
Height	.292	.748	.709
Weight	.090	-3.7153	.8911
Body mass index	.084	-1.626	.344
Hip circumference	.000	-5.922	.822
Waist circumference	.081	-3.152	.790
Mid arm circumference	.023	-.853	.374
Triceps skin fold thickness	.462	-.807	1.097
Aspartate aminotransferase	.000	-9.773	1.269
Alanine aminotransferase	.000	-6.152	1.625
Age	.000	-8.662	.835
High-density lipoprotein	.072	15.401	.995
Triglycerides	.000	26.070	2.218

Table 3: Chi-square test for advanced fibrosis vs. hypertension and diabetes mellitus.

	Diabetes mellitus > 10 yrs			Hypertension		
	Absent	Present	Total	Absent	Present	Total
Advanced						
Absent	1256	136	1392	1276	116	1392
Present	31	194	225	157	68	225
Total	1287	330	1617	1433	184	1617
p value		≤0.001			≤0.001	

Table 4: Logistic regression analysis of significant variables for advanced fibrosis.

	Coefficient of beta	S.E.	Wald	Df	Sig.	Exp (B)
Hip circumference	0.044	.008	26.261	1	.000	1.044
Aspartate aminotransferase	0.028	.007	16.723	1	.000	1.028
Alanine aminotransferase	-.005	.006	.832	1	.362	.995
Diabetes mellitus	3.656	.233	246.380	1	.000	38.699
Hypertension	.466	.260	3.207	1	.073	1.593
Triglycerides	-0.029	.004	43.055	1	.000	.971
Constant	-9.286	1.083	73.503	1	.000	.000

significant in diagnosing advanced fibrosis. Of these, diabetes mellitus for more than ten years, AST, hip circumference, and triglycerides were independent predictors of advanced fibrosis by regression analysis. The coefficient of beta of triglycerides was negative, suggesting a negative association between triglycerides and advanced fibrosis. This negative association was already proven by Jiang et al. [11] in their study on 30752 patients. This can be explained by the fact that the liver is an important site of triglyceride production, and in the initial stages of NAFLD, the triglycerides increase. But as the liver's functions worsen with advanced fibrosis, the triglycerides production by the liver decreases, resulting in an inverse correlation between triglycerides and advanced fibrosis.

The new score has a negative predictive value of 97.92% and a positive predictive value of 39% in predicting advanced fibrosis. This suggests that the new score is an excellent screening tool to rule out advanced fibrosis because of its high negative predictive value.

We developed a new score, the T-HAD score, $(\text{HIP}^* 0.044 + \text{AST}^* 0.028 + \text{DM}^* 3.7) - 0.03^* \text{TGL} + 1$, ($T$ for triglycerides, H for hip Circumference, A for AST, and D for diabetes mellitus for more than ten years).

It has an AUROC of 0.929 in diagnosing advanced fibrosis, compared to 0.819 for FIB-4 and 0.586 for BARD. In the original study, the NFS score had an AUROC of 0.84 [6], BARD had 0.81 [7], FIB-4 had 0.802 [8], ELF had 0.9 [9], and NAFIC had 0.834 [10]. The T-HAD score appears to be better than the available scores in diagnosing advanced fibrosis. The clinical utility of the score lies in the fact that it is easy to calculate and uses only easily available and

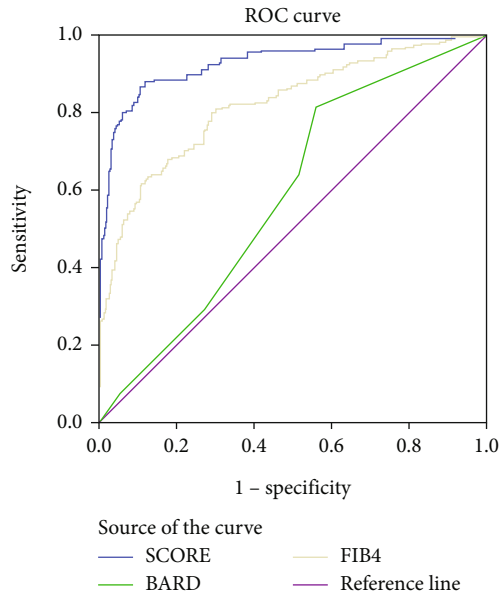

Figure 2: AUROC comparison of the new score/T-HAD score, FIB-4, and BARD score.

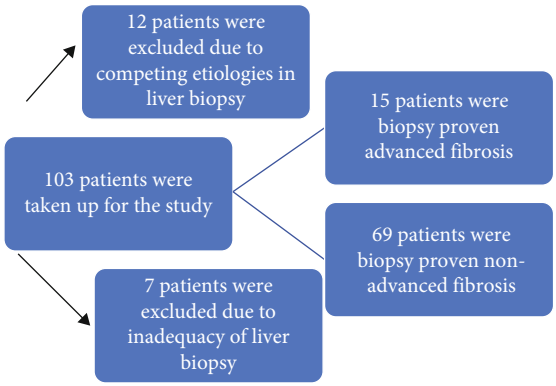

Figure 3: Consort diagram of the validation cohort.

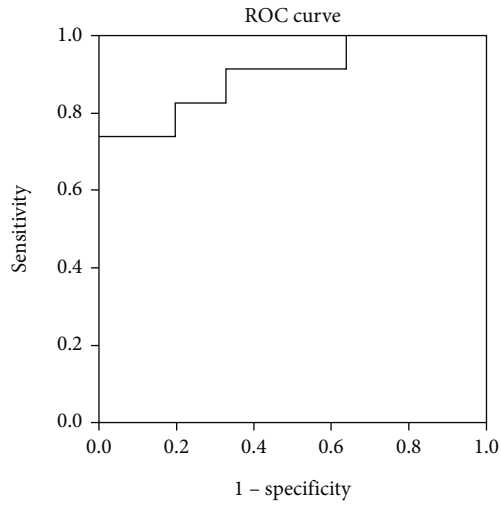

Figure 4: AUROC of new score in a validation cohort of liver biopsy patients.

routinely done investigations (AST and triglycerides) and clinical parameters. It has an AUROC comparable to scores like ELF with costly components like hyaluronic acid, TIMP, and procollagen.

Liver biopsy is the gold standard investigation of advanced fibrosis. The major drawback of this invasive modality is that the volume of tissue assessed is only a mere 1 : 50000 of the volume of the liver. The complications are many and carry a high risk of vascular injuries. Thus, VCTE has become the point of care for diagnosing advanced fibrosis in the cohort of NALFD. It has an AUROC of 0.93 in diagnosing advanced fibrosis [5]. Many studies had shown that the cut off for advanced fibrosis in VCTE is around 10 Kpa with an AUROC > 0.9 [5, 12, 13]. Our new score was validated in a cohort of patients who underwent liver biopsy. The T-HAD had an AUROC of 0.926 in liver biopsy patients, suggesting its reproducibility.

5. Conclusion

(i) T-HAD score is a new diagnostic model which could be used to detect advanced fibrosis in the Asian (Indian) NAFLD patient population

(ii) It is a simple score which can be done on a routine basis, and it would be most ideal in a resource-limited setting like ours

(iii) The new score is an excellent screening tool to rule out advanced fibrosis owing to its very high negative predictive value

5.1. Strengths. The study had a reasonably large sample size considering the liver biopsy validation cohort. The score incorporated simple clinical and biochemical variables which were used in the routine evaluation of NAFLD. The reproducibility of the score was tested in a liver biopsy-proven cohort as well.

5.2. Limitation. A liver biopsy was not done to confirm advanced fibrosis in the patient cohort used to develop the score (liver biopsy is the gold standard for advanced fibrosis). But our score was validated in a liver biopsy cohort to overcome this limitation.

5.3. Future Perspective. A multicenter validation study of the new score is required to assess its reproducibility.

Abbreviations

ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
AUROC:	Area under the receiver operating characteristics
BARD score:	Body mass index AST/ALT ratio and diabetes mellitus score
DM:	Diabetes mellitus
ELF Score:	Enhanced liver fibrosis score
FIB-4:	Fibrosis-4
NAFLD:	Nonalcoholic fatty liver disease
NASH:	Nonalcoholic Steatohepatitis
NFS score:	NAFLD fibrosis score

T-HAD score: Triglycerides, hip circumference, AST, and diabetes mellitus
TE: Transient elastography
VCTE: Vibration-controlled transient elastography.

Data Availability

All data generated during the study were included in the original article.

Disclosure

This study was presented as an abstract in the young investigator award presentation category of the Asia Pacific Digestive Week conference of 2021.

Conflicts of Interest

The authors declare no competing interest.

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