



# Prognostic value of Epstein–Barr virus DNA level for nasopharyngeal carcinoma: a meta-analysis of 8128 cases

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## Abstract

**Background** Plasma levels of Epstein–Barr virus (EBV) DNA have been employed to predict survival outcomes of patients with nasopharyngeal carcinoma (NPC). However, the prognostic value of subsequent EBV DNA levels (mid or post treatment) for NPC is needed to identify by a large cohort of patients. We performed a meta-analysis of studies including data from 8128 patients to evaluate the prognostic value of EBV DNA in NPC patients.

**Methods** We searched PubMed, Web of Science, and the Cochrane library for prospective and retrospective studies. Hazard ratios (HRs) and confidence intervals (CIs) were extracted from the studies or calculated and pooled to assess the association between EBV DNA levels pre-treatment (pre-DNA), mid-treatment (mid-DNA), and post-treatment (post-DNA) on clinical outcomes.

**Results** A total of 22 studies with 8128 patients was included for analysis. Pre-DNA levels predicted overall survival, progression-free survival, distant metastasis-free survival, and local–regional failure survival with HRs (95% CIs) of 2.70 (2.06, 3.54), 2.70 (2.12, 3.44), 3.49 (2.35, 5.17), and 2.00 (1.45, 2.76), respectively, and the corresponding HRs for post-DNA levels were 4.86 (3.30, 7.17), 6.29 (3.41, 11.60), 5.68 (2.71, 11.93), respectively. Mid-DNA levels predicted overall survival and progression-free survival with an HR (95% CI) of 3.02 (1.54, 5.29) and 3.15 (2.05, 4.83). Subgroup analysis showed that the HR of post-DNA wasn't influenced by different detection time of post-DNA ( $P=0.22$ ,  $I^2=33.2\%$ ).

**Conclusion** The EBV DNA levels have a significant prognostic impact in patients with NPC. The effect of post-treatment EBV DNA level dominated that of pre-DNA and mid-DNA levels.

**Keywords** Epstein–Barr virus DNA · Nasopharyngeal carcinoma · Meta-analysis · Prognosis

## Introduction

The ASIRs (age-standardized incidence rates) of nasopharyngeal carcinoma (NPC) in Southeast Asia is high,

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especially in south China, where the ASIR can reach as high as 20/100,000 [1]. The disease often metastasizes, largely due to the network of lymphatic capillaries in the nasopharyngeal mucous membranes. Despite improvements in NPC treatment, particularly concurrent chemoradiation therapy followed by adjuvant chemotherapy, the leading causes of death from NPC remain local recurrence and metastasis [2]. Early diagnosis may improve outcomes, as illustrated by the significant difference between the 10-year survival rates for NPC patients with stage I (up to 98%) and stage II (60%) [3]; however, patients with stage III and IV disease still have poor prognosis, even with combination treatments [4]. Thus, there is an urgent need for diagnostic and prognostic assays that enable early detection and effective monitoring of the disease to allow individualized treatment plans.

The causative agent of NPC is Epstein–Barr virus (EBV), and an increasing number of studies have shown that plasma levels of EBV DNA correlate with prognosis of NPC patients [5, 6]. Real-time reverse-transcription

polymerase chain reaction (qRT-PCR) quantification of EBV DNA levels is commonly used to monitor the progression of NPC and evaluate prognosis. However, most of these studies focused on the detection of the pre-treatment plasm EBV DNA. Actually some researchers have found that subsequent EBV DNA level measurements (mid or post treatment) had greater impact than pre-treatment EBV DNA on clinical outcomes of NPC [7–9]. But these studies incorporated a small cohort of patients and needed a verification of a large sample of patients. Thus, we conducted a systematic meta-analysis of studies measuring pre-, mid-, or post-treatment EBV DNA levels in NPC patients.

## Materials and methods

### Search strategy

This meta-analysis was conducted in accordance with the PRISMA guidelines [10]. We systematically searched PubMed, Web of Science, and the Cochrane library (from January 1, 2010 to last search update September 1, 2018) for prospective and retrospective studies focusing on plasma EBV DNA levels in NPC patients. A combination of keywords “nasopharyngeal carcinoma/cancer/neoplasm” and “Epstein–Barr virus DNA/EBV DNA/Epstein–Barr viral DNA/EBV deoxyribonucleic acid/Epstein–Barr virus deoxyribonucleic acid” in the title or abstract was used in the search. We first selected articles through screening of titles and abstracts; then excluded duplicates and articles not published in English; and finally selected the articles and mined the data. Because this was a meta-analysis, no ethical approval or patient consent was needed.

### Inclusion and exclusion criteria

Studies satisfying the following criteria were included: (1) EBV DNA levels were quantified by RT-PCR or the clearance of EBV DNA was measured; (2) the association between EBV DNA level and survival outcomes (including but not limited to overall survival [OS], disease-free survival [DFS], progression-free survival [PFS], metastasis-free survival [MFS], local–regional failure survival [LRFS], relapse-free survival [RFS], and distant metastasis-free survival [DMFS]), were analyzed; and (3) Kaplan–Meier survival curves and log-rank *P* values of outcomes were reported. Exclusion criteria were studies published as reviews, conference abstracts, correspondence, or case reports. References [11–13] were excluded because the survival information was incomplete.

### Data extraction

Two reviewers screened each study and extracted the data independently. Disagreements were resolved through discussion. The primary data extracted from the articles were: (1) study characteristics (first author, country, study design, number of patients, inclusion period, tumor-node-metastasis classification [TNM] stage, and treatment plan); (2) cut-off values of EBV DNA used to evaluate associations; (3) EBV DNA levels before, during, and after treatment (designated pre-, mid-, and post-DNA levels, respectively); (4) survival outcomes (e.g., OS, PFS, MFS, DMFS, RFS, LRFS); and (5) statistical evaluations, including Cox regression analysis hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values. Data were extracted from the text or tables because figures were often unclear and thus were a potential source of inaccuracy. Additionally, MFS and loco-regional relapse-free survival (LRRFS) reported in some studies were used to represent DMFS and LRFS.

### Data analysis

The quality of studies was assessed by two investigators using the Newcastle–Ottawa Scale (NOS) criteria [14], including patient selection, comparability of the study groups, and assessment of outcomes. The NOS scores ranged from 0 to 9 (allocated as stars) and studies with six or more stars were considered of high quality. Statistical analysis was performed with Review Manager 5.3.5 (Cochrane Collaboration, Oxford, UK). HRs and 95% CIs were used to evaluate the prognostic value of EBV DNA levels. When heterogeneity among the studies was present ( $P < 0.1$ ,  $I^2 > 50\%$ ), the random-effects model (DerSimonian and Laird method) was used; when no heterogeneity was present ( $P \geq 0.1$ ,  $I^2 \leq 50\%$ ), a fixed-effects model was used. The contribution each study made was weighted according to the standard error of that individual estimate. We also performed subgroup analysis of the association between post-DNA levels and OS according to EBV DNA detection time. Sensitivity analysis was performed to examine the effect of variations in study quality. Potential publication bias was examined using Begg’s test.

## Results

### Characteristics of included studies

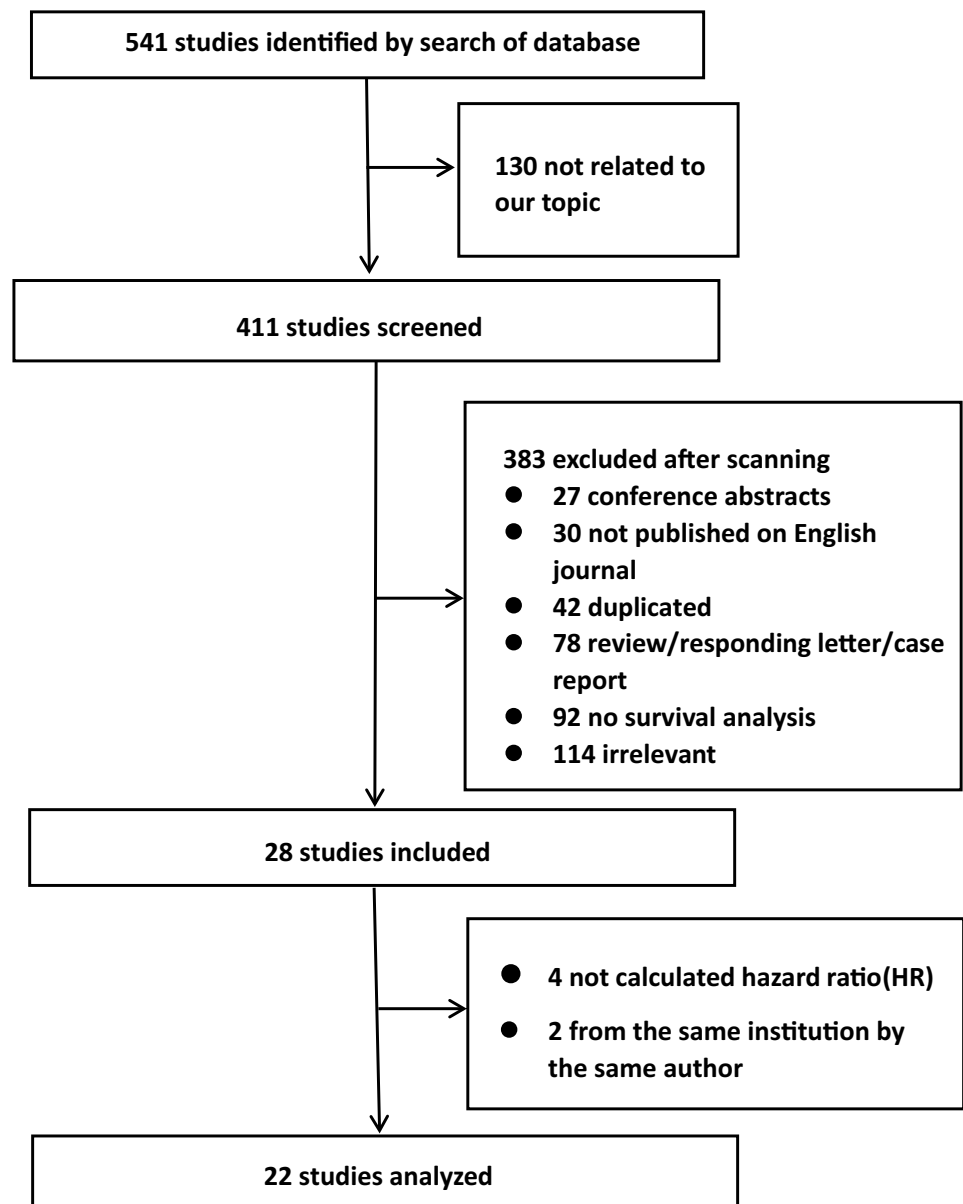
The database search identified 541 articles. After screening of titles and abstracts, 130 articles not related to our topic were removed, leaving 411 articles. Following review, 385

articles were removed based on exclusion criteria: 27 were conference abstracts; 30 were not published in English; 42 were duplicates; 78 were reviews, correspondence, or case reports; survival analysis was not reported in 92; 4 could not be mined for HRs from the data given; 2 were from the same institutions by the same authors; and 114 articles were irrelevant. Finally, a total of 22 articles studying 8128 patients were included in the analysis (Fig. 1).

Table 1 shows a summary of the characteristics of the 22 included studies, which consisted of 12 prospective studies [6–8, 15–23] and 10 retrospective studies [9, 17, 24–32]. The number of participants per study ranged from 34 to 1467. Most participants were newly diagnosed with stage I–IV non-metastatic NPC, but patients with relapsed or metastatic disease were also included. The cut-off value

of pre-DNA for predicting outcomes varied between 0 and 7500 copies/mL, with the most frequently employed values being 1500 and 4000 copies/mL. Most studies adopted 0 copies/ml as the cut-off value of mid-DNA and post-DNA. The EBV DNA levels higher than the cut-off value was defined as high EBV-DNA levels, conversely the EBV DNA levels lower than the cut-off value was low EBV-DNA levels. Fewer studies reported mid-DNA and post-DNA levels compared with pre-DNA levels. A number of indexes were used to describe survival outcome; only OS, PFS, DMFS, and LRFS were analyzed in our meta-analysis. The quality scores of the included publications are shown in Table 1 and detailed scores according to NOS are shown in Supplemental Table 1. A summary of the meta-analysis results is given in Table 2.

**Fig. 1** Flow chart of prospective and retrospective study selection



**Table 1** Characteristics of the eligible studies in the meta-analysis

Study	Study design	N	Inclusion period	TNM stage (1997AJCC)	Cut-off value (copies/ml)			Survival outcome	Treatment plan	Quality score
					pre	mid	Post <sup>†</sup>			
Wang et al,2010 Taiwan	P	34	2005.3-2008.5	Relapse, Metastasis	5000	/	t <sub>1/2</sub> =4	OS	CT+/-RT	★★★★★★
An et al,2011 Guangzhou	P	127	2002.5-2010.4	Relapse, Metastasis	Media (2.33E+5)	/	0	OS, PFS	CT	★★★★★★
Hou et al,2011 Guangzhou	R	69	2002.5-2003.12	I-IV,M0	/	/	0 (1 w)	OS,MFS	Three-dimensional CRT+/- CCRT+/- IMRT	★★★★★★
Hassen et al,2011 Tunisia	p	74	NA	I-IV	/	/	0 (5-8w)	OS	CT+/-RT	★★★★★★★
Hsu et al,2012 Taiwan	P	73	2007.1-2010.2	Relapse, Metastasis	5000	/	t <sub>1/2</sub> =7	OS	CT+/-RT	★★★★★★
Wang et al,2013 Taiwan	P	210	NA	IIb-IV,M0	1500	/	0 (1w)	OS,RFS	NACT+/-IMRT+/-CCRT+/ RT	★★★★★★
Leung et al,2014 HongKong	P	107	2004.6-2006.4	IIb-IVb,M0	4000	0 (4w)	0 (3m)	OS, PFS	CCRT+/-RT	★★★★★
Zhang et al,2015 Guangzhou	P	1467	2007.1-2010.12	I-IV,M0	4000	/	/	OS,PFS,DMFS LRFs	CT+/-IMRT	★★★★★★
Chen et al,2015 Nanjing	R	165	2011.9-2012.7	III-IV,M0	100	/	/	OS,DFS	CCRT+/-IMRT	★★★
Liu et al,2015 Guangzhou	P	185	2009.1-2012.12	III-IV,M0	/	0 (after NACT)	/	PFS,LRFs DMFS	NACT + IMRT + CCRT	★★★★
Shen et al,2015 Guangzhou	R	89	2007.1-2011.12	II-IV,M0	7500	/	/	OS,DMFS,PFS	IMRT+/-Three-dimensio nal CRT +/-CT	★★★★★★★
Zhao et al,2015 Guangzhou	R	637	2006.1-2013.4	I-IV	1500	/	0 (3 m)	OS,RFS	RT+/-induction CT+/-NACT	★★★★★★★
Peng et al,2016 Guangzhou	R	1106	2009.11-2012.2	III-IVb,M0	0	/	/	OS,DMFS,DFS LRRFS	IMRT+/-NACT+/-CCRT	★★★★★
Wang et al,2016 Taiwan	R	125	NA	III-IV,M0	/	/	100 (1w)	OS,DMFS,LRF S	RT +/- induction CT +/- CCRT	★★★★
Lee et al,2016 HongKong	P	260	2010.7-2013.6	I-IV,M0	/	/	0 (8 w)	LFFS,RFFS,DM FS,PFS,CSS,OS	IMRT+/-CCRT+/-NACT	★★★★★★
Chen et al,2016 Guangzhou	P	404	2008.2-2012.12	III-IVb,M0	4000	/	/	PFS,DMFS,OS	RT+/-CCRT	★★★★★★
Lu et al,2016 Guangzhou	P	180	2006.2-2009.12	I-IVb,M0	6800	/	/	OS	IMRT+/-CCRT	★★★★★
Jin et al,2017 Guangzhou	R	1036	2009.11-2012.2	III-IVb,M0	1500	/	/	OS,DMFS,PFS	IMRT+/-CCRT+/-NACT	★★★★★★
Prayongrat et al,2017 Bangkok	R	204	2010.3-2015.9	I-IVb,M0	0	0 (5w)	0 (3m)	PFS,OS	IMRT+/-CT	★★★★★
Chen et al,2018 Guangzhou	P	419	2007.4-2012.11	I-IV,M0	1500	/	/	PFS,OS,DMFS, LRFs	IMRT+/-CCRT+/-NACT	★★★★★
He et al,2018 Guangzhou	R	949	2010.6-2013.10	I-IVb,M0	2500	871	211 (3 m)	OS,DMFS,PFS	IMRT+/-CCRT+/-NACT+/ CT	★★★★★
Lertbutsayanukul et al, 2018 Bangkok	R	208	2010.10-2015.9	I-IVb,M0	2300	/	0 (3 m)	OS,DMFS,PFS	IMRT+/-NACT	★★★★★

1997 AJCC TNM stage = 1997 American Joint Committee on Cancer tumor-node-metastasis staging system

Study design: *P* prospective, *R* retrospective

**Table 1** (continued)

NA not available, “/” in cut-off value columns: not discussed here

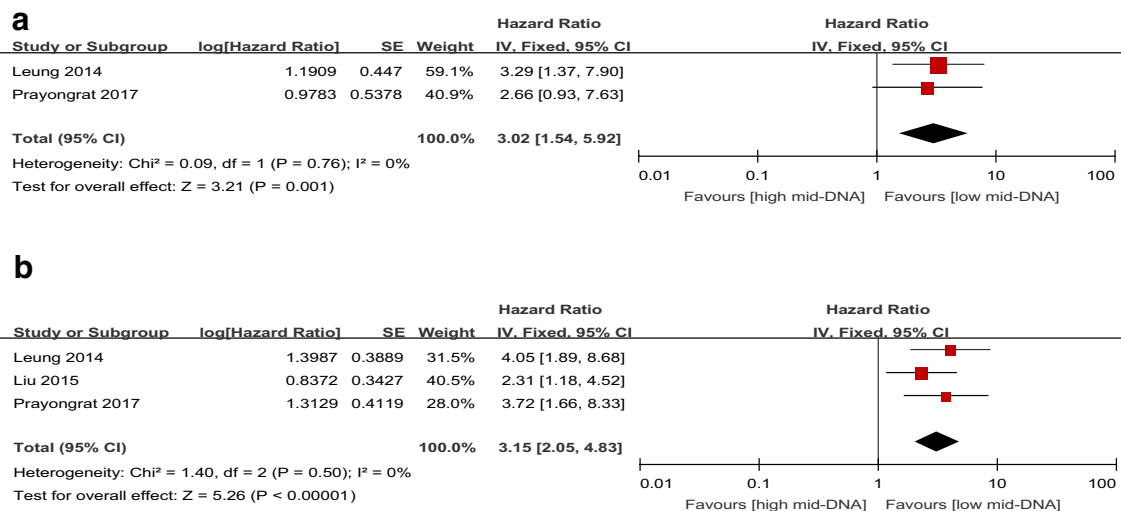
Post<sup>†</sup> the detection time of EBV DNA after treatment in brackets (d=day, w=week, m=month)

IMRT intensity modulated radiation therapy, CCRT concurrent chemoradiation therapy, NACT neoadjuvant chemotherapy, OS overall survival, PFS progression-free survival, DMFS distant metastasis-free survival, LRFS local-regional failure survival, LFFS local failure-free survival, RFFS regional failure-free survival, CSS cancer-specific survival, MFS metastasis-free survival, LFFS local failure-free survival, RFFS regional failure-free survival, CSS cancer-specific survival, MFS metastasis-free survival, RFS relapse-free survival, LRRFS loco-regional relapse-free survival

**Table 2** Summary of meta-analysis results

Outcomes	No of studies	Model	Hazard ratio (95% CI)	P	heterogeneity (P, I <sup>2</sup> )
<b>Pre-DNA</b>					
OS	16	Random	2.70 (2.06, 3.54)	<0.00001	0.0003, 63%
PFS	9	Random	2.70 (2.12, 3.44)	<0.00001	0.03, 53%
DMFS	6	Random	3.49 (2.35, 5.17)	<0.00001	0.03, 61%
LRFS	2	Fixed	2.00 (1.45, 2.76)	<0.0001	0.14*, 54%
<b>Post-DNA</b>					
OS	11	Random	4.86 (3.30, 7.17)	<0.00001	0.005, 60%
PFS	6	Random	6.29 (3.41, 11.60)	<0.00001	0.0006, 77%
DMFS	5	Random	5.68 (2.71, 11.93)	<0.00001	0.010, 70%
<b>Mid-DNA</b>					
OS	2	Fixed	3.02 (1.54, 5.29)	0.001	0.76*, 0%
PFS	3	Fixed	3.15 (2.05, 4.83)	<0.00001	0.50*, 0%

\*P ≥ 0.1 between-study heterogeneity is non-existent



**Fig. 2** Meta-analysis of mid-DNA associated with survival outcomes. **a** Overall survival (OS), **b** progression-free survival (PFS)

**Pre-DNA levels and survival outcome**

We found that high pre-DNA levels predicted poorer prognosis compared with low pre-DNA levels (Supplemental Fig. 1) with HRs (95% CIs) for OS, PFS, DMFS, and LRFS of 2.70 (2.06, 3.54), 2.70 (2.12, 3.44), 3.49 (2.35, 5.17), and 2.00 (1.45, 2.76), respectively. There was significant

between-study heterogeneity (I<sup>2</sup> > 50%, P < 0.1); therefore, we employed a random-effects model for the OS, PFS and DMFS. The risk of distant metastasis was 3-fold higher for patients with high pre-DNA levels compared with low pre-DNA levels.

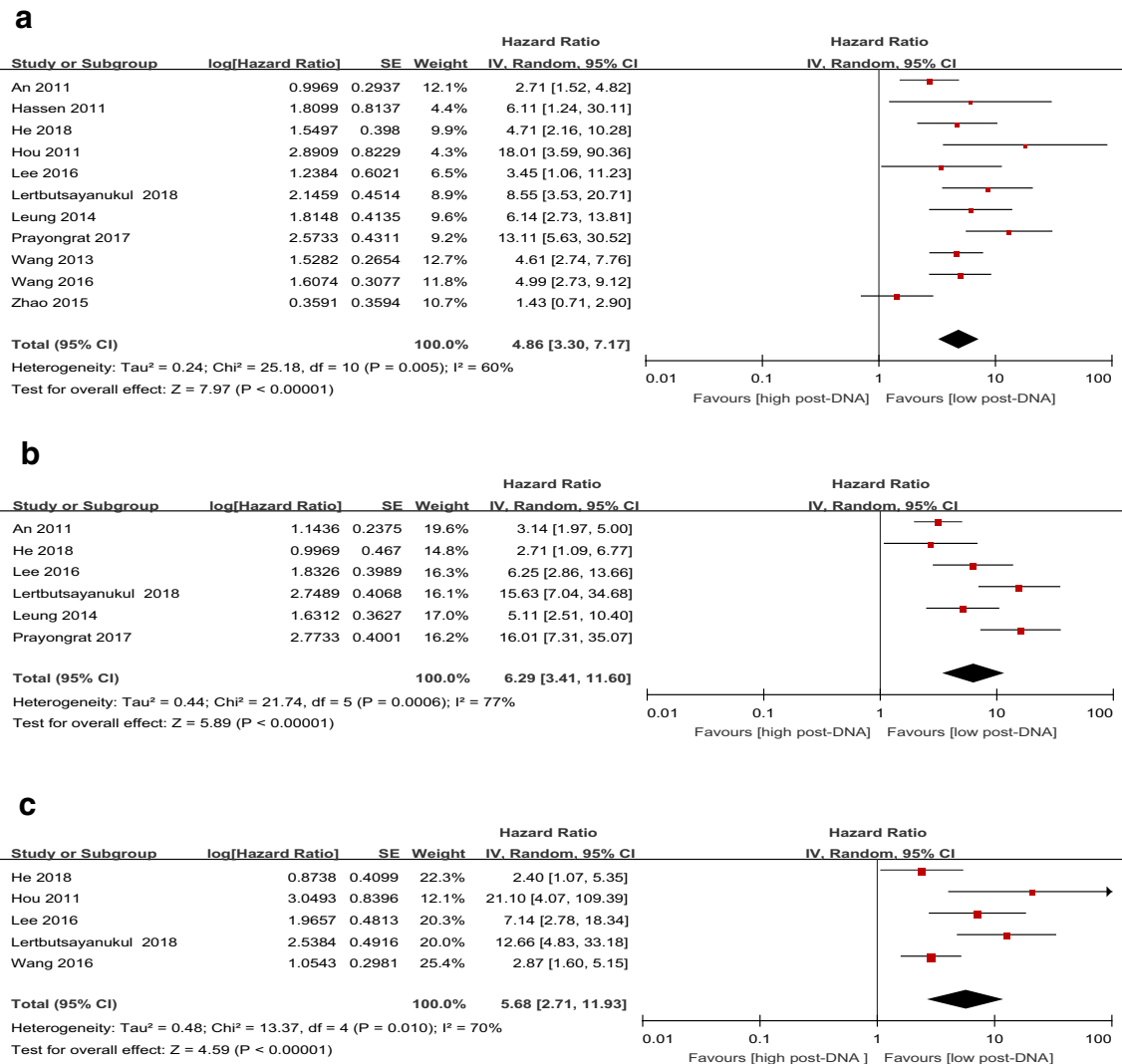
### Mid- and post-DNA levels and survival outcome

Three studies reported mid-DNA levels. High mid-DNA levels were significantly associated with poor OS (pooled HR [95% CI] 3.02 [1.54, 5.29],  $P=0.001$ ) and PFS (3.15 [2.05, 4.83],  $P<0.00001$ ; Fig. 2). For high post-DNA levels, the HRs (95% CIs) for OS, PFS, DMFS were 4.86 (3.30, 7.17), 6.29 (3.41, 11.60), 5.68 (2.71, 11.93), respectively (Fig. 3). The risk of mortality, metastasis was 5–6-fold higher for patients with high post-DNA levels compared with low post-DNA levels. Compared with the meta analysis of pre-DNA levels and mid-DNA levels, the pooled HR of post-DNA was bigger than those obviously (Table 2). Analysis of post-DNA levels showed that patients who have high post-DNA levels have greater probability of bad survival outcomes than patients with high pre-DNA or mid-DNA

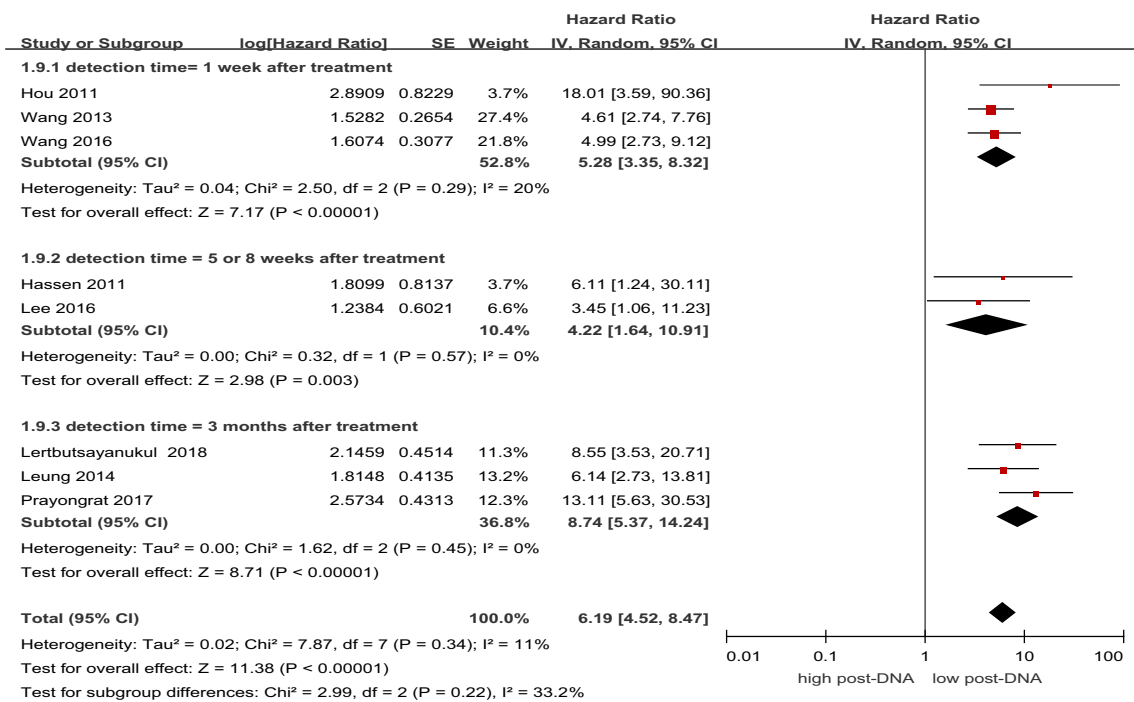
levels. Between-study heterogeneity was detected for OS, PFS, and LRFS ( $I^2>50%$ ,  $P<0.1$ ), and a random-effects model was utilized.

### Subgroup analysis

We examined the association between post-DNA levels and OS in subgroups stratified by detection time of post-treatment EBV DNA ( $\leq 1$  week, 5 or 8 weeks, 3 months). After subdividing, the overall effect of post-DNA levels was also significantly associated with OS ( $P<0.00001$ ). The time at which EBV DNA was detected after treatment varied between 1 day and 3 months; however, we found no difference between subgroups categorized by the detection times ( $P=0.22$ ) (Fig. 4).



**Fig. 3** Meta-analysis of post-DNA associated with survival outcomes. **a** Overall survival (OS), **b** progression-free survival (PFS), **c** distant-metastasis-free survival (DMFS)



**Fig. 4** Subgroup analysis of post-DNA associated with overall survival (OS) subdivided by detection time. 1.9.1: the included studies with detection time of post-DNA=1 week after treatment; 1.9.2: the

included studies with detection time of post-DNA=5 or 8 weeks after treatment; 1.9.3: the included studies with detection time of post-DNA=3 months after treatment

**Table 3** Sensitivity analysis of pre-DNA and post-DNA with survival outcomes

Outcomes	No of studies	Model	Hazard ratio (95% CI)	P	heterogeneity (P*, I <sup>2</sup> )
<b>Pre-DNA</b>					
OS	7	Random	3.10 (2.14, 4.49)	<0.00001	0.03, 58%
PFS	5	Random	2.65 (1.85, 3.81)	<0.00001	0.02, 65%
DMFS	4	Random	3.36 (1.95, 5.78)	<0.0001	0.01, 72%
LRFS	1	Fixed	2.51(1.61, 3.90)	<0.0001	Not applicable
<b>Post-DNA</b>					
OS	5	Fixed	4.00 (2.82, 5.67)	<0.00001	0.22*, 30%
PFS	2	Random	3.63 (1.38, 9.55)	0.009	0.04, 77%
DMFS	2	Fixed	6.43 (3.23, 12.81)	<0.00001	0.75*, 0%

\*P ≥ 0.1 between-study heterogeneity is non-existent

**Sensitivity analysis**

Eleven studies were assessed as being of high quality and 11 were of low quality (Supplemental Table 1). After excluding low-quality studies, we performed a sensitivity analysis of the association between pre-DNA and post-DNA levels and survival outcomes (Supplemental Figs. 2 and 3). Mid-DNA levels were reported in only a few articles and they were not analyzed here. A summary of the meta-analysis results after excluding low quality studies is given in Table 3. It showed high pre-DNA and post-DNA predicted poor OS (HR 3.10 and 4.00), PFS (HR 2.65 and 3.63) and DMFS (HR 3.36 and 6.43), which was in accordance with the results calculated by

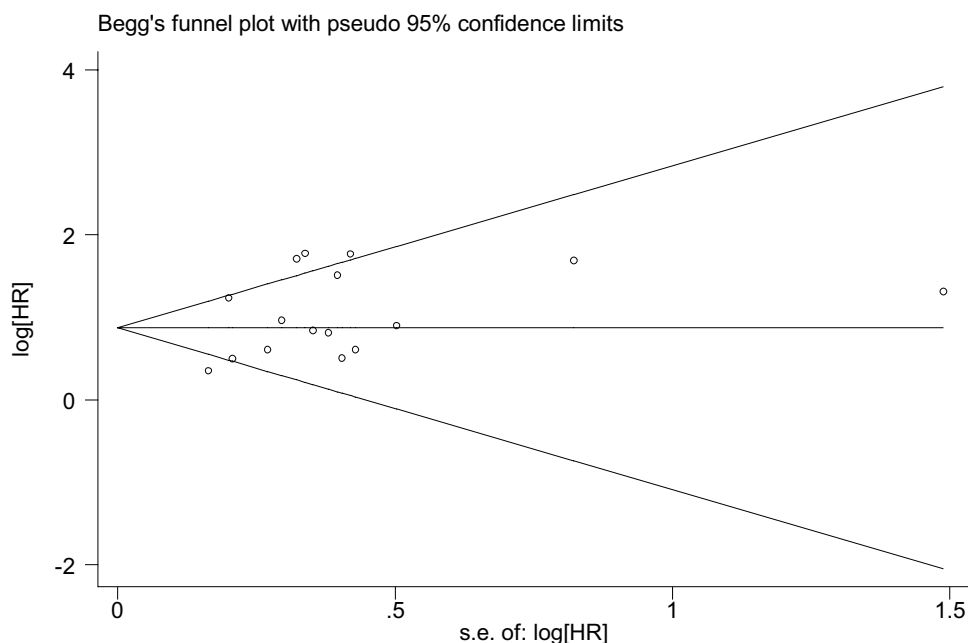
all including studies. Moreover, the heterogeneities between studies disappeared for OS (heterogeneity P=0.22, I<sup>2</sup>=30%) and DMFS (heterogeneity P=0.75, I<sup>2</sup>=0%) of post-DNA after removal of low-quality studies.

**Publication bias**

Begg’s test was employed to assess publication bias, and we found no evidence of bias in the meta-analysis of the 22 studies that examined the association between pre-DNA levels and OS (P=0.392). A funnel plot of the Begg’s test results is shown in Fig. 5.



**Fig. 5** Begg's publication bias plot of 22 studies reported pre-DNA with OS



## Discussion

Measurement of plasma EBV DNA levels is widely used to diagnose NPC and to evaluate treatment and prognosis. In combination with nasopharyngoscopy and nasopharyngeal and neck magnetic resonance imaging, plasma EBV DNA levels are routinely assessed in most clinics. The association between pre-treatment plasma EBV DNA levels and survival outcomes have been investigated in numerous studies for the past years. However, there is an urgent need for incorporating a large sample of patients to identify the prognostic value for NPC of subsequent plasma EBV DNA measurements (mid or post treatment) in intensity-modulated radiation therapy (IMRT) era. Thus, we conducted this meta-analysis of 22 studies and 8128 patients in which EBV DNA levels were associated with survival endpoints. To our knowledge, this is an update to the two previous meta-analyses on the same topic published in 2015 and 2016 [33, 34].

The EBV cut-off values varied among included studies in our meta analysis. The most frequently used cut-off values for pre-treatment EBV DNA were 1500 copies/ml [7, 20, 27, 29] and 4000 copies/ml [8, 17, 18]. Most studies employed 0 copies/ml as the cut-off value for mid-treatment EBV DNA and post-treatment EBV DNA. Although Lertbutsayanukul [31] identified the optimal pre-EBV cut-off value to predict the survival outcome of NPC patients, they also indicated the limitation of their study that they did not conduct the harmonization and standardization of the quantitative plasma EBV measurement between their laboratory with the established centers using common calibrators and PCR master mix. Thus, we employed the different cut-off

values in our including studies to define the high EBV DNA levels and the low EBV DNA levels.

In our meta analysis, the risk of mortality, metastasis was 5–6-fold higher for patients with high post-DNA levels compared with low post-DNA levels, While the risk for patients with high pre-DNA and mid-DNA levels was 2–3-fold higher compared with low pre-DNA and mid-DNA levels. Thus, the prognostic effect of post-treatment DNA level is superior to that of the pre-treatment DNA level or mid-treatment level, which is consistent with the results of the two previous meta-analyses [33, 34]. This is most likely because detection of residual plasma EBV DNA after treatment suggests the possibility of relapse [5]. Most studies employed a cut-off value of 0 copies/mL for evaluation of post-DNA associations. Thus, additional treatment should be considered for NPC patients with detectable EBV DNA levels after basic radiotherapy.

The results of our subgroup analysis of post-DNA levels subdivided by different detection time suggested that HR of post-DNA was not influenced by different detection time. In our included studies, 1 week, 5 or 8 weeks and 3 months after treatment were adopted. Any above detection time point or time point constitution are recommended to use for post-DNA measurement. However, whether patients with persistently detectable subsequent plasma EBV DNA have worse survival outcome was not studied because of lack of associated data. Due to the failure of harmonizing the EBV DNA detection method [35], we did not conduct the subgroup analysis of EBV DNA with survival outcomes subdivided by different cut-off value. Thus, we can not provide the best cut-off value of EBV DNA to predict the prognosis of NPC.



Sensitivity analysis of studies examining the association between post-DNA levels with OS and DMFS benefited by exclusion of low-quality studies to remove heterogeneity. There are some limitations to our study. All of the analyses were based on data extracted from published research, not our own original research, which may have introduced selection and publication bias. The TNM classification of the NPC patients was based on the 1997 American Joint Committee on Cancer/Union for International Cancer Control TNM classification for NPC, but a more recent edition has since been published [36]. It remains unknown whether the results would change based on the updated classification. More studies will be needed to support our conclusions.

In summary, the advantage of the post-treatment plasma EBV DNA level on prognostication may help doctors to decide whether additional treatment after radiotherapy is necessary.

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## Compliance with ethical standards

**Conflict of interest** No conflict of interest exists in the submission of this manuscript.

**Ethical statement** Because our research was a meta analysis, we did not collect any samples of human and animals. No ethical approval or patient consent was needed.

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