



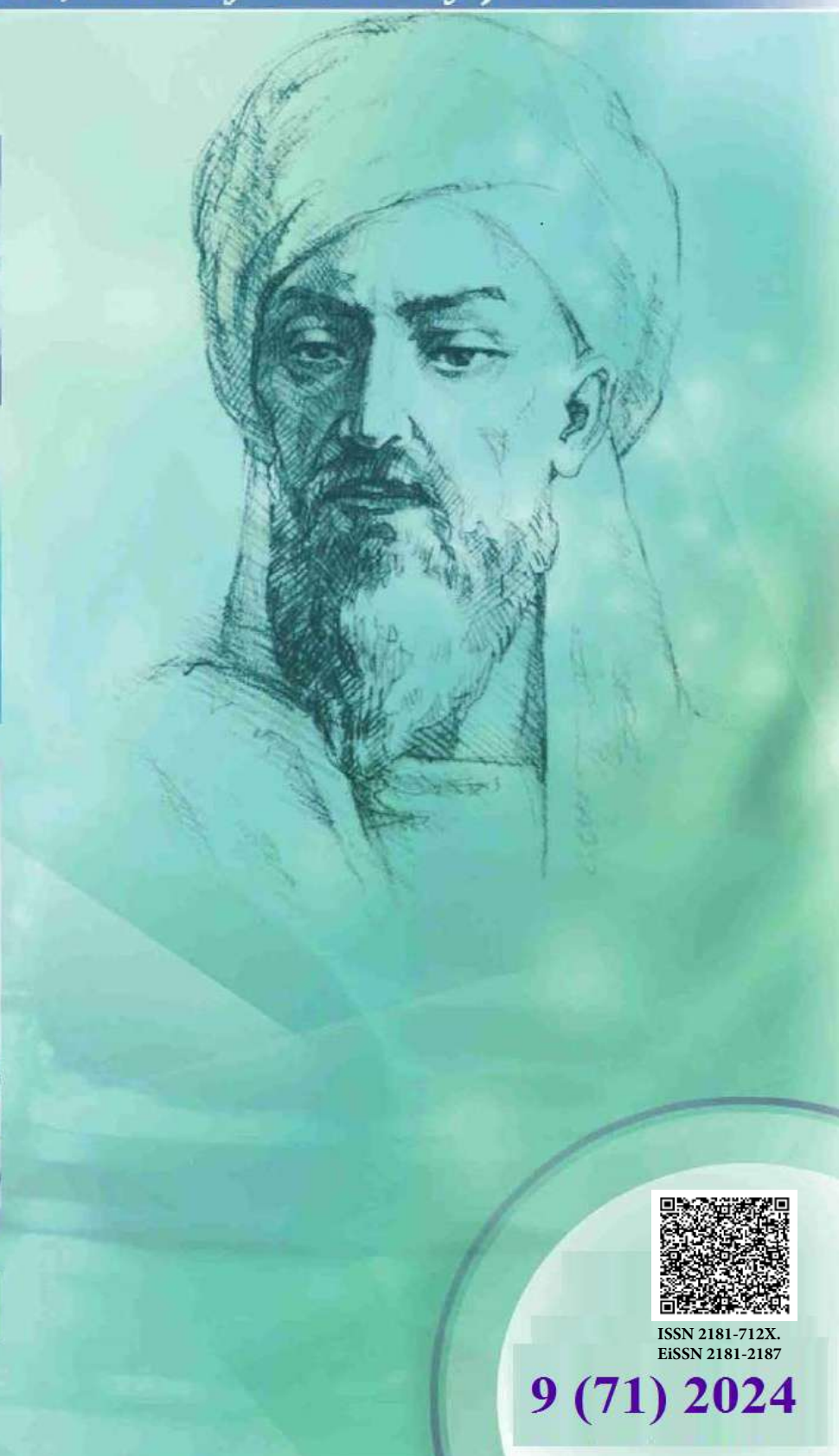
New Day in Medicine
Новый День в Медицине

NDM



TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal



AVICENNA-MED.UZ



ISSN 2181-712X.
EiSSN 2181-2187

9 (71) 2024

Сопредседатели редакционной коллегии:

**Ш. Ж. ТЕШАЕВ,
А. Ш. РЕВИШВИЛИ**

Ред. коллегия:

М.И. АБДУЛЛАЕВ
А.А. АБДУМАЖИДОВ
Р.Б. АБДУЛЛАЕВ
Л.М. АБДУЛЛАЕВА
А.Ш. АБДУМАЖИДОВ
М.А. АБДУЛЛАЕВА
Х.А. АБДУМАДЖИДОВ
Б.З. АБДУСАМАТОВ
М.М. АКБАРОВ
Х.А. АКИЛОВ
М.М. АЛИЕВ
С.Ж. АМИНОВ
Ш.Э. АМОНОВ
Ш.М. АХМЕДОВ
Ю.М. АХМЕДОВ
С.М. АХМЕДОВА
Т.А. АСКАРОВ
М.А. АРТИКОВА
Ж.Б. БЕКНАЗАРОВ (главный редактор)
Е.А. БЕРДИЕВ
Б.Т. БУЗРУКОВ
Р.К. ДАДАБАЕВА
М.Н. ДАМИНОВА
К.А. ДЕХКОНОВ
Э.С. ДЖУМАБАЕВ
А.А. ДЖАЛИЛОВ
Н.Н. ЗОЛотова
А.Ш. ИНОЯТОВ
С. ИНДАМИНОВ
А.И. ИСКАНДАРОВ
А.С. ИЛЪЯСОВ
Э.Э. КОБИЛОВ
А.М. МАННАНОВ
Д.М. МУСАЕВА
Т.С. МУСАЕВ
М.Р. МИРЗОЕВА
Ф.Г. НАЗИРОВ
Н.А. НУРАЛИЕВА
Ф.С. ОРИПОВ
Б.Т. РАХИМОВ
Х.А. РАСУЛОВ
Ш.И. РУЗИЕВ
С.А. РУЗИБОВ
С.А. ГАФФОРОВ
С.Т. ШАТМАНОВ (Кыргызстан)
Ж.Б. САТТАРОВ
Б.Б. САФОВ (отв. редактор)
И.А. САТИВАЛДИЕВА
Ш.Т. САЛИМОВ
Д.И. ТУКСАНОВА
М.М. ТАДЖИЕВ
А.Ж. ХАМРАЕВ
Д.А. ХАСАНОВА
А.М. ШАМСИЕВ
А.К. ШАДМАНОВ
Н.Ж. ЭРМАТОВ
Б.Б. ЕРГАШЕВ
Н.Ш. ЕРГАШЕВ
И.Р. ЮЛДАШЕВ
Д.Х. ЮЛДАШЕВА
А.С. ЮСУПОВ
Ш.Ш. ЯРИКУЛОВ
М.Ш. ХАКИМОВ
Д.О. ИВАНОВ (Россия)
К.А. ЕГЕЗАРЯН (Россия)
DONG JINCHENG (Китай)
КУЗАКОВ В.Е. (Россия)
Я. МЕЙЕРНИК (Словакия)
В.А. МИТИШ (Россия)
В.И. ПРИМАКОВ (Беларусь)
О.В. ПЕШИКОВ (Россия)
А.А. ПОТАПОВ (Россия)
А.А. ТЕПЛОВ (Россия)
Т.Ш. ШАРМАНОВ (Казахстан)
А.А. ЩЕГОЛОВ (Россия)
Prof. Dr. KURBANHAN MUSLUMOV (Azerbaijan)
Prof. Dr. DENIZ UYAK (Germany)

ТИББИЁТДА ЯНГИ КУН НОВЫЙ ДЕНЬ В МЕДИЦИНЕ NEW DAY IN MEDICINE

*Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал*

УЧРЕДИТЕЛИ:

**БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ
МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»**

Национальный медицинский
исследовательский центр хирургии имени
А.В. Вишневского является генеральным
научно-практическим
консультантом редакции

Журнал был включен в список журнальных
изданий, рецензируемых Высшей
Аттестационной Комиссией
Республики Узбекистан
(Протокол № 201/03 от 30.12.2013 г.)

РЕДАКЦИОННЫЙ СОВЕТ:

М.М. АБДУРАХМАНОВ (Бухара)
Г.Ж. ЖАРЫЛКАСЫНОВА (Бухара)
А.Ш. ИНОЯТОВ (Ташкент)
Г.А. ИХТИЁРОВА (Бухара)
Ш.И. КАРИМОВ (Ташкент)
У.К. КАЮМОВ (Тошкент)
Ш.И. НАВРУЗОВА (Бухара)
А.А. НОСИРОВ (Ташкент)
А.Р. ОБЛОКУЛОВ (Бухара)
Б.Т. ОДИЛОВА (Ташкент)
Ш.Т. УРАКОВ (Бухара)

9 (71)

2024

сентябрь

www.bsmi.uz

<https://newdaymedicine.com> E:

ndmuz@mail.ru

Тел: +99890 8061882

UDK 616.36-004-022

IMPORTANCE OF HOMOCYSTEINE IN LIVER DISEASES

Sanokulova Sitora Avazovna Email: sanoqulovasitora94@gmail.com

Bukhara State Medical Institute named after Abu Ali ibn Sino, Uzbekistan, Bukhara c. Gijduvan street
23, e-mail: info@bsmi.uz

✓ Resume

Numerous clinical and epidemiological studies have identified elevated plasma homocysteine levels as a risk factor for atherosclerotic vascular disease and thromboembolism. Hyperhomocysteinemia can develop due to defects in genes that metabolize homocysteine; nutritional conditions leading to a deficiency of vitamins B6, B12 or folic acid; or chronic alcohol use. Homocysteine is an intermediate product of methionine metabolism, which occurs primarily in the liver. Impaired liver function leads to changes in the metabolism of methionine and homocysteine; however, the molecular basis of such changes is not fully understood. In addition, the mechanisms of homocysteine-induced cellular toxicity are not fully defined.

Key words: homocysteine, metabolism, liver, cirrhosis, vitamins B6, B12

ЗНАЧЕНИЕ ГОМОЦИСТЕИНА ПРИ ЗАБОЛЕВАНИЯХ ПЕЧЕНИ

Санокулова Ситора Авазовна Email: sanoqulovasitora94@gmail.com

Бухарский государственный медицинский институт им. Абу Али ибн Сино, Узбекистан, г.
Бухара, улица Гиждуванская, 23, e-mail.ru: info@bsmi.uz

✓ Резюме

Многочисленные клинические и эпидемиологические исследования выявили повышенный уровень гомоцистеина в плазме как фактор риска атеросклеротических заболеваний сосудов и тромбозов. Гипергомоцистеинемия может развиваться из-за дефектов генов, метаболизирующих гомоцистеин; условия питания, приводящие к дефициту витаминов B6, B12 или фолиевой кислоты; или хроническое употребление алкоголя. Гомоцистеин — промежуточный продукт метаболизма метионина, который происходит преимущественно в печени. Нарушение функции печени приводит к изменению метаболизма метионина и гомоцистеина; однако молекулярная основа таких изменений до конца не изучена. Кроме того, механизмы клеточной токсичности, индуцированной гомоцистеином, до конца не определены.

Ключевые слова: гомоцистеин, обмен веществ, печень, цирроз печени, витамины B6, B12.

JIGAR KASALLIKLARIDA GOMOSISTEINNING AHAMIYATI

Sanoqulova Sitora Avazovna Email: sanoqulovasitora94@gmail.com

Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, Ozbekiston, Buxoro sh. Gijduvon kochasi, 23
e-mail: info@bsmi.uz

✓ Rezyume

Ko'pgina klinik-epidemiologik tadqiqotlar qon plazmasidagi gomosisteinning ko'tarilgan darajasini aterosklerotik tomir kasalliklari va tromboemboliya uchun xavf omili sifatida aniqladi. Gipergomosisteinemiya gomosisteinni metabolizatsiya qiluvchi genlardagi nuqsonlar, B6, B12 vitaminlari, foliy kislotasining yetishmasligi yoki surunkali spirtli ichimliklarni iste'mol qilish tufayli rivojlanishi mumkin. Gomosistein metionin metabolizmining oraliq mahsuloti bo'lib, u asosan jigarda uchraydi. Jigar funksiyasining buzilishi esa metionin va gomosistein metabolizmidagi o'zgarishlarga olib keladi. Ammo bunday o'zgarishlarning molekulyar asoslari va gomosistein tomonidan qo'zg'atilgan hujayrali toksiklik mexanizmlari to'liq aniqlanmagan.

Kalit so'zlar: gomosistein, metabolizm, jigar, sirroz, B6, B12 vitaminlari

Relevance

Homocysteine is a sulfur-containing amino acid that is formed as an intermediary in the metabolism of methionine. Extensive evidence suggests that elevated plasma GC concentrations, reflecting impaired cellular metabolism, may be considered an independent risk factor for atherothrombotic vascular disease (reviewed by Refsum et al) [1–4]. This condition has been observed in 20–30% of patients with premature atherosclerosis and in 21% of the general population over a certain age.^{3,4} Three enzymes use GC as a substrate: methionine synthase (MS) and betaine homocysteine methyltransferase (BHMT), which convert homocysteine back to methionine, and cystathionine β -synthase (CBS), the first enzyme in the transsulfuration pathway. The distribution of GCs between them depends on metabolic conditions: when methionine is relatively scarce, GC remethylation is favored by 1,2S-adenosylmethionine (AdoMet), the first metabolite of methionine, modulates GC flux through these metabolic pathways: increased AdoMet levels activate CBS and inhibit MS and BHMT activity. Impaired remethylation or transsulfuration of GC leads to hyperhomocystinemia [5–9]. Such situations may develop due to genetic defects in the enzymes MS, CBS, or methylenetetrahydrofolate reductase (the enzyme that synthesizes the MS cosubstrate 5-methyltetrahydrofolate). Deficiencies of vitamin B6, a CBS cofactor, or folates and vitamin B12, a cosubstrate and cofactor of multiple sclerosis, may also result in along with renal dysfunction, to hyperhomocystinemia [10].

The liver plays a central role in the synthesis and metabolism of homocysteine, given that the majority of dietary methionine is metabolized in this organ, where $\approx 85\%$ of the whole body's transmethylation capacity is located. Accordingly, the liver exhibits a specific expression pattern of genes involved in metabolism methionine and homocysteine [16]. There are 2 genes encoding methionine adenosyltransferase (MAT), the enzyme that converts methionine to AdoMet, one (MAT1A) is expressed exclusively in the liver, and the second gene (MAT2A) is expressed in all tissues. The expression of BHMT and CBS is limited, predominantly in the liver, whereas multiple sclerosis is widely expressed (Figure 1).[5]. Thus, it is possible that HC changes may occur in the event of liver injury. In fact, hyperhomocystinemia has been reported in chronic alcoholics and patients with alcoholic cirrhosis, as well as in experimental models of liver injury. Although there is extensive evidence on the aforementioned genetic and nutritional determinants of hyperhomocystinemia, knowledge of the molecular basis of altered HC metabolism in liver injury is still limited [11].

Purpose of the study: In the present report, we describe our attempt to gain further understanding of the mechanisms of hyperhomocystinemia associated with liver injury, as well as the molecular basis of GC interference with normal cellular function.

Material and methods

DL-GC was from Sigma Chemical Co.. Cell culture media, fetal bovine serum, and antibiotics were from GIBCO-BRL. Anti-tissue inhibitor of metalloproteinase-1 (TIMP-1) monoclonal antibody was from Calbiochem. Anti-proliferating cell nuclear antigen (PCNA) monoclonal antibody was from Santa Cruz Biotechnology. Radioactive isotopes were purchased from Amersham. Restriction enzymes were from Boehringer Mannheim, M-MLV reverse transcriptase was from GIBCO-BRL, and Bio Taq DNA polymerase was from Bioline.

Patients

We observed a group of 120 patients (72 men and 48 women; average age 54 ± 8.5 years) with liver cirrhosis of various etiologies (13 - cirrhosis caused by the hepatitis C virus, 10 - alcoholic cirrhosis, 1 - cirrhosis caused by the hepatitis C virus B, 1 - cryptogenetic cirrhosis, and 1 primary biliary cirrhosis). The control group consisted of 10 patients who underwent cholecystectomy for the treatment of symptomatic gallstone disease and who consented to a liver biopsy at the time of the surgical procedure. Liver samples were immediately frozen and stored at -80°C until processed.

Result and discussions

We measured the expression of liver genes involved in methionine metabolism for the first time. Based on the level of expression compared to the control liver, cirrhotics were divided into 3 groups: group 1 - patients with very low or undetectable expression; Group 2 - patients with an expression level lower than in the control (50% of the expression found in the control); group 3 - patients with expression levels similar to

controls. Human serum albumin (HSA) expression was also measured. The distribution of patients in these groups and by disease etiology (hepatitis C virus or alcoholism). Individual patients with a marked decrease in the expression of a given gene (group 1) tended to do so in the same group for all genes tested. To evaluate whether decreased expression of various genes involved in methionine metabolism is associated with disease severity as measured by the Child-Pugh score, 21 patients were divided into 2 groups. One group (group A) included patients with normal or only decreased mRNA levels for at least 3 of the 5 genes analyzed that are involved in methionine metabolism. The second group (group B) included patients with very low or undetectable mRNA levels of all or 4 of the 5 analyzed genes involved in methionine metabolism. The mean Child-Pugh score was significantly higher in patients with liver cirrhosis in group B (9.0 ± 0.7) than in patients with liver cirrhosis in group A (7.1 ± 0.4 , $P < 0.03$).

The mean serum GC value was significantly higher in patients with liver cirrhosis in group B than in group A (Fig. 1). Accordingly, the mean GC concentration was significantly higher for all patients with cirrhosis (14.1 ± 1.3 $\mu\text{mol/L}$) than for the control group (8.1 ± 0.9 $\mu\text{mol/L}$, $P < 0.03$). Consistent with previous publications fasting serum methionine was higher in patients with cirrhosis (106.3 ± 34.7 $\mu\text{mol/L}$) than in controls (30.8 ± 4.8 $\mu\text{mol/L}$, $P < 0.01$). Differences in methionine concentrations in patients with liver cirrhosis in groups A and B were also statistically significant.

Fig.1.

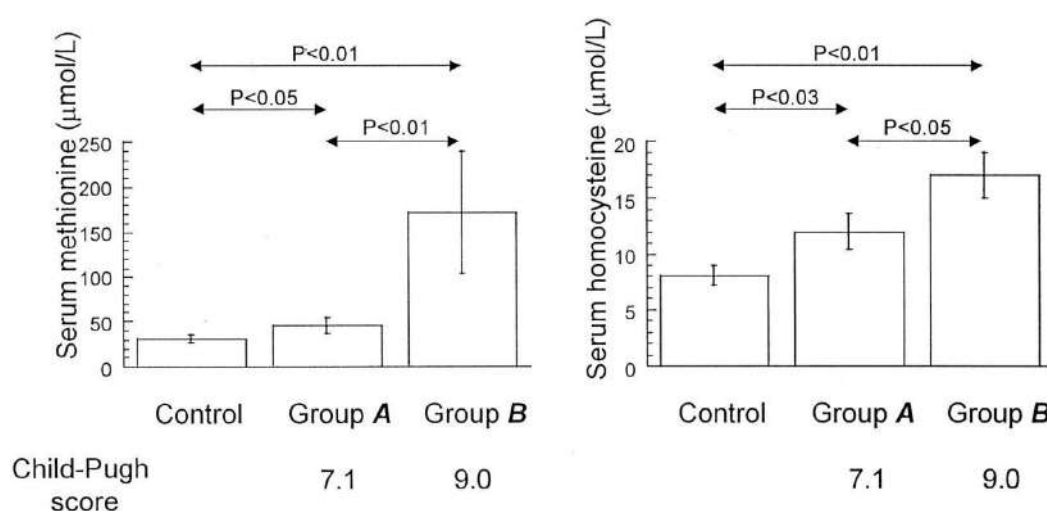


Figure 1. Serum methionine and GC levels in control patients and patients with liver cirrhosis (all 26 patients). Groups A and B are defined in the text.

The second goal of this work was to improve our knowledge of the molecular basis of the cellular effects of GC [11-13]. We observed that GC treatment of quiescent human VSMCs induced the expression of PCNA, a marker of cell proliferation. This effect was also observed when GC was administered to mice and PCNA expression was determined in aortic tissue. We looked for other genes whose expression could be altered by GC in cultured human VSMCs using DDPCR. Cells were quiescent by serum deprivation and then treated with 100 $\mu\text{mol/L}$ GC, a concentration compatible with intermediate hyperhomocystinemia for 24 hours [9]. Using a DDPCR assay, we determined that TIMP-1 is upregulated in response to GC treatment (2-fold induction). This effect was also observed in VSMCs cultured in porcine aorta. Moreover, intraperitoneal administration of GC to mice also resulted in the induction of TIMP-1 expression in the aorta. TIMP-1 plays an important role in the regulation of extracellular matrix (ECM) homeostasis, which is important not only in the vascular wall but also in the liver. We therefore examined the expression of TIMP-1 and $\alpha 1(\text{I})$ procollagen in rat HSCs, observing that both genes are induced by GC in a time- and dose-dependent manner in this cell type. This effect of GC on TIMP-1 expression was also extended to rat hepatocytes and HepG2 cells.

Conclusions

Our results indicate that changes in GC metabolism in human liver cirrhosis can be partly explained by the marked decrease in the expression of key genes involved in its metabolism, namely MS, BHMT and CBS. The expression of these genes was consistently more dysregulated than that of

HSA and was associated with disease severity as measured by the Child-Pugh score. We observe decreased expression of GC metabolizing genes in both alcoholism and hepatitis C virus-induced liver cirrhosis. It has been suggested that impaired GC metabolism in liver cirrhosis may also be associated with decreased availability or use of vitamins B6, B12, or folate, what is possible. However, our current findings of hyperhomocysteinemia in cirrhotic liver have been confirmed in other human and experimental studies in which hyperhomocysteinemia was not associated with altered plasma levels of the aforementioned vitamins.

LIST OF REFERENCES:

1. Finkelstein JD. Methionine metabolism in mammals. //J Nutr Biochem. 1990;1:228-236.
2. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. //Annu Rev Medicine. 1998;49:31-62.
3. Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. //J Am Coll Cardiol. 1996;27:517-527.
4. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly populations. //J Am Med Assoc. 1993;270:2693-2698.
5. Mukhammadieva M.I. (2022). Modern Clinical and Biochemical Characteristics of Liver Cirrhosis Patients of Viral Etiology with Spontaneous Bacterial Peritonitis //Texas Journal of Medical Science. 2022; 86-90 p.
6. Oblokulov Abdurashid Rakhimovich, Mukhammadieva Musharraf Ibrokhimovna Sanokulova, Sitara Avazovna Khadieva, Dora Isakovna. (2023). Clinical and laboratory features of spontaneous bacterial peritonitis in patients with viral liver cirrhosis. //Journal of Advanced Zoology, 2023;44(S2):3744–3750. Retrieved from <http://www.jazindia.com/index.php/jaz/article/view/1716>
7. Oblokulov A.A., Oblokulov A.R., Ergashov M.M. Clinical and laboratory criteria for spontaneous bacterial peritonitis in liver cirrhosis of viral etiology. //Central Asian journal of medical and natural sciences may-jun 2022;3(3):172-177. ISSN: 2660-4159.
8. Ibrokhimovna M.M. (2024). Improvement of Primary Prophylaxis and Treatment of Spontaneous Bacterial Peritonitis Complicated in Virus Etiology Liver Cirrhosis. //Journal of Intellectual Property and Human Rights, 2024;3(4):19-25. Retrieved from <http://journals.academiczone.net/index.php/jiphr/article/view/2506>
9. Elmurodova A.A. (2023). Viral Hepatitis Delta: An Underestimated Threat. //Texas Journal of Medical Science, 2023;26:1-3. Retrieved from <https://zienjournals.com/index.php/tjms/article/view/4610>
10. Oblokulov Abdurashid Rakhimovich Mukhammadieva Musharraf Ibrokhimovna Sanokulova Sitara Avazovna Khadieva Dora Isakovna. (2023). Clinical and laboratory features of spontaneous bacterial peritonitis in patients with viral liver cirrhosis. //Journal of Advanced Zoology, 2023;44(S2):3744–3750. Retrieved from <http://www.jazindia.com/index.php/jaz/article/view/1716>
11. Mukhammadieva M.I. (2022). Modern clinical and biochemical characteristics of liver cirrhosis patients of viral etiology with spontaneous bacterial peritonitis //Texas Journal of Medical Science. 2022; 86-90 p.
12. Sanokulova Sitara Avazovna. (2023). Factors of Development of Hepatorenal Syndrome in Patients with Liver Cirrhosis of Viral Etiology. //Texas Journal of Medical Science, 2023;26:4-9. Retrieved from <https://www.zienjournals.com/index.php/tjms/article/view/4611>
13. Авазовна С.С. (2023). Факторы Развития Гепаторенального Синдрома У Больных Циррозом Печени Вирусной Этиологии. //Amaliy va tibbiyot fanlari ilmiy jurnali, 2023;2(12):1-8. Retrieved from <https://www.sciencebox.uz/index.php/amaltibbiyot/article/view/8673>

Entered 20.08.2024