






Alignment of Physician-Stated vs Clinically Derived Reference Fibrosis Score in Patients with Non-Alcoholic Steatohepatitis: A Real-World European Survey

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Objective: Stratifying disease severity in patients with non-alcoholic steatohepatitis (NASH) is essential for appropriate treatment and long-term management. Liver biopsy is the reference standard for fibrosis severity in NASH, but less invasive methods are used, eg, Fibrosis-4 Index (FIB-4) and vibration-controlled transient elastography (VCTE), for which reference thresholds for no/early fibrosis and advanced fibrosis are available. We compared subjective physician assessment of NASH fibrosis versus reference thresholds to understand classification in a real-world setting.

Methods: Data were drawn from Adelphi Real World NASH Disease Specific ProgrammeTM conducted in France, Germany, Italy, Spain and UK in 2018. Physicians (diabetologists, gastroenterologists, hepatologists) completed questionnaires for five consecutive NASH patients presenting for routine care. Physician-stated fibrosis score (PSFS) based on available information was compared with clinically defined reference fibrosis stage (CRFS) determined retrospectively using VCTE and FIB-4 data and eight reference thresholds.

Results: One thousand two hundred and eleven patients had VCTE (n = 1115) and/or FIB-4 (n = 524). Depending on thresholds, physicians underestimated severity in 16–33% (FIB-4) and 27–50% of patients (VCTE). Using VCTE ≥ 12.2 , diabetologists, gastroenterologists and hepatologists underestimated disease severity in 35%, 32%, and 27% of patients, respectively, and overestimated fibrosis in 3%, 4%, and 9%, respectively (p = 0.0083 across specialties). Hepatologists and gastroenterologists had higher liver biopsy rates than diabetologists (52%, 56%, 47%, respectively).

Conclusion: PSFS did not consistently align with CRFS in this NASH real-world setting. Underestimation was more common than overestimation, potentially leading to undertreatment of patients with advanced fibrosis. More guidance on interpreting test results when classifying fibrosis is needed, thereby improving management of NASH.

Keywords: fibrosis staging, non-alcoholic steatohepatitis, clinically derived reference fibrosis score, physician-stated fibrosis score, real-world evidence

Plain Language Summary

Why Was the Study Done?

The link between type 2 diabetes mellitus and non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is well known. This impacts the risk, severity, and prognosis of these diseases, warranting timely interventions to identify the presence and stage of disease to ensure appropriate management. Although studies have compared vibration-controlled

transient elastography (VCTE) and liver histology findings and demonstrated a good correlation between these methods, the correlation between clinically defined reference thresholds and physician-assessed fibrosis score has not been widely studied. The reliability of physician-assessed fibrosis score warranted further exploration.

What Did the Researchers Do and Find?

Our analysis showed physician-assessed fibrosis scoring to be inaccurate in patients with non-alcoholic steatohepatitis, underestimating and overestimating fibrosis stage compared with reference VCTE and Fibrosis-4 Index (FIB-4) methods. Overall, underestimation was more frequent than overestimation. Scoring misalignment varied with physician specialty, with underestimation greatest among diabetologists and overestimation greatest among hepatologists.

What Do These Results Mean?

Accurate diagnosis and risk stratification of patients are important so that health-care resources can be targeted to those at the greatest risk from their disease. Our findings suggest that more guidance, education and awareness are required to enable effective and accurate interpretation of the test results used to classify a patient's fibrosis stage.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic, often asymptomatic, disease characterized by excessive accumulation of triglycerides in more than 5% of hepatocytes.¹ NAFLD comprises steatosis (non-alcoholic fatty liver [NAFL]), as well as an inflammatory form — non-alcoholic steatohepatitis (NASH) — defined as steatosis plus inflammation and hepatocyte ballooning injury.² In one meta-analysis, NAFLD was estimated to affect 25% of adults globally and 59% of biopsied patients with NAFLD had NASH, resulting in an overall prevalence for NASH of 1.5–6.5%.³ It has been estimated that 12% of adults in the UK⁴ and 14% of adults in the USA have NASH.⁵ A recent structured literature review reported that NASH affects 3–5% of the global population, with most patients having several other comorbidities.⁶

High-quality data on rates of disease progression to NASH are sparse, although two dual biopsy studies indicated that both NAFL and NASH have the capacity to progress to advanced fibrosis, with the greatest risk being in patients with type 2 diabetes mellitus (T2DM) and hypertension.^{7,8} Greater levels of hepatic fibrosis are associated not only with liver-related morbidity but also with cardiovascular disease and all-cause mortality.⁹ In the absence of effective licensed pharmaceutical therapies specifically targeting liver disease, treatment involves controlling underlying risk factors of NASH, including cardiovascular disease, T2DM and obesity, as well as making lifestyle changes (diet and exercise), in particular weight loss.¹⁰ Accurate diagnosis and risk stratification of patients are thus important so that health-care resources can be targeted to those at the greatest risk from their disease.

Liver biopsy is currently the reference standard for identifying steatohepatitis and then grading and staging the disease.² This procedure has several limitations, including sampling error, cost and risk of complications.¹¹ In the real-world setting, physicians do not always have access to, or wish to use, this invasive diagnostic method and, as a result, non-invasive tests have emerged as a means to assess liver fibrosis,^{12,13} including measurement of liver stiffness by vibration-controlled transient elastography (VCTE; FibroScan) as a surrogate measure of hepatic fibrosis.^{14,15} Although more accessible than liver biopsy, VCTE is also subject to some limitations; in particular, fibrosis staging using this technique might be less accurate in older, obese, or hypertensive patients, or in those who have T2DM.^{14,16} Based on the results of studies correlating median liver stiffness derived from non-invasive tests with histological fibrosis stage according to the NASH Clinical Research Network (CRN) Scoring system,¹⁷ thresholds for staging fibrosis have been reported, with sensitivity and specificity values for each derived threshold.^{15,18,19} When applied in standard clinical settings, VCTE and Fibrosis-4 Index (FIB-4) scores have a high negative predictive value and might be used to exclude patients with advanced fibrosis, minimizing unnecessary liver biopsies.²⁰ However, VCTE results require interpretation by supervising clinicians and are open to misinterpretation, such that liver disease severity might be over- or underestimated.²¹ The FIB-4 is another non-invasive method for stratifying patients into those with versus without advanced hepatic fibrosis using the patient's age, aspartate transaminase (AST) level, alanine transaminase (ALT) level and platelet count.²² FIB-4 score is influenced to a greater extent by age than VCTE.²³

Despite recommendations by professional societies,^{2,24} NAFLD remains underdiagnosed and many physicians do not routinely use formal risk-stratification tools to aid triage and management of these patients.^{25–27} Therefore, physicians might underestimate NAFLD severity in the real-world setting. The aim of this analysis was to determine the alignment of physicians' subjective assessment of fibrosis stage (physician-stated fibrosis score, PSFS) in patients with a diagnosis of NASH in the real world against a clinically defined reference fibrosis stage (CRFS) that was calculated using the above-mentioned published reference thresholds for VCTE and FIB-4.^{15,18,19} A secondary aim was to identify physician specialty, patient liver biopsy status, and other patient demographic and clinical factors associated with alignment/misalignment between PSFS and CRFS. Finally, sensitivity analyses were done to determine if the following influenced the degree of alignment: (i) inclusion of patients for whom VCTE is suboptimal; (ii) timing of VCTE, ie, at diagnosis versus most recent test result; and (iii) whether or not patients had a liver biopsy in their diagnostic pathway, as this has the potential to supersede VCTE or FIB-4 assessments.

Methods

Study Design and Participants

Data were drawn from the Adelphi Real World NASH Disease Specific Programme (DSP) conducted in five European countries (France, Germany, Italy, Spain and the UK) between January and March 2018. DSPs are point-in-time surveys of physicians and their patients presenting in real-world clinical settings and have been described in detail and validated elsewhere.^{28–30}

Physicians

Eligible physicians were hepatologists (France, Italy and the UK), gastroenterologists (Germany, Italy, Spain and the UK), gastroenterologists with a subspecialization in hepatology (Germany and Spain), hepato-gastroenterologists (France only), endocrinologists (all countries) and diabetologists (all countries). Physicians were managing ten or more patients with NASH per month and personally responsible for NASH management decisions. Patients had to be aged 18 years or older, with a physician-confirmed diagnosis of NASH obtained via liver biopsy and/or non-invasive test. In this analysis, patients had to have both a PSFS plus a VCTE test and/or data enabling retrospective calculation of a FIB-4 score. Patients could not be participating in NASH clinical trials at the time of data collection.

The survey was performed in accordance with relevant guidelines and in line with the principles of the Declaration of Helsinki; ethics approval was obtained from Freiburg Ethics Commission International (Approval No. 017/1931). All patients provided written informed consent for use of their data, which were anonymized and aggregated. No medication was provided and no tests or investigations were performed as part of this research. No hypothesis was developed or tested.

Patient Sample and Data Collection

Physicians completed questionnaires for the next five consecutive consulting patients with a diagnosis of NASH of any fibrosis stage presenting for routine care. This number of patients was chosen to maximize the number of physicians sampled, while minimizing the burden on each physician.

The questionnaire collected patient demographic and clinical information and details of patient care, including diagnostic tests used, fibrosis score and VCTE reporting.

Outcomes

PSFS

Physicians were asked to classify the patient's fibrosis score at diagnosis (if known) and their current fibrosis score (F0 to F4). The PSFS was based on a summation of available clinical information and routinely ordered investigations, including a combination of non-liver and liver-specific tests as the physician deemed appropriate for that patient. Fibrosis scores are typically applied as per the NASH CRN fibrosis scoring system,¹⁷ however, physicians were not provided with any criteria for use in this assignment.

CRFS

This was a retrospectively assigned, objective fibrosis stage derived from published reference non-invasive test data and established thresholds.^{15,18,19} Using these systems, individual patient fibrosis scores were dichotomized using thresholds I–VIII as shown in Figure 1A. Thresholds were applied at the 80% or 90% level depending on the scoring system used and were defined by either sensitivity (testing correctly to identify the disease — a true positive), specificity (ability to identify patients without disease — a true negative), or Youden's Index (the threshold that optimizes a biomarker's differentiating ability when equal weight is given to sensitivity and specificity).³¹ This generated eight CRFS binary variables defining no fibrosis/early fibrosis or advanced fibrosis/cirrhosis. Patients with indeterminate NASH, ie, those identified via the 90% sensitivity and specificity ranges who did not clearly fall into the advanced fibrosis/cirrhosis category or the no fibrosis/early fibrosis category, were also included in subsequent sizing of patient fibrosis groups.

FIB-4

If the patient's age, AST and ALT levels and platelet count were recorded, FIB-4 scores were calculated retrospectively as previously described,²² irrespective of whether the physician had documented a FIB-4 score. Only FIB-4 scores within the range 0.05–10 were included.

In patients for whom a VCTE test result was available, the median liver stiffness (kPa) was captured to the nearest whole number.

Objectives

The primary objective was to determine how well PSFS aligned with CRFS using a variety of reference thresholds. The secondary objective was to identify physician specialty, patient liver biopsy status, and other demographic and clinical factors associated with alignment/misalignment between PSFS and CRFS.

Statistical Analysis

In the primary analysis, patients were grouped according to their PSFS as F0–F2 versus F3/F4. When categorizing patients as having early versus advanced fibrosis, we referred to 80–90% thresholds for each of the eight CRFS variables as defined in Figure 1B. Proportions within each of the four groups were reported as: (i) aligned, CRFS of no/early fibrosis and PSFS both F0–F2; (ii) aligned, CRFS of advanced fibrosis and PSFS both F3/4; (iii) physician underestimated, PSFS F0–F2 but CRFS of advanced fibrosis; or (iv) physician overestimated, PSFS F3/4 but CRFS of no/early fibrosis.

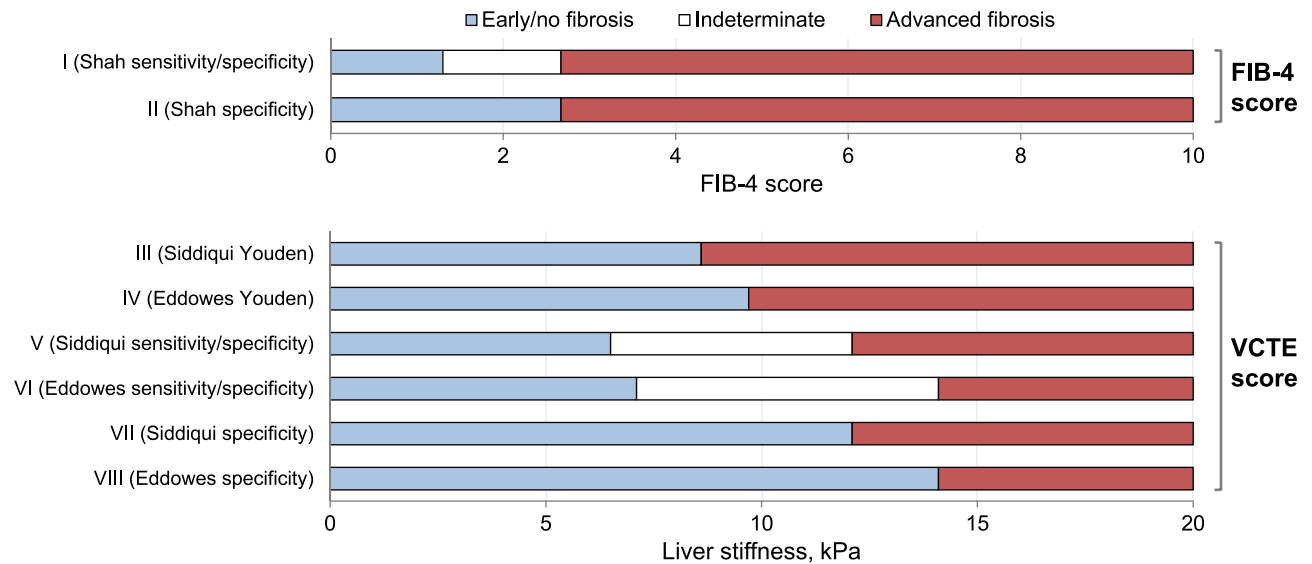
The secondary objective was to identify factors associated with alignment or misalignment between PSFS and CRFS. Alignment was assessed according to treating physician specialty (gastroenterologist, hepatologist, diabetologist), liver biopsy performed (yes, no), and key patient clinical and demographic characteristics, including age (>65 years, ≤65 years), key comorbidities (hypertension, metabolic conditions [any of metabolic syndrome, T2DM, insulin resistance or hyperglycemia]), and ethnicity (White/Caucasian, Asian, Hispanic/Latino, Afro-Caribbean, other). Statistically significant differences were identified using univariate tests (*t*, chi-squared, Fisher's exact and log rank tests). P-values of <0.05 were considered statistically significant; summary statistics were used to provide the size and direction of the difference.

Three sensitivity analyses were undertaken to test the assessment of alignment of fibrosis score:

I. VCTE-Suitable Cases

This involved exclusion of certain patient subgroups based on the recognition that VCTE might not be accurate enough in certain subgroups of patients, ie, patients aged ≥65 years, patients who are morbidly obese (body mass index [BMI] ≥35 kg/m²), patients with T2DM and patients with physician-reported hypertension. In this sensitivity analysis, the primary analysis was re-run including only patients who did not fall into any of the above categories to establish the degree of disconnect when accounting for these patient subgroups. This sensitivity analysis was conducted using the patient's most recent test results, which were assumed to have been performed reasonably close to the survey data collection timepoint and therefore to reflect the patient's condition at the time of the consultation.

A



B

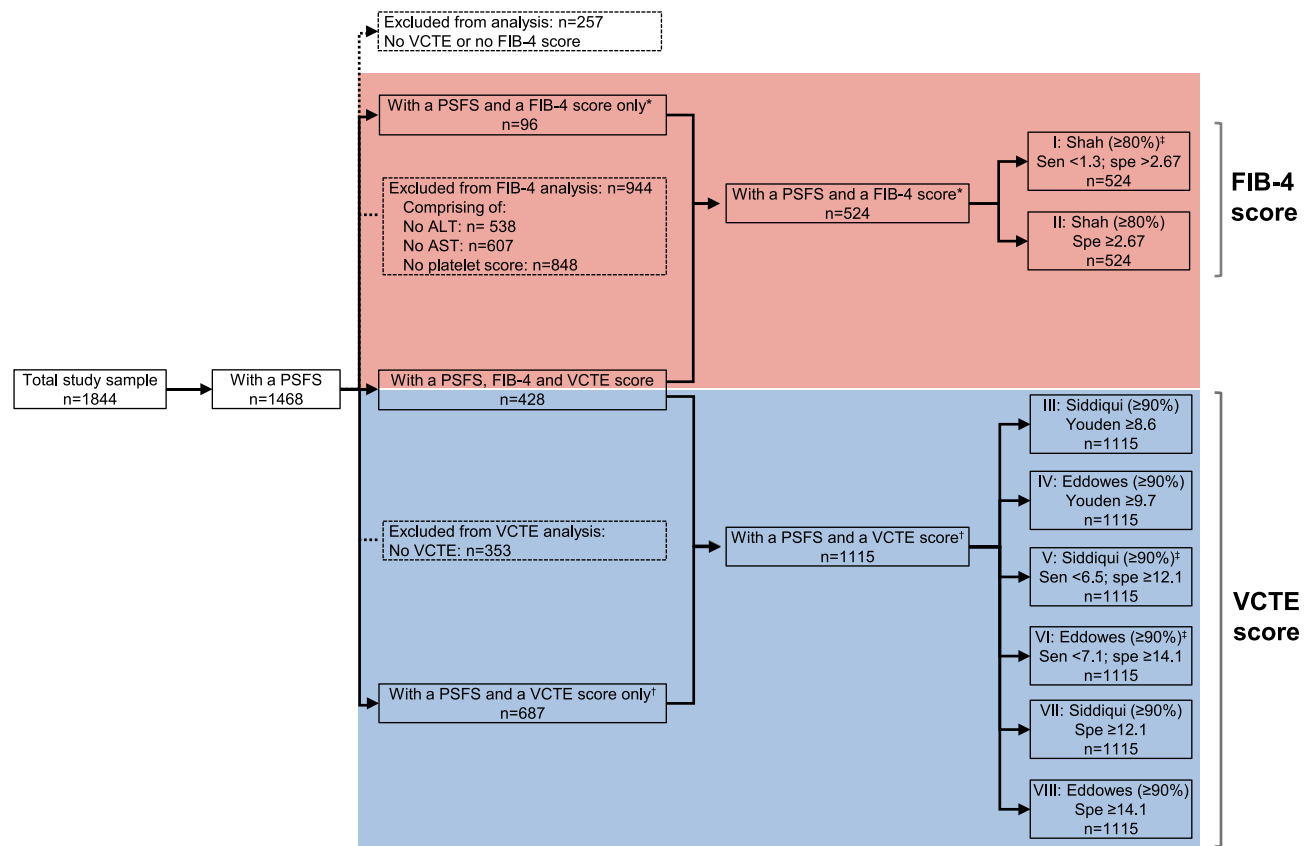


Figure 1 (A) Correlation of FIB-4 and VCTE scores with fibrosis stage according to published thresholds. Thresholds were applied at the 80% threshold for FIB-4 and 90% threshold for VCTE and defined by either sensitivity, specificity, or Youden’s Index. Patients with indeterminate non-alcoholic steatohepatitis were also included in subsequent sizing of patient fibrosis groups. **(B)** Study flow using these thresholds. Patient cohorts were generated using the thresholds described in key references for the presence of advanced fibrosis (specificity; true positive) and absence of advanced fibrosis (sensitivity; true negative). In some cases, upper and lower limits were applied, omitting an “indeterminate” group of patients in whom the presence or absence of advanced fibrosis could not be confirmed. Youden’s Index is the threshold that optimizes the biomarker’s differentiating ability when equal weight is given to sensitivity and specificity. *A FIB-4 score could not be derived if any one of the four components required (ALT, AST, platelet count, or age) was not available. Patients were excluded if their derived FIB-4 score was >10. Only the most recent FIB-4 score was available. †VCTE scores were available at diagnosis and most recent. ‡Indicates scoring systems that include indeterminate patients.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 Index; PSFS, physician-stated fibrosis score; Sen, sensitivity; Spe, specificity; VCTE, vibration-controlled transient elastography.

2. VCTE Results at Diagnosis

As the timing of the above test results could not be confirmed, this sensitivity analysis was repeated using the VCTE test result and PSFS obtained at diagnosis, where available, to assess whether the pattern of misalignment was consistent over time. Tests and assessments upon which diagnosis was based would have been undertaken not long before diagnosis and therefore can be assumed to be time relevant. As the physician only recorded the patient's most recent AST level, ALT level and platelet count data in the questionnaire, FIB-4 calculations could only be generated using the most recent test results, thereby limiting the second sensitivity analysis to VCTE scores.

3. Liver Biopsy

This analysis was performed to assess whether the degree of alignment might be influenced if a patient had undergone a liver biopsy, as this clinical assessment could supersede the FIB-4 or VCTE assessment and subsequent fibrosis assignment. Hence, analysis was repeated for those patients who had undergone a liver biopsy versus those who had not.

Results

Patients

The analysis population included 1844 patients, 1468 (80%) of whom had a PSFS. Despite current guidelines,²⁴ 257 patients had neither a VCTE score nor enough data to calculate a FIB-4 score and were excluded from the analysis. The analysis cohort therefore comprised 1211 patients. Overall, 524 patients (36%) had data enabling the calculation of a FIB-4 score and comprised the FIB-4 cohort ([Figure 1B](#)). A further 1115 patients (76%) had a VCTE score and comprised the VCTE cohort ([Figure 1B](#)). A subgroup of patients (n = 428) had both a VCTE score and a FIB-4 score and were included in the VCTE and FIB-4 cohorts. Patient characteristics are shown in [Table 1](#).

Overall, 494 patients (39%) were being managed by a hepatologist, 472 patients (41%) were being managed by a gastroenterologist and 245 patients (20%) were being managed by a diabetologist. Patient characteristics according to treating physician are shown in [Supplemental Table 1](#). Patients managed by a hepatologist or gastroenterologist appeared to be older and had a higher BMI than those treated by a diabetologist (both $p < 0.05$). Concomitant metabolic factors (T2DM, insulin resistance, metabolic syndrome, hyperglycemia), hypertension and dyslipidemia were more common in patients treated by diabetologists (all $p < 0.0001$). Liver biopsy was more commonly performed in patients treated by gastroenterologists/hepatologists versus diabetologists ($p < 0.05$). Among the 694 NASH patients with concomitant T2DM, 498 patients (72%) were currently managed by a hepatologist or gastroenterologist and 196 patients (28%) were being managed by a diabetologist.

A total of 583 patients had undergone a liver biopsy and 531 patients had not. A higher proportion of patients with no liver biopsy had physician-stated F0–2 fibrosis than those with a liver biopsy whereas more patients with a liver biopsy had physician-stated F3/4 fibrosis. Characteristics of these patients are shown in [Supplemental Table 2](#). A higher proportion of patients undergoing a liver biopsy had a BMI >35 kg/m² (34% [n=215/638] vs 24% [n=136/573] for those with no biopsy), hypertension (55% [n=354/638] vs 44% [n=252/573], respectively), or a metabolic condition — T2DM, insulin resistance, metabolic syndrome, hyperglycemia or any combination (74% [n=470/638] vs 65% [n=370/573], respectively).

Fibrosis Stage

Physician-Stated and Clinically Defined Reference Fibrosis Assessment

As assessed by their physician, 204/1468 patients (14%) were considered to have fibrosis score F0, 565 patients (38%) were F1, 378 patients (26%) were F2, 203 patients (14%) were F3 and 118 patients (8%) were F4. Overall, 1147/1468 patients (78%) had a PSFS of F0–F2, indicating no fibrosis or early fibrosis and 321/1468 patients (22%) had a PSFS of F3/F4, indicating advanced fibrosis or cirrhosis.

Table 1 Patient Demographics and Clinical Characteristics

Characteristic	VCTE Cohort (n=1115)	FIB-4 Cohort (n=524)
Mean age (years) (SD)	55.2 (10.9)	56.2 (11.2)
Male sex, n (%)	658 (59.0)	304 (58.0)
Ethnicity, n (%)		
White/Caucasian	954 (85.6)	436 (83.2)
Asian	58 (5.2)	22 (4.2)
Hispanic/Latino	37 (3.3)	20 (3.8)
Afro-Caribbean	23 (2.1)	17 (3.2)
Other	43 (3.9)	29 (5.5)
Mean BMI (kg/m ²) (SD)	32.7 (6.2)	33.0 (5.7)
BMI (kg/m ²) n (%)		
25–30	256 (23.0)	122 (23.3)
30–35	539 (48.3)	244 (46.6)
≥35	320 (28.7)	158 (30.2)
Mean platelet count (×10 ⁹ /L) (SD)	(n=494) 212 (87)	(n=524) 212 (80)
Mean alanine transaminase level (μg/L) (SD)	(n=737) 119 (377)	(n=524) 102 (290)
Mean aspartate transaminase level (μg/L) (SD)	(n=677) 82 (206)	(n=524) 72 (91)
Mean disease duration (years) (SD)	1.4 (2.3)	1.9 (2.8)
Concomitant conditions, n (%) ^a	(n=797)	(n=436)
Metabolic ^b	757 (67.9)	411 (78.4)
Hypertension	548 (49.1)	287 (54.8)
Dyslipidemia	491 (44.0)	284 (54.2)
Anxiety	183 (16.4)	124 (23.7)
Physician specialty, n (%)		
Hepatologist	447 (40.1)	272 (51.9)
Gastroenterologist	457 (41.0)	151 (28.8)
Diabetologist	211 (18.9)	101 (19.3)
Mean FIB-4 score (SD)	(n=428) 2.3 (1.5)	2.4 (1.6)
Mean fibrosis score (kPa) (SD)		(n=428) 17.9 (14.9)
Testing (ever): liver biopsy, n (%)	583 (52.3)	267 (51.0)
Hepatologist	229 (51.2)	145 (53.3)
Gastroenterologist	258 (56.5)	80 (53.0)
Diabetologist	96 (45.5)	42 (41.6)

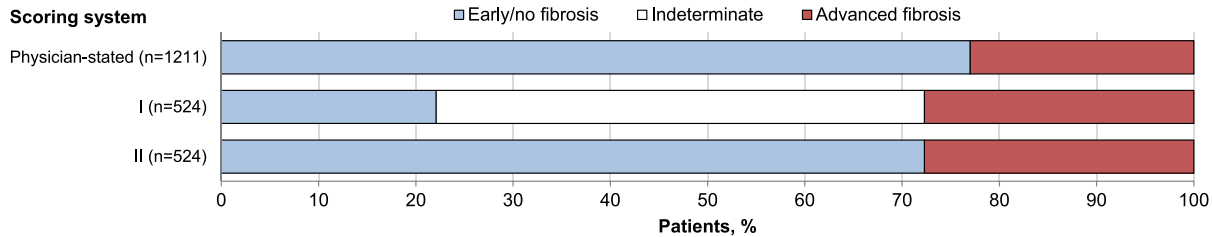
Notes: The two groups were neither mutually exclusive nor was one contained within the other, hence statistical validation could not be performed. A total of 428 patients had a VCTE and a FIB-4 test result and were included in both groups; 257 patients had neither a VCTE nor a FIB-4 test result and were not included. ^aMost common conditions, occurring in >10% of patients overall. ^bMetabolic=presence of any of metabolic syndrome, T2DM, insulin resistance, or hyperglycemia.

Abbreviations: BMI, body mass index; FIB-4, Fibrosis-4 Index; SD, standard deviation; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

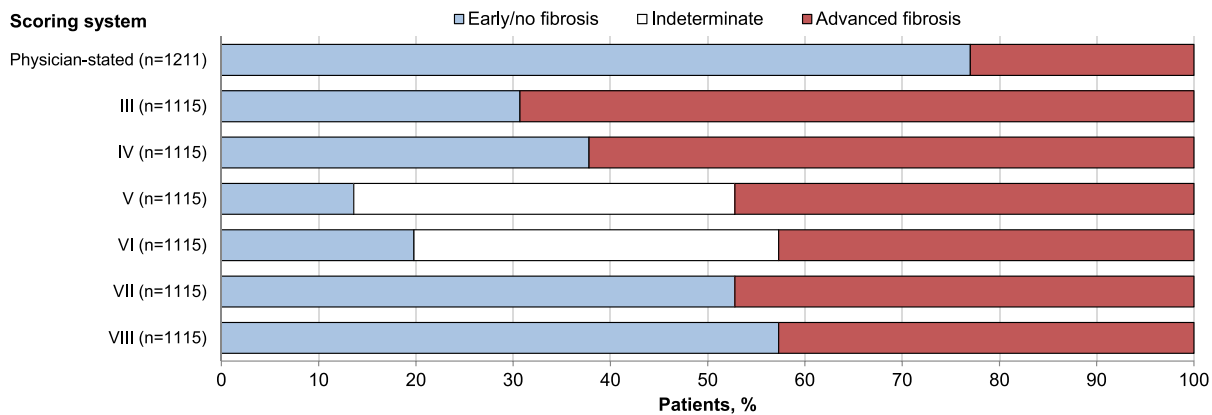
FIB-4 scores were calculated for 524 patients. The mean FIB-4 score was 2.36 (standard deviation [SD] 1.56). Assignment of physician-stated F0–F2 and F3/F4 scores and published FIB-4 thresholds is shown in Figure 2A.

Among the 1115 patients with an up-to-date VCTE scan, the mean liver stiffness was 19.5 kPa (SD 16.0). Assignment of F0–F2 and F4/F4 categorization according to physician assessment and published VCTE thresholds are shown in Figure 2B.

A



B



C

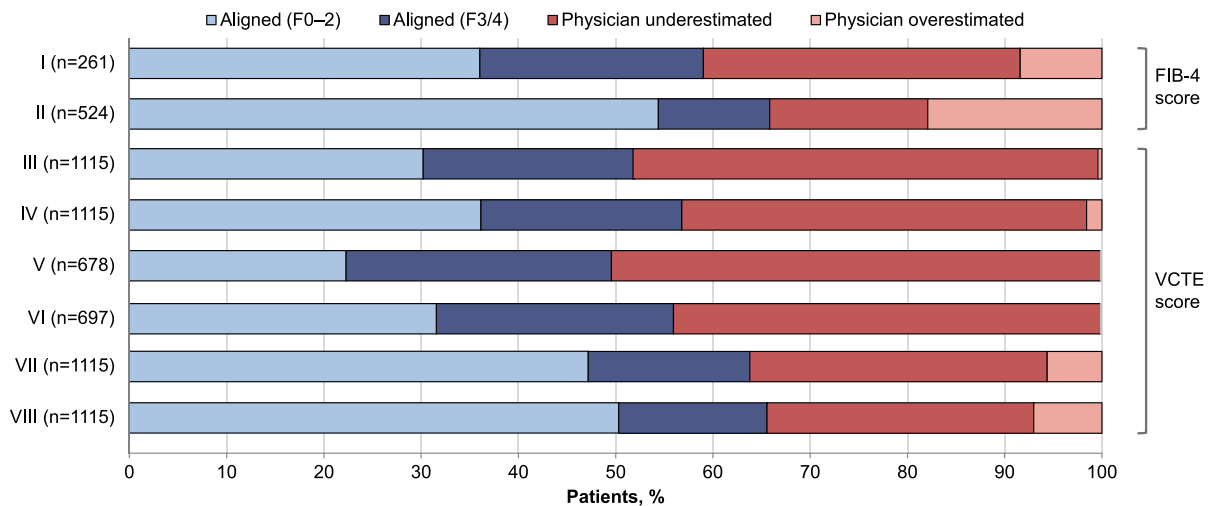


Figure 2 Physician-stated fibrosis score according to published scoring systems. **(A)** Patients with a FIB-4 score and a PSFS; the PSFS is for the 524 patients with a FIB-4 score. **(B)** Patients with a VCTE score and a PSFS; the PSFS is for the 1115 patients with a VCTE score. **(C)** Alignment of PSFS and CRFS scoring according to published scoring systems. Scoring systems as previously published:^{15,18,19} I: Shah (FIB-4 90% Sen<1.3, Spe>2.67); II: Shah (FIB-4 90% Spe>2.67); III: Siddiqui (VCTE Youden 8.6); IV: Eddowes (VCTE Youden 9.7); V: Siddiqui (VCTE 90% Sen<6.5, Spe≥12.1); VI: Eddowes (VCTE 90% Sen<7.1, Spe≥14.1); VII: Siddiqui (VCTE 90% Spe≥12.1); VIII: Eddowes (VCTE 90% Spe≥14.1). All values are kPa. F0–2 indicates no fibrosis/early fibrosis; F3/4 indicates advanced fibrosis or cirrhosis.

Abbreviations: CRFS, clinically defined reference fibrosis score; FIB-4, Fibrosis-4 Index; PSFS, physician-stated fibrosis score; Sen, sensitivity; Spe, specificity; VCTE, vibration-controlled transient elastography.

Alignment of Physician-Stated and Clinically Defined Reference Fibrosis Scores

Alignment of PSFS and FIB-4 scores was greatest using the Shah specificity only threshold (n=345/524; 66%; [Figure 2C](#), scoring system II), although this also resulted in the highest fibrosis overestimation of all eight scoring systems (n=94/524; 18%; [Figure 2C](#)).

Alignment of PSFS and VCTE scores was greatest using Eddowes specificity only (n=731/1115; 66%; scoring system VIII) and lowest for Siddiqui sensitivity/specificity (n=336/678; 50%; scoring system V). Where results were not aligned, underestimation of the patient's fibrosis was more common than overestimation. The extent of underestimation varied between the various derived approaches: this was greatest with the Siddiqui sensitivity/specificity threshold (n=341/678; 50%; scoring system V) and lowest with Eddowes specificity only (n=306/1115; 27%; scoring system VIII).

Alignment According to Treating Physician Specialty

The extent of misalignment of PSFS and available VCTE score according to physician specialty, specifically underestimation by physicians, is shown in [Figure 3A](#) (Siddiqui VCTE specificity ≥ 12.2 threshold) and [Supplemental Figure S1A](#) (all thresholds). Underestimation according to the specificity ≥ 12.2 threshold was 35% (n=73/211) among diabetologists, 32% (n=146/457) among gastroenterologists and 27% (n=122/447) among hepatologists ([Figure 3A](#)). Underestimation was greatest among diabetologists and lowest among hepatologists across almost all thresholds examined ([Supplemental Figure S1A](#)). Conversely, overestimation according to the Siddiqui VCTE specificity ≥ 12.2 threshold was greatest among hepatologists (9% [n=39/447]) versus diabetologists (3% [n=7/211]) and gastroenterologists (4% [n=17/457]). Differences in underestimation rates across physician specialties were statistically significant ($p < 0.05$) for all but two VCTE thresholds ([Supplemental Figure S1A](#)).

A similar pattern was observed when alignment of PSFS and FIB-4 score was analyzed according to physician specialty, with hepatologists generally having a higher rate of overestimation, especially when applying both the sensitivity and specificity ranges ([Supplemental Figure S1A](#)).

Alignment According to Patient Liver Biopsy Status

The extent of misalignment of PSFS and CRFS according to liver biopsy status is shown in [Figure 3A](#) (Siddiqui VCTE specificity ≥ 12.2 threshold) and [Supplemental Figure S1B](#) (all thresholds). Rates of under- and overestimation were higher in patients who had undergone a liver biopsy than those without a biopsy, particularly when VCTE thresholds were considered. To investigate whether this was influenced by physician specialty or a disease effect, we examined alignment rates according to physician specialty and whether patients had undergone liver biopsy. Among diabetologists, underestimation rates were 36% (n=35/96) for patients with a liver biopsy and 33% (n=38/115) for those without, whereas among hepatologists/gastroenterologists, underestimation rates were 32% (n=155/487) for patients with a liver biopsy and 27% (n=113/417) for those without; [Figure 3B](#). Overestimation rates in hepatologists/gastroenterologists were 7% (n=33/487) for patients with a liver biopsy and 6% (n=23/417) for those without, whereas the overestimation rate in diabetologists was 5% (n=5/96) for patients with a liver biopsy and 2% (n=2/115) for those without.

Alignment According to Other Patient Demographic and Clinical Factors

Other confounding factors that could contribute to alignment or misalignment between PSFS and CRFS are shown in [Figure 3A](#). Overestimation of fibrosis severity appeared to be more common in older versus younger patients, and in Asian and Afro-Caribbean patients.

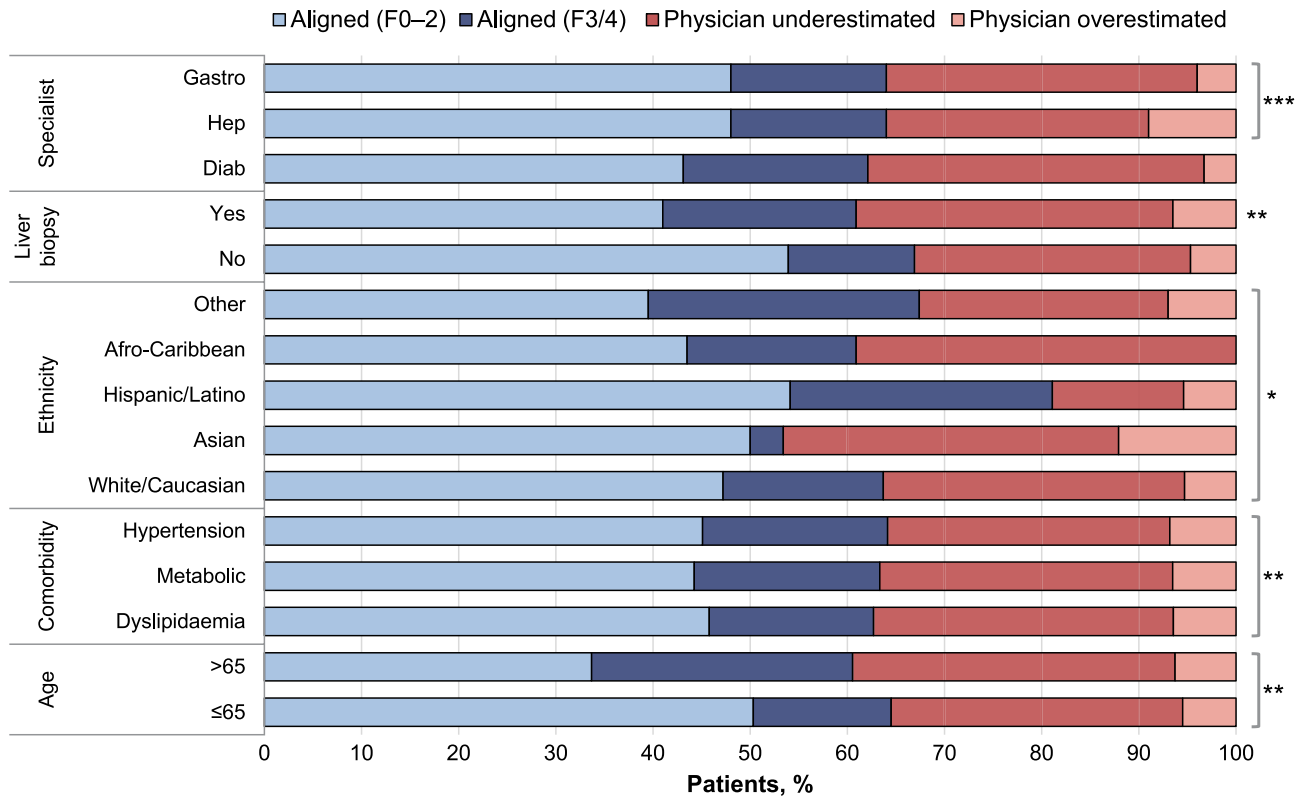
Sensitivity Analyses

Results of the sensitivity analyses are shown in [Figure 4](#). Exclusion of VCTE-unsuitable patients only minimally influenced the degree of misalignment ([Figure 4A](#)). Results did not appear to be sensitive to the timepoint used in most groups ([Figure 4B](#)). Statistically significant differences were seen between patients with a liver biopsy and those with no liver biopsy in two VCTE groups — VII and VIII ([Figure 4C](#)).

Discussion

This comprehensive real-world analysis of alignment between PSFS and two CRFS approaches, FIB-4 and VCTE, applied a range of reference thresholds to identify patients with advanced fibrosis. Our analysis showed that misalignment of PSFS and CRFS was common in the real world, regardless of the threshold retrospectively applied. Physicians

A



B

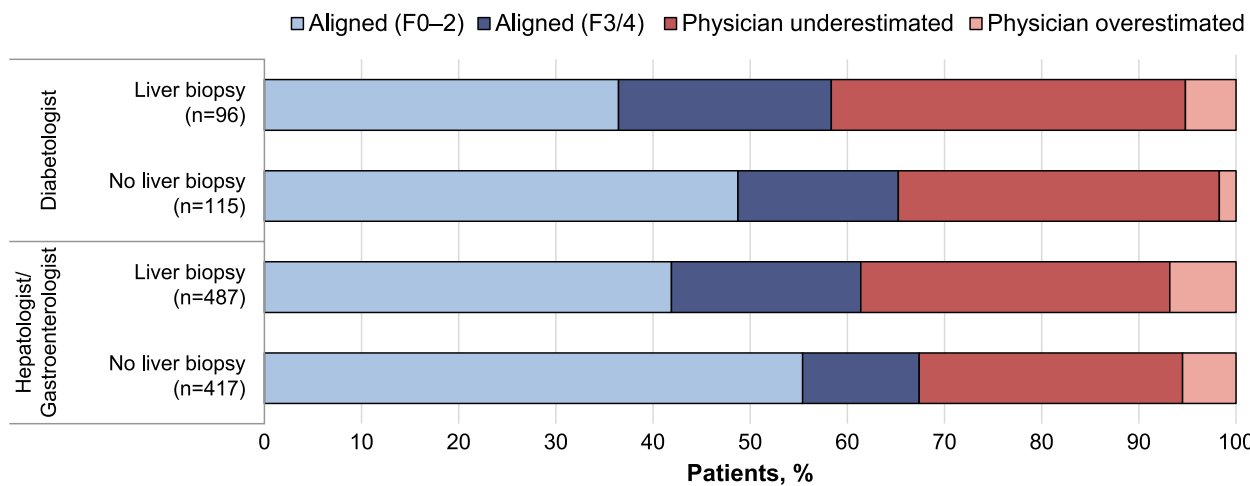


Figure 3 Alignment of PSFS and CRFS scoring according to published scoring systems. All values are kPa. **(A)** Alignment of fibrosis using PSFS versus VCTE scores using the Siddiqui (VCTE specificity ≥ 12.1) threshold according to age, comorbidity, ethnicity, treating physician specialty and whether liver biopsy had been performed (VCTE cohort; n=1115); **(B)** alignment rates according to physician specialty and whether patients had undergone liver biopsy (VCTE cohort; n=1115). F0-2 indicates no fibrosis/early fibrosis; F3/4 indicates advanced fibrosis or cirrhosis. Metabolic indicates presence of any of: metabolic syndrome, T2DM, insulin resistance or hyperglycemia. **(A)** *p < 0.05, **p < 0.01, ***p < 0.0001. **(B)** **p < 0.001 for liver biopsy vs non-invasive testing.
Abbreviations: CRFS, clinically defined reference fibrosis score; Diab, diabetologist; Gastro, gastroenterologist; Hep, hepatologist; PSFS, physician-stated fibrosis score; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

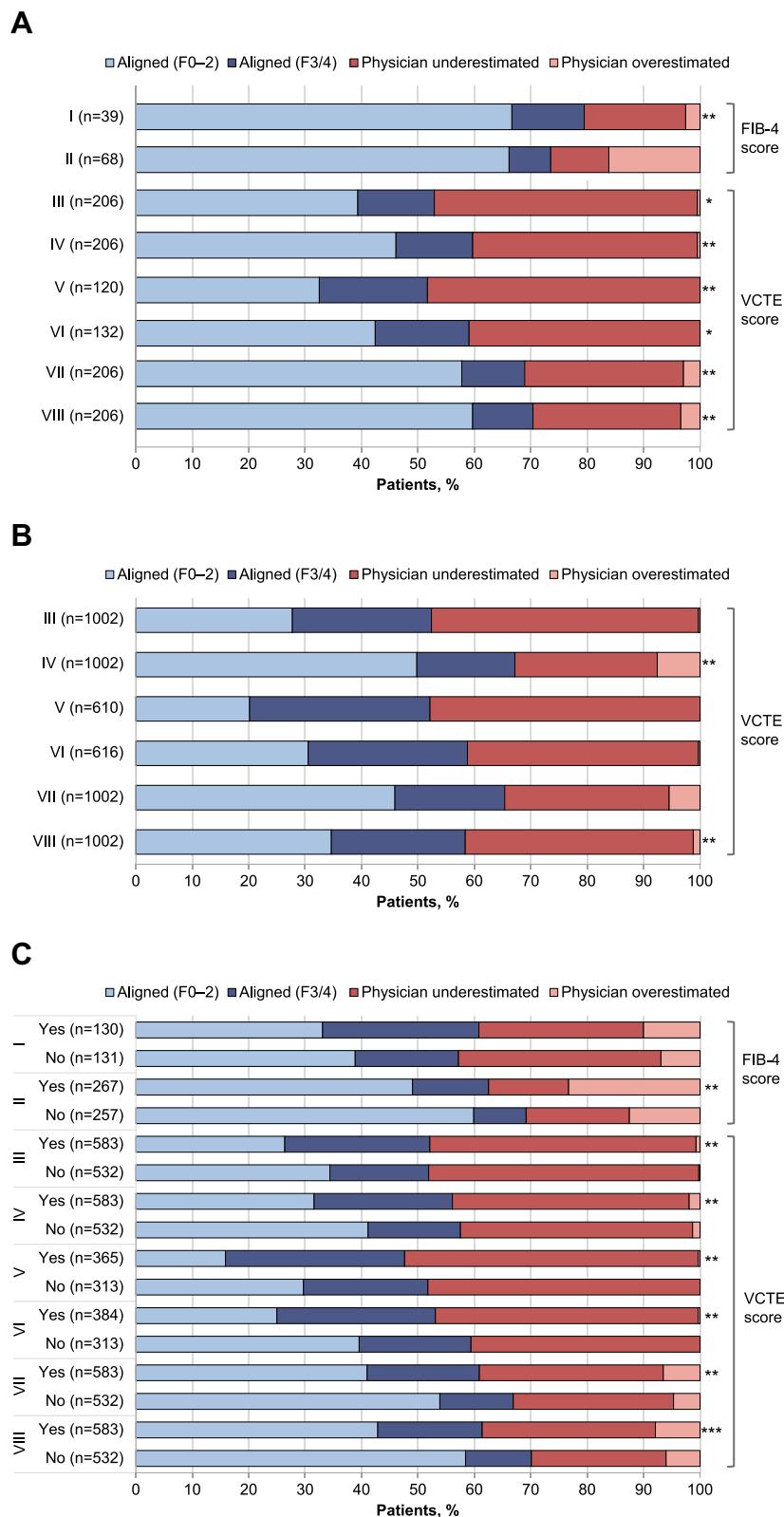


Figure 4 Alignment between PSFS and CRFS: sensitivity analyses. **(A)** VCTE-suitable patients (excludes patients: aged ≥ 65 years; who are morbidly obese [body mass index ≥ 35 kg/m²]; with T2DM; or with physician-reported hypertension) versus VCTE non-suitable patients; **(B)** at-diagnosis VCTE data; and **(C)** liver biopsy versus no liver biopsy. F0-2 indicates no fibrosis/early fibrosis; F3/4 indicates advanced fibrosis or cirrhosis. **(A)** * $p < 0.05$, ** $p < 0.01$ vs VCTE-unsuitable patients. **(B)** ** $p < 0.01$ vs current VCTE data. **(C)** ** $p < 0.01$; *** $p < 0.0001$ for liver biopsy vs no liver biopsy. Scoring systems as previously published.^{15,18,19} All values are kPa.

Abbreviations: CRFS, clinically defined reference fibrosis score; FIB-4, Fibrosis-4 Index; PSFS, physician-stated fibrosis score; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

underestimated disease severity compared with FIB-4 scores in 16–33% of patients depending on the threshold used and in 27–50% of patients when VCTE scores were used as the reference standard. As expected, underestimation was minimized when the highest thresholds with greater specificity but lower sensitivity were used, eg, the Siddiqui and Eddowes specificity thresholds of 12.1 kPa and 14.1 kPa, respectively. This is in line with other studies correlating liver biopsy findings with VCTE scores, where better prediction of significant liver fibrosis occurred at higher thresholds.³² Caballería et al reported that almost two-thirds of patients with a VCTE score of ≥ 9.2 kPa had significant liver fibrosis and 95.8% of patients with scores of < 9.2 kPa had F0 or F1 disease.³² Similarly, Eddowes et al found the highest F4 threshold accuracy at the maximum Youden's Index of 13.6 kPa.¹⁵

Analysis of the extent of fibrosis underestimation among the different physician specialties identified more underestimation among diabetologists than in gastroenterologists or hepatologists. Conversely, hepatologists had higher overestimation rates than diabetologists or gastroenterologists. However, more patients treated by hepatologists had undergone a liver biopsy compared with other physician specialties and hepatologists may have had additional knowledge of test results that accurately staged patients for advanced fibrosis. Therefore, this observation might be influenced by some specialists having additional data to support their assessment of disease severity than indicated by non-invasive markers. Nonetheless, underestimation was considerable in all physician specialties, suggesting that education initiatives providing physicians with additional training in how to select and interpret results of non-invasive biomarkers and risk-stratification tools are important, potentially enhancing delivery of optimal, personalized patient-management approaches.

Other intrinsic patient factors, such as age, comorbidities and ethnicity, affected alignment of PSFS and CRFS. Underestimation was more common in older patients and those with metabolic conditions, in agreement with previous reports.¹⁶ The underlying causes for this are likely multifactorial. Patients with metabolic syndrome are most commonly treated by diabetologists, who had the highest underestimation rates and lowest liver biopsy rates in this study. Obesity — another factor associated with less accurate VCTE measurement — is also more common in metabolic patients. Under- and overestimation of fibrosis severity varied according to ethnicity, with higher rates in Afro-Caribbean and Asian patients. This might relate to a misconception that less overweight patients are unlikely to have advanced disease, particularly relevant to Asian patients who are less likely to have a high BMI at presentation.

Our sensitivity analyses supported the validity of the primary analysis. The extent of alignment of VCTE and PSFS was similar in the overall population and in VCTE-suitable patients (ie excluding patients aged ≥ 65 years and those with BMI ≥ 35 kg/m², T2DM or hypertension, for whom VCTE is known to be less accurate). In contrast, the extent of alignment of FIB-4 and PSFS increased when these VCTE-suboptimal patients were removed from the analysis, hence allowing for (and confirming) more accurate fibrosis assessment. Results appeared to be unaffected by timepoint at which the data were collected and did not vary widely when data obtained at diagnosis or the most recent data were used. In contrast, however, availability of liver biopsy test results resulted in lower alignment rates versus no liver biopsy.

Some potential study limitations and strengths warrant consideration. Identification of patients with NASH was based on the physician's judgment, as no formal definitions or guidelines were provided to physicians; this is likely to be representative of physicians' real-world patient classification. Although patients were selected for this analysis based on availability of FIB-4 and/or VCTE results, some physicians had access to additional testing information for their patient, eg, liver biopsy results. Severity assessment in these cases might have been influenced by liver biopsy interpretation, but we could not assess liver biopsy results for further verification. Nonetheless, the value of non-invasive testing has been demonstrated by others.^{12,33–35} Physicians recorded the most recent test values with no date stamp for the test. Hence, values were assumed to be the current test value. Recall bias, a common limitation of surveys, might have affected physician responses to questionnaires. However, as physicians had access to patient medical records, this is unlikely to have influenced our findings. Finally, although our results are generalizable to the consulting population, the methodology required consecutively consulting patients to be included. Therefore, it is possible that patients who consulted the physician more frequently had a greater chance of inclusion.

Real-world studies such as the present analysis are increasingly being used to generate data that offer a more representative but complementary assessment to randomized controlled studies.^{29,36,37} They are inclusive of populations usually excluded from trials (ie, those who are older or presenting with cardiovascular comorbidities), thus enhancing external validity and generalizability of findings. This analysis provides an insight into diagnostic approaches in clinical practice, where outcomes vary

according to physician specialty, accessibility of tests and patient characteristics. Indeed, even the absence of tests and procedures identified in this analysis, such as the apparently low use of FIB-4 as a triage tool, provides information on how patients are being managed by their health-care providers.

Conclusions

This comparison of PSFS and CRFS for staging NASH-associated fibrosis suggests that physician-estimated fibrosis score does not consistently align with established biomarker reference thresholds, resulting in many patients being assigned an incorrect, often lower, fibrosis stage. Although both over- and underestimation of disease severity are undesirable, underestimation, and failure to identify patients with advanced disease, is potentially the greater concern as it denies patients the opportunity for effective, focused clinical care — be that lifestyle modification or pharmaceutical treatment as drugs become available. This inaccuracy, which could adversely affect testing and referral choices alongside overall patient management, remained the case even when patients with body habitus less well suited to acquiring accurate VCTE data were removed from the analysis. These results highlight the importance of applying risk-stratification tools and assessment with standardized interpretation of findings. Further education might be needed to improve NAFLD patient triage to ensure optimal delivery of individual patient management in clinical care.

Data Sharing Statement

All data relevant to the analysis are included in the article. All data that support the findings of this survey are the intellectual property of Adelphi Real World. The datasets generated during and/or analyzed during the current study are available upon reasonable request to Victoria Higgins at Victoria. Higgins@adelphigroup.com.

Ethics Approval and Informed Consent

Ethics approval was obtained from Freiburg Ethics Commission International (Approval No. 017/1931). All patients provided written informed consent for use of their data, which were anonymized and aggregated.

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Disclosure

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