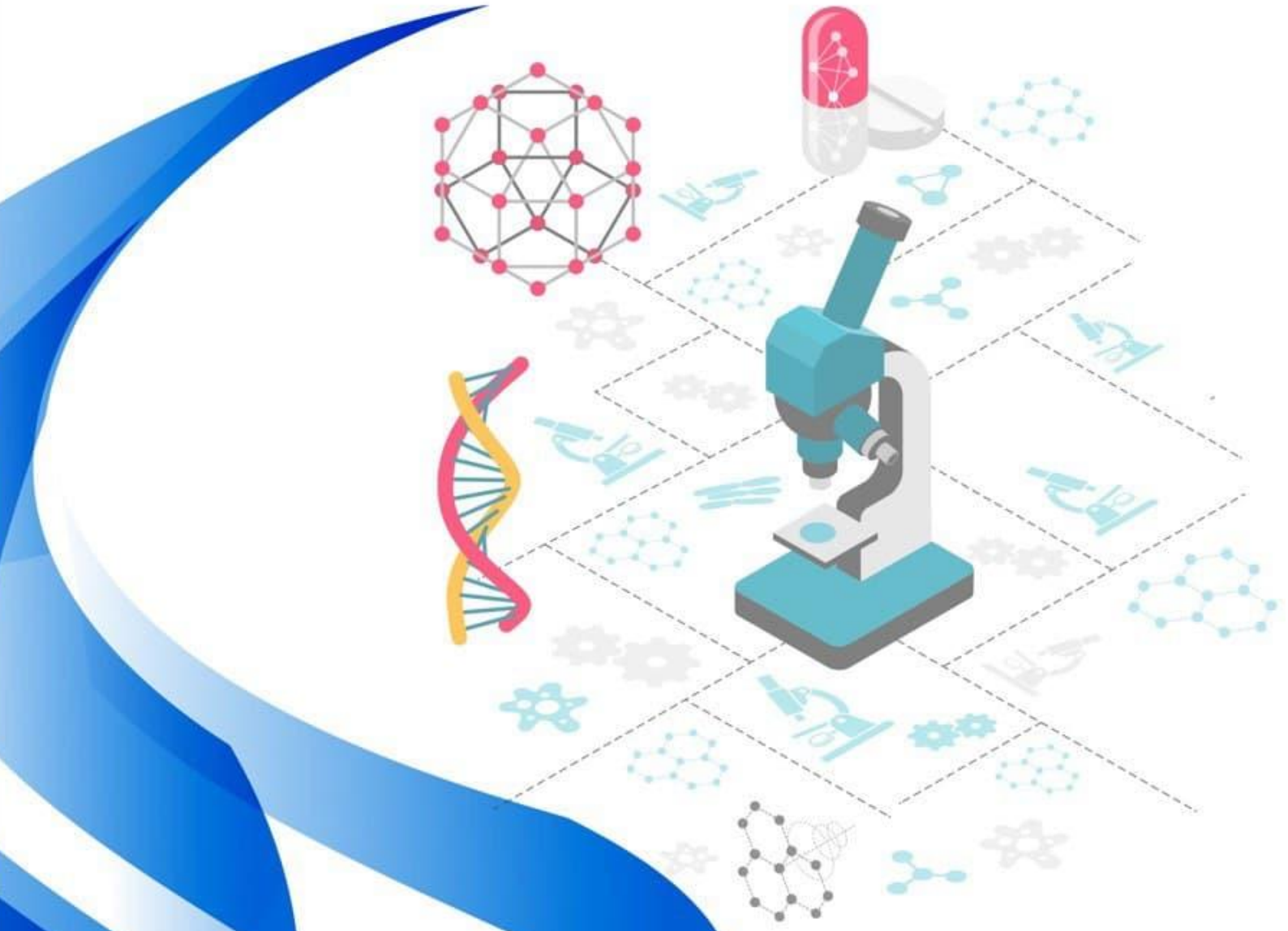
ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR



Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017

Editorial board

Institute of Nuclear Medicine and Allied Sciences (INMAS), India
Brig SK Mazumdar Marg, Timarpur, New Delhi, Delhi 110054 India

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017

HEPATOCARDIORENAL SYNDROME

Jumaeva Madina Fakhritdinovna

Bukhara State Medical Institute The Republic of Uzbekistan

Abstract. Accumulating evidence on the pathophysiology of hepatorenal syndrome has challenged the conventional model of liver-kidney connection. While liver cirrhosis is traditionally considered the origin of a cascade of pathophysiologic mechanisms directly affecting other organs such as the kidney, emerging data point to the heart as the potential mediator of the untoward renal effects. Herein, we briefly review the often-overlooked contribution of the heart to circulatory dysfunction in hepatorenal syndrome and put forward evidence arguing for the involvement of systemic inflammation and endothelial dysfunction in this setting. The temporality of cardiorenal interactions in hepatorenal syndrome and the observed beneficial effects of portosystemic shunting on these pathways lend further support to the notion that cardiac involvement plays a key role in the development of renal dysfunction in severe cirrhosis. The disturbances traditionally bundled within hepatorenal syndrome could represent a hepatic form of cardiorenal syndrome whereby the liver affects the kidney in part through cardiorenal pathways. This new model has practical implications and calls for a shift in the focus of diagnostic and therapeutic approaches to renal dysfunction in advanced cirrhosis.

Keywords. Hepatorenal syndrome · Cardiorenal syndrome · Cirrhosis · Cirrhotic cardiomyopathy

Introduction. Hepatorenal syndrome (HRS) is a serious event during the course of decompensated cirrhosis. Although the most characteristic feature of the

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017
syndrome is a functional renal failure due to intense renal vasoconstriction, it is a more generalized process affecting the heart, brain and splanchnic organs.

HRS is a clinical condition that usually occurs in patients with advanced liver disease and portal hypertension that is characterized by a combination of disturbances in circulatory and kidney function [6] . The major abnormality in the systemic circulation is markedly reduced total SVR, which leads to a low arterial pressure. Kidney function is markedly impaired because of a severe reduction of renal blood flow. The reduction in renal blood flow is pathogenically related to the impairment in the systemic circulatory function. HRS occurs predominantly in the setting of cirrhosis, but it may also develop in other types of severe chronic liver diseases, such as alcoholic hepatitis, or in acute liver failure [7, 8] . Because of its functional nature and lack of structural changes in the kidneys HRS is, theoretically, reversible if the mechanisms leading to the active renal vasoconstriction are corrected.

There are two types of HRS. Type 1 HRS is characterized by a rapidly progressive impairment of the circulatory and renal functions associated with a very poor prognosis (median survival rate lower than 2 weeks). Type 2 HRS is characterized by a steady impairment of the circulatory and renal functions with a median survival of 6 months. The pathogenesis of HRS is a deterioration of the effective arterial blood volume due to splanchnic arterial vasodilation and a reduction in venous return and cardiac output. It is therefore not surprising that the syndrome can be reversed by the simultaneous administration of intravenous albumin and arterial vasoconstrictors. Intrarenal mechanisms are important as well and require prolonged improvement of the circulatory function to be deactivated. Long-term administration of intravenous albumin and vasoconstrictors or correction of portal hypertension with a transjugular intrahepatic portacaval shunt are effective treatments of HRS, and many serve as a bridgepatients

Although the untoward impact of liver dysfunction on the heart and circulatory system has long been recognized, the advent of newer technology and biomarkers has

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017
recently allowed for a more precise evaluation and monitoring of cardiocirculatory function. As such, our understanding of the previously undetected changes taking place in the setting of severe liver disease has dramatically improved. Cirrhotic cardiomyopathy defines a specific form of cardiac dysfunction characterized by blunted contractile responsiveness to stress stimuli and altered diastolic relaxation with electrophysiological abnormalities, in the absence of a knowncardiac disease [1].

Traditional teaching of HRS views the kidney and the heart as 2 separate complications of worsening liver disease with distinct pathophysiologic pathways. However, emerging data points to these 2 organs as being mechanistically entangled; cardiac dysfunction could mediate impairment in renal function (i.e., cardiorenal syndrome [CRS]) in a subset of these patients [2]. Herein, the arguments in favor of frequently underappreciated CRS in the setting of HRS are put forward, and the clinical and therapeutic implications of this notion are briefly mentioned If we hypothesize that cardiac dysfunction has a contributory role in the subsequent development of renal impairment in the setting of advanced cirrhosis, then it is expected to precede

HRS. In the study by Ruiz-del-Arbol , those cirrhotic patients who subsequently developed HRS already had stigmata of cardiac dysfunction (e.g., lower stroke volume) prior to the decline in renal function. Moreover, low cardiac output at baseline, along with increased plasma renin activity, were found to be the only independent predictors for the development of HRS. Similarly, in another study, more patients developed HRS in the group with baseline low cardiac index (i.e., < 1.5 L/min/m2) as measured by gated myocardial perfusion imaging [3]. These observations on the temporal pattern of cardiac and renal dysfunction make it plausible that involvement of the heart contributes to the pathogenesis of HRS rather than being a mere consequence of it [4].

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017

Cardiac Contribution to Circulatory Dysfunction in HRS

In the earlier stages of cirrhosis, circulatory homeostasis is maintained by the development of hyperdynamic circulation characterized by increased cardiac output, heart rate, and plasma volume. Due to normal or increased cardiac output, it was previously assumed that the heart remains largely intact during the disease process; low systemic vascular resistance and arterial underfilling (i.e., central hypovolemia) were thought to be the sole mechanisms of circulatory dysfunction in cirrhosis. However, it is now recognized that in the later stages, the progressive decline in the afterload is no longer followed by an increase in cardiac output, hence contributing to the hemodynamic derangement. The lack of appropriate cardiac response to hemodynamic and neurohormonal stress was reported by Nazar et al. [3] who observed no difference in the left ventricular function and heart rate among patients with compensated cirrhosis, patients with ascites, and those with HRS despite marked differences in mean arterial pressure and plasma norepinephrine concentration. In a longitudinal study on cirrhotic patients with refractory ascites, baseline markers of cardiac function (e.g., cardiac output and stroke volume) were found to be significantly lower in those patients who subsequently developed HRS and further decreased at the time of HRS [4].

Interestingly, systemic vascular resistance remained unchanged between baseline and follow-up in these patients. The neurohormonal activity was also higher in those patients whose cirrhosis progressed to HRS, which, in the face of unchanged systemic vascular resistance but disturbed cardiac output, points to the heart as the main driving factor. In another study, patients with cirrhosis who developed renal failure in the course of spontaneous bacterial peritonitis had a lower cardiac output than those without renal dysfunction [5]. After resolution of the infection, patients with renal failure had an even lower cardiac output. Overall, current evidence suggests that cardiac inotropic and chronotropic dysfunction is a key component of

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017
the circulatory dysfunction observed in HRS. Maladaptive neurohormonal activation represents the key pathophysiologic mechanism linking cardiac dysfunction to HRS. It is also the cornerstone of the pathways involved in the development of CRS [6]. In patients with cardiac dysfunction, a number of factors, such as low cardiac output and use of diuretics, can lead to elevated levels of neurohormones and their downstream renal adverse consequences, such as reduction in glomerular filtration rate and impaired sodium and water excretion (low forward flow) [7]. Moreover, increased cardiac right-sided pressures could result in renal venous congestion and further deterioration in renal hemodynamics and function (high backward pressure) [8, 9]. As such, cardiac dysfunction could contribute to further deterioration of renal function in HRS, whereby there is already a tendency for activation of the neurohormonal axis.

Inflammation and Cardiorenal Interactions in HRS

Hemodynamic and neurohormonal mechanisms have long dominated the literature on the pathophysiology of HRS. However, emerging data points to systemic inflammation and endothelial dysfunction, not only as a trigger for hepatorenal pathways (e.g., splanchnic arterial vasodilation), but also as a direct contributor to derangements of the extrahepatic organs, particularly the heart. Cirrhosis is associated with features of inflammation, including increased markers of macrophage activation, proinflammatory cytokines, systemic oxidative
stress, and activated circulating monocytes and neutrophils [10]. The degree of inflammation and endothelial dysfunction, stemming from translocation of bacteria and pathogen-associated molecular patterns from the intestine, parallels the severity of liver, circulatory, and renal dysfunction [16]. Besides, HRS is often precipitated by bacterial infections, especially if a profound inflammatory response develops [17]. In animal models of decompensated cirrhosis, oxidative stress and tumor necrosis factor α have been shown to induce alterations of β-receptor signaling and impaired systolic

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017
dysfunction [18]. Serum levels of lipopolysaccharide-binding protein, a marker of exposure to bacterial endotoxin, are also independently associated with left ventricular diastolic dysfunction [19]. These observations, coupled with the strong evidence on the central role of endothelial dysfunction in CRS, make it conceivable that inflammation would represent a less well studied link in the liver-heart-kidney connection [20, 21].

Accordingly, in addition to being a potent plasma expander, albumin is known to possess significant anti-inflammatory properties [22]. In cirrhotic rats, albumin increases cardiac contractility by counteracting myocardial oxidative stress and inflammation [18]. In spontaneous bacterial peritonitis, albumin, but not hydroxyethyl starch, increased systemic vascular resistance and left ventricular stroke work index, illustrating the presence of a mechanism beyond volume expansion [23]. In support of this notion, the rate of HRS and mortality decreases by more than half in cirrhotic patients with spontaneous bacterial peritonitis if albumin is added to antibiotics [24]. As such, the beneficial impact of albumin on the treatment of HRS could conceivably be through improvement in inflammatory state and endothelial dysfunction, a common mechanism within cardiorenal interactions.

Temporality of Cardiorenal Interactions in HRS

If we hypothesize that cardiac dysfunction has a contributory role in the subsequent development of renal impairment in the setting of advanced cirrhosis, then it is expected to precede HRS. In the study by Ruiz-del-Arbol [4], those cirrhotic patients who subsequently developed HRS already had stigmata of cardiac dysfunction (e.g., lower stroke volume) prior to the decline in renal function. Moreover, low cardiac output at baseline, along with increased plasma renin activity, were found to be the only independent predictors for the development of HRS. Similarly, in another study, more patients developed HRS in the group with baseline low cardiac index (i.e., < 1.5

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017
L/min/m2) as measured by gated myocardial perfusion imaging [25]. These observations on the temporal pattern of cardiac and renal dysfunction make it plausible that involvement of the heart contributes to the pathogenesis of HRS rather than being a mere consequence of it [26].

Cardiorenal Interactions after Portosystemic Shunting

A subset of patients with cirrhosis receive a transjugular intrahepatic portosystemic shunt (TIPS) to alleviate portal hypertension. Immediately after the procedure, blood from the splanchnic bed and portal system is unloaded into the systemic circulation. As renal veinsdrain directly into the systemic circulation, intrarenal hemodynamics are not expected to be directly affected unless there is a change in renal perfusion. There is avid evidence on the salutary impact of TIPS on renal function, including improved urinary sodium excretion (indicative of ameliorated renal perfusion) as well as an increase in clearance of creatinine [27]. Based on recent data, cardiorenal interplay is the key mediator of the beneficial renal effects of TIPS, as it significantly enhances cardiac inotropy, leading to increased central
blood volume and renal perfusion [28]. Furthermore, the benefits of TIPS could partly be explained by improvement in endothelial function that follows mitigation of systemic inflammation through lowering pressures and shear stress in the portal system and hindering of the intestinal translocation of bacteria. Since the effect of venous congestion with end-stage liver cirrhosis and addition of TIPS may indeed reflect entirely different physiologic mechanisms, future studies are needed to investigate the 2 distinct profiles of renal dysfunction in the setting of simultaneous liver and cardiac dysfunction.

Pragmatic Implications of Cardiorenal Interactions in HRS

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017

In view of the evidence on the contribution of the heart to a host of pathophysiologic features in HRS, systematic evaluation and monitoring of cardiac function should be recommended to these patients, even to those without apparent cardiac impairment. While diastolic dysfunction is observed in as high as 58% of cirrhotics, left ventricular systolic function is commonly latent and is typically diagnosed in the face of blunted responsiveness to hemodynamic or pharmacologic stress [3]. If disturbed, it could have a significant prognostic value by identifying the subgroup at higher risk for subsequent development of HRS. Newer imaging

techniques may identify patients with subclinical cardiac dysfunction more accurately than conventional methods. Two-dimensional speckle-tracking echocardiography allows assessment of left ventricular regional myocardium and global strain by tracking natural acoustic markers (i.e., speckles) and is less likely to be dependent on preload or afterload compared to standard echocardiography. Using this technique has revealed that reduced longitudinal systolic function is common in cirrhosis patients despite having a normal ejection fraction [29].

The conventional treatments of HRS (i.e., albumin and vasoconstrictors) have important cardiac benefits and, therefore, might portend their salutary impact on the kidney in part through cardiorenal mechanisms. Since there is downregulation of β-adrenergic receptors in cirrhosis, β-agonists have commonly been considered unhelpful. However, there are reports of the successful use of cardiac inotropes to reverse renal dysfunction in refractory HRS, further emphasizing the significant contribution of cardiorenal pathways [30]. It remains to be clarified whether emerging treatments with potential benefit in heart failure (e.g., empagliflozin, urodilatin, and urocortin) would also find applications in HRS. In a phase II randomized controlled trial, serelaxin, the recombinant human relaxin-2 with cardioprotective effects in acute heart failure, significantly improved renal blood flow in patients with cirrhosis and ascites [31].

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017

Summary and Conclusion

Accumulating evidence on the pathophysiology of HRS has challenged the conventional model of liver-kidney connection. There are several facts to consider: (1) The heart is commonly involved in the course of cirrhosis and HRS, albeit with variable degrees of severity and presentations. (2) The circulatory dysfunction in HRS is in part due to cardiac impairment. (3) Cardiac dysfunction in cirrhotic patients who subsequently develop HRS frequently exists prior to the decline in renal function. (4) HRS and CRS share a number of cardinal pathophysiologic pathways, namely neurohormonal activation and endothelial dysfunction. (5) The treatments known to improve renal dysfunction in HRS also have direct beneficial effects on cardiorenal mechanisms. As such, the disturbances traditionally bundled within the HRS definition could represent a hepatic form of CRS (i.e., hepatocardiorenal syndrome) where the liver affects the kidney in part through cardiorenal pathways. This new model has practical implications and calls for a shift in the focus of prevention, treatment, and prognostication of renal dysfunction in advanced cirrhosis and HRS. It is noteworthy that the interactions between the heart and the kidney in the setting of CRS, as well as those between the liver and the kidney in HRS, are multifactorial, complex, and not entirely understood. Therefore, due to the sparsity of the data, the aforementioned arguments in support of the involvement of the heart in these interactions are to be considered a hypothesis that would need to be evaluated in future studies.

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/ Universal IMPACT factor 7
Volume 11 Issue 1
JAN-APR 2022
https://doi.org/10.5281/zenodo.6473017

References

1. Møller S, Lee SS. Cirrhotic cardiomyopathy. J Hepatol. 2018 Apr;S0168-8278(18)30017-5. Epub 2018 Apr 28.
2. Krag A, Gluud LL. Cross-talk between the liver, heart and kidney - another piece in the puzzle. J Gastrointestin Liver Dis. 2014 Jun; 23(2): 119–21.
3. Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Ginès P, Moreira V, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology. 2005 Aug; 42(2): 439–47.
4. Ruiz-del-Arbol L, Urman J, Fernández J, González M, Navasa M, Monescillo A, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology. 2003 Nov; 38(5): 1210–8.
5. Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut. 2010 Jan; 59(1): 105–10.
6. McCullough PA, Kellum JA, Mehta RL, et al. ADQI Consensus on AKI Biomarkers and Cardiorenal Syndromes. Contrib Nephrol. 2013; 182.
7. Arroyo V, Gines P, Gerbes AL, Dudley FJ,Gentilini P, Laffi G, et al: Defi nition and diagnosticcriteria of refractory ascites and hepatorenalsyndrome in cirrhosis. InternationalAscites Club. Hepatology 1996; 23: 164–176.
8. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O: Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: A double-blind, placebo-controlled trial. Gastroenterology 2000; 119: 1637–1648.
9. Ellis AJ, O'Grady JG: Clinical disorders or renal function in acute liver failure; in Arroyo V, Gines P, Rodes J, Schrier RW (eds): Ascites and renal dysfunction in liver disease. Malden, Blackwell Science, 1999, pp 63–78.
10. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction

in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012 Sep; 60(12): 1031–42.

11. Ronco C, McCullough PA, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al.; Acute Dialysis Quality Initiative (ADQI) consensus group. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2010; 165: 54–67.
12. Haase M, Müller C, Damman K, Murray PT, Kellum JA, Ronco C, et al. Pathogenesis of cardiorenal syndrome type 1 in acute decompensated heart failure: workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2013; 182: 99–116.
13. Kazory A, Elkayam U. Cardiorenal interactions in acute decompensated heart failure: contemporary concepts facing emerging controversies. J Card Fail. 2014 Dec; 20(12): 1004–11. Cardiorenal Med 2019;9:1–7 7
14. Kazory and Ronco: Hepatorenal Syndrome or Hepatocardiorenal Syndrome: Revisiting Basic Concepts in View of Emerging Data www.karger.com/crm DOI: 10.1159/000492791 © 2018 S. Karger AG, Basel
15. Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al.; CANONIC Study Investigators of the EASLCLIF Consortium and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology. 2016 Oct; 64(4): 1249–64.
16. Navasa M, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. Hepatology. 1998 May; 27(5): 1227–32.
17. Fasolato S, Angeli P, Dallagnese L, Maresio G, Zola E, Mazza E, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology. 2007 Jan; 45(1): 223–9.

18. Bortoluzzi A, Ceolotto G, Gola E, Sticca A, Bova S, Morando F, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology. 2013 Jan; 57(1): 266–76.
19. Karagiannakis DS, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Frequency and severity of cirrhotic cardiomyopathy and its possible relationship with bacterial endotoxemia. Dig Dis Sci. 2013 Oct; 58(10): 3029–36.
20. Virzì GM, Zhang J, Nalesso F, Ronco C, McCullough PA. The Role of Dendritic and Endothelial Cells in Cardiorenal Syndrome. Cardiorenal Med. 2018; 8(2): 92–104.
21. McCullough PA, Kellum JA, Haase M, Müller C, Damman K, Murray PT, et al. Pathophysiology of the cardiorenal syndromes: executive summary from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2013; 182: 82–98.
22. Zhang WJ, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res. 2002 Sep; 55(4): 820–9.
23. Fernández J, Monteagudo J, Bargallo X, Jiménez W, Bosch J, Arroyo V, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology. 2005 Sep; 42(3): 627–34.
24. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999 Aug; 341(6): 403–9.
25. Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut. 2010 Jan; 59(1): 105–10.

26. McCullough PA, Kellum JA, Mehta RL, et al. ADQI Consensus on AKI Biomarkers and Cardiorenal Syndromes. Contrib Nephrol. 2013; 182.
27. Guevara M, Ginès P, Bandi JC, Gilabert R, Sort P, Jiménez W, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology. 1998 Aug; 28(2): 416–22.
28. Busk TM, Bendtsen F, Poulsen JH, Clemmesen JO, Larsen FS, Goetze JP, et al. Transjugular intrahepatic portosystemic shunt: impact on systemic hemodynamics and renal and cardiac function in patients with cirrhosis. Am J Physiol Gastrointest Liver Physiol. 2018 Feb; 314(2):G275–86.
29. Altekin RE, Caglar B, Karakas MS, Ozel D, Deger N, Demir I. Evaluation of subclinical left ventricular systolic dysfunction using two-dimensional speckle-tracking echocardiography in patients with non-alcoholic cirrhosis. Hellenic J Cardiol. 2014 Sep-Oct; 55(5): 402–10.
30. Mocarzel LO, Bicca J, Jarske L, Oliveira T, Lanzieri P, Gismondi R, et al. Cirrhotic Cardiomyopathy: Another Case of a Successful Approach to Treatment of Hepatorenal Syndrome. Case Rep Gastroenterol. 2016 Oct; 10(3): 531–7.
31. Snowdon VK, Lachlan NJ, Hoy AM, Hadoke PW, Semple SI, Patel D, et al. Serelaxin as a potential treatment for renal dysfunction in cirrhosis: preclinical evaluation and results of a randomized phase 2 trial. PLoS Med. 201
32. Akhmedova N.Sh ., Ergashov BB, Nuralieva HO, Safarova GA The influence of collected modified risk factors on the development and progression of chronic kidney disease // International Journal of Current Research and Reviews Volume 13 * Issue 02 • January 2021 Pages 13-17.
33. Ziyoda Rakhmonovna Sohibova, Gulnoz Avazkhonovna Safarova. Modern ideas about the importance of macro- and microelements in the physiology and pathology of the body (review). Journal of Biomedicine and Practice 2020,

Volume 6, Issue 5, pp.238-243 http://dx.doi.org/10.26739/2181-9300-2020-6-38

34. Assessment of vasorenal hemodynamics in patients with chronic kidney disease in combination with arterial hypertension. Mukhamedzhanova Mastura Khayatovna, Safarova Gulnoz Avazkhanovna. Problems of Biology and Medicine 2020, No. 6 (124) 87-90 pages. UDC: 616.1 + 615.2.03 + 613.1 [in Russian]
35. Makhmudov Ravshan Barraevich, Safarova Gulnoz Avazkhonovna, (2021). Clinical Cases Of Aplastic Anemia Associated With Hepatitis. American Journal of Medical Sciences and Pharmaceutical Research, 3(04), 195-199. Doi: https://doi.org/10.37547/TAJMSPR/vol. 03 edition 04-28
36. Features of the vasorenal vascular resistance index indicators in monitoring the progression of chronic kidney disease. Safarova Gulnoz Avazkhonovna, Mukhamedzhanova Mastura Khayatovna, Ubaydova Dilafruz Saddikovna. Asian Journal of Pharmaceutical and Biological Research 2231-2218 http://www.ajpbr.org / Volume 10. Issue 2. MAY-AUGUST 2021. 10.5281/zenodo.5519192 Pages 78-84
37. Safarova GA Changes in vasorenal hemodynamics in patients with chronic kidney disease in combination with hypertension. Asian Journal of Pharmaceutical and Biological Research 2231-2218 http://www.ajpbr.org /Volume 10. Issue 2. MAY-AUGUST 2021 10.5281/zenodo.5464135 Page 66-71
38. Features of anemia in patients with chronic liver diseases. Ismatova MN, Mukhamedzhanova MH// American Journal of Medical Sciences and Pharmaceutical Research 2021 (April 30) pp.189-194
39. Clinical features of the comorbid state of arterial hypertension and bronchial asthma. Mukhamedjanova Mastura Khayatovna, Jumaeva Madina Fakhriddinovna, Nurova Nigora Sadilloevna. Asian Journal of Pharmaceutical

and Biological Research 2231-2218. http://www.ajpbr.org/Volume 10. Issue 3. SEPT-DEC 2021. 10.5281/zenodo.5571846

40. Makhmudova LI, Safarova GA, Mukhamedjanova M.Kh., Sulaimonova GT Assesment of changes in the quality of life in patients with irritable bowel syndrome. // Problems of biology and medicine - 2021 - No. 6 - P. 57-61
41. Anemia in patients with interference and interpretation of modern therapy. Mukhamedjanova MH NDM 4 (36)2021 P150-152
42. NS Shadjanova, UK Abdullaeva New opportunities in the treatment of chronic lymphocytic leukemia // Asian journal of pharmaceutical and biological research. 2021 Vol. 10 Iss. 3 P.11-15
43. SHAJANOVA Nigora Saidjanovna , EGAMOVA Sitora Kobilovna , UMUROVA Nigora Mavlonovna Metabolism in the organism in elderly persons with iron deficiency anemia // Journal of Biomedicine and Practice. 2020. Vol.2 Iss. 5
44. Shadzhanova NS, Ismatova MN prevalence and causing factors of bronchial asthma in the bukhara region // Actual problems of the humanities and natural sciences / 2017. Volume 2 No. 2
45. Shadzhanova NS, Ismatova MN Status of kidney function and some indicators of hemostasis in women with mild pre-eclampsia // Actual problems of the humanities and natural sciences 2018. Volume 11 No. 2
46. Safarova GA Indicators of kidney damage in type II diabetes mellitus in preclinical stages. // Infection, immunity and pharmacology №6/2021 ISSN 2181-5534 Pages 162-167
47. Safarova GA Features of the clinical course of covid-19 in comorbid conditions (A literature review) // New day in medicine 6 (38) 2021 ISSN 2181-712X. EISSN 2181-2187 pages 88-95
48. Mukhamedjanova M.Kh., Safarova GA Evaluation of vasorenal hemodynamics in patients with chronic kidney disease in association with

arterial hypertension // Problems of biology and medicine 2020, no. 6 (124) P. 87-90. UDC: 616.1+615.2.03+613.1

49. Safarova GA, Mukhamedjanova M.Kh.. The value of Doppler ultrasound in the management of patients with acute kidney injury from various causes.Asian journal of Pharmaceutical and biological research 2231-2218 Vol. 11 Issue 1 JAN-APR 2022 https://doi.org/10.5281/zenodo.6460952