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High CONUT score predicts poor survival and postoperative HBV reactivation in HBV-related hepatocellular carcinoma patients with low HBV-DNA levels

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ABSTRACT

Background: Postoperative hepatitis B virus (HBV) reactivation (PHR) is associated with resection-induced immunosuppression in patients with HBV-related hepatocellular carcinoma (HCC). Controlling Nutritional Status (CONUT) score is an effective index for evaluating immune-nutrition function. However, the value of COUNT in predicting PHR in HBV-HCC patients remains unknown.

Methods: Totally, 209 HCC patients were enrolled.

Results: Preoperative immune function ($CD3^+CD4^+$, $CD3^+CD8^+$, IgG and IgM) in patients with high CONUT score was significantly worse than that in patients with low CONUT score ($P<0.05$). Blood test results on postoperative day 7 showed the same trend. In addition, patients with high CONUT score experienced a significantly larger decrease in the proportions of $CD3^+CD4^+$ and $CD3^+CD8^+$ than those with low CONUT score ($P<0.05$). In patients with high CONUT score, the incidence of overall complications was also significantly higher ($P=0.029$) and hospital-stay was significantly longer ($P=0.020$). Besides, overall survival and recurrence free survival in patients with high CONUT score were significantly worse than those in patients with low CONUT score (48.32 *vs.* 38.12 months, $P<0.001$; 36.08 *vs.* 27.03 months, $P=0.001$). The incidence of PHR was significantly higher in patients with high COUNT score ($P<0.001$), and CONUT score was strongly associated with PHR ($P<0.001$). Additionally, the fellow subgroup results also demonstrated that COUNT score was more effective in predicting PHR in patients with HBV-DNA level <500 copies/ml than patients with HBV-DNA 500–1000 copies/ml.

Conclusion: CONUT score is an effective indicator predicting survival and PHR in HBV-HCC patients, especially in those with HBV-DNA levels <500 copies/ml.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most lethal malignant tumor worldwide and is the second leading cause of cancer-related death [1]. For HCC patients, hepatitis B virus (HBV) infection is the important causative risk factor in Asia-Pacific regions [2–4]. In China, more than 90% HCC patients are infected with HBV [5].

Although there are many effective treatments for HCC, surgical resection remains the only radical therapy at present [6]. Despite tremendous improvements in preoperative diagnosis, surgical techniques, and radiofrequency ablation procedures for HCC, overall survival (OS) of HCC patients remains unsatisfactory [7] mainly due to the high recurrence rate [8]. We previously found that postoperative HBV reactivation (PHR) was the independent risk factor of HCC recurrence [9]. Ample evidence has shown that antiviral therapy could significantly reduce the incidence of PHR and the HCC recurrence rate [10,11], but antiviral therapy is only available for patients with high HBV-DNA levels ($>10^3$ copies/ml) according to the guidelines and large sample studies [12,13]. Antiviral therapy is not usually recommended for HCC patients with low HBV-DNA levels ($<10^3$ copies/ml) and the incidence of PHR is not that rare [9]. The exact mechanism of how PHR occurs is not clear, though our previous finding suggested that PHR may be associated with resection-induced immunosuppression in patients with HBV-related HCC [14].

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Malnutrition is frequent noticed in different cancer patients, and HCC patients are at a special increased risk for malnutrition [15,16]. It was reported that 30–40% HCC patients presented with varying degrees of malnutrition [17]. Studies have demonstrated that HCC patients with the impaired nutritional status such as lower body mass index (BMI), hypoalbuminemia or ascites are often accompanied with poor survival outcomes [18–20]. However, no current recommendation is available to assess the nutritional status for HCC patients. Therefore, the development of methods to evaluate the nutritional status and predict clinical outcome of HCC patients is of considerable significance. Controlling Nutritional Status (CONUT) score, which consists of the serum albumin (ALB) concentration, total lymphocyte count (TLC), and total cholesterol (TC) concentration [21], has been widely used in evaluating nutrition status and predict the clinical outcome of many malignancies [22–24].

We previously found that the immune function in patients with PHR was impaired [14], and CONUT score has proved to be a good tool to assess the immune-nutritional status [23,25]. But whether HCC patients with malnutrition were more likely to develop PHR remained ambiguous. In this study, we enrolled resectable HCC patients with low HBV-DNA levels ($<10^3$ copies/ml) without receiving preoperative antiviral therapy, and analyzed the relation between the immune-nutritional status and the incidence of PHR, in an attempt to explore the predictive value of COUNT score in the enrolled resectable HCC patients with low HBV-DNA levels.

Patients and methods

Ethics statement

This study was approved by the Institutional Review Board of Guangxi Medical University, and it was conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines. All patients enrolled in this study signed written consent for their information to be stored in hospital databases and used for this research. During data collection, patient records were anonymized. We previously mentioned it in our former study [14].

Patients

From 2012 to 2013, 209 HCC patients were admitted to our center. The inclusion criteria were 1) patients aged 18–75 years; 2) HBV related HCC patients with low HBV-DNA levels ($<10^3$ copies/ml) and without receiving preoperative antiviral therapy [26]; 3) patients with Child-Pugh stage A or B; 4) patients who were diagnosed with resectable primary HCC [27]; and 5) HCC was confirmed by postoperative pathology. The diagnose of HCC was confirmed according to the criteria of the criteria of the European Association for the Study of the Liver [28].

Preoperative management

A baseline assessment of white blood count (WBC), HBV-DNA, serum levels of alanine aminotransferase (ALT), total bilirubin (TBil), albumin, TC, alpha-fetoprotein (AFP), the proportions of several T lymphocyte subpopulations ($CD3^+CD4^+$, $CD3^+CD8^+$), and serum levels of immunoglobin G (IgG), IgM was performed within one week preoperatively. The tumor size, operating time and blood loss was recorded during operation.

Serum HBV-DNA levels were quantified using the PCR-based Care HBV V2 Assay Kit (Qiagen, Shenzhen, China) using 500 copies/ml as the lower limit of detection [14].

CONUT score was a sum of serum ALB, TLC, and TC [21]. In our study, we defined CONUT score <3 as "low CONUT", and CONUT score ≥3 as "high CONUT" [23,29].

Postoperative management

The results of blood tests including WBC, HBV-DNA, serum levels of ALT, TBil and ALB, the proportions of $CD3^+CD4^+$ and $CD3^+CD8^+$, serum levels IgG and IgM on postoperative day 7 were compared between patients in low and high CONUT scores. The immune function on postoperative day 7 was "subtracted" from baseline values and the difference between the two groups were compared to determine whether immune function had recovered postoperatively from the baseline levels.

A 10-fold increase in HBV-DNA levels compared with preoperative levels as well as detectable level of HBV-DNA postoperatively with undetectable level at baseline was defined as PHR within postoperative 1 month [30]. Antiviral therapy was given to patients once upon the detection of PHR.

Statistical analysis

All data analyses were performed by SPSS 21.0 (IBM, Chicago, USA) and P value < 0.05 was defined as the threshold of statistical significance. Normally distributed data were expressed as mean ± standard deviation (SD), and asymmetrically distributed data were expressed as median (range). Differences in outcomes between two groups were assessed using independent-samples t tests for measurement data or χ^2 test for frequency of various attributes between groups. Risk factor analysis was identified by univariate logistic regression, and following multivariate analysis using a stepwise logistic model. We used Kaplan-Meier method for survival analysis. Receiver operating characteristic (ROC) curve was also performed to compare the predictive value of CONUT score for the incidence of PHR and all area under the ROC curve (AUC) was analyzed between subgroups [14].

Results

Characteristics of the study population

Of the 209 HCC patients who satisfied the inclusion and exclusion criteria and enrolled in this study, 135 patients were defined as low CONUT score Group, and the other 74 patients as high CONUT score Group (Table 1). Patients in high CONUT score group had significantly worse ALB and TC levels and worse immune function (lower proportions of $CD3^+CD4^+$, $CD3^+CD8^+$; lower serum IgG and IgM levels); there were also more Child-Pugh B grade and more advanced stage patients in this group (all $P < 0.05$).

Short-term outcomes

On postoperative day 7, patients in high CONUT score group had significantly a worse immune-nutritional status indicated by lower levels of ALB, lower proportions of $CD3^+CD4^+$, $CD3^+CD8^+$, and lower serum IgG and IgM levels (all $P < 0.05$). After subtracting the results on postoperative day 7 from the baseline values, patients in high CONUT score group experienced a significantly larger decrease in the proportions of $CD3^+CD4^+$ and $CD3^+CD8^+$ as compared with those in low CONUT group (all $P < 0.05$).

Moreover, COUNT was also found to be a good indicator of postoperative complications. Patients in low COUNT group suffered a significantly lower incidence of overall postoperative complications ($P = 0.029$) and had a shorter length of hospital stay ($P = 0.020$) (Table 2).

Table 1
Characteristics of HBV-related HCC patients with high or low CONUT score.

	Low CONUT score (n = 135)	High CONUT score (n = 74)	P
Mean age ± SD, yr	54.08 ± 11.05	51.62 ± 11.72	0.133
Males, n (%)	108 (80.0%)	64 (86.5%)	0.240
Leukocyte, 10^9/L	7.00 ± 1.66	7.18 ± 1.60	0.445
Total bilirubin, μmol/L	13.10 (8.70–18.50)	13.50 (9.37–19.50)	0.712
Albumin, g/L	38.02 ± 2.68	35.58 ± 3.61	<0.001
Alanine Transaminase, U/L	42.90 (26.00–63.70)	47.55 (27.30–62.60)	0.610
Total cholesterol, mg/dL	202.36 ± 22.40	164.92 ± 41.30	<0.001
AFP, ng/mL	261.00 (180.00–386.00)	296.00 (192.75–496.25)	0.909
$CD3^+CD4^+$, %	32.66 ± 6.50	24.17 ± 4.42	<0.001
$CD3^+CD8^+$, %	25.42 ± 6.09	22.65 ± 5.92	0.002
IgG, g/L	18.06 ± 8.43	15.40 ± 5.61	0.028
IgM, g/L	1.57 ± 0.58	1.30 ± 0.58	0.001
Blood loss, mL	300.00 (150.00–400.00)	300.00 (200.00–825.00)	0.101
Operating time (min)	198.00 ± 64.59	211.21 ± 66.46	0.163
Tumor size, cm	6.57 ± 2.83	6.78 ± 3.54	0.631
Child-Pugh Score A/B, n (%)	127 (94.1%)/8 (5.9%)	45 (60.8%)/29 (39.2%)	<0.001
BCLC tumor stage A/B/C, n (%)	88 (65.2%)/29 (21.5%)/18 (13.3%)	38 (51.4%)/11 (14.9%)/25 (33.8%)	0.002

Table 2
Short-term outcomes of HBV-related HCC patients with high or low CONUT score.

	Low CONUT score (n = 135)	High CONUT score (n = 74)	P
Leukocyte, 10^9/L	8.93 ± 2.92	8.27 ± 2.90	0.118
Total bilirubin, μmol/L	28.20 (17.60–37.70)	28.40 (16.45–39.05)	0.792
Albumin, g/L	35.89 ± 2.99	34.99 ± 2.69	0.032
Alanine Transaminase, U/L	73.10 (53.30–99.70)	73.50 (51.00–112.25)	0.136
$CD3^+CD4^+$, %	30.67 ± 9.69	20.08 ± 6.63	<0.001
$CD3^+CD8^+$, %	22.61 ± 6.06	17.42 ± 4.42	<0.001
IgG, g/L	13.42 ± 5.74	11.37 ± 4.89	0.010
IgM, g/L	1.27 ± 0.67	1.06 ± 0.49	0.018
Difference of $CD3^+CD4^+$, %	2.20 (−0.6–4.50)	4.75 (2.58–5.70)	<0.001
Difference of $CD3^+CD8^+$, %	4.20 (−3.30–9.00)	4.95 (−2.10–11.75)	0.044
Difference of IgG, g/L	3.00 (0.10–7.00)	3.75 (0.80–6.80)	0.583
Difference of IgM, g/L	0.38 (−0.27–0.83)	0.02 (−0.20–0.71)	0.606
Postoperative HBV reactivation, n (%)	7 (5.2%)	24 (32.4%)	<0.001
Incidence of overall postoperative complications, n (%)	80 (59.3%)	55 (74.3%)	0.029
Hospital stay, days	18.83 ± 5.19	20.76 ± 6.50	0.020

Overall survival and recurrence-free survival

Survival analysis showed that patients in low CONUT score group had significantly better OS than patients in high COUNT score group (48.32 ± 1.23 *vs.* 38.12 ± 2.00 months, $P < 0.001$) (Fig. 1). And 1-, 3- and 5-year OS rate was 98.5%, 73.6%, 44.0% in low COUNT score group *vs.* 94.6%, 44.9%, 31.3% in high COUNT score group respectively. Univariate and multivariate analyses using the Cox regression model showed that CONUT score was the independently risk factor associated with OS (HR = 1.62, 95%CI 1.05–2.51, $P = 0.030$). Other prognostic factors were AFP level, Child-Pugh score, tumor size, BCLC tumor stage, HBV-DNA level, and PHR (all $P < 0.05$) (Supplement Table 1).

Similarly, recurrence-free survival (RFS) was also compared between the two groups and found that patients in low CONUT score group had significantly higher RFS than patients in high COUNT score group (36.08 ± 1.14 *vs.* 27.03 ± 1.88 months, $P = 0.001$) (Fig. 1). The 1-, 3- and 5-year RFS rate was 92.6%, 44.0%, 9.6% in low

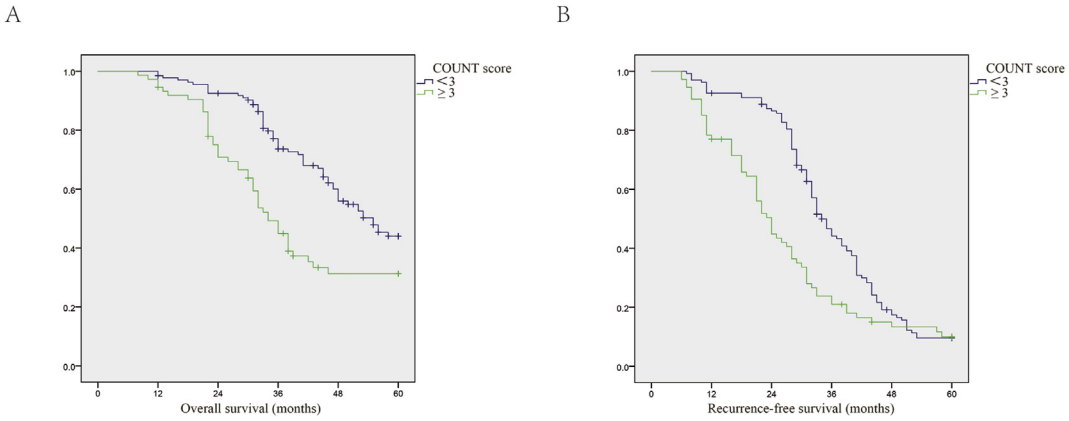

Fig. 1. Survival outcomes in HCC patients with low/high CONUT score. A. overall survival B. recurrence-free survival.

COUNT score group *vs.* 77.0%, 21.0%, 10.0% in high COUNT score group respectively. CONUT score was also the independent risk factor associated with RFS (HR = 1.54, 95%CI 1.10–2.16, $P = 0.011$). Other risk factors associated with RFS were AFP level, Child-Pugh score, BCLC tumor stage and PHR (all $P < 0.05$) (Supplement Table 2).

The value of COUNT score in predicting postoperative HBV reactivation

PHR occurred in 31 patients (14.8%), and the incidence of PHR in high CONUT score group was significantly higher than that in low CONUT score group (24/74, 32.4% *vs.* 7/135, 5.2%, $P < 0.001$) (Table 2). Logistic regression analysis showed that CONUT score was strongly correlated with PHR ($P < 0.001$). Other independent risk factors associated with PHR were HBV-DNA levels, tumor size and BCLC tumor stage (all $P < 0.05$) (Table 3). The results indicated that patients with an impaired immune-nutrition status had a significantly higher incidence of PHR.

The lower limit of HBV-DNA detection was 500 copies/ml in our center. However, researchers defined HBV-DNA less than 1000 copies/ml as undetectable according to the guidelines and large sample studies. Thus we divided HCC patients into two subgroups, patients with HBV-DNA<500 copies/ml and patients with HBV-DNA levels from 500 to 1000 copies/ml. ROC curve was performed to compare the predictive value of CONUT score in these two groups and analyzed AUC for the outcome of PHR. AUC was 0.854 (95%CI 0.778–0.930) and 0.677 (95%CI 0.549–0.804) for patients with undetectable HBV-DNA levels (<500 copies/ml) and patients with low HBV-DNA levels (500–1000 copies/ml) respectively. (Fig. 2).

Discussion

Our previous study suggested that PHR may be associated with resection-induced immunosuppression in patients with HBV-related HCC [14]. Malnutrition is common in HCC patients [17], and believed to be associated with impaired immune function [31]. But the relation between PHR and immune-nutritional function remains unknown. CONUT score consists of both immune and nutritional indicators and may serve as a detector of predicting PHR in HBV-related HCC. Thus, we conducted this study by enrolling HBV-related HCC patents with low HBV-DNA levels and analyzed short/long-term outcomes in patients with different CONUT scores. It was found that OS and RFS were significantly worse in patients with high CONUT score. In addition, HCC patients with high CONUT score had a higher incidence of postoperative complications and were more likely to develop PHR, indicating that CONUT score had a strong relation with PHR. Subgroup analysis further proved that COUNT score was more effective to predict PHR in patients with HBV-DNA levels<500 copies/ml than patients with HBV-DNA 500–1000 copies/ml.

Two kind systems are currently available to assess the nutritional status of cancer patients, one is largely based on some subjective parameters, the other is totally based on the objective parameters. For score systems largely based on some subjective parameters, like Nutritional Risk Screening Score 2002 [32], and Subjective Global Assessment [33]. Above score systems needed the patients to recall the general condition of food intake or the loss of appetite within 6 months. All these indices were mostly influenced by subjective parameters of different patients, thus might easily give rise to a huge bias thus leading to an inaccurate result. There were many sore systems based on objective parameters, however, only few of them could evaluate the immune nutrition status of patients. ALB, BMI or other single indexes could also represent the nutritional status of HCC patients. However, they may be not be comprehensive enough and therefore cannot represent the immune function of HCC patients. For comprehensive objective evaluation systems, prognostic nutrition index (PNI) and CONUT score are two most common used evaluating tools. PNI is the significant prognostic factor for evaluating short-term outcomes or OS of patients with HCC after hepatectomy [34,35]. PNI and CONUT both used ALB and TLC, two objective parameters for calculating. Compared with PNI, CONUT also included TC into consideration. A high CONUT score rather PNI was found to be an independent predictor of in-hospital mortality for HCC patients after hepatectomy [36]. COUNT score is totally based on three objective parameters (ALB, TLC, and TC). Serum ALB is known as a predictor of the immune-nutritional status, especially for HBV-related HCC patients [37]. Hypoalbuminemia has proved to be strongly associated with cachexia and poor perioperative outcomes in different malignancies [38,39]. TLC, an immunological indicator, combining with neutrophil or monocyte count has proved to be an effective detector to predict survival in HCC patients [40]. Serum TC level was reported to be correlated with OS in HCC patients [41]. Besides, the liver is also a key organ involved in lipid metabolism [42]. Based on the above evidence, CONUT seems to be a good option for evaluating the immune-nutritional function in HCC patients.

We previously found that preoperative immune function of HCC patients was suppressed when compared with healthy controls [14]. In this study, we found that patients with high CONUT score not only had a significantly worse nutritional status but a poorer immune function preoperatively. After the shock of hepatectomy, the postoperative immune function of patients with high COUNT score remained poor as compared with patients with low COUNT score. In addition, the recovery ability of immune function from the baseline value to postoperative day 7 in patients with higher CONUT score was also worse. Likewise, patients with poor immune-nutritional function seemed to have a higher incidence of postoperative complications and longer hospital stay. Child-Pugh score system is the most popular model to evaluate liver reserve function and assess the candidates eligible for hepatectomy at present but it not concerns about the immune-nutritional function. A systematic review on head and neck cancer patients also found that patients with a better immune-nutrition status had fewer complications [43].

Table 3
Risk factors associated with postoperative HBV reactivation using logistic regression model.

Factor	Univariate Analysis			Multivariate Analysis		
	HR	95% Confidence Interval	P	HR	95% Confidence Interval	P
CONUT score (<3, ≥3)	8.78	3.56–21.66	<0.001	7.66	2.47–23.80	<0.001
HBV DNA (<500,500–1000)	4.25	1.85–9.78	0.001	3.34	1.18–9.44	0.023
Child-Pugh Score (A/B)	10.94	4.67–25.64	<0.001	1.92	0.64–5.73	0.242
Tumor size, (<5, 5–10, >10)	3.33	1.78–6.25	<0.001	2.93	1.36–6.32	0.006
BCLC tumor stage (A/B/C)	3.53	2.16–5.76	<0.001	2.23	1.25–4.00	0.007

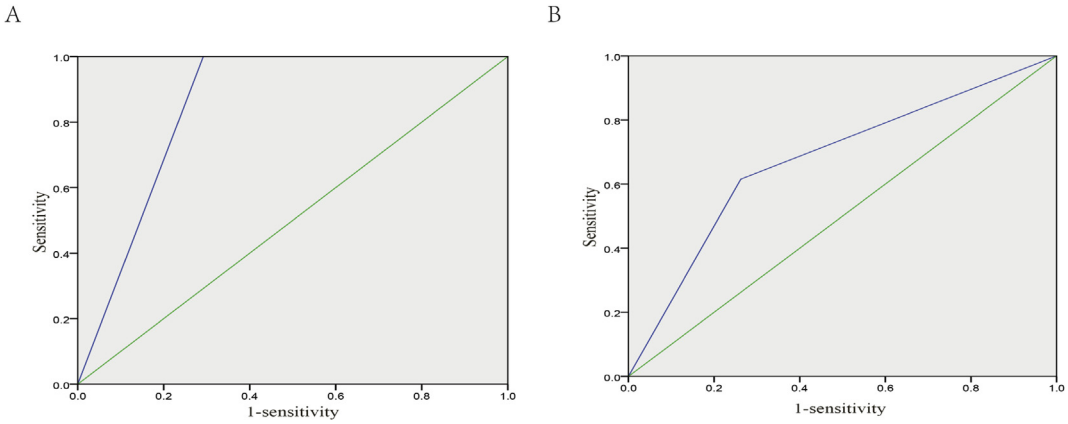

Fig. 2. Receiver operating characteristic curves and the area under the curve for PHR in HCC patients with different HBV-DNA levels. A. ROC curves of patients with HBV DNA levels less than 500 copies/ml.B. ROC curves of patients with HBV DNA levels 500–1000 copies/ml.

Nevertheless, nutritional supplement has already been proved to improve clinical features and laboratory data in HCC patients. Perioperative or postoperative supplementation of a branched-chain amino acid-enriched nutrient-mixture is clinically beneficial in reducing the morbidity associated with postoperative complications and in shortening the duration of hospitalization of HCC patients undergo liver resection [44,45]. In addition, branched-chain amino acid supplementation is beneficial for cirrhotic patients after radiofrequency ablation to relieve mental stress and reduce the risks for intrahepatic recurrence and complications [46]. Additional perioperative immune-nutrition therapy still could bring beneficial effects on clinical outcomes and immune status [47], addressing the importance of taking perioperative immune-nutrition status into consideration.

CONUT score is an effective detector of predicting OS and RFS in HCC patients. We found that patients with a damaged immune-nutrition status had significantly poor OS and RFS. Our initial literature review also retrieved other studies evaluating the survival of HCC patients using CONUT score [36,48,49]. Takagi et al. found that high CONUT score was an independent prognostic risk factor associated with OS, mortality and complications [36,49]. Similarly, Harimoto et al. also reported that HCC patients with high CONUT score had worse survival outcomes [48]. However, not all enrolled HCC patients in above studies were HBV infected. Knowing that HBV infection is the major risk factor of HCC and PHR is an independent prognostic factor of HCC in Asia-Pacific regions [9], our study focused on HBV-related HCC patients and highlighted the relation between immune-nutritional function and PHR.

According to the guidelines, antiviral therapy is not recommended in patients with HBV-DNA less than 1000 copies/ml. Nevertheless, our previous study observed that a certain number of patients with low HBV-DNA levels were still at risk of developing PHR. Similarly, Huang et al. also pointed out that PHR was common after partial hepatectomy for HBV-related HCC with a preoperative low HBV-DNA level of less than 1000 copies/ml [30]. However, they recommended that routine prophylactic antiviral treatment should be given before partial hepatectomy. In consequence, whether antiviral therapy is available for patients with HBV-DNA less than 1000 copies/ml still remains controversial. Our results indicated that PHR was associated with hepatectomy-induced immunosuppression. Furthermore, COUNT score could well predict the immune-nutrition status of HCC patients and was strongly correlated with PHR. The incidence of PHR was significantly higher in patients with high COUNT score. Based on this finding, we should care more about the low HBV-DNA patients with an impaired immune-nutrition status, and further antiviral therapy might be needed, other than patients with a better immune-nutrition status. In our center, the lower limit detection of HBV-DNA is 500 copies/ml. We divided patients into 2 subgroups (patients with HBV-DNA levels less than 500 copies/ml and patients with HBV-DNA 500–1000 copies/ml) and the results further proved that COUNT score was more effective to predict PHR in patients with HBV-DNA levels<500 copies/ml than patients with HBV-DNA 500–1000 copies/ml.

Several limitations still exist in this study. First, the retrospective design is the biggest limitation of our study, though we expanded our sample size to minimize the selection bias. Second, we failed to interfere with immune-nutrition status in patients with malnutrition and evaluate the benefits of immune-nutritional therapy. We have already planned a similar clinical trial with a better design, a larger sample size and a longer follow-up period.

In conclusion, CONUT score is an effective indicator predicting the survival and PHR rate in HBV-related HCC patients, especially in patients with HBV-DNA levels less than 500 copies/ml.

Conflicts of interest

The authors disclose no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.11.007.

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