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The Staging of Newly Diagnosed Hepatocellular Carcinoma in Romania. A National Multicentric Study

Rareș Crăciun[1,2], Horia Ștefănescu[2], Ioan Sporea[3], Larisa Daniela Săndulescu[4], Liana Gheorghe[5], Anca Trifan[6], Zeno Spârchez[1,2], Mirela Dănilă[3], Ion Rogoveanu[4], Răzvan Cerban[5], Camelia Cojocariu[6], Bogdan Procopeț[1,2], Roxana Șirli[3], Cristiana Marinela Urhut[4], Dana Crișan[1,7], Călin Burciu[3], Nadim Al-Hajjar[8,9], Mircea Grigorescu[1,2] on behalf of the Romanian HCC Registry

1) Dept. of Internal Medicine, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca; 2) Dept. of Gastroenterology, Prof. Dr. O. Fodor Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca; 3) Dept. of Gastroenterology and Hepatology, Victor Babeș University of Medicine and Pharmacy, Timișoara; 4) Dept. of Gastroenterology, Research Center of Gastroenterology and Hepatology, Craiova University of Medicine and Pharmacy, Craiova; 5) Center of Gastroenterology and Hepatology, Fundeni Clinical Institute, Carol Davila University of Medicine and Pharmacy, Bucharest; 6) Institute of Gastroenterology and Hepatology, Emergency Clinical Hospital St. Spiridon, Grigore T. Popa University of Medicine and Pharmacy, Iasi; 7) Dept. of Gastroenterology, Clinical Municipal Hospital, Cluj-Napoca; 8) Dept. of Surgery, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca; 9) Dept. of Surgery, "Prof. Dr. O. Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania

Address for correspondence:
Horia Ștefănescu
Dept. of Gastroenterology, Prof. Dr. O. Fodor Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania
horia.stefanescu@irgh.ro

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ABSTRACT

Background & Aims: Hepatocellular carcinoma (HCC) is a significant public health issue, with an increasing incidence and prevalence and a high incidence-to-mortality ratio. The prognosis of HCC depends on two competing factors, tumor burden and underlying liver disease severity, encompassed in the Barcelona Clinic Liver Cancer (BCLC) classification. To assess HCC staging and the way staging affects eligibility for treatment at the time of the first diagnosis in Romania in the setting of opportunistic diagnosis, in the absence of a national HCC screening policy.

Methods: Data regarding HCC staging, underlying liver disease, and eligibility for treatment at the time of diagnosis was analyzed using a prospectively maintained multicentric database, which included patients from the five largest tertiary care hepatology units in the country between June 2016 and February 2020.

Results: A consecutive series of 477 patients was included. The distribution within BCLC classes was as follows: very early (0) 7.1%, early (A) 34.3%, intermediate (B) 19.4%, advanced (C) 14.2%, terminal (D) 24.7%. At the time of the diagnosis, 198 (41.5%) were eligible for a curative intent treatment, while 359 (75.2%) were eligible for a disease-modifying therapy. 228 patients (47.8%) had decompensated liver disease at the time of diagnosis, the most common decompensating event being ascites (78.1%).

Conclusions: A large proportion of HCC cases are diagnosed at the time of a decompensating event, severely restricting the therapeutic potential. Proactive diagnostic strategies should be implemented to improve the rate of actionable diagnosis.

Key words: hepatocellular carcinoma – diagnosis – staging – liver cancer – liver disease.

Abbreviations: ALD: alcohol-related liver disease; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; MAFLD: metabolic dysfunction-associated liver disease; MELD: Model for End-Stage Liver Disease; NAFLD: non-alcoholic fatty liver disease.

INTRODUCTION

Hepatocellular carcinoma (HCC) represents a substantial public health issue, as recent reports suggest a surge in both incidence and prevalence, with figures expected to rise in the next decades [1]. As of the 2020s, the landscape of HCC appears to be facing substantial shifts in etiology and risk factors (generated by improved control of viral hepatitis, counterbalanced by a higher burden of alcohol-related liver disease and the ongoing obesity epidemic), as well as an expanded therapeutic armamentarium, with the advent of immunotherapy in HCC [2]. However, despite isolated improvements in regional dynamics, primary liver cancer still accounts for the sixth most common malignancy while disproportionately accounting for the third most common cause of cancer-related mortality, according to the latest GLOBOCAN 2020 report [3]. These statistics reflect an incidence-to-mortality ratio disappointingly close to 1 [4]. The high mortality might be partially explained by the fact that, in contrast to other primary cancers, the prognosis of patients with HCC is influenced by two major competing risk factors: the severity of the underlying liver disease and tumor staging [5, 6].

Given its prognostic profile, HCC probably represents the epitome of a disease suited for screening. Most of the cases occur in well-defined high-risk populations (advanced liver disease), the screening method is usually

accessible and generates minimal additional burden on care [ultrasonography (US)], and early diagnosis is amendable with multiple curative intent solutions, hence the consensus recommendation for bi-annual US surveillance [2, 7-9]. Thus, the essential element in conferring a good prognosis is detection in the very early and early stages (BCLC 0 and A) in which a survival exceeding five years is expected, in opposition to intermediate (B), advanced (C), and terminal (D) stages, with an expected survival of 2.5 years, two years, and three months, respectively [2].

However, real-life data from the United States and Europe suggest multiple failure points in HCC surveillance, leading to late-stage diagnosis and dim prognosis. According to recent reports, less than half of the patients newly diagnosed with HCC received regular outpatient care in the year prior, and less than 25% of the patients were enrolled in guideline-based surveillance protocols, leading to ineligibility for curative intent therapies in more than 50% of the cases [10-12].

According to the 2020 GLOBOCAN report, Romania ranks second among all European countries in terms of primary liver cancer burden, trailing only neighboring Moldova, with an age-standardized rate per 100.000 (ASR) of 8.8 for incidence and 8.1 for mortality [1, 3]. As of 2023, Romania had no healthcare policy-based HCC surveillance system, and screening for HCC was performed at the discretion of practicing clinicians in a non-standardized manner. The first multicentric national HCC registry was initiated in 2016, upon the collaboration of five hepatology units in regional tertiary-care facilities, with the goals of detecting real-life challenges in HCC management, providing a fact-based rationale for public health policy, and ultimately improving HCC care.

The aim of the present study was to assess the staging and clinical profile of Romanian patients with HCC at the time of their first diagnosis, based on data collected from five hepatology units.

METHODS

Study Population

A consecutive series of patients were included at the time of their first HCC diagnosis using a prospectively maintained multicentric database. All tertiary care hepatology units in the country were formally invited to participate in the registry. Five centers responded to the invitation, which, patient-volume-wise, were the five largest centers in the country. Consequently, enrollment took place in these five referral centers.

The timeframe for enrollment was between June 2016 and February 2020. Patients enrolled since March 2020 were excluded to avoid potential biases related to the adjustments in care imposed by the COVID-19 pandemic. The inclusion criteria were age over 18 years-old, first diagnosis of HCC (including patients referred from secondary-care facilities within a six-week timeframe) and signed written informed consent. To avoid potential selection biases, patients were only enrolled by practicing gastroenterologists to avoid skewing the data towards either end of the disease severity spectrum (curative – surgery, advanced disease – oncology). Patients with a prior history of HCC, either fully treated or with ongoing disease, were excluded.

The diagnosis of HCC was established either using two concordant contrast-enhanced sectional imaging techniques, fulfilling the Li-RADS 5 criteria for patients with cirrhosis [13], or by pathology in non-cirrhotic patients or if imaging was inconclusive.

Patients' Characteristics

Patients' demographics and clinical, laboratory, and imaging data were collected upon enrollment. Clinical variables included the Eastern Cooperative Oncology Group (ECOG) performance status [14] and decompensating events. Underlying liver disease etiology was classified as viral (hepatitis B or C), alcohol-related, non-alcoholic fatty liver disease (NAFLD), other (i.e., autoimmune, cholestatic, hemochromatosis, Wilson's, etc.), or unclassified. Liver disease staging was recorded using the Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) score. Hepatocellular carcinoma was staged according to the latest available BCLC classification at the time of enrollment [15]. The imaging data consisted of tumor burden assessment (number and size of HCC nodules) and the presence of vascular invasion.

Statistical Analysis

The statistical analysis was supervised by a certified biomedical statistician and was performed using the Statistical Product and Service Solution (SPSS®) software, version 28.0 (IBM®, Armonk, New York, USA). Data normality was assessed using the Shapiro-Wilk test. We used mean ± standard deviation (SD) and median plus interquartile range (IQR) for reporting normally distributed and non-normally distributed variables, respectively. We compared means using the Student's t¬-test, and medians using the Mann-Whitney U test. According to the sample size, categorical variables were analyzed using either Fischer's exact test or the Chi-squared test. The threshold value for statistical significance was set at $p < 0.05$.

Ethical Considerations

The study protocol was approved by all five Institutional Review Boards. Given the prospective observational nature of the study, written informed consent was obtained for anonymized personal data use, according to the European Union General Data Protection Regulation (GDPR).

RESULTS

Baseline Characteristics

A consecutive series of 477 patients from five tertiary-care hospitals was included. The baseline characteristics of the patients and their underlying liver disease at the time of HCC diagnosis are summarized in Table I.

Hepatocellular Carcinoma Staging and Tumor Characteristics

The HCC staging was reported using the BCLC classification. At the time of diagnosis, 198 (41.5%) of the patients were eligible for curative intent treatment options (surgery, percutaneous thermal ablation, liver transplantation). Of the remaining patients, 161 (33.7%) were ineligible due to

Table I. Baseline characteristics and underlying liver disease

Age (years)	64.9 ± 11.1
Gender, male (n, %)	335 (70.2)
Liver disease etiology (n, %)	
Viral hepatitis C	232 (48.6)
Viral hepatitis B	111 (23.2)
Alcohol-related liver disease	89 (18.6)
Non-alcoholic fatty liver disease	10 (2.1)
Other	35 (7.3)
Child-Pugh class (n,%)	
A	249 (52.2)
B	137 (28.7)
C	91 (19.1)
MELD score	11 (8-16)
Prior history of LD decompensation (n, %)	162 (33.9)
Performance status n(%)	
ECOG 0	91 (23.4)
ECOG 1	171 (43.5)
ECOG 2	89 (22.6)
ECOG 3	39 (9.9)
ECOG 4	3 (0.8)
Decompensated at the time of HCC diagnosis (n,%)	228 (47.8)
Decompensating event (n, %)	
Ascites	178 (78.1)
Portal hypertension-related bleeding	50 (21.9)
Hepatic encephalopathy	33 (14.4)

Variables with a normal distribution were expressed as mean ± standard deviation; non-normal variables were expressed as median and inter-quartile range; MELD: model for end-stage liver disease; LD: liver disease; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma.

tumor progression (intermediate – BCLC B or advanced – BCLC C stage) and 118 (24.7%) due to underlying liver disease staging or poor performance status (BCLC – D). A description of HCC staging at the time of diagnosis is depicted in Table II.

Table II. Hepatocellular carcinoma staging and tumor characteristics

BCLC staging (n, %)	
0	34 (7.1)
A	164 (34.3)
B	93 (19.4)
C	68 (14.2)
D	118 (24.7)
Eligible for curative-intent treatment (n, %)	198 (41.5)
Eligible for any type of disease modifying treatment (n, %)	359 (75.2)
Number of nodules (n, %)	
Solitary	262 (61)
Two	67 (15.6)
Three	36 (8.3)
Exceeding three nodules	64 (14.9)
Size of the largest nodule (n, %)	
< 3 cm	144 (33.1)
3-5 cm	129 (29.7)
> 5 cm	162 (37.2)
Portal invasion (n, %)	78 (18.1)

BCLC: Barcelona Clinic Liver Cancer classification

Eligibility for Curative Intent Solutions at the Time of Diagnosis

Age (p=0.68) and liver disease etiology (p=0.66) were not significantly associated with very early (BCLC 0) and early (BCLC A) diagnosis and implicitly with eligibility for curative-intent treatment options. Those ineligible for curative therapy had a higher MELD score (14.18 ± 6.78 vs. 10.3 ± 3.45, p<0.001), Child-Pugh score (7.9 ± 2.4 vs. 5.95 ± 1.3, p<0.001), were more likely to have a prior history of liver disease decompensation (38.86% vs. 20.1%, p<0.001), or to be decompensated at the time of HCC diagnosis (62.26% vs. 22.61%, p<0.001).

A subgroup analysis was performed for patients with solitary nodules, as these patients are the most frequent beneficiaries of curative intent therapy. From 79 patients with solitary nodules < 30 mm, 17 (21.51%) were not eligible for curative intent therapy due to liver disease staging or current decompensation. The percentages of those ineligible for curative intent therapy significantly increased when the size threshold was set at 50 mm, as 44 of the 142 patients (30.98%) in this category did not qualify for surgery or loco-regional therapies. Moreover, when analyzing patients who, strictly on nodule number, size, or lack of vascular invasion, would have been classified as BCLC 0 or A (286, 59.95%), only 198 (69.23%) were actually classified as BCLC 0 or A when accounting for liver disease staging, HVPG, or performance status.

DISCUSSION

The current study retrospectively analyzed the data from the five largest hepatology units in Romania, a country with the second-highest liver disease burden, HCC prevalence, and HCC-related mortality in Europe [1, 3]. The main findings of the study point in two critical directions: a relatively low rate of early-stage diagnosis (41.5%) and a significant proportion of patients diagnosed with HCC during hospitalization for a decompensating event (47.8%). In this light, the critical points for discussion are, on the one hand, to identify the roots of these worrying figures within the specific epidemiological background and, on the other hand, to analyze potential methods that might improve the outcomes of HCC patients.

Our findings resemble the results from a Swedish registry of a similar scale, which reported a combined diagnostic rate for BCLC 0 and A of 36%, with a relatively lower rate of BCLC D cases (12% vs. 24.7% in our study) [12]. Comparable results were obtained by a German study group, which reported a 34.3% rate of BCLCA 0 and A staging at diagnosis, while 11.4% were classified BCLC D. Similarly, while not using the BCLC classification, a 30-year retrospective analysis of data from the United States NCI Surveillance, Epidemiology, and End Results database revealed a 50.8% of localized disease, a 12.7% prevalence of tumors < 2 cm (corresponding to BCLC 0). However, underlying liver disease staging was not reported, nor was data regarding the eligibility for curative intent solutions other than surgery, which was 23% [16]. Other smaller-scale studies have reported even lower rates of early HCC diagnosis, with a Malaysian study reporting only 19.8% of HCCs in this category [17]. Until now, we are unaware of any similar endeavors on an Eastern European population.

Besides tumor burden, the specific therapy in HCC is strongly determined by the staging of the underlying liver disease. Our study revealed that up to half of the patients were diagnosed with HCC while being decompensated,

rendering most of the disease-altering therapeutic strategies contraindicated until a better control of the liver disease was reached. The rate of decompensation at the time of HCC diagnosis was also retrospectively analyzed on over 15,000 patients from the English National Cancer Registration Database, along with eligibility for various treatment options. According to the published data, 46.6% of the patients who had their cirrhotic or non-cirrhotic status available were decompensated at the time of diagnosis [18]. This figure strikingly resembles the 47.8% rate of decompensation in our study. The same study reported a curative-intent therapeutic approach in 20%, while 10.5% of the patients in the compensated group and 16.5% in the decompensated group were not eligible for active treatment [18].

Our data result from opportunistic HCC diagnosis, as during the data collection, there was no national healthcare system-based strategy for liver disease screening or HCC screening strategies in high-risk populations, and consequently, these patients were followed up on a provider-by-provider basis. However, a lack of a formally recommended nationwide surveillance protocol might not be the main contributor to late diagnosis. Despite the largely congruent societal guidelines (North American, European, and Asian), which all strongly recommend bi-annual US surveillance [2, 7-9], the effectiveness of this strategy has faced some scrutiny in recent years.

The two main caveats of the current HCC surveillance strategies are a lack of adherence and the intrinsic limitations of US as a screening method, and our team has discussed these issues *in extenso* in a previous article [19]. *In breve*, the strongest argument regarding the effectiveness of US-based HCC surveillance comes from relatively old large-scale Asian randomized controlled data, which compared two populations, one enrolled in a bi-annual surveillance program, while the other relied on opportunistic diagnosis. The patients in the surveillance arm had a 37% reduction in HCC-related mortality [20], yet such designs are unlikely to be replicated due to ethical concerns. Two large retrospective meta-analyses supported these figures, which revealed relatively high sensitivities for HCC detection, in the range of 84-95% for any stage HCC [21, 22]. Yet the diagnosis of HCC should not be the sole objective of a screening strategy, and the results of a positive screening result should be actionable. In this light, data from the largest available meta-analysis published by Tzatzeva et al. [22] revealed a significant reduction in sensitivity for early-stage HCC: 47% (with a 95% confidence interval of 33-61%). Moreover, a North American study revealed that only 37.2% of patients with HCC had regular outpatient care in the year prior to HCC diagnosis, of which less than a quarter (24.7%) were undergoing regular guideline-based bi-annual US surveillance [10]. Even more worrying are the data reported by Singal et al. in 2015, which suggested that less than 2% of patients with cirrhosis received bi-annual US surveillance, citing racial, social, and clinical determinants for surveillance ineffectiveness [11]. These data suggest that however effective, HCC surveillance is most frequently underused in real-life scenarios.

Another aspect worth discussing is the epidemiology of the underlying liver disease. As highlighted in the 2023 update of the global burden of liver disease, the relative control of viral liver disease in developed countries, along with an increase in metabolic dysfunction-associated liver disease (MASLD) prevalence and a relative increase in alcohol-related liver disease (ALD) [23], might translate into different patterns of HCC development and initial presentation.

According to our data, approximately 70% of the patients had viral liver disease. From an epistemological standpoint, there is a higher likelihood that patients with previously documented viral liver disease (most of whom require therapy) will be more compliant with regular follow-up and enrollment in surveillance programs. On the other hand, patients with MASLD might be unaware of their underlying liver disease, as a plethora of metabolic and cardiovascular conditions might overshadow MASLD. In contrast, patients with ALD might have decreased access and compliance to medical care due to the cumulative effects of stigma and specific behavioral patterns [24]. Our data was collected in the first years of interferon-free regimens for HCV. Since then, there has been a relative control of HCV-related disease burden both due to therapy and the natural history of advanced liver disease, and recently developed models suggest a high probability of HCV containment in Romania by 2030 [25, 26]. Moreover, we cannot exclude a bias in the etiology reporting, as we observed a relatively low prevalence of ALD-associated HCC. This might have been generated due to an underreporting of combined etiologies (such as viral + ALD), given that Romania has one of the highest rates of per capita alcohol consumption in Europe [27], along with a relatively high stigma for alcohol use disorders [28]. In this light, a present-day analysis might reveal a substantially different pattern of underlying liver disease etiologies in patients diagnosed with HCC.

Despite providing the first valuable dataset regarding HCC disease and patient profile at diagnosis, we acknowledge that our study has significant limitations. Some of the limitations are inherent to registry-type designs, which are especially prone to bias in HCC due to heterogeneity in the diagnostic pathway between centers and on a patient-by-patient basis (concordant contrast-enhanced sectional imaging, pathology, resection specimens, biomarkers) [29]. The most glaring limitation of our study is related to the lack of reporting on the actual therapeutic choice and long-term follow-up. However, this was not the initial scope of this project. Furthermore, the study's design could have been enhanced by comparison with a cohort of patients undergoing standard bi-annual US surveillance to assess the impact of a regular screening program on the rate of actionable early diagnosis and, ultimately, to help guide local healthcare policy in the most effective direction. Unfortunately, such a cohort was not available at the time of patient recruitment.

CONCLUSIONS

Our study revealed that opportunistic HCC diagnosis in a setting with a high at-risk liver disease population leads to a large proportion of patients diagnosed at the time of a decompensatory event, thus limiting their eligibility for a curative-intent therapeutic solution. Moreover, the rate of early diagnosis (BCLC 0 and A) is relatively low, while up to a quarter of the patients are diagnosed with terminal HCC, unactionable from a therapeutic standpoint.

Conflicts of interest: None to declare.

Authors' contributions: M.G., H.S. and B.P., conceived and designed the study. I.S., L.D.S., L.G., A.T., Z.S., M.D., I.R., R.C., C.C., R.S., C.M.U., C.B., D.C. and N.A. collected data. R.C performed the statistical analysis, analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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