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ORIGINAL ARTICLE

Characteristics and Outcomes of Hepatocellular Carcinoma in Patients with Autoimmune Hepatitis

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Abstract

Background The incidence of HCC in patients with autoimmune hepatitis (AIH) is low and, due to the paucity of data in the literature, a thorough characterization of these patients is missing.

Aim To describe the main characteristics and outcome of patients with AIH and HCC.

Methods Among patients with HCC included in the Italian Liver Cancer (ITA.LI.CA) database during the period 2009–2022, we selected those with AIH, and we described their liver disease characteristics, modality of HCC diagnosis, tumor stage, treatment, and outcome.

Results Among 10,026 patients with HCC, we identified 23 patients (0.2%) with AIH (43.5% males, 69.6% aged > 65 years, 91.0% with cirrhosis). Fifteen patients (65.2%) had co-factors of liver disease [8 patients (34.8%) metabolic dysfunction-associated steatotic liver disease, 4 patients (17.4%) alcohol abuse, 3 patients (13.0%) AIH/Primary Biliary Cholangitis overlap syndrome]. Tumors diagnosed under surveillance (60.9%) were more frequently uninodular (85.7% *vs* 66.6%, $p = 0.146$) and Milan-in (85.7% *vs* 44.4%, $p = 0.066$) than those diagnosed outside surveillance. Treatment with curative intent was more frequent among patients under surveillance (78.6% *vs* 33.3%, $p = 0.077$). Median overall survival was 41.7 months and was remarkably longer in patients under surveillance than in those diagnosed outside surveillance (68.2 *vs* 27.4 months, $p = 0.032$).

Conclusion AIH accounts for a minimal fraction of patients with HCC, and in most patients, risk co-factors for HCC are present. In patients with AIH, too, surveillance is associated with better tumor stage, higher access rate to potentially curative treatments, and improved survival.

Keywords Surveillance · Oncological outcomes · Risk stratification · Autoimmune hepatitis

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by immune-mediated hepatocellular injury that can lead to cirrhosis and liver failure when left untreated [1]. AIH is marked by the presence of autoantibodies, elevated serum immunoglobulin G, and interface hepatitis on histological examination and its pathogenesis is believed to result from a complex interplay of genetic predisposition and environmental triggers, eventually leading to an aberrant immune response against hepatocytes [1].

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, typically arising in the context of chronic liver disease and cirrhosis, which are major risk factors for its development. HCC is commonly associated with chronic viral hepatitis, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), while its occurrence in patients with autoimmune liver diseases is considered a rare event [2]. Indeed, the cumulative incidence of HCC is low in patients with AIH, with an annual incidence of 0.09% during the first 10 years

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and of 0.46% in patients with cirrhosis in the same time interval [3–5]. The low incidence of HCC—well below the threshold of a cost-effectiveness surveillance even in patients with cirrhosis—questions the recommendation of universal monitoring in these patients, calling for studies that may help identify the subgroup of patients eligible for a cost-effective surveillance, in particular when limited resources need to be adequately allocated [5–7]. In this regard, a recent large, multicenter study in patients with AIH, in addition to confirming the overall low incidence of HCC (1.44 cases/1000 patient years), has shown that older age, obesity, excessive alcohol intake, presence of cirrhosis, and concomitant presence of Primary Sclerosing Cholangitis are the co-factors that increase the likelihood of developing HCC [5, 8].

These epidemiological considerations indicate that a systematic implementation of surveillance for HCC in patients with AIH is not appropriate, highlighting the importance of a finer stratification of these patients by individual HCC risk to implement a personalized surveillance aimed at optimizing available resources and improving patients' prognosis [9, 10]. Therefore, in this study we exploited the Italian Liver Cancer (ITA.LI.CA) database with the aim to describe the demographic and clinical characteristics, treatment, and outcome of patients with HCC superimposed on AIH and to assess the impact of additional risk factors for HCC in this population.

Material and Methods

Patients

In this study, among the 10,026 patients with HCC included in the ITA.LI.CA database and in a collaborative center database (Papa Giovanni XXIII Hospital, Bergamo, Italy) between 2009 and 2022, we identified 23 patients (0.2%) with AIH as underlying liver disease. The year of inception (2009) was selected as the cut-point when systemic treatment for HCC was made available in Italy, allowing us to presenting a clinical scenario including also this therapeutic option [11–14].

The ITA.LI.CA dataset is a prospective, multicenter database initiated in 1998 that now comprises real-world data from over 10,000 patients with HCC across the main Italian liver centers. It was established to capture comprehensive clinical information on HCC management in clinical practice, with data collected in a standardized, semi-anonymous manner via an online platform and updated biennially. This extensive dataset includes detailed demographic, clinical, and treatment data, enabling the evaluation of epidemiological trends, prognostic factors, and therapeutic outcomes [14].

The database management adheres to Italian privacy laws. While patient consent is not legally required for retrospective data analysis in Italy, all patients provided written informed consent for each diagnostic and therapeutic procedure, as well as for the anonymous recording of their clinical data in the ITA.LI.CA database. The Institutional Review Board of the ITA.LI.CA Coordinating Center approved the use of this database for scientific research (approval number 99/2012/O/Oss), and the study was conducted in accordance with the ethical principles outlined in the 1975 Declaration of Helsinki.

Methods

The diagnosis of AIH was made by means of a combination of clinical evaluation, laboratory testing, and histological examination, according to established guidelines [15].

Diagnosis of cirrhosis was made through medical history, physical examination, and laboratory test results, along with unequivocal radiological evidence, or was based on liver histology, when available.

The diagnosis of HCC was based on characteristic imaging features obtained by dynamic computed tomography, magnetic resonance imaging, or contrast-enhanced ultrasound, and/or histology, according to the guidelines available at the time of patient enrollment [16].

The following variables were considered: age, sex, presence of clinically significant portal hypertension (CSPH), serum bilirubin levels, other causes of liver disease, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS, categorized as 0/1), Model for End-stage Liver Disease (MELD) score, HCC number (subdivided into uninodular *vs* multinodular), size of the largest lesion, presence of macrovascular invasion, presence of extra-hepatic spread, serum alpha-fetoprotein (AFP), HCC treatment modality, time to HCC recurrence (early: ≤ 2 years from curative treatment), median follow-up duration, overall survival (OS), and cause of death. CSPH was defined by the presence of esophageal varices or history of endoscopic band ligation or a platelet count below 100×10^9/L. OS was calculated from the date of HCC diagnosis to the date of death, while patients lost to follow-up were censored at the last visit, with adjustments for lead-time using appropriate formulas.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation (SD) or median and interquartile ranges (25th–75th), and discrete variables as absolute and relative frequencies. The distribution of the variables was tested using standard procedures such as Levene's test and the Kolmogorov–Smirnov test. Comparisons of continuous variables were made with the Student's *t* test, and changes over time were assessed using ANOVA. Discrete variables were compared with the χ^2 test. Differences between groups were evaluated using

unpaired *t* tests, Wilcoxon, Mann–Whitney *U* (for variables not normally distributed), or Fisher's exact tests (when comparing proportions), as appropriate. Relationships among variables were assessed with the Spearman correlation coefficient.

Survival was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. The HR was calculated using Cox proportional hazards model.

A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS v27.0 (Apache Software Foundation, Chicago, Illinois, USA), R (the R Project, R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria and EZR: https://github.com/jinkim3/ezr) and Stata Statistical Software: Release 1 (StataCorp. 2023. College Station, TX: StataCorp LLC).

Results

Main Demographic and Clinical Characteristics

The main features of the 23 patients included in the study are summarized in Table 1. Male patients ($n = 10$) represented 43.5% of the population, and all patients were > 60 years old, with 69.6% of patients aged > 65 years old. Cirrhosis was present in 21 patients (91.0%) at the time of HCC diagnosis and 7 patients (30.0%) had altered aminotransferases. Most patients had well-compensated liver disease (Child–Turcotte–Pugh class A: 15 patients, 65.2%) with a median MELD score of 11 (9–13), while the prevalence of CSPH was 73.9% ($n = 17$). The median age at AIH diagnosis was 54.9 years (IQR 54.4–56.6 years).

Table 1 Main demographic and clinical characteristics of the study population

Characteristics	Data
Sex, male	10 (43.5)
Age, years	67.2 (65.0–71.6)
Body Mass Index, Kg/m^2	26.2 (24.7–33.2)
ECOG Performance Status, score	
0	19 (82.6)
1	4 (17.4)
ALT, $n \times$ ULN	1 (1–2)
Platelet count, $\times 10^9$/L	84 (65–109)
Mode for End-stage Liver Disease score	11 (9—13)
Child–Turcotte–Pugh score	
A	15 (65.2)
B	7 (30.4)
C	1 (4.3)
Esophageal varices	
Absent	11 (47.8)
Present/large	12 (52.2)/8 (34.8)

Data are expressed as median and interquartile range or number of patients and proportion

ECOG Eastern Cooperative Oncology Group

Overall, 15 patients (65.2%) had concomitant conditions that can cause liver damage and among them, 8 patients (34.8%) had features compatible with MASLD, 4 patients (17.4%) reported alcohol abuse, and 3 patients (13.0%) had an overlap AIH/Primary Biliary Cholangitis.

As far as treatment of AIH is concerned, 19 patients (82.6%) were on immunosuppressive therapy—4 patients on steroid monotherapy, 11 on azathioprine monotherapy, and 4 on a combination of steroids and azathioprine—while 4 patients did not receive any immunosuppressive treatment due to potential risks associated with advanced cirrhosis.

Tumor Burden and Diagnosis

At diagnosis, 16 patients (69.6%) had tumors within the Milan criteria; HCC was uninodular in 18 patients (78.3%); 3 patients (13.0%) presented extra-hepatic spread, while none macro-vascular invasion.

Most HCC diagnoses were made during surveillance ($n = 14$, 60.9%), while in 8 patients (34.8%), HCC was detected incidentally and in 1 patient (4.3%) due to symptoms.

Table 2 reports the characteristics of HCC according to the modality of diagnosis. Patients whose tumor was diagnosed outside surveillance showed a non-significantly higher prevalence of multinodular HCC (44.4% *vs* 14.2%; $p = 0.146$) and extra-hepatic spread (33.3% *vs* 0%; $p = 0.068$). The majority ($n = 12$, 85.7%) of patients under HCC surveillance had tumors within the Milan criteria, while this figure decreased to 44.4% (4 patients) among those diagnosed outside surveillance, although the difference was not statistically significant ($p = 0.066$).

Outcome Analysis: Treatments, Oncological Response, Recurrence, and Overall Survival

The most frequent initial treatments for HCC were those with curative intent (14 patients, 60.9%) that were applied in 78.6% of patients under surveillance ($n = 11$) and in 33.3% of patients not under surveillance ($n = 3$, $p = 0.077$). Among potentially curative treatments, ablative procedures were used in 9 patients (39.1%), liver resection in 4 patients (17.4%), and liver transplantation in 1 patient (4.3%). Seven patients (30.4%) underwent trans-arterial chemoembolization and only 2 patients (8.7%) were considered not eligible for any anti-cancer therapy and were therefore managed by best supportive care.

Table 2 Hepatocellular carcinoma characteristics subdivided according to the modality of diagnosis

Characteristics	All patients $n=23$	Under surveillance $n=14$ (60.9%)	Outside surveillance $n=9$ (39.1%)	p
Number of nodules				
Uninodular	18 (78.2)	12 (85.7)	5 (66.6)	0.146
Multinodular	5 (21.8)	2 (14.2)	4 (44.4)	
Maximum diameter (cm)	3.0 (1.5–3.3)	2.8 (1.8–3.2)	3.0 (1.5–4.0)	0.600
α-fetoprotein level (ng/mL)	3.2 (2.5–20.0)	4.0 (2.9–20.0)	2.8 (2.0–3.6)	0.209
Macro-vascular invasion (present)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Extra-hepatic spread (present)	3 (13.0)	0 (0.0)	3 (33.3)	0.068

Data are expressed as median and interquartile range or number of patients and proportion

Among the 14 patients who underwent curative treatments, 5 patients (35.7%) experienced early HCC recurrence, while among the 7 patients who underwent transarterial chemoembolization, stable disease was observed in 3 patients (42.9.0%), while 4 patients (57.1%) experienced disease progression. During a median follow-up of 41.6 months (IQR 27.4–92.3), 18 patients (78.3%) died. The cause of death was HCC progression in 8 patients (34.8%), liver failure in 7 (30.4%), variceal bleeding in 2 (8.7%), and spontaneous bacterial peritonitis in 1 patient (4.3%). Among the 18 patients who died, 6 (33.3%) had features compatible with MASLD, 4 (22.2%) reported alcohol abuse, and 2 (11.1%) patients exhibited an overlap of AIH/ Primary Biliary Cholangitis.

Overall, the median OS was 41.7 months (95% CI, 4.6–78.7), and it was significantly and remarkably longer in patients under surveillance [68.2 months (95% CI 30.9–87.5)] than in those with an incidental or symptomatic diagnosis of HCC [27.4 months (95% CI 14.5–40.2); HR 3.23 (95% CI 1.10–10.6), $p=0.032$, Fig. 1].

Discussion

The management of patients with HCC represents a clinical challenge due to the complexity of disease and to the multiparametric nature of the choice of treatment [17–19]. This challenge becomes even more evident when considering

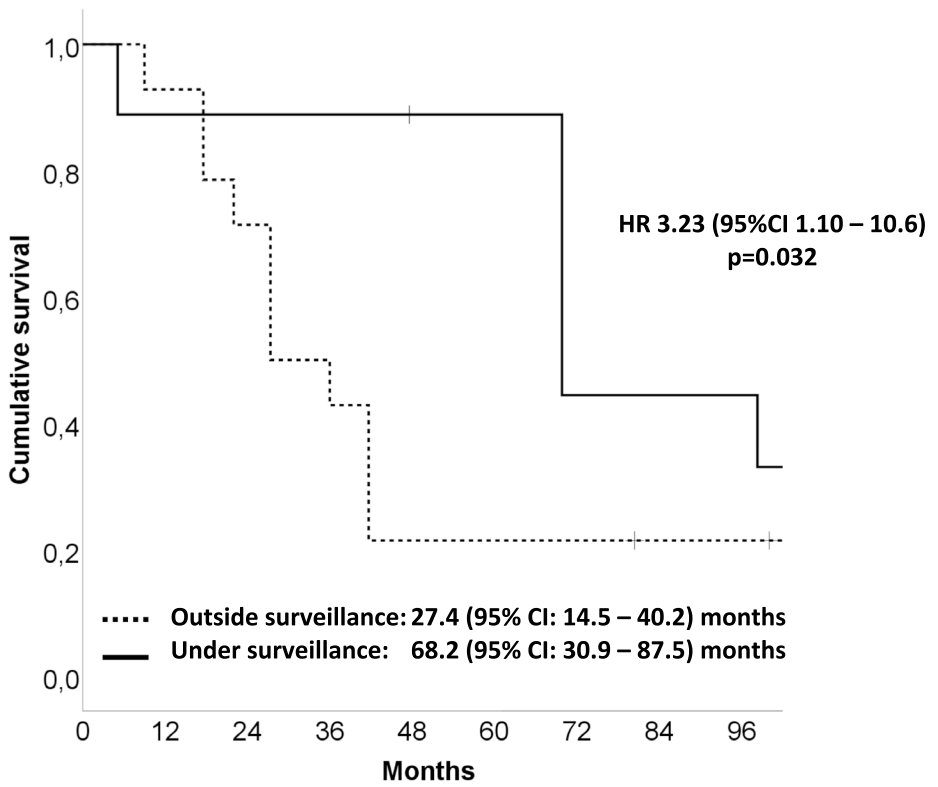

Fig. 1 Kaplan–Meier survival curve of patients, subdivided according to the modality of diagnosis

patients with chronic liver disease due to rare etiologies, such as AIH, which accounts for only 1.28 cases per 100,000 inhabitant years and has a yearly incidence of HCC in patients with cirrhosis as low as 0.46% [20]. Therefore, data and description of patients with AIH and HCC are limited, primarily deriving from small, retrospective studies with very long accrual data [4–6]. Therefore, it is difficult to draw definite conclusions regarding clinical picture and outcome of this "orphan" condition.

Given the reported low risk of oncological progression, costs and potential harms of surveillance for early detection of HCC, routine surveillance is considered not cost-effective in these patients [10]. Nevertheless, our study showed that surveillance was associated with improved access to curative treatments and with better survival, and some AIH patients may indeed have a risk of HCC above the threshold of cost-effectiveness, thus calling for a personalized rather than universal surveillance in this population. However, due to the above-mentioned limitations, precise indications for a personalized surveillance based on the risk assessment ("risk-stratified" surveillance) for AIH patients are yet not available.

Therefore, to provide an updated picture of patients with HCC superimposed on AIH, we evaluated a large cohort of patients with HCC (10,026 patients) among whom only 23 subjects had an AIH-associated HCC, resulting in a prevalence of 0.2% which robustly confirms that AIH is a very rare cause of this tumor since AIH is a rare disease and uncommonly progresses to HCC. Furthermore, it is important to note that in 15 of these 23 cases (65.2%), the etiology of liver disease was not exclusively AIH but included other well-known risk factors that may heighten the risk of carcinogenesis such as MASLD and alcohol abuse, thereby underscoring the significant contribution of co-factors in the development of HCC in patients with AIH.

Notably, we also observed that (a) no patient with HCC was younger than 60, and approximately three-quarter of patients were elderly (> 65 years); (b) the prevalence of male sex greatly exceeded that reported in AIH without HCC, where the female/male ratio is typically 3:1, and this finding aligns with that previously reported by Dakhoul et al. [5], where men represented 40% of patients with AIH and HCC; (c) the vast majority (91.0%) of patients had cirrhosis; and (d) two-third of patients had, beyond AIH, at least one additional etiological factor for chronic liver disease, as 34.8% met the criteria for MASLD, 17.4% had a history of alcohol abuse, and 13.0% presented with an AIH/Primary Biliary Cholangitis syndrome. A limitation of our study is that our cohort did not include AIH patients without HCC contemporarily followed at the participating centers and, hence, we could not compare the prevalence of these characteristics between the two AIH populations (with *vs.* without HCC). Despite the limitation represented by the lack of "denominator" (patients with AIH without HCC), we feel that some useful indications can be drawn from our findings: HCC in patients with AIH seems to be more prevalent in elderly males with cirrhosis, and with concomitant factors for chronic liver disease. Our findings align with recent data from the multicenter, retrospective, observational study by Colapietro et al. [6], who analyzed over 1400 patients diagnosed with AIH. Moreover, our data are also in line with those accrued across the globe in both older and recent series of patients with AIH and HCC, that report an association between HCC and cirrhosis in 100% (1971–2007) and 90% (2000–2014) of patients [4, 5]. These clinical characteristics associated with the risk of HCC may serve to assemble specific risk scores for patients with AIH to optimize surveillance strategies, focusing on well-defined subgroups where cost-effectiveness of surveillance may be acceptable.

Due to the presence of liver cirrhosis, most of our patients were under surveillance for HCC, according to the recommendations of national and international guidelines and, also in this etiological category of patients, we observed—with statistical limitations inherent to the relatively small series—that surveillance was associated with an improved outcome [8, 15]. Indeed, patients under surveillance had better HCC staging at diagnosis, and were much more frequently treated with curative intent as compared to patients diagnosed with HCC outside surveillance (78.6% *vs.* 33.3%). Noteworthy, these findings were associated with very high response rates and a very low rate of early recurrence following curative treatment, eventually leading to a statistically significant and clinically meaningful extension of median OS (more than 3 years) for patients whose HCC was detected under surveillance as compared to the counterpart.

Therefore, while we await the development of dedicated HCC risk calculators for patients with AIH, our findings suggest that surveillance for HCC is more justifiable in patients with established cirrhosis. However, given the overall low incidence rates of HCC in AIH—even among those with cirrhosis—the cost-effectiveness of routine surveillance remains uncertain. In pre-cirrhotic patients, surveillance should be individualized and based on a case-by-case assessment, considering additional risk factors, such as sex, age (> 60 years), and presence of co-factors.

One of the primary limitations of this study is the small sample size, which reduces the statistical power of our findings. This limitation imposes caution in drawing definitive conclusions regarding the generalizability of the results. Additionally, the retrospective nature of the study may introduce bias, as patient data were collected over an extended period across multiple institutions. Lastly, the study is based on data from a cohort enrolled in single country, which may not fully represent the global population of patients with AIH and HCC. Finally, a further limitation of this study is

that the diagnosis of MASLD was based on clinical criteria, and although biopsy data were available from AIH diagnoses, these historical data—often obtained more than one year before the HCC diagnosis—preclude a systematic re-evaluation of the histological findings. Despite its limitations, our study offers significant insights into an "orphan" scenario. The high level of detail provided on patient characteristics, tumor burden and outcomes adds depth to the understanding of HCC in AIH patients, especially regarding the potential benefits of surveillance in this population. Lastly, our findings are in line with the recent literature, strengthening the clinical relevance and suitability of its contents.

To conclude, our data confirm that the prevalence of AIH-associated HCC is very low, and that some demographic and clinical characteristics, such as older age, male sex presence of liver cirrhosis, and presence of co-factors of liver damage, increase the oncologic risk of AIH patients, and, hence, may help focus personalized and cost-effective surveillance programs. Moreover, also in patients with AIH, surveillance for HCC is associated with better tumor staging at diagnosis, higher access to potentially curative treatments, and improved survival.

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Author Contributions Edoardo G. Giannini and Andrea Pasta contributed for conceptualization, literature search, figures, study design, data collection, data analysis, writing first draft, and had access and verified data. Maria Corina Plaz Torres, Giulia Pieri, Ciro Celsa, Angelo Sangiovanni, Nora Cazzagon, Mauro Viganò, Fabio Piscaglia, Claudia Campani, Gabriele Missale, Gianpaolo Vidili, Giorgia Ghittoni, Filippo Pelizzaro, Francesco Giuseppe Foschi, Filomena Morisco, Lorenzo Lani, Gianluca Svegliati-Baroni, Francesco Azzaroli, Carlo Saitta, Maurizia Rossana Brunetto, Rodolfo Sacco, Francesca Romana Ponziani, Sara Boninsegna, Gerardo Nardone, Andrea Martini, Andrea Mega, David Sacerdoti, Daniela Magalotti, Alessandro Vitale, Laura Bucci, and Franco Trevisani contributed for resources, investigation, data collection, data analyses, and writing-review and editing. All authors approved the final draft submitted.

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Data Availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The Institutional Review Board of the ITA.LI.CA Coordinating Center approved the use of this database for scientific research (approval number 99/2012/O/Oss), and the study was conducted in accordance with the ethical principles outlined in the 1975 Declaration of Helsinki.

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