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The evolutionary scenario of hepatocellular carcinoma in Italy: an update

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Abstract

Background & Aims: Epidemiology of hepatocellular carcinoma is changing worldwide. This study aimed at evaluating the changing scenario of aetiology, presentation, management and prognosis of hepatocellular carcinoma in Italy during the last 15 years.

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‡See Appendix for the Italian Liver Cancer (ITA.LI.CA) group.

Methods: Retrospective analysis of the ITA.LI.CA (Italian Liver Cancer) database including 5192 hepatocellular carcinoma patients managed in 24 centres from 2000 to 2014. Patients were divided into three groups according to the date of cancer diagnosis (2000–2004, 2005–2009 and 2010–2014).

Results: The main results were as follows: (i) progressive patient aging; (ii) progressive expansion of non-viral cases and, namely, of "metabolic" hepatocellular carcinomas; (iii) increasing proportion of hepatocellular carcinoma diagnosed during a correct (semi-annual) surveillance programme; (iv) favourable cancer stage migration; (v) increased use of radiofrequency ablation to the detriment of percutaneous ethanol injection; (vi) improved outcomes of ablative and transarterial treatments; (vii) improved overall survival (adjusted for the lead time in surveyed patients), particularly after 2009, of both viral and non-viral patients presenting with an early- or intermediate-stage hepatocellular carcinoma.

Conclusions: During the last 15 years several aetiological and clinical features of hepatocellular carcinoma patients have changed, as their management. The observed improvement of overall survival was owing both to the wider use of semi-annual surveillance, expanding the proportion of tumours that qualified for curative treatments, and to the improved outcome of loco-regional treatments.

KEYWORDS

epidemiology, hepatocellular carcinoma, survival, treatment

The incidence of hepatocellular carcinoma (HCC) is growing in most countries[1] and this tumour is the current leading cause of mortality of patients with cirrhosis.[2] B- and/or C-related chronic hepatitis and chronic alcoholic liver disease represent the main risk factors for the development of HCC. HCC is less frequent in settings such as non-alcoholic fatty liver disease (NAFLD), cholestatic diseases or inherited disorders.[3] In high-income countries, however, this scenario is changing. Indeed, vaccination and therapy for hepatitis B virus (HBV) infection,[4] prevention campaigns for sexual and iatrogenic transmission of HBV and hepatitis C virus (HCV), and the availability of potent antiviral agents for HCV[5] are reducing the burden of chronic viral liver disease.[6,7] Conversely, as a result of the rising prevalence of metabolic disorders in the general population, both NAFLD-associated cirrhosis and HCC are escalating too.[8–10]

Primary liver cancers, most (>80%) of which are represented by HCC, are highly lethal: the 5-year age-standardized survival rate reported by nine population-based Italian registries is <20%.[11] However, curative treatments can greatly improve the prognosis, provided that HCC is detected at an early stage with surveillance programmes.[12] Continuous refinements of treatments for underlying viral infections, complications of cirrhosis and the tumour itself, including the advent of Sorafenib after 2008, have also contributed to improve HCC prognosis.[13,14]

This study was aimed at updating the scenario of HCC in Italy described in a previous study,[6] comparing the epidemiological and clinical features collected over the last three *quinquiennia* by a large number of centres with different levels of expertise in the field of liver disease.

Key points

- Increased number of HCCs ensuing in non-viral patients;
- Continuous increment of semi-annual surveillance implementation;
- Changing of therapeutic options and improvement of loco-regional treatments outcomes;
- Continuous improvement of survival.

1 | PATIENTS AND METHODS

1.1 | Patients

We analysed the data of the Italian Liver Cancer database, currently including 6477 HCC patients consecutively evaluated from January 1987 to December 2014 at 24 medical institutions. Data were collected prospectively and updated every 2 years.

For the purposes of this study, we included 5,192 patients diagnosed with HCC from January 1st 2000 to December 31st 2014. Patients were allocated into three groups according to the year of diagnosis: G1=2000–2004 (1147 [22.1%] patients); G2=2005–2009 (1,624 [31.3%]) and G3=2010–2014 (2421 [46.6%]). The number of patients recruited in each centre ranged from 37 to 642. The 7 primary referral centres recruited 1580 (30.4%) patients, and the 17 tertiary referral centres enrolled 3612 (69.6%) patients. However, it is worth

noting that all the tertiary referral centres also function as primary (local) hospital.

Analysed variables were as follows: age, gender, aetiology of the underlying liver disease, presence of cirrhosis, Child–Pugh [C–P] class, modality of HCC diagnosis, surveillance interval, serum alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC) tumour stage,[15] modality of treatment and patient survival. All these variables were available in >80% of cases, with the exception of AFP (quoted in 76.3% of patients).

1.2 | Liver disease aetiology and diagnosis

The liver disease aetiology was classified as:

- HBV, if patients were HBV surface antigen (HBsAg) carriers (±hepatitis delta virus [HDV])
- HCV, if patients were positive for serum anti-HCV antibody
- multiviral, if patients were 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 cause of liver injury
- NAFLD/non-alcoholic steatohepatitis (NASH), according to the American Association for the study of the liver (AASLD) practice guidelines[16]
- cryptogenic, if the patients did not show positivity of HBV surface antigen (HBsAg) or anti-HCV antibody, alcohol abuse, autoimmune or genetic liver diseases
- multi-aetiology, if there was a combination of: (i) alcohol abuse or non-alcoholic NAFLD + viral infection(s) (multi-aetiological–viral subgroup); (ii) alcohol abuse+other non-viral disease (multi-aetiologic–non-viral subgroup)
- other aetiology, which included haemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, primary biliary cholangitis and sclerosing cholangitis.

Patients were also classified as "viral" or "non-viral", according to HBsAg and anti-HCV antibody status.

The NAFLD/NASH diagnosis was established by ultrasound features (bright liver) in 120 (66.3%), by histology in 19 (10.5%), by laparoscopy in 8 (4.4%), whereas in 34 (18.8%) patients the information was not reported.

The presence of cirrhosis was confirmed by histology in 585 (12.6%) patients and by laparotomy/laparoscopy in 47 (1%); in the remaining cases, this diagnosis was made unequivocally by clinical, laboratory, endoscopic and imaging technique findings (presence of oesophageal varices at endoscopy, and/or dilated portal trunk, collateral porto-systemic vessels, nodular margins of the liver at ultrasound and typical laboratory results).

1.3 | Modality of hepatocellular carcinoma diagnosis

Hepatocellular carcinoma diagnosis was classified as:

- under surveillance, if HCC was detected during an ultrasound (US)-based surveillance programme (±AFP determination) started at least 1 year prior to HCC diagnosis. Patients were subgrouped according to the interval of surveillance (≤7, 12±1 months). To minimize the effect of *length bias*, patients under surveillance were maintained in their original group even if the scheduled US was anticipated by the occurrence of symptoms.
- incidental, when diagnosis was performed during investigations for other diseases or for a general check-up outside regular surveillance;
- symptomatic, if HCC diagnosis followed the appearance of cancer-related symptoms or was performed in patients outside regular surveillance.

1.4 | Diagnosis and staging of hepatocellular carcinoma

Diagnosis of HCC was based on typical features in one or more imaging techniques (dynamic computed tomography [CT], magnetic resonance imaging [MRI], contrast enhanced ultrasound [CEUS]) and/or histological findings, according to the European and American guidelines available at the time of patient recruitment. Before 2001, we utilized the non-invasive diagnostic criteria proposed by the Italian Association of the Study of the Liver.[17]

Cancer burden was assessed by liver CT and/or MRI, whereas further investigations aimed at detecting extra-hepatic involvement were performed routinely in patients with advanced HCC or in candidates for liver transplantation (LT). In the other cases, these imaging techniques were performed when clinically indicated. HCC was staged according to Barcelona Clinic Liver Cancer (BCLC) criteria as: very early, early, intermediate, advanced and end stage.[15]

1.5 | Treatment

If patients were submitted to multiple treatments, they were classified according to the most effective one, following this hierarchic order: LT, hepatic resection, radiofrequency ablation (RF), percutaneous ethanol injection ablation (PEI), transarterial chemoembolization [(TACE), selective or superselective], Sorafenib or other systemic therapy and palliation. Patients treated with transarterial embolization were included in the TACE group.

1.6 | Lead-time estimation

For each period, patients diagnosed with HCC during a surveillance programme or incidentally were challenged against those with a symptomatic diagnosis for lead-time estimation [18] (see Data S1: Supplementary methods). The mean±standard deviation (SD) of lead time for patients under surveillance and diagnosed incidentally was, respectively, 8.1±1.5 months and 3.4±0.5 months in G1; 8.3±2 months and 3.5±0.8 in G2 and 7.6±2.8 months and 3.3±0.8 in G3.

1.7 | Statistical analysis

Continuous data are expressed as mean value±SD and discrete variables as absolute and relative frequencies. Comparisons of continuous variables among the three periods were made using ANOVA or the Kruskal–Wallis tests, as appropriate. Comparison between two periods was made with the *t*-test or the Mann–Whitney *U*-test. Discrete variables were compared with the X^2 test or Fisher's exact test, as appropriate. The lead-time-adjusted actuarial survivals were calculated according to the Kaplan–Meier method and compared by the log-rank test. The survival rates at 1, 3 and 5 years were also reported. A two-tailed *P* value <.05 was considered statistically significant. All statistical analyses were performed with SPSS v23.0 (Apache Software Foundation, Chicago, Illinois, USA).

1.8 | Ethics

The ITA.LI.CA database management conforms to the current Italian legislation on privacy, and this study conforms to the ethics guidelines of the Declaration of Helsinki. All patients provided informed consent to having their data recorded in an anonymous way in the ITA.LI.CA database. This study was approved by the ethics committee/institutional board of the participating centres. See Data S1: Supplementary Material.

2 | RESULTS

2.1 | Demographic factors, aetiology and extra-tumoral liver disease (Table 1)

Age at diagnosis increased over time so that the tumour incidence peak shifted from the 65–69 age group in the first period (Group 1: G1) to the 70–74 age group in the last two periods (G2, G3) (Fig. 1). Such an increment involved both viral patients (from 67.3 in G1 to 68.1 years in G3; *P*=.003) and non-viral patients (from 65.3 in G1 to 67.9 in G3; *P*<.001). The great predominance of male gender (around 74%) did not change over time.

A progressive and significant decrease occurred in the number of viral cases (about 4% *per quinquennium*), and this was compensated by a reciprocal increase in the number of non-viral cases. HCV infection remained the main risk factor in all periods, but its prevalence significantly decreased during the two-first periods, remaining stable thereafter. However, to minimize the impact of geographical factors, a subanalysis was performed after the exclusion of 494 patients (9.5% of the total sample size) included in the database by five Centers located in Southern Italy (where the prevalence of HCV infection is exceedingly high), which joined the ITA.LI.CA network in the last period (Figure S1). This subanalysis confirmed that the 4% drop/*quinquennium* of HCV-positive cases also involved the last period (from 48.0% to 42.6%, *P*=.001). The prevalence of HBV infection and viral–multi-aetiology also decreased in the last 5 years.

Among non-viral patients, "pure" alcoholic and "other causes" cases significantly decreased in the last period, whereas NAFLD/cryptogenic (from 1.1% to 12.6%) and non-viral–multi-aetiological tumours (from 0.02% to 4.9%) strikingly increased over time.

In our series, HCC was usually associated with established cirrhosis (92.6%), even though this association was less frequent in non-viral than in viral patients (81.1% vs 93.9%, *P*<.001). Figure 2A reports the percentage of cirrhotic patients according to aetiology. Therefore, the increasing prevalence of non-viral cases in the last period led to a significant rise of tumours that developed in livers without cirrhosis (Table 1 and Fig. 2B).

Diabetes and excess weight/obesity were remarkably more prevalent among non-viral than viral patients (Figure S2).

The C–P class B distribution significantly increased in the last period to the detriment of C–P class A (Table 1). A subanalysis excluding patients coming from Southern Italy (who joined the ITA.LI.CA network in the last period) confirmed this trend.

2.2 | Modality of hepatocellular carcinoma diagnosis, stage and treatment (Table 1)

Hepatocellular carcinoma was diagnosed under surveillance in more than half of the cases, and this proportion steadily and significantly increased over the three periods from 55.0% to 61.6%, at the expense of incidental detection (from 32.8% to 25.5%) (Fig. 3A). The most commonly employed surveillance was semi-annual, and this modality progressively increased over time from 79.8% to 87.7% (*P*<.001) (Fig. 3B). A rise in the frequency of HCCs detected during surveillance occurred in both viral and non-viral patients, but only reached statistical significance in the former group (from 62.0% to 64.7% to 67.1% [*P*<.001] in viral patients; from 33.2% to 40.4% to 42.8 [*P*=.070] in non-viral patients).

Overall, 59.4% of patients had elevated AFP levels (>10 ng/mL). The prevalence of AFP-producing tumours declined progressively during the observation periods, and this was mainly owing to cases with a moderate AFP elevation (11–200 ng/mL). Non-viral HCCs were far more often associated with normal AFP than viral cases, especially in patients with very early or Milan-in[19] tumours, in whom the prevalence of AFP-secreting HCCs was halved (Fig. 4).

Very early (BCLC 0) HCCs significantly increased over time. This was mainly evident in the last period, when a drop in intermediate- (BCLC B) and end-stage (BCLC D) tumours also occurred. Early (BCLC A) HCCs decreased during the first two periods, remaining stable thereafter. Advanced (BCLC-C) HCCs showed a specular trend.

Significant changes also occurred in cancer size at diagnosis: small tumours (≤2 cm) increased in the first two periods, intermediate-size tumours (2.1–5 cm) progressively decreased, whereas large cancers (>5 cm) increased.

In all periods, a small percentage of patients with HCC underwent LT, falling to 2.9% in the last period, and surgical resections slightly increased only in the first two periods. The percentage of patients undergoing LT was two-fold as higher as in tertiary referral centres than in primary centres (4.4% vs 2.3%) (*P*<.001). Moreover, this percentage ranged from 0% to 15.7% among the 24 centres. Instead, the use of RF steadily increased at the expense of PEI. TACE-treated patients remained stable around 30%. Lastly, the number of patients managed with non-evidence-based ("other") treatments declined after 2009, likely because of a shift of these cases towards Sorafenib (Table 2).

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

	Available cases n (%)	G1: 2000–2004 n (%) 1147 (22.1)	G2: 2005–2009 n (%) 1624 (31.3)	G3: 2010–2014 n (%) 2421 (46.6)	*P*
Age (mean±SD), years	5192 (100)	66.8±9.5	67.4±10.2	68.3±10.6	<.001 G1 vs G2=.047 G1 vs G3<.001 G2 vs G3=.002
Gender (M/F)	5192 (100)	864/283 (75.3/24.7)	1213/411 (74.7/25.3)	1212/609 (74.8/25.2)	.927
Aetiology	5135 (98.9)	1141	1606	2388	<.001
Viral aetiology	3658 (72.2)	884 (77.5)	1160 (72.2)	1614 (67.6)	<.001 G1 vs G2=.002 G1 vs G3<.001 G2 vs G3=.002
HBV (±HDV)	497 (9.7)	113 (9.9)	186 (11.6)	198 (8.3)	G1 vs G2=.164 G1 vs G3=.114 G2 vs G3<.001
HCV	2525 (49.2)	624 (54.5)	771 (48.0)	1130 (47.3)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3=.670
Multiviral	104 (2.0)	33 (2.9)	36 (2.2)	35 (1.5)	G1 vs G2=.283 G1 vs G3=.004 G2 vs G3=.069
Multi-aetiology	532 (10.4)	114 (10.0)	167 (10.4)	251 (10.5)	G1 vs G2=.728 G1 vs G3=.635 G2 vs G3=.909
Non-viral aetiology	1477 (27.3)	257 (22.5)	446 (27.8)	774 (32.4)	<.001 G1 vs G2=.002 G1 vs G3<.001 G2 vs G3=.002
Alcohol	805 (15.6)	190 (16.7)	290 (18.1)	325 (13.6)	G1 vs G2=.339 G1 vs G3=.014 G2 vs G3<.001
NAFLD/NASH	181 (3.5)	4 (0.3)	43 (2.7)	134 (5.6)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3<.001
Cryptogenic	227 (4.4)	9 (0.8)	54 (3.4)	164 (6.9)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3<.001
Multi-aetiology	133 (2.6)	2 (0.02)	14 (0.9)	117 (4.9)	G1 vs G2=.018 G1 vs G3<.001 G2 vs G3<.001
Other	131 (2.5)	52 (4.5)	45 (2.8)	34 (1.4)	G1 vs G2=.011 G1 vs G3<.001 G2 vs G3=.002
Cirrhosis	5038 (97.0)				<.001
Yes	4665 (92.6)	1042 (94.3)	1483 (94.6)	2140 (90.4)	G1 vs G2=.704 G1 vs G3<.001 G2 vs G3<.001
Child–Pugh Class	3948 (84.6)				<.001
Class A	2489 (63.0)	547 (62.6)	844 (67.3)	1098 (60.4)	G1 vs G2 =.026 G1 vs G3=.268 G2 vs G3<.001
Class B	1221 (30.9)	270 (30.9)	321 (25.6)	630 (34.6)	G1 vs G2 =.007 G1 vs G3=.054 G2 vs G3<.001
Class C	238 (6.0)	57 (6.5)	90 (7.2)	91 (5.0)	G1 vs G2=.561 G1 vs G3=.105 G2 vs G3=.012

Data are presented as mean±standard deviation (SD) and as number and percentage (%). HBV, hepatitis B virus; HDV hepatitis D virus; HCV, hepatitis C virus; NAFLD/NASH, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

Treatment distribution over the three periods was also evaluated in each BCLC tumour stage (Figure S3). RF was the prevalent treatment for BCLC 0+A, and its use increased over time up to 37.7% of cases to the detriment of PEI. TACE prevailed in BCLC B, with an increased use in the last period (up to 51.7% of cases) to the detriment of PEI, palliation and other treatment options. Moreover, about 20% of patients underwent resection and, in the last period, about 10% were treated with Sorafenib. In BCLC-C, about 25% of patients underwent TACE without significant changes over time. Instead, "other" treatments progressively decreased from the leading position to an uncommon option, whereas Sorafenib increased after 2009, almost matching TACE prevalence.

2.3 | Survival

The median lead-time-adjusted overall survival (OS) progressively increased across the three periods assessed in this study; such an improvement became statistically significant in the last 5 years (from 30.7 months [95% CI 27.7–33.7] to 32.2 months [28.9–35.6] to 40.4 months [34.3–46.5] [P<.001]). The corresponding 1, 3 and 5-year survival rates were as follows: 72.3%, 73.2%, 73.6%, and 44.2%, 47.0%, 51.2% and 27.7%, 33.0%, 39.2% respectively. The improvement in survival occurred in both viral and non-viral patients (Fig. 5).

A subanalysis of OS of patients stratified by BCLC tumour stage revealed that prognosis significantly improved in very early/early and intermediate HCCs, but not in advanced stages (Fig. 5). Nevertheless, it should be noticed that prognosis significantly improved in the subgroup of BCLC-C patients belonging to Child–Pugh class A (lead-time-adjusted OS: 18.3 months [14.6–21.9] in the first period, 21.3 months [17.1–25.6] in the second and 27.4 months [20.8–33.9] in the last one; P=.016).

A subanalysis of survival with patients stratified by treatments showed that the prognosis of patients undergoing percutaneous ablation and TACE significantly improved over the three periods (P=.001 and P=.002, respectively) (Fig. 6).

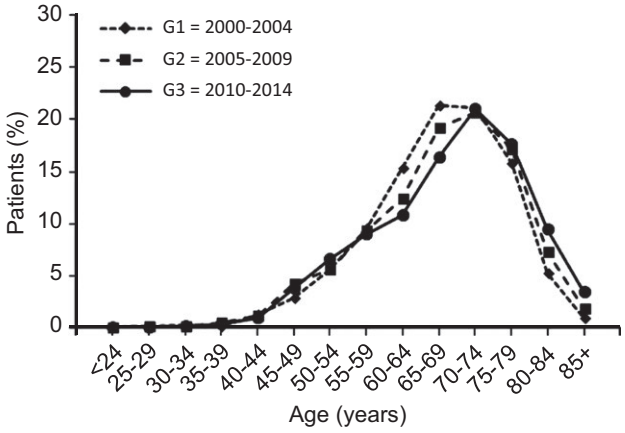

FIGURE 1 Temporal trend of age distribution of patients with hepatocellular carcinoma. In the two last periods the age tumour incidence peak at shifted from 65–69 to 70–74 years

2.4 | Centre-related effect on clinical features

Considering the difference in referral level of the 24 ITA.LI.CA centres we analysed the prevalence of patients diagnosed with HCC during surveillance, the distribution of BCLC cancer stage and the survival according to referral level of centres (primary vs tertiary). The results are reported in Data S1: Supplementary material.

3 | DISCUSSION

3.1 | Hepatocellular carcinoma patients are older and metabolic disorders are a growing cause of hepatocellular carcinoma

This study shows that the already reported[6,7] ageing of HCC patients in Western countries has continued in the last 5 years. Such a

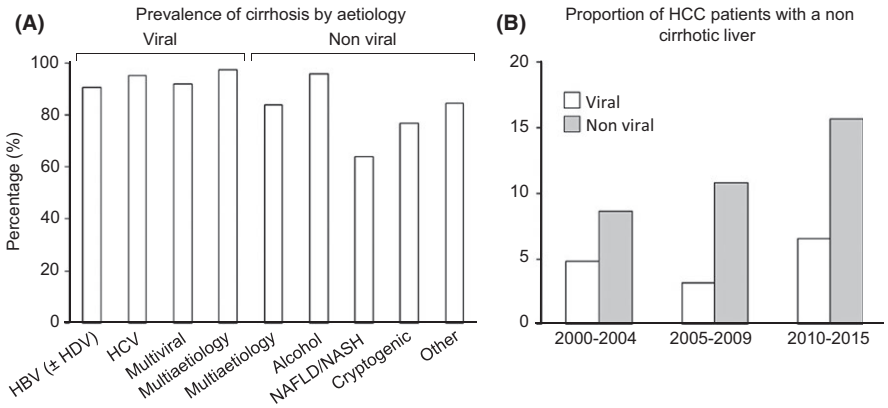

FIGURE 2 Prevalence of cirrhosis in patients recruited during the entire period (2000–2014) according to the aetiology of hepatocellular carcinoma (HCC). Viral cases (in whom aetiology was exclusively viral or included at least one viral infection) showed a significantly higher prevalence (93.9%) of cirrhosis than non-viral ones (81.1%) (P<0.001). Notably, among viral cases all etiological subgroup showed a prevalence of cirrhosis >90%, while, among non-viral cases, only alcoholic patients had almost invariably an underlying cirrhosis (A). Proportion of HCC patients with a non-cirrhotic liver. HCC development in a non-cirrhotic liver is increasing over time, particularly among patients with a non-viral aetiology (from 8.6% in G1 to 15.6% in G3, P=0.004) (B)

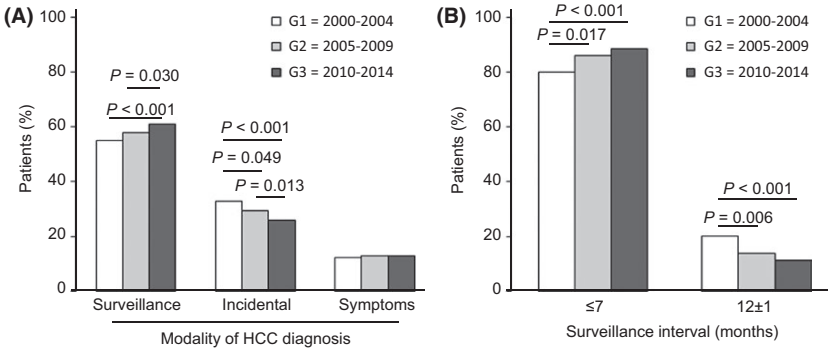

FIGURE 3 Modality of HCC diagnosis (A) and surveillance interval (B) of patients with HCC across the periods: 2000–2004, 2005–2009 and 2010–2014

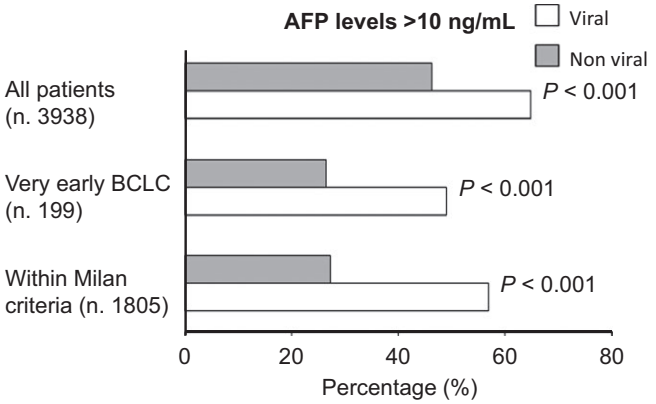

FIGURE 4 Prevalence of patients with alpha-fetoprotein levels >10 ng/mL according to viral and non-viral aetiology in the whole population, in very early BCLC stage and according to Milan criteria

phenomenon cannot be simply attributed to the ageing of the general population but also to the vanishing "cohort effect" of HCV. In fact, HCV infection in Italy reached its maximal diffusion in the 6th and 7th decade of the last century, and started to be efficiently controlled in the '90s, when routine screening testing identified HCV carriers.[20] The efficient control of viral replication by nucleot(s)ide analogues in almost all HBV patients and the achievement of sustained viral response in some HCV carriers contributed to the ageing of our HCC cohort, as these effects of antiviral treatments slow down, rather than prevent, hepatic carcinogenesis.[21]

Another consequence of the vanishing cohort effect in HCV-positive patients, as already shown by the 2012 ITA.LI.CA report,[6] is the declining relative importance of HCV infection as a risk factor for HCC. The apparent arrest of this decline in the last period does not conflict with our interpretation, as it is likely attributable to the contribution of five Centers located in Southern Italy—where HCV infection is highly prevalent (Figure S1)—which joined the ITA.LI.CA network after 2009. In fact, excluding the cases from these centres, the relative prevalence of HCV-related HCCs decreased over the entire study period.

Not surprisingly, HCCs developing in the setting of NAFLD and cryptogenic liver disease are breaking out even in Italy, where about 13% of HCCs currently have these backgrounds. This indirectly confirms the growing role of metabolic disorders, such as obesity and diabetes, as promoters of hepatic carcinogenesis in high-income countries.[7–10] Noticeably, our data show a decrease in the prevalence of "pure" alcoholic HCCs in the last 5 years. This is likely owing not only to a reduction in alcohol consumption[22] but also to the shift of a proportion of alcoholic patients towards the non-viral–multi-aetiological group including those with a combined aetiology (alcohol plus metabolic disorders). This evolutionary scenario foresees that the number of non-viral tumours will match or even overcome that of HCV-related tumours in the next future. Therefore, an efficient primary prevention in high-income countries should rely on both the prevention/cure of infectious hepatitis and the implementation of nationwide educational campaigns aimed at fighting the risky use of alcohol and food, and at promoting physical activity.

3.2 | At-risk patients are more surveyed resulting in a favourable cancer stage migration

Hepatocellular carcinomas detected during regular surveillance are increasing, and this trend was associated with a growing use of 3–6 monthly programmes (Fig. 3). This suggests that healthcare providers are becoming progressively more aware of the usefulness of surveillance in reducing HCC-related mortality.[12,23–25] Nevertheless, although the percentage of HCCs detected during surveillance in our series (around two-thirds) is much higher than in the USA,[26] it remains lower than in Japan, where this practice is managed through a national health programme.[27]

Interestingly, in all periods, viral patients were surveyed more frequently than non-viral cases (approximately 65% vs 38.5%), indicating that the aetiology influences the decision of implementing regular surveillance.[28] Indeed, although the *efficacy* of surveillance has been proven to be similar in viral and non-viral patients,[29] its *effectiveness* is lower in the latter group, as the condition of these patients is more influenced by "external" factors, such as: (i) a lower probability of being identified as carriers of liver disease; (ii) a lower probability of being under the care of gastroenterologists/hepatologists; (iii) a lower perception by care providers of HCC risk; (iv) a limited willingness and adherence to regular surveillance by alcoholic patients and (v) more frequent competing clinical concerns.

The brisk increase in "metabolic" HCCs and their propensity to develop before the establishment of cirrhosis is responsible for the

TABLE 2 Features of hepatocellular carcinoma

	Available n (%)	G1: 2000–2004 n (%) 1147 (22.1)	G2: 2005–2009 n (%) 1624 (31.3)	G3: 2010–2014 n (%) 2421 (46.6)	*P*
AFP	3956 (76.3)				.019
≤10 ng/mL	1605 (40.6)	362 (37.0)	518 (40.9)	725 (42.3)	G1 vs G2=.058 G1 vs G3=.010 G2 vs G3=.536
11–200 ng/mL	1554 (39.3)	422 (43.1)	502 (39.7)	630 (36.8)	G1 vs G2=.098 G1 vs G3=.001 G2 vs G3=.106
>200 ng/mL	797 (20.1)	194 (19.8)	245 (19.4)	358 (20.9)	G1 vs G2=.781 G1 vs G3=.511 G2 vs G3=.304
BCLC	4238 (81.6)				<.001
0	245 (5.8)	17 (1.8)	72 (5.4)	156 (7.9)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3=.005
A	1649 (38.9)	394 (42.6)	499 (37.2)	756 (38.3)	G1 vs G2=.010 G1 vs G3=.029 G2 vs G3=.512
B	714 (16.8)	211 (22.8)	209 (15.6)	294 (14.9)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3=.594
C	1235 (29.1)	221 (23.9)	413 (30.8)	601 (30.5)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3=.844
D	395 (9.3)	82 (8.9)	148 (11.0)	165 (8.4)	G1 vs G2=.092 G1 vs G3=.655 G2 vs G3=.010
Cancer size	4562 (87.9)				<.001
≤2 cm	1300 (28.5)	259 (25.0)	421 (30.1)	620 (29.1)	G1 vs G2=.005 G1 vs G3=.015 G2 vs G3=.518
from 2.1 to 5 cm	2336 (51.2)	595 (57.4)	718 (51.4)	1023 (48.1)	G1 vs G2=.003 G1 vs G3<.001 G2 vs G3=.052
>5.0 cm	926 (20.3)	182 (17.6)	258 (18.5)	486 (22.8)	G1 vs G2=.568 G1 vs G3<.001 G2 vs G3=.002
Treatment	4608 (88.8)				<.001
LT	172 (3.7)	40 (3.7)	72 (4.8)	60 (2.9)	G1 vs G2=.178 G1 vs G3=.233 G2 vs G3=.003
Resection	710 (15.4)	144 (13.4)	237 (15.9)	329 (16.1)	G1 vs G2=.082 G1 vs G3=.048 G2 vs G3=.874
Radiofrequency ablation	959 (20.8)	174 (16.2)	304 (20.4)	481(23.5)	G1 vs G2=.007 G1 vs G3<.001 G2 vs G3=.026
PEI	395 (8.6)	170 (15.8)	117 (7.8)	108 (5.3)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3=.002
TACE	1408 (30.6)	316 (29.5)	441 (29.6)	651 (31.8)	G1 vs G2=.944 G1 vs G3=.169 G2 vs G3=.149
Sorafenib	226 (4.9)	1 (0.1)	35 (2.3)	190 (9.3)	G1 vs G2<.001 G1 vs G3<.001 G2 vs G3<.001
Palliation	442 (9.6)	97 (9.0)	163 (10.9)	182 (8.9)	G1 vs G2=.117 G1 vs G3=.899 G2 vs G3=.045

(*continues*)

TABLE 2 (continued)

	Available n (%)	G1: 2000–2004 n (%) 1147 (22.1)	G2: 2005–2009 n (%) 1624 (31.3)	G3: 2010–2014 n (%) 2421 (46.6)	*P*
Others	296 (6.4)	131 (12.2)	122 (8.2)	43 (2.1)	G1 vs G2=.001 G1 vs G3<.001 G2 vs G3<.001

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

rising number of non-cirrhotic HCCs (Fig. 2). This finding highlights a very topical problem, i.e. the urgent need to identify, among NAFLD patients without cirrhosis, appropriate candidates for a *cost-effective* surveillance. Indeed, it would be unrealistic—and incorrect—to implement surveillance for all NAFLD patients, who represent about 30% of Italian population.

Regarding HCC burden, we observed a quite peculiar finding, i.e. the significant increase in both tiny (≤2 cm) and large (<5 cm) tumours. The first finding, likely owing to the use of semi-annual surveillance in viral cases, explains the increased prevalence of BCLC 0 stage at diagnosis. Instead, the increment of large HCCs may be as a result of two causes: (i) the rising proportion of NAFLD/NASH and cryptogenic cases, which are surveyed more rarely; (ii) the increased prevalence of Child–Pugh B patients, as the liver echo pattern becomes progressively coarser with the advancement of cirrhosis, making it more difficult to recognize small HCCs.[30]

Changes in both aetiology and diagnosis of HCC likely affected AFP levels at diagnosis. Namely, patients with a normal AFP value increased over time, a finding attributable to the growing number of both early stage and non-viral HCCs, which frequently do not produce AFP (Fig. 4).

3.3 | Patients with hepatocellular carcinoma show an evolving therapeutic scenario

Liver transplantation represents a "niche", accounting for less than 5% of cases in all three periods, and its prevalence even declined in the last one, probably owing to: (i) the progressive patient ageing; (ii) the growing number of non-cirrhotic cases, manageable with resection in most cases; (iii) the increase in both tiny tumours—not representing an indication for LT [31]—and advanced cancers to the detriment of the optimal candidates (BCLC A stage). The limited use of LT in unselected

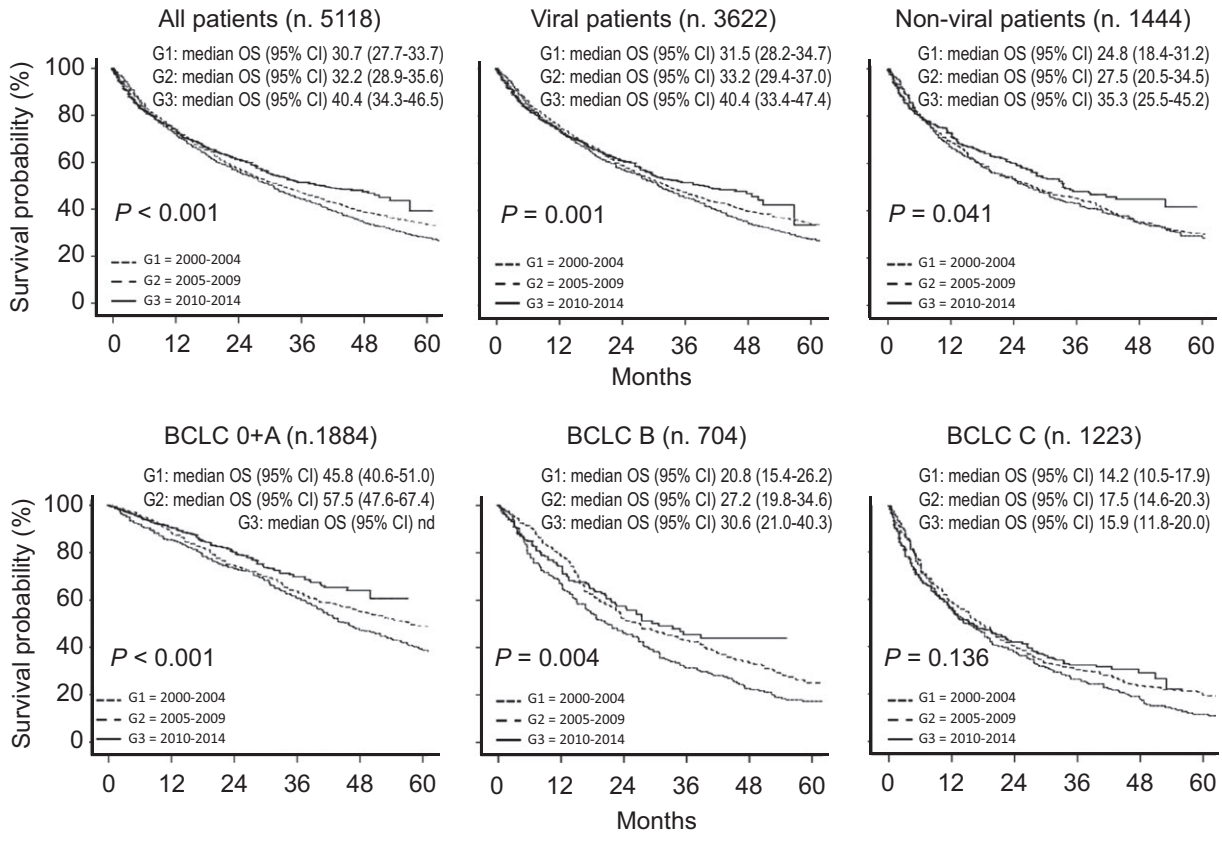

FIGURE 5 Temporal trend of the lead-time adjusted overall survival of all, viral and non-viral patients, and by Barcelona Clinic Liver Cancer (BCLC) stage

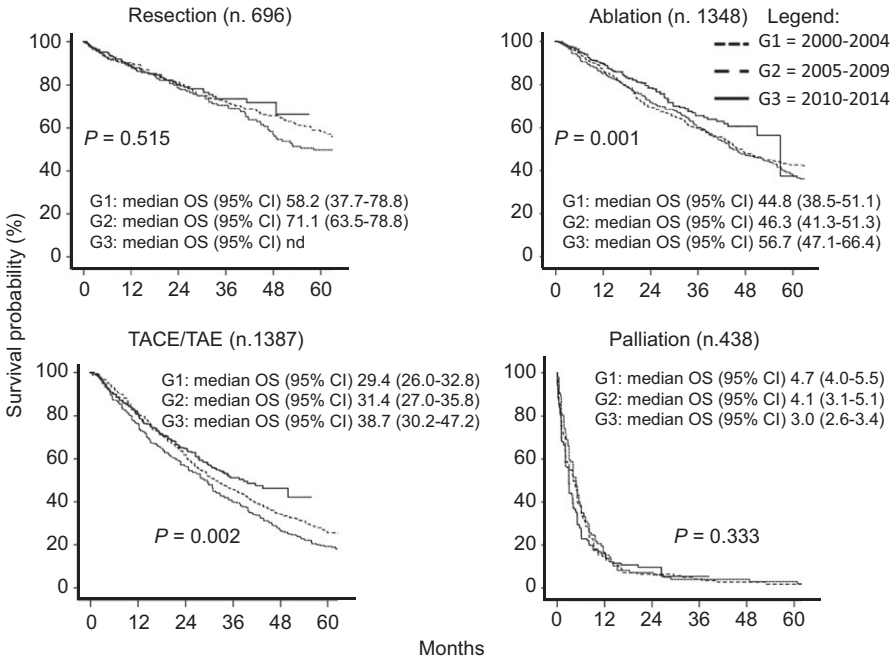

FIGURE 6 Temporal trend of lead-time adjusted overall survival of patients treated with resection, percutaneous ablation, transarterial chemoembilization/embolization (TACE/TAE) and palliation

HCC patients has been recently confirmed by an international study enrolling more than 18,000 patients across different regions of the world.[32]

Resection and, far more substantially, RF increased over the three periods to the detriment of PEI, as RF has been proved to be superior.[33,34]

As a whole, TACE prevalence did not significantly change over time. However, its use for optimal candidates, i.e. BCLC B patients, increased, suggesting that patient selection has become more adherent to the recommendations.[23]

Lastly, the final period was characterized by an impressive increment of the use of Sorafenib, which became available at the end of 2008. Our data indicate that this drug has replaced non-evidence-based therapies but, even in the Sorafenib era, about 10% of HCC patients remain not amenable to any active oncologic treatment.

3.4 | Patients with hepatocellular carcinoma survive longer

Patient survival significantly increased after 2009 (Fig. 5). This improvement was likely caused by the combination of three events: (i) the increased prevalence of very early HCCs; (ii) the replacement of PEI by the more effective RF[33,34] and (iii) the refinement of patient selection for each treatment, ensuring better outcomes [35] (Fig. 6). Moreover, survival improved in all treatable BCLC stages except the advanced stage, where this trend did not reach statistical significance despite the advent of Sorafenib. The apparent "shortcoming" of this standard-of-care therapy may be explained considering the effect of a "dilutional" bias. Indeed, 42.0% of our BCLC-C patients belonged to Child–Pugh class B, a condition preventing the National Health System repaid Sorafenib prescription and, de facto, its use in clinical practice. Moreover, some Child–Pugh A patients may be not qualified for sorafenib owing to comorbidities. As a matter of fact, Child–Pugh A patients showed a better OS after the advent of sorafenib.

In conclusion, the updated revision of the ITA.LI.CA database indicates that several changes have occurred in HCC features and management. The most striking ones are as follows: (i) the fast-growing prevalence of tumours related to metabolic disorders and cryptogenic liver disease, highlighting the need of specific programmes of primary prevention; (ii) the favourable stage migration as a result of the wider and more appropriate surveillance of patients at risk; (iii) the changes in treatment options, with a modest increase in resections, and the preferential use of RF to the detriment of PEI; (iv) the refinement of all therapeutic approaches, likely accounting for the improved survival observed in the last *quinquennium*.

3.5 | Limitation

The first limitation of this study relies on its retrospective nature that makes some results incomplete, such as BMI, prevalence of obesity and diabetes, and may suffer from unintended biases.

A selection bias may derive by the fact that it was not a population-based investigation but a clinical study, making it possible that in tertiary referral centres (e.g. university hospitals) the viral aetiology was overrepresented as compared with NAFLD/alcoholic aetiologies, and a correct surveillance was more frequently applied. However, this bias was limited by the fact that ITA.LI.CA centres include seven first-level hospitals, and the tertiary centres also act as local hospitals.

Lastly, it should be pointed out that 1779 patients (34% of the entire population) had been already included in our previous study.[6] Therefore, the current update includes 3413 newly diagnosed HCCs and, in our

view, the partial patient overlap represents, rather than a limitation, a benchmark to which challenge the evolutionary scenario of this cancer.

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All the authors revised it critically and approved the final version to be submitted.

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ABBREVIATIONS

AASLD, American Association for the study of the liver; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CEUS, contrast enhanced ultrasound; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; ITA.LI.CA, Italian Liver Cancer; LT, liver transplantation; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OS, overall survival; PEI, percutaneous ethanol injection ablation; RF, radiofrequency ablation; SD, standard deviation; TACE, transarterial chemoembolization.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

APPENDIX

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