

# Body composition parameters and comorbidities as markers of clinically significant liver fibrosis (F2, F3 stages) in patients with metabolic dysfunction-associated steatotic liver disease

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**Abstract.** The global incidences of metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity are increasing. Liver fibrosis stage is considered the strongest predictor of disease-specific mortality in MASLD. **Aim.** This study aimed to examine the possible associations between body composition parameters assessed by bioimpedance analysis (BIA), comorbidities, and clinically significant liver fibrosis (F2, F3) in Ukrainian patients with MASLD. **Material and methods.** It was an observational study involving adult patients aged  $\geq 18$  years with a diagnosis of MASLD and liver steatosis, confirmed by ultrasound imaging, who underwent liver shear-wave elastography for assessment of liver fibrosis and body composition assessment. Logistic regression analysis was performed to determine possible factors associated with clinically significant liver fibrosis (F2, F3). **Results.** The study included 79 patients with a mean age of  $45.66 \pm 14.26$  years, and 64.6% were female. The body mass index (BMI) median was  $31.9 \text{ kg/m}^2$  (Q1, Q3: 29.25, 37.3) and clinically significant liver fibrosis (F2, F3) was observed in 15.2% of patients ( $n=12$ ). Patients with F2, F3 stages had higher BMI (median= $37.55$ ; Q1, Q3: 33.11, 42.45) than patients without clinically significant liver fibrosis (median= $31.2$ ; Q1, Q3: 28.63, 35.35;  $p=0.0027$ ). Excessive visceral fat level was associated with clinically significant liver fibrosis (F2, F3) (odds ratio [OR]= $5.74$ , 95% confidence interval (CI): 1.41-23.29,  $p=0.0145$ ). We found that type 2 diabetes (T2D) was significantly associated with clinically significant liver fibrosis (F2, F3) in patients with MASLD (OR= $4.15$ , 95% CI: 1.15-14.99,  $p=0.0297$ ) and this association remained significant after adjustment for age and sex, as well as in the multivariable model. **Conclusion.** We demonstrated that a high-

er visceral fat level was associated with clinically significant liver fibrosis (F2, F3), suggesting that the presence of excessive visceral fat accumulation determined with BIA may be used as a potential marker of clinically significant liver fibrosis (F2, F3) in patients with MASLD. Our study also confirmed the link between T2D and significant liver fibrosis (F2, F3) in Ukrainian adults with MASLD. These findings demonstrate the importance of timely screening of this category of patients for liver fibrosis, as recommended by the current guidelines.

**Keywords:** metabolic dysfunction-associated steatotic liver disease, liver fibrosis, visceral fat, bioimpedance analysis, body mass index.

MASLD affects approximately 30% of the world's population, and its prevalence is anticipated to increase in the near future [1, 2]. According to previous research, liver fibrosis stage is considered the strongest predictor of disease-specific mortality in MASLD [3]. Moreover, studies have shown that advanced liver fibrosis is prevalent among outpatients with T2D, demonstrating the need for systematic screening [4]. The rising global incidence of MASLD co-exists with the worldwide increase in overweight and obesity [5]. Previous studies have demonstrated the association between body composition parameters and hepatic fibrosis in patients with sarcopenic obesity and non-alcoholic fatty liver disease; the use of the index skeletal muscle mass to visceral fat area ratio in MASLD; and the body composition assessment in patients with MASLD using BIA, a non-invasive technique widely used in clinical practice and research [6-10].

This study aimed to examine the possible associations between body composition parameters assessed by BIA, comorbidities, and clinically significant liver fibrosis (F2, F3 stages) in Ukrainian patients with MASLD.

## Material and methods

**Ethical approval.** The study protocol was approved by the Ethic Committee of the Bogomolets National Medical University, Kyiv, Ukraine (Protocol number 152). Participants gave their informed consent during the primary data collection.

**Design of the study.** It was an observational study involving patients with MASLD. Participants were recruited from outpatients who received medical care in KNE «Kyiv Municipal Consultative and Diagnostic Centre» in Ukraine in period from January 2022 to June 2024. The inclusion criteria for participation in the study

were as follows: adult patients aged  $\geq 18$  years with a diagnosis of MASLD and liver steatosis confirmed by ultrasound imaging, who underwent liver elastography for assessment of liver fibrosis and body composition. Exclusion criteria were pregnancy, breast-feeding, patients with liver cirrhosis, daily alcohol intake of more than 30 g per day for men and 20 g per day for women, acute or chronic liver diseases (hepatitis B, hepatitis C, etc.) other than MASLD [11]. The diagnosis of MASLD was based on the criteria defined by the American Association for the Study of Liver Diseases, which are consistent with the EASL–EASD–EASO Clinical Practice Guidelines [11, 12]. As some patients were diagnosed with non-alcoholic fatty liver disease, we evaluated them in accordance with the new nomenclature and criteria.

**Assessment of liver steatosis and fibrosis.** Two experienced physicians performed abdominal ultrasound examination and shear-wave elastography to confirm liver steatosis and assess liver stiffness, respectively; with determination of liver fibrosis stages (F0, F1, F2, F3, F4) following the manufacturer's instructions and current recommendations (Hitachi Aloka Arietta S70) [13-15].

**Body composition assessment.** Weight and height were measured with further BMI calculation. Weight to the nearest 100 g and body composition parameters were assessed by an experienced dietitian using the BIA scale (Tanita BC-545N, Japan). The following body composition parameters were assessed: body fat (%), visceral fat level (1-59 range: low to high), muscle mass (kg), total body water (%), and bone mass (kg). Following the manufacturer's recommendations, a visceral fat level  $>12$  was considered an excessive level of visceral fat.

**Statistical Analysis.** Categorical variables were presented as number of cases and percentages. Continuous variables were checked for

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normality using the Shapiro-Wilk test and histograms. Normally distributed continuous variables were expressed as mean  $\pm$  standard deviation (SD) and non-normally distributed variables as medians with 25<sup>th</sup> and 75<sup>th</sup> percentiles (Q1 and Q3). The t-test (for normally distributed data) and Mann-Whitney U test (for non-normally distributed data) were used to assess the differences between groups. We used the chi-squared test to analyse categorical data. Logistic regression analysis was performed to determine possible factors associated with clinically significant liver fibrosis (F2, F3). As most variables did not follow a normal distribution, we used the Spearman rank correlation coefficient ( $\rho$ ,  $r_s$ ) for the correlation analysis. The sample size was defined as at least 59 participants (10 participants with stages F2, F3 and 49 participants without clinically significant fibrosis, stages <F2) with a power set of 80% ( $p < 0.05$ ), and the null hypothesis was that the mean difference in BMI between participants with clinically significant liver fibrosis and without would be 5 or less, with SD 5 for both groups and the ratio 1:5. A p-value of  $< 0.05$  was considered statistically significant; 95% CI for an OR, which does not include 1.0, was considered to be statistically significant at the 5% level. Data was analysed using MedCalc® Statistical Software version 20.215 [16]. We assessed 84 patients with MASLD for eligibility, five of whom were excluded due to the absence of some necessary data.

## Results

The study included 79 patients with a mean age of  $45.66 \pm 14.26$  years, and 64.6% were female. The median BMI was  $31.9 \text{ kg/m}^2$  (Q1, Q3: 29.25, 37.3) and clinically significant liver fibrosis (F2, F3 stages) was observed in 15.2% of patients ( $n=12$ ). The main clinical characteristics of participants are summarised in **Table 1**.

Based on results of liver fibrosis severity stages assessed by patients with shear-wave elastography were divided in two groups: patients without clinically significant liver fibrosis (<F2) and patients with clinically significant liver fibrosis (F2, F3 stages). There was no difference in age and sex of participants between the groups (**Table 2**). However, patients with F2, F3 stages had higher BMI (median= $37.55$ ; Q1, Q3:  $33.11$ ,

**Table 1.** The main clinical characteristics of participants

Characteristics	Results
Age (years), mean $\pm$ SD	45.66 $\pm$ 14.26
	Sex, n (%)
Female	51 (64.6%)
Male	28 (35.4%)
	Liver fibrosis (n=79)
<F2	67
F2, F3	12
F4	0
BMI (median: Q1, Q3), kg/m <sup>2</sup>	31.9 (29.25, 37.30)
	BMI category, n (%)
<18.5 kg/m <sup>2</sup>	0 (0%)
18.5 to <25 kg/m <sup>2</sup>	1 (1%)
25.0 to <30 kg/m <sup>2</sup>	24 (29%)
30 to < 35 kg/m <sup>2</sup>	29 (37%)
35 to < 40 kg/m <sup>2</sup>	14 (18%)
$\geq 40 \text{ kg/m}^2$	12 (15%)
	Comorbidities, n (%)*
Arterial hypertension	4 (5%)
T2D	19 (24%)
Prediabetes	1 (1.27%)
GERD	3 (3.8%)
Gout	7 (8.86%)
Hypothyroidism	16 (20.25%)

Note. \* – some patients have more than one comorbidity.

42.45) than patients without clinically significant liver fibrosis (median= $31.2$ ; Q1, Q3:  $28.63$  to  $35.35$ ;  $p=0.0027$ ). Moreover, visceral adiposity level was also significantly higher in patients with F2, F3 stages (median= $16.5$ , Q1, Q3:  $12.5$ ,  $22$ ;  $p=0.0015$ ), but not the total fat (%) content.

To further assess the associations between clinically significant liver fibrosis (F2, F3) and body composition parameters as well as comorbidities, the univariate logistic regression analysis was performed (**Table 3**).

**Table 2.** Comparison of body composition parameters and comorbidities between patients without clinically significant liver fibrosis (<F2) and with clinically significant liver fibrosis (F2, F3).

	Without clinically significant liver fibrosis (<F2) (n=67)	Clinically significant liver fibrosis (F2, F3) (n=12)	p
Age (years), mean±SD	45.97±14.18	43.92 ±15.25	0.6489*
Sex (male), n (%)	22 (32.8%)	6 (50%)	0.2553***
Arterial hypertension, n (%)	3 (4.5%)	1 (8.3%)	0.5772***
T2D, n (%)	13 (19.4%)	6 (50%)	0.0232***
Prediabetes, n (%)	1 (1.5%)	0	0.6721***
GERD, n (%)	3 (4.5%)	0	0.4577***
Gout, n (%)	5 (7.5%)	2 (16.7%)	0.3046***
Hypothyroidism, n (%)	13 (19.4%)	3 (25%)	0.6589***
BMI, median (Q1, Q3), kg/m <sup>2</sup>	31.2 (28.63, 35.35)	37.55 (33.11, 42.45)	0.0027**
Fat, median (Q1, Q3), %	37.6 (32.625, 44.45)	40.85 (34.45, 45.65)	0.3529**
Visceral fat, median (Q1, Q3), level	10.5 (7.5, 13)	16.5(12.5, 22)	0.0015**
Water, median (Q1, Q3), %	46.2 (41.3, 48.65)	43.25 (40, 47.45)	0.1852**
Muscle mass, median (Q1, Q3), kg	53.6 (47.78, 61.15)	64.8(53, 79.05)	0.0188**
Bone mass, median (Q1, Q3), kg	2.8 (2.525, 3.2)	3.4 (2.8, 4.1)	0.021**

Note. \* T-test, \*\* Mann-Whitney rank test, \*\*\* A Chi-square test.

**Table 3.** Markers of clinically significant liver fibrosis (F2, F3), using binary logistic regression analysis

Marker	Unadjusted		
	OR	95% CI	p
Age	0.9898	0.9475 to 1.0339	0.6444
Sex (male)	2.0455	0.5912 to 7.0766	0.2584
Arterial hypertension	1.9394	0.1846 to 20.3742	0.5809
T2D	4.1538	1.1510 to 14.9912	0.0297
Prediabetes	0.0000	-	-
Gastroesophageal reflux disease	7.2266 × 10 <sup>-9</sup>	-	0.9984
Gout	2.48	0.4221 to 14.5693	0.3147
Hypothyroidism	1.3846	0.328 to 5.8449	0.6578
BMI	1.1663	1.0517 to 1.2934	0.0036
Fat, %	1.0402	0.9675 to 1.1185	0.2862
Visceral fat, level	1.2137	1.0712 to 1.375	0.0024
Water, %	0.9276	0.8284 to 1.0386	0.1924
Muscle mass, kg	1.0701	1.0177 to 1.1251	0.0081
Bone mass, kg	4.1669	1.4632 to 11.8668	0.0075

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Markers, which were associated with clinically significant liver fibrosis in univariate logistic regression analysis, also remained significant after adjustment for age and sex (Model (1), **Table 4**).

**Table 4.** Model (1). Adjusted for age, sex

Marker	OR	95% CI	p
T2D	6.1107	1.3949 to 26.7699	0.0163
BMI	1.2094	1.0727 to 1.3634	0.0019
Visceral fat, level	1.3421	1.1166 to 1.6131	0.0017
Muscle mass, kg	1.1414	1.0364 to 1.2571	0.0072
Bone mass, kg	15.944	2.1911 to 116.0214	0.0062

However, in the multivariable model (Model (2), **Table 5**), only associations between T2D (OR=8.7661, 95% CI: 1.3231 to 58.0791), visceral adiposity (OR=1.1966, 95% CI: 1.0511 to 1.3623) and clinically significant liver fibrosis were statistically significant.

**Table 5.** Model (2). Multivariable model

Marker	OR	95% CI	p
T2D	8.7661	1.3231 to 58.0791	0.0244
BMI	1.0885	0.9562 to 1.2390	0.1997
Visceral fat, level	1.1966	1.0511 to 1.3623	0.0067
Muscle mass, kg	0.5987	0.2246 to 1.5959	0.3051
Bone mass, kg	$2.08 \times 10^5$	0.0002 to $1.76 \times 10^{14}$	0.2431

In the univariate regression model, excessive visceral fat (visceral fat levels higher than 12) was associated with clinically significant liver fibrosis (F2, F3) (OR=5.74, 95% CI: 1.41 to 23.29,  $p=0.0145$ ). After adjustment for age and sex, the association remained significant (OR=8.71, 95% CI: 1.69 to 44.81,  $p=0.0096$ ). Bone mass (kg) correlated with weight (kg) of the participants ( $rs=0.749$ ,  $p<0.0001$ ), visceral adiposity level ( $rs=0.457$ ,  $p<0.0001$ ), BMI ( $rs=0.424$ ,  $p=0.0001$ ). Muscle mass (kg) also correlated with weight (kg) of the participants ( $rs=0.741$ ,  $p<0.0001$ ),

visceral adiposity level ( $rs=0.453$ ,  $p<0.0001$ ), BMI ( $rs=0.415$ ,  $p=0.0001$ ). This may explain why the OR for bone and muscle mass were significant in the univariate logistic regression analysis, but not in the multivariable model (2).

## Discussion

Liver fibrosis is considered to be linked to fat mass, as well as to visceral fat, in patients with non-alcoholic fatty liver disease [17]. Visceral adipose tissue dysfunction, for example, contributes to metabolic syndrome and therefore may lead to further deterioration of liver function and fibrosis progression [18]. Our findings that visceral fat was associated with liver fibrosis (F2, F3) are consistent with results of the study conducted in Spain demonstrated the association between highest quartile of visceral adiposity index, BMI  $\geq 30$  kg/m<sup>2</sup>, and abdominal obesity with the prevalence of MASLD and liver fibrosis, as well as with fibrosis progression [19].

T2D is considered to be the major determinant of fibrosis progression in patients with MASLD [11]. Our study confirmed that T2D is associated with clinically significant liver fibrosis in Ukrainian adults with MASLD, even after adjustment for possible confounders such as age and sex, as well as other factors such as body composition parameters. Impaired fasting glucose is one of the parameters used in the non-alcoholic fatty liver disease fibrosis score however, some studies suggest T2D, rather than prediabetes, to be a risk factor for clinically significant liver fibrosis [20, 21]. As most patients in our study had T2D and only one participant had prediabetes, we could not establish the association between prediabetes and significant liver fibrosis.

## Conclusion

We consider BIA to be useful for body composition assessment in patients diagnosed with MASLD. We also suggest that the presence of excessive visceral fat accumulation determined with BIA may be used as a potential marker of clinically significant liver fibrosis (F2, F3) in patients with MASLD. Our study confirmed the link between T2D and significant liver fibrosis (F2, F3) in Ukrainian adults with MASLD, additionally indicating the importance of timely

screening of this category of patients for liver fibrosis, as recommended by the current guidelines.

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## Abbreviation

- BIA** – bioimpedance analysis  
**BMI** – body mass index  
**CI** – confidence interval  
**MASLD** – metabolic dysfunction-associated steatotic liver disease  
**OR** – odds ratio  
**T2D** – type 2 diabetes

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## Параметри складу тіла та коморбідність як маркери клінічно значущого фіброзу печінки (F2, F3 стадії) у пацієнтів із метаболічно-асоційованою стеатотичною хворобою печінки

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**Резюме.** Глобальна захворюваність на метаболічно-асоційовану стеатотичну хворобу печінки (МАСХП) та ожиріння зростає. Стадія фіброзу печінки вважається найсильнішим предиктором смертності при МАСХП, що зумовлена захворюванням. **Мета.** Дослідження мало на меті вивчити можливі зв'язки між параметрами складу тіла, оціненими за допомогою біоімпедансного аналізу, супутніми захворюваннями та клінічно значущим фіброзом печінки (F2, F3) в пацієнтів із МАСХП в Україні. **Матеріал і методи.** Це було обсерваційне дослідження за участю дорослих пацієнтів віком  $\geq 18$  років із діагнозом МАСХП та стеатозом печінки, підтвердженим

## Оригінальні дослідження

ультразвуковим дослідженням, яким проводили еластографію печінки методом зсувної хвилі для оцінки фіброзу печінки та оцінку складу тіла. Для визначення можливих факторів, пов'язаних із клінічно значущим фіброзом печінки (F2, F3), було проведено логістичний регресійний аналіз. **Результати.** Дослідження включало 79 пацієнтів середнього віку  $45,66 \pm 14,26$  років, 64,6% із них були жінки. Медіана індексу маси тіла становила  $31,9 \text{ кг/м}^2$  (Q1, Q3: 29,25; 37,3), а клінічно значущий фіброз печінки (F2, F3) спостерігався в 15,2% пацієнтів ( $n=12$ ). Пацієнти зі стадіями F2, F3 мали вищий індекс маси тіла (медіана= $37,55$ ; Q1, Q3: 33,11; 42,45), ніж пацієнти без клінічно значущого фіброзу печінки (медіана= $31,2$ ; Q1, Q3: 28,63; 35,35;  $p=0,0027$ ). Надмірний рівень вісцерального жиру був пов'язаний із клінічно значущим фіброзом печінки (F2, F3) (співвідношення шансів= $5,74$ ; 95% довірчий інтервал: від 1,41 до 23,29;  $p=0,0145$ ). Ми виявили, що цукровий діабет 2-го типу був суттєво пов'язаний із клінічно значущим фіброзом печінки (F2, F3) у пацієнтів із МАСХП (співвідношення шансів= $4,15$ , 95% довірчий інтервал: 1,15–14,99,  $p=0,0297$ ), і цей зв'язок залишався значущим після поправки на вік і стать, а також у багатоваріантній моделі.

**Висновок.** Ми продемонстрували, що вищий рівень вісцерального жиру був пов'язаний із клінічно значущим фіброзом печінки (F2, F3), тож ми розглядаємо надмірне накопичення вісцерального жиру, визначене за допомогою біоімпедансного аналізу, у ролі потенційного маркера клінічно значущого фіброзу печінки (F2, F3) у пацієнтів із МАСХП. Наше дослідження також підтвердило зв'язок між цукровим діабетом 2-го типу та значним фіброзом печінки (F2, F3) у дорослих із МАСХП в Україні. Ці дані свідчать про важливість своєчасного скринінгу фіброзу печінки для цієї категорії пацієнтів, як це рекомендовано сучасними настановами.

**Ключові слова:** метаболічно-асоційована стеатотична хвороба печінки, фіброз печінки, вісцеральний жир, біоімпедансний аналіз, індекс маси тіла.

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