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REVIEW

Efficacy of Nucleoside Analogs for Chronic Hepatitis B Virus-Related Hepatocellular Carcinoma After Curative Treatment: A Meta-Analysis

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Abstract

Background and Aim The efficacy of nucleoside analogs (NAs) for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after curative treatment remains unclear. The present study aimed to evaluate the efficacy of these agents by conducting a comprehensive meta-analysis of available studies.

Methods We searched several databases including Pubmed, Embase, Cochrane Library, Clinical Trials, and Web of Science, according to PRISMA guidelines. We considered all randomized controlled trials and cohort studies that met the inclusion criteria. Statistical analyses were conducted using Review Manager 5.3 and Stata 14.0.

Results Twenty-one studies with 8752 participants were included in the final analysis. The pooled data showed that patients treated with NAs had significantly lower 1- and 3-year HCC recurrence rates (relative risk [RR] 0.76, 95% confidence interval [CI] 0.65–0.90; $P=0.001$ and RR 0.79, 95% CI 0.71–0.88; $P<0.001$, respectively), but there was no difference in 5-year recurrence rates (RR 0.87, 95% CI 0.74–1.03; $P=0.10$). Regarding overall survival (OS), patients treated with NAs had significantly higher 1-, 3-, and 5-year OS rates (RR 1.05, 95% CI 1.02–1.08; $P=0.003$; RR 1.25, 95% CI 1.16–1.34; $P<0.001$; and RR 1.28, 95% CI 1.18–1.39; $P<0.001$, respectively).

Conclusion NA therapy has the potential to reduce the risk of early recurrence and improve OS in patients with HBV-related HCC after curative treatment, compared with placebo or no treatment. Further research including more homogeneous studies with large sample sizes is required to improve the reliability of these conclusions.

Keywords Nucleoside analog · Hepatocellular carcinoma · Curative treatment · Meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumor and the second-leading cause of cancer-related deaths worldwide [1]. In addition to liver transplantation, there are currently two treatment options for patients eligible for curative treatment: Partial hepatectomy represents a potentially curative therapy in patients with a solitary tumor of any size with no evidence of gross vascular invasion [2], while ablation, including radiofrequency ablation (RFA), microwave ablation, percutaneous ethanol injection, and acetic acid ablation, can be used in patients with Child–Pugh class A early-stage HCC (either a single tumor ≤ 5 cm or multiple tumors (up to 3 tumors) each ≤ 3 cm) [3–10]. These curative therapies have improved the overall survival (OS) rate, with some studies reporting a 5-year survival rate of > 50% [11–13] in patients undergoing liver resection and 70% for RFA [9]. However, the recurrence rate in patients after curative treatment remains poor, and some studies suggested that

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5-year recurrence rates in patients after resection and RFA were all > 70% [12, 14, 15]. Adjuvant treatments that can reduce recurrence and further prolong survival are thus of major significance.

About 54.4% of HCC cases can be attributed to hepatitis B virus (HBV) infection [16]. Moreover, some studies of patients with chronic HBV-related HCC undergoing curative treatment reported that tumor recurrence increased in line with levels of HBV DNA. Several studies have investigated the association between the administration of nucleoside analogs (NA) and prognosis, including prolonged survival and decreased recurrence rates [17–20]. However, conclusions based on studies with small sample sizes are not convincing, and it is therefore necessary to carry out a meta-analysis to summarize and analyze the accumulated evidence to reach a more credible conclusion. In the present study, we retrieved and analyzed 21 studies including 8752 participants, which enabled us to conduct subgroup analyses according to study signs, type of curative treatment, and sample size. More comprehensive data and further research could help to identify the short- and long-term effects of NAs in patients with HBV-related HCC, in addition to providing credible evidence for clinicians.

Methods

Search Strategy and Selection Criteria

We conducted a systematic literature search of electronic databases including Pubmed, Embase, Cochrane Library, Clinical Trials, and Web of Science, in accordance with PRISMA guidelines [21], on April 15, 2018. The search terms included "hepatocellular carcinoma," "liver cancer," "liver neoplasms," "HCC," "hepatitis B," "hepatitis B virus," "HBV," "curative treatment," "resection," "hepatectomy," "ablation," "percutaneous ethanol injection," "radiofrequency ablation," "microwave ablation," "acetic acid ablation," "antiviral," "nucleotide," "nucleoside," "lamivudine," "adefovir," "entecavir," "telbivudine," and "tenofovir." The search had no limitation on publication dates, but was restricted to articles published in English. We additionally manually searched primary references included in the earlier meta-analyses and continued to monitor the scientific literature after completing the formal search.

We considered all randomized controlled trials (RCTs) and cohort studies if they met the following inclusion criteria: (1) study population definitely diagnosed with HBV-related HCC; (2) treated for HCC by resection or ablation; (3) adjuvant postoperative treatment included NAs for treatment group and placebo or no treatment for control group; and (4) available results for HCC recurrence rate or OS rate. Studies were excluded if the patients suffered from coinfection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus. Two independent investigators screened the titles, abstracts, and full texts of the retrieved articles. Differences in opinion were resolved by discussion or arbitration by the third author.

Data Extraction

Two reviewers extracted relevant data independently using a standardized data extraction form. The extracted data included information on study design, mean age, sample size, tumor size, proportion of cirrhosis, α-fetoprotein, HBV DNA level, tumor stage, Child–Pugh class, curative treatment, NA type, treatment duration, follow-up duration, and specific data associated with HCC recurrence rate and OS rate.

Quality Assessment

The quality and risk of bias of the RCTs were evaluated using the Cochrane Collaboration tool [22]. The quality of cohort studies was assessed using the modified Newcastle Ottawa Scale (NOS), which evaluated the studies in terms of sample selection, comparability, and outcomes [23]. The NOS gives a maximum score of 9 points, and studies with a score > 5 were considered as high quality.

Data Analysis

Statistical analyses were conducted using Review Manager 5.3 and Stata 14.0. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were used to evaluate the association between NAs and clinical benefit in patients with HBV-related HCC after curative treatment. In terms of incorporating summary time-to-event data into the meta-analysis, reported hazard ratios (HRs) were directly considered as RRs, and if HRs were not reported, published data from the original papers were used to calculate the HR using a spreadsheet developed by Tierney et al. [24]. We tested heterogeneity using Cochran's Q statistic and Higgins I^2 statistic. A value of $P > 0.05$ was considered to indicate no significant heterogeneity, $I^2 \leq 25\%$ indicated little heterogeneity, $I^2 > 25\%$ and $\leq 50\%$ moderate heterogeneity, $I^2 > 50\%$ and $\leq 75\%$ substantial heterogeneity, and $I^2 > 75\%$ considerable heterogeneity [25]. A fixed-effects model was used if the heterogeneity was categorized as low or moderate and a random-effects model if it was considered to be substantial or considerable. We further investigated the possible reasons for any heterogeneity by subgroup analyses based on study design, sample size, and the type of curative treatment. Funnel plots and Egger's test were used to assess publication bias. Two-tailed P values < 0.05 were considered statistically significant.

Results

Study Description

Our search identified 690 citations after the removal of duplicate references. A total of 114 abstracts and 34 full texts were further reviewed after review of the titles. Among the 34 potentially relevant studies, the following publications were excluded: one case report [26], five reviews [27–31], two studies [32, 33] referring to non-curative treatment with transarterial chemoembolization, and five studies [34–38] without relevant data to conduct a meta-analysis. Finally, 21 studies, including three studies [39–41] identified by manual search of previous meta-analyses, were confirmed. The 22 trials (one study [42] consisted of two trials) included 20 cohort studies [17–20, 39–54] and two RCTs [42, 55]. All the studies adjusted for important factors between the treatment and control groups, making the two groups comparable. The studies included 8752 participants, including 2288 patients exposed to NA in the treatment groups and 6464 exposed to placebo or without treatment in the control groups. The study screening process is shown in Fig. 1.

Among the included studies, 13 [17, 39–42, 44–47, 49–51, 54, 55] ($n=7789$) adopted resection as a curative therapy, three studies [19, 52, 53] ($n=731$) adopted ablation, and the remaining four studies [18, 20, 43, 48] ($n=232$) adopted resection and/or ablation without further distinction. Among the trials included in this meta-analysis, lamivudine was the primary antiviral agent, except in one trial [55] that only used entecavir and adefovir. In the 21 trials using lamivudine, patients in 11 [17–20, 41–45, 47] took lamivudine as antiviral monotherapy and those in the other 10 [39, 40, 46, 48–54] used it in combination with other antiviral drugs such as entecavir, adefovir, and tenofovir. We assessed the risk of bias of the two RCTs as unclear based on the Cochrane Collaboration tool. The other 20 cohort studies were assessed as high quality by the NOS (Table S). The main characteristics are summarized in Table 1.

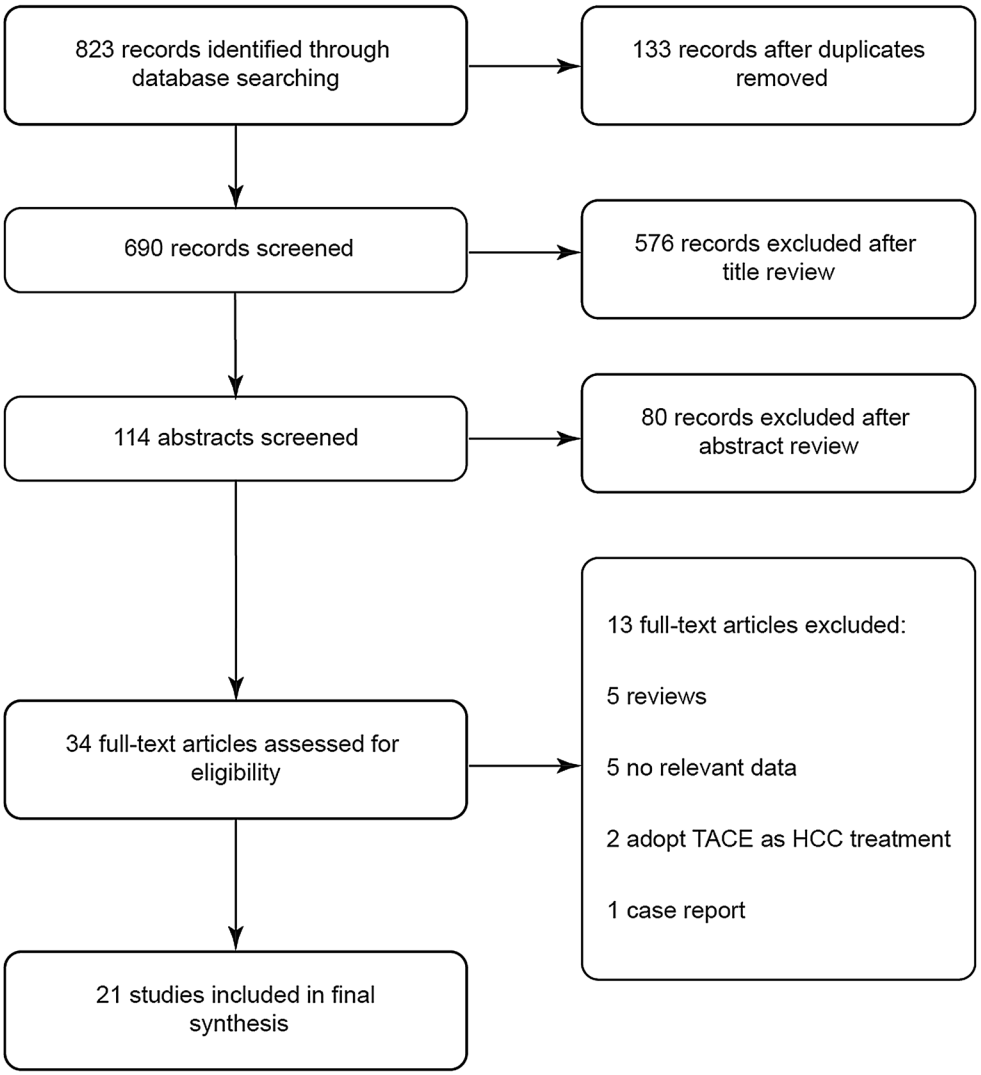

Fig. 1 Flowchart of study screening process. TACE = transarterial chemoembolization; HCC = hepatocellular carcinoma

Table 1 Characteristics of the included studies and quality score

Study, year	Country	Study type	Sample size (T/C)	Age (T/C)	Cirrhosis (%) (T/C)	Tumor size (cm) (T/C)	Tumor stage (I/II/III/IV)*	Child–Pugh class (A/B/C)	Curative treatment	AFP (ng/ml) (T/C)	HBV DNA level (T/C)	NAs type	Treatment duration (months)	Follow-up duration (months) (T/C)	Quality assessment*
Kubo 2007	Japan	Prospective cohort	14/10	55/55	43.0/40.0	2.4/2.8	5/9/10/0	19/5/0	Resection	NA	6.0/6.0 LGE/mL	LAM	32.0	36.7/7.3	7
Kuzuya 2007	Japan	Retrospective cohort	16/33	60/61	NA	NA	25/19/5/0	16/33/0	Resection / RFA	37/37	6.2/4.1 Log copies/mL	LAM	22.7	38.4/32.4	7
Yoshida 2008	Japan	Retrospective cohort	33/71	57/59	NA	2.6/2.8	NA	NA	RFA	16/12	33/45 LGE/mL	LAM	NA	33.0/47.0	8
Chuma 2009	Japan	Retrospective cohort	20/30	56/56	70.0/83.3	2.1/1.7	19/27/4	44/6/0	Resection / RFA	26.7/20.7	6.0/5.9 Log copies/mL	LAM	NA	35.5/49.2	8
Koda 2009	Japan	Retrospective cohort	22/14	59/60	NA	NA	NA	NA	Resection/ RFA	NA	5.7/5.2 LEG/mL	LAM,	NA	NA	7
Li 2010	China	Prospective cohort	43/36	46/45	55.8/69.4	7.1/8.5	13/27/39/0	49/16/4	Resection	177.1/188.1	NA	LAM	NA	12.0/12.0	7
Chan 2011	China	Retrospective cohort	42/94	57/55	74.0/56.0	9.3/9.0	NA	42/0/0	Resection	26/303.5	NA	LAM	NA	NA	7
Wu 2012	China	Retrospective cohort	518/4051	54/55	48.6/38.7	NA	NA	NA	Resection	NA	NA	LAM/ ETV/ TEL	17.4	31.7/26.2	8
Urata 2012	Japan	Retrospective cohort	46/13	57/58	31.0/53.0	2.8/3.4	NA	52/7/0	Resection	NA	4.1/6.1 Log copies/mL	LAM/ ETV/ ADV	NA	37.0/37.0	7
Yang 2012	China	Prospective cohort	142/188	NA	NA	NA	NA	NA	Resection	NA	$> 10^4$ copies/mL	LAM/ ETV/ ADV	NA	NA	8
Ke 2013	China	Retrospective cohort	141/141	49/50	81.6/81.6	4.5/5.0	NA	NA	Resection	NA	$(1.66/1.08) * 10^4$ IU/mL	LAM	12.0	24.0/22.8	6
*Yin 2013(a)	China	Cohort study	215/402	50/50	47.0/35.8	NA	NA	601/16	Resection	NA	4.51/3.81 Log copies/mL	LAM	NA	24.0/24.0	8
*Yin 2013(b)	China	RCT	81/82	48/49	24.7/28.0	NA	NA	162/1	Resection	NA	4.88/4.57 copies/mL	LAM	NA	40.0/40.0	unclear
Yan 2013	China	Retrospective cohort	35/25	45/47	NA	4.7/5.0	22/29/9	35/25	Resection	234/247	$(> 10^5)/(\leq 10^4)$ copies/mL	LAM	NA	36.0/36.0	6

Table 1 (continued)

Study, year	Country	Study type	Sample size (T/C)	Age (T/C)	Cirrhosis (%) (T/C)	Tumor size (cm) (T/C)	Tumor stage (I/II/III/IV)*	Child–Pugh class (A/B/C)	Curative treatment	AFP (ng/ml) (T/C)	HBV DNA level (T/C)	NAs type	Treatment duration (months)	Follow-up duration (months) (T/C)	Quality assessment*
Nishikawa 2014	Japan	Retrospective cohort	65/32	56/61	58.5/46.9	2.8/3.2	23/49/25	NA	Resection/ablation	30.5/17.7	NA	LAM/ADV/ETV	NA	59.0/48.0	7
Huang 2015	China	RCT	100/100	51/51	NA	4.9/5.1	BCLC	NA	Resection	226.2/149	> 2000 IU/Ml	ADV, ETV	NA	60.0/60.0	Unclear
Chong 2015	China	Cohort study	157/150	56/55	52.7/66.1	NA	NA	NA	Resection	NA	> 2000 IU/Ml	LAM/ADV/ETV	NA	39.0/430	8
Sakamoto 2015	Japan	Retrospective cohort	62/100	55/60	NA	3.7/5.7	NA	NA	Resection	NA	3.8/3.5 log copies/mL	LAM/ADV/ETV	NA	32.0/12.0	7
Chen 2016	China	Retrospective cohort	192/253	48/49	NA	4.7/5.4	366/79	NA	Resection	NA	NA	LAM/TDF/ADV	79.0	36.0/36.0	7
Lee 2016	China	Retrospective cohort	133/266	60/60	72.9/72.9	NA	NA	NA	RAF	NA	NA	LAM/TDF/ADV	17.8	29.0/29.0	8
Sohn 2016	Korea	Retrospective cohort	125/103	55/55	83.0/83.0	2.1/2.2	NA	193/35	RAF	NA	5.3/2.8 log IU/ml	LAM/TDF/ADV	60.1	144.0/144.0	8
Wei 2017	China	Retrospective cohort	86/40	51/50	73.0/76.0	8.0/8.9	NA	121/5	Resection	NA	NA	LAM/ETV	NA	30.6/30.6	7

*Yin 2013(a), *Yin 2013(b): Yin 2013 is a two-stage longitudinal study and consisted of two trials. Yin 2013(a) is a cohort study and Yin 2013(b) is a randomized control trial

*Quality assessment: The quality and risk of bias of randomized controlled trials are classified as low risk, unclear risk, and high risk by the Cochrane Collaboration's tool. The cohort studies are assessed by Newcastle Ottawa Scale (with a maximum score of 9 points)

RCT randomized control trial, *NA* not available, *RAF* radiofrequency ablation, *LAM* lamivudine, *ADV* adefovir, *ETV* entecavir, *TLV* telbivudine, *TDF* tenofovir

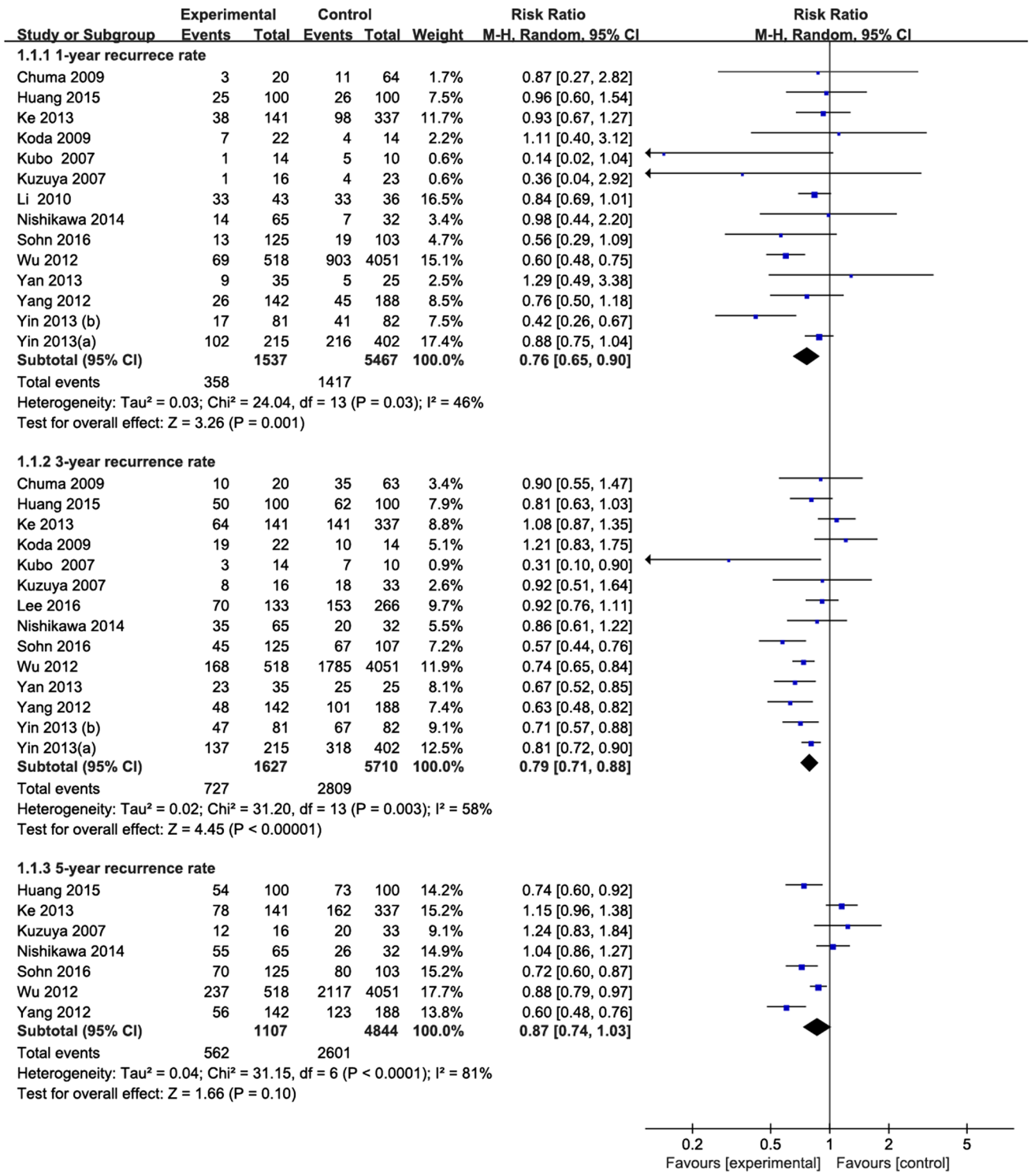

Fig. 2 Forest plot showing the effect of NA therapy on recurrence rate in patients with chronic hepatitis B-related hepatocellular carcinoma after curative treatment

NA Therapy and HCC Recurrence Rate

The pooled data showed that patients treated with NAs had significantly lower 1- and 3-year HCC recurrence rates (RR 0.76, 95% CI 0.65–0.90; $P = 0.001$ and RR 0.79, 95% CI 0.71–0.88; $P < 0.001$, respectively), but there was no significant difference in 5-year recurrence rates between the treated and control groups (RR 0.87, 95% CI 0.74–1.03;

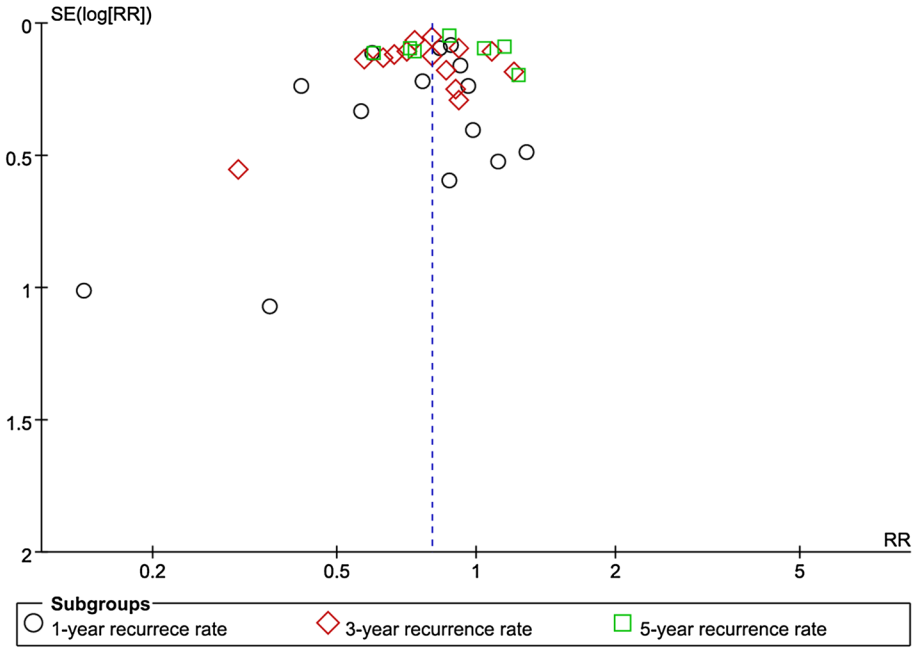

Fig. 3 Funnel plot showing publication bias in studies in relation to recurrence rate

$P = 0.10$). There was moderate heterogeneity ($I^2 = 46\%$, $P = 0.03$) in terms of 1-year HCC recurrence rate, substantial heterogeneity ($I^2 = 58\%$, $P = 0.003$) in 3-year recurrence rate, and considerable heterogeneity ($I^2 = 81\%$, $P < 0.001$) in 5-year recurrence rate (Fig. 2). We found no evidence of publication bias or small-study effect by Egger's test (1-year recurrence rate: $P = 0.522$; 3-year recurrence rate: $P = 0.968$; 5-year recurrence rate: $P = 0.974$) or by visualization of funnel plots (Fig. 3).

NA Therapy and OS Rate

Pooled data showed that treatment with NA significantly improved 1-year OS (RR 1.05, 95% CI 1.02–1.08; $P = 0.003$), 3-year OS (RR 1.25, 95% CI 1.16–1.34; $P < 0.001$), and 5-year OS (RR 1.28, 95% CI 1.18–1.39; $P < 0.001$). There was considerable heterogeneity among studies in relation to 1-year OS ($I^2 = 79\%$, $P < 0.001$) and 3-year OS ($I^2 = 79\%$, $P < 0.001$), and substantial heterogeneity ($I^2 = 60\%$, $P = 0.001$) among studies in relation to 5-year OS (Fig. 4). We detected some publication bias and a small-study effect by Egger's test (1-year OS: $P = 0.021$; 3-year OS: $P = 0.018$; 5-year OS: $P = 0.043$) and by visualization of the funnel plot (Fig. 5).

Subgroup Analyses by Study Design, Curative Treatment, and Sample Size

Subgroup Analysis by Study Design

We pooled the data from cohort studies and RCTs. In the NA therapy group of cohort studies, the 1- and 3-year recurrence rates were significantly decreased by 21% and 20%, respectively, and 1-, 3-, and 5-year OS rates were significantly improved by 5, 23, and 27%, respectively. However, there was no significant difference in 5-year recurrence rates between the treated and control groups. There was a slight reduction in heterogeneity in the groups in relation to 1-year recurrence rate and 1-year OS, but not in relation to 3- and 5-year recurrence and OS rates. In the subgroup of RCTs, the meta-analysis demonstrated a significant difference between the groups for 3-year but not 1-year OS, or 1- or 3-year recurrence rates. There was no evidence of heterogeneity between the studies in relation to 3-year recurrence rate, while the heterogeneity in relation to 1-year recurrence rate and 1- and 3-year OS rates was similar to those before subgroup analysis (Table 2).

Subgroup Analysis According to Curative Treatment

In the subgroup adopting resection as the curative treatment, the pooled results demonstrated that NA therapy decreased both the 1- and 3-year recurrence rates by 24%, and improved the 1-, 3-, and 5-year OS rates by 6, 26, and 29%, respectively. However, there was no significant difference in 5-year recurrence rates. The heterogeneity among studies was slightly reduced in relation to 1-, 3-, and 5-year OS rates, but not 1-, 3-, or 5-year recurrence rates. In the subgroup of studies using RFA, the meta-analysis demonstrated no significant difference between the treatment and control groups for 3-year recurrence rate and 1-, 3-, and 5-year OS rates. There was no evidence of heterogeneity in relation to 1- and 3-year recurrence rates, while heterogeneities in

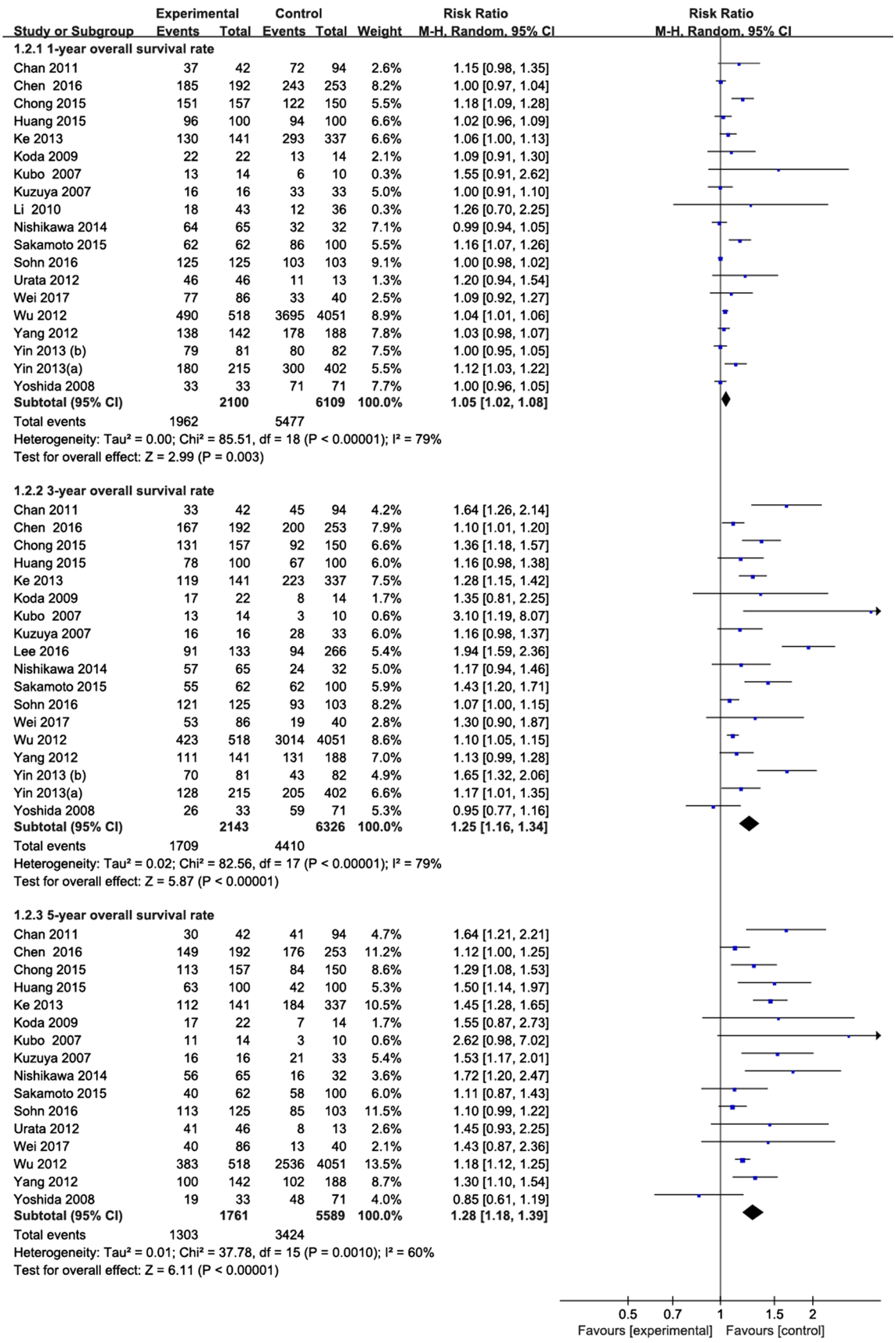

Fig. 4 Forest plot showing effect of NA therapy on overall survival rate in patients with chronic hepatitis B-related hepatocellular carcinoma after curative treatment

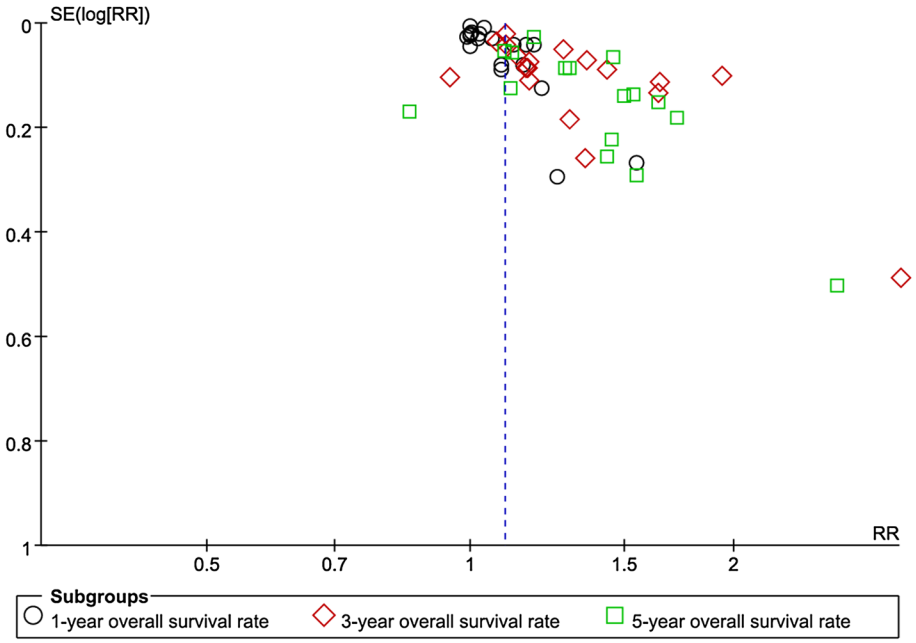

Fig. 5 Funnel plot showing publication bias in studies in relation to overall survival rate

relation to 1-, 3-, and 5-year OS rates were significantly reduced compared with before subgroup analysis (Table 2).

Subgroup Analysis Excluding Trials with Small and Too Large Sample Sizes

We defined a small sample size as < 100 patients in the trial. After excluding trials with small sample sizes [17, 18, 20, 39, 43, 44, 47, 48] and the study by Wu et al. [46], which had an obviously larger sample size (4569) than the other trials, we pooled the remaining studies and found significant differences between the therapy and control groups. Specifically, 1-, 3-, and 5-year recurrence rates were reduced in the therapy group by 23, 22, and 22%, respectively, while 1-, 3-, and 5-year OS rates were improved by 4, 27, and 24%, respectively. Heterogeneity among studies was not significantly reduced in relation to any of the outcomes (Table 2).

Side Effects of NA Therapy

We were unable to conduct a meta-analysis of the adverse effects because of insufficient data. Among the included studies, 24.6–39.4% of cases in six studies [17–19, 42, 43, 48] reported lamivudine-resistant tyrosine-methionine-aspartate-aspartate (YMDD) mutants after lamivudine therapy. Furthermore, 31.3–66.7% of YMDD patients in three studies [18, 39, 43] exhibited breakthrough hepatitis, which was controlled by administration of other kinds of NAs. No serious adverse effects were reported in the included studies, except for one patient who suffered from transient anorexia after the administration of lamivudine [42].

Discussion

This systematic review and meta-analysis of pooled data from 22 trials (20 cohort studies and 2 RCTs) demonstrated that NA therapy could reduce the early recurrence rate (by 24% and 21% at 1 and 3 years, respectively) and improve OS (by 5, 25, and 28% at 1, 3, and 5 years, respectively) in patients with HBV-related HCC after curative treatment. These results were consistent with the conclusions derived from cohort studies and studies with curative resection. In the subgroup of cohort studies, NAs reduced the 1- and 3-year recurrence rates by 21% and 20%, respectively, and improved the 1-, 3-, and 5-year OS rates by 5, 23, and 27%, respectively. In the subgroup of studies that adopted curative resection, NAs reduced the 1- and 3-year recurrence rates by 24% and improved the 1-, 3-, and 5-year OS rates by 6, 26, and 29%, respectively. However, NAs failed to reduce late recurrence in the overall and cohort studies, or in the studies using radical resection. To the best of our knowledge, five previous meta-analyses have assessed the association between NA therapy and the prognosis of patients with chronic HBV-related HCC after curative treatment [56–60]. Compared with the present study, the meta-analyses by Wong et al. [56], Sun et al. [57], Zhou et al. [58], and Liu et al. [60] showed that NAs could prolong OS and decrease recurrence, but did not differentiate between the short-term and long-term effects of NA therapy. Although Xia et al.

Table 2 Summary of the results of subgroup analysis based on study design, the kind of curative treatment, and sample size

Subgroup	No. of studies	Treatment group events/total	Control group events/total	RR (95% CI)	*P* value	Cross-study heterogeneity			
						χ^2	*df*	I^2 (%)	*P*
Subgroup analysis based on study design									
Cohort study									
1-year recurrence	12	316/1356	1350/5285	0.79 (0.68,0.92)	0.002	16.38	11	33	0.13
3-year recurrence	12	630/1446	2680/5528	0.80 (0.71,0.90)	0.0003	302.26	11	64	0.001
5-year recurrence	6	508/1007	2528/4744	0.89 (0.74,1.08)	0.24	28.88	5	83	< 0.0001
1-year OS	17	1787/1919	5303/5927	1.05 (1.02,1.09)	0.002	87.07	16	82	< 0.00001
3-year OS	16	1561/1962	4300/6144	1.23 (1.14,1.33)	< 0.00001	71.50	15	79	< 0.00001
5-year OS	15	1240/1661	3382/5489	1.27 (1.17,1.37)	< 0.00001	35.23	14	60	0.001
RCT									
1-year recurrence	2	42/181	67/182	0.64 (0.28,1.43)	0.27	5.87	1	83	0.02
3-year recurrence	2	97/181	129/182	0.75 (0.64,0.88)	0.0004	0.60	1	0	0.44
1-year OS	2	175/181	174/182	1.01 (0.97,1.05)	0.70	0.31	1	0	0.58
3-year OS	2	148/181	110/182	1.37 (0.98,1.94)	0.07	5.91	1	83	0.02
Subgroup analysis based on the kind of curative treatment									
Resection									
1-year recurrence	9	320/1289	1372/5231	0.76 (0.63,0.92)	0.005	21.75	8	63	0.005
3-year recurrence	8	540/1246	2506/5195	0.76 (0.68,0.86)	< 0.00001	17.45	7	60	0.01
5-year recurrence	4	425/901	2475/4676	0.83 (0.66,1.04)	0.10	20.75	3	86	0.0001
1-year OS	14	1702/1839	5225/5856	1.06 (1.03,1.10)	0.0002	39.56	13	67	0.0002
3-year OS	12	1381/1749	4104/5807	1.26 (1.16,136)	< 0.00001	42.84	11	74	< 0.0001
5-year- OS	11	1082/1500	3247/5336	1.29 (1.19,1.40)	< 0.00001	21.80	10	54	0.02
Ablation									
3-year recurrence	2	115/258	220/373	0.73(0.46,1.16)	0.18	7.40	1	86	0.007
1-year OS	2	158/158	174/174	1.00(0.98,1.02)	1.00	0	1	0	1.00
3-year OS	3	238/291	246/440	1.25(0.78,2.02)	0.36	56.52	2	96	< 0.00001
5-year OS	2	132/158	133/174	1.01(0.78,1.30)	0.95	2.41	1	58	0.12
Subgroup analysis excluding trials with small and too large sample sizes									
1-year recurrence	6	221/804	445/1212	0.77 (0.61,0.96)	0.05	10.85	5	54	0.02
3-year recurrence	7	461/937	909/1482	0.78 (0.68,0.90)	0.004	19.11	6	69	0.0006
5-year recurrence	4	258/508	438/728	0.78 (0.59,1.03)	< 0.0001	22.36	3	87	0.08
1-year OS	11	1142/1219	1553/1770	1.04 (1.00,1.08)	< 0.00001	58.54	10	83	0.04
3-year OS	12	1052/1351	1241/2036	1.27 (1.14,1.41)	< 0.00001	68.09	11	84	< 0.00001
5-year OS	9	666/923	749/1286	1.24 (1.11,1.39)	0.0009	26.26	8	70	0.0002

RCT randomized controlled trial, *OS* overall survival rate, *RR* risk ratio, *CI* confidence interval, *df* degrees of freedom

[59] tried to identify short- and long-term effects, it did not exclude the effect of studies with small sample sizes. Moreover, the previous conclusions were based on fewer studies and smaller sample sizes, which may have reduced the credibility of the results.

In the current meta-analysis, we found that NA therapy significantly decreased the early recurrence rate at 1 and 3 years after curative treatment. Early recurrence can be attributed to dissemination of the initial HCC [61–63]. Furthermore, a high viral concentration has been reported to lead to aggressive behavior of HCC resulting in tumor recurrence via intrahepatic metastasis and growth [39, 64]. NA therapy may thus have decreased the early recurrence rate by inhibiting viral replication and decreasing the viral concentration. However, we failed to find any effect of NA therapy on late recurrence. These results were consistent with the meta-analysis conducted by Xia et al. [59], which reported that NA therapy failed to reduce the late recurrence rate, but decreased the 1- and 3-year recurrence rates by 23% and 19%, respectively. There are two possible reasons for this result. First, although NAs could delay the progression of recurrence, they do not exert any antitumor effect. If any micrometastases that were not detected before partial hepatectomy persisted in the remnant liver,

the HCC would still be likely to relapse. Alternatively, the observed results may have been due to small-study effects. When we excluded studies [18, 48] with sample sizes <100, the pooled results showed a significant reduction in late recurrence rate. However, further studies should be conducted to verify the stability of this conclusion.

Our meta-analysis revealed that NA therapy could significantly improve OS rates in patients with HBV-related HCC at 1, 3, and 5 years after liver resection or ablation, in accordance with the conclusions of previous meta-analyses. These improvements may have two possible explanations. First, the reduced and postponed recurrence of HCC may delay disease progression and correspondingly increase survival time. Second, NA administration could effectively improve liver function, as demonstrated by improvements in indicators such as albumin, aspartate aminotransferase, and alanine aminotransferase compared with levels at baseline [43]. An improved liver reserve would thus allow more kinds of salvage therapy to be administered in the event of HCC recurrence, including resection and ablation, while patients with less liver reserve would have fewer treatment options and thus shorter survival.

In the subgroup analysis according to study design, the pooled results from cohort studies were consistent with those of the overall analysis in relation to survival rate and recurrence rate. However, NA therapy failed to display any significant benefits in recurrence or OS rates using pooled data from RCTs [42, 55], possibly due to the small number of trials and small sample sizes. In the subgroup analysis according to type of curative treatment, analysis of pooled data from studies using curative resection produced the same conclusions as analysis of the cohort subgroup study, while the pooled results from RFA studies showed no significant difference between the treatment and control groups in terms of 3-year recurrence rate and 1-, 3-, and 5-year OS rates. However, further studies are needed to validate these conclusions, which were derived from only three studies.

This study was subject to several limitations. First, given that all but two of the included studies were cohort studies, this may have resulted in selection and performance biases that could reduce the credibility of the conclusions. Second, the heterogeneities of the pooled studies for recurrence rate and OS were significant, and subgroup analyses according to study design, curative treatment, and sample size failed to decrease this significance. The most probable reason for the significant heterogeneities among the included studies was differences in HBV DNA levels, which have been shown to be associated with the prognosis of HBV-related HCC after curative treatment. Other reasons, such as tumor size, the percent of cirrhosis, and treatment duration, may also partially explain the source of the heterogeneities. Third, there was evidence of publication bias and a small-study effect in relation to OS, which may derive from the authors' inclinations to publish positive rather than negative results.

In conclusion, this meta-analysis of 2288 participants exposed to NAs showed that NA therapy could reduce the early recurrence rate and improve OS compared with placebo or no treatment in patients with HBV-related HCC after curative treatment. Overall, NA was well tolerated, with few serious adverse effects. However, in view of the heterogeneity and publication bias identified in this study, further research including more homogeneous studies with larger sample sizes is needed to improve the reliability of the conclusions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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