Original Article

An Echocardiographic Evaluation of Cardiopulmonary Evaluation of Cardiopulmonary Functions in Patients with Cirrhosis of Liver and Correlation with Severity of Disease

Hari Prasad Panthi[1], Dinesh Koirala[2], Rahul Pathak[2*], Brindeswari Kafle Bhandari[2], Anurag Jha[2], Rabin Hamal[2], Mohan Bhusal[2], Manoj Lamsal[2], Susmita Gyawali[3]

[1]Department of Internal Medicine, Maharajgunj Medical Campus,
Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal
[2]Department of Gastroenterology, Maharajgunj Medical Campus,
Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal
[3]Institute of Medicine, Central Department of Public Health, Kathmandu, Nepal

Keywords: Cirrhosis, cirrhotic cardiomyopathy, hepatopulmonary syndrome, portopulmonary hypertension, transthoracic contrast echocardiography

Abstract

Background: Cirrhosis is the end result of varieties of chronic liver disease. A large proportion of patients with cirrhosis develop cardiopulmonary complication. The aim of this study was to evaluate the cardiopulmonary functions of patient with cirrhosis of liver and to correlate these abnormalities with CTP and MELD score.

Methods: The study involved 81 cirrhotic patients admitted in Department of Gastroenterology of TUTH over a period of one year. The diagnosis of cirrhosis was established and clinical evaluation and investigation done.

Results: The mean age of cirrhotic patients included in the study was 52 years. Alcohol was most common cause of cirrhosis (75.31%). The mean CTP score and MELD score was 10.02±1.77 and 23.59±7.53 respectively. Thirty patients (37.03%) had prolonged QTc interval, which had statistically significant association with alcohol as etiology of cirrhosis (p = 0.04). More than half (50.62%) of patients had diastolic dysfunction but it was not statistically significantly associated with CTP and MELD-Na score. Seven patients had evidence of intrapulmonary shunting, which had statistically significant association with MELD-Na score (p =0.01). Similarly, total 5 patients (6.17%) had PPHTN but there was no statistically significant association with CTP and MELD-Na score. Seventeen patients had dilated left atrium with no statistically significant association with CTP score and MELD-Na score.

Conclusion: There was significant incidence of cardiopulmonary abnormalities in cirrhotic patients. Every patient with decompensated cirrhosis irrespective of severity of disease should be evaluated for cardiopulmonary complication with a noninvasive, real-time, rapid imaging transthoracic contrast echocardiography.

Introduction

Cirrhosis of liver, final pathway for a wide varieties of chronic liver disease is a pathological entity defined as diffuse hepatic fibrosis with replacement of normal liver architecture by nodules.1 Transition from compensated asymptomatic cirrhosis to decompensated cirrhosis occur at rate of 5% to 7% per year.2 Patient with cirrhosis can develop extra-hepatic cardiopulmonary complication. Common cardiopulmonary complication includes hepatopulmonary syndrome (HPS), portopulmonary hypertension (PPHTN), hepatic hydrothorax and cirrhotic cardiomyopathy (CCM).3 Presence of these complication significantly increases morbidity and mortality in these patient. Being asymptomatic in initial stage are often ignored but early identification of these complication is associated with better management and improve survival and quality of life of patient. Various study showed that sizable proportion of patient with cirrhosis have cardiopulmonary complication but data are not uniform and we are lacking data regarding prevalence of these complication in our community. So this study will act as a bridge to large scale study in future along with early diagnosis and management of complications.

*Corresponding Author:
Dr. Rahul Pathak, MD, DM
Department of Gastroenterology
Maharajgunj Medical Campus
Tribhuvan University Teaching Hospital, Institute of Medicine
Email: dr.rahuliom@gmail.com
ORCID ID (Rahul Pathak: 0000-0002-9748-2717)
ORCID ID (Dinesh Koirala: 0000-0002-5556-2786)
ORCID ID (Susmita Gyawali: 0000-0001-5787-7354)

Methods

This was a hospital-based, descriptive, observational, cross sectional study conducted at Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine (IOM) and Manmohan Cardiovascular and Transplant Centre, Nepal. Patients attending Gastroenterology Ward and Out Patient Department of TUTH were included in the study for a period of 1 year. Ethical clearance for the study was obtained from the Institutional Review Committee (IRC) of IOM. Sample size was calculated by applying following formula: N= Z2 x P (1 – P)/D2. Sample size was calculated 81.

A total of 81 patients aged 16 years and above with a diagnosis of chronic liver disease (CLD) regardless of etiology meeting the inclusion criteria were enrolled in the study. Informed consent was taken from all the participants. A detailed history was obtained and physical examinations were conducted in all the patients. Demographic profiles, presenting features of CLD, stigmata of liver cirrhosis and laboratory and imaging results were noted in a pre-designed proforma. Patient with known cardiac disease like ischemic heart disease, congenital heart disease, rheumatic heart disease, hypertension etc. and patients taking medication which may lead to cardiomyopathy like cyclophosphamide, prednisolone, lithium, chlorpromazine, fluphenazine, haloperidol were excluded from the study. For the severity of the disease, we used Child Turcotte Pugh (CTP) score and Model for End-stage Liver Disease (MELD) score. A 12 lead ECG was taken and QTc was calculated using Bazzet's formula. Transthoracic contrast echocardiography was done. During echocardiography various parameters like systolic function, diastolic function, dimension of heart chambers were studied. Agitated 8ml of normal saline with 2ml of air was given via three way. If microbubbles appeared in the left heart in three to eight heart beats after its appearance in the right atrium, it signifies the presence of intrapulmonary shunting. All patients received standard of care treatment.

IBM SPSS Statistics version 20 and Microsoft excel 2016 were used for data entry and statistical analysis. Descriptive statistics were used for analysis. In descriptive statistics, frequencies, mean and standard deviation were computed.

Results

A total of 81 patients with a diagnosis of CLD meeting the inclusion criteria were enrolled in the study. The mean age of the patients included in the study was 52 years (SD±12.01). Majority of the patients were of middle adulthood age group (40 to 65 (n=52; 64.2%). The age distribution of the patients is represented in Figure 1.

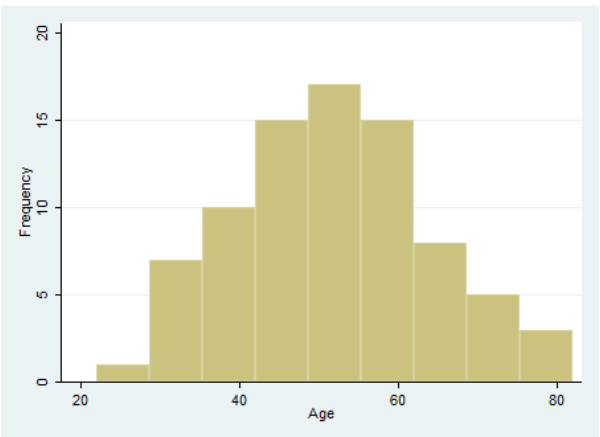

Figure 1. Histogram representation of age of patients (n=81)

Most of the patients (64.2 %, n=52) were male and 35.8% (n=29) were female. Table 1 shows that etiology for the liver cirrhosis in majority of cases was alcohol i.e. 75.31%.

Table 1. Distribution of the etiology of liver cirrhosis among patients (n=81)

Etiology of liver cirrhosis	Frequency	Percentage (%)
Alcohol	61	75.31
Non-alcoholic Steatohepatitis (NASH)	7	8.64
Hepatitis B	3	3.70
Hepatitis C	2	2.47
Hemochromatosis	2	2.47
Secondary Biliary Cirrhosis	2	2.47
Chronic Budd Chiari	1	1.23
Cryptogenic	3	3.70

Majority of the patients were of CTP C class (65.43%). CTP A and CTP B comprised 2.47% and 32.10% respectively. Table 2 shows MELD Na score distribution among these patients where maximum patients score ranged from 20-29.

Table 2. Table showing MELD Na score distribution among liver cirrhosis patients (n=81)

MELD Na score	Frequency	Percentage (%)
0-9	3	3.70
10-19	19	23.46
20-29	41	50.62
30-39	18	22.22

QTc interval was assessed in the patients which is depicted in Table 3. The table shows that 20.99 % of the male and 16.05% of female had prolonged QTc interval where cut off point for QTc interval was < 440 millisecond in male and < 460 millisecond in female. This demonstrated that 37.03% (n=30) of patient with cirrhosis of liver have prolonged QTc interval.

Table 3. Gender wise distribution of QTc interval among liver cirrhosis patients (n=81)

Sex	QTc interval	Frequency	Percentage (%)
Male	Normal	35	43.21
	Prolonged	17	20.99
Female	Normal	16	19.75
	Prolonged	13	16.05

On analyzing, there was no association between QTc interval and CTP score (p=0.06) at 5% level of significance. Also, there was no association between QTc interval and MELD Na score (p=0.1045) at 5% level of significance. Hence, QTc interval is statistically not associated with both CTP score and MELD Na score in liver cirrhosis patients. Regarding etiology, there was statistically significant association between QTc interval and alcohol related etiology of cirrhosis (p=0.04) at 5% level of significance.

Echocardiography was done in all patients which revealed reduced

ejection fraction in just 1.23% patients (n=1). However, diastolic dysfunction was present in 50.62% patients, among which most had grade I diastolic dysfunction (Table 4).

Table 4. Diastolic dysfunction based on echocardiography among liver cirrhosis patients (n=81)

Variables	Frequency	Percentage (%)
Normal	40	49.38
Grade I	35	43.21
Grade II	5	6.17
Grade III	1	1.23

On reviewing, there was no association between diastolic dysfunction and CTP class (p=0.06) and MELD Na score (p=0.69) at 5% level of significance. Similarly, there was no association between diastolic dysfunction and alcohol related etiology (p=0.94) at 5% level of significance. It was found that 8.64% (n=7) of patient have evidence of intrapulmonary shunt. But, there was no significant association between intrapulmonary shunt and CTP class (p=0.87) at 5% level of significance. However, there was statistically significant association between intra- pulmonary shunt and MELD Na score (p=0.01) at 5% level of significance but there was no association between intra pulmonary shunt and alcohol related etiology (p=0.8) at 5% level of significance. Also, there was no association between intra pulmonary shunt and esophageal varices (p=0.58) at 5% level of significance. Pulmonary artery pressure was evaluated in all patients which is shown in figure 2.

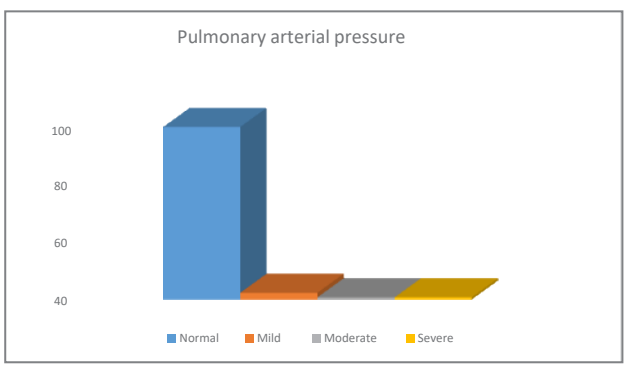

Figure 2. Columnar chart showing the distribution of pulmonary arterial pressure among liver cirrhosis patients (n=81)

On analyzing, there was no association between pulmonary arterial pressure and CTP class (p=0.37) and MELD Na score (p=0.58) at 5% level of significance. Also, there was no association between pulmonary arterial pressure and esophageal varices (p=0.65) at 5% level of significance. No abnormal dilation of cardiac chamber was found in 77.78% of the patients whereas 20.22% have abnormal left atrium and ventricle dilation.

Table 5. Dilated chamber findings based on echocardiography in liver cirrhosis patients (n=81)

Variables	Frequency	Percentage (%)
Not dilated	63	77.78
Left atrium dilated	17	20.99
Right Atrium/ Right Ventricle dilated	1	1.23

There was no association between dilated cardiac chamber and CTP class (p=0.40) and MELD Na score (p=0.49) at 5% level of significance. There was no association between dilated cardiac chamber and alcohol related etiology (p=0.73) at 5% level of significance.

Discussion

Cirrhosis of liver is one of the major public health problem in Nepal.4 Though complications of portal hypertension dominate clinical presentation of cirrhotic patients, cardiopulmonary complications are not uncommon in cirrhotic patients and contribute more than one fourth of cause of death in cirrhotic patients.

In this study, the mean age of the patients was 52 years ±12.01 years. Highest proportion of patient in middle adulthood group (40-65 years). Male is to female ratio was 1.79. A study done in Western Nepal by Tara Ballav Adhikari et al also revealed alcohol consumption frequency as well as amount was significantly higher among men than women and the highest proportion of patient in middle adulthood group (40-65 years).5

ECG abnormalities have been commonly seen in cirrhosis. Among which prolongation of QT interval is thought to reflect cardiac dysfunction secondary to cirrhosis through undetermined mechanism.6 In our study, we calculated the QTc interval of all patients using Bazett's formula after recording QT interval from leads II, V5 and V6, QT interval was measured from the beginning of QRS complex to the end point of T-wave and the longest interval was identified. We found that 30 patients (37.03%) out of 81 had prolonged QTc interval, which was significantly lower than what Lelili Pourafkari et al, found in their study.7 In our study we found that there was no statistically significant association between QTc interval and CTP class and MELD-Na score. Moreover, it was found that QTc interval prolongation can be found in early, well-compensated cirrhosis as well as late stages of the disease. This result can also be implicated in daily clinical practice as detection of prolonged QTc interval help clinician to think about cirrhotic cardiomyopathy even in early course of disease. However, there was statistically significant association between prolonged QTc interval and alcohol as etiology of cirrhosis of liver. Likewise, in a study by Bal et al., QTc prolongation was more commonly seen in patients with alcoholic cirrhosis (60%) as compared with non-alcoholic cirrhosis, and alcoholic etiology was an independent predictor of QT-interval prolongation.6

In our study, we studied various parameters like systolic function, diastolic function, dimension of heart chambers, pulmonary artery pressure and saline bubble contrast for evidence of IPVDs and intrapulmonary shunting during transthoracic contrast echocardiography. The most common cardiac abnormality that ocurs among cirrhotic patients is left ventricular diastolic dysfunction (LVDD) related to development of myocardial fibrosis, hypertrophy and sub endothelial edema.8 Diastolic dysfunction occurs when the passive elastic traits of the myocardium are reduced due to the increased myocardial mass and changes in the extracellular collagen.9 It is most commonly assessed by studying the diastolic trans-mitral flow pattern. An increased atrial contribution to late ventricular filling, leading to a reduced E wave to A wave ratio suggests Grade 1 diastolic dysfunction.10 In our study diastolic dysfunction was present in 41 patients (50.62%) out of 81 patients but there was no statistically significant association between diastolic dysfunction with CTP class, MELD Na score and alcohol as etiology of cirrhosis of liver, these finding were consistent with conclusion of systemic review done by Leva Stundiene et al.8 An association between liver disease severity and diastolic dysfunction and an improvement in diastolic dysfunction after paracentesis has also been reported.11 In a study done by Lee et al, the survival rate was substantially lower in patients with LVDD than in those without LVDD.12

In our study, only one patient had systolic dysfunction as measured by ejection fraction at rest. The normal or supra-normal ejection fraction in cirrhosis is due to hemodynamic changes in patients with cirrhosis. Even when the LV systolic function is normal at rest, cirrhosis patients are susceptible for cardiac failure under conditions of stress.3 This is due to the presence of under-recognized subclinical LV systolic dysfunction especially blunted response to stress. The presence of subclinical LV dysfunction carries prognostic significance, especially if the patient is a prospective candidate for hepatic transplantation.13 After liver transplantation, rapid hemodynamic changes may worsen preexisting congestive heart failure and almost 25% of patients undergoing liver transplant have high risk for postoperative pulmonary edema.14 Since we had not done stress echocardiography in our study, patients with subclinical systolic dysfunction may have been missed and explained the reason for very low incidence of systolic dysfunction.

A lower prevalence of positive bubble contrast test (8.65%) for intrapulmonary shunt, signifying presence of IPVDs and/or direct shunt was found in our study which was slightly lower than what Ferreira pp et al.15 Paul Roberto Pavarino et al gave three injections of agitated saline and was observed by two cardiologists at same time via transesophageal echocardiography (TEE) to increase the sensitivity of test.16 However, we gave only one injection of agitated saline and observed by only one cardiologist via transthoracic echocardiography. This may be one reason for lower prevalence of intrapulmonary shunting in our study. However, different studies have shown variable prevalence of hepatopulmonary syndrome ranging from as low as 4% to as high as 47%.17 Thus a larger scale study is required to establish the actual prevalence of the hepatopulmonary syndrome in our part of world. Presence of intrapulmonary shunting was not associated significantly with CTP class, size of esophageal varices and alcohol as etiology of cirrhosis, which was similar to study result found by Krowka MJ et al.18 However, there was statistically significant association between intrapulmonary shunting and MELD-Na score (P value = 0.01) in our study, this finding was similar to Kumar et al found in his study.19 The only effective treatment which can modify the syndrome's natural history is liver transplantation. Although it is usually asymptomatic, HPS imparts a high risk of pre-transplantation mortality, independently of the severity of liver disease. While there is variable data concerning survival rates after liver transplantation, comparing survival rates between cirrhotic patients with HPS and matched for the severity of liver disease by MELD and Child- Pugh score classification and age patients without HPS, who did not undergo liver transplantation, patients with HPS had a worse 5-year survival (23% vs 63%, P = 0.0003).20 So it is imperative to look for hepatopulmonary syndrome in patient with decompensated cirrhosis even in the absence of symptoms suggestive of HPS.

Using tricuspid regurgitant peak velocity that helps in estimating the right atrial pressure by inferior venacava changes on inspiration, and by using Bernoulli equation, estimates the right ventricular systolic pressure.21 We found that 5 patients (6.17%) had pulmonary arterial hypertension, out of which 3 patients had mild pulmonary artery hypertension, one had moderate and one had severe pulmonary hypertension. Presence and severity of portopulmonary hypertension was not associated significantly with severity of liver disease, as measured by CTP class, MELD-Na score. These results are consistent with the result of study done by Kawut SM et al.22 PPHTN causes progressive stress to the right ventricle, leading to right ventricular dysfunction, progressive chronic cor-pulmonale and eventually death. The degree of right ventricular dysfunction correlates highly with survival and mortality in patients with PPHTN.20 Because of the high mortality associated with attempting to perform liver transplantation in patients with severe PPHTN, which is related to hemodynamic instability, screening for PPHTN should occur before the liver transplantation procedure is planned. The single most important test to screen for PPHTN is the two dimensional transthoracic echocardiogram (TTE) as we have done in our study. Thus, it is recommended that TTE screening in all symptomatic patients with liver disease, and routinely as part of liver transplantation evaluation due to the high morbidity and mortality risk associated with performing transplantation in patients with PPHTN.21

Though all cardiac chambers may be dilated in cirrhotic patients, different studies showed that left atrial enlargement is most eminent one. Left ventricular diastolic dysfunction can lead to an elevation in left ventricular filling pressure, resulting in increased preload in the left atrium after left ventricle relaxation. The left ventricular filling pressure must be adjusted to meet the needs of increased atrial wall tension (resulting from increased thickness); moreover, the increases in left ventricular filling pressure may promote myocardial hypertrophy and result in left atrial enlargement.9 Prevalence of left atrial enlargement was 20.99% in our study which was lower than that of the study done by Xiaopeng Li et al (55%).3 Since our exclusion criteria excluded the patients with primary heart disease, the left atrial enlargement observed in our study reflects CCM-related left ventricular diastolic dysfunction and disruptions of left ventricular filling pressures.

Conclusion

Cirrhosis of liver is one of common presentation in department of Gastroenterology, TUTH. Alcohol was most common cause of cirrhosis of liver in Nepal. Although cirrhosis can present in all age group, it is common in young adulthood. Sizable proportion of patients with cirrhosis of liver have electrophysiological abnormality especially prolonged QTc interval (37.03%), systolic dysfunction (1.23%), diastolic dysfunction (50.62%), portopulmonary hypertension (6.17%), intrapulmonary shunting (8.64%) or dilated left atrium (20.99%). Most of these abnormalities, except for intrapulmonary shunting with MELD Na score and dilated left atrium with alcohol related etiology, have no statistically significant association with severity and underlying etiology of cirrhosis. Though patient may remain asymptomatic at rest, these cardiopulmonary complications can have significant implication in stressful events such as infection, TIPS and liver transplantation. So early detection of subclinical cardiac changes is important to reduce morbidity and mortality in cirrhotic patients. Since severity of cirrhosis of liver does not correlate well with presence or absence of underlying cardiopulmonary complications except for intrapulmonary shunting with MELD Na score, every patient with decompensated cirrhosis irrespective of severity of disease should be evaluated for cardiopulmonary complication. Being a non-invasive, real- time, rapid imaging technology with a high accuracy for diagnosing cardiac abnormalities, transthoracic contrast echocardiography is the method of choice for screening.

Conflict of interest: None declared.

References

1. Sharma A, Nagalli S. Chronic Liver Disease. StatPearls [Internet]. 2022; [Article]
2. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis q. J Hepatol. 2018;69(2):406–60. [Article]
3. Xiaopeng Li, Shanshan Yu, Lu Li, Donggang Han, Shejiao Dai YG. Cirrhosis-related changes in left ventricular function and correlation with the model for end-stage liver disease score. Int J Clin Exp Med. 2014;7(12):5751–7. [Article]

4. Shrestha SM. Liver Diseases in Nepal. Kathmandu Univ Med J. 2005;3(10):178–80. [Article]
5. Adhikari TB, Rijal A, Kallestrup P, Neupane D. Alcohol consumption pattern in western Nepal: Findings from the COBIN baseline survey. BMC Psychiatry. 2019;19(1):1–8. [Article]
6. Bal JS, Thuluvath PJ. Prolongation of QTc interval: Relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver Int. 2003;23(4):243–8. [Article]
7. Pourafkari L, Ghaffari S, Nazeri L, Lee JB, Masnadi-Shirazi K, Tajlil A, et al. Electrocardiographic findings in hepatic cirrhosis and their association with the severity of disease. Cor Vasa. 2017;59(2):e105–13. [Article]
8. Stundiene I, Sarnelyte J, Norkute A, Aidietiene S, Liakina V, Masalaite L, et al. Liver cirrhosis and left ventricle diastolic dysfunction: Systematic review. World J Gastroenterol. 2019;25(32):4779–95. [Article]
9. Piyush O. Somani, Qais contractor, Ajay S. Chaurasia PMR. Diastolic dysfunction characterizes cirrhotic cardiomyopathy. Indian Heart J. 2014;66(6):649–55. [Article]
10. Pompilio Faggiano, Enrico Vizzardi, Emanuela Pulcini, Diego Maffeo, Francesco Fracassi, Savina Nodari LDC. The study of left ventricular diastolic function byDoppler echocardiography: the essential for theclinician. Hear J. 2007;3(1):42–50. [Article]
11. Pozzi M, Carugo S, Boari G, Pecci V, De Ceglia S, Maggiolini S, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology. 1997;26(5):1131–7. [Article]
12. Soon Kyu Lee, Myeong Jun Song, Seok Hwan Kim and HJA. Cardiac diastolic dysfunction predicts poor prognosis in patients with decompensated liver cirrhosis. Clin Mol Hepatol. 2018;24:409–16. [Article]
13. Barman PM, VanWagner LB. Cardiac Risk Assessment in Liver Transplant Candidates: Current Controversies and Future Directions. Hepatology. 2021;73(6):2564–76. [Article]
14. Paolo Feltracco, Cristiana Carollo, Stefania Barbieri, Tommaso Pettenuzzo CO. Early respiratory complications after liver transplantation. World J Gastroenterol. 2013;19(48):9271–81. [Article]
15. Palmireno Pinheiro Ferrerira Edmundo José Nasri Camara, Rogério Luis Porto de Paula, Cláudio Celestino Zollinger, Andréa Ribeiro Cavalcanti PLB. Prevalence of hepatopulmonary syndrome in patients with decompensated chronic liver disease and its impact on short-term survival. Arq Gastroenterol. 2015;45(1):1–6. [Article]
16. Pavarino PR, Dos Reis Corbucci HA, De Marchi CH, Da Mata PF, Fernandes De Godoy M. Contrast echocardiography in the diagnosis of intrapulmonary vascular dilations in candidates for liver transplantation. Arq Bras Cardiol. 2004;82(6):515–22. [Article]
17. Soulaidopoulos S, Cholongitas E, Giannakoulas G, Vlachou M, Goulis I. Review article: Update on current and emergent data on hepatopulmonary syndrome. World J Gastroenterol. 2018;24(12):1285–98. [Article]
18. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: Results from a 10-year screening algorithm. Hepatology. 2006;44(6):1502–10. [Article]
19. Kapoor N, Mehta V, Singh B, Karna R, Kumar S, Kar P. Prevalence of cirrhotic cardiomyopathy and its relationship with serum pro-brain natriuretic peptide, hepatorenal syndrome, spontaneous bacterial peritonitis, and mortality. Indian J Gastroenterol. 2020;39(5):481–6. [Article]
20. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: Impact of liver transplantation. Vol. 41, Hepatology. 2005. p. 1122–9. [Article]
21. Filho VGM and BM. Echocardiography in Chronic Liver Disease: Systematic Review. Arq Bras Cardiol. 2013;100(3):376–85. [Article]
22. Steven M. Kawut, Michael J. Krowka, James F. Trotter, Kari E. Roberts, Raymond L. Benza, David B. Badesch, Darren B. Taichman, Evelyn M. Horn, Steven Zacks, Neil Kaplowitz, Robert S. Brown, Jr. MBF. Clinical risk factors for portopulmonary hypertension. Hepatology. 2008;48(1):196–203. [Article]