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Risk of hepatocellular carcinoma development in long-term nucles(t)ide analog suppressed patients with chronic hepatitis B

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Abstract

Aim: In long-term nucleos(t)ide analog (NA) suppressed patients with chronic hepatitis B (CHB), hepatocellular carcinoma (HCC) can still develop. Few data exist on the incidence and the predictors of HCC development beyond the first five years in long-term treated patients. To assess the prevalence, incidence, and risk factors for HCC development in a real-life cohort of successfully NA-treated CHB patients for more than five years.

Methods: All CHB patients under NAs for ≥ 60 months with stable virologic response were enrolled. HCC surveillance was carried out using liver ultrasound and dosing of serum alpha-fetoprotein every year in patients with CHB and every six months in cirrhotic patients. The baseline PAGE-B score was calculated for each patient.

Results: 343 patients (76% male, 86% HBeAg-negative, 30% cirrhotic) were enrolled. During a median (IQR) follow-up of 144 (105-182) months, 21 patients (6%) developed HCC despite virologic suppression (incidence rate 40 cases/1000 person-years follow-up). In multivariate analysis, higher PAGE B score [adjusted Hazard Ratio, aHR 1.26 (95%CI: 1.13-1.54), P = .022] and cirrhosis [aHR 9.71 (95%CI: 2.02-46.48), P = .005] were predictors of HCC development. PAGE B score showed a significant association with HCC (R^2 0.225, P < .001) and good prognostic capacity (AUC 0.863) of HCC.

Conclusions: Our results confirm that in successfully NA-treated CHB patients, sustained viral replication suppression does not abolish the risk of HCC. The PAGE-B score could be a useful tool for identifying high-risk subjects.

Keywords: Chronic hepatitis B, nucleos(t)ide analogs, hepatocellular carcinoma, PAGE-B score, entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide

INTRODUCTION

Worldwide hepatocellular carcinoma (HCC) remains a leading cause of morbidity and mortality in patients with chronic hepatitis B (CHB), despite the availability of safe and effective therapies, with an estimated 350,000 deaths per year[1,2]. Currently, due to their high potency and barrier to resistance development, Entecavir (ETV), Tenofovir dispoproxil fumarate (TDF), and Tenofovir alafenamide (TAF) are the third-generation nucleos(t)ide analogs (NAs) recommended as first-line monotherapy by all international guidelines for treating CHB[3-5]. These drugs achieve sustained on-treatment viral suppression in more than 95% of patients, resulting in several clinical benefits such as prevention of cirrhosis and liver decompensation, improvement of liver histology, and often reversion of histologic cirrhosis. However, HCC can still develop despite sustained virological response, and it is currently the major complication in the long-term management of CHB patients. Literature data show that in non-cirrhotic patients treated with ETV or TDF, annual HCC incidence ranges from 0% to 1.4% in Asian patients and from 0.1% to 1.0% in predominantly Caucasian populations. In cirrhotic patients treated with ETV or TDF, hepatocellular carcinoma rates are around 4 to 5 times higher, ranging from 0.9% to 5.4% in Asians and from 1.5% to 5.2% in Caucasians[6]. Limited data are available on the incidence and predictive factors of HCC development beyond the first 5 years of NA therapy. A multicenter European cohort study showed that the HCC risk decreased after 5 years of ETV/TDF therapy[7].

Current guidelines identify patients with cirrhosis as a high-risk group requiring close HCC surveillance. Regular abdominal ultrasonography (US), with or without the assay of serum alpha-fetoprotein (AFP) levels, is recommended for early diagnosis of HCC in order to improve the applicability of curative therapies and ultimately the patient's prognosis[8,9].

Sundry predictive factors have been associated with an increased risk of HCC appearance in patients with chronic hepatitis B. These include host factors (male sex, older age), virological factors (high serum HBV DNA levels, HBeAg/anti-HBe status, genotype C, pre-core and core promoter mutations), and disease status-related factors (serum alanine aminotransferase levels, presence of cirrhosis or advanced fibrosis, comorbidities as diabetes and overweight)[10-13].

Up to now, several HCC risk prediction scores, including different baseline parameters, have been elaborated to estimate the mild-long term risk prediction of HCC development in CHB patients[14,15]. In 2016, an HCC risk score (named PAGE-B score) was developed and validated by Papatheodoridis *et al.*[16]. This score, including only the baseline patient age, gender, and platelet levels, stands for a simple and trusty score predicting the 5-year HCC risk in Caucasian patients treated with ETV/TDF therapy. The authors showed that PAGE-B scores ≤ 9 imply no or minimal 5-year HCC risk, while PAGE-B scores ≥ 10 and particularly ≥ 18 indicate increased HCC risk requiring constant and careful surveillance. In particular, the cut-off point of 10 in the PAGE-B score offered 100% sensitivity and negative predictive value (NPV) for HCC prediction in both the derivation and validation datasets.

Our study aimed to assess the incidence and predictive risk factors of late HCC occurrence in a real-life cohort of CHB patients treated with NAs for at least 5 years and to verify the exactness of the PAGE B-risk score.

METHODS

Study population

This was a retrospective observational cohort study including 343 consecutive CHB patients undergoing antiviral treatment with NAs between 1996 and 2016 in three Italian Hospitals: 1. Clinic of Infectious Diseases, University of Foggia, Foggia 2. Infectious Diseases Unit, "F. Perinei" Hospital, Altamura 3. Clinic of Infectious Diseases, University of Bari, Bari.

In total, 403 CHB patients were starting antiviral therapy, and a diagnosis of cirrhosis was assessed in 133/403 patients (33%). During the first five years, 28/403 patients (6.95%) developed HCC, 32 patients were lost to follow up and the remaining 343 patients were enrolled in this study. Patients with Hepatitis D Virus (HDV) and Hepatitis C Virus (HCV) co-infections were also included. All patients were negative for HIV infection.

Alcohol use by men or women was categorized as none/mild if they declared a mean daily alcohol use of < 20 g or < 10 g, moderate if they declared a mean daily alcohol use of 20-60 g or 10-40 g, and abuse in case of daily alcohol use of > 60 g or > 40 g, respectively.

CHB patients with drug addiction were excluded from the study.

Study objectives and endpoints

Our study aimed to assess the prevalence and the incidence of HCC beyond 5 years of treatment in a cohort of virologically suppressed CHB patients long-term treated with NAs (≥ 60 months) and to identify predictive factors of HCC. All patients with HCC occurrence within the first 5 years of treatment were excluded.

The secondary objective of the study was to verify in our real-life cohort of CHB patients the predictive value of the PAGE B-risk score.

Follow-up of participants

At each Center, all patients were treated with NAs and followed up according to international clinical practice guidelines. Every 6-12 months, the patients underwent clinical examinations and routine laboratory tests. Serum HBV-DNA levels were determined every six months by polymerase chain reaction assays (sensitivity 12-13 IU/mL). Virological response was defined as undetectable HBV DNA during treatment.

Surveillance for HCC development was performed every six months in patients with liver cirrhosis or a family history of HCC and every 12 months in non-cirrhotic patients by abdominal ultrasonography and alpha-fetoprotein levels. The diagnosis of HCC was based on standard histological and/or compatible radiological findings. The follow-up was considered the time between study entry and the latest clinical-virological information available. The score PAGE-B was calculated for each patient at the start of therapy with NAs.

Statistical analysis

The prevalence of patients with HCC was calculated as the number of patients identified as the target population, divided by the total number of patients enrolled over the years 1996-2016.

The incidence of the target population was calculated as new cases divided by the total number of person-years follow-up (PYFU) in the study period. Follow-up will be calculated at the time of the last available visit.

Sociodemographic, clinical and virological features of the study population were collected and are presented in terms of the number of subjects, percentages of categorical variables and mean (± Standard Deviation, SD) or median (Inter Quartile Range, IQR) for continuous variables in accordance to their parametric of non-parametric distribution. The chi-square test and Kruskal-Wallis tests were used, as appropriate, to compare patients with HCC occurrence to the whole population with CHB.

Univariate and Multivariate Cox regression analysis was performed to calculate the effects of patient characteristics on the HCC occurrence in the target population during treatment with NAs.

A binomial logistic regression model was used to assess the predictive value of the PAGE B-risk score for developing HCC, by correlating the incidence of HCC with the PAGE-B values. Predictive measures were calculated and graphically expressed using a Receiver Operator Characteristic (ROC) curve.

A P-value < 0.05 was considered statistically significant. Analysis was performed using the Jamovi package 2.3.2.

RESULTS

Overall, 343 CHB patients consecutively treated with NAs for at least five years, predominantly males (76%), mean age (± SD) 48 (± 12) years, were enrolled in the study [Table 1].

A co-infection with other hepatitis viruses was present in 31 patients (9%), in particular, a co-infection with HDV and HCV was present in 21 and 6 patients, respectively; a triple infection HBV/HDV/HCV was present in 4 cases. At baseline before starting NA therapy, the severity of liver disease was classified according to findings from liver biopsies in 286/343 patients (83.4%). In these patients, histological data excluded not-HBV-related causes of liver damage. A diagnosis of cirrhosis (clinical or histological) was present in 105 patients (31%).

Alcohol use was reported as none/mild in 295/343 patients (86%). A history of previous drug addiction was reported only in 11/343 patients (3%). Most patients started therapy with LAM (197 patients, 57%). A family history of HCC was reported in 50 cases (14%).

Clinical outcomes

All patients were followed for a median (IQR) of 144 (105-182) months. During treatment, no patient with chronic hepatitis progressed to cirrhosis, and none of the patients with portal hypertension presented with bleeding esophageal varices. In our study, only one cirrhotic patient with HBV/HDV co-infection, despite the HBV virologic response to ETV, presented liver decompensation with ascites, liver failure, and hepatic encephalopathy requiring liver transplantation. Interestingly, Hepatitis B surface antigen loss was reported in 13 patients (3.8%) after a median period of 142 (101-216) months. These patients discontinued NA therapy after a period of 12 months, irrespective of anti-HBs seroconversion, and none of them showed HBV reactivation.

Table 1. Baseline features of the study population. Chi square test/Fisher exact test and parametric/non parametric ANOVA were used to compare variables of long-term nucleos(t)ide treated patients with and without HCC according to their distribution. A *P* < 0.05 was considered as statistically significant

Variables	Total (N = 343)	Patients without HCC (N = 322)	Patients with HCC (N = 21)	*P*-value
Age, years, mean (± SD)	48 (± 12)	48 (± 12)	54 (± 8)	**.004**
Male gender, *n* (%)	262 (76)	241 (74)	21 (100)	**.009**
Coinfections, *n* (%) - HBV/HDV - HBV/HDV/HCV - HBV/HCV	 21 (6.1) 4 (1.6) 6 (1.7)	 18 (5.6) 4 (1.2) 6 (1.8)	 3 (14) 0 (0) 0 (0)	 .45
Cirrhosis, *n* (%)	105 (31)	86 (27)	19 (90)	**< .001**
HBeAg negative, *n* (%)	295 (86)	276 (85)	19 (90)	.54
Alcohol use, *n* (%) - None/mild - Moderate - Abuse	 295 (86) 42 (12) 6 (2)	 276 (85.8) 40 (12.4) 6 (1.8)	 19 (90.5) 2 (9.5) 0	.54
Initial NA, *n* (%) - LAM - ETV - ADV + LAM - TDF - ADV	 197 (57) 117 (34) 10 (3) 7 (2.5) 11 (3)	 183 (57) 114 (35) 8 (2.5) 6 (2.5) 10 (3)	 14 (67) 3 (15) 2 (9) 1 (4.5) 1 (4.5)	.199
Duration of NA therapy, months, median (IQR)	144 (105-182)	144 (105-182)	151 (144-181)	.08
Rescue Therapy, *n* (%)	184 (54)	167 (51)	17 (80)	**.01**
Family history of HCC, *n* (%)	50 (14)	43 (13)	7 (33)	**.01**
PAGE-B score[15], median (IQR) - cut-off point of ≥ 18, *n* (%)	14 (10-18) 101 (30)	14 (10-18) 82 (24)	18 (18-21) 19 (6)	**< .001** **< .001**

N: Number; HBV: hepatitis B virus; HDV: hepatitis D virus; HCV: hepatitis C virus; NA: nucleos(t)ide analog; LAM: lamivudine; ETV: entecavir; ADV: adefovir; TDF: tenofovirdisoproxil fumarate; HCC: hepatocellular carcinoma; SD: standard deviation; IQR: inter quartile range.

Hepatocellular carcinoma was diagnosed in 21/343 (6%) patients, with an incidence rate of 40 x1000 PYFU. Notably, the prevalence of HCC diagnosis was significantly higher in subjects with liver cirrhosis (19/105 patients, 0.18%) than in those without liver cirrhosis (2/238 patients, 0.008%, $P < .001$). Similarly, while an incidence rate of 14 cases of HCC/1000 PYFU was noticed among subjects with cirrhosis, a remarkably lower rate was reported in individuals without cirrhosis (0.6 cases/1000PYFU).

All subjects with HCC were males, the mean age was 56 (± 6) years, and all except two were cirrhotic. In these two patients, the biohumoral data (liver function tests, serum albumin levels, platelets count) and instrumental procedures (Fibroscan and/or abdominal ultrasonography) excluded the presence of cirrhosis at the time of HCC development.

In particular, one patient had a family history of HCC as a risk factor for HCC development; the remaining CHB patient with obesity and metabolic syndrome had a liver biopsy showing severe nonalcoholic fatty liver disease.

Patients were virologically suppressed by a mean duration of therapy of 80 (± 46) months. At the time of diagnosis, HCC appeared already as multifocal lesions in 5 patients (24%), with portal vein thrombosis in 4

of them (27%). Serum alpha-fetoprotein levels were in the normal range in 13 subjects (62%). The main features of the 21 patients at the moment of HCC occurrence are reported in Table 2.

Overall, 11 patients with HCC died (52%). Of the remaining 10 individuals, two patients underwent liver transplantation, 7 patients, who were more than 65 years old at the time of diagnosis of HCC, underwent chemotherapy with sorafenib (1 patient), hepatic resection (1 patient), Transarterial Chemoembolization (TACE) (2 patients), Transarterial Radiofrequency Ablation (TARF) (2 patients). Three patients who were less than 65 years old underwent first-line therapy with TARF and are currently without HCC recurrence. One patient did not receive any treatment.

At multivariate analysis corrected for age, duration of nucleos(t)ide treatment, mean PAGE-B score, HCC family history, the presence of co-infections and liver cirrhosis, only higher PAGE B score [aHR 1.26 (95%CI: 1.13-1.54), P = .022] and presence of cirrhosis [aHR 9.71 (95%CI: 2.02-46.48), P = .005] were predictors of HCC development [Table 3].

PAGE-B score

A binomial logistic regression model was calculated to assess the predictive value of the PAGE B-risk score for developing HCC, by correlating the incidence of HCC with the PAGE-B values. PAGE B score showed an association with HCC occurrence (R^2 = 0.225, P < .001). The good prognostic capacity of the score was observed [Accuracy: 0.936, Sensitivity: 0.997, Area Under the ROC Curve (AUC) 0.863]. No significant differences were carried out when comparing baseline PageB score with Page B at 5 years of treatment.

Predictive measures are graphically reported in the Receiver Operator Characteristic (ROC) curve in Figure 1.

DISCUSSION

This study assessed in a real-life cohort of virologically suppressed CHB patients treated with long-term NAs the risk and predictors of late HCC development.

Firstly, our results confirm the favourable impact of viral suppression on the natural history of HBV-related liver disease. In fact, no patient with chronic hepatitis progressed to cirrhosis, and no patient with portal hypertension diagnosis presented with bleeding esophageal varices. Only one patient with HBV/HDV-related cirrhosis developed liver decompensation due to the active Delta infection, resulting in the need for liver transplantation.

Moreover, long-term NA treatment in a few patients achieved a functional cure (HBsAg loss), the primary endpoint of future therapeutic strategies for chronic hepatitis B.

Nevertheless, in our cohort of patients, the persistent viral replication suppression does not abolish the risk of HCC, especially in those with advanced liver disease. In fact, a late HCC development was still diagnosed in 21 patients (6%), regardless of successful long-term treatment. Most patients with HCC (16/21) received TDF as rescue therapy after a virological breakthrough due to LAM resistance. The remaining five patients received TDF (2 cases) or ETV (3 cases) from the start.

Limited data are available on the incidence and predictive factors of late HCC occurrence in CHB patients beyond the first 5 years of NA therapy. Papatheodoridis *et al.* showed that after 5 years of ETV/TDF therapy, the HCC risk decreased. They reported 1,951 Caucasian patients under NA treatment for a median

Table 2. Main characteristics of 21 long-term NA-treated patients at HCC development

Characteristics	HCC-Patients (N = 21)
Age, years, mean (± SD)	56 (± 6)
Cirrhosis, *n* (%)	19 (90)
Undetectable HBV DNA, months, mean (±SD)	80 (± 46)
Alfha-fetoprotein, ng/mL, median (±SD)	4.3 (6.60-199)
Alfha-fetoprotein, ng/mL - < UNL* *n* (%) - > UNL *n* (%)	 13 (62) 8 (38)
Type of HCC, *n* (%) - 1 lesion - Multifocal	 16 (76) 5 (24)
Portal vein thrombosis, *n* (%)	4 (27)
Dead, n (%)	11 (52)

N: Number; UNL: upper limit of normal; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; SD: standard deviation; IQR: inter quartile range; * ULN: 7 ng/mL.

Table 3. Univariate and multivariate Cox regression analysis assessing predictors of HCC development during median 144 months of NUC therapy in the study population

Variables	HR (95%CI)	*P*-value	aHR (95%CI)	*P*-value
Age, mean (SD)	1.07 (1.03-1.11)	**.001**	1.00 (0.95-1.06)	.892
PAGE B score, mean (SD)	1.44 (1.25-1.66)	**< .001**	1.26 (1.13-1.54)	**.022**
Presence of Coinfections	3.04 (0.89-10.38)	.076	0.74 (0.49-6.09)	.390
Family History of HCC	2.61 (1.05-6.48)	**.039**	1.27 (0.49-3.29)	.064
Liver Cirrhosis	26.28 (6.10-113.20)	**< .001**	9.71 (2.02-46.48)	**.005**

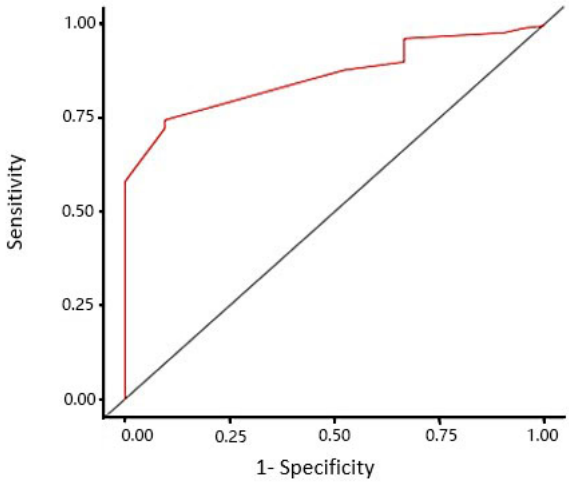
HR: Hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval; SD: standard deviation; NA: nucleos(t)ide analog; HCC: hepatocellular carcinoma.

period of 6.8 years, an overall yearly HCC incidence rate of 1.22% within and 0.73% after the first 5 years ($P = 0.050$)[7].

In this study, the overall incidence of HCC at 5-15 years (6%) was higher than that reported by Papatheodoridis *et al.* at 5-10 years (1.4%). This result could be explained by the difference in baseline patient characteristics and risk factors for HCC development between the two study populations. In fact, our study included a higher number of patients with cirrhosis, with a family history of HCC, and with HDV-HCV co-infections. In multivariate analysis, the diagnosis of cirrhosis at baseline and a family history of HCC were significantly associated with HCC occurrence.

Noteworthy, there were no female patients with HCC in our study, suggesting that male gender is a risk factor for HCC development.

As already known, more than half of our HCC patients HCC showed normal serum levels of alpha-fetoprotein at diagnosis, suggesting a limited value of this serum cancer marker and a great need for better tumor markers. Moreover, in 24% of patients, HCC showed characteristics of multifocal lesions already at diagnosis, representing one of the main reasons for the exclusion from the liver transplant list.



Predictive Measures

Accuracy	Specificity	Sensitivity	AUC
0.936	0.00	0.997	0.863

Figure 1. Receiver Operator Characteristic (ROC) curve representing the predictive measures of PAGE-B score toward the incidence of HCC among CHB patients in the study cohort. The cut-off value was set at 0.5.

Considering these results, having a simple score predicting the development of HCC is crucial. Until March 2019, seven scores were investigated in Asian (n = 6) or Caucasian (n = 1) CHB-treated patients. All scores performed well for HCC development prediction in the derivation and validation cohorts (c-statistic: 0.76-0.95) and generally classified patients into low, medium, and high HCC risk groups[16-22].

Recently, Shen *et al.* published a meta-analysis including 21,561 patients and 14 predictive scores[14]. The authors showed that in CHB-treated patients, the HCC risk scores exhibit good performance in predicting the mild-long term HCC risk development. Serum HBV DNA levels are an unimportant factor in these scores; in contrast, the presence of cirrhosis or surrogates of advanced fibrosis (such as APRI index, Liver stiffness, and serum albumin levels) retains an important role.

An ideal HCC risk score should be uncomplicated, inexpensive, and not difficult to calculate; thus, it should include commonly available parameters. Papatheodoridis *et al.* have developed and validated an HCC risk score (named PAGE-B score) in Caucasian CHB patients treated with ETV or TDF, based only on the patient's age, gender, and platelet count without the need for mathematical calculation. In our study, the PAGE-B score was strongly associated with the incidence of new HCC cases, as all HCC patients, except two, had a baseline score greater than 18. The test was also strongly predictive of HCC development, showing excellent accuracy and sensitivity.

Our study has some limitations: the retrospective nature of the study, the diagnosis of HCC was based on ultrasonographic findings performed by different radiologists, and all of our patients were from the same geographic area. Nevertheless, the long median duration of follow-up in our patients makes the results of considerable significance.

In conclusion, our results confirm that in a real-life setting, HCC can still occur despite long-term virological suppression. The PAGE-B score could be a helpful tool for identifying high-risk subjects, thus supporting clinicians in the prediction and decisions on HCC surveillance in CHB patients.

DECLARATIONS

Authors' contributions

Conceptualization: Fasano M, Santantonio TA
Methodology: Fasano M, Santantonio TA, Poliseno M,
Data curation: Fasano M, Poliseno M, Ieva FRP, Milella M, Ciarallo M, Caccianotti B
Writing-original draft preparation: Fasano M, Santantonio TA
Writing-review and editing: Fasano M, Santantonio TA
Supervision: Santantonio TA
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Databases having sociodemographic, clinical and virological features of the study population are available at each Center.

Financial support and sponsorship

None.

Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Ethical approval was waived by the local ethics committee. All patients sign an informed consent at the presentation in which they agree to collect and use their personal data anonymously for research purposes.

Consent for publication

All patients sign an informed consent at the presentation in which they agree to collect and use their personal data anonymously for research purposes.

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