

Original paper

Applicability of attenuation imaging and shear wave elastography in non-invasive assessment of liver steatosis and fibrosis in adult patients

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Abstract

Purpose: The study aims to assess whether: 1) shear wave elastography (2D-SWE) and attenuation imaging (ATI) can confirm or dispute ultrasonographic (USG) diagnosis of liver steatosis, 2) there is a correlation between 2D-SWE and ATI results, and 3) which blood tests and liver condition indices are most related to a higher F index among participants.

Material and methods: A group of 117 participants (hepatitis B and hepatitis C negative) with B-mode USG-diagnosed fatty liver was examined using ATI and 2D-SWE. Blood tests were performed, and data were analysed for normality, model fitting, and the identification of predictors for a higher F index. The likelihood ratio test assessed variables and their odds ratio in relation to the fibrosis-4 index (FIB-4), followed by interaction analysis with reference patients.

Results: ATI and 2D-SWE provided more accurate liver diagnostics than USG. F2-F3 stages correlated with older age, higher glucose, aspartate aminotransferase (AST), FIB-4, De Ritis, AST to platelet ratio index (APRI), and γ -glutamyl transpeptidase (GGTP). The model showed that AST was a strong indicator of higher F index. Univariate analysis revealed that higher odds for F2-F3 stages were associated with elevated glucose, FIB-4, De Ritis, ATI, AST, and APRI. Compared to S0, values greater than S1 were linked to a higher F index. Interaction analysis showed that only FIB-4-GGTP was significant, with higher GGTP reducing the impact of FIB-4.

Conclusions: ATI and 2D-SWE may complement USG in assessing liver condition. Key predictors for a higher F index include S index, AST, glucose, De Ritis, and FIB-4, with APRI being moderately relevant.

Key words: attenuation imaging, non-alcoholic fatty liver disease, shear wave elastography, ultrasonography.

Introduction

Hepatic steatosis is probably the most common pathological liver condition in the adult population [1,2]. Its epidemiology varies across the globe, with the lowest occurrence rates in sub-Saharan Africa and the highest (> 25% in adult population) in the Middle East and South America [3]. Wong *et al.* [4] noted an even a higher rate of 38% among adults who are suspected to be stricken with this condition. The potential of liver steatosis to transform into more serious diseases, such as hepatic cirrhosis, liver failure, or

hepatocellular carcinoma, requires vigilance of both medical practitioners and patients for early and correct diagnosis before it can lead to fatal conditions [5]. Moreover, liver steatosis is blamed for its wider psychosomatic negative effects because it is associated, on the one hand, with such diseases as hypertension, diabetes, and metabolic syndrome and, on the other hand, stress, anxiety, and higher risk of depression [6]. Despite the pressing need to detect it, medical staff encounter problem in accuracy (sensitivity, specificity) of various imaging methods in the early stages of steatosis, as well as when there are symptoms of fibrosis

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in liver parenchyma. Geethakumari *et al.* [7], in their systematic review, reported that ultrasonography (USG) offers good accuracy in medium to higher grades of steatosis; however, they suggest that, in lower levels of fat, technologies that use the attenuation rate are a more plausible option to decrease the rate of false positive or negative results. To improve the accuracy of liver assessment directed onto various stages of progressing steatosis or fibrosis, shear wave elastography [8,9] and attenuation imaging (ATI) [10–12] are suggested as promising options.

This research is worthy of attention because it presents visible differences in liver assessment directed towards liver fibrosis and steatosis, between USG and more state-of-the-art imaging methods, i.e. shear wave elastography (SWE) and ATI. Therefore, it may provide more clues for the improvement of liver diagnostics in the future. The general purpose of this research is to investigate how the application of various ultrasonography methods, both proven (USG) and novel ones (SWE and ATI), along with blood tests in a group of patients may affect the diagnostic outcome and how they could be treated as a possible non-invasive alternative to biopsy. What is more, these shall be confronted with what has been obtained in blood tests conducted on the patient group. The blood tests were carried out to check glucose levels and the basic indicators for liver assessment (cholesterol fractions, alanine transaminase [ALT], aspartate aminotransferase [ASP], and other indicators), and liver assessment ratios and indexes (De Ritis ratio, Fibrosis-4 index [FIB-4], etc.) have been calculated based on these results.

Material and methods

The study presented in this publication was approved by the Bioethics Committee of Wrocław Medical University, no. 355/2021 (number of consent).

Written consent forms regarding participation in the study were collected and retained from all the participants.

The patients underwent USG imaging diagnostics of their livers (B-mode – where liver parenchyma is juxtaposed to renal parenchyma, for comparison), and they underwent standard tests for active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection – all of which were confirmed negative. The patients underwent basic

anthropometric measurement (weight and height) and blood tests (platelets, liver tests, lipid profile) prescribed for patients with various hepatic conditions. Following this, each participant was checked with ATI and 2D-SWE imaging to reconfirm the initial USG result, whilst also checking liver steatosis and fibrosis. Patients fasted before the examination for at least 6 hours. Both measurements were conducted with use of Canon Aplio A (Canon Medical Systems Corporation, Japan) with a 1–8-MHz curvilinear probe in a supine position and through intercostal spaces. The measurement regions of interest (ROI) of 2D-SWE were placed inside the sample box, which was set at least 1 cm below the liver capsule. ROI used in the SWE examinations was set at a diameter of 10 mm, and in ATI it was adjusted to the minimum size. First, ATI evaluation was performed. Five consecutive acquisitions per patient with a reliable measurement coefficient (R^2 value) of 0.90 or higher was considered as reliable. Second, 5 consecutive 2D-SWE liver stiffness acquisitions per patient were obtained with the IQR/median less than 30%. The median values of both ATI and 2D-SWE were used for the statistical analysis. Additionally, based on the blood test results and anthropometric measurement, various indicators were calculated:

- body mass index (BMI), based on weight and height,
- blood test results: fasting blood glucose levels, blood platelets (PLT), ALT, upper limit of normal ALT, AST, upper limit of normal AST, ALP, g-glutamyl transpeptidase (GGTP), bilirubin, total cholesterol (TC) level, high-density lipoprotein (HDL), low-density lipoprotein (LDL) fraction levels, and triglycerides (TG),
- hepatic dysfunction testing (liver condition) indicators: v/ALT, FIB-4, APRI, de Ritis ratio, and GGTP.

Furthermore, based on ATI and SWE acquisitions and results obtained (SWE median value in kPa, ATI median value in dB/cm/MHz), index values for fibrotic and steatotic transformation were designated (F index value according to METAVIR scoring system for SWE median results for each participant, and S index value for liver cirrhosis based on ATI median result for each participant).

In Table 1, METAVIR scoring is presented with a description of how each score relates to each fibrosis stage and how each score is assigned according to intervals of SWE measurements.

Table 1. Classification of fibrosis stages according to the METAVIR scoring system based on shear wave elastography (SWE) measurement values [15–17]

METAVIR score	Fibrosis stage	Liver stiffness measures in SWE (median value in kPa)
F0	No fibrosis can be detected	> 2.5 kPa and ≤ 7 kPa
F1	Fibrosis exists with expansion of portal zones	
F2	Fibrosis exists with expansion of most portal zones and occasional bridging	> 7 kPa and ≤ 9.5 kPa
F3	Fibrosis exists with expansion of most portal zones, marked bridging and occasional modules	> 9.5 kPa and ≤ 12.5 kPa
F4	Presence of cirrhosis	> 12.5 kPa

In Table 2, the steatosis scoring system is presented, with each score assigned a specific steatosis stage and the interval results of ATI measurements.

Data preprocessing and visualisation were performed with Python 3.10.7 (packages: pandas 1.4.4, numpy 1.21.4, matplotlib 3.5.3, seaborn 0.11.2). Statistics were computed with use of Statistica 13.3 on license by Wrocław Medical University. The normality distribution was checked with use of the Q-Q plots and analysis of skewness. Homoscedasticity was checked with the Levene test. Basic group-wise comparison of values of the selected parameters was based on the results from t test (with Cochran-Cox correction if necessary), Mann-Whitney U, and χ^2 tests. In the case of a low (< 5) estimated count in any contingency table cell, Yates correction for continuity was applied.

Logistic regression was applied to investigate the association between the studied parameters and the odds of observing higher values of the F index among the population. Some variables (referred to as 'effects') did not show linearity vs. log (odds) as checked with the Box-Tidwell test. Such effects were transformed with the log1.15 function. The multivariate model candidate was derived based on the stepwise elimination algorithm (Appendix A). Possible interactions were checked for with the likelihood ratio (LR) type 1 test. Subsequently, selected interactions were explored with logistic regression models of full factorial design with each interaction analysed in a separate model. Due to the low sample size ($N = 13$) for the subgroup of participants with F2-F3 index value (more severe stages of fibrosis), additional goodness of fit of the model was tested.

Table 3 shows an almost even distribution of participants within the group according to sex. What may be of importance, only 22.2% of the whole group is represented by participants of age < 40 years. Furthermore, < 30% of participants had had no chronic diseases and had reported no intake of medications. Therefore, in general, the whole group demonstrates a dominating pattern for comorbidity (chronic diseases) and drug intake, with highly visible participation of persons who have had at least two chronic diseases and at least two medications administered.

Table 4 shows that the most common chronic conditions among participants were blood hypertension (40.4%), diabetes (12.8%), and hypothyroidism (9.6%). On average, each participant with at least one reported chronic disease was stricken with 1.84 chronic morbidities.

Inclusion and exclusion criteria

The selection of patients recruited for the study was based on a simple criterion of having a positive USG result for liver steatosis. Yet, what is substantial for this study, this diagnosis is considered *a priori* as insufficient, or likely as a falsely positive result [13,14], which required further procedures to verify it.

Table 2. Classification of steatosis states based on ATI measurement values [18,19]

Steatosis score	Steatosis stage	ATI measurement results (value in dB/cm/MHz)
S0	No steatosis	≤ 0.62
S1	Mild steatosis	0.63-0.69
S2	Moderate steatosis	0.70-0.74
S3	Severe steatosis	≥ 0.75

Table 3. Basic statistical description of the group of participants (sex, age, chronic diseases, medication intake)

Variable	Number of participants	%
Sex		
Male	60	51.3
Female	57	48.7
Age		
< 40	26	22.2
41-60	48	41.0
> 60	43	36.8
Chronic/no chronic diseases		
No chronic diseases	32	27.4
Various chronic diseases:	85	72.7
2 or more chronic disease	49	41.9
3 or more chronic diseases	19	16.2
Regular medication intake/no intake		
Participants with no medication intake	30	25.6
Participants with intake of at least 1 medication	87	74.4
Participants with intake of > 1 medication	63	53.8
Participants with intake of > 2 medications	40	34.2

The whole group of participants, consisting of 117 patients (100% of the group), had had hepatic steatosis confirmed beforehand with USG, which was used as an inclusion criterion. Patients whose USG imaging results appeared to have been negative and falsely negative were automatically excluded from the study.

Results

Table 5 presents basic descriptive statistics presenting the obtained results within each variable. Values for normality distribution have been presented for the following variables: age, glucose, ALT, AST, FIB-4, APRI, De Ritis Index, ALP, GGPT, bilirubin, TG, LDL, median value from SWE, and median value from ATI. The average value with standard deviation was calculated for BMI, PLT, and TC. These values, along with the obtained skewness, were calculated for two subgroups of patients: those with

Table 4. Chronic disease characteristics among participants

Type of disease	Number of participants	%
Blood hypertension	63	40.4
Diabetes	20	12.8
Hypothyroidism	15	9.6
Insulin resistance	12	7.7
Hepatitis B (resolved)	5	3.2
Hepatitis C (with sustained viral response)	5	3.2
Hashimoto disease	4	2.6
Asthma	4	2.6
Psoriasis	3	1.9
Glaucoma	3	1.9
Podagra	2	1.3
Rheumatoid arthritis	2	1.3
Polycystic ovary syndrome	2	1.3
Wilson disease, depression, undifferentiated connective tissue disease, Churg-Strauss disease, polyneuropathy, heart failure, post-cerebral vascular accident state, supraventricular tachycardia atopic dermatitis, chronic obstructive lung disease, gastroesophageal reflux disease, prediabetic state, Sjogren syndrome, leukopaenia, peripheral polyneuropathy, cancer (breast, uterus)	Only 1 occurrence per condition (total 16 occurrences)	10.2
Total		100
156 occurrences		
1.33 per participant		
1.84 per participant with at least 1 chronic disease		

F index value F0-F1, and those with F index value F2-F3. A *p*-value for statistical significance for each variable was calculated for the whole group.

Table 6 shows the population sample split into two groups based on their F index. The first subgroup consists of patients diagnosed with no hepatic fibrosis (F0) or minimum fibrotic changes in liver parenchyma (F1), while the second subgroup consists of participants with more significant states of progression of hepatitis fibrosis (F2-F3). Significant differences in values were spotted in context of: age (*p* = 0.027), glucose concentration (*p* = 0.018), AST activity (*p* = 0.002), FIB-4 (*p* < 0.001), APRI (*p* = 0.003), de Ritis index (*p* = 0.025), GGTP activity (*p* = 0.038), and measurements from the used devices (SWE and ATI, respectively: *p* < 0.001, *p* = 0.035). The values of these parameters were higher in the group of higher F index (F2-F3). Importantly, FIB-4 shows the highest level of statistical significance among all the variables (*p* < 0.001), which may be a good basis to additionally check the effects of interactions of FIB-4 with other variables on the odds of seeing F2-F3 indexes (conducted further in Tables 9 and 10).

The values of the corrected Akaike Information Criterion (AICc) constitute only a slightly larger value than the AIC value, which may be a good predictor of the quality of the employed logistic regression model.

To indicate the fit of the model, several measures for the goodness of fit were calculated. The goodness of fit of the model with regard to F2-F3 values among the whole group of participants was checked against the pseudo-R-squared value tests. The obtained values (Cox-Snell R^2 = 0.228761 and Nagelkerke R^2 = 0.450166) may be a good measure of whether the designed model has a high goodness of fit.

As the next step, an elimination stepwise process was conducted (Appendix A) to determine multivariate model candidates with the most significant impact on the odds of observing higher F values among the participants. While AST, ALT, and glucose have been determined as the most promising candidates in the process, in Table 7 their impact on observing these values was checked on the example of the reference patient.

Table 7 presents the odds of observing higher F index in a reference patient. The algorithmically-derived model (Table 7, Figure 1) featured three effects: AST (*p* = 0.001), ALT (*p* = 0.003), and glucose (*p* = 0.003). Therefore, these three parameters, simultaneously, modulated the odds of observing higher values of the F index (F2-F3). The baseline odds for a patient with typical AST, ALT, and glucose values (26.69 IU/l, 35 IU/l, 93 mg/dl, respectively), were 0.031 (*p* < 0.001), meaning that only 3.1% of such patients would show F index values higher

Table 5. Normality distribution in two subgroups of patients (first group: F0-F1 index value, second group: F2-F3 index value)

Variable	F index: F0-F1 (N = 104)		F index: F2-F3 (N = 13)		p
	Values	Skewness	Values	Skewness	
Age	{42, 53, 62}*	−0.15	{60, 62, 66}*	−1.98	0.027
BMI	[29.00 ± 4.48]**	0.51	[29.71 ± 4.83]**	0.37	0.597
Glucose	{86, 93, 101}*	2.18	{87, 110, 148}*	0.85	0.018
PLT	[242.86 ± 60.94]**	0.62	[209.62 ± 71.57]**	−0.45	0.072
ALT	{24, 35, 50}*	2.14	{24, 41, 55}*	1.12	0.532
AST	{24, 27, 35}*	4.34	{28, 41, 61}*	0.61	0.002
FIB-4	{0.78, 1.01, 1.46}*	2.61	{1.28, 1.79, 2.60}*	1.88	< 0.001
APRI	{0.26, 0.34, 0.46}*	7.17	{0.40, 0.61, 1.07}*	1.28	0.003
De Ritis Index	{0.64, 0.79, 1.00}*	1.04	{0.76, 1.08, 1.20}*	1.89	0.025
ALP	{67.0, 79.5, 96.0}*	4.33	{63.0, 80.0, 111.0}*	0.30	0.757
GGTP	{20, 31, 64}*	3.10	{38, 48, 74}*	2.68	0.038
Bilirubin	{0.49, 0.68, 0.85}*	2.07	{0.59, 0.65, 0.74}*	1.70	0.955
TChol	[193.15 ± 39.71]**	0.28	[188.92 ± 51.04]**	1.19	0.618
HDL	[51.86 ± 12.26]**	0.74	[48.92 ± 14.31]**	0.35	0.309
TG	{89, 112, 146}*	1.72	{79, 120, 188}*	3.00	0.622
LDL	{96.0, 117.5, 136.0}*	0.36	{95.0, 112.0, 134.0}*	−0.58	0.338
Median value from SWE (kPa)	{4.4, 4.7, 5.4}*	0.43	{7.2, 7.2, 7.7}*	1.50	< 0.001
Median value from ATI (dB/cm/MHz)	{0.56, 0.60, 0.66}*	0.59	{0.60, 0.68, 0.74}*	−0.64	0.035
Sex: Female	48 (47.06%)	–	8 (61.54%)	–	0.491
Sex: Male	54 (52.94%)	–	5 (38.46%)	–	–
F index: F0 - F1	104 (100%)	–	–	–	–
F index: F2	–	–	12 (92.31%)	–	–
F index: F3	–	–	1 (7.69%)	–	–
S index: S0	60 (57.69%)	–	4 (30.76%)	–	–
S index: S1	27 (25.96%)	–	3 (23.08%)	–	–
S index: S2	8 (7.69%)	–	1 (7.69%)	–	–
S index: S3	9 (8.65%)	–	4 (30.76%)	–	–

*Results presented in the following order: {first quartile, median, third quartile}.

**Results presented in the following order: [mean ± standard deviation].

Table 6. Goodness of fit of the tested model

	F category (merged) – measurements of goodness of fit (Arkusz1631) Distribution: binomial, binding function: LOGIT Modelled probability F category (merged) = F2-F3 (sample for the analysis)		
	Df	Stat.	Stat/Df
Deviation	110	51.297913	0.466345
Scalable deviation	110	51.297913	0.466345
Pearson χ^2	110	168.618930	1.532899
Scalable Pearson χ^2	110	168.618930	1.532899
Akaike information criterion (AIC)	59,297913		
Corrected Akaike information criterion (AICc)	59.664886		
Bayesian information criterion (BIC)	70.242707		
Cox-Snell R ²	0.228761		
Nagelkerke R ²	0.450116		
Log (number of variants)	−25.648957		

Table 7. Odds of observing higher F index values among participants (reference patients) depending on assumed increase of aspartate aminotransferase (AST), alanine transaminase (ALT), or glucose

Effect	Tested phenomenon	β	β SE	Wald	Odds or OR	Odds or OR –95% CI	Odds or OR 95% CI	<i>p</i>
Intercept	The odds of observing a higher F index in a reference patient (AST = 26.69, ALT = 35.00, glucose = 93.00)	–3.479	0.619	31.546	0.031	0.009	0.104	< 0.001
AST	Fold difference in the odds upon each consecutive 15% increase in AST activity	0.758	0.219	12.010	2.133	1.390	3.274	0.001
ALT	Fold difference in the odds upon each one-unit increase in ALT activity	–0.062	0.021	8.614	0.940	0.902	0.980	0.003
Glucose	Fold difference in the odds upon each one-unit increase in glucose concentration	0.042	0.014	9.024	1.043	1.015	1.072	0.003

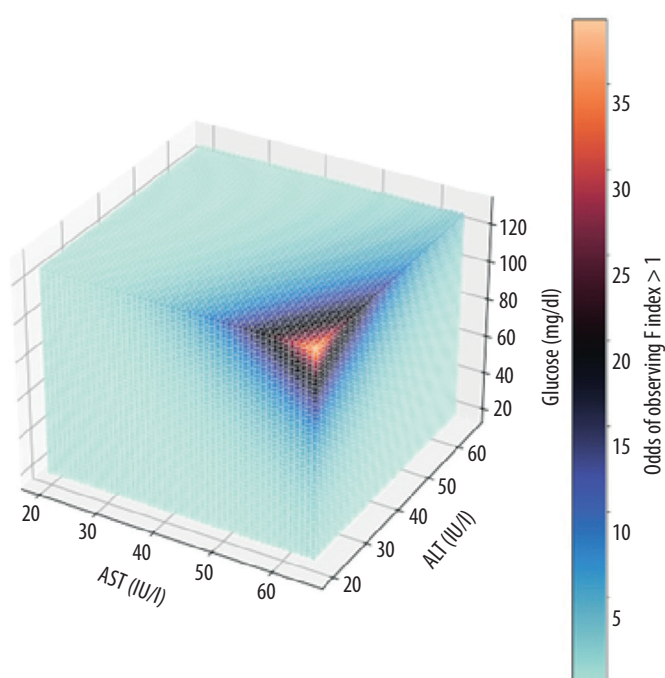


Figure 1. Odds of observing higher F index depending on increase of AST and ALT activity and glucose levels – visual presentation

than 1. Out of the three aforementioned effects, the one associated with AST was the strongest one, increasing the baseline odds 2.133-fold with every one-unit increase in AST. Conversely, the effect of a one-unit increase in ALT decreased the baseline odds by approximately 6%. Elevation of glucose concentration by one unit increased the baseline odds by 4.3%. The tendency of changing odds for all three effects is also presented in Figure 1.

Figure 1 shows a three-dimensional presentation of how the odds ratio is shaped depending on the level of AST, ALT, and glucose, with some obvious and expected results on AST and glucose, as predictors of higher F index. The higher F index with a negative tendency in ALT levels may be surprising, but this outcome will be discussed later if there is any evidence in the literature confirming a similar observation.

Univariate analysis of how each variable may impact the odds of observing a higher F index is presented in Table 8.

The above calculations are accompanied with visual presentation on whisker plots in Figure 2.

In Figure 2, in univariate analysis, the odds of observing a higher F index among the patients increased with the following: glucose concentration (3.8% increase per 1 mg/dl increase, $p = 0.001$), FIB-4 (2.32-fold increase per one-unit increase, $p = 0.004$), de Ritis index (7.07-fold increase per one-unit increase, $p = 0.008$), ATI value (45.7% increase per increase by 0.05, $p = 0.034$), AST (31% increase per 15% increase in AST, $p = 0.003$), and APRI (21.8% increase per 15% increase in APRI, $p = 0.003$). Moreover, compared to the S0 index, values higher than S1 (S2–S3) were associated with 4.609-fold higher odds of spotting higher F2–F3 index values ($p = 0.036$), which may be an obvious observation since fibrosis is a change in liver parenchyma that occurs after steatotic changes and may progress concurrently.

Due to FIB-4 being a good candidate to see odds of higher F index ($p > 0.001$ – see: Table 5).

The results of the performed likelihood test ratio in Table 9, show that the best candidate pairs to check how the odds of a higher F index change upon interactions between them are as follows: FIB-4 and PLT (p [LR] = 0.0168), FIB-4 and AST log 1.15 (p [LR] = 0.0193), FIB-4 and GGTP (p [LR] = 0.027), and FIB-4 and APRI (p [LR] = 0.0406).

These interactions were tested in the next step, which was analysis of interaction on four reference patients (Tables 10A–D for respective interactions among reference patients).

The initial analysis of interactions revealed that GGTP*FIB-4, PLT*FIB-4, AST*FIB-4, and APRI*FIB-4 are candidates for further analysis ($p = 0.027$, $p = 0.017$, $p = 0.019$, $p = 0.0406$, respectively). However, upon exploring the full factorial models containing these interactions along with the effects taking part in them (Table 10), only GGTP ($p = 0.036$, Table 10A) and PLT ($p = 0.018$, Table 10B) appeared to significantly modulate the effect

Table 8. Univariate analysis of effects

Variable	Estimate	Standard	Wald statistic	Upper boundary	Bottom boundary	p	OR	Confidence interval OR –95%	Confidence interval OR 95%
Sex	–0.588	0.604	0.948	–1.771	0.595	0.3302	0.556	0.170	1.814
BMI	0.034	0.064	0.285	–0.091	0.160	0.5937	1.035	0.913	1.173
*Glucose	0.037	0.011	10.906	0.015	0.059	0.0010	1.038	1.015	1.061
PLT	–0.009	0.005	3.201	–0.020	0.001	0.0736	0.991	0.980	1.001
ALT	0.005	0.009	0.270	–0.013	0.023	0.6036	1.005	0.987	1.023
*FIB-4	0.841	0.289	8.465	0.275	1.408	0.0036	2.320	1.316	4.089
*De Ritis index	1.956	0.740	6.979	0.505	3.407	0.0082	7.070	1.657	30.174
ALP	0.002	0.008	0.053	–0.014	0.017	0.8175	1.002	0.986	1.018
GGTP	0.004	0.003	1.825	–0.002	0.011	0.1768	1.004	0.998	1.011
Bilirubin	–0.066	0.816	0.007	–1.665	1.533	0.9351	0.936	0.189	4.630
TG	0.005	0.003	2.798	–0.001	0.011	0.0944	1.005	0.999	1.011
*ATI (per 0.05 increase)	0.376	0.178	4.481	0.028	0.725	0.0343	1.457	1.028	2.064
S category: S1	0.782	0.744	1.103	–0.677	2.241	0.2936	2.185	0.508	9.398
*S category: S2-S3	1.528	0.728	4.410	0.102	2.954	0.0357	4.609	1.107	19.187
*log1.15 (AST)	0.270	0.092	8.577	0.089	0.450	0.0034	1.310	1.093	1.569
*log1.15 (APRI)	0.197	0.066	8.934	0.068	0.327	0.0028	1.218	1.070	1.386
log1.15 (TCchol)	–0.096	0.190	0.254	–0.468	0.277	0.6143	0.909	0.626	1.319
log1.15 (HDL-Chol)	–0.180	0.176	1.042	–0.525	0.165	0.3073	0.835	0.591	1.180
log1.15 (LDL-Chol)	–0.118	0.123	0.924	–0.359	0.123	0.3365	0.889	0.699	1.131

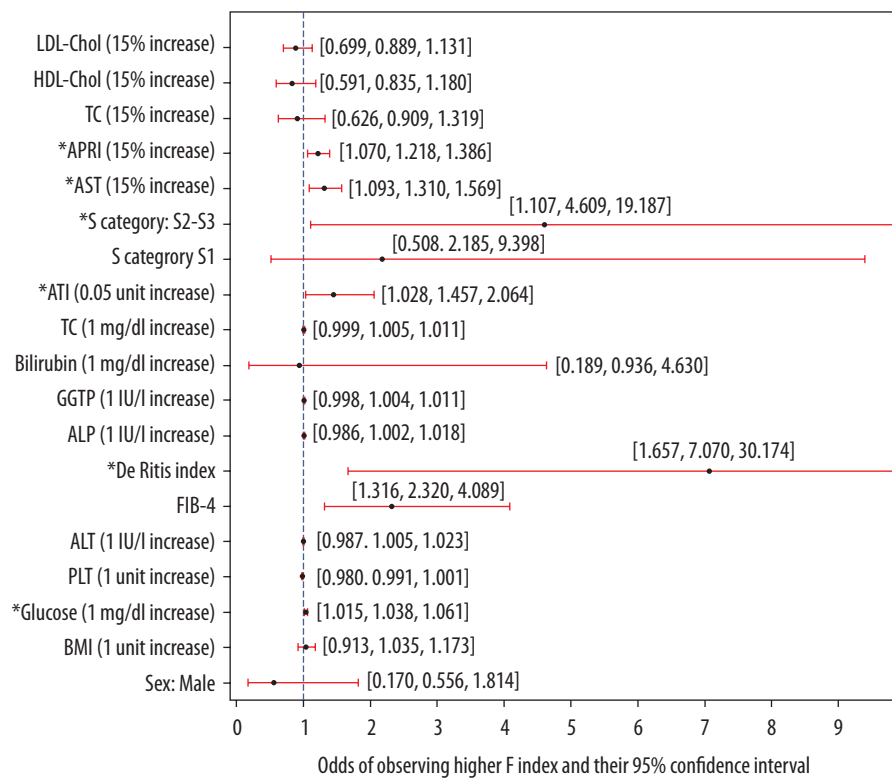


Figure 2. Univariate analysis of effects – visual presentation

Table 9. Results of likelihood ratio type 1 test

Variable 1	Variable 2	χ^2	<i>p</i> (LR)
GGTP	ALP	6.922	0.0085
De Ritis Index	Bilirubin	5.8381	0.0157
FIB-4	PLT	5.7125	0.0168
FIB-4	AST log 1.15	5.4757	0.0193
FIB-4	GGTP	4.8932	0.027
TG	ALP	4.5146	0.0336
TG	HDL log 1.15	4.3297	0.0375
HDL log 1.15	Bilirubin	4.2796	0.0386
PLT	BMI	4.2263	0.0398
APRI log 1.15	BMI	4.212	0.0401
BMI	Bilirubin	4.2022	0.0404
FIB-4	APRI log 1.15	4.193	0.0406
ALT	TChol log 1.15	4.1079	0.0427
Glucose	PLT	3.8539	0.0496
FIB-4	ALT	3.804	0.0511
Age	LDL log 1.15	3.5722	0.0588
S category (merged)	GGTP	3.5491	0.0596
Sex	TChol log 1.15	3.5263	0.0604
Sex	Bilirubin	3.2644	0.0708
TChol log 1.15	ALP	3.189	0.0741
Age	GGTP	3.0169	0.0824
FIB-4	BMI	3.0028	0.0831
GGTP	TChol log 1.15	2.8239	0.0929
ALT	Bilirubin	2.7317	0.0984
AST log 1.15	BMI	2.6524	0.1034
APRI log 1.15	AST log 1.15	2.6015	0.1068
HDL log 1.15	ALP	2.5651	0.1092
ATI median value (dB/cm/MHz)	TChol log 1.15	2.5235	0.1122
De Ritis Index	ATI median value (dB/cm/MHz)	2.2646	0.1324
TG	Sex	2.2475	0.1338
Median value ATI (dB/cm/MHz)	GGTP	2.2043	0.1376
Median value from ATI (dB/cm/MHz)	Sex	2.1252	0.1449
LDL log 1.15	ALT	2.0537	0.1518
LDL log 1.15	ALP	2.0161	0.1556
S category (merged)	TChol log 1.15	2.0136	0.1559
PLT	Bilirubin	1.9663	0.1608
Glucose	APRI log 1.15	1.962	0.1613
FIB-4	ATI median value (dB/cm/MHz)	1.8966	0.1685
AST log 1.15	S category (merged)	1.8963	0.1685
FIB-4	S category (merged)	1.8484	0.174
Glucose	De Ritis Index	1.8114	0.1783
APRI log 1.15	S category (merged)	1.7885	0.1811
Sex	ALP	1.7329	0.188

Table 9. Cont.

Variable 1	Variable 2	χ^2	<i>p</i> (LR)
ATI median value (dB/cm/MHz)	LDL log 1.15	1.6496	0.199
HDL log 1.15	Sex	1.5622	0.2113
HDL log 1.15	TChol log 1.15	1.5018	0.2204
De Ritis Index	S category (merged)	1.4475	0.2289
Age	HDL log 1.15	1.4152	0.2342
De Ritis Index	ALT	1.394	0.2377
S category (merged)	LDL log 1.15	1.3823	0.2397
S category (merged)	ALT	1.352	0.2449
TG	ATI median value (dB/cm/MHz)	1.3191	0.2508
PLT	HDL log 1.15	1.2249	0.2684
AST log 1.15	TChol log 1.15	1.2136	0.2706
TG	Bilirubin	1.2021	0.2729
PLT	ALT	1.1886	0.2756
GGTP	HDL log 1.15	1.1317	0.2874
APRI log 1.15	ATI median value (dB/cm/MHz)	1.1203	0.2899
Glucose	Age	1.1012	0.294
AST log 1.15	ATI median value (dB/cm/MHz)	1.0984	0.2946
HDL log 1.15	ALT	1.0595	0.3033
TG	GGTP	1.0385	0.3082
LDL log 1.15	Bilirubin	1.0228	0.3119
AST log 1.15	Sex	0.9802	0.3222
ALP	Bilirubin	0.959	0.3274
AST log 1.15	HDL log 1.15	0.9487	0.3301
TG	S category (merged)	0.9216	0.337
AST log 1.15	PLT	0.8994	0.3429
De Ritis Index	LDL log 1.15	0.885	0.3468
APRI log 1.15	ALT	0.8792	0.3484
APRI log 1.15	Bilirubin	0.8278	0.3629
De Ritis Index	ALP	0.756	0.3846
Sex	ALT	0.7433	0.3886
S category (merged)	Sex	0.7417	0.3891
Glucose	AST log 1.15	0.739	0.39
HDL log 1.15	LDL log 1.15	0.6869	0.4072
APRI log 1.15	HDL log 1.15	0.6687	0.4135
Sex	BMI	0.6579	0.4173
FIB-4	ALP	0.5845	0.4446
S category (merged)	HDL log 1.15	0.5817	0.4457
TG	ALT	0.5611	0.4538
De Ritis Index	TG	0.5537	0.4568
Glucose	Sex	0.5521	0.4575
AST log 1.15	De Ritis Index	0.5447	0.4605
APRI log 1.15	TChol log 1.15	0.5412	0.4619
FIB-4	HDL log 1.15	0.5263	0.4681
FIB-4	LDL log 1.15	0.5066	0.4766

Table 9. Cont.

Variable 1	Variable 2	χ^2	p (LR)
FIB-4	Glucose	0.4949	0.4817
Glucose	LDL log 1.15	0.4779	0.4894
LDL log 1.15	TChol log 1.15	0.4574	0.4988
Age	S category (merged)	0.456	0.4995
S category (merged)	BMI	0.4456	0.5044
BMI	ALT	0.4409	0.5067
Sex	LDL log 1.15	0.4194	0.5172
De Ritis Index	TChol log 1.15	0.4139	0.52
PLT	GGTP	0.404	0.525
AST log 1.15	Bilirubin	0.4017	0.5262
GGTP	BMI	0.3871	0.5338
FIB-4	Bilirubin	0.3787	0.5383
De Ritis Index	PLT	0.3757	0.5399
AST log 1.15	Age	0.3689	0.5436
GGTP	Sex	0.3486	0.5549
TG	Age	0.3357	0.5623
APRI log 1.15	Sex	0.323	0.5698
Age	PLT	0.3095	0.578
APRI log 1.15	Age	0.3011	0.5832
Glucose	GGTP	0.2939	0.5877
HDL log 1.15	BMI	0.291	0.5896
S category (merged)	Bilirubin	0.2852	0.5933
GGTP	ALT	0.2727	0.6016
ATI median value (dB/cm/MHz)	PLT	0.2716	0.6023
ALT	ALP	0.2704	0.6031
LDL log 1.15	BMI	0.2471	0.6192
PLT	S category (merged)	0.2218	0.6377
TG	PLT	0.21	0.6468
APRI log 1.15	PLT	0.2087	0.6478
Glucose	TG	0.2038	0.6517
Glucose	BMI	0.2021	0.653
ATI median value (dB/cm/MHz)	BMI	0.1976	0.6567
FIB-4	TG	0.1874	0.6651
APRI log 1.15	ALP	0.1591	0.69
De Ritis Index	HDL log 1.15	0.1458	0.7025
TChol log 1.15	Bilirubin	0.1449	0.7035
Age	Bilirubin	0.1354	0.7129
Glucose	HDL log 1.15	0.1343	0.714
AST log 1.15	ALP	0.1306	0.7178
APRI log 1.15	De Ritis Index	0.1254	0.7233
TG	LDL log 1.15	0.114	0.7356
BMI	ALP	0.1129	0.7368
Glucose	ALT	0.1104	0.7397
Glucose	ALP	0.1079	0.7426

Table 9. Cont.

Variable 1	Variable 2	χ^2	p (LR)
Glucose	TChol log 1.15	0.1065	0.7442
FIB-4	Sex	0.103	0.7482
PLT	LDL log 1.15	0.1014	0.7501
GGTP	Bilirubin	0.0903	0.7638
APRI log 1.15	TG	0.0744	0.7851
Glucose	S category (merged)	0.0718	0.7887
Age	ALP	0.0713	0.7895
AST log 1.15	LDL log 1.15	0.0648	0.799
ATI median value (dB/cm/MHz)	ALT	0.0633	0.8014
APRI log 1.15	LDL log 1.15	0.0608	0.8052
S category (merged)	ALP	0.0523	0.8191
APRI log 1.15	GGTP	0.051	0.8213
Glucose	Bilirubin	0.0365	0.8485
FIB-4	Age	0.0352	0.8512
AST log 1.15	ALT	0.0336	0.8547
De Ritis Index	Age	0.0291	0.8644
PLT	TChol log 1.15	0.0232	0.8789
TG	TChol log 1.15	0.0231	0.8791
De Ritis Index	BMI	0.0173	0.8953
AST log 1.15	GGTP	0.0124	0.9113
GGTP	LDL log 1.15	0.0117	0.914
ATI median value (dB/cm/MHz)	HDL log 1.15	0.0111	0.9159
ATI median value (dB/cm/MHz)	S category (merged)	0.0079	0.9292
De Ritis Index	Sex	0.0071	0.9327
De Ritis Index	GGTP	0.0063	0.9368
ATI median value (dB/cm/MHz)	ALP	0.0051	0.9432
PLT	Sex	0.0033	0.9542
FIB-4	De Ritis Index	0.0022	0.9622
ATI median value (dB/cm/MHz)	Bilirubin	0.0016	0.9682
Glucose	ATI median value (dB/cm/MHz)	0.0013	0.9708
AST log 1.15	TG	0.0011	0.9736
BMI	TChol log 1.15	0.0009	0.9755
Age	Sex	0.0008	0.9769
ATI median value (dB/cm/MHz)	Age	0.0006	0.9798
Age	TChol log 1.15	0.0005	0.9816
Age	BMI	0.0004	0.9841
FIB-4	TChol log 1.15	0.0002	0.9882
Age	ALT	0.0002	0.9892

of FIB-4 on the odds of observing higher F index among the study participants, while the modulation by AST and APRI was on the brink of statistical significance ($p = 0.064$ and $p = 0.053$, respectively; Table 10C-D). According to the model (Table 10A), each one-unit increase

in GGTP activity decreased the effect of FIB-4 on the odds of observing higher F index by approximately 1.11%. Conversely, this FIB-4-associated change in the odds would increase by 1.1% with every one-unit elevation in PLT.

Table 10. Changes in impact of FIB-4 on the odds of observing higher values of the F index – results from analysis of interactions

Table 10A. Interaction 1. Reference patient: FIB-4 = 1, GGTP = 32								
Effect/interaction	Tested phenomenon (estimate)	β	β SE	Wald statistic	Estimate	Estimate –95% CI	Estimate 95% CI	<i>p</i>
Intercept	The odds of observing a higher F index among a reference patient (FIB-4 = 1, GGTP = 32)	–3.119	0.545	32.723	0.044	0.015	0.129	< 0.001
FIB-4 c 1	Fold difference in the odds upon each one-unit increase in FIB-4	2.075	0.716	8.391	7.967	1.957	32.442	0.004
GGTP c 32	Fold difference in the odds upon each one-unit increase in AST	0.006	0.004	1.862	1.006	0.997	1.015	0.172
FIB-4 c 1*GGTP c 32	Fold modulation of the FIB-4 effect on the odds upon each one-unit increase in GGTP	–0.011	0.005	4.396	0.989	0.980	0.999	0.036
Table 10B. Interaction 2. Reference patient: FIB-4 = 1, PLT = 236								
Effect/interaction	Tested phenomenon	β	β SE	Wald statistic	Estimate	Estimate –95% CI	Estimate 95% CI	<i>p</i>
Intercept	The odds of observing a higher F index among a reference patient (FIB-4 = 1, PLT = 236)	–3.213	0.565	32.373	0.040	0.013	0.122	< 0.001
FIB-4 c 1	Fold difference in the odds upon each one-unit increase in FIB-4	2.686	0.863	9.681	14.668	2.702	79.638	0.002
PLT c 236	Fold difference in the odds upon each one-unit increase in PLT	0.012	0.008	2.274	1.012	0.996	1.028	0.132
FIB-4 c 1*PLT c 236	Fold modulation of the FIB-4 effect on the odds upon each one-unit increase in GGTP	0.011	0.005	5.563	1.011	1.002	1.021	0.018
Table 10C. Interaction 3 - Reference patient: FIB-4 = 1, AST = 26.69								
Effect/interaction	Tested phenomenon	β	β SE	Wald statistic	Estimate	Estimate –95% CI	Estimate 95% CI	<i>p</i>
Intercept	The odds of observing a higher F index among a reference patient (FIB-4 = 1, AST = 26.69)	–3.167	0.552	32.944	0.042	0.014	0.124	< 0.001
FIB-4 c 1	Fold difference in the odds upon each one-unit increase in FIB-4	1.555	0.573	7.360	4.734	1.540	14.557	0.007
AST log 1.15 c 23.5	Fold difference in the odds upon each consecutive 15% increase in AST activity	0.299	0.144	4.313	1.349	1.017	1.790	0.038
FIB-4 c 1*AST log 1.15 c 23.5	Fold modulation of the FIB-4 effect on the odds upon each one-unit increase in GGTP	–0.171	0.093	3.425	0.843	0.703	1.010	0.064
Table 10D. Interaction 4 – Reference patient: FIB-4 = 1, APRI = 0.37								
Effect/interaction	Tested phenomenon	β	β SE	Wald statistic	Estimate	Estimate –95% CI	Estimate 95% CI	<i>p</i>
Intercept	The odds of observing a higher F index among a reference patient (FIB-4 = 1, APRI = 0.37)	–2.879	0.471	37.325	0.056	0.022	0.142	< 0.001
FIB-4 c 1	Fold difference in the odds upon each one-unit increase in FIB-4	1.627	0.637	6.523	5.090	1.460	17.742	0.011
APRI log 1.15 c -7.16	Fold difference in the odds upon each one-unit increase in APRI	0.109	0.109	0.986	1.115	0.900	1.381	0.321
FIB-4 c 1*APRI log 1.15 c -7.16	Fold modulation of the FIB-4 effect on the odds upon each one-unit increase in GGTP	–0.094	0.049	3.737	0.910	0.827	1.001	0.053

c – assumed value for each variable employed in each interaction.

Discussion

The above analysis indicates that the use of USG among patients may not be sufficient for effective diagnosis of liver steatosis and fibrosis among adult patients. Classical USG, in particular, is not very effective at detecting and assessing liver fibrosis, which is a condition indicating more developed or complicated progression of liver disease.

The study shows that after the recruitment of patients whose post-USG diagnosis detected liver steatosis, additional imaging with the use of SWE and ATI showed that USG alone delivered false positive results in some participants. The additional imaging procedures that employed ATI for liver steatosis and SWE for liver fibrosis have shown that 64 patients (60 from the subgroup with F0-F1 index and 4 from the subgroup with F2-F3 index) were confirmed to have no liver steatosis (S0), while 30 further participants had only had a mild steatosis (S1 – 27 participants with F0-F1 index and 3 participants with F2-F3 index).

This general observation is confirmed by various studies, which suggest that ATI and SWE extend imaging diagnostics, because USG may be, in some cases, inaccurate (falsely positive results towards liver steatosis) [20-22]. However, these studies are based on imaging techniques only, while Ijima [23] in industry-financed analysis (for Canon, producer of ATI imaging devices), and later Tada *et al.* [19], have concluded in a similar manner for ATI, i.e. that its diagnostic value in checking liver steatosis is comparable to that offered by biopsy.

Ma *et al.* [24] indicate that both ATI and SWE are effective at diagnosing both liver fibrosis and steatosis as the main and most common associated conditions. However, these authors concluded that ATI may be even more effective, but this observation may be subject to type of liver disease (they worked with metabolic dysfunction-associated steatotic liver disease). In addition, Yazdani *et al.* [25] suggest that SWE is effective at diagnosing liver steatosis, stating that it is a plausible alternative to invasive methods such as biopsy.

On the other hand, among the participants of this study who were diagnosed with liver steatosis based on USG imaging, this was only re-confirmed with ATI imaging among 8 participants (diagnosed with S1-S3 steatosis stage) among the whole subgroup with F2-F3 values ($N = 13$). This may suggest that SWE and ATI imaging combined were effective at the more credible evaluation of liver condition, while they both may be effective at cross-examining the liver to check whether there is not only steatosis but also fibrosis, and – also very important – which patients may be affected by both liver conditions at the same time. Many authors confirm such effectiveness of cross-examination of liver condition, with the use of ATI and SWE at the same time (also variants of SWE technology: pointed SWE or two-dimensional SWE) [16,26,27].

As an extension for this discussion, more in-depth observations could also be presented. Yuri *et al.* [28] assessed whether ATI may be affected by liver fibrosis, but they rejected this assumption, thus demonstrating that ATI is highly steatosis-sensitive, and its imaging capability is not affected by fibrosis as an additional factor blurring (falsely enhancing or diluting) the ATI measurement results. The same should apply to SWE; however, the effectiveness of both ATI and SWE may be negatively affected by additional factors not included in this study (inflammatory activity) [29].

Based on the normality distribution, this study confirms that ATI and SWE results are statistically significant ($p < 0.001$ and 0.035 , respectively). But what comes out of the results is that there are some promising predictors for higher F index value (F2-F3) and S index value (S2-S3), and these are as follows: age, glucose levels, AST, GGPT activity, as well as liver function indicators: FIB-4, De Ritis Index, and APRI.

Additional statistical procedures show that the most promising candidates for prediction of F2-F3 index value (more developed fibrosis) are: AST, ALT and glucose levels. What this shows the odds of observing higher F value is based on the assumption that AST and glucose levels are higher, while ALT levels. AST, however is the most strong predictor elevating odds of observing F2-F3 value more than ALT or glucose. These results, namely, high AST/low ALT linkage, may indirectly show that de Ritis index, too, may be associated with higher F value (De Ritis Index is merely a proportion between AST and ALT levels: the higher AST, or lower ALT, the higher the value of the Ritis index is).

Regarding the age, correlation with higher S or F index is confirmed by plethora of sources, so that the term coined for the condition is age-related hepatic steatosis [30-32], hence, the above study does not deliver any new results on this long-standing and well-proved correlation between age and liver steatosis.

What the study shows is an interesting linkage between high AST and glucose, low ALT which at the time are responsible for high odds of observing F2-F3 index among the participants, according to this study. What is seen in literature, high AST is broadly confirmed as a predictor for the progression of fatty liver disease, and fibrosis and steatosis as its main symptoms [33-35]. The same applies to high AST along with high ALT [36-39]. Yet, correlation between ALT, AST and glucose, altogether, in patients liver steatosis is rarely studied, but if so, it is rather conducted with a different research goal in mind (what roles they have in leading to prediabetes and diabetes) [33,40,41].

Yet, the literature may give some initial response to this observation, as there are opinions that ALT may be a weaker predictor in hepatic conditions (steatosis or fibrosis), than have so far been thought since: its levels decrease with age progression among patients, also its

levels increase at the beginning of steatosis and then they may decrease [42,43]. Weak value of ALT in predicting liver steatosis or fibrosis comes from a wider 2017–2018 NHANES study [44].

The result of, somewhat contradictory to the results seen in literature, specifically with regard to ALT levels, may be: 1) correct, if this is related to high values of De Ritis ratio, which are a good predictor for more developed stage of steatosis and fibrosis in liver, 2) correct if they describe a general tendency within the group of participants where older patients prevail (see Table 3), 3) incorrect, basing on the low sample size, specifically, number of participants who have had F2–F3 index and low ALT levels (> 30) at the same time ($N = 8$). Hence, such a linkage needs to be verified in further studies.

FIB-4 index may also be a good predictor for seeing F2–F3 among participants, as it is confirmed through the high statistical significance of results in univariate analysis, which also presents that its increase leads to higher odds of observing higher F index among participants. Its impact was examined in pairs (interactions) with GGPT, platelet count, AST and APRI value, where two former interactions have come out to be statistically significant, while two latter ones were on the brink of statistical significance.

Higher FIB-4 value along with increased GGPT ratios are confirmed in literature [45], however value of GGPT in diagnosing liver steatosis and fibrosis may be inferior to De Ritis index, APRI, or AST levels [46]. Interaction of FIB-4 and platelet count leading to higher F index in the study shows only a minimum positive change (1.1% increase). However, results from the literature do not judge the impact of this pair, i.e. unidirectionally. Zijstra *et al.* [47] observed correlation between decreasing PLT levels along with increasing FIB-4 index when liver fibrosis was progressing in observed patients. Malladi *et al.* [48] confirmed the observation of Zijstra *et al.* [47] on the lower levels of PLT, but they indicated that a decrease of PLT in patients with progressing steatosis and – particularly – fibrosis is accompanied with increased PLT activation, which means that the explanatory value of PLT for various liver diseases (also where there is both steatotic and fibrotic transformation of liver tissue) is not with serum PLT level but with PLT concentration in the liver tissue and its proinflammatory and pro-fibrous activity.

The main limitation of this study is that within the whole group of participants, individuals diagnosed with an F2–F3 index value may have been underrepresented ($N = 13$) in comparison to individuals who had an F0–F1 index value ($N = 104$). This drawback encountered during the recruitment of participants for the study has – at least in part – been mitigated with the series of statistical tests conducted. Another limitation of this study may be related to the assumed reference patient approach (Table 7 and Table 10), which is related to a ‘hypothetical participant’, which may not give comparable results to studies

where the same interactions have been studied on larger sample sizes.

Suggestions for future study:

- Because there was a significant share of participants with blood hypertension, it may be reasonable to research various publications studying relationship between blood hypertension and liver steatosis and cirrhosis [49]; the same approach could be given to the comparison of patients with chronic disease vs. healthy patients, or patients with intake of at least one drug vs. patients not taking any drugs.
- Re-examination of significance of ALT levels in determining higher F index, but on a larger group of participants with $F > 1$ index value.
- The effects of measuring liver fibrosis and steatosis with SWE and ATI, respectively, should be compared to the results of liver biopsy in further studies (alongside the same set of blood tests among two compared groups of patients) to determine the extent to which SWE-ATI, following USG initial examination, is accurate when confronted with liver biopsy (non-invasive vs. invasive approach).

Conclusions

ATI and SWE are plausible, ultrasound-based imaging techniques that may be considered as an alternative or supplementary to USG. Utility of both imaging techniques in checking liver condition among adult patients is especially important because in USG false positive results may be obtained regarding liver steatosis, and it is relatively ineffective in detecting liver fibrosis. In the study, a relationship between higher F index and higher S index was also presented, which means that the study participants who had their liver steatosis (S2–S3) confirmed in ATI would also have confirmed liver fibrosis in more progressed stages (F2–F3) at the same time. This reaffirms the fact that fibrosis follows steatosis when liver condition deteriorates, but there are also other various reasons for liver tissue to become fibrous (drug intake, other chronic disease), which may be clearly read from the statistics (Tables 3–5).

The results of the study show that the blood tests conducted among the patients examined with ATI–SWE, which included determining the glucose levels, the basic indicators for liver assessment (cholesterol fractions, ALT, ASP, etc.), and liver assessment ratios and indexes (De Ritis ratio, FIB-4, etc.), suggest that the most promising predictors for higher F index are as follows: high AST level, high glucose level (although not widely confirmed in literature), high FIB-4 value, and moderately higher APRI and higher GGTP ratio. A separate mention should be made here for lower ALT levels as a good predictor to seeing higher F index alongside elevated AST and glucose levels, which may be related to the fact that its diagnostic value may be overestimated, especially in situations

when the ALT level does not explain deteriorating liver condition (in elderly patients and patients with more progressed liver fibrosis).

Disclosures

1. Institutional review board statement: The study was approved by the Bioethics Committee of Wrocław Medical University (approval number 355/2021).

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Appendix A. Stepwise elimination algorithm

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 1	Sex	0.264	0.608			Included in the model
	S category (merged)	0.094	0.954			Included in the model
	Age	0.255	0.614			Included in the model
	BMI	0.667	0.414			Included in the model
	Glucose	2.427	0.119			Included in the model
	PLT	0.034	0.855			Included in the model
	ALT	3.202	0.074			Included in the model
	FIB-4	0.109	0.741			Included in the model
	De Ritis Index	0.202	0.653			Included in the model
	ALP	0.854	0.355			Included in the model
	GGTP	2.338	0.126			Included in the model
	Bilirubin	0.123	0.726			Included in the model
	TG	2.969	0.085			Included in the model
	ATI median value (dB/cm/MHz)	0.013	0.909			Included in the model
	AST log 1.15	0.155	0.693			Included in the model
	APRI log 1.15	0.001	0.981			Excluded from the model in this step
	TChol log 1.15	1.228	0.268			Included in the model
	HDL log 1.15	0.081	0.776			Included in the model
	LDL log 1.15	1.270	0.260			Included in the model
Step 2	Sex	0.273	0.602			Included in the model
	S category (merged)	0.101	0.951			Excluded from the model in this step
	Age	0.427	0.513			Included in the model
	BMI	0.723	0.395			Included in the model
	Glucose	2.510	0.113			Included in the model
	PLT	0.696	0.404			Included in the model
	ALT	3.444	0.063			Included in the model
	FIB-4	0.882	0.348			Included in the model
	De Ritis Index	0.336	0.562			Included in the model
	ALP	0.923	0.337			Included in the model
	GGTP	2.329	0.127			Included in the model
	Bilirubin	0.123	0.725			Included in the model
	TG	3.069	0.080			Included in the model
	ATI median value (dB/cm/MHz)	0.014	0.905			Included in the model
	AST log 1.15	4.095	0.043			Included in the model
	LDL log 1.15	1.517	0.218			Included in the model
	TChol log 1.15	1.468	0.226			Included in the model
	HDL log 1.15	0.091	0.763			Included in the model
	APRI log 1.15			0.001	0.981	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 3	Sex	0.295	0.587			Included in the model
	HDL log 1.15	0.113	0.737			Excluded from the model in this step
	Age	0.414	0.520			Included in the model
	BMI	0.803	0.370			Included in the model
	Glucose	3.110	0.078			Included in the model
	PLT	0.712	0.399			Included in the model
	ALT	3.968	0.046			Included in the model
	FIB-4	0.816	0.366			Included in the model
	De Ritis Index	0.310	0.578			Included in the model
	ALP	1.076	0.300			Included in the model
	GGTP	2.398	0.121			Included in the model
	Bilirubin	0.147	0.701			Included in the model
	TG	3.273	0.070			Included in the model
	ATI median value (dB/cm/MHz)	0.139	0.709			Included in the model
	AST log 1.15	4.982	0.026			Included in the model
	LDL log 1.15	1.727	0.189			Included in the model
	TChol log 1.15	1.653	0.199			Included in the model
	S category (merged)			0.101	0.951	Excluded from the model in previous step(s)
	APRI log 1.15			0.007	0.934	Excluded from the model in previous step(s)
Step 4	Sex	0.189	0.664			Included in the model
	TChol log 1.15	1.793	0.181			Included in the model
	Age	0.457	0.499			Included in the model
	BMI	0.752	0.386			Included in the model
	Glucose	3.114	0.078			Included in the model
	PLT	0.639	0.424			Included in the model
	ALT	4.032	0.045			Included in the model
	FIB-4	0.768	0.381			Included in the model
	De Ritis Index	0.319	0.572			Included in the model
	ALP	0.957	0.328			Included in the model
	GGTP	2.452	0.117			Included in the model
	Bilirubin	0.089	0.765			Excluded from the model in this step
	TG	4.896	0.027			Included in the model
	ATI median value (dB/cm/MHz)	0.153	0.696			Included in the model
	AST log 1.15	4.990	0.025			Included in the model
	LDL log 1.15	1.822	0.177			Included in the model
	HDL log 1.15			0.113	0.736	Excluded from the model in previous step(s)
	S category (merged)			0.125	0.939	Excluded from the model in previous step(s)
	APRI log 1.15			0.038	0.846	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 5	Sex	0.128	0.721			Included in the model
	TChol log 1.15	1.854	0.173			Included in the model
	Age	0.479	0.489			Included in the model
	BMI	0.820	0.365			Included in the model
	Glucose	3.074	0.080			Included in the model
	PLT	0.576	0.448			Included in the model
	ALT	3.954	0.047			Included in the model
	FIB-4	0.657	0.418			Included in the model
	De Ritis Index	0.303	0.582			Included in the model
	ALP	0.918	0.338			Included in the model
	GGTP	2.354	0.125			Included in the model
	LDL log 1.15	1.824	0.177			Included in the model
	TG	4.437	0.035			Included in the model
	ATI median value (dB/cm/MHz)	0.101	0.751			Excluded from the model in this step
	AST log 1.15	4.921	0.027			Included in the model
	Bilirubin			0.090	0.765	Excluded from the model in previous step(s)
	HDL log 1.15			0.052	0.820	Excluded from the model in previous step(s)
	S category (merged)			0.135	0.935	Excluded from the model in previous step(s)
	APRI log 1.15			0.030	0.863	Excluded from the model in previous step(s)
Step 6	Sex	0.149	0.699			Excluded from the model in this step
	TChol log 1.15	1.885	0.170			Included in the model
	Age	0.439	0.508			Included in the model
	BMI	0.771	0.380			Included in the model
	Glucose	3.032	0.082			Included in the model
	PLT	0.519	0.471			Included in the model
	ALT	3.734	0.053			Included in the model
	FIB-4	0.572	0.449			Included in the model
	De Ritis Index	0.246	0.620			Included in the model
	ALP	0.957	0.328			Included in the model
	GGTP	2.281	0.131			Included in the model
	LDL log 1.15	1.812	0.178			Included in the model
	TG	4.808	0.028			Included in the model
	AST log 1.15	4.725	0.030			Included in the model
	ATI median value (dB/cm/MHz)			0.101	0.750	Excluded from the model in previous step(s)
	Bilirubin			0.037	0.847	Excluded from the model in previous step(s)
	HDL log 1.15			0.074	0.785	Excluded from the model in previous step(s)
	S category (merged)			0.209	0.901	Excluded from the model in previous step(s)
	APRI log 1.15			0.021	0.884	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 7	AST log 1.15	4.688	0.030			Included in the model
	TChol log 1.15	2.048	0.152			Included in the model
	Age	0.496	0.481			Included in the model
	BMI	0.640	0.424			Included in the model
	Glucose	2.933	0.087			Included in the model
	PLT	0.418	0.518			Included in the model
	ALT	3.579	0.058			Included in the model
	FIB-4	0.521	0.470			Included in the model
	De Ritis Index	0.274	0.601			Excluded from the model in this step
	ALP	0.971	0.324			Included in the model
	GGTP	2.249	0.134			Included in the model
	LDL log 1.15	1.867	0.172			Included in the model
	TG	4.482	0.034			Included in the model
	Sex			0.150	0.699	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.123	0.726	Excluded from the model in previous step(s)
	Bilirubin			0.003	0.957	Excluded from the model in previous step(s)
	HDL log 1.15			0.003	0.954	Excluded from the model in previous step(s)
	S category (merged)			0.234	0.889	Excluded from the model in previous step(s)
	APRI log 1.15			0.015	0.903	Excluded from the model in previous step(s)
Step 8	AST log 1.15	5.266	0.022			Included in the model
	TChol log 1.15	2.242	0.134			Included in the model
	Age	0.597	0.440			Included in the model
	BMI	0.994	0.319			Included in the model
	Glucose	2.727	0.099			Included in the model
	PLT	0.239	0.625			Excluded from the model in this step
	ALT	5.095	0.024			Included in the model
	FIB-4	0.459	0.498			Included in the model
	TG	4.482	0.034			Included in the model
	ALP	1.264	0.261			Included in the model
	GGTP	2.451	0.117			Included in the model
	LDL log 1.15	2.167	0.141			Included in the model
	De Ritis Index			0.280	0.597	Excluded from the model in previous step(s)
	Sex			0.182	0.670	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.042	0.837	Excluded from the model in previous step(s)
	Bilirubin			0.002	0.965	Excluded from the model in previous step(s)
	HDL log 1.15			0.002	0.962	Excluded from the model in previous step(s)
	S category (merged)			0.090	0.956	Excluded from the model in previous step(s)
	APRI log 1.15			0.199	0.656	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 9	AST log 1.15	5.524	0.019			Included in the model
	TChol log 1.15	2.019	0.155			Included in the model
	Age	0.550	0.458			Included in the model
	BMI	1.051	0.305			Included in the model
	Glucose	2.986	0.084			Included in the model
	LDL log 1.15	1.981	0.159			Included in the model
	ALT	5.359	0.021			Included in the model
	FIB-4	0.290	0.590			Excluded from the model in this step
	TG	4.303	0.038			Included in the model
	ALP	1.269	0.260			Included in the model
	GGTP	2.687	0.101			Included in the model
	PLT			0.242	0.623	Excluded from the model in previous step(s)
	De Ritis Index			0.104	0.747	Excluded from the model in previous step(s)
	Sex			0.064	0.800	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.025	0.875	Excluded from the model in previous step(s)
	Bilirubin			0.001	0.969	Excluded from the model in previous step(s)
	HDL log 1.15			0.005	0.941	Excluded from the model in previous step(s)
	S category (merged)			0.086	0.958	Excluded from the model in previous step(s)
	APRI log 1.15			0.146	0.702	Excluded from the model in previous step(s)
Step 10	AST log 1.15	11.179	0.001			Included in the model
	TChol log 1.15	2.389	0.122			Included in the model
	Age	0.837	0.360			Excluded from the model in this step
	BMI	0.859	0.354			Included in the model
	Glucose	2.818	0.093			Included in the model
	LDL log 1.15	2.277	0.131			Included in the model
	ALT	8.118	0.004			Included in the model
	GGTP	2.836	0.092			Included in the model
	TG	4.398	0.036			Included in the model
	ALP	1.373	0.241			Included in the model
	FIB-4			0.308	0.579	Excluded from the model in previous step(s)
	PLT			<0.001	0.986	Excluded from the model in previous step(s)
	De Ritis Index			0.055	0.815	Excluded from the model in previous step(s)
	Sex			0.035	0.851	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.002	0.961	Excluded from the model in previous step(s)
	Bilirubin			0.020	0.888	Excluded from the model in previous step(s)
	HDL log 1.15			0.029	0.864	Excluded from the model in previous step(s)
	S category (merged)			0.019	0.990	Excluded from the model in previous step(s)
	APRI log 1.15			0.063	0.801	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 11	AST log 1.15	11.483	0.001			Included in the model
	TChol log 1.15	2.692	0.101			Included in the model
	ALP	1.896	0.169			Included in the model
	BMI	0.704	0.401			Excluded from the model in this step
	Glucose	5.921	0.015			Included in the model
	LDL log 1.15	2.409	0.121			Included in the model
	ALT	8.599	0.003			Included in the model
	GGTP	3.241	0.072			Included in the model
	TG	4.900	0.027			Included in the model
	Age			0.859	0.354	Excluded from the model in previous step(s)
	FIB-4			0.610	0.435	Excluded from the model in previous step(s)
	PLT			0.042	0.838	Excluded from the model in previous step(s)
	De Ritis Index			0.059	0.808	Excluded from the model in previous step(s)
	Sex			0.056	0.812	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.004	0.953	Excluded from the model in previous step(s)
	Bilirubin			0.012	0.915	Excluded from the model in previous step(s)
	HDL log 1.15			0.082	0.775	Excluded from the model in previous step(s)
	S category (merged)			0.029	0.985	Excluded from the model in previous step(s)
	APRI log 1.15			0.185	0.667	Excluded from the model in previous step(s)
Step 12	AST log 1.15	11.025	0.001			Included in the model
	TChol log 1.15	2.333	0.127			Included in the model
	ALP	1.786	0.181			Excluded from the model in this step
	TG	4.703	0.030			Included in the model
	Glucose	6.357	0.012			Included in the model
	LDL log 1.15	1.980	0.159			Included in the model
	ALT	8.098	0.004			Included in the model
	GGTP	3.437	0.064			Included in the model
	BMI			0.722	0.395	Excluded from the model in previous step(s)
	Age			0.721	0.396	Excluded from the model in previous step(s)
	FIB-4			0.334	0.564	Excluded from the model in previous step(s)
	PLT			<0.001	0.995	Excluded from the model in previous step(s)
	De Ritis Index			0.227	0.633	Excluded from the model in previous step(s)
	Sex			0.017	0.898	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.050	0.822	Excluded from the model in previous step(s)
	Bilirubin			0.020	0.888	Excluded from the model in previous step(s)
	HDL log 1.15			0.125	0.723	Excluded from the model in previous step(s)
	S category (merged)			0.055	0.973	Excluded from the model in previous step(s)
	APRI log 1.15			0.060	0.807	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 13	AST log 1.15	10.831	0.001			Included in the model
	TChol log 1.15	1.679	0.195			Included in the model
	GGTP	2.323	0.127			Included in the model
	TG	3.120	0.077			Included in the model
	Glucose	5.679	0.017			Included in the model
	LDL log 1.15	1.270	0.260			Excluded from the model in this step
	ALT	8.475	0.004			Included in the model
	ALP			1.730	0.188	Excluded from the model in previous step(s)
	BMI			0.553	0.457	Excluded from the model in previous step(s)
	Age			1.168	0.280	Excluded from the model in previous step(s)
	FIB-4			0.493	0.483	Excluded from the model in previous step(s)
	PLT			0.000	0.983	Excluded from the model in previous step(s)
	De Ritis Index			0.446	0.504	Excluded from the model in previous step(s)
	Sex			0.001	0.976	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.048	0.826	Excluded from the model in previous step(s)
	Bilirubin			0.022	0.881	Excluded from the model in previous step(s)
	HDL log 1.15			0.000	0.999	Excluded from the model in previous step(s)
	S category (merged)			0.090	0.956	Excluded from the model in previous step(s)
	APRI log 1.15			0.074	0.786	Excluded from the model in previous step(s)
Step 14	AST log 1.15	10.603	0.001			Included in the model
	TChol log 1.15	0.414	0.520			Excluded from the model in this step
	GGTP	2.455	0.117			Included in the model
	TG	3.385	0.066			Included in the model
	Glucose	6.912	0.009			Included in the model
	ALT	8.273	0.004			Included in the model
	LDL log 1.15			1.372	0.241	Excluded from the model in previous step(s)
	ALP			0.866	0.352	Excluded from the model in previous step(s)
	BMI			0.154	0.695	Excluded from the model in previous step(s)
	Age			1.195	0.274	Excluded from the model in previous step(s)
	FIB-4			0.800	0.371	Excluded from the model in previous step(s)
	PLT			0.159	0.690	Excluded from the model in previous step(s)
	De Ritis Index			0.349	0.555	Excluded from the model in previous step(s)
	Sex			0.037	0.848	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.140	0.709	Excluded from the model in previous step(s)
	Bilirubin			0.050	0.824	Excluded from the model in previous step(s)
	HDL log 1.15			0.432	0.511	Excluded from the model in previous step(s)
	S category (merged)			0.336	0.846	Excluded from the model in previous step(s)
	APRI log 1.15			0.426	0.514	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score p	Status
Step 15	AST log 1.15	10.605	0.001			Included in the model
	ALT	8.015	0.005			Included in the model
	GGTP	2.582	0.108			Excluded from the model in this step
	TG	3.869	0.049			Included in the model
	Glucose	8.658	0.003			Included in the model
	TChol log 1.15			0.417	0.518	Excluded from the model in previous step(s)
	LDL log 1.15			0.003	0.957	Excluded from the model in previous step(s)
	ALP			0.938	0.333	Excluded from the model in previous step(s)
	BMI			0.188	0.665	Excluded from the model in previous step(s)
	Age			1.407	0.236	Excluded from the model in previous step(s)
	FIB-4			0.981	0.322	Excluded from the model in previous step(s)
	PLT			0.300	0.584	Excluded from the model in previous step(s)
	De Ritis Index			0.254	0.614	Excluded from the model in previous step(s)
	Sex			0.078	0.780	Excluded from the model in previous step(s)
	ATI (dB/cm/MHz)			0.033	0.855	Excluded from the model in previous step(s)
	Bilirubin			0.058	0.809	Excluded from the model in previous step(s)
	HDL log 1.15			0.576	0.448	Excluded from the model in previous step(s)
	S category (merged)			0.227	0.893	Excluded from the model in previous step(s)
	APRI log 1.15			0.614	0.433	Excluded from the model in previous step(s)
Step 16	AST log 1.15	10.467	0.001			Included in the model
	ALT	7.695	0.006			Included in the model
	Glucose	9.847	0.002			Included in the model
	TG	1.250	0.264			Excluded from the model in this step
	GGTP			2.119	0.145	Excluded from the model in previous step(s)
	TChol log 1.15			0.515	0.473	Excluded from the model in previous step(s)
	LDL log 1.15			0.023	0.881	Excluded from the model in previous step(s)
	ALP			0.008	0.929	Excluded from the model in previous step(s)
	BMI			0.290	0.590	Excluded from the model in previous step(s)
	Age			1.505	0.220	Excluded from the model in previous step(s)
	FIB-4			0.944	0.331	Excluded from the model in previous step(s)
	PLT			0.060	0.807	Excluded from the model in previous step(s)
	De Ritis Index			0.211	0.646	Excluded from the model in previous step(s)
	Sex			0.251	0.616	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.190	0.663	Excluded from the model in previous step(s)
	Bilirubin			0.270	0.604	Excluded from the model in previous step(s)
	HDL log 1.15			0.999	0.318	Excluded from the model in previous step(s)
	S category (merged)			0.292	0.864	Excluded from the model in previous step(s)
	APRI log 1.15			0.299	0.585	Excluded from the model in previous step(s)

Appendix A. Cont.

Step	Effect (variable)	Wald statistic	Wald p	Score statistic	Score <i>p</i>	Status
Step 17	AST log 1.15	12.010	0.001			Included in the model
	ALT	8.614	0.003			Included in the model
	Glucose	9.024	0.003			Included in the model
	TG			4.694	0.030	Excluded from the model in previous step(s)
	GGTP			0.026	0.871	Excluded from the model in previous step(s)
	TChol log 1.15			0.062	0.803	Excluded from the model in previous step(s)
	LDL log 1.15			0.000	0.987	Excluded from the model in previous step(s)
	ALP			0.016	0.900	Excluded from the model in previous step(s)
	BMI			0.167	0.683	Excluded from the model in previous step(s)
	Age			0.619	0.431	Excluded from the model in previous step(s)
	FIB-4			0.151	0.697	Excluded from the model in previous step(s)
	PLT			0.005	0.946	Excluded from the model in previous step(s)
	De Ritis Index			0.204	0.652	Excluded from the model in previous step(s)
	Sex			0.038	0.845	Excluded from the model in previous step(s)
	ATI median value (dB/cm/MHz)			0.708	0.400	Excluded from the model in previous step(s)
	Bilirubin			0.094	0.759	Excluded from the model in previous step(s)
	HDL log 1.15			2.060	0.151	Excluded from the model in previous step(s)
	S category (merged)			1.428	0.490	Excluded from the model in previous step(s)
	APRI log 1.15			0.017	0.895	Excluded from the model in previous step(s)