

# Socioeconomic disparities in access to a hepatocellular carcinoma screening program in Brazil

Izabelle Venturini Signorelli,\* Patrícia Lofêgo Gonçalves, Luciana Lofêgo Gonçalves, Luiz Sérgio Emery Ferreira, Ana Tereza Parpaiola Mendonça, Gustavo Leite Franklin, Maria da Penha Zago Gomes

Universidade Federal do Espírito Santo, Hospital Universitário Cassiano A Moraes, Serviço de Gastroenterologia, Vitória/ES, Brazil.

**OBJECTIVES:** Cirrhotic patients must receive an abdominal ultrasound every 6 months as part of hepatocellular carcinoma (HCC) screening. The aim of this study was to assess if HCC screening was performed as recommended by the literature and to observe the differences between the private and public services in Brazil.

**METHODS:** We analyzed data from the HCC screenings of 253 cirrhotic patients from the University Hospital (n=177) and private sector (n=76) in Vitória, ES, Brazil.

**RESULTS:** Ultrasound screening was performed every 13.1 months on average (SD 9.02). In 37 out of 253 patients, the screenings were performed close to the recommended frequency; 16 were performed every 6 months, and 21 were mostly performed during the follow-up period every 6 months. In the remaining 216 cases, ultrasounds were not performed according to the guidelines; for 106 patients, less than 50% of all ultrasounds were performed every 6 months and 110 patients showed an interval greater than one year. Patients from the private sector received ultrasound screenings near the ideal in 28.9% of cases, while patients from the University Hospital received ultrasounds in only 8.4% of cases ( $p < 0.0001$ ). HCC was diagnosed in 30 patients (11.8%). For these 30 patients, 11 screenings were properly performed within 6 months (36.6%) and only 1 out of the 11 (9%) met the criteria for transplant. In the remaining 19 patients who did not receive the screening within 6 months, 6 (31.5%) did not meet the criteria for transplant.

**CONCLUSION:** HCC screening in our environment was irregularly performed, mainly in the public service setting, which prevented early diagnosis in a large number of patients.

**KEYWORDS:** Hepatocellular Carcinoma; Mass Screening; Diagnosis; Liver Cirrhosis.

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\*Corresponding author. E-mail: [izabellesignorelli@gmail.com](mailto:izabellesignorelli@gmail.com)

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and represents more than 90% of all primary liver cancer cases (1,2). The World Health Organization considers HCC to be the third most common cause of death by cancer in humans (3). Nearly 90% of HCC cases are associated with liver cirrhosis, especially those associated with the hepatitis B and C viruses (HBV and HCV, respectively) and alcoholism; however, any type of cirrhosis is a risk factor for tumor development (1,2).

Despite considerable progress in the treatment of HCC, the prognosis remains poor because most patients present with

advanced liver disease when they are diagnosed, preventing the use of therapeutic curative measures (4). Thus, HCC screenings in high-risk populations aim to reduce mortality because they may enable the identification of tumors at earlier stages and the use of therapeutic curative measures. Combining alpha-fetoprotein (AFP) measurement and abdominal ultrasound (US) improves HCC detection rates. It was initially suggested that US screenings should be conducted at 6-month intervals based on tumor doubling times. Shorter time intervals, such as every 3 months, may increase the detection of smaller nodules but have shown no significant effects on survival (5).

HCC screening is recommended for patients with cirrhosis of any etiology, Child-Pugh A and B (or Child-Pugh C if awaiting a liver transplant), non-cirrhotic disease with either a chronic HBV diagnosis or a family history of HCC and chronic carriers of HCV with advanced hepatic fibrosis (Metavir 3) (2). The objective of this study was to assess if HCC screening was performed as recommended by the literature and to observe whether the differences between public and private services interfere with early HCC diagnosis.

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## MATERIALS AND METHODS

This was a descriptive, cross-sectional study from October 2012 to May 2014 that used a retrospective analysis of the medical records of 253 cirrhotic patients. In total, we recruited 177 (70.0%) patients who required services from a reference unit at the Study of Liver Diseases University Hospital Cassiano A Moraes (UH) and 76 patients (30.0%) who required services from the private sector (PS). The follow-up was performed using the same criteria for both services. We included cirrhotic patients with any etiology who had been followed for at least 6 months within the last 10 years.

Demographic data, etiologies of cirrhosis, time intervals between cirrhosis diagnosis and HCC detection, time intervals between the US screenings during follow-up and the ultrasonography findings at every examination were retrieved from each record.

Liver cirrhosis was diagnosed according to clinical data in addition to an imaging method (i.e., computed tomography [CT] or nuclear magnetic resonance imaging [NMR], US), endoscopy or pathology. Alcohol abuse was defined as more than 60 g of ethanol intake per day for men and more than 30 g per day for women for at least 10 years. Persistent HBV infection was assessed by evaluating HBsAg and HCV infection using anti-HCV antibodies associated with PCR (polymerase chain reaction) to identify the RNA virus. Cirrhosis secondary to nonalcoholic steatohepatitis was diagnosed by the presence of metabolic syndrome after excluding other possible causes of chronic liver disease. Metabolic syndrome was diagnosed according to the criteria of the Brazilian Society of Endocrinology and Metabolism (6).

To characterize the time interval between abdominal US screenings during the follow-up program in private and public services, patients were separated into the following groups: 1) US every 6 months, defined as all US examinations performed within a time interval of 6 months; 2) most US within 6 months, defined as when more than 50% of all US screenings performed during follow-up were conducted every 6 months; 3) minority of US within 6 months, defined as when less than 50% of all US screenings performed during follow-up were conducted every 6 months; or 4) US after more than 1 year, defined as when more than 50% of all US screenings were performed with an interval of 1 year or more.

All patients had access to AFP measurement tests. The cut-off value of serum AFP was 10 ng/ml. Values over 10 ng/ml were considered to be abnormal and were suspicious for the presence of HCC. The size of the nodule evaluated at the time of HCC diagnosis was categorized as follows: 1) two or three nodules up to 3 cm, 2) one nodule up to 5 cm and 3) one nodule greater than 5 cm. Laboratory tests (HBsAg, anti-HCV antibodies, PCR for HCV RNA and serum AFP) were performed at the University Hospital for public sector patients and privately owned laboratories for private sector patients.

Patients were considered to have received regular medical follow-ups if they went to doctors' appointments at least every 12 months.

The software Statistical Package for the Social Sciences (SPSS, version 17.0 IBM, Chicago, IL, USA) was used for statistical analysis. Frequencies were compared by chi square test or exact Fisher test. Student's *t* test was utilized to compare age. A *p* value less than 0.05 was considered significant.

## Ethical considerations

This study was approved by the ethics committee of the Federal University of Espírito Santo under registration number 254.604.

## RESULTS

The US screening was performed every 13.1 months on average (SD 9.02). Among UH patients, the mean interval between US was of 14.9 months and 11.4 months among PS patients ( $p < 0.001$ ).

Demographic data, etiologies of liver cirrhosis, and regularity of US by the origin of the patients are shown in Table 1. The main isolated cause of cirrhosis was chronic alcoholism (42.4% versus 24.9% HBV and 18.1% HCV;  $p = 0.018$ ) in the UH group and HCV infection (38.2% versus 27.6% alcoholism and 10.5% HBV;  $p < 0.05$ ) in the PS group. The time intervals between US examinations were higher in the UH group than in the PS group ( $p < 0.05$ ). In addition, the time interval between US was significantly higher among patients who did not receive regular follow-ups (Table 2).

The mean time of follow-up was 65.43 months (SD 47.44; median 49). Thirty patients had an HCC diagnosis (11.8%), and the mean time between liver cirrhosis diagnosis and HCC diagnosis was  $43.7 \pm 36.4$  months (median 26 months).

During follow-up, 35 patients had a nodule identified by US and four patients had nodules identified by CT or MR to confirm suspicions after US or AFP. HCC was diagnosed in 26 of the 35 patients through nodule identification by US and HCC was diagnosed in all four patients through nodule identification by another imaging method. Among the 30 cases of HCC, 16 were from the UH and 14 from PS. The size and number of nodules detected during the follow-up period are shown in Tables 3 and 4 according to service type and frequency of US screening, respectively. An HCC diagnosis was established with greater frequency when the abdominal US was performed as recommended in the literature ( $p = 0.006$ ), and the greatest number of cases was identified among patients with HCV cirrhosis (12 cases HCV, 9 ethanol, 6 HBV, 2 NASH and 1 cryptogenic;  $p = 0.021$ ).

AFP was higher than 10 ng/ml in 47 patients; of these, 17 had HCC. However, in 13 cases of HCC (43.3%), the AFP level was normal. In three patients whose US did not show any nodules, the AFP levels were notably elevated, and other imaging methods were used to demonstrate HCC.

Table 4 shows the distribution of nodule size in relation to the frequency of abdominal US screening. Patients who had US screenings performed at time intervals longer than 1 year had the most cases with nodules larger than 5 cm identified at the time of diagnosis.

## DISCUSSION

Despite considerable progress in the treatment of HCC, the prognosis remains poor because most patients present with advanced liver disease when they are diagnosed, preventing the use of therapeutic curative measures (4). Our results confirm that screening performed irregularly does not allow early diagnosis of HCC in a high percentage of patients (7,8). The procedure of performing an abdominal US every 6 months for cirrhotic patients is cost effective (9), and this recommendation is internationally accepted, including by the public health system of Brazil (2,10).

**Table 1** - Demographic data, etiologies of liver cirrhosis and regularity of ultrasound performance according to type of public and private patients.

Variables	Groups*		All cases (n=253)	p-value**
	UH (n=177)	PS (n=76)		
<b>Gender n (%)</b>				
Male	131 (74)	52 (68.4)	183	0.417
<b>Age (mean ± SD)</b>	52.00 ± 12.05	56.00 ± 12.03	52.65 ± 12.2	0.553
<b>Cirrhosis etiology n (%)</b>				
Alcoholism	75 (42.4)	21 (27.6)	96 (37.9)	0.018
HBV	28 (15.8)	7 (9.2)	35 (13.8)	0.113
HBV + alcoholism	16 (9.1)	1 (1.3)	17 (6.7)	0.016
HCV	23 (12.9)	22 (28.9)	45 (17.7)	0.002
HCV + alcoholism	9 (5.2)	7 (9.3)	16 (6.3)	0.169
NASH	14 (7.9)	8 (10.5)	22 (8.6)	0.324
Others	12 (6.7)	10 (13.2)	22 (8.6)	0.148
<b>Regular follow-up n (%)</b>				
Yes	129 (72.8)	52 (68.4)	181 (71.5)	0.497
No	48 (27.2)	24 (31.6)	72 (28.5)	
<b>Time between US***n (%)</b>				
US every 6 months	8 (4.5)	8 (10.5)	16 (6.3)	0.045
US most in 6 months	7 (3.9)	14 (18.4)	21 (8.3)	0.002
US minority in 6 months	71 (40.2)	35 (46.1)	106 (41.8)	0.192
US over 1 year	91 (51.4)	19 (25.0)	110 (43.4)	0.001

\* UH=University Hospital; PS=private sector

\*\* Comparison between UH versus PS

\*\*\* US=Ultrasound

**Table 2** - Evaluation between regular medical appointment and ultrasound performance for hepatocellular carcinoma screening.

Variables	Regular medical appointment		p-value
	Yes (n=181)	No (n=72)	
<b>Time between US n (%)</b>			
US every 6 months	13 (7.2)	3 (4.2)	0.199
US most in 6 months	19 (10.4)	2 (2.8)	0.019
US minority in 6 months	91 (50.5)	14 (19.4)	<0.001
US over 1 year	58 (31.9)	53 (73.6)	<0.001

**Table 3** - Size and number of nodules of hepatocellular carcinoma diagnosed in patients with liver cirrhosis who were followed-up at the University Hospital or private sector in Vitória, ES, Brazil.

Nodule size	Group		p-value
	UH n=16	PS n=14	
<b>2 or 3 nodule up to 3 cm n (%)</b>	5 (31.2%)	7 (50%)	0.358
<b>1 nodule 3 up to 5 cm n (%)</b>	7 (43.8%)	4 (28.6%)	0.584
<b>Larger than 5 cm n (%)</b>	4 (25.0%)	3 (21.4%)	0.706

\* Hepatocellular carcinoma

\*\* UH=University Hospital; PS=private sector

The public health system in Brazil does not specifically recommend whether a US should be performed with or without AFP evaluation. Our results showed that although the AFP results were normal in 43% of diagnosed HCC cases, high serum AFP was observed in three HCC cases with normal US. For this reason, we believe that AFP measurement is a tool that must be performed with US to screen for HCC in cirrhotic patients; however, many authors have suggested otherwise (11).

Despite the effectiveness of the procedure, there was great scheduling irregularity of HCC screening in the studied sample, especially in the public service setting. As Table 1 shows, half of the patients from the public service setting received US at

intervals greater than 12 months. The adherence to screening observed here (50%) was inferior to that reported in a Californian study by Wong et al. (12) who described 64.2% to be ideal, and our adherence was also much lower than the 74.7% observed in 884 patients with liver cirrhosis at a public service hospital in the city of São Paulo (13). Patient adherence to screening partly depends on the attending physician, who must request tests and convince the patient of the importance and benefits of screening. At UH, the team of professionals who worked in the liver unit is composed of experienced gastroenterologists and hepatologists who are attentive to the needs and importance of HCC screening in cirrhotic patients. However, patients' adherence may be influenced by other factors, including difficulties in scheduling appointments and tests that are generally performed long after they were requested in the public system of health in Espírito Santo. This delay may negatively influence patients' adherence to the screening programs.

When we compared the patients from the UH and PS groups, adherence was significantly greater in the private group partly due to an enhanced ability to perform the screening without delay. Another factor that might have negatively influenced patients' adherence in the UH group was that patients with cirrhosis of an alcoholic etiology formed the majority of this group. Indeed, alcoholics are known to be poorly adherent to medical care (14).

In this study, regular follow-up was shown to be a relevant factor associated with regular US examinations. This observation agreed with data that were previously reported by Wong et al. (12), who demonstrated that the number of annual doctors' appointments was the only positive predictor for US examination in a screening program of cirrhotic patients.

In conclusion, our results showed that adherence to HCC screening in cirrhotic patients in our environment was low, mostly among patients attending public service centers. Poor adherence was likely due to the lengthy time between test requests and fulfillments.



**Table 4** - Number and size of hepatocellular carcinoma nodules diagnosed in cirrhotic patients by ultrasonography.

Frequency of Ultrasound	Number and size of nodules					
	2 or 3 nodules ≤ 3 cm		1 nodule ≤ 5 cm		1 nodule > 5 cm	
	n	%	n	%	n	%
US every 6 months	2	40.0	2	40.0	1	20.0
US most in 6 months	5	83.3	1	16.7	-	-
US minority in 6 months	1	12.5	5	62.5	2	25.0
US over 1 year	4	36.4	3	27.3	4	36.4
Total	12	40.0	11	36.7	7	23.3

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## AUTHOR CONTRIBUTIONS

Signorelli IV and Zago-Gomes MP contributed to the study conception, design, data analysis, and interpretation and wrote and edited the article. Signorelli IV, Zago-Gomes MP and Gonçalves LL reviewed and approved the final article. Signorelli IV, Gonçalves PL, Gonçalves LL, Ferreira LS, Mendonça AT, Franklin GL and Zago-Gomes MP contributed to data acquisition.

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