Original Article

Prognostic significance of pyruvate kinase M2 expression in esophageal squamous cell carcinoma and its meta-analysis

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Background: Pyruvate kinase 2 (PKM2) is a key enzyme in the glycolysis pathway and has been reported to be associated with the development of esophageal squamous cell carcinoma (ESCC). However, the prognostic value of PKM2 in ESCC remains undetermined.

Methods: This study aimed to investigate the clinicopathological significance of PKM2 expression in ESCC. A comprehensive and systematic literature search was conducted using the PubMed, Embase, Medline, and Cochrane library databases. The quality of studies and potential for bias were appraised, and meta-analysis was performed to assess the prognostic impact of PKM2 on overall survival (OS).

Results: A total of 5 studies with 781 participants were eligible and enrolled. Patients with high PKM2 expression were associated with poor prognosis in ESCC [hazard ratio (HR) =1.72, 95% confidence interval (CI): 1.41–2.09; P<0.01]. Furthermore, upregulated PKM2 was significantly associated with lymph node metastasis [odds ratio (OR) =2.38, 95% CI: 1.68–3.35; P<0.01], clinical stage (OR =3.29, 95% CI: 2.27–4.77; P<0.01), and tumor (T) classification (OR =2.92, 95% CI: 2.05–4.16, P<0.01).

Discussion: High PKM2 expression denotes worse OS in ESCC patients, and correlates with the lymph node metastasis, clinical stage, and T classification. However, further studies are warranted to assess how PKM2 can be implemented as a reliable staging element in clinical practice and whether it could provide a new target for therapeutic intervention.

Keywords: Esophageal squamous cell carcinoma (ESCC); pyruvate kinase 2 (PKM2); overall survival (OS); meta-analysis; prognosis

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Introduction

Esophageal cancer (EC) is among the most common gastrointestinal tract tumors. According to the most recent International Agency for Research on Cancer (IARC) report, 455,800 new EC cases (3% of all cancers) were reported and 400,200 deaths due to EC (5% of all cancer deaths) occurred worldwide in 2012 (1). China has one of the highest rates of EC in the world, with an average of about 150,000 deaths per year due to EC. Esophageal squamous cell carcinoma (ESCC) is the predominant type of EC in China (2). Clinical treatment methods include surgical treatment, radiotherapy, chemotherapy, endoscopic treatment, traditional Chinese medicine antitumor

treatment, palliative treatment, and others. Although these traditional treatments have been used in clinical practice for many years, the prognosis of patients with ESCC has remained poor, with an overall 5-year survival rate of 18% (3). Therefore, new efficient prognostic markers need to be identified for risk estimation in ESCC patients.

Numerous oncological studies have focused on cancer metabolism due to the aberrant feature of energy production. Tumor cells acquire the vast majority of energy from glycolysis and lactic acid fermentation regardless of sufficient oxygen supply; this unique phenomenon is known as the Warburg effect, or aerobic glycolysis (4). Pyruvate kinase (PK) is one of the main rate-limiting enzymes in glycolysis. There are 2 isoenzymes, M-type and I-type, and the M-type has M1 and M2 isoforms (PKM1 and PKM2). The PKM1 and PKM2 isoforms are different in their expression and function (5). The PKM2 isoform is mainly expressed in differentiated tissues, such as those of the lung, adipose tissue, retina, and islet, and is also expressed in cells with a high nucleic acid synthesis rate, such as normal proliferating cells, embryonic cells, and tumor cells (6). There have been several findings which have alerted researchers to the potential role of PKM2 in tumorigenesis. Sizemore *et al.* (7) confirmed that the serine/threonine kinase ataxia telangiectasia-mutated (ATM) phosphorylates nuclear PKM2 at T328 following DNA damage, leading to the accumulation of PKM2 in the nucleus. Increased nuclear pT328-PKM2 level is associated with significantly worse survival in glioblastoma patients, so using PKM2-targeting strategies can not only disrupt cancer metabolism but can also inhibit an important mechanism of resistance to genotoxic therapies. For ESCC, PKM2 is overexpressed in ESCC tissues and cell lines (8), and PKM2 overexpression is associated with poor prognosis of ESCC (9-14).

However, the clinical significance of PKM2 expression remains controversial due to conflicting clinical evidence. Hence, we performed a meta-analysis to clarify the prognostic significance of PKM2 in ESCC and offer referential information for future clinical practice. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-442) (15).

Methods

Search strategy

The PubMed, Embase, Medline, and Cochrane Library databases were searched with the key phrases "esophageal squamous cell carcinoma" OR "oesophageal squamous cell carcinoma" OR "ESCC" AND "pyruvate kinase M2 OR PKM2". Google Scholar and the latest conferences were also searched.

Selection criteria

The literature inclusion criteria were as follows: (I) patients in the original study histopathologically diagnosed with ESCC; (II) assessment of the expression of PKM2 with immunohistochemistry (IHC); (III) analysis of the associations of PKM2 with disease-specific survival (DSS), disease-free survival (DFS), progression-free survival (PFS), or overall survival (OS); and (IV) full text available. The exclusion criteria were as follows: Kaplan-Meier survival curve was not used for survival analysis in the original literature, or the data were incomplete and hazard ratio (HR) data could not be obtained.

Literature screening, data extraction, and quality evaluation

The retrieved literature was independently screened by two investigators (Q Zhang and S Zheng) by title and abstract for inclusion in the review. If the suitability of an article was uncertain, the full text was assessed. Disagreements were resolved through discussion or review by a third investigator (L Yang). The following information was extracted from the enrolled studies: general information (including the first author's name, year of publication, article name, and publication details), number of participants, clinical features of participants, detection method, antibody, cutoff value of high and low expression of PKM2, high expression rate of PKM2, OS, estimate of the HRs, and 95% confidence intervals (CIs). If the HR was not directly provided in the original literature, a request was sent to the author via email. If the authors did not respond, the data were extracted from the article's survival curve. The Newcastle-Ottawa Scale (NOS) was used by the two investigators to

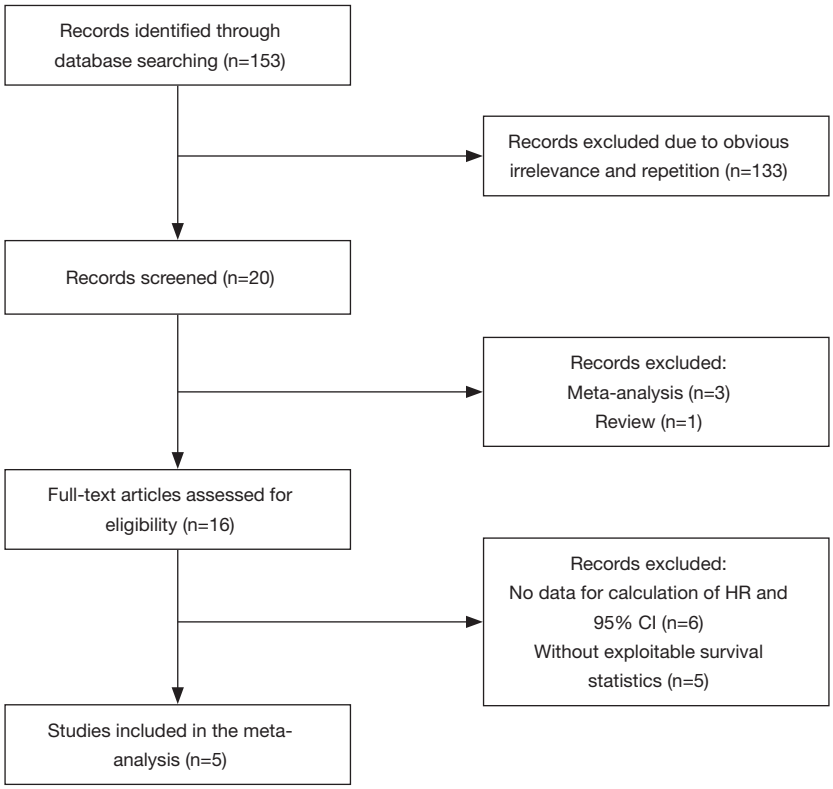

Figure 1 Flow diagram of study selection process and specific reasons for exclusion in this meta-analysis.

assess the quality of the original studies. Disagreements were resolved through discussion or reviewed by the third investigator. The NOS evaluates randomized, case-controlled, and cohort studies by evaluating population selection, comparability, exposure evaluation, or outcome evaluation. It contains 8 items, and the evaluation of literature quality is based on the semi-quantized principle of the star system, with a full score of 9. All studies with NOS scores of 6 or above are considered high quality.

Statistical analysis

Review Manager 5.3 (RevMan, Cochrane Collaborative, Oxford, UK) software was used in the meta-analysis. The software allowed the results to be presented graphically. Heterogeneity between studies was assessed by chi-squared (χ^2)-based Q test and I^2 tests, where I^2 >50% or P<0.05 was considered to indicate significant heterogeneity. Publication bias was estimated using funnel plots and Egger's test through the software Stata 14.0 (StataCorp, College Station, TX, USA). A P value <0.1 was considered to indicate statistically significant publication bias.

Results

The selection of research participants and their characteristics

The processes of identifying and selecting studies are presented in *Figure 1*. Through the preliminary search, a total of 153 studies were screened out. By reading the titles and abstracts of these articles, repetitive or irrelevant studies were excluded. After a detailed review of the remaining 16 studies that potentially met the inclusion criteria, 5 articles comprising 781 participants were finally included in the meta-analysis. The OS was documented in all studies. According to the NOS literature quality assessment scale, the quality score of all the studies was 7, indicating that the quality of the studies was relatively high (*Table 1*).

Association of PKM2 expression with OS

It has been reported that PKM2 is a key molecule in the metastasis of cancer and is overexpressed in various cancer tissues in comparison with paired normal adjacent tissue (NAT). However, there has been a lack of summary of

Table 1 Main characteristics of the 5 included studies in the meta-analysis

Study year	Country	Technology	Sample size	Age median	Gender (F/M)	PKM2 (L/H)	Follow-up (months)	Outcome	HR (95% CI)	Cutoff value	NOS score
Fukuda 2015, (10)	Japan	IHC	205	NA	30/175	101/104	47.9±43.4	OS	1.850 (1.200–2.780)	Score ≥6	7
Li 2014, (11)	China	IHC	141	60	54/87	82/59	NA	OS	1.214 (0.728–2.026)	Score ≥0.75	7
Zhan 2013, (12)	China	IHC	210	NA	48/162	43/167	Overall 72.0	OS	1.748 (1.277–2.395)	Score ≥4	7
Zhang 2013, (13)	China	IHC	86	65 (41–81)	22/64	24/62	NA	OS	2.358 (1.156–4.812)	Score ≥4	7
Ma 2019, (14)	China	IHC	139	NA	32/107	36/103	NA	OS	1.754 (1.070–2.876)	Score ≥3	7

CI, confidence interval; HR, hazard ratio; OR, odds ratio; IHC, immunohistochemistry; NOS, Newcastle-Ottawa Scale; NA, not available; OS, overall survival; PKM2, pyruvate kinase M2; F, female; M, male; H, high; L, low.

different studies on PKM2 in ESCC to provide the reader with extensive information on the clinical impact of PKM2 in ESCC. Consequently, we meta-analyzed the expression of PKM2 in ESCC in the present study. Among the 5 included articles, different antibody manufacturers were used, and the dilution ratio was 1:100, except in the study of Zhang *et al.* (13), in which the ratio was 1:30. The IHC method used was either the EnVision (Agilent Technologies, Santa Clara, CA, USA) method or the streptavidin peroxidase (SP) method. The scoring systems mainly included staining intensity and the percentage of positive cells. The staining intensity of 5 articles was scored as follows: 0, negative; 1, weak; 2, moderate; and 3, strong. The percentage of positive cells was scored slightly differently between the 5 articles (Table S1). Therefore, the definition of the cutoff value in the 5 articles was different. For Fukuda *et al.* (10), Zhan *et al.* (12), and Zhang *et al.* (13), the cutoff value was defined as the median value multiplied by the intensity score and the percentage of positive cells score. For Ma *et al.* (14), the cutoff value was the median of the staining intensity score plus the percentage of positive cells score. For Li *et al.* (11), the cutoff value was defined by combining the weighted score generated by the multiplication of the intensity score and the percentage of positive cells score and statistical analysis. All of them qualified PKM2 expression as "low" when the immunoreactive score (IRS) was less than the cutoff value and "high" when it was higher than the cutoff value.

We found that analysis of PKM2 expression in all cases showed that overexpression of PKM2 was associated with poor prognosis in patients with ESCC (HR =1.72, 95% CI: 1.41–2.09; P<0.01; *Figure 2A*).

Association of PKM2 expression with clinicopathological features

Positivity of PKM2 and its overexpression were significantly different between ESCC and its paired normal controls (OR =21.18, 95% CI: 6.46–69.47; P<0.01) and significantly different between lymph node metastasis and non-metastasis (OR =2.38, 95% CI: 1.68–3.35; P<0.01; *Figure 2B,C*). The positivity and overexpression of PKM2 were significantly associated with clinical stage I–II and clinical stage III–IV (OR =3.29, 95% CI: 2.27–4.77; P<0.01) and significantly associated with T classification (OR =2.92, 95% CI: 2.05–4.16; P<0.01; *Figure 2D,E*). However, PKM2 positivity and overexpression were not significantly associated with tumor differentiation (OR =1.40, 95% CI: 0.79–2.48; P=0.25; *Figure 2F*). Together, these data indicate that PKM2 overexpression could significantly correlate with lymph node metastasis, clinical stage, and T classification in tissues of ESCC.

Heterogeneity analysis

Heterogeneity among the studies was analyzed by χ^2 test and I^2 test, and heterogeneity was found in correlation analysis of PKM2 expression between ESCC and NAT (P<0.05; I^2 =86%) and tumor differentiation (P<0.05; I^2 =63%). Therefore, the random effects model was used to analyze PKM2 expression between ESCC and NAT and tumor differentiation, and the fixed effects model was used for other correlation analyses.

Publication bias

Begg's funnel plots were created to assess the publication

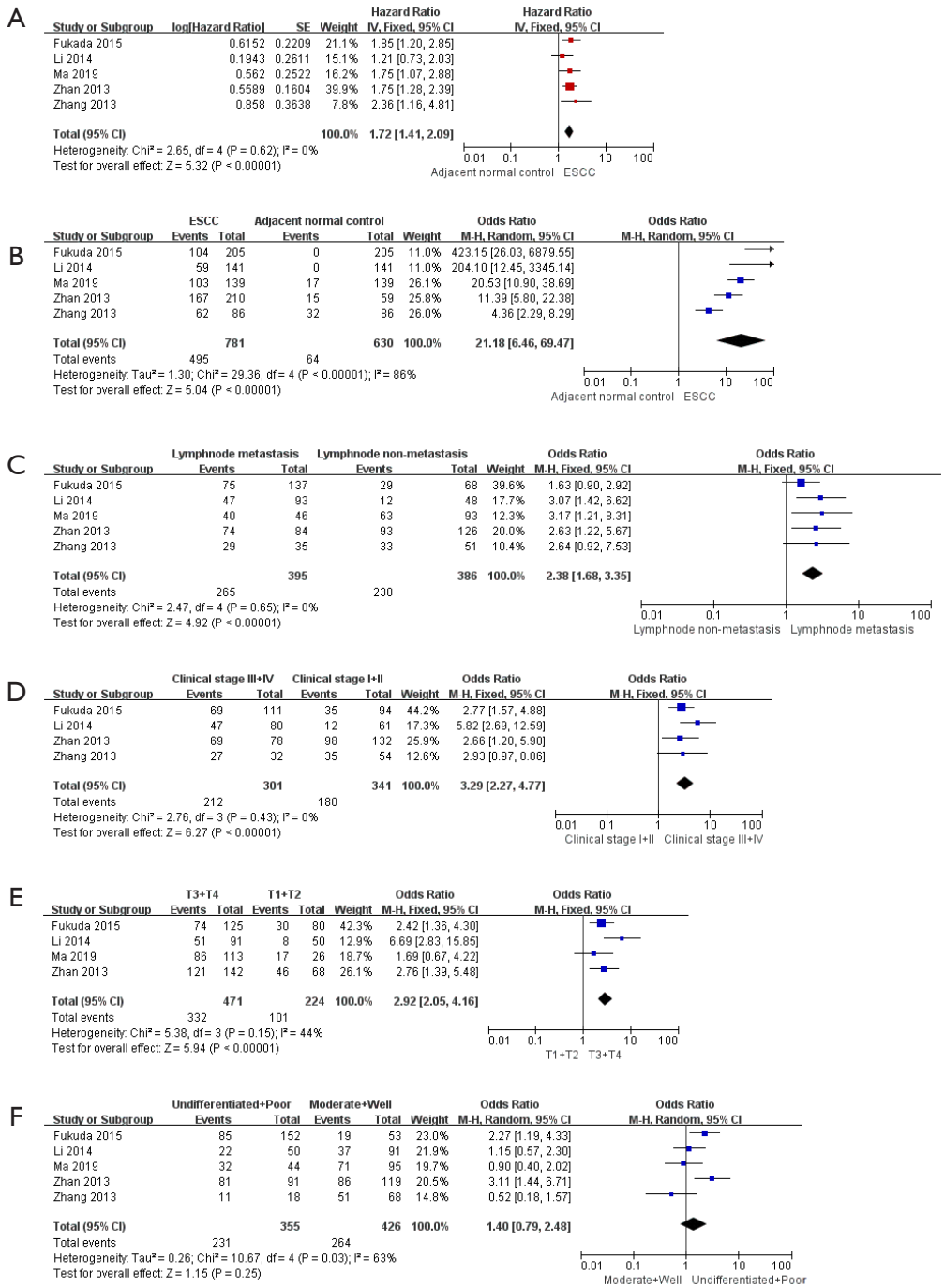

Figure 2 Difference for the association of PKM2 in ESCC. (A) Forest plot of overall association between PKM2 overexpression and OS in ESCC (fixed effects). (B) Forest plot of the association between PKM2 expression in ESCC and paired NAT (random effects). (C) Forest plot of the association between PKM2 expression in lymph node metastasis and non-metastasis tissues (fixed effects). (D) Forest plot of the association of PKM2 expression in clinical stage (fixed effects). (E) Forest plot of the association of PKM2 expression in T classification of ESCC (fixed effects). (F) Forest plot of the association of PKM2 expression in differentiated degree of ESCC (random effects). The square and the horizontal lines correspond to the study-specific ORs or HRs and 95% CIs. The diamond represents the summary of ORs or HRs and 95% CIs. ESCC, esophageal squamous cell carcinoma; NAT, normal adjacent tissue; PKM2, pyruvate kinase 2; OS, overall survival; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

bias of the articles. The peaks of the funnel plots did not reveal any evidence of obvious asymmetry (*Figure 3*). For the accuracy of the results, Egger's test was used to further evaluate publication bias, with the results showing no publication bias among the studies (P>0.05; *Table 2*).

Discussion

It is currently understood that PKM2 plays an important role in the glucose metabolism of malignant tumors, and the PKM2-mediated Warburg effect can provide sufficient energy and a large number of metabolic intermediates for the rapid proliferation of tumor cells (16). The reason is that under the regulation of various factors, PKM2 can switch between the highly active tetramer and the less active dimer (17), with the tetramer having PK activity, and the dimer having protein kinase activity (18). The activity of PKM2 is regulated by a variety of posttranslational modifications, such as phosphorylation, acetylation, small ubiquitin-like modifier (SUMO)-ylation, hydroxylation, and oxidation, which prefer the formation of dimer PKM2 in tumor cells (18,19). Mutations of PKM2 can also change its activity (20). A study showed that PKM2 activity is downregulated by the oxidation of C358 by reactive oxygen species (ROS) or hypoxia, leading to switching of the flux of glucose into the pentose phosphate pathway and glycolytic biosynthesis to generate nicotinamide adenine dinucleotide phosphate (NADPH) for ROS detoxification and tumor progression (21). Cytoplasmic PKM2 is a stable tetramer form, and nuclear PKM2 is a dimer form that plays the role of protein kinase and uses phosphoenolpyruvate (PEP) as a phosphate donor (22). In the nucleus, STAT3 is phosphorylated at tyrosine 705 by PKM2.

The above studies have suggested that PKM2 figures prominently in the emergence and development of malignant tumors. However, the prognostic value of PKM2 in ESCC has not yet been determined. Therefore, the relationship between PKM2 expression and ESCC prognosis and clinicopathological parameters was systematically evaluated and summarized in this meta-analysis. The results showed that PKM2 was expressed differently in ESCC and paired NAT, and the prognostic analysis suggested that PKM2 overexpression was related to the poor prognosis of ESCC. It was also suggested that PKM2 overexpression correlates with lymph node metastasis, clinical stage, and T classification in ESCC tissues.

Similarly, some studies have suggested that PKM2 can be used as a prognostic marker for pancreatic ductal adenocarcinoma (PDAC), breast cancer, hepatocellular carcinoma (HCC), and gallbladder carcinoma (23-25). However, the prognostic value of PKM2 remains controversial. We performed this meta-analysis to provide a more comprehensive and direct understanding of whether PKM2 can be used as a prognostic marker for ESCC. In addition, as lymph node metastasis is the most important prognostic factor in ESCC (26), accurate nodal staging is crucial for the treatment of ESCC (27). Some studies report PKM2 expression to not be associated with lymph node metastasis in ESCC (10,12,13). Therefore, a meta-analysis combining the results of several studies enabled a more comprehensive overview. Our study showed that PKM2 overexpression correlates with lymph node metastasis of ESCC, suggesting that PKM2 may be a molecular target for lymph node metastasis of ESCC. It is also controversial whether PKM2 is associated with tumor differentiation in ESCC. Our results showed that PKM2 was not associated with tumor differentiation.

An interesting finding was that strong PKM2 expression significantly correlated with poor response to chemotherapy. Fukuda *et al.* (10) showed that strong PKM2 expression significantly correlated with decreased OS in patients who received neoadjuvant chemotherapy followed by surgery, and PKM2 expression was not affected by the neoadjuvant chemotherapy. Therefore, the therapeutic value of PKM2 should be systematically assessed. Liu *et al.* (28) reported that the PKM2 inhibitor shikonin inhibited proliferation and glycolysis and induced cell apoptosis in HCC cells. James *et al.* (29) reported that PKM2 inhibitor shikonin reduced PDAC cell proliferation, cell migration, and induced cell death. Tang *et al.* (30) reported that shikonin enhances sensitization of gefitinib against wild-type epidermal growth factor receptor (EGFR) non-small cell lung cancer via inhibition of the PKM2/STAT3/cyclinD1 signal pathway. Another study reported that shikonin has a significant antitumor effect in EC by regulating the HIF1α/PKM2 signal pathway (31). Considering the complex function of PKM2 in cell biology, measures that inhibit or silence PKM2 possibly cause a wide range of effects in the human body, especially in patients who are chemotherapy resistant.

Despite producing valuable findings, there were a few limitations to our study. First, although we did not find any obvious evidence for publication bias from funnel plots and Egger's tests, this meta-analysis was based on formally published articles with principally positive results. Hence,

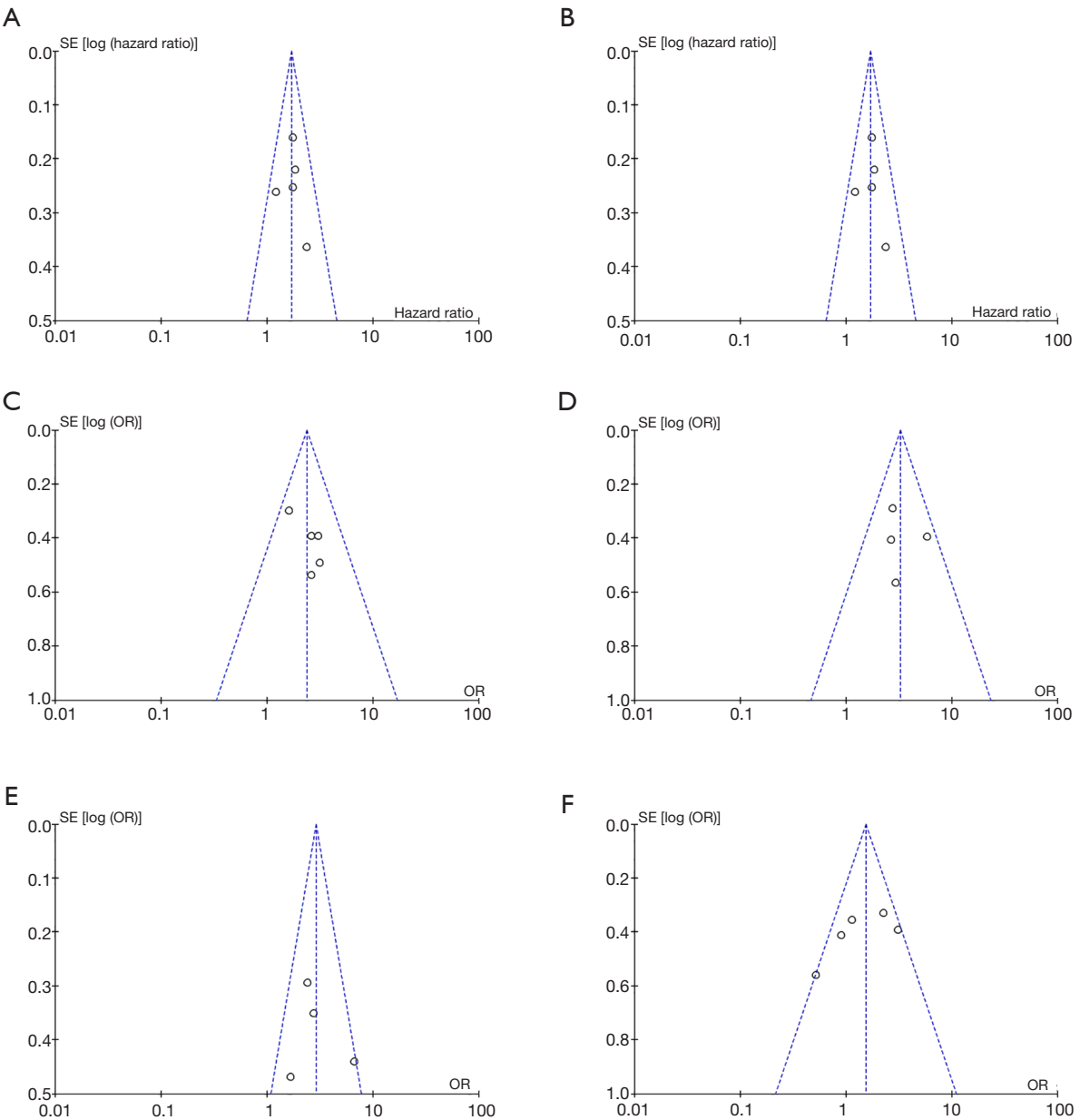

Figure 3 Funnel plots for publication bias in an association analysis of PKM2 expression among different clinicopathological parameters. (A) Funnel plot of overall association between PKM2 overexpression and OS in ESCC. (B) Funnel plot of the association between PKM2 expression in ESCC and paired NAT. (C) Funnel plot of the association between PKM2 expression in lymph node metastasis and non-metastasis tissues. (D) Funnel plot of the association of PKM2 expression in clinical stage. (E) Funnel plot of the association of PKM2 expression in T classification of ESCC. (F) Funnel plot of the association of PKM2 expression in differentiated degree of ESCC. PKM2, pyruvate kinase 2; ESCC, esophageal squamous cell carcinoma; OS, overall survival; NAT, normal adjacent tissue; OR, odds ratio.

there was a potential publication bias that might have lowered the accuracy and validity of the results. Second, due to some relatively small sample-sized studies and some missing information, the quality of the included studies was not uniform.

In summary, the present study suggests that PKM2 is crucial for the development of ESCC and that PKM2 overexpression is associated with poor prognosis of ESCC

Table 2 Results of Egger's test

Comparison	*t*	P value	95% CI
ESCC and NAT	1.65	0.197	2.838–8.966
Lymph node metastasis	2.20	0.115	1.206–6.622
Clinical stage	0.26	0.820	10.255–11.571
T classification	0.38	0.740	16.753–20.005
Tumor differentiation	1.47	0.237	18.106–6.649

ESCC, esophageal squamous cell carcinoma; NAT, normal adjacent tissue; CI, confidence interval.

and correlates with lymph node metastasis, clinical stage, and T classification. There is potential for PKM2 as a potential prognostic biomarker and therapeutic target for ESCC.

Conclusions

The present study demonstrated that PKM2 plays a crucial role in ESCC. The level of PKM2 is significantly associated with ESCC prognosis and tumor-node-metastasis staging. Additional research is needed to investigate how PKM2 promotes metastasis during ESCC carcinogenesis.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-442

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-442). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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