

Article

Blood-Based Non-Invasive Tests of Hepatic Fibrosis in Autoimmune Hepatitis: Application among Selected Patients Leads to Higher Accuracy

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Abstract: Background. Assessment of liver fibrosis is essential to guide treatment in autoimmune hepatitis (AIH), but non-invasive tests (NITs) showed poor accuracy. Our study aims to evaluate the performance of NITs among different AIH presentations. Methods. Monocentric retrospective study among 122 AIH patients. NITs were compared to histological grading of liver fibrosis. We performed an accuracy analysis among acute (jaundice and/or transaminases > 10 times upper limit of normal) and non-acute patients. Results. A significant difference in the distribution of NIT values for each Ishak stage was found for spleen-diameter-to-platelet-count ratio (SD/PC) ($p < 0.001$), fibrosis-4-score (FIB-4) ($p = 0.002$), AST-to-ALT ratio (AAR) ($p = 0.002$), red-blood-cell-width-distribution-to-platelet-count ratio (RDW/PC) ($p = 0.008$) and AST-to-platelet-count ratio (APRI) ($p = 0.029$). The AUC for advanced fibrosis of SD/PC, FIB-4, RDW/PC, APRI and AAR were, respectively, 0.814, 0.770, 0.768, 0.708 and 0.694. The AUC of SD/PC, FIB-4 and APRI in non-acute subgroup were 0.902, 0.834 and 0.758, while in acute patients they were 0.754, 0.724 and 0.716. RDW/PC and AAR weren't different among the two subgroups. Conclusions. For SD/PC, FIB-4 and APRI, diagnostic accuracy is higher in patients with non-acute presentation. In this context, SD/PC and FIB-4 showed an overall performance that could be of interest in clinical practice alongside other non-invasive techniques.

Keywords: autoimmune hepatitis; fibrosis; non-invasive test; FIB-4; spleen diameter; platelet count



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1. Introduction

Autoimmune hepatitis (AIH) is defined as an immune-mediated inflammation of the liver, characterized by the presence of hypergammaglobulinemia, autoantibodies and interface hepatitis on biopsy [1]. AIH has a wide spectrum of clinical manifestations, ranging from asymptomatic forms and forms with non-hepatospecific symptoms, to forms of acute hepatitis (occasionally leading to liver failure) and presentations with symptoms of advanced liver disease or portal hypertension [2].

Assessment of liver fibrosis stage is essential to determine prognosis, guide treatment strategies, evaluate their effectiveness, and to suggest the need for regular screening for complications of cirrhosis [1]. Liver biopsy is considered the gold standard for the evaluation of liver fibrosis stage, but it is limited by sampling variability and its intrusiveness, with a reported risk of death of 0.2% and of severe bleeding of 0.6% [3]. Moreover, it has high costs, and it is unacceptable to patients to undergo periodic biopsies to monitor liver fibrosis stage [4]. Liver stiffness measurement with vibration controlled or shear wave-based elastography methods is widely accepted as the most accurate non-invasive method for detection of fibrosis in AIH [5,6], but it still has a relatively high cost and 5–10% failure rate [4], and it seems to be affected by inflammation activity of acute forms of AIH [5,7].

Several non-invasive tests, including laboratory and radiological tests, have been proposed, but unlike studies in chronic viral hepatitis or NAFLD, they showed contrasting data about their diagnostic accuracy among AIH patients. Moreover, at the day there are no studies taking into account the different performances of these tests in acute and non-acute AIH clinical subsets.

2. Materials and Methods

This is a retrospective study among 122 AIH patients at the time of diagnosis, from the Center of Autoimmune Diseases of the Liver and Biliary System, Policlinico di Sant'Orsola, University of Bologna. AIH diagnosis was defined in accordance with guidelines of the International Autoimmune Hepatitis Group. Patients with primary biliary cholangitis, primary sclerosing cholangitis, overlap syndromes or other forms of liver disease were excluded. Patients with inadequate liver biopsy were also excluded. Demographic and clinical data, blood chemistry, abdominal ultrasound and histological data were collected after reviewing the outpatient records.

Clinically, the presentation of AIH was arbitrarily defined as “acute” when there was evidence of acute hepatitis with jaundice and, under the laboratory profile, when transaminases 10 times the normal limit and/or a value of total bilirubin greater than 5 mg/dl were found. The presentation was defined as “non-acute” when non-specific symptoms were present (such as asthenia, weight loss, amenorrhea, fever, nausea, loss of appetite) or in case of asymptomatic presentation, without “acute” laboratory features.

Biochemical and hematological parameters collected included white blood cells (WBC), neutrophils, lymphocytes, red blood cells (RBC), hemoglobin (Hb), mean corpuscular volume (MCV), red blood cell volume distribution width (RDW), platelet count (PC), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and their respective increase from the upper limit of norm (ULN), alkaline phosphatase, gamma-glutamyltransferase and albumin. From abdominal ultrasound reports we collected spleen diameter (SD). All patients underwent liver biopsy, and the samples obtained were analyzed by expert pathologists of the Polyclinic. Liver fibrosis stage was assessed according to Ishak. Advanced fibrosis (AF) was defined as Ishak stage equal or greater than 4. Since there was only one patient with Ishak = 6, he was grouped to Ishak 5.

All the evaluations (abdominal ultrasound, laboratory analyses) were performed on average 23 days before the liver biopsy; all patients were treatment-naive at the time of the investigations. Non-invasive tests (NIT) calculated are fibrosis 4 score (FIB-4), AST to PC ratio (APRI), AST to ALT ratio (AAR), RDW to PC (RDW/PC), SD to PC ratio (SD/PC).

Data are presented as medians with interquartile ranges (IQRs) and n (%) unless otherwise stated. Comparisons between two groups were made using Mann–Whitney U-test and chi-square test as appropriate. The correlation between NIT values and fibrosis stages was estimated using ANOVA Kruskal–Wallis test. Diagnostic value of each NIT was assessed by the area under the receiver operating characteristic curve (AUC). Comparison AUCs and 95% confidence intervals (CIs) were performed using the nonparametric Delong test. A value of $p < 0.05$ was considered significant. Youden's index was used to identify the optimum cut-off point of the AUCs. Positive and negative predictive values (PPV and NPV) and likelihood ratios (LRs) for the appropriate cut-offs were calculated. Data were analyzed using JASP statistics software version 0.11.1.0 and easyROC, a web-tool for ROC curve analysis (ver. 1.3.1). Diagnostic performance is considered acceptable for AUC greater than 0.7 [8] and of value in clinical practice for AUC greater than 0.8 [9].

3. Results

Mean age was 49 years (33.25–58.00) and female sex accounted for 73.70% of patients involved. Histological Ishak stage was 1 in 27, 2 in 41, 3 in 27, 4 in 17 and 5 in 10 patients. Advanced fibrosis (Ishak stage ≥ 4) was observed in 27 patients (22.1%). 63 patients (51.63%) presented with an acute form of hepatitis. Comparison between laboratory features and NITs among absent/minimal fibrosis and advanced fibrosis groups is presented in Table 1.

Table 1. Comparison of collected data and derived non-invasive tests of fibrosis among Ishak 0–3 and Ishak ≥ 4 patients.

	Missing	Ishak 0–3 (n = 95)	Ishak ≥ 4 (n = 27)	p-Value
Age	0	47.0 (31.0–57.5)	57.0 (42.0–60.5)	0.099
WBC	16	5.90 (5.05–7.60)	5.46 (4.37–6.78)	0.127
Neutrophil	20	3.14 (2.59–4.05)	2.63 (2.05–3.82)	0.095
Lymphocyte	20	1.95 (1.50–2.54)	2.05 (1.49–2.39)	0.684
RBC	18	4.60 (4.23–4.87)	4.50 (4.24–4.87)	0.846
Hb	16	13.40 (12.60–14.50)	12.90 (12.10–14.20)	0.279
MCV	21	89.00 (84.78–91.83)	88.10 (85.80–91.00)	0.962
PC	17	245.50 (187.00–290.00)	177.00 (130.00–222.00)	<0.001
RDW	40	13.90 (13.40–15.00)	14.10 (13.90–16.75)	0.027
MPV	46	9.20 (8.20–11.00)	9.60 (8.85–10.70)	0.579
AST	2	254.00 (95.00–739.00)	488.00 (279.00–982.50)	0.044
AST/ULN	2	7.00 (2.70–20.10)	13.00 (7.50–23.70)	0.077
ALT	2	434.00 (124.00–962.00)	650.00 (317.50–986.00)	0.341
ALT/ULN	2	11.22 (3.00–27.00)	14.00 (8.15–23.90)	0.704
GGT	9	79.50 (29.75–137.00)	151.00 (68.00–190.00)	0.014
ALP	14	132.50 (81.25–219.25)	172.00 (127.25–238.25)	0.165
Albumin	14	40.00 (36.85–42.00)	36.00 (34.53–39.00)	0.003
SD	21	11.00 (10.00–12.50)	13.80 (12.70–14.53)	<0.001
FIB-4	17	2.21 (1.21–4.53)	6.17 (3.32–11.03)	<0.001
APRI	17	0.04 (0.01–0.11)	0.11 (0.05–0.12)	0.002
AAR	17	0.70 (0.59–0.89)	0.97 (0.71–1.24)	0.002
RDW/PC	20	0.06 (0.05–0.08)	0.09 (0.06–0.13)	<0.001
SD/PC	29	0.04 (0.04–0.06)	0.08 (0.06–0.10)	<0.001

AAR = AST to ALT ratio; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APRI = AST to platelet count ratio; AST = aspartate aminotransferase; FIB-4 = fibrosis 4 score; GGT = gamma-glutamyl transpeptidase; Hb = hemoglobin; MCV = mean corpuscular volume; MPV = mean platelet volume; PC = platelets count; RBC = red blood cells; RDW = red blood cell volume distribution width; RDW/PC = red blood cell volume distribution width to platelet count ratio; SD = spleen diameter (SD); SD/PC = spleen diameter to platelet count ratio; ULN = upper limit of norm; WBC = white blood cells.

Distribution of NITs for each Ishak stage is shown on Figure 1. Using Kruskal–Wallis test, we found a significant difference among the different stages of fibrosis when comparing the values for SD/PC ($p < 0.001$), FIB-4 ($p = 0.002$), AAR ($p = 0.002$), RDW/PC ($p = 0.008$) and APRI (0.029).

According to the results of receiver operating characteristics curves analysis (Table 2), the best performance for the diagnosis of AF was seen for SD/PC (AUC = 0.814; 95% CI 0.719–0.909), followed by FIB-4 (AUC = 0.770; 95% CI 0.670–0.870), RDW/PC (AUC = 0.768; 95% CI 0.640–0.896), APRI (AUC = 0.708, 95% CI 0.592–0.823) and AAR (AUC = 0.694; 95% CI 0.568–0.819) (ROC curves analysis in Table 3 and Figure 2). Statistical comparison of the curves with DeLong test did not show statistical superiority of one of these tests (not shown in tables), due to the limitation of the sample.

For each NIT we identified the best cut-off by Youden's index and its performance (Table 3). For SD/PC, optimal cut-off was calculated at 0.054 (cm/unit $\times 10^9$ /L), where it gives high sensitivity and NPV, with a good specificity (88.0%, 94.0% and 68.9%), keeping a PPV of more than 50%. FIB-4 and APRI (optimal cut-off calculated at the maximum of Youden's index 2.00 and 6.04 respectively) showed great ability to rule out AF with good sensitivity and NPV (96.0% and 97.5%, 70.8% and 88.7% and respectively), but quite low specificity and PPV (48.7% and 36.9% and 68.8% and 40.5% respectively). RDW/PC and AAR (optimal cut-off calculated at 0.087 and 0.93 respectively) showed high NPV (both close to 90%), keeping a good specificity (85.9% and 87.7% respectively).

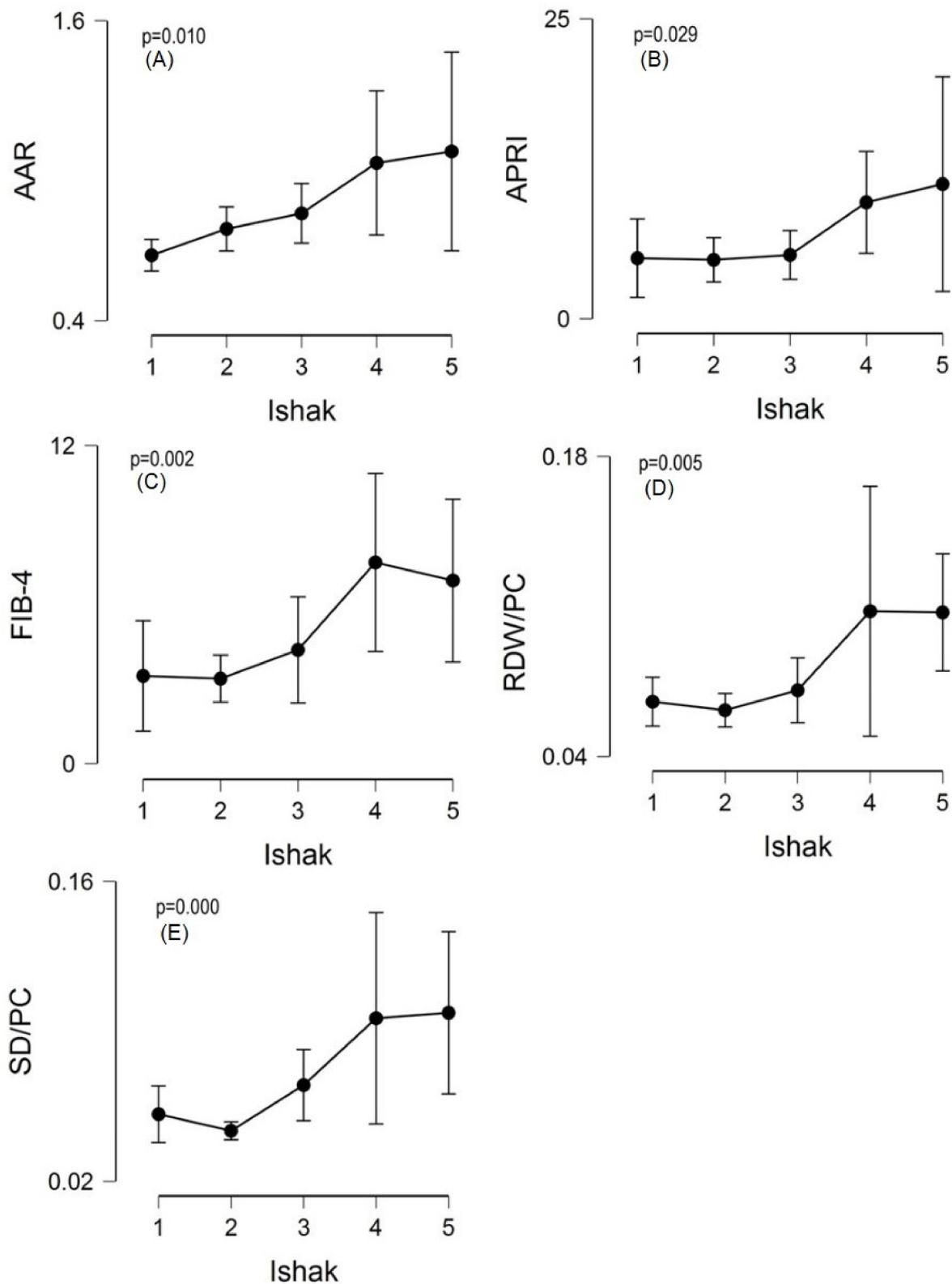


Figure 1. Correlation between non-invasive tests and fibrosis stages. Plot of (A) AAR, (B) APRI, (C) FIB-4, (D) RDW/PC, (E) SD/PC score values for fibrosis stages. The point through the middle of each line represents the median. The length of the line represents the interquartile range.

Table 2. Areas under the receiver operating characteristic curves of non-invasive tests for the prediction of advanced fibrosis among all patients, acute and non-acute AIH.

Test	Population	AUC	95% CI	Z	p-Value
FIB-4	All patients (n = 105)	0.770	(0.670–0.870)	5298.42	<0.001
	Acute (n = 56)	0.724	(0.567–0.881)	2792.685	0.005
	Non-acute (n = 49)	0.834	(0.679–0.990)	4206.383	<0.001
APRI	All patients (n = 105)	0.708	(0.592–0.823)	3.522	<0.001
	Acute (n = 56)	0.716	(0.553–0.879)	2.605	0.009
	Non-acute (n = 49)	0.758	(0.579–0.938)	2.816	0.005
AAR	All patients (n = 120)	0.694	(0.568–0.819)	3022.145	0.003
	Acute (n = 62)	0.674	(0.500–0.848)	1958.879	0.050
	Non-acute (n = 58)	0.697	(0.500–0.894)	1969.192	0.049
RDW/PC	All patients (n = 82)	0.768	(0.640–0.896)	4114.128	<0.001
	Acute (n = 41)	0.773	(0.614–0.933)	3362.831	0.001
	Non-acute (n = 41)	0.733	(0.506–0.959)	201.469	0.044
SD/PC	All patients (n = 93)	0.814	(0.719–0.909)	6478.971	<0.001
	Acute (n = 49)	0.754	(0.606–0.902)	3371.503	0.001
	Non-acute (n = 44)	0.902	(0.814–0.990)	8988.844	<0.001

AAR = AST to ALT ratio; APRI = AST to platelet count ratio; AUC = area under the receiver operating characteristic curve; CI = confidence intervals; FIB-4 = fibrosis 4 score; RDW/PC = red blood cell volume distribution width to platelet count ratio; SD/PC = spleen diameter to platelet count ratio.

Table 3. Cut-off and diagnostic performance of non-invasive tests for determination of advanced fibrosis among all patients, acute and non-acute.

Test	Population	Cut-Off	Sensitivity	Specificity	PPV	NPV	LR pos	LR neg
FIB-4	All patients	2.000	0.960	0.487	0.369	0.975	1.873	0.082
	Non-acute	3.300	0.818	0.872	0.643	0.944	6.382	0.209
	Acute	6.200	0.643	0.756	0.474	0.861	2.636	0.472
APRI	All patients	6.044	0.708	0.688	0.405	0.887	2.267	0.424
	Non-acute	3.422	0.636	0.842	0.538	0.889	4.03	0.432
	Acute	7.232	0.846	0.548	0.367	0.92	1.87	0.281
AAR	All patients	0.930	0.593	0.787	0.444	0.871	2.785	0.518
	Non-acute	0.934	0.583	0.848	0.5	0.886	3.833	0.491
	Acute	0.825	0.733	0.66	0.407	0.886	2.154	0.404
RDW/PC	All patients	0.087	0.632	0.859	0.571	0.887	4.491	0.429
	Non-acute	0.061	0.889	0.594	0.381	0.95	2.188	0.187
	Acute	0.087	0.700	0.800	0.538	0.889	3.5	0.375
SD/PC	All patients	0.054	0.880	0.691	0.512	0.94	2.85	0.174
	Non-acute	0.062	0.909	0.853	0.667	0.967	6.182	0.107
	Acute	0.045	0.929	0.588	0.481	0.952	2.255	0.121

AAR = AST to ALT ratio; APRI = AST to platelet count ratio; FIB-4 = fibrosis 4 score; LR neg = likelihood ratio negative; LR pos = likelihood ratio positive; NPV = negative predictive values; PPV = positive predictive values; RDW/PC = red blood cell volume distribution width to platelet count ratio; SD/PC = spleen diameter to platelet count ratio.

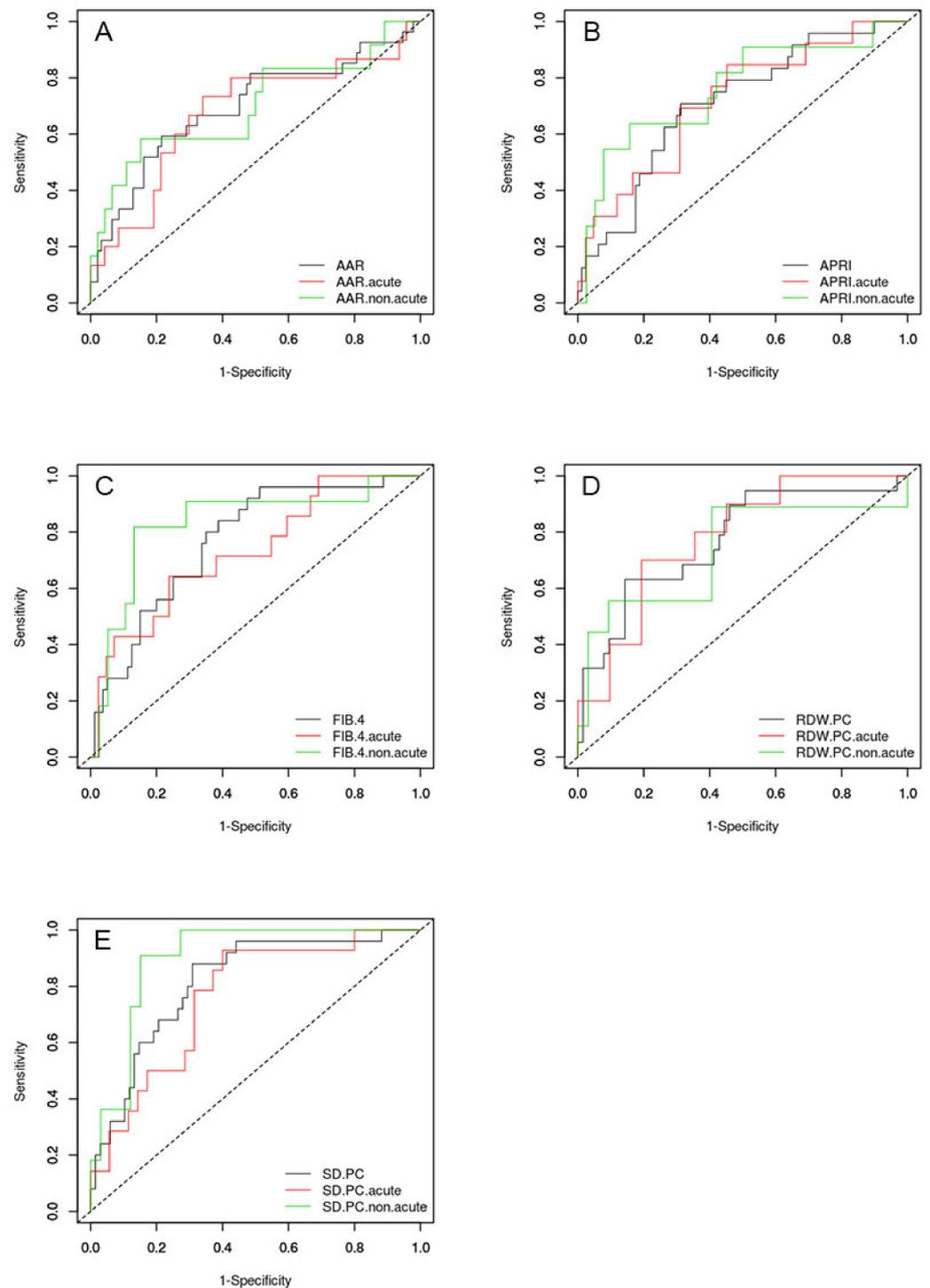


Figure 2. Receiver operator characteristics curves of non-invasive tests for the diagnosis of advanced fibrosis. AUC for (A) AAR: entire population = 0.694, acute patients = 0.674, non-acute patients = 0.697, (B) APRI: entire population = 0.708, acute patients = 0.716, non-acute patients = 0.758, (C) FIB-4: entire population = 0.770, acute patients = 0.724, non-acute patients = 0.834, (D) RDW/PC: entire population = 0.768, acute patients = 0.773, non-acute patients = 0.733, (E) SD/PC: entire population = 0.814, acute patients = 0.754, non-acute patients = 0.902. Black line = entire population, red line = acute patients, green line = non-acute patients.

The performance of NITs in identifying AF in patients with non-acute presentation and patients with acute hepatitis was compared using ROC curves analysis (Table 2, Figure 2).

The AUCs of SD/PC (non-acute AUC = 0.902, CI 95% 0.814–0.990; acute AUC = 0.754, CI 95% 0.606–0.902), FIB-4 (non-acute AUC = 0.834, CI 95% 0.679–0.990; acute AUC = 0.724, CI 95% 0.567–0.881) and APRI (non-acute 0.758, 95% CI 0.579–0.938; acute AUC = 0.716, 95% CI 0.553–0.879) are higher in non-acute patients. Comparison with DeLong test did not show statistical significance ($p = 0.12$, $p = 0.37$, and $p = 0.73$ respectively). AUCs of AAR and RDW/PC did not show relevant differences in the two subsets of patients. Best cut-off for FIB-4 in the non-acute group is 3.3, where it keeps high sensitivity and NPV, giving higher specificity and PPV compared to the general population set. For SD/PC, in non-acute patients the best cut-off was 0.06, where it has a NPV of 96.7% (Table 3).

4. Discussion

The central driver of hepatic fibrosis in AIH is adaptive immune response, which triggers the extrinsic pathway of hepatocyte apoptosis, inducing myofibroblast transformation of Kupffer and stellate cells, which in turn expands the extracellular matrix [10]. This process is now recognized as dynamic, since there is a high potential for fibrosis regression in AIH if liver inflammation is effectively controlled [1,10]. There is agreement that assessment of hepatic fibrosis in addition to complete biochemical remission may help to assure a lack of disease progression over the long term, and may reduce the need for follow-up liver biopsy [11,12]. In this context, our work aims to evaluate the performance of blood-based NITs that, to date, have given contrasting results in literature. Moreover, we wanted to clarify whether they are affected by different forms of presentation of AIH. In Table 4 we summarize the literature for blood-based NITs among AIH and other chronic liver diseases (CLD) [13–20].

Table 4. Literature review of non-invasive tests' performance among different chronic liver diseases and AIH.

NIT	Article Type	CLD	N	AUC	Cut-Off	Diagnostic Accuracy
FIB-4 [13]	Metanalysis	CHB	3139	0.80 (0.74–0.91)	0.5	SE 73%, SP 55%
FIB-4 [14]	Review	NAFLD	686	0.80–0.86	1.3	NPV 90–95%
FIB-4 [15]	Retrospective multicenter	NAFLD	1904	NR	3.25	PPV 75%
FIB-4 [16]	Retrospective monocentric	CHC	798	0.84	1.37	SE 75%, SP 71%
FIB-4 [17]	Retrospective monocentric	AIH	108	0.64 (0.53–0.74)	NR	NR
FIB-4 [18]	Retrospective monocentric	AIH	76	0.74 (0.62–0.86)	3.21	SE 24%, SP 78%
FIB-4 [5]	Metanalysis	AIH	421	0.76 (0.72–0.79)	2.37	SE 74%, SP 71%
FIB-4 [19]	Retrospective monocentric	AIH	45	0.76 (0.61–0.90)	NR	SE 60%, SP 76%
RDW/PC [4]	Metanalysis	Various	1489	0.83 (± 0.03)	2.26	SE 77%, SP 74%
RDW/PC [19]	Retrospective monocentric	AIH	45	0.79 (0.65–0.92)	0.07	SE 78%, SP 70%
AAR [15]	Retrospective multicentre	NAFLD	1904	0.68 (0.66–0.71)	0.24	SE 86%, SP 61%
AAR [19]	Retrospective monocentric	AIH	45	0.71 (0.56–0.86)	0.85	SE 54%, SP 73%
AAR [18]	Retrospective monocentric	AIH	76	0.73 (0.61–0.85)	0.77	SE 82%, SP 57%
AAR [14]	Review	NAFLD	174	0.83–0.90	1.0	SE 59%, SP 71%
AAR [5]	Metanalysis	AIH	252	0.73 (0.69–0.76)	0.8	NPV 93%, PPV 44%
APRI [16]	Retrospective monocentric	CHC	798	0.82	NR	SE 84%, SP 64%
APRI [13]	Metanalysis	CHB	3139	0.76 (0.68–0.87)	NR	NR
APRI [20]	Retrospective monocentric	NAFLD	111	0.85	NR	NR
APRI [14]	Review	NAFLD	175	0.56–0.67	0.98	SE 75%, SP 86%
APRI [15]	Retrospective multicentre	NAFLD	1904	NR	0.84	NPV 84%, PPV 37%
APRI [5]	Metanalysis	AIH	506	0.74 (0.70–0.78)	NR	SE 75%, SP 65%
APRI [17]	Retrospective monocentric	AIH	108	0.65 (0.54–0.75)	NR	SE 72%, SP 64%
APRI [18]	Retrospective monocentric	AIH	76	0.71 (0.58–0.83)	2.13	SE 43%, SP 89%
SD/PC [18]	Retrospective monocentric	AIH	76	0.88 (0.80–0.97)	0.84	SE 83%, SP 63%
					0.001	SE 88%, SP 85%

AAR = AST to ALT ratio; AIH = autoimmune hepatitis; APRI = AST to platelet count ratio; AUC = area under the receiver operating characteristic curve; CHB = chronic hepatitis B; CHC = chronic hepatitis C; CLD = chronic liver disease; FIB-4 = fibrosis 4 score; NAFLD = non-alcoholic fatty liver disease; NIT = non-invasive tests; NPV = negative predictive values; NR = not reported; PPV = positive predictive values; RDW/PC = red blood cell volume distribution width to platelet count ratio; SE = sensitivity; SD/PC = spleen diameter to platelet count ratio; SP = specificity.

The main result of our study is that the diagnostic performance of SD/PC, FIB-4, RDW/PC and APRI can be considered acceptable (AUC greater than 0.7), but only SD/PC

and FIB-4 in the non-acute subset have accuracies that could be of value in clinical practice (AUC greater than 0.80) [9].

In more detail, the best performance was seen for SD/PC, which showed a good correlation with different fibrosis stages and a good accuracy (AUC = 0.814) that is higher among non-acute AIH, reaching an AUC of 0.902. For FIB-4 we found an AUC of 0.770, which is higher in non-acute patients (AUC = 0.834). For RDW/PC we obtained an AUC of 0.768, which was not affected by acute onset, while for APRI we found an AUC of 0.708, and a mildly better performance among non-acute patients (AUC = 0.758). For AAR we identified an AUC of 0.694, which is too low for the application in clinical practice. As shown by our results, the main application of these tests is mainly in the exclusion of AF, since at the best cut-off calculated they all show great sensitivity and NPV. Overall, specificity and PPV were quite low for all the NITs at the optimal cut-off, which means that up to 60% of patients will be misdiagnosed as having an advanced form of liver disease.

Interestingly, our study is the first that evaluate the performance of NITs among different presentation of AIH. Regarding the identification of acute-onset AIH, there is no globally accepted definition nor unique serological parameters that could help in the differentiation. In our study, we apply the “acute” definition provided by a multicenter Italian study, in which our cohort was partially included [2]. Although increasingly recognized, in the literature there are no exclusion criteria for acute forms of AIH, and treatment status is not often clear, two biases that inevitably affect the results. Our study suggests that at least for SD/PC, FIB-4 and APRI, application in a well-stratified cohort may show better performance. Performance presented in the literature for AIH is lower than what we found among non-acute patients (Table 4). Probably, large meta-analyses fail to demonstrate a benefit in using these tests given the great heterogeneity of AIH manifestations. Our results cannot be ascribed to a greater prevalence of AF in the non-acute patients, since Ishak stage ≥ 4 was comparable between the two subgroups ($p = 0.886$) (Supplementary material, Table S1). The obvious explanation of the different performances is that tests directly proportional to AST level (such as FIB-4 and APRI) will fail in acute patients. Speculating on the performance of SD/PC, we found that SD, PC and their ratio are not different between acute and non-acute patients; this means that in some acute patients, reactive splenomegaly unrelated to portal hypertension can lead the test to underperform.

Comparing our results to the literature (Table 4), we can see that performance of NITs for the diagnosis of AF in AIH (especially if applied in selected patients) seems in line to what has been published in literature for other CLDs where these tests are routinely used. Moreover, we must acknowledge that studies among chronic viral hepatitis have a higher prevalence of advanced fibrosis (as high as 33.5% for CHB and 44% for CHC) that affects diagnostic accuracy rising pre-test probability [9–11]. In contrast, in our study the prevalence of AF was 22.1%, which is more similar to that reported for metabolic forms (28%) [11]. Finally, cut-offs identified by our study are comparable to those reported in literature, except for APRI, whose reported cut-off (APRI = 0.5) is not suitable for our cohort, since the prevalence of acute forms of AIH leads to higher AST levels and an inevitably higher ratio.

There is a broad consensus that in AIH the most adequate method for staging hepatic fibrosis is hepatic elastography by VCTE or 2DSWE, which in all studies proved to be superior to blood-based NITs. As in other CLDs, this method offers the chance to obtain a real-time estimate of the degree of hepatic fibrosis, and, from the available data, it does not seem significantly affected by the activity of the disease [5,6,21]. Nevertheless, blood-based NITs do not incur additional expense, involve routinely available data, and are highly reproducible, so they could be widely implemented with relative ease. Given these specifications, they could represent an adjunctive tool in the hand of the physician, aware of their limitations and of their field of application.

Limitations of this study are that it is monocentric, retrospective and that performance is evaluated at the time of diagnosis, when biopsy is necessarily obtained. Regarding RDW/PC, it may be useful to know folate, vitamin B12 and iron levels to contextualize

results and to minimize false positives, but we can indirectly state that none of the 122 patients included were under supplementation at the time of diagnosis. Future study should apply these NITs in a longitudinal manner to evaluate reliability for the diagnosis of fibrosis stage during follow-up.

5. Conclusions

Our study shows that, in a wide cohort of AIH patients, blood-based NITs have an overall acceptable performance. Higher accuracy was seen for FIB-4, SD/PC and RDW/PC, while for SD/PC, FIB-4 and APRI diagnostic performance is higher when applied among patients with non-acute presentation. In this context, SD/PC and FIB-4 showed an overall performance that is consistent (AUC > 0.8) and could be of interest in clinical practice alongside other non-invasive techniques. Comparing these results with available literature, their diagnostic accuracy is comparable to what was reported about other forms of CLDs. Cut-offs identified in the literature are suitable among AIH patients except for APRI, and generally they lead to high NPV that permits excluding advanced fibrosis. Future studies should take into account the great heterogeneity of AIH presentations and should exclude patients with an acute hepatitis. Longitudinal application of these scores might be helpful to non-invasively monitor progression of liver fibrosis alongside the complete biochemical response to exclude the evolution of the disease despite treatment.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/gastroent13030029/s1>, Table S1: Comparison of collected data and derived non-invasive tests of fibrosis among acute and non-acute AIH patients.

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