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Evaluation of liver stiffness measurement–based scores in liver transplantation recipients

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Abstract

Combining bioclinical parameters with liver stiffness measurement (LSM) has improved the diagnostic performance of vibration-controlled transient elastography (VCTE) for detection of advanced fibrosis in patients with chronic liver disease. However, this approach has not yet been tested in liver transplantation (LT) recipients. Thus, the aim of this study was to evaluate the diagnostic performance of combining LSM-based scores with LSM alone for the detection of advanced fibrosis in LT recipients. Adult LT recipients with a liver biopsy, VCTE, and clinical data necessary to construct LSM-based fibrosis models (FibroScan-AST [FAST], AGILE-3+, and AGILE-4) were included (n = 132). The diagnostic statistics for advanced fibrosis (fibrosis stage 0–2 vs. 3–4) were determined by optimal cut-off using the Youden index. The area under the receiver operating characteristic curve (AUROC) for LSM was 0.94 (95% confidence interval [95% CI], 0.89–0.99), FAST was 0.65 (95% CI, 0.50–0.79), AGILE-3+ was 0.90 (95% CI, 0.83–0.97), and AGILE-4 was 0.90 (95% CI, 0.83–0.97). No statistically significant differences were noted between the AUROC of LSM versus LSM-based scores. The false-positive rates for AGILE-3 + and AGILE-4 were 14.5% and 11.8% compared with 8.3% for LSM alone. The false-positive rates in LSM-based scores were higher among patients with diabetes mellitus, higher AST levels, and lower platelet counts. The LSM-based scores did not improve the diagnostic performance of LSM alone in LT recipients for the detection of advanced fibrosis. This lack of improvement in diagnostic performance results from the impact of immunosuppression on bioclinical profile and underscores the importance of developing LSM-based scores that are specific to LT patients.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CPM, clinical prediction model; FAST, FibroScan-AST; FIB-4, Fibrosis-4 Index; IQR, interquartile range; LSM, liver stiffness measurement; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; VCTE, vibration-controlled transient elastography.

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INTRODUCTION

Hepatic fibrosis is a key predictor of clinical outcomes in liver transplantation (LT) recipients.[1] Advanced hepatic fibrosis has been associated with both liver- and nonliver-related outcomes and is a surrogate for graft cirrhosis and hepatic decompensation.[2,3] While assessment of hepatic fibrosis had historically required a liver biopsy fibrosis, this has now become less prevalent in clinical practice due to the invasiveness of protocolized liver biopsies. However, nowadays, noninvasive testing methods such as transient elastography and clinical prediction models (CPMs) can be readily deployed in clinical practice.[4]

Vibration-controlled transient elastography (VCTE) measures the speed of mechanically generated shear waves across the liver to derive a liver stiffness measurement (LSM), a marker of hepatic fibrosis.[5,6] The CPM uses routinely available laboratory tests and anthropometric data to provide a point-of-care fibrosis assessment, and thus, does not increase health care–related cost.[7,8] In a head-to-head comparison performed recently, VCTE outperformed CPM for the detection of hepatic fibrosis.[9] However, it remains currently unknown whether combining CPM with VCTE can improve the diagnostic accuracy of this noninvasive biomarker. Moreover, models incorporating LSM and clinical parameters such as the FibroScan-AST (FAST) score, AGILE-3+, and AGILE-4 have demonstrated excellent diagnostic performance in patients with chronic liver disease. These LSM-based models incorporate laboratory parameters (aminotransferases and platelet count) and comorbid conditions such as advanced age and diabetes mellitus status, which are associated with an increased risk of advanced hepatic fibrosis, to provide a more dynamic noninvasive fibrosis assessment than LSM alone. However, the diagnostic performance of these LSM-based models in LT recipients also currently remains unknown.

This study aims to evaluate the diagnostic performance of the combination of CPM and LSM versus LSM-based noninvasive fibrosis models versus LSM alone in LT recipients according to the regulatory guidance in biomarker development. As LT recipients have a significantly different biochemical profile than non-LT patients (serum aminotransferases, platelets, diabetes mellitus status), we hypothesize that LSM alone will be noninferior to LSM-based fibrosis models and a combination of CPM and LSM. We tested this hypothesis in a prospective cohort of LT recipients with histological fibrosis assessment.

PATIENTS AND METHODS

Study design

Adults aged ≥ 18 years were prospectively enrolled into a natural history study of LT recipients at the Hume-Lee Transplant Center at Virginia Commonwealth University. Study participants who had a qualifying liver biopsy with fibrosis assessment VCTE within 6 months were eligible for inclusion. Those with documented cirrhosis on a previous liver biopsy who only underwent VCTE were also included in the analysis. All research was conducted in accordance with both the Declaration of Helsinki and the Declaration of Istanbul. All patients gave written consent to participate in the study. This is part of a larger study evaluating clinical outcomes in patients following LT and was approved by the institutional review board at Virginia Commonwealth University. The manuscript was reviewed and approved by all authors prior to submission.

Patient population

Adult patients with a liver biopsy and VCTE in the natural history study were included in this analysis. Patients with active use of more than mild alcohol consumption, which is defined as consuming more than one standard drink/day in women and two standard drinks/day in men, were excluded. Additional exclusion criteria were active therapy for hepatitis C virus, untreated hepatitis C virus, acute cellular rejection, chronic rejection, cholestatic hepatitis, having implantable cardiac devices, pregnancy, ascites, dialysis, and heart failure. Only patients with well-compensated cirrhosis and no clinical manifestation of portal hypertension were included. Patients with decompensated cirrhosis were excluded as the fibrosis stage is often evident in patients with signs or symptoms of portal hypertension and these models offer little utility in those cases. Only patients who had a liver biopsy, successful VCTE, and necessary laboratory studies to construct the CPM within 6 months were included in the analysis.

Liver biopsy

The decision to perform a liver biopsy was at the discretion of the treating physician (transplantation hepatology or transplantation surgery) based on his/her clinical assessment. All liver biopsies were scored by a histopathologist blinded to the clinical data. Hepatic fibrosis was quantified from stages 0 to 4.[10] Moderate fibrosis was defined as the presence of fibrosis stage 2 or greater and advanced fibrosis as fibrosis stage 3 or greater. Fibrosis stage 4 was graft cirrhosis.

Vibration-controlled transient elastography

VCTE was performed using the FibroScan 502 Touch software (Echosens, Paris, France) as described previously.[11] In brief, after an overnight fast, patients were placed in the supine position with their right arm in

maximal abduction and measurements taken over the right hepatic lobe through the intercostal space.[5] All studies were started using the M probe, with the XL probe used only if prompted by the 502 Touch software. An LSM examination was considered unreliable if the interquartile range (IQR)/median was >30%, while technical failure was defined as the inability to obtain ten valid measurements.

Selection of clinical prediction models

The Fibrosis-4 Index (FIB-4) is the most validated CPM in chronic liver disease and has recently demonstrated reasonable diagnostic performance in LT recipients.[9] Thus, FIB-4 was used in conjunction with LSM using LT-specific cutoff values. The LSM-based models included FAST, AGILE-3+, and AGILE-4, which have emerging data on their diagnostic performance in chronic liver disease; however, there are no data regarding their performance in LT recipients. The mathematical formula to calculate these scores is presented in Table S1. Thus, LT-specific cutoff values for FAST, AGILE-3+, and AGILE-4 were derived to be used in this study.

Plan of analysis

Summary statistics including means, standard deviations, and percentages were presented as appropriate. Continues variables were compared using Student *t* test and χ^2 test for qualitative data. The LSM and FIB-4 values used for identification of advanced fibrosis were those published in the LT cohort.[9,11] As the LSM-based fibrosis scores (i.e., AGILE-3+/4, FAST) do have LT-specific cutoff values, these cutoffs were derived in the current cohort at Youden index and at maximum sensitivity and specificity according to best practices in biomarker science. The diagnostic statistics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) cross validated (using the jack-knife procedure) using area under the receiver operating characteristic curve (AUROC) and 95% confidence interval (CI) were reported. Diagnostic statistics for increasing pairwise fibrosis stages (0 vs. 1–4; 0–1 vs. 2–4; 0–2 vs. 3–4; and 0–3 vs. 4) were determined at optimal cutoffs using (1) Youden index, (2) sensitivity fixed at 90%, and (3) specificity fixed at 90%. The AUROCs of the CPM were ranked from the highest to the lowest. The Delong test was used to directly compare the AUROC of LSM with the CPM.[12,13] The number of patients correctly and incorrectly identified using LSM and CPM was obtained. A test of marginal homogeneity was performed by comparing the misclassification of VCTE against CPM. Two-sided p values < 0.05 were considered statistically significant. All statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA) and R software version 3.0.1 (R Foundation for Statistical Computing).

RESULTS

Study population

The clinical characteristics of the study cohort are presented in Table 1. In brief, a total of 132 patients (N) had a liver biopsy, VCTE, and CPM successfully completed. The most common etiologies of chronic liver disease leading to the need for LT were chronic hepatitis C (32%), nonalcoholic steatohepatitis (21%), and alcohol-associated cirrhosis (14%). The mean age of the cohort was 56.4 (standard deviation 12.7) years and 56% and 92 (70%) of the patients were men and Whites, respectively. The mean body mass index was 31.5 (standard deviation 19.8) kg/m^2 and obesity was noted in 40%. Diabetes mellitus and dyslipidemia were reported in 41% and 53% of the patients, respectively. The median time from LT to liver biopsy was 59 months (IQR, 21–130). The median time between liver biopsy and VCTE was 42 (IQR, 19–93) days. The most common indications for liver biopsy were elevated liver enzymes (n = 79) and elevated LSM (n = 29). The distributions of fibrosis stage 0, stage 1, stage 2, stage 3, and stage 4 were 49%, 31%, 3%, 8%, and 8%, respectively. An XL probe was needed in 44 (33%) patients that underwent VCTE.

Using FIB-4 and LSM to detect advanced hepatic fibrosis

The individual diagnostic performance of LSM and FIB-4 is presented in Table 2. In the sequential schema, using a FIB-4 cutoff value of 1.73 first reduced the number of patients requiring LSM from 132 to 49. In the second step, an LSM cutoff value of 12.2 kPa further excluded 37 patients from a liver biopsy consideration. This approach reduced the need for 120 liver biopsies; however, 12 patients (9%) with underlying advanced fibrosis were missed (10 with FIB-4 and 2 with VCTE) due to the sequential approach. In the combinational approach, patients with LSM $\leq$ 12.20 and FIB-4 $\leq$ 1.73 were excluded from biopsy consideration. This approach avoided a liver biopsy in 66 patients; however, the false-negative rate was 3%.

To better understand the relationship between FIB-4 and LSM, the concordance between FIB-4 and LSM to predict the presence of advanced fibrosis was evaluated. As noted in Figure 1, when FIB-4 and LSM were low, the likelihood of advanced fibrosis was 3%. By contrast, when LSM and FIB-4 were high, the likelihood

TABLE 1 Clinical characteristics of the study cohort

	N/% median/interquartile range
Demographics	
Number of participants (*N*)	132
Age (years)	56.4 ± 12.7
Gender (%male)	56%
Ethnicity	
Caucasian	92 (70%)
African American	34 (26%)
Etiology of liver disease	
Hepatitis C	42 (32%)
Nonalcoholic steatohepatitis	28 (21%)
Alcoholic cirrhosis	19 (14%)
Medical co-morbidities	
Body mass index (kg/m^2)	31.5 ± 19.8
Diabetes (%)	41%
Dyslipidemia (%)	53%
Hypertension (%)	80%
Obesity (%)	40%
Laboratory	
ALT (IU/L)	74.5 ± 79.4
AST (IU/L)	65.8 ± 71.7
Alkaline phosphatase (IU/L)	178.1 ± 186.8
Bilirubin (mg/dl)	1.25 ± 1.50
Hemoglobin (g/dl)	12.6 ± 2.19
Platelet (×10^3/μl)	177.2 ± 75.0
Histology	
Fibrosis	
Stage 0	65 (49%)
Stage 1	41 (31%)
Stage 2	4 (3%)
Stage 3	11 (8%)
Stage 4	11 (8%)
VCTE probe (XL probe)	44 (33%)
Liver stiffness measurement (kPa)	11.4 ± 12.1
Controlled attenuation parameter (dB/m)	254.2 ± 73.4
Time from transplant to VCTE (months)	99 ± 100

Note: Data are presented as *n* (%) or % or mean (standard deviation), or median (IQR).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography.

of advanced fibrosis was 83%. The concordance of these two noninvasive tests allows for risk-stratification of patients to determine if a liver biopsy is necessary. For example, a liver biopsy can be avoided in patients who will be low-risk (i.e., low FIB-4 and low LSM) for advanced hepatic fibrosis. By contrast, high-risk patients (i.e., concordant high FIB-4 and high LSM) are likely to have advanced hepatic fibrosis and thus a confirmatory liver biopsy is needed. However, in the setting of discordant results, the likelihood of advanced fibrosis ranged from 27% in patients with elevated FIB-4 but low LSM to 47% in patients with elevated LSM but low FIB-4.

Diagnostic performance of AGILE-3+, AGILE-4, and FAST

The diagnostic performance of AGILE-3+ and AGILE-4 in predicting the presence of advanced fibrosis in LT recipients is depicted in Table 2. The median AGILE-3+ and AGILE-4 values for each fibrosis stage are plotted in Figure 2. The AUROCs for detecting advanced fibrosis were 0.90 (95% confidence interval [95% CI], 0.83–0.97) with AGILE-3+ compared with 0.94 (95% CI, 0.89–0.99) with LSM alone. The cutoff value of 0.82 had an NPV of 0.96 and a PPV of 0.53 for the detection of advanced fibrosis. By fixing specificity at 90%, the cutoff value of 0.86 improved PPV to 0.56 at the expense of lower NPV (Tables S2 and S3). Using AGILE-3+ and AGILE-4 scores, a total of 47 and 53 biopsies would have been avoided. However, this would still be associated with 4 (3%) and 4 (3%) false negatives for AGILE-3+ and AGILE-4, respectively.

The AGILE-4 cutoff value, as determined by Youden index, of 0.36 had an AUROC of 0.90 (95% CI, 0.83–0.97) with a PPV of 0.57 and an NPV of 0.95. Cutoff values at fixed 90% specificity or sensitivity led to marginal improvement in both NPV and PPV. The diagnostic performance of AGILE-3+ and AGILE-4 was similar to that of LSM alone ($p = 0.15$ and 0.18, respectively).

Similar to AGILE-3+ and AGILE-4, FAST did not significantly improve the diagnostic performance of LSM alone. The AUROC for FAST to detect advanced fibrosis was 0.65 (95% CI, 0.50–0.79) with a PPV of 0.27 and an NPV of 0.89. Using the FAST score would have avoided 47 biopsies; however, this would still be associated with 12 (9%) false negatives.

In the sensitivity analysis, the study results were not affected if the analysis was restricted to only patients having a liver biopsy and VCTE within 90 days.

Misclassification with AGILE-3+ and AGILE-4

The misclassification between AGILE-3+ and AGILE-4 resulted largely from false positives, where the false positive rates were 14.55% for AGILE-3+ and 11.82% for AGILE-4. This was evaluated further by plotting the component of these scores against false-positive rates (Figures 3 and 4). The false-positive rates were signifi-

TABLE 2 Diagnostic performance of VCTE, Fibrosis-4, and composite scores for the detection of hepatic fibrosis

Fibrosis stage	AUROC (95% CI)	Cutoff	Sensitivity	Specificity	PPV	NPV	*p* value vs. LSM
LSM							
0 vs. 1–4	0.81 (0.73–0.88)	7.00	0.81	0.69	0.73	0.78	Reference
0–1 vs. 2–4	0.88 (0.81–0.96)	10.50	0.81	0.82	0.53	0.95	Reference
0–2 vs. 3–4	0.94 (0.89–0.99)	12.20	0.86	0.89	0.61	0.97	Reference
FIB-4							
0 vs. 1–4	0.59 (0.49–0.69)	3.40	0.33	0.88	0.73	0.56	<0.001
0–1 vs. 2–4	0.62 (0.51–0.73)	1.73	0.81	0.43	0.26	0.90	<0.001
0–2 vs. 3–4	0.62 (0.50–0.75)	2.52	0.59	0.66	0.26	0.89	<0.001
FAST							
0 vs. 1–4	0.67 (0.57–0.76)	0.33	0.75	0.60	0.66	0.70	<0.001
0–1 vs. 2–4	0.63 (0.50–0.76)	0.52	0.58	0.68	0.31	0.87	<0.001
0–2 vs. 3–4	0.65 (0.50–0.79)	0.52	0.59	0.67	0.27	0.89	<0.001
AGILE-3+							
0 vs. 1–4	0.76 (0.68–0.84)	0.66	0.58	0.86	0.81	0.67	0.15
0–1 vs. 2–4	0.88 (0.82–0.95)	0.68	0.85	0.76	0.47	0.95	0.98
0–2 vs. 3–4	0.90 (0.83–0.97)	0.82	0.82	0.85	0.53	0.96	0.15
AGILE-4							
0 vs. 1–4	0.80 (0.72–0.87)	0.11	0.73	0.77	0.77	0.74	0.73
0–1 vs. 2–4	0.86 (0.79–0.94)	0.17	0.85	0.71	0.42	0.95	0.49
0–2 vs. 3–4	0.90 (0.83–0.97)	0.36	0.77	0.88	0.57	0.95	0.18

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; FAST, FibroScan-AST; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; VCTE, vibration-controlled transient elastography.

cantly higher among patients with diabetes mellitus at 30% (vs. 3% for non–type 2 diabetes mellitus) for AGILE-3+ and 22% (vs. 5% for non–type 2 diabetes mellitus) for AGILE-4. No significant differences were noted with regard to sex and false-positive rates for both AGILE-3+ and AGILE-4. The false-positive rates for AGILE-3+ increased with higher aspartate aminotransferase (AST) and lower platelet counts (Figure 3). Similarly, for AGILE-4, the false-positive rates increased with higher alanine aminotransferase and AST and lower platelet counts.

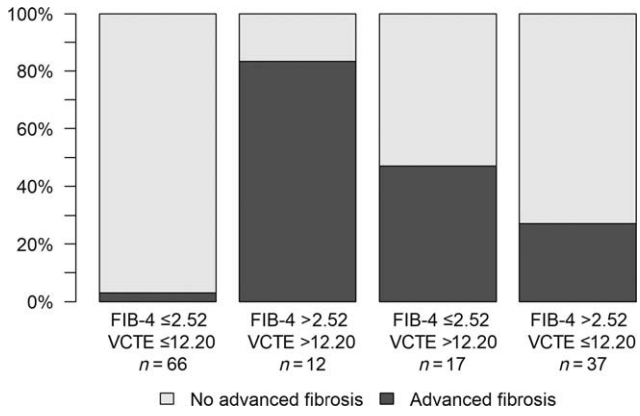

FIGURE 1 Concordance of FIB-4 and LSM versus likelihood of advanced fibrosis

DISCUSSION

Innovations in noninvasive biomarkers for the assessment of hepatic fibrosis in LT recipients are essential in identifying patients at risk for fibrosis progression while minimizing the unnecessary procedural risk of liver biopsy. VCTE has excellent diagnostic performance in non-LT populations and emerging data demonstrate excellent performance of VCTE in combination with CPM or fibrosis scoring schema that readily incorporate LSM such as FAST, AGILE-3+, and AGILE-4.[14] In this study, we evaluated the diagnostic performance of these strategies for detecting the presence of advanced fibrosis in LT recipients.

Study findings in the context of published literature

The LSM had excellent diagnostic performance for the detection of hepatic fibrosis in LT as previously reported.[11,15] A sequential approach of FIB-4 first followed by VCTE has the potential to avoid a significant number of VCTE and liver biopsy procedures; however, there is a nearly 1 in 10 chance of missing advanced hepatic fibrosis. By contrast, the likelihood of missing advanced hepatic fibrosis with a simultaneous approach using LSM and FIB-4 reduces the false-negative rates; however, this is at the

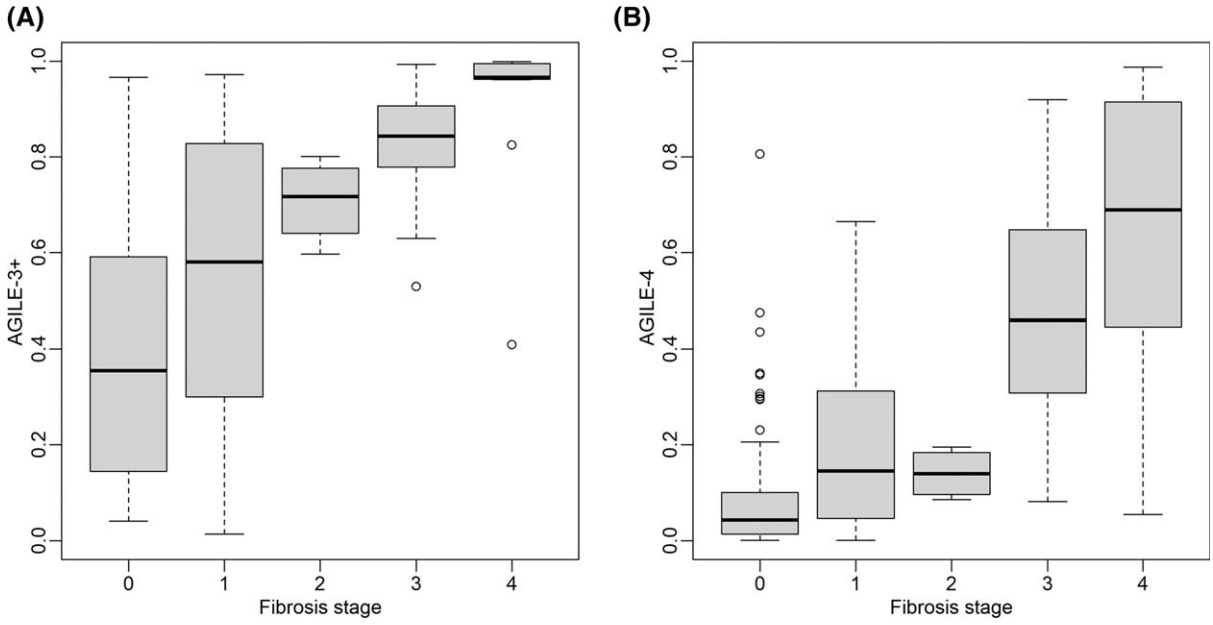

FIGURE 2 (A) Median AGILE-3+ score for each fibrosis stage; (B) median AGILE-4 score for each fibrosis stage

expense of performing VCTE in all patients while biopsy could only be avoided in half as many patients as the sequential approach.

Recently, significant efforts have been made to improve the diagnostic performance of LSM by incorporating the clinical profile of the patient into fibrosis assessment. The AGILE-3+, AGILE-4, and FAST scores use clinical parameters associated with fibrosis progression age, diabetes mellitus status, AST, and platelet counts to improve the detection of hepatic fibrosis noninvasively.[14] These models have shown excellent diagnostic performance in non-LT population, particularly, in patients with NAFLD. The diagnostic performance of these LSM-based models in the LT population, however, did not improve over LSM alone. This results from the disproportionately higher prevalence of diabetes mellitus in LT recipients and older age of patients who receive LT.[3,16,17] Moreover, laboratory-based parameters such as AST and platelet counts that have a high predictive value for the detection of advanced fibrosis in non-LT (or general population) are less helpful in LT recipients because of their exposure to chronic immunosuppression, which can affect serum aminotransferase levels and platelet counts.[18–20]

Impact of study findings on clinical practice

This study confirms that noninvasive testing can be used in LT recipients to identify at-risk patients.[9,11,15] Moreover, the use of CPMs can lead to further refinement of noninvasive strategies. The sequential strategy using FIB-4 followed by VCTE has the added benefit of reducing health care cost by avoiding patients who may have low FIB-4 values. By contrast, the combination strategy (FIB-4 + VCTE) lowered the false-negative rate for the presence of advanced fibrosis from 9% to 3%; however, in this strategy, all patients required VCTE. Thus, the optimal strategy to be adopted in clinical practice would depend on the clinical question and patient population. Moreover, these strategies require further validation in prospective cohorts before they can be adopted in clinical practice.

The VCTE-based scores combine LSM with “at-risk” clinical and biochemical parameters and have shown significant improvement over VCTE alone in nontransplantation settings.[14] In this study, the LSM-based scores, AGILE-3+ and AGILE-4, did not significantly improve the diagnostic performance of LSM. This discrepancy between non-LT and LT population is multifactorial. Because of chronic exposure to immunosuppression, LT recipients are at a much higher rate of metabolic comorbid conditions, which can occur relatively early following LT.[17,21,22] This is different from non-LT patients in whom the exposure to comorbid conditions such as obesity and diabetes mellitus may be much longer. This is evident when false-positive rates are plotted against these metabolic and biochemical risk factors. Therefore, LSM-based scores currently do not show improvements over LSM alone and there is thus a need to develop LSM-based scores that are specific for LT population. Finally, this study was not designed to compare the performance of VCTE with other modalities for measuring elastography (B-mode ultrasound or magnetic resonance); however, the diagnostic performance of VCTE seems similar to that of published literature.[23–25]

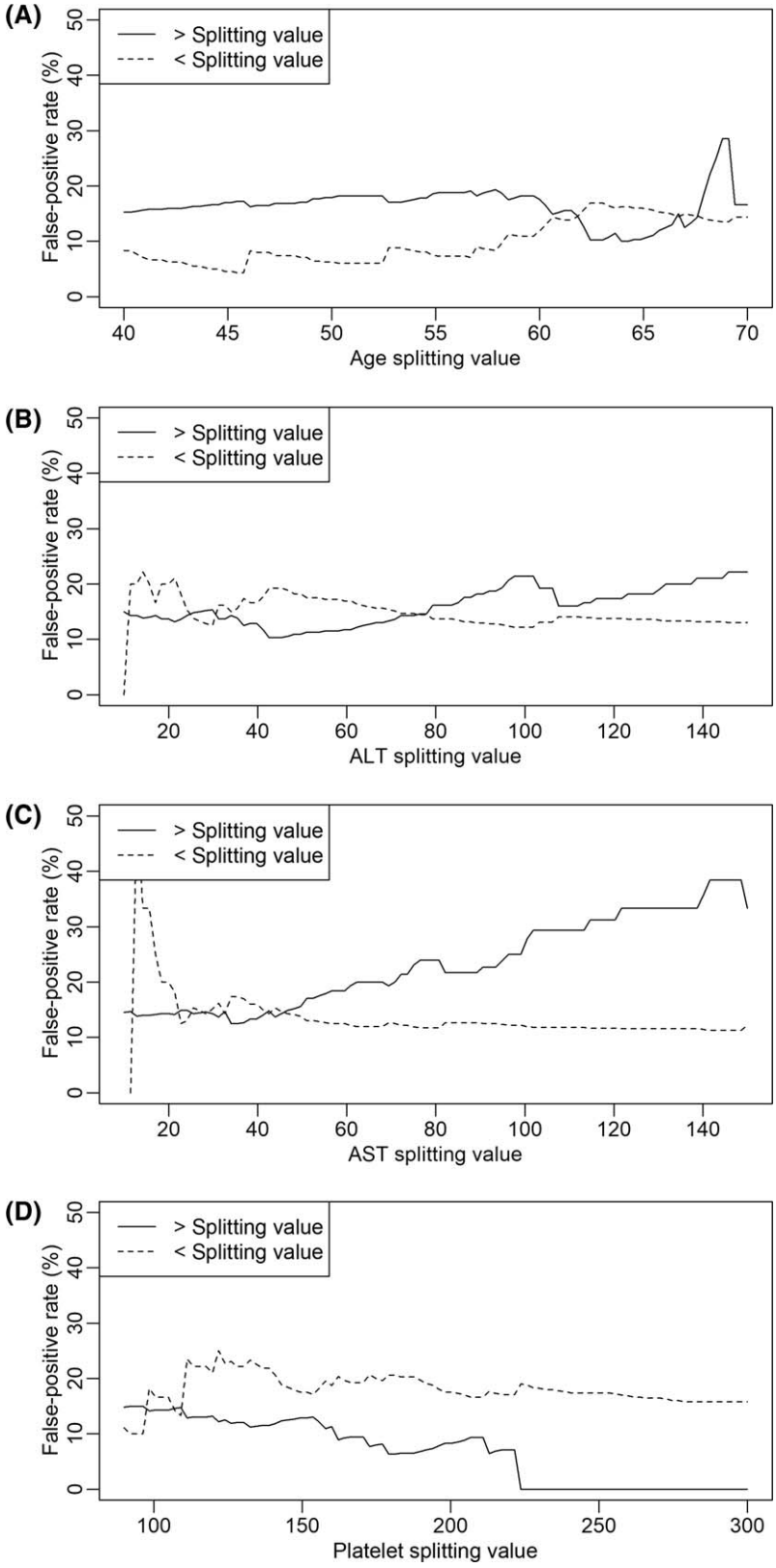

FIGURE 3 (A) Age splitting value versus false-positive rate (%) using AGILE-3+; (B) ALT splitting value versus false-positive rate (%) using AGILE-3+; (C) AST splitting value versus false-positive rate (%) using AGILE-3+; (D) platelet splitting value versus false-positive rate (%) using AGILE-3+

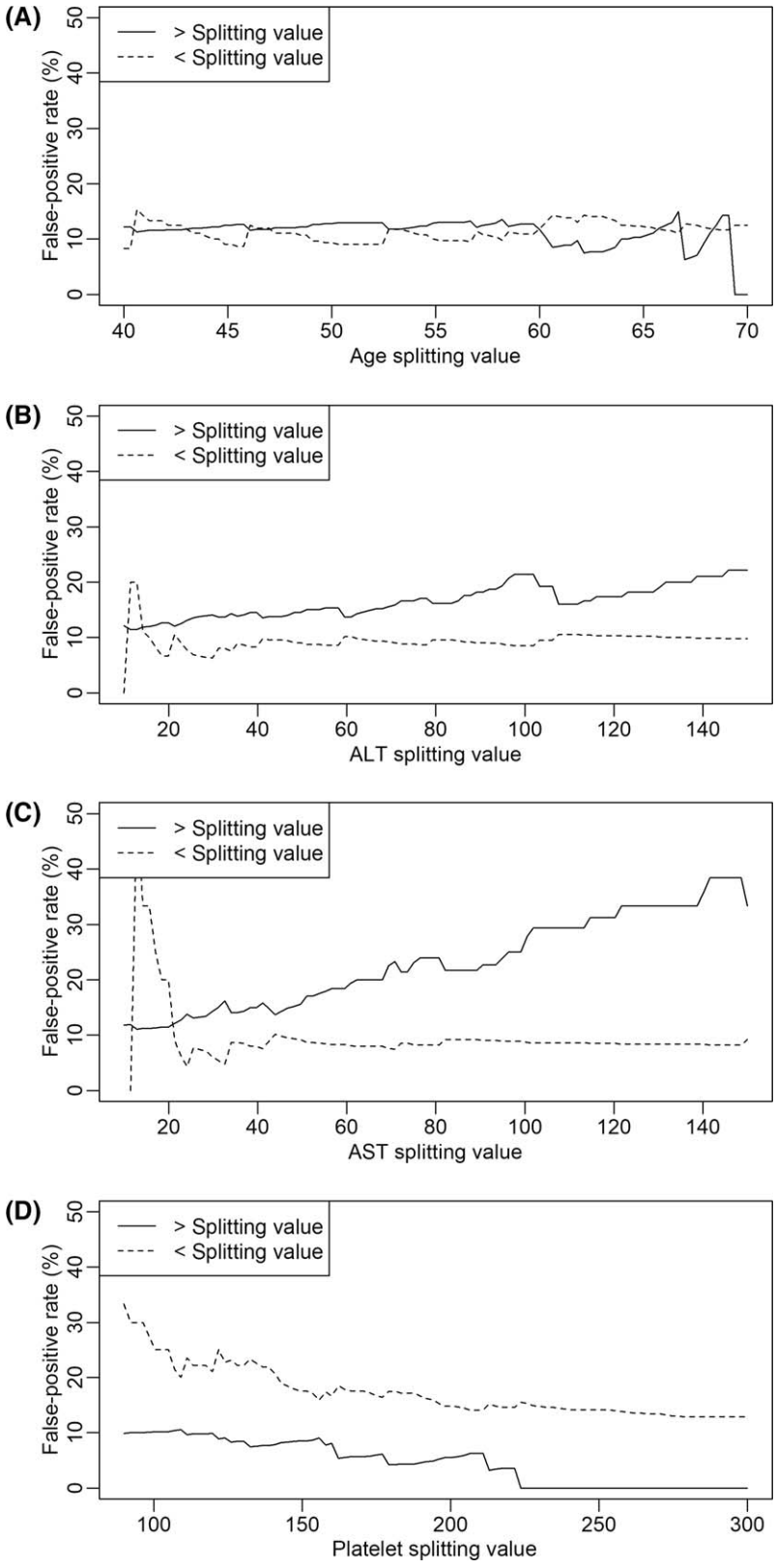

FIGURE 4 (A) Age splitting value versus false-positive rate (%) using AGILE-4; (B) ALT splitting value versus false-positive rate (%) using AGILE-4; (C) AST splitting value versus false-positive rate (%) using AGILE-4; (D) platelet splitting value versus false-positive rate (%) using AGILE-4

Well-designed, prospective studies are required to truly compare the diagnostic performance of different modalities for measuring fibrosis in LT recipients.

Study strengths and limitations

This study used histological assessment in a large cohort of LT recipients who underwent simultaneous noninvasive fibrosis assessment via VCTE and CPM to compare diagnostic performance. Statistical methods in accordance with emerging biomarker development technology were employed to define the context of use and limitations of these noninvasive fibrosis biomarkers. As such, the study results have the potential to be readily adopted in clinical practice. Identification of advanced fibrosis is clinically significant, but the prevalence of advanced fibrosis in the study cohort was relatively low. This results from the fact that LT recipients are at competing risk of increased mortality from nonliver-related causes such as cardiovascular disease, malignancy, and infection that reduce the likelihood that they would develop advanced fibrosis.[16,26] The study analysis could have been expanded to include patients with moderate fibrosis (stage 0–1 vs. stage 2–4 fibrosis); however, there is a relatively small number of patients with stage 2 fibrosis and it is unlikely that the study results would have been significantly different if the analysis compared patients with moderate (vs. nonmoderate) fibrosis. The study included a mixed etiology of chronic liver disease rather than a single etiology. In routine clinical practice, patients seen in the transplantation hepatology clinic have mixed etiologies of chronic liver disease, and thus, the population studied is reflective of what is commonly encountered in transplantation hepatology setting. The study did not provide data linking VCTE to clinical events but instead used liver histology as a surrogate and is a limitation. Future studies are thus necessary to demonstrate the relationship between VCTE and clinical events. This study also did not use the LT-specific fibrosis assessment and a future direction of the current findings is to validate these findings using an allograft-specific score.[27]

In summary, LSM-based scores do not improve the diagnostic performance over LSM alone. This underscores the challenges of quantifying hepatic fibrosis in LT recipients and the need to develop LSM-based scores that are specific to the LT population.

AUTHOR CONTRIBUTIONS

Mohammad Shadab Siddiqui, Chandra S. Bhati, and Mark Muthiah conceptualized this study. Mohammad Shadab Siddiqui, Chandra S. Bhati, and Vaishali Patel oversaw patient recruitment. Anh T. Bui performed statistical analysis; Tamoore Arshad, Michael Tseng, Austin Miller, Marie-Claire Evans, Taseen Syed, and Dylan Vainer extracted relevant data. Michael O. Idowu performed pathology review; Mohammad Shadab Siddiqui and Tamoore Arshad prepared the manuscript. All authors revised the manuscript.

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CONFLICT OF INTEREST

Mark Muthiah consults for Astellas and Roche.

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