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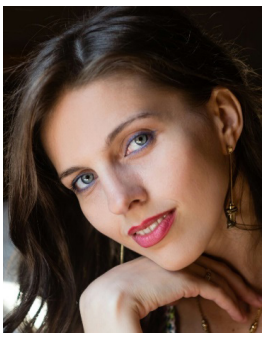

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Peculiarities of the Ukrainian Model of Fracture Risk Assessment (FRAX®) Among Patients with liver Cirrhosis Accompanied by Impaired Bone Mineral Density: Its Diagnostic and Prognostic Value

Introduction. Among the polymorbid lesions, patients with liver cirrhosis (LC) often have impaired bone mineral density (IBMD) [1, 8–10, 13, 21], the most severe manifestation of which is osteoporosis. However low-energy fractures are known to occur not only in the presence of osteoporosis, but also in case of osteopenia, and sometimes in case of normal bone mineral density (BMD). Diagnosis of bone lesions usually requires expensive and not always available laboratory and instrumental examinations.

For decades, scientists around the world have been working on solving this problem, elucidating etiological and pathogenetic mechanisms, researching cause-and-effect relationships, searching for improved and generally available methods of diagnosis, and, accordingly, prevention and treatment, which are extremely important economic and social elements in modern global health care system.

Among the factors causing bone fractures, several main ones have been figured out, which are the basis of the Fracture Risk Assessment (FRAX®) tool. Today, this is one of the most accessible risk assessment methods for the 10-year expectancy of fractures. This method can be used both with the use of BMD data or based only on patient anamnesis, namely gender, age, presence of fractures in the past, confirmed rheumatoid arthritis, possible secondary osteoporosis, use of glucocorticoids, bad habits (smoking, alcohol abuse), parental femur fracture, height and body weight (body mass index, BMI) [11].

Depending on the country of use and the system of providing medical care, there are certain differences in the thresholds according to the FRAX® model, which make it possible to immediately prescribe treatment, indicate the need of bones additional examination, or exclude necessity of both [4, 12]. Ukraine has implemented its own model of the FRAX® tool since 2016 [19], but the age-specific evaluation thresholds for Ukraine were first developed and launched only in 2019 [18].

Despite certain global achievements in the study of bone diseases, the problem of osteoporotic fractures and evaluation thresholds for intervention in patients with LC remains obscure so far; similarly, the Ukrainian FRAX® model was never used in patients with LC in Ukraine. This option determined the purpose of our study.

The aim of the study. To find out the peculiarities of the Ukrainian model of Fracture Risk Assessment, its diagnostic and predictive value for its implementation in patients with liver cirrhosis accompanied with impaired bone mineral density.

Materials and methods. After signing voluntary consent to participate in the study, in compliance with the Helsinki Declaration of Human Rights and the Council of Europe Convention on Human Rights and Biomedicine, 90 patients with LC [17] of various etiologies were randomly assigned, among whom the majority (61.11 %) were patients with alcoholic LC.

27 of these participants were women and 63 – men at the age from 18 to 66 years (27 young adults (18–44 years old), 53 – middle-aged (45–59 years old) and 10 – elderly (60–74 years old)). All of them were receiving inpatient treatment at the Lviv Regional Hepatological Center (Communal Non-Commercial Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital") in 2016–2020.

The bone tissue condition was examined using calcaneal quantative ultrasound (CQUS) [2] ("Sonost-2000" device). T-score was indicated, and if its value was <-1.0 standard deviation (SD), IBMD was diagnosed, or IBMD was excluded if T-score was ≥-1.0 SD. If the T-score was within -1.0 and -2.5 SD, osteopenia was diagnosed, and if T-score was ≤-2.5 SD, osteoporosis was detected [22].

Based on the obtained results, the patients were stratified into an experimental group (EG) (patients with IBMD

– 72 (80.00 %)), which was divided into two subgroups – EG A (patients with osteopenia – 46 (63.89 %)) and EG B (patients with osteoporosis – 26 (36.11 %)), and into the comparison group (CG) (patients with BMD within the normal range – 18 (20.00 %)) according to the bone tissue condition.

Examining the features of the Ukrainian FRAX® model and its diagnostic characteristics for bone disorders, an adapted online calculator [https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=uk#notes] was used to obtain the percentage value of the 10-year probability of major osteoporotic fractures.

The following risk factors were analysed: gender (female and male), age (young (18–44 years old), middle-aged (45–59 years old) and elderly (60–74 years old)), presence of fractures in the anamnesis, diagnosed rheumatoid arthritis, possible secondary osteoporosis (this risk factor is inherent in all the examined participants due to liver damage), use of glucocorticoids at a dosage of 5.0 mg per day or more in terms of prednisolone for more than three months, femur fractures among parents, smoking, alcohol abuse (3 units or more per day), height (tall (170.0 cm or more for women; 175.0 cm or more for men), medium (155.0–169.0 cm for women and 160.0–174.0 cm for men), short (less than 155.0 cm for women and less than 160.0 cm for men)), body weight (BMI 18.5–24.9 kg/m² – normal, BMI 25.0–29.9 kg/m² – overweight). All investigated parameters were marked with "yes" or "no" signs.

To determine evaluation thresholds, the recommendations of V. Povoroznyuk and co-researchers [18] were used, which were based on the percentage values of the probability of osteoporotic fractures according to the age of the patients, without taking into account BMD (if the examinee was younger than 40 years old, the obtained values were estimated in correspondance to a 40-year-old person).

Due to the patients' age three thresholds were established: upper threshold, the percentage values above which make it possible to prescribe antiosteoporosis treatment without conducting additional examinations; intermediate values of fracture risk, which require additional investigation of bones state and the fracture risk reassessment; lower threshold, the percentage values below which do not entail an additional examination of BMD and, correspondingly, treatment (table 1) [18].

Table 1

The evaluation thresholds of the 10-year probability of osteoporotic fractures according to the Ukrainian model of Fracture Risk Assessment for making a decision about the prescription of treatment or the necessity of additional bones examination

Age, years	Lower threshold, **%**	Upper threshold, **%**
1	2	3
40	2.40	6.60
45	2.70	7.30
50	3.10	8.10
55	3.50	9.10

Table 1 (continued)

1	2	3
60	4.00	10.00
65	4.40	11.00
70	5.00	12.00
75	6.00	13.00
80	6.70	13.00
85	6.90	13.00
90	6.00	12.00

Notes: Values above the upper threshold require the prescription of treatment; intermediate values of fracture risk including values of upper and lower thresholds are prerequisite for additional examination of BMD; values below the lower threshold do not require further examination or treatment.

The research was conducted in two stages. At the *first stage*, the features of the criteria (risk factors), wich are used to calculate the cumulative percentage of the 10-year fracture probability (*first step*), and evoluation thresholds according to the Ukrainian FRAX® model (*second step*) amoung patients with LC with bone disorders were explored.

For this purpose, the incidence of features in groups were esteblished. Their share of the total number of patients with LC was defined. Significant differences between groups were detected by R. Fisher's exact test calculating ($p < 0.050$) [16]. Stochastic associations between features and IBMD or its manifestations were investigated with the help of J. Yule's coefficient of association (YCA) and / or contingency coefficient (CC). A stochastic association was considered substantial if YCA was ≥0.50 or ≤-0.50 and CC was ≥0.30 or ≤-0.30. A positive value of the coefficients indicated a direct association, and a negative value – a negative one [7, 23].

At the *second stage*, the risk factors of osteoporotic fractures and the evaluation thresholds according to the Ukrainian FRAX® model, which have certain peculiarities (have statistically significant difference, or a substantial direct stochastic association with a certain bone disorder), are selected to determine diagnostic characteristcs (the diagnostic value (sensitivity and specificity), predictive value (positive and negative predictive values), likelihood ratio (positive and negative likelihood ratios)) (*first step*) [6, 15], and the most valuable (simultaneously confirmed by R. Fisher's exact test ($p < 0.050$) and have a substantial direct stochastic association with certain IBMD (YCA ≥0.50 and/or CC ≥ 0.30) – to determine the post-test probability of certain bone disorders among all patients with LC (*second step*) [15, 20]. The post-test probability was calculated on the basis of the pre-test probability (prevalence) of bone disorders (obtained using CQUS) and the likelihood ratio (obtained at the previous step of the study). The selected values of the pre-test probability of IBMD were 80.00 %, osteopenia – 51.11 %, osteoporosis – 28.89 %.

The obtained results are depicted using E. Bayes' theorem nomogram [3, 14], which is an advanced version of

T. Fagan's nomogram [5] for a quick assessment of the applied test result, which indicates disease prevalence, likelihood ratio, test sensitivity and specificity.

Statistical processing of the research results was executed on a personal computer using the Microsoft Excel program and the Real Statistics Resource Pack add-in [24].

Results and discussion. The results of the *first stage*, dedicated to discovering the peculiarities of the fracture probability risk factors [https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=uk#notes]. and the evaluation thresholds according to the Ukrainian FRAX® model [18], are shown in table 2.

Table 2

Characteristics of gender, age, previous fractures and other risk factors of fractures, evaluation thresholds according to the Ukrainian model of Fracture Risk Assessment among patients with liver cirrhosis with impaired bone mineral density (including osteopenia and osteoporosis) and normal bone mineral density

Features		Total number of cases (n, %) N=90		Frequency of cases in the studied groups (n, %)								The result of R. Fisher's exact test (p) and J. Yule's coefficient of association (YCA)							
				EG (IBMD)						CG (normal BMD) N=18		EG (IBMD) – CG (normal BMD)		EG A (osteopenia) – CG (normal BMD)		EG B (osteoporosis) – CG (normal BMD)		EG A (osteopenia) – EG B (osteoporosis)	
				Total (IBMD) N=72		EG A (osteopenia) N=46		EG B (osteoporosis) N=26											
		n	%	n	%	n	%	n	%	n	%	p	YCA	p_1	YCA_1	p_2	YCA_2	p_3	YCA_3
1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Fracture risk factors	Female	27	30.00	22	81.48	14	51.85	8	29.63	5	18.52	1.000	0.07	1.000	0.06	1.000	0.07	1.000	-0.01
	Male	63	70.00	50	79.37	32	50.79	18	28.57	13	20.63	1.000	-0.07	1.000	-0.06	1.000	-0.07	1.000	0.01
	Young adults (18–44 years old)	27	30.00	22	81.48	16	59.26	6	22.22	5	18.52	1.000	0.07	0.769	0.16	0.738	-0.12	0.425	0.28
	Middle-aged adults (45–59 years old)	53	58.89	42	79.25	25	47.17	17	32.08	17	32.08	1.000	-0.06	0.781	-0.14	1.000	0.09	0.458	-0.23
	Elderly (60–74 years old)	10	11.11	8	80.00	5	50.00	3	30.00	2	20.00	1.000	0.00	1.000	-0.01	1.000	0.02	1.000	-0.03
	Previous fractures	24	26.67	23	95.83	10	41.67	13	54.17	1	4.17	0.034*	0.78^	0.159	0.65^	0.002*	0.89^	0.019*	-0.57^
	Rheumatoid arthritis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-	-	-	-	-	-
	Secondary osteoporosis	90	100.00	72	80.00	46	51.11	26	28.89	18	20.00	-	-	-	-	-	-	-	-
	Use of glucocorticoids	6	6.67	5	83.33	2	33.33	3	50.00	1	16.67	1.000	0.12	3.000	-0.13	0.634	0.38	0.344	-0.48
	Smoking	28	31.11	23	82.14	12	42.86	11	39.29	5	17.86	1.000	0.10	1.000	-0.04	0.361	0.31	0.192	-0.35
	Alcohol abuse	77	85.56	62	80.52	40	51.95	22	28.57	15	19.48	0.719	0.11	0.703	0.14	1.000	0.05	1.000	0.10
	Femur fractures among parents	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-	-	-	-	-	-
	Tall height (170.0 cm or more for women; 175.0 cm or more for men)	31	34.44	23	74.19	15	48.39	8	25.81	8	25.81	0.407	-0.26	0.399	-0.25	0.525	-0.29	1.000	0.04
	Medium height (155.0–169.0 cm for women and 160.0–174.0 cm for men)	53	58.89	45	84.91	28	52.83	17	32.08	8	15.09	0.188	0.35	0.272	0.32	0.222	0.40	0.802	-0.10
	Short height (less than 155.0 cm for women and less than 160.0 cm for men)	6	6.67	4	66.67	3	50.00	1	16.67	2	33.33	0.595	-0.36	0.615	-0.28	0.558	-0.52^	1.000	0.27
	Normal body weight (BMI 18.5–24.9 kg/m²)	46	51.11	41	89.13	25	54.35	16	34.78	5	10.87	0.035*	0.55^	0.093	0.51^	0.036*	0.61^	0.625	-0.15
	Overweight (BMI 25.0–29.9 kg/m²)	44	48.89	31	70.45	21	47.73	10	22.73	13	29.55	0.035*	-0.55^	0.093	-0.51^	0.036*	-0.61^	0.625	0.15

Table 2 (continued)

1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Evoluation thresholds	Values above the upper evaluation threshold according to the Ukrainian FRAX® model	14	15.56	13	92.86	4	28.57	9	64.29	1	7.14	0.286	0.58^	1.000	0.24	0.031*	0.80^	0.010*	-0.70^
	Intermediate values of fracture risk according to the Ukrainian FRAX® model	62	68.89	53	85.48	37	59.68	м	25.81	9	14.52	0.085	0.47	0.028*	0.61^	0.542	0.23	0.100	0.44
	Values below the lower evaluation threshold according to the Ukrainian FRAX® model	14	15.56	6	42.86	5	35.71	1	7.14	8	57.14	0.001*	-0.80^	0.005*	-0.74^	0.002*	-0.90^	0.408	0.51^

Notes: N – the total number of patients; n – the incident of the studied characteristic; % – relative frequency of cases and its percentage share in each group; p – the value of R. Fisher's exact test (EG and CG); p_1 – the value of R. Fisher's exact test (EG A and CG); p_2 – the value of R. Fisher's exact test (EG B and CG); p_3 – the value of R. Fisher's exact test (EG A and EG B); * – statistically significant difference between the frequency of cases in groups ($p < 0.050$); YCA – the value of J. Yule's coefficient of association to confirm the stochastic association between the feature and IBMD; YCA_1 – the value of J. Yule's coefficient of association to confirm the stochastic association between the feature and osteopenia; YCA_2 – the value of J. Yule's coefficient of association to confirm the stochastic association between the feature and osteoporosis; YCA_3 – the value of J. Yule's coefficient of association to confirm the stochastic association between the feature and osteopenia or osteoporosis in case of its negative value; ^ – a substantial direct stochastic association between the feature and a certain bone disorder (YCA ≥0.50 or ≤-0.50).

According to the results of the *first step*, there were 27 (30.00 %) women, 22 (81.48 %) of whom had IBMD, among all examined patients with LC. 14 (51.85 %) women had osteopenia, 8 (29.63 %) – osteoporosis, 5 (18.52 %) women's BMD was within the normal range. However, men predominated in the number of examined patients (63 (70.00 %) patients), 50 (79.37 %) of which had IBMD. 32 (50.79%) men had osteopenia, 18 (28.57%) – osteoporosis, and 13 (20.63%) men's BMD was within the normal range. The number of females and males did not statistically significantly differ among groups ($p > 0.050$), and the stochastic association between bone disorders and gender was not substantial (YCA <0.50 and >-0.5).

The analysis of age showed that the majority of patients with LC were middle-aged (53 (58.89 %)), a bit less – young (27 (30.00 %)), the least – elderly (10 (11.11 %)). Among young patients IBMD was detected in 22 (81.48 %) of them, 16 (59.26 %) of whom had osteopenia, and 6 (22.22 %) had osteoporosis. 5 (18, 52 %) young patients had BMD within the normal range. 42 (79.25 %) middle-aged patients had IBMD (25 (47.17 %) – osteopenia; 17 (32.08 %) – osteoporosis), and 17 (32.08 %) participants had normal BMD. Among the elderly, the frequency of bone disorders was eight (80.00 %) cases (five (50.00 %) and three (30.00 %), respectively), and there was no IBMD in only two (20.00 %) cases. There was no significant difference between groups ($p > 0.050$) or substantial stochastic association between age and IBMD manifestations (YCA <0.50 and >-0.5).

24 (26.67 %) patients with LC happened to have fractures in anamnesis. 23 (95.83%) of them had IBMD (10 (41.67 %) – osteopenia; 13 (54.17 %) – osteoporosis) and 1 (4.17%) – did not. There was a statistically significant difference in the frequency of cases in EG and CG ($p = 0.034$), as well as in EG B and CG ($p = 0.002$), and EG A and EG B ($p = 0.019$). Substantial direct stochastic association between the presence of previous fractures in the anamnesis and all the manifestations of IBMD (including osteopenia and osteoporosis) was found (EG and CG: YCA = 0.78; EG A and CG: YCA = 0.65; EG B and CG: YCA = 0.89). Comparing osteopenia and osteoporosis shows that previous fractures have association with osteoporosis (EG A and EG B: YCA = -0.57).

Any patient with LC has not been detected to have rheumatoid arthritis. On the other hand, due to liver damage, the probability of secondary osteoporosis is inherent in all (100.00 %) patients with LC.

Six (6.67 %) patients with LC were treated with glucocorticoids at a dosage of 5.0 mg per day or more at the time of examination, five (83.33 %) of them had IBMD (two (33.33 %) – osteopenia; three (50.00 %) – osteoporosis) and one (16.67 %) had BMD within the normal range. Neither statistically significant difference nor substantial stochastic association with the manifestations of IBMD was recorded ($p > 0.050$; YCA <0.50 and >-0.5).

Smoking was a bad habit of 28 (31.11 %) patients with LC, 23 (82.14 %) of whom had IBMD (12 (42.86 %) – osteopenia; 11 (39.29%) – osteoporosis) and 5 (17.86%) – BMD within the normal range. There was no statistically significant difference between groups ($p > 0.050$) or substantial stochastic association of smoking with IBMD manifestations recorded (YCA <0.50 and >-0.5).

Alcohol was a risk factor for 77 (85.56 %) patients with LC. 62 (80.52%) of them had IBMD (40 (51.95 %)

– osteopenia; 22 (28.57 %) – osteoporosis) and 15 (19.48 %) did not have bone disorders. There was no statistically significant difference between groups and no substantial stochastic association between excessive alcohol consumption and any manifestation of bone disorders ($p > 0.050$; YCA <0.50 and >- 0.5) recorded.

While studying the frequency of femur fractures among parents of patients with LC, not a single case was recorded.

31 (34.44 %) patients with LC were tall. 23 (74.19 %) of them had IBMD, in particular osteopenia – 15 (48.39 %) and osteoporosis – 8 (25.81 %), and 8 (25.81 %) had BMD within the normal range. Medium height was most frequently recorded among patients with LC (53 (58.89 %) cases). 45 (84.91 %) of them were detected to have IBMD (28 (52.83 %) – osteopenia; 17 (32.08 %) – osteoporosis), 8 (15.09 %) patients with LC of medium height had normal BMD. Among patients with LC, only six (6.67 %) were of short stature. Four (66.67 %) of them had IBMD (three (50.00 %) – osteopenia, one (16.67 %) – osteoporosis) and two (33.33 %) had normal BMD. In no case was the height statistically significantly different between the groups ($p > 0.050$), and only between osteoporosis and short height was a substantial negative stochastic association (YCA = -0.52).

When examining body weight, 46 (51.11 %) patients with LC were found to have normal body weight and 44 (48.89 %) were overweight. 41 (89.13 %) patients with IBMD (25 (54.35 %) patients with osteopenia and 16 (34.78 %) – with osteoporosis) and 5 (10.87 %) patients without IBMD were detected to have normal weight. On the contrary, 31 (70.45 %) patients with IBMD were overweight (21 (47.73 %) of them with osteopenia and 10 (22.73 %) – with osteoporosis) and 13 (29.55 %) – with BMD within the normal range. At the same time, the frequency of having normal body weight was statistically significantly different in EG and CG (p = 0.035) and in EG B and CG ($p = 0.036$). Substantial direct stochastic assotiation between having normal body weight and bone disorders was found (EG and CG: YCA = 0.55; EG A and CG: YCA = 0.51; EG B and CG: YCA = 0.61). Overweight, which was also statistically significantly different in EG and CG ($p = 0.035$) and in EG B and CG ($p = 0.036$), was characterized by a substantial negative stochastic assotiation with IBMD and its manifestations (EG and CG: YCA = -0.55; EG A and CG: YCA = -0.51; EG B and CG: YCA = -0.61), indicating that this feature is inherent in patients without bone disorders.

The *second step of the first stage* of the study showed the following results: the values above the upper evaluation threshold were observed in 14 (15.56 %) patients with LC. Among them, 13 (92.86 %) had IBMD (4 (28.57 %) – osteopenia; 9 (64.29 %) – osteoporosis) and only 1 (7.14 %) had no bone disorders. There was a statistically significant difference in the frequency of cases in EG B and CG (p = 0.031) and in EG A and EG B ($p < 0.010$). Substantial stochastic assotiation between values above the upper evaluation threshold and IBMD (EG and CG: YCA = 0.58), and osteoporosis in particular, was recorded (EG B and CG: YCA = 0.80; EG A and EG B: YCA = -0.70).

The intermediate values of fracture risk were indicated in 62 (68.89 %) patients with LC. 53 (85.48 %) of them had bone disorders, and most frequently they were patients with osteopenia (37 (59.68 %)). Osteoporosis was present in 16 (25.81 %) patients, and the smallest number of examined patients with intermediate values of fracture risk was found in CG (9 (14.52 %). Only the frequency of cases in EG A and CG was statistically significantly different ($p = 0.028$), and a substantial direct stochastic assotiation was recorded only between intermediate values of fracture risk and osteopenia (EG A and CG: YCA = 0.61).

The values below the lower evaluation threshold were recorded for 14 (15.56 %) patients with LC. IBMD was present in six (42.86 %), while osteopenia was observed in five (35.71 %). The values below the lower evaluation threshold were recorded least often for patients with osteoporosis (one case (7.14 %)), and most often for patients without IBMD (eight (57.14 %)). A statistically significant difference between EG and CG (p = 0.001), as well as EG A and CG ($p = 0.005$), and EG B and CG ($p = 0.002$) was noted. The values below the lower evaluation threshold are characterized by substantial negative stochastic assotiation with all manifestations of IBMD (EG and CG: YCA = -0.80; EG A and CG: YCA = -0.74; EG B and CG: YCA = -0.90), suggesting that the values below the lower evaluation threshold most likely indicate BMD to be within the normal range.

So, the risk factors for osteoporotic fractures in patients with LC were detected with frequency of 0.00–100.00 %, and the evaluation thresholds according to the Ukrainian FRAX® model – with a frequency of 15.56–68.89 %. None of the patients had a history of confirmed rheumatoid arthritis and a femur fracture among their parents, but due to the presence of liver damage, all patients with LC had risk of secondary osteoporosis (100.00 %), most of them had intermediate values of fracture risk (68.89 %), and the rest – with the same frequency had values both above upper and below lower evaluation thresholds according to the Ukrainian FRAX® model.

Although patients with bone disorders were more predisposed to osteoporotic fractures due to mentioned risk factors, significant differences were found between the frequency of previous fractures in patients with IBMD and normal BMD, osteoporosis and normal BMD, and osteopenia and osteoporosis; between the frequency of cases of normal body weight, as well as overweight in LC patients with IBMD and normal BMD, and osteoporosis and normal BMD. The evaluation thresholds according to the Ukrainian FRAX® model also differed significantly: values above the upper evaluation threshold – in patients with osteoporosis and normal BMD, and in patients with osteopenia and osteoporosis; intermediate values of fracture risk – in patients with osteopenia and normal BMD; values below the lower evaluation threshold – in patients with all manifistations of IBMD and normal BMD.

Bone disorders had a substantial direct stochastic association in the following cases: IBMD in general – with the presence of previous fractures in the anamnesis, normal

body weight and values above the upper evaluation threshold according to the Ukrainian FRAX® model; osteopenia – with the presence of previous fractures in the anamnesis, normal body weight and intermediate values of fracture risk according to the Ukrainian FRAX® model; osteoporosis – with the presence of previous fractures in the anamnesis, normal body weight and values above the upper evaluation threshold according to the Ukrainian FRAX® model. In addition, all manifestations of bone disorders were detected to have substantial negative stochastic association with overweight and values below the lower evaluation threshold according to the Ukrainian FRAX® model, as well as osteoporosis with short height. As a result, BMD can be suggested to be within the normal range.

The results of the *second stage* of the study are shown in the table 3.

Table 3

Diagnostic characteristics of fracture risk factors and evaluation thresholds according to the Ukrainian model of Fracture Risk Assessment in patients with liver cirrhosis with impaired bone mineral density including osteopenia and osteoporosis

Features		Studied groups	TP	FN	FP	TN	Se, %	Sp, %	PPV, %	NPV, %	LR+	LR-	DA, %	p_1	p_2	YCA	CC
Fracture risk factors	Previous fractures	EG	23	49	1	17	31.94	94.44	95.83	25.76	5.75	0.72	44.44	0.034*		0.78^	0.24
		EG A	10	36			21.74		90.91	32.08	3.91	0.83	42.19	0.159	0.019*	0.65^	0.19
		EG B	13	13			50.00		92.86	56.67	9.00	0.53	68.18	0.002*		0.89^	0.47^
	Normal body weight (BMI 18.5–24.9 kg/m²)	EG	41	31	5	13	56.94	72.22	89.13	29.55	2.05	0.60	60.00	0.035*		0.55^	0.23
		EG A	25	21			54.35		83.33	38.24	1.96	0.63	59.38	0.093	0.625	0.51^	0.24
		EG B	16	10			61.54		76.19	56.52	2.22	0.53	65.91	0.036*		0.61^	0.33^
	Overweight (BMI 25.0–29.9 kg/m²)	EG	31	41	13	5	43.06	27.78	70.45	10.87	0.60	2.05	40.00	0.035*		-0.55	-0.23
		EG A	21	25			45.65		61.76	16.67	0.63	1.96	40.63	0.093	0.625	-0.51	-0.24
		EG B	10	16			38.46		43.48	23.81	0.53	2.22	34.09	0.036*		-0.61	-0.33
Evaluation thresholds	Values above the upper evaluation threshold according to the Ukrainian FRAX® model Intermediate values of fracture risk according to the Ukrainian FRAX® model	EG	13	59	1	17	18.06	94.44	92.86	22.37	3.25	0.87	33.33	0.286		0.58^	0.14
		EG A	4	42			8.70		80.00	28.81	1.57	0.97	32.81	1.000		0.24	0.05
		EG B	9	17			34.62		90.00	50.00	6.23	0.69	59.09	0.031*	0.010*	0.80^	0.34^
	Values above the upper evaluation threshold according to the Ukrainian FRAX® model Intermediate values of fracture risk according to the Ukrainian FRAX® model	EG	53	19	9	9	73.61	50.00	85.48	32.14	1.47	0.53	68.89	0.085		0.47	0.20
		EG A	37	9			80.43		80.43	50.00	1.61	0.39	71.88	0.028*		0.61^	0.30^
		EG B	16	10			61.54		64.00	47.37	1.23	0.77	56.82	0.542	0.100	0.23	0.11
	Values above the upper evaluation threshold according to the Ukrainian FRAX® model	EG	6	66	8	10	8.33	55.56	42.86	13.16	0.19	1.65	17.78	0.001*		-0.80	-0.40
		EG A	5	41			10.87		38.46	19.61	0.24	1.60	23.44	0.005*	0.408	-0.74	-0.38
		EG B	1	25			3.85		11.11	28.57	0.09	1.73	25.00	0.002*		-0.90	-0.49

Notes: TP – true positive test results; FN – false negative test results; FP – false positive test results; TN –true negative test results; Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio; DA – diagnostic accuracy; p_1 –the value of R. Fisher's exact test if studied groups compared with the comparison group (EG and CG; EG A and CG; EG B and CG); p_2 – the value of R. Fisher's exact test if comparing EG A with EG B; * – statistically significant difference between the frequency of cases in groups ($p < 0.050$); YCA – the value of J. Yule's coefficient of association to confirm the stochastic association between the studied feature and a certain bone disorder; CC – the value of the contingency coefficient to confirm the stochastic association between the studied feature and a certain bone disorder; ^ – a substantial direct stochastic association between the studied feature and a certain bone disorder (YCA ≥0.50 or CC ≥0.30).

The first step of the second stage. There were more cases of fracture in the anamnesis of patients with IBMD than in patients without IBMD (EG and CG: $p = 0.034$), and more often in patients with osteoporosis than in patients with normal BMD or osteopenia (EG B and CG: $p = 0.010$; EG A and EG B: $p = 0.019$), and significant direct stochastic association was observed with IBMD overall (YCA = 0.58) including osteopenia (YCA = 0.65; CC = 0.19) and osteoporosis (YCA = 0.89; CC = 0.47). Therefore, diagnostic test indicators were studied for IBMD including osteopenia and osteoporosis. Sensitivity of previous fractures for IBMD is 31.94%, for osteopenia – 21.74 %, for osteoporosis – 50.00 %; specificity – 94.44 % for each of the manifestations of IBMD. Positive predictive value of the factor for IBMD is 95.83 %, for osteopenia – 90.91 %, for osteoporosis – 92.86 %, and negative predictive values are 25.76 %, 32.08 %, and 56.67 %, respectively. Positive likelihood ratio for IBMD corresponds to 5.75, for osteopenia – 3.91, for osteoporosis – 9.00; negative likelihood ratio for IBMD is 0.72, for osteopenia – 0.83, and for osteoporosis – 0.53.

Normal body weight was significantly more common for patients with IBMD, including patients with osteoporosis, than for patients with normal BMD (EG and CG:

$p = 0.035$; EG A and CG: $p = 0.036$), and has substantial direct stochastic association with IBMD (YCA = 0.55), including osteoporosis (YCA = 0.61; CC = 0.33). Sensitivity of the factor for IBMD is 56.94 %, for osteoporosis – 61.54 %; specificity – 72.22 % for both. Positive predictive value of normal body weight for IBMD is 89.13 %, for osteoporosis it is 76.19 %, and negative predictive values are 29.55 % and 56.52 %, respectively. Positive likelihood ratio for IBMD corresponds to 2.05, for osteoporosis – 2.22; negative likelihood ratio for IBMD is 0.60 and for osteoporosis – 0.53.

Overweight, on the contrary, was significantly more often recorded in patients with BMD within normal range than in patients with IBMD, including osteoporosis (EG and CG: $p = 0.035$; EG A and CG: $p = 0.036$), and the stochastic assotiation was substantial but negative for all manifestations of bone disorders (EG and CG: YCA = -0.55; EG A and CG: YCA = -0.51; EG B and CG: YCA = -0.61, CC = - 0.33), which indicates that this feature most likely denotes normal BMD rather than IBMD manifestations.

The analysis of evaluation thresholds according to the Ukrainian FRAX® model confirmed that values above the upper threshold are significantly more often observed in patients with osteoporosis than in patients with normal BMD and osteopenia (EG B and CG: $p = 0.031$; EG A and EG B: $p < 0.010$), and substantial direct stochastic association exists between the upper threshold and IBMD (YCA = 0.58), including osteoporosis (YCA = 0.80; CC = 0.34). The sensitivity of values above the upper evaluation threshold for IBMD is 18.06 %, for osteopenia – 8.70 %, for osteoporosis –34.62 %; specificity – 94.44 % for each of the manifestations of bone disorders. Predictive value indicators are following: positive predictive value for IBMD – 92.86 %, for osteopenia – 80.00 %, for osteoporosis – 90.00 %; negative predictive values are 22.37 %, 28.81 % and 50.00 %, respectively. Positive likelihood ratio for IBMD is 3.25, for osteopenia – 1.57, for osteoporosis – 6.23; negative likelihood ratios are 0.87, 0.97 and 0.69, respectively.

According to the Ukrainian FRAX® model, patients with osteopenia significantly more often had intermediate values of fracture risk than patients with normal BMD (EG A and CG: $p = 0.028$), and there was substantial direct stochastic association only with osteopenia (EG A and CG: YCA = 0.61; CC = 0.30), therefore, the value of intermediate values of fracture risk is significant only for osteopenia. Sensitivity of intermediate values of fracture risk for osteopenia reaches 80.43 %; specificity – 50.00 %; positive predictive value – 80.43 %; negative predictive value – 50.00 %; positive likelihood ratio is 1.61; negative likelihood ratio is 0.39.

Values below the lower evaluation threshold were significantly more frequently elicited among patients without IBMD than among patients with bone disorders (EG and CG: $p = 0.001$; EG A and CG: $p = 0.005$; EG B and CG: $p = 0.002$), and substantial stochastic association was negative with all manifestations of IBMD (EG and CG: YCA = -0.80; CC = -0.40; EG A and CG: YCA = -0.74; CC = -0.38; EG B and CG: YCA = -0.90; CC = -0.49). Sensitivity for IBMD is 8.33 %, for osteopenia – 10.87 %, for osteoporosis – 3.85 %; and specificity is 55.56 % for each of the manifestations of IBMD. Positive predictive value for IBMD is 42.86 %, for osteopenia – 38.46 %, for osteoporosis – 11.11 %; negative predictive values are 13.16 %, 19.61 % and 28.57 %, respectively. Positive likelihood ratio for IBMD is 0.19, for osteopenia – 0.24, for osteoporosis – 0.09; negative likelihood ratios are 1.65, 1.60, and 1.73, respectively. The obtained results of diagnostic characteristics of values below the lower evaluation threshold for each of the IBMD manifestations are very low, but the significant differences with a margin of error of 0.10–0.20 % and the presence of a very strong negative stochastic association with all bone disorders suggest that values below the lower evaluation threshold are most likely typical for BMD within normal range.

To determine the post-test probability of bone disorders in *the second step of the second stage*, markers were selected which were simultaneously confirmed by several criteria of statistical reliability. Among the risk factors for fractures and the evaluation thresholds according to the Ukrainian FRAX® model, the most valuable markers are following: the presence of previous fractures in the anamnesis – for IBMD in general and osteoporosis in particular, normal body weight – for IBMD in general and osteoporosis in particular, values above the upper evaluation threshold according to the Ukrainian FRAX® model – for osteoporosis, intermediate values of fracture risk according to the Ukrainian FRAX® model – for osteopenia.

If a patient with LC has 80.00 % probability of IBMD and 28.89 % probability of osteoporosis before the test, then if there are previous fractures in anamnesis, the post-test probability of IBMD reaches 95.83 % (positive likelihood ratio is 5.75), and of osteoporosis – 78.52 % (positive likelihood ratio is 9.00). If there is no previous fractures in patient's anamnesis, the post-test probability of IBMD will still remain rather high and will be 74.24 % (negative likelihood ratio is 0.72), while the post-test probability of osteoporosis will be only 17.70 % (negative likelihood ratio is 0.53) (fig. 1, 2).

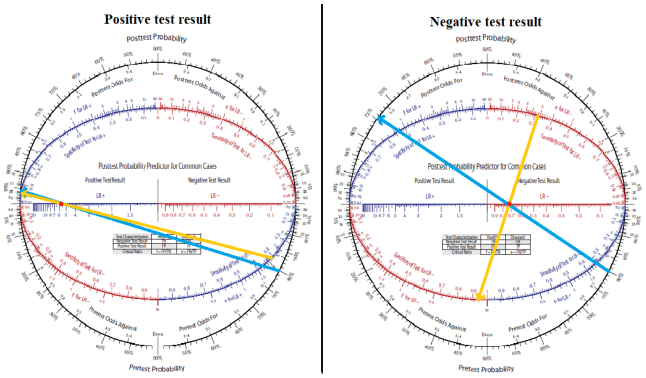

Fig. 1. The post-test probability of impared bone mineral density in the presence and absence of previous fractures in the anamnesis.

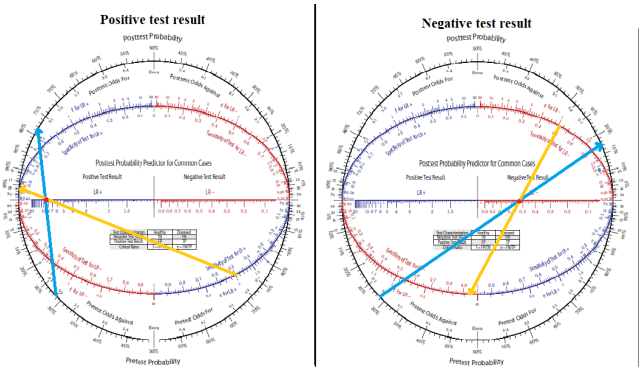

Fig. 2. The post-test probability of osteoporosis in the presence and absence of previous fractures in the anamnesis.

Notes: →– sensitivity and specificity of the test; → – post-test probability of IBMD in case of 80.00 % IBMD prevalence (fig. 1), and post-test probability of osteoporosis in case of 28.89 % osteoporosis prevalence (fig. 2).

If the pre-test probability of IBMD is 80.00 %, and positive and negative likelihood ratios are 2.05 and 0.60, respectively, then the probability of IBMD in a patient with LC who has normal body weight will be equal to 89.13 %, and in the absence of normal body weight, the probability of IBMD will be 70.45 % (fig. 3). For osteoporosis, normal body weight has positive likelihood ratio of 2.22, and negative likelihood ratio of 0.53. Therefore, if the pre-test probability of osteoporosis in patients with LC has a value of 28.89 %, then in the presence of normal body weight, the probability of this diagnosis will be 47.37 %, and in the absence of normal body weight, the probability of osteoporosis will be equal to 17.79 % (fig. 4).

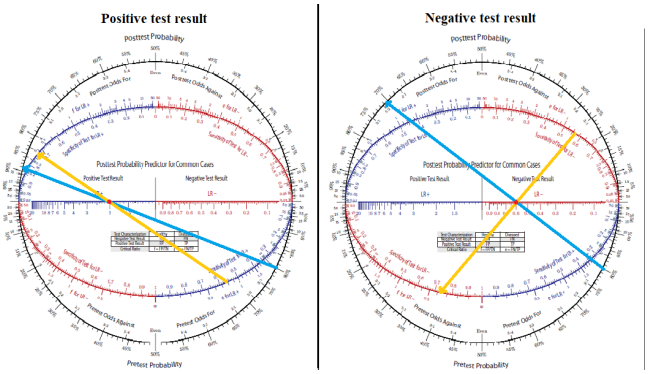

Fig. 3. The post-test probability of impared bone mineral density in the presence and absence of normal body weight.

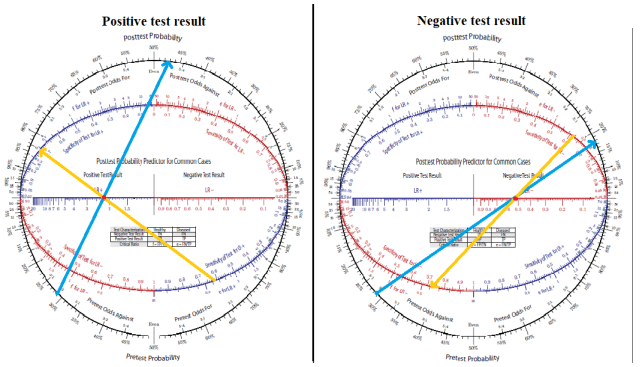

Fig. 4. The post-test probability of osteoporosis in presence and absence of normal body weight.

Notes: → – sensitivity and specificity of the test; → – post-test probability of IBMD in case of 80.00 % IBMD prevalence (fig. 3), and post-test probability of osteoporosis in case of 28.89 % osteoporosis prevalence (fig. 4).

If the value of the obtained test result is above the upper evaluation threshold according to the Ukrainian FRAX® model, there will be 71.68 % probability of osteoporosis (positive likelihood ratio is 6.23), and if the value above the upper evaluation threshold is not recorded, then the probability of osteoporosis will be quite low and will be 21.95 % (negative likelihood ratio is 0.69) (fig. 5).

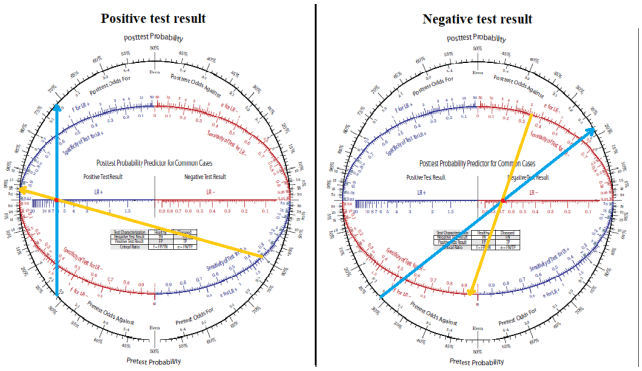

Fig. 5. The post-test probability of osteoporosis in the presence and absence of values above the upper evaluation threshold according to the Ukrainian model of Fracture Risk Assessment.

Notes: → – sensitivity and specificity of the test; →– post-test probability of osteoporosis in case of 28.89 % osteoporosis prevalence.

The pre-test probability of osteopenia in patients with LC according to the results of CQUS is 51.11 %. If positive likelihood ratio for intermediate values of fracture risk according to the Ukrainian FRAX® model is known to be 1.61, then in case of intermediate values of fracture risk detection in patient with LC, the probability of osteopenia will be 62.71 %. Negative likelihood ratio (0.39) indicates that if there have been no intermediate values of fracture risk recorded, the post-test probability of osteopenia is much lower than before the test, and is equal to 29.03 % (fig. 6).

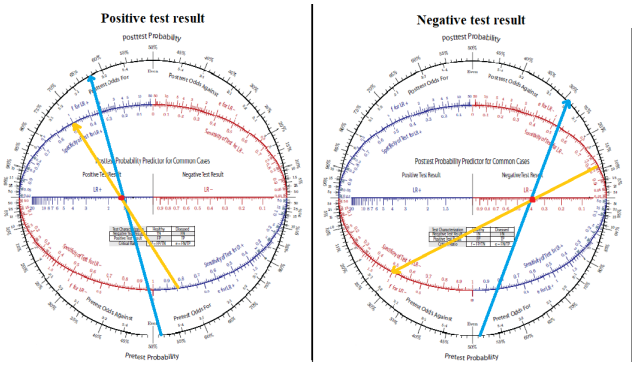

Fig. 6. The post-test probability of osteopenia in the presence and absence of intermediate values of fracture risk according to the Ukrainian model of Fracture Risk Assessment

Notes: → – sensitivity and specificity of the test; → – post-test probability of osteopenia in case of 51.11 % osteopenia prevalence.

So, the discovered fracture risk factors and evaluation thresholds according to the Ukrainian FRAX® model are mainly single-vector markers, i.e. those that either confirm the diagnosis if they are detected, or deny it if they are absent.

Valuable for confirming IBMD in general are the highly specific previous fractures and the medium specific normal body weight of a patient with LC. To eliminate osteopenia, medium-specific intermediate values of fracture risk according to the Ukrainian FRAX® model are valuable. For osteoporosis, highly specific previous fractures, weakly sensitive but medium-specific normal body weight, and highly specific values above the upper evaluation threshold according to the Ukrainian FRAX® model are valuable, which, if present, are most likely to confirm the diagnosis of osteoporosis. Overweight, and especially the values below the lower evaluation threshold, is most likely characteristic of BMD within normal range.

Conclusions. The use of the Ukrainian model of Fracture Risk Assessment (FRAX®) for patients with liver cirrhosis accompanied with impaired bone mineral density has certain peculiarities and value. In particular, presence of previous fractures in the anamnesis will most likely confirm impaired bone mineral density in general and osteoporosis in particular.

The presence of normal body weight might indicate impaired bone mineral density, while its absence indicate the absence of osteoporosis. The presence of values above the upper evaluation threshold according to the Ukrainian FRAX® model will make it possible to correctly diagnose osteoporosis and prescribe the appropriate treatment. Intermediate values of fracture risk, which require additional examination of the bones state, deny the diagnosis of osteopenia, if absent.

References

1. Abrahamovych MO, Farmaha ML. Treatment of the liver cirrhosis: modern principles, considering syntropic co- and mulAbrahamovych MO, Farmaha ML. Treatment of the liver cirrhosis: modern principles, considering syntropic co- and multimorbid lesions of other organs and systems of organs. Lviv Clinical Bulletin. 2013;2(2):37-45). (Ukrainian) https://doi.org/10.25040/lkv2013.02.037
2. Abrahamovych UO, Abrahamovych OO, Tsyhanyk LV, Synenkyi OV, Guta SI. Comparative evaluation of bone mineral density based upon the results of ultrasound osteodensitometry, X-ray Osteodensitometry, and dual-energy X-ray Absorptiometry tests in premenopausal women with systemic lupus erythematosus. Lviv Clinical Bulletin. 2017;1(17):32-37). (Ukrainian) https://doi.org/10.25040/lkv2017.01.032
3. Abushouk AI. Evolution of Fagan's Nomogram; a Commentary. Emerg (Tehran). 2016;4(3):114-115.
4. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014 Oct;25(10):2359-81. https://doi.org/10.1007/ s00198-014-2794-2. https://doi.org/10.1007/s00198-014-2794-2
5. Fagan TJ. Letter: Nomogram for Bayes theorem. N Engl J Med. 1975; 293:257. https://doi.org/10.1056/NEJM197507312930513
6. Gadetska S, Dubnitskiy V, Khodyrev A. Specialized programmable calculator for laboratory test clinical informativeness estimate. Adv Inf Syst. 2020;4(2):80-4. https://doi.org/10.20998/2522-9052.2020.2.12. (Ukrainian) https://doi.org/10.20998/2522-9052.2020.2.12
7. Gamma Coefficient (Goodman and Kruskal's Gamma) & Yule's Q [Internet]. https://www.statisticshowto.com/gamma-coefficient-goodman-kruskal/
8. Gokcan H, Akdogan M, Demir SO, Kacar S, Cam P, Kaplan M et al. Prevalence and characteristics of bone disease in cirrhotic patients. Hepatol Forum. 2020;2:48-52. https://doi.org/10.14744/hf.2020.2020.0007
9. Guañabens N, Parés A. Osteoporosis in chronic liver disease. Liver Int. 2018;38(5):776-785. https://doi.org/10.1111/liv.13730
10. Jeong H, Kim D. Bone Diseases in Patients with Chronic Liver Disease. Int J Mol Sci. 2019;20(17):4270. https://doi.org/10.3390/ijms20174270
11. Kanis JA. Assessment of osteoporosis at the primary health care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School. 2007. Available from: https://www.sheffield.ac.uk/FRAX/pdfs/WHO_ Technical_Report.pdf.
12. Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3-44. https://doi.org/10.1007/s00198-018-4704-5
13. Khadim M, Mubashir W, Irshad A, Hospital S, Khan RY. Prevalence of Osteoporosis in Liver Cirrhosis. Asian J Multidiscip Stud. 2019;7(9):2348-7186.
14. Marasco J, Beach P, Doerfler R, Roschier L. Doc, What Are My Chances? UMAP Journal. 2011;32:279-98.
15. Mandell BF. Understanding medical tests and test results. MSD Manual Professional Version; 2021; Modified 2022:1-5. https://www.msdmanuals.com/professional/special-subjects/clinical-decision-making/understanding-medical-tests-and-test-results
16. McDonald JH. Book: Biological Statistics (McDonald). Open Education Resource (OER) LibreTexts Project (https://LibreTexts.org) 2022:270. https://stats.libretexts.org/Bookshelves/Applied_Statistics/Book%3A_Biological_Statistics_(McDonald)
17. Order of the Ministry of Health of Ukraine No. 271 dated 13.06.2005 "On approval of protocols for the provision of medical care in the specialty "Gastroenterology". https://zakon.rada.gov.ua/rada/show/v0271282-05#Text (Ukrainian)
18. Povoroznyuk VV, Grygorieva NV, Kanis JA et al. Ukrainian FRAX: criteria for diagnostics and treatment of osteoporosis. Pain Joints Spine 2019;9(4):9-16.
19. Povoroznyuk VV, Grygorieva NV, Kanis JA, McCloskey EV, Johansson H. Ukrainian Version of FRAX: from Creation to Validation. Bol', sustavy, pozvonočnik. 2016;(3):5-14. https://doi.org/10.22141/2224- 1507.3.23.2016.85000. (Ukrainian).

20. Ranganathan P, Aggarwal R. Understanding the properties of diagnostic tests - Part 2: Likelihood ratios. Perspect Clin Res. 2018;9(2):99-102. https://doi.org/10.4103/picr.PICR_41_18
21. Saeki C, Takano K, Oikawa T, Aoki Y, Kanai T, Takakura K et al. Comparative assessment of sarcopenia using the JSH, AWGS, and EWGSOP2 criteria and the relationship between sarcopenia, osteoporosis, and osteosarcopenia in patients with liver cirrhosis. BMC Musculoskelet Disord. 2019;20(1):1-12. https://doi.org/10.1186/s12891-019-2983-4
22. WHO Study Group Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep. 1994;843:5-6. https://apps.who.int/iris/handle/10665/39142
23. Yule GU. On the methods of measuring association between two attributes. J R Stat Soc. 1912;75(6):579. https://doi.org/10.2307/2340126
24. Zaiontz C. Real Statistics Using Excel. 2020. www.real-statistics.com

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Conflict of interest
The authors of this article argue that there is no conflict of interest.

Peculiarities of the Ukrainian Model of Fracture Risk Assessment (FRAX®) Among Patients with Liver Cirrhosis Accompanied by Impaired Bone Mineral Density: Its Diagnostic and Prognostic Value

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Introduction. The problem of osteoporotic fractures and the evaluation thresholds for intervention in patients with liver cirrhosis (LC) remains obscure so far. Ukrainian model of fracture risk assessment (FRAX®) has never been implemented among patients with LC in Ukraine.

The aim of the study. To find out the peculiarities of the Ukrainian model of Fracture Risk Assessment, its diagnostic and prognostic value for implementation among patients with liver cirrhosis accompanied by impaired bone mineral density.

Materials and methods. 90 patients with LC (27 women and 63 men aged 18 to 66 years) were randomly assigned into the study. Stratification into groups was based on information about bone condition. 72 patients were included into an experimental group (EG, patients with impaired bone mineral density (IBMD), which was divided into two subgroups – EG A (patients with osteopenia, 46) and EG B (patients with osteoporosis, 26). Control group (CG) included 18 patients without IBMD.

The peculiarities of the fracture risk factors and evaluation thresholds according to the Ukrainian FRAX® model (2019) amoung patients with LC with bone disorders were established (significant differences between frequency of features in groups and substantial stochastic associations of features with IBMD or its manifestations were investigated). The diagnostic characteristcs (diagnostic value, predictive value, likelihood ratio) of the detected features for IBMD in general, osteopenia and osteoporosis in particular, were revealed, and after that the post-test probability of certain bone disorders was determined among all patients with LC in the case of applying the identified features.

The results. It was found that although most of the risk factors occurred more often in patients with bone disorders, significant differences were detected only between the frequency of previous fractures in EG and CG, including EG B and CG, and EG A and EG B; between the frequency of cases of normal body weight, as well as overweight in EG and CG, including EG B and CG. The evaluation thresholds according to the Ukrainian FRAX® model also differed significantly: the values above the upper evaluation threshold – in EG B and CG and in EG A and EG B; the intermediate values of fracture risk – in EG A and CG; the values below the lower evaluation threshold – in EG and CG, as well as in EG A and CG and in EG B and CG, including. Bone disorders had a substantial direct stochastic association in the following cases: IBMD in general – with the previous fractures, normal body weight and values above the upper evaluation threshold; osteopenia – with the previous fractures, normal body weight and intermediate values of fracture risk; osteoporosis – with the previous fractures, normal body weight and values above the upper evaluation threshold. All manifestations of bone disorders had substantial negative stochastic association with overweight and values below the lower evaluation threshold, as well as osteoporosis with short height (indicates that features are inherent for normal bone mineral density).

It was found out that fracture risk factors and evaluation thresholds according to the Ukrainian FRAX® model are mainly single-vector markers, since they can confirm the disease being detected, or deny it in the case they are absent. The previous fractures are highly specific for IBMD, especially for osteoporosis, and can be useful for confirming these disorders being present in patient with LC. The normal body weight is medium-specific for IBMD and for osteoporosis, but can be more useful for indicating IBMD if it is present, and excluding osteoporosis being

absent. The values above the upper evaluation threshold according to the Ukrainian FRAX® model are highly specific for osteoporosis and can confirm osteoporisis being present. The intermediate values of fracture risk according to the Ukrainian FRAX® model are medium-specific for osteopenia, but can be more useful for excluding osteopenia if they are absent. The overweight, especially the values below the lower evaluation threshold, will most likely indicate normal bone mineral density.

Conclusions. The use of the Ukrainian model of Fracture Risk Assessment (FRAX®) has certain peculiarities and can be valuable tool for detecting or excluding impaired bone mineral density in patients with liver cirrhosis.

Keywords: cirrhosis, osteopenia, osteoporosis, Fracture Risk Assessment, Ukrainian FRAX, intervention threshold.

Особливості української моделі оцінки ризику перелому (Fracture Risk Assessment – FRAX®) у хворих на цироз печінки з порушенням мінеральної щільности кісткової тканини та її діагностична і прогностична цінність

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Вступ. Проблему остеопорозних переломів і меж втручання у хворих на цироз печінки (ЦП) досі не розв'язано, а використання української моделі оцінки ризику перелому (FractureRiskAssessment – FRAX®) у хворих на ЦП в Україні не вивчали взагалі.

Мета. З'ясувати особливості української моделі оцінки ризику перелому, її діагностичну й передбачувану цінність для застосування у хворих на цироз печінки з порушенням мінеральної щільности кісткової тканини.

Матеріали й методи. Після підписання добровільної згоди на участь у дослідженні, із дотриманням Гельсінкської декларації прав людини та Конвенції Ради Європи про права людини і біомедицину, в рандомізований спосіб у дослідження залучено 90 хворих на ЦП (27 жінок і 63 чоловіки віком від 18 до 66 років), які у період з 2016 до 2020 року лікувались у Комунальному некомерційному підприємстві Львівської обласної ради «Львівська обласна клінічна лікарня». Стратифікація на групи відбувалась на основі інформації про стан кісток. 72 хворих увійшли в дослідну групу (ДГ) (хворі з порушенням мінеральної щільности кісткової тканини (ПМЩКТ), яку поділено на дві підгрупи – ДГ А (хворі з остеопенією (46)) і ДГ Б (хворі на остеопороз (26)). Групу порівняння (ГП) сформовано з 18 хворих без ПМЩКТ.

Вивчаючи особливості української моделі FRAX® (2019), виявляли статистично достовірні відмінності між групами та наявність істотного стохастичного зв'язку з певним ураженням кісток чинників ризику переломів (стать, вік, наявність попередніх переломів, ревматоїдний артрит у анамнезі, вторинний остеопороз, використання глюкокортикоїдів, переломи стегнової кістки у батьків, шкідливі звички (куріння і зловживання алкоголем), зріст і маса тіла) та меж втручання (верхня межа, показники вище якої дають змогу призначати антиостеопорозне лікування, не проводячи додаткові обстеження; проміжні показники ризику переломів, які є підставою для додаткового дослідження, і нижня межа, показники нижче якої можуть свідчити, що немає потреби в додатковому дослідженні структури кісток і відповідно в лікуванні) без урахування показників мінеральної щільности кісткової тканини (МЩКТ). Після цього визначали діагностичні характеристики (діагностичну й передбачувану цінність, відношення правдоподібности) виявлених ознак для ПМЩКТ загалом і остеопенії й остеопорозу зокрема та посттестову ймовірність певного ураження кісток серед усіх хворих на ЦП у разі застосування їх.

Результати. Виявлено, що хоча більшість чинників ризику частіше траплялася у хворих із ураженням кісток, достовірні відмінності зафіксовані лише між частотою попередніх переломів у ДГ і ГП, у тому числі ДГ Б і ГП та ДГ А і ДГ Б; між частотою випадків нормальної маси тіла, а також надмірної маси тіла у хворих ДГ і ГП, у тому числі ДГ Б і ГП. Межі втручання відповідно до української моделі FRAX® також достовірно відрізнялися: верхня межа – у хворих ДГ Б і ГП та у хворих ДГ А і ДГ Б; проміжні показники – у хворих ДГ А і ГП; нижня межа – у хворих ДГ і ГП, а також у хворих ДГ А і ГП й ДГ Б і ГП в тому числі. Ураження кісток мали істотний прямий стохастичний зв'язок у таких випадках: ПМЩКТ загалом – із наявністю попередніх переломів у анамнезі, нормальною масою тіла та верхньою межею втручання згідно з українською моделлю FRAX®; остеопенія – із наявністю попередніх переломів у анамнезі, нормальною масою тіла та проміжними показниками ризику остеопорозних переломів згідно з українською моделлю FRAX®; остеопороз – із наявністю попередніх переломів у анамнезі, нормальною масою тіла й верхньою межею втручання

згідно з українською моделлю FRAX®. Окрім цього, виявлено істотний обернений стохастичний зв'язок між усіма проявами ураження кісток і надмірною масою тіла та нижньою межею втручання згідно з українською моделлю FRAX®, а також між остеопорозом і низьким зростом, що вказує на характерність цих ознак для МЩКТ у межах норми.

З'ясовано, що чинники ризику переломів і межі втручання відповідно до української моделі FRAX® переважно є одновекторними маркерами, тобто такими, що або підтверджують хворобу в разі виявлення їх, або спростовують наявність хвороби, якщо їх немає. Цінними для підтвердження ПМЩКТ загалом є високоспецифічна наявність попередніх переломів і середньоспецифічна нормальна маса тіла хворого на ЦП. Для виключення остеопенії цінними є середньоспецифічні проміжні показники ризику переломів відповідно до української моделі FRAX®. Для остеопорозу цінними є високоспецифічна наявність попередніх переломів, слабкочутлива, але середньоспецифічна нормальна маса тіла й високоспецифічні показники вище верхньої межі втручання відповідно до української моделі FRAX®, що за наявности найімовірніше підтвердять діагноз остеопорозу. Наявність у хворого надмірної маси тіла, а особливо – нижньої межі втручання, найімовірніше вказуватиме на МЩКТ у межах норми.

Висновки. Застосування української моделі оцінки ризику перелому має певні особливості та може бути цінною для виявлення чи виключення порушення мінеральної щільности кісткової тканини у хворих на цироз печінки, завдяки чому можна обрати правильну тактику курації такого хворого.

Ключові слова: цироз печінки, остеопенія, остеопороз, українська модель FRAX®, оцінка ризику перелому, межі втручання.

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