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The changing scenario of hepatocellular carcinoma in Italy: an update

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Abbreviations: AASLD, American Association for the Study of the Liver; AFP, alpha-foetoprotein; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; ITA.LI.CA, Italian Liver Cancer; LT, liver transplantation; MAR, missing at random; MCAR, missing completely at random; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SD, standard deviation; TACE, transarterial chemoembolization; US, ultrasound.

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Abstract

Background and aims: Epidemiology of hepatocellular carcinoma (HCC) is changing in most areas of the world. This study aimed at updating the changing scenario of aetiology, clinical presentation, management and prognosis of HCC in Italy during the last 15 years.

Methods: Retrospective analysis of the Italian Liver Cancer (ITA.LI.CA) database included 6034 HCC patients managed in 23 centres from 2004 to 2018. Patients were divided into three groups according to the date of cancer diagnosis (2004-2008, 2009-2013 and 2014-2018).

Results: The main results were: (i) a progressive patient ageing; (ii) a progressive increase of non-viral cases and, particularly, of 'metabolic' and 'metabolic + alcohol' HCCs; (iii) a slightly decline of cases diagnosed under surveillance, but with an incremental use of the semiannual schedule; (iv) a favourable cancer stage migration; (v) an increased use of radiofrequency ablation to the detriment of percutaneous ethanol injection; (vi) improved outcomes of ablative and transarterial treatments; (vii) an improved overall survival (adjusted for the lead time in surveyed patients) in the last calendar period, particularly in viral patients; (viii) a large gap between the number of potential candidates (according to oncologic criteria and age) to liver transplant and that of transplanted patients.

Conclusions: During the last 15 years several aspects of HCC scenario have changed, as well as its management. The improvement in patient survival observed in the last period was likely because of a larger use of thermal ablation with respect to the less effective alcohol injection and to an improved management of intermediate stage patients.

KEYWORDS
epidemiology, hepatocellular carcinoma, survival, treatment

1 | INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is growing in most countries, and this tumour is currently the leading cause of mortality in cirrhotic patients.[1] Worldwide, chronic viral hepatitis and alcoholic liver disease remain the main risk factors for HCC development, although in high-income countries non-alcoholic fatty liver disease (NAFLD)-associated HCCs are escalating, because of the rising prevalence of metabolic disorders.[2-4] Conversely, vaccination and therapy for hepatitis B virus (HBV) infection,[5] prevention campaigns for sexual and iatrogenic transmission of HBV and hepatitis C virus (HCV) and the availability of effective antiviral agents against HCV are reducing the burden of chronic viral liver disease.[6-9]

Primary liver cancers, most (>80%) of which are HCCs, are highly lethal tumours leading to a 5-year age-standardized survival rate <20% even in developed countries, as reported by nine population-based Italian registries.[10] However, provided that HCC is detected at an early stage, curative treatments can greatly improve prognosis.[11] In addition, continuous refinements of treatments for underlying viral infections, complications of cirrhosis and tumour itself, including the advent of several lines of effective systemic therapy and immunotherapy, have also contributed to improve HCC prognosis.[12,13]

This study was aimed at updating the epidemiological and clinical scenario of HCC we described in two previous reports,[8,14] comparing the pertinent features collected over the last three *quinquiennia* by 23 centres spread around our country.

2 | PATIENTS AND METHODS

2.1 | Patients

We analysed the data of the Italian Liver Cancer (ITA.LI.CA) registry, currently including 7816 patients consecutively diagnosed with HCC and followed-up from January 1987 to December 2018 by 23 ITA.LI.CA centres (9 acting as primary and 14 as tertiary referral centres). Data were collected prospectively and updated every two years, as described in previous reports.[8,14]

For this study, we enrolled 6034 patients diagnosed with HCC from January 1st 2004 to December 31th 2018. Patients were subdivided into three groups according to the year of cancer diagnosis: G1 = 2004-2008 [n. 1135 (18.8%) patients], G2 = 2009-2013 [n. 2355 (39.0%)] and G3 = 2014-2018 [n. 2544 (42.2%)]. The patients recruited in each centre ranged from 80 to 676. The patient enrolment rate of primary and tertiary referral centres was 1989 (33.0%) and 4045 (67.0%) respectively.

We analysed the following variables: age, gender, aetiology, presence of cirrhosis, Child-Pugh class, modality of HCC diagnosis, surveillance interval, alpha-foetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC) stage,[15] treatment and patient survival. All these variables were available in >80% of cases, except for AFP (quoted in 77.7% of patients). No missing data imputation was conducted because data were not missing at random, but were systematically incomplete or not recorded in some patients (see Statistical analysis paragraph).

Key points

- Increased number of HCCs ensuing in a non-viral chronic liver disease
- Increment of the implementation of semiannual surveillance
- Evolution of therapeutic management with an improved outcome of loco-regional treatments
- Improved survival, particularly in viral patients

2.2 | Aetiology and diagnosis of liver disease

The aetiology of liver disease was classified as:

- HBV, if patients were HBV surface antigen (HBsAg) carriers [± hepatitis delta virus (HDV)];
- HCV, if positive for serum anti-HCV antibody;
- multiviral (HBV + HCV±HDV), if infected by both HBV (±HDV) and HCV;
- alcoholic, if the daily ethanol intake was more than 60 g for women and 80 g for men, for >10 years, in the absence of any other liver injury;
- non-alcoholic fatty liver (NAFLD), according to the criteria proposed by the American Association for the Study of the Liver (AASLD)[16];
- alcohol + NAFLD, if there was a combination of alcohol abuse and fatty liver;
- cryptogenic, if HBsAg, anti-HCV antibody, alcohol abuse, autoimmune or genetic liver diseases were absent;
- multiaetiology, if there was a combination of viral infection(s) and alcohol abuse or NAFLD [in the analyses where aetiology was dichotomized as 'viral' or 'non-viral', this group was included in the viral group (see below)];
- other aetiology, which included hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, primary biliary cirrhosis and sclerosing cholangitis.

Patients were also divided into 'viral' and 'non-viral', according to the presence/absence of HBsAg and/or anti-HCV antibody.

All cases classified as NAFLD had a fatty liver at ultrasound (US) or magnetic resonance imaging (MRI), and the absence of all other causes of liver damage. In 40 (13.4%) of them the liver damage was also evaluated by histology.

The diagnosis of cirrhosis was confirmed by histology in 354 (6.7%) patients, and by laparotomy or laparoscopy in 37 (0.7%); otherwise it was made unequivocal by clinical, laboratory, endoscopic and imaging findings.

2.3 | Modality of HCC diagnosis

The type of HCC diagnosis was classified as:

- under surveillance: if HCC was detected during an US-based surveillance program (±AFP determination) started at least one year prior to HCC diagnosis. Patients were subgrouped according to the interval of surveillance (≤7 months vs 12 ± 1 months). In order to minimize the *length bias*, patients under surveillance were maintained in their original group even if the scheduled US examination was anticipated by the occurrence of symptoms;
- incidental: if diagnosis was made during investigations for other diseases or for a general check-up, outside regular surveillance;
- symptomatic: if HCC was detected through investigations motivated by the occurrence of cancer symptoms in patients outside surveillance.

2.4 | Diagnosis and staging of HCC

Diagnosis of HCC was established according to histological findings or to the typical features in one or more imaging techniques [dynamic computed tomography (CT) and/or MRI] as proposed by the versions of European and American guidelines available at the time of cancer diagnosis. In particular, for nodules between 1 and 2 cm, diagnosis was based on typical HCC features in two diagnostic imaging modalities and for lesions >2 cm in one modality until 2011, when we adopted the updated AASLD guidelines allowing to diagnose HCC if the typical features are observed in one imaging technique for all nodules ≥1 cm.[17]

Cancer burden was assessed by liver CT and/or MRI, while further investigations aimed at detecting an extra-hepatic tumoural spread were performed routinely in patients with advanced HCC or in candidates for liver transplantation (LT). Otherwise, these imaging techniques were executed if clinically indicated. HCC was staged according to BCLC staging system.[15]

Patients aged ≤70 years and without extra-hepatic spread and vascular invasion were also evaluated as potential candidates to LT according to the Milan criteria[18] and the Metroticket 2.0 model[19] in order to compare the theoretical amenability rate to LT attainable with these two selection models.

2.5 | Treatment

Most patients underwent multiple treatments. For the purpose of this investigation, they were classified according to the most effective one, based on this hierarchy: LT, hepatic resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), sorafenib, other systemic therapies and palliation. Patients treated with transarterial embolization and transarterial radioembolization were included in the TACE group.

2.6 | Lead-time estimation and statistical analysis

Patients diagnosed with HCC during a surveillance program or incidentally were challenged against those with a symptomatic diagnosis for lead-time-estimation (see Supplementary Methods).

Continuous data were expressed as mean value ± standard deviation (SD) and discrete variables as absolute and relative frequencies. Comparisons of continuous variables among the three periods were made using ANOVA. Discrete variables were compared with the chi-squared test.

The lead-time adjusted survival was estimated using Kaplan-Meier method and compared between groups using the log-rank test. The percentages of patients surviving at 1, 3 and 5 years were also reported.

The statistical assumptions concerning missing data, ie missing at random (MAR) or missing completely at random (MCAR) were tested to determine whether data imputation was feasible.

A two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed with SPSS v25.0 (Apache Software Foundation, Chicago, IL, USA).

2.7 | Ethics

The ITA.LI.CA database management is compliant with the current Italian legislation on privacy, and the study conforms to the ethical guidelines of the Declaration of Helsinki. All patients provided informed consent to having their data entered into the ITA.LI.CA database with an anonymized identification number. The study design was approved (protocol n. 99/2012/O/Oss) by the Independent Ethic Committee of S. Orsola-Malpighi Hospital of Bologna, that operates as coordinating centre of the ITA.LI.CA network. In all the remaining centres, data inclusion into ITA.LI.CA registry was approved by the local ethics committees.

3 | RESULTS

3.1 | Demographic characteristics, aetiology and liver function (Table 1)

In all calendar periods HCC incidence peaked at age 70-74 years (Figure 1). However, the mean age at diagnosis increased over time so that in the G3 period patients were significantly older than in the previous ones. The ageing of HCC population was also confirmed by the shift towards right of the age distribution of incident cases (Figure 1), with a modest increase in viral patients (from 66.6 years in G1 to 67.9 years in G3; $P = .023$) and a larger one in non-viral patients (from 65.8 years in G1 to 69.0 years in G3; $P < .001$). Instead, the great predominance of male gender (around 77%) did not change over time.

Viral aetiology prevailed in all periods, but viral cases progressively and significantly decreased over time, with a compensatory increment in non-viral patients, who raised up to 37.2% in G3. The lowering of viral aetiology was mainly produced by the attenuation of the HCV impact that progressively decreased from 48.8% to 43%. The prevalence of both HBV and multiviral infections also declined. In order to assess the current role played on aetiology by the patient area of residence, we assessed the viral/non-viral ratio in North, Centre and South areas of our country in G3 period. Viral cases largely prevail everywhere, but with a significantly higher predominance in South Italy (Figure S1).

Among non-viral patients, 'pure' alcoholic HCCs remarkably declined over time (from 20% to 13.3%), with a mirror raise of alcoholic + NAFLD cases (from 0.7% to 8%). 'Pure' NAFLD cases also strikingly increased (from 1.5% to 7.1%), with a similar change in cryptogenic liver disease (from 0.9% to 4.1%).

When the subgroup of patients aged ≤65 years (n. 2260) was analysed, we found that the number of non-viral HCCs equaled that of HCV-related ones since the G2 period (Figure S2A). Although non-viral tumours increased even among older patients, HCV infection remained the main cause of HCC in all calendar periods (Figure S2B).

In the overall population established cirrhosis was present in most HCC cases (90.2%). Nevertheless, cirrhosis was less prevalent in non-viral than in viral patients (88.3% vs 92.8%, $P < .001$), particularly in metabolic cases (Figure 2A). The prevalence of tumours arising in a non-cirrhotic liver progressively increased over time (from 4.9% to 12.0%) in both viral and non-viral settings (Figure 2B).

Diabetes and overweight/obesity were remarkably more common in non-viral than viral patients, achieving their highest prevalence in NAFLD and alcoholic + NAFLD cases (Figure S3).

About two-third of patients belonged to Child-Pugh class A in all periods, and the prevalence of this class significantly increased over time to the detriment of class C, particularly from G1 to G2.

3.2 | Modality of HCC diagnosis, cancer stage and treatment (Table 2)

Overall, 63% of HCCs were detected under surveillance. In particular, diagnosis under surveillance was much more common in viral

TABLE 1 Demographic factors, aetiology of liver disease and liver function of patients with hepatocellular carcinoma

	Available cases, n (%)	G1 2004-2008, n (%)	G2 2009-2013, n (%)	G3 2014-2018, n (%)	p
		1135 (18.8)	2355 (39.0)	2544 (42.2)	
Age (mean ± SD), years	6034 (100)	66.3 ± 10.3	67.2 ± 10.7	68.3 ± 10.8	G1 vs G3 < 0.001 G2 vs G3 = 0.001
Gender (M/F)	6034 (100)	859/276 (75.7/24.3)	1827/528 (77.6/22.4)	1973/571 (77.6/22.4)	
Aetiology	5815 (96.4)	1110 (19.1)	2272 (39.1)	2433 (41.8)	*P* < .001
Viral aetiology	3871 (66.6)	797 (71.8)	1545 (68.0)	1529 (62.8)	*P* < .001
HBV (± HDV)	558 (9.6)	130 (11.7)	222 (9.8)	206 (8.5)	G1 vs G3 = 0.007
HCV	2625 (45.1)	542 (48.8)	1037 (45.6)	1046 (43.0)	G1 vs G3 = 0.004
HBV + HCV (± HDV)	101 (1.7)	26 (2.3)	46 (2.0)	29 (1.2)	G1 vs G3 = 0.031
Multiaetiology	587 (10.1)	99 (8.9)	240 (10.6)	248 (10.2)	
Non-viral aetiology	1944 (33.4)	313 (28.2)	727 (32.0)	904 (37.2)	*P* < .001
Alcohol	886 (15.2)	222 (20.0)	340 (15.0)	324 (13.3)	G1 vs G2 = 0.001 G1 vs G3 < 0.001
Alcohol + NAFLD	310 (5.3)	8 (0.7)	108 (4.8)	194 (8.0)	G1 vs G2 < 0.001 G1 vs G3 < 0.001 G2 vs G3 < 0.001
NAFLD	297 (5.1)	17 (1.5)	108 (4.8)	172 (7.1)	G1 vs G2 < 0.001 G1 vs G3 < 0.001 G2 vs G3 = 0.002
Cryptogenic	207 (3.6)	10 (0.9)	98 (4.3)	99 (4.1)	G1 vs G2 < 0.001 G1 vs G3 < 0.001
Other	244 (4.2)	56 (5.0)	73 (3.2)	115 (4.7)	G1 vs G2 = 0.027 G2 vs G3 = 0.024
Cirrhosis	5865 (97.2)	1085 (18.5)	2312 (39.4)	2468 (42.1)	*P* < .001
Yes	5292 (90.2)	1032 (95.1)	2088 (90.3)	2172 (88.0)	G1 vs G2 < 0.001; G1 vs G3 < 0.001; G2 vs G3 = 0.032
Child-Pugh class	5305 (87.9)	957 (18.0)	2036 (38.4)	2312 (43.6)	*P* < .001
Class A	3462 (65.3)	586 (61.2)	1333 (65.5)	1543 (66.7)	G1 vs G3 = 0.008
Class B	1544 (29.1)	285 (29.8)	607 (29.8)	652 (28.2)	
Class C	299 (5.6)	86 (9.0)	96 (4.7)	117 (5.1)	G1 vs G2 < 0.001 G1 vs G3 < 0.001 G2 vs G3 = 0.031

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; NAFLD, non-alcoholic fatty liver disease.

than in non-viral patients (71.1% vs 52.1%, *P* < .001, data not shown). In G3, this diagnosis barely decreased (from 64.4% in G1 to 65.6% G2 and to 60.9% in G3), with a reciprocal gain of the incidental detection of the tumour (from 21.3% to 23.3% to 26.8%) (Figure 3A).

Among surveyed patients, the proportion of those screened every 6 months prevailed, raising from G1 to G2 (from 83.0% to 90.4%) and thereafter remaining unchanged (89.4%) (Figure 3B).

An abnormal (>10 ng/mL) AFP level was found in 54.2% of patients. The prevalence of AFP-producing tumours declined over time, mainly because of a decrease in those causing a moderate (11-200 ng/mL) elevation.

A 'bidirectional' change in the distribution of cancer size was noted, as both small (≤2 cm) and large (>5 cm) tumours increased at the expenses of intermediate-size nodules (2.1-5 cm).

The prevalence of very early and early (BCLC 0 and A) HCCs significantly increased over time so that they accounted for 54.9% of all HCCs in G3. This change was associated with a drop of both intermediate and end-stage (BCLC B and D) tumours.

From the whole population, we selected 2303 patients (38.2%) fulfilling the *fundamental* features for assuming an application to LT (*ie* age ≤ 70 years, absence of macrovascular invasion and extrahepatic cancer spread). In 1733 (75.2%) of them the Metroticket 2.0 parameters (number and size of nodules and AFP value) were specified, and 1446 (83.4%) of them fulfilled the oncological conditions predicting a 5-year overall mortality <50% after LT according to this model (Figure 4). Such a theoretical amenability did not significantly change over time (G1 82.5%, G2 82.9% and G3 84.4%). When we tested the Milan criteria (1 nodule ≤5 cm or

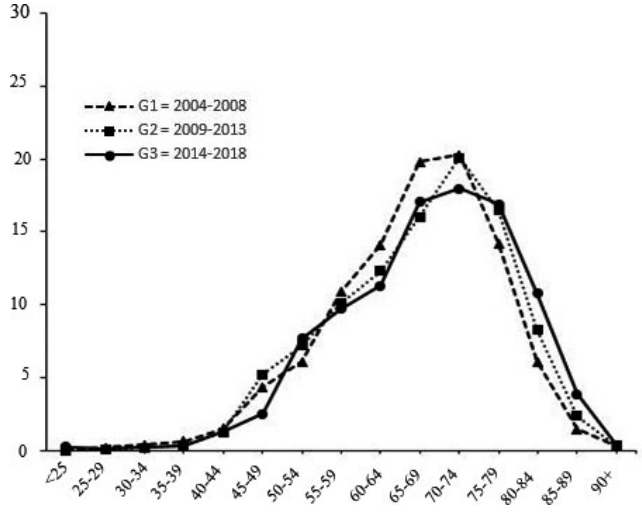

FIGURE 1 Temporal trends of age distribution in patients with hepatocellular carcinoma. In all calendar periods the tumour incidence peaked at 70-74 years of age. However, the curves progressively shifted from left to right over time, leading to a significant increase in mean patients' age at the time of cancer diagnosis (see also Table 1)

up to 3 nodules each ≤3 cm) in the same 2303 patients fulfilling the fundamental criteria for amenability to LT, 2097 (91.1%) had the Milan parameters specified, and 1573 (75.0%) of them fulfilled these criteria.

3.3 | Treatment (Table 2)

LT was performed in a minimal percentage of cases (around 5.5%) in all calendar periods, without significant changes during the study period.

In the whole period of study, considering the patients fulfilling the *fundamental* criteria for the eligibility to LT, among the 1446 Metroticket 2.0-in patients only 163 patients (11.3%) underwent LT. Among the 1573 Milan-in patients, 176 patients (11.2%) were transplanted.

We also performed a subanalysis selecting patients not eligible to alternative curative options because of a poor liver function according to two arbitrarily defined conditions: Child-Pugh score > B7 and/or presence of ascites. Among Metroticket 2.0-in patients, 490 (33.9%) fulfilled this definition, and only 81 (16.5%) of them underwent LT. Among Milan-in patients, the corresponding figures were 474 (30.1%) and 76 patients (16%) respectively.

Resected patients fluctuated around 17% of cases, peaking at 19% in G2. RFA was utilized in 27.6% of the population, with a progressive increase over time up to 31.6% in G3, while PEI use progressively diminished from 13.0% to 4.0%.

The percentage of patients treated with TACE did not change significantly, fluctuating around 25% in the three periods.

Sorafenib treatment markedly increased, mainly across G1 and G2, at the detriment of non- evidence-based therapies ('other'). Lastly, about 8% of patients underwent palliative therapy, and this percentage significantly decreased in the last period (6.1%).

When the treatment distribution by BCLC stage was analysed (Figure S4), in stage 0 + A patients, RFA accounted for most cases, with a progressive increase up to 43.6% of cases in G3; resection was performed in about 25% of patients, and LT in <10% of cases. In stage B patients, TACE strikingly prevailed, with figures fluctuating around 43%. About 20% of these patients underwent resection and, in G3, 7.2% of them underwent sorafenib therapy. In stage C patients, sorafenib (not available in G1) accounted for 20.4% of cases in G2 and 29.8% in G3 ($P < .001$).

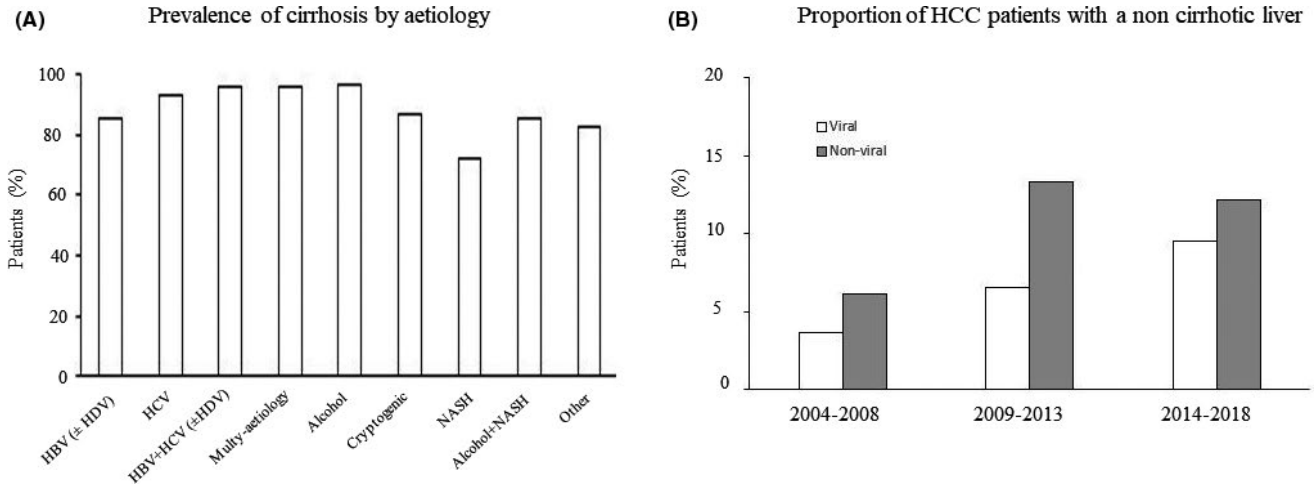

FIGURE 2 Prevalence of cirrhosis in patients recruited during the entire period (2004-2018) according to the aetiology of hepatocellular carcinoma (HCC). (A) Viral cases showed a significantly higher prevalence (92.8%) of cirrhosis than non-viral ones (88.3) ($P < .001$). Among viral cases, all aetiological subgroup showed a prevalence of cirrhosis >85%, while, among non-viral cases, only alcoholic patients had almost invariably an underlying cirrhosis. (B) The proportion of HCC patients with a non-cirrhotic liver increased over time, particularly in non-viral patients (6.2% in G1, 13.3% in G2 and 12.8% in G3)

TABLE 2 Oncological characteristics and treatment of patients with hepatocellular carcinoma

	Available cases, n (%)	G1 2004-2008, n (%)	G2 2009-2013, n (%)	G3 2014-2018, n (%)	p
	6034 (100)	1135 (18.8)	2355 (39.0)	2544 (42.2)	
Serum AFP	4690 (77.7)	923 (19.7)	1751 (37.3)	2016 (43.0)	$P < .001$
≤10 ng/mL	2151 (45.9)	348 (37.7)	770 (44.0)	1033 (51.2)	G1 vs G2 = 0.006 G1 vs G3 < 0.001 G2 vs G3 < 0.001
11-200 ng/mL	1701 (36.3)	404 (43.8)	651 (37.2)	646 (32.0)	G1 vs G2 = 0.003 G1 vs G3 < 0.001 G2 vs G3 = 0.003
>200 ng/mL	838 (17.9)	171 (18.5)	330 (18.8)	337 (16.7)	
Cancer size	5435 (90.1)	1006 (18.5)	2072 (38.1)	2357 (43.4)	$P = .008$
≤2 cm	1610 (29.6)	273 (27.1)	599 (28.9)	738 (31.3)	G1 vs G3 = 0.047
From 2.1 to 5 cm	2686 (49.4)	544 (54.1)	1018 (49.1)	1124 (47.7)	G1 vs G2 = 0.030 G1 vs G3 = 0.002
>5.0 cm	1139 (21.0)	189 (18.8)	455 (22.0)	495 (21.0)	
Number of nodules	5748 (95.3)	1085 (18.9)	2228 (38.8)	2435 (42.4)	$P < .001$
1 nodule	2971(51.7)	523 (48.2)	1182 (53.1)	1266 (52.0)	G1 vs G2 = 0.026
2-3 nodules	1775 (30.9)	300 (27.6)	680 (30.5)	795 (32.6)	G2 vs G3 = 0.009
>3 nodules	543 (9.4)	171 (15.8)	177 (7.9)	195 (8.0)	G1 vs G2 < 0.001 G1 vs G3 < 0.001
Massive/ infitrative	459 (8.0)	91 (8.4)	189 (8.5)	179 (7.4)	
BCLC stage	5671 (94.0)	1043 (18.4)	2221 (39.2)	2407 (42.4)	$P < .001$
0	336 (5.9)	33 (3.2)	149 (6.7)	154 (6.4)	G1 vs G2 < 0.001 G1 vs G3 < 0.001
A	2441 (43.0)	405 (38.8)	869 (39.1)	1167 (48.5)	G1 vs G3 < 0.001 G2 vs G3 < 0.001
B	865 (15.3)	197 (18.9)	342 (15.4)	326 (13.5)	G1 vs G2 = 0.037 G1 vs G3 < 0.001
C	1598 (28.2)	294 (28.2)	697 (31.4)	607 (25.2)	G2 vs G3 = 0.001
D	431 (7.6)	114 (10.9)	164 (7.4)	153 (6.4)	G1 vs G2 = 0.002 G1 vs G3 < 0.001
Main treatment	5381 (89.2)	1033 (19.2)	2151 (40.0)	2197 (40.8)	$P < .001$
LT	288 (5.4)	61 (5.9)	124 (5.8)	103 (4.7)	
Resection	963 (17.9)	161 (15.6)	408 (19.0)	394 (17.9)	
RFA	1486 (27.6)	220 (21.3)	572 (26.6)	694 (31.6)	G1 vs G2 = 0.004 G1 vs G3 < 0.001 G2 vs G3 = 0.001
PEI	376 (7.0)	134 (13.0)	154 (7.2)	88 (4.0)	G1 vs G2 < 0.001 G1 vs G3 < 0.001 G2 vs G3 < 0.001
TACE	1333 (24.8)	273 (26.4)	501 (23.3)	559 (25.4)	
Sorafenib	366 (6.8)	0 (0.0)	167 (7.8)	199 (9.1)	G1 vs G2 < 0.001 G1 vs G3 < 0.001
Palliation	437 (8.1)	100 (9.7)	203 (9.4)	134 (6.1)	G1 vs G3 = 0.001 G2 vs G3 < 0.001
Other	132 (2.5)	84 (8.1)	22 (1.0)	26 (1.2)	G1 vs G2 < 0.001 G1 vs G3 < 0.001

Abbreviations: AFP, alpha-foetoprotein; BCLC, Barcelona Clinic Liver Cancer; LT, liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

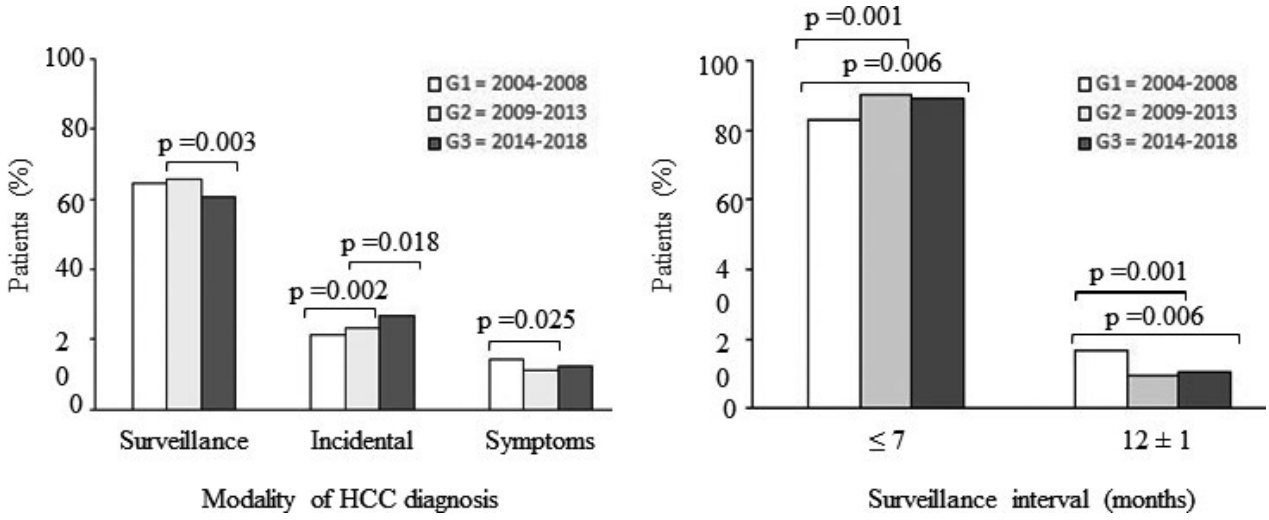

FIGURE 3 Modality of cancer diagnosis (A) and surveillance interval (B) in patients with hepatocellular carcinoma across the calendar periods

3.4 | Survival

The calculated lead times (mean ± SD) for patients under surveillance and for those diagnosed incidentally were, respectively:

- G1: 7.3 ± 1.5 and 3.2 ± 0.7 months
- G2: 8.4 ± 2.5 and 4.1 ± 1.1 months
- G3: 7.2 ± 2.3 and 2.9 ± 0.7 months.

After adjustment for the lead-time, the median overall survival (OS) increased in G3 [from 34.5 months (95% CI 30.4-38.5) to 32.1 months (95% CI 29.4-34.8) to 42.8 months (95% CI not

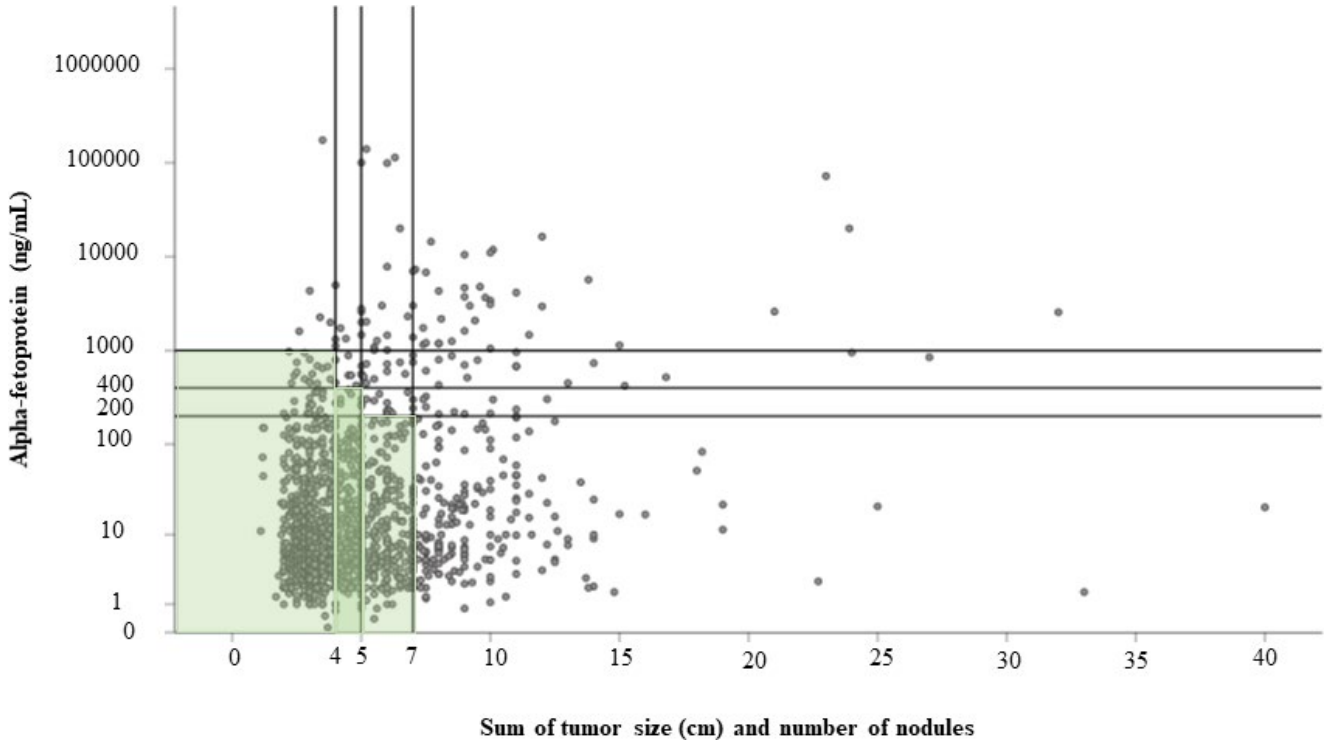

FIGURE 4 Distribution of cases diagnosed with hepatocellular carcinoma during the whole period of study according to the Metroticket 2.0 model. The green area includes the 1446 (83.4%) out of 1733 patients fulfilling the transplantation criteria for this model (*ie* with an expected 5-year survival rate >50%). This theoretical amenability to transplantation did not significantly change over time (G1 82.5%, G2 82.9% and G3 84.4%)

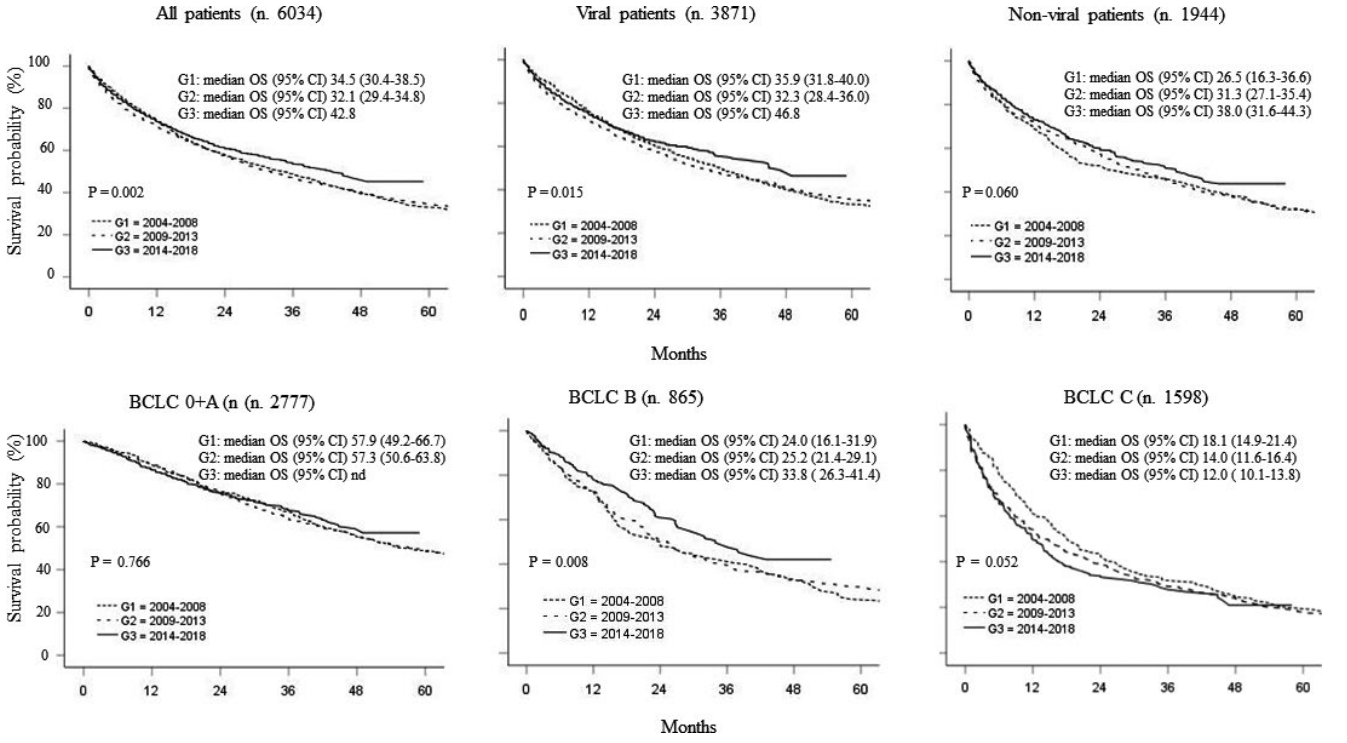

FIGURE 5 Temporal trend of the lead-time adjusted overall survival of all, viral and non-viral patients (Top), and by Barcelona Clinic Liver Cancer (BCLC) stage (Bottom)

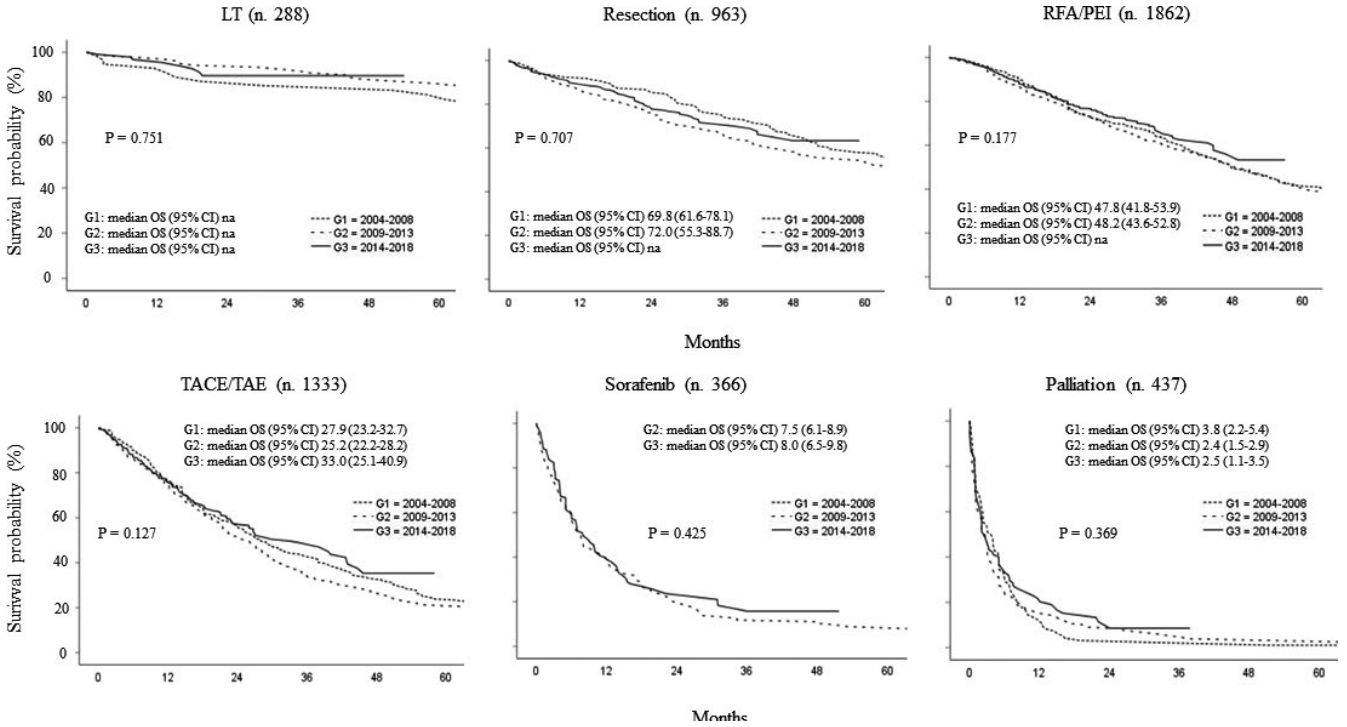

FIGURE 6 Temporal trend of lead-time adjusted overall survival of patients according to the main treatment (LT, liver transplantation, RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE/TAE transarterial chemoembolization/embolization). Sorafenib group contains only two calendar periods since this therapy became available in 2018

reached)]. The corresponding 1, 3 and 5-year survival rates for G1, G2 and G3 were: 73.7%, 71.8%, 73.6%, and 48.7%, 47.1%, 53.4%, and 33.3%, 34.5% (not calculable for G3) respectively.

In G3, OS improved in the whole population and in viral patients, while the improvement did not reach statistical significance in non-viral patients (Figure 5).

A subgroup analysis by BCLC stage revealed that OS significantly improved in G3 for BCLC B patients (Figure 5), while it significantly decreased for BCLC C patients from G1 to G3 ($P = .006$).

A subgroup analysis by treatment showed that TACE improved OS from G2 to G3 [from 25.2 months (95% CI 22.2-28.2) to 33.0 months (95% CI 25.1-40.9); $P = .019$], whereas resected patients showed an improvement in OS between G1 and G2 [from 69.8 months (95% CI 61.6-78.1) to 72.0 months (95% CI 55.3-88.7); $P = .013$] (Figure 6).

4 | DISCUSSION

This study shows that the already reported[8,14] ageing of HCC population and decreasing aetiological impact of viral infections (particularly HCV infection) are continuing. The ageing of our HCC population could simply reflect the similar trend observed in the Italian population, in which the life expectancy of males increased from 77.9 years in 2004 to 80.6 years in 2017, and that of females from 83.6 years to 84.9 years (https://www.istat.it/it/archivio/230627; last access 21/10/2020). Nonetheless, it cannot be excluded that the ageing of HCC patients also reflects a slowdown of hepatic carcinogenesis leading to a delayed tumour occurrence because of the efficient control of viral replication by nucleot(s)ide analogues in HBV patients and the achievement of a sustained virological response in an increasing proportion of HCV carriers.[20,21]

However, in our country HCV remains the main cause of HCC, still accounting for 43% of cases in the last period analysed. The reduced relevance of HCV can be explained by the waning of the *baby boomer* population in which HCV has extensively circulated before the 1990s. Our assumption is supported by the finding that the prevalence of this infection was remarkably lower in the subset of patients aged ≤65 years. Another causal factor could be the availability of several antiviral therapies (interferon, direct antiviral agents and nucleot(s)ide agents) that, resolving the necro-inflammatory activity of liver disease, reduce the risk of HCC in patients with advanced fibrosis or cirrhosis.[7,22-25]

The viral aetiology tends to be replaced by metabolic promoters, such as obesity and diabetes.[3,4,26,27] which were much more common in non-viral patients (Figure S3). Namely, among non-viral patients, 'pure' alcoholic cases almost halved over time (from 20% to 13.3%), likely because of a shift towards mixed alcoholic + NAFLD cases (from 0.7% to 8%), and 'pure' NAFLD -associated HCCs strikingly increased (from 1.5% to 7.1%) as well as those ensuing in cryptogenic cirrhosis (from 0.9% to 4.1%), that frequently results from a burned-out non-alcoholic steatohepatitis.[28]

The growing impact of non-viral aetiology was particularly manifested in patients aged ≤65 years, in whom it reached the same magnitude of HCV after 2008 (Figure S2). It is also worth noting that in our country the ratio between viral and non-viral aetiologies was unevenly distributed, since viral infections still accounts for 76% of HCCs in the South area, while this figure dropped to about 60% in the other areas (Figure S1). Taken together, these data should guide the primary prevention of HCC not only towards the prevention and cure of viral hepatitis, but also towards hammering campaigns against the risky use of alcohol and promoting healthy life-styles.

The prevalence of cirrhosis progressively declined over time (from 95.1% to 88.0%) as possible consequence of the growing proportion of HCCs due to a 'metabolic' aetiology. In fact, cirrhosis was less common in non-viral than in viral patients (88.3% vs 92.8%, $P < .001$) and particularly in the setting of NAFLD (Figure 2A), where its prevalence may fall until 50%.[29] More intriguingly, we found that the association with cirrhosis declined even in viral patients (Figure 2B). This unexpected result, that needs to be confirmed, could be attributed to a 'peculiar' (*ie* not strictly cirrhosis-dependent) carcinogenesis in patients who benefit of antiviral therapy.

A number of the epidemiological changes we observed could also explain the shift towards Child-Pugh class A to the detriment of Child-Pugh class C.

Overall, about 63% of HCCs were diagnosed in patients under surveillance and, among them, the relative proportion of tumours detected under a semiannual program increased after the first period (Figure 3B), suggesting a growing adherence of physicians to guideline recommendations. However, it is worth noting that the overall percentage of HCCs detected during surveillance slightly decreased in the last period, being counterbalanced by a gain in incidental diagnoses (Figure 3A). This phenomenon may have two explanations: first, a discontinuation of surveillance and/or a growing use of an inconsistent surveillance programs in non-viraemic HBV patients and in those with cured HCV; second, the mounting proportion of metabolic and metabolic + alcoholic patients who are more frequently diagnosed with HCC outside surveillance compared to HCV carriers,[29,30] owing to the absence of specific recommendations for non-cirrhotic NAFLD and the low compliance to surveillance of alcoholic patients.[31] In line with this assumption, in our study the diagnosis of HCC under surveillance was more frequent in viral than in non-viral patients. The decline of diagnoses under surveillance conflicts with what we observed in the investigation that ended in 2014,[14] and we think that this initial inversion of tendency needs to be accurately monitored in the future.

Regarding HCC burden, the bidirectional change of cancer size we previously reported[14] was confirmed in the present survey: intermediate-size (2.1-5 cm) nodules progressively decreased in favour of both small (≤2 cm) and large (>5 cm) tumours. This can be the integrate result of two phenomena: first, the increasing proportion, among surveyed patients, of semiannual surveillance and advancements in diagnostic tools, allowing the detection of tiny lesions[32]; second, the mounting prevalence of patients who are not considered good candidates for a cost-effective surveillance, leading to a decreased application of surveillance itself in patients with a chronic liver damage and, consequently, a late HCC diagnosis.

The distribution of BCLC stages was characterized by a shift from intermediate-advanced-terminal stages towards early stages. Despite this encouraging result, likely promoted by the effect of antiviral therapy on liver function (leading to an increasing percentage of Child-Pugh class A, $P = .008$) and by the mounting use of

semiannual surveillance (expanding the number of paucifocal tumours, $P < .001$), the subtle - but alarming - rise of the percentage of incidental diagnosis casts some doubts on the possibility to further expand the number of early HCCs in a risk population mainly formed by non-viral or viral-cured patients who tend to escape from scheduled surveillance.

Overall, 46% of HCCs were associated with a low (≤10 ng/mL) AFP level, and the proportion of these tumours increased over time, as a possible consequence of the mutating aetiological scenario. In fact, the production of AFP is greater in viral than in metabolic or alcoholic HCCs.[29,33,34] This should have important implications in designing further studies aimed at assessing the performance - and choose a valid threshold value - of AFP as a surveillance marker.

Even in this updated survey, LT represented a 'therapeutic niche', only accounting for about 5% of all treatments in the whole HCC population, with minimal changes over time. In order to shed more light on the causes of this shortage, we assessed the theoretical percentage of patients amenable to LT according to the Milan and the Metroticket 2.0 criteria,[18,19] obtaining two interesting results: first, the Metroticket 2.0 model expanded by 10% the theoretical amenability to LT achieved with Milan criteria; second, the number of potential candidates to LT (based on permissive oncological criteria and an age ≤70 years) was exceedingly higher compared to the number of actually transplanted subjects that accounted for about 11% of them, regardless of the criteria tested (Figure 4). One of the main reasons of this striking discrepancy may rely on the amenability to alternative curative treatments which narrows the LT benefit and contribute to graft sparing. We tested this assumption with a subanalysis that selected patients not eligible to non-transplant curative treatments because of an advanced liver dysfunction (arbitrary defined as Child-Pugh score > B7 and/or presence of ascites). For these subjects, the rate of LT, although higher than that observed in the overall population of theoretically transplantable patients, remained low, being 16%. Therefore, the striking discrepancies we observed between potential and actual use of LT for HCC patients would indicate that other unmeasured factors, such as major comorbidities, graft shortage and under-referral to transplant centres represent the main causes curbing the use of LT in clinical practice. As a matter of fact, these data suggest that, even if we were theoretically capable to diagnose almost all HCCs at a stage fulfilling the LT criteria, many other factors (clinical and organizational) would limit its use.

Resection rate accounted for about 18% of treatments without significant changes over time, while the rate of RFA (overall 27.6%) continuously increased reaching 31.6% in the last period. This trend was explained, at least in part, by the abandonment of the less effective PEI, and was confined to BCLC 0 + A stages, in which RFA represented the most used treatment. It is also conceivable that the progressive ageing of our patients has favoured the choice of this moderately invasive approach.

Overall, TACE prevalence stabilized around 25% and, as expected, showed a maximum utilization in BCLC B stage (44.1% in the last period).

Lastly, sorafenib largely replaced palliation and other treatments after 2008, when it became available in clinical practice, ranking as the leading therapy for BCLC C patients in the last calendar period (30% of cases).

Notably, in both BCLC B and C stages the proportion of curative treatments was similar to that of the therapy recommended for each stage by the BCLC system,[35] demonstrating once more that a rigid stage-dependent strategy is unacceptable and is replaced by a patient-tailored approach aimed at offering the most effective therapy whenever possible.[36-38]

The survival of our HCC patients ameliorated in the last calendar period, with a more evident improvement in the viral group. However, considering cancer stage, only BCLC B patients significantly improved their prognosis likely because of the increased use of RFA (to the detriment of less effective PEI), the therapeutic refinements of TACE, the use of radioembolization in suboptimal candidates to TACE[39] and the possibility to treat with sorafenib patients not amenable to locoregional treatments or those in whom locoregional therapies had failed. Conversely and unexpectedly, in the advanced stage survival significantly decreased in the last period (when 30% of cases received sorafenib) with respect to the first one (when this evidence-based therapy was not available). This prompted us to investigate the causes of such a finding with a sensitive analysis which showed, as possible explanation, that BCLC C patients presented in the last calendar period a worst Child-Pugh class distribution, a decreased prevalence of single tumours, an increase in large (>5 cm) lesions, and a rise of cases with caval vein invasion and extrahepatic spread (Table S3).

Our study has several limitations linked to its retrospective nature. Firstly, the presence of missing data is an unavoidable pitfall of multicenter database grounded on clinical practice. Data imputation was not performed, because the statistical assumptions concerning the random missingness of data did not hold. However, more than 78% provided complete data allowing meaningful comparisons among the three time periods based on the available data.

Another limitation may derive from the selection bias, because this is not a population-based study but a clinical study enrolling patients referring to both tertiary and primary centres.

Lastly, some differences between time periods, although statistically significant, may be considered not clinically meaningful, particularly when they are transient, like the increased prevalence of BCLC C stage in G2. However, for most variables the observed trend, although modest, was unidirectional and continued over the entire period of observation, reaching the statistical significance between G1 and G3. In our opinion, these evolutionary changes can indicate what we should expect in the forthcoming scenario of HCC.

In conclusion, our study, once more, indicates that HCC scenario is continuously and rapidly evolving in terms of aetiology, clinical presentation, management and treatment outcome. Therefore, we think that this scenario needs to be continuously monitored in order to know where we are and where changes will bring the clinical history of this cancer.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Trevisani F, Garuti F, Neri A, Avanzato F and Rampoldi D participated in the conception and design of the article and drafted it. All the authors revised it critically and approved the final version to be submitted.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX

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