IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2019; 10(1): 131-137. doi: 10.7150/jca.28216

Research Paper

Prognostic Value of PDZ-Binding Kinase/T-LAK Cell-Originated Protein Kinase (PBK/TOPK) in Patients with Cancer

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Received: 2018.06.30; Accepted: 2018.10.24; Published: 2019.01.01

Abstract

Background: PDZ-binding kinase/T-LAK cell-originated protein kinase (PBK/TOPK) plays a critical role in tumorigenesis and cancer progression. However, the prognostic roles in cancer patients are inconsistent or even controversial. Therefore, we performed a meta-analysis to investigate the prognostic value of PBK/TOPK in cancers.

Methods: Literature search was performed using several online databases (PubMed, Web of Science, Embase, Cochrane Library, and Google Scholar, National Knowledge Infrastructure and Wanfang) for eligible articles published up to May 1, 2018. The relationship between PBK/TOPK expression and prognosis in cancers was investigated by using pooled hazard ratios (HRs) with 95% confidence intervals (CIs) through STATA 12.0 software.

Results: Totally 20 eligible studies were included in this meta-analysis. The pooled results showed that carriers with high protein expression of PBK/TOPK were significantly associated with poor OS (HR: 1.69, 95% CI: 1.33-2.04) in various cancers, and patients with increased PBK/TOPK protein expression were significantly correlated with inferior RFS (HR: 1.63, 95% CI: 1.02-2.24) and short DFS (HR: 1.69, 95% CI: 1.16-2.23).

Conclusions: The findings suggest that PBK/TOPK protein expression might serve as a prognostic tumor marker in cancers.

Key words: PBK/TOPK, solid tumor, prognosis, meta-analysis

Introduction

PBK (PDZ-binding kinase), also known as T-lymphokine–activated killer cell-originated protein kinase (TOPK), is a 322 amino-acid and mitogen-activated serine/threonine protein kinase **[1-2]**. PBK/TOPK protein is generally difficult to detect in normal tissues but frequently elevated in cancer tissues, such as breast cancer, lymphoma and bladder cancer **[3-5]**. Furthermore, PBK/TOPK has been reported to play vital roles in inflammation, cell apoptosis, and cell-cycle regulation and high expression of PBK/TOPK contributes to tumor growth, proliferation, and metastasis **[6-9]**. Accumulating evidence has reported that PBK/TOPK protein expression was correlated with clinical outcomes in various solid cancers, such as colorectal cancer, cholangiocarcinoma and lung cancer **[10-12]**. However, the potential prognostic value of PBK/TOPK in human solid tumors is inconsistent and even contradictory**.** For example, Hayashi et al **[13]** reported that over-expression of TOPK protein was significantly related with poor prognosis in glioma, which was consistent with the results conducted in lung adenocarcinoma by Wei et al **[12]**, but there was no significant association between PBK/TOPK protein expression and OS in prostate, gastric and epithelial ovarian cancer **[14-16]**. Conversely, PBK/TOPK up-regulation was reported to be correlated with longer overall survival in cholangiocarcinoma

and oral squamous cell carcinoma **[10,17].**

To date, there is no study to comprehensively assess the correlation between PBK/TOPK protein expression and prognosis in cancer patients. And considering the limited number of individual study and varied results. Herein, we conducted the meta-analysis with published data to clarify the influence of high PBK/TOPK expression and its impact on the outcomes of different cancers as well as provide an overview of the current roles of PBK/TOPK in tumor prognosis and as a promising therapeutic target.

Materials and Methods

Search strategy and study selection

The literature search was performed by two authors (Zhang Y and Wang R) in the electronic platforms of PubMed, Web of Science, Embase, Cochrane Library, Google scholar, Wanfang and National Knowledge Infrastructure (CNKI). The last search date was May 1, 2018. The search strategy was used as: 'PDZ binding kinase', 'PBK', 'TOPK', 'T-LAK cell-originated protein kinase', 'lymphokine-activated killer T-cell-originated protein kinase', 'Nori-3 protein', 'TOPK' and 'cancer', 'tumour', 'carcinoma', 'neoplasm', 'tumor', 'neoplasia'. Article language was limited to English and Chinese. The references of all relevant articles were manually reviewed to find potentially relevant studies.

Inclusion criteria

(1) studies concerning the prognostic values of PBK/TOPK protein expression in tissues from primary solid cancer; (2) studies with complete information for assessment of hazard ratios (HRs) and their 95% confidence intervals (CIs) for overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) or recurrence-free survival (RFS); (3) original articles in English or Chinese.

Exclusion criteria

(1) articles focused on hematologic neoplasms; (2) study only detected the mRNA expression of PBK/TOPK; (3) letters, editorials, case reports, reviews, comments or abstracts.

Data extraction and quality assessment

The following extracted information was recorded by two independent authors (Zhang Y and Wang R): first author's surname, publication year, number of sample size, number of patients with overexpression of PBK/TOPK protein, country or region, clinical stage or tumor grade, detection method, cut-off value, analytical method, HRs with their 95 % CIs for OS/RFS/DFS/PFS.

To evaluate the quality of studies, the Newcastle-Ottawa Scale (NOS) was applied. We assigned the studies of high quality a scored ≥6.

Statistical analysis

In the meta-analysis, the pooled HRs and their 95% CIs were calculated to investigate the impact of PBK/TOPK expression on the survival of patients using STATA (Version 11.0; StataCorp, College Station, TX). I^2 test and Q test were used to assess heterogeneity among the studies, $P_{het}<0.10$ and/or $I^2 > 50\%$ indicates obvious heterogeneity among studies, and then the random effect model was used for significant heterogeneity. Otherwise, a fixed-effect model was applied. Egger's test and Begg's test were conducted to assess potential publication bias. Sensitivity analysis was carried out to explore the stability of the combined results. A p-value < 0.05 was considered as statistically significant.

Results

The study selection procedure is outlined in **Figure 1**. According to the selection criteria, the potential relevant full-texts were reviewed and further examined. Finally, 20 **[10-29]** eligible studies which fulfilled all inclusion criteria were selected into this systematic review and meta-analysis.

Up to 3470 participants from 20 studies were enrolled in this meta-analysis. The included articles were published from 2010 to 2018. The sample size varied from 24 to 520. A total of 20 studies investigated the association of PBK/TOPK expression with overall survival (OS) **[10-29]**, and for the correlations between PBK/TOPK expression and secondary outcomes, 2 studies reported progression-free survival (PFS) **[13, 16]**, 3 studies focused on recurrence-free survival (RFS) **[12, 20, 28]** and 4 studies covered disease-free survival (DFS) **[18, 22, 24, 29].** As for cancer type, 12 different kinds of human solid cancers were investigated, including colorectal cancer (CRC) **[10, 22, 25]**, cholangiocarcinoma (CCA) **[11]**, lung cancer (LC) **[12, 18, 19, 21]**, breast cancer (BC) **[20]**, prostate cancer (PCa) **[14, 28]**, oral squamous cell carcinoma (OSCC) **[17]**, epithelial ovarian cancer (EOC) **[16]**, esophageal squamous cell carcinoma (ESCC) **[23]**, nasopharyngeal carcinoma (NPC) **[24]**, gastric cancer (GC) **[15, 26, 27]**, hepatocellular carcinoma (HCC) **[29]** and glioma **[13]**. The principal characteristics of all included studies are summarized in **Table 1**.

PBK/TOPK protein and OS

A total of 20 studies with 3470 patients reported the relationship between PBK/TOPK protein and OS in various cancers. The random-effects model was applied for large heterogeneity existed ($I^2 = 71.7\%$; P_{het}

=0.000). As shown in **Figure 2**, the overall results showed that high PBK/TOPK expression was significantly correlated with poorer OS in various cancers (HR: 1.69, 95% CI: 1.33-2.04).

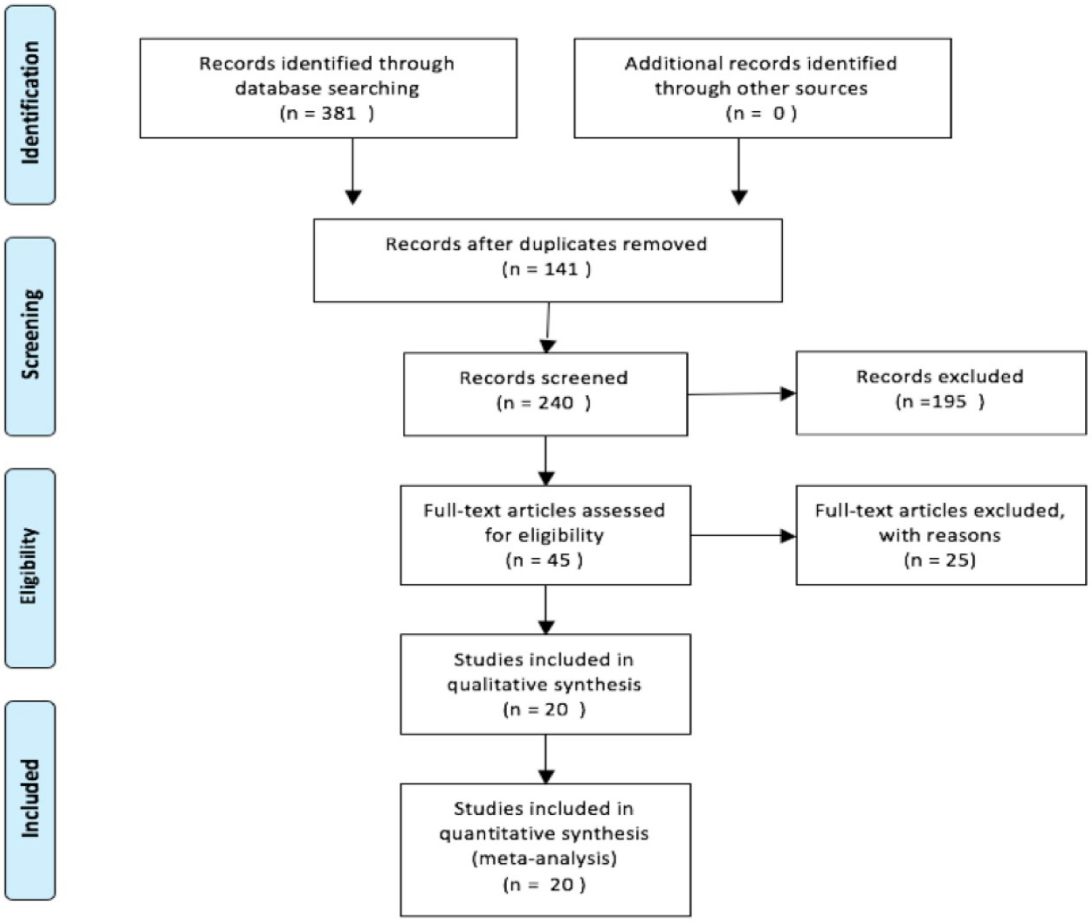

Figure 1. Flow diagram of studies selection procedure.

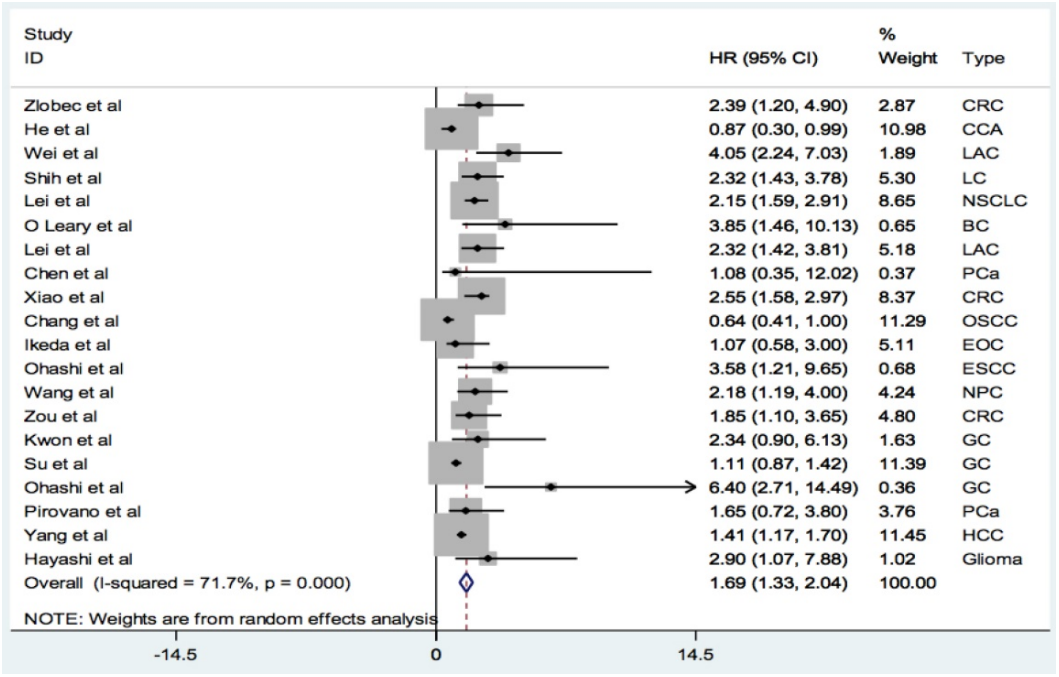

Figure 2. Forest plots of PBK/TOPK protein and OS in various cancers.

Table 1. Characteristics of eligible studies in this meta-analysis.

First author	Year	Cancer type	Country	Sample size	Number of OE	Clinical stage/ tumor grade	Criterion of OE	Test methods	Outcome measures	MVA	NOS score
Zlobec et al [10]	2010	CRC	Switzerland	87	36	NA	diffuse cytoplasmic TOPK staining in >90% of colorectal tumor cells	IHC	OS	Yes	6
He et al [11]	2010	CCA	China	24	11	tumor grade 1-2-3	> the percentages of TOPK-positive cells (10 %)	IHC	OS	Yes	6
Wei et al [12]	2012	LAC	China	203	136	I	IHC score >3	IHC	OS, RFS	Yes	7
Shih et al [18]	2012	LC	China	119	72	I-II-III-IV	IHC score (2, 3)	IHC	OS, DFS	Yes	6
Lei et al [19]	2013	NSCLC	China	279	125	I-II-III-IV	> the median percentage of positively stained cells (11.5%)	IHC	OS	Yes	8
O Leary et al [20]	2013	BC	Ireland	290	104	tumor grade 1-2-3	percentage of cells stained multiplied by intensity score >48	IHC	OS, RFS	Yes	8
Lei et al [21]	2015	LAC	China	127	67	I-II-III-IV	> the average percentages of TOPK-positive cells (13.3%)	IHC	OS	Yes	7
Chen et al [14]	2015	PCa	China	98	NA	NA	immunoreactivity scores (IRS)	IHC	OS	No	6
Xiao et al [22]	2015	CRC	China	186	135	tumor grade 1-2-3	IHC score >3	IHC	OS, DFS	Yes	7
Chang et al [17]	2016	OSCC	China	287	75	I-II-III-IV	mean PBK/TOPK expression score	IHC	OS	Yes	7
Ikeda et al [16]	2016	EOC	Japan	163	84	I-II-III-IV	2+, 3++	IHC	OS, PFS	No	7
Ohashi et al [23]	2016	ESCC	Japan	54	10	0-I-II-III-IV	intensity plus proportion scores ≥5	IHC	OS	Yes	6
Wang et al [24]	2016	NPC	China	185	92	NA	NA	IHC	OS, DFS	Yes	7
Zou et al [25]	2017	CRC	China	80	43	NA	NA	IHC	OS	No	6
Kwon et al [15]	2017	GC	Korea	385	79	I-II-III	+,++	IHC	OS	Yes	8
Su et al [26]	2017	GC	China	79	73	I-II-III-IV	+,++,+++,++++	IHC	OS	No	6
Ohashi et al [27]	2017	GC	Japan	144	24	I-II-III	PBK/TOPK presenting scores ⩾5 tumor cells	IHC	OS	Yes	7
Pirovano et al [28]	2017	PCa	UK	128	NA	NA	> the median score of PBK IHC score	IHC	OS, RFS	Yes	7
Yang et al [29]	2017	HCC	China	520	292	I-II-III-IV	> the median score of PBK IHC	IHC	OS, DFS	Yes	8
Hayashi et al [13]	2018	Glioma	Japan	32	23	II--III-IV	> median percentage of TOPK-positive cells (12.7%)	IHC	OS, PFS	Yes	6

CRC: colorectal cancer; CCA: cholangiocarcinoma; LAC: lung adenocarcinoma; LC: lung cancer; NSCLC: non-small-cell lung cancer; BC: breast cancer; PCa: prostate cancer; OSCC: oral squamous cell carcinoma; EOC: epithelial ovarian cancer; ESCC: esophageal squamous cell carcinoma; NPC: nasopharyngeal carcinoma; GC: gastric cancer; HCC: hepatocellular carcinoma; IHC: immunohistochemistry; OS: overall survival; RFS: recurrence-free survival; PFS: progression-free survival; DFS: disease-free survival; OE: over-expression; MVA: multivariate analysis NA: not available.

We also investigated the prognostic values of PBK/TOPK in several subgroups (**Table 2**). We found that PBK/TOPK expression level could serve as a prognostic biomarker in lung cancer (HR=2.30, 95% CI: 1.79-2.81) and CRC (HR=2.39, 95% CI: 1.81-2.97). However, there was no significant difference but a strong trend between PBK/TOPK expression level and OS in prostate cancer (HR=1.61, 95% CI: 0.12-3.10) and gastric carcinoma (HR=1.13, 95% CI: 0.86-1.41). Furthermore, increased expression of PBK/TOPK was related to poor OS in Asia cohorts (HR=1.65, 95% CI: 1.28-2.03) but no significant association was found for European cohorts (HR=2.08, 95% CI: 0.94-3.23). Interestingly, PBK/TOPK expression could be an independent predictor for OS in multiple cancers (HR=1.88, 95% CI:1.42-2.34).

PBK/TOPK protein and DFS/PFS/RFS

The pooled HR for secondary outcomes in cancer patients are presented in **Table 3**.

Patients with elevated expression of PBK/TOPK protein were significantly associated with inferior RFS (HR: 1.63, 95% CI: 1.02-2.24) and shorter DFS (HR: 1.69, 95% CI: 1.16-2.23), and there was a strong trend but not statistical difference between PBK/TOPK expression and PFS (HR: 2.56, 95% CI: 0.80-4.32).

Publication bias

We performed the Begg's and Egger's test to identify potential publication bias. The visible plots were shown in **Figure 3** and **Figure 4**, the test results all indicated that there was no significant publication bias in this meta-analysis ($Pr_{Begg's\ test} > |z| = 0.538$ (continuity corrected); $Pr_{Egger's\ test} > |z| = 0.111$).

Sensitivity analysis

The results (**Figure 5**) showed that the exclusion of any individual study did not change the statistical significance, suggesting the robustness of our results.

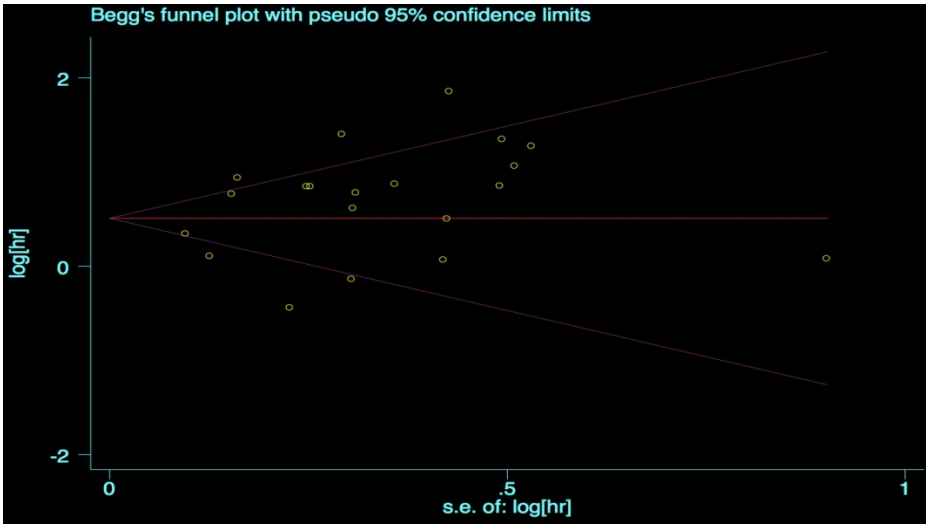

Figure 3. Begg's funnel plot for OS.

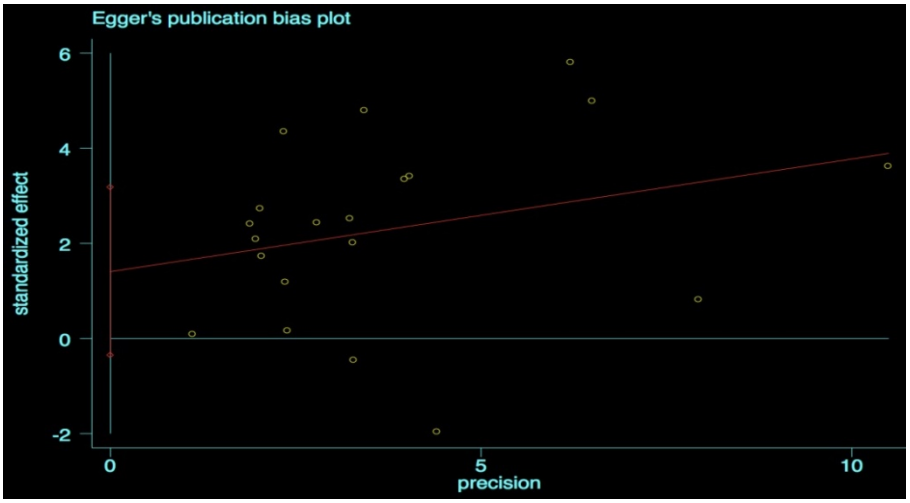

Figure 4. Egger's publication bias plot for OS.

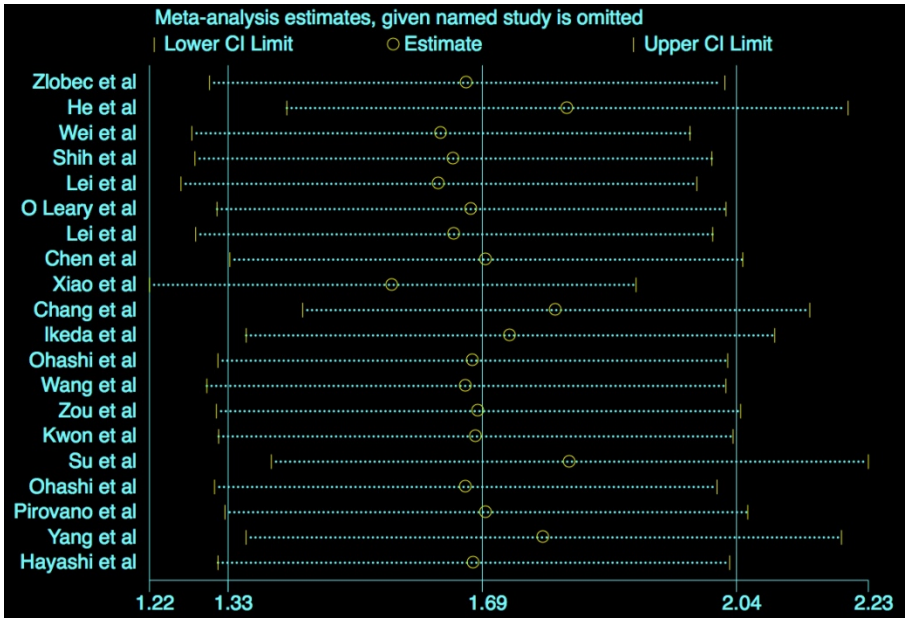

Figure 5. Sensitivity analysis for OS.

Table 2. Meta-analysis results of the relationship between PBK/TOPK protein and OS.

Group/ subgroup	No. of data set	No. of cases	Pooled HR (95%CI)	p-value	Model	P_{het}	I^2 (%)
Overall [10-29]	20	3470	1.69 (1.33-2.04)	<0.001	Random	71.7	0.0
Lung cancer [12, 18, 19, 21]	4	728	2.30 (1.79-2.81)	<0.001	Fixed	0.524	0.0
Prostate cancer [14, 28]	2	226	1.61 (0.12-3.10)	NS	Fixed	0.853	0.0
Gastric carcinoma [15, 26, 27]	3	608	1.13 (0.86-1.41)	NS	Fixed	0.141	49
Colorectal cancer [10, 22, 25]	3	353	2.39 (1.81-2.97)	<0.001	Fixed	0.643	0.0
European cohorts [10, 20, 28]	3	505	2.08 (0.94-3.23)	NS	Fixed	0.593	0.0
Asia cohorts [11-19, 21-27, 29]	17	2965	1.65 (1.28-2.03)	<0.001	Random	0.000	74.9
Multivariate analysis [10-13, 15, 17-24, 27-29]	16	3050	1.88 (1.42-2.34)	<0.001	Random	0.000	77.0

Table 3. Analyses of secondary outcomes for PBK/TOPK protein in tumors.

Secondary outcomes	No. of data set	No. of cases	Pooled HR (95% CI)	p-value	Model	P_{het}	I^2 (%)
RFS [12, 20 ,28]	3	621	1.63 (1.02-2.24)	<0.001	Fixed	0.490	0.0
DFS [18, 22, 24, 29]	4	1010	1.69 (1.16-2.23)	<0.001	Fixed	0.677	0.0
PFS [13, 16]	2	195	2.56 (0.80-4.32)	NS	Fixed	0.594	0.0

Discussion

Since the prognosis potential of PBK/TOPK protein in human solid cancers is inconsistent and debatable, a quantitative meta-analysis is employed in our study. To our knowledge, this is the first meta-analysis to comprehensively evaluate the effect of PBK/TOPK protein level on prognosis in various tumors. By searching against several online databases, a total of 20 observational studies were ultimately included in our work altogether 3470 subjects, containing 12 different cancer types. After analyzing the data extracted from those eligible articles, we revealed that PBK/TOPK protein expression level was associated with clinical outcomes in solid tumors.

The pooled HR results suggested that a high expression level of PBK/TOPK protein was significantly associated with poor OS (HR: 1.69, 95% CI: 1.33-2.04) in human cancers. According to different cancer types, we found the prognostic value of PBK/TOPK in LC (HR=2.30, 95% CI: 1.79-2.81) and CRC (HR=2.39, 95% CI: 1.81-2.97). But no significant differences were found between PBK/TOPK expression and OS in prostate and gastric cancer, this might be for the relatively small number of studies and needed to be explored by future larger studies. As for different ethnicities, the current findings showed that PBK/TOPK expression might be a significant prognostic predictor in Asian patients but not in Caucasian populations, the findings of different ethnic background should be confirmed by future multi-center researches. In addition, we also found that PBK/TOPK protein might be an independent predictor for OS in human cancers (HR=1.88, 95% CI:1.42-2.34). Meanwhile, the relationships between PBK/TOPK protein level and secondary outcomes were also investigated, and PBK/TOPK was found to be a useful prognostic factor for RFS (HR: 1.63, 95% CI: 1.02-2.24) and DFS (HR: 1.69, 95% CI: 1.16-2.23), but not significant for PFS (HR: 2.56, 95% CI: 0.80-4.32). Generally, PBK/TOPK exhibited the potential clinical utility as a candidate molecular marker in human malignancies.

This present study showed that PBK/TOPK expression was associated with patients' clinical outcomes. A number of researches have studied the roles of PBK/TOPK in cancer development, PBK/TOPK acts as an oncogene in multiple cancers and contributes to tumor progression **[8, 21, 23, 30-31].** PBK/TOPK is reported to be highly expressed in cancer tissues and cell lines, and high PBK/TOPK expression tends to indicate higher biological malignant aggressiveness **[19, 32]**. TOPK knockdown could significantly inhibit tumor growth, invasion and metastasis *in vitro* and *in vivo***,** conversely, PBK up-regulation displays multiple tumorigenic properties, it could promote cell growth, metastasis and enhance tumor transformation **[23-26, 30-31]**. PBK/TOPK also correlates with drug response and tumor resistance and showed to be the valid target for antineoplastic kinase inhibitors and serves as a potential therapeutic target for various cancers, such as CRC **[33-36]**, lung cancer **[37-38]**, breast cancer **[39]** and prostate cancer **[40-41]**.

Nevertheless, there are several limitations in our study. First, we only included the studies published in English or Chinese, and most of the studies included came from the Asian countries. Second, the total sample size was not sufficient enough and all enrolled were retrospective studies. Third, the prognostic potentials of PBK/TOPK protein in other special types of cancers were needed for further investing-ation. Fourth, there was obvious heterogeneity for OS. Finally, the definition of PBK/TOPK protein

overexpression varied in different studies.

In summary, the current meta-analysis indicates that elevated PBK/TOPK protein expression is correlated with poor cancer prognosis, and PBK/TOPK protein might be a promising candidate to predicate the cancer survival. If replicated in future larger-scale, multicenter prospective studies, this finding may support the clinical value of PBK/TOPK as a biomarker in tumors.

Competing Interests

The authors have declared that no competing interest exists.

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