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Review Article

PDK1 as a potential prognostic and clinicopathological biomarker in various carcinomas: a meta-analysis

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Abstract: Introduction: Recent studies have confirmed that pyruvate dehydrogenase kinase 1 (PDK1) is dysregulated in various tumors and that PDK1 overexpression is associated with survival and clinicopathological features in patients with cancer. Therefore, this meta-analysis was performed to evaluate prognostic and clinicopathological roles of PDK1 in human tumors. Materials and methods: Electronic databases PubMed and Web of Science were searched (up to December 20, 2017). Results: A total of 2,676 patients from 14 eligible studies were collected and analyzed in this study. Results indicated high that PDK1 expression correlated with poor overall survival (OS) (HR=1.81, 95% CI: 1.42-2.31, *P<0.001*). Moreover, PDK1 was related to T grade (OR=1.72, 95% CI: 1.27-2.31, *P<0.001*). Conclusion: The present meta-analysis showed that high PDK1 expression predicts poor prognosis and T stage, serving as a promising biomarkers for patients with cancer.

Keywords: PDK1, cancer, poor survival, T stage, meta-analysis

Introduction

Cancer continues to be a serious common and frequently encountered disease, threatening human health worldwide [1]. According to statistics, 14.1 million people were diagnosed with cancer and 8.2 million people died in the year 2012 [2]. Despite recent advances in surgical resection, chemotherapy, and targeted drugs, prognosis of cancer remains poor, primarily due to delayed diagnosis, recurrence, and drug resistance. Thus, there is an urgent need for a biomarker which can provide reliable information for tumor diagnosis and prognosis.

PDK1, termed a globular protein, has 556 amino acids polypeptides, belonging to the AGC kinase family [3]. It contains two domains, including an N-terminal serine-threonine kinase domain, together with a C-terminal Pleckstrin Homology (PH) domain. Accordingly, it is capable of regulating activities of numerous AGC kinases, such as Akt, p70S6K, p90RSK, SGK, and some PKC isoforms [3, 4]. Moreover, it has been revealed that PDK1 plays pivotal roles in many biological mechanisms, including cell survival, growth, proliferation, invasion, and migration [5-7]. As demonstrated by numerous research, aberrant expression of PDK1 has been observed in different kinds of cancers, such as gastric carcinoma, hepatocellular carcinoma, colorectal carcinoma, and small-cell lung cancer [6, 8-10]. Elevated PDK1 expression has been observed having a significant correlation with poor prognosis and clinicopathological characteristics, indicating that PDK1 plays pivotal roles in the progression of cancers [8, 9, 11, 12].

Even though a closer association exists between PDK1 expression and clinicopathological characteristics in human cancers, their sample sizes and discrete performances have been quite limited in most studies. Therefore, the present quantitative meta-analysis was carried out to investigate association between PDK1 and clinicopathological characteristics and OS of patients.

Materials and methods

Search strategy

Electronic databases PubMed and Web of Science were searched (up to December 20,

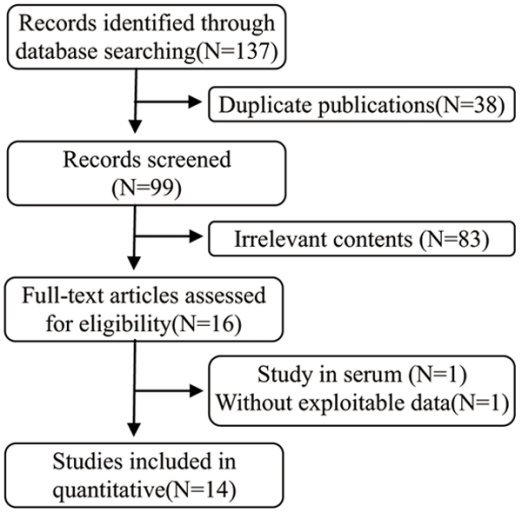

Figure 1. Flow diagram of the study selection process.

2017). The following combined search terms were used: "PDK-1", "Pyruvate dehydrogenase kinase 1", "PDPK-1", "3-phosphoinositide-dependent protein kinase-1", "Cancer", "prognosis", and "outcome". Country, race, and dates were not limited in this search.

Inclusion and exclusion criteria

Two investigators (Lingyun Yang, Ying Zhou) performed assessment and extraction of all qualified research works, independently. Inclusion criteria included: (1) PDK1 expression was identified with the help of immunohistochemistry (IHC) or in situ hybridization (ISH) in human cancer tissues; (2) Association between PDK1 expression and survival of cancer patients was investigated; (3) Patients were grouped in accordance with PDK1 expression; and (4) Related clinicopathologic parameters were provided. Exclusion criteria were: (1) Reviews, letters, case reports, expert opinions, and editorials; (2) Cell and animal studies; (3) Studies without usable data; and (4) Duplicate publications.

Data extraction

Based on inclusion and exclusion criteria, three investigators performed independent extraction of these elements: (1) First authors' last name, (2) Year of publication, (3) Country, (4) Cancer type, (5) Number of cases, (6) Detection method of PDK1, (7) Survival analysis method, and (8) Sources of hazard ratios (HRs) [95% CIs (confidence intervals)]. Engauge Digital 4.1 software was employed for the digitization and extraction of data as prognosis was only plotted as a Kaplan-Meier curve in some articles [13].

Statistical analysis

Association between PDK1 expression and cancer prognosis was performed with the help of pooled HR, together with their 95% CI. OR with their CIs were used for assessment of the impact of PDK1 expression on clinicopathological parameters. Chi-square Q test was employed for checking heterogeneity among the studies involved. If no significant heterogeneity was observed between various studies (I^2<50% or P>0.1), a fixed-effects model was employed. Otherwise, a random-effects model was adopted [14]. Sensitivity analysis was carried out through the omission of a study sequentially. Assessment of publication bias was carried out by Begg's and Egger's test [15]. All statistical analyses were performed using Stata statistical software version 12.0 (Stata Corporation, College Station, Texas, USA).

Results

Literature search and characteristics of included studies

Literature search and characteristics of included studies of 212 qualified research works were employed from PubMed (n=75) and Web of Science (n=137), in accordance with the literature retrieval methodology stated earlier. Of these, 38 articles were excluded due to duplicate publications. A total of 83 references were excluded due to lack of relevance. Assessment of the 16 remaining full-text articles was conducted. According to exclusion criteria, 2 research works were further excluded. Eventually, a total of 14 articles were included in this meta-analysis. As evident from **Figure 1**, an aggregate of 2,676 patients were included in the 14 research works, most in China. Ten different types of cancer were evaluated in this meta-analysis (**Table 1**), with 1 colorectal cancer (CRC) [8], 1 esophageal squamous cell carcinoma (ESCC) [16], 1 gallbladder carcinoma (GBC) [17], 3 gastric carcinomas (GC) [10, 18, 19], 1 hepatocellular carcinoma (HCC) [9], 1 head and neck squamous cancer (HNSCC) [11],

Table 1. Characteristics of studies included in the meta-analysis

First author	Year	Countary	Cancer type	Total number	PDK1 expression				HR	Method	Type of survival data	HR estimate
					High		Low					
					T1-2	T3-4	T1-2	T3-4				
Wigfield SM [11]	2008	UK	HNSCC	140	29	52	29	30	1.83 (0.85-3.95)	IHC	OS	Survival curve
Lin S [20]	2013	China	NPC	52	8	24	15	5	3.1 (0.38-25.67)	IHC	OS	Survival curve
Yang Z [16]	2014	China	ESCC	120	20	45	20	35	1.07 (0.44-2.61)	IHC	OS	Survival curve
Yoon S [8]	2015	Korea	CRC	486	72	254	46	114	1.98 (1.10-3.50)	IHC	OS	Reported
Xiang G [21]	2016	China	NPC	102	42	31	22	7	1.86 (0.20-17.32)	IHC	OS	Survival curve
Liu D [22]	2011	China	NSCLC	142	-	-	-	-	1.15 (0.77-1.70)	IHC	OS	Reported
Kim JG [10]	2013	Korea	GC	621	-	-	-	-	1.34 (0.91-1.96)	IHC	OS	Reported
Hur H [18]	2013	Korea	GC	152	-	-	-	-	5.49 (1.12-27.04)	IHC	OS	Survival curve
Baumunk D [24]	2013	Germany	RCC	91	-	-	-	-	1.85 (1.06-3.23)	IHC	OS	Reported
Lohneis P [23]	2015	Germany	OSC	253	-	-	-	-	1.96 (1.09-3.57)	IHC	OS	Reported
Wang J [9]	2016	China	HCC	128	-	-	-	-	2.68 (2.46-4.42)	IHC	OS	Reported
Lian S [17]	2016	China	GBC	101	-	-	-	-	2.76 (1.85-2.88)	IHC	OS	Reported
Bai X [19]	2016	China	GC	156	-	-	-	-	1 (0.33-3.06)	IHC	OS	Reported
Liu T [6]	2017	China	NSCLC	132	-	-	-	-	1.12 (0.44-2.87)	IHC	OS	Survival curve

Colorectal cancer (CRC), esophageal squamous cell carcinoma (ESCC), gallbladder carcinoma (GBC), gastric carcinoma (GC), hepatocellular carcinoma (HCC), head and neck squamous cancer (HNSCC), nasopharyngeal carcinoma (NPC), nonsmall cell lung cancer (NSCLC), Ovarian Serous Carcinoma (OSC), renal cell carcinoma (RCC), Overall survival (OS).

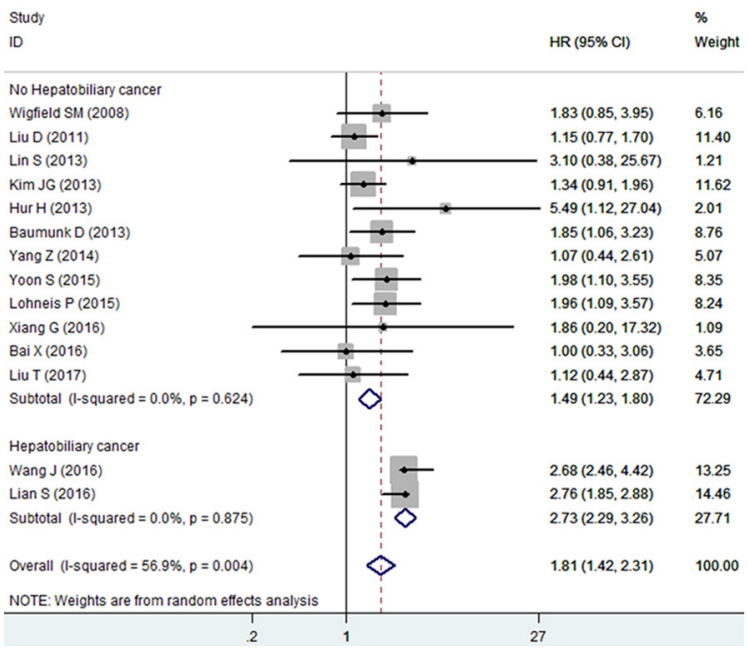

Figure 2. Forest plots for association between PDK1 expression and OS.

2 nasopharyngeal carcinoma (NPC) [20, 21], 2 non-small cell lung cancer (NSCLC) [6, 22], 1 ovarian serous carcinoma (OSC) [23], and 1 renal cell carcinoma (RCC) [24]. Assessment of expression levels of PDK1 was carried out by immunolytic enzyme histochemistry technology.

Association between PDK1 expression and OS

A total of 14 studies, including 2,676 participants, were extracted for the purpose of investigating association between PDK-1 expression and overall survival. Revealed by key findings, high PDK-1 expression group had a poorer outcome (HR=1.81, 95% CI: 1.42-2.31, *P<0.001*) (**Figure 2**). Due to significant heterogeneity (*P* =0.004, I^2=56.9%), a random-effects model was used. Subgroup analysis was performed based on cancer type (other cancers and hepatobiliary cancer). Results revealed significant association between PDK-1 and OS in non-hepatobiliary cancers (HR=1.49, 95% CI: 1.23-1.80, *P<0.001*) and hepatobiliary cancer (HR=2.73, 95% CI: 2.29-3.26, *P<0.001*). Moreover, results also indicated that cancer type was likely to be the source of heterogeneity.

According to present findings, whether in non-hepatobiliary cancers or hepatobiliary cancer, PDK-1 overexpression had an association with shorter OS. Accordingly, PDK-1 constituted an independent factor of OS among cancer patients.

Correlation of PDK1 expression with T stage

Univariate analysis of T stage was performed in 5 research works, aiming to investigate associ-

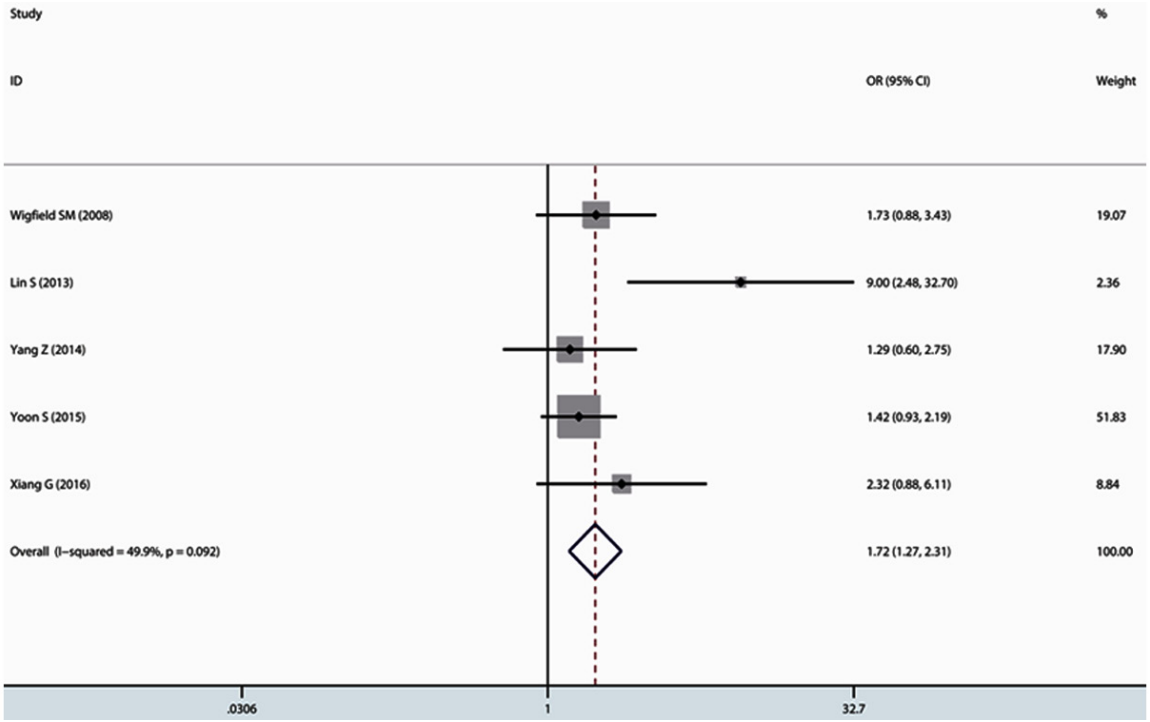

Figure 3. Forest plots for association between PDK1 expression and T stage.

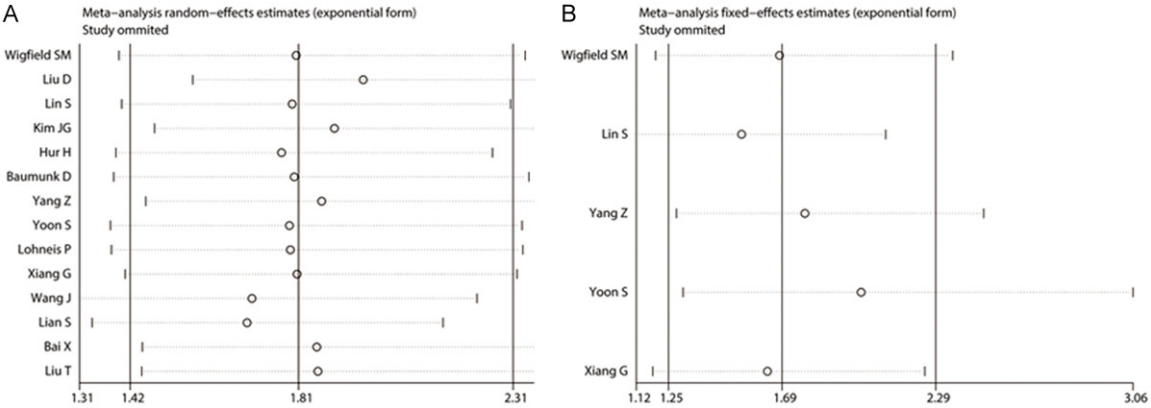

Figure 4. Sensitivity analysis. A. PDK1 expression and overall survival in different cancers. B. PDK1 expression and T stage.

ation of PDK1 expression with T stage of cancers (OR=1.72, 95% CI: 1.27-2.31, *P<0.001*) (**Figure 3**). A fixed-effects model was adopted due to no significant heterogeneity (*P*=0.092, I^2=49.9%). As a result, higher PDK1 expression level was associated with deeper cancer invasion.

Sensitivity analysis and publication bias

Sensitivity analysis of survival rates revealed that individual research works had little impact on results, validating both the stability and credibility of findings (**Figure 4**). As suggested by funnel plot analysis, there was observed no obvious publication bias in survival rates and T stages. Egger's regression test also confirmed that pooled findings had no significant publication bias (**Figure 5**).

Discussion

Cancer exerts serious impact on human health worldwide. Currently, it is among the leading

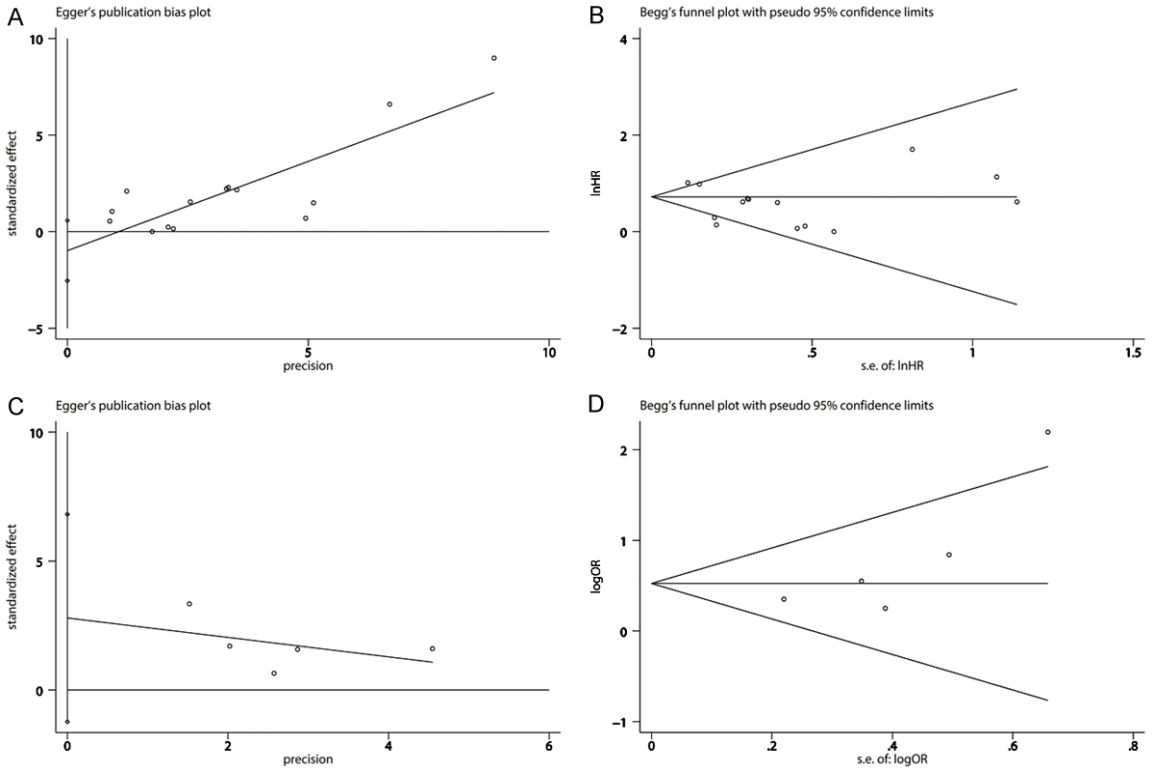

Figure 5. Publication bias. A. Egger's test for PDK1 expression and OS. B.Begg's test for PDK1 expression and OS. C. Egger's test for PDK1 expression and T stage. D. Begg's test for PDK1 expression and T stage.

causes of death in China. However, there remains a lack of diagnostic and prognostic markers for cancers. Thus, discovery of a new biomarker is essential, providing convincing evidence and guiding diagnosis and treatment.

PDK1 is dysregulated in numbers of tumors, playing substantial roles during tumor initiation and progression. Bayascas observed that lowering expression of PDK1 could inhibit tumorigenesis in PTEN+/- mice [25]. Du shed light on the fact that deletion of PDK1 eliminates established spontaneous breast cancer. Instead, overexpression of PDK1 drives tumor metastasis dissemination to the lungs by the means of regulation of the epithelial-mesenchymal transition (EMT) [26]. Also, PDK1 has been considered a critical enzyme of the Warburg Effect. Moreover, aberrant PDK1 expression augments the survival of tumor cells in hypoxia microenvironments, as well as inhibiting apoptosis [27, 28]. As highlighted by some researchers, expression of PDK1 has an association with drug resistance of tumors. Inhibition of PDK1 expression is capable of reversing multiple drug resistance, including temozolomide, MK2206, and BYL719 et al. [7, 29, 30]. According to these findings, PDK1 is likely a therapeutic target. Additionally, it is likely a potential biomarker for cancer.

This meta-analysis was systemically carried out to explore the latent prognostic and clinicopathological roles of PDK1 in cancer. Collection and analyses of an aggregate of 2,676 patients, from 14 eligible research works, were performed. Results revealed significant association between PDK1 expression and poor prognosis (HR=1.81, 95% CI: 1.42-2.31, *P<0.001*), whether in hepatobiliary cancer (HR=2.73, 95% CI: 2.29-3.26, *P<0.001*) or non-hepatobiliary cancers (HR=1.49, 95% CI: 1.23-1.80, *P<0.001*). Moreover, statistical analyses revealed that high PDK1 expression had significant correlation with T stage (OR=1.72, 95% CI: 1.27-2.31, *P*<0.001).

There were still some limitations to the present study. First, most patients in this analysis hailed from China. Accordingly, the data lacked the universality factor. Second, this research

was developed on the basis of published studies, wherein, some negative studies were likely unpublished. Third, antibody sources and definitions of PDK1 overexpression are quite varied in different studies. Ultimately, there exists heterogeneity that cannot be ignored.

Conclusion

The present meta-analysis demonstrates that overexpression of PDK1 has significant correlation with poor overall survival, along with greater invasive depth. Detection of PDK1 expression has the potential to provide evidence, guiding diagnosis and treatment in multiple cancer patients.

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Disclosure of conflict of interest

None.

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