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ORIGINAL ARTICLE

PIWIL2 may serve as a prognostic predictor in cancers: A systematic review and meta-analysis

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Summary

Purpose: *PIWIL2, one of the PIWI gene subfamily, is now thought to be closely related to poor clinical outcomes in various cancers. The aim of this research was to comprehensively estimate its predictive value in the prognosis of cancer patients.*

Methods: *We thoroughly searched PubMed, Web of Science and Embase databases for eligible articles published until April 4th 2019, in which the association between cancer prognosis and PIWIL2 expression level was studied. Study qualities were assessed using NOS criteria. We performed analyses by Stata SE 12.0 and RevMan 5.3. The primary endpoints contained overall survival (OS), cancer-specific survival (CSS), metastasis-free survival (MFS), recurrence-free survival (RFS) and disease-free survival (DFS).*

Results: *Ten studies containing 2116 patients with 8 various solid cancers were finally included. The outcomes indicated that cancer patients with higher PIWIL2 expression level had significant shorter OS (HR:2.20, 95%CI:1.25-3.88, p=0.006), DFS/RFS/MFS (HR:2.96, 95%CI:1.68-5.23, p<0.001), CSS (HR: 2.12, 95%CI: 1.40-3.23, p<0.001) than cancer patients with lower PIWIL2 expression level. What's more, PIWIL2 over-expression was significantly correlated to more lymph node metastasis (LNM) (OR:1.61, 95%CI:1.28-2.02, p<0.001). And PIWIL2 expression was not significantly correlated with age, gender, differentiation, tumor invasion, tumor size, TNM stage and distant metastasis (DM).*

Conclusions: *A higher expression level of PIWIL2 may predict a poorer prognosis of cancer patients. And its prognostic values are not significantly influenced by clinicopathological characters. Therefore, PIWIL2 could serve as a personalized prognostic predictor in cancers in the future.*

Key words: *cancer, clinicopathologic characteristics, meta-analysis, PIWIL2, prognosis*

Introduction

Cancer is a severe public health problem all over the world, and has become the second leading cause of death in the USA [1]. According to the estimates, approximately 18.1 million new cases and 9.6 million deaths of cancer are projected to occur in 2018, and the leading causes of cancer deaths are lung cancer, female breast cancer, gastric cancer, liver cancer, colorectal cancer and prostate cancer [2]. However, cancer mortality continuously decreases with a decline of 26% for all cancers from 1991 to 2015, and the primary reasons include cancer prevention, improvements in screening and early detection, and improvements in cancer treatment in which advances in systemic treatment, such as the development of targeted therapies, play an important role [3]. Numerous

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researches have studied the mechanisms of the occurrence and progression of various cancers, and great achievements have also been made in the prevention, diagnosis and treatment. However, the 5-year overall survival rate is still low in the majority of cancer patients [1]. Therefore, novel biomarkers about various cancers that can help classify the risks of patient outcomes in early stage, identify tumor progression, predict the therapy outcome and prognosis and develop personalized treatment that are urgently needed.

The cancer pathogenesis is complex which involves genetic, epigenetic and environmental factors [4,5]. Researchers have found that the gene expression was dysregulated during cancer progression [6-9]. An important function of small noncoding RNAs is silencing RNA expression through base pairing, in which the Argonaute family is indispensable component [10,11]. The P-element-induced wimpy testis (PIWI) family belongs to the Argonaute family [12]. The PIWI proteins bind to PIWI-interacting RNAs (piRNAs), and piRNAs have been found in tumor tissues and cells [13-16]. By targeting mRNAs, piRNAs can result in their degradation and take part in epigenetic regulation [17,18]. The PIWI gene was initially identified by Cox et al in Drosophila and found that it could play an important role in the asymmetric division and self-renewal of germ-line stem cells [19]. Subsequent researchers found that PIWI proteins were involved in regulating various biological processes such as stem cell self-renewal, spermatogenesis, RNA stability, transposon silencing, translational suppression, and chromatin remodeling [20-22]. In addition, some researches have detected expression of PIWI in different types of animal and human tumor cell lines [23,24], and positive PIWI expression is found in cancer but not in the corresponding normal tissues [25-27]. Recent researches have suggested that deregulation of PIWI gene expression is related to deregulation of cell proliferation, changed apoptosis, genomic instability and tumor invasion, which makes PIWI proteins to be potential biomarkers for different types of cancer [28,29]. PIWIL2 is one of the PIWI gene subfamily which is located on chromosome 8(8p21) [30]. Interestingly, stable PIWIL2 expression was found in precancerous stem cells (pCSCs), which had the potential differentiation for either malignant or benign, so PIWIL2 was considered to regulate the development and differentiation of pCSCs [31]. In addition, positive PIWIL2 gene expression has been found in different human cancers such as lung, prostate, breast, gastric, colorectal and ovarian cancer, and the higher expression level is closely related with an elevated risk of the progression, invasion and metastasis of cancers [32-35].

Accumulating evidence has suggested that PIWIL2 plays an important role in human cancers, so PIWIL2 could be used as a potential marker for diagnosis and predict prognosis and a target for the treatment of cancers in the future. However, neither comprehensive review nor meta-analysis have confirmed the positive clinical value of PIWIL2 expression in cancers. Given the above background, we performed this comprehensive meta-analysis to confirm the association between PIWIL2 expression and clinical outcomes of cancer patients in combination with clinicopathological characters.

Methods

Literature search

The databases Pubmed, Web of Science, and Embase were comprehensively retrieved to identify eligible studies up to April 4th, 2019. The combination of the following strategy was used in the literature search: ("PIWIL2" or "HILI" or "Piwi-Like Protein 2" or "Piwi Like RNA-Mediated Gene Silencing 2") and ("cancer" or "tumor" or "carcinoma"). In addition, the reference lists were also manually reviewed to obtain potential articles. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36] (http://www.prisma-statement.org).

Inclusion criteria

The included articles must meet the following inclusion criteria: (1) investigation based on human cancer; (2) studies reporting the associations of PIWIL2 expression with clinical outcomes [overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), metastasis-free survival (MFS) and cancer-specific survival (CSS)] and clinicopathological characters; (3) studies providing hazard ratios (HRs) and 95% confidence intervals (CIs) for survival analysis, or survival curves to extract these data using the method described by Tierney et al [37]; (4) cancer patients were divided into "positive/high/" group and "negative/low" group. The following studies were excluded: (1) reviews, letters, or case reports; (2) animal or cell experiment studies; (3) studies lacking sufficient information.

Data extraction and quality assessment

Two authors carefully reviewed the full-text, and then independently extracted particular data using previously designed forms. Disagreements were settled by discussing with a third author. The following information was extracted: first author, country, cancer type, number of patients analyzed, specimen type, method of measurement, cut-off value, HR estimated method and HR for survival (OS, CSS, DFS/RFS/MFS) and clinicopathological characters (such as age, gender, differentiation, tumor invasion, tumor size, clinical stage, LNM, and DM).

Besides, the Newcastle-Ottawa Scale (NOS) was applied to determine the quality of the qualified studies with a score ranging from 0 to 9 [38]. With NOS score > 6, the studies were thought to be high-quality.

Sensitivity analysis and publication bias assessment

Sensitivity analyses were also conducted by removing each study in turn to check the stability of the outcomes. Begg's funnel plot was conducted to detect publication bias [39]. The analyses were conducted by Stata SE 12.0 statistical software. P values <0.05 indicated statistical significance.

Statistics

The prognostic value of PIWIL2 overexpression in cancer patients was appraised by combined HRs and corresponding 95% CIs. Combined HRs for OS, CSS and DFS/RFS/MFS were calculated separately. The association between PIWIL2 expression and clinicopathological characters was evaluated by pooled estimates of odds ratios (ORs) and 95% CIs. Heterogeneity across publications was detected by x^2-based Q test and I-squared test. P value <0.1 and I^2 >50% indicated the heterogeneity was significant, and then a random-effect model was used; otherwise, a fixed-effect model was used for the analyses. The analyses were conducted by RevMan 5.3 and Stata SE 12.0 statistical software. P values<0.05 indicated statistical significance.

Results

Search results

After comprehensive searches of PubMed, Embase and Web of Science databases, a total of 270 records were identified. The selecting process is detailed in Figure 1. Next, 118 duplicate articles were excluded, and 152 records remained for further assessment. After screening the titles and abstracts, 133 irrelevant articles were excluded, and the remaining 19 potential studies were then inspected by screening full texts. Finally, 10 studies were qualified for our meta-analysis [40,35,41-44,33,45,46,26].

Characteristics of included studies

2116 patients with 8 types of solid tumors containing colorectal cancer (CRC), breast cancer, glioma, Hilar cholangiocarcinoma, soft tissue sarcoma, non-small cell lung cancer (NSCLC), gastric cancer (GC) and bladder cancer from 10 qualified

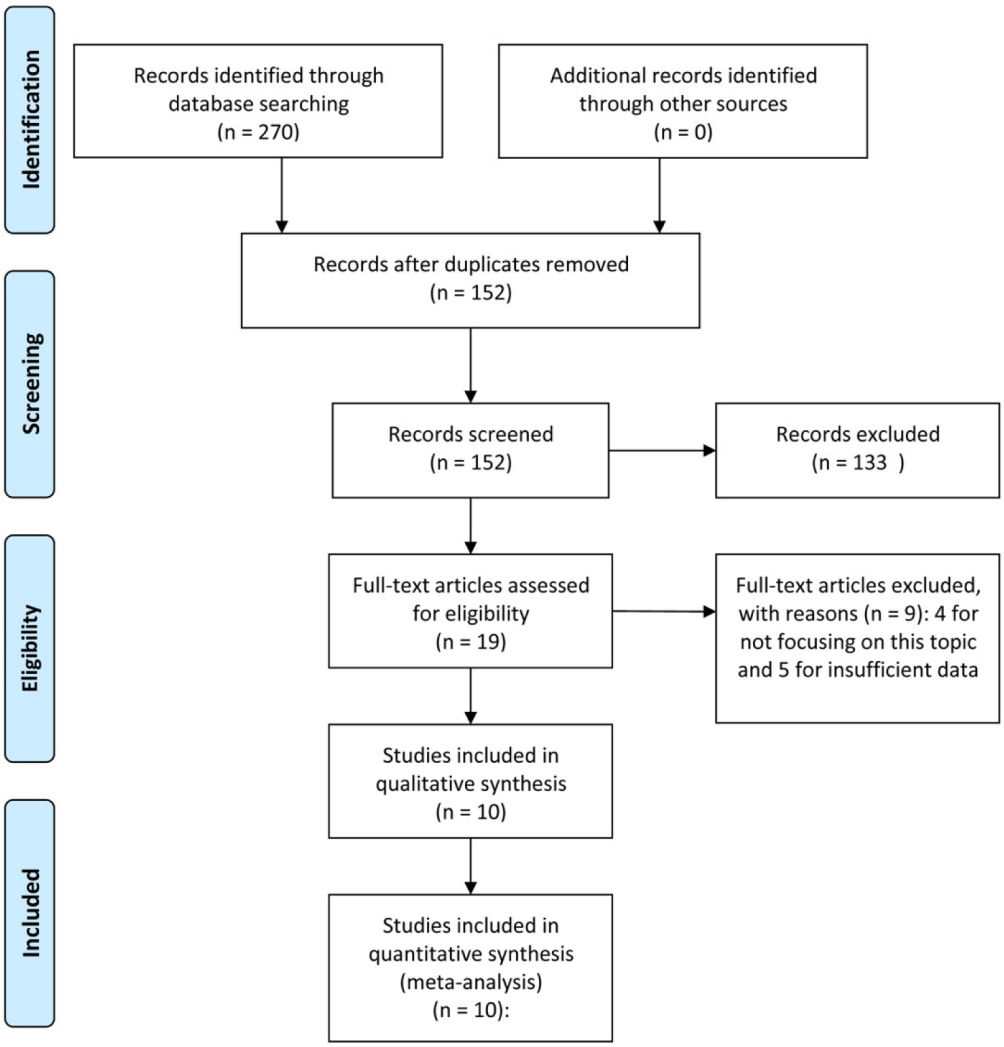

Figure 1. The flow diagram of the selection of qualified studies.

studies with concerned clinical outcomes were finally included in our meta-analysis. The articles were published between 2012 and 2018. Six of the 10 studies were performed in China, and 2 in Germany. The sample sizes ranged from 41 to 1086, 6 studies enrolled more than 100 participants. All studies detected the PIWIL2 expression levels in tissue samples, and patients were categorized into high/positive and low/negative expression groups in the included studies according to the expression levels which were mainly confirmed using immunohistochemistry (IHC). NOS was conducted to estimate the quality of these studies and all eligible studies scored highly (>6). Ten studies provided survival information and 8 studies reported clinicopathological characters. The main characteristics of included studies are summarized in Table 1.

Associations between PIWIL2 over-expression and cancer prognosis

Among the 10 studies evaluating the prognostic value of PIWIL2 overexpression in solid tumors, 6 focused on OS, 5 focused on DFS/RFS/MFS and 2 focused on CSS. As shown in Figure 2 and Table 2, for CSS, a fix-effect model was used to evaluate the pooled HRs with their 95% CIs due to no observation of significant heterogeneity, and for OS or DFS/RFS/MFS, a random-effect model was used to evaluate the pooled HRs with their 95% CIs due to significant heterogeneity. The pooled HRs were 2.20 (95% CIs:1.25-3.88, p=0.006) for OS, indicating that PIWIL2 over-expression was significantly correlated to reduced OS periods. Next, a meta-analysis for DFS/RFS/MFS was conducted and the result revealed that PIWIL2 over-expression group was significantly correlated to shorter DFS/RFS/MFS outcomes (HR=2.96, 95% CIs:1.68-5.23, p<0.001). Finally, grouping according to CSS, the pooled HRs were 2.12 (95% CIs:1.40-3.23, p<0.001) for CSS.

Associations of PIWIL2 over-expression with clinicopathological characteristics

Eight studies with 1839 cancer patients were analyzed for the association of PIWIL2 over-expression with various clinicopathological characters, and the pooled ORs and relative information are shown in Figure 3 and Table 3. The results suggested that PIWIL2 positive expression had no obvious relationship with age (n=7, OR=0.68, 95% CI: 0.28-1.64), gender (n=6, OR=0.77, 95% CI: 0.56-1.08), differentiation (n=7, OR=2.00, 95% CI: 0.57-6.98), tumor invasion (n=5, OR=0.83, 95% CI: 0.33-2.09), tumor size (n=3, OR=1.18, 95% CI: 0.68-2.05), TNM stage (n=5, OR=1.04, 95% CI: 0.50-2.16) and DM (n=4, OR=1.61, 95% CI: 0.92-2.82). However, PIWIL2 over-expression was significantly correlated to more LNM (n=6, OR=1.61, 95% CI: 1.28-2.02).

Analyses of sensitivity and publication biases for PIWIL2 expression and OS or DFS/RFS/MFS

Sensitivity analyses were conducted by using the leave-one-out analyses to evaluate the outcome stability of PIWIL2 expression and OS or DFS/RFS/MFS, and the negative results indi-

Table 1. Main characteristics of included studies

Study (year)	*Country*	*Disease*	*Sample size*	*Positive (n)*	*Sample source*	*Method*	*Cut-off*	*Outcome*	*NOS*
Litwin, 2018	Poland	Breast cancer	101	11	Tissue	IHC	score >8	OS, CF	7
Oh, 2012	Korea	Colorectal cancer	60	44	Tissue	IHC	score >2	CF	7
Chen, 2015	China	Hilar cholangiocarcinoma	41	33	Tissue	IHC	NR	OS, DFS, CF	8
Greither, 2012	Germany	Soft tissue sarcoma	125	63	Tissue	qRT-PCR	median	CSS, CF	9
Li, 2016	China	Glioma	97	62	Tissue	IHC	score >4	OS, CF	8
Li, 2012	China	Colorectal cancer	203	152	Tissue	IHC	score >2	OS, MFS, CF	9
Qu, 2015	China	Non-small cell lung cancer	126	64	Tissue	qRT-PCR	EI >4	OS, DFS, CF	7
Eckstein, 2018	Germany	Bladder cancer	95	45	Tissue	IHC	score >2	CSS, RFS	8
Zhang, 2013	China	Breast cancer	1086	334	Tissue	IHC	>10%	MFS, CF	9
Wang, 2012	China	Gastric cancer	182	NR	Tissue	IHC	score >3	OS	8

NR: not reported; IHC: immunohistochemistry; qRT-PCR: quantitative real time polymerase chain reaction; EI: expression index; NOS: Newcastle-Ottawa Scale; CF: clinicopathological features; OS: overall survival; DFS: disease-free survival; CSS: cancer-specific survival; MFS: metastasis-free survival; RFS: recurrence-free survival

Table 2. Prognostic value of PIWIL2 for survival outcome of solid tumors

Study (year)	*HR*	*Lower CI*	*Upper CI*	*P*	*Statistical method*	*Conclusion*
OS						
Litwin, 2018	1.52	0.56	4.11	0.412	Survival curve	Not significant
Chen, 2015	3.49	1.11	10.99	0.033	Multivariate	Unfavorable
Li, 2016	4.78	2.32	9.85	< 0.001	Multivariate	Unfavorable
Li, 2012	3.31	1.59	6.90	0.001	Multivariate	Unfavorable
Qu, 2015	1.93	1.07	3.50	0.029	Survival curve	Unfavorable
Wang, 2012	0.83	0.45	1.52	0.541	Multivariate	Not significant
Pooled estimate	*2.20*	*1.25*	*3.88*	*0.006*	*Random-effect model*	*Unfavorable*
DFS/RFS/MFS						
Chen, 2015	3.52	1.09	11.36	0.035	Multivariate	Unfavorable
Li, 2012	2.63	1.17	5.81	0.019	Multivariate	Unfavorable
Qu, 2015	1.60	1.08	2.38	0.019	Survival curve	Unfavorable
Eckstein, 2018	3.00	1.45	6.20	0.003	Multivariate	Unfavorable
Zhang, 2013	5.64	3.57	9.59	< 0.001	Multivariate	Unfavorable
Pooled estimate	*2.96*	*1.68*	*5.23*	*< 0.001*	*Random-effect model*	*Unfavorable*
CSS						
Greither, 2012	1.87	1.06	3.32	0.031	Multivariate	Unfavorable
Eckstein, 2018	2.46	1.33	4.54	0.004	Multivariate	Unfavorable
Pooled estimate	*2.12*	*1.40*	*3.23*	*< 0.001*	*Fixed-effect model*	*Unfavorable*

HR: hazard ratio; CI: confidence interval; OS: overall survival; DFS: disease-free survival; CSS: cancer-specific survival; MFS: metastasis-free survival; RFS: recurrence-free survival

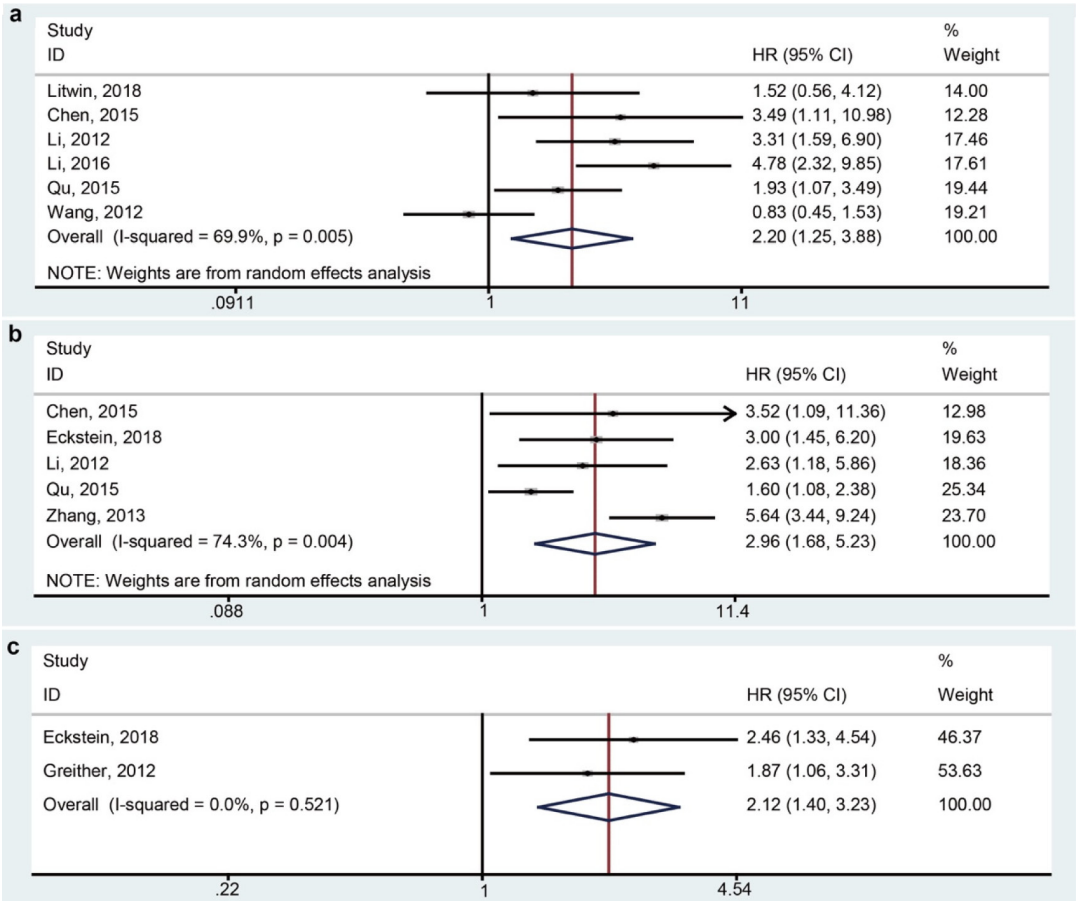

Figure 2. PIWIL2 expression and the survival periods. **(a)** OS. **(b)** DFS/RFS/MFS. **(c)** CSS. HR: hazard ratio, CI: confidence interval, OS: overall survival, DFS: disease-free survival, MFS: metastasis-free survival, RFS: recurrence-free survival.

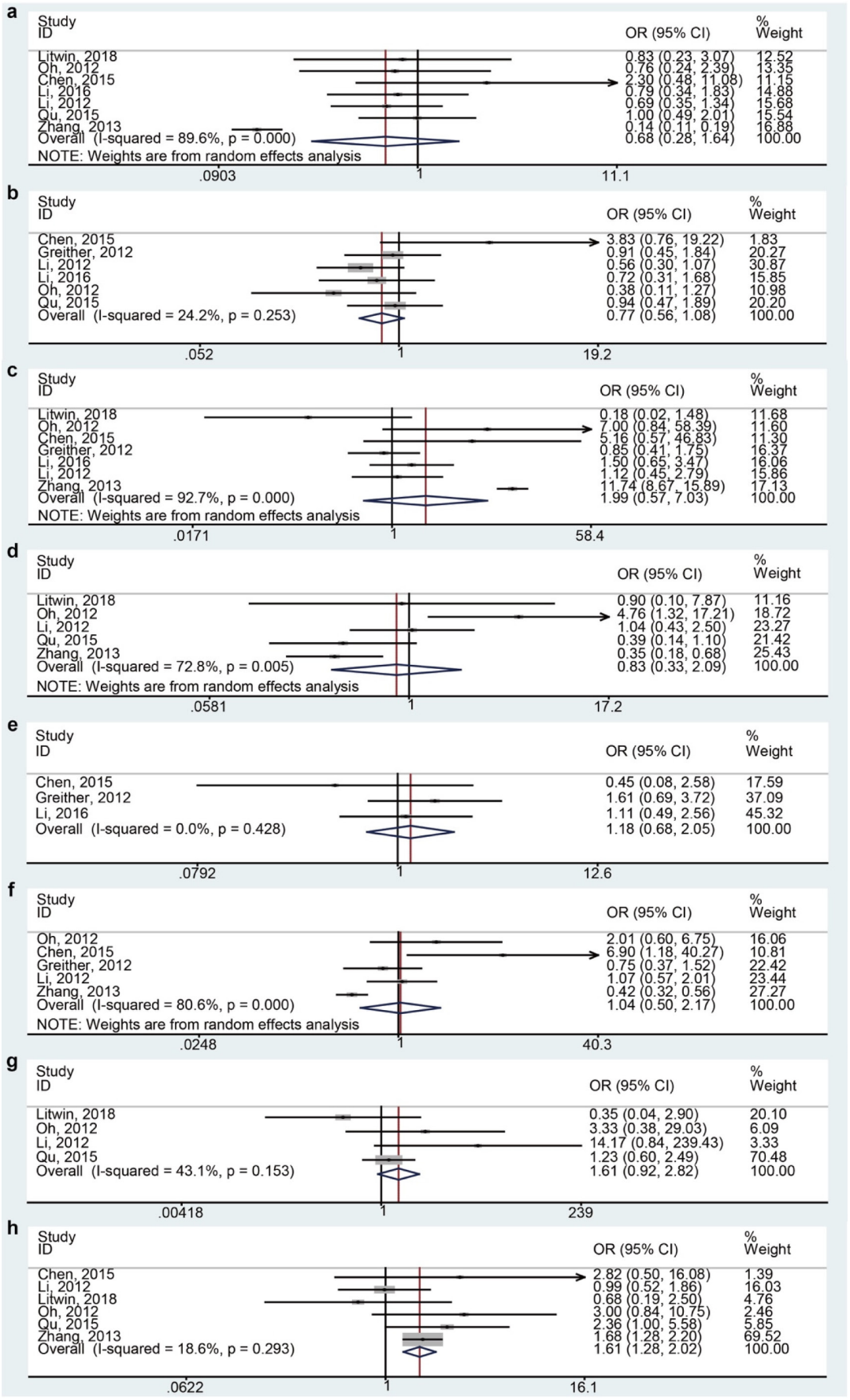

Figure 3. Forest plots of polled ORs for the association between PIWIL2 expression and clinicopathological characters. **(a)** Age. **(b)** Gender. **(c)** Differentiation. **(d)** Tumor invasion. **(e)** Tumor size. **(f)** TNM stage. **(g)** DM. **(h)** LNM. OR: odds ratio, CI: confidence interval, DM: distant metastasis, LNM: lymph node metastasis.

Table 3. Association of PIWIL2 expression and clinicopathological features

Clinicopathological features	*Study (n)*	*Patients (n)*	*Pooled OR (95% CIs)*	*P*	I^2	P_h	*Estimated method*
Age (old vs young)	7	1683	0.68 (0.28-1.64)	0.387	89.5%	<0.001	Random-effect model
Gender (male vs female)	6	652	0.77 (0.56-1.08)	0.129	24.2%	0.253	Fixed-effect model
Differentiation (poor vs good/moderate)	7	1713	2.00 (0.57-6.98)	0.280	92.6%	<0.001	Random-effect model
Tumor invasion (T3/T4 vs T1/T2)	5	1576	0.83 (0.33-2.09)	0.699	72.8%	0.005	Random-effect model
Tumor size (large vs small)	3	263	1.18 (0.68-2.05)	0.557	0%	0.428	Fixed-effect model
TNM stage (III/IV vs I/II)	5	1515	1.04 (0.50-2.16)	0.926	80.5%	<0.001	Random-effect model
DM (yes vs no)	4	490	1.61 (0.92-2.82)	0.097	43.1%	0.153	Fixed-effect model
LNM (yes vs no)	6	1617	1.61 (1.28-2.02)	< 0.001	18.6%	0.293	Fixed-effect model

OR: odds ratio; CIs: confidence intervals; DM: distant metastasis; LNM: lymph node metastasis

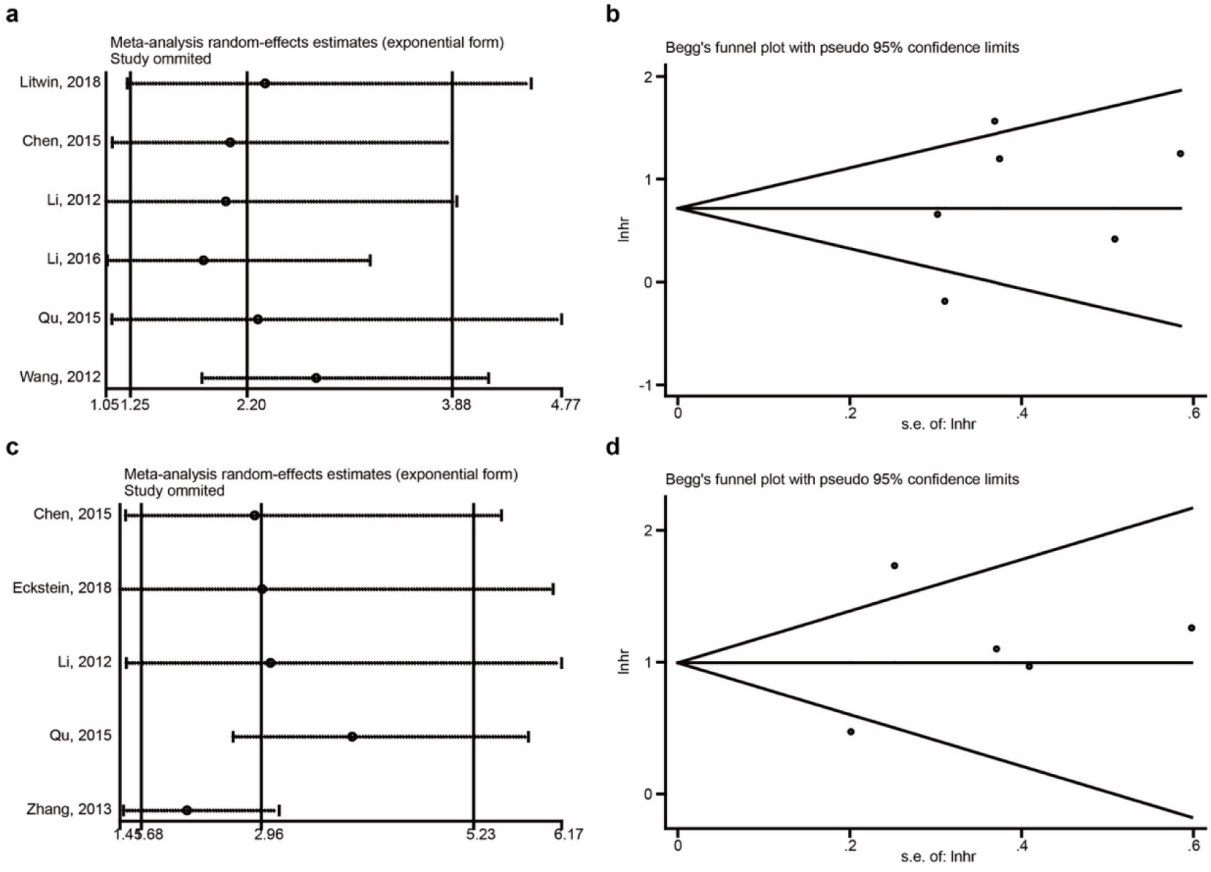

Figure 4. Sensitivity analyses and Begg's funnel plots of the publication biases. **(a)** PIWIL2 expression and OS. **(b)** OS. **(c)** PIWIL2 expression and DFS/RFS/MFS. **(d)** DFS/RFS/MFS. OS: overall survival, DFS: disease-free survival, MFS: metastasis-free survival, RFS: recurrence-free survival.

cated that the pooled HRs were stable and credible (Figure 4a and c). Begg's funnel plots were conducted to analyze the publication biases, and no significant publication biases for OS or DFS/RFS/MFS were identified (p>0.05) (Figure 4b and d).

Discussion

Overexpression of PIWIL2 had been discovered to facilitate cancer progression and predict poor prognosis of patients in various cancers. Plenty of clinical researches have explored the value to predict prognosis of PIWIL2 overexpression. However, nearly all of these researches, which included limited number of subjects of specific cancer, have come to incomprehensive conclusions.

The current meta analysis is the first comprehensive review of all qualified published clinical researches in regard to the positive influence of PIWIL2 expression level on prognosis of 8 types of solid tumors in combination with clinicopathological characters. Survival data of 2116 cancer patients included in 10 different studies were systematically estimated. In summary, the overall results specifically suggested that the higher PIWIL2 expression was associated with a poorer prognosis in cancers, with results of the poorer OS (pooled HR=2.20, 95% CIs: 1.25-3.88, p=0.006), poorer DFS/RFS/MFS (pooled HR=2.96, 95% CIs: 1.68-5.23, p<0.001) and poorer CSS (pooled HR=2.12, 95% CIs: 1.40-3.23, p<0.001). As for clinicopathological characters, the results suggested that PIWIL2 overexpression had no obvious relationship with age, gender, differentiation, tumor invasion, tumor size, TNM stage and DM, but was significantly correlated to more LNM (n=6, OR=1.61, 95% CI: 1.28-2.02).

For now, this study is the most full-scale meta analysis and systematic review which scientifically revealed the potential prognostic role of PIWIL2 expression level in cancers. The results convincingly confirmed the present main viewpoint that overexpression of PIWIL2 was associated with the OS, DFS, RFS, MFS, CSS and LNM. What's more, two important implications in this study were put forward. Firstly, PIWIL2 overexpression could be a common poor prognostic biomarker in cancers. In this study, we involved 8 types of cancers, including CRC, breast cancer, glioma, Hilar cholangiocarcinoma, soft tissue sarcoma, bladder cancer, GC, and NSCLC, which could mean the results were universal and this finding could be applied to at least these 8 types of solid tumors. Secondly, it signified the potential to exploit PIWIL2 as a worthy treatment target for solid tumors.

Many researches have explored the action mechanisms of PIWIL2 on tumorigenesis and tumor progression in different cancers. Specific changes in mRNA expression levels and methylation levels are considered to be crucial factors in tumorigenesis [47,48]. Initially, it has been found that PIWIL2 was mainly expressed in breast cancer stem cells and inhibited apoptosis through activating the Stat3/Bcl-XL pathway, and PIWIL2 was stably expressed in precancerous stem cells (pCSCs) in breast cancer, which might participate in the regulation of pCSC development and differentiation [31,32]. Several researches had found that high expression of PIWI and piRNAs could lead to abundant DNA methylation, silencing of tumor-suppressor genes and an abnormal 'stem-like' state of cancer cells [18,49,50]. What's more, PIWIL2 had been suggested to take an important part in the pathological process of various malignant tumors [51]. Subsequently, more studies in different cancer cell lines revealed that PIWI proteins were closely related to important features of cancer such as chromatin modifications, genomic instability and mutations, cell proliferation, invasion and metastasis [22,52,33,34,44]. Therefore, numerous data have shown the abundant expression of PIWI genes in various cancer types, revealing that PIWI proteins and related piRNAs are involved in tumorigenesis [27,53].

However, our study has several limitations. Firstly, all of the qualified studies are retrospective and reported positive outcomes. Secondly, among the included studies, the methods assessing PIWIL2 expression and defining positive is inconsistent. Thirdly, the sample size in the included studies is relatively small. Fourthly, due to insufficient data for a single cancer, it could not be analyzed in subgroups. Finally, the majority of subjects included in the study are from China, which may weaken the generalization of conclusions.

In the further, well-designed, prospective, multicenter randomized control studies with data of cost analysis, longer duration and larger sample size, and fundamental researches surveying mechanisms of PDE5-Is treating LUTS/BPH and lower ureteric stones, are required to help better demonstrate the advantages as well as drawbacks of combination drug therapies. Clinical trials on the basis of the highest quality standard and method should be encouraged to ensure that the results have statistical significance and clinical relevance at the same time.

In the further, high-quality and well-designed studies with sufficient and standard data of prognosis of different cancers are required to help reveal the prognostic value of PIWIL2 for cancers or single cancers.

Conclusions

To sum up, the association of higher PIWIL2 expression in solid tumor tissues with poorer survival was specifically confirmed in this review and meta analysis. We suggested that PIWIL2 overexpression is a valuable predictor for poor cancer prognosis in OS, CSS, DFS, RFS, MFS and LNM, while its prognostic values are not significantly influenced by clinicopathological characters. Therefore, PIWIL2 is a valuable marker for prognosis of cancers. But whether it would be a promising target for treating solid tumors still needs to be scientifically studied.

Authors' contribution

Weigang Hu, Xifeng Sun and Tao Ye contributed to conception and design; Weigang Hu, Xifeng Sun, Tao Ye and Shaoqiang Feng contributed to literature searches and data extractions; Qiongfang Ruan, Maomao Xi, Xueqing Zhou, Min Li, Ziqing Ye and Xueting Cheng contributed to data analysis and statistical practices; Weigang Hu, Xifeng Sun, Tao Ye and Weiguo Xie contributed to manuscript preparations and revisions. Weigang Hu, Xifeng Sun and Tao Ye are contributors responsible for the overall content as guarantors.

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Conflict of interests

The authors declare no conflict of interests.

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