Original Paper

Evaluation of Hepatocellular Carcinoma Patients: Interim Analysis of Cases from a Tertiary Referral Center in Craiova, Romania

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ABSTRACT: Although medicine is constantly evolving, hepatocellular carcinoma remains a pathology with a poor prognosis due to the frequent delayed diagnosis and the aggressiveness of the disease. Aim: Our objective was to evaluate liver function and stage of disease of newly diagnosed HCC patients. Methods: We conducted a retrospective study between July 2016 and January 2021 and we included hospitalized patients within the Department of Gastroenterology of the Emergency County Hospital of Craiova. We identified 119 newly diagnosed patients and we collected data from patient history, contrast-enhanced imaging and laboratory analysis. Results: 81 patients were diagnosed in BCLC Stage A and B. Liver function was not significantly modified, despite 91.5% of the patients presented with elevated AST levels. Because of the cirrhotic liver already affected, 73 patients had thrombocytopenia. Contrast-enhanced ultrasound was performed in 79 patients, as a complementary imaging exploration. Alfa-fetoprotein values could not be correlated with the severity of disease. Conclusions: Early diagnosis was mostly established. It is mandatory for treatment management and overall survival to follow a rigorous surveillance of patients at risk for HCC.

KEYWORDS: *Hepatocellular carcinoma, Surveillance, Diagnosis, Contrast-enhanced imaging, Alfa-fetoprotein.*

Introduction

Hepatocellular carcinoma (HCC) is an important global health issue due to the increased death rate in the past few years. Based on data from the GLOBOCAN report in 2018, liver cancer is the sixth most common malignancy worldwide.

Thus, with 842,000 new cases and 782,000 death per year, HCC is a disease with a high rate of incidence and mortality [1].

About 75% of all primary liver cancer confirm a hepatocellular carcinoma.

The diagnosis is based on the contrast-enhanced imaging criteria for tumor description and alpha-fetoprotein (AFP) measurement [2].

In early stages, abdominal ultrasound and AFP may be useful to detect HCC lesions [3].

The pathological evidence is not mandatory, except for non-cirrhotic patients, which liver biopsy is the main option to proof HCC characteristics [4-6].

Men are two to three times more frequently affected by liver cancer than women [1].

Because of the development of the heath system, HCC prevention, early diagnosis, treatment and surveillance determined an improvement in the benefit of patient management [7].

The most common risk factor for HCC is cirrhosis associated to chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), which causes 80% of cases annually [8,9].

The involvement of Hepatitis E virus (HEV) as a promotor of HCC is not completely elucidated [10].

Due to the improvement in HBV and HCV management and treatment, the incidence of hepatocellular carcinoma is radically reduced worldwide.

Comorbidities and environmental factors, excess alcohol consumption, nonalcoholic fatty liver disease, metabolic liver disease, type 2 diabetes and obesity, co-carcinogens are also risk factors that should pay attention of [4,11].

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Aim

The purpose of our study was to assess the grade of liver dysfunction and the stage of HCC at diagnosis.

Due to access to a center of excellence and advanced technology, patients were able to benefit from a quick and accurate diagnosis.

Moreover, on account of the multidisciplinary approach, patients received specialized treatment in optimal time.

Material and Methods

We included 119 consecutive patients newly diagnosed with HCC from the Department of Gastroenterology, Emergency County Hospital of Craiova-a major referral center for gastrointestinal diseases in the Oltenia region.

Most of the subjects presented ambulatory accusing mild to moderate asthenia, weight loss and appetite disorder.

Three patients addressed to Emergency Department with main symptoms including diffuse abdominal pain, muscle defense, fever.

After laboratory analysis and imaging exploration, they were diagnosed with acute abdomen from HCC rupture.

Most of the patients had risk factors as liver cirrhosis.

Therefore, they were diagnosed with malignant tumors during surveillance.

Included patients were newly diagnosed at the Department of Gastroenterology of Craiova.

Diagnosis was established using the typical vascular hallmarks of HCC on contrast-enhanced imaging criteria.

For imaging description of the lesions, we used Computed tomography (CT) and Magnetic resonance imaging.

The findings were correlated with clinical data extracted from patient history.

Diagnostic algorithm did not used serum AFP determination or contrast-enhanced ultrasound (CEUS).

Our study was subjected for review to the Ethics Board of the Emergency County Hospital of Craiova; being a retrospective analysis, we were granted permission to review medical records on-site, without extracting any personal identification data.

We performed a descriptive analysis of the lot, presenting continuous variables as median (min, max).

Statistical tests were applied as appropriate (chi-square test, calculation of odds ratio and relative risk, two-way ANOVA where appropriate), p values below 0.05 being considered statistically significant.

Data was analyzed and reports generated by using the demo version of GraphPad Prism (Graphpad, USA).

Results

Our lot included significantly more males (89 subjects), compared to 30 females (2.96:1 ratio, $p<0.05$).

Most patients were above 50 years old (one patient was 41 y.o.), with median ages of 68.27 (minimum 41, maximum 83).

We found no difference in the median age between genders (67.6 y.o for male and 70.2 y.o for females, $p>0.05$).

Histograms of age distributions per total lot and among the two genders are presented in Figures 1 and 2.

Figure 1. Histogram representation of overall age distribution in our lot.

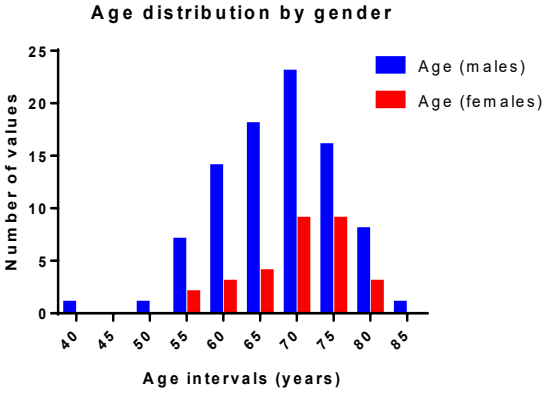

Figure 2. Combined gender-age histogram of our patient lot.

Statistical results as well as descriptive data are presented in Table 1.

Table 1. Statistics regarding age and gender distribution within our lot. We found no significant differences between mean and median ages pertaining to either men or women.

	Men	Women	P value
Total number of values	89	30	P<0.05
Minimum	41.0	56.0	P<0.05
Median	69.0	71.5	Not significant
Maximum	83.0	81.0	Not significant
Mean	67.6067	70.2667	Not significant
Std. Deviation	7.80969	7.09022	Not significant
Std. Error of Mean	0.827826	1.29449	Not significant

Regarding the number of tumors, most patients (n=65, 54.6%) had one tumor, 19 (15.96%) two and 10 three (8.4%); 25 patients (21%) presented multicentric HCC.

The majority of patients were Child-Pugh A (65 patients, 54.6%).

As for Barcelona Clinic for Liver Cancer (BCLC) staging, we had 43 stage A, 38 stage B, 26 stage C and 12 stage D.

We found significant statistical differences between the two genders, in regards of Child-Pugh score distribution (P=0.0089, two-way ANOVA) and the BCLC staging class (p=0.0384, two-way ANOVA).

Data is presented in Table 2 and Figure 3.

Table 2. Case distribution according to Child-Pugh scores and BCLC staging, per gender.

		BCLC Staging				
Child Pugh Score		**A**	**B**	**C**	**D**	**TOTAL**
A	***Men***	19	14	12	0	45
	Women	9	8	2	1	20
	Total	65				
B	***Men***	9	10	8	2	29
	Women	2	2	1	0	5
	Total	34				
C	***Men***	3	2	3	7	15
	Women	1	2	0	2	5
	Total	20				
TOTAL		43	38	26	12	119

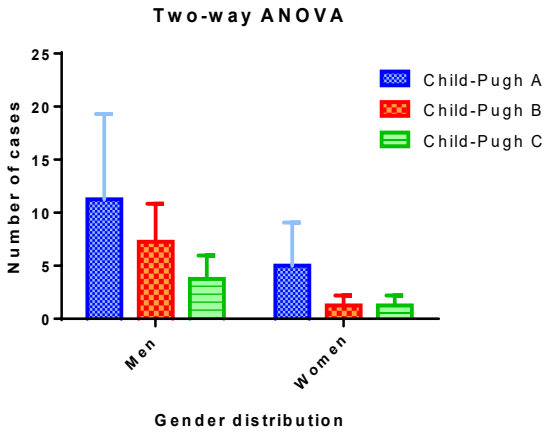

Figure 3. Gender distribution according to Child-Pugh score.

We found 109 subjects with elevated AST levels (normal range 5-34U/l), of which 64 also exhibited elevated ALT values (normal range 3-55U/l).

We also found 22 patients with lower albumin levels (below 2.8g/dl), 62 with abnormally low hemoglobin (below 12.6g/dl), six patients (four male) having below 8g/dl and thus requiring blood transfusions.

We also investigated coagulation parameters, finding lower thrombocyte counts in 73 patients (below 150,000 per cubic millimeter).

Six patients also had lower international normalized ratio (INR) values.

These values correlated well with lower performance scores and worse prognostic values [odds ratio 4.34 (3.1-9.12), relative risk of 3.41 (2.61-8.96)].

Also, overall, worsen liver function correlated with higher BCLC stages (100% of stage C and D patients had at least one modified value, p<0.001).

We evaluated liver encephalopathy in these patients; only seven displayed a suggestive clinical signs, while 72 patients did not have ascites.

However, 38 patients (3.93%) had minimum ascites identified on ultrasound, five moderate and six significant ascites.

Overall, the presence of these factors associated with a higher BCLC class and thus with worse prognosis (odds ratio, p<0.05).

We also found 50 patients with esophageal varices (42%), half of them (25 patients) also exhibiting ascites.

The presence of these complications also correlated with disease severity (p<0.001).

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Alfa-fetoprotein levels were recorded for 89 patients, of which we found 28 with elevated levels (above 400ng/ml); we found a mean value of 1508.1 (SD±308.2).

Higher values did not correlate with disease severity or any serological parameter (Correlation test, p>0.05-Table 3).

Table 3. AFP levels did not correlate with any other parameter.

AFP *versus*	***AST***	***ALT***	***GGT***	***Albumin***	***Hb***	***Tumor size***	***BMI***	***Child Pugh***	***MELD***
r	0.009	0.004	0.055	-0.061	0.098	0.077	0.152	0.070	-0.034
P value	0.928	0.968	0.610	0.592	0.359	0.500	0.259	0.509	0.774
P summary **ns=not significant**	ns	ns	ns	ns	ns	ns	ns	ns	ns

As for known risk factors, we found 51 patients with hepatitis C virus infection, 34 with hepatitis B viral exposure and 38 admitted alcohol abuse.

Seven HCV patients also consumed large quantities of alcohol, compared to only three HVB subjects which were mild alcohol consumers.

We could not identify any common risk factors in 10 patients.

Alcohol consumption correlated well with gender (35 male patients, Table 4), being more prevalent in men (odds ratio 0.0521, p<0.05).

Table 4. Alcohol consumption in our lot, interpreted by gender distribution.

Alcohol	**Yes**	**No**	**Total**
Male	35	54	89
Female	3	27	30
Total	38	81	119

The most frequent localization of the tumors was the right lobe of the liver.

From 119 patients, 82 of them presented lesions in the right lobe (68.9%), 13 in the left lobe and in 23 cases HCC tumors interested the whole liver.

Only one patient had the caudate lobe affected.

Median body mass index was 24.54 kg/m^2, at the superior limit of healthy weight (normal range 18.5-25kg/m^2), ruling out malnutrition.

We had 81 patients diagnosed with early BCLC A and B HCC, which could be correlated with the normal nutrition status described above.

According to the quality of life of our patients, 84.8% had a good performance status (Eastern Cooperative Oncology Group-ECOG=0-2) and 18 subjects had ECOG performance status 3-4.

Discussions

There are several studies about finding the best strategy to diagnose as early as possible the liver malignant tumours.

Although the rate of early diagnosis is decent, there is always a need of improved surveillance methods [12].

The progression of HCC is fast and with an unfavorable prognosis, although development of hepatocellular carcinoma as an end-stage liver disease is a long process [13,14].

The poor prognosis of HCC highlights a 5-year survival rate under 20% [15].

Hence, a proper surveillance is the key of an early diagnosis that could benefit to a curative treatment.

Patients' stratification into risk groups is a method for an efficient screening and surveillance.

Prognostic factors that influence the HCC growth rate could not yet been determined, although there are few studies that researched the subject [13].

In our study, risk factors correlated with gender distribution.

Males were almost three times more affected than women, due to the life habits such as alcohol abuse.

Moreover, HCV and HBV infection incidence is higher in males than in females.

The main recommendation of EASL guidelines is screening with abdominal ultrasound with or without serum AFP value for targeting population at risk of developing hepatocellular carcinoma [6].

For this fact, it is mandatory to use a quality ultrasound system.

The sensitivity is about 94%, as studies demonstrated [16].

Half of the primary liver malignancies are diagnosed when the surgery is no longer an option, usually at advanced stages [17].

Although in absence of a national screening program, 68% of the patients were diagnosed in BCLC A and B stages.

Therefore, monitoring patients with a predisposition to develop HCC favored their early detection.

BCLC staging system is the main tool, which combines hepatocellular carcinoma treatment alternative with tumor characteristics, liver function and performance status [18].

The treatment options are determined by the stage of the disease.

The surgery (resection, liver transplantation) and also percutaneous local ablative treatment could be potentially curative for early-diagnosed HCC.

Transarterial chemoembolisation is mostly reserved for BCLC B patients with a good performance status. On the other hand, multiple tyrosine kinase inhibitors (mTKIs) such as sorafenib, regorafenib, cabozantinib, lenvantinib and immune checkpoint inhibitors such as pembrolizumab and nivolumab demonstrated a good response in advanced HCC patients [2].

The BCLC D patients with poor performance status in advanced stages of disease benefit only of best supportive care [19].

The degree of liver failure was not dramatically expressed, although most patients had ethanolic or viral liver cirrhosis. Portal and parenchymal decompensation was not frequently encountered in our study.

Serum AFP dosage is a diagnostic and prognostic factor with a high association with existence and progression of hepatocellular carcinoma.

Despite AFP measurement showed high level in a significant number of patients, we could not find a correlation between AFP value and tumor dimension or disease stage.

Multiple imaging diagnostic system are used in order to provide HCC findings.

The Liver Imaging Reporting and Data System (LI-RADS) is the most thorough of them, which includes ultrasound LI-RADS, contrast enhanced LI-RADS, computed tomography/magnetic resonance imaging LI-RADS [20-22].

CEUS is an imaging tool combining ultrasound and contrast agents, in order to evidence the benign or malignant hallmarks of the lesions.

It is considered a second-line diagnostic method in noninvasive diagnosis for HCC [21].

CEUS is not yet a standard in HCC diagnosis; however, it can be useful in certain circumstances.

The high specificity of CEUS LI-RADS-5 in the diagnosis of HCC demonstrates the usefulness of this imaging modality [22].

Our department of Gastroenterology benefits from a high performance CEUS system, which is useful in the detection of HCC lesions.

Although CEUS is not considered a usual method of diagnosis, this exploration has been suitable as a complementary technique.

Conclusions

Early detection of HCC is the keypoint of an effective treatment.

However, in the group of patients diagnosed with HCC in this study, the aim was to monitor the liver function for the efficacy of a subsequent therapeutic protocol.

Conflict of interests

None to declare.

Acknowledgements

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