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ORIGINAL ARTICLE

LncRNA PANDAR is a Novel Prognostic Biomarker in Patients with Cancer: a Meta-Analysis

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SUMMARY

Background: **Mounting evidence from recent studies has revealed the association of lncRNA PANDAR expression levels with outcomes in several types of cancer. However, inconsistent results have also been reported, which rationalized a meta-analysis of available data to analyze the prognostic value of lncRNA PANDAR.**
Methods: **From inception to May 26, 2018, electronic literature databases including PubMed (medline), the Cochrane Library, ScienceDirect, Springer, ISI Web of Knowledge, Wiley Online library, BioMed Central, and Embase were searched for literature collections. The hazard ratios (HR) with 95% confidence interval (95% CI) were utilized to calculate pooled effect size.**
Results: **A total of 1,132 cancer patients were enrolled in the present meta-analysis to assess the prognostic value of PANDAR in various carcinomas. Promoted PANDAR expression was demonstrated to significantly predict unfavorable OS (HR = 1.77, 95% CI: 1.12 - 2.80, p = 0.014) by the random effects model. According to the stratified analyses and meta-regression results, the heterogeneity of present analysis may be attributed to the differences of cancer resources. Furthermore, over-expression of PANDAR was revealed to be effectively predictive of cancer progression (HR = 1.70, 95% CI: 1.41 - 2.05, p < 0.00001) and LNM (HR = 1.71, 95% CI: 1.39 - 2.10, p < 0.00001).**
Conclusions: **The present findings indicate that increased PANDAR is associated with poor OS in patients with general carcinomas and may serve as a useful clinical prognostic biomarker.**
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KEY WORDS

cancer, prognosis, long non-coding RNA, PANDAR

INTRODUCTION

Carcinoma is a major health problem and the leading cause of mortality worldwide [1]. According to 2017 Cancer Statistics, an estimated 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States [2]. In the past few decades, the mechanisms underlying carcinogenesis and tumor progression have been widely investigated, while the molecular mechanisms still remain obscure and the therapy shows less effectiveness. Therefore, many researchers are devoted to identifying new clinical biomarkers for

the prognosis and targeted therapy of cancer patients [3-6].

The human genome sequencing project has revealed that 90% of the genome can be transcribed, but only less than 2% is subsequently translated, which means that the vast majority of genome undergoes transcription to various types of RNA species [7]. More and more evidence has shown that long non-coding RNAs (lncRNAs) were cancer-specific and function as oncogenes or tumor suppressors [8,9]. Their ability to regulate essential pathways for tumorigenesis and progression employs them as promising clinical biomarkers and therapeutic targets [10,11].

PANDAR (promoter of CDKN 1A antisense DNA damage activated RNA), which was first reported by Hung, underlies chromosomal instability and metastatic progression in various cancers [12].

Recently, PANDAR has been reported to be strikingly up-regulated in multiple cancer tissues and could serve as a promising biomarker to evaluate the prognosis of different tumors [13,14]. However, most studies evaluating the prognostic value of PANDAR in general cancers have been limited by controversial results and small sample sizes. Therefore, we performed a quantitative meta-analysis to assess the prognostic role of PANDAR in various cancers.

MATERIALS AND METHODS

Search strategy

Electronic databases including PubMed (medline), ScienceDirect, Springer, the Cochrane Library, Wiley Online library, BioMed Central, Embase, and ISI Web of Knowledge were comprehensively searched to identify relevant articles from inception to May 26, 2018. These studies were gathered using the following keywords in variably combinations: ("long non coding RNA-" or lnc RNA-,") and ("PANDAR" or "PANDA") and ("cancer" or "tumor") and ("prognosis" or "prognostic" or "metastasis" or "progression"). In addition, the previous reviews and reference lists of the relevant studies were also searched for further congruent articles.

Inclusion and exclusion criteria

The following criteria decided to which studies could be selected: 1) Patients with unambiguous diagnosis confirmed for cancer; 2) Appraisal of PANDAR in tissues or serum in the studies; 3) Studies with sufficient information to calculate HR or make a 2 x 2 contingency table.

Studies should be excluded if: 1) Literature does not refer to PANDAR; 2) Similar results from the same author, excluding earlier and smaller sample data; 3) Literature without two classifications of PANDAR expression levels for survival outcome; 4) Presentations without original data such as: talks, letters, reviews, correspondence, advice from experts, reports, editorials, basic research, animal experiments, and expert opinions.

Data extraction and Quality Assessment

The essential information extracted from identified articles was carefully completed and double-checked by two independent investigators (LYT and JRL). Any discrepancy was resolved by consulting with a third investigator (YYZ). The following information was collected from each individual article: (1) First author, publication year, tumor type, patient residency, follow-up time; (2) PANDAR assessment method and specimen resources; (3) Other information including: HR and 95% CI of PANDAR expression value for overall survival (OS), patient number for tumor metastasis or progression. If only Kaplan-Meier curves were provided in these articles, the essential index such as hazard ratio and 95% CI were extracted from the graphical plots following the published procedures [15,16].

Quality assessment

Following the critical review checklists proposed by MOOSE and PRISMA, the present analysis was systematically assessed for the quality of all eligible studies (Table S1 and S2). The quality assessment was constructed on the following points: (I) sufficient description of the cancer. (II) clear introduction of study design. (III) good description of PANDAR measurement and cutoff value. (IV) good description of tumor outcomes. (V) sufficient period of follow-up time. All points should be mentioned from the collected articles.

Statistical analysis

All data analysis was measured by Review Manage Software (RevMan 5.3) and STATA 12.0 (Stata Corporation). The value of HR and 95% confidence interval were calculated based on the impact of PANDAR levels on the prognosis and metastasis of cancer patients. Heterogeneity was defined as the value of I^2 statistics. The fixed-effects model was used to evaluate the connection between PANDAR levels with overall survival or metastasis when there was no obvious heterogeneity among the included studies ($I^2 < 50\%$) [17-19]. Publication bias was evaluated by constructing a funnel plot and a Begg's linear test. Individual study was assessed by sensitivity analysis.

RESULTS

Screening of the literature

The processes of literature screening and study selection is presented as Figure 1. After preliminary searching of electronic databases, 282 relevant articles concerning PANDAR and clinical outcomes were retrieved. All of these articles mentioned that PANDAR participated in carcinogenesis or tumor progression. After manually reviewing the titles and abstracts, 257 articles were removed because they were review articles, letters, basic research, or studies not related to the current analysis. Full texts and reference lists of all of the eligible articles were further carefully checked by two authors, and

Table 1. Summary of the eight included studies.

Study	Origin of population	Study design	Disease	n	Stage	Detection method	Survival analysis	Metastasis analysis	Hazard ratios	Follow-up months
Han 2015 [20]	China	R	NSCLC	140	I/II, II/IV	qRT-PCR	OS	NA	HR/K-M	60
Peng 2015 [21]	China	R	HCC	482	I/II, II/IV	qRT-PCR	OS	NA	HR/K-M	60
Lu 2016 [22]	China	R	CRC	124	I/II, II/IV	qRT-PCR	OS	LNM	HR/K-M	60
Ma 2016 [23]	China	R	GC	100	I/II, II/IV	qRT-PCR	OS/DFS	LNM	HR/K-M	36
Li 2017 [24]	China	R	CRC	102	I/II, II/IV	qRT-PCR	OS	LNM	HR/K-M	60
Xu 2017 [25]	China	R	ccRCC	62	I/II, II/IV	qRT-PCR	OS	LNM	HR/K-M	40
Xu 2017 [26]	China	R	CCA	67	I/II, II/IV	qRT-PCR	OS	LNM	HR/K-M	60
Zhan 2016 [27]	China	R	BC	55	I/II, II/IV	qRT-PCR	NA	LNM	NA	NA

Study design is described as retrospective (R), NSCLC - non-small cell lung cancer, HCC - hepatocellular carcinoma, CRC - colorectal cancer, GC - gastric cancer, ccRCC - clear cell renal cell carcinoma, CCA - cholangiocarcinoma, BC - breast cancer, OS - overall survival, DFS - disease-free survival, LNM - lymph node metastasis.

Table 2. Characteristics of studies included in the lymph node metastasis analysis.

Study	Year	No. of patients	Method	Cutoff	PANDAR high		PANDAR low	
					Metastasis	Total	Metastasis	Total
Lu [22]	2016	124	qRT-PCR	median	42	62	30	62
Ma [23]	2016	100	qRT-PCR	median	58	73	15	27
Li [24]	2017	102	qRT-PCR	median	19	51	5	51
Xu [25]	2017	62	qRT-PCR	median	4	34	0	28
Xu [26]	2017	67	qRT-PCR	median	32	40	12	27
Zhan [27]	2016	55	qRT-PCR	median	1	17	1	38

Table 3. Characteristics of studies included in the tumor progression analysis.

Study	Year	Number	Method	Cutoff	III - IV		I - II	
					PANDAR high	Total	PANDAR high	Total
					Event	Total	Event	Total
Lu [22]	2016	124	qRT-PCR	median	48	78	14	46
Ma [23]	2016	100	qRT-PCR	median	34	39	39	61
Li [24]	2017	102	qRT-PCR	median	39	63	12	39
Xu [26]	2017	67	qRT-PCR	NA	35	52	5	15
Zhan [27]	2016	55	qRT-PCR	median	15	17	22	38

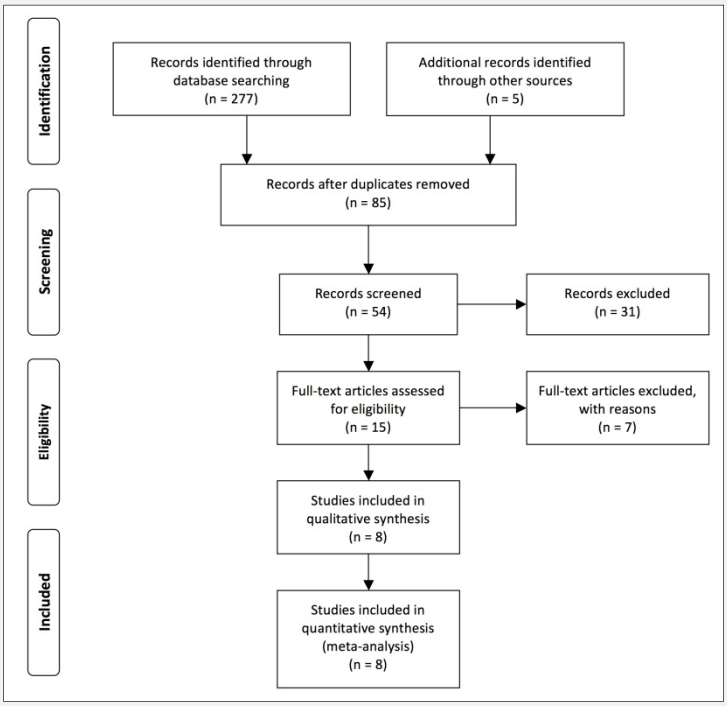

Figure 1. Flow diagram of the study search and selection process.

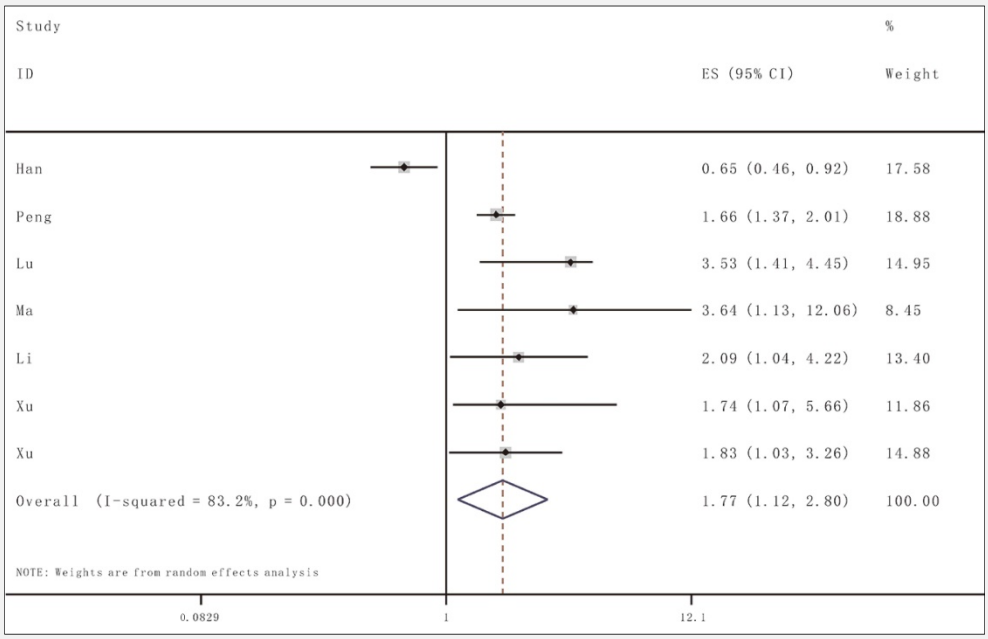

Figure 2. Forest plot for the association between PANDAR expression levels with overall survival (OS).

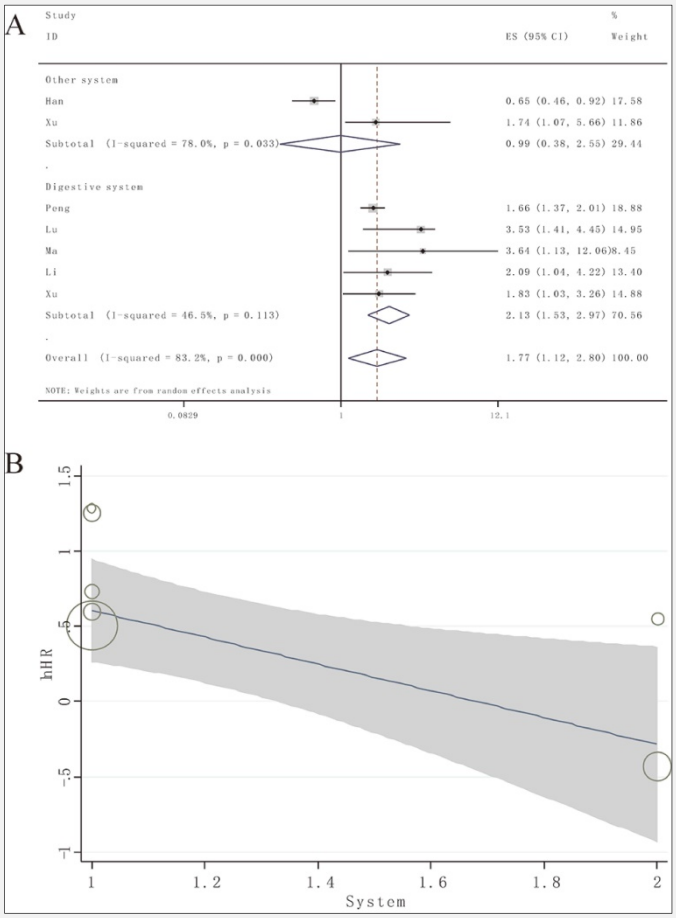

Figure 3. Stratified analyses and meta-regression analysis for the association between PANDAR expression with overall survival (OS).

(A) Subgroup analysis of HRs of OS by factor of cancer resources. (B) Meta regression analysis for assessment of the heterogeneity scores. Variable of suspected heterogeneity was cancer resources.

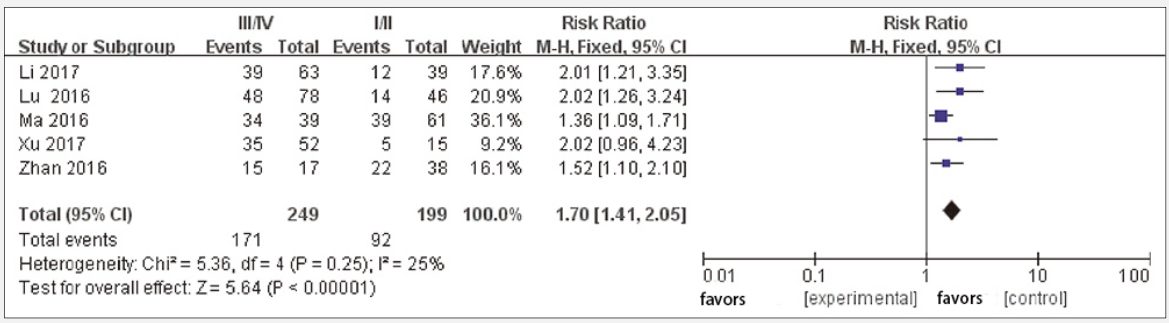

Figure 4. Forest plot for the association between PANDAR expression with TNM stage (III/IV vs. I/II).

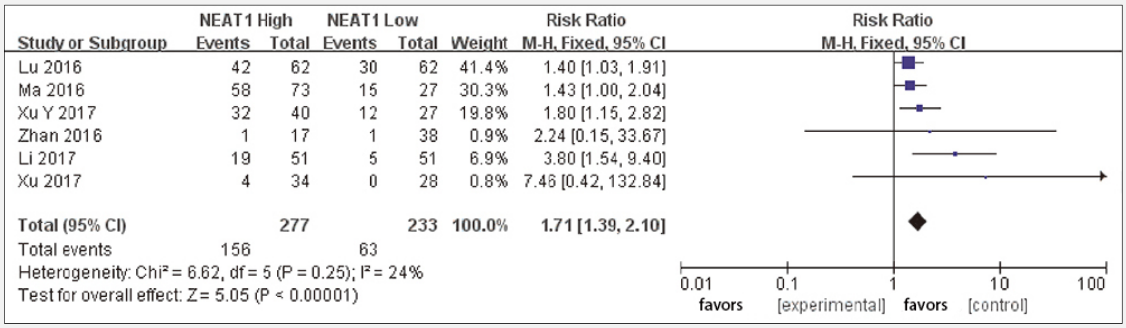

Figure 5. Forest plot for the association between PANDAR expression with lymph node metastasis.

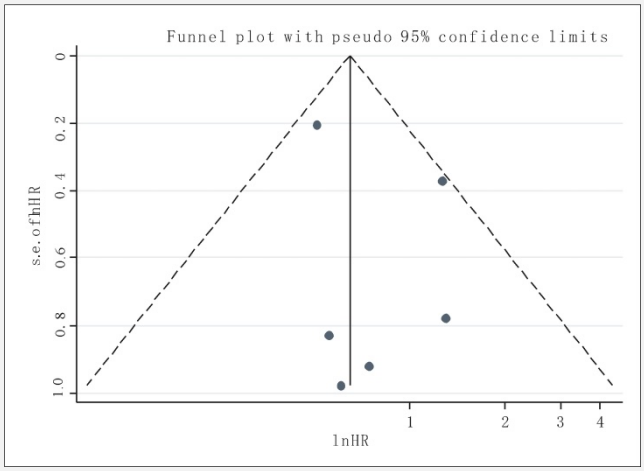

Figure 6. Funnel plot of the publication bias for overall survival.

17 articles were then excluded because the survival data could not be applied in the study. Finally, 8 articles were involved in the present analysis.

Characteristics of the analyzed articles

The main features and basic information of included literature were summarized in Table 1 [20-27]. All studies were retrospective and examined the expression of PANDAR in cancerous tissue. A total of 1,132 patients were divided into high or low PANDAR group according to the detection results with median applied for cut-off value in most studies. The enrolled articles were from China and related to seven kinds of carcinoma, including non-small cell lung cancer, hepatocellular carcinoma, colorectal cancer, gastric cancer, clear cell renal cell carcinoma, cholangiocarcinoma, and breast cancer.

Main results

As presented in Figure 2, Higgins I-squared statistic among included studies for OS was 83.2%. A random effects model (Inverse Variance method) was utilized to analyze the pooled HR and its 95% CI in the presence of between-study heterogeneity. We found that high expression levels of PANDAR may be associated with unfavorable OS outcome in various human cancers, with the pooled HR of 1.77 (95% CI: 1.12 - 2.80, p = 0.014) regardless the resources of cancer (Figure 2).

Afterwards the stratified analyses and meta-regression

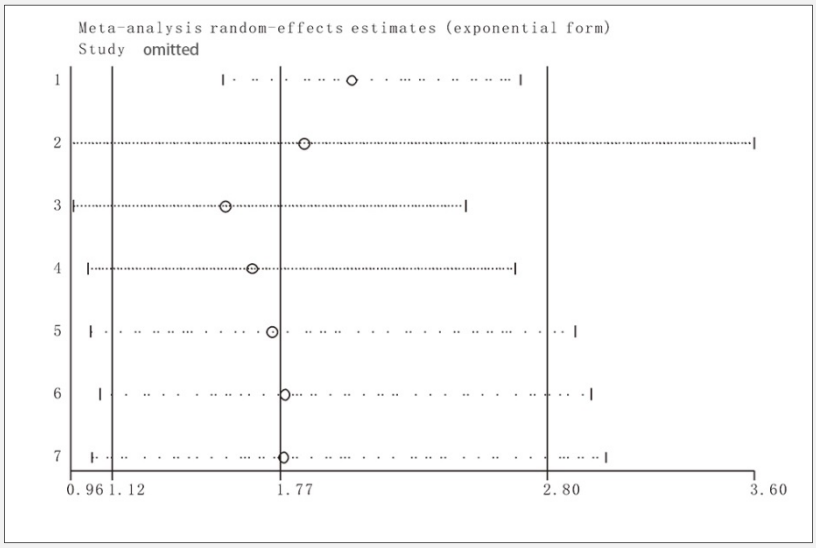

Figure 7. Sensitivity analyses of studies concerning PA NDAR and overall survival.

models were performed by factor of cancer resources to specify the source of the significant heterogeneity. Subgroup analysis suggested that promoted PANDAR levels could be associated with worse outcome in digestive system (HR = 2.13, 95% CI: 1.53 - 2.97, $p < 0.0001$) (Figure 3A). No significant heterogeneity was presented in digestive system carcinomas during stratified analyses. Subsequently, meta-regression results revealed that the differences of cancer resources was a significant factor for the heterogeneity of the primary results ($p = 0.021$) (Figure 3B).

Next, the prognostic role of PANDAR with metastasis and progression was further explored in various carcinomas. Figure 4 and 5 represented the forest plots of the pooled articles assessing the prognostic value of PANDAR expression levels on tumor stage and lymph node metastasis. Elevated PANDAR manifested itself as inclined to lymph node metastasis (LNM) (HR = 1.71, 95% CI: 1.39 - 2.10, $p < 0.00001$) and tumor progression (HR = 1.70, 95% CI: 1.41 - 2.05, $p < 0.00001$), respectively. Characteristics of articles included in the LNM and TNM stage analysis were presented in Table 2 and 3.

Publication bias

Subsequently, publication bias of the pooled articles was evaluated by funnel assay and Egger's test. $p < 0.05$ indicates the presence of publication bias. Figure 6 exposed a nearly symmetrical funnel plot and the results of Egger's test was 0.553 for OS of all enrolled articles, indicating that there was no significant publication bias in the present meta-analysis.

Sensitivity analysis

Finally, the results of sensitivity analysis suggested that the differences between studies may not induce our conclusions instability (Figure 7).

DISCUSSION

Previous research supposed that lncRNAs were transcriptional noise because most lack protein coding capability [8,28]. Recent studies have demonstrated that lncRNAs are involved in tumor development and progression by regulating cell proliferation, differentiation, migration, invasion, and apoptosis [29,30]. Along with the rapid development of high-throughput sequencing techniques, tremendous achievements had been made especially in early diagnostic and accurate prognostic biomarkers as well as targeted therapy for cancer patients [31,32].

After Hung et al. discovered that PANDAR was induced in a p53-dependent manner after DNA damage limiting the expression of pro-apoptotic genes, the molecular mechanism that underlies tumorigenesis and progression has gradually been elucidated [12]. First, the crosstalk between PANDAR and pivotal transcription factors or signaling pathways revealed the biological mechanism of PANDAR in modulation of diverse cellular processes. Several experiments demonstrated that PANDAR interacts with the transcription factor NF-YA, consequently promoting tumorigenesis and metastatic progresses of multiple cancers [12]. Besides, PANDAR exerts potential regulatory function in cell

cycle processes. Recent studies manifested that PANDAR contributes to tumor progression through regulatory function in G1/S transition by suppressing p16 (INK4A) expression [33]. Furthermore, knockdown of PANDAR expression activated apoptosis signaling by receptor-mediated and mitochondrial pathways and correlated with the regulation of caspase-3, caspase-9, Bax, and Bcl-2 [26]. Additionally, PANDAR was found to repress the transcription of senescence-promoting genes that might be mediated by interacting with polycomb repressive complexes (PRC1 and PRC2) [34]. Accumulating evidence suggested that elevated PANDAR was considered as an effective worse biomarker in the prognosis of different cancers, such as cholangiocarcinoma, breast cancer, colorectal cancer, gastric cancer, clear cell renal cell carcinoma, and hepatocellular carcinoma [21-27]. However, Han et al. found that low expression of PANDAR predicts a poor prognosis in NSCLC by affecting cell apoptosis by regulating Bcl-2 [20]. Since the prognostic values of PANDAR in various cancers still remains controversial, the present meta-analysis was conducted to investigate the potential prognostic value of PANDAR in various carcinomas. A total of eight articles including 1,132 cancer patients were enrolled in the present analysis, and the results suggest that promoted PANDAR levels effectively predict worse prognosis, tumor progression, and LNM in patients with different types of cancer. The results showed a pooled HR was 1.77 (95% CI: 1.12 - 2.80, $p = 0.014$), 1.70 (95% CI: 1.41 - 2.05, $p < 0.0001$) and 1.71 (95% CI: 1.39 - 2.10, $p < 0.0001$) for OS, tumor progression and LNM, respectively.

To our knowledge, the current study is the first meta-analysis in assessing the expression levels of PANDAR in the prognosis of different carcinomas. Yet several limitations should be considered in its application. To start with, the cutoff value of PANDAR expression is ambiguous. Although most of the studies have defined a median as the cutoff of PANDAR levels, the accurate values may be different in these studies. In addition, some of the HR are estimated by reconstructing survival curves rather than directly obtaining them from the primary studies, which may contaminate our conclusions to a certain extent. Finally, the number of involved articles is relatively small, which leads to insufficient studies to be conducted in subgroup analyses.

In summary, our study has provided convincing evidence supporting over-expression of PANDAR was effective in predicting unfavorable prognosis in different kinds of cancer patients. Given the limitations described above, more clinical studies with specific cutoff values are necessary to focus on the relationship between PANDAR levels and cancer patient prognosis.

CONCLUSION

The present findings indicate that increased PANDAR is associated with poor OS in patients with general carcinomas and may serve as a useful clinical prognostic biomarker.

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Declaration of Interest:
All the authors declare there is no conflict of interest in this research.

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