CorSalud 2018 Abr-Jun;10(2):106-112

CorSalud

Cuban Society of Cardiology

Original Article

Cardiocentro Ernesto Che Guevara Santa Clara Cuba

Correlates of diastolic function in patients with alcoholic liver cirrhosis

Ruxandra Deliu[1]*, MD; Ionuț Donoiu[2]✉, MD, PhD; Constantin Militaru[2], FESC, MD, PhD; Octavian Istrătoaie[2], MD, PhD; and Tudorel Ciurea[3], MD, PhD

[1] University of Medicine and Pharmacy. Craiova, Romania.
[2] Department of Cardiology, University of Medicine and Pharmacy. Craiova, Romania.
[3] Department of Gastroenterology, University of Medicine and Pharmacy. Craiova, Romania.
* PhD Student.

Este artículo también está disponible en español

ARTICLE INFORMATION

Received: October 28, 2017
Accepted: November 30, 2017

Competing interests
The authors declare no competing interests

Acronym
NT-proBNP: N-terminal pro brain natriuretic peptide

✉ *I Donoiu*
Department of Cardiology, Craiova University of Medicine and Pharmacy, 2 Petru Rareș Street, 200349 Craiova, Romania.
E-mail address:
ionut.donoiu@umfcv.ro

ABSTRACT

Introduction: There are few established correlations between echocardiographic and biological parameters, and the severity of hepatic alcoholic disease; and even fewer prognostic correlations.

Objective: The present study is aiming at establishing correlations between severity of hepatic alcoholic disease and cardiac structural and functional alterations, as well as their prognostic implications.

Method: We investigated a group of 50 patients with liver cirrhosis of alcoholic etiology, classified by Child-Pugh score. Routine laboratory tests and transthoracic echocardiography were performed, NT-proBNP level was measured in each.

Results: We found that patients with more severe liver dysfunction have a significantly worse diastolic profile. The peak early diastolic filling velocity of the left ventricle (E wave) was significantly higher, with lower tissue Doppler velocities at annular level and high ratio between E and e', which point to the severity of the diastolic dysfunction. When comparing the indexed volumes of heart cavities, we did not find significant differences regarding left atrium indexed volume, left ventricle end-diastolic or end-systolic indexed volumes. Patients with Child class B liver disease had significantly lower levels of NT-proBNP.

Conclusions: This study is revealing the significant association between diastolic dysfunction of the left ventricle and severity of the alcoholic liver cirrhosis, as well as the correlation between E/e' ratio value, Child-Pugh class and also higher values of NT-proBNP. The benefit is that patients with alcoholic cirrhosis can be also classified according to the existence and severity of left ventricular diastolic dysfunction so that these patients could benefit from a stricter monitoring and closer follow-up.

Key words: Liver cirrhosis, Alcoholic liver disease, Cardiac function, Echocardiography

Correlaciones de la función diastólica en pacientes con cirrosis hepática alcohólica

RESUMEN

Introducción: Existen pocas correlaciones establecidas entre los parámetros ecocardiográficos y biológicos con la gravedad de la enfermedad hepática alcohólica,

y aún menos parámetros asociados al pronóstico.
Objetivo: Establecer la asociación entre la gravedad de la enfermedad hepática alcohólica y las alteraciones estructurales y funcionales cardíacas, así como sus implicaciones pronósticas.
Método: Se investigó un grupo de 50 pacientes con cirrosis hepática de origen alcohólico, clasificados según la puntuación Child-Pugh. A todos los pacientes se les realizaron pruebas de laboratorio de rutina, determinación de los niveles de NT-proBNP, y ecocardiograma transtorácico.
Resultados: Los pacientes con disfunción hepática más grave tuvieron un perfil diastólico significativamente peor. La velocidad máxima de llenado protodiastólico del ventrículo izquierdo (onda E) fue significativamente más alta, con velocidades inferiores en el Doppler tisular a nivel del anillo, y una relación E/e' elevada, lo que apunta a la gravedad de la disfunción diastólica. No se encontraron diferencias significativas con respecto a los volúmenes indexados de la aurícula izquierda y del ventrículo izquierdo en telediástole y telesístole. Los pacientes con enfermedad hepática en clase B de Child tuvieron niveles significativamente más bajos de NT-proBNP.
Conclusiones: Existe asociación significativa entre la disfunción diastólica del ventrículo izquierdo y la gravedad de la cirrosis hepática alcohólica, así como entre el valor de la relación E/e', la clase de Child-Pugh y los valores más elevados de NT-proBNP. Los pacientes con cirrosis alcohólica también se pueden clasificar según la existencia y gravedad de la disfunción diastólica del ventrículo izquierdo, de modo que estos pacientes puedan beneficiarse de una evaluación más certera y un seguimiento más estrecho.
Palabras clave: Cirrosis hepática, Hepatopatía alcohólica, Función cardíaca, Ecocardiografía

INTRODUCTION

While it is a well-known fact that alcohol in excess is harmful for the heart, there is overwhelming amount of data that prove the beneficial effect on cardiovascular system in normal and diseased patients, depending on the dose. In a meta-analysis of 34 prospective studies, published in 2006, Di Castenuovo *et al.*[1] showed that between total mortality and alcohol consumption there is a J-shaped relationship. Low-moderate alcohol consumption has beneficial effects and lowers total mortality, but when the consumption exceeds this level it becomes increasingly harmful.

The pathological entity called "alcoholic cardiomyopathy" is a consequence to long-term heavy alcohol consumption and it takes the form of non-ischemic dilated cardiomyopathy.

Alcohol has many pathophysiological effects on the heart, like myocyte apoptosis, toxicity on mitochondria and myocyte sarcoplasm[2,3], changes in calcium sensitivity in myofilaments[4] and others, by which it produces structural and functional abnormalities.

Genetic factors like polymorphisms in genes that control alcohol metabolism, like alcohol dehydrogenase[5], or genes that encode angiotensin-converting enzyme[6] might play an important role as triggers in pathogenesis of alcoholic cardiomyopathy[7].

Several studies have shown that left ventricle diastolic dysfunction is a consistently echocardiographic finding in cirrhotic patients and precedes systolic dysfunction, as both dysfunctions precede clinical symptoms and signs of heart failure[8].

There are few established correlations between echocardiographic parameters, biological parameters and the severity of hepatic alcoholic disease and even fewer prognostic correlation.

The present study is aiming at establishing correlations between severity of hepatic alcoholic disease and cardiac structural and functional alterations, as well as their prognostic implications.

METHOD

We investigated a group of 50 patients with alcoholic liver cirrhosis as diagnosed by histology or clinical, laboratory and ultrasonography findings.

Inclusion and exclusion criteria

Inclusion criteria were: alcoholic liver cirrhosis at any stage of the evolution. Exclusion criteria were: other causes of cirrhosis - viral liver disease, autoimmune liver disease; structural or ischemic heart disease, chronic heart failure, history of hypertension; transjugular porto-systemic shunt; systemic infection; chronic respiratory disease and treatment with drugs that could affect cardiac function or circulatory parameters (oncologic treatment).

Routine laboratory tests and abdominal ultrasound were performed in all patients included. Plasma level of NT-proBNP was also measured in all patients by electro-chemiluminescence method. Cut-off value given by the laboratory was 150 pg/ml. Child-Pugh score was calculated for every patient included in this study.

A 12 lead ECG was performed in all patients and QT interval measurement was corrected using Bazzet's formula.

Echocardiography

Transthoracic echocardiography (General Electric Vivid 7, USA) was used to assess diastolic dysfunction, chambers' diameters and volumes, left ventricular systolic function. In each patient, we used 2D mode in order to measure diameters of both left and right heart cavities, atrial volumes, left ventricle end-diastolic and end-systolic volumes, ejection fraction by using Simpson's formula. We used color Doppler and continuous wave Doppler to assess valvular regurgitations. We used pulsed wave Doppler to measure peak early diastolic filling (E wave), peak late diastolic filling, deceleration time of E wave and E/A ratio. Tissue Doppler imaging was used to assess peak early mitral annular velocity in both septal (e' septal) and lateral (e' lateral) left ventricle wall. The average between e' septal and e' lateral was obtained (e' average). We calculated E/e' average ratio. Pulmonary artery systolic pressure was also estimated.

We used the echocardiographic criteria latest updated by American Society of Echocardiography in collaboration with European Association for Cardiovascular Imaging to assess diastolic dysfunction[9-11]:

- Grade 1: E < 50 cm/sec, E/A < 0.8.
- Grade 2: E/A = 0.8 - 2.0 and at least 2 criteria of the following: E/e' > 14, tricuspid regurgitation velocity > 2.8 m/s and/or LA indexed volume > 34 ml/m^2.
- Grade 3: E/A > 2.

For the rest of the measurements, cut-off values given by the European Society of Cardiology guidelines in echocardiography were used.

Statistical processing

Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT 2014 add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA).

The data obtained were recorded in Microsoft Excel files, then processed statistically in order to analyze the relationships between clinical and paraclinical data of patients.

Data processing –descriptive batch analysis based on various parameters and their graphical representation– was performed in MS Excel using the Functions-Statistical, Pivot Tables, Chart and Data Analysis menu functions. To perform the normality tests (Shapiro-Wilks and Anderson-Darling) and complex statistical tests (the Z test for proportions, the Chi square test, the Mann-Whitney-Wilcoxon test, the calculation of the rho Spearman correlation coefficient) we used XLSTAT module or we performed it with SPSS program.

To characterize the numerical data used in this paper, we used fundamental statistical indicators: arithmetic mean and standard deviation, as well as imputation indicators, minimum, maximum, median, quarks (percentiles).

Student's *t* test, comparing the averages for 2 batches has a result named *p*, which is a numerical value between 0-1. The interpretation of the *p* values is, as in any statistical test, as follows:

- p<0.05: the difference between the two averages of the batches is significant (95% confidence).
- p<0.01: the difference between the two averages of the batches is significant (99% confidence).
- p<0.001: the difference between the two averages is highly significant (99.9% confidence).
- p>0.05: the difference between the two averages is insignificant.

RESULTS

We included 50 patients, 78% men, median age was

58.4 ± 8.6 years. There were 5 patients in class A Child (10%), 27 in class B (54%) and 18 patients in class C (36%). Given the small number of patients in class A, and the similar profile of measured parameters, we decided to analyze this group together with those in Class Child B (patients in class A and B will be referred as class B in the next pages).

There were no significant differences between patients with class Child B and C regarding age, blood pressure, heart rate, liver enzymes, renal function, or serum sodium and potassium (**Table 1**).

By analyzing the diastolic function through mitral filling pattern and tissue doppler mitral annular velocities, we found that patients with more severe liver dysfunction have a significantly worse diastolic profile (**Table 2**). The peak early diastolic filling velocity of the left ventricle (E wave) was significantly higher, with lower tissue doppler velocity in the interventricular septum (e'), and high ratio between E and e', when measured on both septal and lateral wall, and also when considering the mean of e'.

When comparing the indexed volumes of heart cavities, we did not find significant differences regarding left atrium indexed volume, left ventricle end-diastolic or end-systolic indexed volumes, or right atrium indexed volume.

Comparing the distribution according to the E/A ratio between Child B and Child C patients, we found no significant difference (*p* Chi square=0.278) (**Figure 1**).

Patients with Child class C liver disease had higher levels of NT-proBNP (611.81 ± 337.81 vs 384.00 ± 263.29 pg/ml, p=0.017) (**Figure 2**).

By analyzing the correlations of parameters of diastolic function we found several significant relationships with clini cal, biological and electrocardiographic features, especially with NT-proBNP levels (**Table 3**). The most powerful correlation, excepting age, of E/A ratio was with gamma-glutamyl transpeptidase levels. For E/e', we found a relatively weak, but significant correlation with potassium and NT-proBNP.cal, biological and electrocardiographic features, especially with NT-proBNP levels (**Table 3**). The most powerful correlation, excepting age, of E/A ratio was with gamma-glutamyl transpeptidase levels. For E/e', we found a

Table 1. Patients characteristics, according to Child classification.

Variables	Child B	Child C	*p*
Age (years)	59.66 ± 9.48	56.17 ± 6.46	0.171
Male sex (%)	81.25	72.22	0.459
Heart rate (bpm)	80.63 ± 13.97	81.28 ± 9.71	0.861
sBP (mmHg)	122.34 ± 23.04	128.33 ± 22.43	0.377
AST (U/L)	84.31 ± 85.74	95.22 ± 80.76	0.661
ALT (U/L)	67.44 ± 125.06	37.78 ± 30.67	0.329
GGT (U/L)	582.00 ± 549.91	481.78 ± 663.58	0.568
Creatinine (mg/dl)	0.87 ± 0.32	0.72 ± 0.13	0.071
eGFR (ml/min/1.73m^2)	89.97 ± 23.32	100.81 ± 11.12	0.070
Sodium (mmol/l)	136.47 ± 2.87	134.39 ± 4.80	0.060
Potassium (mmol/l)	4.43 ± 0.62	4.21 ± 0.90	0.305

ALT; alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; sBP, systolic blood pressure.

Table 2. Comparison of diastolic function parameters and chambers volumes.

Variables	Child B	Child C	p
E wave (m/s)	0.71 ± 0.13	0.79 ± 0.12	0.043
e' lateral (cm/s)	11.14 ± 3.21	8.85 ± 3.53	0.231
e' septal (cm/s)	7.26 ± 1.41	6.27 ± 1.23	0.016
E/e' mean	9.83 ± 3.34	11.81 ± 2.70	0.037
E/e' lateral	6.41 ± 2.96	8.37 ± 3.45	0.039
E/e' septal	9.83 ± 3.34	11.81 ± 2.70	0.037
LAVi (ml/m^2)	42.70 ± 13.54	44.98 ± 14.03	0.574
LVEDVi (ml/m2)	65.47 ± 26.22	71.42 ± 15.70	0.385
LVESVi (ml/m2)	17.35 ± 13.67	24.86 ± 15.68	0.083
RAVi (ml/m2)	30.95 ± 12.08	30.54 ± 7.85	0.898

LAVi - left atrium indexed volume; LVEDVi - left ventricle end-diastolic indexed volume; LVESVi - left ventricle end-systolic indexed volume; RAVi - right atrium indexed volume.

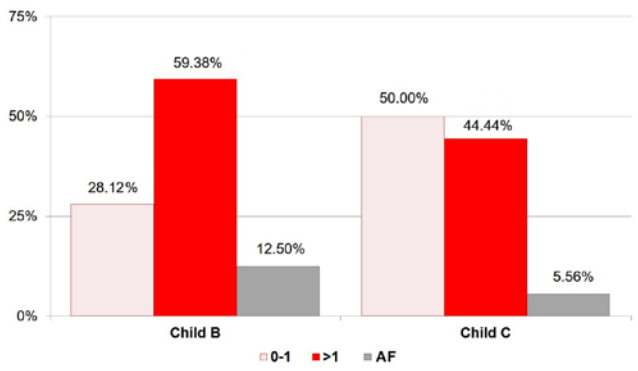

Figure 1. E/A ratio distribution depending on Child class. FA, atrial fibrillation.

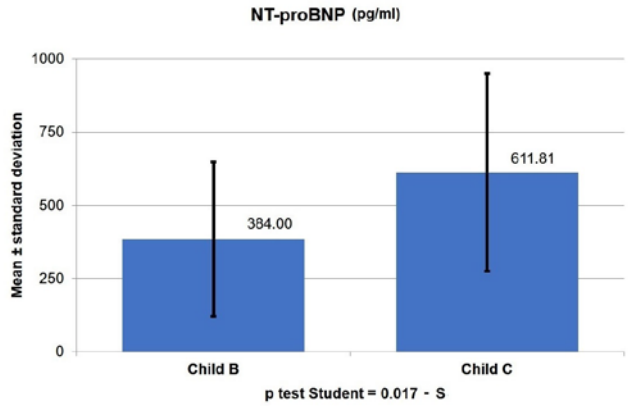

Figure 2. NT-proBNP values according to Child class.

relatively weak, but significant correlation with potassium and NT-proBNP.

DISCUSSION

In our study a significant number of cirrhotic patients had diastolic dysfunction and its severity is correlated with the degree of liver failure. 26 patients had grade 1 diastolic dysfunction, 1 patient had grade 2 diastolic dysfunction and 5 patients had atrial fibrillation (diastolic pattern not identifiable by common methods), thus 54% had diastolic dysfunction identifiable by pulsed wave Doppler and tissue Doppler imaging. We showed that there is no significant difference in terms of E/A ratios between Child-

Table 3. Pearson correlations between diastolic function parameters and clinical/biological variables.

Variables	E	A	E/A	e' septal	E/e' septal	e' lateral	E/e' lateral	E/e' mean
Age	0.001	0.259	-0.026	-0.255	**0.301**	**-0.481**	**0.423**	**0.366**
sBP	-0.120	**0.284**	-0.259	-0.180	0.083	-0.077	-0.116	-0.042
AST	-0.146	-0.022	-0.158	-0.053	0.003	0.080	-0.167	-0.106
ALT	-0.077	0.048	-0.250	-0.138	0.125	-0.039	-0.033	0.056
GGT	**-0.284**	0.184	**-0.308**	-0.102	-0.186	-0.103	-0.155	-0.193
Creatinine	-0.156	0.068	-0.076	-0.193	0.001	-0.149	-0.006	0.024
eGFR	0.099	-0.204	0.108	0.263	-0.124	0.209	-0.085	-0.127
Sodium	-0.047	-0.090	-0.048	0.117	-0.152	-0.071	-0.067	-0.088
Potassium	-0.206	**-0.299**	-0.014	0.023	-0.220	-0.034	-0.251	**-0.310**
NT-proBNP	**0.335**	**0.368**	-0.015	0.002	**0.323**	0.028	0.262	**0.368**
Heart rate	0.004	-0.084	0.061	0.075	0.020	0.019	0.059	-0.062
QRS duration	0.081	-0.018	-0.029	0.128	0.037	0.057	-0.026	0.075
QTc	-0.046	0.261	**-0.289**	-0.162	0.188	-0.038	-0.157	0.006

ALT - alanine aminotransferase; AST - aspartate aminotransferase; eGFR - estimated glomerular filtration rate; GGT - gamma-glutamyl transpeptidase; sBP - systolic blood pressure. All values in bold type have $p<0.05$.

Pugh classes. While E/A ratio is a variable that is largely influenced by preload and afterload conditions, E/e' average is a parameter linked to left atrial pressure, thus severity of diastolic dysfunction. Accordingly, we used tissue Doppler imaging to detect e' on septal wall and e' on lateral wall at the mitral annulus level, then we used E/e' average ratio to detect severity of diastolic dysfunction, which is a less load-dependent parameter, thereby a more accurate tool to assess myocardial dysfunction[9-11].

The peak early diastolic filling velocity of the left ventricle (E wave) was significantly higher, with lower tissue doppler velocity in the interventricular septum (e'), and high ratio between E and e', when measured on both septal and lateral wall, and also when considering the mean of e' in Child C class comparing with Child B class. Therefore, liver disease severity as classified by Child class it is found to be in direct positive correlation with the severity of left ventricle diastolic dysfunction and also with a poorer prognosis, as shown in other studies of the matter[12,13].

The study of Karagiannakis et al. found that diastolic dysfunction and low albumin levels are strongly associated with poor prognosis in cirrhotic patients regardless of etiology and that the correlation is stronger after first year of follow-up. Accordingly, in our study we found that diastolic dysfunction is correlated with the severity of the cirrhosis, therefore with the prognosis of the patients.

Therefore, E/e´ ratio as a marker of severity of diastolic dysfunction could be used to stratify patients with alcoholic liver cirrhosis in order to establish which ones need more careful and close monitoring and longer follow-up.

Measuring the indexed volumes of the heart cavities, we found no statistically significant correlation between the measurements and the Child-Pugh score, nor with routine laboratory tests. This is in accordance with the results of other studies that concluded that diastolic dysfunction precedes systolic dysfunction in liver diseases[14,15].

It is known fact that B-type natriuretic peptide is associated with the prognosis and cardiac dysfunction in cirrhotic patients as shown in studies of Henrikssen in 2003[16] and Pimenta in 2010[17]. In this regard, our study found that higher values of N-terminal proBNP are associated with more severe liver disease and that there are also correlated with diastolic dysfunction.

CONCLUSIONS

This study is revealing the significant association between diastolic dysfunction of the left ventricle and severity of alcoholic liver cirrhosis, as well as the correlation between E/e' ratio value, as a marker of severity of diastolic dysfunction, Child-Pugh class and also higher values of NT-proBNP, as a marker of cardiac dysfunction. The benefit from this study is that patients with alcoholic cirrhosis can be also classified according to the existence and severity of left ventricle diastolic dysfunction so that these patients could benefit from a stricter monitoring and closer follow-up.

REFERENCES

1. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: An updated meta-analysis of 34 prospective studies. Arch Intern Med. 2006;166(22):2437-45.
2. Capasso JM, Li P, Guideri G, Malhotra A, Cortese R, Anversa P. Myocardial mechanical, biochemical, and structural alterations induced by chronic ethanol ingestion in rats. Circ Res. 1992;71(2):346-56.
3. Schoppet M, Maisch B. Alcohol and the heart. Herz. 2001;26(5):345-52.
4. Delbridge LM, Connell PJ, Harris PJ, Morgan TO. Ethanol effects on cardiomyocyte contractility. Clin Sci (Lond). 2000;98(4):401-7.
5. Hines LM, Stampfer MJ, Ma J, Gaziano JM, Ridker PM, Hankinson SE, *et al.* Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. N Engl J Med. 2001;344(8):549-55.
6. Fernández-Solá J, Nicolas JM, Oriola J, Sacanella E, Estruch R, Rubin E, *et al.* Angiotensin-converting enzyme gene polymorphism is associated with vulnerability to alcoholic cardiomyopathy. Ann Intern Med. 2002;137(5 Part 1):321-6.
7. Djoussé L, Gaziano JM. Alcohol consumption and heart failure: A systematic review. Curr Atheroscler Rep. 2008;10(2):117-20.
8. Iacovoni A, de Maria R, Gavazzi A. Alcoholic cardiomyopathy. J Cardiovasc Med (Hagerstown). 2010;11(12):884-92.
9. Klein AL, Burstow DJ, Tajik AJ, Zachariak PK, Bailey KR, Seward JB. Effects of age on left ven

tricular dimensions and filling dynamics in 117 normal persons. Mayo Clin Proc. 1994;69(3):212-24.
10. Kazankov K, Holland-Fischer P, Andersen NH, Torp P, Sloth E, Aagaard NK, *et al*. Resting myocardial dysfunction in cirrhosis quantified by tissue Doppler imaging. Liver Int. 2011;31(4):534-40.
11. Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva AP, Valente J, *et al*. Systolic and diastolic dysfunction in cirrhosis: A tissue-Doppler and speckle tracking echocardiography study. Liver Int. 2013;33(8):1158-65.
12. Karagiannakis DS, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Diastolic cardiac dysfunction is a predictor of dismal prognosis in patients with liver cirrhosis. Hepatol Int. 2014;8(4):588-94.
13. Ruíz-del-Árbol L, Achécar L, Serradilla R, Rodríguez-Gandía MÁ, Rivero M, Garrido E, *et al*. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. Hepatology. 2013;58(5): 1732-41.
14. Moller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J. 2013;34(36):2804-11.
15. Alqahtani SA, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. Semin Liver Dis. 2008;28(1):59-69.
16. Henriksen JH, Gotze JP, Fuglsang S, Christensen E, Bendtsen F, Moller S. Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease. Gut. 2003;52(10):1511-7.
17. Pimenta J, Paulo C, Gomes A, Silva S, Rocha-Gonçalves F, Bettencourt P. B-type natriuretic peptide is related to cardiac function and prognosis in hospitalized patients with decompensated cirrhosis. Liver Int. 2010;30(7):1059-66.