AP&T Alimentary Pharmacology and Therapeutics

Comparison between alcohol- and hepatitis C virus-related hepatocellular carcinoma: clinical presentation, treatment and outcome

L. Bucci*, F. Garuti*, V. Camelli*, B. Lenzi*, F. Farinati†, E. G. Giannini‡, F. Ciccarese§, F. Piscaglia*, G. L. Rapaccini**, M. Di Marco††, E. Caturelli‡‡, M. Zoli*, F. Borzio¶¶, R. Sacco***, M. Maida†††, M. Felder‡‡‡, F. Morisco§§§, A. Gasbarrini**, S. Gemini****, F. G. Foschi††††, G. Missale‡‡‡‡, A. Masotto§§§§, A. Affronti†††, M. Bernardi*, F. Trevisani* & for the Italian Liver Cancer (ITA.LI.CA) Group[1]

*Bologna, Italy.
†Padova, Italy.
‡Genova, Italy.
§Zingonia, Italy.
**Roma, Italy.
††Seriate, Italy.
‡‡ Viterbo, Italy.
¶¶Milano, Italy.
***Pisa, Italy.
†††Palermo, Italy.
‡‡‡Bolzano, Italy.
§§§Napoli, Italy.
****Ancona, Italy.
††††Faenza, Italy.
‡‡‡‡Parma, Italy.
§§§§ Negrar, Italy.

Correspondence to:
Prof. F. Trevisani, Semeiotica Medica, Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum-University of Bologna, Via Albertoni, 15, 40138 Bologna, Italy.
E-mail: franco.trevisani@unibo.it

[1]See Appendix.

Publication data
Submitted 1 July 2015
First decision 14 August 2015
Resubmitted 15 October 2015
Accepted 4 November 2015
EV Pub Online 14 December 2015

This article was accepted for publication after full peer-review.

SUMMARY

Background
Hepatitis C virus (HCV) and alcohol abuse are the main risk factors for hepatocellular carcinoma (HCC) in Western countries.

Aim
To investigate the role of alcoholic aetiology on clinical presentation, treatment and outcome of HCC as well as on each Barcelona Clinic Liver Cancer (BCLC) stage, as compared to HCV-related HCCs.

Methods
A total of 1642 HCV and 573 alcoholic patients from the Italian Liver Cancer (ITA.LI.CA) database, diagnosed with HCC between January 2000 and December 2012 were compared for age, gender, type of diagnosis, tumour burden, portal vein thrombosis (PVT), oesophageal varices, liver function tests, alpha-fetoprotein, BCLC, treatment and survival. Aetiology was tested as predictor of survival in multivariate Cox regression models and according to HCC stages.

Results
Cirrhosis was present in 96% of cases in both groups. Alcoholic patients were younger, more likely male, with HCC diagnosed outside surveillance, in intermediate/terminal BCLC stage and had worse liver function. After adjustment for the lead-time, median (95% CI) overall survival (OS) was 27.4 months (21.5–33.2) in alcoholic and 33.6 months (30.7–36.5) in HCV patients ($P = 0.021$). The prognostic role of aetiology disappeared when survival was assessed in each BCLC stage and in the Cox regression multivariate models.

Conclusions
Alcoholic aetiology affects survival of HCC patients through its negative effects on secondary prevention and cancer presentation but not through a greater cancer aggressiveness or worse treatment result. In fact, survival adjusted for confounding factors was similar in alcoholic and HCV patients.

Aliment Pharmacol Ther 2016; **43**: 385–399

doi:10.1111/apt.13485

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most frequent malignancy among men and the ninth among women, and represents the second cause of death from cancer.[1] The majority of HCCs occurs in patients with liver cirrhosis, with an annual incidence ranging from 1% to 8%.[2] In Western countries, hepatitis C virus (HCV) and alcohol intake represent the main risk factors for this tumour.[2] However, in developed countries, a divergent secular trend for these two risk factors is expected: the number of HCV-related HCCs will decrease in the next decades due to either the end of the 'cohort effect' of this infection or the availability of new potent anti-viral agents, able to cure HCV infection.[3, 4] Conversely, the number of alcohol-related HCCs is supposed to remain stable or even to increase due to a greater alcohol consumption among young people.[5] Indeed, according to recent epidemiological trends, the number of HCCs associated with a hazardous alcohol intake and metabolic disorders is expected to equal or even overcome HCV-related tumours over the next decade in many developed countries.[6]

A grimmer prognosis of alcoholic patients can be presumed as compared to non-alcoholic cases, due to their lower adherence to surveillance programmes[7–9] and the greater incidence of traumatic events, several comorbidities and other tumours.[10] This clinical profile may increase the overall mortality and restrain the feasibility of HCC treatments.

Despite the growing importance of alcohol abuse among HCC risk factors and its potential effects on tumour management, so far the impact of alcoholic aetiology on HCC prognosis and management remains unsettled. In fact, one study showed a more advanced tumour stage in alcoholic than in virus-related HCCs, but the low sample size limited the robustness of results regarding survival by tumour stage at diagnosis.[11] Reddy *et al.*[12] compared the outcome of curative treatments in HCC patients with non-alcoholic steatohepatitis vs. a combined group of alcoholic and HCV-related cases, thus making it impossible to ascertain the outcome of alcoholic cases. Two other Eastern studies report clinical features and prognosis of alcoholic patients with HCC. However, the Korean investigation was biased by a small sample size, while the Japanese study did not provide any comparative data with viral HCCs.[13, 14] Moreover, survival analyses of all these articles were biased by confounding factors.

In the present study, we used data of the Italian Liver Cancer (ITA.LI.CA) database to answer the following two questions:

(i) Does alcoholic aetiology affect clinical presentation, treatment and outcome of HCC as compared with tumours associated to HCV infection?
(ii) Is the effect of alcoholic aetiology detectable in all/-some BCLC stages?

PATIENTS AND METHODS

Patients

We retrospectively analysed data of the ITA.LI.CA database. This registry collects data generated by the field-practice of 20 Italian centres spread throughout the country. At the time of this analysis, the database included 5439 consecutive patients, diagnosed with HCC between January 1987 and 31 December 2012. Patients' data are collected prospectively and updated every 2 years. After data collection and before statistical evaluation, the consistency of the data set is checked by the group coordinator (F.T.) and, if clarifications or additional information are needed, the data are resubmitted to the relevant centre.

For this study, we selected patients:

(i) diagnosed with an HCC due to hazardous alcohol intake (daily alcohol intake >80 g for men and 60 g for women, for more than 10 years), without other known causes of liver diseases, or to HCV infection (revealed by the presence of serum antibody anti-HCV) without other known causes of liver damage and with BCLC stage reported;
(ii) diagnosed in the current century (from 1 January 2000 to 31 December 2012).

The selection process of patients is illustrated in Figure 1. Among the 2215 enrolled patients, 573 (25.9%) had alcoholic liver disease and 1642 (74.1%) were infected by HCV.

Underlying liver disease

The presence of cirrhosis was ascertained by histology in 49 (9.0%) and 247 (16.1%) of alcoholic and HCV patients, respectively. In the remaining cases it was based on clinical, ultrasound, endoscopic and laboratory features. In patients deemed noncirrhotic cases, the characteristics of the extratumoural liver were assessed by histology.

The severity of liver dysfunction was graded according to Child–Pugh classification[15] and Model of End Liver Disease (MELD, Model of End-Stage Liver Disease).[16]

Diagnosis and staging of HCC

The type of HCC diagnosis was classified as:

(i) under surveillance, when the tumour was detected during a follow-up based on liver ultrasonography performed at least once per year;
(ii) incidental, when an asymptomatic tumour was discovered outside surveillance;
(iii) symptomatic, when HCC was suspected because of symptom development or worsening of the previous clinical status.

These data were reported in >95% of cases.

The final diagnosis of HCC was based on histology and/or cytology in 39 (7.0%) alcoholic patients and 90 (5.5%) HCV patients. In the remaining cases, it was based on typical radiological features at contrast-enhanced imaging techniques (multiphase computed tomography or magnetic resonance imaging) according to recommendations of Western guidelines.[17, 18]

Tumour gross pathology was classified as: single, multifocal and infiltrating/massive. HCC stage was defined according to Barcelona Clinic Liver Cancer (BCLC) criteria as: very early, early, intermediate, advanced and end stage.[2, 18] The tumour stage was also assessed according to American Joint Committee on Cancer/Union for International Cancer Control-tumour, node, metastasis (AJCC/UICC-TNM) staging system.[19]

Comorbidity and performance status

Comorbidities were assessed using the age-adjusted Charlson Comorbidity Index.[20] Performance status (PS) was graded according to the Eastern Cooperative Oncology Group (ECOG).[21]

Lead-time estimation

Patients diagnosed with HCC during a 3- to 7-month or 8- to 13-month surveillance programme, or incidentally or at the time of cancer symptom occurrence (outside any surveillance programme) were used for lead-time estimation.[22] We assumed an exponential tumour growth during the sojourn time as it best reflects the tumour growth kinetics over the range of sizes the majority of HCCs are detected at in screening programmes.[23] Briefly, the mean size of tumour detected under surveillance, incidentally or outside any surveillance programmes were used for sojourn time calculation.[24] The mean size values of tumour detected under 3- to 7-month and 8- to 13-month surveillance, incidentally and because of symptoms were: 2.8, 3.9, 4.1 and 5.2 cm respectively. Tumour growth rate was derived by the tumour volume doubling time[25, 26] and the transition rate to symptomatic disease was used to calculate lead-time by the appropriate formula.[27, 28] The mean ± standard deviation (s.d.) of lead-time was 7.5 ± 2.1 months for patients under 3- to 7-month surveillance, 3.7 ± 0.8 months for those under 8- to 13-month surveillance and 3.1 ± 0.7 for incidentally diagnosed tumours.

Statistical analysis

Continuous data are expressed as mean ± s.d. Categorical data are expressed as absolute and relative frequencies. The Mann–Whitney *U*-test or Student *t*-test and chi-squared test with Fisher's exact test were used to compare variables, as appropriate.

Overall survival (OS) was calculated from the date of HCC diagnosis to death, with values censored at the end of the observation period (31 December 2012) or at the last patient contact (drop-outs). Moreover, due to the higher proportion of HCV-related HCCs detected during surveillance, OS analysis was repeated after lead-time adjustment. OS was also evaluated in the subgroup of patients undergoing regular surveillance. Survival estimates were obtained by Kaplan–Meier analysis and compared with the Cox model. As potential predictors of survival, we tested in the Cox model the following vari-

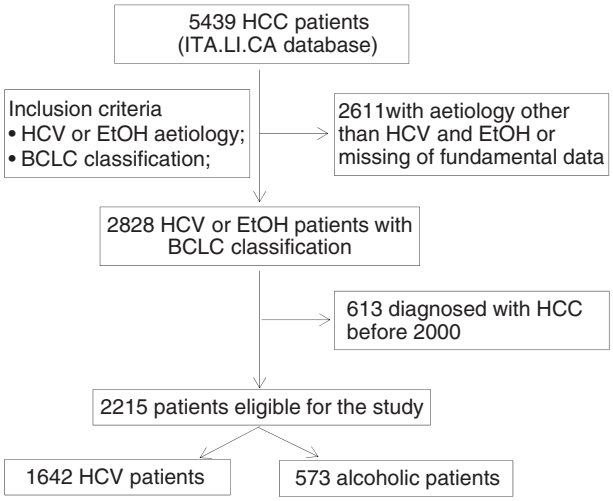

Figure 1 | Flow diagram of patient selection. HCC, hepatocellular carcinoma; ITA.LI.CA, Italian Liver Cancer; EtOH, ethanol; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer.

ables (reported in >75% of cases): age, gender, aetiology, active smoking habit, type of HCC diagnosis, Charlson comorbidity score, presence of diabetes, Child–Pugh score and classes, MELD score, presence of oesophageal varices, alpha-fetoprotein (AFP) level (categorised as ≤20, 21–200, >200 ng/mL), tumour gross pathology, size of the dominant lesion, presence of portal vein thrombosis (PVT), presence of metastases, BCLC and AJCC/UICC-TNM HCC stage and HCC treatment. Patients with multiple types of treatment were categorised as the treatment modality with the highest likelihood of cure, as follows: surgical options [liver transplant (LT) and hepatic resection], percutaneous ablation (radiofrequency and ethanol injection), transarterial treatments [chemoembolization (TACE) and embolization (TAE)], sorafenib and other/palliation. Patients who underwent different treatments were allocated to the most effective one.

Variables resulted to be associated at univariate analysis ($P \leq 0.10$) with lead-time adjusted OS were entered in Cox multivariate forward stepwise regression models to identify the independent prognostic factors. For each prognostic factor, the adjusted hazard ratio (HR) and 95% confidence interval (CI) were reported. Child–Pugh score, PVT and metastases were not included in the Cox multivariate models as part of the BCLC staging system. A second multivariate analysis including AJCC/UICC-TNM staging system and Child–Pugh classification instead of BCLC staging system was also performed. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS 22.0 statistical package (SPSS Inc., Chicago, IL, USA). This study conforms to the ethics guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of our department.

RESULTS

A total of 2215 HCC patients were included in the study (Figure 1). The underlying liver disease was reported in 98.0% of patients. HCC ensued in a cirrhotic liver in 96.3% of alcoholic subjects and 96.6% of HCV patients. The second most common liver disease was fatty liver (1.6%) in alcoholic cases and chronic hepatitis (3.1%) in HCV patients. Fibrosis, other causes of liver disease and normal liver accounted for the remaining cases.

Table 1 reports baseline characteristics of patients. On average, alcoholic subjects were 4 years younger, more likely males and active smokers. They showed diabetes more frequently than viral cases. Body mass index (BMI) was also higher in alcoholic patients but this data was available in only 40% of cases.

Alcoholic patients had a more advanced cirrhosis, as indicated by a significantly higher MELD and Child–Pugh scores, as well as a higher frequency of oesophageal varices. In this group, HCC was more frequently diagnosed outside surveillance programmes (38.1% vs. 68.9%; Figure 2a) and the tumour was larger, more frequently multifocal or infiltrating/massive (56.7% vs. 42.1%) and associated with PVT. Therefore, very early and early BCLC stages as well as AJCC/UICC-TM Stage I were less common, while intermediate and terminal BCLC stages and AJCC/UICC-TM Stage III were more frequent among alcoholic patients. The prevalence of advanced BCLC HCCs did not differ between two groups (Figure 2b,c).

Despite the worse stage distribution, alcoholic patients showed lower AFP levels.

Relationship between surveillance and tumour burden

In order to scrutinise the role played by surveillance on HCC presentation, a sub-analysis on patients diagnosed under surveillance was performed. The mean ± s.d. interval of surveillance was 6.4 ± 2.2 months for HCV patients and 5.9 ± 2.5 for alcoholic cases ($P = 0.01$). The percentage of surveyed patients undergoing 3- to 7-month interval surveillance largely prevailed and did not differ between alcoholic and HCV cases (87.7% vs. 87.9%, respectively; $P = 0.952$). Nevertheless, solitary HCCs were less frequent in alcoholic cases (55.4% vs. 64.3%, respectively; $P = 0.022$).

Tumour treatment

Aetiology influenced treatment distribution in the whole population (Table 1). Namely, among alcoholic patients the most common treatment was palliation (30.4% of cases), a choice adopted in only 19.8% of HCV patients, while viral cases were deemed to be eligible for ablative procedures more frequently than their counterpart (34.0% vs. 25.5%). These differences were due to a different management of patients with advanced (BCLC C) HCCs (palliation: 45.4% of alcoholic patients vs. 29.6% of HCV patients; ablation: 16.6% vs. 28.8%, respectively; $P = 0.001$), while, in the other BCLC stages, treatments distribution did not significantly differ between the two aetiological groups. TACE/TAE represents the second most common therapy in both groups without differences between the two groups.

Table 1 | Demographic and clinical features of studied patients

	HCV patients, *n* = 1642 (74.1%)	Alcoholic patients, *n* = 573 (25.9%)	*P*-Value
Age (years)			
Mean ± s.d.	70.7 ± 8.8	66.7 ± 8.8	<0.001
≤71, *n* (%)	795 (48.4)	405 (70.7)	<0.001
>71, *n* (%)	847 (51.6)	168 (29.3)	
Gender			
Male, *n* (%)	1002 (61.0)	523 (91.3)	<0.001
Active smokers			
Available data, *n* (%)	1239 (75.4)	438 (76.4)	<0.001
Yes, *n* (%)	216 (17.4)	163 (37.2)	
BMI (kg/m^2)			
Available data, *n* (%)	653 (39.8)	233 (40.7)	<0.001
Mean ± s.d.	24.8 ± 3.8	26.3 ± 3.5	<0.001
Underweight, *n* (%)	16 (2.5)	1 (0.4)	
Normal range, *n* (%)	359 (55.0)	91 (39.1)	0.122
Overweight, *n* (%)	226 (34.6)	108 (46.4)	<0.001
Obese, *n* (%)	52 (8.0)	33 (14.2)	0.001
Charlson Comorbidity Index			
Mean ± s.d.	4.5 ± 1.7	4.4 ± 2.0	0.188
Diabetes			
Available data, *n* (%)	1429 (87.0)	502 (87.6)	<0.001
Yes, *n* (%)	366 (25.6)	191 (38.0)	
MELD score			
Available data, *n* (%)	1584 (96.5)	560 (97.7)	<0.001
Mean ± s.d.	10.4 ± 4.3	11.7 ± 4.6	
Child–Pugh			
Mean ± s.d.	6.3 ± 1.6	6.7 ± 1.8	<0.001
A, *n* (%)	1125 (68.5)	318 (55.5)	
B, *n* (%)	433 (26.4)	205 (35.8)	
C, *n* (%)	84 (5.1)	50 (8.7)	
AFP (ng/mL)			
Available data, *n* (%)	1394 (84.9)	525 (91.6)	<0.001
≤20, *n* (%)	674 (48.4)	346 (65.9)	
21–200, *n* (%)	458 (32.9)	96 (18.3)	
>200, *n* (%)	262 (18.8)	83 (15.8)	
Gross pathology			
Single, *n* (%)	950 (57.9)	248 (43.3)	0.001
Multifocal, *n* (%)	597 (36.4)	266 (46.4)	
Infiltrating/massive, *n* (%)	95 (5.8)	59 (10.3)	
Main nodule size (cm)			
Available data, *n* (%)	1613 (98.2)	550 (96.0)	<0.001
Mean ± s.d.	3.3 ± 2.0	4.1 ± 2.7	
PVT			
Yes, *n* (%)	204 (12.4)	100 (17.5)	0.003
Metastases			
Yes, *n* (%)	40 (2.4)	17 (3.0)	0.540
Oesophageal varices			
Available data, *n* (%)	1339 (81.5)	481 (83.9)	0.037
Yes, *n* (%)	718 (53.6)	285 (59.3)	
ECOG-PS			
0	1123 (68.4)	363 (63.4)	0.171
1	342 (20.8)	140 (24.4)	
2	117 (7.1)	47 (8.2)	
3	52 (3.2)	22 (3.8)	
4	8 (0.5)	1 (0.2)	

Table 1 | (Continued)

	HCV patients, *n* = 1642 (74.1%)	Alcoholic patients, *n* = 573 (25.9%)	*P*-Value
BCLC staging system			
Very early, *n* (%)	103 (6.3)	16 (2.8)	<0.001
Early, *n* (%)	671 (40.9)	176 (30.7)	
Intermediate, *n* (%)	228 (13.9)	116 (20.2)	
Advanced, *n* (%)	511 (31.1)	197 (34.4)	
End-stage, *n* (%)	129 (7.9)	68 (11.9)	
AJCC/UICC-TNM staging system			
Stage I, *n* (%)	876 (53.3)	228 (39.8)	<0.001
Stage II, *n* (%)	498 (30.3)	180 (31.4)	
Stage III, *n* (%)	239 (14.6)	149 (26.0)	
Stage IV, *n* (%)	29 (1.8)	16 (2.8)	
Treatment			
Available data, *n* (%)	1605 (97.7)	550 (96.0)	<0.001
OLT, *n* (%)	35 (2.2)	6 (1.1)	
Resection, *n* (%)	174 (10.8)	62 (11.3)	
Ablation, *n* (%)	546 (34.0)	140 (25.5)	
TACE/TAE, *n* (%)	493 (30.7)	159 (28.9)	
Sorafenib, *n* (%)	39 (2.4)	16 (2.9)	
Others/palliation, *n* (%)	318 (19.8)	167 (30.4)	

BMI, body mass index; MELD, Model of End Liver Disease; AFP, alpha-fetoprotein; PVT, portal vein thrombosis; ECOG-PS, Eastern Cooperative Oncology Group- Performance status; BCLC, Barcelona Clinic Liver Cancer; AJCC/UICC-TNM, American Joint Committee on Cancer/Union for International Cancer Control-tumour, node, metastasis; OLT, orthotopic liver transplant; TACE/TAE, transarterial chemoembolization/transarterial embolization.

Data are presented as mean ± standard deviation (s.d.) and as number and percentage (%).

Relationship between tumour burden and liver function

In order to investigate whether the greater liver dysfunction of alcoholic patients was due to their larger tumour burden, a sensitivity analysis was performed in the subset of patients with tumours fulfilling Milan criteria (single lesion ≤5 cm or up to 3 lesions ≤3 cm each, without vascular invasion or extra-hepatic spread),[29] which do not remarkably affect hepatic function. A significantly lower proportion of alcoholic patients meets the Milan criteria compared to HCV patients (33.5% vs. 47.1% respectively, $P < 0.001$) but, among those satisfying the Milan criteria, alcoholic patients showed a higher MELD and Child scores (mean ± s.d.: 11.4 ± 4.2 vs. 9.8 ± 3.8 and 6.5 ± 1.7 vs. 6.0 ± 1.3, $P \leq 0.001$, respectively) and a less favourable Child–Pugh class distribution (class A: 59.1% vs. 75.8%, class B: 33.5% vs. 21.7%, class C: 7.4% vs. 2.5%, $P \leq 0.001$) compared to their HCV counterpart.

Survival

Over a median follow-up of 22.3 months (95% CI: 2.0–92.3 months), 1216 (54.9%) patients died: 866 (71.2%) belonged to the HCV group, and 350 (28.8%) to the alcoholic group. The causes of death were: cancer progression (54.6% in alcoholic vs. 54.3%, in viral patients), hepatic failure (10.6% vs. 10.9%), haemorrhage (2.0% vs. 1.3%), infections (0.6% vs. 1.5%), renal failure (1.1% vs. 0.5%), other causes (4.3% vs. 3.2%) and unknown (26.6% vs. 28.4%).

The median OS was 38.6 months (95% CI: 35.7–41.4) in the whole population. It was significantly lower in alcoholic patients [32.4 months (26.6–38.3)] than in HCV patients [40.6 months (37.7–43.5) ($P = 0.002$)] (Figure 3a). Survival rates at 1, 3, 5, 7 and 10 years were 72.9 ± 0.02%, 47.1 ± 0.02%, 31.7 ± 0.02%, 20.9 ± 0.02%, 12.3 ± 0.03% and 83.2 ± 0.01%, 54.8 ± 0.014%, 28.6 ± 0.015%, 23.9 ± 0.15%, 15.7 ± 0.02% respectively. After lead-time adjustment, the median OS decreases to 31.7 months (95% CI: 29.0–34.4) in the whole population. It remained significantly lower in alcoholic patients [27.4 months (21.5–33.2)] compared to HCV patients [33.6 months (30.7–36.5)] ($P = 0.021$) (Figure 3b). Survival rate at 1, 3, 5, 7 and 10 years were 67.1 ± 0.02%, 43.7 ± 0.02%, 26.3 ± 0.02%, 19.3 ± 0.02%, 13.4 ± 0.02% and 74.9 ± 0.01%, 47.7 ± 0.01%, 29.9 ± 0.01%, 20.9 ± 0.01%, 15.5 ± 0.02% respectively.

The OS of all surveyed patients and that of patients undergoing 3- to 7-month surveillance (Figure 3c,d,

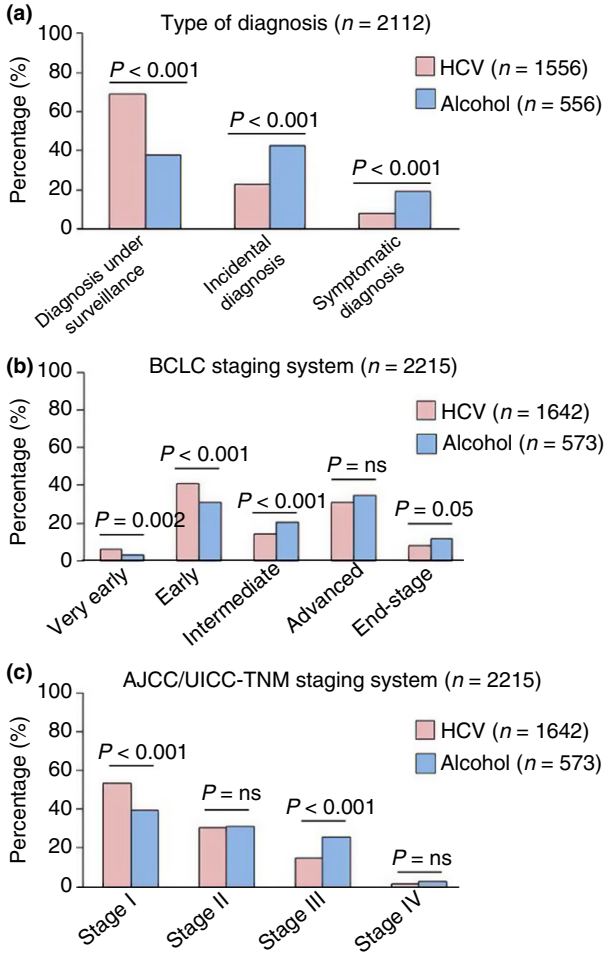

Figure 2 | Type of diagnosis (available in 2110 cases) in HCV-related and alcohol-related HCC patients (a). Distribution of BCLC (b) and of AJCC/UICC-TNM (c) stages in HCV-related and alcohol-related HCC patients.

respectively) were also compared. Median OS of all surveyed patients was 52.8 months (95% CI: 39.8–65.7) in alcoholic patients and 46.7 months (95% CI: 43.3–50.0) in HCV patients (P = 0.529), while median OS of 3- to 7-month surveyed patients was 59.8 months (95% CI: 46.3–73.3) in alcoholic patients and 47.7 months (95% CI: 44.1–51.2) in HCV patients (P = 0.790).

At univariate analysis, alcoholic aetiology, age, active smoking, HCC diagnosis outside surveillance, MELD and Child–Pugh scores, Child–Pugh class B and C, tumour gross pathology, oesophageal varices, PVT, metastases, AFP >20 ng/mL, nodule size, BCLC and AJCC/UICC-TNM staging systems as well as treatment type were associated with the lead-time adjusted OS (Table 2). As data regarding smoking, AFP and oesophageal varices were available in less than 90% of cases (Table 1), the inclusion of all the variables associated with survival at the univariate analysis in a single multivariate Cox model would have reduced the sample to 50.6% of the initial population. Therefore, we launched four multivariate models (each including at least 65.1% of cases). All the models were also adjusted for gender. The 'core' model (Model 1: 82.6% of cases) included aetiology, age, gender, type of diagnosis, MELD score, tumour gross pathology, nodule size, BCLC stage and treatments. We added to this model: AFP (Model 2: 72.8% of cases) or oesophageal varices (Model 3: 69.8%) or active smoking (Model 4: 65.1%). Variables independently associated with survival in all the four models were: age (HR, hazard ratio 1.02, 95% CI: 1.01–1.02), MELD (HR 1.03, 95% CI: 1.02–1.05), tumour diameter (HR 1.07, 95% CI: 1.03–1.10), BCLC stages beyond the very early one [early (HR 3.89, 95% CI: 2.07–7.32), intermediate (HR 4.77, 95% CI: 2.47–9.20), advanced (HR 5.32, 95% CI: 2.81–10.06) and terminal (HR 6.65, 95% CI: 3.39–13.05)] and treatment [surgical (HR 0.27, 95% CI: 0.21–0.34), ablation (HR 0.37, 95% CI: 0.30–0.45), TACE (HR 0.44, 95% CI: 0.37–0.52) and sorafenib (HR 0.40, 95% CI: 0.40–0.93)]. In addition, AFP (21–200 ng/mL: HR, 1.24; 95% CI: 1.07–1.44; >200 ng/mL: HR 1.50, 95% CI: 1.24–1.78), oesophageal varices (HR 1.46, 95% CI: 1.27–1.69) or smoking (HR 1.30, 95% CI: 1.11–1.52) resulted to be independent prognostic factors when added to Model 1 (Table 2). When the BCLC stages were substituted with the AJCC/UICC-TNM stages, and the Child–Pugh classification was included, the results did not substantially differ (see Table S1).

The analysis of lead-time adjusted survival, according to BCLC and AJCC/UICC-TNM stratification, did not show differences between alcoholic and viral patients. Median OS was: for very early/early BCLC stage 53.4 months (95% CI: 47.0–59.8) in alcoholic and 51.9 months (95% CI: 45.1–58.6) in HCV patients (P = 0.997); for intermediate BCLC stage, 24.0 months (95% CI: 13.9–34.1) and 23.7 months (95% CI: 18.8–29.1) (P = 0.972); for advanced BCLC stage, 15.2 months (95% CI: 10.4–20.0) and 19.8 months (95% CI: 15.0–24.5) (P = 0.303); for end BCLC stage, 5.1 months (95% CI: 2.1–8.1) and 6.3 months (95% CI: 4.8–7.7) (P = 0.656), respectively (Figure 4).

Median OS was: for AJCC/UICC-TNM Stage I, 47.3 months (95% CI: 37.7–56.9) in alcoholic and 45.8 months (95% CI: 41.3–50.3) in HCV patients (P = 0.772); for Stage II, 32.1 months (95% CI: 21.1–43.0) and 27.0 months (95% CI: 21.4–32.6) (P = 0.757); for Stage III, 7.1 (95% CI: 5.0–9.2) and 8.7 months (95% CI: 6.1–11.3) (P = 0.752); for Stage IV, 8.1 months (95%

CI: 2.7–13.5) and 12.8 months (95% CI: 0.25–25.4) (P = 0.884) respectively (Figure 5).

DISCUSSION

Our large multicentre study provided a comprehensive comparison between HCCs caused by hazardous alcohol consumption and HCV infection, the two main risk factors for this cancer in Western and Japanese people.[2]

The higher preponderance of males among alcoholic patients, attributable to the greater propensity of this sex towards hazardous alcohol consumption, is a well-known information.[30] Another result in line with most – but not all[7] – previous investigations[13, 31, 32] is the younger age of alcoholic patients. As both risk factors are encountered in adulthood age rather than in infancy, a possible explanation relies on a faster progression towards cirrhosis in alcoholic cases, possibly due to the

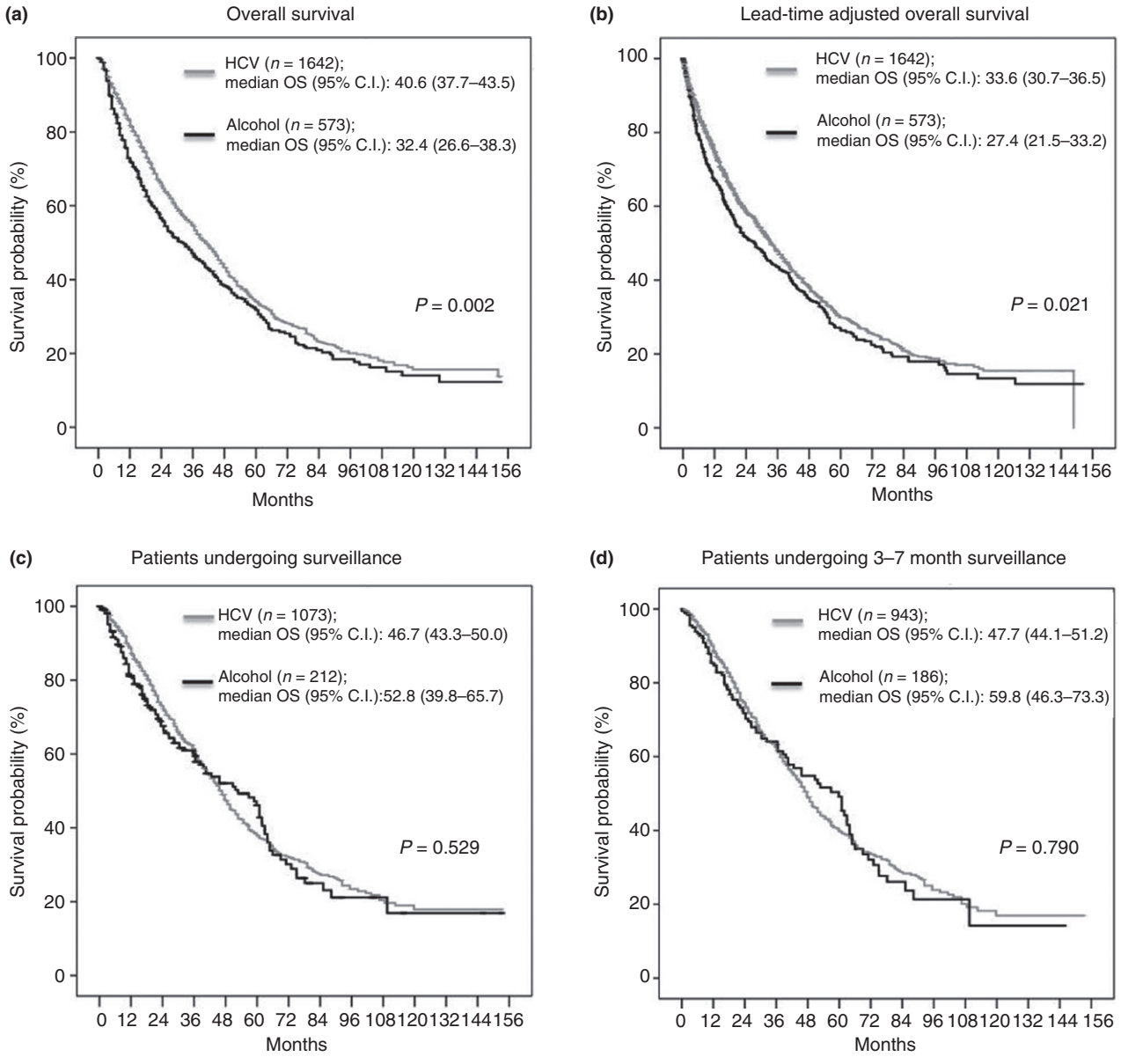

Figure 3 | Overall survival (a), lead-time adjusted overall survival (b), overall survival of all regularly surveyed patients (n = 1285) (c) and overall survival of 3- to 7-month surveyed patients (n = 1129) (d) according to aetiology.

Table 2 | Univariate and multivariate Cox proportional hazard regression analysis of factor affecting the lead-time adjusted survival

		Multivariate analysis			
	Univariate analysis	Model 1	Model 2	Model 3	Model 4
Aetiology		NS	NS	NS	NS
Alcoholic	1.13 (1.00–1.28)				
Age at diagnosis	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.02 (1.01–1.03)	1.01 (1.01–1.02)
Gender		ns	ns	ns	ns
Male	0.99 (0.87–1.12)				
Active smokers		NA	NA	NA	
Yes	1.31 (1.13–1.51)				1.30 (1.11–1.52)
Type of diagnosis		ns	ns	ns	ns
Incidental	1.29 (1.13–1.46)				
Symptomatic	1.89 (1.59–2.24)				
Charlson Comorbidity Index	1.02 (0.98–1.05)	NA	NA	NA	NA
Diabetes		NA	NA	NA	NA
Yes	0.99 (0.86–1.13)				
MELD score	1.08 (1.06–1.09)	1.03 (1.02–1.05)	1.04 (1.02–1.05)	1.03 (1.01–1.04)	1.03 (1.01–1.05)
Child–Pugh Class		NA	NA	NA	NA
B	2.01 (1.78–2.27)				
C	3.38 (2.75–4.16)				
Child–Pugh score	1.28 (1.25–1.32)	NA	NA	NA	NA
AFP level (ng/mL)		NA		NA	NA
21–200	1.32 (1.15–1.51)		1.24 (1.07–1.44)		
>200	2.52 (2.16–2.93)		1.50 (1.24–1.78)		
Gross pathology				ns	
Multifocal	1.65 (1.47–1.86)	1.17 (1.01–1.35)	1.10 (0.95–1.28)		1.12 (0.96–1.32)
Infiltrating/Massive	4.35 (3.57–5.30)	1.62 (1.18–2.21)	1.54 (1.18–2.13)		1.65 (1.17–2.33)
Main nodule size, cm	1.16 (1.13–1.18)	1.07 (1.03–1.10)	1.05 (1.01–1.09)	1.10 (1.01–1.14)	1.05 (1.01–1.09)
PVT		NA	NA	NA	NA
Yes	2.65 (2.29–3.07)				
Metastases		NA	NA	NA	NA
Yes	2.26 (1.66–3.07)				
Oesophageal varices		NA	NA		NA
Yes	1.69 (1.48–1.92)			1.46 (1.27–1.69)	
BCLC classification					
Early	3.60 (2.07–6.25)	3.89 (2.07–7.32)	4.00 (2.05–7.78)	3.33 (1.71–6.49)	3.76 (1.85–7.62)
Intermediate	6.72 (3.84–11.75)	4.77 (2.47–9.20)	4.89 (2.45–9.77)	4.00 (2.01–7.96)	5.00 (2.40–10.42)
Advanced	7.93 (4.57–13.78)	5.32 (2.81–10.06)	5.47 (2.79–10.71)	4.16 (2.12–8.15)	5.39 (2.64–11.00)
End stage	15.55 (8.83–27.40)	6.65 (3.39–13.05)	5.90 (2.89–10.04)	5.60 (2.74–11.45)	7.01 (3.29–14.96)
AJCC/UICC-TNM classification		NA	NA	NA	NA
Stage II	1.50 (1.31–1.71)				
Stage III	3.21 (2.77–3.73)				
Stage IV	3.26 (2.31–4.59)				
Treatment					
Surgical options	0.15 (0.12–0.19)	0.27 (0.21–0.34)	0.28 (0.21–0.36)	0.25 (0.19–0.33)	0.23 (0.17–0.31)
Ablation	0.21 (0.18–0.25)	0.37 (0.30–0.45)	0.38 (0.31–0.47)	0.33 (0.27–0.42)	0.36 (0.29–0.46)
TACE/TAE	0.32 (0.28–0.37)	0.44 (0.37–0.52)	0.44 (0.36–0.53)	0.43 (0.35–0.52)	0.43 (0.36–0.53)
Sorafenib	0.68 (0.47–1.00)	0.61 (0.40–0.93)	0.54 (0.34–0.85)	0.66 (0.43–1.04)	0.56 (0.34–0.93)

Values are expressed as HR (95% CI).

HR, hazard ratio; CI, confidence interval; ns, nonsignificant; NA, not assessed; MELD, model of end-stage liver disease; AFP, alpha-foetoprotein; PVT, portal vein thrombosis; BCLC, Barcelona Clinic Liver Cancer; AJCC/UICC–TNM, American Joint Committee on Cancer/Union for International Cancer Control–tumour, node, metastasis; TACE, transarterial chemoembolization; TAE, transarterial embolization.

Model 1 included: aetiology, age, gender, type of diagnosis, MELD score, tumour gross pathology, nodule size, BCLC stage and treatments; Model 2: model 1 + AFP; Model 3: model 1 + oesophageal varices; Model 4: model 1 + active smoking. Reference categories: HCV aetiology; female gender; no smoking; surveillance diagnosis; no diabetes; Child–Pugh class A; AFP ≤20 ng/mL; single nodule HCC; no PVT; no metastases; no oesophageal varices; very early BCLC stage; palliation.

frequent presence of 'cofactors' of liver damage. Indeed, these patients more frequently associate diabetes and overweight/obesity which, beside representing well-established risk factors for HCC, can accelerate the progression of liver damage in alcoholic and non-alcoholic liver disease.[33, 34] Moreover, metabolic cofactors and tobacco smoking – another custom more frequent in alcoholic patients – have a synergistic effect on HCC risk,[35–37] which is expected to anticipate cancer development in the natural history of liver disease. This anticipation, however, seems to conflict with the more progressed cirrhosis found in alcoholic patients, which cannot be considered a simple epiphenomenon of their larger tumour burden. In fact, this difference was also observed in the subgroup of early HCCs. Therefore, it can be surmised that alcohol itself is an oncogenic factor less efficient than HCV requiring the establishment of advanced cirrhosis for priming carcinogenesis. However, this oncologic advantage would be overridden by an accelerated progression of the underlying liver disease due to insulin resistance, overweight/obesity and smoking, resulting in a younger age of alcoholic patients at the time of HCC detection.

Our study confirmed two other well-known characteristics of alcoholic HCCs. First, cancer was detected outside any surveillance programme much more frequently than in HCV patients,[8, 9, 11] with a doubling of symptomatic cases. This disadvantage can be ascribed to both a lower patient awareness of – and/or a lower interest for – their risk status and a poorer adherence to surveillance with respect to viral patients.[7, 8] A delayed cancer diagnosis was probably the main cause of the greater tumour burden and the poorer survival seen in alcoholic subjects. However, it should not be disregarded that, even among surveyed patients, multinodularity was more frequent in the alcoholic group indicating possible different carcinogenetic patterns between alcoholic and HCV patients.

Both the different oncologic status and liver function may account for the worse therapeutic scenario of the alcoholic group, in which curative treatments (LT, resection or ablation) were less frequently applied than in viral HCCs, while palliation was more common (Table 1). However, this difference was also caused by a more conservative management of alcoholic patients bearing an advanced HCC, 45% of whom underwent just palliation (vs. 29% of HCV cases).

This could depend on a significant higher prevalence of some comorbidities (overweight/obesity, heart disease) and the higher Child–Pugh score of alcoholic BCLC C patients (data not presented). Another cause might rely on a poorer socio-economical status of alcoholic patients.[38] In this respect, it is likely that the patient income had a limited impact as, in Italy, the access to diagnostic procedures and treatments of cancer patients is totally in charge to the National Health System, guarantying the same degree of assistance to all citizens. Instead, a different degree of acceptance of medical care and management between alcoholic and viral patients can be surmised.

Although not strictly pertinent to the study aim, it should be pointed out that our 708 BCLC C patients showed a median OS of 18.3 months, a figure higher than those reported in Western randomised and field-practice studies.[39–41] This can be explained considering that 62.1% of our BCLC C patients were allocated to this stage just because of a PS > 0, in the absence of the relevant oncologic hallmarks, i.e. vascular invasion or extrahepatic tumour spread. Therefore, a number of these patients underwent curative treatments or TACE. As a result, in such a BCLC C subset with a favourable oncologic status the median OS reached 28.0 months (95% CI: 22.2–33.8), while the figure falls to 8.2 months (95% CI: 5.1–11.2) in patients with at least one tumoural hallmark of the advanced stage. This result lends support to those of a recent study showing that the prognostic accuracy of the BCLC staging system improved if a PS 1 was not considered preclusive for patient allocation to early or intermediate stage.[42] Based on these considerations, the Italian Association for the Study of the Liver recommends not allocating HCC patients to BCLC stage C just because of PS 1.[43]

The second established characteristic of alcoholic HCCs we confirmed is the low production of AFP.[31, 44] This production depends on both tumoural and extratumoural factors, and one of them is the tumour burden.[45, 46] The combination of lower AFP values with larger tumours seen in alcoholic cases would indicate that the effect of aetiology prevailed over that of tumour volume. Pragmatically, the clinical message coming from the different propensity to produce AFP by nonviral and viral HCC patients is that physicians should take into account such a phenomenon when they decide to use this marker as a surveillance test for HCC.[44, 47]

The main result of our study concerns patient survival. Alcoholic patients had a significantly shorter OS compared to HCV patients. This difference was confirmed when the survival of patients with HCC diagnosed during surveillance or incidentally was adjusted for the lead-time, showing that the advantage was not a

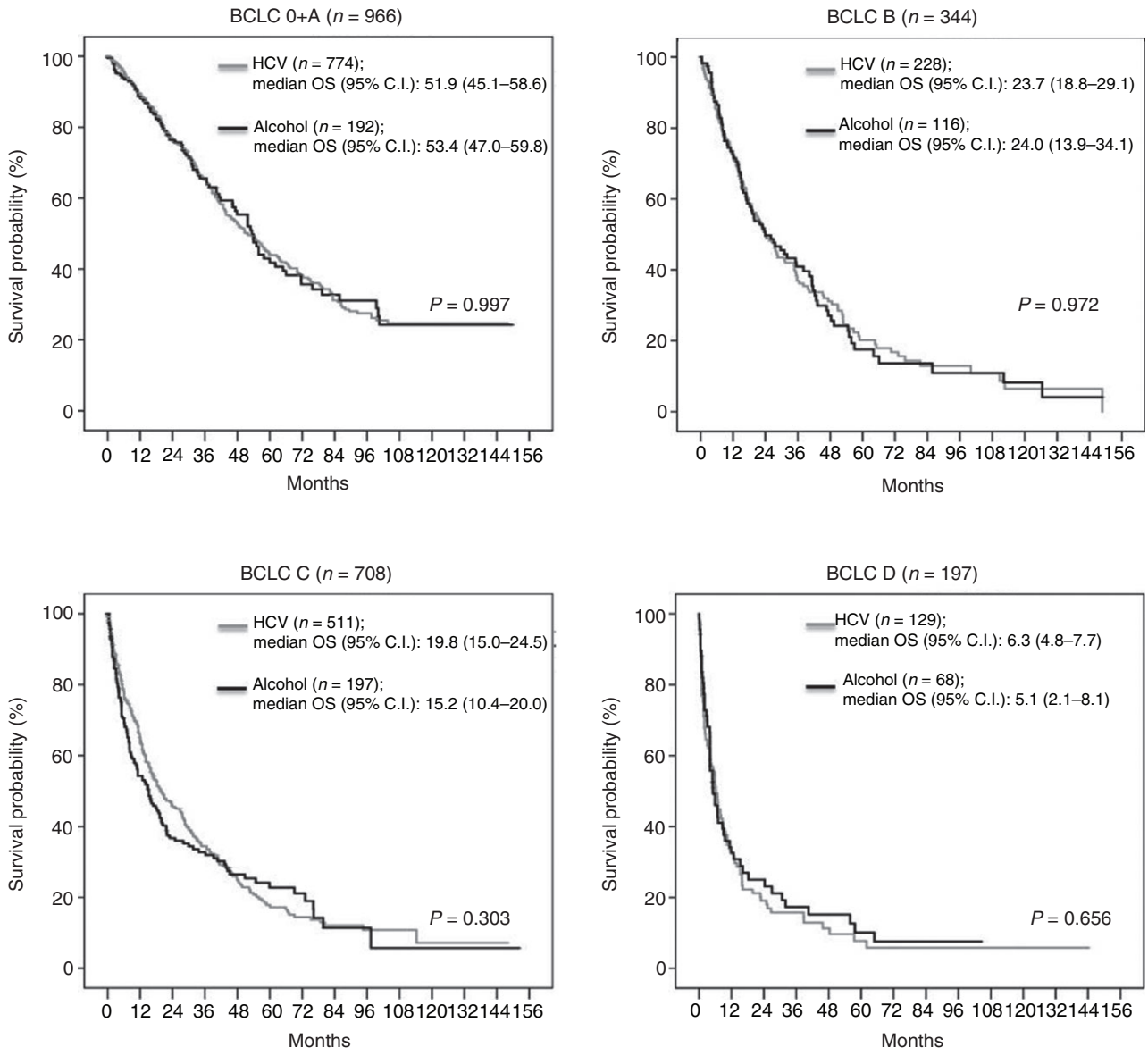

Figure 4 | Lead-time adjusted overall survival by BCLC stage in patients with HCV-related and alcohol-related HCC. The survival probability in each BCLC stage did not differ according to the tumour aetiology.

spurious effect caused by an anticipated diagnosis, due to surveillance, but it was due to the higher proportion of surveyed patients in the HCV group. In fact, the difference in OS between aetiological groups disappeared in the subset of surveyed patients.

Our study clearly indicate that the poorer prognosis of alcoholic patients depends on the more advanced cancer stage as the role of aetiology disappeared not only when survival was adjusted for all the confounding factors (multivariate analyses) but also when patients were stratified by BCLC or by AJCC/UICC-TNM stage. Our result conflicts with a previous demonstration that alcoholic patients with early stage HCC survive longer than the HCV counterpart, a difference that vanished in the advanced stage.[11] However, this study was biased by a very low sample size and by no adjustments for confounding factors. Therefore, it can be concluded that alcoholic aetiology worsens the HCC prognosis, with respect to HCV-associated cases, by delaying the time of its diagnosis, and not by affording the tumour a greater biological aggressiveness or worsening treatment results, regardless of the stage at which the tumour is detected.

This study has some limitations. The first one relies on its retrospective nature that cannot fully exclude

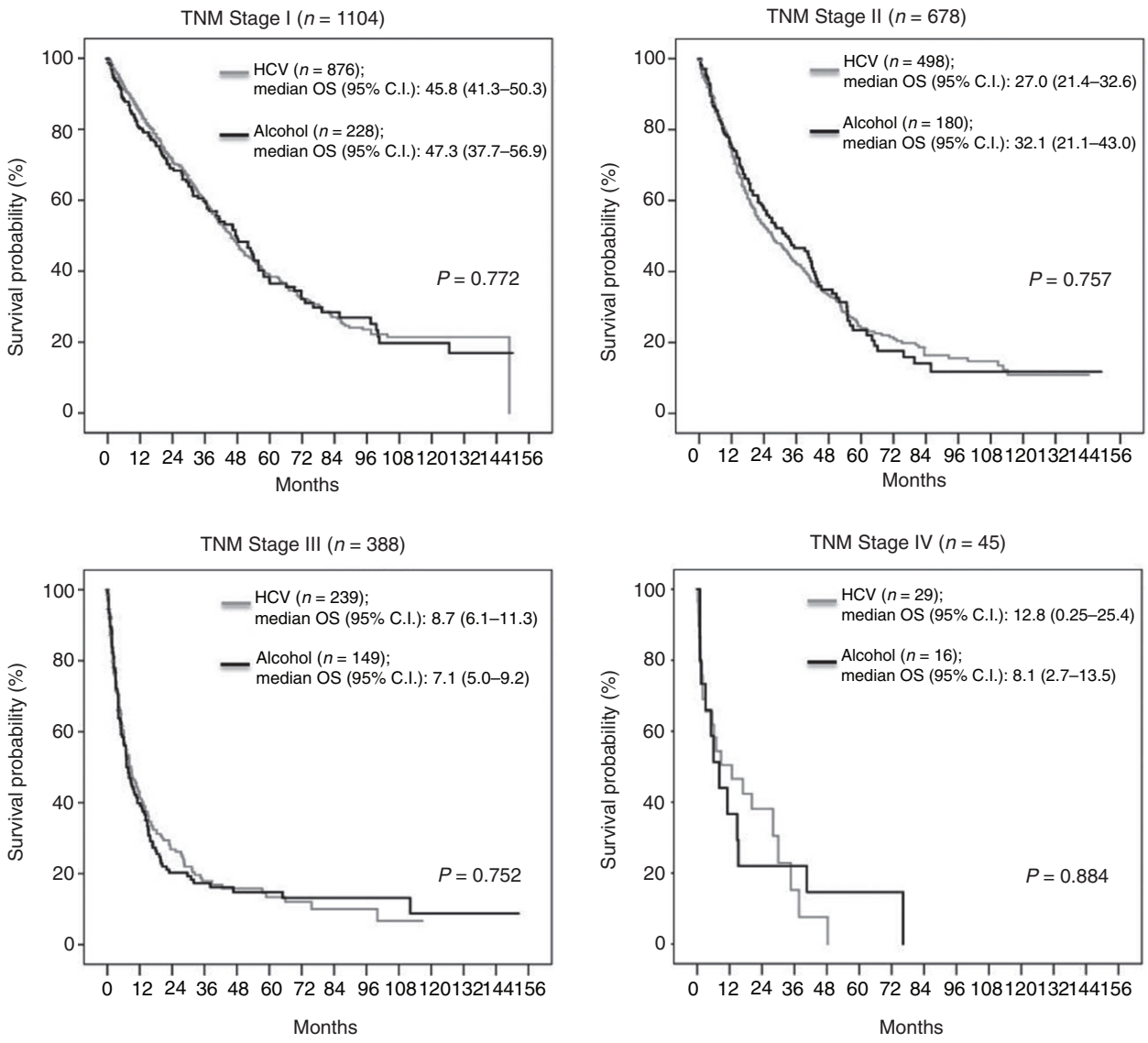

Figure 5 | Lead-time adjusted overall survival by AJCC/UICC-TNM stage in patients with HCV-related and alcohol-related HCC. The survival probability in each AJCC/UICC-TNM stage did not differ according to the tumour aetiology.

unintended biases. The second limitation is the incompleteness of data regarding abstinence from alcohol. This drawback did not allow us to assess whether abstinent cases have a better prognosis, as it is probable, than active drinkers and, more intriguingly, than HCV patients. Our clinical practice indicates that only a minority (about 20–25%) of alcoholic patients (usually wine drinkers without addiction) continue to drink after HCC diagnosis. Therefore, our results can be considered representative of a population mainly consisting of abstinent patients, and cannot be extrapolated to active drinkers.

As far as causes of death are concerned, we did not find differences between alcoholic and viral patients but the lack of information in one-third of cases weakens the robustness of the comparison. This incompleteness is not surprising for a registry generated by the clinical practice, as a number of patients died at their primary referral hospitals – i.e. outside the ITA.LI.CA network – making it impossible to precisely identify the event responsible for death. On the other hand, in the pertinent literature we did not find data to challenge our results.

Finally, it should be mentioned that the advent of new direct anti-viral drugs,[3, 4] able to eradicate HCV

infection in most patients, will likely improve not only the epidemiologic burden of HCV-related tumours[48] but also prognosis of HCCs caused by HCV infection through two mechanisms: (i) by reducing after curative approaches, the late cancer recurrences which are more frequent in a setting of active liver disease,[49] as already observed in patients treated with interferon[50]; (ii) by a long-term preservation of liver function, resulting in a lower cirrhosis-related mortality and a greater chance of receiving curative treatments if cancer recurs. In this forthcoming scenario, our data regarding alcoholic HCC will likely remain a benchmark, whereas the changing history of HCV-related neoplasms will need an up-date.

In conclusion, alcoholic aetiology adversely affects HCC prognosis through a delayed cancer detection, frequently made outside any surveillance programme and in a setting of an advanced liver cirrhosis. Consequently, HCC stage is more advanced and less frequently amenable to curative therapies. These features, rather than a greater cancer aggressiveness or worse treatment results, justify the poorer prognosis of Western alcoholic patients with respect to HCV-infected patients.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Multivariate Cox proportional hazard regression analysis of factors affecting the lead-time adjusted survival.

AUTHORSHIP

Guarantor of the article: Professor Franco Trevisani.

Author contributions: L. Bucci, F. Garuti, V. Camelli, B. Lenzi and F. Trevisani participated in the conception and design of the article and drafted the paper. All the authors revised the article critically, and approved the final version to be submitted.

ACKNOWLEDGEMENTS

We thank Ing. A.M. Morselli-Labate for his statistical assistance and revision of the manuscript.

Declaration of personal interests: All the authors declared that they do not have any conflict of interest or financial interest regarding the subject of the article.

Declaration of funding interests: This study was supported by grants (Ricerca fondamentale orientata 2007/2008 and 2008/2009) from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR). The no profit ITA.LI.CA Association received funding from Bayer Health Care for the ITA.LI.CA database up-date.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359–86.
2. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908–43.
3. Cholongitas E, Papatheodoridis GV. Sofosbuvir: a novel oral agent for chronic hepatitis C. *Ann Gastroenterol* 2014; **27**: 331–7.
4. Koff RS. Review article: the efficacy and safety of sofosbuvir, a novel, oral nucleotide NS5B polymerase inhibitor, in the treatment of chronic hepatitis C virus infection. *Aliment Pharmacol Ther* 2014; **39**: 478–87. Review.
5. Rüütel E, Sisask M, Värnik A, *et al.* Alcohol consumption patterns among adolescents are related to family structure and exposure to drunkenness within the family: results from the SEYLE project. *Int J Environ Res Public Health* 2014; **11**: 12700–15.
6. Santi V, Buccione D, Di Micoli A, *et al.* The changing scenario of hepatocellular carcinoma over the last two decades in Italy. *J Hepatol* 2012; **56**: 397–405.
7. Henrion J, Libon E, De Maeght S, *et al.* Screening for hepatocarcinoma in a cohort with cirrhosis mainly of alcoholic origin. *Gastroenterol Clin Biol* 2003; **27**: 534–9.
8. Edenvik P, Davidsdottir L, Oksanen A, Isaksson B, Hultcrantz R, Stal P. Application of hepatocellular carcinoma surveillance in a European setting. What can we learn from clinical practice? *Liver Int* 2014; **35**: 1862–71.
9. Eskesen AN, Bjøro K, Aandahl EM, Line PD, Melum E. Low use of surveillance and early diagnosis of hepatocellular carcinoma in Norway – a population-based cohort study. *Cancer Epidemiol* 2014; **38**: 741–7.
10. Rehm J, Mathers C, Popova S, Thazorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223–33.
11. Schütte K, Bornschein J, Kahl S, *et al.* Delayed diagnosis of HCC with chronic alcoholic liver disease. *Liver Cancer* 2012; **1**: 257–66.
12. Reddy SK, Steel JL, Chen HW, *et al.* Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology* 2012; **55**: 1809–19.
13. Lee SS, Jeong SH, Byoun YS, *et al.* Clinical features and outcome of cryptogenic hepatocellular carcinoma compared to those of viral and alcoholic hepatocellular carcinoma. *BMC Cancer* 2013; **13**: 335.
14. Tateishi R, Okanoue T, Fujiwara N, *et al.* Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. *J Gastroenterol* 2015; **50**: 350–60.
15. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646–9.
16. Kamath PS, Wiesner RH, Malinchoc M, *et al.* A model to predict survival in

patients with end-stage liver disease. *Hepatology* 2001; **33**: 464–70.
17. Bruix J, Sherman M, Llovet JM, *et al.*; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421–30.
18. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208–36.
19. Vauthey JN, Lauwers GY, Esnaola NF, *et al.* Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 2002; **20**: 1527–36.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.
21. Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.
22. Cucchetti A, Trevisani F, Pecorelli A, *et al.* Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. *J Hepatol* 2014; **61**: 333–41. doi:10.1016/j.jhep.2014.03.037
23. Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures from mass screening programmes. *Biometrics* 1984; **40**: 1–14.
24. Duffy SW. *Screening, Sojourn Time. Encyclopedia of Biostatistics*. Hoboken: John Wiley & Sons, Ltd., 2005. http://dx.doi.org/10.1002/0470011815.b2a04052
25. Furlan A, Marin D, Agnello F, *et al.* Hepatocellular carcinoma presenting at contrast-enhanced multi-detectorrow computed tomography or gadolinium-enhanced magnetic resonance imaging as a small (≤ 2 cm), indeterminate nodule: growth rate and optimal interval time for imaging follow-up. *J Comput Assist Tomogr* 2012; **36**: 20–5.
26. Kubota K, Ina H, Okada Y, Irie T. Growth rate of primary single hepatocellular carcinoma: determining optimal screening interval with contrast enhanced computed tomography. *Dig Dis Sci* 2003; **48**: 581–6.
27. Duffy SW, Nagtegaal ID, Wallis M, *et al.* Correcting for lead-time and length bias in estimating the effect of screen detection on cancer survival. *Am J Epidemiol* 2008; **168**: 98–104.
28. Prevost TC, Launoy G, Duffy SW, Chen HH. Estimating sensitivity and sojourn time in screening for colorectal cancer: a comparison of statistical approaches. *Am J Epidemiol* 1998; **148**: 609–19.
29. Mazzaferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–9.
30. Wagoner KG, Blocker J, McCoy TP, Sutfin EL, Champion H, Wolfson M. Free alcohol use and consequences: gender differences among undergraduates. *Am J Health Behav* 2012; **36**: 446–58.
31. Trevisani F, Magini G, Santi V, *et al.* Impact of etiology of cirrhosis on the survival of patients diagnosed with hepatocellular carcinoma during surveillance. *Am J Gastroenterol* 2007; **102**: 1022–31.
32. Toshikuni N, Izumi A, Nishino K, *et al.* Comparison of outcomes between patients with alcoholic cirrhosis and those with hepatitis C virus-related cirrhosis. *J Gastroenterol Hepatol* 2009; **24**: 1276–83.
33. Raynard B, Balian A, Fallik D, *et al.* Risk factors of fibrosis in alcohol-induced liver disease. *Hepatology* 2002; **35**: 635–8.
34. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. *Am J Med* 2007; **120**: 829–34.
35. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol* 2005; **42**: 218–24.
36. N'Kontchou G, Paries J, Htar MT, *et al.* Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. *Clin Gastroenterol Hepatol* 2006; **4**: 1062–8.
37. Trichopoulos D, Bamia C, Lagiou P, *et al.* Hepatocellular carcinoma risk factors and disease burden in a European cohort: a nested case-control study. *J Natl Cancer Inst* 2011; **103**: 1686–95.
38. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology* 2010; **52**: 132–41.
39. Llovet JM, Ricci S, Mazzaferro V, *et al.* SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378–90.
40. Iavarone M, Cabibbo G, Piscaglia F, *et al.* SOFIA (SOraFenib Italian Assessment) study group. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011; **54**: 2055–63.
41. Ganten TM. Final analysis of overall survival per subgroups of HCC patients in the prospective, non-interventional INSIGHT study treated with sorafenib. *Ann Oncol* 2014; **25**: iv210–53. doi:10.1093/annonc/mdu334.113
42. Hsu CY, Lee YH, Hsia CY, *et al.* Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system. *Hepatology* 2013; **57**: 112–9.
43. Bolondi L, Cillo U, Colombo M, *et al.*; Italian Association for the Study of the Liver (AISF). Position paper of the Italian Association for the Study of the Liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma. *Dig Liver Dis* 2013; **45**: 712–23.
44. Trevisani F, D'Intino PE, Morselli-Labate AM, *et al.* Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol* 2001; **34**: 570–5.
45. Marrero JA, Su GL, Wei W, *et al.* Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in American patients. *Hepatology* 2003; **37**: 1114–21.
46. Giannini EG, Sammito G, Farinati F, *et al.* Determinants of alpha-fetoprotein levels in patients with hepatocellular carcinoma: implications for its clinical use. *Cancer* 2014; **120**: 2150–7.
47. Gopal P, Yopp AC, Waljee AK, *et al.* Factors that affect accuracy of α-fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2014; **12**: 870–7.
48. Younossi ZM, Kanwal F, Saab S, *et al.* The impact of hepatitis C burden: an evidence-based approach. *Aliment Pharmacol Ther* 2014; **39**: 518–31.
49. Cucchetti A, Piscaglia F, Caturelli E, *et al.* Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. *Ann Surg Oncol* 2009; **16**: 413–22.
50. Singal AK, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2010; **32**: 851–8.

APPENDIX: OTHER MEMBERS OF THE ITA.LI.CA GROUP

Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum – Università di Bologna: Luigi Bolondi, Maurizio Biselli, Paolo Caraceni, Alessandro Cucchetti, Marco Domenicali, Annagiulia Gramenzi, Donatella Magalotti, Anna Pecorelli, Carla Serra, Laura Venerandi; Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova: Alessia Gazzola, Francesca Murer, Caterina Pozzan, Veronica Vanin; Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia: Paolo Del Poggio, Stefano Olmi; Unità Operativa di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia: Claudia Balsamo, Elena Vavassori; Dipartimento di Medicina Clinica e Sperimentale, Università di Padova: Luisa Benvegnù; Dipartimento di Malattie Apparato Digerente e Medicina Interna, Azienda ospedaliero-universitaria di Bologna, Unità Operativa di Radiologia: Alberta Capelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli; Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma: Giulia Bosco; Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo: Paola Roselli; Unità Operativa di Medicina Protetta, Ospedale Belcolle, Viterbo: Serena Dell'Isola, Anna Maria Ialungo, Elena Rastrelli; Dipartimento di Medicina Interna, Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova: Alessandro Moscatelli, Gaia Pelagatta, Antonino Picciotto, Vincenzo Savarino; Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Gastroenterologia, Università di Palermo: Maria Rosa Barcellona, Calogero Cammà, Giuseppe Cabibbo, Andrea Costantino; Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna 2, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo: Roberto Virdone; Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano: Andrea Mega; Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma: Emanuele Rinninella; Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa: Valeria Mismas; Dipartimento di Medicina Interna; Ospedale per gli Infermi di Faenza, Faenza: Anna Chiara Dall'Aglio, Valentina Feletti, Arianna Lanzi, Federica Mirici Cappa, Elga Neri, Giuseppe Francesco Stefanini, Stefano Tamberi; Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma: Elisabetta Biasini, Emanuela Porro; Dipartimento di Medicina Clinica e Chirurgia, Unità di Gastroenterologia, Università di Napoli "Federico II", Napoli: Maria Guarino; Clinica di Gastroenterologia, Università Politecnica delle Marche, Ancona: Gianluca Svegliati Baroni, Laura Schiadà; Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar: Maria Chiaramonte, Fabiana Marchetti, Matteo Valerio.