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Review

p53, latent membrane protein 1, bcl-2, and prognosis in nasopharyngeal carcinoma: a meta-analysis

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Summary. The controversy of (p53) in nasopharyngeal carcinoma persists, despite the fact that many studies have been conducted on its correlation with latent membrane protein 1 (LMP1), bcl-2, and prognosis. To better understand this postulated relationship, a meta-analysis was performed based on existing relevant studies. A total of 19 individual studies with a total of 1189 patients were included in the meta-analysis. Overall, the results revealed a significant association of p53-positive status with a poor 5-year survival of nasopharyngeal carcinoma (NPC) patients as the risk difference (RD) was -0.17 (95% CI, -0.31, -0.03; P=0.02, Pheterogeneity=0.01).The overall odds ratio (OR) for LMP1 in the p53 positive group vs. negative group revealed that a significantly elevated risk of positive LMP1 in the former was achieved (OR 5.52 95% CI, 2.66-11.46; P<0.00001, Pheterogeneity=0.78). Similarly, a strong correlation between bcl-2 and p53 was found with an OR 6.85 (95% CI, 2.37-19.74; P=0.0004, Pheterogeneity=0.48). However, there did not appear to be any correlations with clinical parameters such as gender, tumor site, lymph node metastasis, pathological type and TNM stage. In conclusion, p53 expression is related to the survival of nasopharyngeal carcinoma. It can be considered as the auxiliary detection index in treatment and prognosis of nasopharyngeal carcinoma.

Key words: p53, Latent membrane protein 1(LMP1), bcl-2, Nasopharyngeal carcinoma (NPC), Prognostic significance

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Introduction

Nasopharyngeal carcinoma (NPC) is the most commonly diagnosed type of head and neck cancer in Southeast Asia, especially in the southern provinces of China (Wei and Sham, 2005). Despite advances in radiation oncology, patients with advanced NPC have a low 5-year overall survival (Langendijk et al., 2004; Cao et al., 2011). Recent work has focused on identifying molecular markers that would predict the 5-year survival rate of patients.

p53 plays an important role in cell cycle arrest and the induction of apoptosis. It is one of the most frequently studied tumor suppressor genes that becomes inactivated during the development of many malignancies including NPC. The expression of p53 detected by immuno-histochemistry is reported to be highly expressed in NPC patients (Sheu et al., 1995). p53 mutations or deletions which are resistant to degradation occur at a high frequency in the majority of tumor types. Cells without mutations do not show immuno-histochemical staining of p53 because there is

no accumulation in the cell (Fontanini et al., 1994).

The prognostic role of p53 expression in NPC cancer has been investigated in many studies. Several reports have suggested that NPC patients without p53 expression survive longer and that p53 is an indicator of poor prognosis (Masuda et al., 1998; Xu and Zhang, 2001; Wang et al., 2006; Zhang et al., 2015). In contrast to these studies, several papers have shown that p53 expression is not related to survival (Zhou et al., 1998; Fulya et al., 2004; Mo et al., 2004; Liu and Ji, 2011) . Such contradictory findings indicate the true clinical significance of p53 in the prognosis of NPC is still unclear. Therefore, the aim of this study was to assess the association between p53 with clinicopathological parameters and prognosis, which may be useful for planning the management and assessing the prognosis.

Materials and methods

Search strategy

Two electronic databases (PubMed and Embase) and the Chinese National Knowledge Infrastructure (CNKI) were searched (last search was updated on 25 March 2015). No language restriction was applied, and we also screened the references of the relevant studies to check for other potentially relevant articles. The terms: 'p53' and 'nasopharyngeal carcinoma or NPC' were used as the search keywords. Because NPC is a characteristic tumor with regional distribution properties, especially in Southern China, studies in Chinese were also included. Only published studies with full-text articles were included. When the same patient population was included in several publications, only the most recent or complete study was used in the meta-analysis.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) p53 expression was measured by immunohistochemistry; (2) the correlation between p53 and LMP1, Bcl-2 or clinical prognostic parameters was evaluated; (3) sufficient published data was used to estimate an odds ratio (OR) with a 95% confidence interval (CI); (4) 5-year survival rates between different expressions of p53 in NPC cancer were compared and the risk difference (RD) for 5-year survival rates according to p53 expression were reported or calculated from the presented data. Studies were excluded if (1) they were case reports, letters, and reviews without original data, or were animal or laboratory studies; (2) the samples came from lymph nodes; (3) the outcomes of interest were not reported and it was impossible to calculate outcomes from the originally published data, (4) they were repeated studies based on the same database or patients.

Data extraction

Data were carefully extracted from all eligible studies by two of the authors (Guang-Da Yang and Zhi-Chao Wang), according to the inclusion criteria listed above. The following data were collected from each study: first author's surname, publication date, study method, sample size, turmor size, lymph node metastasis, total number of patients with positive p53 and negative p53, and number of patients divided by gender, pathological type, TNM stage and 5-year overall survival in those with and without p53, respectively. Because several articles showed survival data indirectly with a Kaplan-Meier curve, the software GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer.com/) was applied to digitize and extract the data. We did not define a minimum number of patients for inclusion in our meta-analysis. The cut-off score of the p53 positive group varied among the different studies. We defined the p53 positive group according to the original articles.

Statistical analysis

Odd ratios with 95% CI were used to assess the correlation of p53 with LMP1, bcl-2, and clinical parameters. We used risk difference (RD) to assess the prognosis of p53 for 5-year survival rates in NPC patients. Heterogeneity was confirmed by an X_2-based Q-test. A P-value greater than 0.10 for the Q-test indicated a lack of heterogeneity among the studies; therefore, the OR estimate or RD for each study was calculated using the fixed-effects model. Otherwise, the random-effects model was used. The significance of the pooled OR or RD was determined by the Z-test and a $P \leq 0.05$ was considered to be statistically significant. An estimate of potential publication bias was performed using the funnel plot with a Begg's test, and the funnel plot asymmetry on the natural logarithm scale of the OR or RD was measured using a linear regression approach. All statistical tests were performed with Review Manager Version 5.0 (The Cochrane Collaboration, Oxford, England).

Results

Study characteristics

Through electronic screening, 156 potentially relevant articles consistent with our search terms were identified. After exclusion of the trials that were out of the scope of our meta-analysis, 32 studies were considered eligible for inclusion. Upon further review, 8 were excluded because it was not possible to allow for the comparison of different p53 expression levels in NPC cancer due to insufficiently reported data, and an additional 5 were excluded because their data were used in other studies. The flowchart of our selection procedure and the study designs are summarized in Fig. 1. A total of 19 studies (Kanavaros et al., 1995; Kouvidou et al., 1995; Sheu et al., 1995; Masuda et al., 1998; Zhou et al., 1998; Murono and Park, 1999; Niemhom et al., 2000; Ho et al., 2001; Xu and Zhang,

2001; Chen et al., 2004; Fulya et al., 2004; Mo et al., 2004; Shao et al., 2004; Cheng et al., 2005; Wang et al., 2006; Liu and Ji, 2011; Mehdi et al., 2011; Tabyaoui et al., 2013; Zhang et al., 2015) were included in the meta-analysis (Table 1).

Of the included 19 studies, eleven studies assessed patients from China, three from Japan, one from Morocco, one from Greece and China, one from Algeria, one from Turkey and one from Greece. The total number of patients included was 1189, ranging from 11 to 125 patients per study. These eligible studies were published between 1995 and 2015.

Correlation with clinical information

The meta-analysis of gender in the p53-positive vs. negative groups did not attain statistical significance (OR 0.65 95% CI, 0.40-1.05; P=0.08, $P_{heterogeneity}$=0.78). The overall OR for tumor site and lymph node metastasis in the p53-positive vs. negative subgroups was 0.69 (95% CI, 0.25-1.91; P=0.48, $P_{heterogeneity}$=0.001) and 1.38 (95% CI, 0.50-3.80; P=0.54, $P_{heterogeneity}$=0.06), respectively. The overall OR for TNM stage or pathological type in the p53-positive vs. negative subgroups did not show any positive finding (OR 1.19 95% CI, 0.54-2.61; P=0.66, $P_{heterogeneity}$=0.07 and OR 1.40 95% CI, 0.93-2.12; P=0.11, $P_{heterogeneity}$=0.37, respectively) (Table 2, Fig. 2).

Correlation with LMP1 and bcl-2

The overall OR for LMP1 in p53 positive group vs. negative group revealed a significantly elevated risks of positive LMP1 in the former (OR 5.52 95% CI, 2.66-11.46; P<0.00001, $P_{heterogeneity}$=0.78). Similarly, a strong correlation between bcl-2 and p53 was observed by OR 6.85 (95% CI, 2.37-19.74; P=0.0004, $P_{heterogeneity}$=0.48) (Table 2 and Fig. 3).

Correlation with prognostic parameters

The information concerning the association between p53 expression and 5-year survival of nasopharyngeal

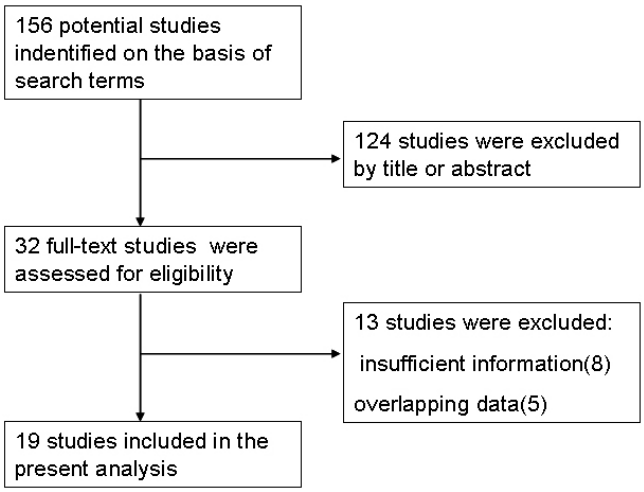

Fig. 1. Flow chart showing the selection of the 19 studies included in the meta-analysis.

Table 1. Main characteristics of all studies included in the meta-analysis.

Reference	N	Country	Detection method	Cut off value	Features
Kanavaros et al., 1995	59	Greece and China	IHC	hight, low	p53 and MDM2 cell differentiation
Sheu et al., 1995	101	China	IHC	>10% cell, positive	There was no correlation of p53 with clinical parameters
Kouvidou et al., 1995	44	Greece	IHC	hight, low	p53 and bc~2 cell differentiation
Masuda et al., 1998	22	Japan	IHC	>5% cell, postive	p53 was a prognostic factor
Zhou et al., 1998	125	China	IHC	>25% cell, postive	There was no correlation of p53 with clinical parameters
Murono and Park, 1999	54	Japan	IHC	>10% cell, postive	Association of EBV infection with p53 protein accumulation
Sopaporn, 2000	53	Japan	IHC	>10% cell,postive	CO-expression of p53 and bc~2 correlate to the presence of EBV
Xu and Zhang, 2001	58	China	IHC	>10% cell, postive	p53 protein is related to the time of survival
Ho et al., 2001	68	China	IHC	>10% cell, postive	p53 overexpression and radiotherapy inNPC
Chen et al., 2004	42	China	IHC	>5% cell, postive	p53 was be found to be independent of clinical stage
Mo et al., 2004	80	China	IHC	>30% cell, postive	p53 have no relation with NPC stage and prognosis
Fulya et al., 2004	81	Turkey	IHC	>10% cell, postive	There was no correlation of p53 with clinical parameters and prognosis
Shao et al., 2004	87	China	IHC	p53+++ ++,p53 + -	p53 accumulation in NPC was correlated to LMP1
Cheng et al., 2005	59	China	IHC	>5% cell, postive	p53 was a prognostic factor
Wang et al., 2006	79	China	IHC	>10% cell, postive	There was no correlation of p53 with clinical parameters and prognosis
Mehdi et al., 2011	11	Algeria	IHC	3+ (High); 1 +(Weak) and 2+ (Low).	p53 and bc~2 cell differentiation
Liu and Ji, 2011	47	China	IHC	hight, low	There was no correlation of p53 with clinical parameters and prognosis
Tabyaouil et al., 2013	23	Morocco	IHC	>10% cell, postive	LMP1 and p53 in NPC
Zhang et al., 2015	96	China	IHC	Negative (-) and positive (+) to (+++)	Positive expression of p53 was associated with a poor prognosis

IHC, immunohistochemistry; EBV, Epstein-Barr virus; NPC, Nasopharyngeal carcinoma; LMP1, Latent membrane protein 1.

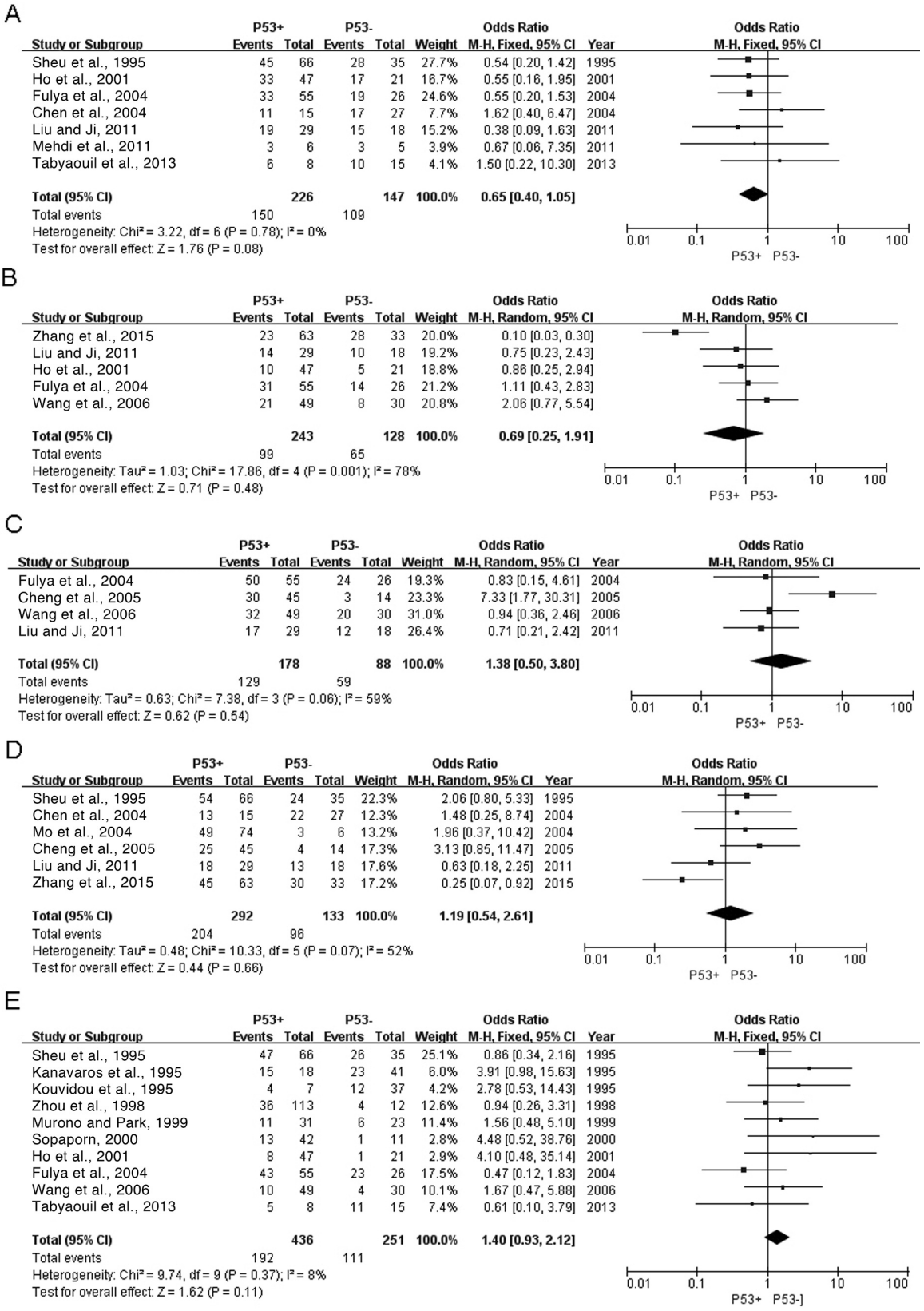

Fig. 2. Forest plot showing association of p53-positive status (p53+) and Clinical Information in nasopharyngeal carcinoma: **A**) gender; **B**). tumor site; **C**). Lymph node metastasis; **D**) TNM stage; **E**) pathological type.

Table 2. Outcomes of the meta-analysis.

Parameters	No. Studies	Sample Size		Heterogeneity	OR(RD)	95% CI of Overall Effect	P
		p53+	p53-				
Gender	7	226	147	P=0.78, I^2=0%	0.65	0.40-1.05	P=0.08
Tumor site	5	243	128	P=0.001, I^2=78%	0.69	0.25-1.91	P=0.48
Lymph node metastasis	4	178	88	P=0.06, I^2=59%	1.38	0.50-3.80	P=0.54
TNM stage	6	292	133	P=0.07, I^2=52%	1.19	0.54-2.61	P=0.66
Pathological type	10	436	251	P=0.37, I^2=8%	1.4	0.93-2.12	P=0.11
bcl-2	3	55	53	P=0.48, I^2=0%	6.85	2.37-19.74	P=0.0004
LMP1	3	99	57	P=0.78, I^2=0%	5.52	2.66-11.46	P<0.00001
5-year survival	8	432	156	P=0.01, I^2=61%	RD(-0.17)	(-0.31- -0.03)	P=0.02

LMP1, Latent membrane protein 1; OR, odds ratio; RD, risk difference.

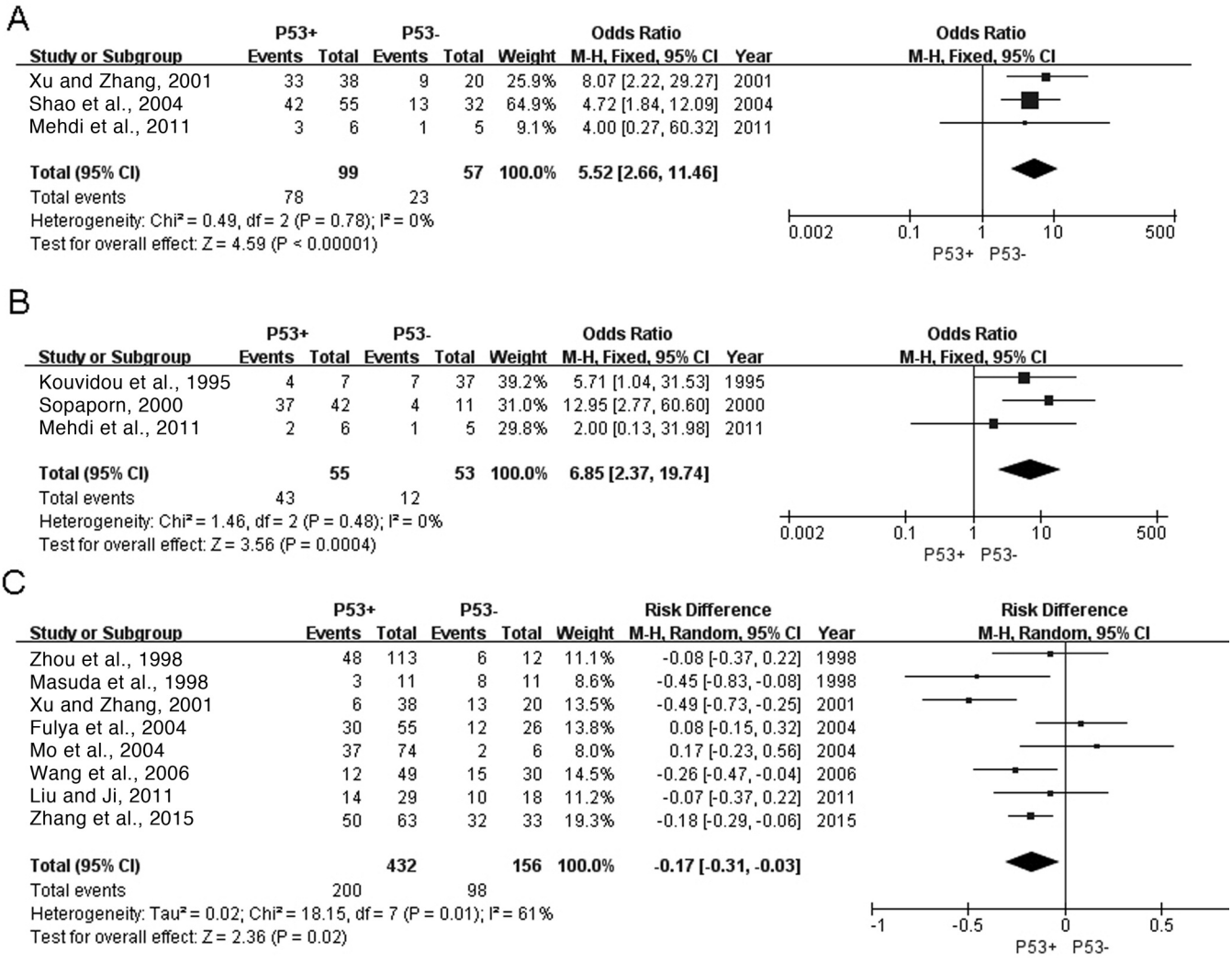

Fig. 3. Forest plot showing association of p53-positive status (p53+) **(A)**, LMP1 **(B)**, bcl2 and 5-year survival **(C)**.

carcinoma was revealed by the analysis of eight eligible studies. The combined analysis showed that the 5-year survival rate for patients with positive expression of p53 was 46.30% (200/432) compared to 62.82% (98/156) for patients with negative expression of p53. Meta-analysis results showed that compared to patients with negative expression of p53, those who had positive expression of p53 had significantly poorer OS (RD=-0.17, 95% CI, -0.31, -0.03; P=0.02, $P_{heterogeneity}$=0.01). (Table 2 and Fig. 3).

Publication bias

A Begg's funnel plot and an Egger's test were performed to assess publication bias. The results showed that no publication bias was present for all comparisons. An important publication bias was identified for 5-year survival. As shown in Fig. 4, the funnel plots of the p53-positive status analysis for the association with 5-year survival confirmed a symmetric distribution and suggested that there was no publi-cation bias.

Discussion

In this meta-analysis, the relationship between p53 immunohistochemical expression on the one hand and gender, tumor site, lymph node metastasis, pathological type, TNM stage and survival was statistically analyzed in order to investigate the association between positive expression of p53 and prognosis of NPC. The present meta-analysis has combined 19 publications representing 1,189 patients to yield statistics, showing the following results: The p53-positive expression was closely related to LMP1 (OR 5.52 95% CI, 2.66-11.46; P<0.00001, Pheterogeneity=0.78) and bcl2 (OR 6.85 95% CI, 2.37-19.74; P=0.0004, Pheterogeneity=0.48). Patients with positive expression of p53 had poorer 5-year survival (p=0.02). However, no correlation was observed between p53 expression and clinicopathological features including gender, tumor site, lymph node metastasis, pathological type and TNM stage.

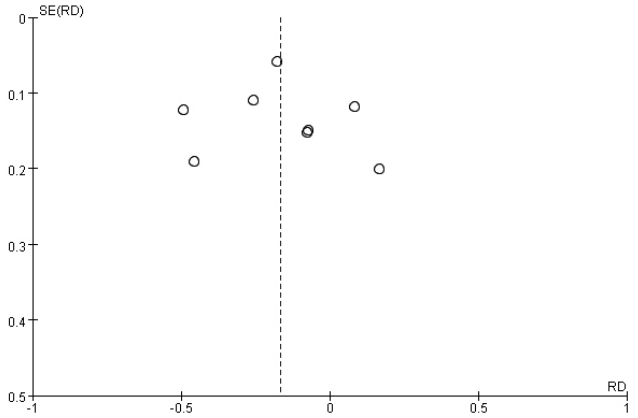

Fig. 4. Begg's funnel plots for publication bias test on the association of p53-positive status with 5-year survival of nasopharyngeal carcinoma patients.

Tumor suppressor gene p53, one of the most tumor relevant genes, is the most frequently mutated gene in human tumor (Ecke et al., 2010). Mutant p53 protein not only loses the primitive function of tumor suppression, but also may contribute to radiotherapy and chemotherapy resistance (Wang et al., 2010). p53 protein is overexpressed, which is the main product detected by immunohistochemistry (IHC) due to the longer half-life of mutant-type p53 protein, and its content is very high in nuclei. The overexpression of the p53 gene is involved in selective tolerance of tumor cells to chemotherapeutic drugs. The multidrug resistance associated gene of tumor cells is mainly mdrl, and the mutant p53 gene protein can enhance the promoter activity. In order to obtain a good therapeutic effect, mdrl unrelated drugs, such as paclitaxel, may be used for malignant tumors with overexpression of p53 (Gan et al., 1996). Interestingly, our study found that p53 overexpression is related to LMP1 and bcl-2, although only three studies were analyzed, respectively. The LMP1 gene is a well-known and important oncogene in EBV and is a poor prognostic biomarker in NPC patients (Chen et al., 2015). In addition, our previous studies indicated that LMP1 could induce chemoresistance and radioresistance in NPC cells (Yang et al., 2013, 2014, 2016). The bcl-2 protein has been reported to be up-regulated in vitro by LMP1 in epithelial cells (Sarac et al., 2001). This may indicate that overexpression of p53 can induce chemoresistance and radioresistance in NPC throught LMP1 and bcl2. In addition, Koch et al, have found a radioresistance correlation between p53 overexpression and squamous cell carcinoma of the head and neck (HN-SCC) (Koch et al., 1996).

Thus more large-scale studies or meta-analyses on this issue need to be conducted. Based on the above data, our updated meta-analysis was worthwhile and comprehensive.

Our meta-analysis indicated a significant role of p53 detection by IHC in predicting 5-year survival of NPC. The study showed that the 5-year survival rate of patients with positive expression of p53 was lower than that of patients with negative expression of p53, which may be related to the sensitivity of tumor cells with overexpression of p53 to radiotherapy and chemotherapy.

However, it would be too speculative to make a verdict on the association of p53 overexpression and NPC because there are still several issues that should be considered. Distinctive heterogeneity of the studies used in the meta-analysis is the first and most important problem in our analysis. In the studies that we included, the IHC techniques used to detect protein expression were not the same, including antibody type and concentration, as well as the cut-off value used.

Moreover, lack of specific criteria for assessing p53 positivity according to different types of cancer is an issue that should be addressed in the future. There were additional differences in age, tumor histological type, grade, stage, tumor size and therapy in patients. The excision method of the tissues (surgical or endoscopic excision) evaluated for p53 expression may also have affected this result. These factors could contribute to the heterogeneity. Therefore, it is essential to develop more extensive large-scale studies with bead-array technology in the future. In addition, the small size of the included patient cohorts led to a lack of power in identifying the correlation between the proposed prognostic factors and outcome. The studied populations may not have accurately represented the p53 expression data in the global population. Lastly, in some studies, the RD and their corresponding 95% CIs were indirectly calculated from other survival data or extracted from the survival curves, which may have bias our results. All of these factors might partly influence the significance of p53 expression in the survival and the clinicopathological analysis.

In conclusion, this meta-analysis found that p53 expression is related to LMP1 and bcl-2 and that no correlation exists between p53 overexpression and other common clinicopathological parameters. In addition, overexpression of p53 detected by immunohistochemistry was related to poorer survival of NPC patients. To strengthen our findings, well-designed prospective studies are required to explore the relationship between p53 expression and survival of NPC.

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Conflicts of interest. The authors have declared no conflicts of interest.

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