Review Article

Prognostic and Clinicopathological Value of PINX1 in Various Human Tumors: A Meta-Analysis

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PINX1 (Pin2/TRF1 interacting protein X1, an intrinsic telomerase inhibitor and putative tumor suppressor gene) may represent a novel prognostic tumor biomarker. However, the results of previous studies are inconsistent and the prognostic value of PINX1 remains controversial. Therefore, we conducted a meta-analysis to determine whether PINX1 expression is associated with overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), recurrence-free survival (RFS), and clinicopathological characteristics in patients with malignant tumors. A systematic search was performed in the PubMed, Web of Science, and Embase databases in April 2018. Quality assessment was performed according to the modified Newcastle-Ottawa Scale. Pooled odds ratios (ORs) and hazard ratios (HRs) with 95.0% confidence intervals (CIs) were calculated to determine the relationship between PINX1 expression and OS, DSS, DFS/RFS, and clinicopathological characteristics. Due to the heterogeneity across the included studies, subgroup and sensitivity analyses were performed. Fixed-effects models were used when the heterogeneity was not significant and random-effects models were used when the heterogeneity was significant. Fourteen studies of 16 cohorts including 2,624 patients were enrolled. Low PINX1 expression was associated with poor OS (HR: 1.51, 95.0% CI: 1.03–2.20; \(P = 0.035\)) and DFS/RFS (HR: 1.78, 95.0% CI: 1.28–2.47; \(P = 0.001\)) but not DSS (HR: 0.80, 95.0% CI: 0.38–1.67; \(P = 0.548\)). Low PINX1 expression was also associated with lymphatic invasion (OR: 2.23, 95.0% CI: 1.35–3.70; \(P = 0.002\)) and advanced tumor-node-metastasis stage (OR: 2.43, 95.0% CI: 1.29–4.57; \(P = 0.006\)). No significant associations were observed between low PINX1 expression and sex, depth of invasion, grade of differentiation, and distant metastasis. Low PINX1 expression was associated with poor OS and DFS/RFS and lymphatic invasion and advanced tumor-node-metastasis stage, suggesting that PINX1 expression may be a useful predictor of prognosis in patients with malignant tumors.

1. Introduction

A hallmark of cancer cells is their limitless division and maintenance of stable telomere lengths through activation of specific telomere maintenance mechanisms [1]. Telomeres, regions of repetitive DNA at the end of a chromosome, maintain chromosome integrity and genome stability, preventing double-strand breaks that can lead to aberrant chromosomal rearrangements [2–4]. Aberrations in telomere biology play a pivotal role in oncogenesis and in maintaining the potential of cancer cells to divide infinitely. In the last 15 years, researchers have proposed strategies to target telomerase or telomeric structure as a prospective approach to cancer therapy. PINX1 (Pin2/TRF1 interacting protein XI) is a newly cloned gene mapped to chromosome 8p23.1. It encodes a 45-kDa nucleolar protein containing 328 amino acids that suppresses telomerase activity, resulting in telomere shortening [5, 6]. PinXI is an interacting protein of telomeric repeat
factor 1 (TRF1) that maintains telomere integrity by regulating TRFI stability. Human telomerase reverse transcriptase may act as a regulator of TRFI homeostasis in a PinX1-dependent manner [7, 8].

PinX1 is a haploinsufficiency telomerase inhibitor and putative tumor suppressor gene [7, 9, 10]. The most frequently deleted region correlates with tumorigenicity and tumor invasion, migration, and differentiation. Several recent studies [10–19] have shown that low PinX1 expression is associated with poor survival and different clinicopathological characteristics in various types of cancer, including colorectal cancer, ovarian carcinoma, breast cancer, non-small cell lung cancer, bladder urothelial carcinoma, renal cell carcinoma, and prostate cancer. However, conflicting results exist for some types of malignant tumors, including glioma, esophageal squamous cell carcinoma, and cervical squamous cell carcinoma [20–22]. Therefore, the precise prognostic role of PinX1 in malignant tumors remains controversial.

Therefore, we conducted this first meta-analysis to determine the prognostic and clinicopathological value of low PinX1 expression in patients with various types of malignant tumors.

2. Materials and Methods

2.1. Literature Search Strategy. A systematic search was performed in the PubMed, Web of Science, and Embase databases in April 2018. Search terms included “PinX1” OR “PinX1 protein” OR “Pin2-interacting protein 1” OR “liver putative tumor suppressor” AND “cancer” OR “tumor” OR “neoplasm” OR “carcinoma” OR “malignancy”. The published language was limited to English. A manual search was conducted to identify all potentially eligible studies, including references cited in original studies.

2.2. Inclusion and Exclusion Criteria. Eligible publications for inclusion met the following criteria: (1) studies reporting the relationship between PinX1 expression and overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS)/recurrence-free survival (RFS) in patients with malignant tumors; (2) related clinicopathological data available; (3) studies published in English; (4) two groups of patients established based on PinX1 expression; and (5) sufficient information or data available to calculate odds ratios (ORs) or hazard ratios (HRs) with 95.0% confidence intervals (CIs). The exclusion criteria included the following: (1) comments, letters, abstracts, reviews, case reports, meta-analyses, and duplicate studies; (2) studies with insufficient information or data to calculate ORs or HRs with 95.0% CIs; (3) studies conducted only on human cell lines or animals.

2.3. Data Extraction and Quality Assessment. Two independent investigators reviewed all eligible articles and carefully extracted the data. A third investigator was responsible for reconciling disagreements when the results were inconsistent. The extracted information included the name of the first author and year of publication, country, tumor type, study design, number of cases, mean age of the patients, method of analyzing PinX1 expression, cutoff value, number of cases expressing PinX1, outcome measures, and follow-up time. When prognostic data from univariate and multivariate analyses were available, only the latter were extracted because of the accuracy in accounting for confounding factors. Only when Kaplan-Meier curves were presented for OS, DSS, and DFS/RFS without HRs or 95.0% CIs was the survival data extracted using Engauge Digitizer software (version 4.1, available to download from http://digitizer.sourceforge.net/).

Two independent investigators assessed the quality of each study according to the modified Newcastle-Ottawa Scale (NOS) [24]. NOS scores were calculated based on selection, comparability, and ascertainment of the outcome of interest. Studies with NOS scores of ≥6 were considered high-quality studies [25].

2.4. Statistical Analyses. All statistical analyses were conducted using Stata software (version 12.0; Stata Corporation, College Station, TX, USA). To determine whether PinX1 expression was associated with tumor prognosis, HRs and 95.0% CIs were calculated for the quantitative aggregation of survival data. When included studies did not provide HRs and corresponding 95.0% CIs, methods developed by Parmar [26], Williamson [27], and Tierney [28] were applied to extract data from survival curves. Regarding the relationship between PinX1 expression and the clinicopathological characteristics of malignant tumors, ORs and 95.0% CIs were used to calculate the pooled results. A $P < 0.05$ was considered statistically significant. The heterogeneity of the included studies was detected using Chi-square tests and I² statistics. $I^2 > 50.0\%$ with $P < 0.05$ indicated statistically significant heterogeneity. Pooled ORs and HRs were calculated using fixed-effects or random-effects models. Publication bias was assessed visually (by evaluating the symmetry of funnel plots) and formally (using Egger’s and Begg’s tests). Funnel plot asymmetry and $P < 0.05$ indicated significant publication bias. Sensitivity analysis was used to confirm the reliability and stability of the meta-analysis.

3. Results

3.1. Literature Search. In the initial search, 514 studies were aggregated and analyzed from the PubMed, Web of Science, and Embase databases. Duplicates ($n = 240$) were removed. The titles and abstracts were screened, leaving 56 studies for detailed analysis. After meticulously reviewing the full texts, 42 studies were excluded. Finally, 14 eligible studies containing 2,624 patients [10–23] were included in the meta-analysis. A flow chart of the screening process is shown in Figure 1.

3.2. Study Characteristics. A total of 14 studies with 16 cohorts were extracted. The baseline characteristics of the studies are summarized in Table 1. Finally, 2,624 patients with malignant tumors were enrolled in the subsequent analysis. The included studies (published between 2008 and 2017) were all conducted in China. The sample size across all eligible studies ranged from 40 to 583. All of the included studies were retrospective analyses that were published in English. Qian et al. [21] and Tian et al. [18] each conducted 2 studies. Therefore, we labeled them as Qian 1 and Qian 2 and Tian
| Study          | Country   | Type of malignancy | Study design | No. of patients | Mean age (years) | Test method | Cutoff value | No. of cases with PINX1 expression | Outcome measures | Median follow-up time (months) | NOS score |
|---------------|-----------|--------------------|--------------|----------------|-----------------|-------------|--------------|-----------------------------------|------------------|-------------------------------|-----------|
| Bai 2015 [20] | China     | Glioma             | R            | 583            | 47              | IHC + TMA   | Staining index ≤ 4     | 217                  | 366                        | OS*MA, DSS*MA | 60                            | 7         |
| Cai 2010 [11] | China     | Ovarian carcinoma  | R            | 157            | 51              | IHC + TMA   | Stained cells <60.0%   | 53                   | 104                        | OS*UA, NA       | NA                            | 6         |
| Deng 2015 [12]| China     | Colorectal cancer  | R            | 83             | 58              | IHC         | Staining index ≤ 4     | 36                   | 47                         | OS*UA, DFS*UA  | NA                            | 6         |
| Feng 2017 [14]| China     | Breast cancer      | R            | 59             | 50              | IHC + TMA   | Stained cells <62.5%   | 35                   | 24                         | NA, NA          | 6                             | 6         |
| Li 2015 [10]  | China     | Renal cell carcinoma | R          | 353            | NA              | IHC + TMA   | Staining index ≤ 3     | 203                  | 150                        | OS*MA, DFS*MA  | 60                            | 5         |
| Liu 2013 [16] | China     | Bladder urothelial carcinoma | R     | 187            | 60              | IHC + TMA   | Stained cells <50.0%   | 83                   | 104                        | OS*UA, RFS*UA | 92                            | 7         |
| Ma 2008 [23]  | China     | Gastric cancer     | R            | 90             | NA              | IHC         | Staining index ≤ 3     | 38                   | 52                         | NA, NA          | 5                             |           |
| Qian 2013 [21]| China     | Esophageal cancer  | R            | 98             | 55              | IHC         | Stained cells <50.0%   | 40                   | 58                         | DSS*MA, NA     | 7                             |           |
| Qian 2016 [13]| China     | Colorectal cancer  | R            | 86             | 55              | IHC         | Stained cells <50.0%   | 52                   | 34                         | OS*MA, DFS*MA | NA                            | 7         |
| Rong Shi 2014 [17] | China     | Prostate cancer    | R            | 40             | 67              | IHC + TMA   | Stained cells <60.0%   | 27                   | 13                         | NA, NA          | 5                             |           |
| Mei Lin Shi 2015 [15] | China   | Breast cancer      | R            | 405            | NA              | IHC + TMA   | Staining index ≤ 3     | 212                  | 193                        | OS*MA, DSS*MA | 60                            | 7         |
| Tian 2014 [22]| China     | Cervical carcinoma | R            | 122            | 46              | IHC         | Stained cells <50.0%   | 53                   | 69                         | OS*UA, DSS*MA | NA                            | 6         |
| Tian 2017 [18]| China     | Non-small cell lung cancer | R     | 93             | 56              | IHC         | Stained cells <65.0%   | 56                   | 37                         | OS*UA, NA      | 6                             |           |
| Tian 2017 [18]| China     | Non-small cell lung cancer | R     | 51             | 56              | IHC         | Stained cells <65.0%   | 27                   | 24                         | OS*UA, NA      | 6                             |           |
| Wang 2017 [19]| China     | Non-small cell lung cancer | R     | 158            | 61              | IHC         | Stained cells <50.0%   | 117                  | 41                         | OS*UA, DFS*UA  | NA                            | 7         |

* Staining index = staining intensity × proportion of immune-positive cells.

DFS, disease-free survival; DSS, disease-specific survival; IHC, immunohistochemistry; MA, multivariate analysis; NA, not available; No., number; NOS, Newcastle-Ottawa Quality Assessment Scale; OS, overall survival; R, retrospective; RFS, recurrence-free survival; TMA, tissue microarray; UA, univariate analysis.
1 and Tian 2, respectively. PINX1 expression in tissue specimens was quantified using immunohistochemistry (IHC) or IHC and tissue microarray (TMA). Cutoff values were determined using the staining index or percentage of stained cells. Two studies [12, 13] reported on colorectal cancer, 2 [14, 15] reported on breast cancer, 2 [18, 22] reported on non-small cell lung cancer, and 1 each reported on glioma [20], ovarian carcinoma [11], renal cell carcinoma [10], bladder urothelial carcinoma [16], gastric cancer [23], esophagus cancer [21], prostate cancer [17], and cervical carcinoma [22].

Ten studies with 11 cohorts [10–13, 15, 16, 18–20, 22] reported on OS, 4 studies with 5 cohorts [10, 15, 20, 21] reported on DSS, and 3 studies [12, 13, 19] reported on DFS. Because only 1 study [16] reported on RFS, DFS and RFS were combined to calculate the pooled HR and 95.0% CI. The mean NOS score of the included studies was 6.2 (range, 5.0–7.0), suggesting that the quality of the included studies was adequate (Table 2).

3.3. Associations Between PINX1 Expression and OS. OS was analyzed in 10 studies with 11 cohorts [10–13, 15, 16, 18–20, 22]. Due to the existence of heterogeneity ($I^2 = 85.4\%, P < 0.001$), a random-effects model was used to calculate the pooled HR. Our meta-analysis indicated that low PINX1 expression was associated with significantly poorer OS (HR: 1.51, 95.0% CI: 1.03–2.20; $P = 0.035$) (Figure 2(a)).

Owing to severe heterogeneity, subgroup analyses stratified by tumor type, sample size, test method, cutoff value, type of analysis, and NOS score were conducted to investigate the association between PINX1 expression and OS in patients with various types of malignant tumors (Table 3). In a subgroup analysis of tumor type, low PINX1 expression was associated with significantly poorer OS for colorectal cancer (HR: 2.28, 95.0% CI: 1.46–3.56; $P < 0.001$) and non-small cell lung cancer (HR: 1.48, 95.0% CI: 1.06–2.08; $P = 0.023$). However, no significant associations were observed between low PINX1 expression and other types of malignant tumors (HR: 1.36, 95.0% CI: 0.74–2.50; $P = 0.322$). Moreover, the prognostic significance of low PINX1 expression for OS was poorer with respect to sample size (> 150) (HR: 1.70, 95.0% CI: 1.15–2.50; $P = 0.007$) and test method (IHC + TMA) (HR: 1.72, 95.0% CI: 1.05–2.84; $P = 0.032$). No significant differences were observed in any other subgroup analyses.

3.4. Associations Between PINX1 Expression and DSS. Four studies with 5 cohorts [10, 15, 20, 21] reported associations between PINX1 expression and DSS. The results of the meta-analysis using a random-effects model ($I^2 = 90.8\%, P < 0.001$) showed that low PINX1 expression was not associated with significantly poorer DSS (HR: 0.80, 95.0% CI: 0.38–1.67; $P = 0.548$) (Figure 2(b)).
3.5. Associations Between PINX1 Expression and DFS/RFS. Four studies [12, 13, 16, 19] reported associations between PINX1 expression and DFS/RFS. A fixed-effects model was used to calculate the pooled HR and 95.0% CI because no significant heterogeneity was observed ($I^2 = 9.4\%$, $P = 0.346$). The results of the meta-analysis showed that low PINX1 expression was associated with significantly poorer DFS/RFS (HR: 1.77, 95.0% CI: 1.30–2.42; $P = 0.001$) (Figure 2(c)).

3.6. Publication Bias and Sensitivity Analysis. Begg’s funnel plot (Figures 3(a)–3(c)) and Egger’s test were used to assess the potential publication bias of the OS, DSS, and DFS/RFS studies included in this meta-analysis. The symmetrical shape of the funnel plots and the $P$ values from Begg’s and Egger’s tests indicated that there was no significant publication bias for OS, DSS, and DFS/RFS ($P = 0.755$ and $P = 0.914$, $P = 0.221$ and $P = 1.000$, and $P = 0.336$, respectively).
Table 2: Newcastle-Ottawa quality assessment scale.

| First Author | Year | Selection | Comparability | Outcome | Total |
|--------------|------|-----------|---------------|---------|-------|
| Bai [20]     | 2015 | ⭐⭐⭐⭐     | ⭐             | ⭐⭐⭐⭐   | 7     |
| Cai [11]     | 2010 | ⭐         | ⭐⭐           | ⭐⭐⭐⭐   | 6     |
| Deng [12]    | 2015 | ⭐⭐         | ⭐⭐           | ⭐⭐⭐    | 6     |
| Feng [14]    | 2017 | ⭐         | ⭐⭐           | ⭐⭐⭐⭐   | 6     |
| Li [10]      | 2015 | ⭐⭐⭐       | ⭐             | ⭐⭐⭐    | 5     |
| Liu [16]     | 2013 | ⭐⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 7     |
| Ma [23]      | 2008 | ⭐⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 7     |
| Qian 1 [21]  | 2013 | ⭐⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 7     |
| Qian 2 [21]  | 2013 | ⭐⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 7     |
| Qian [13]    | 2016 | ⭐⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 7     |
| Rong Shi [17]| 2014 | ⭐⭐⭐       | ⭐             | ⭐⭐⭐⭐   | 5     |
| Meilin Shi [15]| 2015 | ⭐⭐⭐       | ⭐             | ⭐⭐⭐⭐   | 7     |
| Tian [22]    | 2014 | ⭐⭐⭐       | ⭐             | ⭐⭐⭐⭐   | 6     |
| Tian 1 [18]  | 2017 | ⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 6     |
| Tian 2 [18]  | 2017 | ⭐         | ⭐⭐⭐          | ⭐⭐⭐⭐   | 6     |
| Wang [19]    | 2017 | ⭐⭐⭐       | ⭐             | ⭐⭐⭐⭐   | 7     |

Table 3: Subgroup analysis of pooled HRs for overall survival in patients with low PINX1 expression.

| Stratified analysis                  | No. of cohorts | No. of patients | Pooled HR (95.0% CI) | P value | Heterogeneity |
|-------------------------------------|----------------|-----------------|----------------------|---------|---------------|
|                                     |                |                 |                      |         | I² (%)        |
| Tumor type                          |                |                 |                      |         | P value       |
| Colorectal cancer                   | 2              | 169             | 2.28 (1.46 – 3.56)   | <0.001  | 0.0           |
| Non-small cell lung cancer          | 3              | 302             | 1.48 (1.06 – 2.08)   | 0.023   | 0.0           |
| Other                               | 6              | 1,807           | 1.36 (0.74 – 2.50)   | 0.931   | <0.001        |
| Sample size                         |                |                 |                      |         |               |
| ≤150                                | 4              | 435             | 1.23 (0.52 – 2.88)   | 0.635   | 94.5          |
| >150                                | 7              | 1,843           | 1.70 (1.15 – 2.50)   | 0.007   | 88.2          |
| Test method                         |                |                 |                      |         |               |
| IHC only                            | 6              | 568             | 1.34 (0.73 – 2.46)   | 0.341   | 80.4          |
| IHC + TMA                           | 5              | 1,710           | 1.72 (1.05 – 2.84)   | 0.032   | 85            |
| Cutoff value                        |                |                 |                      |         |               |
| Staining index ≤4                   | 4              | 1,424           | 0.30 (-0.22 – 0.82)  | 0.255   | 85.5          |
| Stained cells ≤65.0%                | 7              | 854             | 0.49 (-0.12 – 1.10)  | 0.116   | 83.8          |
| Type of analysis                    |                |                 |                      |         |               |
| Univariate                          | 7              | 851             | 1.61 (0.86 – 3.03)   | 0.136   | 87.8          |
| Multivariate                        | 4              | 1,427           | 1.40 (0.86 – 2.29)   | 0.178   | 87.3          |
| NOS score                           |                |                 |                      |         |               |
| ≤6                                  | 6              | 859             | 1.48 (0.83 – 2.65)   | 0.186   | 84.7          |
| >6                                  | 5              | 1,419           | 1.55 (0.87 – 2.74)   | 0.134   | 84.9          |

CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; No., number; NOS, Newcastle-Ottawa Quality Assessment Scale; TMA, tissue microarray.

To determine the influence of each study on the pooled HRs for OS, DSS, and DFS/RFS and to verify the robustness of our results, sensitivity analysis was performed by omitting one study at a time and calculating the pooled HRs for the remaining studies. The results of the sensitivity analysis indicated that no significant effect on pooled HRs was observed after excluding any single study, suggesting that the results of this meta-analysis were relatively robust (Figures 3(d)–3(f)).

3.7 Associations Between PINX1 Expression and Clinicopathological Characteristics. Nine [10, 12, 13, 16, 18–21, 23], 11 [10–19, 21], 12 [10–19, 21, 23], 11 [11–18, 21–23], 10 [10–14, 17–20, 23], and 5 [11, 17–19, 21] studies reported associations between PINX1 expression and sex, depth of invasion, lymph node metastasis, tumor differentiation, tumor-node-metastasis (TNM) stage, and distant metastasis, respectively. Associations between low PINX1 expression and clinicopathological characteristics are summarized in Table 4. The
Table 4: Meta-analysis of low PINX1 expression and clinicopathological characteristics of malignant tumors.

| Clinicopathological characteristic | No. of cohorts | OR (95.0% CI) | \( P \) value | \( I^2 \) (%) | \( P \) value | Model |
|-----------------------------------|----------------|---------------|----------------|---------------|---------------|-------|
| Sex (male vs. female)             | 9              | 0.84 (0.65 – 1.09) | 0.168 | 23.1 | 0.238 | Fixed |
| Depth of invasion (T3–4 vs. T1–2) | 11             | 1.57 (0.88 – 2.78) | 0.126 | 81.1 | <0.001 | Random |
| Lymph node metastasis (yes vs. no) | 12             | 2.23 (1.35 – 3.70) | 0.002 | 77.5 | <0.001 | Random |
| Tumor differentiation (poor vs. well) | 11             | 1.35 (0.91 – 2.02) | 0.140 | 59.7 | 0.006 | Random |
| TNM stage (III–IV vs. I–II)       | 10             | 2.43 (1.29 – 4.57) | 0.006 | 83.6 | <0.001 | Random |
| Distant metastasis (yes vs. no)   | 5              | 2.64 (0.87 – 8.01) | 0.087 | 85.1 | <0.001 | Random |

CI, confidence interval; No., number; OR, odds ratio; TNM, tumor-node-metastasis.

Figure 3: Begg’s funnel plot of publication bias for (a) overall survival, (b) disease-specific survival, and (c) disease-free/recurrence-free survival and sensitivity analysis for (d) overall survival, (e) disease-specific survival, and (f) disease-free/recurrence-free survival.

results of the pooled analysis showed that low PINX1 expression was associated with lymph node metastasis (OR: 2.23, 95.0% CI: 1.35–3.70; \( P = 0.002 \)) and advanced TNM stage (OR: 2.43, 95.0% CI: 1.29–4.57; \( P = 0.006 \)). However, no significant associations were observed between low PINX1 expression and sex (OR: 0.84, 95.0% CI: 0.65–1.09; \( P = 0.168 \)), depth of invasion (OR: 1.57, 95.0% CI: 0.88–2.78; \( P = 0.126 \)), grade of differentiation (OR: 1.35, 95.0% CI: 0.91–2.02; \( P = 0.140 \)), and distant metastasis (OR: 2.64, 95.0% CI: 0.87–8.01; \( P = 0.087 \)).

4. Discussion

The human PINX1 gene comprises 7 exons. It maps to a region that is frequently associated with loss of heterozygosity in cancer [29–33]. PinX1 is an interacting protein of TRF1 that regulates TRF1 stability to maintain telomere integrity [7, 8]. The human PINX1 gene is a telomerase inhibitor and putative tumor suppressor gene that inhibits telomerase activity and shortens the length of telomeres to suppress tumor growth [34]. In addition, low PINX1 expression has been shown to affect chemoradiotherapy sensitivity in cancer cells [21, 22, 35]. The association between PINX1 dysregulation and carcinogenesis has been described in several reports. However, low PINX1 expression plays various roles in tumor progression and its prognostic value in patients with malignant tumors remains controversial. To date, no meta-analyses have been conducted to determine the prognostic value of low PINX1 expression in patients with malignant tumors. Therefore, we conducted a meta-analysis of 14 studies containing 2,624 patients to determine the prognostic value of PINX1 expression for survival in patients with malignant tumors. Furthermore, this is the first meta-analysis to determine whether PINX1 expression is associated with patient outcomes.

The pooled results of the meta-analysis showed that low PINX1 expression was associated with significantly poorer OS and DFS/RFS, but not DSS, in patients with malignant tumors. To investigate the cause of heterogeneity, subgroup analyses were performed according to the tumor type, sample
size, test method, cutoff value, type of analysis, and NOS score. The results of the subgroup analysis showed that low PINX1 expression was associated with significantly poorer OS in colorectal cancer, non-small cell lung cancer, sample size (> 150), and test method (IHC + TMA). Therefore, PINX1 expression is a potential biomarker of prognostic significance for OS and DFS/RFS in colorectal cancer and non-small cell lung cancer. However, studies of other malignant tumors are limited and not all of the included studies involved all types of malignant tumors. Therefore, more eligible studies are needed to validate the prognostic value of PINX1 expression in other types of malignant tumors. Sample sizes and test methods caused heterogeneity in the results. Therefore, the standard sample size and test method should be verified based on further eligible studies.

The pooled results for OS and DFS/RFS showed that low PINX1 expression was associated with poor prognosis, suggesting that PINX1 may function as a tumor suppressor gene in malignant tumors. However, among the 14 studies included in this meta-analysis, 3 [20–22] reported on cervical squamous cell carcinoma, esophageal squamous cell carcinoma, and glioma where PINX1 expression has been reported to have an opposite prognostic effect compared to the pooled outcome. Meanwhile, high PINX1 expression has been reported to be associated with response to chemoradiotherapy. It has also been reported to be an independent predictor of poor survival in cervical and esophageal squamous cell carcinomas [21, 22]. The potential reasons are as follows. First, only a single study reported the prognostic value of PINX1 expression in each of the following: cervical squamous cell carcinoma, esophageal squamous cell carcinoma, and glioma, respectively [20–22]. The small sample size may have introduced bias. Moreover, the relationship between PINX1 expression and response to chemoradiotherapy was considered a clinical parameter in cervical and esophageal squamous cell carcinomas, the mechanism of which has not been determined [21, 22]. Therefore, the results may have statistical flaws and larger sample sizes may be needed to address this bias. Hence, we conducted a meta-analysis to increase the sample size and to reduce bias in assessing the prognostic value of PINX1 expression in various types of malignant tumors. Second, the genetic background of PINX1 may be different in different types of tumors and the role of PinX1 in tumorigenesis complicated and may be tumor type-specific. Furthermore, the mechanism of PinX1 may change in response to chemoradiotherapy, which may influence the prognosis of patients with malignant tumors. Hence, the results of our meta-analysis should be interpreted with caution. Further eligible studies are needed to determine the prognostic value of PINX1 expression in various types of malignant tumors.

With respect to the clinicopathological characteristics, we showed that low PINX1 expression was associated with lymph node metastasis and advanced TNM stage. This suggests that low PINX1 expression is linked to enhanced invasion and migration capacity and reduced survival. Previous studies [10, 15, 16, 36, 37] have described the molecular mechanisms in vitro. PinX1 inhibits invasion, migration, and cell proliferation by suppressing the NF-κB/MMP-9 signaling pathway and MMP-2 via NF-κB-dependent transcription, as well as inhibiting telomerase activity via the p16/cyclin DI pathway and the Mad/1-c-Myc pathway and increasing the apoptotic index. Therefore, low PINX1 expression promotes tumor proliferation, invasion, and migration. However, no significant differences were observed for sex, depth of invasion, grade of differentiation, and distant metastasis. Our findings suggest that PinX1 may facilitate the invasion and migration of malignant tumors. However, further studies are needed to verify the contradictory results and to confirm an association between PINX1 expression and sex, depth of invasion, grade of differentiation, and distant metastasis.

This is the first meta-analysis to evaluate the prognostic value of PINX1 expression in patients with malignant tumors. However, there are several limitations, which mean caution must be taken when interpreting the results. First, all of the included studies were published in English, which may have resulted in publication bias. Second, the included studies did not involve all types of malignant tumors (some types of malignant tumors were reported in only a single study), which suggests that more high-quality studies were necessary to accurately determine the prognostic value of PINX1 expression in patients with malignant tumors. Third, different biological characteristics and molecular mechanisms associated with different types of malignant tumors may generate potentially inconsistent findings. Fourth, some data were extracted from survival curves in the included studies which may be less reliable than data obtained directly. Finally, all of the patients included in this meta-analysis were Asian. Therefore, it is necessary to validate our findings in different populations.

5. Conclusions
In this meta-analysis, we showed that low PINX1 expression was associated with significantly poorer OS, DFS/RFS, and clinicopathological characteristics in patients with various types of malignant tumors. We highlight the important role of PinX1 in malignant tumors and reveal the potential for PINX1 expression to serve as a biomarker for malignant tumors.

Conflicts of Interest
The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors’ Contributions
Hao Liang, Zhiyong Xiong, and Ying Li contributed equally to this work.

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