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AP&T Alimentary Pharmacology and Therapeutics

Von Willebrand Factor as a new marker for non-invasive assessment of liver fibrosis and cirrhosis in patients with chronic hepatitis C

A. Maieron*,†, P. Salzl†, M. Peck-Radosavljevic†, M. Trauner†, S. Hametner*, R. Schöfl*, P. Ferenci† & M. Ferlitsch†

*Division of Gastroenterology and Hepatology, Internal Medicine IV, Elisabeth Hospital Linz, Linz, Austria.
†Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University Vienna, Vienna, Austria.

Correspondence to:
Dr M. Ferlitsch, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria.
E-mail: monika.ferlitsch@meduniwien.ac.at

Publication data
Submitted 14 September 2013
First decision 1 October 2013
Resubmitted 30 October 2013
Accepted 6 November 2013
EV Pub Online 5 December 2013

SUMMARY

Background
Staging of liver fibrosis in patients with chronic hepatitis C (CHC) is recommended prior to anti-viral therapy. As vWF-Ag was shown as a predictor of portal hypertension, decompensation and mortality in patients with liver cirrhosis, we performed this study to investigate if vWF-Ag is able to predict different fibrosis stages and if it is comparable to other fibrosis scores.

Aim
To investigate if vWF-Ag is able to predict different fibrosis stages and if it is comparable to other fibrosis scores.

Methods
We analysed 294 patients with chronic hepatitis C who underwent biopsy. We assessed stage of liver fibrosis according to Metavir, measured vWF-Ag and calculated different fibrosis scores (APRI, FCI, FORNS, FI, Fib-4) and compared them by AUCs. We also calculated a new score: vWF-Ag/thrombocytes (VITRO score) for prediction of fibrosis.

Results
vWF-Ag levels were increasing with stage of fibrosis: F0: vWF-Ag was median 136.5%, FI 140.6%, FII 157.5%, FIII 171.0%, FIV 252.0%; $P < 0.001$. vWF-Ag and VITRO score produced AUCs of 0.7 and 0.72 for ≥F2, comparable to the AUCs of APRI, Fib-4, FORNS with 0.75, 0.65 and 0.64 ($P > 0.05$). For ≥F3 AUCs were 0.79 and 0.86 for vWF-Ag and VITRO score, comparable with AUCs of 0.79, 0.86 and 0.87 for APRI, Fib-4 and FORNS. Cirrhosis shows AUCs of 0.84 and 0.89 for vWF-Ag and VITRO score, APRI, Fib-4 and FORNS showed similar results with AUCs of 0.82, 0.88 and 0.87.

Conclusions
vWF-Ag and VITRO score offer an easy possibility to evaluate the stage of fibrosis to diagnose subclinical cirrhosis in patients with chronic hepatitis C. Both vWF-Ag and VITRO score show equal performance in comparison to other fibrosis scores assessed in our study.

Aliment Pharmacol Ther 2014; **39**: 331–338

doi:10.1111/apt.12564

INTRODUCTION

Hepatitis C is a major health problem; 130–210 million individuals suffer from chronic hepatitis C (CHC)[1, 2] and about 20% will develop liver cirrhosis and hepatocellular carcinoma (HCC) within the next 10–20 years.[3, 4] The currently recommended therapy of chronic hepatitis C is pegylated interferon-alpha (PegINF), ribavirin with or without direct-acting anti-virals (DAA) with response rates up to 79% in treatment-naïve patients.[5, 6] According to EASL guidelines, treatment should be initiated at least in patients with advanced fibrosis (Metavir score ≥F3) and is strongly considered in patients with moderate fibrosis (F2). Thus, assessment of liver fibrosis is needed prior to anti-viral therapy. However, patients' wish might be another important factor. It is crucial to identify patients with cirrhosis, as these patients have the most urgent need for anti-viral therapy, but their treatment response is inferior to patients with milder fibrosis stages[7] and risk for adverse events is higher.[8] Liver biopsy is considered the 'gold standard' for determination of fibrosis stage, but has drawbacks like sample size, sampling error, high cost, inter- and intra-observer variance.[9] Furthermore, it is associated with patient discomfort, although the risk of major complications is low, but also includes mortality (1/4000–1/10000).[10, 11] Up to 40% of patients do not agree to liver biopsy.[12] Therefore, many non-invasive fibrosis tests have been developed. These indirect biomarkers of fibrosis are composed of easy available variables with one or more fibrosis-predicting panels like AST to platelet ratio index (APRI); fibrose index (FI), fibrosis cirrhosis index (FCI), FIB 4 score and Forns Index.[13] They all show adequate diagnostic performance in detection of cirrhosis, with AUROCs between 0.81 and 0.89 and moderate diagnostic performance for advanced fibrosis, with AUROCs between 0.77 and 0.85.[13–15]

Transient Elastography (TE) has also the ability to assess fibrosis. TE detects cirrhosis (AUROC 0.87–0.98) more adequately than significant fibrosis (AUROC 0.75–0.93).[13]

Van Willebrand factor (vWF) is a large important adhesive protein for both platelet adhesion and aggregation. Estimation of vWF-Ag is a well-established method with small inter-laboratory variability.[16] vWF is mediated by two platelet membrane receptors, glycoprotein (Gp) 1b and Gp IIb/IIIa, in a co-ordinated and synergistic manner.[17, 18] For adhesion of vWF to Gp 1b, large vWF-multimers are needed. Adhesion of platelets results in activation of Gp IIa/IIIb and release of platelet-activating mediators, such as adenosine diphosphate and thromboxane A2, finally leading to the development of a platelet plug.[17, 19] vWF-Ag is released by activated endothelial cells and therefore represents an indicator of endothelial cell activation[20] and plays a crucial role in high shear stress depending on primary haemostasis. The endothelium plays a crucial role in many vascular diseases and endothelial dysfunction is a fundamental component of the increased hepatic vascular tone of cirrhotic livers.[21, 22] Activation of thrombocytes and endothelium finally leads to platelet aggregation and, probably, to microthrombotic events. Those events lead to increased portal pressure and furthermore might lead to worsening of fibrosis. As vWF-Ag is elevated in liver disease it might be a key player in establishing liver fibrosis.[18, 23] vWF-Ag was established as a valuable marker for prediction of varices, portal hypertension and mortality in patients with liver cirrhosis.[17, 24] None of the mentioned fibrosis scores shows a relationship with complications of liver disease, such as decompensation, portal hypertension and mortality.[17, 25] However, this additional information might be crucial for assessing patients' risk during interferon-based anti-viral therapy.[26] Although such markers of fibrosis are good, they are not perfect, establishing new markers of fibrosis is still necessary.

vWF-Ag increases with every Child–Pugh stage.[27] Furthermore, vWF-Ag predicts response to anti-viral therapy.[28]

As vWF-Ag is a valuable non-invasive marker in patients with liver cirrhosis, we performed this study to:

(i) Explore whether vWF-Ag is able to predict fibrosis stage in patients with CHC

(ii) Compare the value of vWF-Ag with other fibrosis scores like APRI, FCI, FI, FIB-4 and FORNS.

PATIENTS AND METHODS

We analysed and reviewed the data of patients with PCR and histologically documented CHC retrospectively. Patients admitted to the Divisions of Gastroenterology at the Medical University of Vienna and Elisabethinen Hospital Linz (academic teaching hospital) were included. All patients who were enrolled at Medical University of Vienna and Elisabethinen Hospital Linz in two prospective trials were analysed.[29, 30] The studies were approved by the local ethics committee (Meduniwien, Vienna, Austria; ML 17131, M 78023) in accordance with the Declaration of Helsinki. Written informed consent was obtained from every study participant.

Two hundred and ninety-four patients with the following criteria were included in this study: (i) HCV antibodies and HCV RNA positivity, (ii) liver biopsy to assess severity of liver damage, (iii) availability of laboratory test results allowing the calculation of APRI, FCI, FI, FIB-4 and FORNS. Patients with severe cardiopulmonary and/or renal failure, active infections, diabetes mellitus ($HbA1_c$ >7.5%), with HIV and/or HBV coinfections, HCC, age >75 and liver transplantation were excluded.

Liver biopsy was taken via Menghini technique.[31] All liver tissues samples were evaluated by board-certified pathologists unaware of the patient`s clinical history. All biopsies had a minimal length of 25 mm. The degree of fibrosis was scored according to the METAVIR system.[32] No fibrosis was defined as F0, mild fibrosis as F1, moderate fibrosis as F2, severe fibrosis as F3 and cirrhosis as F4. Significant fibrosis was defined according to EASL criteria to F2–F4 and advanced fibrosis was defined ≥F3.

Laboratory parameters including AST, ALT, γGT, platelets, ALP, bilirubin, albumin, cholesterol were taken routinely prior to liver biopsy. Age of the patient was set at the time of liver biopsy. Non-invasive fibrosis scores were calculated according to the following formulae, as represented in Table 1:

Plasma levels of vWF-Ag were measured as described before:[33] using a fully automated STA analyser and vWF-LIA Test (Diagnostic Stargo, Paris, France).

We also calculated a new score dividing vWF-Ag by Platelets (vwF-Ag/PLT). We compared APRI, FCI, FI, FIB-4, FORNS, vWF-Ag and vWF-Ag/Plt among the groups: no/nonsignificant fibrosis (F0/F1), significant fibrosis (≥ F2), advanced fibrosis (≥F3) and cirrhosis (= F4).

Statistical analysis

Statistical analyses were performed using SPSS 19.0. Descriptive statistics are provided as median and IQR or percentage. Differences of fibrosis scores among different fibrosis stages were assessed by Mann–Whitney *U*-test. Receiver operating characteristic curves were created for the assessment of the predictive fibrosis scores for stages of fibrosis. Area under the curve (AUC), sensitivity, specificity, positive (PPV) and negative (NPV) predictive value were calculated. The value with the best sensitivity and specificity in AUC analysis (Youden Index) was chosen as best cut-off. AUCs were compared using the Hanley McNeil approach. All *P*-values reported are two-sided and *P*-values <0.05 are considered significant.

Table 1 | Calculation of different fibrosis scores

Fibrosis Scores	Calculation
FCI[14]	(ALP × Bili)/(Alb × platelet)
FI[15]	8-0.01 × platelet(10^3/μL)−Alb(g/dL)
FIB-4[43]	[age(years) × GOT(U/L)]/[platelet(10^9/L) × GPT(U/L)^{½}]
FORNS[36]	7.811−3.131 × ln platelet + 0.781 × ln GGT + 3.647 × ln age−0.014 × cholesterol
APRI[44]	(AST/upper limit of normal)/platelet(10^9/L) × 100
VITRO score	vWF-Ag/plt

RESULTS

Patients' characteristics

Two hundred and ninety-four patients with chronic hepatitis C (193 male, 101 female, median age 49 years, IQR 42–56) were included. Twelve patients (4.08%) were histologically classified as fibrosis stage 0 (F0), 31 (10.54%) as fibrosis stage I (F1), 138 (46.94%) as fibrosis stage II (F2), 24 (8.16%) as fibrosis stage III (F3) and 89 (30.27%) as fibrosis stage IV (F4). All cirrhotic patients were classified as Child–Pugh A. The patients' characteristics are summarised in Table 2.

vWF-Ag as predictor for fibrosis:

Median VWF-Ag level in all patients populations' was 219% (IQR 115.0–218.0). vWF-Ag levels were increasing

Table 2 | Patients' characteristics

Characteristics		IQR
Demographic data		
Age (years)	49	42–56
Male gender	193 (65.6%)	
Laboratory data		
vWF-Ag%	219	115–218
Serum albumin (mg/dL)	4.35	4.07–4.58
Total bilirubin (mg/dL)	0.7	0.53–0.92
Aspartate aminotransferase (IU/L)	48	33–81
Alanine aminotransferase (IU/L)	69	42–115
GGT (IU/L)	58	30–114
Platelet count (10^9/L)	216	176–261
Prothrombin time (%)	94	83-105
Fibrosis stage, *n* (%)		
F0	12 (4.08)	
F1	31 (10.54)	
F2	138 (46.94)	
F3	24 (8.16)	
F4	89 (27.30)	

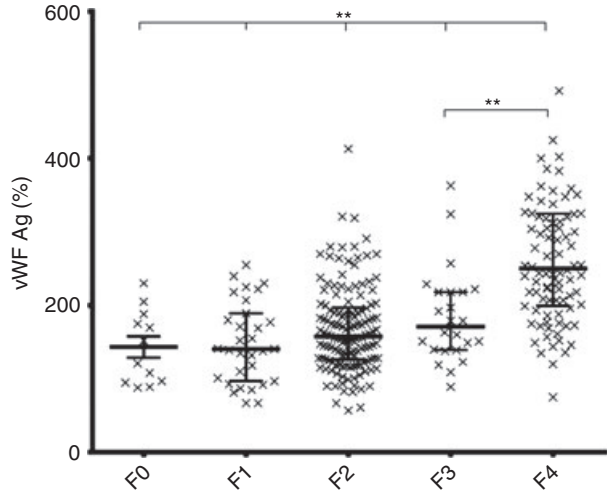

Figure 1 | Dotplots for vWF-Ag according to fibrosis stage showing mean values and IQRs. $P < 0.001$ for all fibrosis stages, F3 vs. F4 $P < 0.0001$.

with stage of fibrosis: in patients with fibrosis stage 0, vWF-Ag was median 136.5% (IQR 96.0–181.5); in fibrosis stage I, 140.6% (IQR 97.0–189.0); in fibrosis stage II, 157.5% (IQR 127.0–196.0); in fibrosis stage III, 171.0% (IQR 139.5–218.0) and in fibrosis stage IV, 252.0% (IQR 201.0–325.0); $P < 0.001$. Figure 1 shows vWF-Ag levels throughout different fibrosis stages.

The diagnostic performance of vWF-Ag predicting liver fibrosis was analysed by AUROC. AUROC for significant fibrosis (≥F2) was 0.7 (95% CI 0.616–0.778), for advanced fibrosis (≥F3) 0.79 (95% CI 0.734 – 0.842) and for cirrhosis 0.84 (95% CI 0.784–0.885).

The most discriminant cut-off value to rule out cirrhosis was vWF-Ag <192% with a sensitivity of 78.7%, a specificity of 73.7%, PPV of 56.5% and a NPV of 93.2%.

A new, non-invasive score: von Willebrand factor-Ag/thrombocytes – VITRO score

To increase the diagnostic performance of vWF-Ag, we divided vWF-Ag by thrombocytes.

The mean values for the VITRO score increased constantly with the fibrosis stage (F0 = 0.58; F1 = 0.67; F2 = 0.71; F3 = 0.95; F4 = 1.62 all $P < 0.05$). This is shown in Figure 2.

Diagnostic performances of vWF-Ag and VITRO score in *comparison to APRI, FCI, FI, FIB-4 and FORNS:*

Table 3 shows the median values of different fibrosis scores (vWF – Ag, FCI, FI, FIB-4, FORNS, APRI, VITRO score) according to fibrosis stages (0–IV) as well as for significant fibrosis (≥F2) and advanced fibrosis (≥F3).

The diagnostic performance of vWF-Ag predicting liver fibrosis in comparison to other fibrosis scores was analysed by AUROC: with 0.703, vWF-Ag is one of the best markers to differentiate patients with fibrosis (F1-F4) from patients without fibrosis (F0). None of the existing fibrosis scores is good in distinguishing mild or no fibrosis (F0, F1) from significant fibrosis (≥F2); vWF-Ag shows an AUROC of 0.7 (IQR 0.592–0.781). In our sample, APRI score performed best with an AUROC of 0.752 (IQR 0.679–0.826) to distinguish between ≤F1 and ≥F2. The diagnostic performance of vWF-Ag in comparison to other fibrosis scores to differentiate from significant fibrosis (≥F2) is comparable to all the other scores. APRI score is performing best in our group, with an AUROC of 0.75 (IQR: 0.681–0.813); however, not significantly better than vWF-Ag with an AUROC of 0.7 (IQR 0.616–0.778) ($P = 0.2$) or VITRO score with an AUROC of 0.72 (IQR: 0.647–0.79) ($P = 0.3$), which are performing as third and second best.

For advanced fibrosis (≥F3), FORNS and VITRO score were performing best, with an AUROC 0.87 (IQR: 0.826–0.911) and 0.86 (IQR 0.813–0.903; $P = 0.4$) respectively; vWF-Ag shows an AUROC of 0.79 (IQR: 0.734–0.842; $P > 0.05$).

Each fibrosis score, including vWF-Ag, is able to distinguish between cirrhosis (F4) and no cirrhosis (≤F3). In our cohort, VITRO score had the best performance analysed by AUROC 0.89 (IQR: 0.853–0.933). Fib-4 and FORNS were also performing well in detecting cirrhosis,

Table 3 | Median values of different fibrosis scores according to fibrosis stages

Median	F0	F1	F2	F3	≥F2	≥F3	F4
APRI	0.47	0.44	0.64	0.86	0.533	0.763	1.82
FCI	0.04	0.05	0.04	0.07	0.059	0.054	1.12
FI	1.49	1.31	1.3	1.67	1.33	1.26	2.4
FIB-4	1.28	1.09	1.06	1.59	1.183	1.181	3.08
FORNS	4.52	4.47	4.42	6.17	4.746	4.532	7.4
vWF-Ag (%)	136.5	140.6	157.5	171	147.3	163.1	252
vWF/plt	0.58	0.67	0.71	0.95	0.67	0.76	1.62

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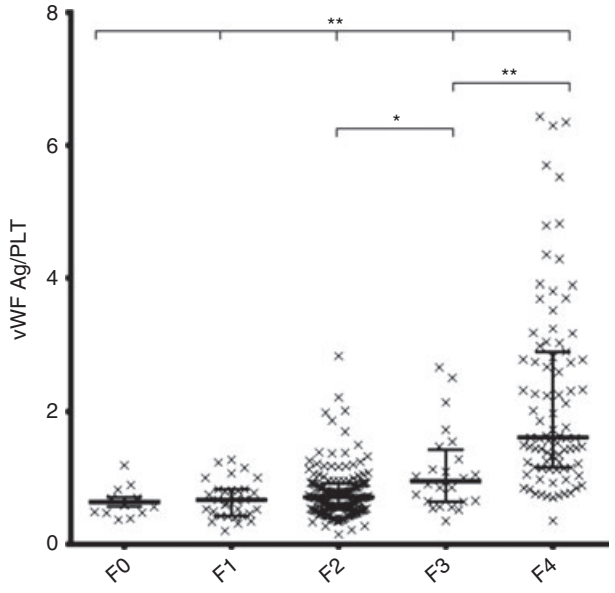

Figure 2 | Dotplots for VITRO score according to fibrosis stage showing mean values and IQRs. $P < 0.05$ for all fibrosis stages, F2 vs. F3 $P < 0.05$, F3 vs. F4 $P < 0.0001$.

with AUROCs of 0.88 (IQR: 0.842–0.932) and 0.87 (IQR: 0.833–0.916) respectively. AUROCs for all the calculated fibrosis scores throughout the different groups of fibrosis are shown in Table 4.

The results of the different AUROCs for vWF-Ag, VITRO score and the best performing score in each fibrosis group are shown in Figure 3 (a–d).

Cut-off values for detecting advanced fibrosis and cirrhosis for vWF-Ag/Plt (VITRO) were calculated as follows:

The cut-off for significant Fibrosis (≥ F3) was 0.97 with sensitivity of 0.77, specificity of 0.81, a PPV of 0.72 and a NNP of 0.86.

For cirrhosis, we identified a cut-off of 1 with sensitivity 0.83, a specificity of 0.79, a PPV of 62.5 and a NNP of 91.5. With VITRO score, we correctly diagnosed 79.9% of the cases with advanced fibrosis and 79.9% of the cases with cirrhosis.

DISCUSSION

This study clearly demonstrates the diagnostic value of vWF-Ag as a novel non-invasive biomarker in the assessment of liver fibrosis. We were able to show vWF-Ag as predictor of advanced fibrosis (F3) and cirrhosis (F4) in patients with CHC with a NPV of 91.5%. The AUROC of vWF-Ag is 0.79 for advanced fibrosis and 0.84 for detecting cirrhosis. It is remarkable that a single, simple-to-obtain, cheap laboratory parameter shows comparable AUROCs compared with the other established fibrosis scores. Even in diagnosing significant fibrosis, vWf-Ag shows comparable results with the other fibrosis markers.

If vWF-Ag is divided by platelet counts, the diagnostic accuracy increases to an AUROC of 0.86 for advanced fibrosis and 0.89 for cirrhosis respectively. These values are within the best in our cohort, and VITRO score was performing best to identify cirrhosis and allows discriminating between cirrhosis and noncirrhosis, with a simple cut-off value of 1.

Throughout the literature, most fibrosis scores show poor performance in detecting mild fibrosis stages. vWF-Ag and VITRO score show comparable results, but no significant improvement in detection of mild fibrosis stages.[13–15, 34–36] As transient elastography shows a lack of accuracy in distinguishing among F1, F2 and F3, evaluating the precise stage of fibrosis still remains the domain of liver biopsy.[37] vWF-Ag and VITRO score gain diagnostic accuracy in detecting significant fibrosis and cirrhosis.

The introduction of vWF-Ag and VITRO score facilitates assessing liver disease by verifying whether vWF-Ag levels are higher than thrombocytes counts.

A vWF-Ag less than the platelet count excludes cirrhosis with 91.5% certainty, in our study.

Table 4 | AUROCs for different fibrosis scores throughout the different groups of fibrosis

	AUROC (95% confidence interval)			
SCORES	F0 vs. F1234	F01 vs. F234	F012 vs. F34	F4 vs. F0123
APRI	0.704 (0.585–0.823)	0.747 (0.681–0.813)	0.791 (0.736–0.847)	0.821 (0.766–0.876)
FCI	0.739 (0.601–0.876)	0.662 (0.573–0.75)	0.84 (0.792–0.887)	0.864 (0.82–0.909)
FI	0.569 (0.438–0.701)	0.623 (0.544–0.702)	0.843 (0.797–0.89)	0.874 (0.831–0.917)
FIB-4	0.551 (0.435–0.666)	0.648 (0.575–0.721)	0.863 (0.818–0.909)	0.887 (0.842–0.932)
FORNS	0.623 (0.499–0.747)	0.634 (0.559–0.71)	0.869 (0.826–0.911)	0.874 (0.833–0.916)
vWF-Ag (%)	0.703 (0.565–0.841)	0.697 (0.616–0.778)	0.788 (0.734–0.842)	0.835 (0.784–0.885)
vWF/plt	0.728 (0.613–841)	0.718 (0.647–0.790)	0.858 (0.813–0.903)	0.893 (0.853–0.933)

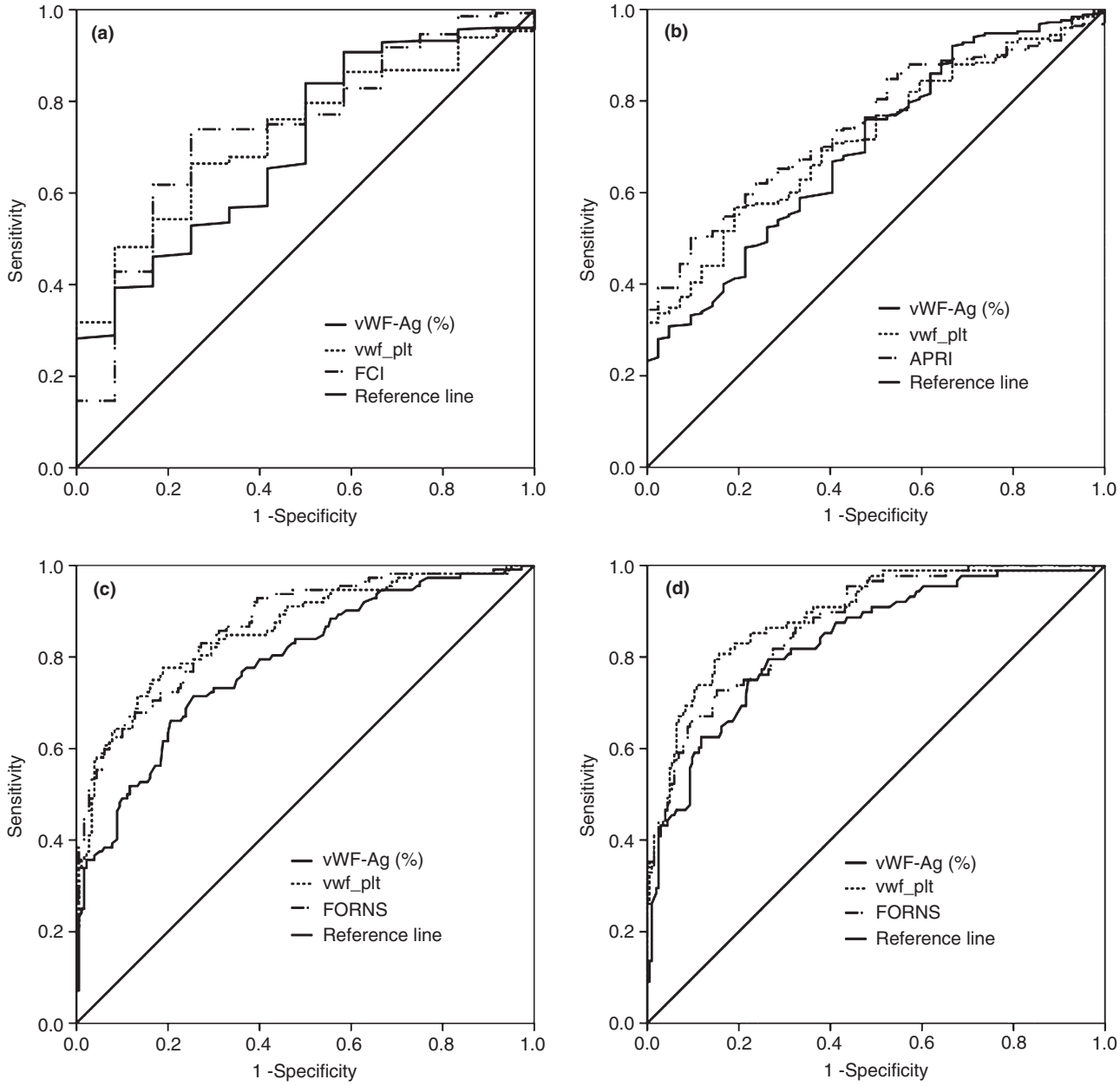

Figure 3 | The results of the different AUROCs for vWF-Ag, VITRO score and the best performing score in each fibrosis group are shown in A–D. (a) Receiver operating characteristics (ROC) curves for vWF-Ag, VITRO score and FCI in the diagnosis of mild fibrosis (≥F1): AUC vWF-Ag = 0.703, VITRO score = 0.728 and FCI = 0.739 ($P > 0.05$). (b) Receiver operating characteristics (ROC) curves for vWF-Ag, VITRO score and APRI in the diagnosis of significant fibrosis (≥F2): AUC vWF-Ag = 0.697, VITRO score = 0.718 and APRI = 0.747 ($P > 0.05$). (c) Receiver operating characteristics (ROC) curves for vWF-Ag, VITRO score and FORNS in the diagnosis of advanced fibrosis (≥F3): AUC vWF-Ag = 0.788, VITRO score = 0.858 and FORNS = 0.869 ($P > 0.05$). (d) Receiver operating characteristics (ROC) curves for vWF-Ag, VITRO score and FORNS in the diagnosis of cirrhosis (F4): AUC vWF-Ag = 0.835, VITRO score = 0.893 and FORNS = 0.874 ($P > 0.05$).

Assessing coagulopathy in patients with liver disease is essential and part of the daily routine. vWF-Ag can be assessed from the same blood samples. As mentioned before, vWF-Ag provides crucial additional information and therefore slightly increased costs might be justified.

Liver biopsy is commonly used as reference method for assessing liver fibrosis. However, it is an invasive pro-

cedure with associated morbidity and carries significant costs,[38] and has limitations such as sampling variability depending on the biopsy's length in up to 30% of patients [39] as well as inter- and intra-observer variability. For larger biopsies, these values were, respectively, 0.95 and 0.99 for detecting significant fibrosis and cirrhosis.[13, 40]

Transient elastography can also be used to assess fibrosis; however, it is usually only available in specialised centres and therefore cannot be used in assessing liver fibrosis on a large scale. The AUROCs for transient elastography are up to 0.91 for severe fibrosis and 0.97 for cirrhosis. Another limitation for using transient elastography seems the applicability with 80%. In up to 20% transient elastographies, measurement failed, mainly because of obesity.[13]

It has been recently shown that there are discrepancies among the histological staging, APRI score and transient elastography. It seemed that transient elastography was performing best in that study and that transient elastography could identify additional cases of cirrhosis.[41] Due to the increased costs, non-invasive tests like ELF test, Hepascore and Fibrometer are not widely used, although they show adequate performance, with AUROC of up to 0.9 for the detection of cirrhosis.[14] It has been lately shown that these costly tests do not perform better than APRI score in predicting significant fibrosis in CHC patients.[13, 42]

Limitation of the study

One clear limitation of this study is that we do not have transient elastography data. However, when transient elastography is not available, a cheap and simple tool in evaluating liver fibrosis is needed.

vWF-Ag and VITRO score provide robust data, in particular, for distinguishing cirrhosis from other fibrosis stages with a simple, and widely available, laboratory test.

The combination of vWF-Ag and VITRO score in combination with TE could further increase the diagnostic accuracy, especially in differentiating mild from moderate or advanced stages of fibrosis. Therefore, future prospective studies should be performed to reach a higher diagnostic accuracy. vWF-Ag and VITRO score should also be evaluated in different populations to diminish the need of liver biopsy.

In conclusion, vWF-Ag and VITRO score offer an easy possibility to evaluate stage of fibrosis and to diagnose subclinical cirrhosis in hepatitis C patients in our clinical routine work. Both vWF-Ag and VITRO score show equal performance in comparison to the other fibrosis scores assessed in our study.

AUTHORSHIP

Guarantor of the article: Monika Ferlitsch.

Author contributions: M.F. designed the study. A.M., P.S., S.H. collected the data. A.M., P.S., S.H., M.F. analysed and interpreted the data. A.M., S.H. wrote the manuscript. M.PR., M.T., R.S., P.F. carried out a critical revision of the paper and gave important intellectual input. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENT

Declaration of personal interests: Peter Ferenci is a member of the global advisory board and of the speaker's bureau of Roche, Basel, Switzerland, and of Rottapharm-Madaus, Monza, Italy. He is also advisor to Boehringer Ingelheim, Vertex/Tibotec, Gilead, Novartis, GSK and MSD. He has also received an unrestricted research grant from Roche Austria. Michael Trauner serve as speakers for Roche Austria and MSD Austria. Andreas Maieron serve as speakers for Roche Austria and MSD Austria, Boehringer Ingelheim, Gilead and BMS.

Declaration of funding interests: None.

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