Clinical and laboratory parameters associated with li-rads as diagnostic of liver nodule in patients with cirrhosis

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer in the world. Clinical and laboratory evaluation of a cirrhotic patient with a liver nodule may show alterations suggesting malignancy. There is a lack of questions related to diagnosis of HCC and evaluation of liver imaging reporting and data system (LI-RADS) could be a tool for early diagnosis of HCC. This aims to confirm an association between clinical and laboratory characteristics in cirrhotic patients with hepatic nodule after LI-RADS categorization.

Methods: A cross-sectional retrospective study was performed with 62 patients grouped according to LI-RADS algorithm. Differences between groups were confirmed using association tests and the Kappa test was employed to provide further confirmation.

Results: Associations were observed after univariate analysis with higher values of aspartate aminotransferase (AST) (P=0.008), alanine aminotransferase (ALT) (P=0.019), alkaline phosphatase (ALP) (P=0.0052), gamma glutamyl transferase (GGT) (P=0.0023), alpha-fetoprotein (AFP) (P=0.0001), nodule size (P=0.0001) and age (P=0.007) in LR 5 group compared to LR 3. Univariate analysis also revealed higher levels for the LR5 group of ALP (P=0.0228), AFP (P=0.022) and age (P=0.046) in relation to LR 1+2 group. AFP also had higher serum levels in the LR 4 group compared to LR 1+2 (P=0.004). After multivariate analysis, higher levels in LR5 group of nodule size (P=0.047) and ALP (P=0.027) were observed in relation to LR3, and were therefore considered predictors of HCC diagnosis.

Conclusions: The study suggests that the combination of clinical-laboratory and radiological factors, such as heightened serum levels of ALP and hepatic nodule size, may support the screening of HCC in cirrhotic patients with hepatic nodules using the LI-RADS algorithm.

Keywords: Hepatocellular carcinoma (HCC); liver imaging reporting and data system (LI-RADS); liver cirrhosis; liver nodule

Introduction

Hepatocellular carcinoma (HCC) is one of the most common types of cancer in the world (1). Cirrhosis of the liver is the main risk factor for its development; chronic viral hepatitis the most common cause of HCC (2). Most patients are diagnosed at the advanced and intermediate stages of the Barcelona Clinic Liver Cancer (BCLC) classification, for which palliative treatments are advised (3).

Cirrhotic patients with clinical decompensation may raise suspicion of HCC. The clinical presentation depends on the stage of the liver disease and on the stage of the tumor. In general, the symptomatology may be related to tumor growth (abdominal pain or constitutional symptoms—weight loss, abdominal distension, nausea, anorexia) or liver disease decompensation, increased alkaline phosphatase (ALP), bilirubin (BT), and alpha-fetoprotein (AFP), recent-onset ascites, acute intra-abdominal bleeding, encephalopathy and hematemesis/melena (4,5). AFP has a prognostic value, but is not sufficiently accurate for screening and diagnosis. The American Association for the Study of Liver Diseases (AASLD) recommends screening using ultrasonography with or without AFP for HCC in cirrhotic patients every 6 months (6).

The diagnosis of hepatic lesions can be made using imaging methods (7). The liver imaging reporting and data system (LI-RADS) was developed with the aim of standardizing the interpretation of computed tomography (CT) and magnetic resonance imaging (MRI) of patients at risk of developing HCC cancer. CT and MRI are the definitive diagnostic methods for HCC. LI-RADS aims to aid interpretation and communication among physicians (8). LI-RADS also provides an algorithm that categorizes liver nodules from definitely benign (LR 1) to clearly HCC (LR 5). The definition of indeterminate nodules may be broad and could be benign or require follow-up without a biopsy. LR 1 and LR 2 include benign and probably benign categories, which encompass cysts, hemangiomas, perfusion abnormalities, hepatic fat deposition, and areas of fibrosis or scarring. LI-RADS expands the "indeterminate" category in relation to intermediate and probable HCC (LR categories 3 and 4, respectively). Other classifications of LI-RADS, such as LR-NC, involve cases in which categorization is not possible, owing to degradation or omission of the imaging sequence. LR-TIV categorizes a definition of tumors in veins, LR-M categorizes nodules that are probably cancer but is not specific for HCC. LR 5 involves hepatic nodules

that are definitely HCC (9). The main imaging features characterized and used in this diagnostic algorithm include image hyper-reduction in the arterial phase, tumor size (diameter), portal phase washout, enhancement and nature of the capsule and the growth pattern of the nodule (8). LI-RADS has already been validated in Brazil by the Brazilian College of Radiology and Diagnostic Imaging, but is still very rarely used. The aim of the present study was to identify the clinical and laboratory characteristics of cirrhotic patients with hepatic nodules applying the LI-RADS algorithm categorization.

Methods

Patient selection

A cross-sectional and observational study and group comparison were carried out with 74 (*Figure 1*) cirrhotic patients with hepatic nodules undergoing CT or MRI with contrast between 2017 and 2018, at Hospital Oswaldo Cruz/University, Pernambuco and the Liver and Transplantation Institute of Pernambuco.

Patients aged under 18 years were excluded from the study, along with those classified according to the LI-RADS as LR-M or LR-TIV algorithm, those who did not provide the clinical, laboratory and radiological data needed to analyze the proposed variables and those who underwent any treatment of the hepatic nodule, be it surgery, chemoembolization or radio-ablation.

The radiological findings used for diagnosis of hepatic cirrhosis were presence of heterogeneity and hepatic surface nodularity, hypertrophy of the caudate lobe, segmental atrophy in the right lobe, signs of portal hypertension, and others described in the literature (10,11).

Patients eligible for the study were categorized according to the LI-RADS algorithm and classified into four groups: Group 1 (LR 1 + LR 2, definitely and probably benign, respectively) 13% (n=8), Group 2 (LR 3, n=18), Group 3 (LR 4, probably HCC), 16% (n=10) and Group 4 (LR 5, definitely HCC) 42% (n=26).

The necessary clinical, radiological and laboratory patient information was collected from medical records. These were registered age, ascites, encephalopathy, portal hypertension, diabetes, history of alcoholism and/or smoking, and MELD and CHILD calculations performed. Laboratory tests were carried out within a maximum of 30 days between collection and radiological imaging. The laboratory analysis included aspartate aminotransferase (AST), alanine aminotransferase
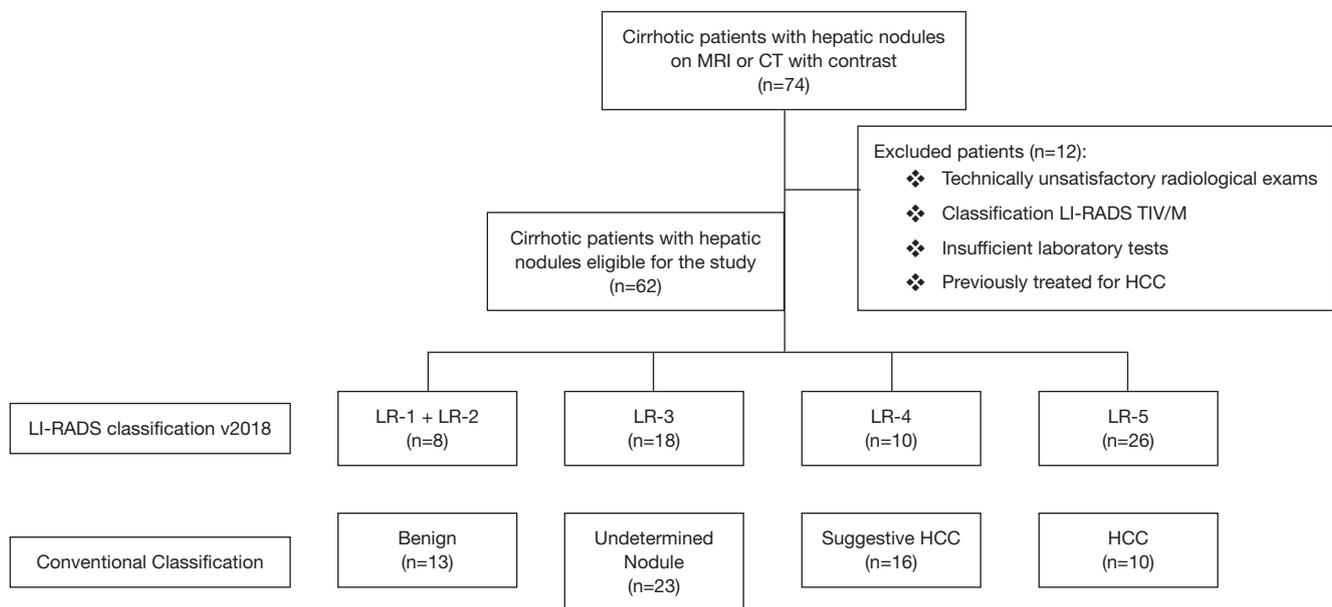
Figure 1 Diagram of study population eligible for the study. HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; CT, computed tomography; MRI, magnetic resonance imaging.

(ALT), ALP, gamma glutamyl transferase (GGT), BT, AFP, platelets and albumin (ALB). The serological profile included serology for hepatitis B (HBsAg, anti-HBs, total anti-HBc) and hepatitis C (anti-HCV). Diagnosis of hepatitis C was carried out using HCV-RNA screening in patients testing positive for anti-HCV. Patients were also evaluated for nodule size and number hepatic nodules being classified as uni- or multinodular (≥2 nodules).

All patients agreed to participate in the study by signing a consent form. The present study was approved by the local ethics committee (UPE-HUOC) under CAAE number: 82265517.4.0000.5207.

Radiological images

The radiological examinations were conducted using the following contrast devices: a Philips MRI, Model: Achieva 1.5, Channels: 16 and a Philips CT, Model: Ingenuity, Channels: 128. The digital storage system was PACS (Onis®, JP).

Interpretation of images

Conventional radiological analysis versus LI-RADS v2018 algorithm

Two radiologists, with radiology experience and no access to the clinical and laboratory results of the patients,

analyzed the radiological images. The classification of hepatic nodules was performed on two different occasions after MRI or CT with contrast. The first evaluation was performed by conventional diagnosis, classifying the hepatic nodule according to AASLD guidelines, currently the most commonly used in Brazil, and the second classification, conducted by another radiologist, followed the LIRADS/v2018 algorithm.

According to AASLD criteria, HCC can be diagnosed radiologically by CT or MRI scans without biopsy if typical imaging features are present (6). HCC is detected in contrast-enhanced CT or MRI scans when nodular hepatic lesions present a specific vascular profile of hyper-enhancement during the arterial phase and washout during the venous and/or late portal phases. In the arterial phase, the HCC shows greater intensity compared to the surrounding liver parenchyma, whereas in its venous phase it has lower intensity (12,13).

LI-RADS version 2018 provides updated criteria for small LR-5 nodules (10–19 mm and a simplified definition of threshold growth. These updates represent an important milestone in achieving consistency and integration of the clinical practice guidelines for AASLD hepatocellular carcinoma in 2018. The classification of hepatic nodules according to the LI-RADS algorithm includes five major criteria. (I) Hyper-enhancement of the nodule in the arterial

phase reflects the angiogenesis process, a key component of HCC pathogenesis (14,15). (II) Washout can be evaluated in the portal or late venous phase if an extracellular contrast agent is administrated in MRI or CT This is one of the most reliable features. (III) "Capsule appearance" or "capsule" is defined as a uniform and pointed hyper-enhancement ring around most or all of a nodule (16). The degree of enhancement typically increases from early phases to late, reflecting the slow flow of intracapsular vessels. (IV) Size of the hepatic nodule is defined as the dimension of the greatest length from external to outer border including the capsule, if present. (V) Threshold growth is defined as ≥50% increase in mass size in ≤6 months (14,17).

Statistical analysis

The existence of associations between categorical variables was evaluated using Pearson's Chi-square test and Fisher's exact test. Differences were considered significant at P<0.05. The magnitude of these associations was estimated by odds ratio (OR), using 95% confidence intervals. For comparison of continuous variables, between the two groups, Student's *t*-test or the non-parametric Mann-Whitney test was applied, and for comparison between more than two groups were applied ANOVA or Kruskal Wallis test was used, as appropriate. The PRISMStatistics v.6.0 program (GraphPad Software, San Diego, California, USA) was used for these analyzes. Logistic regression was employed to adjust the OR for possible confounding factors, using the SPSS V.22 program. The Kappa concordance coefficient was used to describe the agreement between the radiological reports performed by the conventional method and the reports performed following the LI-RADS v2018 algorithm on the same sample. A kappa value of 0 indicates no agreement, kappa values of 0.01–0.20 represent slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good, almost perfect agreement 0.81–0.99 and 1 perfect agreement (18).

Results

Clinical features

The final study sample included 62 cirrhotic patients with a hepatic nodule, 30 (48%) women and 32 (52%) men. Patients were divided into groups according to categorization of radiological images according to the LI-RADS algorithm (LR 1+2, LR 3, LR 4 and LR 5). clinical characteristics (gender, portal hypertension, ascites, diabetes mellitus, smoking and/or alcoholism, HBV, HCV, CHILD and MELD), and number of nodules, and possible association with HCC was investigated. Of the patients covered, HCV was found in 41.93% (n=26), HBV in 8% (n=5), ascites in 43.5% (n=27), portal hypertension in 64.5% (n=40), encephalopathy in 1.6% (n=1), DM in 29% (n=18), a history of alcoholism in 46.7% (n=29) and a history of smoking in 19.3% (n=12). The mean age in years for the groups was LR 1 and 2: 62±9.8 years, LR 3: 59±14.9 years, LR 4: 64±7.7 years and LR 5: 70±9.4 years (*Table 1*). There was a statistically significant positive correlation for the age variable in LR 5 group compared to the LR 1+2 groups (P=0.046) and also when compared to LR 3 (P=0.007). Nodule size showed a statistically significant correlation with larger nodules in LR 1+2 *vs.* LR 3 group (P=0.037) and in LR 3 *vs.* LR 5. There were larger nodules in the LR 5 group when compared to the LR 3 group (P=0.0001).

The Child classification was evaluated in only 53 patients, owing to incomplete data, and the patients were classified as follows: Child A 64.2% (n=34), B 32% (n=17) and C 3.8% (n=2) (*Table 1*). No statistically significant difference between the groups in this study was observed for the other clinical variables.

Laboratory characteristics

The laboratory variables classified according to groups classified after radiological imaging using the LI-RADS algorithm presented statistical significance with progressively higher serum levels for the LR 5 group when compared to the LR 3 group for GGT (P=0.0023), AFP (P=0.0001), ALP (P=0.0052), AST (P=0.008) and ALT (P=0.019) (*Table 2*).

The ALP analysis presented statistical significance of higher serum levels for the LR 5 group when compared to LR 1+2 (P=0.0228) and LR 3 (P=0.0052). The AFP in the present study showed higher serum levels for the LR 4 group compared to LR 1+2 (P=0.004) and higher serum levels for the LR 5 group compared to LR 1+2 (P=0.022) and LR 3 (P=0.0001) (*Figure 2*).

Kappa analysis

Kappa index analysis was performed to ascertain whether there was concordance correlation between conventional diagnosis and LI-RADS. The result for Group D (conventional diagnosis—HCC *vs.* LR 5), was kappa 0.328,

Table 1 Clinical and epidemiological data of cirrhotic patients with hepatic nodules by LI-RADS algorithm

Clinical features (N=62)	LR 1+2 (N=8)	LR 3 (N=18)	LR 4 (N=10)	LR 5 (N=26)	P				
					LR 1+2 vs. LR 3	LR 1+2 vs. LR 4	LR 1+2 vs. LR 5	LR 3 vs. LR 5	LR 4 vs. LR 5
Males (n=32), n [%]	4 [50]	9 [50.0]	5 [50]	14 [53.8]	0.99	0.99	0.99	0.99	0.99
Age, years, mean ± SD	62±9.8	59±14.9	64±7.7	70±9.4	0.667	0.530	0.046	0.007	0.118
Nodules, n [%]					0.667	0.99	0.99	0.75	0.99
Uninodular	4 [50]	12 [66.7]	6 [60]	15 [57.7]					
Multinodular	4 [50]	6 [33.3]	4 [40]	11 [42.3]					
Size larger nodule (cm), median [range]	2.55 [1–12]	1.4 [0.6–2.5]	3.05 [0.9–7.2]	4.5 [1–17]	0.037	0.614	0.065	0.0001	0.208
HBV (n=5), n [%]	0	3 [16.7]	1 [10]	1 [3.8]	–	–	–	–	0.484
HCV (n=26), n [%]	2 [25]	4 [22.2]	4 [40]	16 [61.5]	0.99	0.638	0.110	0.370	0.285
Ascites (n=27), n [%]	4 [50]	7 [38.9]	3 [30]	13 [50.0]	0.682	0.630	0.99	0.546	0.456
PH (n=40), n [%]	6 [75]	12 [66.7]	7 [70]	15 [57.7]	0.99	0.99	0.443	0.750	0.706
Encephalopathy (n=1), n [%]	0	1 [5.6]	0	0	–	–	–	–	–
DM (n=18), n [%]	2 [25]	6 [33.3]	2 [20]	8 [30.8]	0.601	0.99	0.99	0.99	0.689
Alcoholic/ex-alcoholic (n=29), n [%]	4 [50]	9 [50.0]	6 [60]	10 [38.5]			0.67	0.541	0.285
Smoking/ex-smoker (n=12), n [%]	0	3 [16.7]	3 [30]	6 [23.1]	–	–	–	–	0.685
MELD, median [range]	7 [6–12]	9 [6–17]	10 [6–20]	9 [6–16]	0.205	0.177	0.114	0.95	0.495
Child#, n [%]									
A (n=34)	4 [50]	11 [61.1]	6 [60]	13 [50.0]					
B (n=17)	2 [25]	3 [16.7]	2 [20]	10 [38.5]	0.99	0.99	0.99	0.419	0.438
C (n=2)	0	1 [5.6]	1 [10]	0					

#, Child-Pugh score. LI-RADS, liver imaging reporting and data system; HCV, hepatitis C virus; HBV, hepatitis B virus; PH, portal hypertension; DM, diabetes mellitus.

P=0.007 and kappa 0.369, P<0.0001 was observed for Group C (conventional-suspected diagnosis HCC vs. LR 4) and Group D (Tables 3,4).

Multivariate analysis

A binary logistic regression of the forward stepwise type was performed to check for possible predictors of HCC in the LR 5 and LR 3 groups, including the variables that were significant in univariate analysis (age, GGT, AST, ALT, AFP, ALP and nodule size). After the test, only nodule size (P=0.047) and ALP (P=0.027) were predictors of HCC

diagnosis (Table 5).

Discussion

The present study evaluated the relation between clinical, laboratory and radiological factors and the LI-RADS algorithm on diagnosis of HCC. This is one of the first studies to evaluate these factors together. Recently, the incidence of HCC has been increasing exponentially. Clinical practice shows that analysis of individual patients is fundamental. Factors related to liver disease, liver function, portal hypertension, comorbidities and the tumor should all

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Table 2 Laboratory data of cirrhotic patients with hepatic nodules by LI-RADS algorithm

Laboratory data	LR 2+1 (N=8)	LR 3 (N=18)	LR 4 (N=10)	LR 5 (N=26)	P				
					LR 1+2 vs. LR 3	LR 1+2 vs. LR 4	LR 1+2 vs. LR 5	LR 3 vs. LR 5	LR 4 vs. LR 5
Albumin (g/dL), mean ± SD	4±0.5	3.9±0.7	3.7±0.5	3.65±0.7	0.814	0.227	0.221	0.168	0.936
Bilirubin total, (mg/dL), median (range)	0.93 (0.46–6.7)	1.03 (0.3–3.7)	1.47 (0.4–6.9)	1.11 (0.59–8.4)	0.987	0.714	0.473	0.362	0.977
Alkaline phosphatase (U/L), median [range]	92.7 [73–173]	100 [36–164]	152 [54–233]	160 [72–577]	0.857	0.228	0.0228	0.0052	0.664
GGT (U/L), median [range]	80 [28–756]	72.5 [19–191]	99 [12–284]	159 [21–1,298]	0.962	0.489	0.117	0.0023	0.192
INR, mean ± SD	1.07±0.13	1.22±0.19	1.30±0.28	1.15±0.21	0.079	0,065	0.364	0.207	0.098
AFP (ng/mL), median [range]	2.92 [0.92–23]	2.65 [0.84–6.18]	30.7 [3.0–4.498.0]	19.5 [0.9–51,000.0]	0.503	0.004	0.022	0.0001	0.371
ALT (U/L), median [range]	35 [12,9–87]	30 [11–86]	35 [15–113]	48 [17–159]	0.964	0.403	0.073	0.019	0.431
AST (mg/dL), median [range]	43.5 [15.5–125]	43 [22–71]	62.5 [17–94,7]	57 [22–191]	0.883	0.468	0.140	0.008	0.248
Platelets (mg/dL), median [range]	111,000 [1,000–336,000]	147,000 [63,000–554,000]	135,000 [40,000–204,000]	123,000 [49,000–382,000]	0.424	0.982	0.584	0.337	0.413

LI-RADS, liver imaging reporting and data system; GGT, gamma glutamyl transferase; INR, international standard ratio; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

be considered.

Univariate analysis showed that the occurrence of HCC was statistically significant for age >50 years, hepatic nodule size and heightened levels of enzymes such as ALP, GGT, AFP, ALT and AST. Age presented data similar to those described in literature, revealing a progressive increase in age for groups with the greatest likelihood of occurrence of HCC. Another study evaluating HCC mortality conducted in Brazil revealed that 84.7% of patients were aged 50 years or older (19). The multivariate analysis of the present study also revealed that a larger size of the hepatic nodule and higher levels of ALP were strong predictors of HCC occurrence.

The size of the nodule presented a statistical correlation for LR 1+2 *vs.* LR 3 and LR 3 *vs.* LR 5, although the size of the nodule in the LR 1+2 group was higher in relation to LR 3. This may be explained by the presence of a 12 cm hepatic hemangioma in a patient with LR 1 classification. Multivariate analysis of LR 5 and LR 3 patients demonstrated that larger nodule size was associated with the occurrence of HCC, independent of other confounding factors. Pawlik *et al.* in a multicenter study of 1,073 HCC patients, observed that tumor size and number of nodules were associated with microvascular invasion, capsular invasion, tumor size, satellite nodules, invasive behavior, and that tumor size can predict its histological grade (20). Tumor size is an independent risk factor for HCC patient survival and prognosis. Genetic alterations and pathological features are associated with tumor size in HCC (21,22). The presence of tumor recurrence and metastasis may be more commonly observed in patients with larger HCC.

Analysis of prognostic factors or biomarkers that help predict survival and make clinical decisions is urgently needed. Some serum hepatic enzymes, ALT, AST, ALP, GGT and AFP, are routinely required in cirrhotic patients with hepatic nodules. Of these, ALP and GGT are not as widely used as AFP, which has been reported as a predictor in the diagnosis of HCC, although with low sensitivity (23,24). ALP, a hydrolase enzyme, may be associated with tumor patient prognosis and is found mainly in the liver, bile duct and bone (24). Serum ALP levels increase during pregnancy or under some pathological conditions, including cholangiocarcinoma, HCC, biliary cirrhosis, and liver injury (25). Some tumor cells exhibited heightened ALP activity in the nucleolus during cell cycles, and ALP may play an important role in cell cycle regulation, cell proliferation and tumor formation (26). The participation of ALP in tumor formation represents both a direct and an
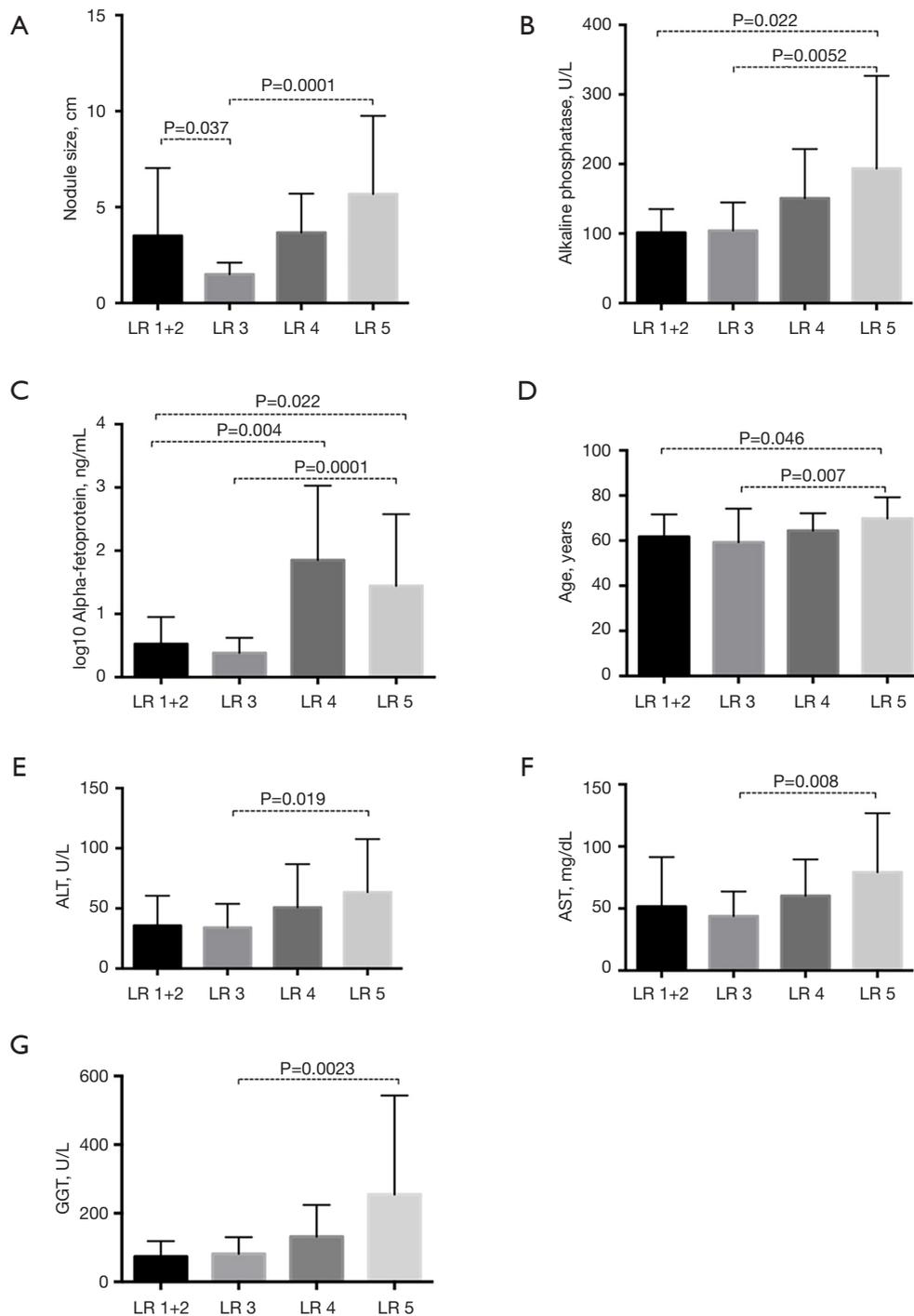
Figure 2 Distribution of clinical-laboratory data of patients after radiological staging according to LI-RADS algorithm. (A) Descriptive analysis of nodule size *vs.* LI-RADS; (B) descriptive analysis of Alkaline Phosphatase *vs.* LI-RADS; (C) descriptive analysis log10 alpha-fetoprotein *vs.* LI-RADS; (D) descriptive analysis age *vs.* LI-RADS; (E) descriptive analysis ALT *vs.* LI-RADS; (F) descriptive analysis AST *vs.* LI-RADS; (G) descriptive analysis GGT *vs.* LI-RADS. LI-RADS, liver imaging reporting and data system.

Table 3 Correlation of cirrhotic patients with hepatic nodules with conventional radiological diagnosis versus LI-RADS

Conventional radiological diagnosis	LR 1+2	LR 3	LR 4	LR 5	P value Kappa category
Benign nodule, N=13 [%]	4 [30.7]	7 [53.8]	2 [15.5]	0	0.061
Undetermined nodule, N=23 [%]	5 [22]	9 [39]	2 [8.6]	7 [30.4]	0.179
Suggestive HCC, N=16 [%]	0	1 [6]	6 [38]	9 [56]	0.007
HCC, N=10 [%]	0	1 [10]	0	9 [90]	<0.001
Total =62	9 [14.5]	18 [29]	10 [16.1]	25 [40.4]	

LI-RADS, liver imaging reporting and data system; HCC, hepatocellular carcinoma.

Table 4 Kappa values for the categories analyzed by HCC radiological classification

Classification	A	B	C	D	Kappa general
Kappa category (95% CI)	0.232 (0.475–0.011)	0.168 (0.413–0.077)	0.328 (0.567–0.09)	0.369 (0.576–0.162)	0.274 (0.409–0.139)
P value Kappa	0.061	0.179	0.007	<0.001	<0.001

Group A: Conventional (Undetermined) *vs.* LR 3; Group C: Conventional Diagnosis (Suspected HCC) *vs.* LR 4; Group D: Conventional Diagnosis (Benign) *vs.* LR 1+2; Group B: (HCC) *vs.* LR 5. HCC, hepatocellular carcinoma.

Table 5 Binary forward stepwise logistic regression comparing LR 3 and LR 5 for factors involved in HCC

Variables*	P value	OR	95% CI
Size of nodule	0.047	1.104	1.001–1.218
Alkaline phosphatase	0.027	1.036	1.004–1.069

*, variables included in the equation: age, GGT, AST, ALT, AFP. HCC, hepatocellular carcinoma; GGT, gamma glutamyl transferase; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

indirect inflammatory reaction and this may be predictive of the prognosis in HCC patients (27).

Xu *et al.* in a study with 172 HCC patients undergoing hepatic resection, followed up for 10 years, found that ALP, GGT and tumor size were independent predictors of lower overall survival and tumor-free survival. A further in-depth analysis showed that patients with heightened levels of ALP and GGT had significantly greater risk of death and tumor recurrence according to the Kaplan-Meier analysis, indicating a potential predictive role of ALP and GGT in the prognosis of HCC patients after liver resection (28). ALP is also one of the fundamental elements in the HCC staging system used by the Chinese University's Prognostic Index (CUPI) (29).

Abnormal expression of GGT has been found in a number of human tumors (30). GGT is found in healthy adults and is secreted primarily by Kupffer hepatic cells and endothelial cells of the bile duct. Its expression increases in tissue with HCC. It has been reported that GGT sensitivity is 74.0% for the detection of larger size HCC and 43.8% for smaller-size HCC. Sensitivity can be significantly increased by simultaneous determination of GGT and AFP (31). GGT is an oxidative stress flag related to the origin of pro-oxidant reactions and producing endogenous reactive hydrogen species in tumor cells, and plays an important role in the formation of tumors, cell proliferation and apoptosis (32-34). GGT catalyzes the transpeptidation and hydrolysis of the glutamyl group of glutathione and participates in biotransformation, nucleic acid metabolism and genesis (35). In addition to being easily obtained in routine tests, ALP and GGT can also predict the prognosis in patients with HCC (36). Overall, the results of the studies showed that high levels of ALP and GGT had a close relationship with tumor recurrence, formation and progression (27).

The relative risk of HCC increases with the severity of liver damage, indicated by heightened levels of ALT and AST. A cohort study conducted in 2013 with 5,555 men in Taiwan showed that increased levels of liver enzymes were associated with overall mortality and cancer mortality, in particular HCC-related mortality. Increased liver enzymes, AST or ALT or GGT, were independently associated with higher overall cancer mortality and HCC-specific mortality (37).

AFP is a fetal component protein produced during the embryonic period by the visceral endoderm of the gestational sac and subsequently by the liver (38). In the

present study, AFP-related univariate analysis showed a statistically significant difference between LR 1+2 groups *vs.* LR 4, LR 1+2 *vs.* LR 5, and LR 3 *vs.* LR 5. AFP has been routinely used to aid diagnosis of HCC. Heightened levels may be a poor prognostic factor in HCC patients. Progressively higher levels of AFP have been associated with a more aggressive molecular subclass of HCC and abnormal or altered genesis of hepatic cells (39,40).

The present study also found a concordance correlation between conventional diagnosis and LI-RADS using Kappa index analysis. A significant correlation was observed only in group C (conventional-suspected diagnosis HCC *vs.* LR 4) and Group D (conventional diagnosis—HCC *vs.* LR 5), kappa 0.328, P=0.007 and kappa 0.369, P<0.0001, respectively (*Tables 3,4*). The 2018 version of LI-RADS is more judicious regarding AASLD criteria alone for non-invasive diagnosis of HCC in high-risk patients, providing important and complementary information on the likelihood of HCC and enabling possible changes in management of these patients.

LI-RADS was created as a dynamic system with regular updates to maintain best practices based on the latest evidence and specialized multidisciplinary consensus. LI-RADS is consistent with the National Comprehensive Cancer Network (NCCN) guidelines. The new version of LI-RADS has now been integrated into the 2018 AASLD guidelines for clinical practice. This represents an important step towards general endorsement of LI-RADS (17).

The fundamental importance of the present study lies in the evaluation of factors associated with HCC and the LI-RADS algorithm. However, the limitation relating to the low number of patients in our series may have affected the power of the analysis and consequently the extrapolation of results. Studies with a larger sample of patients are needed to confirm the role of the markers in HCC evolution to be incorporated in diagnostic and prognostic HCC algorithms.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tgh.2020.01.05). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients agreed to participate in the study by signing a consent form. The present study was approved by the local ethics committee (UPE-HUOC) under CAAE number: 82265517.4.0000.5207. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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