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Analysis of features associated with difficulty in screening and early diagnosing hepatocellular carcinoma in risk patients

Análise das características associadas à dificuldade de rastreamento e diagnóstico precoce do carcinoma hepatocelular em pacientes de risco

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Abstract

Introduction: *Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor. Through biannual screening with abdominal ultrasound (USG) and alpha-fetoprotein (AFP) in high-risk patients, an early diagnosis can be performed when there are proposals for curative treatment. Nevertheless, the existence of access barriers to HCC screening tests negatively impacts the prognosis of patients with chronic liver diseases.* ***Objectives:*** *This study aimed to evaluate the determinants that hinder access to screening and early diagnosis, through abdominal US, in patients at risk for HCC or already diagnosed with the cancer.* ***Methods:*** *Descriptive and cross-sectional study where, to assess the main factors associated with this difficulty in patients, a questionnaire was designed that addresses the most prevalent factors.* ***Results:*** *During the study period, 60 patients were evaluated. In a first analysis, it was observed that most patients were male sex (54%) and mean age was 59 years. The most observed etiology of chronic liver disease was alcohol (48%) followed by C virus infection (32%). Although 42.86% of patients deny difficulties in performing the screening tests, factors such as financial (12.50%) and lack of knowledge about the disease (10.71%) were identified as hindering factors. It was noted that 62% of patients diagnosed with HCC had no prospect for curative treatment.* ***Discussion:*** *When early diagnosed, HCC has curative treatment options, such as liver transplantation, with the lesser purpose of guaranteeing better quality of life for the patient. Even though, difficult access to the exam or lack of knowledge about the disease delay the follow-up of this patient and, accordingly, limit therapeutic strategies.* ***Conclusion:*** *A joint action of different levels of health care to solve the main problems represented in the difficulty of screening for HCC can help in the early diagnosis of cancer and, therefore, curative treatment options for the patient.*

Keywords: *Hepatocellular carcinoma, Screening, Early diagnosis, Early detection of cancer, Risk factors*

Resumo

Introdução: *O carcinoma hepatocelular (CHC) é o tumor maligno primário mais comum do fígado. Através do rastreamento semestral com ultrassonografia (USG) abdominal e alfafetoproteína (AFP), em pacientes de risco, seu diagnóstico pode ser realizado de maneira precoce, quando há propostas de tratamento curativo. Entretanto, a existência de inúmeras barreiras de acesso aos exames de rastreamento do CHC impacta negativamente no prognóstico dos pacientes portadores de hepatopatias crônicas.* ***Objetivo:*** *O estudo teve como objetivo avaliar os determinantes que dificultam o acesso ao rastreamento e diagnóstico precoce, através da USG abdominal, em pacientes de risco para CHC ou já diagnosticados com a neoplasia.* ***Métodos:*** *Trata-se de um estudo descritivo e transversal, onde, para avaliar os principais fatores associados a essa dificuldade nos pacientes, foi aplicado um questionário que aborda estes fatores mais prevalentes.* ***Resultados:*** *Durante o período de estudo, 60 pacientes foram abordados. Em uma primeira análise, foi observado que a maioria dos pacientes era do sexo masculino (54%) e idade média de 59 anos. Da doença hepática crônica, a etiologia mais observada foi álcool (48%) seguida da infecção pelo vírus C (32%). Apesar de 42,86% dos pacientes negarem dificuldades para realização dos exames de rastreio, fatores como financeiro (12,50%) e desconhecimento da doença (10,71%) foram apontados como dificultadores. Dos pacientes com CHC, foi notado que, ao diagnóstico, 62,5% não tinha perspectiva de tratamento curativo.* ***Discussão:***

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Quando diagnosticado precocemente, o CHC possui opções de tratamento curativo, como o transplante hepático, com intuito secundário de garantir melhor qualidade de vida ao paciente. Entretanto, a dificuldade de acesso ao exame ou o desconhecimento da doença retardam o acompanhamento deste paciente e, consequentemente, limitando as estratégias terapêuticas. ***Conclusão:*** *A ação conjunta dos diferentes níveis de atenção de saúde para solucionar os principais problemas envolvidos na dificuldade de rastreio para o CHC podem auxiliar no diagnóstico precoce do câncer e, portanto, opções de tratamento curativo ao paciente.*

Palavras chave: *Carcinoma hepatocelular, Rastreamento, Diagnóstico precoce, Detecção precoce do câncer, Fatores de risco*

Introduction

Hepatocellular carcinoma (HCC) is the most usual primary malignant tumor of the liver. It is supposed to portray 5% of all cancer cases in the world; it is the fifth most common type of cancer in men and the eighth in women. In 2008, beyond 748,000 new cases of HCC were recorded on a global scale, besides roughly 696,000 deaths from this disease. As stated in DataSUS data, between July 2014 and June 2015, 5,487 new cases of HCC were registered in Brazil, they included, 88% had not been formerly diagnosed with underlying diseases that predispose them, which may evidence the underreporting of these diseases failure to monitor on them and delayed diagnosis of HCC[1-4].

This tumor is resulting from a chronic aggression to liver cells, with greater susceptibility in male patients, and as a rule, in patients aged around 60 years. The primary risk factors for HCC are chronic hepatitis B virus (HBV) infections, patients with advanced fibrosis caused by the hepatitis C virus (HCV) and non-alcoholic fatty liver disease (NAFLD), besides liver cirrhosis of any etiology. The majority of patients who develop cancer have underlying liver cirrhosis, and in Brazil, the main etiology of cirrhosis is closely related to chronic HCV infection in 70% of cases [2,5].

Considering that HCC is a silent and immensely aggressive disease, screening patients in risk groups is the most effective way to warranty early diagnosis, the possibility of cure, and enhanced survival rate for these patients. Screening of patients with hepatitis B, F3 fibrosis as a consequence of NAFLD or chronic HCV infection and compensated cirrhotic patients of any etiology should be performed utilizing abdominal USG, every 6 months. This imaging test is inexpensive, non-invasive and effective, with a sensitivity of 58% to 89% and a specificity greater than 94%. Alpha-fetoprotein has a low specificity, as it may be high as a result of the necroinflammatory activity of hepatitis viral, being a more efficient test for screening in cases of non-viral cirrhosis, nevertheless, it is widely used, together with the abdominal US, for the purpose of increasing the sensitivity of the screening[5-7, 9-10,12].

The diagnosis of HCC commences with an ultrasound finding of a suspected liver nodule, which may be closely related to an increased serum alpha-fetoprotein (AFP) level. In cases of suspicion, the demonstration, in complementary diagnostic tests of hypervascularization, in the arterial phase, and in contrast whitening or washout, in the late phases after enhancement, rises the probability of HCC by 65 times[5,7].

Accordingly, this finding can ideally be obtained over dynamic, non-invasive radiological methods, for instance, computed tomography (CT) and nuclear magnetic resonance (NMR). After a positive diagnosis for HCC, the staging for the tumor must be defined and, at present, in Brazil, it is recommended that the staging system developed by the Barcelona Clinic Liver Cancer (BCLC) be accustomed for tumor classification. As reported by the BCLC, HCC is classified into five stages, in line with the size and location of the tumor, symptoms and the patient's liver function, they are: stage 0 (very early), stage A (initial), stage B (intermediate), stage C (advanced) and stage D (terminal)[13-16].

Therapeutic options for HCC rely on the stage at which the tumor was diagnosed as well as on the presence or absence of other comorbidities. Conceivably curative procedures, characteristic of early stages of HCC, comprise liver transplantation and surgical resection of the tumor, which is the first-line treatment in non-cirrhotic patients diagnosed in the early stages of the disease. Patients in stage 0 or A, not eligible for surgical resection or awaiting liver transplantation, are indicated for radiofrequency ablation or chemical ablation by percutaneous ethanol injection, both of which help to prevent tumor progression. When HCC is already intermediate, the principal advised procedure is transarterial catheter chemoembolization which purposes to prevent tumor progression. In advanced stages, available treatments, besides not allowing a cure, present high mortality rates. Sorafenib, oral chemotherapy, is a first-line therapeutic option with scientific evidence of survival gain for cases of unresectable HCC. Nevertheless, new drugs as the combined use of atezolizumab with bevacizumab have already been studied and had better outcomes than the isolated use of sorafenib. Terminal patients, stage D in agreement with the BCLC classification, should receive palliative care, without anticancer treatment, for the sake of ensuring only a better quality of life for the patient[10-11,13].

At present, in Brazil, access to early diagnosis and treatment of HCC is not fairly warranted for the entire population. Access barriers include stigmas around underlying diseases, absence of awareness campaigns, variation in quality and type of care between different establishments in the public system, fragmentation of the referral and counter-referral system between the different levels of care in the SUS, distance patient--health facility, the time to schedule exams and the delay in starting treatment, with an average of 76.3 days of waiting between diagnosis and the first treatment. Contrarily, data analysis from DataSUS between July 2014 and June 2015 indicated that merely 9.8% of patients with HCC are diagnosed at an early stage, and 62.2% receive the diagnosis when just palliative care is feasible [4, 17-19].

As a result, when HCC is detected in its early stages, it is potentially curable and, for this reason, it is required to establish and implement measures that remove access barriers to early diagnosis of the disease[14,20-22].

Material and methods

This is an exploratory, descriptive and longitudinal study that was performed over a 12-month period by medical students at the School of Higher Sciences of Santa Casa de Misericórdia de Vitória (EMESCAM), in the Hepatology outpatient clinics of the teaching hospital Hospital Santa Casa de Misericórdia de Vitória (HSCMV), from the approval of the Research Ethics Committee (CEP), with the Certificate of Presentation for Ethical Appreciation (CAAE) number 26435119.1.0000.5065.

A questionnaire that addresses sociodemographic aspects and screening of determinants that hinder the screening and early diagnosis of HCC in patients followed up at the Hepatology outpatient clinic was conducted. Men and women were included, without age limitation, diagnosed with chronic infection by virus B, advanced fibrosis (F3) and patients with non-alcoholic fatty liver disease (NAFLD) or chronic infection by virus C who also have this degree of liver disease, together with patients in stage of liver cirrhosis regardless of etiology. Patients with neurocognitive disorders that interfere with autonomy or independence, and who are not able to decide for themselves were excluded.

Categorical variables were analyzed using frequencies and percentages, and associations were verified using the chi-square test or Fisher's exact test (in the case of expected values less than 5 and tables in the 2 x 2 matrix form). Numerical variables were analyzed by data summary measures such as mean and standard deviation, and the comparison between groups was performed using the Student's t-test for independent samples, since the Kolmogorov-Smirnov test showed a normal distribution ($p>0.05$).

Associations and comparisons were considered significant in the case of p-value < 0.05.

Data were tabulated in an EXCEL spreadsheet and analyzed in the IBM SPSS Statistics (Statistical Package for Social Sciences) version 27 program.

Result

Throughout the study period, 60 patients were approached through a questionnaire and divided, first, into two groups: non-cirrhotic and cirrhotic. Table 1 shows the sociodemographic aspects of the research participants, including data such as age and gender, in addition to information regarding the underlying chronic liver disease.

Table 2 was built from information regarding outpatient follow-up in the Hepatology service and possible difficulties encountered in tracking HCC, with most patients (76%) undergoing regular and biannual follow-up with abdominal US for screening HCC. When asked about the understanding of the importance of the imaging exam, the most obtained answers were "liver assessment" or "disease follow-up".

The profile of patients diagnosed with hepatocellular carcinoma was also analyzed and placed in Table 3.

Discussion

HCC, the most common primary malignant tumor of the liver, can be tracked through a biannual surveillance program using alpha-fetoprotein (AFP) and abdominal ultrasonography (USG) measurements that allow for early diagnosis of cancer, when there are still curative and treatment options and the opportunity to offer a better quality of life to the patient [1].

This field, cross-sectional and descriptive study analyzed the factors, not only socio-epidemiological of patients with indication for screening, but also factors that hinder the access to biannual surveillance to the HCC. In general, most patients participating in the research were male, with an average age of 59 years, having completed elementary school (1st to 9th grade) and, as marital status, "married or living as married", different from the data found in the study by Steel et al[6].

Among the observed etiologies, alcohol was found in 48% of cases, as in other descriptive and observational studies such as Souza et al. (2021), with a causal relationship between the amount and duration of consumption with the onset of chronic liver disease. According to the 2018 report of the World Health

Table 1

Analysis of the epidemiological profile of patients participating in the research.

Variables analyzed	*Groups*		*All cases (n = 50)*
	Non-cirrhotic (n = 9)	*Cirrhotic (n = 41)*	
Male gender n (%)	5 (10)	22 (44)	27 (54)
Age (average ± SD)	54 ± 9.22	59 ± 11.45	59 ± 11.16
Education n (%)			
Elementary school (1st to 9th grade)	6 (12)	25 (50)	31 (62)
High School (Former 2nd degree)	2 (4)	8 (14)	10 (20)
University education	1 (2)	4 (8)	5 (10)
None (0 years)	0 (0)	3 (6)	3 (6)
Marital status n (%)			
Never married	1 (2)	5 (10)	6 (12)
Married or live like married	6 (12)	22 (44)	28 (56)
Widower (Widow)	1 (2)	8 (16)	9 (18)
Separated	1 (2)	2 (4)	3 (6)
Divorced	0 (0)	4 (8)	4 (8)
Etiology of chronic liver disease			
Alcohol	12 (24)	12 (24)	24 (48)
HBV	3 (6)	9 (18)	12 (24)
HCV	6 (12)	10 (20)	16 (32)
HCV + Alcohol	0 (0)	1 (2)	1 (2)
Alcohol + HBV + HCV	0 (0)	1 (2)	1 (2)
NASH	0 (0)	5 (10)	5 (10)
Others	0 (0)	3 (6)	3 (6)
Child n (%)			
A	--	22 (55)	22 (55)
B	--	16 (40)	16 (40)
C	--	2 (5)	2 (5)
MELD (min ± max)	--	6 ± 21	6 ± 21
Complications associated with liver cirrhosis			
Esophageal varices	--	23 (29.11)	
HDA	--	7 (8.86)	
Ascites	--	18 (22.78)	
Encephalopathy	--	12 (15.19)	
Hepatorenal syndrome	--	3 (3.80)	
Others	--	6 (7.60)	
Absence of complications	--	10 (12.66)	

Sources: The authors.

Organization (WHO), a daily consumption of alcohol above 80 grams for more than 10 years increases the risk of developing liver cirrhosis[23-24].

Viral etiologies also had an important etiological role for chronic liver diseases, with emphasis on HCV infections (32%) and HBV infection (24%), as the 2nd

Table 2

Analysis of the outpatient follow-up of patients participating in the research.

Variables analyzed	*Groups*		*All cases (n = 50)*	*p-value*
	Non-cirrhotic (n = 9)	*Cirrhotic (n = 41)*		
Frequency of consultations n (%)				
1st time	1 (2)	5 (10)	6 (12)	0.011b
≤ 6 months	4 (8)	33 (66)	37 (74)	
7 to 12 months	4 (8)	2 (4)	6 (12)	
>12 months		1 (2)	1 (2)	
Regular follow-up with USG				
Yes	7 (14)	31 (62)	38 (76)	1.000a
No	2 (4)	10 (20)	12 (24)	
Understand the Importance of USG				
Yes	6 (12)	23 (46)	29 (58)	0.716a
No	3 (6)	18 (36)	21 (42)	
Greater difficulty in performing the examination				
Finantial		7 (12.50)	7 (12.50)	0.912b
Forgetfulness		2 (3.57)	2 (3.57)	
Exam scheduling	3 (5.36)	11 (19.64)	14 (25)	
Transport to the site		2 (3.57)	2 (3.57)	
No prior knowledge of the disease	1 (1.79)	5 (8.93)	6 (10.71)	
Result release		1 (1.79)	1 (1.79)	
No dificulty	5 (8.93)	19 (33.93)	24 (42.86)	

Source: The Authors. a Fisher exact test. b Chi-square Test

and 3rd prevalent etiologies, respectively, different from the study of cohort by Paranaguá-Vezozzo et. al (2014) who places these infections as the two main ones involved in chronic liver disease. It is worth noting that the chronic carrier status asymptomatic to hepatotropic viruses often delays early diagnosis and treatment, so that this etiology is investigated in an already established liver cirrhosis or in its more advanced course of HCC. With specific antiviral treatment, the risk of progression to HCC is reduced, but not eradicated, which justifies the outpatient and careful monitoring of these patients, even after reaching the sustained virological response (SVR), in cases of hepatitis C, or starting to drug therapy with tenofovir or entecavir for cases of hepatitis B[9,25-27].

Concerning the group of patients with HCC, the majority (75%) had a previous diagnosis of liver cirrhosis, as shown by other national scientific studies such as Carrilho et al[13], with alcohol and viruses as the main etiologies involved. In this study, it was observed that half of the patients who received the diagnosis of HCC were not followed up in a specialized Hepatology outpatient service and some were still unaware of the underlying liver disease[13].

It was seen in this same group that the absence of biannual screening and low adherence to the follow-up of liver disease influenced a late diagnosis of cancer and no prospect of curative treatment in 62.5% of cases. This same conclusion is demonstrated by the most frequent staging of the disease: BCLC D in half of the observations, considered the end stage of the disease, with no proposal for curative treatment and with an estimated survival time of 3 months [27].

Accordingly, by understanding that HCC is a primary liver tumor which can be tracked and treated in the early stages of evolution, systematized lines of care can become a tool to overcome difficulties encountered until the diagnosis of this cancer. Given the fact that a significant portion of patients had an unknown diagnosis of a chronic liver disease, primary health care has an important role in providing screening tests (quick tests) for viral hepatitis, which have become prevalent causes of chronic liver disease and HCC in this study and in other publications such as Gomes et al[1] and

Table 3

Analysis of the profile of patients diagnosed with hepatocellular carcinoma (HCC).

Variables analyzed	*Groups*		*All cases (n = 8)*
	Non-cirrhotic (n = 2)	*Cirrhotic (n = 6)*	
Gender n (%)			
Male	2 (25.0)	1 (12.5)	3 (37.5)
Female	0 (0.0)	5 (62.5)	5 (62.5)
Age (average)	47	61	58
Etiology of chronic liver disease n (%)			
Alcohol		2 (25)	2 (25)
HBV	1 (12.5)	1 (12.5)	2 (25)
HCV	1 (12.5)		1 (12.5)
HCV + Alcohol		1 (12.5)	1 (12.5)
NASH		1 (12.5)	1 (12.5)
Others		1 (12.5)	1 (12.5)
Frequency of consultations n (%)			
1st time	1 (12.5)	3 (37.5)	4 (50)
≤ 6 months	1 (12.5)	2 (25)	3 (37.5)
>12 months		1 (12.5)	1 (12.5)
Regular follow-up with USG			
No	1 (12.5)	4 (50)	5 (62.5)
Yes	1 (12.5)	2 (25)	3 (37.5)
Understand the importance of the USG			
No	1 (12.5)	4 (50)	5 (62.5)
Yes	1 (12.5)	2 (25)	3 (37.5)
BCLC to diagnosis			
BCLC 0	1 (12.5)		1 (12.5)
BCLC A		2 (25)	2 (25)
BCLC C	1 (12.5)		1 (12.5)
BCLC D	1 (12.5)	3 (37.5)	4 (50)
Is there time for curative treatment?			
Yes		3 (37.5)	3 (37.5)
No	2 (25)	3 (37.5)	5 (62.5)
AFP values at diagnosis (min ± maximum)	2 ± 80.000	73 ± 481.74	

Source: The Authors.

Kirstein, Vogel[3], in addition to raising awareness about alcohol abuse and the importance of controlling metabolic factors such as blood pressure[1,3,26].

Regarding the level of secondary care, encouraging outpatient follow-up in specialized care to adapt to the biannual HCC tracking has a positive impact, demonstrated in this study ($p<0.05$) and by Signorelli et al. [20], focusing on health prevention at the secondary level.

Even though 42.86% of patients answered that they did not find it difficult to perform the exam, there are still problems to overcome in this scenario. Given that "exam scheduling" was present in most observations, the role of secondary care with a focus on adapting to the demand of this profile of patients through greater availability of places for the USG exam can be a strategy of positive impact for this problem.

Finally, tertiary care would be aimed at secondary and tertiary prevention for patients at risk or with an established diagnosis. There is a wide range of available therapeutic options depending on the stage of the disease, including, for example, promising systemic therapies with the use of Sorafenib or, according to the most recent studies, the association of atezolizumab and bevacizumab for advanced HCC in BCLC stage C[1,5,11,18,27].

By ensuring the joint action of the different levels of health care, it is expected, consequently, to open new perspectives of quality of life, not only for patients with a previous diagnosis of HCC, but also for patients with chronic liver disease. The impact on quality of life by virtue of cancer is negative and may include, for example, emotional changes and social isolation in the patient, as demonstrated in studies by Bianchi et al[7] and Steel et al[6].

When cancer is still at an early stage, it can present itself as a single nodule, with a diameter less than 2 cm and asymptomatically, which reiterates the importance of screening for early diagnosis and offering curative therapies[1].

Conclusion

In the setting of chronic liver disease, biannual screening for HCC through abdominal USG and AFP is essential for early diagnosis of cancer. When in early stages, it is possible to offer curative therapies to patients, with a positive impact on quality of life. As noted in this study, the greatest difficulties encountered by patients in performing the exams are found in the lack of knowledge about the underlying liver disease and financial problems. The combined action of different levels of health care services (primary, secondary and tertiary) can be a tool to overcome these adversities and, thus, allow an early diagnosis of cancer and propitiate a better quality of life for the patient.

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