SHORT COMMUNICATION

Diastolic dysfunction in patients with liver cirrhosis: A short-term, observational study at a Malaysian hospital

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SUMMARY

Cirrhotic cardiomyopathy is a recognised complication of liver cirrhosis and predicts poor outcomes. Detection of diastolic dysfunction, an early indicator of left ventricular dysfunction can help identify those patients at risk of disease progression. In our study we showed that there was a high prevalence of diastolic dysfunction amongst patients with liver cirrhosis at our outpatient clinic, with the majority being Child-Pugh A/low MELD score. Multiple regression analysis indicated that age and sodium levels were significantly associated with the presence of diastolic dysfunction. This further reinforces the importance of dietary sodium restriction amongst patients with liver cirrhosis.

KEY WORDS:

Child-Pugh score, Cirrhotic cardiomyopathy, Liver cirrhosis, MELD score, Sodium restriction

INTRODUCTION

Cirrhotic cardiomyopathy (CC) was first described in patients who had a history of alcoholism, inadequate diet and liver cirrhosis.[1] These patients had elevated resting cardiac output and increased stroke volume, but with a normal blood pressure and low systemic vascular resistance. Chronic activation of the renin-angiotensin system results in increased fluid retention,[2,3] and in late stages of CC cardiac output decreases whilst left ventricular (LV) filling pressure increases.[4] Diastolic dysfunction (DD) is present when despite having a normal ejection fraction and systolic LV function, there are abnormalities of LV relaxation, filling and compliance.[5]

Presence of CC predicts poor prognosis among chronic liver disease patients who undergo invasive procedures such as trans-jugular intrahepatic portosystemic shunt insertion or liver transplantation. However, irreversible CC presents at a late stage, and thus early detection of LV dysfunction may assist in prognostication. DD may be present in patients with liver cirrhosis and is an important early marker for LV dysfunction.

METHODOLOGY

A cross-sectional, prospective, observational study involving patients with liver cirrhosis was conducted from December 2018 until March 2019. After obtaining informed consent subjects were recruited from the outpatient Gastroenterology Clinic of Hospital Universiti Sains Malaysia (HUSM). Echocardiography assessment was subsequently performed once the relevant demographic, clinical and laboratory data were recorded. We primarily aimed to identify the presence of DD and its associated factors among patients with liver cirrhosis on follow-up at HUSM. We also assessed LV function parameters in relation to different stages of liver cirrhosis via Child-Pugh and Model for End-stage Liver Disease (MELD) score calculations.

Ethical approval was obtained from the Universiti Sains Malaysia Human Research Ethics Committee (USM/JEPeM/18080372).

Inclusion criteria were adults aged from 18-80 years old with liver cirrhosis. Liver cirrhosis was diagnosed based on typical history and physical examination findings, with supporting features on radiographic and laboratory investigations. Exclusion criteria were patients who had a history of cardiac disease, those who had active infection or sepsis (e.g., spontaneous bacterial peritonitis), or those who were previously diagnosed to have hepatocellular carcinoma. Echocardiography was performed by trained personnel using a GE Vivid S70 Cardiovascular Ultrasound machine. Recommendations from the American Society of Echocardiography (2016) were used to assess the presence and severity of DD according to the following table.[6]

Data was analysed using IBM Statistical Package for Social Sciences (SPSS) version 24. Normality of the numerical variables were checked using graphical methods (histogram with overlying normal curve) and numerical methods (Fisher coefficient of skewness). Variables which had p-values <0.25 or of clinical importance were selected for subsequent statistical analysis.

To identify and establish the relationships between variables and the outcome, multiple logistic regression was applied. Forward selection and backward elimination methods were

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Table I: Grading of LV diastolic dysfunction

	Normal	Grade I	Grade II	Grade III
LV relaxation	Normal	Impaired	Impaired	Impaired
LAP	Normal	Low or normal	Elevated	Elevated
Mitral E/A ratio	≥0.8	≤0.8	>0.8 to <2	>2
Average E/e' ratio	<10	<10	10–14	>14
Peak TR velocity (m/sec)	<2.8	<2.8	>2.8	>2.8
LA volume index	Normal	Normal or increased	Increased	Increased

LV: left ventricle, LAP: mean left atrial pressure, TR: tricuspid regurgitation, LA: left atrium

Table II: Demographic and clinical characteristics of study subjects related to diastolic dysfunction (n = 33)

Characteristics	Total (n=33) n (%)	DD present (n=26) n (%)	DD absent (n=7) n (%)
Age (year)[a]	60(15)	61(7)	49(31)
Sex			
Male	16(48.5)	12(75.0)	4(25.0)
Female	17(51.5)	14(82.4)	3(17.6)
Race			
Malay	23(69.7)	17(73.9)	6(26.1)
Chinese	8(24.2)	8(100.0)	0
Siamese	2(6.1)	1(50.0)	1(50.0)
Medical History			
Hypertension			
Yes	13(39.4)	13(100.0)	0
No	20(60.6)	13(65.0)	7(35.0)
T2DM[b]			
Yes	8(24.2)	7(87.5)	1(12.5)
No	25(75.8)	19(76.0)	6(24.0)
Hyperlipidaemia			
Yes	11(33.3)	10(90.9)	1(9.1)
No	22(66.7)	16(72.7)	6(27.3)
Aetiology			
Viral	19(57.7)	16(84.2)	3(15.7)
NAFLD[c]	9(27.3)	7(77.8)	2(22.2)
Alcoholic	2(6.0)	1(50.0)	1(50.0)
Autoimmune	1(3.0)	0	1(100.0)
Others	2(6.0)	2(100.0)	0
Clinical ascites			
Present	11(33.3)	9(34.6)	2(28.6)
Absent	22(66.7)	17(65.4)	5(71.4)

[a] median (Interquartile range), [b] Type 2 Diabetes Mellitus, [c] non-alcoholic fatty liver disease

Table III: Proportion of subjects with diastolic dysfunction as compared to severity of chronic liver disease classified according to Child-Pugh and MELD score (n=33)

	Total sample	Child Pugh A n (%)	Child Pugh B n (%)	Child Pugh B n (%)
DD absent	7 (21.2)	3 (42.9)	4 (57.1)	0
DD grade 1	20 (60.6)	12 (60.0)	6 (30.0)	2 (10.0)
DD grade 2	4 (12.1)	2 (50.0)	2 (50.0)	0
DD grade 3	2 (6.1)	0	2 (100.0)	0
	Total sample	**MELD score <10 n (%)**	**MELD score >10 n (%)**	
DD absent	7 (21.2)	3 (42.9)	4 (57.1)	
DD grade 1	20 (60.6)	10 (50.0)	10 (50.0)	
DD grade 2	4 (12.1)	2 (50.0)	2 (50.0)	
DD grade 3	2 (6.1)	2 (100.0)	0	

DD: diastolic dysfunction; MELD: Model for End-stage Liver Disease

used to obtain a preliminary main effects model. Multicollinearity was checked using correlation matrix and standard error of regression coefficients. Interactions between the variables were also tested. Once a preliminary final model was established, the model fitness was tested using Hosmer Lemeshow test, classification table, as well as checking the area under the Receiver Operating Characteristics (ROC) curve. The final model included all significant variables with adjusted odds ratio and 95% confidence intervals. Level of significance was set at p-value <0.05.

RESULTS

Thirty-three patients were enrolled during the study period. The median age of the subjects was 60 years. Twenty-six subjects (78.8%) had DD (0.64-0.94, 95% CI), with 13 of them having a concomitant diagnosis of hypertension. The most common aetiology for liver cirrhosis was viral hepatitis (n=19, 57.7%) (Table II). Subjects were mostly Child-Pugh score A (n=17, 51.5%), a similar number had a MELD score of less than 10. The number of subjects categorised according to severity of liver disease and grade of diastolic dysfunction are summarised in Table III.

Regarding medications, 20 out of 33 the studyβ subjects were on diuretics (60.6%). DD was present in 18. -blockers were used in 25 subjects (75.8%); 19 of them had DD. Angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) were used in 6 subjects (18.2%), with all of them having DD. Calcium channel blockers (CCB) were used in 4 subjects (12.1%), all of them had DD as well.

Following backward and forward linear regression analysis, a final fit model was performed for age and sodium. These were significant in multiple regression analyses as well; subjects with liver cirrhosis had a 1.2 likelihood of having DD/year (CI%: 1.030, 1.295), whilst for sodium levels an increase of 1 mmol/L would translate to 1.6 the odds of having DD (CI%: 1.024, 2.532).

DISCUSSION

The proportion of our subjects with DD was high at 78.8% (64-95% CI) despite the majority of them being Child-Pugh A/low MELD score. Traditional cardiovascular risk factors, e.g. older age, Type 2 diabetes mellitus (T2DM), hypertension and hyperlipidaemia have been recognised to contribute to the diastolic dysfunction seen in CC, with the latter two being independent predictors of worse outcomes post liver transplantation.[7-9] In this study, 13 of the subjects with DD had hypertension, seven had T2DM and 10 hyperlipidaemia, which may confound the aetiology of DD. Nevertheless, the fact that overall, approximately 80% of subjects with liver cirrhosis had DD highlights the importance of acknowledging this entity and taking the appropriate steps to reduce progression towards CC.

It was also shown that only nine out of the 26 subjects with CC had ascites on physical examination, indicating that the majority had detectable DD on echocardiography despite not having significant liver decompensation. When assessed according to Child-Pugh score; 14/17 (82.4%) of Child-Pugh A subjects, 10/14 (71.4%) of Child-Pugh B and 2/2 (100%) of Child-Pugh C subjects had DD. This meant that DD was present in high numbers irrespective of Child-Pugh liver status, in keeping with a study that showed that there was no association of severity of liver disease and diastolic dysfunction in a case vs control group.[10] It is also recognised that Child Pugh C patients have a significant risk of having diastolic dysfunction; both of the two Child Pugh C subjects in this study had DD.[9]

From the study results it can be seen that a large number of subjects with DD were also on diuretic, β-blocker, CCB, ACEi and/or ARB medications. The first should not be surprising as spironolactone and frusemide combinations are often used βto control ascites in the setting of liver cirrhosis. Non-selective – blockers, e.g., propranolol is also used for the treatment of oesophageal varices, which is a common complication of the portal hypertension seen in liver cirrhosis. However, as pointed out earlier the subjects may also have underlying hypertension, necessitating the use of CCB, ACEi and/or ARB drugs for blood pressure control. Thus, the impact of medications as a confounding factor on the presence of DD cannot be ruled out, as these medications may also variably alter cardiac haemodynamics depending on the severity of the underlying liver disease. Renal status could be another possible confounder. The presence of concomitant renal disease may affect overall body fluid volume, which could influence measurement of echocardiographic parameters. However, creatinine clearance values were not obtained for the subjects who were enrolled in this study.

Multiple logistic regression analysis showed that age and sodium levels were significantly associated with DD (p=0.014 and 0.039 respectively). With regards to the relationship between sodium and extracellular volume (ECV), an increased sodium level leads to ECV expansion, activating the renin–angiotensin system which leads to higher cardiac output.[11] It is recommended that patients with ascites practice moderate sodium restriction (80-120mmol sodium/day or 4.6-6.9g salt/day),[12-15] which is equivalent to one/one and a half of teaspoons of salt per day. Patients with liver cirrhosis should have a detailed assessment of dietary intake, and relevant advice given.[14]

CONCLUSION

This brief study on patients with liver cirrhosis at our outpatient clinic showed that DD was common regardless of liver disease severity. The findings also reinforce the importance of sodium restriction in preventing DD progression.

REFERENCES

1. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. The J Clin Invest 1953; 32(10): 1025-33.
2. Pudil R, Pelouch R, Praus R, Vasatova M, Hulek P. Heart failure in patients with liver cirrhosis. Cor et Vasa 2013; 55(4): e391-e6.
3. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Postgrad Med J 2009; 85(999): 44-54.
4. Ruiz-del-Arbol L, Achecar L, Serradilla R, Rodriguez-Gandia MA, Rivero M, et al. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. Hepatol 2013; 58(5): 1732-41.

5. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000; 101(17): 2118-21.
6. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur J Echocardiogr 2016; 17(12): 1321-60.
7. Raval Z, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, et al. Cardiovascular risk assessment of the liver transplant candidate. J Am Coll Cardiol 2011; 58: 223-31.
8. Johnston SD, Morris JK, Cramb R, Gunson BK, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation 2002; 73(6): 901-6.
9. Papastergiou V, Skorda L, Lisgos P, Papakonstantinou N, Giakoumakis T, et al. Ultrasonographic prevalence and factors predicting left ventricular diastolic dysfunction in patients with liver cirrhosis: is there a correlation between the grade of diastolic dysfunction and the grade of liver disease?. The Sci World J 2012; 2012: e615057.
10. Somani PO, Chaurasia AS, Rathi PM. Diastolic dysfunction characterizes cirrhotic cardiomyopathy. Indian Heart J 2014; 66(6): 649-55.
11. Drenjancevic-Peric I, Jelakovic B, Lombard JH, Kunert MP, Kibel A, et al. High-salt diet and hypertension: focus on the renin-angiotensin system. Kidney Blood Press R 2011; 34(1): 1-11.
12. The Korean Association for the Study of the Liver. KASL clinical practice guidelines for liver cirrhosis: ascites and related complications. Cli Mol Hepatol 2018; 24(3): 230-77.
13. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69(2): 406-60.
14. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019; 709(1): 172-93.
15. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. J Hepatol 2013; 57(4): 1651-3.