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Original Article

Prognostic value of p53 expression in childhood nephroblastoma: a meta-analysis

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Abstract: Background: Nephroblastoma is a heterogeneous disease and the most common neoplasm of the kidney in children. The purpose of this study was to evaluate the prognostic value of tumor suppressor p53 expression in childhood nephroblastoma. Methods: Relevant studies published between January 2000 and 2015 were searched and retrieved using Medline, Web of science, PubMed and CNKI. The odds ratio (OR) and risk ratio (RR) with their 95% confidence interval (CI) were employed to calculate the strength of value. Results: Total 12 articles were finally screened out, including 415 children with nephroblastoma. Overall, our result detected that the frequency of p53 expression was much higher in advance stage (III+IV+V) than that in early stage (I-II) (53.9% versus 13.1%), and indicated that p53 expression was associated with tumor stages (OR=5.90, 95% CI=3.54-9.85, P<0.00001). Subgroup analysis by ethnicity showed that p53 expression increased the tumor risk in both Asian and non-Asian populations (P<0.00001). P53 expression was positively correlated with unfavorable histological type (OR=31.87, 95% CI=10.14-100.14, P<0.00001) as well. Furthermore, p53 expression increased the metastasis of nephroblastoma (OR=5.59, 95% CI=2.43-12.86, P<0.00001), and decreased the overall survival (RR=4.87, 95% CI=2.18-10.88, P=0.0001). No significant association was found between p53 expression and gender, recurrence and histological components of patients with nephroblastoma. Conclusions: Our results indicated that p53 expression could be used as an indicator to predict the poor prognosis and a reference index to determine the clinical stages and histological types of the tumor.

Keywords: Nephroblastoma, p53, expression, prognosis

Introduction

Nephroblastoma, also known as Wilms' tumor, is an embryonal type of renal cancer that histologically mimics renal embryogenesis [1]. It is composed of a variable mixture of stromal, blastemal, and epithelial elements. Nephroblastoma is the most common solid malignant neoplasms in children [2], and comprises approximately 8% of all childhood cancers and 90% of paediatric renal tumors [3]. The incidence is around 1 in 10000 Caucasian children. This disease can be diagnosed in adolescents or adults as well, but it is extremely rare that accounts for less than 1% of all renal tumors [4]. Although the advances during the last decades in surgical techniques, anesthesia, and supportive care have dramatically improved the survival rates for children with nephroblastoma to greater than 90% [5, 6], and decreased the overall relapse rate to less than 15%, the overall long-term survival for patients with recurrent disease remains at approximately 50% [7]. Furthermore, nephroblastoma is a heterogeneous disease. Differentiating nephroblastoma in the high- and low-risk patients is a prerequisite to implement better therapeutic approaches and predict the prognosis [8]. Therefore, identifying biomarkers in the aetiology of nephroblastoma is vital in improvement of the risk stratification and the outcomes for patients with unfavourable histology and recurrent disease.

Prognostic factors are now shown to be associated with predicting outcome in patients with nephroblastoma [9, 10]. The tumor suppressor p53 is located on human chromosome 17p13.1 and is one of the studied prognostic factors. It can both activate and repress gene expression, and regulate key stages of metastatic progression, such as cell migration and invasion [11, 12]. P53 plays a crucial role in coordinating cellular processes to genome instability [13]. It

also functions to integrate cellular responses to stress, guide cancer treatment and predict prognosis [14], and is critical for suppression of spontaneous tumorigenesis [15]. The p53 signaling is involved in regulating cancer prevention and aging [16], and its mutants might play a role in the development of new therapeutic approaches in a broad range of cancer types [17]. Evidences have shown that p53 expression were significantly associated with an advanced stage and poor disease-specific survival of malignant tumors, such as gastric cancer [18], diffuse large B-cell lymphoma [19], and upper urinary tract urothelial carcinoma [20].

Several studies have identified the prognostic value of p53 expression in nephroblastoma, however, the results remain contradictory. Sredni et al. showed that overall survival was higher in patients with p53 negative than with p53-positive cases, and p53 expression was associated with advanced disease and relapse in Wilms' tumor [21]; Govender et al. proved that p53 expression predicted poor prognosis [22]; Djuricić et al. discovered that the immune-expression of p53 was significantly higher in the blastemal and epithelial than in the stromal component, and was significantly correlated to histological prognostic types [23]. While D'angelo found no correlation between p53 expression and tumor stages or prognosis in individuals with histologically favorable Wilms' tumor [24]; Das et al. demonstrated that p53 expression did not show any significant difference among the histological components, and was not associated with stages of Wilms' tumor [25]. Moreover, p53 staining and scoring system might be used in distinguishing between preoperative chemotherapy and direct surgery in patients with Wilms' tumor [26]. In addition, the incidence rates are discrepant in different populations [27], and the outcomes for certain patient subgroups, including those with unfavorable histologic and molecular features, bilateral disease, and recurrent disease, remain low survival rate [28]. Therefore, we conducted the present meta-analysis to evaluate the role of p53 expression in predicting clinical tumor stages and determining prognosis among childhood nephroblastoma.

Methods

Search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [29], we comprehensively searched the electronic databases of Medline, Web of science, PubMed and CNKI (China National Knowledge Internet) to retrieve relevant articles published between January 2000 and 2015. The following terms: "nephroblastoma or Wilms' tumor", "p53", "children or infant", "expression", and "prognosis" as well as their combinations were employed as the searching words. Their equivalents of Chinese characters were used in Chinese libraries. We also manually searched the references of included studies to obtain more related articles.

Inclusion criteria

Eligible articles should meet the following criteria: 1) assessing the value of p53 expression on prognosis of patients with nephroblastoma; 2) patients with nephroblastoma were less than 14 years old, and pathology confirmed; 3) clinical stages (I, II, III, IV, V) and histological type (Favorable histology, FH; Unfavorable histology, UH) of nephroblastoma cases were graded according to the standard of the National Wilms' Tumor Study Group [30]; 4) the p53 expression was measured by immunohistochemistry (IHC); and 5) when the same authors or laboratories reported two or more articles on the same issue or population, only the most recent full-text was included.

Data extraction

Three of our authors determine the quality of individual included studies independently to reach a consensus on each item. The first author, published year, country, ethnicity, mean age, positive number of p53 expression in different disease stages and histological types, and definition of positivity (cut-off value) were extracted from each study.

Statistical analysis

The pooled odds ratio (OR) and risk ratio (RR) with their 95% confidence interval (CI) were employed to measure the value of p53 expression on prognosis of nephroblastoma patients. The Z test was used to estimate the effect (*P*-value less than 0.05 was considered significant). Heterogeneity between studies was calculated by the Q test and the I^2 test. When the *p*-value of the Q test was more than 0.01 and I^2 of the I^2 test less than 50%, the fixed-effect model was used, otherwise the random-effect model was used. The RevMan 5.2 program was used to perform all the analysis.

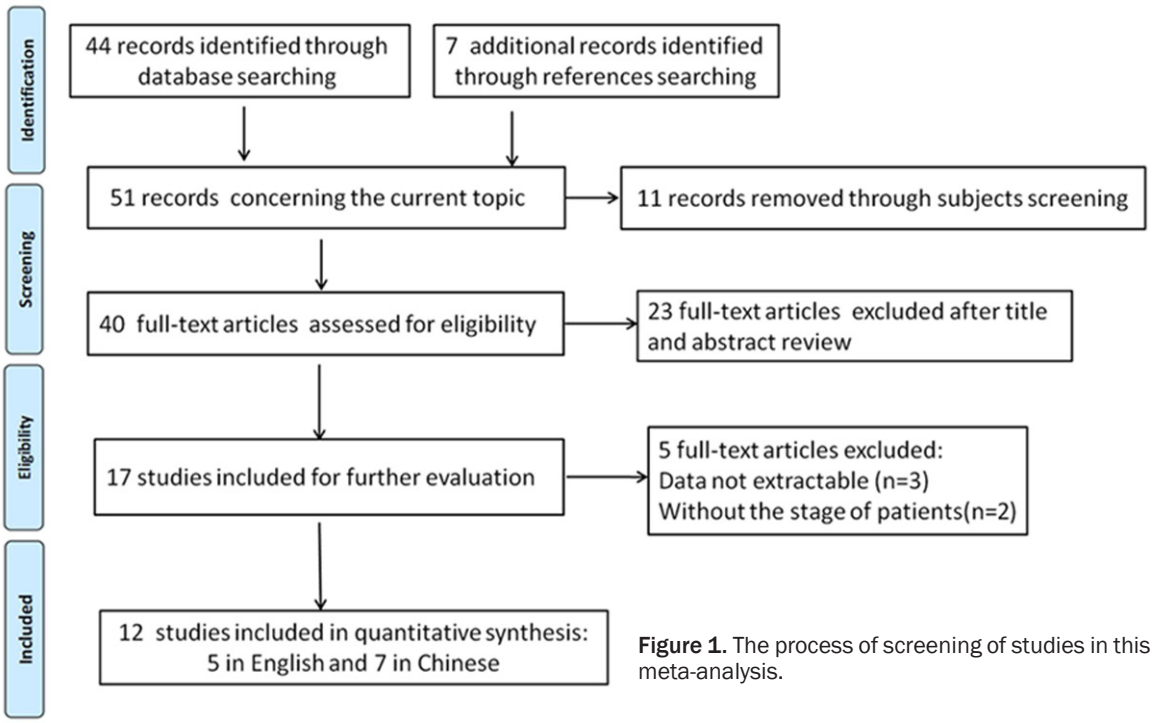

Figure 1. The process of screening of studies in this meta-analysis.

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

First author	Year	Country	Ethnicity	Age (month)	Clinical stages				Histological types				Cut-off value
				Mean (range)	I+II		III+IV+V		FH		UH		
					P	T	P	T	P	T	P	T	
Meng YL	2000	China	Asian	-(8-120)	2	33	6	13	3	40	5	6	-
Beniers AJ	2001	Netherlands	Caucasian	50 (6-88)	2	14	5	7	-	-	-	-	25%
Zhao L	2001	China	Asian	42 (5-168)	3	23	8	13	6	30	5	6	>10%
Cui SP	2003	China	Asian	-(21-144)	2	10	3	10	-	-	-	-	>5%
Sun CZ	2003	China	Asian	41 (10-156)	2	21	5	11	2	25	5	7	>10%
Qu JR	2006	China	Asian	37.2 (3-144)	2	19	6	9	-	-	-	-	>5%
Wu HF	2010	China	Asian	-(5-96)	6	23	2	5	3	22	5	6	>10%
Agarwal S	2011	India	Asian	31 (4-72)	1	8	16	22	17	30	-	-	>20%
Jadali F	2011	Iran	Asian	36 (4-96)	9	19	15	25	13	33	11	11	>25%
Zhang LJ	2011	China	Asian	35.9 (3-132)	4	43	6	14	-	-	-	-	>25%
Franken J	2013	Belgium	Caucasian	45 (36-109)	1	37	4	11	-	-	-	-	>5%
Hodorova I	2013	Slovak Republic	Caucasian	-(7-120)	2	24	0	1	-	-	-	-	>10%

-, not available; P, positive number of p53 expression; T, total number; FH, favorable histology; UH, unfavorable histology.

Results

Characteristics of included studies

After applying the inclusion criteria, we finally screened out twelve relevant studied, including 415 children with nephroblastoma. The selection process was presented in **Figure 1**. The twelve articles (five in English [26, 31-34] and seven in Chinese [35-41]) were conducted in six countries (India, Netherlands, Iran, China, Belgium, Slovak Republic). The sample size ranged from 21 to 57. The p53 expression was all measured by HIC method, and was detected in 27.0% of all cases (112/415). The main characteristics of included studies were listed in **Table 1**.

Correlation of p53 expression on clinical stages, histological types and predominant histological components in patients with nephroblastoma

All the twelve articles estimated the effect of p53 expression on clinical stage of clinical

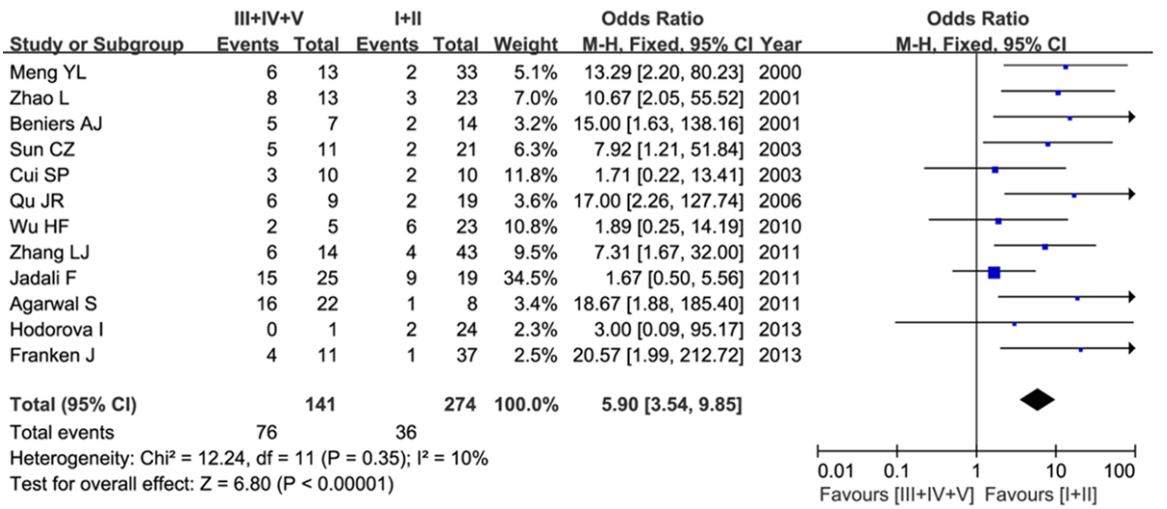

Figure 2. Forest plot of p53 expression on clinical stages of nephroblastoma.

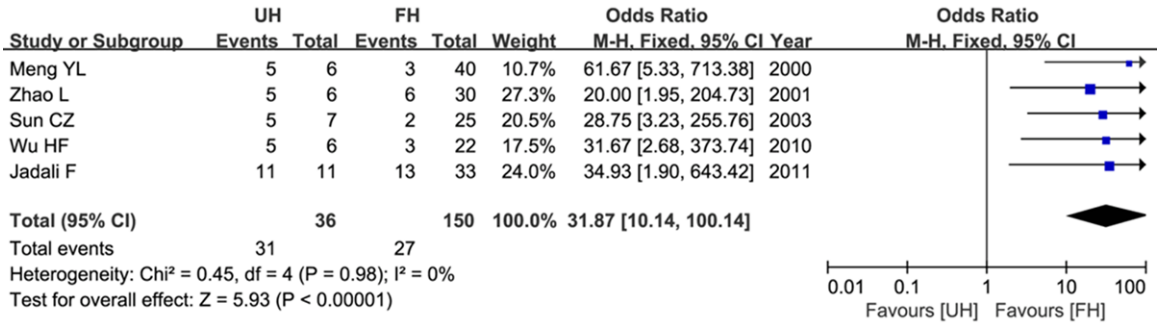

Figure 3. Forest plot of p53 expression on histological types of patients with nephroblastoma (FH, favorable histology; UH, unfavorable histology).

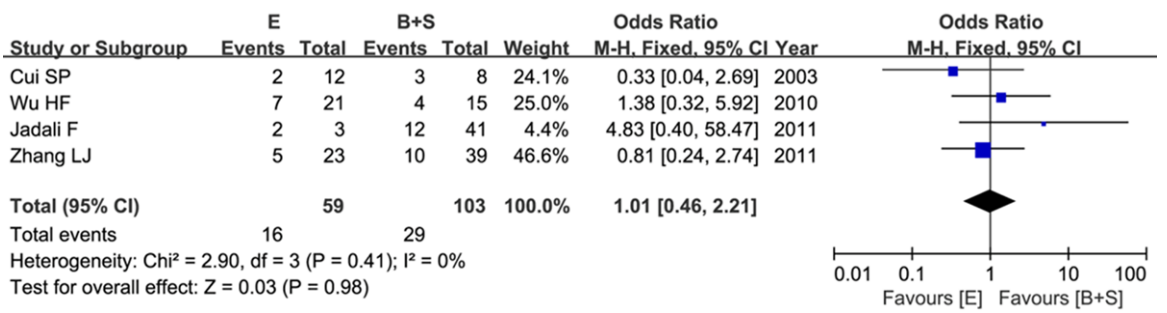

Figure 4. Correlation of p53 expression on predominant histological components in patients with nephroblastoma (E, epithelial parts; B, blastemal parts; S, sromal parts).

stages of tumor. No significant heterogeneity was observed between studies (P=0.35, I^2= 10%). We divided patients into two groups: early stage (I-II) and advance stage (III+IV+V) which included 274 and 141 patients, respectively. We found that the frequency of p53 expression was much higher in advance stage than that in early stage (53.9% versus 13.1%). Our result demonstrated that p53 expression was associated with tumor stages (OR=5.90, 95% CI=3.54-9.85, P<0.00001) as shown in **Figure 2**, indicating that p53 expression might

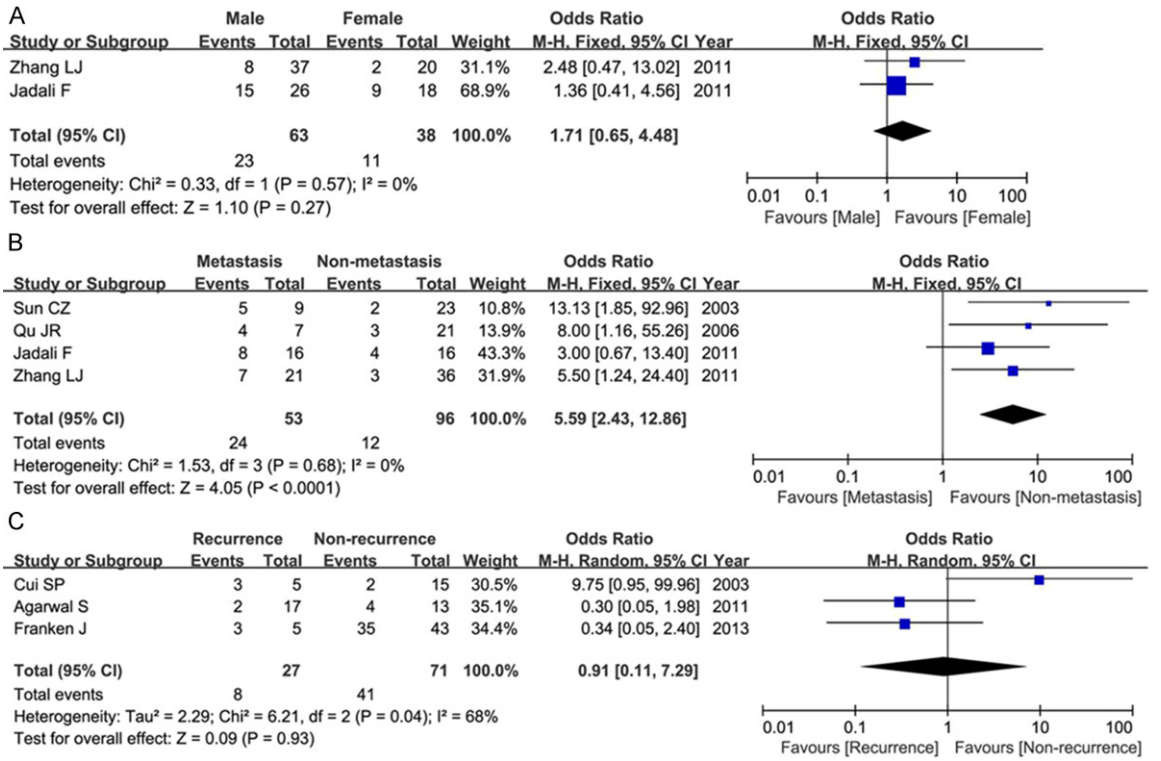

Figure 5. Correlation of p53 expression on gender (A), tumor metastasis (B) and recurrence rate (C) of nephroblastoma patients.

be increased the risk of nephroblastoma. Subgroup analysis by ethnicity showed that p53 expression was related with tumor stages in both Asian (OR=5.27, 95% CI=3.04-9.13, P<0.00001) and non-Asian (OR=13.20, 95% CI=3.32-52.56, P=0.0003) population.

Five articles concerned on the histological types, including 186 patients. We also divided patients into two groups: FH group and UH group. The p53 was expressed higher in UH group than that in FH group (86.1% versus 18.0%) as well. Our analysis showed that p53 expression was positively related with histological types (OR=31.87, 95% CI=10.14-100.14, P<0.00001) as shown in **Figure 3**.

With respect to the predominant components in histology of tumors, our result from four included studies found that there was no difference between p53 expression and components of tumor histology (Epithelial parts versus Blastemal+Stromal parts: OR=1.01, 95% CI= 0.46-2.21, P=0.98) in the fixed-effect model as shown in **Figure 4**.

Association between p53 expression and gender, tumor metastasis and recurrence of patients with nephroblastoma

Only two articles discussed the gender issue, including 63 males and 38 females. Although the p53 expression was higher in male patients than that in females (36.5% versus 28.9%), our result did not detect a relationship between sex and p53 expression in nephroblastoma cases (OR=1.71, 95% CI=0.65-4.48, P=0.27) in the fixed-effect model as shown in **Figure 5A**. Four studies including 149 patients concerned on the tumor metastasis. Our results showed that p53 expression was correlated with metastasis of nephroblastoma (OR=5.59, 95% CI=2.43-12.86, P<0.00001) in the fixed-effect model as shown in **Figure 5B**. Three articles focused on the tumor recurrence rate, containing 98 patients. Our results demonstrated the difference of p53 expression between recurrence and non-recurrence groups was not statistically significant (OR=0.91, 95% CI=0.11-7.29, P=0.93) in the random-effect model as shown in **Figure 5C**.

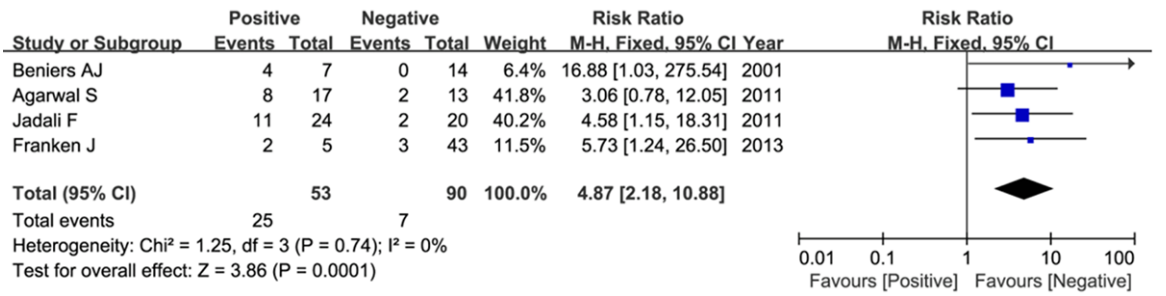

Figure 6. Meta-analysis of p53 expression on overall survival of nephroblastoma patients.

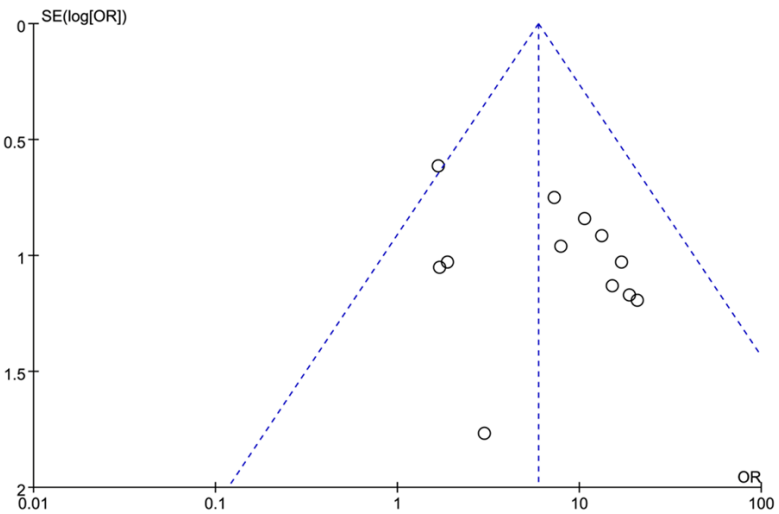

Figure 7. Funnel plot of P53 expression on clinical stages of patients with nephroblastoma.

Association between p53 expression and overall survival of nephroblastoma patients

Four articles were screened out, including 143 patients. Our result proved that the p53 expression was significantly associated with decreased the overall survival (RR=4.87, 95% CI=2.18-10.88, P=0.0001) in a fixed-effect model as shown in **Figure 6**, suggesting that p53 might be an indicator of poor prognosis for nephroblastoma patients.

Sensitivity analysis and publication bias

To verify whether individual single study influenced the overall result in each comparison or not, we omitted each study every time. The result showed that the pooled OR and RR were not statistics significantly changed. The funnel plot was not obvious asymmetry as shown in **Figure 7**, suggesting that there were no publication biases in this meta-analysis.

Discussion

In this meta-analysis, we identified 12 articles. Our results found that p53 expression was associated with clinical advance stages and unfavorable histological types of nephroblastoma. Furthermore, p53 expression increased the metastasis of nephroblastoma and decreased the overall survival. No relationship was found between p53 expression and gender, tumor recurrence and histologic components in patients with nephroblastoma. These results indicated that p53 might be an independent prognostic factor in nephroblastoma in children.

P53 can regulate cellular metabolism, control cell survival and death, and induce mitochondrial changes through transcription-dependent and transcription-independent mechanisms following stress signals such as hypoxia, oncogene activation and DNA damage [42]. It can also regulate necrotic cell death and autophagic activity including mitophagy, and has a much wider influence on mitochondrial integrity and function [43]. P53 is the barrier to cancer stem cell formation [44]. It plays a role in glial cell function of health and disease, and functions as a potential target for therapeutic intervention in neurodegeneration as well [45]. Caspase recruitment domain can suppresses cell death by antagonizing p53 function through suppressing p53 expression, and combined p53 activation and caspase recruitment domain inhibition can augment apoptosis induc-

tion [46]. Furthermore, the p53-mediated miRNAs could contribute to tumor suppression by controlling the expression of central components of multiple processes, and in turn, p53 itself is under the control of miRNAs, which indicate that these pathways are important for the initiation and progression of tumors [47]. Numerous studies have confirmed that expression of p53 was common in human malignant tumors, and might be implicated in oncogenesis and cancer therapy [48, 49]. Koi et al. demonstrated that the high proliferative activity of postmenopausal endometrial glandular cells might be associated with p53 overexpression and conditions of low apoptotic cell death [50]. Besides, low p53 expression could counteract the age-dependent decline in endothelial function [51]. Therefore, p53 expression in tumors might have diagnostic, prognostic, and therapeutic implications.

Nephroblastoma is a malignant neoplasm and is the most common renal tumor of childhood. Patients with high risk or low risk disease are treated with different therapy regimens. Although stage and histology are the most known prognostic factors in nephroblastoma, challenges remain in identifying novel molecular, histological and clinical risk factors for stratification of treatment intensity. Evidences from previous studies on the role of p53 expression in nephroblastoma were not consistent. Huang et al. showed that p53 accumulation in FH nephroblastoma was associated with angiogenesis and clinically aggressive disease [52]. Lahoti et al. found that p53 immunopositivity strongly correlated with recurrence/metastasis in Wilms' tumors [53]. Skotnicka-Klonowicz et al. suggested that the index of p53 expression was not an independent prognostic factor in Wilms' tumor in children, but this determination may be helpful in identifying high-risk and low-risk patients [54]. Percicote et al. did not detect a relationship between p53 expression and tumor stages, but identified that mean immunoexpression of p53 was higher in tumors treated with preoperative chemotherapy when compared with tumors not treated with this procedure with statistical significance [55]. Madjd et al. showed that p53 expression were not associated with tumor stage and UH in pediatric Wilms' tumor [56]. Furthermore, p53 mutations were shown to be associated with improved risk stratification in diffuse anaplasia of Wilms' tumours and predicted poor outcome [57]. Andrade et al. demonstrated an association between p53 mutation and age at diagnosis, as well as risk of development of Wilms' tumor [58].

Several limitations were presented in this study. First of all, the sample size in each included study was small. Second, the cut-off value for p53 expression positive was different. Third, most of the study subjects were Asian population, while other ethnicities should be included. Fourth, it's not clear that whether patients with nephroblastoma received any therapy or not. Last, we only concerned on patients less than 14 years old, other age group were needed as well. All the above points might influence the reliable of our results.

In conclusion, our results found that p53 expression in childhood nephroblastoma might be an indicator of poor prognosis. Future well-designed studies with more population are still needed to further evaluate the prognostic value of p53 expression in nephroblastoma.

Disclosure of conflict of interest

None.

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