Received: 14 March 2018 | Accepted: 17 July 2018

DOI: 10.1002/jcp.27179

ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

Clinicopathological and prognostic value of lncRNA PANDAR expression in solid tumors: Evidence from a systematic review and meta-analysis

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Funding information
Mashhad University of Medical Sciences, Grant/Award Number: 961403

Abstract

PANDAR (promoter of CDKN1A antisense DNA damage activated RNA) has been shown to be aberrantly expressed in many types of cancer. Considering conflicting data, the current study was aimed to assess its potential role as a prognostic marker in malignant tumors. A comprehensive literature search of PubMed, Medline, and Web of Science was performed to identify all eligible studies describing the use of PANDAR as a prognostic factor for different types of cancer. Data related to overall survival (OS) and clinicopathologic features were collected and analyzed. The pooled hazard ratio (HR) and odds radio (OR) with a 95% confidence interval (CI) were used to estimate associations. Ten original studies containing 1,231 patients were included. The results showed that in patients with cancer, high PANDAR expression is correlated with lymph node metastasis (LNM; OR = 2.57; 95% CI, 1.76–3.81; $p < 0.001$), tumor stage (OR = 2.90; 95% CI, 1.25–6.75; $p = 0.013$), and tumor size (OR = 1.79; 95% CI, 1.11–2.91; $p = 0.018$). However, sensitivity analysis further demonstrated a significant association between high PANDAR expression and OS, both in multivariate and univariate analysis models (pooled HR 2.01; 95% CI, 1.17–3.44 and pooled HR 2.62; 95% CI, 1.98–3.47, respectively), after omitting one study. These results suggested that PANDAR expression might be indicative of advanced disease and poor prognosis in patients with cancer. Further studies are necessary to determine the value of this risk stratification biomarker in clinical management of patients with cancer.

KEYWORDS
long noncoding RNA (lncRNA), meta-analysis, neoplasms, promoter of CDKN1A antisense DNA damage activated RNA (PANDAR), prognosis

1 | INTRODUCTION

Cancer is a leading cause of death in most regions worldwide, particularly in less developed countries. The global burden of cancer is expected to grow due to the population aging and largely due to inability of early detection methods (Jemal et al., 2011). Despite the ongoing advances in management and treatment of patients with cancer, the 5-year survival rate is still low in many types of cancer (Torre, Siegel, Ward, & Jemal, 2016). This low survival rate is attributed to the fact that many cancers are diagnosed at advanced rather than early stages with poor prognosis. Therefore, identification and validation of specific and sensitive biomarkers for cancer detection in early stages are crucial to reduce cancer-related mortality. Recently, considering the advances in functional genomic and the emergence of new nucleic acid–base molecules including cell-free DNAs, exosome, and noncoding RNAs, there has been growing

interest among researchers to explore the potential utility of these molecules as cancer diagnostic and prognostic biomarkers. Noncoding RNAs including microRNAs, long noncoding RNAs (lncRNAs) and circular RNAs, which are significantly upregulated or downregulated in various types of cancer, have received a broad attention as biomarkers for cancer management (Gibb, Brown, & Lam, 2011; Mattick & Makunin, 2006; Ono, Lam, Nagahara, & Hoon, 2015; Santosh, Varshney, & Yadava, 2015).

LncRNAs are a new class of RNA transcripts greater than 200 nucleotides in length with no ability to be translated into protein (Frith et al., 2006). They are originally by-products of Pol II transcription and for a long time were thought to be transcriptional noise with no biological function (Wapinski & Chang, 2011). However, numerous studies indicated that lncRNAs are not the "dark matter" of the genome and are involved in a wide range of biological processes including cell growth, proliferation, differentiation, apoptosis, and cell cycle progression (Djebali et al., 2012; Quinn & Chang, 2016; Schmitt & Chang, 2016). A growing body of evidence has also demonstrated a strong association between aberrant expression of lncRNAs and the development of diverse human diseases (Wapinski & Chang, 2011). Indeed, dysregulation of lncRNA has been reported in various types of cancer, due to interaction with oncogenic and tumor-suppressing pathways, suggesting that they are major players in tumor initiation, progression, and metastasis (Schmitt & Chang, 2016). From the functional point of view, lncRNAs can be divided into tumor suppressor and oncogene classes (Bhan, Soleimani, & Mandal, 2017). Functional lncRNAs have been known as a promising biomarker for cancer diagnosis and prognosis, and could also be potential therapeutic targets (Bolha, Ravnik-Glavač, & Glavač, 2017).

PANDAR (promoter of CDKN1A antisense DNA damage activated RNA) is a novel noncoding RNA with 1,506 nucleotides in length mapping to chr6p21.2 (Hung et al., 2011). Hung and Wang for the first time reported that DNA damage could induce five lncRNAs from the CDKN1A promoter in a p53-dependent manner (Hung et al., 2011). These lncRNAs, including PANDAR, interact with a regulatory subunit of nuclear transcription factor Y to reduce the expression of proapoptotic genes in human fibroblasts. It has been indicated that PANDAR contributes to cell proliferation, migration, invasion, and apoptosis in many types of cancer cells. Recently, an increasing number of studies have shown that upregulation of PANDAR is associated with poor prognosis and promotes tumorigenesis in various types of cancer (Chen, Yang, Wang, & He, 2017; Kotake et al., 2017; Z. Li et al., 2017; X. Li, Wang, Sun, Fan, & Cui, 2017; Lu et al., 2017; Ma, Xu, Huang, & Shu, 2016; Peng & Fan, 2015; Xu, Tong et al., 2017; Xu, Jiang, & Cui, 2017; Zhan et al., 2016). However, some other studies have indicated a reciprocal trend especially for non-small-cell lung cancer (NSCLC), clear cell renal cell carcinomam (ccRCC), and hepatocellular carcinoma (HCC) (Han et al., 2015; Peng et al., 2017; Puvvula et al., 2014; Wu et al., 2016). Taken together, the prognostic value of PANDAR in patients with cancer is still in doubt. Conducting a systematic review and meta-analysis may clarify to what extent this molecule might be of prognostic significance. Therefore, we conducted a comprehensive meta-analysis of all previously published data based on the robust evidence of the expression and impact of PANDAR in tumorigenesis, aiming to evaluate the prognostic value of PANDAR in tumor metastasis, progression, and survival.

2 | METHODS

2.1 | Literature search strategy and study selection

An electronic search of PubMed, Medline, and Web of Science was performed to identify all relevant studies up to January 2018. The search terms included ("LncRNA-PANDAR" OR "PANDA" OR "lincRNA" OR "noncoding RNA") AND ("cancer" OR "carcinoma" OR "neoplasm" OR "prognosis" OR "prognostic" OR "survival" or "recurrence" OR "tumor") with English language restriction. Our search was supplemented with an additional manual search of reference lists of all retrieved articles. Two authors (HM-M and YR) independently screened the titles and abstracts of all citations for relevance and eligibility. Abstracts, unpublished reports, review articles, letters, case reports, editorials, and comments, and animal studies were excluded. When duplicate studies were retrieved, the most recent or informative study was included. Studies were considered eligible if they met the following criteria: (a) measured the tissue expression of lncRNA-PANDAR among patients of any type of human cancer; (b) assessed the association of lncRNA-PANDAR expression with survival; and (c) provided sufficient data to estimate hazard ratios (HRs) and their 95% confidence intervals (CI). All studies that did not meet the inclusion criteria, and those with lack of sufficient data to estimate HRs with 95% CI were excluded. If data could not be extracted or calculated from the original article, the study was also excluded.

2.2 | Data extraction and quality assessment

The articles that fulfilled all inclusion criteria were qualitatively evaluated by two investigators (HM-M and YR) in accordance with the Newcastle–Ottawa scale (NOS) scoring system and then processed for data extraction. Any disagreements were resolved through discussion with a third investigator (M-SH). Briefly, for each study, the following data were recorded: The first author's surname and year of publication, country, ethnicity, number of patients, number of high PANDAR expression group, and low expression group, tumor type, clinical stage of tumor, treatment data, study design, detection method, cutoff values, disease-free survival, and overall survival (OS). If data from any of the earlier categories were not reported in the primary study, items were treated as "not stated." It was necessary that each eligible study was provided with enough information to extract or calculate the natural logarithm of the HR and its variance for meta-analysis. All analyses were based on previously published studies; thus, no ethical approval or patient consent was required.

2.3 | Statistical analysis

The pooled HRs or odds ratios (ORs) with 95% CI were used to assess the impact of PANDAR expression on survival and prognosis of patients with cancer. Pooled HRs and ORs were directly extracted from the published data. When a study did not directly provide HR and 95% CI values, the survival information was extracted from Kaplan–Meier curves and used to estimate HR. Statistical heterogeneity among different studies was measured by using the chi-square-based Cochran's Q and I^2 statistic, with significant heterogeneity defined as $I^2 > 50\%$ and $p < 0.05$. When a distinct heterogeneity was present, the random-effect model was used; otherwise, the fixed-effects model was applied. Moreover, sensitivity analyses were performed to assess the stability of the results by removing each study in sequence. The meta-regression analysis was also applied to estimate the sources of heterogeneity. Potential publication bias was evaluated by using funnel plots, Begg's test, and Egger's linear regression test. Statistical analysis was conducted using Comprehensive Meta-analysis version 3 software (Biostat, Englewood, NJ; Borenstein, Hedges, Higgins & Rothstein, 2005). Statistical significance was defined as a p-value less than 0.05.

3 | RESULTS

3.1 | Literature search analysis

The flow chart diagram of the article screening process for lincRNA PANDAR is shown in Figure 1. Our initial search revealed a total of 44 articles. After simultaneous screening of titles and abstracts, 24 irrelevant or duplicate articles were excluded. A more detailed review of the abstracts based on inclusion and exclusion criteria resulted in 11 eligible papers for systematic review; of these, one article was excluded due to insufficient data to estimate HR or OR for further analysis (Zhang, Yin, Sun, & Han, 2017). Finally, based on inclusion and exclusion criteria, a total of 10 articles with 1,231 patients were included in the current meta-analysis (Han et al., 2015; Huang, Xie, Ma, Zhao, & Gao, 2017; Jiang et al., 2017; X. Li et al., 2017; Lu et al., 2017; Ma et al., 2016; Peng & Fan, 2015; Xu, Jiang et al., 2017; Xu, Tong et al., 2017; Zhan et al., 2016). The main characteristics of the selected studies are summarized in Table 1. All studies have been conducted in China and were published between 2015 and 2017. Nine different types of cancer were evaluated in those studies including one ccRCC, one cholangiocarcinoma (CCA), two colorectal cancer (CRC), one bladder cancer (BC), one pancreatic ductal adenocarcinoma (PDAC), one HCC, one NSCLC, one gastric cancer (GC), and one cervical cancer. Preoperative treatment information was not reported in two studies, and for the other eight studies, no treatment was taken. PANDAR expression was measured in tumor specimens using the qRT-PCR method. All studies comprised two groups of high and low PANDAR expression. Not all studies examined OS or other clinicopathological features. Eight studies investigated the association of PANDAR with OS, five studies with distance metastasis (DM), eight studies with lymph node metastasis (LNM), nine studies with tumor stage, and six studies with tumor size. According to the NOS scoring system, all included studies were of good quality (Table 2).

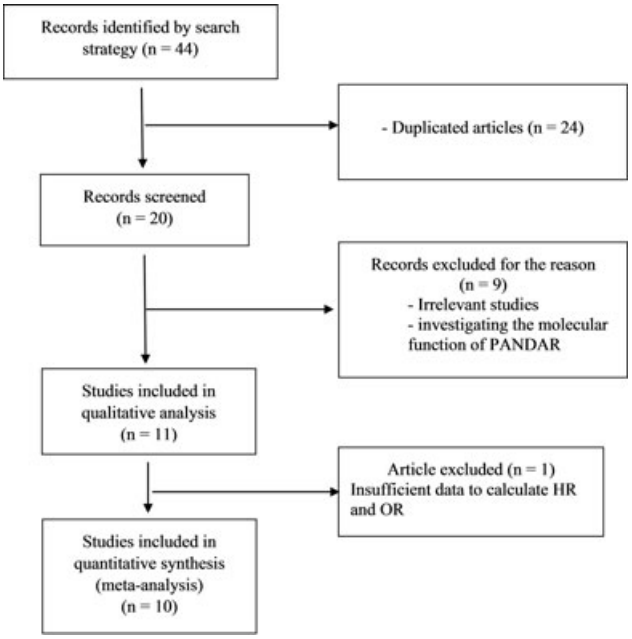

FIGURE 1 Flow diagram of study selection process. HR: hazard ratio; OR: odds ratio; PANDAR: promoter of CDKN1A antisense DNA damage activated RNA

3.2 | Association between PANDAR expression and OS

The association between PANDAR expression and the OS of different cancer types was reported in eight studies in a total of 1,145 patients. All these eight studies conducted multivariate analysis of OS, whereas only seven studies reported both multivariate and univariate analysis for OS. A significant association was observed between PANDAR and OS in patients with cancer in the univariate model (pooled HR 2.17; 95% CI, 1.10–4.30; $p = 0.026$) but not in the multivariate model (pooled HR 1.69; 95% CI, 0.93–3.09; $p = 0.085$) (Figure 2). Heterogeneity was significant in studies that examined the association between PANDAR and OS. Reflecting the presence of significant heterogeneity, sensitivity analysis was performed to explore the studies that affect the meta-results. Repeating the meta-analysis while omitting one study identified the study conducted by Han et al. (2015) as a source of heterogeneity. After excluding the Han study, the observed heterogeneity disappeared, but a significant association between PANDAR and OS was emerged both in multivariate and univariate analysis models (pooled HR 2.62; 95% CI, 1.98–3.47 and pooled HR 2.01; 95% CI, 1.17–3.44, respectively; Table 3). In addition, in meta-regression results, we did not find any evidence of covariates significantly affecting OS. These results suggested that patients with cancer with elevated expression of PANDAR might be correlated with a shorter OS. Therefore, upregulated PANDAR expression might be developed as an independent factor of OS among patients with cancer in China.

TABLE 1 Basic characteristics of the included studies

Study/year	Age (high/low)	Country	Tumor type	Histological grade (high/low)	Tumor size (high/low)	Sample size (n)	Male (high/low) Female (high/low)	TNM stage of tumor (high/low)	Preoperative treatment	Cutoff value	PANDAR expression						Survival analysis	HR (95% CI) (high/low)	Method
											High (n)			Low (n)					
											Total	LNM	DM	Total	LNM	DM			
Xu, Jiang et al. (2017)	<60 6/12 ≥ 60 28/16	China	ccRCC	G1-G2 18/12 G3-G4 16/16	–	62	22/17 12/11	I (13/17) II–IV (21/11)	No	Median	34	4	3	28	0	0	Univariate Multivariate	1.74 (1.07–5.66) 1.13, (1.08–5.12)	qRT-PCR
Xu, Tong et al. (2017)	<60 22/19 ≥60 18/8	China	CCA	Well 12/10 poor 28/17	–	67	19/10 21/17	I–II 5/10 III–IV 35/17	No	NA	40	32	12	27	12	9	Univariate Multivariate	2.228 (1.269–3.913) 1.830 (1.026–3.264)	qRT-PCR
X. Li et al. (2017)	<60 19/23 ≥60 32/28	China	CRC	Well/moderately 29/33 Poorly/undifferentiated 22/18	<5 cm 27/28 ≥5 cm 24/23	102	31/27 20/24	I–II 12/27 III–IV 39/24	No	Median	51	19		51	5		Multivariate	3.09 (0.84–7.89)	qRT-PCR
Zhan et al. (2016)	<60 14/6 ≥60 23/12	China	BC	G1 11/12 G2,G3 26/6	<3 cm 11/10 ≥3 cm 26/8	55	27/13 10/5	I–II 22/16 III–IV 15/2	NA	Mean	37	1	–	18	1	–	NP	NP	qRT-PCR
Jiang et al. (2017)	<60 6/8 ≥60 11/6	China	PDAC	Well/moderately 4/6 Poorly/undifferentiated 13/8	–	31	7/9 10/5	I–II 2/7 III–IV 15/7	No	NA	17	11	10	14	11	2	NP	NP	qRT-PCR
Lu et al. (2017)	<60 22/29 ≥60 40/33	China	CRC	Well 35/48 poor 27/14	<5 cm 33/42 ≥5 cm 29/13	124	39/36 23/26	I–II 14/32 III–IV 48/30	No	Median	62	42	17	62	30	11	Univariate Multivariate	3.641 (1.77–4.96) 3.532 (1.41–4.45)	qRT-PCR

(Continues)

TABLE 1 (Continued)

Study/year	Age (high/low)	Country	Tumor type	Histological grade (high/low)	Tumor size (high/low)	Sample size (n)	Male (high/low) Female (high/low)	TNM stage of tumor (high/low)	Preoperative treatment	Cutoff value	PANDAR expression						Survival analysis	HR (95% CI) (high/low)	Method
											High (n)			Low (n)					
											Total	LNM	DM	Total	LNM	DM			
Peng et al. (2015)	<60 206/104 ≥60 120/52	China	HCC	Well 247/124 poor 79/32	<5 cm 184/98 ≥5 cm 142/58	482	251/127 75/29	I–II 140/37 III–IV 186/119	No	NA	326	–	–	156	–	–	Univariate Multivariate	3.95 (1.46–17.24) 0.60 (0.28–1.19)	qRT-PCR
Han et al. (2015)	-	China	NSCLC	-	–	140	–	–	–	Mean	70	–	–	70	–	–	Univariate Multivariate	0.56 (0.39–0.80) 0.65 (0.46–0.92)	qRT-PCR
Ma et al. (2016)	<50 35/13 ≥50 38/14	China	GC	Well 48/20 poor 25/7	<5 cm 39/14 ≥5 cm 34/13	100	41/17 32/10	I–II 39/22 III–IV 34/5	NA	NA	73	58	5	27	15	1	Univariate Multivariate analysis	4.61 (1.54–13.83) 3.68 (1.13–12.06)	qRT-PCR
Huang et al. (2017)	≤40 20/18 >40 18/12	China	CC	Well 10/15 poor 28/15	<4 cm 13/22 ≥4 cm 25/8	68	0/0 38/30	I–II 12/18 III–IV 26/12	No	Average fold change = 4.7	38	22	–	30	14	–	Univariate Multivariate analysis	2.46 (1.18–5.14) 3.19 (1.09–4.87)	qRT-PCR

Note. BC: bladder cancer; CC: cervical cancer; CCA: cholangiocarcinoma; CRC: colorectal cancer; ccRCC: clear cell renal cell carcinoma; GC: gastric cancer; HCC: hepatocellular carcinoma; NSCLC: non-small-cell lung cance; PDAC: pancreatic ductal adenocarcinoma.

TABLE 2 Study quality according to the NOS scale

Study/year	Quality score	Adequate of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment	Nonresponse rate
Xu, Jiang et al. (2017)	7	*	*	*	NA	**	*	*	NA
X. Li et al. (2017)	7	*	*	*	NA	**	*	*	NA
Zhan et al. (2016)	7	*	*	*	NA	**	*	*	NA
Jiang et al. (2017)	7	*	*	*	NA	**	*	*	NA
Lu et al. (2017)	7	*	*	*	NA	**	*	*	NA
Peng and Fan 2015	7	*	*	*	NA	**	*	*	NA
Han et al. (2015)	7	*	*	*	NA	**	*	*	NA
Ma et al. (2016)	7	*	*	*	NA	**	*	*	NA
Huang et al. (2017)	7	*	*	*	NA	**	*	*	NA
Xu, Tong et al. (2017)	7	*	*	*	NA	**	*	*	NA

Note. The quality of the article is through the number of stars (*). All items get one star at most, except for two stars for comparability. NA: not available; NOS: Newcastle–Ottawa scale.

3.3 | Association between PANDAR expression and clinicopathological characteristics of cancer

To explore the association of PANDAR expression with clinicopathological features of patients with cancer, further meta-analyses were done for the studies that described tumor features including LMN, DM, histological grade, size of tumor, and tumor stage. The pooled ORs and 95% CIs of clinicopathological parameters in human solid tumors are shown in Table 3. Meta-results revealed that the high PANDAR expression was associated with positive LNM (OR = 2.57; 95% CI, 1.76–3.81; $p < 0.001$), larger tumor size (OR = 1.78; 95% CI, 1.35–2.35; $p = 0.018$), advanced TNM stage (OR = 2.90; 95% CI, 1.25–6.75; $p = 0.013$), poor histological grade (OR = 1.83; 95% CI, 1.36–2.47; $p < 0.001$), and older age (OR = 1.36; 95% CI, 1.05–1.76; $p = 0.021$) (Figures 3-6 and Table 3). However, other clinicopathological characteristics such as gender (OR = 0.964; 95% CI, 0.72–1.285; $p = 0.806$) and DM ($OR = 1.76$, 95% CI, 0.98–3.16, $p = 0.06$) showed no significant correlation with PANDAR expression (Table 3). These results were strengthened due to relatively little heterogeneity across studies.

3.4 | Sensitivity analysis and publication bias

Begg's funnel plot and Egger's test are usually used to detect the publication bias of selected articles. However, due to the limited number of studies included in this meta-analysis, only Egger's linear regression test was applied. Egger's test results provided no statistical evidence of publication bias across the included studies in all comparison models ($p > 0.05$). Moreover, sensitivity analysis, assessing the effect of each study on the overall results of meta-analysis, revealed no single study that altered the overall pooled ORs in all groups. This indicates the stability and robustness of the results.

4 | DISCUSSION

LncRNAs have recently attracted major research interest for their regulatory roles in nearly all aspects of cell biology including differentiation, development, and proliferation (Shi, Sun, Liu, Yao, & Song, 2013). Experimental data also revealed that abnormal expression of lncRNAs was associated with various human diseases, including cancer (Kwok & Tay, 2017; Lalevee & Feil, 2015; Wapinski & Chang, 2011). Notably, these lncRNAs have key roles in gene regulation and thus affect the progression of cancer via both oncogenic and tumor-suppressive pathways (Li, Meng, Bai, & Wang, 2016). Due to the progressive nature of most cancers towards metastasis including LMN and DM, the identification of novel biomarkers with better diagnostic and prognostic performance for accurate prediction of metastasis risk is vital for improving patient outcomes. In this case, lncRNAs with their critical roles in tumor development may represent a promising source of biomarkers to predict tumor metastasis and prognosis (Qi & Du, 2013). To date, several cancer-related lncRNAs have been identified, which may be

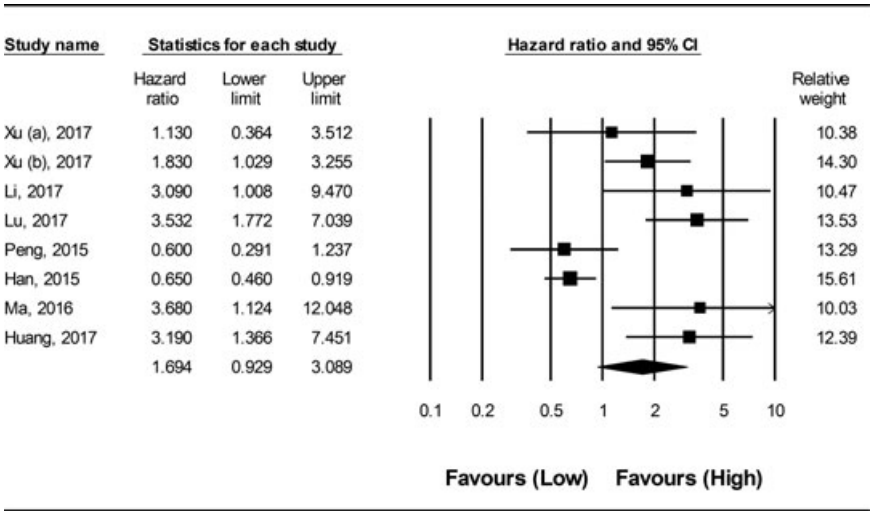

FIGURE 2 Forest plot showing the association between OS and PANDAR expression in different cancer types (multivariate model). OS: overall survival; PANDER: promoter of CDKN1A antisense DNA damage activated RNA

used as novel biomarkers for the prediction of tumor prognosis or therapeutic targets in human cancer (Fan, Fang et al., 2017; Fan, Ye at al., 2017; Liu, Pan, Xia, Qiu, & Zhu, 2016; Serghiou, Kyriakopoulou, & Ioannidis, 2016; Zhang et al., 2014; Zhu, Liu, Ma, & Zhang, 2015).

Previous studies have demonstrated that PANDAR, as a novel cancer-related lncRNA, is dysregulated in many types of cancer including NSCLC, CRC, CCA, osteosarcoma, renal cell carcinoma, breast cancer, thyroid cancer, and other types of cancer. The expression levels and the exact role of PANDAR in tumorigenesis in different types of cancer are still controversial and remain to be clarified. In two studies, PANDAR was found to function as a tumor suppressor factor by regulating Bcl-2, and low PANDAR expression to be associated with poor prognosis in patients with NSCLC (Han et al., 2015; Zhang et al., 2017). By contrast, some other studies demonstrated an oncogenic role for PANDAR in promoting tumorigenesis in various types of cancer where upregulated PANDAR was correlated with advanced tumor progression in bladder (Zhan et al., 2016), gastric (Ma et al., 2016), and breast cancers (Sang et al., 2016).

The interesting observation to be noted is the controversial results even for the same tissue type of cancer. In a study by them,

TABLE 3 Results of association between high levels of lincRNA PANDAR and characteristics of patients with cancers

Stratified analysis		No. of studies	No. of patients	Test of association: Pooled HR/OR (95% CI)	*p*-value	Test of heterogeneity: I^2 (%)	*p*-value	Model
Overall survival	Univariate	7	1,043	2.17 (1.10–4.30)	0.026	87.86	0.000	R
		6 (without Han, 2015)	903	2.62 (1.98–3.47)	0.000	2.38	0.401	F
	Multivariate	8	1,145	1.69 (0.93–3.09)	0.085	81.73	0.000	R
		7 (without Han, 2015)	1,005	2.01 (1.17–3.44)	0.011	64.75	0.009	R
Gender (male vs. female)		8	1,023	0.96 (0.72–1.29)	0.806	0.000	0.672	F
Age (≥60 vs.<60)		9	1,091	1.36 (1.05–1.76)	0.021	0.000	0.698	F
		7 (without Ma and Huang)	923	1.40 (1.05–1.85)	0.020	0.000	0.534	F
Tumor size (large vs. small)		6	931	1.79 (1.11–2.91)	0.018	56.22	0.044	R
		5 (without Zhan)	876	1.69 (1.01–2.86)	0.050	60.89	0.037	R
Histological grade (poorly and others vs. well and moderately)		9	1,091	1.78 (1.35–2.35)	0.000	9.42	0.357	F
		7 (without Xu (a) and Zhan)	974	1.83 (1.36–2.47)	0.000	0.000	0.846	F
		2 (Xu(a) and Zhan	117	1.72 (0.25–11.74)	0.578	83.24	0.150	R
LNM (yes vs. no)		8	609	2.59 (1.76–3.81)	0.000	33.38	0.162	F
DM (yes vs. no)		5	384	1.76 (0.98–3.16)	0.06	27.90	0.236	F
Tumor stage (III+IV vs. I+II)		9	1,091	2.90 (1.25–6.75)	0.013	86.25	0.000	R
		8 (without Peng)	609	3.66 (2.51–5.32)	0.000	0.000	0.983	F

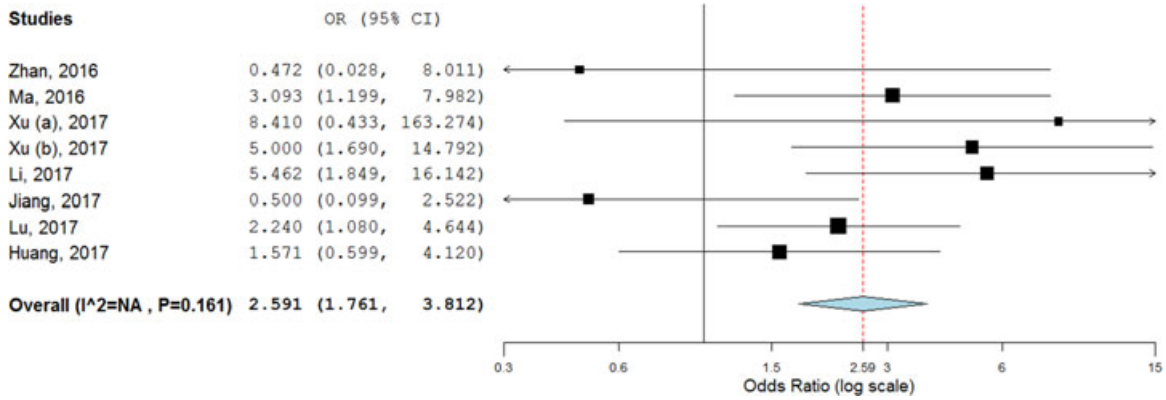

FIGURE 3 Forest plot for the association between LNM and PANDAR expression in different cancer types. LNM: lymph node metastasis; PANDER: promoter of CDKN1A antisense DNA damage activated RNA [Color figure can be viewed at wileyonlinelibrary.com]

Puvvula et al. (2014) found that PANDAR had a reduced level of expression in HCC. Also, Peng and Fan, (2015) revealed that PANDAR was overexpressed in HCC. The same results were found for the ccRCC. In the study conducted by Xu, Tong et al. (2017), PANDAR expression was significantly upregulated in tumor tissue, whereas Wu et al. (2016) uncovered a decreased level of PANDAR in serum of patients with ccRCC. These studies indicate that PANDAR's biological functions in human cancer are controversial.

Despite these controversial discussions, several research works have been done on understanding the biological function of PANDAR in several types of cancer. PANDAR knockdown in various cell lines exhibited contradictory conclusions. Few studies demonstrated that the silencing of PANDAR led to a significant decrease in cell proliferation and invasion and greater apoptosis (Peng & Fan, 2015; Sang et al., 2016; Xu, Jiang et al., 2017; Xu, Tong et al., 2017). Likewise, PANDAR overexpression has increased tumor cell proliferation in cell culture and also accelerated carcinogenesis in the xenograft tumor model (Peng et al., 2017). It has been proposed that this tumor-promoting activity of PANDAR may mediate through the transcriptional regulation of target genes involved in the cellular senescence-to-immortality transition (Peng et al., 2017; Puvvula et al., 2014; Sang et al., 2016). These results indicate that PANDAR has a crucial role in cell-fate decision beyond apoptosis. So, considering these conflicting reports, the underlying mechanisms regarding the role of PANDAR in human cancer remain largely unclear, and PANDAR may act as a common molecular biomarker. Therefore, this comprehensive meta-analysis was designed to explore the clinicopathological significance and actual prognostic value of PANDAR in patients with cancer.

Ten studies that met the requirements, comprising 1,231 patients with various types of cancer, were included and analyzed in our work. Our meta-analysis results showed that higher PANDAR expression might be indicative of advanced disease and poor prognosis in patients with cancer. Because there was a significant heterogeneity across the studies included, sensitivity analysis was performed to explore the source of heterogeneity. Accordingly, it was found that the Han study significantly affected the pooled OS, thereby excluded from OS analysis (Han et al., 2015). Combining HRs from Cox multivariate analyses revealed that PANDAR expression was an independent prognostic factor of OS in patients with cancer. It should be taken into account that due to significant correlation between low PANDAR expression and HCC cancer patient's prognosis in Han study, the prognostic value of low PANDAR expression in HCC might be of utmost importance. Furthermore, our results demonstrated that high PANDAR expression in tumor tissue was significantly correlated with LNM, tumor size, TNM stage, and histological grade. However, further studies on the possible relationship between PANDAR expression and DM are needed.

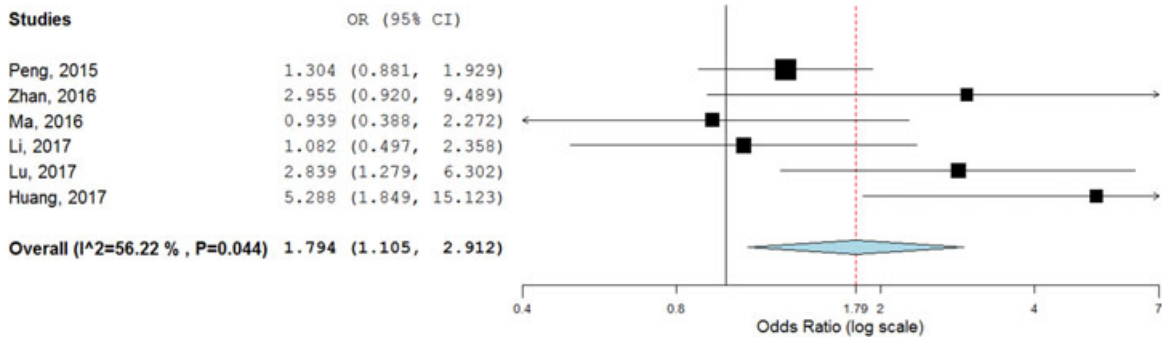

FIGURE 4 Forest plot for the association between tumor size and PANDAR expression in different cancer types. PANDER: promoter of CDKN1A antisense DNA damage activated RNA [Color figure can be viewed at wileyonlinelibrary.com]

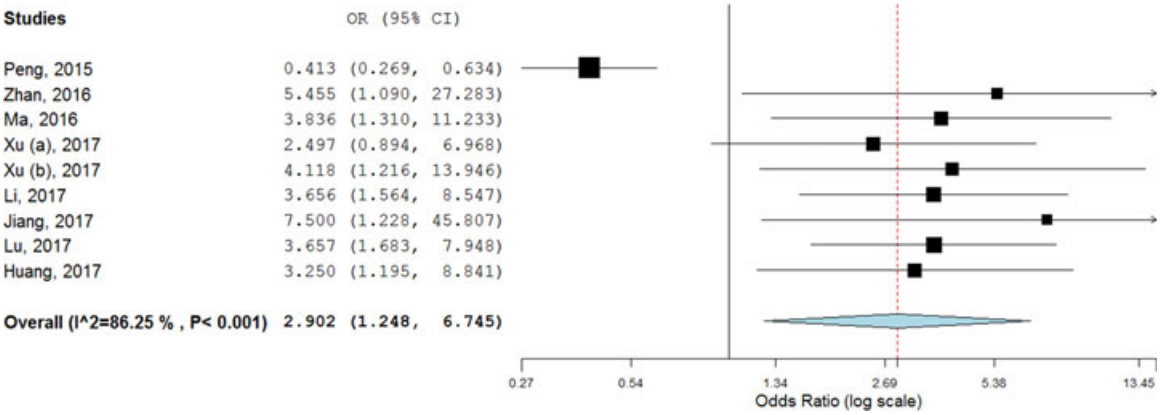

FIGURE 5 Forest plot showing the association between Tumor stage and PANDAR expression in different cancer types. PANDER: promoter of CDKN1A antisense DNA damage activated RNA [Color figure can be viewed at wileyonlinelibrary.com]

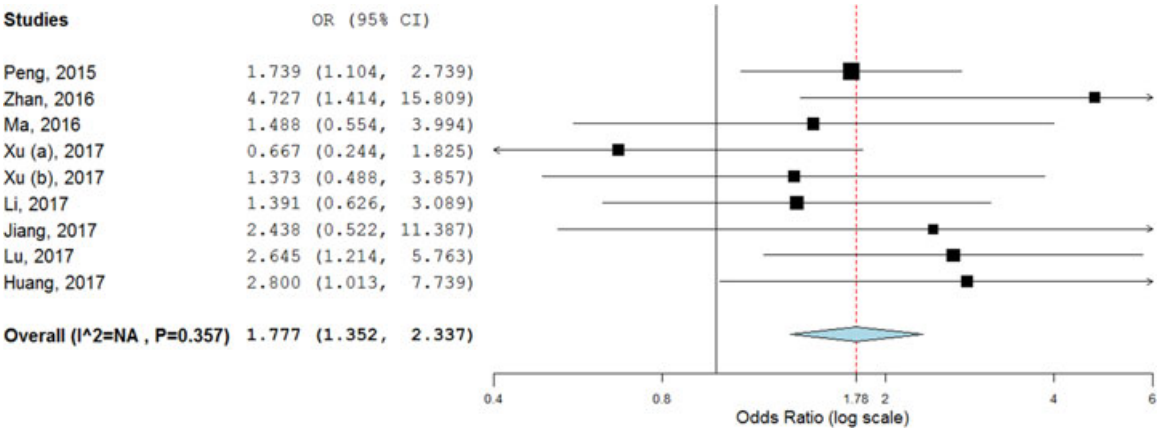

FIGURE 6 Forest plot for the association between histological grade and PANDAR expression in different cancer types. PANDAR: promoter of CDKN1A antisense DNA damage activated RNA [Color figure can be viewed at wileyonlinelibrary.com]

It should be noted that our study has some limitations. First, all included studies have been conducted in China, which limits the generalizability to some extent. Second, the sample size and the number of studies included in the meta-analysis were relatively small, which could have influenced the pooled results. Third, selection bias may exist in exclusion of studies due to a lack of pertinent information and language restriction. A bias may also exist in favor of published articles with positive results, and this type of publication bias may have led to overestimations in this meta-analysis. Forth, each study varied regarding the cutoff value for high and low PANDAR expression, also for other categories such as age, histological grade and size of the tumor. Finally, a difference in protocols for treatment after surgery in various studies might have a great impact on survival outcomes and thus resulted in some heterogeneity.

In conclusion, it is shown that high PANDAR expression is associated with poor OS in patients with different types of cancer. It is also correlated with cancer clinicopathological features, such as LNM, advanced TNM stage, tumor size, and histological grade. PANDAR expression may be used as a promising biomarker to predict prognosis and clinical pathology in patients with cancer. However, more studies in different populations with various ethnicities are required to achieve a more persuasive conclusion.

ACKNOWLEDGMENT

We thank for the financial support of this study provided by a Grant from the Mashhad University of Medical Sciences (No. 961403).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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How to cite this article: Mehrad-Majd H, Akhtari J, Haerian M-S, Ravanshad Y. Clinicopathological and prognostic value of lncRNA PANDAR expression in solid tumors: Evidence from a systematic review and meta-analysis. *J Cell Physiol*. 2019;234: 4206–4216. https://doi.org/10.1002/jcp.27179