SPLENIC ARTERY SYNDROME AFTER LIVER TRANSPLANTATION – PREDICTIVE FACTORS: EXPERIENCE OF A CENTER

SÍNDROME DA ARTÉRIA ESPLÊNICA APÓS TRANSPLANTE HEPÁTICO – FATORES PREDITIVOS: EXPERIÊNCIA DE UM CENTRO

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ABSTRACT

Splenic artery syndrome (SAS) is described as a decrease in hepatic artery (HA) flow associated with increased flow in the splenic artery (SA). The present study aim was to identify predictive factors of SAS. A retrospective study was conducted in 70 patients, undergoing liver transplantation (LT) between 03/2010 until 08/2016. The case group (n=27) corresponded to the patients who developed SAS and the control group (n=43) to the patients who didn't develop. The donor, recipient and graft variables were collected. Significant differences were observed in relation to spleen volume 1137,4±512,9) cm^3 vs 523,9±258,1cm^3, spleen volume/liver volume ratio 0,9±0,3 vs 0,4±0,2, difference in caliber between SA and HA 2,1±1,6mm vs 0,8±1,5mm, and the ratio between spleen volume and body mass index (BMI) of the recipient 47,9±24,5 vs 18,9±8,8 between the case and control group respectively. In case group the mean difference between pre-embolization and post-embolization resistive index (RI) was 0.2±0.1, which demonstrates a significant improvement after embolization of the SA ($p<0.001$, CI: 95% 0.11-0.25). In logistic regression, the retained variable was only the spleen volume ($p<0.05$), and the cut-off point was 1023.9 cm^3. It's possible to conclude that spleen volume is a risk factor for SAS. It's also important to note that significant differences between groups were evident in relation to the ratio spleen volume/liver volume and difference in caliber between SA and HA in the pre-LT. In this sense, it's relevant in future studies to develop a prospective methodological design in order to analyze the predictive value of these variables.

Key words: *Liver Transplant; Splenic Artery; Embolization; Vascular Diseases.*

ABBREVIATIONS

BMI – Body Mass Index;
BSAi – Body Surfasse Area index;
CHUC – Hospital and University Center of Coimbra;
CT – Computerized Tomography;
GRWR – Graft to recipiente weight ratio;
HA – Hepatic Artery;
LT – Liver Transplantation;
RI – Resistive Index;
SA – Splenic Artery;
SAE – Splenic Artery Embolization;
SAS – Splenic Artery Syndrome

INTRODUCTION

Splenic artery syndrome (SAS) is one of the arterial complications that occur after liver transplant, and it is described as a decrease in hepatic artery (HA). This phenomenon is still unclear and controversial[1], however, it is responsible for non-hypoperfusion hepatic artery occlusion after liver transplant. SAS is an underdiagnosed condition with an estimated incidence of 0.6% to 10.1%[2-5], however there are no established diagnostic criteria. The clinical reasoning for the evaluation of the risk of the patients to develop this phenomenon is focused in clinical, laboratory and imaging findings. In recent years, the diagnosis of SAS has been confirmed by a significant improvement in HA flow after SA embolization[3-6].

Regarding the treatment, there are two modalities: prophylactic treatment performed during transplantation, which consists of ligation of the SA and the treatment performed after liver transplant that it is usually translated by the splenic artery embolization (SAE). SAE[7] is the treatment performed, most of the time but it is also possible to resort to occlusion of the SA by balloon and surgical techniques[3]. Although prophylactic treatment allows a reduction of complications, it is an intervention that is not risk-free, since it prolongs surgical time, associating with infarct areas in the spleen and increases the risk of pancreatic complications[2,8]. Therefore, it is urgent to identify the patients with higher risk of developing SAS to promote the prevention. This retrospective clinical investigation aimed to identify possible factors that predispose to the appearance of this phenomenon in transplanted patients. The information resulting from this study may contribute to the improvement of decision making for prophylactic treatments, based on the identification of risk variables.

METHODS

Retrospective study based on information from patients over 18 years of age who underwent liver transplantation (LT) at the Hospital and University Center of Coimbra (CHUC) between March of 2010 until August of 2016. The case group (n = 27) corresponded to individuals who developed SAS and control group (n = 43) to those who did not develop. Patients that realized ligation of SA during LT were excluded. Recipient, donor and graft variables was obtained. With the use of computerized tomography (CT) images, the volume of the liver, spleen volume, and SA and HA caliber was calculated. The vessel gauge (SA and HA) was measured using sectional studies after administration of intravenous contrast. The volume of the spleen and liver were calculated by volumetric sectional imaging studies, and the volumes were made using Osirix Lite 7.0.4 software. The data collected were grouped according to the characteristics of each variable, based on classifications described in the literature, the ratios (spleen volume/liver volume, spleen volume/recipient BMI, caliber of the SA/HA) and the difference in size between SA and HA were calculated. The data treatment was performed using SPSS statistical software, version 22. The statistical analysis considered a level of significance of 5%.

In order to identify possible predictive factors in the development of SAS, *Stepwise Backward Conditional logistic regression* will be performed. In the Univariate analysis, a significance value of $p > 0.250$ will be considered, in order not to exclude relevant variables.

RESULTS

Between 1st of March of 2010 until 31st of August of 2016, 370 patients were transplanted in CHUC, 70 of whom were excluded because they were transplant patients of pediatric age and 5 by embolization of SA. Of the non-excluded transplant patients (n = 295), 27 (9.2%) developed SAS.

Graft receptor

The case group (n = 27) and the control group (n = 43) were composed mainly of males. Regarding the variable points in the MELD score, the mean in the case group was 18.1(±5.3) versus 17.3 (±9.3) in the control group, revealing no significant differences between groups (p=0.62). Regarding the causes of transplantation, in the case group 33.3% occurred for cirrhosis (22.2% alcoholic and 11.1% viral), 29.6% due to hepatocellular carcinoma and 37% other causes. In the control group, 34.9% occurred due to cirrhosis (30.2% alcoholic cirrhosis and 4.7% viral cirrhosis), 32.6% for hepatocellular carcinoma and 32.6% for other causes. As for the ratio of the donor's body surface to the body surface of the recipient (BSAi), the mean was 1.0 (±0.1) and 1.2 (±0.1) in the case group and control respectively, and there were no significant differences between groups (p=0.70).

Computer Tomography

Regarding the SA caliber variable, in the cases the mean was 7.4 (±1.1) mm. In the control group the mean was 6.2 (±1.3) mm. The mean of the HA variable was 5.1 (±0.8) mm in the cases versus 5.6 (±1.4) mm in the control group. As regards the variable difference between SA and HA, in cases, the value mean was 2.1 (±1.6) mm, whereas in the control group it was 0.8 (±1.5) mm, revealing significant differences between groups (p=0.012, CI: 95% 0.3 – 2.3) (Figure 1). In the case group, the mean of the ratio between SA and HA caliber was 1.5 (±0.4) and in the control group was 1.2 (±0.3), revealing significant differences between the groups (p=0.015).

As to the variable spleen volume, the mean was 1137.4 (±512.9) cm^3 vs 523.9 (±258.1) cm^3 in the case and control group, respectively, with differences significant (p<0.001). In relation to liver volume, in cases the mean volume was 1489.2 (±480.2) cm^3, whereas in the control group it was 1492.6 (±354.1) cm^3, there is no significant difference (p=0.87, CI: 95% –258.7-251.9). As for the ratio spleen volume/ liver volume, the mean was 0.9 (±0.3) in the case group and 0.4 (±0.2) in the control group, revealing significant differences between the groups (p=0.018) (Figure 1).

The mean of the variable ratio between spleen volume and recipient BMI was 47.9 (±24.6) and 18.9 (±8.8) in the case and control group, respectively. Regarding this ratio, there were significant differences between groups (p<0.001 CI: 95% 20,7 –42,9) (Figure 1).

EcoDoppler

The mean of the variable difference between pre-embolization RI and post-embolization was 0.2 (±0.1). The results showed significant differences between RI before and after embolization of the SA (p<0.001, CI: 95% 0.1-0.2), indicating an improvement in the clinical picture.

Graft

Regarding the ratio between graft and recipient weight (GRWR), the mean was 0.02 (±0.005) corresponding to 2.1% and 0.02 (±0.005) corresponding to 2.0% in the case group and control respectively, with no significant differences (p=0.55). The treatment of SAS by embolization of SA, taking into account the median and excluding outliers, occurred on the 5th day after transplantation, with the minimum value was 2 days and the maximum of 87 days.

Logistic regression

In the logistic regression, the variables with clinical plausibility were inserted, namely: spleen

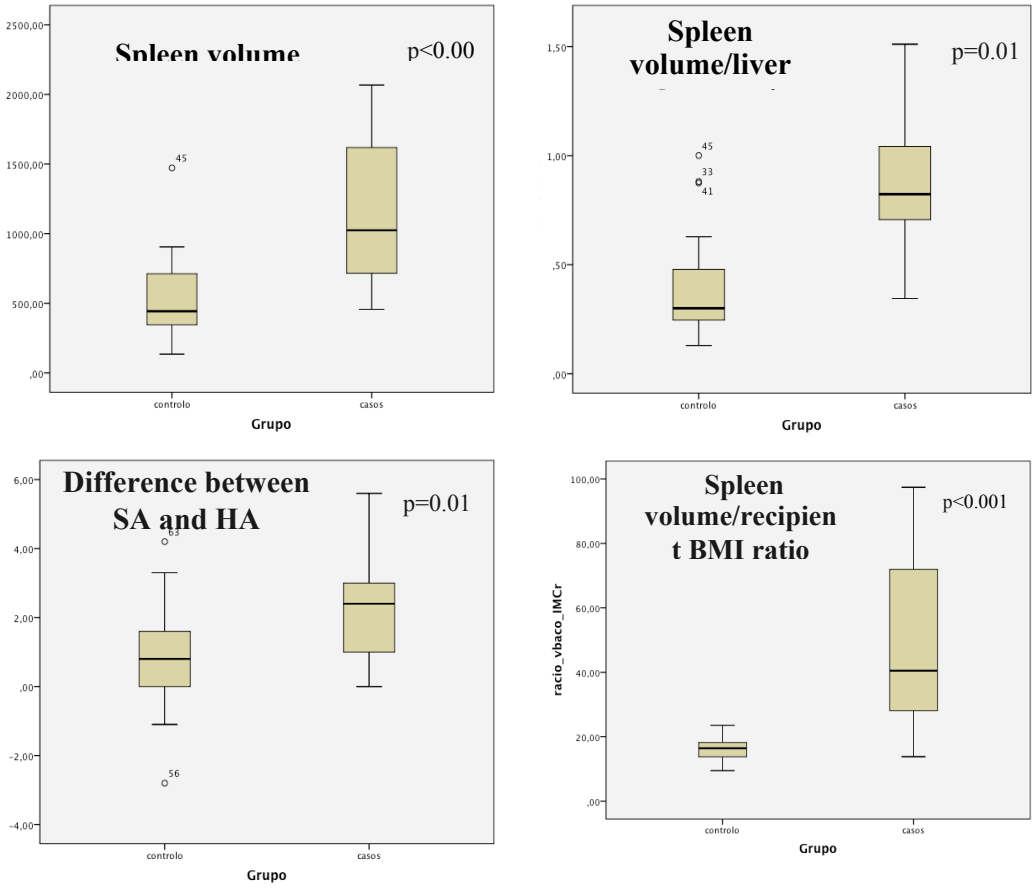

Figure 1 – **Comparison between case and control group variable.**

Table 1 – **Comparison between case and control group variable.**

	Case group	Control group	P Value
Spleen volume	1137.4 (±512.9)	523.9 (±258.1)	←0.001
Spleen volume/liver volume ratio	0.9 (±0.3)	0.4 (±0.2)	0.018
Difference between SA and HA	2.1 (±1.6)	0.8 (±1.5)	0.012
BSAi	1.0 (±0.1)	1.2 (±0.1)	0.702
SA/HA ratio	1.5 (±0.4)	1.2 (±0.3)	0.015
GRWR	0.02 (±0.005)	0.02 (±0.005)	0.553
Spleen volume/ receptor BMI ratio	47.9 (±24.6)	18.9 (±8.8)	←0.001
Native Liver volume	1489.2 (±480.2)	1492.6 (±354.1	0.871
Score MELD	18.1(±5.3)	17.3 (±9.3)	0.616

Subtitle: BMI – Body Mass Index; BSAi – Body Surfasse Area index; GRWR – Graft to recipiente weight ratio; HA – Hepatic Artery; SA – Splenic Artery.

volume, ratio of spleen volume/liver volume, difference between the SA and the HA and the ratio of the donor and recipient body surface.

In the univariate analysis all variables were included, revealing that the variable ratio between body surfaces is not associated with the development of SAS ($p<0.250$). Thus, the multivariate analysis included the variables of the spleen volume, difference size between SA and HA and ratio between spleen volume and liver volume.

In the final model, only the variable retained was the spleen volume ($p<0.05$). A volume of the larger spleen is associated with an increased risk of developing SAS. The cut-off point was estimated from the area of the ROC curve, with an accuracy of 87.6%, for a sensitivity of 50% and specificity of 97%, was 1023.9 cm^3.

DISCUSSION

The phenomenon of SAS is still poorly documented and clarified, however, incidence valor are beginning to gain prominence due to the clinical consequences for the sickness and health expenditures. The incidence of splenic artery syndrome in this study was 9.2%, and this result is in line with the results published in studies incidence values on the order of 0.6 to 10.1%[3, 5, 9]. Given a difficulty to recognize the clinical indicators for the diagnosis of SAS, the number of days until diagnosis is an important variable to be analyzed, considering the clinical repercussions of the same. According to the results of the literature published, most SAS patients are diagnosed in the first 2 months after transplantation[7]. Considering the results of the present study, we can observe that 50% of the patients who developed SAS were diagnosed and the 5th day after transplantation. In relation to these results, we can infer that the diagnosis of SAS in this center occurs mostly in an immediate post-transplant phase. However, in the context of this study, the clinical and economic repercussions of the diagnosis at different times cannot be inferred. Graft weight ratios on receiver weight (GRWR) of less than 0.8% are associated with an increased risk of graft dysfunction[7, 10]. In this study, in both groups, this ratio presented higher values, fulfilling the requirements to avoid graft dysfunction.

In this study, it was verified that the spleen volume and the spleen volume/liver volume ratio of the pre-transplant period were higher in the group of cases when the control, which meets the published literature[11]. According to a study by *Grieser C.* values of spleen volumes greater than 829 ml had 75% accuracy for the development of SAS[12, 3, 8]. In the present study, logistic regression results allow us to conclude that spleen volume is a risk factor for SAS development, the greater spleen volume higher the possibility of the patients develop SAS. It was found cut-off a spleen volume of 1023.9 cm^3, for sensitivity of 50% and specificity of 97%, from which the risk of developing SAS increases.

According to previous studies, an SA caliber higher than HA is associated with an increased risk for the development of SAS[7]. In the present study, it was concluded that SA was superior to AH in all patients in the group of cases for whom the measurement was possible. Although significant differences were found between the calibers of the arteries and spleen volume/liver volume ratio between case and control group, these variables were not verified as a predictive factor.

It was possible to conclude that the MELD score, liver volume and BSAi were not statistically significant and were not associated with a higher risk of developing the complication. Taking into account the published literature[12], graft dysfunction can be influenced by the ratio between the donor's body surface and the body surface area index (BSAi). BSAi of less than 0.78 or greater than 1.24 presents a greater risk for graft dysfunction[12]. In the presence of BSAi less than 0.78, vascular resistance is increased, which may alter the fluxes and aggravate

ischemia/reperfusion injury. In the present study, the mean of the BSAi variable was 1.0 (± 0.1) and 1.2 (± 0.1) in the case and control group, respectively, being within the considered adequate values (12) (0,78-1,24) to avoid graft dysfunction.

As to the cause of liver transplantation, there were significant differences in the frequency of liver transplantation due to cirrhosis of viral cause between the case group and the control group. This result has not yet been reported in any of the referenced studies, however, the higher frequency of liver cirrhosis due to viral cirrhosis in the group of cases is highlighted.

LIMITATIONS OF THE STUDY

This study was a retrospective, non-randomized study consisting of a heterogeneous population with a small number of patients. The heterogeneity of the clinical record conditioned the categorization of the variables. Given the nature of the present study, there was a high rate of missing values, limiting statistical analysis, particularly in logistic regression.

In conclusion, the results of this study demonstrate that spleen volume seems to be a risk factor for the development of SAS. The present study also allows us to conclude that the spleen volume/liver volume ratio, the difference of size between SA and HA, the ratio between SA and HA and the ratio of spleen volume to BMI of the recipient, in pre-transplantation, presented differences between the group of cases and controls. Beyond also demonstrated that embolization of the splenic artery is an effective treatment for this complication in this series.

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