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ORIGINAL RESEARCH

The effect of antiviral therapy on patients with hepatitis B virus-related hepatocellular carcinoma after curative resection: a systematic review and meta-analysis

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Xu-Xiao Chen[1,2]
Jian-Wen Cheng[1,2]
Ao Huang[1,2]
Xin Zhang[1,2]
Jian Wang[1,2]
Jia Fan[1,2]
Jian Zhou[1,2]
Xin-Rong Yang[1,2]

[1]Liver Surgery Department, Liver Cancer Institute, Zhongshan Hospital, [2]Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai, People's Republic of China

Background and aim: Studies suggest that antiviral therapy performed after curative resection improves the postoperative prognosis of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC), but the evidence has been contradictory. The aim of this meta-analysis was to assess the effect of antiviral therapy with nucleoside analogs (NAs) after curative resection on the long-term postoperative survival of patients with HBV-related HCC.

Materials and methods: MEDLINE, PubMed, Embase, and Cochrane Library were systematically searched up to August 2017 with no limits. Outcome measures were the primary parameter of overall survival (OS) after radical resection of HBV-related HCC and the secondary parameter of postoperative recurrence-free survival (RFS).

Results: A total of 9,009 patients (2,546 of whom received antiviral therapy and 6,463 received no treatment) were included. The pooled analysis revealed that antiviral therapy was associated with significantly improved OS (hazard ratio [HR]: 0.58; 95% confidence interval [CI]: 0.51–0.67; $P<0.00001$) and RFS (HR: 0.68; 95% CI: 0.63–0.74; $P<0.00001$). Moderate heterogeneity among studies for both OS and RFS was observed, which disappeared or decreased after pooling studies using one type of NA as antiviral drug. In the subgroup analysis, antiviral therapy significantly prolonged both OS (HR: 0.69; 95% CI: 0.52–0.92; $P=0.01$) and RFS (HR: 0.58; 95% CI: 0.49–0.70; $P<0.00001$) in patients with high baseline HBV DNA level (≥20,000 IU/mL) with no heterogeneity, but not in patients with low baseline HBV DNA level (<20,000 IU/mL).

Conclusion: Antiviral therapy with NAs confers significant survival benefits in patients with HBV-related HCC after curative resection, especially in patients with high baseline HBV DNA level (≥20,000 IU/mL).

Keywords: hepatocellular carcinoma, hepatitis B virus, antiviral therapy, recurrence, survival

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths in the modern world, and its incidence continues to increase.[1] Chronic hepatitis B virus (HBV) infection remains a major cause of HCC development (especially in Asia) either through direct transactivation, viral integration, or indirectly through inflammation, fibrosis, or cirrhosis.[2,3] Growing evidence has shown that antiviral therapy with nucleoside analogs (NAs) can reduce the risk of HCC development in patients with chronic HBV infection.[4,5] According to the current guidelines for the management of HCC, surgical resection should be considered as the first-line treatment for patients

Correspondence: Xin-Rong Yang
Liver Surgery Department, Liver Cancer Institute, Zhongshan Hospital, Fudan University, No 180, Fenglin Road, Shanghai 200032, People's Republic of China
Tel/fax +86 21 6403 7181
Email yang.xinrong@zs-hospital.sh.cn

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with resectable tumors and preserved liver function.[6,7] With advances in surveillance programs, early diagnosis, and surgical technologies, the long-term postoperative survival of patients with early-stage HCC has improved, but is still unsatisfactory due to the high recurrence rate. Therefore, how to decrease HCC recurrence after curative resection merits further attention.

In patients with resected HBV-related HCC, factors including high viral replication status, active inflammation, subsequent damage, and regeneration of hepatocytes are associated with an increased risk of recurrence and adverse long-term survival outcomes.[8–10] Further, sustained low HBV load predicts good long-term recurrence-free survival (RFS) and overall survival (OS).[11] Recently, several pioneering studies used antiviral therapy with NAs (NA therapy) to treat patients with HBV-related HCC after curative resection and assessed the effect of such therapy on the long-term postoperative survival outcomes.[12–36] Some trials reported significant postoperative survival benefits, but others failed to confirm such outcomes. Indeed, the previous meta-analyses on this issue did not exclude patients who received NA therapy before the diagnosis of HBV-related HCC, which may affect the natural course of HBV-related HCC.[37] Compared to locoregional therapy including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transcatheter arterial embolization (TAE), surgical resection can usually achieve relatively complete elimination of HCC lesions and satisfied margin of normal liver tissue which is very important to avoid potential tumor tissue remnant and potentially benefits the prognosis of patients.[38–40] Patients who received locoregional treatments instead of curative resection for the initial treatment of HCC had not been excluded in the previous meta-analyses, which may have potentially biased the interpretation of survival outcomes.[41–45] Otherwise, non-English articles were all excluded in previous meta-analyses, and this search strategy may not be sufficiently comprehensive since HBV infection is the main cause of HCC in Asia-Pacific region, and Chinese, Korean, and Japanese articles may contribute significantly to the meta-analysis. Therefore, to investigate this important issue, we performed a more comprehensive meta-analysis to evaluate the effect of NA therapy after curative resection on the long-term postoperative survival of patients with HBV-related HCC.

Materials and methods

Data sources and search strategy

A systematic literature search was performed up to August 2017 using MEDLINE, PubMed, Embase, and Cochrane Library with no limits. The search strategy involved the Medical Subject Heading (MeSH) terms: "hepatitis B," "HBV," "antiviral," "nucleotide," "nucleotide analog," "lamivudine," "adefovir," "entecavir," "telbivudine," "hepatocellular carcinoma," "HCC," "liver cancer," "hepatic cancer," "liver resection," "surgical resection," "radical resection," "curative resection," "hepatic resection," and "hepatectomy," combined with free text words. The bibliographies of all retrieved review articles and primary studies were manually searched for more relevant studies. For studies with duplicate publications from the same cohort, the most recent comprehensive publication was included.

Study selection

All clinical studies, including randomized controlled trials (RCTs) and prospective or retrospective cohort studies, were selected if they met the following criteria: 1) enrolled patients who were diagnosed with HBV-related HCC and underwent curative resection as the initial treatment; 2) enrolled patients underwent no other forms of antitumor therapy before curative resection, such as local ablation therapy, regional or systemic chemotherapy, molecular target therapy, or immunotherapy; 3) consisted of one or more groups treated with NA therapy and an untreated control group; 4) reported at least long-term results of OS or RFS for outcome measures; 5) had been published with full-text accessible.

Studies were excluded if they met one or more of the following criteria: 1) included patients who received NA therapy before the diagnosis of HBV-related HCC; 2) included patients with combined infection of other hepatitis viruses; 3) included patients with drug abuse or alcohol consumption; 4) nonhuman studies, abstracts, editorials, letters, case reports, reviews, and studies not clearly reporting the outcomes of interest.

Outcome measures

The primary analysis focused on OS of HBV-related HCC after curative resection, and postoperative RFS served as secondary outcome.

Data extraction

Parameters regarding the following information were extracted in a standardized data extraction form: 1) study characteristics: reference, year of publication, country of origin, and study design; 2) patient characteristics: sample size, age, gender, hepatitis B e-antigen (HBeAg) status, and Child–Pugh classification; 3) tumor characteristics: tumor size and number; 4) outcomes of the antiviral therapy group and the control group: OS and RFS;

5) potential sources of heterogeneity. Any discrepancy in the extraction process was resolved by discussion and consensus.

Quality assessment

The quality of each trial was assessed independently by two study investigators (X-XC and X-RY). The Jadad scale was used to score the methodological quality of RCTs based on the following items: randomization (0−2 points), blinding (0−2 points), and dropouts and withdrawals (0−1 point). A modified Newcastle–Ottawa Scale was used to assess non-RCTs across the following three factors: patient selection (0−2 stars), comparability of the cohort (0−2 stars), and outcome assessment (0−2 stars).[46]

Statistical analysis

The meta-analysis was performed by using Review Manager (version 5.2), which was provided by the Cochrane Collaboration (The Nordic Cochrane Centre, Copenhagen, Denmark). Long-term outcomes (survival analysis) were analyzed by calculating the hazard ratio (HR) with 95% confidence interval (95% CI). HRs of the OS or RFS were calculated and combined using the data extracted from Kaplan–Meier curves; HR <1 represented survival benefits favoring the antiviral therapy group. A random-effect model (DerSimonian and Laird's method) was used to compare the overall effect estimates.

Statistical heterogeneity was explored by the χ^2 and I^2 statistics. $I^2<25\%$ was considered to reflect low heterogeneity, an I^2 value between 25% and 50% was considered to reflect moderate heterogeneity, and $I^2>50\%$ was considered to reflect high heterogeneity. Heterogeneity was considered statistically significant when the Cochrane Q test $P<0.10$. Two-sided value of $P<0.05$ was considered statistically significant. A funnel plot was conducted to screen for potential publication bias.

In addition, a sensitivity analysis was performed to assess the effect of individual studies on the pooled estimates. To anticipate potential heterogeneity among the included studies, subgroup analysis was performed for the following study-related variables if the necessary data were provided: 1) NA type; 2) viral load (baseline HBV DNA level ≥20,000 IU/mL versus <20,000 IU/mL); 3) fully preserved hepatic function (Child class A).

Results

Characteristics of identified studies

A total of 360 potentially relevant studies were identified through database searching and other sources. After detailed screening, based on the inclusion and exclusion criteria, 25 references involving 26 studies (two RCTs and 24 non-RCTs) were included for the final meta-analysis.[12–36] One study was a two-stage longitudinal clinical study, which included a first-stage non-RCT to assess the effect of NA therapy on the postoperative prognosis of HBV-related HCC and a second-stage RCT to validate the initial result.[20] Furthermore, propensity score matching (PSM) analysis was performed in one retrospective study to reduce patient selection bias, and we only extracted the data after PSM for the current meta-analysis.[15] The detailed study screening and selection process is shown in Figure 1.

A total of 9,009 patients with resected HBV-related HCC were included in the analysis, 2,546 of whom received NA therapy (antiviral therapy group), whereas the other 6,463 patients received no treatment (control group). Table 1 lists the baseline characteristics of the included studies and the main features of the enrolled patients.

Antiviral therapy and virological response

In the 26 included studies, lamivudine was the most commonly used antiviral drug, followed by entecavir and adefovir. When lamivudine resistance occurred, adefovir was added or entecavir was used instead. Three studies reported HBV DNA suppression rates, and NA therapy was associated with significantly higher HBV DNA suppression rate at 1, 2, 3, and 5 years.[13,14,16,26,29,36] In the antiviral therapy group, the HBV DNA suppression rate ranged from 51.3% to 87.2% at 1 year, from 62.7% to 98.0% at 2 years, from 67.2% to 91.7% at 3 years, and 92.8% at 5 years of NA therapy. The cumulative HBeAg seroconversion rate at 1 year ranged from 12.0% to 57.2% in the antiviral therapy group.[14,16]

Primary outcome: OS

A total of 17 studies reported the comparative data for postoperative OS. Meta-analysis of these studies revealed that the NA therapy was significantly associated with higher OS (HR: 0.58; 95% CI: 0.51–0.67; $P<0.00001$; Figure 2A). Moderate heterogeneity was detected in the analysis ($P=0.04$, $I^2=40\%$). However, after pooling studies using one type of NA, no heterogeneity was observed within subgroups of studies (Figure 3).

While the subgroup analysis of patients with high baseline HBV DNA level (≥20,000 IU/mL) showed stable results (HR: 0.69; 95% CI: 0.52–0.92; $P=0.01$) with no heterogeneity among studies, the subgroup analysis of patients with low baseline HBV DNA level (<20,000 IU/mL) indicated no significant difference between the antiviral therapy group

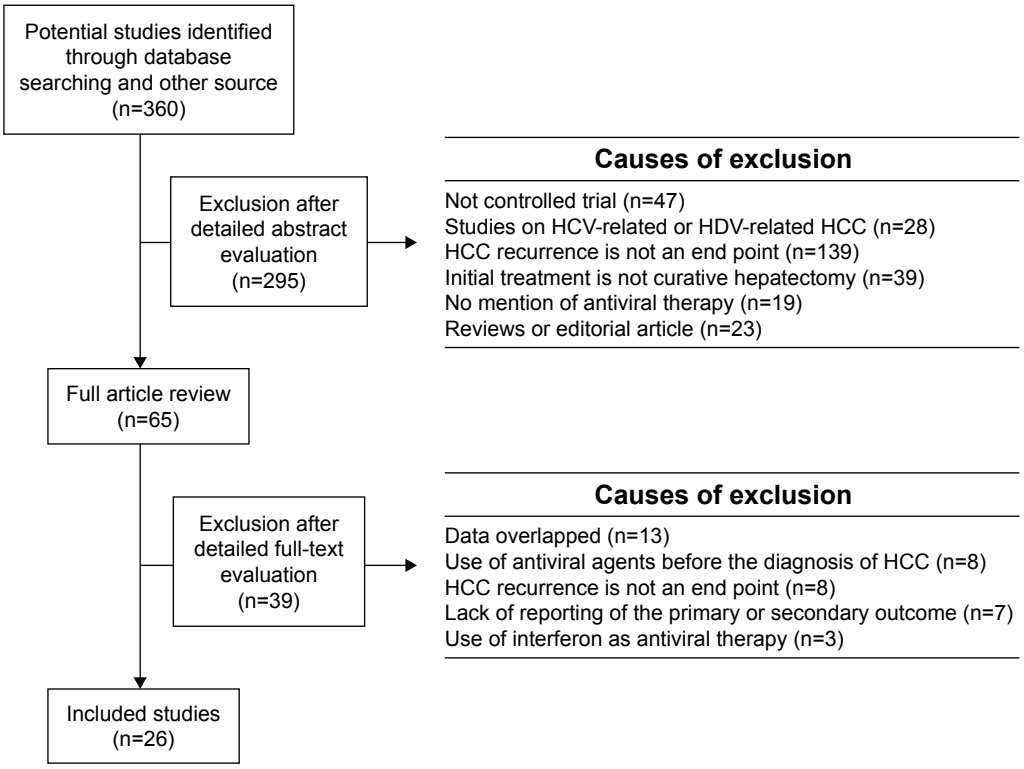


Figure 1 Flowchart of search strategy for meta-analysis study selection.
Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus.

and the control group (HR: 0.80; 95% CI: 0.38–1.68; P=0.56; Figure 4A). Stratified meta-analysis of fully preserved hepatic function (Child class A) showed stable results with no heterogeneity (Figure 5A).

Secondary outcome: RFS

The selected 25 studies reported the comparative data for postoperative RFS. Meta-analysis of these studies showed that patients with NA therapy had a significantly increased RFS after surgery (HR: 0.68; 95% CI: 0.63–0.74; P<0.00001). Moderate heterogeneity was detected in the analysis (P=0.08, I^2=30%; Figure 2B). However, after pooling studies using one type of NA, only a little heterogeneity was observed within subgroups of studies (Figure 6).

According to subgroup analysis, patients with high baseline HBV DNA level showed stable results (HR: 0.58; 95% CI: 0.49–0.70; P<0.00001) with on heterogeneity among studies, whereas results from patients with low baseline HBV DNA level showed no significant difference between the antiviral therapy group and the control group (HR: 0.86; 95% CI: 0.51–1.46; P=0.57) with moderate heterogeneity among studies (Figure 4B). Stratified meta-analysis of fully preserved hepatic function (Child class A) showed stable results with high heterogeneity (Figure 5B).

Liver function reserve at HCC recurrence and subsequent treatment for recurrence

Two studies reported significantly better liver function in the antiviral therapy group compared to the control group at the time of HCC recurrence.[13,15] Similarly, several studies reported significantly improved liver function in the antiviral therapy group compared to the control group at 6 months after surgery;[20,25,26,28] Li et al's[16] study also reported a significant residual liver volume improvement in the antiviral therapy group compared to the control group at 6 months after surgery. Two studies reported a significantly higher amenability rate of radical retreatment (eg, surgical resection or local ablation therapy) for HCC recurrence in the antiviral therapy group due to better liver function reserve than that of the control group.[13,15]

Publication bias

Figure 7 illustrates a funnel plot of the included studies comparing postoperative RFS in HBV-related HCC patients with or without NA therapy. Visual inspection of the funnel plot revealed asymmetry, and Begg's test for publication bias showed statistically significant results which indicated

Table 1 Baseline characteristics of the studies included for meta-analysis

Study	Study type	NA type	Arms	Cases	Age (years)[a]	Gender (M/F)	HBV DNA level (log copies/mL)[a]	HBeAg (±)	Tumor size (cm)[a]	No of tumors (S/M)	Tumor stage[b]	Child–Pugh (A/B/C)	Follow-up duration (months)[a]	Quality score
Chan et al (2011)[12]	Pro–retro	LAM, ETV	Treatment	42	57	31/11	N/A	N/A	9.3	N/A	11/14/16/0 (AJCC)	42/0/0	N/A	4[c]
			Control	94	55	74/20	N/A	N/A	9.0	N/A	28/18/48/0 (AJCC)	84/10/0	N/A	
Chen et al (2016)[22]	Retro	LAM, ETV	Treatment	192	47	172/20	N/A	48/144	4.7	176/16	151/41/0 (TNM)	192/0/0	74[d]	4[c]
			Control	253	49	218/35	N/A	35/218	5.4	232/21	215/38/0 (TNM)	253/0/0		
Chen (2015)[24]	Pro	LAM	Treatment	45	52.2	39/6	N/A	N/A	N/A	37/8	38/5/2/0 (AJCC)	41/4/0	N/A	4[c]
			Control	40	51.9	36/4	N/A	N/A	N/A	35/5	34/5/1/0 (AJCC)	38/2/0	N/A	
Cheng et al (2011)[35]	Retro	LAM	Treatment	50	45.3	38/12	5.56 (5.53–5.64)	N/A	N/A	N/A	N/A	N/A	N/A	4[c]
			Control	43	42.2	32/11	5.68 (5.50–5.83)	N/A	N/A	N/A	N/A	N/A	N/A	
Chong et al (2015)[13]	Pro–retro	LAM, ETV	Treatment	254	55	222/32	N/A	42/212	3.5	198/56	168/50/34/2 (AJCC)	243/10/1	39.2 (0.2–163.9)	5[c]
		ADV, LdT	Control	150	56	125/25	N/A	12/138	3.8	118/32	97/26/27/0 (AJCC)	145/4/1	43.3 (0.1–151.2)	
Ding et al (2014)[36]	Retro	ETV	Treatment	74	47.2	56/18	5.21	N/A	N/A	N/A	N/A	54/20/0	N/A	4[c]
			Control	39	46.5	30/9	5.02	N/A	N/A	N/A	N/A	31/8/0	N/A	
Fang et al (2012)[25]	Retro	LAM	Treatment	26	48.9	20/6	6.38	N/A	N/A	N/A	N/A	N/A	41	4[c]
			Control	30	50.0	23/7	6.55	N/A	N/A	N/A	N/A	N/A	20	
Huang et al (2015)[14]	RCT	ADV	Treatment	100	50.6	90/10	N/A	51/49	4.9	100/0	8/60/0 (BCLC [0/A/B])	100/0/0	60 (4–70)[d]	3[e]
			Control	100	50.5	89/11	N/A	50/50	5.1	100/0	8/59/0 (BCLC [0/A/B])	100/0/0		
Huang et al (2016)[26]	Retro	LAM, ETV	Treatment	45	N/A	N/A	4.72	N/A	N/A	N/A	N/A	45/0/0	11 (3–34)[d]	4[c]
		ADV	Control	33	N/A	N/A	4.25	N/A	N/A	N/A	N/A	33/0/0		
Ke et al (2013)[15]	Retro	LAM	Treatment	141	48.9	129/12	4.97	15/126	4.5	102/39	107/23/11 (BCLC [A/B/C])	141/0/0	24 (2–65)	5[c]
			Control	141	49.7	127/14	4.78	16/125	5.0	107/34	105/26/10 (BCLC [A/B/C])	141/0/0	23 (1–73)	
Li et al (2010)[16]	Pro	LAM, ADV	Treatment	43	46	34/9	6.49 (4.04–7.38)	38/5	7.1	N/A	9/17/17 (TNM)	28/14/1	12	4[c]
			Control	36	45	30/6	7.27 (3.45–8.32)	27/9	8.5	N/A	4/10/22 (TNM)	21/12/3	12	
Lin et al (2016)[27]	Retro	ETV	Treatment	35	54.2	26/9	7.48	N/A	N/A	N/A	N/A	28/7/0	54	4[c]
			Control	25	2.5	20/5	6.94	N/A	N/A	N/A	N/A	20/5/0	38	
Qian et al (2016)[28]	Retro	LAM, ADV	Treatment	70	N/A	58/12	6.70	N/A	6.5	N/A	N/A	70/0/0	N/A	4[c]
			Control	65	N/A	52/13	6.71	N/A	6.6	N/A	N/A	65/0/0	N/A	
Su et al (2013)[17]	Retro	LAM, ETV	Treatment	62	52	56/6	5.89 (4.83–7.15)	9/53	2.7	48/14	40/15/5 (BCLC [A/B/C])	N/A	N/A	4[c]

(*Continued*)

Table 1 (*Continued*)

Study	Study type	NA type	Arms	Cases	Age (years)[a]	Gender (M/F)	HBV DNA level (log copies/mL)[a]	HBeAg (±)	Tumor size (cm)[a]	No of tumors (S/M)	Tumor stage[b]	Child–Pugh (A/B/C)	Follow-up duration (months)[a]	Quality score
			Control	271	58	232/39	5.48 (4.09–7.83)	28/243	4.2	144/127	142/83/44 (BCLC [A/B/C])	N/A	N/A	
Tian et al (2015)[29]	Retro	LAM, ETV	Treatment	29	57.8	18/11	4.7	N/A	2.8	11/18	N/A	25/4/0	28.6[d]	4[c]
		ADV	Control	21	58.3	14/7	6.1	N/A	3.4	8/13	N/A	18/3/0		
Wang et al (2015)[30]	Retro	LAM, ETV	Treatment	76	53.7	58/18	5.46	N/A	6.1	64/12	35/30/11 (TNM)	N/A	30.3	4[c]
		ADV	Control	80	51.3	57/23	5.40	N/A	5.5	71/9	32/28/10 (TNM)	N/A	18.4	
Wei et al (2016)[23]	Retro	LAM, ADV	Treatment	86	50.8	79/7	6.9 (2.0–8.8)	14/72	8.0	27/59	0/36/50 (TNM)	82/4/0	30.6 (3.3–73.2)[d]	4[c]
			Control	40	50.0	35/5	5.7 (2.0–6.7)	6/34	8.9	15/25	0/22/18 (TNM)	39/1/0		
Wu et al (2012)[18]	Retro	LAM, ETV	Treatment	518	54.4	435/83	N/A	N/A	N/A	N/A	N/A	N/A	32	4[c]
		LdT	Control	4,051	54.6	3,335/716	N/A	N/A	N/A	N/A	N/A	N/A	26	
Xu et al (2016)[31]	Retro	N/A	Treatment	29	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4[c]
			Control	82	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Yang et al (2010)[32]	Retro	LAM	Treatment	30	22/8	N/A	N/A	N/A	N/A	N/A	27/2/1 (TNM)	29/1/0	26.2[d]	4[c]
			Control	30	23/7	N/A	N/A	N/A	N/A	N/A	21/7/2 (TNM)	26/4/0		
Yang et al (2012)[19]	Pro	LAM, ETV	Treatment	142	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	49.1[d]	4[c]
		ADV	Control	188	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
Yao et al (2016)[33]	Retro	LAM, ADV	Treatment	76	53.9	54/22	5.43	N/A	N/A	N/A	N/A	N/A	30.4	4[c]
			Control	80	52.3	55/25	5.40	N/A	N/A	N/A	N/A	N/A	18.5	
*Yin et al (2013a)[20]	Pro	LAM, ETV	Treatment	215	50.1	194/21	4.51	80/135	N/A	184/31	6/159/50 (BCLC [0/A/B])	209/6/0	24[d]	5[c]
		ADV	Control	402	50.3	336/66	3.82	100/302	N/A	351/51	6/296/98 (BCLC [0/A/B])	392/10/0		
*Yin et al (2013b)[20]	RCT	LAM, ETV	Treatment	81	47.9	74/7	4.88	41/40	N/A	71/10	4/67/10 (BCLC [0/A/B])	80/1/0	40[d]	3[e]
		ADV	Control	82	49.4	70/12	4.57	26/56	N/A	64/18	2/58/22 (BCLC [0/A/B])	82/0/0		
Zhang (2015)[34]	Pro	LAM	Treatment	45	52.2	39/6	N/A	N/A	N/A	37/8	38/5/2 (TNM)	41/4/0	N/A	4[c]
			Control	40	51.9	36/4	N/A	N/A	N/A	35/5	34/5/1 (TNM)	38/3/0	N/A	
Zhang et al (2014)[21]	Retro	ETV	Treatment	40	N/A	26/14	N/A	N/A	4.6	40/0	N/A	33/6/1	N/A	5[c]
			Control	47	N/A	31/16	N/A	N/A	4.8	47/0	N/A	37/10/0	N/A	

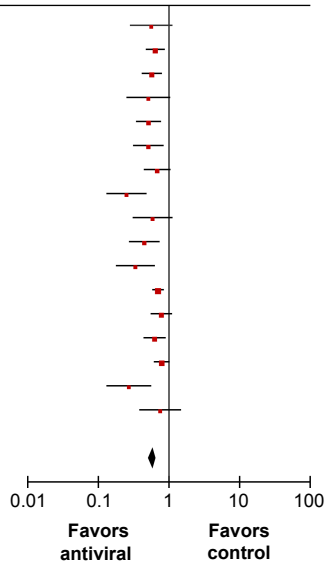
Notes: [a]Mean, median, or median (range). [b]Tumor stage containing AJCC with form (I/II/III/IV), TNM with form (I/II/III), and BCLC (0/A/B or A/B/C). [c]Modified Newcastle–Ottawa scale (0–6 stars). [d]The follow-up duration of all patients in the study. [e]Jadad scale (0–5 points). *Study of Yin et al (2013)[20] was a two-stage longitudinal clinical study which included a first stage pro study and a second stage RCT. Therefore, the first stage pro study was defined as Yin et al (2013a)[20] and the second stage RCT was defined as Yin et al (2013b)[20].

Abbreviations: ADV, adefovir dipivoxil; AJCC, American Joint Committee on Cancer; BCLC, Barcelona clinic Liver Cancer; ETV, entecavir; HBeAg, Hepatitis B e-antigen; HBV, hepatitis B virus; LAM, lamivudine; LdT, telbivudine; M/F, male/female; NA, nucleoside analog; N/A, not available; Pro, prospective; RCT, randomized controlled trial; Retro, retrospective; S/M, single/multiple.

A

Study or subgroup	Log (HR)	Antiviral therapy SE	Antiviral therapy Total	Control Total	Weight (%)	HR IV, random, 95% CI
Chan et al (2011)[12]	–0.5798	0.3537	42	94	3.1	0.56 (0.28–1.12)
Chen et al (2016)[22]	–0.4463	0.1575	192	253	8.8	0.64 (0.47–0.87)
Chong et al (2015)[13]	–0.5604	0.1678	254	150	8.3	0.57 (0.41–0.79)
Ding et al (2014)[36]	–0.6733	0.3638	74	39	2.9	0.51 (0.25–1.04)
Huang et al (2015)[14]	–0.6675	0.2084	100	100	6.5	0.51 (0.34–0.77)
Ke et al (2013)[15]	–0.6733	0.254	141	141	5.0	0.51 (0.31–0.84)
Li et al (2010)[16]	–0.3857	0.2221	43	36	6.0	0.68 (0.44–1.05)
Su et al (2013)[17]	–1.3863	0.3336	62	271	3.4	0.25 (0.13–0.48)
Tian et al (2015)[29]	–0.5351	0.3317	29	21	3.4	0.59 (0.31–1.12)
Wang et al (2015)[30]	–0.8062	0.255	76	80	5.0	0.45 (0.27–0.74)
Wei et al (2016)[23]	–1.0966	0.324	86	40	3.5	0.33 (0.18–0.63)
Wu et al (2012)[18]	–0.3567	0.0959	518	4,051	12.5	0.70 (0.58–0.84)
Yang et al (2012)[19]	–0.2485	0.1783	142	188	7.8	0.78 (0.55–1.11)
Yao et al (2016)[33]	–0.4691	0.1851	76	80	7.5	0.63 (0.44–0.90)
*Yin et al (2013a)[20]	–0.2357	0.1319	215	402	10.3	0.79 (0.61–1.02)
*Yin et al (2013b)[20]	–1.3093	0.3729	81	82	2.8	0.27 (0.13–0.56)
Zhang et al (2014)[21]	–0.2877	0.3469	40	47	3.2	0.75 (0.38–1.48)
Total (95% CI)			**2,171**	**6,075**	**100**	**0.58 (0.51–0.67)**

Heterogeneity: τ^2=0.03; χ^2=26.89, *df*=16 (*P*=0.04); I^2=40%
Test for overall effect: *Z*=7.84 (*P*<0.00001)



B

Study or subgroup	Log (HR)	Antiviral therapy SE	Antiviral therapy Total	Control Total	Weight (%)	HR IV, random, 95% CI
Chan et al (2011)[12]	–0.4155	0.2306	42	94	2.9	0.66 (0.42–1.04)
Chen et al (2016)[22]	–0.0305	0.1245	192	253	6.8	0.97 (0.76–1.24)
Chen (2015)[24]	–0.297	0.3001	45	40	1.8	0.74 (0.41–1.34)
Cheng and Lv (2011)[35]	–0.4082	0.219	50	43	3.1	0.66 (0.43–1.02)
Chong et al (2015)[13]	–0.3147	0.1262	254	150	6.7	0.73 (0.57–0.93)
Ding et al (2014)[36]	–0.5987	0.3155	74	39	1.7	0.55 (0.30–1.02)
Fang et al (2012)[25]	–0.9086	0.3812	26	30	1.2	0.40 (0.19–0.85)
Huang et al (2015)[14]	–0.399	0.1827	100	100	4.1	0.67 (0.47–0.96)
Huang et al (2016)[26]	–0.5086	0.2205	45	33	3.1	0.60 (0.39–0.93)
Ke et al (2013)[15]	–0.1054	0.146	141	141	5.6	0.90 (0.68–1.20)
Li et al (2010)[16]	–0.2107	0.1793	43	36	4.2	0.81 (0.57–1.15)
Lin et al (2016)[27]	–1.1841	0.3932	35	25	1.1	0.31 (0.14–0.66)
Qian et al (2016)[28]	–0.685	0.2324	70	65	2.8	0.50 (0.32–0.79)
Su et al (2013)[17]	–0.5798	0.1846	62	271	4.0	0.56 (0.39–0.80)
Tian et al (2015)[29]	–0.5351	0.3317	29	21	1.5	0.59 (0.31–1.12)
Wang et al (2015)[30]	–0.4291	0.1767	76	80	4.3	0.65 (0.46–0.92)
Wei et al (2016)[23]	–0.4005	0.1809	86	40	4.2	0.67 (0.47–0.96)
Wu et al (2012)[18]	–0.2744	0.072	518	4,051	10.8	0.76 (0.66–0.88)
Xu et al (2016)[31]	–0.6038	0.4061	29	82	1.1	0.55 (0.25–1.21)
Yang et al (2012)[19]	–0.6349	0.1436	142	188	5.7	0.53 (0.40–0.70)
Yao et al (2016)[33]	–0.3479	0.1574	76	80	5.1	0.71 (0.52–0.96)
*Yin et al (2013a)[20]	–0.2485	0.0852	215	402	9.6	0.78 (0.66–0.92)
*Yin et al (2013b)[20]	–0.734	0.1759	81	82	4.3	0.48 (0.34–0.68)
Zhang (2015)[34]	–0.2942	0.2752	45	40	2.1	0.75 (0.43–1.28)
Zhang et al (2014)[21]	–0.5108	0.2606	40	47	2.3	0.60 (0.36–1.00)
Total (95% CI)			**2,516**	**6,433**	**100**	**0.68 (0.63–0.74)**

Heterogeneity: τ^2=0.01; χ^2=34.37, *df*=24 (*P*=0.08); I^2=30%
Test for overall effect: *Z*=8.87 (*P*<0.00001)

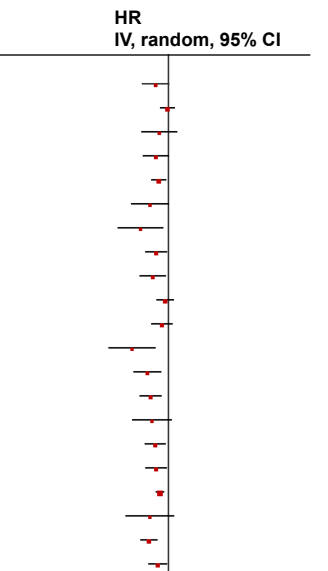


Figure 2 Forest plots for postoperative survival outcomes.
Notes: (**A**) Meta-analysis of OS. (**B**) Meta-analysis of RFS. *Study of Yin et al (2013)[20] was a two-stage longitudinal clinical study which included a first stage pro study and a second stage RCT. Therefore, the first stage pro study was defined as Yin et al (2013a)[20] and the second stage RCT was defined as Yin et al (2013b)[20].
Abbreviations: CI, confidence interval; HR, hazard ratio; IV, inverse variance; OS, overall survival; RFS, recurrence-free survival; SE, standard error.

possibility of publication bias (*z*=2.73, *P*=0.006). Subsequently, trim and fill method was used to correct and identify whether the asymmetry funnel plot was caused by publication bias. The results showed that no study was missing in the iterative algorithm and the effect size of the meta-analysis after trimming and filling was exactly same as the primary results, which indicated that there was no publication bias and the asymmetry funnel plot may not be caused by publication bias.

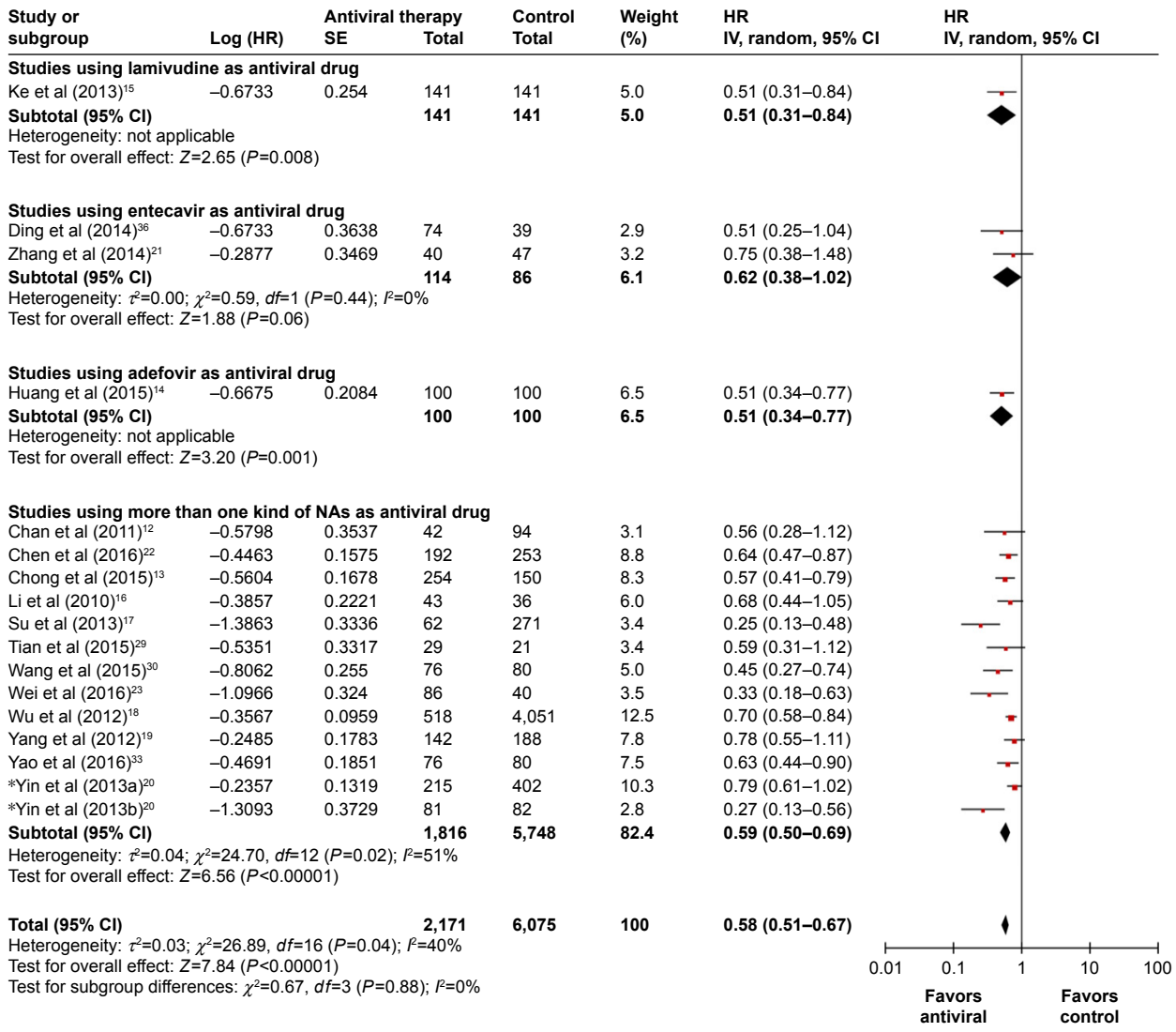


Figure 3 Stratified meta-analysis of OS according to the type of NAs.
Note: *Study of Yin et al (2013)[20] was a two-stage longitudinal clinical study which included a first stage pro study and a second stage RCT. Therefore, the first stage pro study was defined as Yin et al (2013a)[20] and the second stage RCT was defined as Yin et al (2013b)[20].
Abbreviations: CI, confidence interval; HR, hazard ratio; IV, inverse variance; NAs, nucleoside analogs; OS, overall survival; SE, standard error.

Discussion

Tumor recurrence is the most common cause of mortality for HCC patients after curative resection.[47] Despite the advances in surveillance programs, surgical technologies, and multidisciplinary treatments, there are still no adjuvant therapy options that effectively prevent HCC recurrence after curative resection. Most of the well-known risk factors for HCC recurrence, such as tumor characteristics, liver cirrhosis, and alpha fetoprotein level, are irreversible.[48] However, HBV status is an important risk factor for HCC recurrence that can be reversed by NA therapy. Thus, the exact effect of NA therapy on patients with HBV-related HCC after curative resection becomes a subject of great interest to hepatobiliary surgeons or physicians, and several studies have been performed recently, but the results are inconsistent. Otherwise, there is still not enough convincing evidence to support this issue because of the potential bias mentioned earlier in the previous studies or meta-analyses. Therefore, we conducted the current study, a more comprehensive meta-analysis, to assess the exact effect of NA therapy after curative resection on the long-term survival of patients with HBV-related HCC as far as possible.

The current meta-analysis demonstrated that NA therapy significantly improved the RFS of patients after surgical resection for HBV-related HCC, which suggested that NA therapy can prevent or delay the recurrence of HBV-related HCC. Recent studies have demonstrated that sustained viremia may impair tumor immune surveillance and favor the development of hepatocellular carcinogenesis,[49,50]

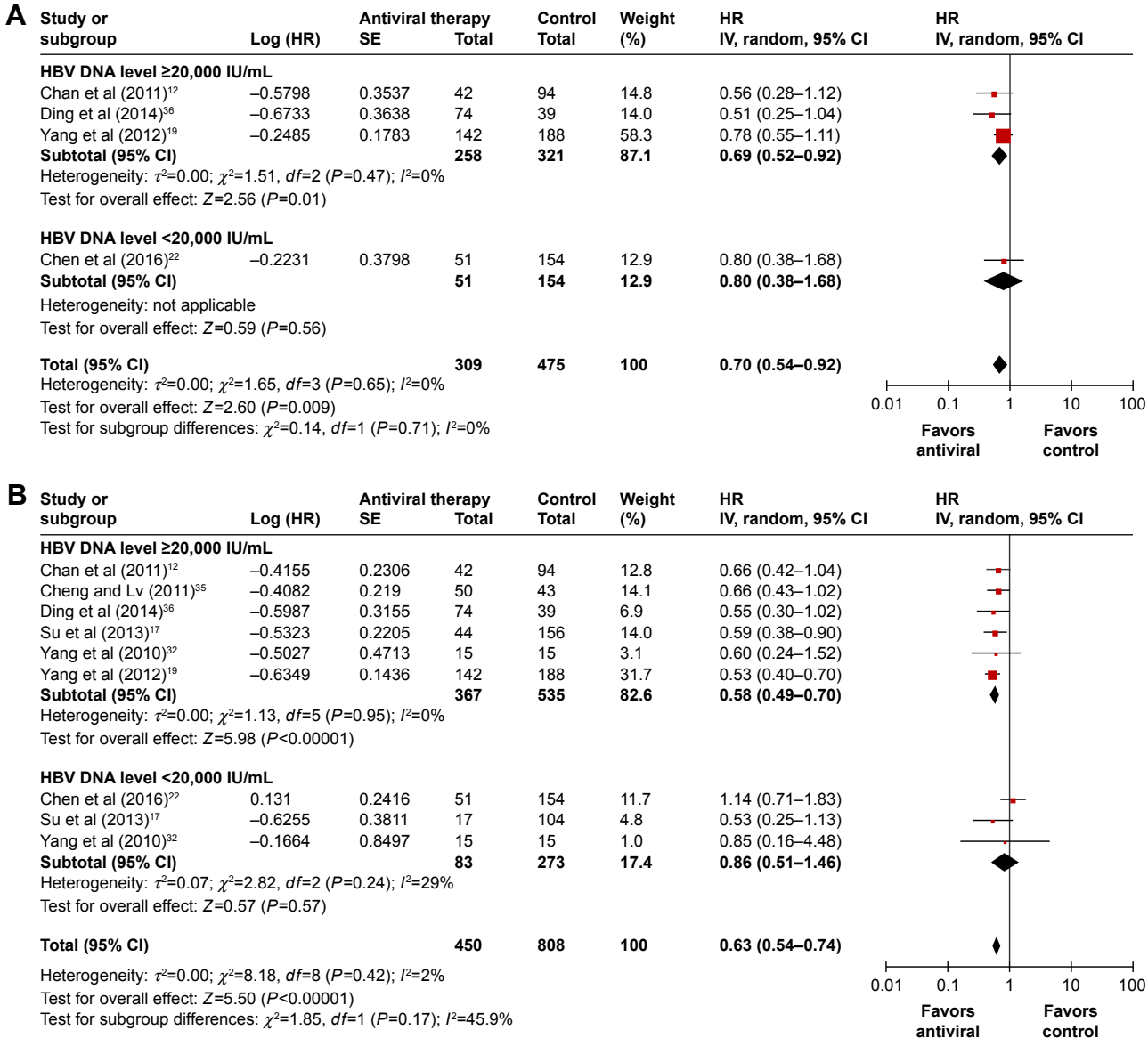


Figure 4 Stratified meta-analysis of postoperative survival outcomes according to viral load (baseline HBV DNA level ≥20,000 IU/mL versus <20,000 IU/mL).
Notes: (**A**) Meta-analysis of OS. (**B**) Meta-analysis of RFS.
Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; IV, inverse variance; OS, overall survival; RFS, recurrence-free survival; SE, standard error.

and chronic hepatitis activity and liver inflammation induced by immune response were associated with HCC recurrence after radical resection.[51,52] Similarly, other studies found that high HBV load and HBV mutation promote the growth and metastasis of HCC,[17,53,54] and the HBV X protein promotes the invasive and metastatic potential of HCC.[20,55–57] Therefore, the beneficial effect of NA therapy on HCC recurrence may be associated with the inhibition of these viral factors. Due to moderate heterogeneity that was detected among eligible studies, subgroup analyses were performed. After pooling studies using one type of NAs, only a little heterogeneity was observed. That may be partly attributed to the different viral suppression effect of different types of NAs which can further affect the tumor recurrence of HBV-related HCC. In the subgroup analyses of patients with different viral load, NA therapy can significantly prolong RFS in patients with high baseline HBV DNA level (≥20,000 IU/mL) with no heterogeneity, but not in patients with low baseline HBV DNA level (<20,000 IU/mL) with moderate heterogeneity. The results indicated that HCC patients with low baseline HBV DNA level may not significantly benefit from NA therapy as patients with high baseline HBV DNA level did. However, as there was moderate heterogeneity in the subgroup analysis of patients

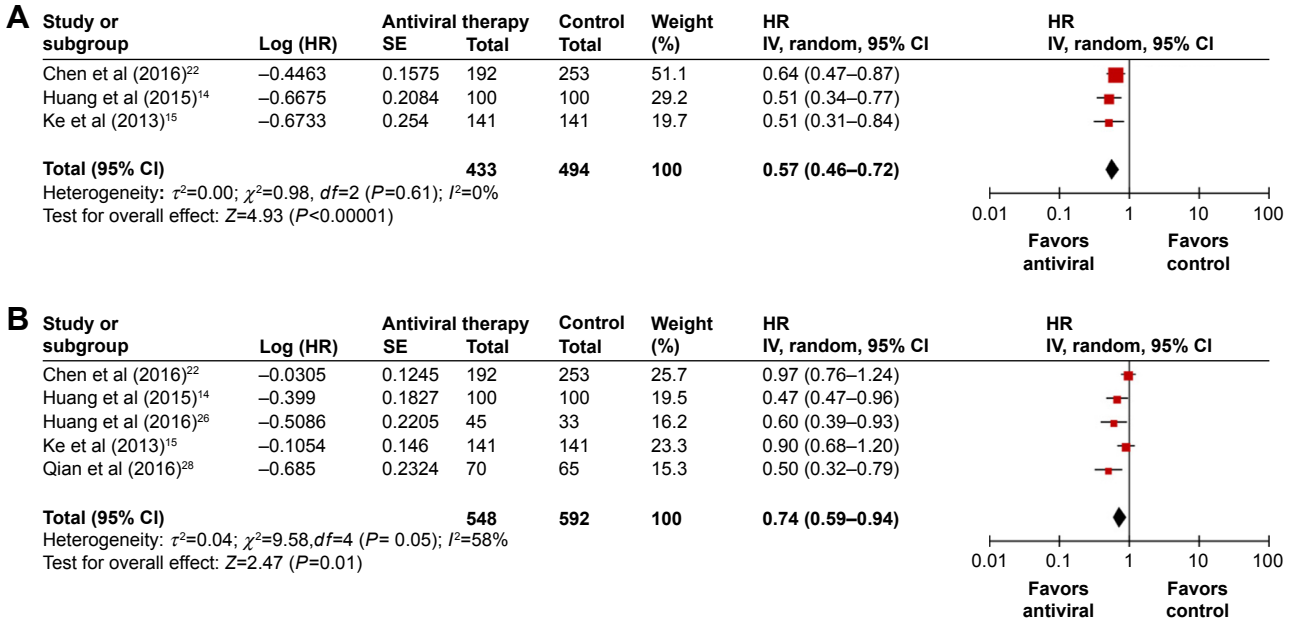


Figure 5 Subgroup analysis on patients with fully preserved hepatic function (Child class A).
Notes: (**A**) Meta-analysis of OS. (**B**) Meta-analysis of RFS.
Abbreviations: CI, confidence interval; HR, hazard ratio; IV, inverse variance; OS, overall survival; RFS, recurrence-free survival; SE, standard error.

with low baseline HBV DNA level (<20,000 IU/mL), the findings are not conclusive and further high-quality studies are needed.

In this study, we also found that NA therapy can significantly improve the OS of patients with HBV-related HCC after surgical resection. The beneficial effect of NA therapy in preventing or delaying HCC recurrence contributes to better OS. Further, several studies have reported that NA therapy is effective in suppressing viral replication, modulating liver function, and increasing residual liver volume after radical resection.[13,15,16,20] These effects may not only affect survival directly but also significantly improve the tolerance of patients to receive subsequent therapy (especially repeat surgical resection) after HCC recurrence which leads to a significant improvement in OS. Subgroup analyses were also conducted because of the moderate heterogeneity among studies. After pooling studies using one type of NA, no heterogeneity was observed among studies. In the subgroup analyses of patients with different viral load, NA therapy can significantly prolong OS in patients with high baseline HBV DNA level (≥20,000 IU/mL) with no heterogeneity, but not in patients with low baseline HBV DNA level (<20,000 IU/mL) with moderate heterogeneity. Smaller size was one factor that led to nonsignificant groups of patients with low baseline HBV DNA level (<20,000 IU/mL). Moreover, it has been identified that HCC patients with persistently low HBV DNA levels had better survival results compared to those with high HBV DNA levels. After antiviral therapy, groups of HCC patients with high HBV DNA levels always could achieve a more substantial reduction in HBV DNA load, as compared to groups of HCC patients with low HBV DNA levels. Therefore, HCC patients with low HBV DNA levels may not significantly benefit from antiviral therapy compared to patients with high HBV DNA levels. However, as only one study was included in the subgroup analysis of patients with low baseline HBV DNA level (<20,000 IU/mL), more quality studies are needed to draw a definitive conclusion.

Nonetheless, there are several limitations to the current meta-analysis. First, most of the included studies were non-RCTs; the potential confounding factors in these studies may decrease the reliability of the results, even for the well-analyzed cohort studies. Second, several indirect data acquisition methods were used in the meta-analysis, which may have effects on the outcomes. Finally, moderate heterogeneity existed in the meta-analysis; the variation in HBV status, type of NA therapy, Child–Pugh class, and tumor stage may be responsible for the heterogeneity.

Conclusion

The current meta-analysis suggests that antiviral therapy with NAs significantly improves the survival outcomes of patients with HBV-related HCC after curative resection, especially for patients with high HBV DNA level. To further

Study or subgroup	Log (HR)	Antiviral therapy SE	Total	Control Total	Weight (%)	HR IV, random, 95% CI
Studies using lamivudine as antiviral drug						
Chen (2015)[24]	–0.297	0.3001	45	40	1.8	0.74 (0.41–1.34)
Cheng and Lv (2011)[35]	–0.4082	0.219	50	43	3.1	0.66 (0.43–1.02)
Fang et al (2012)[25]	–0.9086	0.3812	26	30	1.2	0.40 (0.19–0.85)
Ke et al (2013)[15]	–0.1054	0.146	141	141	5.6	0.90 (0.68–1.20)
Zhang (2015)[34]	–0.2942	0.2752	45	40	2.1	0.75 (0.43–1.28)
Subtotal (95% CI)			**307**	**294**	**13.8**	**0.75 (0.60–0.93)**
Heterogeneity: τ^2=0.01; χ^2=4.49, *df*=4 (*P*=0.34); I^2=11%						
Test for overall effect: *Z*=2.61 (*P*=0.009)						
Studies using entecavir as antiviral drug						
Ding et al (2014)[36]	–0.5987	0.3155	74	39	1.7	0.55 (0.30–1.02)
Lin et al (2016)[27]	–1.1841	0.3932	35	25	1.1	0.31 (0.14–0.66)
Zhang et al (2014)[21]	–0.5108	0.2606	40	47	2.3	0.60 (0.36–1.00)
Subtotal (95% CI)			**149**	**111**	**5.1**	**0.51 (0.35–0.73)**
Heterogeneity: τ^2=0.01; χ^2=2.13, *df*=2 (*P*=0.34); I^2=6%						
Test for overall effect: *Z*=3.68 (*P*=0.0002)						
Studies using adefovir as antiviral drug						
Huang et al (2015)[14]	–0.399	0.1827	100	100	4.1	0.67 (0.47–0.96)
Subtotal (95% CI)			**100**	**100**	**4.1**	**0.67 (0.47–0.96)**
Heterogeneity: not applicable						
Test for overall effect: *Z*=2.18 (*P*=0.03)						
Studies using more than one kind of NAs as antiviral drug						
Chan et al (2011)[12]	–0.4155	0.2306	42	94	2.9	0.66 (0.42–1.04)
Chen et al (2016)[22]	–0.0305	0.1245	192	253	6.8	0.97 (0.76–1.24)
Chong et al (2015)[13]	–0.3147	0.1262	254	150	6.7	0.73 (0.57–0.93)
Huang et al (2016)[26]	–0.5086	0.2205	45	33	3.1	0.60 (0.39–0.93)
Li et al (2010)[16]	–0.2107	0.1793	43	36	4.2	0.81 (0.57–1.15)
Qian et al (2016)[28]	–0.685	0.2324	70	65	2.8	0.50 (0.32–0.79)
Su et al (2013)[17]	–0.5798	0.1846	62	271	4.0	0.56 (0.39–0.80)
Tian et al (2015)[29]	–0.5351	0.3317	29	21	1.5	0.59 (0.31–1.12)
Wang et al (2015)[30]	–0.4291	0.1767	76	80	4.3	0.65 (0.46–0.92)
Wei et al (2016)[23]	–0.4005	0.1809	86	40	4.2	0.67 (0.47–0.96)
Wu et al (2012)[18]	–0.2744	0.072	518	4,051	10.8	0.76 (0.66–0.88)
Xu et al (2016)[31]	–0.6038	0.4061	29	82	1.1	0.55 (0.25–1.21)
Yang et al (2012)[19]	–0.6349	0.1436	142	188	5.7	0.53 (0.40–0.70)
Yao et al (2016)[33]	–0.3479	0.1574	76	80	5.1	0.71 (0.52–0.96)
*Yin et al (2013a)[20]	–0.2485	0.0852	215	402	9.6	0.78 (0.66–0.92)
*Yin et al (2013b)[20]	–0.734	0.1759	81	82	4.3	0.48 (0.34–0.68)
Subtotal (95% CI)			**1,960**	**5,928**	**76.9**	**0.68 (0.62–0.75)**
Heterogeneity: τ^2=0.01; χ^2=23.67, *df*=15 (*P*=0.07); I^2=37%						
Test for overall effect: *Z*=7.62 (*P*<0.00001)						
Total (95% CI)			**2,516**	**6,433**	**100**	**0.68 (0.63–0.74)**
Heterogeneity: τ^2=0.01; χ^2=34.37, *df*=24 (*P*=0.08); I^2=30%						
Test for overall effect: *Z*=8.87 (*P*<0.00001)						
Test for subgroup differences: χ^2=3.37, *df*=3 (*P*=0.34); I^2=11.0%						

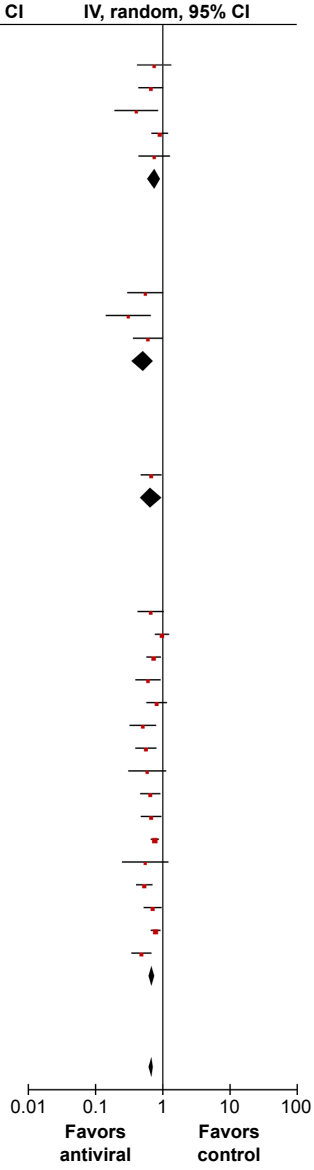


Figure 6 Stratified meta-analysis of RFS according to the type of NAs.
Note: *Study of Yin et al (2013)[20] was a two-stage longitudinal clinical study which included a first stage pro study and a second stage RCT. Therefore, the first stage pro study was defined as Yin et al (2013a)[20] and the second stage RCT was defined as Yin et al (2013b)[20].
Abbreviations: CI, confidence interval; HR, hazard ratio; IV, inverse variance; NAs, nucleoside analogs; RFS, recurrence-free survival; SE, standard error.

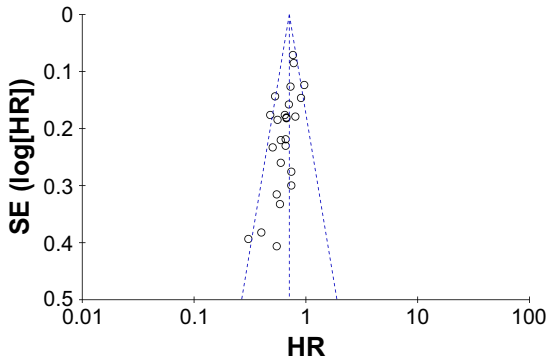


Figure 7 Funnel plot for the results from included studies comparing RFS in HBV-related HCC patients who received antiviral therapy or no treatment.
Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; RFS, recurrence-free survival; SE, standard error.

investigate the promising effects of antiviral therapy with NAs on patients with low HBV DNA level, high-quality studies are needed.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009;27(9):1485–1491.
2. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;132(7):2557–2576.
3. Wan S, Civan J, Rossi S, Yang H. Profiling HBV integrations in hepatocellular carcinoma. *Hepatobiliary Surg Nutr*. 2013;2(2):124–126.
4. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol*. 2010;53(2):348–356.
5. Shamliyan TA, MacDonald R, Shaukat A, et al. Antiviral therapy for adults with chronic hepatitis B: a systematic review for a National Institutes of Health Consensus Development Conference. *Ann Intern Med*. 2009;150(2):111–124.
6. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):i41–i48.
7. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908–943.
8. Hung IF, Poon RT, Lai CL, Fung J, Fan ST, Yuen MF. Recurrence of hepatitis B-related hepatocellular carcinoma is associated with high viral load at the time of resection. *Am J Gastroenterol*. 2008;103(7):1663–1673.
9. Yeh CT, So M, Ng J, et al. Hepatitis B virus-DNA level and basal core promoter A1762T/G1764A mutation in liver tissue independently predict postoperative survival in hepatocellular carcinoma. *Hepatology*. 2010;52(6):1922–1933.
10. Chen L, Zhang Q, Chang W, Du Y, Zhang H, Cao G. Viral and host inflammation-related factors that can predict the prognosis of hepatocellular carcinoma. *Eur J Cancer*. 2012;48(13):1977–1987.
11. An HJ, Jang JW, Bae SH, et al. Sustained low hepatitis B viral load predicts good outcome after curative resection in patients with hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2010;25(12):1876–1882.
12. Chan AC, Chok KS, Yuen WK, et al. Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus-related hepatocellular carcinoma. *Arch Surg*. 2011;146(6):675–681.
13. Chong CC, Wong GL, Wong VW, et al. Antiviral therapy improves post-hepatectomy survival in patients with hepatitis B virus-related hepatocellular carcinoma: a prospective-retrospective study. *Aliment Pharmacol Ther*. 2015;41(2):199–208.
14. Huang G, Lau WY, Wang ZG, et al. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. *Ann Surg*. 2015;261(1):56–66.
15. Ke Y, Ma L, You XM, et al. Antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after radical hepatectomy. *Cancer Biol Med*. 2013;10(3):158–164.
16. Li N, Lai EC, Shi J, et al. A comparative study of antiviral therapy after resection of hepatocellular carcinoma in the immune-active phase of hepatitis B virus infection. *Ann Surg Oncol*. 2010;17(1):179–185.
17. Su CW, Chiou YW, Tsai YH, et al. The influence of hepatitis B viral load and pre-S deletion mutations on post-operative recurrence of hepatocellular carcinoma and the tertiary preventive effects by anti-viral therapy. *PLoS One*. 2013;8(6):e66457.
18. Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308(18):1906–1914.
19. Yang T, Lu JH, Zhai J, et al. High viral load is associated with poor overall and recurrence-free survival of hepatitis B virus-related hepatocellular carcinoma after curative resection: a prospective cohort study. *Eur J Surg Oncol*. 2012;38(8):683–691.
20. Yin J, Li N, Han Y, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *J Clin Oncol*. 2013;31(29):3647–3655.
21. Zhang ZY, Zhou ZQ, Zhou GW. Higher efficacy of antiviral therapy after major hepatectomy in patients with hepatitis B virus-related hepatocellular carcinoma of less than 3 cm. *Eur J Gastroenterol Hepatol*. 2014;26(10):1116–1124.
22. Chen JL, Lin XJ, Zhou Q, Shi M, Li SP, Lao XM. Association of HBV DNA replication with antiviral treatment outcomes in the patients with early-stage HBV-related hepatocellular carcinoma undergoing curative resection. *Chin J Cancer*. 2016;35:28.
23. Wei Q, Tian H, Luo HX, et al. Better prognosis of hepatic resection combined with antiviral therapy for HBV-related hepatocellular carcinoma with BCLC Stage B/C. *Asian J Surg*. Epub 2016 Jun 16.
24. Chen Y. Role of antiviral treatment in hepatitis related liver cancer recurrence. *Chin J Biochem Pharm*. 2015;35:97–99.
25. Fang L, Zhou Y, Wang Y, Li XY. Influence of antiviral therapy on the clinical postoperative prognosis of primary liver cancer with positive HBV DNA. *Clin Med Eng*. 2012;19:1079–1081.
26. Huang LL, Zheng Q, Liu YR. Influence of antiviral therapy on the tumor recurrence in patients with hepatitis B virus related hepatocellular carcinoma after radical resection. *J Chin Physician*. 2016;18:1220–1222.
27. Lin Q, Li MJ, Li HQ, Wei Q. Clinical study of entecavir on treating hepatitis B related hepatic carcinoma after radical operation. *Chin J New Clin Med*. 2016;9:139–142.
28. Qian H, Xie P, Tan ZH. Effect of antiviral therapy on the clinical outcome of hepatitis B virus related hepatocellular carcinoma after curative resection. *Chin J Surg Integr Tradit West Med*. 2016;22:11–14.
29. Tian YH, Yang HC, Peng Y, Ma H, Li Y, Li GY. The impact of antivirus of prognosis after liver resection for hepatitis B-related hepatocellular carcinoma. *Chin J Bases Clin Gen Surg*. 2015;22:1187–1191.
30. Wang BQ, Xue F, Tong Q, et al. Recurrence-free survival and overall survival in patients with hepatitis B-related liver cancer receiving antiviral therapy. *J Pract Hepatol*. 2015;18:132–135.
31. Xu MY, Song SP, Lan YH, et al. Effect of nucleos(t)ide analog antiviral treatment on the pathological differentiation and prognosis of hepatitis B virus-related hepatocellular carcinoma. *Chin J Infect Dis*. 2016;34:723–726.
32. Yang M, Xiao L, Shi XM. A study of antiviral therapy in prevention of tumor recurrence after curative treatment of hepatocellular carcinoma. *Med J Chin PLA*. 2010;35:726–728.
33. Yao HB, Wen MB, Hua YP, Huang G, Li GH. Efficacy of nucleoside analogues antiviral therapy on clinical outcome for HBV-related primary hepatic carcinoma patients after hepatectomy. *J Pract Med*. 2016;32:2468–2470.
34. Zhang XY. The role of antiviral treatment in HBV related liver cancer recurrence. *J Trop Med*. 2015;15:946–949.
35. Cheng F, Lv L, Sun BC, et al. A study of antiviral therapy in prevention of tumor recurrence after radical liver resection of hepatocellular carcinoma with high load of hepatitis B virus DNA. *Acta Univ Med Nanjing*. 2011;31(882–4):888.
36. Ding C, Pan F, Hu HZ, et al. Efficacy of antiviral therapy in hepatocellular carcinoma patients with HBV DNA levels after radical resection. *J Clin Hepatol*. 2014;30:656–659.
37. Zhou Y, Zhang Z, Zhao Y, Wu L, Li B. Antiviral therapy decreases recurrence of hepatitis B virus-related hepatocellular carcinoma after curative resection: a meta-analysis. *World J Surg*. 2014;38(9):2395–2402.
38. Wong TC, Lo CM. Resection strategies for hepatocellular carcinoma. *Semin Liver Dis*. 2013;33(3):273–281.

39. Sasaki A, Kai S, Iwashita Y, Hirano S, Ohta M, Kitano S. Microsatellite distribution and indication for locoregional therapy in small hepatocellular carcinoma. *Cancer*. 2005;103(2):299–306.
40. Chen X, Chen Y, Li Q, Ma D, Shen B, Peng C. Radiofrequency ablation versus surgical resection for intrahepatic hepatocellular carcinoma recurrence: a meta-analysis. *J Surg Res*. 2015;195(1):166–174.
41. Wong JS, Wong GL, Tsoi KK, et al. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2011;33(10):1104–1112.
42. Qu LS, Liu JX, Kuai XL, Xu ZF, Jin F, Zhou GX. Significance of viral status on recurrence of hepatitis B-related hepatocellular carcinoma after curative therapy: a meta-analysis. *Hepatol Res*. 2014;44(7):750–760.
43. Xia BW, Zhang YC, Wang J, Ding FH, He XD. Efficacy of antiviral therapy with nucleotide/nucleoside analogs after curative treatment for patients with hepatitis B virus-related hepatocellular carcinoma: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol*. 2015;39(4):458–468.
44. Liu GM, Huang XY, Shen SL, Hu WJ, Peng BG. Adjuvant antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after curative treatment: a systematic review and meta-analysis. *Hepatol Res*. 2016;46(1):100–110.
45. Yuan P, Chen P, Qian Y. Evaluation of antiviral therapy performed after curative therapy in patients with hepatitis B virus-related hepatocellular carcinoma: an updated meta-analysis. *Can J Gastroenterol Hepatol*. Epub 2015 Nov 30.
46. Wei M, He Y, Wang J, Chen N, Zhou Z, Wang Z. Laparoscopic versus open hepatectomy with or without synchronous colectomy for colorectal liver metastasis: a meta-analysis. *PLoS One*. 2014;9:e87461.
47. Regimbeau JM, Abdalla EK, Vauthey JN, et al. Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. *J Surg Oncol*. 2004;85(1):36–41.
48. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer*. 2000;89(3):500–507.
49. Kubo S, Hirohashi K, Tanaka H, et al. Virologic and biochemical changes and prognosis after liver resection for hepatitis B virus-related hepatocellular carcinoma. *Dig Surg*. 2001;18:26–33.
50. Kubo S, Hirohashi K, Tanaka H, et al. Effect of viral status on recurrence after liver resection for patients with hepatitis B virus-related hepatocellular carcinoma. *Cancer*. 2000;88:1016–1024.
51. Hoshida Y, Villanueva A, Kobayashi M, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *N Engl J Med*. 2008;359(19):1995–2004.
52. Ko S, Nakajima Y, Kanehiro H, et al. Significant influence of accompanying chronic hepatitis status on recurrence of hepatocellular carcinoma after hepatectomy. Result of multivariate analysis. *Ann Surg*. 1996;224(5):591–595.
53. Huang Y, Wang Z, An S, et al. Role of hepatitis B virus genotypes and quantitative HBV DNA in metastasis and recurrence of hepatocellular carcinoma. *J Med Virol*. 2008;80(4):591–597.
54. Huang Y, Tong S, Tai AW, Hussain M, Lok AS. Hepatitis B virus core promoter mutations contribute to hepatocarcinogenesis by deregulating SKP2 and its target, p21. *Gastroenterology*. 2011;141(4):1412–1421.
55. Ou DP, Tao YM, Tang FQ, Yang LY. The hepatitis B virus X protein promotes hepatocellular carcinoma metastasis by upregulation of matrix metalloproteinases. *Int J Cancer*. 2007;120(6):1208–1214.
56. Cheng AS, Wong N, Tse AM, et al. RNA interference targeting HBx suppresses tumor growth and enhances cisplatin chemosensitivity in human hepatocellular carcinoma. *Cancer Lett*. 2007;253(1):43–52.
57. Liu H, Xu L, He H, et al. Hepatitis B virus X protein promotes hepatoma cell invasion and metastasis by stabilizing Snail protein. *Cancer Sci*. 2012;103(12):2072–2081.