ASSESSMENT OF HEPATOPULMONARY SYNDROME PREVALENCE AND EPIDEMIOLOGICAL PROFILE IN OUTPATIENTS WITH LIVER CIRRHOSIS

AVALIAÇÃO DA PREVALÊNCIA DA SÍNDROME HEPATOPULMONAR E DO PERFIL EPIDEMIOLÓGICO EM PACIENTES AMBULATORIAIS COM CIRROSE HEPÁTICA

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ABSTRACT

Hepatopulmonary Syndrome (HPS) is a complication from portal hypertension. It is a priority on the liver transplant list, which is the treatment of choice. Prevalence can reach 32% in cirrhotic patients, the result of microvascular changes, presenting an altered ventilation-perfusion relationship. Diagnosis depends on gasometric and imaging criteria. Retrospective study following the Hepatopulmonary outpatient from January 2019 to June 2023. Variables analyzed: age, sex, etiology, MELD and Child-Pugh score and gasometric parameters. Patients were classified: with or without a diagnosis of HPS. The Severity of HPS is defined based on PaO2 values. We included 105 patients. 62.85% are men. Child A, 80%, B 16.19%, and C 3.8%. The average age was 57.8 years, and the average MELD was 10.7 points. The etiology of cirrhosis: HCV in 57.14%, NASH in 18.09%, alcohol in 6.66%. HBV cirrhosis, mixed etiology, and other etiologies 5.71% each. Gasometric analysis: 71% had increased GA-aO2. 32.38% had a HPS diagnosis. The group with HPS: 73.52% were men, average MELD of 11.6 points, average age of 55.8 years. Child-Pugh: 73.52% were classified as A, 26.47% as B, and none as C. The severity of HPS: 67.64% patients with mild HPS, 29.41% with moderate HPS, none with severe HPS, and 2.94% with very severe HPS. The research results demonstrated the epidemiological profile and prevalence of HPS at 32.38%.

KEYWORDS: Alveolar arterial oxygen gradient; Hypoxemia; Hypocapnia.

RESUMO

A Síndrome Hepatopulmonar (SHP) é uma complicação da hipertensão portal. É prioridade na lista do transplante de fígado, sendo o tratamento de escolha. A prevalência pode chegar a 32% em pacientes cirróticos, resultado de alterações microvasculares, apresentando relação ventilação-perfusão alterada. O diagnóstico depende de critérios gasométricos e de imagem. Estudo retrospectivo acompanhando ambulatório de Hepatopulmonar no período de janeiro de 2019 a junho de 2023. Variáveis analisadas: idade, sexo, etiologia, escore MELD e Child-Pugh e parâmetros gasométricos. Os pacientes foram classificados: com ou sem diagnóstico de SHP. A gravidade do HPS é definida com base nos valores de PaO2. Incluímos 105 pacientes. 62,85% são homens. Criança A, 80%, B 16,19% e C 3,8%. A idade média foi de 57,8 anos e o MELD médio foi de 10,7 pontos. A etiologia da cirrose: HCV em 57,14%, NASH em 18,09%, álcool em 6,66%. Cirrose HBV, etiologia mista e outras etiologias 5,71% cada. Análise gasométrica: 71% apresentaram GA-aO2 aumentado. 32,38% tiveram diagnóstico de SHP. Grupo com HPS: 73,52% eram homens, MELD médio de 11,6 pontos, idade média de 55,8 anos. Child-Pugh: 73,52% foram classificados como A, 26,47% como B e nenhum como C. A gravidade da HPS: 67,64% pacientes com HPS leve, 29,41% com HPS moderada, nenhum com HPS grave e 2,94% com HPS muito grave HPS. Os resultados da pesquisa demonstraram o perfil epidemiológico e a prevalência da SHP em 32,38%.

PALAVRAS-CHAVE: Gradiente alveolar arterial de oxigênio; hipoxemia; hipocapnia.

1. INTRODUCTION

Hepatopulmonary syndrome (HPS) is the most common cause of respiratory failure in patients with chronic liver disease[1], without primary heart or lung disease. It is a clinical syndrome consisting of a triad: 1 - advanced liver dysfunction / portal hypertension / congenital systemic portal shunts[2], 2 - intrapulmonary vascular dilation and 3 - impairment of arterial oxygenation[3], with concentrations below normal levels and/or increased alveolar-arterial gradient in oxygen partial pressure. In this context, chest radiography can be useful to assess the presence of another lung disease, as can spirometry. Likewise, the echocardiogram can also rule out primary heart disease or even intracardiac shunt, which would also result in the appearance of contrast (bubbles) in the left heart early, until the third cycle, while in the intrapulmonary

shunt the bubbles would appear in the left heart, in a later, after the fourth cardiac cycle.

HPS is found in approximately 11% to 32% of patients with chronic liver disease, particularly those with cirrhosis[4], with great variation in prevalence depending on the population studied, the diagnostic criteria and methods used, such as echocardiography with transthoracic or transesophageal contrast, perfusion scintigraphy or pulmonary angiography, and the cutoff determined as a reference to define hypoxemia and increased alveolar-arterial oxygen gradient.

In a study carried out by Barbosa *et al* (2018).[9], it was demonstrated that the prevalence of HPS in patients with liver cirrhosis was 10.1% ($p<0.001$), in accordance with the results described in previous studies.

HPS is most frequently found in patients with chronic parenchymal liver disease, however, it can also be found in patients with non-cirrhotic portal hypertension[5], a fact that suggests that portal hypertension is a predominant factor in the genesis of HPS.

Although the causes of HPS are unknown, it appears to result from an imbalance between vasoconstrictors and vasodilators, such as nitric oxide (NO), and hepatic factors that inhibit or stimulate the growth of vascular cells, such as hepatocyte growth factor (HGF) or vascular endothelial growth factor (VEGF). HPS results from microvascular changes in pulmonary gas exchange[6], through diffuse dilations at the pre-capillary level or capillaries, ranging from 15 to 500 μm (functional shunt) or arteriovenous communications (true shunt)[7]. Recent evidence has shown that pulmonary angiogenesis would also act as a contributing factor in the pathophysiology of HPS[2]. These vascular changes compromise the ventilation-perfusion relationship (V/Q). Combined with the hyperdynamic state present in liver dysfunction, they lead to an increase in blood flow in the pulmonary territory, with greater perfusion. Even if ventilation remains unchanged, this reduction in the time for gas exchange occurs.

The diagnosis of HPS has a negative impact on the prognosis of patients with liver cirrhosis, doubling the risk of mortality 2. It is important to highlight that there is no relationship described between the severity of liver disease and the presence of hepatopulmonary syndrome[3, 13].

Diagnosis

HPS screening should be carried out in all patients with chronic liver disease, especially those on the liver transplant list. A review by the International Liver Transplant Society, carried out by Krowka *et al.* (2016)[2] , defined the diagnosis of HPS as the recognition of the components of the syndrome's triad based on the following criteria: elevation in the alveolar-capillary oxygen gradient greater than 15 mmHg in younger patients at 64 years of age or 20 mmHg for those aged 65 years or over in an upright position at rest; recognition of intrapulmonary vascular changes via transthoracic echocardiography with contrast (bubbles); and presence of liver dysfunction, with greater prevalence in liver cirrhosis with portal hypertension. A recent study carried out by Barbosa et al, highlighted the possibility of using transesophageal echocardiography to detect intrapulmonary vasodilation in cases of inconclusive transthoracic echocardiography, associated with changes in the alveolar-arterial oxygen gradient or even hypoxemia, without primary heart or lung disease that justify these changes[9].

It is important to differentiate HPS from portopulmonary hypertension (PPH), as these two conditions are often confused. Regarding the pathophysiological aspect of these conditions, in PPH there is mainly vasoconstriction in the lung bed in addition to changes in the vessel like what occurs in primary pulmonary hypertension, including plexogenic arteriopathy; while in HPS, as mentioned above, one of the main elements of the triad is precisely pulmonary vasodilation associated with arteriovenous shunts. We can classify the severity based on PaO2 values: ≥80mmHg (mild); <80 and ≥60mmHg (moderate); <60 and ≥50 (Severe); < 50mmHg (Very Severe) 26. Clinically, in HPS, hypoxemia is more severe, with PaO2 possibly being less than 50mmHg, and accompanied by orthodeoxia[3,11]. On clinical examination, in HPS cyanosis and digital clubbing may occur and there is no involvement of the right ventricle. In PPH, what predominates clinically is right heart dysfunction.

The diagnosis of both has a negative impact on the prognosis of cirrhotic patients, increasing the mortality rate, in portopulmonary hypertension due to right ventricular failure and its complications[11], and in HPS due to a set of factors involving progressive hypoxemia and the action of vasoactive substances and inflammatory[12].

A recent study carried out by Forde et al, highlighted the specificity of reduced oxygen saturation in the diagnosis of HPS and its lack of sensitivity, constituting an ineffective method for screening HPS using pulse oximetry in liver transplant candidates[10].

Clinical manifestations

Rodriguez-Roisin and Krowka [3] highlighted the association between the presence of vascular spiders and more significant systemic and pulmonary vasodilation. All patients with HPS had telangiectasia, however, this was also found in patients without HPS in large proportions. It is believed that vascular spiders can be considered a cutaneous marker of pulmonary vasodilation.

In a study, Barbosa *et al.* (2018)[9] observed that the

signs on physical examination described in the literature as the greatest predictors of HPS, telangiectasia, digital clubbing and central cyanosis were present in different proportions, with telangiectasia being present in all patients with HPS (10%), and in 66% of the entire sample.

Platypnea is defined as dyspnea when moving from the supine to orthostatic position and orthodeoxia, as a drop in the partial pressure of oxygen greater than 5% or 3 mmHg, are also among the most common findings in HPS, found in around 25% of patients[2]. A large cohort study showed more frequent cyanosis and the presence of flapping in patients with HPS, when compared to patients with chronic liver disease without HPS[12].

Barbosa *et al.* (2018)[9] observed that 74.6% of patients presented hypocapnia, reflecting the hyperventilation that is common in cirrhotic patients, probably due to a compensatory mechanism directly related to the ventilation/perfusion disorder; being a determining factor for preferentially using the alveolar-arterial oxygen gradient, instead of PaO2, as it incorporates the partial pressure of carbon dioxide in addition to the concentration of inspired oxygen[15, 16, 17].

In the literature, findings regarding hypoxemia are discrepant. According to some authors, the prevalence of arterial hypoxemia in cirrhotic patients varies from 22 to 70% in different patient populations[19]. Possible factors responsible for these differences may be related to laboratory variation, selection of the group of patients studied, and different cut-offs used to define hypoxemia. Another study referring to HPS in 80 patients who were candidates for liver transplantation 18 found hypoxemia, defined as PaO2 less than 80 mmHg in only 8 (10%) patients, among those diagnosed as having HPS, only 2 (2.5%) had hypoxemia. The prevalence of HPS was 17.5%. Rodriguez-Roisin & Krowka (2004) showed that the presence of hypoxemia with a PaO2 lower than 60mmHg when associated with telangiectasia, digital clubbing and cyanosis strongly suggests HPS[3].

Treatment

The main element of symptomatic treatment is oxygen therapy. Several therapeutic modalities have been used in HPS, without satisfactory results or still requiring more clinical studies to better define their results, such as almitrine, indomethacin, tamoxifen, somatostatin analogues, sympathomimetics, beta-blockers, methylene blue, pentoxifylline and plasmapheresis[20, 21, 22, 23].

A large review of 73 cases of HPS [11] demonstrated that 82% of patients (adults and pediatrics) normalize their oxygenation changes within 9 to 15 months after liver transplantation, with normalization of contrast echocardiography and scintigraphy. Therefore, we can deduce that the only effective treatment to date is liver transplantation, with better results when carried out in the early stages of the disease. PaO2 below 60mmHg is used as an indicative parameter for prioritizing the patient on the liver transplant list[14]. Survival in 5 years after transplantation is 76%[13], and recurrence of the disease after this approach is rare.

To evaluate the prevalence of HPS and the epidemiological profile of outpatients with liver cirrhosis at HCFMB Unesp Botucatu, São Paulo, Brazil.

2. METHODS

The study was carried out at the Hepatopulmonary Syndrome outpatient clinic of the Júlio de Mesquita Filho University Hospital (Unesp), in Botucatu, in the State of São Paulo, Brazil.

The study approach was documentary in nature, descriptive with a quantitative approach based on contemporary or retrospective documents, considered scientifically authentic. For the study, we used the electronic medical records of adult patients over 18 years of age, being monitored at the Hepato-pulmonary outpatient clinic from January 2019 to June 2023, due to its ease of access and because it contains all the variables necessary to carry out the research, such as: age, sex, etiology, complementary exams. Examinations conducted within a year of each other were considered for statistical analysis.

The data were analyzed using descriptive statistics with table presentation, obtaining an epidemiological profile of the Hepato-pulmonary outpatient clinic.

A total of 157 medical records were evaluated, corresponding to all consultations carried out during the studied period, of which 105 were included in the research as the entire investigation had already been completed.

Exclusion criteria: patients who were still under investigation and had not undergone all diagnostic tests were excluded from the study.

Patients evaluated at this outpatient clinic had a diagnosis of chronic liver disease, being evaluated regarding epidemiological aspects: Etiology of cirrhosis, age, sex, Child-Pugh and Model End-Stage Liver Disease (MELD) scores, presence of hypocapnia in arterial blood gas analysis, hypoxemia and abnormal of alveolar oxygen gradient.

The etiological analysis was divided into: Virus C, Virus B, NASH, Alcoholic, Mixed (composed of more than one etiology, regardless of the cause), and others (Biliary, cystic fibrosis, autoimmune, hemochromatosis and cryptogenic).

Patients diagnosed with Hepatopulmonary Syndrome were those who presented an increase in the alveolar oxygen gradient associated with the imaging examination compatible with the presence of intrapulmonary shunt, either by transthoracic echocardiography with positive microbubble contrast from the 3rd cardiac cycle, perfusion scintigraphy pulmonary or transesophageal echocardiogram contrasted with microbubble.

Of the gasometrical parameters, we considered the presence of hypoxemia to be those with PaO2 values

below 80mmHg, and hypocapnia to those with PCO2 below 35mmHg. The alveolar oxygen gradient was calculated using the formula:

GA-aO2=Fio2x(P atmospheric-PH2O)-(PO2/0.8)-PCO2

Where we consider the water pressure (PH2O) as equal to 47mmHg and atmospheric pressure as equal to 760mmHg.

We consider the cutoff values for gradient change depending on age with the following parameter: The altered gradient: >15mmHg in patients up to 64 years old, and >20mmHg in patients over 64 years old.

Regarding the severity of HPS, we classified it based on PaO2 values: ≥80mmHg (mild); <80 and ≥60mmHg (moderate); <60 and ≥50 (Severe); < 50mmHg (Very Severe)[26].

3. RESULTS

We evaluated 157 patients, of which 52 patients were excluded because they did not present all diagnostic tests, making it impossible to confirm or exclude hepatopulmonary syndrome.

Of the 105 patients included in the research, 66 were male (62.85%). Among them, 84 (80%) had Child A, 17 (16.19%) had Child B and 4 (3.8%) had Child C.

The average age of the patients evaluated was 57.8 years, and the average Meld evaluated for these patients was 10.7 points.

In the etiological assessment, the main etiology evaluated was cirrhosis resulting from viral Hepatitis C, with 60 (57,14%) patients, followed by non-alcoholic fatty liver disease with 19 (18.09%) patients. The third most prevalent etiology was alcohol, with 7 (6.66%) patients. Cirrhosis due to viral hepatitis B, mixed etiology, and other etiologies presented 6 (5.71%) patients each.

Of these 105 patients included, 23 (21.9%) had hypoxemia, 52 (49.52%) had hypocapnia in blood gas tests, and 75 (71%) had increased alveolar oxygen gradient, but only 34 (32.38%) showed changes in imaging tests, intrapulmonary shunt, for diagnostic criteria for hepatopulmonary syndrome.

In the evaluation of the HPS group, a total of 25 men (73.52%) were observed, with an average MELD of 11.6 points, with an average age of 55.8 years. Of these patients, 19 (55.88%) had hypocapnia and 11 (32.35%) had hypoxemia. Regarding the Child-Pugh assessment, we observed 25 (73.52%) Child A patients with HPS, which would correspond to 30.12% of all 83 Child A patients in the research, 9 (26.47%) Child B patients with HPS and no Child C patient met the diagnostic criteria for HPS. Regarding etiology, we observed 17 (50%) patients with HCV with HPS, 5 (14.70%) patients with alcoholic etiology with HPS, 4 (11.76%) patients with NASH with HPS, 3 (8.8%) patients with virus B with HPS, 3 (8.8%) patients with mixed etiology with HPS, and only 2 (5.88%) patients with other etiologies with HPS.

When evaluating the severity of the HPS group, we observed a prevalence of 23 (67.64%) patients with mild HPS, 10 (29.41%) patients with moderate HPS, no patients with severe HPS and only 1(2.94%) with very severe HPS.

In the global analysis of etiologies, the etiology with the highest prevalence of HPS was alcoholic, being present in 5 than 7 patients (71.42%) of the sample, followed by viral hepatitis B with 3 of 6 patients (50%), mixed etiology with 3 of 7 patients (42,85%), other etiologies with 2 of 6 patients (33%), viral hepatitis C with 17 of 60 patients (28,33%) and finally, the etiology with the lowest prevalence of HPS was due to NASH, with 4 of 19 patients (21.05%) of the sample.

Table 1. Epidemiological assessment of the entire studied population (N=105 patients). HCV: Viral hepatitis C; HBV: Viral hepatitis B; NASH: Non-alcoholic steato hepatitis; OH: alcoholic. **Source**: the author.

Parameter studied (N=105)	Number	Percentage of total sample
Male	66	62.85%
Women	39	37.15%
Child A	84	80%
Child B	17	16.19%
Child C	4	3.80%
Median MELD	9	
Medium MELD	10,781	
Middle Ages	57,819	
Negative image for intrapulmonary shunt	54	51.42%
Positive image for intrapulmonary shunt	51	48.57%
Obstructive Spirometry	21	20%
Restrictive Spirometry	11	10.47%
Normal Spirometry	69	65.71%
Mixed disorder spirometry	two	1.90%
HCV etiology	60	57.14%
HBV etiology	6	5.71%
NASH etiology	19	18.19%
Etiology OH	7	6.66%
Etiology Others	6	5.71%
Mixed Etiology	6	5.71%
Hypocapnia	52	49.52%
Boosted Gradient	75	71%
Hypoxemia	23	21.90%

Table 2. Epidemiological assessment of the entire population with hepatopulmonary syndrome studied (N=34 patients). HPS: hepatopulmonary syndrome; HCV: Viral hepatitis C; HBV: Viral hepatitis B; NASH: Non-alcoholic steato hepatitis; OH: alcoholic. **Source**: the author.

Parameters studied in HPS patients	Number	Percentage
Number of SHP patients	34	32.38%
Average MELD SHP	11.6176	
Average age SPH	55.8235	
SHP Child A	25	73.52%
SHP Child B	9	26.47%
SHP Child C	0	0%
SHP Men	25	73.52%
SHP Women	9	26.48%
HCV etiology with HPS	17	50%
HBV etiology with HPS	3	8.80%
NASH etiology with HPS	4	11.76%
Etiology OH with SHP	5	14.70%
Etiology Others with HPS	two	5.88%
Etiology Mixed with HPS	3	8.80%
SPH with Hypocapnia	19	55.88%
HPS with Hypoxemia	11	32.35%
Light SHP Gradient (PaO2 >80)	23	67.64%
SPH Gradient Moderate (PaO2 <80 >=60)	10	29.41%
Severe SPH Gradient (PaO2 <60 >=50)	0	0.00%
Very Severe SPH Gradient (PaO2 <50)	1	2.94%

Table 3. Comparative assessment between subgroups to define hepatopulmonary syndrome for each etiology. HPS: hepatopulmonary syndrome; HCV: Viral hepatitis C; HBV: Viral hepatitis B; NASH: Non-alcoholic steato hepatitis; OH: alcoholic. **Source**: the author

Assessment of subgroups with HPS	Total for each etiology	Total SHP by etiology	Percentage
HVC	56	17	30.35%
HBV	6	3	50%
NASH	19	4	21.05%
OH	7	5	71.42%
Others	6	two	33.33%
Mixed	6	3	50%

4. DISCUSSION

According to the literature, HPS can affect patients of any age group and is not associated with clinical-demographic factors such as age, sex, smoking, and the etiology of liver cirrhosis[6, 24].

We can observe a higher prevalence in males in cases of cirrhosis, as well as in the HPS group, which is corroborated by the work carried out by Parolin et al. In our study, the average age at assessment of patients in general was 58 years, with a minimum age of 24 years and a maximum of 74 years, and in patients with HPS the average age was 55.8 years, with a minimum age of 24 years and a maximum of 71 years. Comparing with the work carried out by Parolin et al, whose average age was 46.19 years in this patient profile, varying between 19 and 66 years. In this research we present a more advanced age profile[25].

Based on the Child-Pugh assessment, given the conflicting data in comparison with the literature, which demonstrates a higher prevalence of HPS in patients with chronic liver disease in more advanced stages, we believe that such a prevalence of low scores (Child A) corresponds to patients evaluated on an outpatient basis, referred from the hepatology clinic, not necessarily on the liver transplant list.

The low MELD value corroborates the profile of patients assessed at the outpatient level, predominantly Child A. Such sampling may have had an influence on the predominance of this profile, even with the SPH complication, however, it is possible to observe an important percentage increase in the participation of Child B patients, as well as an increase in mean Meld in the HPS group, demonstrating a relationship with the prevalence of HPS in more advanced stages of the disease. However, it is important to highlight that 67.64% of patients with HPS criteria presented the mild form of the disease, that is, without the presence of hypoxemia (defined by PaO2 below 80mmHg), thus it is possible to note a considerable prevalence (30 .12%) of the entire Child A population studied, which are patients with not so advanced disease and without hypoxemia, going somewhat against the other studies studied, and can be questioned as an underdiagnosed condition in this patient profile, or as a diagnosis late. Consequently, the active search for HPS is emphasized in all cirrhotic patients, regardless of the severity of the disease or inclusion on the transplant list.

From the etiological profile, we believe that this discrepancy is due to the large flow of referrals of patients with hepatitis C, however, with the new epidemiological profile, we have recently seen an increase in NASH cases.

As pointed out by Rodríguez-Roisin *et al.* (2008)[3], and by Moller *et al.* (1998)[19] whose presence of hypoxemia can occur in 22 to 70% of patients with chronic liver disease, we found a total of 23 (21.9%) of the patients studied.

In patients with HPS, unlike what was presented by Martinez (2001)[18], we had a result of 19 (55.88%) patients with hypocapnia, being closer to the result shown by Barbosa et al.

We present 75 (71.42%) patients with increased alveolar arterial oxygen gradient, but, of these, 34 patients met diagnostic criteria for HPS, corresponding to 32.38% of the patients evaluated. Such sampling is consistent with the results presented by Castro (1996)[4].

Furthermore, when assessing severity, we observed a prevalence of mild HPS, which is consistent with the sample studied, since the worsening of liver function directly affects the scores, as well as the natural evolution and severity of the disease.

In patients with Hepatopulmonary Syndrome (HPS), a shift in prevalence patterns by etiology was evident compared to the previous study. HCV-related cirrhosis remained the primary etiology, likely influenced by a sampling bias that predominantly included patients with cirrhosis due to hepatitis C. However, the second most prevalent etiology for HPS was attributed to alcohol, despite having a significantly smaller overall sample size compared to fatty liver disease. It is crucial to highlight the limitation of these data in inferring this condition as more frequently leading to HPS due to the small number of patients in the sample with alcoholic liver cirrhosis. This suggests that the etiology of cirrhosis may directly influence the risk of developing HPS, indicating that, in the case of alcohol consumption, there is a higher likelihood of such a complication. However, a conclusive statement would require a study with a larger comparative sample.

In this study, we did not evaluate the mortality profile in the last 5 years, due to the great loss in the continuity of these patients in the years of the COVID-19 pandemic, therefore, many were lost to follow-up without having documented the outcome until now.

5. CONCLUSION

HPS is a complication related to portal hypertension, mainly in cirrhotic patients, the severity of which indicates criteria for prioritization on the liver transplant list. The research results demonstrated the epidemiological profile and prevalence of HPS in outpatients with liver cirrhosis at HCFMB UNESP Botucatu-SP, whose prevalence of HPS was 32.38%. We observed a predominance in the male population, and in the alcoholic etiology for the development of HPS and a lower prevalence in the NASH etiology, however, given the heterogeneous sampling and the

small number of individuals in the evaluation, more studies are needed to correlate the etiology and the prevalence of HPS.

Given the absence of predictive scores for its development, it is recommended that HPS be investigated in all cirrhotic patients, regardless of the etiology or degree of development of the disease.

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