Cardiac Magnetic Resonance Evaluation of Patients with Cirrhosis Eligible to Liver Transplantation

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Summary

Background: Liver transplantation (LT) is a huge surgery performed to treat patients with advanced liver cirrhosis and is associated with several risks. For this reason, is necessary to stratify the risk in the pre-transplantation period through the evaluation of myocardial function and ischemia

Objective: To demonstrate the applicability of cardiac magnetic resonance (CMR) in cardiac morphologic and functional evaluation, as well use in the evaluation of myocardial ischemia in pre-transplantation.

Methods: Retrospective, descriptive study. Data from patients with cirrhosis referred to the liver transplant outpatient clinic from January 2014 to July 2016 were analyzed they underwent CMR for cardiac evaluation and as provocative test of myocardial ischemia.

Results: 135 patients were referred of these, 39 performed CMR. The mean age was 60 (50 to 71). About 87% (n = 34) were males. Alcoholic etiology prevailed 56% (n = 22). Most were of CHILD C patients with MELD ≥ 18, (n = 26). CMR showed myocardial ischemia in 03 patients (7,6%). Coronary angiography was performed and presence of severe coronary artery disease (obstruction > 70%) was confirmed, with consequent myocardial revascularization. At a follow-up of 2 years and 7 months, the survival of transplanted patients was 87%, without cardiologic complications.

Conclusions: The realization of CMR in the evaluation of cirrhotic patients in the pre-transplantation proved to be a safe strategy by showing presence of morphologic and functional changes of the cirrhotic cardiomyopathy and the presence of myocardial ischemia. However, more studies should be performed to standardize methods and criteria for cardiovascular evaluation in cirrhotic patients before the liver transplantation. (Arq Bras Cardiol: Imagem cardiovasc. 2017;30(4):119-125)

Keywords: Coronary Artery Disease; Liver Transplantation; Diagnostic Imaging; Magnetic Resonance Spectroscopy.

Introduction

Hepatic cirrhosis is associated with several cardiovascular abnormalities. Cirrhotic cardiomyopathy (CCM) is defined as the presence of a chronic cardiac dysfunction in cirrhotic patients in the absence of a known cardiac etiology, regardless of the etiology of liver cirrhosis.[1,2] These cardiac disorders are mediated by decreased adrenergic beta transduction, increased circulatory inflammatory cardiodepressor mediators and changes in repolarization.[1,2]

All of these abnormalities contribute to potential cardiac complications, especially in patients undergoing liver transplantation due to post-operative stress-induced hemodynamic abnormalities.[1]

CCM, still underdiagnosed, is characterized by diastolic dysfunction, electrical conduction abnormalities, chronotropic incompetence and attenuated systolic contractility in response to physiological abnormalities.[1,2] At rest, patients present increased cardiac output, hyperdynamic state, due to reduced peripheral vascular resistance (post-load) secondary to systemic vasodilation. The main findings in cirrhotic patients in terms of heart disease are increased QTc interval, left ventricular hypertrophy, left atrial enlargement, increased LV end diastolic diameter, diastolic dysfunction and LV systolic dysfunction during stress.[1,2]

It has been described since the 1960s, but was initially erroneously attributed to alcoholic etiology. Only a few decades ago, it was shown that cardiac dysfunction with attenuated stress response is associated with cirrhosis itself, rather than being one of the adverse effects of alcohol.[3,4] The criteria for CCM are described in Table 1.

A few types of imaging tests are used in the diagnostic evaluation of CCM and in the stratification of cardiac risk in the pre-transplantation period.[6]

Of these, cardiac magnetic resonance imaging (CMRI) is considered the gold standard for the assessment of left ventricular (LV) and right ventricular (RV) volumes, systolic function and myocardial mass. Late enhancement sequence in CMRI has the potential to demonstrate subclinical myocardial

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Table 1 – Diagnostic Criteria for Cirrhotic Cardiomyopathy

Diagnostic criteria for cirrhotic cardiomyopathy according to the World Conference of Gastroenterology held in Montreal in 2005
Systolic dysfunction
• Ejection fraction at rest EF < 55%
• Weak cardiac output increase after exercise or pharmacological stress testing
Diastolic dysfunction
• Ventricular filling ratio (E/A ratio) < 1 (corrected age)
• Deceleration time (DT) > 200 ms
• Isovolumetric relaxation time (IRT) > 80 ms
Support criteria
• Electrophysiological abnormalities with QT interval prolongation
• Abnormal chronotropic response
• Electromechanic decoupling
• Left atrial enlargement
• Myocardial mass increase
• Increased brain natriuretic peptide (BNP) and pro-BNP
• Increased troponin I

Source: Karagiannakis, 2014[5]

abnormalities (presence of myocardial fibrosis) before the start of LV systolic dysfunction. Besides this, CMRI has the unique ability to detect myocardial edema, which can be seen in acute myocardial injury.[7] CMRI can help differentiate normal, ischemic, infarcted (viable and non-viable) hearts.[8] It is a noninvasive method with no ionizing radiation, it is capable of offering diagnosis in the early stages of the ischemic cascade, before irreversible damage occurs to the myocardium, being accurate and efficient for the diagnosis of coronary artery disease (CAD) and evaluation of myocardial viability.[9]

Myocardial resonance then is an accurate diagnostic method both for the evaluation of cirrhotic cardiomyopathy and for the presence of ischemic disease in pre-transplant cirrhotic patients. Cardiac status should be evaluated until liver transplantation — to exclude patients who do not have the prerequisites (cardiac reserve) to assist in the preoperative and perioperative management of the transplant, minimizing major fluctuations in preload and afterload and consequent deaths due to cardiac causes: post-reperfusion syndrome, pulmonary hypertension and cardiomyopathy.[10,11]

This study included the evaluation of patients submitted to a pre-transplantation protocol using myocardial resonance imaging for cardiac evaluation, the results of which were associated with the post-transplant results.

Our primary objective was to demonstrate the applicability of CMRI in assessing cardiac function and determining the cardiac repercussion of the cirrhotic state, as well as to demonstrate its use in evaluating the presence of myocardial ischemia in the pre-transplantation period.

Methods

A retrospective, descriptive study was carried out and included collection of data from the electronic medical record (MV PEP), a non-digital system of tests and medical records (X clinic) of all cirrhotic patients referred to the liver transplantation (LT) outpatient clinic from January/2014 to July/2016.

Altogether, data from 135 patients were collected. Of these, 39 underwent CMRI for cardiac evaluation and as a provocative test of myocardial ischemia before the transplant. Among the patients who underwent CMRI, none were excluded.

Patients who did other tests (scintigraphy, stress echocardiogram, exercise test) and those with unavailable or incomplete data were excluded. According to the service protocol, only patients older than 50 are submitted to myocardial evaluation, or older than 40 with risk factors for cardiovascular disease.

The following variables were analyzed: - magnetic resonance imaging: MV and LV dimensions and volumes, LV and RV systolic function, mass, late enhancement for fibrosis and myocardial necrosis, and ischemia. In addition, we describe demographic data (age, sex), etiology of cirrhosis, MELD (Model for End-Stage Liver) on transplantation, comorbidities, renal function and hepatorenal syndrome, in addition to post-transplant data: ICU stay, amine time, sepsis, multiple blood transfusions, cardiac events, hemodialysis and any surgeries undergone by these patients.

These data were compared to data found in the literature. The database used for literature research was PubMed.

Results

Once the patients who did not any meet criteria for the research were excluded, 39 patients underwent cardiac myocardial resonance imaging as a test for cardiac evaluation before the transplant. Of these, 58.9% (n = 23) underwent liver transplantation.

Following the service protocol, all patients older than 50 — or older than 40 with risk factors for coronary disease – eligible for liver transplantation were referred for transthoracic echocardiography, electrocardiography, chest X-ray and ischemia screening, which could be: dobutamine stress echocardiography, perfusion myocardial scintigraphy with dipyridamole stress, exercise test or CMRI. The decision to perform one or another test depended on the availability of the test in the city of origin, health insurance (Public Health System and other private health insurances) or on whether the tests were conducted while the patient was in hospital or at the outpatient clinic. There was no clinical criterion to define which patient would undergo CMRI; all patients who conducted the protocol upon admission underwent CMRI, preferably.

The average age of patients was 60 (ranging from 50 to 71). About 87% (n = 34) were males and 38.5% (n = 15) of the patients had diabetes and SAH.

The etiologies of liver cirrhosis in the patients of this study were: alcohol abuse, 56% (n = 22); hepatitis C (HCV), 18% (n = 7); cryptogenic etiology and NASH, 10% (n = 4) and the others had 1 case each, as shown in the chart below (Figure 1). Of these patients, 38.5% (n = 15) had associated hepatocellular carcinoma (HCC) that motivated the indication of transplantation. The most common association was alcohol abuse 40% (n = 6) and hepatitis C 27% (n = 4) with HCC (Figure 2).

The patients' MELD score ranged from 8 to 36 (mean of 18). Patients with the lowest MELD score generally corresponded to those with exception criteria, such as hepatocellular carcinoma and refractory ascites, who got scores while in line due to a special situation as provided in the Brazilian legislation. Most of them were CHILD C patients with MELD ≥ 18: n = 26 (66.6%).

Patients had the following complications during follow-up: 38.4% (n = 15) gastrointestinal bleeding, 20.5% (n = 8) repetitive ascites, 18% (n = 7) developed hepatorenal syndrome, n = 3 type I; 15% (n = 6) encephalopathy, 10% (n = 4) sepsis, mostly due to SBP; and others. In a follow-up of up to 2 years and 7 months, of the 23 transplanted patients, (n = 3) patients died, and of the 16 pre-transplant patients, (n = 5) died, with a survival rate of 68.8%. The main causes of death in this group were sepsis and hepatorenal syndrome.

Regarding the results found in the CMRI, the main findings are shown in Table 2. An analysis of the table shows that, on average, the patients presented normal ventricular dimensions, mass and systolic function, both men and women. In addition, both sexes also showed a significant increase in heart rate after the injection of dipyridamole (> 20%).

Delayed enhancement sequence revealed septal subendocardial fibrosis in one patient (2.5%, n = 1). This patient had a history AMI.

7.7% (n = 3) patients presented CMRI positive for ischemia and all were confirmed with CAD after coronary angiography.

One patient presented LV morphofunctional abnormalities on CMRI: VE with increased dimensions (LVEDD: 6.8 mm; LVESD: 6.1 mm; LVEDVi: 161 ml/m^2; LVESVi: 105 ml/m^2), severe diffuse hypokinesia, left atrial enlargement (LA: 55 ml/m^2), severe systolic dysfunction (LVEF%: 34) and moderate RV systolic dysfunction (RVEF%: 43). The abnormalities were interpreted as possibly related to the cirrhotic state or secondary to previous alcoholism. In this patient, transplantation was contraindicated, both due to the overall condition of the patient with other comorbidities and to the diagnostic doubts as to alcoholic cardiomyopathy.

Two of the patients with CAD after CMRI and coronary angiography (treated prior to transplantation) were submitted to transplantation, without any cardiac events immediately after the transplant.

In the immediate postoperative period of liver transplantation, 8.6% (n = 02) of the patients presented symptoms suggestive of the Takotsubo's syndrome, one of which had been submitted to MRI and the other to stress echocardiography and exercise test. All of the tests were normal. These patients underwent coronary angiography to investigate the case, without evidence of coronary obstruction.

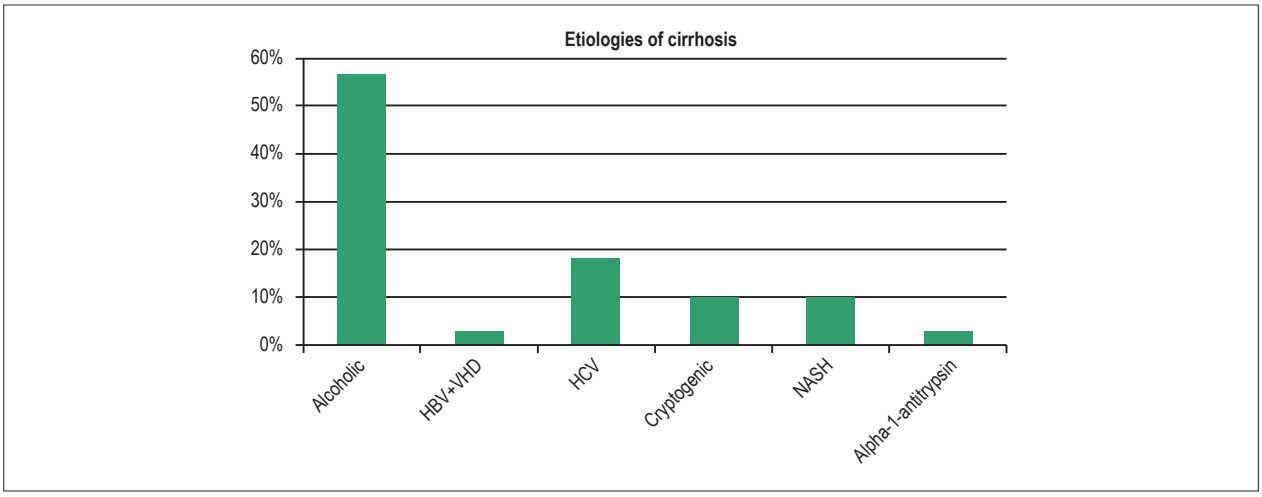

Figure 1 – *Prevalence of etiologies of cirrhosis in patients evaluated for transplant in the research sample. HBV: Hepatitis B virus; VHD: Hepatitis D virus; NASH: Nonalcoholic steatohepatitis; HCV: Hepatitis C virus; Alpha-1-antitrypsin deficiency.*

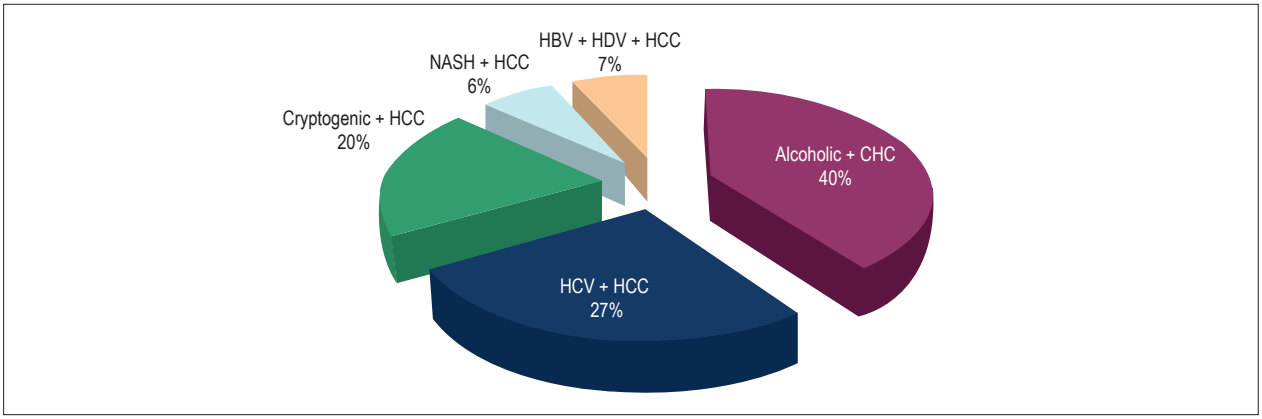

Figure 2 – *HCC patients referred for transplant. HBV: Hepatitis B; HDV: hepatitis D; HCC: hepatocellular carcinoma; NASH: Nonalcoholic steatohepatitis; HCV: hepatitis C.*

Table 2 – Findings of cardiac magnetic resonance imaging (CMRI) in cirrhotic patients before transplant

	Men			Women		
	Value (mean)	SD	RV	Value (mean)	SD	RV
Parameters						
IVS	1.0	0.2	0.7 - 1.2	0.9	0.2	0.7 - 1.2
LVEDD	5.0	0.7	3.7 - 5.3	4.8	0.8	3.7 - 5.3
LVESD	3.0	0.8	2.6 - 3.9	3.0	1.2	2.6 - 3.9
LVEDVi	73.6	24.0	57 - 105	73.1	33.0	56 - 96
LVESVi	25	17.6	14 - 38	27.1	27.8	14 - 34
LVMi	61.2	12.0	49 - 85	59.6	12.5	41 - 82
LVEF%	67.6	10.7	57 - 77	64.2	13.4	57 - 77
RVEDVi	63.5	15.8	61 - 121	58.8	12.1	48 - 112
RVESVi	21.8	9.2	19 - 59	21.0	11.1	12 - 52
RVEF%	65.9	8.5	55 - 72	62.7	11.6	51 - 71
%RHDIPY	21.8	13.6	> 20%	25.1	12	> 20%

IVS: interventricular septum (mm); LVEDD: left ventricular end-diastolic diameter (mm); LVESD: left ventricular end-systolic diameter (mm); LFEDVi: left ventricular end-diastolic volume index (ml/m^2); LVESVi: left ventricular end-systolic volume index (ml/m^2); LVMi: left ventricular mass index (g/m^2); LVEF%: left ventricular ejection fraction; RVEDVi: right ventricular end-diastolic volume index (ml/m^2); RVESVi: right ventricular end-systolic volume index (ml/m^2); RVEF%: right ventricular ejection fraction; %RHDIPY: % heart rate increase after dipyridamole infusion; SD: standard deviation; RV: reference value.[12]

Both progressed with improved cardiac condition while at the hospital. One of these patients died after about 3 months due to other complications (one of them being sepsis) and the other one remained in good clinical condition.

The patients' stay at the intensive care unit was 11 days on average, with a median of 5 (maximum of 113 days, 1 patient only), with mean amine time of one day.

Of the 6 patients who developed sepsis (26%), two also presented cardiac events — Takotsubo's syndrome and renal dysfunction, one requiring dialysis. Major bleeding and coagulation disorder occurred as surgical complications in 26% (n = 6) of the patients, who also had multiple blood transfusions.

Discussion

The main finding of this study was the demonstration of the safety and efficacy of CMRI as a diagnostic method for cirrhotic cardiomyopathy and as a screening test for myocardial ischemia in patients with cirrhosis who will undergo liver transplantation.

Liver transplantation is associated with increased short-and long-term cardiac morbidity.[13] However, it is the only effective therapy for end-stage liver disease and heart failure.[2] It has been demonstrated that liver transplantation can reverse systolic and diastolic dysfunction and QT interval increase after transplantation.[2,14,15]

CMRI is an accurate diagnostic method for assessing cardiac function, as reported in the literature. It can identify the consequences of hyperdynamic circulation and reduced systemic vascular resistance of end-stage cirrhotic patients, in addition to determining the presence of coronary artery disease.[16,17] Therefore, a useful tool to exclude patients with cardiovascular issues and pre and post-surgical planning with circulatory stress management caused by liver transplantation.[16,17]

In our group of patients, only 1 patient (2.5%) was diagnosed with cirrhotic cardiomyopathy: he presented LVEF of 34%, RVEF of 43%, and increased LV volume and mass. Only 7.7% (n = 3) had coronary artery disease. The protocol used for the CMRI scans was perfusion with gadolinium during stress with dipyridamole (0.84 mg/kg/4 min) and at rest after reversal with aminophylline. Studies show that at least one chronic coronary artery lesion occurs in 5% to 26% of all asymptomatic liver transplant candidates.[6,18] Up to 50% of patients with significant CAD will die in the perioperative period from cardiac complications.[6,18,19] Our prevalence of CAD is consistent with the literature and has been confirmed by dipyridamole stress test, although studies have reported that dobutamine is better than vasodilators such as adenosine or dipyridamole to induce ischemia in cirrhotic patients, with good negative predictive value.[20,21]

Myocardial ischemia investigation in patients with severe hepatopathy can be performed by dobutamine stress echocardiography or using a coronary vasodilator drug (dipyridamole or adenosine) causing areas of myocardial hypoperfusion. The latter method is questionable in this population[21] considering that liver disease patients already have a state of systemic and coronary vasodilation secondary to the release of mediators such as nitric oxide, which lead to splanchnic vasodilation and cardiac hyperflow.[11] Thus, it is not known whether dipyridamole or adenosine would cause additional coronary vasodilation and, therefore, infusion disorder. Bhutani S. et al.22 reported low sensitivity of 62% in severe CAD with stenosis > 70% and 54%, with 50% stenosis using adenosine.

In addition, liver disease patients are unable to achieve the target heart rate, either by activation of the sympathetic nervous system with post-synaptic desensitization of β-adrenergic receptors in the sinoatrial node, or by frequently using beta-blockers. [11] One of the indirect ways of inferring the vasodilatory action of dipyridamole during the provocative ischemic test is by raising the heart rate after infusion (reflex tachycardia). An increase of more than 20% is used as a criterion to indicate dipyridamole action. In the studied patients, the men presented an increase of 21.8% (± 13.6%) and the women, 25.1% (± 12%). This finding is an indirect indication that there has been vasodilation caused by dipyridamole in the patients studied and contributes to decreasing the uncertainty regarding this provocative stimulus.

The average age of patients was 60. Transplants are increasingly performed in older patients with multiple comorbidities, which increases the risk of cardiovascular complications.[1] Age >50, male sex, diabetes, and obesity are common risk factors for coronary artery disease on liver transplantation and add up.[16] In our study, most of the patients were males and diabetes mellitus was present in 38% of the patients. In addition, the diagnosis of non-alcoholic steatohepatitis (NASH) independently increases the risk of CAD,[23] and was one of the etiologies of cirrhosis in the reported patients.

Another point to be discussed is the association between the severity of hepatic cirrhosis, measured by scores such as MELD and Child-Pugh, and worse cardiac outcomes (LV systolic and chronotropic dysfunction, diastolic dysfunction).[11] According to Baik et al.,[25] "at least one characteristic of cirrhotic cardiomyopathy is present in patients who achieved Child-Pugh > 8 points." [24,25] Most patients had MELD ≥ 18 and were Child C, justifying an accurate cardiac evaluation.

Studies suggest that cirrhotic cardiomyopathy is an important determinant in the pathogenesis of hepatorenal syndrome (HRS).[3] Circulatory dysfunction and abnormal activation of the systemic and renal neurohormonal regulation lead to HRS in approximately 20% of advanced cirrhotic patients.[26] In contrast to the literature, in all patients with HRS (18%, n = 7), cirrhotic cardiomyopathy criteria were identified. In this context, underdiagnosis is still questioned.

CMRI is a very effective instrument for investigating patients prior to procedures such as LT and placement of transjugular portosystemic intrahepatic shunt (TIPS).[16] There is overload of the cardiocirculatory system during these procedures. Immediately after LT, preload abnormalities occur, as well as after fluid infusion and vena cava blockade, and the heart of CCM patients is unable to respond to this condition.[13] Studies show that pulmonary edema rates occur in 56% of TH receptors after surgery, hemodynamically significant arrhythmias in 27%, and congestive heart failure in up to 5.6%.[27]

Therefore, previous cardiac evaluation is essential. In our study, all patients underwent CMRI with the main objective of pre-transplantation ischemic evaluation. Due to the ability to evaluate parameters such as cardiac morphology, function, myocardial tissue characterization and vascular flow, it was also possible to evaluate myocardial functionality and identify one patient with cardiomyopathy who could not be transplanted. CMRI has proven to have high diagnostic and prognostic performance in CAD, according to the literature[9], as the patients were evaluated, managed and there were no intercurrences related to coronary obstruction in the immediate post-transplant period. Even with 26% of the patients presenting massive bleeding and having undergone multiple blood transfusion.

Finally, two patients presented stress-induced cardiomyopathy — Takotsubo, with no cardiovascular abnormalities previously demonstrated. In fact, up to the present moment, there are no identified predictors of this pathology, but a series of theories about the pathophysiology of which one of the triggers would be stress,[28,29] which makes our results consistent with the literature.

The performance in the analysis of the variables, with excellent results shown in table 2 above, were reproducible in the transplant results, with no cardiac intercurrence and 87% survival in the study period of up to 2 years and 7 months.

Conclusion

Hepatic cirrhosis is a systemic disease and, particularly in more advanced stages, it presents significant involvement of the cardiovascular system.[3] Cirrhotic cardiomyopathy and ischemic diseases are part of this spectrum. Identification of CCM based on well-defined parameters is necessary, as it may be a subclinical condition during the natural course of cirrhosis and is an independent risk factor for various cirrhotic complications such as hepatorenal syndrome.[3]

During the analysis of 39 CRMIs, we observed that cirrhotic patients presented normal ventricular volume, mass and systolic function, as well as adequate chronotropic response after injection of dipyridamole, according to protocols pre-established for the test, showing that it is suitable for ischemic evaluation in this group of patients. However, new protocols with specific stress tests and updated diagnostic parameters are fundamental, mainly for the diagnosis of CCM.

Of the 3 patients who presented ischemic abnormalities, one could be safely ineligible for transplantation; the other 2 had diagnosis confirmed by coronary angiography and were previously treated, successfully undergoing LT, showing that CMRI was safe in the pre-transplant evaluation of these patients. Studies have shown high prevalence of asymptomatic CAD in cirrhotic patients candidates for transplantation.[30] The presence of CAD contributes to post-transplant outcome and cardiovascular complications are the main cause of mortality after transplantation. CMRI also proved to be an effective noninvasive method in this diagnosis.[3]

Therefore, further studies should be performed to standardize methods and criteria for cardiovascular evaluation in cirrhotic patients through CMRI in order to maximize their diagnostic potential in this group of patients.

Authors' contributions

Research creation and design: Ribeiro JA, Reis PP, Falquetto EB, Andrade AMF; Data acquisition: Ribeiro JA, Reis PP; Data analysis and interpretation: Ribeiro JA, Reis PP, Falquetto EB, Andrade AMF; Statistical analysis: Ribeiro JA, Pinto PVA, Falquetto EB; Manuscript drafting: Ribeiro JA, Falquetto EB, Andrade AMF; Critical revision of the manuscript as for important intellectual content: Ribeiro JA, Reis PP, Falquetto EB, Andrade AMF.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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Academic Association

This study is not associated with any graduate programs.

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