Crosstalk between cardiac dysfunction and outcome of liver cirrhosis: Perspectives from evidence-based medicine and holistic integrative medicine

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Liver cirrhosis is primarily characterized by portal hypertension, which can lead to severe splanchnic vasodilatation, manifesting as increased cardiac output and decreased peripheral resistance. Notably, increased cardiac output is insufficient to maintain effective circulatory volume, thus, the vasodilation and its associated hypotension activate the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) resulting in renal vasoconstriction and sodium and fluid retention. Then, cardiac structural and functional changes develop, specifically cardiac hypertrophy and cardiac dysfunction. At present, it has been widely recognized that impaired cardiac contractility in response to stress, diastolic dysfunction, and electrophysiological abnormality, mainly QT interval prolongation, often develop in cirrhotic patients, which is termed cirrhotic cardiomyopathy (CCM).[1] CCM is often latent and asymptomatic in resting state, but becomes obvious under physiological and pathological stress. Accordingly, its prevalence is significantly underestimated in our everyday clinical practice. Recently, there has been a growing body of evidence regarding the interaction between cardiac dysfunction and liver cirrhosis and increased concern from physicians about this topic. In this setting, this paper aims to briefly review the mechanisms of CCM, analyze the association of cardiac dysfunction related indicators, mainly including echocardiography-related parameters, novel serum biomarkers, and QT interval prolongation, with the prognosis of liver cirrhosis based on the currently available evidence, and introduce the concept of holistic integrative medicine to further explain cardiohepatic interactions in the setting of liver cirrhosis.

MECHANISMS OF CCM

According to the theory of contemporary medicine, the mechanisms of CCM have been explored in human and animal studies. There are some potential mechanisms of systolic dysfunction in CCM. First, SNS hyperactivity causes cardiac damage directly and impairs β-adrenergic receptor signaling function, which finally decreases cardiac responsiveness, including chronotropic and inotropic incompetence. Second, cardiac suppressants, such as nitric oxide and inflammatory cytokines, are accumulated due to decreased inactivation of various bioactive substances in cirrhotic patients, thereby promoting cardiomyocyte apoptosis and cell death. Third, increased serum levels of endocannabinoids in cirrhotic patients may lead to negative inotropic action in the myocardium. Several underlying mechanisms of diastolic dysfunction in CCM have also been proposed.[2] First, it has been shown that the content of stiffer

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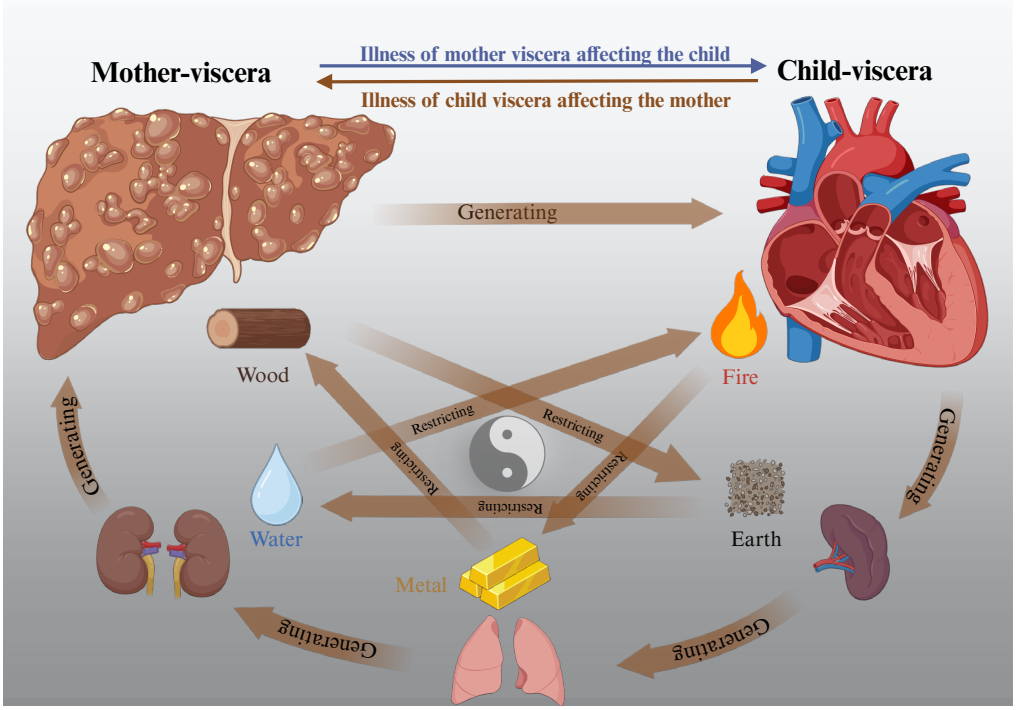

Figure 1: Mutual generation and restriction among five elements and disorder between liver and heart according to the five elements theory. Created using BioRender.com.

collagen I is increased, but that of more compliant collagen III is decreased in cirrhotic rats, subsequently increasing the passive cardiac tension. Second, protein kinase A (PKA) level is decreased in cirrhotic patients, probably impairing the phosphorylation of titin and subsequently increasing the passive tension of the left ventricle. In addition, such a reduction in PKA level may impair the phosphorylation of PKA-dependent cardiac troponin I (cTnI) and decrease the dissociation of calcium from cardiac troponin C (cTnC), which finally prolongs the diastolic time. The major mechanism of electrophysiological abnormality in CCM may be attributed to disrupted fluidity in the cardiomyocyte plasma membrane and subsequent changes in membrane receptor and ion channels.

On the other hand, according to the theory of traditional Chinese medicine (TCM), especially the "five elements theory", a very close association between the heart and liver, two major organs of human beings, has also been recognized for centuries. As mentioned in the ancient "five elements theory", the five elements correspond to five organs of the human body, specifically the liver, heart, kidney, lung, and spleen, and their characteristics are also associated with the physiological functions of the five organs. Mutual generation and restriction among these elements are the basic principle of interaction between these organs, which maintains the coordination and stability of the human system. The illness of the mother's viscera affecting the child's viscera is one of the disorders in mutual generation (Figure 1). In other words, the diseases may be transmitted from the mother viscera to the child viscera. The "five elements theory" can be used to explain the development of cardiac dysfunction caused by liver diseases. In detail, the liver belongs to wood and is considered as the mother of the heart, and the heart belongs to fire and is considered as the son of the liver. In a healthy population, the liver can maintain the free flow of "Qi" throughout the entire body and store blood. By contrast, the cirrhotic liver is characterized by "Qi" stagnation and blood stasis, ultimately compromising effective circulatory volume, which is consistent with the modern pathophysiological understanding of myocardial ischemia and injury caused by portal hypertension. Furthermore, in cirrhotic liver, stagnation can transform into "fire", leading to hyperactivity of "fire" in the heart, which consumes "Yin" in the heart and contributes to cardiomyocyte damage and cardiac dysfunction. This is consistent with the mechanism that increased inflammatory reaction and oxidative stress in cirrhosis are associated with cardiac dysfunction.

PERSPECTIVES FROM EVIDENCE-BASED MEDICINE

Echocardiography-related parameters for the prognosis of cirrhosis

Echocardiography is a convenient non-invasive tool for assessing cardiac structure and function, especially diastolic

dysfunction. Numerous studies have suggested that echocardiography related parameters reflecting diastolic dysfunction, such as left atrium enlargement, increased left atrial volume index, the ratio of mitral inflow early diastolic velocity/early diastolic mitral annular velocity of the septal and lateral sites (E/e') ≥ 10, and the ratio of mitral inflow early diastolic velocity/mitral inflow late diastolic velocity (E/A) ≤ 1, may predict the risk of death in cirrhotic patients (Supplementary Table S1). Except for death as the outcome of interest, our recent study also found that lower right ventricular dimension was associated with further decompensation in patients with decompensated cirrhosis.[3] However, some other studies did not confirm the association of echocardiography-related parameters with the survival of cirrhotic patients.[4] The discrepancy in the relationship of echocardiography-related parameters with a prognosis of liver cirrhosis may be caused by the heterogeneity in study populations, diagnostic criteria for CCM, and echocardiographic techniques (*e.g.*, 2D *vs.* 3D echocardiography *vs.* Tissue Doppler imaging). Additionally, it should be acknowledged that a majority of published studies have explored the effect of diastolic dysfunction, rather than systolic dysfunction, on the outcome of liver cirrhosis. This can be explained by the fact that left ventricular ejection of fraction, a traditional echocardiography-related parameter for systolic dysfunction, is normal in most cirrhotic patients, due to increased cardiac output as their compensatory mechanism. Accordingly, absolute global longitudinal strain < 18 has been added as a new diagnostic criterion for systolic dysfunction by the 2019 Cirrhotic Cardiomyopathy Consortium (CCC) to identify the development of systolic dysfunction as a major component of CCM more comprehensively. However it seems that absolute global longitudinal strain < 18 does not deteriorate the outcome of patients with cirrhosis.

Serum biomarkers of cardiac dysfunction for the prognosis of cirrhosis

Prohormone of brain natriuretic peptide (Pro-BNP), which is secreted by cardiomyocytes in response to ventricular wall stretch, is a sensitive marker for early assessment of cardiac failure. Troponin is a highly specific marker for the identification of myocardial injury. According to the 2005 World Congress of Gastroenterology criteria, increased levels of brain natriuretic peptide (BNP), Pro-BNP, and troponin I were considered as the supportive criteria for CCM. The 2019 CCC criteria have further suggested the importance of serum biomarkers of cardiac dysfunction for the management of CCM.[5] Cumulative evidence has supported the association of elevated serum biomarkers of cardiac dysfunction with poor outcomes in liver cirrhosis.[6] Our recent studies found that increased levels of Pro-BNP and high-sensitivity cardiac troponin T (hs-cTnT) were significantly associated with the severity of liver dysfunction and in-hospital mortality in cirrhotic patients,[7] and that N-terminal Pro-BNP and hs-cTnT might positively correlate with acute decompensating events (Supplementary Table S1).[8]

QT interval prolongation for the prognosis of cirrhosis

QT interval prolongation, the most frequent electrocardiographic abnormality in CCM, indicates the presence of ventricular arrhythmia, which can cause sudden death. However, the incidence of ventricular arrhythmia and its effect on mortality has been insufficiently evaluated in cirrhotic patients, primarily due to the absence of continuous electrocardiogram monitoring and the use of some drugs that may prolong the QT interval, such as quinolones and vasopressin analogs. Our study found that QT interval prolongation was associated with the severity of liver dysfunction in cirrhotic patients.[9] Other studies further demonstrated that cirrhotic patients with QT interval prolongation, especially those with acute gastrointestinal bleeding, had an increased risk of long-term mortality (Supplementary Table S1).

PERSPECTIVES FROM HOLISTIC INTEGRATIVE MEDICINE

In recent years, the concept of holistic integrative medicine, which sufficiently highlights the importance of TCM theory, has been widely accepted for the management of diseases and the improvement of health. It is also of special significance for the management of liver cirrhosis in clinical practice. From the holistic integrative medicine perspective, the management strategy should not be limited to the liver, a single organ, but also to the whole body, including the heart.[10] Specifically, CCM should be treated as a complex disease condition, which requires multidisciplinary management of the underlying liver cirrhosis and the cardiovascular system, as well as the general condition of a cirrhotic patient, including malnutrition, sarcopenia, and frailty.

FUTURE CONSIDERATIONS

With deep infiltration of holistic integrative medicine concepts in clinical practice, cardiohepatic interactions have been increasingly recognized. As shown by the existing evidence, the development of cardiac dysfunction can indicate worse outcomes for patients with liver cirrhosis, suggesting the necessity of incorporating the parameters of cardiac dysfunction into the prognostic model of cirrhosis (Supplementary Table S2). In the future, a comprehensive scoring system that integrates cardiac dysfunction biomarkers with MELD or Child-Pugh scores

could significantly improve the predictive performance of poor prognosis in cirrhotic patients, which needs to be further validated in multicenter cohorts. Notably, non-cardiac factors, such as renal dysfunction, may affect the level of serum biomarkers, which should be further explored. Meanwhile, holistic integrative assessment and management of CCM should be necessary.

Supplementary Information

Supplementary materials are only available at the official site of the journal (www.intern-med.com).

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Author Contributions

Conceptualization: Xingshun Qi; Writing–original draft: Liyan Dong, and Xingshun Qi; Writing–review and editing: Liyan Dong, Xingshun Qi, Huishan Wang, and Daiming Fan; Supervision: Xingshun Qi, Huishan Wang, and Daiming Fan. All authors have made an intellectual contribution to the manuscript and approved the submission.

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Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Conflict of Interest

Xingshun Qi is an Editorial Board Member of the journal. The article was subjected to the standard procedures of the journal, with a review process independent of the editor and his research group.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

Not applicable.

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