ORIGINAL ARTICLE

Prediction of hepatocellular carcinoma through the modified PAGE-B score (mPAGE-B) in patients with chronic hepatitis B: it should be used in clinical practice?

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HIGLIGHTS

• Chronic hepatitis B is a well-defined risk factor for hepatocellular carcinoma, and it is important to implement early detection programs for hepatocellular carcinoma in affected patients. In this study, the data found suggest that the mPAGE-B score can be applied to reduce the number of medical consultations in young patients infected with the hepatitis B virus and aged <40 years.

ABSTRACT – Background – Persistent hepatitis B virus (HBV) infection can lead to hepatocellular carcinoma (HCC) alone, that is, without the development of previous cirrhosis, which makes it of paramount importance to predict the risk patients with chronic hepatitis B have for developing HCC in the future. Thus, the mPAGE-B score was developed in order to predict very low risks of HCC, becoming an important score, since with low risk, patient surveillance can be spread out. **Objective –** The main objective of this study was to predict the risk of HCC according to the mPAGE-B score for patients with chronic hepatitis B, using antiviral therapy. **Methods –** A cross-sectional, descriptive, quantitative, and retrospective study was conducted. Patients with chronic hepatitis B from the Hepatology Outpatient Clinic of the Federal University of the Fronteira Sul/HCPF in Passo Fundo, Rio Grande do Sul, covering a period of 12 years, were analyzed. **Results –** Of the 67 patients submitted to data collection, the mean age at diagnosis was 51.4 (±12.1) years, with a predominance of males (76.1%-n.51). All patients were HBeAg negative at diagnosis and 11 (16.4%) had cirrhosis. Regarding the antiviral regimen, 70.1% used tenofovir disoproxil fumarate (TDF) and 29.9% entecavir (ETV). According to m-PAGE-B stratification, 18 (25%) patients were classified as low-risk, 30 (41.7%) as intermediate-risk, and 19 (26.4%) as high-risk of developing HCC. The probability of developing HCC of these 67 patients in 3 years was 0.4% for low, 2.8% for moderate, and 9% for high risk. In 5 years, the probability was 0.5% for low, 4.4% for moderate, and 14% for high risk. **Conclusion –** This study demonstrates that the mPAGE-B score can be applied to decrease the number of consultations of patients with chronic hepatitis B in specialized outpatient clinics and, based on this population, patients aged ≤40 years may have one consultation per year instead of semi-annual.

Keywords – Chronic hepatitis B; hepatocellular carcinoma; mPAGE-B score.

INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem. According to the World Health Organization (WHO), more than 250 million people worldwide have chronic HBV infection[1]. Although vaccination programs developed in different countries of the world have been important in the fight against hepatitis B, this disease continues to be responsible for significant morbidity and mortality rates[2,3].

Hepatocellular carcinoma (HCC) is a primary malignant liver tumor with hepatocellular differentiation that in most cases develops in patients with chronic liver disease with or without cirrhosis[4]. Patients suffering from chronic hepatitis B develop a relevant morbidity and mortality caused by HCC[5]. Surveillance by ultrasonography has therefore been established in these patients and improves overall survival[6]. Therefore, chronic hepatitis B treatment guidelines recommend HCC surveillance in all patients with liver cirrhosis every 3 to 6 months. In chronic hepatitis B patients without liver cirrhosis a diagnostic screening is generally recommended annually[7]. Although it does not eliminate the risk, long-term HBV antiviral treatment is related to a decrease in the incidence of HCC[8,9]. Several scoring systems have been proposed to quantify HCC risk in patients using antiviral therapy, and the first developed in non-Asian patients was PAGE-B. PAGE-B was developed in 2016 to predict the development of HCC in 5 years in Caucasian patients undergoing HBV treatment, composed by age, sex, and platelet count[10]. Subsequently, Kim et al. (2018) added the level of serum albumin, creating the mPAGE-B score. The authors described an area under the receiver-operating characteristic curve (AUROC) of 0.82 in the prediction of HCC in 5 years in Asians, with better performance than other evaluated scores, such as CU-HCC, GAG-HCC, REACH-B, THRI, and PAGE-B[11].

The difficulty in implementing HCC surveillance in clinical practice is well known. The Covid-19 pandemic has bought additional challenges to proper HCC screening. HCC predictor scores may help prioritize higher-risk patients. In this context, this study aims to know the profile of the mPAGE-B score in patients with hepatitis B on antiviral therapy. This information can provide data that help organize the health services that provide care to this group of patients.

METHODS

Study design

A cross-sectional, descriptive, quantitative, and retrospective study was conducted, and medical records of patients with chronic hepatitis B using antivirals (ETV or TDF) for at least 6 months, attended at the Hepatology Outpatient Clinic of the Federal University of Fronteira Sul/HCPF, Passo Fundo, Rio Grande do Sul from January 1, 2008 to December 31, 2020, were studied. Patients with the following characteristics were excluded: a) co-infected with hepatitis C virus and/or hepatitis D virus; b) co-infected with the human immunodeficiency virus (HIV); c) carriers of other autoimmune and metabolic liver diseases; d) diagnosed with cancer, including HCC, prior to treatment with ETV/TDF; e) HCC and/or liver transplantation in the first 6 months after treatment with ETV/TDF; f) TVT/TDF therapy for less than 6 months; g) follow-up of less than 6 months; h) using ETV/TDF as prophylactic therapy because the patient received rituximab or any other chemotherapy agents.

Data collection

The clinical and epidemiological data collected were sex, age, presence of cirrhosis, family history of HCC, presence of hepatic nodule suggestive of HCC on ultrasound and/or tomography, alpha-fetoprotein (AFP) levels, platelets, albumin, and antiviral in use and time of use of antiviral.

The mPAGE-B score was calculated and the patients were classified into high (≥13 points), intermediate (9–12 points) and low (≤8 points) HCC risk groups (ANNEX I).

All information was kept confidential. Data were collected after approval of the Institutional Ethics Committee (CEP/Atitus). The study is in accordance with the norms of Resolutions No. 466/2012[12] and No. 510/2016[13] of the National Health Council.

Statistical analysis

The mPAGE-B score of each patient was calculated. Statistical analysis was performed using IBM SPSS Statistics version 27 for Windows.

ANNEX I. Table for calculating the mPAGE-B Score. Simple mPAGE-B score formula:

Age (years)	Risk (Score)	Sex	Risk (Score)	Platelets (x10⁹/L)	Risk (Score)	Albumin (g/dL)	Risk (Score)
<30	0	Female	0	>250	0	≥4.0	0
30–39	3	Male	2	200–250	2	3.5–4.0	1
40–49	5			150–200	3	3.0–3.5	2
50–59	7			100–150	4	<3.0	3
60–69	9			<100	5		
≥70	11						

Categorical variables were expressed as absolute and relative frequencies. Numerical variables were expressed as mean ± standard deviation or median (percentile$_{25}$ – percentile$_{75}$).

Finally, the projections derived by Kim et al.[11] were used to estimate the probability of developing HCC in 3 and 5 years.

RESULTS

Patient's characteristics

A total of 133 medical charts of patients diagnosed with chronic hepatitis B were evaluated, and, after exclusion criteria, 67 patients were included in the study (FIGURE 1). The mean age at diagnosis was 51.4 (±12.1) years, with a predominance of males (76.1%-n.51). All patients were HBeAg negative at diagnosis and 11 (16.4%) had cirrhosis.
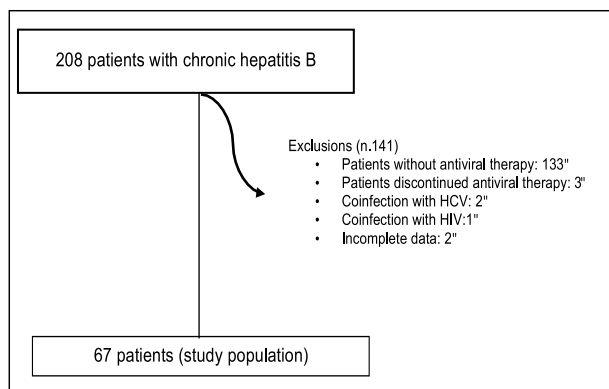

FIGURE 1. Flowchart of study population enrollment.

Regarding the antiviral regimen, 47 (70.1%) used TDF and 20 (29.9%) used ETV.

In the study population, mPAGE-B score had an average of 11.0 (±3.5). According to m-PAGE-B stratification, 18 (25%) patients were classified as low-risk, 30 (41.7%) as intermediate-risk, and 19 (26.4%) as high-risk of developing HCC.

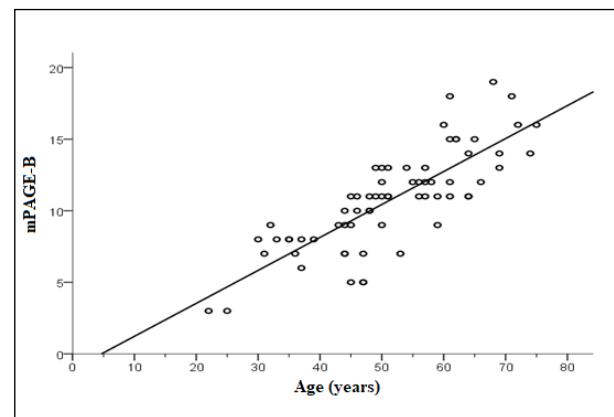A strong and positive correlation was observed between age and score, r=0.81, $P<0.001$, as shown in FIGURE 2.

FIGURE 2. Correlation between age and mPAGE-B score (n=67). The chart markings are indicative of each of the 67 individuals participating in the study and the line describes the lowest sum of error between what was predicted by the line equation and the one observed in reality. The line has a slope that is determined by r (r=0.81 or 81%) which is Pearson's linear correlation coefficient, indicating that there is a strong correlation between age and mPAGE-B.

Furthermore, the score was significantly higher among men (11.5±2.9) than women (8.4±4.1), $P=0.002$, as shown in FIGURE 3.
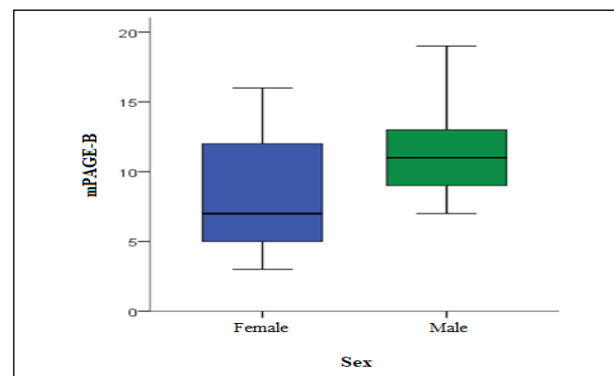

FIGURE 3. Correlation between sex and mPAGE-B score (n=67). The bold black line in the middle of the boxes represents the median. The lower limit of the boxes is percentile$_{25}$ and the upper limit is percentile$_{75}$. The horizontal line that exceeds the box both up and down represents the highest and lowest mPAGE-B values found for each sex, respectively.

TABLE 1 describes the risk classification and the cumulative incidence of HCC expected in 3 and 5 years for the 67 individuals for whom the mPAGE-B score was available.

In addition, TABLE 2 stratifies the risk classification and the cumulative incidence of HCC expected in 3 and 5 years for the 67 individuals according to sex and age, with a conventional age of 40 years and greater than 40 years, for which the mPAGE-B score was available.

DISCUSSION

Of the 67 patients who participated in the study, 76.1% were men and the mean age was 51.4 years. In addition, 16.4% were diagnosed with liver cirrhosis, following characteristics similar to other studies already conducted[11].

We analyzed the association between sex and age in relation to mPAGE-B, showing that there is a strong relationship between these variables and the

TABLE 1. Risk classification (n=67).

Score	Risk category	Frequency	Probability of developing HCC*	
			3 years	5 years
≤8	Low	18 (25.0%)	0.4% (0.3%–0.6%)	0.5% (0.4%–0.8%)
9–12	Moderate	30 (41.7%)	2.8% (2.5%–3.1%)	4.4% (4.0%–4.8%)
≥13	High	19 (26.4%)	9.0 (8.3%–9.6%)	14.0% (13.2%–14.8%)

*HCC: hepatocellular carcinoma. KIM et al. (2018).

TABLE 2. Risk classification stratified by sex and age (n=67).

Score	Risk category	Frequency	Probability of developing HCC*	
			3 years	5 years
Women				
≤8	Low	9 (56.3%)	0.4% (0.3%–0.6%)	0.5% (0.4%–0.8%)
9–12	Moderate	4 (25.0%)	2.8% (2.5%–3.1%)	4.4% (4.0%–4.8%)
≥13	High	3 (18.8%)	9.0 (8.3%–9.6%)	14.0% (13.2%–14.8%)
Men				
≤8	Low	9 (17.6%)	0.4% (0.3%–0.6%)	0.5% (0.4%–0.8%)
9–12	Moderate	26 (51.0%)	2.8% (2.5%–3.1%)	4.4% (4.0%–4.8%)
≥13	High	16 (31.4%)	9.0 (8.3%–9.6%)	14.0% (13.2%–14.8%)
≤40 years				
≤8	Low	11 (91.7%)	0.4% (0.3%–0.6%)	0.5% (0.4%–0.8%)
9–12	Moderate	1 (8.3%)	2.8% (2.5%–3.1%)	4.4% (4.0%–4.8%)
≥13	High	–	9.0 (8.3%–9.6%)	14.0% (13.2%–14.8%)
>40 years				
≤8	Low	7 (17.2%)	0.4% (0.3%–0.6%)	0.5% (0.4%–0.8%)
9–12	Moderate	29 (52.7%)	2.8% (2.5%–3.1%)	4.4% (4.0%–4.8%)
≥13	High	19 (34.5%)	9.0 (8.3%–9.6%)	14.0% (13.2%–14.8%)

HCC: hepatocellular carcinoma. *KIM et al. (2018).

score. This result was already expected, since sex and age are part of the mPAGE-B score.

For the 67 patients who participated in this study, the estimated risk of developing HCC at 3 and 5 years, respectively, was 0.4% and 0.5% for the low risk category (mPAGE-B score ≤8). For the moderate risk category (mPAGE-B score between 9 and 12), the calculated risk was 2.8% and 4.4%. For the high risk category (mPAGE-B score ≥13), the calculated risk was 9% and 14%. This data is very similar to what was reported in four larger studies that also took into account patients with chronic hepatitis B undergoing treatment with NA[11,14-15].

Regarding age, the present study showed that of the patients aged ≤40 years, most have a low risk (91.7%) of developing HCC and none have a high risk. In the cases of patients over 40 years of age, it is noteworthy that the majority (52.7%) have moderate or high risk (34.5%) of developing HCC.

The four studies mentioned above reported that for an mPAGE-B score ≤8 (mild risk of developing HCC) the annual risk of developing HCC was less than 0.2%, in agreement with the present study. Within this context, it is worth noting that, according to the American Association for the Study of Liver Diseases, surveillance for HCC is not cost-effective for patients who have an mPAGE-B risk score ≤8[3].

Therefore, based on the data represented here, approximately a quarter of patients can have their medical follow-up spaced out, saving health system resources.

This study does have some limitations. The sample included a limited number of patients and data were collected retrospectively in just one moment, not allowing the analysis of the incidence of HCC in this group.

However, it is indisputable that despite these limitations, the present study presents extremely pertinent results for the patients assessed, since in the future, with more studies in the area, they may be exempted from the performance of tests, which are usually done for patients at a risk of HCC.

Thus, it is worth remembering that in the clinical practice developed in Brazil, it is still not common to use the mPAGE-B in daily life, since this score is not yet validated for the Brazilian population. A study conducted in Brazil also analyzed the mPAGE-B score and found epidemiological characteristics comparable to our study, such as male predominance and a similar percentage of cirrhosis. In this last study, the prevalence of HCC was 6.7% at a median follow-up time of 9 years, and its occurrence was related to men, older age at HBV diagnosis, higher initial PAGE-B and m-PAGE-B, and the presence of cirrhosis[16].

CONCLUSION

Based on the analysis of the data collected, we can conclude that mPAGE-B is an important risk score for HCC, as it allows the identification of patients at low risk of developing the disease. Using this score, public health strategies can be implemented, reducing the number of consultations and clinical exams. This strategy will allow patients classified as low risk to perform a single annual rather than semiannual consultations, a periodicity that is currently recommended for the follow-up of patients likely to develop HCC. The relevance of this strategy is even more pertinent in a context such as the current COVID-19 pandemic, where there is a demand for social isolation.

Considering the above, we highlight the need for more studies on this subject, so that the mPAGE-B score can be validated in Brazil to provide a greater efficiency in the follow-up of patients with chronic hepatitis B.

Authors' contribution

Frison PR: data collection, analysis, and interpretation, drafting of the manuscript. Fraga RS: study concept and design, study supervision, drafting of the manuscript, critical revision for important intellectual content.

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RESUMO – Contexto – A infecção persistente do vírus da hepatite B (HBV) pode levar ao carcinoma hepatocelular (CHC) de forma independente, ou seja, sem o desenvolvimento de cirrose anteriormente, o que torna de suma importância predizer o risco que os pacientes com hepatite B crônica têm para desenvolver CHC no futuro. Assim, o escore mPAGE-B surgiu com o intuito de prever riscos baixos de CHC, tornando-se um escore de extrema relevância, uma vez que diante de risco baixo, pode-se espaçar a vigilância do paciente. **Objetivo –** O principal objetivo deste trabalho é predizer o risco de CHC, conforme o escore mPAGE-B, para os pacientes com hepatite B crônica em uso de terapia antiviral. **Métodos –** Foi realizado um estudo transversal, descritivo, quantitativo e retrospectivo. Foram analisados pacientes com hepatite B crônica do ambulatório de hepatologia, da Universidade Federal da Fronteira Sul/HCPF, em Passo Fundo, no Rio Grande do Sul, abrangendo um período de 12 anos. **Resultados –** Dos 67 pacientes submetidos à coleta de dados, a média de idade no diagnóstico foi 51,4 (±12,1) anos, com uma predominância do sexo masculino (76,1%-n.51). Todos os pacientes eram HBeAg negativos no diagnóstico e 11 (16,4%) tinham cirrose. Conforme a estratificação do mPAGE-B, 18 pacientes (25%) foram classificados como de baixo risco, 30 (41,7%) como risco intermediário, e 19 (26,4%) como alto risco de desenvolver CHC. A probabilidade de desenvolver CHC desses 67 pacientes em 3 anos é de 0,4% para risco leve, 2,8% para moderado e 9% para alto. Em 5 anos, a probabilidade é de 0,5% para risco leve, 4,4% para moderado e 14% para alto. **Conclusão –** Este estudo demonstra que o mPAGE-B pode ser um escore aplicado para diminuir o número de consultas de pacientes com hepatite B crônica em ambulatórios especializados e, baseado nessa população, talvez os pacientes com idade ≤40 anos possam ter uma consulta por ano ao invés de ser semestralmente.

Palavras-chave – Hepatite B crónica; carcinoma hepatocelular; escore mPAGE-B.

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