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Cytokines in Liver Cirrhosis (Their Importance in Assessing Activity and Decompensation)

Giesiddin K. Mirodzhov, Saodat D. Pulatova*

Institute of Gastroenterology, Dushanbe, Republic of Tajikistan

Aim: studying the role of pro-inflammatory and anti-inflammatory cytokines in the pathogenesis of liver cirrhosis progression.
Materials and methods. The material of the study was the data of clinical-instrumental, biochemical, virological studies of 109 patients with liver cirrhosis of various etiologty, who were hospitalized in the clinic of the Institute of Gastroenterology (Dushanbe, Republic of Tajikistan). The diagnosis of the underlying disease was established according to the clinical recommendations of the Russian Society for the Study of the Liver and the Russian Gastroenterological Association for the diagnosis and treatment of liver fibrosis and cirrhosis and their complications (2021); decompensated liver cirrhosis was established according to the 1996 Child — Pugh classification. The age of the patients ranged from 17 to 79 years (36.9 ± 0.8 years), there were 55 men and 54 women.
Results. Among the examined patients, compensated liver cirrhosis (Class A) according to Child — Pugh was detected in 18 persons, subcompensated (Class B) — in 14, decompensated (Class C) — in 77. The study of the content of pro-inflammatory and anti-inflammatory cytokines in the blood serum of patients with Class A liver cirrhosis showed, that levels of tumour necrosis factor alpha (TNF-α), interleukin-2, interleukin-6 were statistically higher compared to healthy individuals, while the concentration of anti-inflammatory interleukin-10 was lower (30.7 ± 4.7 pg/mL) in comparison with the control group. In patients with Class B liver cirrhosis, the level of TNF-α increased to 75.0 ± 4.5 pg/mL ($p < 0.001$), interleukin-2 — to 328.7 ± 23.9 pg/mL ($p < 0.05$), and interleukin-6 — to 95.4 ± 7.7 pg/mL ($p < 0.001$). Serum interleukin-10 decreased compared with the control group (23.1 ± 2.8 pg/mL; $p > 0.05$). At the decompensated stage of Class C cirrhosis, a huge release of pro-inflammatory cytokines occurs — the content of TNF-α increases by 80 times, of interleukin-2 — by more than 60 times, as for interleukin-10, its content is progressively reduced.
Conclusion. In liver cirrhosis, there is a significant disruption in the synthesis of pro-inflammatory cytokines, which is manifested by a sharp increase in the content of TNF-α, interleukin-2 and interleukin-6. High levels of proinflammatory cytokines in blood serum in liver cirrhosis correlate with the activity and degree of decompensation, which indicates their important role in the pathogenesis and progression of the pathological process.
Keywords: liver cirrhosis, pro-inflammatory and anti-inflammatory cytokines
Conflict of interest: the authors declare that there is no conflict of interest.

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Цитокины при циррозе печени (их значение в оценке активности и декомпенсации)

Г.К. Мироджов, С.Д. Пулатова*

ГУ «Институт гастроэнтерологии» Министерства здравоохранения и социальной защиты населения Республики Таджикистан, Душанбе, Республика Таджикистан

Цель исследования: изучить роль провоспалительных и противовоспалительных цитокинов в патогенезе и прогрессировании цирроза печени.
Материалы и методы. Материалом исследования служили данные клинико-инструментальных, биохимических, вирусологических исследований 109 пациентов с циррозом печени различной этиологии, находившихся на стационарном лечении в клинике ГУ «Институт гастроэнтерологии» в отделении гепатологии. Диагноз основного заболевания устанавливали согласно клиническим рекомендациям Российского общества по изучению печени и Российской гастроэнтерологической ассоциации по диагностике и лечению фиброза

и цирроза печени и их осложнений (2021), декомпенсированный цирроз устанавливали по шкале Чайлда — Пью (1996). Возраст больных колебался от 17 до 79 лет (36,9 ± 0,8 года), мужчин было 55, женщин — 54.
Результаты. Среди обследованных пациентов компенсированный цирроз печени (класс А) по Чайлду — Пью выявлен у 18 чел., субкомпенсированный (класс В) — у 14, декомпенсированный (класс С) — у 77 чел. Изучение содержания провоспалительных и противовоспалительных цитокинов в сыворотке крови пациентов с циррозом печени класса А по шкале Чайлда — Пью показало, что уровни фактора некроза опухоли альфа (ФНО-α), интерлейкина-2 и интерлейкина-6 были достоверно выше по сравнению со здоровыми лицами. У больных с циррозом печени класса В уровень ФНО-α был равен 75,0 ± 4,5 пг/мл ($p < 0,001$), интерлейкина-2 — 328,7 ± 23,9 пг/мл ($p < 0,05$), интерлейкина-6 — 95,4 ± 7,7 пг/мл ($p < 0,001$). При декомпенсированной стадии цирроза класса С происходит огромный выброс провоспалительных цитокинов — содержание ФНО-α увеличивалось в 80 раз, а интерлейкина-2 — более чем в 60 раз.
Выводы. При циррозе печени имеет место значительное нарушение синтеза провоспалительных цитокинов, что проявляется резким повышением содержания ФНО-α, интерлейкина-2 и интерлейкина-6. Высокий уровень провоспалительных цитокинов в сыворотке крови при циррозе печени коррелирует с активностью и степенью декомпенсации, что свидетельствует об их важной роли в патогенезе и прогрессировании патологического процесса.
Ключевые слова: цирроз печени, провоспалительные и противовоспалительные цитокины
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Liver cirrhosis remains one of the most important medical, social and economic problem of the century and occupies a leading place in the structure of diseases of the digestive system. The urgency of the problem of liver cirrhosis is associated with its high prevalence in people of young working age, the lack of effective treatment methods and serious complications, such as bleeding from esophageal varices, ascites-peritonitis, hepatic coma, which become the main cause of death [1–3].

Some scientific studies have shown that cytokines play an important part in the development of the necro-inflammatory process in hepatocytes with the development of liver fibrosis [4–7].

Currently, quite a large amount of scientific material has been accumulated on the participation of tumor necrosis factor alpha (TNF-α) in the development of immunopathological processes that contribute to the progression of liver cirrhosis [8–11]. At the same time, the importance of pro-inflammatory and anti-inflammatory cytokines in the development of decompensation of cirrhosis and its severe complications has not yet been identified.

Materials and methods

The material for the prospective study was data from clinical, instrumental, biochemical, and virological studies of 109 patients with liver cirrhosis of various origin who were hospitalized at the clinic of the Institute of Gastroenterology (Dushanbe, Republic of Tajikistan). The diagnosis of the underlying disease was made in accordance with the clinical recommendations of the Russian Society for the Study of the Liver and the Russian Gastroenterological Association for the diagnosis and treatment of liver fibrosis and cirrhosis and their complications (2021). The age of the patients ranged from 17 to 79 years (36.9 ± 0.8 years); there were 55 men and 54 women.

The control group included 16 healthy individuals (employees of the Institute of Gastroenterology), who also underwent clinical, biochemical and instrumental research methods. Serum levels of pro-inflammatory and anti-inflammatory cytokines (tumor necrosis factor alpha, interleukin-2, interleukin-6, interleukin-10) were determined by enzyme-linked immunosorbent assay in a "sandwich" version. At the same time, to obtain research results, the following reagents were used by OOO Vector-Best (Russia): Interleukin-2 ELISA-Best; Interleukin-6 ELISA-Best; Interleukin-10 ELISA-Best; TNF-α ELISA-Best. Cytokine levels in the control group were at the lower limit of sensitivity of the method and ranged from 1 to 11 pg/mL (average — 0.6–0.7 pg/mL).

Results

Among the examined patients, compensated liver cirrhosis (Class A) according to Child — Pugh was detected in 18 persons, subcompensated (Class B) — in 14, decompensated (Class C) — in 77. The distribution of the examined patients according to the etiology of liver cirrhosis is given in Table 2.

We studied the levels of serum pro-inflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin-2 and interleukin-6) and the anti-inflammatory cytokine interleukin-10 in patients with liver

Table 1. Distribution of examined patients with liver cirrhosis by age and gender (n = 109)

Таблица 1. Распределение обследованных пациентов с циррозом печени по возрасту и полу (n = 109)

Liver cirrhosis class according to Child — Pugh Класс цирроза печени по Чайлду — Пью	Age, years / Возраст, лет													
	<20		20–29		30–39		40–49		50–59		60–69		70–79	
	m / м	f / ж	m / м	f / ж	m / м	f / ж	m / м	f / ж	m / м	f / ж	m / м	f / ж	m / м	f / ж
A (n = 18)	1	–	3	2	2	4	1	3	–	2	–	–	–	–
B (n = 14)	1	–	1	1	5	1	2	3	–	–	–	–	–	–
C (n = 77)	1	–	2	1	14	10	17	15	5	4	4	2	2	–

Note: m — males; f — females.

Примечание: м — мужчины; ж — женщины.

Table 2. General characteristics of the examined patients with liver cirrhosis by etiological factor (n = 109)

Таблица 2. Общая характеристика обследованных пациентов с циррозом печени по этиологии (n = 109)

Liver cirrhosis class according to Child — Pugh Класс цирроза печени по Чайлду — Пью	Etiological factor / Этиологический фактор				
	HBV ВГВ	HCV ВГС	HBV + HDV ВГВ + ВГС	HCV + Ethanol ВГВ + Этанол	%
A (n = 18)	5	5	7	1	16.5
B (n = 14)	2	3	7	2	12.8
C (n = 77)	16	18	41	2	70.6
Total / Всего	23	26	55	5	100

Note: HBV — hepatitis B virus; HCV — hepatitis C virus.

Примечание: ВГВ — вирус гепатита В; ВГС — вирус гепатита С.

cirrhosis of various etiologies, class A (compensated stage) according to the Child — Pugh classification. Eighteen patients (11 women, 7 men) aged from 21 to 74 years (mean age — 47.3 ± 2.4 years) with liver cirrhosis were examined.

A biochemical study of the blood serum of patients with class A liver cirrhosis revealed an increase in the levels of enzymes of the transamination process with a simultaneous significant decrease in the total protein content due to the albumin fraction and prothrombin index (Table 3).

A study of the content of pro-inflammatory and anti-inflammatory cytokines in the blood serum of patients with Child — Pugh class A liver cirrhosis in 18 patients showed that already in the stage of compensation of the disease, the level of pro-inflammatory cytokines, compared with the indicators in the control group, significantly increases. Thus, the level of TNF-α, interleukin-2 (IL-2) and interleukin-6 (IL-6) in patients with class A liver cirrhosis was significantly higher compared to healthy individuals. At the same time, the concentration of anti-inflammatory IL-10 in the blood serum of these patients was lower (30.7 ± 4.7 pg/mL) compared to control individuals (Table 4).

Serum proinflammatory cytokines (TNF-α, IL-6, IL-2) and anti-inflammatory IL-10 were studied in 14 patients (9 men, 5 women) aged 24 to 70 years (mean age — 46.6 ± 2.5 years) with liver cirrhosis class B (subcompensated) according to Child — Pugh. The study showed a statistically significant decrease ($p < 0.01$) in albumin levels (33.6 ± 1.5 g/L) and prothrombin index (59.7 ± 2.0 %) compared with the control group (42.8 ± 0.7 g/L and 90.1 ± 1.2 %). There was an increase in the activity of ALT (41.8 ± 3.8 U/L) and AST (34.4 ± 3.6 U/L) compared with the values of healthy individuals (28.4 ± 1.3 U/L and 23.3 ± 1.4 U/L, respectively) (Table 3).

A study of serum concentrations of pro-inflammatory and anti-inflammatory cytokines in patients with Child — Pugh class B liver cirrhosis showed a significant increase in all studied parameters. Thus, the level of TNF-α increased to 75.0 ± 4.5 pg/mL ($p < 0.001$), IL-2 — to 328.7 ± 23.9 pg/mL ($p < 0.05$), and IL-6 — up to 95.4 ± 7.7 pg/mL ($p < 0.001$). The serum level of anti-inflammatory IL-10 decreased compared to the control group and amounted to 23.1 ± 2.8 pg/mL ($p > 0.05$).

Biochemical parameters and pro-inflammatory cytokines were also studied in the blood serum

Table 3. Biochemical parameters of blood serum of examined patients with liver cirrhosis ($M \pm m$)
Таблица 3. Биохимические показатели сыворотки крови обследованных пациентов с циррозом печени ($M \pm m$)

Parameters Показатели	Healthy persons Здоровые лица ($n = 16$)	Liver cirrhosis class according to Child — Pugh Класс цирроза печени по Чайлду — Пью		
		A ($n = 18$)	B ($n = 14$)	C ($n = 77$)
AST, U/L АСТ, Ед./л	23.3 ± 1.4	45.9 ± 4.7 $p_1 < 0.01$	34.4 ± 3.6 $p_1 > 0.05$ $p_2 > 0.05$	51.6 ± 6.0 $p_1 < 0.001$ $p_2 > 0.05$ $p_3 > 0.05$
ALT, U/L АЛТ, Ед./л	28.4 ± 1.3	53.9 ± 5.8 $p_1 < 0.01$	41.8 ± 3.8 $p_1 > 0.05$ $p_2 > 0.05$	67.4 ± 9.5 $p_1 < 0.001$ $p_2 > 0.05$ $p_3 > 0.05$
Bilirubin, umol/L Билирубин, мкмоль/л	13.5 ± 0.7	23.4 ± 2.6 $p_1 > 0.05$	38.5 ± 1.8 $p_1 > 0.05$ $p_2 < 0.01$	56.3 ± 5.6 $p_1 < 0.001$ $p_2 > 0.05$ $p_3 > 0.05$
Albumin, g/L Альбумин, г/л	42.8 ± 0.7	38.5 ± 1.3 $p_1 > 0.05$	33.6 ± 1.5 $p_1 < 0.01$ $p_2 > 0.05$	27.1 ± 0.7 $p_1 < 0.001$ $p_2 < 0.05$ $p_3 > 0.05$
Prothrombin index, % Протромбиновый индекс, %	90.1 ± 1.2	77.3 ± 2.8 $p_1 < 0.05$	59.7 ± 2.0 $p_1 < 0.01$ $p_2 < 0.05$	40.3 ± 1.3 $p_1 < 0.001$ $p_2 < 0.05$ $p_3 < 0.05$

Note: AST — aspartate aminotransferase; ALT — alanine aminotransferase; p_1 — statistical significance of differences compared with data from healthy people (according to the Kruskal — Wallis H test); p_2 — statistical significance of differences compared with data from the group of patients with Child — Pugh class A liver cirrhosis; p_3 — statistical significance of differences compared with data from a group of patients with Child — Pugh class B liver cirrhosis.
Примечание: АСТ — аспартатаминотрансфераза; АЛТ — аланинаминотрансфераза; p_1 — статистическая значимость различий по сравнению с данными здоровых (по H-критерию Краскела — Уоллиса); p_2 — статистическая значимость различий по сравнению с данными группы пациентов с циррозом печени класса А по Чайлду — Пью; p_3 — статистическая значимость различий по сравнению с данными группы пациентов с циррозом печени класса В по Чайлду — Пью.

of 77 patients (32 women, 45 men) aged from 21 to 74 years (mean age — 47.3 ± 2.4 years) with liver cirrhosis of various etiologies in the decompensation stage (Child — Pugh class C).

The study revealed a significant increase in the level of bilirubin (56.3 ± 5.6 umol/L; $p < 0.001$), enzymes of the transamination process — AST (51.6 ± 6.0 U/l; $p < 0.001$) and ALT (67.4 ± 9.5 U/L; $p < 0.001$) compared with the control group. At the same time, there was a significant decrease in the level of albumin (27.3 ± 0.7 g/L; $p < 0.001$) and prothrombin index (40.3 ± 1.3 %; $p < 0.001$) compared to healthy individuals (Table 3).

Analysis of the level of pro-inflammatory cytokines in patients with class C liver cirrhosis showed a statistically significant increase in the content of TNF-α (85.8 ± 6.5 pg/mL; $p < 0.001$), IL-2 (440.0 ± 12.1 pg/mL; $p < 0.001$), IL-6 (162.7 ± 11.8 pg/mL; $p < 0.001$) compared with the control group. At the same time, the serum level of the anti-inflammatory cytokine IL-10 continued to decrease and amounted to 20.1 ± 1.6 pg/mL ($p > 0.05$) (Table 4).

Discussion

In liver cirrhosis, already in the compensation stage, there is a tendency to increase the activity of transamination enzymes, against the background of a decrease in the content of total protein, its albumin fraction and prothrombin index. At the same time, there is an increase in the level of pro-inflammatory cytokines, which can contribute to the further progression of liver cirrhosis.

With liver cirrhosis in the subcompensation stage (Child — Pugh class B), along with a slight increase in bilirubin levels and a decrease in the prothrombin index, which indicate the initial manifestations of decompensation, there is a moderate increase in the activity of enzymes in the transamination process, which indicate the activity of the process. The results of the study showed that the level of pro-inflammatory cytokines (TNF-α, IL-2, IL-6) in patients with class B liver cirrhosis was significantly increased, and the concentration of anti-inflammatory IL-10 decreased.

Table 4. Content of serum cytokines in examined patients with liver cirrhosis ($M \pm m$)

Таблица 4. Содержание сывороточных цитокинов у обследованных пациентов с циррозом печени ($M \pm m$)

Cytokines Цитокины	Healthy persons Здоровые лица ($n = 16$)	Liver cirrhosis class according to Child — Pugh Класс цирроза печени по Чайлду — Пью		
		A ($n = 18$)	B ($n = 14$)	C ($n = 77$)
TNF-α, pg/mL ФНО-α, пг/мл	1.2 ± 0.1	53.8 ± 4.0 $p_1 < 0.01$	75.0 ± 4.5 $p_1 < 0.001$ $p_2 > 0.05$	85.8 ± 6.5 $p_1 < 0.001$ $p_2 > 0.05$ $p_3 > 0.05$
IL-2, pg/mL ИЛ-2, пг/мл	5.7 ± 0.4	313.5 ± 12.8 $p_1 < 0.05$	328.7 ± 23.9 $p_1 < 0.05$ $p_2 > 0.05$	440.0 ± 12.1 $p_1 < 0.001$ $p_2 < 0.001$ $p_3 < 0.05$
IL-6, pg/mL ИЛ-6, пг/мл	3.5 ± 0.4	30.5 ± 1.8 $p_1 > 0.05$	95.4 ± 7.7 $p_1 < 0.001$ $p_2 < 0.05$	162.7 ± 11.8 $p_1 < 0.001$ $p_2 < 0.001$ $p_3 > 0.05$
IL-10, pg/mL ИЛ-10, пг/мл	32.3 ± 4.7	30.7 ± 4.7 $p_1 < 0.05$	23.1 ± 2.8 $p_1 > 0.05$ $p_2 < 0.001$	20.1 ± 1.6 $p_1 > 0.05$ $p_2 < 0.001$ $p_3 > 0.05$

Note: TNF-α — tumour necrosis factor alpha; IL — interleukin; p_1 — statistical significance of differences compared with data from healthy people (according to the Kruskal — Wallis H test); p_2 — statistical significance of differences compared with data from the group of patients with Child — Pugh class A liver cirrhosis; p_3 — statistical significance of differences compared with data from a group of patients with Child — Pugh class B liver cirrhosis.
Примечание: ФНО-α — фактор некроза опухоли альфа; ИЛ — интерлейкин; p_1 — статистическая значимость различий по сравнению с данными здоровых (по H-критерию Краскела — Уоллиса); p_2 — статистическая значимость различий по сравнению с данными группы пациентов с циррозом печени класса А по Чайлду — Пью; p_3 — статистическая значимость различий по сравнению с данными группы пациентов с циррозом печени класса В по Чайлду — Пью.

During the decompensated stage of class C cirrhosis, a huge release of pro-inflammatory cytokines occurs — the content of TNF-α increases 80 times, IL-2 — more than 100 times and IL-6 — more than 60 times; as for IL-10, its content progressively decreases. Consequently, the level of pro-inflammatory cytokines can be used to judge not only the degree of activity of the process, but also decompensation.

Conclusions

1. In liver cirrhosis, there is a significant disruption in the synthesis of pro-inflammatory and anti-inflammatory cytokines, which is manifested by a sharp increase in the content of TNF-α, IL-2, and IL-6 with a simultaneous decrease in the level of IL-10 in the blood serum.

2. A high level of pro-inflammatory cytokines in the blood serum in liver cirrhosis correlates with the activity and degree of decompensation, which indicates their important role in the pathogenesis and progression of the process.

3. The study of pro-inflammatory and anti-inflammatory cytokines in blood serum in liver cirrhosis is important for the diagnosis and prognosis of decompensation of the pathological process.

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Information about the authors

Giesiddin K. Mirodzhov — Dr. Sci. (Med.), Professor, Academician of the National Academy of Sciences of Tajikistan, Scientific Consultant, Institute of Gastroenterology.
Contact information: mirodzhovg@mail.ru;
734064, Republic of Tajikistan, Dushanbe,
Mayakovskogo str., 2.
ORCID: https://orcid.org/0009-0001-9426-9005

Saodat D. Pulatova* — Cand. Sci. (Med.), Head of the Department of Hepatology, Institute of Gastroenterology.
Contact information: sao_90@mail.ru;
734064, Republic of Tajikistan, Dushanbe,
Mayakovskogo str., 2.
ORCID: https://orcid.org/0009-0007-7729-9329

Сведения об авторах

Мироджов Гиесиддин Кудбиддинович — доктор медицинских наук, профессор, академик Национальной академии наук Таджикистана, научный консультант ГУ «Институт гастроэнтерологии» Министерства здравоохранения и социальной защиты населения Республики Таджикистан.
Контактная информация: mirodzhovg@mail.ru;
734064, Республика Таджикистан, г. Душанбе,
ул. Маяковского, 2.
ORCID: https://orcid.org/0009-0001-9426-9005

Пулатова Саодат Джалолидиновна* — кандидат медицинских наук, заведующая отделением гепатологии ГУ «Институт гастроэнтерологии» Министерства здравоохранения и социальной защиты населения Республики Таджикистан.
Контактная информация: sao_90@mail.ru;
734064, Республика Таджикистан, г. Душанбе,
ул. Маяковского, 2.
ORCID: https://orcid.org/0009-0007-7729-9329

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* Corresponding author / Автор, ответственный за переписку