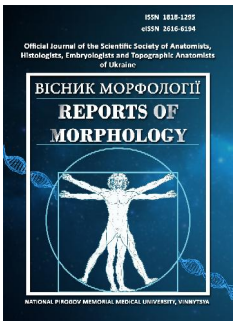
DOI: 10.31393/morphology-journal-2023-29(2)-03 Reports of Morphology, Vol. 29, №2, Pages 18-25

ISSN 1818-1295 eISSN 2616-6194

REPORTS OF MORPHOLOGY

Official Journal of the Scientific Society of Anatomists, Histologists, Embryologists and Topographic Anatomists of Ukraine

journal homepage: https://morphology-journal.com



Serum myostatin and irisin as predictive biomarkers of sarcopenia, malnutrition and mortality in patients with decompensated liver cirrhosis

Motsiuk V. M., Pentiuk N. O.
National Pirogov Memorial Medical University, Vinnytsya, Ukraine

ARTICLE INFO
Received: 31 January 2023
Accepted: 24 February 2023

UDC: 616.74:616.36-004:621.3.088.6

CORRESPONDING AUTHOR
e-mail: pentiuk.na@gmail.com
Pentiuk N. O.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

FUNDING
Not applicable.

Malnutrition and sarcopenia are nowadays considered the main complications of liver cirrhosis (LC). Myokines are signal peptides synthesized in muscles that regulate muscle strength and mass and mediate crosstalk between skeletal muscles and other organs. It is unknown whether circulating myokines can be used as biomarkers of malnutrition and sarcopenia and have independent prognostic value in LC. The purpose of the study was to assess the relationship of serum levels of myokines myostatin and irisin with nutritional status, skeletal muscle status, and survival in decompensated LC patients. 74 patients (55.30±11.40 years) were involved in the prospective study. Nutritional status was assessed using the Patient-Generated Subjective Global Assessment, and skeletal muscle mass was assessed using the Skeletal Muscle Index. The concentration of serum myostatin and irisin was determined by enzyme immunoassay. Statistical data processing was performed in SPSS22 (© SPSS Inc.). It was established that the concentration of serum myostatin and irisin is not related to the LC severity according to the Child-Turcotte-Pugh, Model For End-Stage Liver Disease, and the grade of ascites. Patients with overt encephalopathy have higher myostatin levels. Patients with severe hypoalbuminemia have higher serum myostatin and lower serum irisin levels. The development of malnutrition and sarcopenia in decompensated LC patients is associated with increased serum myostatin concentration and decreased serum irisin concentration. Serum myostatin level can predict sarcopenia (AUC 0.834 in males and 0.827 in females, p<0.01). Serum irisin level can predict severe malnutrition (AUC 0.830, p<0.001). The mortality of patients with high myostatin levels (above 5.25 ng/ml in males and 3.55 ng/ml in females) and low irisin levels (less than 1.72 ng/ml) is significantly higher. In conclusion, the circulating myokines levels may be useful in the assessment of nutritional and skeletal muscle status, and prediction of mortality in LC patients.

Keywords: *myostatin, irisin, malnutrition, sarcopenia, survival, liver cirrhosis.*

Introduction

Malnutrition and its clinical consequence, sarcopenia, are today considered the main complications of liver cirrhosis (LC) [34, 35]. Recent data indicate that malnutrition and loss of skeletal muscle mass are independent factors of poor prognosis and are associated with a decreased quality of life, higher risk of decompensation and acute-on-chronic liver failure [5, 18, 20, 28]. Sarcopenic patients face a higher risk of developing hepatic encephalopathy, infectious complications, and sepsis [13, 16, 23]. It has been demonstrated that malnutrition and sarcopenia are associated with an extended stay at the hospital, increased treatment cost and reduced survival [4, 5, 10, 20].

Currently, there are no effective approaches for the treatment of malnutrition and sarcopenia in LC. Liver transplantation ameliorates portal hypertension and liver failure but does not eliminate nutritional and muscle failure in most cases [7, 31, 36, 37]. The identification of potential therapeutic targets is complicated by the insufficient understanding of the pathophysiology, the lack of assessment tools, and sensitive biomarkers.

In recent years, it has grown evident that skeletal muscles have the properties of an endocrine organ. Muscles synthesize and secrete several signal peptides, myokines, which act in an autocrine, paracrine, or endocrine manner.

Myokines regulate many physiological processes, including energy expenditure, carbohydrate and lipid metabolism, liver functions, insulin sensitivity, and inflammation [15, 32]. Myokines synthesized during physical activity regulate muscle strength and mass and mediate crosstalk between skeletal muscles and other organs, including bones, adipose tissue, blood vessels, the liver, brain [33]. It is assumed that abnormal formation and secretion of myokines can negatively affect skeletal muscle status. However, data on the role of myokines in malnutrition and sarcopenia in LC are limited. Recent research shows that age-related sarcopenia is associated with a decreased level of myokines which promote the growth and differentiation of skeletal muscles (apelin, decorin, insulin-like growth factor-1, irisin), and an increased level of myostatin which promotes catabolism and skeletal muscles atrophy [15]. It is unknown whether circulating myokines can be used as biomarkers of malnutrition and sarcopenia and have independent prognostic value in LC patients.

The purpose of the study was to assess the relationship of serum myokines myostatin and irisin with nutritional status, skeletal muscle status, and survival in decompensated LC patients.

Materials and methods

Between 2019 and 2021, 74 patients, including 29 females and 45 males (mean age 55.30±11.40), hospitalized in Vinnytsia City Clinical Hospital No. 1 due to LC decompensation, were involved in the prospective study.

All subjects were informed about the purpose of the study and provided their written consent. The *Committee on Bioethics* of National Pirogov Memorial Medical University, Vinnytsia (*Protocol No 8 from 17.10.2019*) found that the study does not contradict the basic bioethical standards of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant WHO regulations and Ukrainian law. Viral (HBV, HCV) etiology of LC was confirmed in 8, alcohol-related - in 49, and viral-alcohol-related - in 17 patients. All patients met the criteria of decompensated LC according to the classification of G. D'Amico et al. (2018) [6]. Stage B according to the Child-Turcotte-Pugh (CTP) score was diagnosed in 24 patients, and Stage C - in 50 patients. The Model For End-Stage Liver Disease (MELD) score was 28.50±7.04 and fluctuated between 15.4 to 38.9 points. Acute LC decompensation was the cause of hospitalization in 39 patients. None of the patients had clinical signs of acute infection, gastrointestinal bleeding, or acute-on-chronic liver failure. The follow-up period lasted until June 2022. During this time, 42 patients died due to LC complications.

The nutritional status of patients was assessed using the Patient-Generated Subjective Global Assessment (PG-SGA) [11, 25]. The PG-SGA evaluates the patient's weight loss, food intake and symptoms that affect food intake, activity and functioning, metabolic needs, and data from the patient's nutrition-oriented examination. The overall PG-SGA score allocates patients to three categories: well-nourished (Stage A), moderate/suspected malnutrition (Stage B), and severely malnourished (Stage C). The study used a translated and cross-culturally adapted Ukrainian version of the PG-SGA [27] based on the original v4.3.20 PG-SGA (available at http://pt-global.org).

Skeletal muscle mass was assessed using computed tomography. The cross-sectional skeletal muscle area at the L3 level was visualized and calculated in the range -29 +150 HU using NIH ImageJ version 1.52a software. The result was normalized to height, and the skeletal muscle index (SMI) was calculated [17, 28]. Reference values of SMI for the Ukrainian population were >52.2 and >39.3 cm^2/m^2, in males and females, respectively [22]. A decrease in SMI was considered sarcopenia.

The content of serum myostatin and irisin was determined by enzyme immunoassay using MyBioSource Inc. commercial test systems (San Diego, USA), Cat. No. MBS9716424, MBS2903725. Blood sampling was performed in the morning after a night's rest in the fasting state. Patients were advised to avoid physical exertion for 12 hours before blood sample collection because physical exertion affects the synthesis of myokines.

Statistical data was processed in the SPSS22 software package (©SPSS Inc). The mean, standard deviation, and standard error of the mean were calculated. The parametric Student's t-test and the non-parametric Mann-Whitney U-test were used to assess the intergroup difference, while Spearman rank and Pearson's correlation analysis were used to determine the relationships between values. The prognostic value of myostatin and irisin was analyzed in ROC analysis. Analysis of patient survival was performed using the Kaplan-Meier method. The comparison of survival curves was performed using the Logrank test. Results are demonstrated as M±SD and Me (P_{25} - P_{75}). The difference was considered significant at $p<0.05$.

Results

The percentile distribution of the serum myostatin and irisin is presented in the Table 1. The level of myostatin in males was higher than in females, 5.25 (3.31 - 7.24) versus 3.55 (1.95 - 6.40) ng/ml, respectively. The level of irisin in males and females was not significantly different, 1.52 (1.10 - 3.63) versus 2.04 (1.11 - 3.63) ng/ml, respectively. Myostatin inversely correlated with irisin ($r = -0.407$, $p = 0.000$).

Serum myokines were weakly associated with the severity of the underlying disease (Table 2). Myostatin was significantly higher and irisin was significantly lower in CTP class C compared to class B patients. However, the levels of myostatin and irisin did not correlate with the numeric CTP ($r = 0.228$, -0.268, respectively, $p>0.05$). Patients with overt encephalopathy had higher myostatin levels. Patients with severe hypoalbuminemia had higher myostatin levels and lower irisin levels. Myostatin and irisin weakly correlated with the serum albumin ($r = -0.307$, 0.397,

Table 1. Serum myostatin and irisin levels in patients with decompensated LC.

Variables	M±m	s	Me	P_5	P_{10}	P_{25}	P_{75}	P_{90}	P_{95}
Myostatin, ng/ml	Total LC patients, n=74								
	4.621±0.302	2.60	4.51	0.88	1.15	2.34	6.39	8.11	9.72
	Males, n=45								
	5.251±0.406	2.72	5.25	0.76	1.42	3.31	7.24	9.23	10.20
	Females, n=29								
	3.653±0.368	1.99	3.55*	0.85	0.98	1.95	5.19	6.40	6.94
Irisin, ng/ml	Total LC patients, n=74								
	2.302±0.192	1.65	1.72	0.39	0.66	1.11	3.22	5.24	6.13
	Males, n=45								
	2.142±0.241	1.61	1.52	0.29	0.68	1.10	2.73	5.27	5.94
	Females, n=29								
	2.518±0.323	1.71	2.04	0.34	0.46	1.11	3.63	5.25	6.34

Note: * - p<0.05 comparatively to male patients.

Table 2. Serum myostatin and irisin levels according to LC severity, Me (P_{25}-P_{75}).

Variables		Myostatin, ng/ml	Irisin, ng/ml
CTP	Class B, n=24	2.96 (1.33-6.29)	2.93 (1.20-4.43)
	Class C, n=50	5.15 (3.31-6.46) p=0.036	1.47 (1.07-2.23) p=0.036
MELD	≥29, n=39	4.13 (1.46-6.52)	2.11 (1.24-4.11)
	<29, n=35	4.99 (3.38-6.30) p=0.200	1.45 (0.98-2.53) p=0.070
Ascites	0-1 degree, n=48	4.55 (2.08-6.36)	2.10 (1.19-4.09)
	2-3 degrees, n=26	4.51 (2.88-6.43) p=0.760	1.37 (1.07-2.15) p=0.083
Hepatic encephalopathy	0-1 stage, n=28	3.22 (1.38-5.79)	2.57 (1.20-4.38)
	2-3 stage, n=46	5.19 (3.36-6.71) p=0.008	1.53 (1.05-2.23) p=0.071
Albumin	≥30 g/l, n=37	3.99 (1.53-6.18)	2.24 (1.27-4.07)
	<30 g/l, n=37	5.22 (3.30-6.95) p=0.031	1.45 (0.97-2.18) p=0.016

respectively, p<0.05), but did not correlate with the MELD (r = 0.152, -0.223, respectively, p>0.05) and the severity of ascites (r = -0.036, -0.088, respectively, p>0.05).

Our data shows that malnutrition and loss of skeletal muscle mass are closely associated with elevated serum myostatin and decreased serum irisin levels (Table 3). The content of myostatin in severely malnourished patients was significantly higher than in patients with moderate/ suspected malnutrition or well-nourished patients. Median myostatin concentrations in sarcopenic males and females were more than three times higher than in patients with normal skeletal muscle mass. Myostatin weakly correlated with the numerical PG-SGA score (r = 0.394, p<0.005) and moderately correlated with the radiological SMI (r = -0.644 for males, -0.608 for females, respectively, p<0.005). Serum irisin was more dependent on nutritional status than on skeletal muscle status. The concentration of this myokine significantly decreased with the progress of malnutrition severity and moderately correlated with the numerical PG-SGA score (r = -0.615, p<0.005). Irisin concentrations in sarcopenic males and females were more than half as low as in nonsarcopenic patients. There was a moderate correlation between irisin and SMI in males and females (r = 0.430, 0.408, respectively, p<0.005).

The ROC analysis (Table 4) established that the level of serum myostatin can predict sarcopenia in patients with decompensated LC (AUC 0.834 and 0.827 for males and females, p<0.01, respectively). The cut-offs of myostatin concentration for predicting low SMI in males and females were 4.20 ng/ml (Se 77.1 %, Sp 80.0 %) and 2.72 ng/ml

Table 3. Serum myostatin and irisin levels according to nutritional status and muscle mass in patients with decompensated LC, Me (P_{25} - P_{75}).

Variables			Myostatin, ng/ml	Irisin, ng/ml
PG-SGA	1	*Stage A*. Well-nourished, n=18	2.18 (1.28-4.52)	3.90 (2.91-5.24)
	2	*Stage B*. Moderate/suspected malnutrition, n=26	3.79 (1.24-5.49) $p_{1,2}$=0.163	2.07 (1.34-2.61) $p_{1,2}$=0.003
	3	*Stage C*. Severely malnourished, n=30	6.10 (4.25-7.08) $p_{1,3}$=0.000 $p_{2,3}$=0.013	1.04 (0.71-1.66) $p_{1,3}$=0.000 $p_{2,3}$=0.000
SMI	4	Nonsarcopenic males, n=10	1.53 (0.96-2.72)	4.78 (3.85-5.66)
	5	Sarcopenic males, n=35	6.22 (4.22-7.75) $p_{4,5}$=0.000	1.32 (1.05-2.05) $p_{4,5}$=0.000
	6	Nonsarcopenic females, n=9	1.34 (0.99-2.18)	4.22 (3.30-5.36)
	7	Sarcopenic females, n=20	4.90 (3.30-6.07) $p_{6,7}$=0.000	1.50 (0.91-2.18) $p_{6,7}$=0.000

Table 4. The area under curves for malnutrition and sarcopenia prediction according to serum myokines levels in patients with decompensated LC.

Variables			AUC	p
Severe malnutrition: *Stage C* PG-SGA	Myostatin (all patients, n=74)	0.652	0.036	0.501-0.802
	Irisin (all patients, n=74)	0.830	0.000	0.712-0.914
Sarcopenia: SMI ≤52,2 cm²/m² for males; SMI ≤39,3 cm²/m² for females	Myostatin (males, n=45)	0.834	0.003	0.674-0.995
	Myostatin (females, n=29)	0.827	0.007	0.667-0.987
	Irisin (all patients, n=74)	0.639	0.074	0.478-0.794

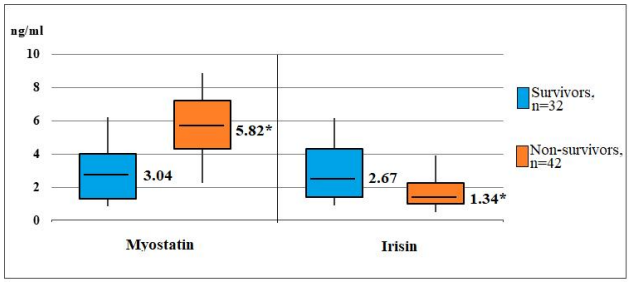


Fig. 1. Serum myostatin and irisin levels according to survival status of patients with decompensated liver cirrhosis. The upper and lower limits of the boxes correspond to P_{25} and P_{75}, the lines outside the boxes - P_{10} and P_{90}, and the line inside the boxes - Me; P_{10}, P_{25}, P_{75}, P_{90}, - percentiles. * - p<0.005.

(Se 85.0 %, Sp 77.8 %), respectively. A low concentration of serum irisin can predict malnutrition (AUC 0.830, p<0.001). The cut-off of irisin concentration for predicting severe malnutrition according to the PG-SGA was 1.78 ng/ml (Se 83.3 %, Sp 72.1 %).

During the follow-up (Me 367 (82-569) days), no patient was lost to analysis, and 42 (56.8%) patients died due to LC complications. Deceased patients had significantly higher myostatin and lower irisin levels at baseline than patients who survived (Fig. 1). We allocated patients into groups with relatively high (higher than Me) and relatively low (lower than Me) myokine levels to determine the relationship between circulating myokine and survival. Kaplan-Meier analysis showed that the overall survival of patients with high (higher than 5.25 ng/ml in males and 3.55 ng/ml in females) myostatin was significantly lower (Fig. 2). The estimated survival time in the high myostatin group was 272.0±42.8 (95% CI: 188-355) versus 654.0±58.1 (95% CI: 541-798) days in the low myostatin group. Patients with low irisin (less than 1.72 ng/ml in males and females) had significantly lower survival than patients with high irisin.

Discussion

To the best of our knowledge, the presented work is one of the few studies of circulating levels of myokines as biomarkers of malnutrition and sarcopenia in patients with LC. We focused on a high-risk cohort of patients. All subjects had MELD scores of more than 15 points. About half of them died during the follow-up. More than 70 % of patients were diagnosed with malnutrition and sarcopenia.

In our study, the serum levels of myostatin and irisin in decompensated LC patients were weakly associated with the severity of the underlying disease. Although CTP class C patients had higher myostatin and lower irisin levels than CTP class B patients, we found no correlation between myokine levels and CTP and MELD. Patients with minimal and pronounced ascites had similar levels of myostatin and irisin. Previously, Nishikawa H. et al. (2017) showed that the concentration of serum myostatin of CTP class B and C patients was higher than that of CTP class A patients [24]. M. Kukla et al. (2020) did not find a difference in the serum irisin between LC patients depending on CTP, MELD, and ascites [14]. M. Pazgan-Simon et al. (2020) demonstrated that the serum irisin in patients with LC and hepatocellular carcinoma (HCC) is lower compared to controls, but not related to the LC severity and the stage of

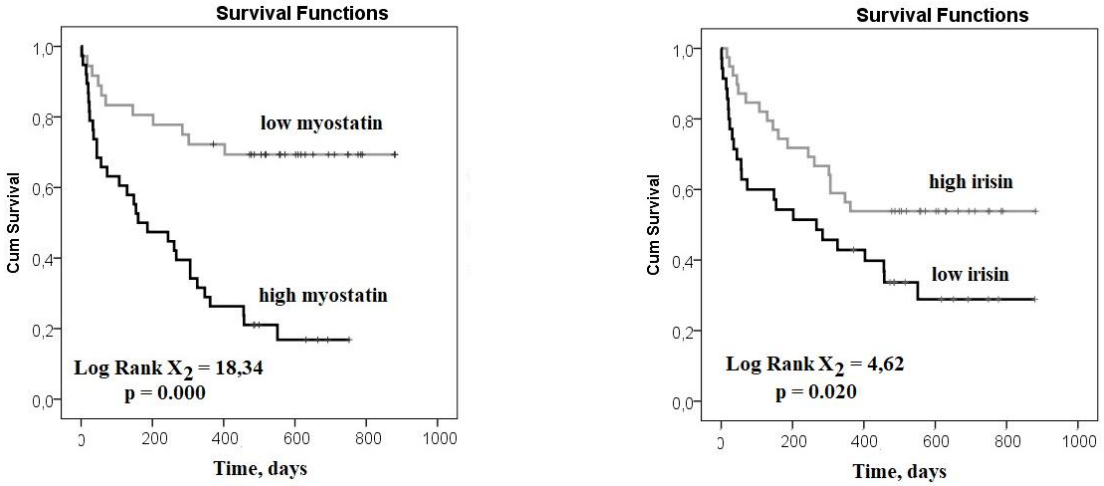


Fig. 2. Kaplan-Meier analysis for survival according to the serum myokines levels.

HCC [26]. The deterioration of liver function and the worsening of portal hypertension are unlikely to have a pivotal effect on the serum myokines in LC patients.

In our study, patients with overt hepatic encephalopathy had higher serum myostatin than patients with minimal encephalopathy. This observation is consistent with previous findings of an association between hepatic encephalopathy and skeletal muscle atrophy. M. Merli et al. (2013) demonstrated that ammonia content in venous blood is higher in patients with sarcopenia [19]. It is assumed that hyperammonemia is associated with the depletion of the branched-chain amino acids pool required for muscle tissue formation, activation of muscle autophagy, and increased expression of myostatin [9]. On the other hand, sarcopenia promotes hyperammonemia and hepatic encephalopathy, as up to 50% of circulating ammonia is detoxified in skeletal muscles [17].

Our data demonstrate that severe malnutrition and sarcopenia in decompensated LC patients are associated with an increase in serum myostatin. Myostatin was the first among the identified myokines and acts as a powerful negative regulator of myogenesis [33]. Experimental studies have shown that animals with a knockout of the myostatin gene have pronounced hypertrophy of skeletal muscles [21, 33]. Existing data suggest that myostatin activates several intracellular signalling pathways to inhibit the proliferation and differentiation of muscle satellite cells, decrease protein synthesis, and stimulate protein degradation in muscle fibres [38]. In clinical studies, high levels of myostatin are associated with muscle wasting, myopathy, and sarcopenia in elderly patients with renal failure and fractures [8, 39, 42].

In our study, myostatin was moderately correlated with the radiological SMI and weakly correlated with the numerical PG-SGA in males and females. We showed that the concentration of serum myostatin (cut-off 4.20/2.72 ng/ml in males/females) can predict sarcopenia in decompensated LC patients (AUC>0.800, p<0.01). A negative relationship between high levels of myostatin and skeletal muscle mass was demonstrated in a retrospective study by H. Nishikawa et al. (2017). The study included 198 Japanese LC patients, 59% of them had a viral aetiology of the disease, 62% - compensated LC, 38% - decompensated LC, and 20% - had HCC. It was established that the concentration of serum myostatin was negatively correlated with the radiological index of the psoas muscle [24]. Later, S. Sato et al. (2021) found a negative correlation between myostatin levels and SMI in patients with viral but not alcohol-related LC [30]. Recently, S. Boga, et al. (2022) using regression analysis demonstrated that a high level of myostatin is an independent predictor of sarcopenia in LC in the Turkish population [2]. The relationship between circulating levels of myostatin and muscle wasting was more pronounced in decompensated patients [2].

Our data suggest that serum irisin was less dependent on muscle condition than myostatin. Sarcopenic LC patients had lower levels of this myokine than patients with normal skeletal muscle mass. Irisin was weakly correlated with SMI and had limited value in predicting sarcopenia in ROC analysis. Previously, M. Kukla et al. (2020) did not find an association between irisin concentration and midarm muscle circumference and transversal psoas muscle index in a similar cohort of patients [14]. However, in another multicenter retrospective study involving 262 LC patients of mainly viral aetiology, it was established that irisin decreases in sarcopenic patients, correlates with SMI, and is an independent predictor of sarcopenia in regression analysis [41].

Our data show that the level of serum irisin was more dependent on the nutritional status of LC patients than on the skeletal muscle status. The concentration of this myokine decreased significantly even in patients with moderate/suspected malnutrition and continued to decrease in severely malnourished patients. Irisin moderately correlated with the numerical PG-SGA score, and the concentration of serum irisin (cut-off 1.78 ng/ml) predicted severe malnutrition according to the PG-SGA (AUC 0.830, p<0.001). The latest data demonstrated that irisin is secreted not only in skeletal muscles but also in adipose tissue, which allows it to be classified as an adipomyokine [3, 29]. The biological effects of irisin are related to energy expenditure, thermoregulation, and the transformation of white adipose tissue into brown adipose tissue [29]. Irisin is an insulin-sensitizing hormone, as it promotes the assimilation of glucose by skeletal muscles, reduces lipogenesis and gluconeogenesis in the liver, and activates lipid oxidation and glycolysis [32]. Anti-inflammatory properties of this regulatory peptide were recently discovered: irisin inhibits the expression of pro-inflammatory cytokines tumor necrosis factor-alpha and interleukin-6 and reduces the migration of macrophages in adipose tissue [1]. Pointing to the important role of irisin in the regulation of metabolism and energy expenditure, we suggest that the loss of adipose and muscle tissue in malnourished LC patients is closely associated with a decline in serum irisin.

We aimed to evaluate the relationship between myokine levels and prognosis in decompensated LC patients. In the Kaplan-Meier analysis, we showed that a high level of myostatin and a low level of irisin have a negative impact on patient survival. Literature data on the prognostic value of myokines in patients with end-stage liver disease are limited and contradictory. A recent retrospective study by J.H. Kim et al. (2020) involving 1077 alcohol-related LC patients is noteworthy. Patients with high serum myostatin levels were shown to have a significantly higher 5-year risk of HCC than patients with low serum myostatin levels (HR 7.53, p<0.001) [12]. S. Yoshio et al., 2021 showed that high-level serum myostatin is an independent predictor of mortality in patients with HCC associated with nonalcoholic fatty liver disease, regardless of muscle status [40]. H. Nishikawa et al. (2017) demonstrated that the 5-year

and 7-year cumulative survival of LC patients with high-level serum myostatin were significantly lower than that of patients with low-level serum myostatin (53% and 39%, versus 78% and 73%, respectively) [24]. However, a recent study by S. Boga et al. (2022) demonstrated that decreased irisin levels were associated with increased cirrhosis-related 4-year mortality in CTP class A patients, while myostatin did not show good prognostic value [2].

In conclusion, the circulating myokines levels may be useful in the assessment of nutritional and skeletal muscle status, and prediction of mortality in LC patients.

Further prospective studies are needed to confirm the prognostic value of myokines in LC patients.

Conclusions

1. The serum myokines myostatin and irisin levels in decompensated LC patients are not related to the LC severity according to the CTP, MELD score, and the degree of ascites. Patients with overt encephalopathy have higher serum myostatin. Patients with severe hypoalbuminemia have higher serum myostatin and lower serum irisin.

2. Malnutrition and sarcopenia are associated with an increase in serum myostatin and a decrease in serum irisin. The myostatin concentration can predict sarcopenia in LC (AUC 0.834 in males, 0.827 in females, $p<0.01$). The irisin concentration can predict severe malnutrition (AUC 0.830, $p<0.001$).

3. An increase in serum myostatin and a decrease in serum irisin are associated with worsening patients' survival. The overall mortality of patients with high levels of serum myostatin (above 5.25 ng/ml in males and 3.55 ng/ml in females) and low levels of serum irisin (less than 1.72 ng/ml) is significantly higher.

References

[1] Askari, H., Rajani, S. F., Poorebrahim, M., Haghi-Aminjan, H., Raeis-Abdollahi, E., & Abdollahi, M. (2018). A glance at the therapeutic potential of irisin against diseases involving inflammation, oxidative stress, and apoptosis: An introductory review. *Pharmacological Research,* 129, 44-55. doi: 10.1016/j.phrs.2018.01.012

[2] Boga, S., Yildirim, A. E., Ucbilek, E., Koksal, A. R., Sisman, S. T., Durak, I., … & Alkim, C. (2022). The effect of sarcopenia and serum myokines on prognosis and survival in cirrhotic patients: a multicenter cross-sectional study. *European Journal of Gastroenterology & Hepatology,* 34(12), 1261-1268. doi: 10.1097/MEG.0000000000002461

[3] Bostrom, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., … & Spiegelman, B. M. (2012). A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature,* 481(7382), 463-468. doi: 10.1038/nature10777

[4] Chapman, B., Goh, S. K., Parker, F., Romero, S., Sinclair, M., Gow, P., … & Testro, A. (2022). Malnutrition and low muscle strength are independent predictors of clinical outcomes and healthcare costs after liver transplant. *Clinical Nutrition ESPEN,* 48, 210-219. doi: 10.1016/j.clnesp.2022.02.013

[5] Dajti, E., Renzulli, M., Ravaioli, F., Marasco, G., Vara, G., Brandi, N., … & Colecchia, A. (2022). The interplay between sarcopenia and portal hypertension predicts ascites and mortality in cirrhosis. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, S1590-8658(22)00789-7. Advance online publication. doi: 10.1016/j.dld.2022.11.011

[6] D'Amico, G., Morabito, A., D'Amico, M., Pasta, L., Malizia, G., Rebora, P., & Valsecchi, M. G. (2018). Clinical states of cirrhosis and competing risks. *Journal of Hepatology,* 68(3), 563-576. doi: 10.1016/j.jhep.2017.10.020

[7] Dasarathy, S. (2013). Posttransplant sarcopenia: an underrecognized early consequence of liver transplantation. *Digestive Diseases and Sciences,* 58(11), 3103-3111. doi: 10.1007/s10620-013-2791-x

[8] de Sire, A., Baricich, A., Reno, F., Cisari, C., Fusco, N., & Invernizzi, M. (2020). Myostatin as a potential biomarker to monitor sarcopenia in hip fracture patients undergoing a multidisciplinary rehabilitation and nutritional treatment: a preliminary study. *Aging Clinical and Experimental Research,* 32(5), 959-962. doi: 10.1007/s40520-019-01436-8

[9] Di Cola, S., Nardelli, S., Ridola, L., Gioia, S., Riggio, O., & Merli, M. (2022). Ammonia and the Muscle: An Emerging Point of View on Hepatic Encephalopathy. *Journal of Clinical Medicine*, 11(3), 611. doi: 10.3390/jcm11030611

[10] Hassan, E. A., Makhlouf, N. A., Ibrahim, M. E., Dabbous, H. M., Salah, M. A., Aboalam, H. S., … & Salama, M. A. R. (2022). Impact of Sarcopenia on Short-Term Complications and Survival After Liver Transplant. *Experimental and Clinical Transplantation: Official Journal of the Middle East Society for Organ Transplantation,* 20(10), 917-924. doi: 10.6002/ect.2022.0293

[11] Jager-Wittenaar, H., & Ottery, F. D. (2017). Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. *Current opinion in Clinical Nutrition and Metabolic Care,* 20(5), 322-329. doi: 10.1097/MCO.0000000000000389

[12] Kim, J. H., Kang, S. H., Lee, M., Youn, G. S., Kim, T. S., Jun, B. G., … & Suk, K. T. (2020). Serum Myostatin Predicts the Risk of Hepatocellular Carcinoma in Patients with Alcoholic Cirrhosis: A Multicenter Study. *Cancers,* 12(11), 3347. doi: 10.3390/cancers12113347

[13] Krell, R. W., Kaul, D. R., Martin, A. R., Englesbe, M. J., Sonnenday, C. J., Cai, S., & Malani, P. N. (2013). Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society,* 19(12), 1396-1402. doi: 10.1002/lt.23752

[14] Kukla, M., Skladany, L., Menzyk, T., Derra, A., Stygar, D., Skonieczna, M., … & Koller, T. (2020). Irisin in Liver Cirrhosis. *Journal of clinical medicine,* 9(10), 3158. doi: 10.3390/jcm9103158

[15] Kwon, J. H., Moon, K. M., & Min, K. W. (2020). Exercise-Induced Myokines can Explain the Importance of Physical Activity in the Elderly: An Overview. *Healthcare* (Basel, Switzerland), 8(4), 378. doi: 10.3390/healthcare8040378

[16] Lee, D. U., Fan, G. H., Ahern, R. R., & Karagozian, R. (2021). The effect of malnutrition on the infectious outcomes of hospitalized patients with cirrhosis: analysis of the 2011-2017 hospital data. *European Journal of Gastroenterology & Hepatology,* 32(2), 269-278. doi: 10.1097/

MEG.0000000000001991

[17] Levitt, D. G., & Levitt, M. D. (2018). A model of blood-ammonia homeostasis based on a quantitative analysis of nitrogen metabolism in the multiple organs involved in the production, catabolism, and excretion of ammonia in humans. *Clinical and Experimental Gastroenterology,* 11, 193-215. doi: 10.2147/CEG.S160921

[18] Mauro, E., Crespo, G., Martinez-Garmendia, A., Gutierrez-Acevedo, M. N., Diaz, J. M., Saidman, J., … & Gadano, A. (2020). Cystatin C and Sarcopenia Predict Acute on Chronic Liver Failure Development and Mortality in Patients on the Liver Transplant Waiting List. *Transplantation,* 104(7), e188-e198. doi: 10.1097/TP.0000000000003222

[19] Merli, M., Giusto, M., Lucidi, C., Giannelli, V., Pentassuglio, I., Di Gregorio, V., ... & Riggio, O. (2013). Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. *Metabolic Brain Disease*, 28(2), 281-284. doi: 10.1007/s11011-012-9365-z

[20] Montano-Loza, A. J., Duarte-Rojo, A., Meza-Junco, J., Baracos, V. E., Sawyer, M. B., Pang, J. X., ... & Myers, R. P. (2015). Inclusion of Sarcopenia Within MELD (MELD-Sarcopenia) and the Prediction of Mortality in Patients With Cirrhosis. *Clinical and translational gastroenterology,* 6(7), e102. doi: 10.1038/ctg.2015.31

[21] Mosher, D. S., Quignon, P., Bustamante, C. D., Sutter, N. B., Mellersh, C. S., Parker, H. G., & Ostrander, E. A. (2007). A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. *PLoS genetics,* 3(5), e79. doi: 10.1371/journal.pgen.0030079

[22] Motsiuk, V. M., & Pentiuk, N. O. (2021). Діагностичне та прогностичне значення показників товщини та площі поперекового м'язу у хворих на цироз печінки, ускладений саркопенією [Diagnostic and prognostic value of indicators of the thickness and area of the lumbar muscle in patients with liver cirrhosis complicated by sarcopenia]. *Вісник Вінницького національного медичного університету - Reports of Vinnytsia National Medical University,* 25(4), 551-558. doi: 10.31393/reports-vnmedical-2021-25(4)-06

[23] Nardelli, S., Lattanzi, B., Torrisi, S., Greco, F., Farcomeni, A., Gioia, S., Merli, M., & Riggio, O. (2017). Sarcopenia Is Risk Factor for Development of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt Placement. *Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association,* 15(6), 934-936. doi: 10.1016/j.cgh.2016.10.028

[24] Nishikawa, H., Enomoto, H., Ishii, A., Iwata, Y., Miyamoto, Y., Ishii, N., … & Nishiguchi, S. (2017). Elevated serum myostatin level is associated with worse survival in patients with liver cirrhosis. *Journal of Cachexia, Sarcopenia and Muscle*, 8(6), 915-925. doi: 10.1002/jcsm.12212

[25] Ottery, F. D. (1996). Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* (Burbank, Los Angeles County, Calif.), 12(1 Suppl), S15-S19. doi: 10.1016/0899-9007(96)90011-8

[26] Pazgan-Simon, M., Zuwala-Jagiello, J., Menzyk, T., Bator, M., Derra, A., Lekstan, A., … & Kukla, M. (2020). Serum betatrophin and irisin levels in hepatocellular carcinoma. *Journal of Physiology and Pharmacology: an Official Journal of the Polish Physiological Society,* 71(1), 1. doi: 10.26402/jpp.2020.1.11

[27] Pentiuk, N. O., Motsiuk, V. M., & Ferree, A.S. (2021). Адаптація та валідизація україномовної версії шкали оцінки нутритивного стану Patient-Generated Subjective Global Assessment (PGSGA) у хворих на цироз печінки [Adaptation and validation of the Ukrainian version of the Patient-Generated Subjective Global Assessment (PGSGA) nutritional status scale in patients with liver cirrhosis]. *Сучасна гастроентерологія - Modern Gastroenterology,* 117(1), 58-66. doi: 10.30978/MG-2021-1-58

[28] Praktiknjo, M., Clees, C., Pigliacelli, A., Fischer, S., Jansen, C., Lehmann, J., … & Trebicka, J. (2019). Sarcopenia Is Associated With Development of Acute-on-Chronic Liver Failure in Decompensated Liver Cirrhosis Receiving Transjugular Intrahepatic Portosystemic Shunt. *Clinical and Translational gastroenterology,* 10(4), e00025. doi: 10.14309/ctg.0000000000000025

[29] Rodriguez, A., Becerril, S., Ezquerro, S., Mendez-Gimenez, L., & Fruhbeck, G. (2017). Crosstalk between adipokines and myokines in fat browning. *Acta Physiologica* (Oxford, England), 219(2), 362-381. doi: 10.1111/apha.12686

[30] Sato, S., Namisaki, T., Murata, K., Fujimoto, Y., Takeda, S., Enomoto, M., … & Yoshiji, H. (2021). The association between sarcopenia and endotoxin in patients with alcoholic cirrhosis. *Medicine,* 100(36), e27212. doi: 10.1097/MD.0000000000027212

[31] Shen, W., Punyanitya, M., Wang, Z., Gallagher, D., St.-Onge, M.-P., Albu, J., Heymsfield, S. B., Heshka, S. (2004) Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. *J. Appl. Physiol.,* 97, 2333-2338. doi: 10.1152/japplphysiol.00744.2004

[32] Senesi, P., Luzi, L., & Terruzzi, I. (2020). Adipokines, Myokines, and Cardiokines: The Role of Nutritional Interventions. *International Journal of Molecular Sciences,* 21(21), 8372. doi: 10.3390/ijms21218372

[33] Severinsen, M. C. K., & Pedersen, B. K. (2020). Muscle-Organ Crosstalk: The Emerging Roles of Myokines. *Endocrine Reviews,* 41(4), 594-609. doi: 10.1210/endrev/bnaa016

[34] Tandon, P., Montano-Loza, A. J., Lai, J. C., Dasarathy, S., & Merli, M. (2021). Sarcopenia and frailty in decompensated cirrhosis. *Journal of Hepatology*, 75(Suppl 1), S147-S162. doi: 10.1016/j.jhep.2021.01.025

[35] Traub, J., Reiss, L., Aliwa, B., & Stadlbauer, V. (2021). Malnutrition in Patients with Liver Cirrhosis. *Nutrients,* 13(2), 540. doi: 10.3390/nu13020540

[36] Tsien, C., Garber, A., Narayanan, A., Shah, S. N., Barnes, D., Eghtesad, B., … & Dasarathy, S. (2014). Post-liver transplantation sarcopenia in cirrhosis: a prospective evaluation. *Journal of Gastroenterology and Hepatology,* 29(6), 1250-1257. doi: 10.1111/jgh.12524

[37] van Vugt, J. L. A., Buettner, S., Alferink, L. J. M., Bossche, N., de Bruin, R. W. F., Darwish Murad, S., … & Izermans, J. N. M. (2018). Low skeletal muscle mass is associated with increased hospital costs in patients with cirrhosis listed for liver transplantation-a retrospective study. *Transplant International: Official Journal of the European Society for Organ Transplantation,* 31(2), 165-174. doi: 10.1111/tri.13048

[38] Verzola, D., Barisione, C., Picciotto, D., Garibotto, G., & Koppe, L. (2019). Emerging role of myostatin and its inhibition in the setting of chronic kidney disease. *Kidney International,* 95(3), 506-517. doi: 10.1016/j.kint.2018.10.010

[39] Widajanti, N., Soelistijo, S., Hadi, U., Thaha, M., Aditiawardana, Widodo, Firdausi, H., … & Syakdiyah, N. (2022). Association between Sarcopenia and Insulin-Like Growth Factor-1, Myostatin, and Insulin Resistance in Elderly Patients Undergoing Hemodialysis. *Journal of Aging Research,* 2022, 1327332. doi: 10.1155/2022/1327332

[40] Yoshio, S., Shimagaki, T., Hashida, R., Kawaguchi, T., Tsutsui, Y., Sakamoto, Y., … & Kanto, T. (2021). Myostatin as a fibroblast-activating factor impacts on postoperative outcome in patients with hepatocellular carcinoma. *Hepatology research: the Official Journal of the Japan Society of Hepatology,* 51(7), 803-812. doi: 10.1111/hepr.13667

[41] Zhao, M., Zhou, X., Yuan, C., Li, R., Ma, Y., & Tang, X. (2020). Association between serum irisin concentrations and sarcopenia in patients with liver cirrhosis: a cross-sectional study. *Scientific Reports,* 10(1), 16093. doi: 10.1038/s41598-020-73176-z

[42] Zunner, B. E. M., Wachsmuth, N. B., Eckstein, M. L., Scherl, L., Schierbauer, J. R., Haupt, S., … & Moser, O. (2022). Myokines and Resistance Training: A Narrative Review. *International Journal of Molecular Sciences,* 23(7), 3501. doi: 10.3390/ijms23073501

МІОСТАТИН ТА ІРИСИН СИРОВАТКИ КРОВІ ЯК ПРОГНОСТИЧНІ БІОМАРКЕРИ САРКОПЕНІЇ, МАЛЬНУТРИЦІЇ ТА СМЕРТНОСТІ У ХВОРИХ НА ДЕКОМПЕНСОВАНИЙ ЦИРОЗ ПЕЧІНКИ

Моцюк В.М., Пентюк Н.О.

Мальнутриція та саркопенія сьогодні розглядаються як основні ускладнення цирозу печінки (ЦП). Міокіни є сигнальними пептидами, котрі синтезуються у м'язах, здійснюють регуляцію м'язової сили та маси, а також забезпечують зв'язок між скелетними м'язами та іншими органами. Невідомо, чи можуть циркулюючі міокіни слугувати біомаркерами мальнутриції та саркопенії й мати самостійну прогностичну цінність у хворих на ЦП. Метою нашого дослідження стало оцінити зв'язок сироваткових рівнів міокінів міостатину та ірисину з нутритивним станом, станом скелетних м'язів та виживанням хворих на декомпенсований цироз печінки. До проспективного дослідження увійшли 74 хворих (середній показник віку хворих становив 55,30±11,40 роки). Нутритивний стан оцінювали за шкалою сукупного суб'єктивного оцінювання стану пацієнта (Patient-Generated Subjective Global Assessment), масу скелетних м'язів оцінювали за індексом скелетних м'язів (Skeletal Muscle Index). Вміст міостатину та ірисину в сироватці крові визначали методом імуноферментного аналізу. Статистичну обробку даних проводили у SPSS22 (© SPSS Inc.). Встановлено, що вміст міостатину та ірисину у хворих на декомпенсований ЦП не пов'язаний із важкістю ЦП за шкалами Child-Turcotte-Pugh, Model For End-Stage Liver Disease та ступенем асциту. Пацієнти з маніфестною енцефалопатією мають вищий рівень міостатину, а пацієнти з тяжкою гіпоальбумінемією - вищі рівні міостатину та нижчі рівні ірисину в сироватці крові. Розвиток мальнутриції та саркопенії у хворих на декомпенсований ЦП асоціюється з підвищенням концентрації міостатину та зниженням концентрації ірисину в сироватці крові. Сироватковий рівень міостатину може прогнозувати саркопенію (AUC 0,834 у чоловіків та 0,827 у жінок, p<0,01), сироватковий рівень ірисину може прогнозувати тяжку мальнутрицію (AUC 0,830, p<0,001). Загальна смертність пацієнтів з високими рівнями міостатину (вище 5,25 нг/мл у чоловіків та 3,55 нг/мл у жінок) та низькими рівнями ірисину (менше 1,72 нг/мл) є достовірно вищою. Таким чином, оцінка циркулюючих рівнів міокінів може бути корисною для оцінки нутритивного стану, стану скелетних м'язів та прогнозу у хворих на ЦП.

Ключові слова: *міостатин, ірисин, мальнутриція, саркопенія, виживаність, цироз печінки.*