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ORIGINAL PAPERS

The utility of the macro-aggregated albumin lung perfusion scan in the diagnosis and prognosis of hepatopulmonary syndrome in cirrhotic patients candidates for liver transplantation

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ABSTRACT

Background: The macro-aggregated albumin lung perfusion scan (^{99m}Tc-MAA) is a diagnostic method for hepatopulmonary syndrome (HPS).

Aim: To determine the sensitivity of ^{99m}Tc-MAA in diagnosing HPS, to establish the utility of ^{99m}Tc-MAA in determining the influence of HPS on hypoxemia in patients with concomitant pulmonary disease and to determine the correlation between ^{99m}Tc-MAA values and other respiratory parameters.

Methods: Data from 115 cirrhotic patients who were eligible for liver transplantation (LT) were prospectively analyzed. A transthoracic contrast echocardiography and ^{99m}Tc-MAA were performed in 85 patients, and 74 patients were diagnosed with HPS.

Results: The overall sensitivity of ^{99m}Tc-MAA for the diagnosis of HPS was 18.9% (14/74) in all of the HPS cases and 66.7% (4/6) in the severe to very severe cases. In HPS patients who did not have lung disease, the degree of brain uptake of ^{99m}Tc-MAA was correlated with the alveolar-arterial oxygen gradient (A-a PO_2) ($r = 0.32$, $p < 0.05$) and estimated oxygen shunt ($r = 0.41$, $p < 0.05$) and inversely correlated with partial pressure of arterial oxygen (PaO_2) while breathing 100% O_2 ($r = -0.43$, $p < 0.05$). The ^{99m}Tc-MAA was positive in 20.6% (7/36) of the patients with HPS and lung disease. The brain uptake of ^{99m}Tc-MAA was not associated with mortality and normalized in all cases six months after LT.

Conclusions: The ^{99m}Tc-MAA is a low sensitivity test for the diagnosis of HPS that can be useful in patients who have concomitant lung disease and in severe to very severe cases of HPS. It was not related to mortality, and brain uptake normalized after LT.

Key words: Cirrhosis. Ascites. Contrast echocardiography. Pulmonary vascular diseases. Perioperative care.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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INTRODUCTION

HPS is characterized by the presence of intrapulmonary vascular dilations (IPVD), which cause a physiologic shunt that decreases the alveolar-arterial oxygen gradient (A-a PO2) and can produce hypoxemia in patients with liver disease (1,2). Thoracic contrast echocardiography (TCE), which is a non-invasive and sensitive method for diagnosing IPVD, is considered to be the gold standard for diagnosing HPS (1,3). The ^{99m}Tc-MAA can also diagnose and quantify IPVD, but its sensitivity is lower; however, there are few studies that have compared the two techniques (4-8).

The ability of this method to quantify IPVD by determining the brain uptake of ^{99m}Tc-MAA makes it attractive for stratifying the severity of HPS. In this context, there are some studies linking the increased brain uptake of ^{99m}Tc-MAA to increased mortality among HPS patients (6-8). In an attempt to validate its ability to quantify IPVD, its correlations with different respiratory parameters that could measure HPS severity, such as the PaO_2 while breathing 100% oxygen, A-a O_2, estimated degree of oxygen shunt and corrected diffusing capacity for carbon monoxide (DLCOco), have been analyzed; however, the information is scarce and inconclusive (5-9).

When HPS was first defined, no existing concomitant cardiopulmonary diseases were required for its diagnosis (10). Subsequently, it was observed that HPS could be present in patients with lung disease. Because IPVD are frequent in cirrhotic patients without HPS, they are often detected by TCE, and the problem arises of determining whether hypoxemia in patients with pulmonary disease is due to IPVD or to HPS (3). It has been speculated that ^{99m}Tc-MAA may be useful for assessing the contribution of

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HPS to hypoxemia in patients with concomitant pulmonary disease (5).

LT is capable of reversing the HPS quickly, except for some of its parameters, such as DLCOco (11-16). There are scarce data on the changes in the uptake of ^{99m}Tc-MAA in the brain after LT (8).

The objectives of our study were the following: a) to determine the sensitivity of ^{99m}Tc-MAA for diagnosing HPS in cirrhotic patient candidates for LT; b) to establish the utility of ^{99m}Tc-MAA in determining the influence of HPS on hypoxemia in patients with concomitant pulmonary disease; and c) to examine the correlation between ^{99m}Tc-MAA values and other respiratory parameters that can define HPS severity and the influence of ^{99m}Tc-MAA values on pre- and post-LT survival.

MATERIALS AND METHODS

Selection of patients

All of the adult patients with cirrhosis who were evaluated for a first LT at the Hospital Universitario Virgen del Rocío in Seville (Spain) for a period of five years were prospectively included in the study. Candidates who were evaluated for re-transplantation were excluded. To be included in the study, patients signed an informed consent form which was in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of the hospital. Patients whose results from an arterial blood gas analysis in the supine position were compatible with a diagnosis of HPS were selected. These results are part of a larger study, and some of its findings have been previously published (16).

Hepatopulmonary syndrome

Blood gas studies

An arterial blood gas analysis was performed while the patients were in the supine position and breathing room air. The samples were analyzed using a gasometer (ABL-500 gasometer, Radiometer, Copenhagen, Denmark), and the A-a PO_2 was calculated using the following formula: A-a PO_2 = [(BP - 47) FIO_2 - $PaCO_2$/0.8] - PaO_2, where BP is barometric pressure, FIO_2 is the fraction of inspired O_2, $PaCO_2$ is the partial pressure of carbon dioxide, and PaO_2 is the partial pressure of arterial oxygen. The intrapulmonary shunt size was determined by studying the ratio of PaO_2 in the arterial blood when a second blood gas analysis was performed while the patients were breathing with FIO_2 = 1 (100% O_2) for 15 minutes through a face mask with a reservoir. The shunt was determined from the nomogram devised by Chiang (17).

Transthoracic contrast echocardiography

All of the patients whose blood gas analysis results were compatible with a HPS diagnosis received a TCE, which was performed by two cardiologists from our hospital. A 10 ml saline serum solution was shaken in two 10 ml syringes that were connected to a three-way valve. The solution was injected into a peripheral vein of the upper limb through a 20G catheter. An apical four-chamber image was taken with a variable-frequency transducer (2.1-4.2 MHz) that had a Philips iE-33 scanner (Royal Philips Electronics, Amsterdam, the Netherlands) to detect the presence of micro-bubbles. The presence of micro-bubbles between the fourth and sixth beat after the injection in the left chambers was considered as a positive result.

Macro-aggregated albumin lung perfusion scan

A ^{99m}Tc-MAA was performed in the patients whose blood gas analysis results were compatible with a HPS diagnosis. The scan was performed by injecting 100,000 particles (1.3 to 2.1 mCi in size) of albumin macro-aggregates labeled with Tc 99 (TechneScan LyoMAA; Tyco Healthcare, Madrid, Spain; 95% of the particles have a diameter between 10 and 100 μm) through a peripheral vein while the patient was in the sitting position. Then, the patient was placed in the supine position, and images were obtained of each half of the head and of the anterior and posterior thorax using a parallel hole collimator, with a 20% window centered at the technetium peak of 140 keV for five minutes, and a gamma camera (Apex SPX Helix, Elscint, Haifa, Israel). The regions of interest were drawn around the brain and lungs, and the radiation counts of those areas were recorded. The extrapulmonary shunt fraction, assuming that 13% of the cardiac output is delivered to the brain, was calculated using the geometric mean of technetium (GMT) counts around the brain and lung in the following formula: (GMTbrain)/(GMTbrain + GMTlung). The scan was considered to be positive when the fraction of the extrapulmonary shunt in the brain was greater than or equal to 6%; the shunt fraction was quantitatively recorded in all cases (4,5).

Hepatopulmonary syndrome and orthodeoxia criteria

HPS was defined according to the following criteria: a) PaO_2 < 70 mmHg and/or A-a $PO_2 \geq 20$ mmHg while the patient was in a supine position (6,8,11,18,19); b) a positive TCE; and c) evidence of cirrhotic liver disease. Patients were classified into the following four degrees of HPS severity according to the level of PaO_2: mild ($PaO_2 \geq 80$ mmHg), moderate ($PaO_2 < 80$ mmHg and ≥ 60 mmHg), severe ($PaO_2 < 60$ mmHg and ≥ 50 mmHg), and very severe (PaO_2 < 50 mmHg) (1). Orthodeoxia occurred when arterial blood gas PaO_2 in seated patients (after spending at least 20 minutes standing or seated) was reduced by $\geq 5\%$ or ≥ 4 mmHg compared with the values for patients in the supine position.

Studies of lung function

The patients performed spirometric tests according to the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) recommendations, and values from a Mediterranean population were used as a reference. A pneumotachograph spirometer (Masterlab, Erich Jaeger GmbH, Würzburg, Germany) was used for the tests. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and the FEV1/FVC ratio were recorded. Patients were considered to have obstructive lung disease when the FEV1/FVC ratio was less than 70% or when the FEV1 was less than 80% of the reference

value. Patients were diagnosed with restrictive lung disease when their FVC was less than 80% from baseline or with mixed lung disease when they had both criteria. DLCO values (expressed in mmol/min/kPa) and DLCO values adjusted for alveolar volume (expressed in mmol/min/kPa/l) and hemoglobin (DLCOco) were obtained. All lung function tests followed SEPAR recommendations and used reference values for the Mediterranean population.

Post LT follow-up

A ^{99m}Tc-MAA was performed in patients with HPS every three to six months after LT until the values returned to normal.

Survival analysis

The date of death, transplantation or last follow-up at the hospital before the end of the study was considered to be the last date of the transplant waiting list period. The date of death or last visit to the hospital before the end of the study was considered to be the last date in the post-transplant period.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs), and categorical variables are expressed as numbers (n) and percentages (%). Comparisons between categorical variables were performed using the Chi-squared test or Fisher's exact test, and comparisons between continuous variables were performed with Student's t test or Mann-Whitney test. The relationships between variables were assessed by the Spearman correlation coefficient. Survival analyses were performed using the Kaplan-Meier method and Cox regression. The statistical analysis was performed with SSPS version 15.0 (SSPS Inc., Chicago, IL, USA).

RESULTS

A total of 316 of the 367 patients examined were enrolled in the study. A total of 115 (36.4%) patients had blood gas analysis results that were compatible with HPS, and each of these patients received a TCE. A ^{99m}Tc-MAA was carried out in 85 (73.9%) patients who had alterations in their blood gas analysis that were compatible with HPS. There were no significant differences in clinical findings between the two groups except the presence of HPS was more frequent in the study sample. Figure 1 shows an outline of the study.

Patient characteristics

The study sample included 115 patients; 92 (80%) were men and 23 (20%) were women. The median age was 55 years (IQR: 49-60). The etiology of cirrhosis was alcohol in 61 (53%) patients, hepatitis C virus (HCV) in 11 (9.6%) patients, alcohol and HCV in 17 (14.8%) patients, hepatitis B virus (HBV) in 4 (3.5%) patients, HBV and alcohol in 7 (6.1%) patients, and other causes in 15 (13%) patients. The distribution of cirrhosis severity according to the Child-Pugh classification was the following: class A, 17 (14.8%) patients; class B, 47 (40.9%) patients; and class C, 51 (44.3%) patients. The median model for end-stage liver disease (MELD) index was 16 (IQR: 12-19). Eighty-one (70.4%) patients were diagnosed with HPS.

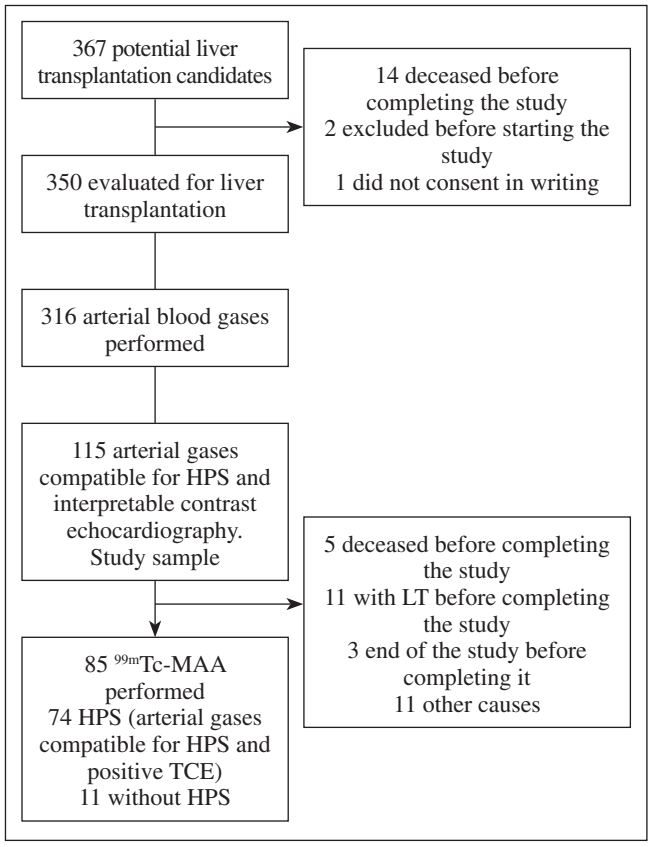

Fig. 1. Study flowchart. HPS: Hepatopulmonary syndrome. LT: Liver transplantation. ^{99m}Tc-MAA^{99m}: ^{99m}Tc-macro-aggregated albumin lung perfusion scan. TCE: Transthoracic contrast echocardiography.

Comparative study between ^{99m}Tc-MAA and TCE for the diagnosis of HPS

A ^{99m}Tc-MAA and a TCE were performed in 85 patients who had arterial blood gas analysis results that were compatible with HPS. The time interval between the two procedures was less than one month. No adverse events were observed during either procedure. Seventy-four (87%) patients were diagnosed with HPS according to an arterial blood gas analysis (59/74) (79.7%) with only an A-a $PO_2 \geq 20$ mmHg without $PaO_2 < 70$ mmHg) and a positive TCE result. The following distribution of HPS severity was observed: 29 mild cases (39.2%), 39 moderate

cases (52.7%), five severe cases (6.8%), and one very severe case (1.4%). Only 14 (18.9%) patients with HPS had a positive ^{99m}Tc-MAA; thus, the overall sensitivity of the ^{99m}Tc-MAA in diagnosing HPS was 19%. The specificity was 100%, none of the 11 patients with negative TCE had a positive ^{99m}Tc-MAA. The negative predictive value was 15%, and the positive predictive value was 100%. The ^{99m}Tc-MAA was positive in 10/68 (14.7%) mild to moderate cases of HPS *versus* 4/6 (66.7%) severe or very severe cases; this difference was statistically significant ($p = 0.01$).

A statistically significant association ($p < 0.05$) was observed between the ^{99m}Tc-MAA and platelet count, $PaCO_2$ in the supine position, PaO_2 while breathing 100% oxygen, the degree of estimated oxygen shunt and DLCOco. ^{99m}Tc-MAA was also associated with hypersplenism and orthodeoxia; however, these associations were on the verge of statistical significance ($p = 0.06$). In the multivariate study, DLCOco and $PaCO_2$ in the supine position remained independent predictors of a positive ^{99m}Tc-MAA (Table I).

Correlation of brain uptake in ^{99m}Tc-MAA with variables associated with HPS

The brain uptake of ^{99m}Tc-MAA in patients with HPS was not significantly correlated with PaO_2 while breathing room air, A-a PO_2, or DLCOco. However, the brain uptake of ^{99m}Tc-MAA was inversely correlated with PaO_2 while breathing 100% oxygen ($r = -0.42$, $p < 0.01$) and $PaCO_2$ ($r = -0249$, $p < 0.05$), and was positively correlated with the degree of oxygen shunt ($r = 0.42$, $p < 0.01$). When exclusively analyzing HPS patients who did not have underlying lung disease, a statistically significant weak positive correlation was observed with A-a PO_2 ($r = 0.32$, $p < 0.05$) and the degree of oxygen shunt ($r = 0.41$, $p < 0.05$), and an inverse correlation was observed with PaO_2 while breathing 100% O_2 ($r = -0.43$, $p < 0.05$). However, the brain uptake of ^{99m}Tc-MAA was not correlated with PaO_2 while breathing room air, $PaCO_2$, or DLCOco (Fig. 2).

Correlation between the brain uptake of ^{99m}Tc-MAA and the parameters of liver function and of portal hypertension

The brain uptake of ^{99m}Tc-MAA was not correlated with the Child-Pugh classification of cirrhosis severity, MELD index or levels of total bilirubin, albumin, international normalized ratio (INR) and platelet count.

Role of ^{99m}Tc-MAA in patients with concomitant lung disease

Among the HPS patients, there were no significant differences in a positive ^{99m}Tc-MAA between the patients who had concomitant respiratory disease and those who did not ($p = 0.77$). ^{99m}Tc-MAA was positive in seven of the 34 (20.6%) patients who had coexisting respiratory disease and in seven of the 40 (17.5%) without respiratory disease. When stratified by the severity of HPS, the ^{99m}Tc-MAA was positive in 4/25 (13.8%) mild or moderate cases *versus* 3/5 (60%) severe or very severe cases ($p = 0.048$). ^{99m}Tc-MAA was negative in 27 of the 34 (79.4%) patients who had coexisting respiratory disease and in 33 of 40 (82.5%) without respiratory disease.

Statistically significant differences were observed between a positive ^{99m}Tc-MAA and the value of PaO_2 while breathing 100% O_2, degree of estimated oxygen shunt and DLCOco in patients with HPS and concomitant lung disease. These differences were not observed among patients who had HPS but did not have pulmonary disease (Table II).

Pre-LT and post-LT mortality of HPS patients

Mortality in the pre-transplantation or the post-transplantation periods was not associated with positive ^{99m}Tc-MAA results, shunt values obtained by ^{99m}Tc-MAA, PaO_2 while breathing room air or 100% oxygen, A-a PO_2, degree of oxygen shunt calculated, or DLCO. These associations were also negative when the two periods were jointly analyzed. Two patients with ^{99m}Tc-MAA > 20% received transplants, and one of them died.

Changes in ^{99m}Tc-MAA post- transplantation

Ten patients who had HPS and a positive ^{99m}Tc-MAA result received a transplant, and two of them died. A new ^{99m}Tc-MAA was performed during the first six months post-LT in six of the eight survivors, and the result was negative for all of them.

DISCUSSION

This study prospectively analyzed the utility of the standardized ^{99m}Tc-MAA for the diagnosis and prognosis of HPS and its relationship to other respiratory parameters associated with. This makes it one of the largest collections studied to date in the literature.

^{99m}Tc-MAA sensitivity in the diagnosis of HPS

This study found that the ^{99m}Tc-MAA has a low sensitivity (19%) for diagnosing HPS compared to the sensitivity of TCE. However, the sensitivity changed with the severity of HPS; it increased to 66.7% in severe and very severe cases. The ^{99m}Tc-MAA results were never positive

Table I. Characteristics in HPS patients with positive and negative ^{99m}Tc-MAA

Variable	*Total (n = 74)*	*Negative ^{99m}Tc-MAA (n = 60)*	*Positive ^{99m}Tc-MAA (n = 14)*	*p**
Age (y, p25-p75)	54 (49-60)	54.5 (48.7-61)	52 (49-64.5)	0.934
Sex, male (%)	58 (78.4)	47 (78.3)	11 (78.6)	0.984
Smoker	51 (68.9)	41 (68.3)	10 (71.4)	0.822
BMI	25 (24-28)	26 (25-28.2)	24 (23.5-32)	0.727
AHT history	8 (11.6)	5 (8.9)	3 (23.1)	0.151
DM history	19 (25.7)	15 (25)	4 (28.6)	0.783
Alcohol consumption	56 (75.7)	46 (76.7)	10 (71.4)	0.681
HCV	22 (29.7)	15(25)	7 (50)	0.065
HBV	5 (6.8)	5 (8.3)	0 (0)	0.627
Hepatocarcinoma	18 (24.7)	14 (23.7)	4 (28.6)	0.705
Ascites	69 (93.2)	55 (91.7)	14 (100)	0.263
Encephalopathy	34 (45.9)	26 (43.3)	8 (57.1)	0.351
Esophageal varices	272 (86)	200 (86.6)	72 (90)	0.426
Hypersplenism	46 (62,2)	34 (56,7)	12 (85,7)	0.065
Child-Pugh class (A/B/C)	12/27/35	10/22/28	2/5/7	0.966
Child-Pugh score	9 (8-10)	8 (7-10)	9 (8-10)	0.038
Total bilirubin (mg/dl)	2.9 (1.5-5.4)	2.7 (1.4-5)	2.6 (2.1-5.1)	0.809
INR	1.4 (1.25-1.61)	1.42 (1.32-1.57)	1.45 (1.37-1.64)	0.159
Albumin (g/dl)	2.8 (2.4-3.2)	2.9 (2.5-3.3)	3 (2.4-3.1)	0.365
Creatinine (mg/dl)	0.9 (0.7-1.1)	0.9 (0.75-1.16)	0.86 (0.74-1.18)	0.307
Hemoglobin (g/dl)	10.7 (9.5-12.2)	10.7 (9.8-12.1)	11.5 (9.5-12.3)	0.456
Leukocytes (1/mm$^{3)}$	4,630 (3,237-7,325)	4,670 (3,300-7,070)	4,310 (3,340-6,390)	0.355
Platelets (10^3/mm^3)	88 (59-120)	93 (69-130)	85 (73-99)	0.048
MELD score	15.5 (12-19)	15 (12-19)	16 (13-17)	0.242
PaO_2 (mmHg)	76 (71.7-84)	79 (74-84)	80 (57-89)	0.539
$PaCO_2$ (mmHg)	33 (30-35)	34 (32-35)	32 (30-34)	0.039
A-a PO_2	29.5 (23.7-38)	28.5 (22-34)	29 (25-55)	0.275
PaO_2 on 100% oxygen (mmHg)	582 (430-614.5)	596.5 (463-621)	427 (280-602)	0.020
Oxygen shunt estimated	5.65 (3.8-12.5)	4.75 (2.8-11.1)	13 (4.4-19.1)	0.019
Severe or very severe HPS	6 (8.1)	2 (3.3)	4 (28.6)	0.010
Respiratory disease	34 (46.6)	27 (45,8)	7 (50)	0.775
FEV1 (%)	84 (71.7-96.5)	84.5 (73-95)	82 (80-104)	0.284
FVC (%)	90 (79.7-105)	90 (81-105)	101 (90-110)	0.277
Tiffeneau index (%) (FEV1/FVC x 100)	74 (69-80)	74.5 (68-79)	79 (66-80)	0.275
TLC (%)	94 (83-107)	96.5 (83-107)	93.2 (82-109)	0.479
DLCOco (%)	79 (66.2-94)	80.2 (73-96)	64 (41-79)	0.021
Orthodeoxia	15/52 (28.8)	9/40 (22.5)	6/12 (50)	0.065

A-a PO_2: Alveolar-arterial oxygen gradient; AHT: Arterial hypertension; BMI: Body mass index; DLCOco: Carbon monoxide diffusing capacity adjusted for hemoglobin concentration; DM: diabetes mellitus; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HPS: Hepatopulmonary syndrome; INR: International normalized ratio; MELD: Model for end-stage liver disease; $PaCO_2$: Partial carbon dioxide pressure; PaO_2: Partial oxygen pressure; TLC: Total lung capacity. p* refers to the p value for patients with negative or positive ^{99m}Tc-MAA.

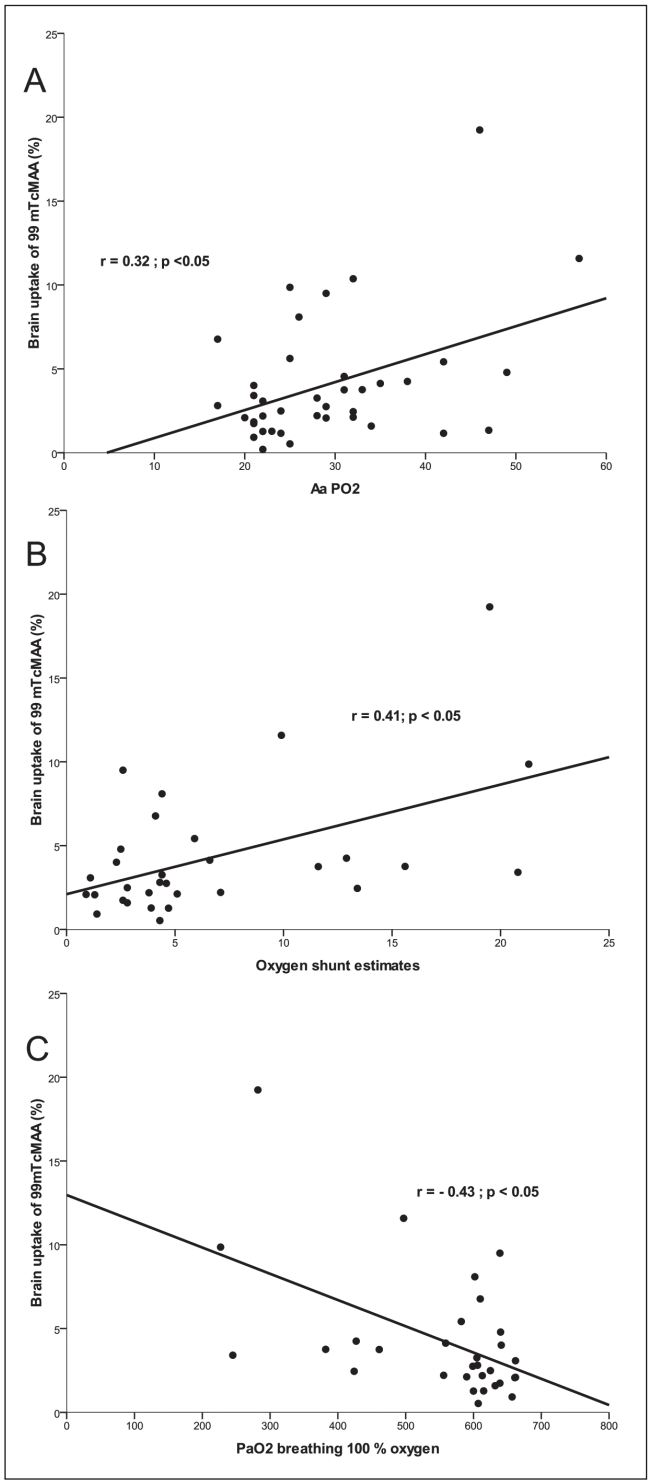

Fig. 2. Correlation of the MAA shunt fraction with: alveolar-arterial gradient (A); oxygen shunt estimates (B); and arterial PaO_2 while breathing 100% oxygen (C). Hepatopulmonary syndrome patients without intrinsic lung disease.

when the TCE results were negative. This low sensitivity is also observed in HPS patients without lung disease. In this analysis, the confusing implication of lung disease on oxygenation abnormality and possible false positive cases of HPS (hypoxemia or altered A-a PO_2 caused by lung disease and positive TCE) are avoided.

Abrams et al. established the diagnostic utility of ^{99m}Tc-MAA in adults with HPS through two studies published in 1995 and 1998 (4,5). In the first study, the ^{99m}Tc-MAA was demonstrated to be negative (i.e., it established a minor shunt fraction equal to 6%) in healthy patients and in patients who had lung disease and hypoxemia without cirrhosis. Moreover, ^{99m}Tc-MAA was also negative in normoxemic cirrhotic patients who had a positive TCE result, and ^{99m}Tc-MAA was found to have a negative predictive value of 93% (4). The second study analyzed 25 patients with HPS, and 21 (84%) of them had severe or very severe HPS (10 severe and 11 very severe). The study found that the ^{99m}Tc-MAA had a sensitivity of 84%, with the four negative cases corresponding to a moderate case and three mild cases. The ^{99m}Tc-MAA was also found to be negative in hypoxemic patients who had lung disease but did not have cirrhosis. The study concluded that a positive ^{99m}Tc-MAA is specific to the presence of severe or very severe HPS (5). Krowka et al. also found that the ^{99m}Tc-MAA had a very high sensitivity of 96% in a group of 25 patients with HPS; 19 (76%) of the patients had severe or very severe HPS (6). In a sample of 25 HPS patients, in which 15 (60%) had severe or very severe HPS, Arguedas et al. obtained a sensitivity of 76% (7). Swanson et al. studied the use of ^{99m}Tc-MAA in 37 patients with HPS; although they did not specify its diagnostic sensitivity, they observed that the ^{99m}Tc-MAA was never negative if patient hypoxemia was less than or equal to 50 mmHg (8).

The sensitivity of the ^{99m}Tc-MAA in our study is significantly lower than that reported in the literature. This can be explained by a difference in the characteristics of the HPS patient populations; our sample predominantly consisted of mild to moderate HPS cases, whereas the samples in the other studies mainly consisted of severe or very severe cases. This difference can be explained by the selection of HPS patients. In our study, HPS patients were selected in a systematic way as part of the pre-transplantation evaluation. In contrast, the other studies were performed in clinical patients or the population characteristics were not specified. In our study and in the study by Abrams et al., the ^{99m}Tc-MAA was observed to be positive much more frequently in patients with severe or very severe HPS than in patients with mild to moderate HPS. However, the ^{99m}Tc-MAA was positive in 14.7% of mild to moderate cases in our study, which indicates that a positive ^{99m}Tc-MAA result is not specific to the presence of severe or very severe HPS, as had previously been indicated (5).

In our study, the low sensitivity of ^{99m}Tc-MAA and the significant number of HPS cases that were not diagnosed by ^{99m}Tc-MAA despite a positive TEC suggest against the systematic use of the ^{99m}Tc-MAA as a diagnostic tool for HPS. Another issue is its use as a prognostic measure or

Table II. Differences in PaO_2 on 100% oxygen, oxygen shunt estimated and DLCOco in HPS patients

	With lung disease (n = 24)			*Without lung disease (n = 31)*		
	Negative ^{99m}Tc-MAA (n = 19)	*Positive ^{99m}Tc-MAA (n = 5)*	*p*	*Negative ^{99m}Tc-MAA (n = 25)*	*Positive ^{99m}Tc-MAA (n = 6)*	*p*
PaO_2 on 100% oxygen (mmHg)	549 (447-601)	399 (242.5-433)	0.012	606.5 (564.7-639.7)	602 (254-624)	0.202
Oxygen shunt estimated	7.6 (4.4-11.6)	14.6 (12.8-21)	0.012	4.3 (2.5-6.4)	4.4 (3.3-20.4)	0.211
DLCOco (%)	78 (64-94)	41 (35.5-60.5)	0.003	85 (75.5-99)	85 (74.5-98)	0.499

DLCOco: Carbon monoxide diffusing capacity adjusted for haemoglobin concentration; PaO_2: Partial oxygen pressure; ^{99m}Tc-MAA: ^{99m}Tc-macroaggregated albumin lung perfusion scan.

in assessing the role of HPS in patients with cirrhosis and concomitant lung disease; this will be discussed below.

Correlation of the brain uptake in ^{99m}Tc-MAA with respiratory function parameters associated with HPS

A weak positive correlation was observed between the degree of brain uptake of ^{99m}Tc-MAA and the A-a PO_2 and calculated degree of oxygen shunt, whereas an inverse correlation was found with PaO_2 while breathing 100% O_2. The degree of brain uptake of ^{99m}Tc-MAA was not correlated with PaO_2 while breathing room air or with DLCOco. The calculated degree of oxygen shunt and PaO_2 while breathing 100% O_2 were also associated with a positive ^{99m}Tc-MAA in the univariate analysis but not in the multivariate analysis.

In this sense, the results are contradictory between the different studies. Abrams et al. found a strong negative correlation with PaO_2 while breathing room air but not with PaO_2 while breathing 100% O_2 in a sample of 21 patients (6). Krowka et al., however, observed a negative correlation with PaO_2 while breathing 100% O_2 but a positive correlation with A-a PO_2 (similar to our study) and with PaO_2 while breathing room air. There was no correlation observed with DLCO (7). Arguedas et al. observed a strong negative correlation with PaO_2 while breathing room air, a positive correlation with A-a PO_2 and, similar to our study, a weak correlation with PaO_2 while breathing 100% O_2 (8). Finally, Swanson et al. found the same correlations with PaO_2 while breathing room air, A-a PO_2 and PaO_2 while breathing 100% O_2 (9). The ^{99m}Tc-MAA was not correlated with the calculated degree of oxygen shunt in any of the studies (Table III).

One explanation of why the brain uptake of ^{99m}Tc-MAA was not correlated with PaO_2 in the supine position and, to a lesser extent, with A-a PO_2 in our study is, once again, the difference in the severity of HPS in our patient sample compared to that of the samples in other studies. Considering the results of these studies together, we observe that the correlation between the estimated shunt by ^{99m}Tc-MAA and PaO_2 while breathing 100% oxygen is independent of HPS severity; however, A-a PO_2 and PaO_2 while breathing room air are dependent on the severity of HPS.

Correlation with parameters of liver function and portal hypertension

The level of brain uptake of ^{99m}Tc-MAA was not correlated with any parameters of liver function or the indirect parameters of portal hypertension. This finding is consistent with those of other studies (5,6,20).

Utility of ^{99m}Tc-MAA in patients with HPS and concurrent respiratory pathology

The ^{99m}Tc-MAA was positive in the same proportion of HPS patients with and without respiratory disease. This

Table III. Correlations between brain uptake of ^{99m}Tc-MAA and HPS related parameters

Study	*n*	*PaO_2 on room air*	*PaO_2 on 100% oxygen*	*A-a PO_2*	*DLCOco*	*Oxygen shunt estimated*
Abrams et al. (6)	21	r = -0,73*	r = -0.23	r = 0.77*		
Krowka et al. (7)	25	r = -0.57*	r = -0.41*	r = 0.59*	r = 0.05	
Arguedas et al. (8)	24	r = -0.74*	r = -0.43*	r = 0.71*		
Swanson et al. (9)	37	r = -0.62*	r = -0.46*	r = 0.64*		
Grilo et al.	74	r = -0.11	r = -0.42*	r = 0.21	r = -0.20	r = 0.42*
	40+	r = -0.17	r = -0.42*	r = 0.32*	r = -0.05	r = 0.41*

A-a PO_2: Alveolar-arterial oxygen gradient; PaO_2: Partial oxygen pressure; DLCOco: Corrected diffusing capacity for carbon monoxide. *p < 0.05. +HPS patients without associated lung disease.

comparison has not been previously conducted, and it allows us to conclude that the results of the ^{99m}Tc-MAA are not influenced by the presence of concomitant lung disease, even in patients with HPS. The negative results of the ^{99m}Tc-MAA in hypoxemic and non-cirrhotic lung disease (5) patients have been previously described. This observation is important because the use of ^{99m}Tc-MAA in patients with HPS who also have lung disease is recommended to assess the degree to which HPS influences hypoxemia in these patients. We observed that the ^{99m}Tc-MAA was positive in 20% of HPS patients with coexisting lung disease and increased to 60% in severe and very severe cases. Although this observation is based on few patients, it supports the recommendation of using ^{99m}Tc-MAA to detect patients with HPS and coexisting lung disease, especially in patients with severe or very severe HPS. A positive ^{99m}Tc-MAA result supports the diagnosis of HPS. Another issue is how a negative ^{99m}Tc-MAA result in such patients should be interpreted. This may entail cirrhotic patients with mild or moderate HPS, in whom the sensitivity of ^{99m}Tc-MAA is low. Another possibility is that patients do not really have HPS, but that their hypoxemia is due to concomitant lung disease. Other studies have shown that a positive TCE result is more frequent than the actual presence of HPS; thus, patients with concomitant lung disease and hypoxemia may be misdiagnosed with HPS (8,21-23). In this sense, other parameters suggestive of HPS should be evaluated by diagnostic tests. In the group of HPS patients with concomitant lung disease, our study found statistically significant differences in the values of DLCOco, calculated shunt and PaO_2 while breathing 100% oxygen, between the patients with positive and negative ^{99m}Tc-MAA. These findings suggest that hypoxemia in patients with negative ^{99m}Tc-MAA results is not associated with the presence of HPS. These differences were not observed in patients without concomitant lung disease. Krowka et al. also found significantly lower levels of PaO_2 while breathing 100% oxygen in patients who had lung disease and HPS compared to those of HPS patients without lung disease; however, they did not link it to ^{99m}Tc-MAA results (6).

Pre- and post-LT mortality

We found no association between overall mortality and the levels of ^{99m}Tc-MAA, PaO_2 while breathing room air or 100% oxygen, degree of calculated shunt, nor DLCOco, in HPS patients who were either on the active transplant waiting list or in the post-transplantation period. Arguedas et al. and Swanson et al. found that a lower PaO_2 and higher brain uptake of ^{99m}Tc-MAA were associated with increased post-transplantation mortality (7,8). However, Gupta et al. did not observe increased post-transplantation mortality in patients with severe HPS compared to the other HPS patients (14). Iyer et al. observe that survival after LT was not associated with PaO_2 levels at the time of HPS diagnosis (24). In our study, two patients who had a brain uptake of ^{99m}Tc-MAA > 20% received a transplant, and one of them died. Therefore, we can neither affirm nor deny the prognostic value of ^{99m}Tc-MAA in patients with severe or very severe HPS, but we can note that in mild and moderate HPS cases, ^{99m}Tc-MAA is not useful in determining the risk of mortality.

Changes in MAA post-transplantation

The shunt values measured with ^{99m}Tc-MAA in HPS patients who had a positive ^{99m}Tc-MAA result normalized in the first six months post-transplantation. This quick normalization of ^{99m}Tc-MAA results is consistent with previously published results from the same sample of patients, in which the symptoms of HPS were completely reversed in 100% of cases during the first 12 months after LT and in 8% of cases during the first six months. Because the ^{99m}Tc-MAA is less sensitive than TCE in detecting IPVD, it seems logical that its results normalize earlier than those of TCE. Swanson et al. also observed a normalization of the ^{99m}Tc-MAA scan in 20 patients by 12 months after LT (8).

One of the limitations of this study is that patients enrolled came from only one center, which limits the application of its findings to other populations due to possible genetic or environmental differences in the study population. Another limitation is the relatively small sample size, although it is the largest reported in the literature. It must also be highlighted that our study predominantly included mild to moderate cases, so the findings primarily apply to this group of patients. However, it is noteworthy that the results of this study are based on a standardized HPS screening in cirrhotic patients who were eligible for LT and, therefore, are of great interest in this context.

In conclusion, the ^{99m}Tc-MAA is a low sensitivity test for the diagnosis of IPVD that defines the presence of HPS compared to the TCE, and we do not advise its widespread use as a diagnostic test. However, it might be useful in the diagnosis of HPS in patients who have concomitant lung disease to determine the role of HPS in hypoxemia, especially patients with severe and very severe HPS. In cases of mild to moderate HPS, the ^{99m}Tc-MAA value was moderately correlated with PaO_2 while breathing 100% oxygen and the calculated shunt but not with PaO_2 while breathing room air or A-a PO_2. The ^{99m}Tc-MAA values were not related to mortality in patients with mild to moderate HPS and normalized soon after LT.

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