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ORIGINAL ARTICLE

Elevated lactate impairs the efficacy of antiviral treatment on post-hepatectomy survival for advanced stage hepatitis B virus—related hepatocellular carcinoma

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KEYWORDS
Hepatitis B virus;
Hepatocellular carcinoma;
Nucleotide and nucleotide analogues;
Lactate

Summary
Background: Nucleoside and nucleotide analogues (NAs) have a risk of mitochondrial toxicity and then inducing the increase of lactate. We aim to evaluate the impact of lactate on the effects of NAs therapy in hepatitis B virus-related hepatocellular carcinoma (HCC) patients after curative liver resection.
Materials and methods: Five hundred and fifty-seven HBV-related HCC patients were divided into the treatment and control group according to whether they received NAs therapy or not. Perioperative and prognosis data were retrospectively reviewed.
Results: The treatment group had a better overall survival rate (OS) than the control group ($P = 0.017$). The recurrence-free survival rate (RFS) did not significantly differ between the two groups ($P = 0.174$). NAs could improve the OS of early stage HCC patients ($P = 0.028$), as well as the OS of advanced stage HCC patients with low level of lactate in subgroup analysis stratified against the level of lactate ($P = 0.037$). Advanced stage HCC patients in the treatment group had a higher value of lactate than those in the control group ($P = 0.024$). Besides, advanced stage HCC patients had a higher value of lactate than early stage HCC patients in the treatment group ($P < 0.001$), as well as in the control group ($P < 0.001$).
Conclusions: NAs could improve the long-term outcomes of HBV-related HCC patients after curative liver resection. However, the improvement effect of NAs therapy is counteracted by the adverse effect of elevated lactate in advanced stage HBV-related HCC patients.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer-related death [1,2]. The curative hepatic resection remains the mainstay of treatment for HCC. However, the long-term survival is discouraging because of high incidence of recurrence, which is reported up to 70% during the first 5 years after hepatectomy [3].

Hepatitis B Virus [4] infection has been one of the major risk factors for HCC. Recently years, quite a few studies have declared that nucleoside and nucleotide analogues (NAs), the antiviral treatment drugs, could reduce the HCC incidence in HBV-infected patients and improve the prognosis of HBV-related HCC [5—8]. However, there also have some studies indicated that not every HBV-related HCC patient is suitable to receive antiviral therapy [9—13]. NAs have the potential to induce mitochondrial toxicity for its affection of human DNA polymerase and the extra-hepatic effects of NAs have been reported in some studies [14—17]. Therefore, the Food and Drug Administration requires all NAs to carry the ''black box'' warning the development of lactic acidosis for their mitochondrial toxicity [16]. The ''Warburg effect'', a phenomenon of accelerated conversion of pyruvate to lactate in tumor cells, has been discovered since 1924. And recently, some studies have reported that the increase of lactate correlate with incidence of distant metastases and bad prognosis [18—22]. However, whether the lactate produced during the antiviral treatment with NAs in HBV-related HCC patients after curative liver resection could affect the long-term outcomes has not been defined. In this study, we aim to evaluate the impact of lactate on the effects of antiviral treatment with NAs in HBV-related HCC patients after curative liver resection.

Patients and methods

Study population

There were 2216 patients underwent liver resection for HCC at the Center of Hepatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST) from Jan. 1, 2005 to Dec. 31, 2012. Of them, 557 consecutive HBV-related HCC patients who underwent curative liver resection were enrolled retrospectively in this study. The inclusion criteria were:

- positive test for hepatitis B surface antigen and negative test for antibodies to hepatitis C;
- liver function of Child-Pugh class A or class B;
- no lymph node and distant metastasis;
- no previous treatment of HCC;
- no previous history of antiviral treatment;
- no diabetes mellitus;
- detailed and precise follow-up records.

The patients in the treatment group received either lamivudine (LAM) with a dosage of 100 mg/d, adefovir (ADV) with a dosage of 10 mg/d, entecavir (ETV) with a dosage of 0.5 mg/d, or combination therapy of them after admission for operation. The indication for antiviral treatment were performed basically based on the Guideline of prevention and treatment for chronic B (2010 Version) [23]:

- for Hepatitis B e Antigen (HBeAg)-positive patients, the value of HBV-DNA $\geq 10^5$ copies/mL; or for HBeAg-negative patients, HBV-DNA $\geq 10^4$ copies/mL; and alanine aminotransferase (ALT) $\geq$ two folds the upper limit of normal;
- for patients with compensated cirrhosis, HBV-DNA $\geq 10^4$ copies/mL for HBeAg-positive patients, and HBV-DNA $\geq 10^3$ copies/mL for HBeAg-negative patients, irrespective of the level of ALT;
- for patients with cirrhosis in the decompensation period, they should receive antiviral treatment once HBV-DNA is detected.

The patients in the treatment group received lamivudine (LAM) with a dosage of 100 mg/d, adefovir (ADV) with a dosage of 10 mg/d, entecavir (ETV) with a dosage of 0.5 mg/d, or combination therapy of them after curative liver resection. This study was approved by the Institutional Review Boards of Tongji hospital, Tongji Medical College, HUST.

Data collection and follow-up

The clinical and pathologic characteristics were retrospectively collected from the database maintained by Tongji Hospital. Major resection was defined as equal to or more than three Couinaud segments resection. Taking the concentration of patients' blood lactate measured by arterial blood gas analysis before discharged as the value of lactate. After curative liver resection, all patients were undertaken regular follow-up examination of serum alpha - fetoprotein (AFP), liver function and ultrasonogrphy every 4—6 weeks, and chest radiography every 8—12 weeks during the first 2 years. Thereafter, the intervals changed to 3—6 months.

Statistical analysis

All the data were analyzed with SPSS version 21.0 software (SPSS, Chicago, IL). Continuous variables were expressed as the mean $\pm$ standard deviation (SD) and categorical variables were expressed as the number and percentage. Comparisons of continuous variables were performed using Mann—Whitney *U*-test, while Pearson Chi^2 analysis or Fisher's exact test were used to compare categorical variables. The overall survival rate (OS) and recurrence-free survival rate (RFS) were estimated by the Kaplan—Meier method and were compared with the log-rank test. After the univariate analysis, the significant variables associated with the OS and RFS were then used for multivariate analysis using the Cox's proportional hazards model. The binary logistic regression model was used for univariate and multivariate analysis to determine the variables associated with high level of lactate. $P < 0.05$ was considered to be significant difference.

Table 1 Characteristics of patients in the treatment and control group.

Variables	Treatment group($n=189$)	Control group($n=368$)	P
Age (year)	53.1 ± 11.6	52.2 ± 11.6	0.381
Gender (male)	161 (85.2%)	309 (84%)	0.708
HBeAg (positive)	35 (18.5%)	75 (20.4%)	0.602
HBV-DNA ($\log_{10}$ IU/mL)	4.2 ± 1.3	4.2 ± 1.2	0.781
ALT (U/L)	45.4 ± 55.2	42.9 ± 54.8	0.612
ALB (g/L)	38.7 ± 5.3	38.5 ± 5.0	0.735
Lactate (mmol/L)	1.28 ± 0.23	1.24 ± 0.39	0.134
TBIL (umol/L)	15.1 ± 12.1	15.2 ± 14.7	0.910
PT (s)	14.0 ± 1.0	14.1 ± 1.0	0.096
AFP (≥ 20 ng/mL)	120 (63.5%)	230 (62.5%)	0.819
MELD	4.5 ± 3.1	4.5 ± 3.2	0.996
Child—Pugh class (A)	181 (95.8%)	347 (94.3%)	0.459
Ascites (yes)	29 (15.3%)	72 (19.6%)	0.221
Cirrhosis			0.871
No	28 (14.8%)	59 (16.0%)	
Mild	112 (59.3%)	220 (59.8%)	
Yes	49 (25.9%)	89 (24.2%)	
Tumor number (multiple)	76 (40.2%)	126 (34.2%)	0.165
Tumor diameter (≥ 3 cm)	173 (91.5%)	329 (89.4%)	0.424
Tumor encapsulation			0.381
Complete	96 (50.8%)	207 (56.3%)	
Incomplete	36 (19.0%)	69 (18.7%)	
Absence	57 (30.2%)	92 (25.0%)	
BCLC stage			0.275
A	105 (55.6%)	230 (62.5%)	
B	55 (29.1%)	88 (23.9%)	
C	29 (15.3%)	50 (13.6%)	
Operation time (min)	246 ± 75	251 ± 81	0.416
Type of hepatectomy (major)	131 (69.3%)	244 (66.3%)	0.474
Inflow occlusion (yes)	127 (67.2%)	240 (65.2%)	0.641
Blood loss (mL)	442 ± 438	411 ± 501	0.475
Blood transfusion (yes)	41 (21.7%)	85 (23.1%)	0.708

HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ALT: alanine aminotransferase; ALB: albumin; TBIL: total bilirubin; DBIL: direct bilirubin; PT: prothrombin time; AFP: α-fetoprotein; MELD: model for end-stage liver disease; BCLC: Barcelona Clinic Liver Cancer.

Results

The clinical and pathologic characteristics in the two groups

189 (33.9%) patients received antiviral treatment (treatment group) and 368 patients (66.1%) had no antiviral treatment (control group) after curative liver resection (Supplementary Figure 1). All clinical and pathologic characteristics showed no significant difference between the two groups (Table 1). The value of lactate ≥ 1.25 mmol/L (the median value of lactate for all enrolled patients) was defined as high level of lactate.

Factors associated with the OS and RFS of HCC patients after curative liver resection

The 1-, 3-, and 5-year OS were 88.3%, 63.4% and 33.3%, respectively, in the treatment group, and were 85.0%, 55.0% and 24.8%, respectively, in the control group. The OS in the treatment group was significantly improved in contrast to the control group ($P=0.017$) (Fig. 1b). The 1-, 3-, and 5-year RFS were 63.9%, 41.7% and 41.1%, respectively, in the treatment group, and were 62.3%, 33.6% and 32.7%, respectively, in the control group. There was no statistical difference of RFS between the two groups ($P=0.174$) (Fig. 1a). The patients with low level of lactate had a better OS ($P<0.001$) and RFS ($P<0.001$) than patients with high level of lactate (Fig. 1c—d). Multivariate Cox analysis indicated that the level of lactate ($P<0.001$), tumor number ($P=0.031$), Barcelona Clinic Liver Cancer (BCLC) stage ($P=0.001$) and antiviral treatment ($P=0.017$) significantly predicted OS (Table 2), and the level of lactate ($P<0.001$) and BCLC stage ($P<0.001$) significantly predicted RFS (Table 3).

The effects of antiviral treatment in HCC patients after stratification with the BCLC stage

NAs significantly improved the OS ($P=0.028$) of patients with early stage (BCLC stage A/B) HCC (Fig. 2b), but

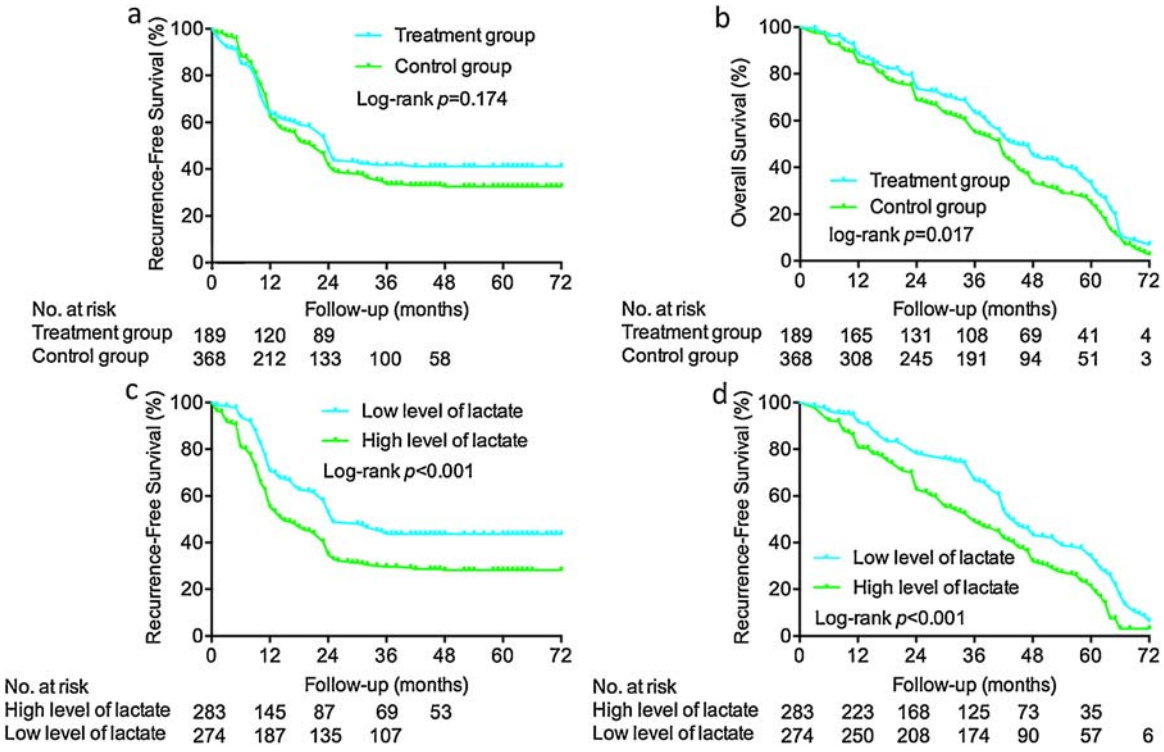

Figure 1 Comparison of post-operative survival (a, b) between the treatment group and the control group, and (c, d) between the patients with high (lactate ≥ 1.25 mmol/L) and low levels of lactate.

Table 2 Factors significantly associated with overall survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (≧ 53 vs. < 53 y)	1.064	0.876—1.291	0.940			
Gender (male vs. female)	1.134	0.862—1.492	0.367			
HBeAg (positive vs. negative)	1.032	0.810—1.315	0.798			
HBV-DNA (≧ 4 vs. < 4 $\log_{10}$ IU/mL)	1.078	0.886—1.311	0.452			
ALT (≧ 40 vs. < 40 U/L)	1.034	0.841—1.271	0.751			
ALB (≧ 35 vs. < 35 g/L)	0.885	0.689—1.135	0.336			
Lactate (≧ 1.25 vs. < 1.25 mmol/L)	1.583	1.298—1.929	0.000*	1.578	1.291—1.929	0.000*
TBIL (≧ 17 vs. < 17 umol/L)	1.140	0.915—1.420	0.242			
PT (≧ 13 vs. < 13 s)	1.164	0.864—1.568	0.318			
AFP (≧ 20 vs. < 20 ng/mL)	1.069	0.875-1.306	0.512			
MELD (≧ 4.6 vs. < 4.6)	1.037	0.853—1.259	0.717			
Child—Pugh class (B vs. A)	1.028	0.648-1.630	0.906			
Ascites (yes vs. no)	1.188	0.924—1.526	0.179			
Cirrhosis (yes vs. no/mild)	0.991	0.793—1.240	0.940			
Tumor number (multiple vs. single)	1.354	1.104—1.661	0.004*	1.269	1.022-1.575	0.031*
Tumor diameter (≧ 3 vs. < 3 cm)	1.049	0.759—1.495	0.771			
Tumor encapsulation (complete/incomplete vs. absence)	0.908	0.730—1.128	0.383			
BCLC stage (C vs. A/B)	1.896	1.454—2.473	0.000*	1.598	1.206—2.117	0.001*
Operation time (≧ 233 vs. < 233 min)	1.032	0.692—1.538	0.891			
Type of hepatectomy (major vs. minor)	1.218	0.994—1.493	0.057			
Inflow occlusion (yes vs. no)	1.210	0.913—1.536	0.210			
Blood loss (≧ 388 vs. < 388 ml)	2.108	0.651—6.848	0.211			
Blood transfusion (yes vs. no)	1.432	0.842—2.429	0.311			
Antiviral treatment (yes vs. no)	0.807	0.655—0.993	0.043*	0.775	0.629—0.955	0.017*

HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ALT: alanine aminotransferase; ALB: albumin; TBIL: total bilirubin; DBIL: direct bilirubin; PT: prothrombin time; AFP: α-fetoprotein; MELD: model for end-stage liver disease; BCLC: Barcelona clinic liver cancer.
* $P < 0.05$.

Table 3 Factors significantly associated with recurrence-free survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (≧53 vs. <53 y)	1.057	0.854—1.309	0.611			
Gender (male vs. female)	1.164	0.860—1.576	0.326			
HBeAg (positive vs. negative)	1.067	0.817—1.395	0.634			
HBV-DNA (≧4 vs. <4 $\log_{10}$ IU/mL)	1.158	0.935—1.434	0.179			
ALT (≧40 vs. <40 U/L)	1.107	0.884—1.386	0.378			
ALB (≧35 vs. <35 g/L)	0.969	0.739—1.270	0.819			
Lactate (≧1.25 vs. <1.25 mmol/L)	1.614	1.300—2.003	0.000*	1.551	1.248—1.929	0.000*
TBIL (≧17 vs. <17 umol/L)	1.099	0.861—1.401	0.449			
PT (≧13 vs. <13 s)	1.077	0.787—1.475	0.642			
AFP (≧20 vs. <20 ng/mL)	1.113	0.889-1.393	0.350			
MELD (≧4.6 vs. <4.6)	1.111	0.896—1.376	0.338			
Child—Pugh class (B vs. A)	0.978	0.583-1.642	0.938			
Ascites (yes vs. no)	1.241	0.948—1.624	0.116			
Cirrhosis (yes vs. no/mild)	1.049	0.819—1.342	0.707			
Tumor number (multiple vs. single)	1.351	1.085—1.682	0.007*	1.242	0.990—1.558	0.061
Tumor diameter (≧3 vs. <3 cm)	1.141	0.789—1.651	0.484			
Tumor encapsulation (complete/incomplete vs. absence)	0.838	0.661—1.062	0.144			
BCLC stage (C vs. A/B)	1.996	1.508—2.643	0.000*	1.728	1.290—2.314	0.000*
Operation time (≧233 vs. <233 min)	1.107	0.631—1.946	0.721			
Type of hepatectomy (major vs. minor)	1.166	0.931—1.461	0.182			
Inflow occlusion (yes vs. no)	1.345	0.741—2.440	0.331			
Blood loss (≧388 vs. <388 mL)	1.571	0.842—2.924	0.155			
Blood transfusion (yes vs. no)	1.303	0.706—2.406	0.299			
Antiviral treatment (yes vs. no)	0.859	0.683—1.079	0.190			

HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ALT: alanine aminotransferase; ALB: albumin; TBIL: total bilirubin; DBIL: direct bilirubin; PT: prothrombin time; AFP: α-fetoprotein; MELD: model for end-stage liver disease; BCLC: Barcelona Clinic Liver Cancer.
* $P < 0.05$.

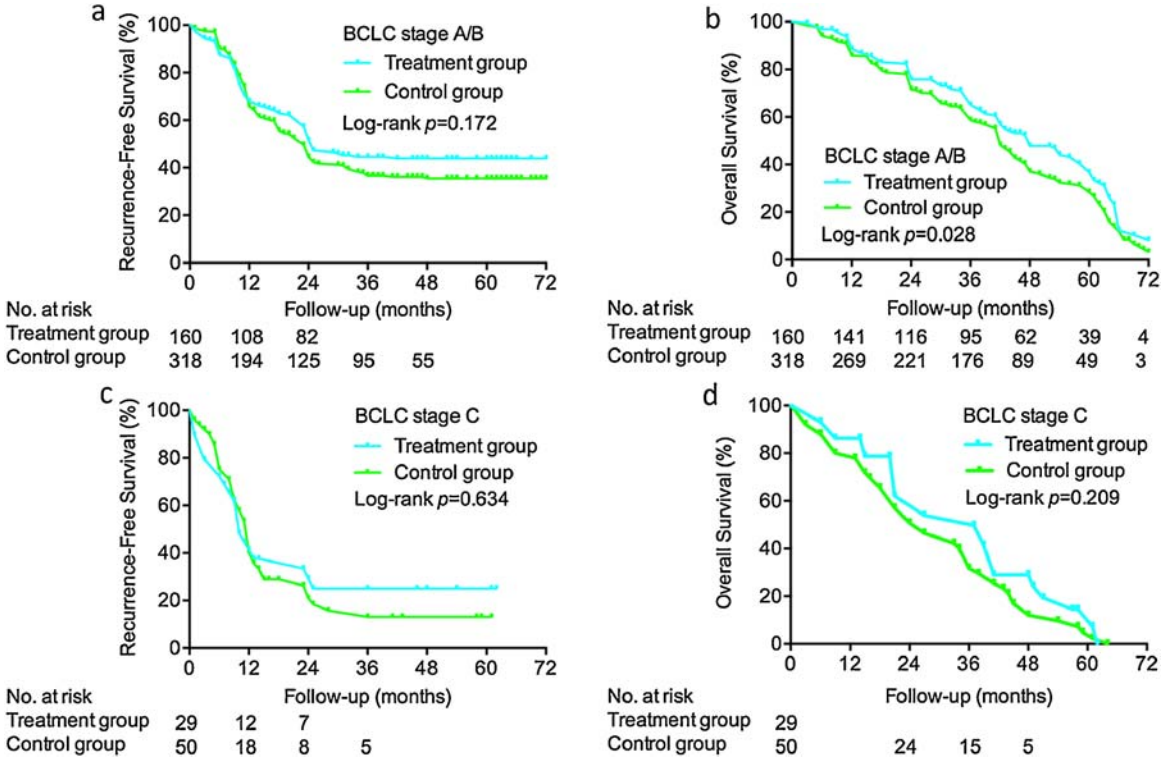

Figure 2 Comparison of post-operative survival between patients with different Barcelona Clinic Liver Cancer (BCLC) stages: a and b: patients with early stage hepatocellular carcinoma (HCC); c and d: patients with advanced stage HCC.

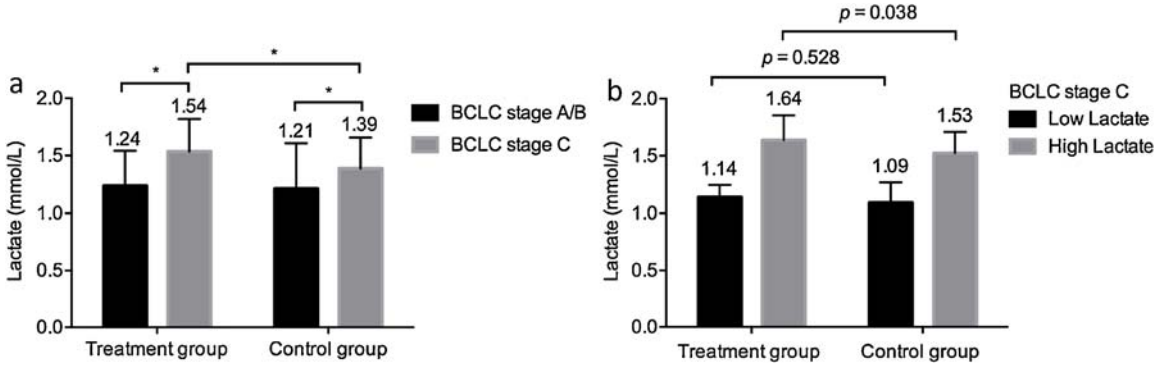

Figure 3 Comparison of the value of lactate between the treatment group and the control group: a: the value of lactate for patients with different Barcelona Clinic Liver Cancer (BCLC) stages; b: the value of lactate for advanced stage hepatocellular carcinoma (HCC) patients with different the levels of lactate (*, $P < 0.05$).

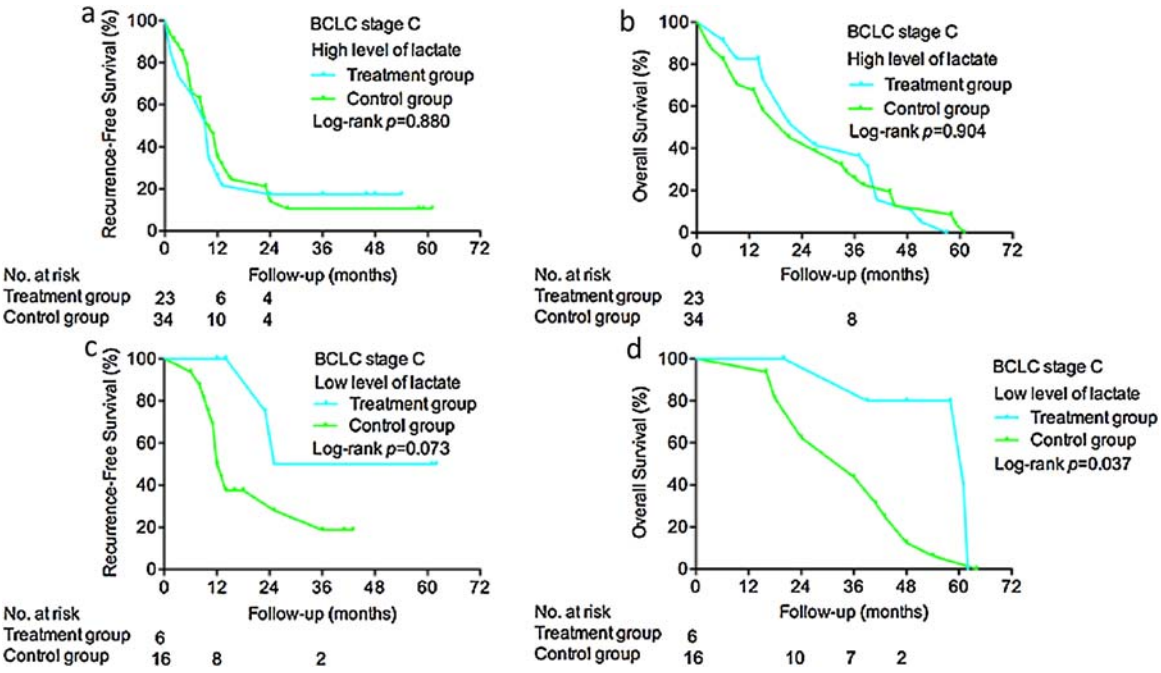

Figure 4 Comparison of post-operative survival for advanced stage hepatocellular carcinoma (HCC) patients between the treatment group and the control group after stratification with the level of lactate: a and b: patients with high level of lactate (lactate $\geq$ 1.25 mmol/L); c and d: patients with low level of lactate.

there was no significant difference of RFS ($P = 0.172$) for these patients between the two groups (Fig. 2a). Neither the OS ($P = 0.209$) nor the RFS ($P = 0.634$) of patients with advanced stage (BCLC stage C) HCC showed significant difference between the two groups (Fig. 2c—d). Although all clinical and pathologic characteristics including the value of lactate had no significant difference between the two groups (Table 1), the advanced stage HCC patients in the treatment group had a higher value of lactate than those in the control group (1.54 ± 0.28 mmol/L vs. 1.39 ± 0.27 mmol/L, $P = 0.024$). Furthermore, the advanced stage HCC patients had a higher value of lactate than the early stage HCC patients in the treatment group (1.54 ± 0.28 mmol/L vs. 1.24 ± 0.31 mmol/L, $P < 0.001$), as well as in the control group (1.39 ± 0.27 mmol/L vs. 1.21 ± 0.40 mmol/L, $P < 0.001$). Comparison of the value of lactate between the two groups in the early stage HCC patients showed no significant difference (1.24 ± 0.31 mmol/L vs. 1.21 ± 0.40 mmol/L, $P = 0.463$) (Fig. 3a).

The impact of elevated lactate on the effects of NAs therapy in advanced stage HCC patients after curative liver resection

Subgroup analysis stratified against the level of lactate in advanced stage HCC patients showed that NAs significantly improved the OS of advanced stage HCC patients with low level of lactate ($P = 0.037$) (Fig. 4d), but could not improve the OS of advanced stage HCC patients with high level of lactate ($P = 0.904$) (Fig. 4b). Comparison of RFS

Table 4 Factors significantly associated with the value of lactate.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (≧53 vs. <53 y)	0.964	0.692—1.344	0.831			
Gender (male vs. female)	1.191	0.753—1.883	0.455			
HBeAg (positive vs. negative)	0.868	0.572—1.319	0.508			
HBV-DNA (≧4 vs. <4 $\log_{10}$ IU/mL)	1.017	0.729—1.419	0.922			
ALT (≧40 vs. <40 U/L)	0.908	0.637—1.294	0.592			
ALB (≧35 vs. <35 g/L)	0.806	0.528—1.231	0.319			
TBIL (≧17 vs. <17 umol/L)	1.023	0.698—1.498	0.908			
PT (≧13 vs. <13 s)	1.400	0.842—2.326	0.195			
AFP (≧20 vs. <20 ng/mL)	0.945	0.670—1.333	0.749			
MELD (≧4.6 vs. <4.6)	0.885	0.635—1.234	0.470			
Child—Pugh class (B vs. A)	0.776	0.366—1.646	0.509			
Ascites (yes vs. no)	0.667	0.432—1.031	0.068			
Cirrhosis (yes vs. no/mild)	1.075	0.732—1.580	0.711			
Tumor number (multiple vs. single)	1.258	0.890-1.779	0.194			
Tumor diameter (≧3 vs. <3 cm)	1.079	0.618—1.883	0.789			
Tumor encapsulation (complete/incomplete vs. absence)	0.886	0.609—1.290	0.528			
BCLC stage (C vs. A/B)	2.889	1.711—4.877	0.000*	2.707	1.560—4.696	0.000*
Operation time (≧233 vs. <233 min)	1.547	0.861—2.785	0.046*	1.221	0.605—2.467	0.702
Type of hepatectomy (major vs. minor)	1.460	1.022—2.086	0.038*	1.154	0.788—1.692	0.461
Inflow occlusion (yes vs. no)	1.583	0.876—2.850	0.006*	1.781	1.115—3.410	0.020*
Blood loss (≧388 vs. <388 mL)	2.04	1.16—3.71	0.015*	1.513	0.512—5.134	0.473
Blood transfusion (yes vs. no)	2.16	1.22—3.95	0.007*	1.691	1.113—2.568	0.013*
Antiviral treatment (yes vs. no)	1.292	0.909—1.837	0.154			

HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; ALT: alanine aminotransferase; ALB: albumin; TBIL: total bilirubin; DBIL: direct bilirubin; PT: prothrombin time; AFP: α-fetoprotein; MELD: model for end-stage liver disease; BCLC: Barcelona Clinic Liver Cancer.
* $P < 0.05$.

between the two groups showed no significant difference in advanced stage HCC patients with high level of lactate ($P = 0.880$), as will as in advanced stage HCC patients with low level of lactate ($P = 0.073$) (Fig. 4a and c). In addition, the advanced stage HCC patients with high level of lactate in the treatment group had a higher value of lactate than those in the control group (1.64 ± 0.22 mmol/L vs. 1.53 ± 0.18 mmol/L, $P = 0.038$), but no significant difference of the value of lactate was observed in advanced stage HCC patients with low level of lactate between the two groups (1.14 ± 0.10 mmol/L vs. 1.09 ± 0.17 mmol/L, $P = 0.528$) (Fig. 3b).

Factors associated with the increase of lactate in HCC patients after NAs therapy

Univariate analysis indicated that the BCLC stage, operation time, type of hepatectomy, inflow occlusion, blood loss and blood transfusion could significantly predicted the increase of lactate in HCC patients after NAs therapy ($P < 0.05$), while just the BCLC stage ($P < 0.001$), inflow occlusion ($P = 0.020$) and blood transfusion ($P = 0.013$) remained the predictive factors of the increase of lactate in multivariate analysis (Table 4).

Discussion

Nucleoside and nucleotide analogues (NAs), the antiviral treatment agent, have a great proven efficacy in reducing HCC incidence in HBV-infected patients and improving the prognosis of HBV-related HCC [24,25]. However, there also is a different view that not every HBV-related HCC patient is suitable to receive antiviral therapy, which brings some uncertainties to the effects of antiviral treatment [9—13].

In this study, we found that antiviral treatment with NAs could significantly improve the OS, rather than the RFS, of HBV-related HCC patients after curative liver resection, which was similar to the results of some studies [12,13,26]. However, subgroup analysis stratified against BCLC stage showed that the long-term outcomes improvement effect of NAs was only observed in early stage HCC patients. For advanced stage HCC patients, there was no significant difference of OS or RFS between the two groups. Although the similar results had also been reported in some studies and were attributed to the tumor factors, the exact reasons have not been discovered [12,13,27].

NAs therapy may benefit the prognosis of HBV-related HCC patients in many ways, such as suppressing HBV replication and reactivation, improving the liver function, thereby reducing the risk of HCC incidence and prolonging the recurrence-free survival and overall survival [11,28]. Whatever, the basic mechanism of NAs is inhibiting the HBV-DNA

polymerase. Despite it is believed that the NAs have low-level activity against human mitochondrial DNA polymerase, the extra-hepatic conditions like myopathy, nephropathy, neuropathy and lactic acidosis due to mitochondrial toxicity are not rare in patients during NAs therapy [5,14]. Lange and colleagues have reported severe lactic acidosis during ETV therapy in patients with impaired liver function [Model for End-stage Liver Disease (MELD) Score $\geq$ 20] firstly in 2009, which have also been reported in cases thereafter [17,29—31]. Lactate is transformed from pyruvate in the cytosol, and pyruvate could also be converted by pyruvate dehydrogenase in mitochondria to acetyl coenzyme A that involved in the highly oxygen-dependent Krebs cycle to produce energy [32—34]. Thus, anything influencing the function of mitochondria or oxygen supply could reduce the activity of Krebs cycle and therefore accelerate the conversion of pyruvate to lactate [32,35]. Recently, some studies have reported that the value of lactate would increase after hepatectomy due to the hypoperfusion resulted from intraoperative inflow occlusion and low central venous pressure management, and the elevated lactate is considered as an early predictor of post-operative adverse outcomes [21,22,33,35,36]. Similarly in this study, patients with high level of lactate had a worse OS and RFS compared with patients with low level of lactate, and the factors BCLC stage, inflow occlusion, and blood transfusion could predict the increase of lactate in multivariate analysis. Besides, although the value of lactate between the two groups had no significant difference, subgroup analysis stratified against BCLC stage revealed that the advanced stage HCC patients in the treatment group had a higher value of lactate than those in the control group, which may mean that NAs could induce the increase of lactate in advanced stage HCC patients. Furthermore, the advanced stage HCC patients had a higher value of lactate than the early stage HCC patients in the treatment group, as well as in the control group. Simultaneously, comparison of liver function and surgery-related variables, which were associated with the post-operative increase of lactate in some studies, showed no significant difference between the two groups in early stage HCC patients, as well as in advanced stage HCC patients (data not shown) [35,36].

Considering the mitochondrial toxicity of NAs and the ''Warburg effect'' that both could induce the increase of lactate, it is not difficult to understand why the advanced stage HBV-related HCC patients had a higher value of lactate after NAs therapy. Similarly, that patients with high level of lactate had a worse OS and RFS compared with patients with low level of lactate could be attributed to the elevated lactate promoting tumor grows, progression, and metastasis. And the reason why NAs therapy could not improve the outcomes of the advanced stage HBV-related HCC patients, while subgroup analysis stratified against the level of lactate showed the advanced stage HBV-related HCC patients with low level of lactate had a better OS in the treatment group than those in the control group, is the improvement effect of NAs therapy was counteracted by the adverse effect of elevated lactate.

There are limitations in this study. Firstly, the effects of various NA agents were not explored because some patients took combination therapy with LMV and ADV or ETV and some patients changed to take other type of NAs or combination therapy halfway for the LMV resistance. Secondly, although totally 557 patients were enrolled in this study, there were only 22 (6 in the treatment group and 16 in the control group) advanced stage HCC patients with low level of lactate. This small size might have weakened the conclusion. Finally, this was a retrospective study in single-center. Despite of a relatively large number of patients enrolled, there inevitably was some bias in this study. However, with a great proven efficacy of NAs' reducing HCC incidence and improving prognosis of HCC in HBV-infected patients, it would not be ethical to perform prospective placebo-control studies. Thus, more evidence from basic research and multi-centric studies with larger sample size is needed.

In conclusion, antiviral treatment with NAs could benefit the long-term outcomes of HBV-related HCC patients after curative liver resection. However, the improvement effect of NAs therapy is counteracted by the adverse effect of elevated lactate in advanced stage HBV-related HCC patients. The progression of HCC and NAs therapy could induce the increase of lactate in advanced HCCs. And the elevated lactate is a predictor of bad prognosis for HBV-related HCC patients after curative liver resection.

Author's contribution

WGZ, JPZ designed this study. JPZ, JJW, SSC and YXZ collected the data and analysis. JPZ, JJW wrote the draft. WGZ revised the draft. All approved the final version for publication.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2018.08.008.

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