

**PROGNOSTIC SIGNIFICANCE OF CLINICAL, PATHOGENETIC, AND GENETIC FACTORS IN HEPATORENAL SYNDROME IN THE KHOREZM REGION OF UZBEKISTAN****ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ КЛИНИЧЕСКИХ, ПАТОГЕНЕТИЧЕСКИХ И ГЕНЕТИЧЕСКИХ ФАКТОРОВ ПРИ ГЕПАТОРЕНАЛЬНОМ СИНДРОМЕ В ХОРЕЗМСКОЙ ОБЛАСТИ УЗБЕКИСТАНА****O'ZBEKISTONNING XORAZM VILOYATIDA GEPATORENAL SINDROMDA KLINIK, PATOGENETIK VA GENETIK OMILLARNING PROGNOSTIK AHAMIYATI**

*Samadova A., Arsalan M.A., Ro'zmetov N.A. - Urgench Branch of Tashkent Medical Academy  
Jabbarov A.A.- Tashkent Medical Academy*

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**Abstract.** *Hepatorenal syndrome (HRS) is a serious consequence of advanced liver disease that causes kidney failure. The purpose of this study is to assess the clinical, pathogenetic, and genetic factors that influence the development and prognosis of hepatorenal syndrome in the Khorezm region of Uzbekistan. A retrospective research of 50 patients diagnosed with HRS at regional hospitals investigated the role of genetic predisposition, pathogenetic processes, and clinical markers. The findings indicate a strong link between specific genetic markers, pathogenetic variables, and clinical outcomes, which could enhance the prognosis and care of patients with hepatorenal syndrome in the region.*

**Keywords:** *Hepatorenal, pathogenesis, prognosis, Predisposition, genetics*

**Аннотация.** *Гепаторенальный синдром (ГРС) - серьезное последствие прогрессирующего заболевания печени, вызывающее почечную недостаточность. Цель настоящего исследования - оценить клинические, патогенетические и генетические факторы, влияющие на развитие и прогноз гепаторенального синдрома в Хорезмской области Узбекистана. В ходе ретроспективного исследования 50 пациентов с диагнозом ГРС в областных больницах изучена роль генетической предрасположенности, патогенетических процессов и клинических маркеров. Полученные результаты свидетельствуют о наличии тесной связи между специфическими генетическими маркерами, патогенетическими переменными и клиническими исходами, что может улучшить прогноз и лечение пациентов с гепаторенальным синдромом в регионе.*

**Ключевые слова:** *Гепаторенал, патогенез, прогноз, предрасположенность, генетика*

**Annotatsiya.** *Gepatorenal sindrom (HRS) buyrak etishmovchiligiga olib keladigan progressiv jigar kasalligining jiddiy oqibatidir. Ushbu tadqiqotning maqsadi O'zbekistonning Xorazm viloyatida gepatorenal sindromning rivojlanishi va prognoziga ta'sir etuvchi klinik, patogenetik va genetik omillarni baholashdan iborat. Hududiy shifoxonalarda HRS tashxisi qo'yilgan 50 nafar bemorni retrospektiv tekshirishda irsiy moyillik, patogenetik jarayonlar va klinik belgilarning roli o'rganildi. Topilmalar o'ziga xos genetik belgilar, patogenetik o'zgaruvchilar va klinik natijalar o'rtasida kuchli bog'liqlik mavjudligini ko'rsatadi, bu mintaqadagi gepatorenal sindromli bemorlarning prognozi va davolashini yaxshilashi mumkin.*

**Kalit so'zlar:** *Gepatorenal, patogenez, prognoz, moyillik, genetika*

**Introduction.** The association between liver disease and renal failure had been known for more than a century. In 1877, Frerichs, the inventor of modern liver pathology, documented the prevalence of

oliguria in patients with ascites [5, 6]. Flint observed that in most cases of renal failure in cirrhosis, there were no significant histological changes in the kidneys at post-mortem. In 1956, Hecker and Sherlock observed renal failure in nine patients with liver disease who had progressive oliguria, very low urinary sodium excretion, hyponatremia and no proteinuria. The renal failure was eventually found to be functional, as the kidneys of these patients could be successfully transplanted into other patients with chronic renal failure, and the renal failure was reversible after liver transplantation. Hepatorenal syndrome (HRS) is a life-threatening condition characterized by the rapid decline of kidney function in patients with advanced liver cirrhosis or fulminant hepatic failure [11]. This syndrome is closely associated with liver disease, particularly in patients with chronic hepatitis or alcoholic cirrhosis. The Khorezm region of Uzbekistan, known for its high prevalence of liver diseases, faces an increasing burden of HRS cases [2, 3, 11]. Understanding the clinical, pathogenetic, and genetic factors that contribute to the development and progression of HRS is essential for improving diagnosis and treatment. Studies from other parts of the world have demonstrated the importance of these factors in predicting patient outcomes, but little is known about the situation in Uzbekistan, particularly in the Khorezm region. This study aims to fill that gap by exploring the clinical presentations, pathogenetic mechanisms, and genetic markers associated with HRS in the region [9, 10].

#### **Objectives:**

- Evaluation of the clinical manifestations and their significance in the prediction of the prognosis of HRS patients in Khorezm.
- To investigate the pathogenetic mechanisms underlying the development of HRS and their influence on disease progression.
- To identify specific genetic markers that may predispose individuals to HRS and evaluate their prognostic significance.

#### **Literature Review: HRS is classified into two types:**

- a) Type 1 HRS is distinguished by a rapid loss in renal function, which is frequently caused by a triggering event such as infection or acute liver failure.
- b) Type 2 HRS is a more slowly progressing form of the syndrome [1, 4].

The pathogenetic mechanisms underlying HRS include systemic vasodilation, particularly in the splanchnic circulation, and intense renal vasoconstriction. These hemodynamic changes lead to reduced renal perfusion, triggering kidney failure. Several studies have highlighted the role of cytokines and endotoxins in the progression of HRS, while genetic susceptibility is also being explored as a potential contributor [7, 8].

In Uzbekistan, the study of genetic factors influencing liver and renal diseases is still in its infancy. The prevalence of chronic liver diseases, particularly hepatitis, is high in the Khorezm region, which suggests a potential genetic predisposition to HRS that needs further investigation.

#### **Methods: Study Design:**

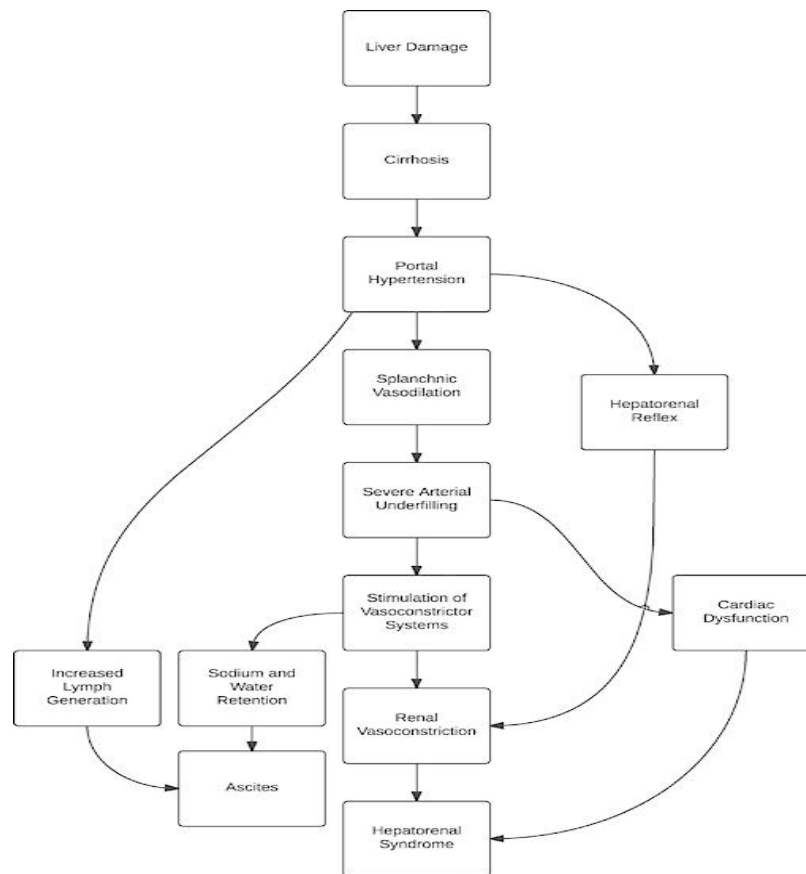
This was a retrospective cohort research undertaken at three main hospitals in Uzbekistan's Khorezm area from 2018 to 2023. The study examined the medical records of patients diagnosed with hepatorenal syndrome.

#### **Inclusion Criteria:**

- Patients diagnosed with liver cirrhosis (Child-Pugh classes B and C).
- Patients presenting with acute renal failure secondary to liver disease.
- Age range: 30–70 years.
- No pre-existing kidney disease or sepsis-related kidney injury.

#### **Data Collection:**

A series of clinical parameters were measured, including blood pressure, renal function (as indicated by creatinine levels), liver function (as indicated by bilirubin and albumin levels), and a number of other important biomarkers (as indicated by sodium levels and platelet count). The pathogenetic data included an analysis of inflammatory markers (C-reactive protein, tumour necrosis factor-alpha), as well as genetic testing for polymorphisms in genes related to liver and kidney function.



**Fig. 1. - Pathogenesis and treatment targets of hepatorenal syndrome**

### Genetic Analysis:

Patients underwent genotyping for specific single-nucleotide polymorphisms (SNPs) associated with HRS. Genetic markers previously associated with liver diseases and renal dysfunction were selected based on global studies. DNA samples were collected from blood samples, and PCR-based methods were used to identify these genetic variations. To determine the frequency of alleles and genotypes of the rs738409 polymorphism of the angiotensinogen-synthesizing PNPLA3 gene, the alleles and genotypes of the rs1800471 polymorphism of the TGFB1 (Transforming Growth Factor B-1) gene, and the alleles and genotypes of the UMOD gene rs4293393T>C polymorphism in groups of Uzbek patients with liver cirrhosis.

### Statistical Analysis:

Data were analyzed using SPSS software (v25). Descriptive statistics (mean, standard deviation) were calculated for continuous variables, and chi-square tests were used for categorical data. Logistic regression models were employed to determine the predictive value of clinical, pathogenetic, and genetic factors on patient outcomes. Kaplan-Meier survival curves were used to estimate survival probabilities.

### Results: Demographic and Clinical Characteristics:

A total of 50 patients were included in the study, of whom 65% were male and the mean age was 53 years. The majority of patients had liver cirrhosis, with aetiology including chronic hepatitis B (45%) or alcoholic liver disease (30%).

a) Clinical Indicators: Elevated serum creatinine (>2 mg/dL) and low sodium levels (<125 mmol/L) were identified as significant predictors of poor outcomes. Ascites and hepatic encephalopathy were frequently observed in the patient cohort.

### Pathogenetic Mechanisms

a) Inflammatory Markers: High levels of C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- $\alpha$ ) were significantly associated with severe HRS progression. Inflammatory processes appeared to exacerbate renal vasoconstriction, accelerating kidney failure.

**Genetic Markers:**

SNP Analysis: Polymorphisms in the TNF- $\alpha$  gene (rs1800629) were related with an increased chance of developing HRS, with a hazard ratio of 2.5 (95% CI: 1.4–4.3,  $p < 0.05$ ). Additionally, variations in the angiotensin-converting enzyme (ACE) gene (rs4343) have been linked to poor renal outcomes in HRS patients.

**Prognostic Significance:**

The combination of high CRP levels ( $>10$  mg/L), the presence of TNF- $\alpha$  polymorphisms, and advanced liver dysfunction (Child-Pugh Class C) provided a strong predictive model for mortality, with an AUC (Area Under the Curve) of 0.87 ( $p < 0.001$ ).

**Discussion:** The results of this study highlight the complex interplay between clinical, pathogenetic, and genetic factors in determining the prognosis of patients with HRS in the Khorezm region of Uzbekistan. Elevated inflammatory markers, particularly TNF- $\alpha$ , appear to play a critical role in the development of HRS by exacerbating renal vasoconstriction (Jung & Chang, 2023).

Moreover, genetic predispositions, particularly SNPs in TNF- $\alpha$  and ACE genes, seem to have significant prognostic value. These findings align with global studies suggesting that genetic variability in inflammatory pathways contributes to differential outcomes in HRS patients (*TNF Tumor Necrosis Factor [Homo Sapiens (Human)] - Gene - NCBI, n.d.*).

**Clinical Implications:** This study implies that early detection of patients with high inflammatory markers and certain genetic risk factors may allow for more focused interventions, such as the use of anti-inflammatory medicines or ACE inhibitors to enhance patient outcomes.

**Table 1.**

**Medications commonly used in the treatment of HRS**

Class	Drug	Action	Comment
Albumin		Intravascular volume expansion	Complimentary component of medical vasoconstrictor therapies
Albumin		Intravascular volume expansion	Complimentary component of medical vasoconstrictor therapies
Vasopressin analogs	Vasopressin, ornipressin	Vasopressin receptor agonist	Some improvement in HRS: serious side effects
	Terlipressin	V1 receptor agonist	Most well-validated vasopressin analog unavailable in United States
Alpha-adrenergic agonists	Noradrenaline	Adrenergic agonist	Benefits comparable to terlipressin: great availability
	Midodrine	Selective alpha adrenergic agonist	Frequently paired with octreotide: less effective than noradrenaline or terlipressin
Somatostatin analog	Octreotide	Inhibits splanchnic blood flow	Improves renal blood flow: decreases GFR
Dopamine agonist	Dopamine		Improves renal blood flow: improvement in renal function

**Abbreviations:** GFR, glomerular filtration rate; HRS, hepatorenal syndrome

**Limitations:**

- a) The study was limited to a specific geographic region, and the findings may not be generalizable to other populations.
- b) The retrospective design may have introduced biases, particularly in the selection of patients for genetic testing.

**Conclusion.** The clinical, pathogenetic, and genetic parameters analysed provide important information on the prognosis of HRS patients in the Khorezm region. The discovery of specific genetic markers and inflammatory pathways that influence disease progression may pave the door for more personalised therapeutic approaches. Future research should examine the therapeutic implications of targeting these pathways to enhance survival rates in patients with HRS.

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