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CLINICAL AND IMMUNOGENETIC FOUNDATIONS FOR EARLY PREDICTION OF DECOMPENSATION PHENOTYPES IN LIVER CIRRHOSIS OF DIFFERENT ETIOLOGIES

Literature Review

Boburjon Abduqoxxorovich Rasulov

Assistant, Department of Pharmacology, Clinical Pharmacology and Medical Biotechnologies, Andijan State Medical Institute, Andijan, Uzbekistan

Jasurbek Baxromovich Ravzatov

PhD, Associate Professor, Department of Family Physician Training, Andijan State Medical Institute, Andijan, Uzbekistan

Abstract

Liver cirrhosis remains one of the leading causes of disability and mortality worldwide, including in Uzbekistan. The clinical severity of cirrhosis is determined not merely by the presence of cirrhotic transformation itself, but also by the development of decompensation phenotypes, including ascites, bleeding from esophageal varices, spontaneous bacterial peritonitis, and hepatic encephalopathy. In recent years, increasing attention has been paid to the role of the Th17/IL-23/IL-17 inflammatory axis and the IL-6 cascade in the pathogenesis of cirrhosis, particularly in relation to fibrosis progression, portal hypertension, disruption of the gut-liver immune axis, and infectious complications. This review systematically analyzes the role of clinical, immunological, and genetic factors in the early prediction of decompensation phenotypes in liver cirrhosis of different etiologies. Particular attention is given to the association of IL-23R, IL-17A, IL-17F, and IL-6 gene polymorphisms with disease course, decompensation phenotypes, and clinical-biochemical parameters. In addition, the scientific and practical prospects of integrating clinical-genetic risk stratification alongside conventional tools such as the Child-Pugh score are discussed.

Keywords: liver cirrhosis, decompensation phenotypes, ascites, variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, IL-23R, IL-17A, IL-17F, IL-6, clinical-genetic prognosis.

INTRODUCTION

Liver cirrhosis represents the final morphological and functional stage of chronic liver disease and is characterized by diffuse fibrosis of the hepatic parenchyma, formation of regenerative nodules, and progressive decline in liver function. In hepatology and internal medicine practice, cirrhosis occupies a special place as a complex disorder associated with high disability rates, frequent hospitalizations, and substantial mortality risk. The clinical significance of cirrhosis is determined not only by its existence as a pathological state, but also by its progression to decompensation and the emergence of severe complications.

In conventional clinical practice, the severity of liver cirrhosis is commonly assessed using the Child-Pugh classification. Although this scoring system remains highly valuable for prognostic evaluation, it does not predict decompensation phenotypes with equal accuracy in all patients. The observation that patients with apparently similar clinical and biochemical characteristics may demonstrate markedly different rates of decompensation and distinct complication profiles suggests an important role for genetic and immunological determinants.

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In recent years, it has become increasingly clear that the pathogenesis of cirrhosis cannot be explained solely by fibrosis and portal hypertension. Current concepts emphasize that chronic systemic inflammation, disruption of the gut-liver immune axis, bacterial translocation, cytokine imbalance, and individual genetic susceptibility are major factors shaping the clinical phenotype of cirrhosis. Within this framework, the Th17/IL-23/IL-17 signaling pathway and the IL-6 cascade have attracted particular interest in relation to decompensated cirrhosis and its complications.

Decompensation Phenotypes in Liver Cirrhosis and Their Clinical Significance

Decompensation phenotypes are among the principal determinants of clinical severity in liver cirrhosis. Ascites, bleeding from esophageal and gastric varices, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome significantly reduce patient survival and worsen quality of life. For this reason, modern hepatology increasingly favors a more refined phenotypic characterization of cirrhosis rather than a simple dichotomy between compensated and decompensated disease.

Ascites is one of the most common manifestations of decompensation and is associated with portal hypertension, arterial vasodilation, activation of the renin-angiotensin-aldosterone system, and disturbances in protein-water homeostasis. Variceal bleeding, in turn, represents a life-threatening complication that is closely related to elevated portal pressure, the size of varices, and abnormalities of the hemostatic system. Spontaneous bacterial peritonitis and hepatic encephalopathy are complex phenotypes linked to systemic inflammation, increased intestinal permeability, ammonia metabolism disturbances, and dysregulated immune responses.

Inflammation and Immune Response in Cirrhosis

Although cirrhosis was long regarded primarily as a fibrotic disorder, it is now increasingly interpreted as an immunometabolic syndrome accompanied by systemic inflammation. Proinflammatory mediators, including IL-6, TNF-α, IL-1β, and members of the IL-17 family, exacerbate functional abnormalities not only within hepatic tissue but throughout the entire organism. In cirrhosis, increased permeability of the intestinal wall and bacterial translocation disrupt the gut-liver immune axis. As a result, endotoxemia and enhanced production of inflammatory mediators develop, contributing to portal hypertension, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy. Thus, decompensation should not be considered merely the consequence of hepatic parenchymal injury, but rather the outcome of complex immunoinflammatory mechanisms.

Pathogenetic Role of the Th17/IL-23/IL-17 Axis

Th17 cells and the related IL-23/IL-17 signaling pathway are known to play a pivotal role in autoimmune, chronic inflammatory, and fibrotic diseases. In the setting of liver cirrhosis, this pathway may promote activation of hepatic stellate cells, intensification of fibrogenesis, amplification of cytokine cascades, and deepening of immune imbalance. IL-17A and IL-17F act as potent proinflammatory cytokines, stimulating neutrophil recruitment, production of inflammatory mediators, and tissue injury. IL-23R is crucial for the differentiation, expansion, and maintenance of Th17 cells.

Accordingly, polymorphisms in IL-23R, IL-17A, and IL-17F genes may be associated with individual variability in inflammatory response, fibrosis progression, and susceptibility to decompensation in cirrhosis. This may be particularly relevant for complications such as ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy, where inherited differences in immune reactivity could partly explain interindividual clinical heterogeneity.

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IL-6 Cascade and Its Clinical-Prognostic Relevance

Among inflammatory mediators, IL-6 occupies a central position in the pathogenesis of liver cirrhosis, being implicated in hepatocyte injury, fibrosis progression, portal hypertension, and systemic inflammatory responses. Elevated IL-6 levels often parallel disease severity, infectious complications, and unfavorable prognosis. In this respect, IL-6 may serve as an informative clinical biomarker.

Polymorphisms in the IL-6 gene may modulate the magnitude of the cytokine response. Consequently, some patients may exhibit a more intense inflammatory reaction, earlier decompensation, and more severe complications. Therefore, combined assessment of IL-6 polymorphisms with clinical and biochemical parameters may contribute substantially to the development of personalized prognostic systems in liver cirrhosis.

Etiology-Specific Mechanisms of Decompensation

The mechanisms underlying decompensation are not identical across all etiological forms of liver cirrhosis. In HBV- and HCV-related cirrhosis, antiviral immune responses, chronic necroinflammation, and persistent activation of immune cells play dominant roles. In cirrhosis arising on the background of nonalcoholic fatty liver disease, metabolic inflammation, insulin resistance, adipokine imbalance, and oxidative stress are particularly important. In alcoholic cirrhosis, by contrast, the toxic effects of ethanol and its metabolites, alterations in the gut microbiota, and endotoxemia-related immune abnormalities appear to predominate.

These differences suggest that the same genetic polymorphism may not exert identical clinical effects across all etiological subtypes. Consequently, prognostic models for cirrhosis should ideally be adapted to disease etiology rather than applied uniformly.

Prospects for Clinical-Genetic Risk Stratification

At present, Child-Pugh and related conventional scoring systems remain the principal instruments for evaluating disease severity in liver cirrhosis. However, these tools do not incorporate immunogenetic characteristics of the patient. For this reason, integrative risk models that combine clinical, laboratory, and genetic data represent one of the most promising directions in modern hepatology.

A clinical-genetic approach may enable earlier identification of high-risk groups, individualization of preventive strategies, and refinement of clinical decision-making. In particular, early recognition of patients at elevated risk for spontaneous bacterial peritonitis, variceal bleeding, or hepatic encephalopathy would have major practical importance. Moreover, evaluation of genetic polymorphisms may provide a solid basis for implementing the principles of personalized medicine in hepatology, especially in stratifying high-risk patients, predicting disease course, and allocating healthcare resources more effectively.

Practical Implications

Early prediction of decompensation risk in liver cirrhosis of different etiologies is of substantial practical significance. If a simple yet reliable risk model combining clinical findings, laboratory parameters, and genetic markers can be developed, it may improve differential follow-up strategies in the work of family physicians, hepatologists, gastroenterologists, and internists. Such a model would be especially valuable for identifying patients at high risk of spontaneous bacterial peritonitis or variceal bleeding before these complications occur.

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In addition, the integration of genetic polymorphism assessment into routine practice may facilitate the implementation of personalized medicine approaches. This would be particularly useful for early risk stratification, individualized monitoring, and more rational distribution of clinical resources.

Conclusion

Decompensation phenotypes in liver cirrhosis of different etiologies are among the principal determinants of disease prognosis. Their development depends not only on hepatic functional insufficiency, but also on systemic inflammation, disruption of the gut-liver immune axis, cytokine imbalance, and individual genetic predisposition. In particular, polymorphisms in IL-23R, IL-17A, IL-17F, and IL-6 genes, when evaluated together with clinical and biochemical indicators, may improve the accuracy of early decompensation risk prediction. Thus, the implementation of a clinical-immunogenetic approach in cirrhosis may provide an important scientific and practical basis for early diagnosis, risk stratification, individualized monitoring, and optimization of complication prevention strategies.

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