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Role of aetiology, diabetes, tobacco smoking and hypertension in hepatocellular carcinoma survival

Elena Raffetti[a,*], Nazario Portolani[b], Sarah Molfino[b], Gian Luca Baiocchi[b], Rosa Maria Limina[a], Giovanni Caccamo[a], Rossella Lamera[a], Francesco Donato[a], for the Brescia HCC Study Group

[a] Unit of Hygiene, Epidemiology and Public Health, Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy
[b] Surgical Clinic, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

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ABSTRACT

Background: Aim of this study was to investigate the role of aetiology, diabetes, tobacco smoking and hypertension in the survival of patients with hepatocellular carcinoma.
Methods: A prospective cohort of 552 patients (81.5% males, mean age 64.4 years) first diagnosed with hepatocellular carcinoma in 1995–2001 in Brescia, Italy, was retrospectively analyzed. Data on the presence of diabetes mellitus, hypertension, heavy alcohol intake and tobacco smoking were obtained from patients' clinical charts or interviews. Survival analysis was performed using univariate and multivariate methods (Cox proportional hazards model).
Results: 33% had a history of heavy alcohol intake, 24.3% had viral hepatitis and 33.5% had both aetiologies. Diabetes, hypertension and tobacco smoking were found in 29.9%, 37.9% and 35.9%, respectively. During follow-up (median 19.9 months), the median survival was 19.9 (95% confidence interval [CI] 16.7–22.8) months. Using multivariate Cox regression models, alcohol-related liver disease and diabetes were found to be associated with mortality, with hazard ratios of 1.32 (95% CI 0.99–1.75) and 1.25 (95% CI 1.02–1.54), respectively. Hypertension and smoking habit did not influence survival.
Conclusions: Alcohol aetiology and the presence of diabetes were positively associated with patient mortality with hepatocellular carcinoma, whereas tobacco smoking and hypertension were not.

1. Introduction

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is the fifth most common cancer in men worldwide [1]. Although the treatment of liver cancer has greatly improved in recent years, the survival rate remains extremely poor. The 5-year survival rate has increased from 2% to almost 12% according to the US Surveillance, Epidemiology, and End Results (SEER) Program [1], and from 8.6% in 1995–1999 to 11.7% in 2000–2007 according to the European Cancer Registry Based Study on Survival and Care of Cancer Patients [2].

Hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol intake are the main global causes of HCC, particularly in southern Europe [1,3,4]. The role of these factors in clinical presentation at diagnosis and survival after therapy has been widely investigated, but conflicting results have been reported so far [5–10].

The role of metabolic factors, such as obesity, diabetes mellitus (DM) and metabolic syndrome, in both HCC occurrence and progression has been increasingly studied worldwide in the past decade [11]. Two recent meta-analyses suggested that pre-existing DM moderately increases the mortality of patients with HCC, with a summary relative risk of 1.3–1.4 [12,13]. However, DM is often associated with other causes of death in these patients, thus requiring a competing-risk analysis to understand its specific role in mortality. Of interest, the impact of DM on overall mortality may also be computed as an attributable risk of death. However, these aspects have not yet been investigated. The effect of DM treatment on the survival of cancer patients has also been debated, as some studies [13] have reported a negative effect of insulin use on survival.

* Corresponding author at: Unit of Hygiene, Epidemiology and Public Health, Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, Viale Europa 11, 25123 Brescia, Italy.
Tel.: +39 030 3717689; fax: +39 030 3717688.
E-mail address: e.raffetti@unibs.it (E. Raffetti).

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Tobacco smoking has been recognized as a risk factor for various cancers, including HCC [14]; further, two recent investigations [15,16] found an association between continued smoking after diagnosis and worse prognosis for HCC.

Lastly, hypertension has been investigated as a possible independent predictor of HCC survival [17], although more conclusive data are required.

The aim of this study was to investigate the association of HCC aetiology, DM, tobacco smoking and hypertension with the severity of liver disease and/or tumour characteristics at HCC diagnosis and their role as independent predictors of the long-term survival of these patients using both non-competitive and competitive risk survival models.

2. Patients and methods

The study prospectively enrolled 552 patients admitted to the two main hospitals in the province of Brescia, Italy, first diagnosed with HCC in 1995–2001, who were below the age of 80, born in Italy, residing in the area, capable of signing an informed consent form and providing valid answers to the interview. Immigrants were excluded because they constituted <5% of the total Italian population with possibly different aetiologies of HCC, particularly aflatoxin exposure, from native-born individuals.

The enrolled patients had also participated in a case–control study on HCC aetiology [3] and some of them in a previous study on HCC survival [9].

Of the patients with HCC, 81% were diagnosed by histology or cytology, 14% by alpha-fetoprotein levels >500 ng/dl and liver lesions observed on sonography or computerized tomography and 5% by imaging tests.

All the clinical and pathologic data were extracted from clinical records. The following tumour characteristics were evaluated: nodule diameter (<2, 2–5 cm and >5 cm), TNM classification [18], tumour morphology (single or multiple nodules), grading, portal vein invasion and treatment. Both HCC and underlying liver disease characteristics were evaluated with Cancer of the Liver Italian Program (CLIP) score, which considers the Child–Pugh stage, tumour morphology and extension, portal vein invasion and alpha fetoprotein serum levels [19,20]. Hypertension and DM were defined based on clinical diagnosis in medical records.

HCC treatments were surgery, including transplantation, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and transarterial chemoembolization (TACE).

Patients with HCC were directly interviewed using a standardized questionnaire including history of alcohol intake. A threshold of 60 and 40 g/day of ethanol was used for men and women, respectively, for at least one decade, to consider past alcohol intake as a possible cause of the underlying liver disease (heavy alcohol intake) [1]. Sera were collected and frozen at −80 °C until tested for hepatitis B surface antigen (HBsAg) and anti-HCV antibodies. Anti-HCV-positive sera were further tested for HCV RNA. Haemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis and other possible causes of liver disease were attributed based on clinical records. The methods used to investigate HCC aetiology have been explained in detail in previous reports of our case–control study [3].

Based on current and past tobacco smoking as assessed in the patient interview, subjects were classified as 'smokers' if they usually smoked at least one cigarette a day, and as 'former smokers' if they had stopped smoking at least one year earlier.

The patients were interviewed and blood samples collected at inclusion.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was approved by the local ethics committee. Written informed consent was obtained from all enrolled patients.

2.1. Statistical analysis

The differences in demographic, aetiological, clinical and pathological features were determined using common statistical methods for mean and proportion comparisons. Survival was calculated from the date of HCC diagnosis to the end of follow-up, namely 31 December 2012. Municipality registers were consulted for data on the vital status at the end of follow-up and the causes of death for all subjects. The causes of death were coded according to the International Classification of Diseases (ICD), 9th revision, and the ICD, 10th revision [21].

The relative survival was estimated using the Ederer II method [22] from Italian life tables of all-cause mortality by age, gender and calendar year [23].

The Kaplan–Meier method was used to model the cumulative survival curves. The association between each variable and patient survival was tested by univariate analysis (log-rank test). In addition, the same variables were tested by multivariate analysis using Cox proportional hazards models. Variables for fitting the most parsimonious model were selected using a backward procedure, with a p-value = 0.05 for retaining each variable in the model; age and gender were retained in the models as possible confounders, regardless of their statistical significance. No major departures from the proportional hazard assumption were detected during graphical checking.

A competing-risk regression [24] with non-liver-related mortality as a competing event was used. To reduce the impact of some missing data on cause of death, competing-risk regression models were adjusted by stabilized inverse probability weights [25], considering the data to be missing at random.

Lastly, various sensitivity analyses were conducted. In particular, the consistency of the effect of DM in subjects undergoing treatment, those with hepatitis virus aetiology or alcohol aetiology and those with normal renal function (serum creatinine 0.4–1.2 mg/dl) was assessed.

The 'adjusted' mortality-attributable risk percentage (AR%) was calculated to evaluate the number and proportion of deaths from DM and HCC aetiology. AR% assesses the impact of an 'exposure' by measuring its contribution to the total 'incidence' under exposure [26]. In the present study, 'exposure' was defined as the presence of DM or alcohol aetiology, and the outcome ('incidence') was mortality (Supplementary Fig. S1). The population-attributable risk percentage (PAR%) is the reduction in incidence that would be achieved if the entire population was not exposed, compared with its current exposure pattern [26] (Supplementary Fig. S1). In this study, mortality PAR% indicates the excess of deaths in HCC from DM or alcohol aetiology. AR% was computed using the following formula: $AR\% = ((\text{relative risk (RR)} - 1)/RR) \times 100$, where RR is the mortality hazard ratio (HR) for DM or alcohol aetiology from a multivariate Cox proportional model [26]. PAR% was calculated using Miettinen's formula: $PAR\% = p \times ((RR - 1)/RR) \times 100$ [27], where p is the proportion of subjects with DM or alcohol aetiology among all those who died and RR is the mortality HR for DM or alcohol aetiology obtained from the adjusted Cox proportional model [26].

All performed tests were two-sided with a p-value of 0.05 to reject the null hypothesis. All the analyses were computed using the Stata 12.0 statistical package (Stata Corporation, College Station, TX, USA).