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IMPACT OF TYPE 2 DIABETES ON HCC APPEARANCE IN PATIENTS TREATED WITH DIRECT ACTING ANTIVIRALS

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Abstract – *Objective:* *Diabetes mellitus is closely associated with chronic HCV infection, which contributes to the 25% of the global hepatocellular carcinoma (HCC) cases. The aim of this study was the assessment of diabetes impact on HCC occurrence in HCV patients treated with Direct Acting Antivirals (DAAs).*

Patients and Methods: *According to Italian ministerial guidelines for DAAs treatment, 208 HCV patients treated with DAAs were enrolled. Abdominal ultrasound was performed before starting antiviral therapy and, thereafter, repeated every six months. HCC and diabetes diagnosis were performed according to the international guidelines. Liver stiffness measurement and all laboratory tests were performed before the treatment.*

Results: *HCC was diagnosed in 31 patients with chronic HCV infection under DAAs interferon-free therapy. The prevalence of diabetes was 32.3%. At the univariate analysis, HCC development was associated with older age (p=0.0007), sex (p<0.0001), liver stiffness (median 35.8 vs. 20.6 kPa; p<0.0001), smoke (p=0.010), metabolic syndrome (p<0.0001), bright liver (p=0.007) and number of focal lesions (p<0.0001). At the multivariate analysis, age (p=0.045), liver stiffness (p=0.007), platelet (p=0.002) count and Child-Pugh B score (p=0.048) at baseline revealed as independent predictors of HCC development. The Kaplan Meier analysis showed a statistically significant difference in terms of HCC cumulative risk based on diabetes mellitus duration, stratified according to metabolic syndrome presence/absence (log-rank p=0.002).*

Conclusions: *Diabetes and MS are two important risk factors associated with cancer. Even in cirrhotic patients who have obtained the viral clearance, a careful ultrasound monitoring is mandatory, especially in inveterate cirrhosis.*

KEYWORDS: *HCC, Diabetes, Direct Acting Antiviral, HCV, Cirrhosis.*

INTRODUCTION

A growing body of evidence suggests that diabetes may be related to an increased risk of cancer. According to the World Health Organization (WHO), cancer represents the second leading cause *of death* worldwide, and diabetes has an estimated global prevalence of approximately the 9%[1-3]. It remains still unclear whether such an association is due either to linking risk factors (e.g. ageing, gender, obesity, physical activity, diet, alcohol and smoking), or to the activity of metabolic disorders typical of diabetes on carcinogenesis (e.g., hyperglycaemia, insulin resistance, hyperinsulinemia).

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Hyperinsulinemia plays a direct role on the activation, survival and mitogenesis of neoplastic cells. Likewise, hyperinsulinemia may increase insulin-like growth factor 1 (IGF-1), which presents stronger mitogenic and anti-apoptotic activities than insulin[4].

Hyperglycaemia may also establish some carcinogenic potential[5], not only by increasing haemoglobin glycosylation, but also providing the metabolic requirements for cell proliferation.

The relative risk conveyed by diabetes is higher (about 2 folds) for liver, pancreas and endometrium cancer, and lower (1.2-1.5 folds) for colon, rectum, breast and bladder cancer[6].

Hepatocellular carcinoma (HCC) incidence is two to three times higher among patients with diabetes mellitus[7-9]. This association is best shown by the presence of other risk factors such as HBV, HCV, or alcoholic cirrhosis[10]. More specifically, DM is closely associated with chronic HCV infection, which contributes to the 25% of the global HCC cases [11,12]. The recent introduction of oral regimens based on direct antiviral agents (DAA) for hepatitis C treatment has improved SVR rates over the 90%, with excellent side effect profiles even in difficult-to-treat population[13].

The main goal of viral clearance is to prevent the disease progression as well as to decrease the risk of chronic HCV, end-stage liver diseases, HCC development and death. This expectation has been rejected by several European studies[14-18], which displayed high-rates of HCC occurrence and recurrence in DAA treated patients who achieved SVR.

The possible explanation proposed by researchers for such a high recurrence rate is the low level of immune surveillance and the down regulation of the interferon genes after the HCV viral load decrease. Therefore, DAA therapy may lead to an increased cell proliferation without checkpoints, hence promoting carcinogenesis[19,20]. Nevertheless, this is just a hypothesis, not supported by randomized controlled trials. On the other side, several studies have disproved the link between DAA therapy and HCC[21-23]. In these study, researchers believe that this association may reflect a selection bias, as recurrent HCCs were simply those previously undetectable, become detectable only after the beginning of DAA therapy.

Moreover, DAA treatments are performed in a wider scenario of patients, including those with advanced cirrhosis, at a highest risk of HCC.

Finally, the question of a possible increase of HCC after DAAs therapy remains still unsolved; hence, further preclinical studies are required. The aim of this study was the assessment of diabetes impact on HCC occurrence in patients with chronic hepatitis C who underwent DAAs treatment.

PATIENTS AND METHODS

Patients

Two hundred and eighty HCV patients were enrolled in two Italian specialized Centers, and followed from April 2015 to June 2016.

HCV-RNA was assessed by Real-time PCR at the beginning as well as at the end of treatment. The technical platform for HCV-RNA detection was based on dual labeled fluorescent probe. The test was performed in accordance with the CE-IVD policy following the manufacturers, by using Real-time PCR with a limit of detection of 15 IU/mL.

The choice of a regimen with DAA (12/24 weeks) was made according to genotype and stage of the liver disease, in agreement with the National Registry of the Italian Medicines Agency Committee (AIFA)[24]. Approved criteria included: patients with Child-Turcotte-Pugh (CTP) class A or B liver cirrhosis without a previous HCC history or with a HCC history with complete radiologic response (after either surgical resection or loco-regional ablation), and patients with a METAVIR F3 fibrosis score result > 12 kPa assessed by liver histology or transient elastography by Fibroscan® (Echosens, Paris, France). The absence of HCV RNA at 12 weeks after the end of therapy was considered as SVR. HCC diagnosis was based on the International guidelines[25]. Patients with no previous HCC history performed an ultrasound screening. Abdominal ultrasonography was performed within ten days before the beginning of DAA therapy; moreover, patients who had previously received curative treatment for HCC also underwent a dynamic and multiphase contrast-enhanced computed tomography (CT).

Patients with uncharacterized nodules (radiographically detectable lesions) as well as patients with HBV and/or HIV co-infection, and patients HCV positive after liver transplant, were excluded.

Antiviral regimens containing interferon were not taken into consideration. An abdominal ultrasound was performed after treatment as well as every six months later, during the follow-up. In the case of appearance of a liver lesion, a CT scan or MRI examination was also performed.

Biochemistry, body mass index (BMI), liver stiffness, presence of co-morbidity and any complications related to cirrhosis were also evaluated.

Diabetes diagnosis shall meet the following criteria of American Diabetes Association (ADA)[26]: glycated hemoglobin test (HbA1c) $\geq$ 6.5%, test performed in a laboratory using a National Glyco-hemoglobin Standardization Program (NGSP) certified method and standardized to the Diabetes Control and Complications Trial (DCCT) assay, or fasting plasma glucose (FPG) $\geq$ 126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for at least 8 h or, in patients showing the classic symp-

toms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL); 11.1 mmol/L or 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The OGTT test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Statistical Analysis

Data are shown as either median and range, in the case of continuous variables or number and percentage, for categorical variables. Differences between groups have been analyzed by Fisher's exact test or x^2-test for categorical variables. Mann-Whitney U test or Kruskal-Wallis test has instead been performed to compare continuous variables. As multivariate analysis, a logistic regression with the stepwise Wald statistic input and a survival analysis were performed. In particular, a Cox regression model was based on diabetes duration and a Kaplan-Meier analysis, to evaluate HCC cumulative risk according to metabolic syndrome presence/absence. *p*-values < 0.05 were considered statistically significant. All analyses were performed with the SPSS software (IBM, Armonk, NY, USA), version 25.

RESULTS

Two hundred sixty-four patients (n = 264) with LSM > 14 kPa completed the follow-up between April 2015 and June 2016. There were 142 men and 122 women, with an average age of 67 [IQR: 61 – 73]. Of these, 204 were cirrhotic (76.9%), whilst the remaining 60 patients had advanced fibrosis (23.1%). Population demographics are shown in Table 1.

Moreover, among the entire cohort of study, 31 patients of 264 with chronic HCV infection under DAAs interferon-free therapy, developed hepatocellular carcinoma (HCC). HCC development was associated with older age (p=0.0007), sex (p<0.0001), liver stiffness (median 35.8 *vs.* 20.6 kPa; p<0.0001), smoke (p=0.010), metabolic syndrome (p<0.0001), bright liver (p=0.007) and number of focal lesions (p<0.0001), as seen in Table 2. Additionally, platelets were significantly lower among patients with HCC both at baseline and SVR (p<0.0001 both). Finally, Child Pugh score revealed significantly higher (Class B) among HCC patients (16.1% *vs.* 4.3% in the control group; p<0.0001).

According to HCC, the presence metabolic syndrome was significantly more prevalent among HCC patients (19.4% *vs.* 3%; p=0.000), whilst diabetes, though more prevalent among HCC patients, did not reach the statistical significance (32.3% *vs.* 18%, p=0.061). BMI, instead, was slightly higher among patients without HCC (median 25 *vs.* 26; p =0.110) (Figures 1-3).

TABLE 1. Baseline characteristics of the entire cohort of study (n = 264).

Parameter	
Age (yrs), median [IQR]	67 [61 – 73]
Sex, n (%)	
Male	142 (53.8)
Female	122 (46.2)
BMI, median [IQR]	25.9 [23.9 – 28]
Smoke, n (%)	11 (4.2)
Potus, n (%)	5 (1.9)
Diabetes, n (%)	52 (19.7)
Metabolic syndrome, n (%)	13 (4.9)
Bright liver, n(%)	
0	140 (53)
1	119 (45.1)
2	5 (1.9)
Focal lesions, n (%)	
0	233 (88.3)
1	23 (8.7)
≥ 2	2 (3)
Liver stiffness (kPa), median [IQR]	21.3 [14 – 32.3]
Platelets, median [IQR]	
T0	120000 [82000 – 165000]
SVR	125000 [89000 – 172000]
Genotype, n (%)	
1	199 (77.2)
2	46 (17.8)
3	7 (2.7)
4	6 (2.3)
Child-Pugh Score, n (%)	
A	249 (94.3)
B	15 (5.7)

*Data are expressed ad either number and percentage or median and interquartile range (IQR).

At the multivariate analysis, conducted through a Wald stepwise logistic regression analysis, age, liver stiffness, Child Pugh B and platelet count at baseline, revealed as independent predictors of HCC development. Data are shown in Table 2.

A Cox Regression Model was also performed, based on diabetes duration, which did not find any statistically significant result (data not shown), whilst a Kaplan Meier analysis showed a statistically significant difference in terms of HCC cumulative risk based on diabetes mellitus duration, stratified according to metabolic syndrome presence/absence (log-rank p=0.002) (Figure 4).

DISCUSSION

The achievement of a high rate of SVR represents the fundamental goal of antiviral therapy, as it allows the necro-inflammatory activity and the progression of fibrosis to be switched off. Unfortunately, the cirrhotic stage does not denote, above all in

TABLE 2. Baseline Characteristics of the cohort of study according to HCC Development: univariate and multivariate analysis (n = 264).

	Univariate Analysis			*Multivariate Analysis*	
Parameter	***Yes (n = 31)***	***No (n = 233)***	***p***	***O.R. [95% C.I.]***	***p***
Age (yrs), median [IQR]	70 [66 – 77]	67 [60.5 – 72]	0.007	1.071 [1.001 – 1.146]	0.045
Sex, n (%)			<0.0001		
Male	14 (45.2)	17 (54.8)			
Female	194 (83.3)	39 (16.7)			
BMI, median [IQR]	25 [22.2 – 27]	26 [24 – 28]	0.110		
Smoke, n (%)	4 (12.9)	7 (3)	0.010		
Potus, n (%)	1 (3.2)	4 (1.7)	0.563		
Diabetes, n (%)	10 (32.3)	42 (18)	0.061		
Metabolic syndrome, n (%)	6 (19.4)	7 (3)	0.000		
Duration of therapy, months, median [IQR]	24 [12 – 24]	12 [12 – 12]	<0.0001		
Liver stiffness (kPa), median [IQR]	35.8 [22 – 45]	20.6 [13.8 – 28]	<0.0001 0.007	0.728 [0.906 – 1.154]	0.007
Bright liver, n(%)					
0	24 (77.4)	118 (50.6)			
1	7 (22.6)	111 (47.6)			
2	–	4 (1.7)			
Focal lesions, n(%)			<0.0001		
0	–	233 (100)			
1	23 (74.2)	–			
≥2	8 (25.8)	–			
Platelets, median [IQR]					
T0	81000 [50000 – 108000]	133000 [87850 – 170750]	<0.0001	1.000 [1.006 – 1.166]	0.002
SVR	97500 [67750 – 122000]	134500 [90000 – 185000]	<0.0001		
Genotype, n (%)			0.975		
1	20 (74.1)	179 (76.8)			
2	5 (18.5)	41 (17.6)			
3	1 (3.7)	6 (2.6)			
4	1 (3.7)	5 (2.1)			
Child Pugh Score, n (%)			0.000	0.268 [0.073 – 0.986]	0.048
A	26 (83.9)	223 (95.7)			
B	5 (16.1)	10 (4.3)			

*Data are expressed ad either number and percentage or median and interquartile range (IQR).

the inveterate phases, a reversible condition[27]. These assumptions are at the basis of the double effect of DAAs: a) HCV clearance with very high SVR rates and b) reduction but not absence of complications.

The appearance of HCC in patients with SVR is one of the most striking evidence sporadically emerged. Several studies[18,19,21,22,28-31] have evaluated HCC risk factors, among which diabetes and metabolic factors were found.

The biological association between DM and HCC in HCV chronic infection may be related to several factors. Many studies[3-6] have demonstrated the role of the insulin resistance (IR) and chronic hyperglycemia in carcinogenesis both in the liver and in other tissues. In particular, the increase of insulin-like growth factor-1 (IGF-1), the oxidative stress and cellular damage, are considered the main mechanisms, which could affect both cancer incidence and prognosis.

In our study, the prevalence of diabetes in patients with HCC appeared after DAA therapy was 32% *vs.* 18% (p=0.061), at the limit of statistical significance. These data apparently do not confirm the significant increase of HCC risk among diabetic patients emerged from other studies. However, this lack of a statistically significant association is more likely due to our too small sample size. In our population, the metabolic syndrome (MS) revealed statistically significant at univariate analysis.

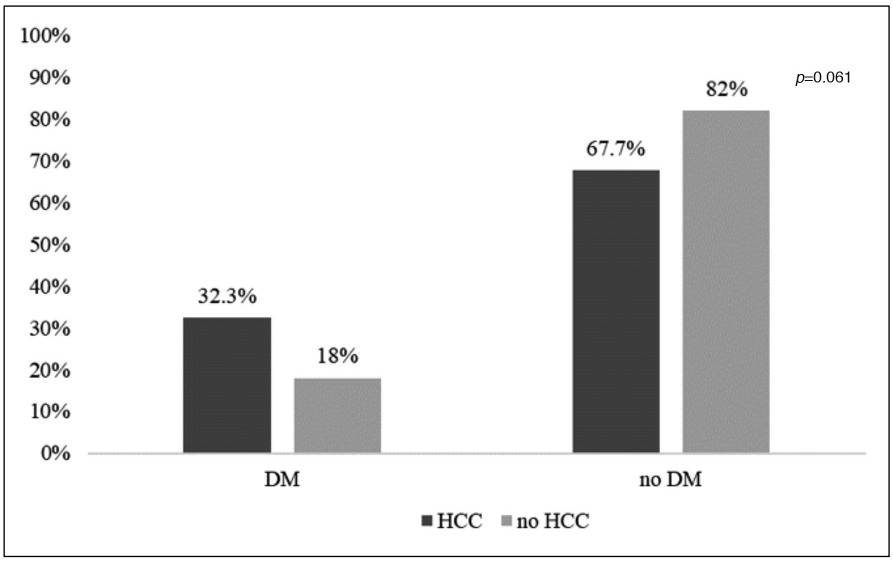

Fig. 1. Diabetes Mellitus (DM) prevalence according to the presence or absence of HCC.

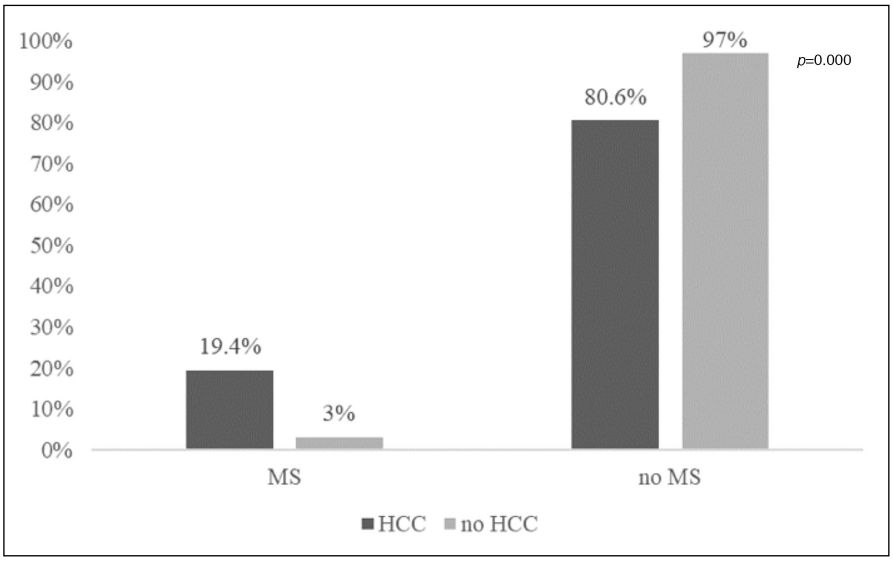

Fig. 2. Metabolic Syndrome (MS) prevalence according to the presence or absence of HCC.

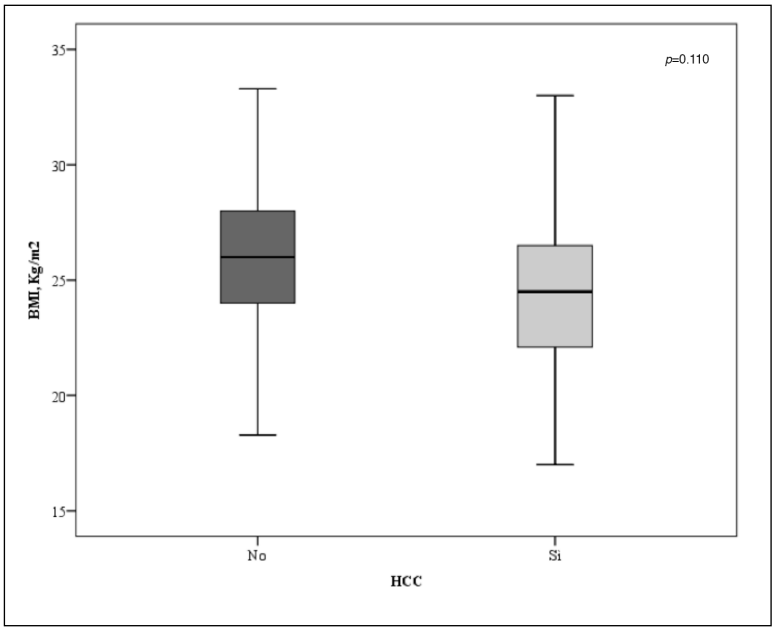

Fig. 3. Box plot showing Body Mass Index changes according to the presence or absence of HCC.

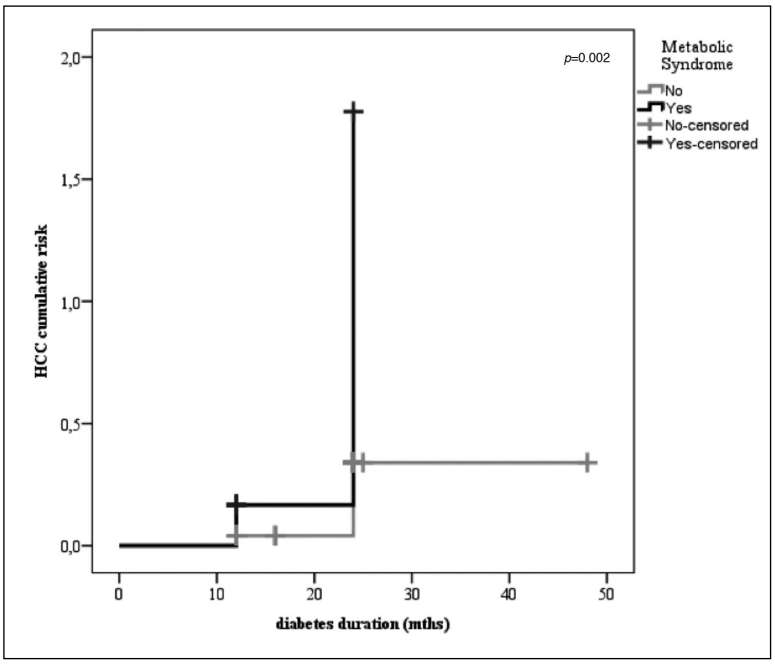

Fig. 4. HCC cumulative risk based on diabetes mellitus duration, stratified according to metabolic syndrome presence/absence (Kaplan-Meyer analysis).

MS represents an important link between hepatic disease and the cardiovascular system; one of the main pathogenetic aspects of this correlation is exemplified by the alteration of the glucose metabolism supported by IR.

Non-alcoholic steatohepatitis (NAFLD) is considered as the hepatic expression of MS and its evolution in non-alcoholic steatohepatitis (NASH) with development of fibrosis, is associated with the risk of HCC even in non-cirrhotic liver[32,33]. Even the bright liver showed a statistical significance at the univariate analysis. Bright liver is an echographic parameter strongly correlated to the presence of fatty liver and represents a useful screening factor both in overweight and lean people.

Multivariate analysis did not confirm MS as an independent risk factor suggesting the need of a synergy between metabolic and hepatic factors to trigger an increased risk of HCC. MS, in fact, plays a role in increasing the risk of HCC onset, as demonstrated by the Kaplan-Meyer analysis, conducted according to the duration of diabetes. These data were confirmed by a recent large cohort study[34]. The Cox proportional hazard model, instead, did not find any risk factor independently associated with our outcome, most likely due to the time covariate, the duration of diabetes, which was uniformly distributed in our population. We did not evaluate the impact of either hypoglycemic or insulin therapy due to the poor influence shown in a similar study[29].

The covariates independently associated with the presence of HCC are those related to advanced liver disease. Thrombocytopenia, Child-Pugh B and high liver stiffness are usually the typical expression of inveterate cirrhosis, as they measure the main hepatic function indices and the fibrosis related liver and portal hypertension status, respectively[35,36]. The well-known correlation to HCC of metabolic, nutritional[37,38], fibrotic factors, can be explained by the increased cellular exposure to the chronic inflammatory stimulus and the activity of the HCV virus on the immune system.

CONCLUSIONS

Finally, diabetes and MS are two important risk factors associated with cancer. HCV virus and NASH properties are IR-related and associated with diabetes and MS. Even in cirrhotic patients who have obtained the viral clearance, a careful ultrasound monitoring is, therefore mandatory, especially in inveterate cirrhosis or in the case of concomitant comorbidities (e.g., diabetes, MS or NAFLD).

Conflict of interests:
All authors declare that they have no conflict of interests.

Ethical Committee:
The study was conducted according to the Institutional requirements and Helsinki Declaration.

Funding:
This is spontaneous and non-sponsored study.

Ethical Statement:
The data presented in this document are the results of our clinical practice: when the patients were enrolled to the antiviral therapy, signed an informed consent on the use of data relating to the treatment.

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