Systematic Review and Meta-Analysis

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Prognostic significance of nuclear Yes-associated protein 1 in patients with nonsmall cell lung cancer

A systematic review and meta-analysis

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Abstract

Background: Nuclear Yes-associated protein 1 (YAP1) has often been regarded as an adverse prognostic indicator in various tumors. Recent studies have associated YAP1 with unfavorable prognosis in nonsmall cell lung cancer (NSCLC). However, due to small sample sizes, the prognostic value of nuclear YAP1 in NSCLC patients is not well understood. In the present study, we evaluated the prognostic role of nuclear YAP1 in NSCLC patients via a systematic review and meta-analysis.

Methods: We searched the PubMed, EMBASE, Cochrane, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Databases for papers investigating the prognostic significance of nuclear YAP1 expression in NSCLC patients. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated with reference to overall survival (OS) and progression-free survival (PFS) of NSCLC patients to provide synthesized estimates of the effects of nuclear YAP1 expression.

Results: Among 414 cases, higher nuclear YAP1 expression presented as a predictive factor of poorer OS (HR = 1.52; 95% CI: 1.11–2.08; $P = .01$; $I^2 = 0.0\%$) and decreased PFS (HR = 2.11; 95% CI: 1.52–2.93; $P < .001$; $I^2 = 44.2\%$) in NSCLC patients. Subgroup analysis revealed shortened OS (HR = 1.63; 95% CI: 1.14–2.34; $P = .007$; $I^2 = 0.0\%$) and worse PFS (HR = 2.25; 95% CI: 1.53–3.30; $P < .001$; $I^2 = 0.0\%$) in patients from Asia with higher nuclear YAP1 expression. Prognosis was also worse in patients with III–IV stage cancer (PFSHR = 2.09; 95% CI: 1.45–3.01; $P < .001$; $I^2 = 58.1\%$) and in patients treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) (OS HR = 1.59; 95% CI: 1.00–2.51; $P = .048$; $I^2 = 15.5\%$, and PFS HR = 2.35, 95% CI: 1.62–3.42; $P < .001$; $I^2 = 0.0\%$).

Conclusion: High expression of nuclear YAP1 was associated with shorter survival outcome in patients with NSCLC.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, CRC = colorectal cancer, EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors, EMT = epithelial-mesenchymal transition, ES = estimated survival, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, NSCLC = nonsmall cell lung cancer, OS = overall survival, PFS = progression-free survival, STAT3 = signal transducer and activator of transcription 3, TEAD = TEA-domain transcription factors, YAP1 = Yes-associated protein 1.

Keywords: meta-analysis, NSCLC, nuclear Yes-associated protein 1, prognosis

1. Introduction

Lung cancer is the most fatal cancer worldwide, leading to 1.61 million deaths annually.[1] Even in recent decades, its 5-year survival rate remains only 13%–16%, which is due to high rates of local recurrence or distal metastasis.[2–4] Nonsmall cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases.[5] The most prevalent histological subtypes of NSCLC are adenocarcinoma and squamous cell carcinoma.[6] Although much effort has been devoted to improve the diagnostic and therapeutic strategies for NSCLC, there is still a long way to go to cure the disease. Understanding molecular pathogenesis is yet incomplete, and effective prognostic markers are not available.[7] Identification of potential prognosis biomarkers is of importance for patient classification and selection of subsequent optimal treatment.

Previous studies have highlighted the prognostic significance of YAP1 in a variety of cancer types, including hepatocellular carcinoma (HCC),[8] gastric cancer (GC),[9] breast cancer,[10] colorectal cancer (CRC),[11] and NSCLC.[12,13] Located at 11q22, YAP1 is widely considered as an essential effector of the Hippo

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signaling pathway.[12] This pathway, initially identified in Drosophila, is linked to tissue homeostasis, organ size control, and tumorigenesis, and is highly conserved in mammals.[14,15] When the Hippo pathway is turned off, cytoplasmic YAP1 is dephosphorylated and accumulates in the nucleus, thus regulating cellular functions.[16,17] Therefore, YAP1 is mainly localized in the tumor cell nuclei.[18] Consistent with these results, another study found that in NSCLC, YAP1 was predominantly localized in the nucleus, and its overexpression was markedly linked to advanced TNM stage, nodal metastasis, and decreased overall survival.[19] Accumulating evidence from studies of NSCLC has confirmed that high expression of YAP1 in the nucleus, rather than the cytoplasm, is related to worse OS and PFS.[16,20,21] Accordingly, our aim in this review was to assess the prognostic significance of YAP1 expression in the nucleus, but not cytoplasm.

With respect to its biological mechanism in cancer, YAP1 has been reported as a tumor suppressor gene or oncogene in various cancer types.[22] For example, Hong et al proposed that YAP acted as an oncogene in NSCLC, promoting cell proliferation and invasion.[20] However, another study indicated that nuclear YAP1 played a role as tumor suppressor that inhibited development of lung squamous cell carcinoma.[23] Therefore, the prognostic effect of nuclear YAP1 in NSCLC remains controversial. We herein carried out a systematic review and meta-analysis to quantitatively determine whether nuclear level of YAP1 correlates with a more unfavorable survival rate in NSCLC patients.

2. Methods

2.1. Search strategy

Ethical approval is not required, as this is a meta-analysis. We conducted a search of the PubMed, EMBASE, Cochrane, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases for relevant studies of nuclear YAP1 in NSCLC updated on November 30, 2018. This was carried out by LZ and GM. The keyword combinations used were as follows: "pulmonary cancers" or "nonsmall cell lung carcinoma" or "NSCLC" or "lung cancer" and "YAP" or "Yes-associated protein 1" or "Yap1 protein" or "YAP protein" or "Yes-associated protein" and "prognosis" or "outcome" or "survival". The electronic search was confined to the English and Chinese languages. We conducted the selection procedure following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[24] Meanwhile, a meta-analysis statement flow chart was applied to the selection of articles (Fig. 1). When there were disagreements in a particular article, the corresponding author was contacted and consulted.

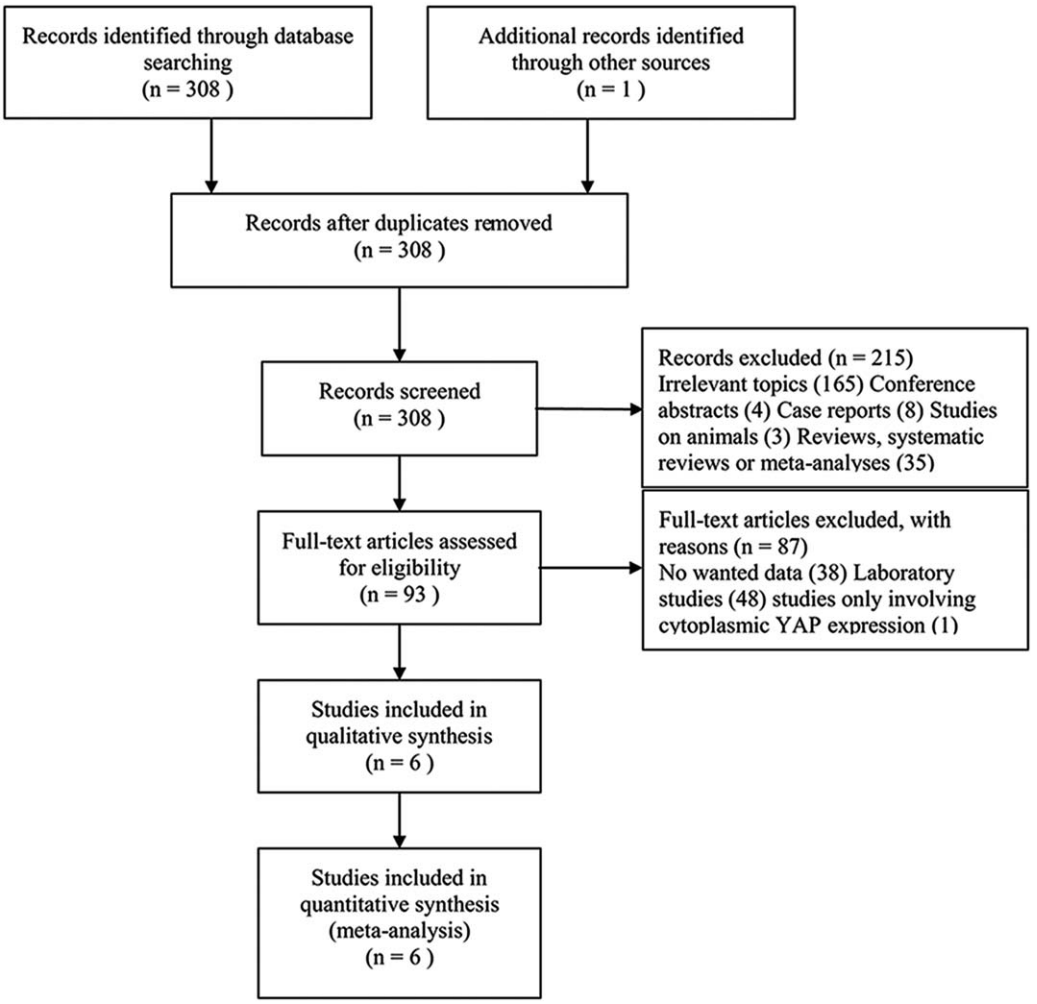

Figure 1. The screening process for eligible studies.

2.2. Eligibility criteria

The following inclusion criteria were set before retrieving and assessing relevant literature:

(1) NSCLC without restriction of stage and pathology type;
(2) the association between nuclear YAP1 expression and patient survival (OS or PFS) was reported;
(3) HRs and 95% CIs for OS and PFS to nuclear YAP1 were reported or could be computed from the data presented; and
(4) NSCLC patients were divided into two groups according to nuclear YAP1 expression level.

Studies were excluded if they were

(1) case reports;
(2) reviews, systematic reviews, or meta-analyses;
(3) conference abstracts;
(4) studies on animals;
(5) studies not assessing nuclear YAP1 or NSCLC;
(6) studies without available data;
(7) laboratory studies, such as studies on signaling pathways, molecular mechanisms, or other in vitro experiments; and
(8) studies only addressing cytoplasmic YAP1 expression but not nuclear YAP expression.

2.3. Data extraction

In accordance with the Cochrane Handbook for systematic reviews, two independent reviewers (LZ and GM) selected the literature and extracted data, with any dispute being resolved by discussion with a third reviewer (JL). Basic information retrieved from the reports included the name of the first author, the year of publication, country, number and gender of patients, median age, smoking history, histological subtype, tumor stage, antibodies applied for detection of nuclear YAP1 expression, cutoff value to define high nuclear YAP1, number of cases with high and low nuclear YAP1 expression, reported survival, HRs from multivariate analysis for survival curves, and therapy. We measured PFS from the start of treatment to clinical/radiographic progression or death by any cause. The definition of OS was the time from diagnosis till death by any cause.

2.4. Methodological assessment

The whole assessment of eligible publications was performed by two reviewers (LZ and GM) independently in light of the Newcastle-Ottawa Scale (NOS) criteria.[25] The score assessed three dimensions of methodology as follows: selection of patients (0 to 4), study comparability (0 to 2), and the ascertainment of outcomes of interest (0 to 3). The NOS scores ranged from 0 to 9 and studies scoring 6 or more were defined as high quality.

2.5. Statistical analysis

Statistical computations were carried out using STATA (version 12, Stata Corporation). The natural logarithms of the HR values and variance statistics were obtained from the survival results for syntheses on the condition that they were given directly. Otherwise, the ln(HR) and variance were calculated from either the HR with 95% CI or the survival curves with P values. When both adjusted and unadjusted HRs were available, the former was preferred. Multivariate survival analyses would likewise take priority over univariate survival analyses. The assessment of heterogeneity among the studies was evaluated by the I^2 statistic test and chi-square-based Q-test, and statistical significance was inferred where $P < .01$. A random-effects model was employed to reduce the influence of heterogeneity if this was detected ($P < .05/I^2 > 50\%$). A fixed-effects model was considered if heterogeneity was absent. The publication bias of pooled studies was evaluated using Begg's test. Insignificant publication bias was inferred where $P > .05$.

3. Results

3.1. Literature selection

Figure 1 depicts the results of our literature screening process. We identified 309 potentially relevant publications, 308 of which were obtained from PubMed, EMBASE, Cochrane, or Web of Science, and others were drawn from the CNKI and Wanfang Databases. After rigorously reading each identified study, we excluded 216 as follows: duplicate studies (n = 1); studies of irrelevant topics (n = 165); conference abstracts (n = 4); case reports (n = 8); studies on animals (n = 3); and reviews, systematic reviews, or meta-analyses (n = 35). Further 87 studies were excluded for the following reasons: studies without sufficient data such as HR or 95% CI of OS or PFS (n = 38); laboratory studies (n = 48); and studies only involving cytoplasmic YAP1 expression (n = 1). Finally, six studies fulfilled all the inclusion criteria of our meta-analysis, including five studies with both OS and PFS rates, and one that only reported OS.

3.2. Study characteristics

A summary of the principal characteristics of the included studies is shown in Table 1.

Altogether, 414 NSCLC patients with median age ranging from 58 to 67 years were included in our analysis. Six studies were published from 2010 to 2018, with two each from China,[19,26] Korea,[20,27] and Spain.[26,28] Smoking history was reported in only two of them. Among six studies, 249 NSCLC patients were confirmed with adenocarcinoma, and the remainder were papillary carcinoma (n = 12), micropapillary carcinoma (n = 2), solid carcinoma (n = 11), squamous cell carcinoma (n = 41), large cell carcinoma (n = 1), adenosquamous carcinoma (n = 1), and other undetermined NSCLC subtypes (n = 97). The six studies included cancers varying in stages from I to IV, and four of them, including 155 patients, had only advanced-stage (III–IV) cancer. The 414 patients included 171 cases involving high nuclear YAP1 expression and 243 cases with low nuclear YAP1 expression. A total of 138 patients in three studies were treated with EGFR-TKIs, including gefitinib, erlotinib, afatinib, and oricotinib, and the remaining cases underwent surgical resection, chemotherapy, or immunotherapy (nivolumab). All eligible studies scored ≥6 on the Newcastle-Ottawa Scale (NOS), with three scored 7, one 8, and one 9.

3.3. Publication bias test

We detected no significant publication bias using Begg's test of the association of high levels of nuclear YAP1 with survival outcomes on OS ($P = 0.06$) (Fig. 2A) or PFS ($P = 0.22$) in NSCLC patients (Fig. 2B).

3.4. Meta-analysis results

3.4.1. The prognostic significance of high nuclear YAP1 to OS and PFS of NSCLC patients. We evaluated the prognostic significance of nuclear YAP1 expression with respect to OS and

Table 1

The main characteristics of all included studies.

Author	Year of publication	Country	Median age	N (F/M)	Histological subtype	Tumor stage	Antibody	N of high nuclear YAP1	N of low nuclear YAP1	Outcome	HR estimation	Therapy	NOS scores
Karachaliou[28]	2018	Spain	64.2	17 (5/12)	ADC (12)/SCC (3)/Large cell carcinoma (1)/adenosquamous (1)	III–IV	NM	12	5	PFS and OS	MA	Platinum based chemotherapy or docetaxel or nivolumab	7
Chaib[26]	2017	Spain	67	47	NSCLC (47)	IIIB–IV	NM	24	23	PFS and OS	MA	EGFR TKI	7
Chaib[26]	2017	China	58	50	NSCLC (50)	IIIB–IV	NM	25	25	PFS and OS	MA	EGFR TKI	7
Kim[27]	2015	Korea	66	167 (88/79)	ADC (167)	I–IV	PO	34	133	PFS and OS	SC	Wedge resection, lobectomy or pneumonectomy	8
Hong[20]	2014	Korea	60.4	41 (29/12)	ADC (16)/Papillary (12) Solid (11)/ Micropapillary (2)/	IIIB–IV	MO	15	26	PFS and OS	SC	EGFR TKI	9
Wang[19]	2010	China	60	92 (43/49)	ADC (54)/SCC (38)	I–IV	RP	61	31	OS	SC	Curative surgical resection	6

ADC = adenocarcinoma, EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, F = female, M = male, MA = multivariate analysis, MO = monoclonal, N = number of patients, NM = not mentioned, NOS = Newcastle-Ottawa Scale, NSCLC = nonsmall cell lung cancer, OS = overall survival, PFS = progression-free survival, PO = polyclonal, RP = rabbit polyclonal, SC = survival curve, SCC = squamous cell carcinoma, YAP1 = Yes-associated protein 1.

PFS. The relationship between OS and expression level of nuclear YAP1 was discussed in six studies (n = 414), and the combined results suggested that high nuclear YAP1 expression was related to worse OS in NSCLC (HR = 1.52; 95%CI: 1.11–2.08; $P = .01$; Fig. 3A). Heterogeneity testing showed $I^2 = 0.0\%$ ($P = .461$), and we therefore used the fixed-effects model for analysis.

PFS was also analyzed in five studies (n = 322), and the combined HR demonstrated that high nuclear YAP1 expression was related to poorer PFS (HR = 2.11; 95% CI: 1.52–2.93; $P < .001$; Fig. 3B). As the heterogeneity was acceptable ($I^2 = 44.2\%$; $P = .127$), HR was computed with fixed-effects model.

3.4.2. Subgroup analysis. The included patients were stratified on the following bases: (I) population (Asian/non-Asian and Chinese/Korean/Spanish); (II) median age (≤65 years old/>65 years old); (III) TNM stages (III–IV); (IV) antibody (polyclonal); and (V) therapy (EGFR-TKIs/non-EGFR-TKIs).

3.4.2.1. Population. In the four of the studies from Asia, including 350 cases, high expression of nuclear YAP1 was significantly correlated with shorter OS (HR = 1.63; 95% CI: 1.14–2.34; $P = .007$; $I^2 = 0.0\%$). Regarding PFS, three studies including 258 Asian patients demonstrated that high nuclear YAP1 expression in patients with NSCLC was associated with shorter PFS (HR = 2.25; 95% CI: 1.53–3.30; $P < .001$; $I^2 = 0.0\%$). In two Korean studies, including 208 patients, decreased OS (HR = 1.93; 95% CI: 1.07–3.45; $P = .028$) and PFS (HR = 2.08; 95% CI: 1.27–3.41; $P = .004$) were correlated with high expression of nuclear YAP1 without heterogeneity ($I^2 = 0.0\%$). However, the pooled results from the remaining two studies, from Spain, were not significant in terms of OS (HR = 1.17; 95% CI: 0.61–2.26; $P = .637$; $I^2 = 31.7\%$) or PFS (HR = 1.80; 95% CI: 0.96–3.36; $P = .066$; $I^2 = 84.7\%$). Likewise, high nuclear YAP1 expression was not significantly linked to decreased OS in 142 NSCLC patients from China in two studies (HR = 1.48; 95% CI: 0.94–2.33; $P = .09$; $I^2 = 27.6\%$).

3.4.2.2. Median age. The median age of included patients was calculated from six eligible studies, four of which included 200 patients whose median age was ≤65 years. The synthesized results in terms of OS and PFS for NSCLC patients with median age ≤6 5years were 1.55 (95% CI: 1.08–2.23; $P = .018$; $I^2 = 34.2\%$) and 1.93 (95% CI: 1.25–2.97; $P = .003$; $I^2 = 70.0\%$), respectively. In the subgroup patients with median age ≥65 years, the aggregated HR was 1.41 (95% CI: 0.76–2.63; $P = .278$) for OS and 2.39 (95% CI: 1.44–3.97; $P = .001$) for PFS, without heterogeneity ($I^2 = 0.0\%$).

3.4.2.3. Tumor stage. Four of the studies, included 155 patients only with stages III–IV NSCLC, while the other studies included stages I–IV NSCLC. Analyses were performed on the subgroup of cases with stages III–IV, and the combined HR showed a significant correlation between high nuclear YAP1 expression and poor PFS (HR = 2.09; 95% CI: 1.45–3.01; $P < .001$; $I^2 = 58.1\%$), but no significant correlation with OS (HR = 1.43; 95% CI: 0.93–2.21; $P = .105$; $I^2 = 31.5\%$).

3.4.2.4. Polyclonal antibodies. The influence of antibodies for nuclear YAP1 in NSCLC was analyzed, including two polyclonal antibodies among 259 cases. The subgroup analysis was conducted on polyclonal antibodies, with combined HR for OS of 1.61 (95% CI: 1.02–2.54; $P = .04$; $I^2 = 0.0\%$).

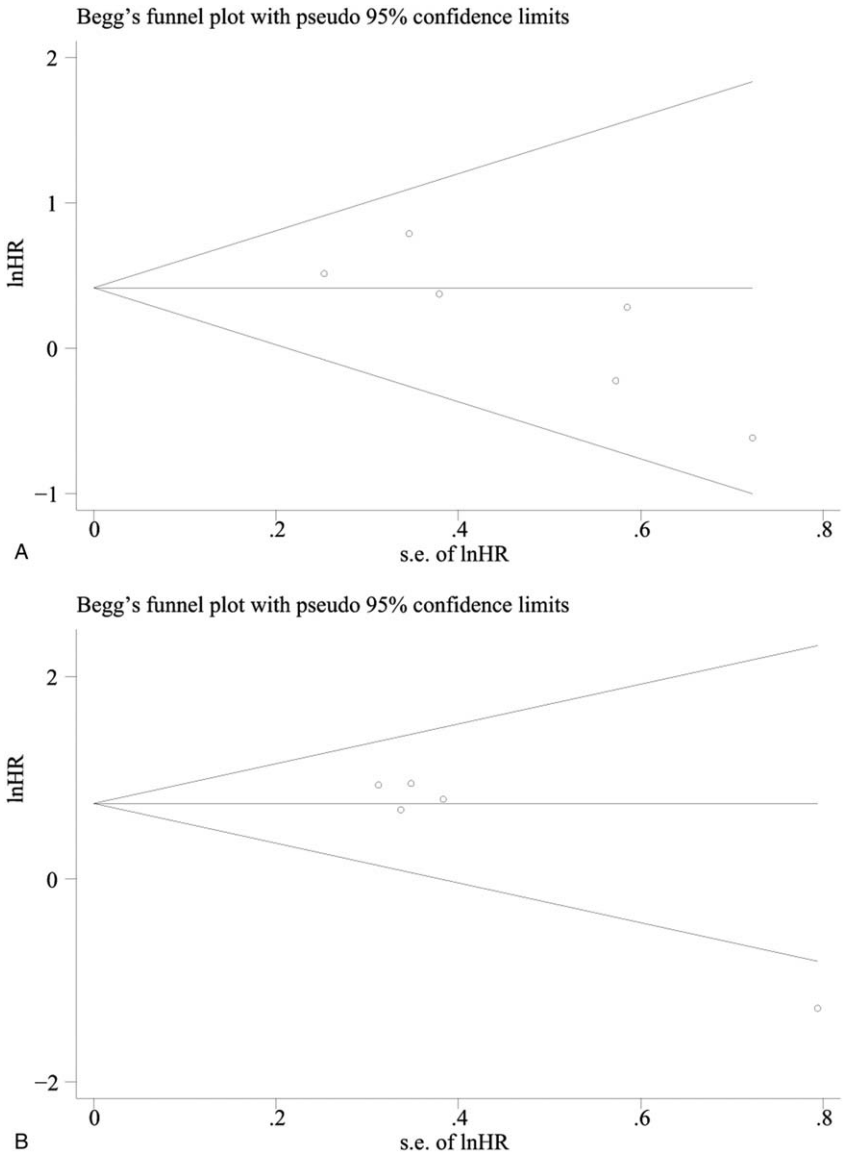

Figure 2. Begg funnel plot showing the publication bias of the included studies for OS (A) and PFS (B) in NSCLC patients prior to EGFR-TKI treatment.

3.4.2.5. Therapy. A total of 138 NSCLC patients in three studies received EGFR-TKI treatment. EGFR-TKI-treated patients with a high level of nuclear YAP1 had higher risk of shortened OS (HR = 1.59; 95% CI: 1.00–2.51; $P = .048$; $I^2 = 15.5\%$) and PFS (HR = 2.35; 95% CI: 1.62–3.42; $P < .001$; $I^2 = 0.0\%$). In contrast, patients without treatment with EGFR-TKIs were not significantly influenced by high nuclear YAP1 expression in either OS (HR = 1.45; 95% CI: 0.94–2.24; $P = .091$; $I^2 = 9.2\%$) or PFS (HR = 1.49; 95% CI: 0.76–2.93; $P = .24$; $I^2 = 81.7\%$).

All summarized results of subgroup analyses are displayed in Table 2.

4. Discussion

To assess the prognostic significance of nuclear YAP1 expression in NSCLC patients, a meta-analysis was performed on six studies published in English language journals, which included 414 NSCLC patients. Overall, the pooled results indicated that NSCLC patients with a high level of nuclear YAP1 were correlated with worse survival outcomes, in terms of both OS and PFS, compared with the low expression group. This association was particularly strong in Chinese and Korean patients but was weaker and nonsignificant in two Spanish studies. In addition, high expression of nuclear YAP1 was significantly correlated with poorer OS and PFS in EGFR-TKI treated cases, but not in EGFR-TKI naïve cases.

Two assumptions may explain the effects of EGFR-TKI treatment. First, 138 NSCLC patients treated with EGFR-TKIs in three studies had higher EGFR-mutation rates, compared with patients not given EGFR-TKI therapy. Second, it has been demonstrated that nuclear YAP1 contributes to EGFR-TKI resistance in NSCLC via disruption of EGFR TKI modulation,[18] possibly leading to worse prognosis in EGFR-mutant patients. On the other hand, EGFR signaling enhanced YAP1 expression and activity through facilitating protein stability, which in turn fostered proliferation and survival of EGFR-mutant NSCLC cells.[29] Accordingly, a combination of YAP1 inhibitors and EGFR-TKIs might play a synergistic role in treatment of EGFR-

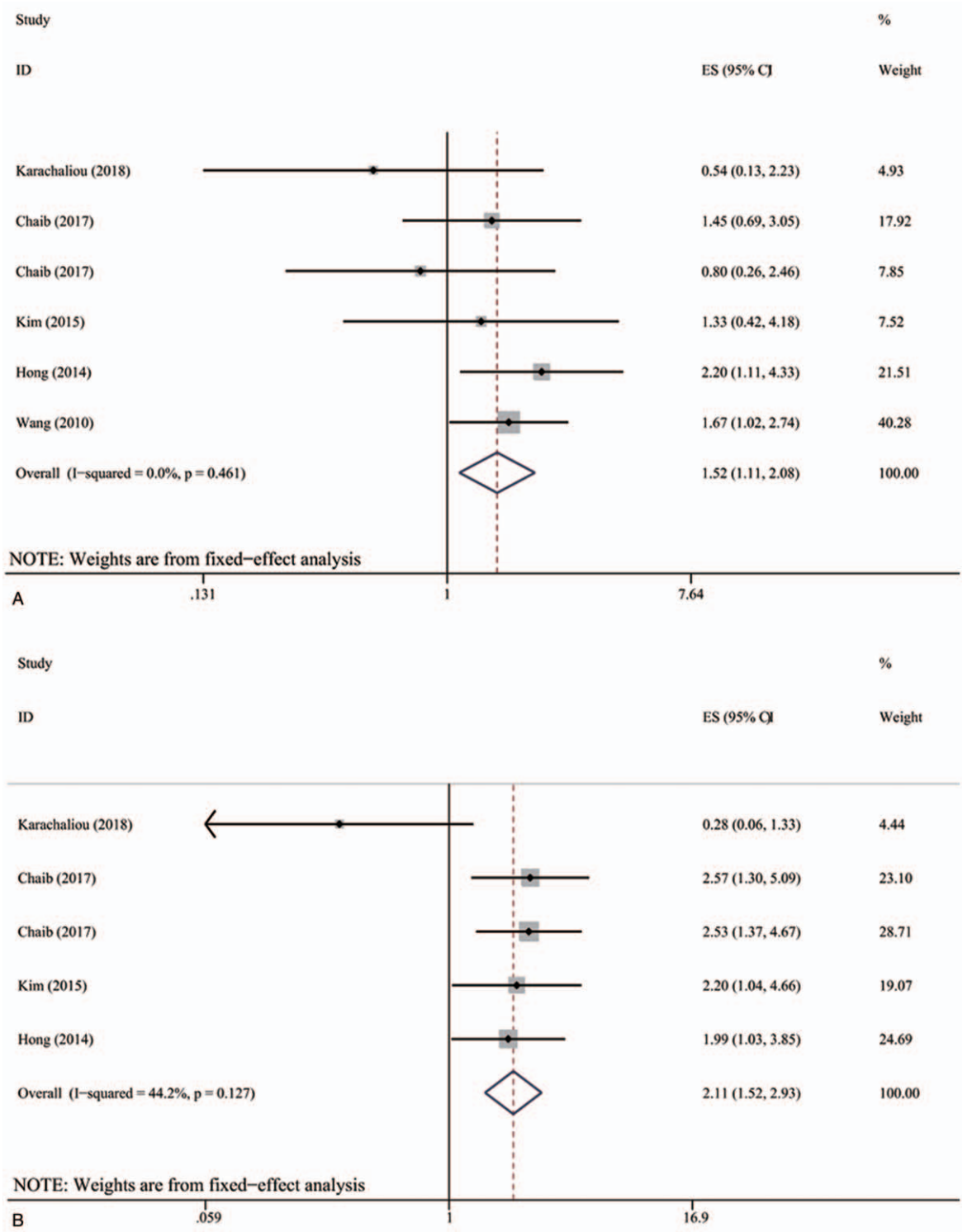

Figure 3. The pooled estimated survival (ES) (HR) for OS (A) and PFS (B) in NSCLC patients before treatment with EGFR TKIs.

mutant NSCLC with promising potential.[24] The interaction between nuclear YAP1 and EGFR in NSCLC was reported to be linked with the STAT3 pathway,[24] and the YAP1 downstream target AXL,[30] but the detailed mechanism could be far more complicated and requires further exploration. Furthermore, Hong's group found that elevated YAP1 expression before, but not after, EGFR-TKI treatment, was significantly correlated with poor outcomes in EGFR-mutant patients.[20] Consistently, our results suggested that YAP1 could be a potential prognostic biomarker of response rate and survival in EGFR-mutant NSCLC patients before EGFR-TKI treatment.

Our subgroup analyses also demonstrated that pooled OS showed no significant difference in Chinese and non-Asian (Spanish) patients who harbored high or low levels of nuclear

Table 2

Results of subgroup analysis of pooled HRs of survival outcomes of NSCLC patients with high nuclear YAP1.

	N of studies	Patients	Model	HR (95% CI)	Log-rank *p*	Heterogeneity (p, I^2)	Conclusion
Total OS	6	414	Fixed	1.52 (1.11–2.08)	0.01	0.461, 0.0%	Positive
Total PFS	5	322	Fixed	2.11 (1.52–2.93)	<0.001	0.127, 44.2%	Positive
Asian OS	4	350	Fixed	1.63 (1.14–2.34)	0.007	0.490, 0.0%	Positive
Asian PFS	3	258	Fixed	2.25 (1.53–3.30)	<0.001	0.870, 0.0%	Positive
Non-Asian (Spanish) OS	2	64	Fixed	1.17 (0.61–2.26)	0.637	0.226, 31.7%	Negative
Non-Asian (Spanish) PFS	2	64	Random	1.80 (0.96–3.36)	0.066	0.011, 84.7%	Negative
Chinese OS	2	142	Fixed	1.48 (0.94–2.33)	0.09	0.240, 27.6%	Negative
Korean OS	2	208	Fixed	1.93 (1.07–3.45)	0.028	0.458, 0.0%	Positive
Korean PFS	2	208	Fixed	2.08 (1.27–3.41)	0.004	0.847, 0.0%	Positive
Median age ≤65 OS	4	200	Fixed	1.55 (1.08–2.23)	0.018	0.207, 34.2%	Positive
Median age ≤65 PFS	3	108	Random	1.93 (1.25–2.97)	0.003	0.036, 70.0%	Positive
Median age >65 OS	2	214	Fixed	1.41 (0.76–2.63)	0.278	0.898, 0.0%	Negative
Median age >65 PFS	2	214	Fixed	2.39 (1.44–3.97)	0.001	0.762, 0.0%	Positive
Tumor stage (III–IV) OS	4	155	Fixed	1.43 (0.93–2.21)	0.105	0.223, 31.5%	Negative
Tumor stage (III–IV) PFS	4	155	Random	1.85 (1.02–3.37)	<0.001	0.067, 58.1%	Positive
Antibody (polyclonal) OS	2	259	Fixed	1.61 (1.02–2.54)	0.04	0.718, 0.0%	Positive
Therapy (EGFR-TKI) OS	3	138	Fixed	1.59 (1.00–2.51)	0.048	0.306, 15.5%	Positive
Therapy (EGFR-TKI) PFS	3	138	Fixed	2.35 (1.62–3.42)	<0.001	0.833, 0.0%	Positive
Therapy (non-EGFR-TKI) OS	3	276	Fixed	1.45 (0.94–2.24)	0.091	0.333, 9.2%	Negative
Therapy (non-EGFR-TKI) PFS	2	184	Random	1.49 (0.76–2.93)	0.249	0.019, 81.7%	Negative

CI = confidence interval, EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, HR = hazard ratio, N = number, NSCLC = nonsmall cell lung cancer, OS = overall survival, PFS = progression-free survival, YAP1 = Yes-associated protein 1.

YAP1. Similarly, no significant correlation was confirmed between PFS and Spanish patients with high nuclear YAP1. The nonsignificant difference in Spanish patients with high nuclear YAP1 expression might result from the fact that in these two studies,[26,28] only mRNA level of YAP1 was detected without further confirmation at the level of protein. Another possible reason for the aberrant results was the small sample sizes of the Chinese and Spanish studies, compared with those from Korea. Additionally, we found an unfavorable influence of nuclear YAP1 expression on OS when polyclonal antibody was used to detect YAP1 expression. However, antibodies for histological detection are so crucial that a larger sample size is needed for liability.

In subgroup analysis of stages III–IV NSCLC, a high level of nuclear YAP1 was significantly correlated with PFS, but not OS. The main explanation may be that the majority of patients with stages III–IV NSCLC were treated with EGFR-TKI. These inconsistent results could also be explained by highly variant characteristics of patients and diverse quality of studies. Furthermore, as mentioned above, this can be at least partly explained by the effects of YAP1 in EGFR-TKI-resistant NSCLC. Consequently, our results revealed that nuclear YAP1 might promote the partial growth of NSCLC cells[19] but didn't affect the overall survival of patients.[27]

The role of YAP1 may be related to its position at the center of the Hippo signaling pathway.[31] Inactivated Hippo signaling leads to YAP1 dephosphorylation, which eventually accumulates in the nucleus where it binds to TEA-domain transcription factors (TEAD), thereby regulating their expression. These transcription factors impact cell proliferation, migration, reprogramming, stemness, epithelial-mesenchymal transition (EMT), differentiation, antiapoptosis, and drug resistance in vitro.[31–33] However, numerous other molecular mechanisms might explain the unfavorable impact of nuclear YAP1 in NSCLC, including involvement of other targets of YAP1, upstream regulators, and microRNAs.[26,31] Some associated pathways are Src family kinase signaling, the signal transducer and activator of transcription 3 (STAT3) pathway,[26] the microtubule affinity-regulating kinase (MAPK),[11] and the EGFR signaling pathway.[20]

Significantly elevated nuclear YAP1 expression has been reported in cancers compared with normal samples,[19] and high expression of YAP1 was reported to promote tumorigenesis and progression of NSCLC.[19,34] Moreover, knockdown of YAP1 was found to repress growth of xenograft tumors and lung metastasis in vivo.[9] In a clinical study including 177 cases of hepatocellular carcinoma, YAP1 was shown to be a promising independent marker for OS and disease-free survival.[29] Silvia et al reported that YAP1 was among the most suitable biomarkers for the identification of normal and tumor lung profiles via Gene Chip technology.[30] Our meta-analysis is consistent with these studies and shows that NSCLC patients with high expression of nuclear YAP1 had elevated risk of worse survival outcome including PFS and OS.

To date, this is the first meta-analysis showing that high expression of nuclear YAP1 is significantly associated with poor prognosis in NSCLC patients. However, this study has several notable limitations. The heterogeneity of our meta-analysis regarding OS and PFS was not high, while practical constraints included the small number of suitable studies and their low sample sizes and the absence of multicenter randomized controlled trials (RCT). Moreover, the cutoff values defining high and low nuclear YAP1 expression, the follow-up period (from 22 to 120 months), and detection methods were inconsistent among the selected studies (Table 1). Also of note, we were not able to verify the reported adverse prognostic association of YAP1 in well-differentiated lung adenocarcinoma[27] owing to a lack of available histological data. Additionally, no significant difference was observed in some of our subgroup analyses, including gender, smoking history, or individuals treated with each TKI (gefitinib, erlotinib, afatinib, or icotinib) due to insufficient background information. Our synthesized results should therefore be considered with caution accordingly.

Although some heterogeneity was indeed detected through subgroup analyses, overall statistics did not exhibit apparent publication bias or heterogeneity in the analysis of the link between survival time and high nuclear YAP1 among six studies. Furthermore, there was no apparent publication bias by Begg's tests, while the P value for OS was marginal ($P = .06$), possibly due to lacking of enough information for data analysis. Additionally, the scores evaluated by the Newcastle-Ottawa Scale were at least 6, meeting our inclusion criterion. All facts above suggest that our pooled results may be reliable to other populations.

In conclusion, high expression of nuclear YAP1, especially detected before EGFR-TKI therapy, indicates poor survival outcome in NSCLC patients. The underlying mechanism is complicated and still unclear, but the interaction between YAP1 and the EGFR signaling pathway may be relevant, as high YAP1 could facilitate the resistance of cancer cells to EGFR-TKIs. Considering the limitations of our analysis, this conclusion should be interpreted with caution. Larger studies with higher quality are expected to further confirm a precise evaluation of the prognostic significance of nuclear YAP1 in NSCLC patients.

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Author contributions

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