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Prevalence and Diagnosis of Incidental Hepatocellular Carcinoma in Surgical Patients Submitted to Liver Transplantation at Santa Isabel Hospital in Blumenau (SC)

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Abstract: **Objectives:** To quantify the frequency of incidental hepatocellular carcinoma (iHCC) and evaluate the reasons for liver transplantation in the study population and the accuracy of imaging tests in diagnosing hepatocellular carcinoma (HCC) in a liver transplant referral center. **Methods:** Retrospective sectional study conducted based on 426 medical records of patients who underwent liver transplantation at the Hospital Santa Isabel in Blumenau (SC), between January 2016 and December 2019. The pathology reports of the explanted livers, the evolution of the patients, and the reports of the imaging exams performed up to six months before the transplant were evaluated. Patients under 18 years of age, history of retransplantation, fulminant liver failure, metabolic liver disease, autoimmune hepatitis, and other etiologies of liver failure with a lower risk of developing HCC were excluded. **Results:** Of the 426 transplant patients, 89 were excluded. Among those included, 190 (56.38%) were transplanted for cirrhosis without previously diagnosed HCC and 147 (43.62%) for previously diagnosed HCC. The frequency of iHCC was 7.89% (15/190). Hepatitis C virus was more frequent among patients with previously diagnosed HCC than among those with iHCC (p = 0.033). Magnetic resonance imaging (MRI) was the most sensitive and least specific test (S = 100%; E = 75.76%). Computed tomography (CT) showed high sensitivity and specificity (S = 93.75%; E = 90%), while ultrasonography showed low sensitivity and high specificity (S = 56.76%; E = 97.86%). **Conclusion:** This study found similar data to the international literature regarding the frequency of iHCC. Ultrasonography was the least sensitive test, while CT and MRI showed higher sensitivity than seen in the literature. The MRI showed lower specificity than most of the references analyzed.

Descriptors: Hepatocellular Carcinoma; Liver Transplantation; Terminal Liver Disease; Liver Neoplasms.

INTRODUCTION

Liver cancer is the fourth leading cause of cancer death in the world. Among its various subtypes, hepatocellular carcinoma (HCC) accounts for 75 to 85% of all malignant neoplasms of the organ.[1] Conditions that lead to cirrhosis, such as alcoholism, viral hepatitis, and nonalcoholic fatty liver disease, are major risk factors for developing HCC.[2]

The diagnosis of HCC is difficult in some patients, especially when the tumor is smaller than 20 mm. The histopathological finding of HCC in the liver explant, not previously diagnosed by imaging or laboratory method in the recipient liver,

characterizes incidental hepatocellular carcinoma (iHCC).[3] The frequency of iHCC is variable, fluctuating from 1 to 10% in study centers.[3-13]

Ultrasonography (USG) is the test of choice for screening HCC in patients with cirrhosis of any etiology. At the same time, computed tomography (CT) and magnetic resonance imaging (MRI) are the best tests for the most accurate diagnosis of the neoplasm. [14] When a nodule larger than 10 mm is found on USG, multiphase examinations (CT or MRI) are performed, preferably with hepatospecific contrast (gadoxetic acid), to better define the lesion.[15]

Cirrhosis consists of the end stage of all chronic liver diseases.[16] The gold standard diagnostic method for liver cirrhosis is biopsy; however, this is an invasive test and has limitations. In the center where this study was conducted, the diagnosis of cirrhosis is made by a combination of laboratory and clinical trials, such as the aspartate aminotransferase to platelet count ratio (Apri) index, assessment of tissue stiffness by liver elastography, and imaging tests, as well as the gold standard technique.[16,17]

Liver transplantation is the main treatment for acute and chronic liver failure and special indications, such as HCC.[18] The Model for End-Stage Liver Disease (Meld) scale estimates the risk of death on the transplant waiting list by analyzing serum bilirubin, prothrombin time, and serum creatinine. This scale is used to organize the liver transplant queue.[19] Because of the rapid evolution of HCC, which Meld does not predict, these patients receive an additional score, according to Ordinance No. 2600 of October 21, 2009, of the Brazilian Ministry of Health.[20,21] Patients not diagnosed with iHCC no longer receive these points, which have the potential to increase their waiting time in the transplant queue and may worsen their prognosis.[4]

In Santa Catarina, 135 liver transplants were performed with a deceased donor, in 2018.[22] The city of Blumenau is a reference in transplants in the state and is home to the Hospital Santa Isabel, which service has 1,456 liver transplants performed by the end of 2020.[23,24] Given this scenario, the present study evaluated the frequency of iHCC and its relation with imaging exams in a reference center.

METHODS

This is a retrospective sectional study developed based on 426 medical records of liver transplantation patients at Santa Isabel Hospital in Blumenau between January 2016 and December 2019. Medical students performed the analysis. The Research Ethics Committee approved the project of the Blumenau Regional University, and all patients signed an informed consent form for liver transplantation from a deceased donor, which included authorization to use the data contained in their medical records for scientific research.

Exclusion criteria were age less than 18 years, retransplantation, fulminant hepatitis, autoimmune hepatitis, drug-induced hepatitis, transplantation at another institution, cholangitis, Budd–Chiari syndrome, polycystic disease, amyloidosis, Caroli disease, schistosomiasis, cystic fibrosis, Rendu–Osler–Weber syndrome, hemochromatosis, hemosiderosis, glycogenosis type 1, liver metastases, tumors other than HCC, and fibrolamellar HCC.

Screening for HCC among the patients was performed with USG every six months. Computed tomography or MRI was done if the patient had a suspicious liver nodule on USG. According to the guidelines of the European Association for the Study of the Liver, the diagnosis of HCC was based on contrast-enhanced multiphase radiological examinations (CT or MRI) and/or biopsy. The typical finding of HCC on these imaging examinations is the combination of hypervascularization in the arterial phase with washout in the portal or late phase.[15,25] All examinations with suspected HCC were considered positive. The pathology reports of the explanted livers, the evolutions of the patients, and the reports of the imaging exams up to six months before transplantation were evaluated.

The patients were initially divided into two groups:

- Transplanted for cirrhosis (TxCi), consisting of those who had cirrhosis but not previously diagnosed HCC at transplantation (pdHCC);
- Transplanted HCC (TxHCC), consisting of those who already had a diagnosis of HCC before transplantation.

The TxCi group was subdivided into the iHCC and cirrhosis only (CiOn) groups, according to the presence or absence of HCC, respectively. The iHCC was defined as the presence of HCC on pathological examination of the explanted liver, not previously diagnosed.

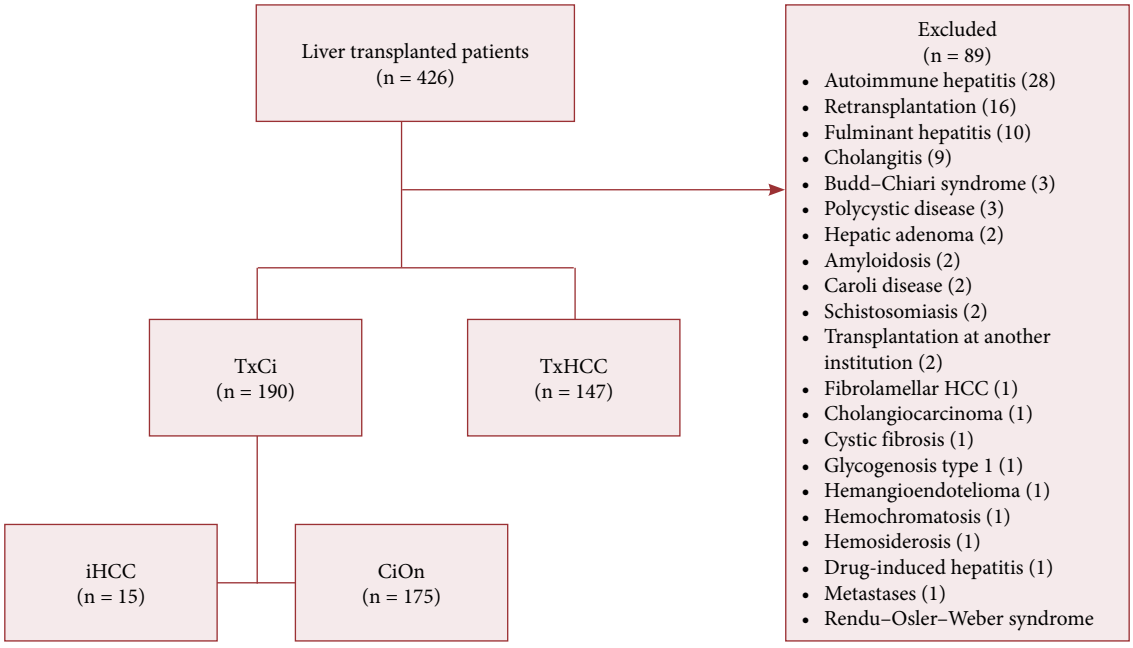
Based on the data obtained, the frequency of the incidental HCC finding was given by the quotient of the number of patients with iHCC by the number of patients in the TxCi group. In addition, the frequency of false-positive HCC diagnoses in the TxHCC group was quantified. The specificity and sensitivity of imaging tests and biopsy in detecting HCC using pathology examination as the gold standard were analyzed. The etiologies of liver diseases that led to transplants were quantified.

The data were organized in descriptive tables containing mainly absolute and relative frequencies (proportions in percentage form). Categorical variables were analyzed with the test of independent proportions. $P < 0.05$ was considered significant. Data analysis occurred with Microsoft Excel 2016 and Epi Info version 7.2.1.0 applications.

RESULTS

Of the 426 patients, 89 were excluded. In the excluded group, the reasons were: autoimmune hepatitis (n = 28; 31.46%), retransplantation (n = 16; 17.98%), fulminant hepatitis (n = 10; 11.23%), and others (n = 35; 39.33%). Among those included, 190 (56.38%) were transplanted for cirrhosis without pdHCC (TxCi) and 147 (43.62%) for pdHCC (TxHCC) (Fig. 1). The frequency of iHCC in the TxCi group was 7.89% (15/190), and the frequency of false-positives in the TxHCC group was 7.48% (11/147) (Table 1).

The most frequent reason for transplantation after HCC was alcoholic cirrhosis, followed by hepatitis C and B in the patients analyzed. The most common etiology in the TxCi and CiOn groups was also alcoholic (48.42 and 50.29%, respectively). In the TxHCC group, viral hepatitis was the most frequent (71.43%). In the iHCC group, there was no prevalent etiology. Alcoholism,



TxCi: cirrhosis transplant group; TxHCC: hepatocellular carcinoma transplant group; iHCC: incidental hepatocellular carcinoma group; CiOn: cirrhosis only group; HCC: hepatocellular carcinoma.

Figure 1. Group division of those included in the study and frequencies of reasons for exclusion.

Table 1. Frequency distribution of patients transplanted for hepatocellular carcinoma and cirrhosis.

Groups	n (%)
Considering all the patients analyzed (n = 337)	
TxCi	190 (56.38)
TxHCC	147 (43.62)
Of those transplanted for cirrhosis (n = 190)	
iHCC	15 (7.89)
CiOn	175 (92.11)
Of those transplanted for HCC (n = 147)	
True positives	136 (92.52)
False positives	11 (7.48)

TxCi: cirrhosis transplant group; TxHCC: hepatocellular carcinoma transplant group; iHCC: incidental hepatocellular carcinoma group; CiOn: cirrhosis only group.

hepatitis C virus (HCV) and metabolic dysfunction-associated fatty liver disease (MAFLD) had the same frequency, 26.67%. In comparison, hepatitis B virus (HBV) and cryptogenic etiology accounted for 20% of each etiologies (Table 2). HCV was more frequent among patients with pdHCC than among those with iHCC (p = 0.033).

A total of 177 USG, 139 MRI, 133 CT, and 19 biopsies were performed. The frequency of performing each exam differed between the groups without statistical significance. In the iHCC group, none of the patients underwent MRI, as opposed to 14.29% of the patients in the CiOn group (p = 0.140). The percentage of patients who had at least one multiphasic contrast-enhanced imaging exam, excluding those who had biopsy, was 45.71% in the CiOn group and 26.67% in the group with iHCC (p = 0.237) (Table 3).

MRI was the most sensitive and least specific test (S = 100%; E = 75.76%). CT showed high sensitivity and specificity (S = 93.75%; S = 90%), while USG, low sensitivity and high specificity (S = 56.76% and S = 97.86%) (Table 4).

Table 2. According to etiologies, the frequency distribution of patients transplanted for hepatocellular carcinoma or cirrhosis.

Etiologies	TxCi (n = 190)	TxHCC (n = 147)	Total (n = 337)
	n (%)	n (%)	n (%)
Alcoholic	92 (48.42)	25 (17.01)	117 (34.72)
HCV	35 (18.42)	75 (51.02)	110 (32.64)
HBV	13 (6.84)	30 (20.41)	43 (12.76)
Cryptogenic	32 (16.84)	8 (5.44)	40 (11.87)
MAFLD	34 (17.89)	16 (10.88)	50 (14.84)
In TxCi (n = 190)			
Etiologies	CiOn (n = 175)	iHCC (n = 15)	Total (n = 190)
	n (%)	n (%)	n (%)
Alcoholic	88 (50.29)	4 (26.67)	92 (48.42)
HCV	31 (17.71)	4 (26.67)	35 (18.42)
HBV	10 (5.71)	3 (20)	13 (6.84)
Cryptogenic	29 (16.57)	3 (20)	32 (16.84)
MAFLD	30 (17.14)	4 (26.67)	34 (17.89)
In TxHCC (n = 147)			
Etiologies	False positives (n = 11)	True positives (n = 136)	Total (n = 147)
	n (%)	n (%)	n (%)
Alcoholic	2 (18.18)	23 (16.91)	25 (17.01)
HCV	7 (63.64)	68 (50)	75 (51.02)
HBV	1 (9.09)	29 (21.32)	30 (20.41)
Cryptogenic	1 (9.09)	7 (5.15)	8 (5.44)
MAFLD	2 (18.18)	14 (10.29)	16 (10.88)

TxCi: cirrhosis transplant group; TxHCC: hepatocellular carcinoma transplant group; HBV: hepatitis B virus; HCV: hepatitis C virus; MAFLD: metabolic dysfunction-associated fatty liver disease; iHCC: incidental hepatocellular carcinoma group; CiOn: cirrhosis only group.

DISCUSSION

The diagnosis of HCC, unlike that of other tumors, can be made by noninvasive, multiphase, contrast-enhanced imaging examinations. This is because of the high pretest probability for HCC in the context of cirrhosis. Noncirrhotic patients, however, need confirmation with biopsy of the lesion.[15] Thus, to maintain the homogeneity of the population regarding pretest probability, only transplant patients with cirrhosis and/or HCC were included in the study.[26,27]

The reference group for calculating the frequency of iHCC varies in the literature, making comparison with other centers difficult. A classic study by Klintmalm was known to show a high prevalence of iHCC (40%). Still, he evaluated the frequency of iHCC in the group of patients with HCC-positive explant histopathology.[28] Choi et al. analyzed the frequency of iHCC only among patients with HBV cirrhosis.[29] Most of the researches consulted do the analysis based on the total number of transplant recipients or the number of patients without pdHCC. The frequency of iHCC in these studies ranges from 1 to 10%.[3-13] In the present study, using the patients without pdHCC (TxCi group) as a reference, the frequency of iHCC was found to be 7.89% (15/190). The value is in line with the range found in the literature. When calculating the frequency of iHCC among all patients in the study population, a frequency of 4.45% (15/337) was obtained.

Table 3. Frequency distribution of patients transplanted for hepatocellular carcinoma or cirrhosis, according to types of examination performed and groups.

Types of exams	TxCi (n = 190)	TxHCC (n = 147)	Total (n = 337)
	n (%)	n (%)	n (%)
In the general group (n = 337)			
MNR	25 (13.16)	114 (77.55)	139 (41.25)
CT	67 (35.26)	66 (44.90)	133 (39.47)
USG	152 (80)	25 (17.01)	177 (52.52)
Biopsy	4 (2.11)	15 (10.20)	19 (5.64)
MNR only	15 (7.89)	57 (38.78)	72 (21.36)
CT only	19 (10)	27 (18.37)	46 (13.65)
USG only	102 (53.68)	0 (0)	102 (30.27)
CT or MRI (without biopsy)	84 (44.21)	132 (89.80)	216 (64.09)
In TxCi (n = 190)			
Types of exams	CiOn (n = 175)	iHCC (n = 15)	Total (n = 190)
	n (%)	n (%)	n (%)
MNR	25 (14.29)	0 (0)	25 (13.16)
CT	63 (36)	4 (26.67)	67 (35.26)
USG	138 (78.86)	14 (93.33)	152 (80)
Biopsy	4 (2.29)	0 (0)	4 (2.11)
MNR only	15 (8.57)	0 (0)	15 (7.89)
CT only	18 (10.29)	1 (6.67)	19 (10)
USG only	91 (52)	11 (73.33)	102 (53.68)
CT or MRI (without biopsy)	80 (45.71)	4 (26.67)	84 (44.21)
In TxHCC (n = 147)			
Types of exams	False positives (n = 11)	True positives (n = 136)	Total (n = 147)
	n (%)	n (%)	n (%)
MNR	8 (72.73)	106 (77.94)	114 (77.55)
CT	7 (63.64)	59 (43.38)	66 (44.90)
USG	2 (18.18)	23 (16.91)	25 (17.01)
Biopsy	1 (9.09)	14 (10.29)	15 (10.20)
MNR only	3 (27.27)	54 (39.71)	57 (38.78)
CT only	3 (27.27)	24 (17.65)	27 (18.37)
USG only	0 (0)	0 (0)	0 (0)
CT or MRI (without biopsy)	10 (90.91)	122 (89.71)	132 (89.80)

TxCi: cirrhosis transplant group; TxHCC: hepatocellular carcinoma transplant group; MRI: magnetic resonance imaging; CT: computed tomography; USG: ultrasonography; iHCC: incidental hepatocellular carcinoma group; CiOn: cirrhosis only group.

Table 4. Diagnostic accuracy of MRI, CT scan, ultrasound, and biopsy for diagnosis of hepatocellular carcinoma among all analyzed patients and frequency distribution of the results of these tests according to the gold standard.

Exam results		AP positive	AP negative	Total	Sensitivity (%)	Specificity (%)
MNR	Positive	106	8	114	100	75.76
	Negative	0	25	25		
	Total	106	33	139		
CT	Positive	59	7	66	93.75	90
	Negative	4	63	67		
	Total	63	70	133		
USG	Positive	21	3	24	56.76	97.86
	Negative	16	137	153		
	Total	37	140	177		
Biopsy	Positive	11	0	11	78.57	100
	Negative	3	5	8		
	Total	14	5	19		

AP: anatomopathologic; MRI: magnetic resonance imaging; CT: computed tomography; USG: ultrasonography.

HBV and HCV account for 32% of infections associated with cancer genesis in developing countries, compared to 19% in developed countries. For example, in Asia and sub-Saharan Africa, there is a high prevalence of chronic hepatitis B, with about 5% of the region's population infected with this virus.[29] Asia is home to 60% of the world's population and 80% of all HCC cases are concentrated there.[30] In Africa, the incidence of HCC is estimated at 19.2 to 28.4 cases per 100,000 people per year, and it accounts for 20% of all malignant diseases.[31] In our study, 43.62% of the patients had pdHCC. Viral hepatitis accounted for 71.43% of the etiologies of transplant patients with pdHCC (TxHCC), with HCV predominating (51.02%).

Current evidence does not indicate that alcohol plays a carcinogenic role in HCC, alcohol-induced cirrhosis is a significant risk factor for carcinoma development, with a five-year cumulative risk of 8%.[32] Hepatitis C is the predominant factor for HCC in North America. In Africa and Asia, hepatitis B is more closely related to cancer genesis, since patients with noncirrhotic hepatitis B in areas endemic for this virus have a 20% increase in the incidence of HCC. MAFLD has increased in incidence in recent years, but its relationship to the onset of liver cancer is not yet well established.[14] In our study, among the diseases associated with pdHCC, hepatitis C (51.02%) was the main one, followed by hepatitis B (20.41%) and alcoholic cirrhosis (17.01%). There were similarities with the profile reported in North American countries.

The correlation between the etiology of cirrhosis and iHCC is controversial. Perez et al. found a higher frequency of cirrhosis caused by HCV in the group with iHCC,[3] and Mourad et al. found the inverse correlation.[4] Two other studies found no differences in the etiology of cirrhosis of patients with iHCC and pdHCC.[11,12] In this study, HCV was more frequent among patients with pdHCC than among those with iHCC ($p = 0.033$). In the group of patients with iHCC; HCV, MAFLD and alcoholism had 26.67% frequency each, while HBV and the cryptogenic etiology, 20% frequency each.

The impact of iHCC on overall survival and disease-free survival is also controversial. In general, the results of the analyzed studies show a worse prognosis than in patients without HCC and similar to that of patients with pdHCC.[3-6,9,12,13] Some studies report longer survival of patients with iHCC than those with pdHCC.[10,33,34]

Perez et al. found higher Child-Pugh scores in patients with iHCC than in those with pdHCC;[3] two other studies showed Meld to be higher in the incidental group.[11,12] Perez et al. also found a similar risk of tumor recurrence between patients with iHCC and pdHCC.[3] Despite the similar prognosis, histopathological analysis of iHCC usually indicates milder disease than in pdHCC. The tumor volume is smaller in iHCC in all the series analyzed, and the rates of multinodular disease and microvascular invasion are similar or lower than in pdHCC.[3,4,12] One possible explanation is that the early stage of the disease in some cases of iHCC is counterbalanced by prioritization and inadequate selection of transplant candidates and the lack of neoadjuvant therapies.[3]

In this study, MRI and CT showed higher sensitivity than what is found in the literature. MRI has demonstrated 100% sensitivity, above the confidence interval of several recent meta-analyses.[35-39] The sensitivity of CT was 93.75%, compared to 76-88% (95% confidence interval - 95%CI) in a large meta-analysis by Chou et al.[36] Hanna et al. found a sensitivity of 57.2-72.8% (95%CI) for CT when using explanted livers as the gold standard. This study, however, evaluated the diagnosis per lesion,[37] and not per patient, as the present work does. The high sensitivity here is probably explained by taking into account all the tests with suspected positive HCC. Our goal was to avoid having lesions with considerable suspicion of HCC classified as iHCC, so as not to overestimate the frequency of the incidental finding.

USG was the test with the lowest sensitivity (57.76%), consistent with other studies showing sensitivity between 46-90 and 38.4-58.4% (95%CI).[36,37] USG was the most specific exam (97.86%), and MRI the least (75.76%). Such a relationship agrees with a previously cited meta-analysis[36]and study by Floriani et al, in which USG showed higher specificity than MRI.[40] The specificity value of NMR, however, is below the confidence interval of most of the papers reviewed.[35,36,38,39] A study by Hanna et al. is the exception, showing specificity for MRI between 70-79% (95%CI), similar to that found in our center.[37] Although the comprehensive criteria for defining the test as positive were applied to all diagnostic modalities, MRI was the only modality that deviated considerably from the standard set by the rest of the literature surveyed.

The occurrence of the incidental finding of HCC has various explanations in the literature. Pretransplant diagnosis of HCC smaller than 20 mm is challenging, and can be mistaken for regenerative or dysplastic nodule. Certain studies have shown that the frequency of iHCC is higher in older patients; the incidental nature is thought to be related to the longer duration of their cirrhosis.[4] The relatively long time on the waiting list, because of the insufficient number of donors for the demand, may contribute to the genesis of iHCC.[41] One possible strategy to decrease the frequency of iHCC, which would result in better selection and prioritization of liver transplant candidates, is the use of protocols with contrast-enhanced multiphase tests for HCC screening in patients who are on the liver transplant waiting list. This strategy is especially useful in the event of a long waiting time.[3] USG does not seem to be a suitable screening method in patients who are on the waiting list for liver transplantation.[42]

CONCLUSION

This study found similar data to those in the international literature regarding the prevalence of iHCC and an etiologic profile similar to that pointed out by North American studies. USG was the least sensitive test. CT and MRI showed higher sensitivity than what is found in the literature. Surprisingly, MRI showed lower specificity than the other tests and most of the references analyzed. The additional accuracy indexes were in agreement with the literature cited. The most common etiology of HCC was HCV cirrhosis. iHCC did not have the most prevalent etiology, with alcoholism, MAFLD, and HCV being the most frequent, in equal proportion.

Despite the low cost and easy access to USG, this method is operator-dependent and has low sensitivity. Because of their greater sensitivity and specificity, Multiphase contrast-enhanced imaging examinations are more effective in screening for HCC. However, costs and availability still make it prohibitive to implement HCC screening with CT or MRI in the liver transplant queue. The gradual price reduction and increased availability of these imaging methods, on the other hand, tend to optimize HCC screening in this context. Efforts are suggested to reduce these costs and increase the availability of such equipment.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Nogara MAS, Stadnick GP and Marques NK; **Conception and design:** Nogara MAS, Stadnick GP and Marques NK; **Technical procedures:** Wiederkher JC and Igreja M; **Analysis and interpretation of data:** Nogara MAS, Stadnick GP and Marques NK; **Statistics analysis:** Stein CE; **Manuscript writing:** Nogara MAS, Stadnick GP and Marques NK; **Critical revision:** Nogara MAS, Stadnick GP and Marques NK; **Final approval:** Nogara MAS.

AVAILABILITY OF RESEARCH DATA

All data were generated or analyzed in the present study.

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