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EVALUATION OF ELASTOGRAPHY IN COMPARISON WITH α 2-MACROGLOBULIN, HAPTOGLOBIN, AND APOLIPOPROTEIN A1 LEVELS IN THE DIAGNOSIS OF LIVER FIBROSIS IN TYPE 2 DIABETES MELLITUS

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This study aimed to comparatively evaluate elastography and serum biomarkers (α 2-macroglobulin, haptoglobin, and apolipoprotein A1) for diagnosing liver fibrosis in patients with type 2 diabetes mellitus. The study included 108 patients: 33 without evident fibrosis (F0–F1) and 75 with fibrosis of varying severity (F2–F4). Age, body mass index, disease duration, liver elastography parameters, and serum biomarker levels were assessed. Statistical analysis included the Mann–Whitney U test, Spearman correlation, ROC analysis, and canonical correlation analysis. Body mass index was significantly associated with fibrosis progression ($p=0.360$; $p<0.001$). Elastography parameters correlated positively with α 2-macroglobulin ($p=0.573$; $p<0.001$) and negatively with haptoglobin ($p=-0.281$; $p=0.003$). Canonical analysis identified liver stiffness and body mass index as the main clinical contributors and α 2-macroglobulin and haptoglobin as the principal biochemical contributors. Combining elastography, physical parameters, and serum biomarkers may improve diagnostic assessment of liver fibrosis in patients with type 2 diabetes mellitus.

Key words: metabolic dysfunction-associated steatotic liver disease, type 2 diabetes mellitus, shear wave elastography, liver fibrosis, serum biomarkers.

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ОЦІНКА ЕЛАСТОГРАФІЇ У ПОРІВНЯННІ З РІВНЯМИ α 2-МАКРОГЛОБУЛІНУ, ГАПТОГЛОБІНУ ТА АПОЛІПОПРОТЕЇНУ А1 У ДІАГНОСТИЦІ ФІБРОЗУ ПЕЧІНКИ ПРИ ЦУКРОВОМУ ДІАБЕТІ 2 ТИПУ

Метою дослідження була порівняльна оцінка еластографії та сироваткових біомаркерів (α 2-макроглобуліну, гаптоглобіну та аполіпопротеїну А1) у діагностиці фіброзу печінки у пацієнтів із цукровим діабетом 2 типу. До дослідження було включено 108 пацієнтів: 33 без виражених ознак фіброзу (F0–F1) та 75 із фіброзом різного ступеня тяжкості (F2–F4). Оцінювали вік, індекс маси тіла (ІМТ), тривалість захворювання, показники еластографії печінки та рівні сироваткових біомаркерів. Статистичний аналіз включав U-критерій Манна–Уїтні, кореляційний аналіз Спірмена, ROC-аналіз та канонічний кореляційний аналіз. ІМТ мав значущий зв'язок із прогресуванням фіброзу ($p=0,360$; $p<0,001$). Показники еластографії позитивно корелювали з рівнем α 2-макроглобуліну ($p=0,573$; $p<0,001$) та негативно – з рівнем гаптоглобіну ($p=-0,281$; $p=0,003$). Канонічний аналіз показав, що основними клінічними факторами були жорсткість печінки та ІМТ, а серед біохімічних показників найбільший внесок мали α 2-макроглобулін та гаптоглобін. Комплексна оцінка даних еластографії, фізичних параметрів та сироваткових біомаркерів може підвищити ефективність діагностики фіброзу печінки у пацієнтів із цукровим діабетом 2 типу.

Ключові слова: метаболічно асоційована стеатотична хвороба печінки, цукровий діабет 2 типу, еластографія зсувною хвилею, фіброз печінки, сироваткові біомаркери.

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as non-alcoholic fatty liver disease (NAFLD), represents one of the most prevalent chronic liver diseases and is increasingly recognized as an important manifestation of systemic metabolic dysfunction [11, 15]. The adoption of the MASLD nomenclature emphasizes the close relationship between hepatic steatosis and cardiometabolic risk factors, including obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) [6, 11]. This association is particularly important because patients with T2DM constitute a population at increased risk of progressive liver disease and clinically significant fibrosis [3, 15].

The relationship between MASLD and T2DM is complex and bidirectional. Insulin resistance, altered lipid metabolism, chronic low-grade inflammation, oxidative stress, and metabolic dysregulation contribute to hepatocellular injury and

promote progression from steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis [3, 6]. The presence and severity of fibrosis are particularly important for prognosis, as advanced fibrosis identifies patients at increased risk of liver-related complications and determines the need for more intensive surveillance and management [12, 13].

Given the high prevalence of metabolic liver disease among patients with T2DM, timely identification of clinically significant fibrosis is essential. Liver biopsy has traditionally been considered the reference standard for fibrosis assessment; however, its invasive nature, sampling variability, limited reproducibility, and potential complications restrict its applicability for population screening and repeated monitoring [4, 7, 9, 12]. Consequently, considerable attention has been directed toward non-invasive methods capable of

identifying patients at increased risk of advanced fibrosis [2, 6, 8].

Imaging-based techniques, particularly elastography, have become important tools for non-invasive assessment of liver fibrosis. Shear wave elastography enables quantitative evaluation of liver stiffness and may provide clinically relevant information regarding the severity of fibrotic changes [1, 16]. Nevertheless, liver stiffness measurements may be influenced by several factors, including inflammation, steatosis, obesity, and other metabolic characteristics; therefore, interpretation of elastographic findings should take the overall clinical context into account [7, 8, 12].

Alongside imaging techniques, serum biomarkers and biomarker-based algorithms have been increasingly investigated for non-invasive assessment of liver fibrosis [4, 9, 13]. Of particular interest are α 2-macroglobulin, haptoglobin, and apolipoprotein A1 (Apo-A1), which are incorporated into established biomarker panels and reflect different aspects of hepatic fibrogenesis, inflammatory response, and metabolic function. Deckmyn et al. demonstrated the clinical relevance of these serum proteins in patients with fatty liver disease, including individuals with T2DM, supporting their potential value in metabolic liver disease assessment [5].

Current evidence increasingly favors sequential or combined diagnostic strategies rather than reliance on a single non-invasive test [2, 3, 6, 14]. Integration of imaging-derived liver stiffness measurements with clinical and biochemical parameters may improve identification of patients with clinically significant fibrosis, facilitate risk stratification, and reduce unnecessary invasive procedures [2, 12–14]. Such an approach may be particularly relevant in patients with T2DM, in whom obesity and metabolic abnormalities can influence both fibrosis progression and the performance of individual non-invasive tests [2, 3, 15].

The purpose of the study was to perform a comprehensive analysis and evaluate the diagnostic effectiveness of a combination of physical, radiological (elastography), and laboratory methods (α 2-macroglobulin, haptoglobin, Apo-A1) in patients with type 2 diabetes mellitus.

Materials and methods. The work was carried out at the following clinics: Republican Clinical Hospital named by Acad. Mirgasimov, Educational Surgery Clinic of Azerbaijan Medical University, Educational Therapeutic Clinic Azerbaijan Medical University in the period of June 2022–November 2024.

An observational cross-sectional study was conducted, including 108 patients aged ≥ 18 years with type 2 diabetes mellitus.

The diagnosis of type 2 diabetes mellitus was established on the basis of clinical and laboratory

criteria in accordance with internationally accepted diagnostic standards. Assessment of metabolic dysfunction-associated steatotic liver disease and the selection of non-invasive methods for liver fibrosis evaluation were performed in accordance with contemporary international recommendations, including the EASL–EASD–EASO Clinical Practice Guidelines for the management of metabolic dysfunction-associated steatotic liver disease (MASLD) [6]. The diagnostic assessment included clinical and anthropometric evaluation, biochemical testing, and non-invasive assessment of liver fibrosis using serum biomarkers and shear wave elastography. Fibrosis severity was categorized using the METAVIR scoring system (F0–F4) and results obtained using the FibroTest. In addition, all patients underwent elastography (EG) using the Supersonic Aixplorer MultiWave system with a 1–6 MHz curved transducer.

According to the METAVIR scoring system, FibroTest values ranging from 0.00 to 0.21 correspond to stage F0 and indicate no evidence of liver fibrosis. Values between 0.22 and 0.27 are classified as F0–F1 and represent a borderline condition. FibroTest values of 0.28–0.31 correspond to stage F1, indicating minimal fibrosis, whereas values of 0.32–0.48 are classified as F1–F2 and indicate mild fibrosis. A FibroTest result ranging from 0.49 to 0.58 corresponds to stage F2 and reflects moderate, clinically significant fibrosis. Values between 0.59 and 0.74 indicate stage F3, characterized by advanced fibrosis. Finally, FibroTest values ranging from 0.75 to 1.00 correspond to stage F4 and are indicative of liver cirrhosis.

Patients were stratified into two groups according to the stage of fibrosis: F0–F1 – without fibrosis or with minimal manifestations of fibrosis ($n=33$), and F2–F4 – with clinical and/or laboratory signs of liver fibrosis ($n=75$). Serum α 2-macroglobulin, haptoglobin, and apolipoprotein A1 concentrations were determined using an automated Cobas c 501 analyzer (Roche Diagnostics, Germany), according to the manufacturer's instructions.

Statistical analysis included the Mann–Whitney U test, Spearman correlation analysis, ROC analysis, and canonical correlation analysis to evaluate multivariate relationships. Calculations were performed using IBM SPSS Statistics software, version 27 [10].

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and generally accepted principles of biomedical research involving human participants. All diagnostic procedures included in the study were performed as part of routine clinical assessment and did not involve additional interventions beyond standard patient management. The confidentiality and anonymity of

patients' personal and medical information were maintained throughout data collection and analysis. Informed consent for the use of clinical and laboratory data for research purposes was obtained from the participants.

Results of the study. A descriptive analysis was conducted for all patients, including age ($p = 0.920$), body mass index (BMI) ($p=0.006$), disease duration ($p=0.438$), as well as biomarkers: $\alpha 2$ -macroglobulin ($p<0.001$), haptoglobin ($p=0.338$), and Apo-A1 ($p=0.522$) (Table 1).

Table 1

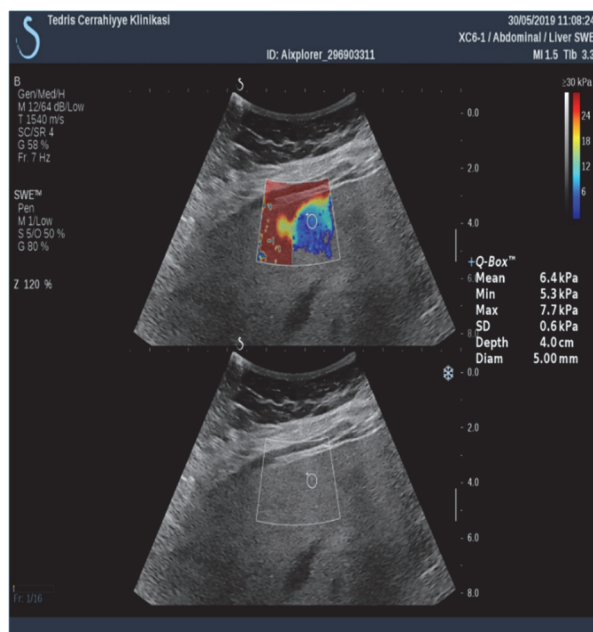
Descriptive analysis of age, body mass index (BMI), and disease duration in patients with type 2 diabetes mellitus

Characteristics	Fibrosis								p
	F0-F1				F2-F4				
	M	Me	Q1	Q3	M	Me	Q1	Q3	
Age	57.8	56.0	52.0	66.0	57.3	58.0	49.0	65.0	0.920
BMI	30.0	30.0	28.0	32.0	32.6	33.0	29.0	36.0	0.006*
Disease duration	11.7	10.0	7.0	16.0	11.3	10.0	4.0	15.0	0.438
α2-macroglobulin	2.94	2.80	2.00	3.40	4.72	4.60	3.60	6.20	<0.001*
Haptoglobin	0.99	0.90	0.70	1.20	0.90	0.90	0.33	1.31	0.338
Apo-A1	1.34	1.35	1.10	1.50	1.28	1.30	0.90	1.63	0.522

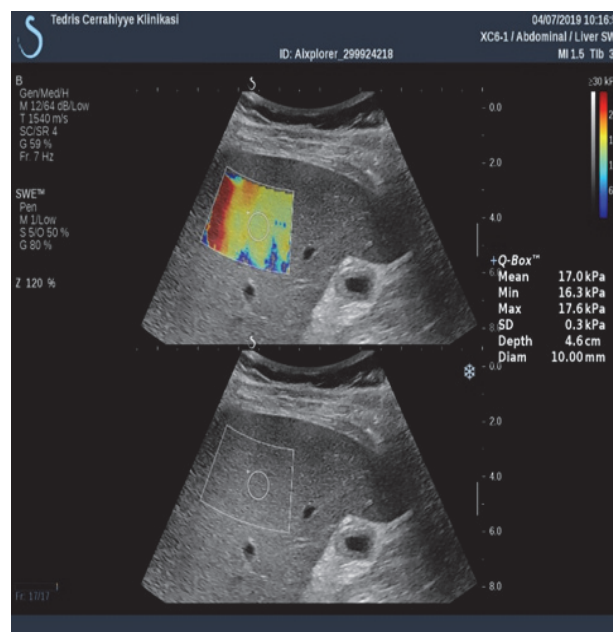
Note: statistical significance of differences was assessed using the Mann-Whitney U test. “*” - the null hypothesis (H_0) was rejected.

According to elastography findings, liver fibrosis stages were classified based on liver stiffness values expressed in kilopascals (kPa). Stage F0, indicating the absence of fibrosis, corresponded to liver stiffness values of 2.0–5.6 kPa. Stage F1 was defined by values ranging from 5.7 to 7.2 kPa, while stage F2 corresponded to 7.3–9.5 kPa. Liver stiffness values of 9.6–12.4 kPa were

classified as stage F3, reflecting advanced fibrosis. Values of ≥ 12.5 kPa corresponded to stage F4, indicating the most severe stage of fibrosis. Fig. 1 illustrates liver stiffness assessed by elastography: liver tissue stiffness and steatosis parameters were within normal ranges. Elastometric examination revealed a liver stiffness of 6.4 kPa, corresponding to fibrosis stage F1.



A



B

Fig. 1. A – Liver elastography result of patient M., age 34 years. Fibrosis stage F1; B – Liver elastography result of patient F., age 67 years. Fibrosis stage F4.

The results of the study demonstrated that higher BMI values were statistically associated with more severe stages of fibrosis ($p=0.006$), whereas patients' age and disease duration did not show statistically significant associations.

Spearman's correlation analysis revealed a

statistically significant positive correlation between $\alpha 2$ -macroglobulin ($\rho=+0.573$; $p<0.001$) and a significant negative correlation between haptoglobin ($\rho=-0.281$; $p=0.003$) and the degree of fibrosis. The correlation between Apo-A1 and fibrosis was not statistically significant (Table 2).

Table 2

Spearman correlation analysis results

	N = 108	Elasto-METAVIR	BMI	$\alpha 2$ -macroglobulin	haptoglobin	Apo-A1
Elasto-METAVIR	ρ (Rho)	1.000	0.360**	0.573**	-0.281**	-0.066
	p		<0.001	<0.001	0.003	0.500
BMI	ρ (Rho)	0.360**	1.000	0.324**	-0.178	-0.210*
	p	<0.001		0.001	0.066	0.029
$\alpha 2$ -macroglobulin	ρ (Rho)	0.573**	0.324**	1.000	-0.149	-0.052
	p	<0.001	0.001		0.124	0.593
haptoglobin	ρ (Rho)	-0.281**	-0.178	-0.149	1.000	0.103
	p	0.003	0.066	0.124		0.290
Apo-A1	ρ (Rho)	-0.066	-0.210*	-0.052	0.103	1.000
	p	0.500	0.029	0.593	0.290	

Note: “*” - the null hypothesis (H_0) was rejected.

ROC analysis demonstrated that $\alpha 2$ -macroglobulin had the highest diagnostic performance among the evaluated serum biomarkers, with an area under the curve (AUC) of 0.806 (standard error [SE] = 0.036; 95 % CI: 0.735–0.877; $p < 0.001$). Haptoglobin showed an AUC of 0.342 (SE = 0.045; 95 % CI: 0.252–0.431; $p = 0.001$), indicating an inverse association with the presence or severity of fibrosis. Apo-A1 demonstrated an AUC of 0.424 (SE = 0.048; 95 % CI: 0.329–0.519); however, its diagnostic performance did not reach statistical significance ($p = 0.118$). Thus, among the analyzed biomarkers, $\alpha 2$ -macroglobulin demonstrated the strongest ability to discriminate patients according to liver fibrosis status (Fig. 2).

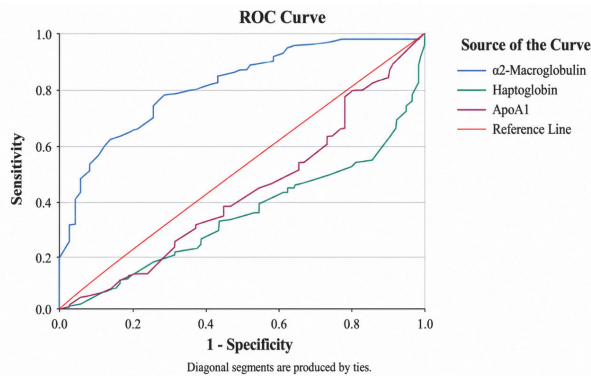


Fig. 2. ROC analysis of $\alpha 2$ -macroglobulin, haptoglobin, and Apo-A1 levels in liver fibrosis among patients with type 2 diabetes mellitus.

To further evaluate the multivariate association between clinical and laboratory parameters, canonical correlation analysis was performed.

Two variable sets were defined: Set 1: Elasto-METAVIR score, BMI Set 2: $\alpha 2$ -macroglobulin, haptoglobin, Apo-A1.

Canonical correlation analysis demonstrated a statistically significant relationship between the clinical and biochemical variable sets ($R_c = 0.539$; $p < 0.001$; Wilks' $\lambda = 0.681$). The first canonical function explained approximately 31.9 % of the total variance, indicating a moderate multivariate association between the two groups of variables.

The canonical variable of the clinical block was predominantly determined by liver stiffness

(loading = -0.891) and body mass index (-0.750), whereas among biochemical markers the greatest contribution was provided by $\alpha 2$ -macroglobulin (-0.880) and haptoglobin (0.536). Apolipoprotein A1 demonstrated a relatively weak contribution. The analysis showed that the combination of “elastography+ $\alpha 2$ -macroglobulin+haptoglobin” demonstrated the highest diagnostic accuracy.

Discussion. The present study demonstrates that the assessment of liver fibrosis in patients with type 2 diabetes mellitus benefits from a multiparametric approach combining clinical characteristics, elastographic measurements, and serum biomarkers. Among the evaluated clinical parameters, BMI showed a statistically significant association with fibrosis severity, whereas age and duration of diabetes were not significantly associated with fibrosis stage. This finding supports the concept that excess adiposity and metabolic dysfunction may play an important role in the progression of liver fibrosis in patients with T2DM. Current evidence indicates that patients with both metabolic liver disease and T2DM represent a particularly high-risk population for progressive fibrosis and its complications [3, 6, 15].

The observed association between higher BMI and more advanced fibrosis is consistent with the current understanding of MASLD as a systemic metabolic disorder rather than an isolated hepatic condition. The EASL-EASD-EASO Clinical Practice Guidelines emphasize obesity and T2DM as major determinants of MASLD progression and recommend targeted assessment for advanced fibrosis in individuals with cardiometabolic risk factors [6]. Similarly, Chan et al. highlighted the importance of metabolic risk stratification in patients with T2DM and obesity and demonstrated the need for non-invasive assessment strategies adapted to this high-risk population [3]. In the present study, the positive correlation between BMI and the Elasto-METAVIR score ($\rho = 0.360$; $p < 0.001$) further supports the relationship between metabolic burden and the severity of fibrotic liver changes.

Elastography constitutes a central component of contemporary non-invasive fibrosis assessment

because it enables quantitative estimation of liver stiffness. Ayonrinde et al. demonstrated the clinical relevance of shear wave elastography in comparison with transient elastography and other markers of fibrosis, supporting its applicability in routine clinical assessment [1]. Zhang et al. also emphasized the value of ultrasound- and magnetic resonance-based elastography as non-invasive imaging techniques for characterizing hepatic fibrosis [16]. Nevertheless, elastography should not necessarily be interpreted as an isolated diagnostic modality. Liver stiffness can be affected by biological and technical factors, and its diagnostic performance may differ according to the underlying liver disease and patient characteristics [7, 8, 12].

An important finding of our study was the significant positive correlation between $\alpha 2$ -macroglobulin levels and fibrosis severity ($p=0.573$; $p<0.001$). Furthermore, $\alpha 2$ -macroglobulin demonstrated the best ROC performance among the serum biomarkers evaluated, with an AUC of 0.806 (95 % CI: 0.735–0.877). These findings indicate that $\alpha 2$ -macroglobulin may provide clinically relevant complementary information for distinguishing patients according to fibrosis status. This observation is supported by Deckmyn et al., who investigated $\alpha 2$ -macroglobulin, Apo-A1, and haptoglobin in patients with fatty liver disease with and without T2DM and demonstrated the clinical relevance of these proteins as components of non-invasive fibrosis assessment [5]. The relatively strong association observed for $\alpha 2$ -macroglobulin in our cohort may reflect its relationship with extracellular matrix remodeling and protease regulation during hepatic fibrogenesis.

Haptoglobin demonstrated a different pattern. Its concentration was negatively correlated with fibrosis severity ($p=-0.281$; $p=0.003$), and ROC analysis yielded an AUC of 0.342 (95 % CI: 0.252–0.431). An AUC below 0.5 should not automatically be interpreted as absence of biological or diagnostic relevance, particularly when the direction of association between a biomarker and the outcome is inverse. In the present study, the negative correlation and ROC findings were directionally consistent, suggesting that decreasing haptoglobin levels were associated with increasing fibrosis severity. Thus, haptoglobin may contribute to fibrosis assessment primarily as part of a multivariable biomarker profile rather than as an independent stand-alone diagnostic test [5].

In contrast, Apo-A1 did not demonstrate a statistically significant association with fibrosis severity in our cohort ($p=-0.066$; $p=0.500$), and its ROC performance was also non-significant (AUC=0.424; $p=0.118$). This finding illustrates an important limitation of individual serum biomarkers: their diagnostic contribution may vary substantially depending on the population, metabolic characteristics, disease spectrum, and prevalence of different fibrosis stages. Current reviews therefore

emphasize that no single serum biomarker or non-invasive test can provide optimal diagnostic performance across all patient populations and clinical settings [4, 7, 9, 13].

This concept is particularly relevant to patients with T2DM. Castera et al., in a prospective head-to-head evaluation of non-invasive scores for fibrotic MASH in patients with T2DM, demonstrated the importance of carefully selecting and combining non-invasive strategies in this high-risk population [2]. Similarly, Sanyal et al. emphasized that non-invasive assessment should be interpreted within a structured clinical pathway rather than as a simple replacement for histological evaluation [12]. Tsochatzis also highlighted the advantages of sequential non-invasive testing, in which complementary methods are used to improve discrimination between low- and high-risk patients [14].

The results of our canonical correlation analysis provide additional support for such an integrated strategy. A statistically significant relationship was identified between the clinical/imaging and biochemical variable sets ($R_c=0.539$; $p<0.001$; Wilks' $\lambda=0.681$). Within the clinical block, liver stiffness and BMI showed the greatest contribution, whereas $\alpha 2$ -macroglobulin and haptoglobin were the dominant variables within the biochemical block. These findings suggest that elastography and serum biomarkers do not merely duplicate the same diagnostic information but may characterize different and complementary components of the fibrotic process.

The combination of elastography with $\alpha 2$ -macroglobulin and haptoglobin therefore appears particularly promising. Contemporary guidelines and reviews increasingly support multistep pathways combining simple serum-based tests with more specific imaging or biomarker methods to improve risk stratification [6–9, 13, 14]. Such strategies are clinically attractive because they may reduce the number of unnecessary invasive procedures while allowing patients at higher risk of advanced fibrosis to be identified for further evaluation and follow-up.

Our findings should nevertheless be interpreted considering several limitations. First, the cross-sectional design does not allow assessment of temporal or causal relationships between metabolic factors, biomarker changes, and fibrosis progression. Second, the sample size was relatively limited, particularly when patients were subdivided according to individual fibrosis stages. Third, histological confirmation by liver biopsy was not available as a reference standard; fibrosis classification was based on non-invasive methods. Finally, the diagnostic thresholds and associations identified in this cohort require external validation before they can be generalized to broader populations of patients with T2DM. These limitations are particularly relevant because the performance of non-invasive fibrosis tests may vary according to disease etiology,

prevalence of advanced fibrosis, obesity, and other patient-related characteristics [7, 9, 12].

Despite these limitations, the study provides clinically relevant evidence supporting a combined diagnostic strategy in patients with T2DM. The significant association of liver stiffness and BMI with fibrosis, together with the diagnostic contribution of α 2-macroglobulin and the inverse association of

haptoglobin, indicates that integrating imaging, metabolic, and biochemical information may provide a more comprehensive assessment than any individual parameter alone. This approach is consistent with the current shift toward non-invasive, sequential, and risk-adapted assessment of liver fibrosis in patients with metabolic liver disease [2, 3, 6, 12–14].

Conclusion

In patients with type 2 diabetes mellitus, a comprehensive assessment combining physical parameters, imaging findings, and serum biomarkers provides a more informative approach to the evaluation of liver fibrosis. Higher BMI was significantly associated with more advanced fibrosis, emphasizing the contribution of metabolic factors to liver disease progression. Elastography provides a non-invasive quantitative assessment of liver stiffness and, when combined with biochemical markers, may enhance fibrosis risk stratification. Among the evaluated serum biomarkers, α 2-macroglobulin demonstrated the strongest association with fibrosis severity and the highest diagnostic performance, whereas haptoglobin showed a significant inverse association with fibrosis. Apo-A1 demonstrated a relatively limited diagnostic contribution. The findings support the complementary value of elastography, BMI, α 2-macroglobulin, and haptoglobin in assessing liver fibrosis in patients with type 2 diabetes mellitus. This combined approach may facilitate earlier identification of patients at increased risk of clinically significant fibrosis and support individualized monitoring and further diagnostic evaluation.

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Conflict of interest. The authors have no conflicts of interest to declare

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