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Review

Clinical usefulness of gastric adenocarcinoma predictive long intergenic noncoding RNA in human malignancies: A meta-analysis

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ABSTRACT

Background: Gastric adenocarcinoma predictive long intergenic noncoding RNA (GAPLINC), a newly identified lincRNA, was reported to be aberrantly expressed in several kinds of cancers and played an important role in tumor progression. This study was performed to systematically estimate the prognostic role of GAPLINC expression in cancer patients.

Methods: Several electronic databases, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wan Fang databases were searched for potential literature (updated to September 3, 2018). The pooled hazard ratios (HRs), odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with a fixed effects model using Stata12.0 software.

Results: The pooled results indicated that elevated GAPLINC was significantly related to shorter overall survival (OS) (HR = 1.66, 95%CI: 1.40–1.93, $p < 0.001$), which was further validated using The Cancer Genome Atlas (TCGA) dataset. Furthermore, high GAPLINC expression was correlated with higher tumor grade (OR = 1.91, 95%CI: 1.35–2.70, $p < 0.001$), positive lymph node metastasis (OR = 2.80, 95%CI: 1.69–4.64, $p < 0.001$), deeper infiltration depth (OR = 2.44, 95%CI: 1.43–4.17, $p = 0.001$) and advanced clinical stage (OR = 3.54, 95%CI: 2.13–5.88, $p < 0.001$).

Conclusions: Our results suggest that elevated GAPLINC was associated with poor clinical outcomes and might serve as a promising prognostic biomarker in cancer survivors.

1. Introduction

Nowadays, the malignant tumor has become one of the great threat to public health, the morbidity and mortality of malignant tumor have been increased year by year [1–3]. Despite recent progress in the diagnosis and treatment of malignant tumor, curative effect and prognosis were not significantly improved [4–7]. Therefore, more and more researchers are concentrating on exploring applicable therapeutic and prognostic targets to improve the curative effect and tumor prognosis.

Long non-coding RNAs (lncRNAs) are one kind of RNAs without protein-coding capacity, Integrative genomic studies have found that human being has over 10,000 long non-coding RNAs [8–11], they are more than 200 nucleotides in length [12], some of them have been confirmed to be related to tumorigenesis and cancer progression, and increasing studies revealed that cancer-related lncRNAs could play the role of oncogene or tumor-suppressing factor [13–15]. Furthermore, accumulating evidence suggests cancer-related lncRNAs could affect cancer development and progression at almost all stages of gene expression [16].

Gastric adenocarcinoma predictive long intergenic noncoding RNA (GAPLINC) is a latest identified 924-bp non-coding RNA, it was first reported to be associated with cancer progression by regulating the expression of CD44 oncogene which acts as a molecular sponge for miR-211-3p in gastric cancer [17]. So far it has been founded to be upregulated and play the role of an oncogene in various types of cancer, such as gastric cancer (GC), colorectal cancer (CRC), and hepatocellular carcinoma (HCC) [17–20]. And more studies have indicated the potential prognostic value of GAPLINC in several kinds of human cancers. However, the limitation of specimen capacity or the difference of research method among these individual studies may result in inaccurate consequences, we need to use all GAPLINC-related published data to launch this meta-analysis so that we can make a synthetic assessment for its association with prognostic value in human solid cancers.

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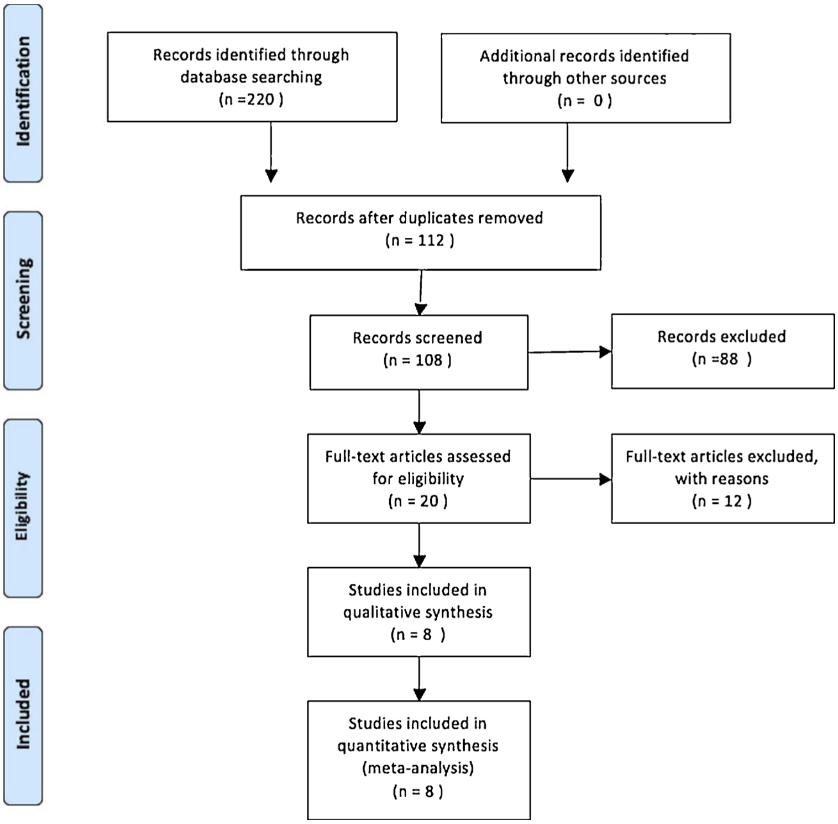

Fig. 1. The literature retrieval procedure of eligible studies.

2. Material and methods

2.1. Search strategy

The literature relevant to the clinical values of GAPLINC in human tumors was searched in the following databases: Web of Science, Embase, PubMed, China National Knowledge Infrastructure (CNKI), Wan Fang bases through September 3, 2018. The key words for search included the following: “GAPLINC”, “LINC01540”, “gastric adenocarcinoma predictive long intergenic noncoding RNA”, “long intergenic non-coding RNA GAPLINC”, “lincRNA GAPLINC”, “carcinoma”, “cancer”, “tumor” and “neoplasm”. The reference lists of relevant articles were also reviewed for additional potentially eligible studies.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows:

1) the expression of GAPLINC in human tumor tissues was measured,
2) cancer patients were divided into two groups based on high and low expression levels of GAPLINC,
3) the associations of GAPLINC expression with overall survival or clinicopathological features were described,
4) HRs with 95%CIs were reported or sufficient data were available for the computation.

Exclusion criteria were as follows:

1) articles that were duplicated or unpublished,
2) papers that were reviews, editorials, letters, expert opinions, and case reports,
3) studies without useful information about survival outcomes.

2.3. Data extraction and quality assessment

The following information was extracted: first author's name, year of publication, country, cancer type, sample size, the detection method of GAPLINC, cutoff values, endpoints, follow-up time. In addition, the clinicopathological parameters also extracted from eligible studies, including gender distribution, tumor differentiation, infiltration depth, lymph node metastasis, clinical stage.

For cancer prognosis, HRs and its corresponding 95%CIs were extracted directly from studies that provided with multivariate analyses, otherwise, the Engauge Digitizer (http://digitizer.sourceforge.net/) software was applied to extract them from Kaplan–Meier curves as described [21–23].

In this study, Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the qualities of the selected studies, each appraised study got a score between 0 and 9, NOS scores of 1–3, 4–6 and 7–9 were defined as low-, intermediate- and high-quality studies, respectively.

2.4. Public data and tools

In order to further assess the prognostic values of GAPLINC in various different human tumors, a free online database, the Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/index.html) was used. This database has a large of RNA sequencing expression data of tumors and normal samples from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects. In this study, we used the GEPIA database to show the expression level of GAPLINC in other cancer types and further analyze its correlation with overall survival (OS) in TCGA dataset. The median expression was the group cutoff, one-way ANOVA was used for differential expression analysis, and the Kaplan–Meier plots were used for survival analysis.

2.5. Statistical analyses

The Stata SE12.0 software was applied to perform all statistical analyses. HRs and 95%CIs were calculated to assess the correlation between GAPLINC and OS, and ORs and 95%CIs were used to explore the relationship between GAPLINC and the clinicopathological characteristics. A P-value from the Chi-square test and I^2 value derived from the Q test were used to determine the heterogeneity among studies. The fixed-effects model was used if no obvious heterogeneity was observed across studies ($I^2 < 50\%$ or $P > 0.05$). Visual plots and Begg's test /Egger's test were used to estimate the publication bias. The sensitivity analysis was used to assess the robustness of the combined results. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of eligible studies

The literature retrieval procedure was shown in Fig. 1. Finally, a total of 8 cohort studies published between 2014–2018 were considered to be eligible and selected for this meta-analysis [17–20,24–27].

All those eight elected studies counted 943 patients with mean sample-size of 117.9, with a range from 33 to 274. Among them, seven studies including 879 patients presented data regarding the association between GAPLINC expression and OS, and the human tumors that were included in this meta-analysis were derived from the following six cancer types: gastric cancer (GC), colorectal cancer (CRC), osteosarcoma, hepatocellular carcinoma (HCC), perihilar cholangiocarcinoma (PHCC) and bladder cancer (BC). All primary cancer tissues and adjacent non-tumor tissue samples were collected from patients in China. The expression of GAPLINC was measured by qRT-PCR in six studies and ISH in two studies. GAPLINC expression was found to be up-regulated in 47.1% to 59.4% tumor tissues. All these articles were written in English and with good-quality (NOS ranged from 5 to 8, mean: 6.63). The main characteristics of the eight identified studies are shown in Table 1.

3.2. Results of the meta-analysis

3.2.1. GAPLINC expression and OS

For calculating the pooled HR and 95%CI for the association between GAPLINC expression and overall survival (OS), the fixed-effects model was applied for no significant heterogeneity existed among studies ($P_{het} = 0.600$, $I^2 = 0.0\%$). As shown in Fig. 2, the pooled results revealed that enforced GAPLINC expression was associated with poor OS in various cancers (HR = 1.66, 95%CI: 1.40–1.93, $p < 0.001$).

Subsequently, we performed subgroup analyses according to sample size and detection method to evaluate the prognostic role of GAPLINC in cancers. As shown in Table 2, high expression of GAPLINC was significantly associated with poor OS when detected using ISH or qRT-PCR as well as in groups with larger than or small than 120.

3.2.2. GAPLINC and clinicopathological features

The clinicopathological parameters collected from the eligible studies are presented in Table S1. The pooled ORs of the associations between increased GAPLINC expression and the clinicopathological features are summarized in Fig. 3. It showed that there was no significant correlation of elevated GAPLINC expression with gender (OR = 1.21, 95%CI: 0.88–1.64, $p = 0.238$). While elevated GAPLINC was significantly correlated with higher tumor grade (OR = 1.91, 95%CI: 1.35–2.70, $p < 0.001$), and the patients with high expression of GAPLINC tend to have lymph node metastasis (OR = 2.80, 95%CI: 1.69–4.64, $p < 0.001$), deeper infiltration depth (OR = 2.44, 95%CI: 1.43–4.17, $p = 0.001$) and advanced clinical stage (OR = 3.54, 95%CI: 2.13–5.88, $p < 0.001$).

Table 1
Characteristics of included studies.

First author	Year	Disease type	Sample size	Percentage of HE	Clinical stage or grade	Judging for HE	Detection method	Endpoints	Follow-up	HR statistics	NOS
Hu Y	2014	GC	90	50%	I-IV	median expression	ISH	OS	≥ 5 years	Reported	7
Liu L	2016	GC	33	48.5%	NA	the ratios of expressions in tissues (2.03)	qRT-PCR	OS	≥ 5 years	Survival curve	6
Zhang M	2016	CRC	64	50%	I-IV	median expression	qRT-PCR	NR	NR	NR	5
Wang HK	2017	HCC	274	47.1%	I-IV	median expression	qRT-PCR	OS	≥ 5 years	Reported	8
Wang XP	2018	PHCC	96	59.4%	I-IV	ROC curve (3.10)	qRT-PCR	OS	≥ 5 years	Reported	6
Yang P	2016	CRC	180	47.2%	1-3 (Grade)	median immunoreactive score ≥6	ISH	OS	≥ 5 years	Reported	8
Zheng Z	2018	BC	80	50%	low-high (Grade)	cut-off value	qRT-PCR	OS	≥ 5 years	Survival curve	6
Liao S	2018	osteosarcoma	126	50%	I-III	median expression	qRT-PCR	OS	≥ 5 years	Reported	7

GC: gastric cancer; HCC: hepatocellular carcinoma; PHCC: perihilar cholangiocarcinoma; CRC: colorectal cancer; BC: bladder cancer; ISH: in situ hybridization; qRT-PCR: quantitative real-time polymerase chain reaction; HE: high expression; ROC: receiver operating characteristic; OS: overall survival, NR: not reported.

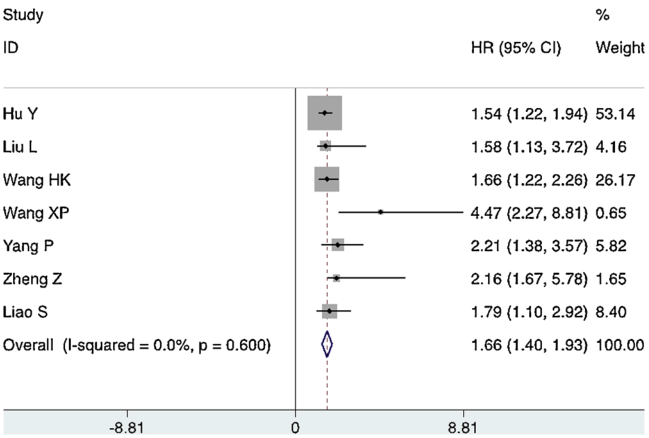

Fig. 2. Forest plot describing the relationship between the high expression of GAPLINC and OS.

Table 2
Subgroup analysis of the association between GAPLINC expression and OS.

Subgroup factor	Divided standard	No. of studies	Pooled HR (95%CI)	*p*-value	Heterogeneity	
					I^2 (%)	P_{het}
Sample size	≥ 120	3	1.77(1.35-2.18)	< 0.001	0.0	0.668
	< 120	4	1.59(1.25-1.93)	< 0.001	10.5	0.340
Detection method	ISH	2	1.61(1.26-1.95)	< 0.001	24.0	0.251
	qRT-PCR	5	1.74(1.33-2.16)	< 0.001	0.0	0.558

3.2.3. *Publication bias*

Visible plots, as well as Begg's and Egger's test, was used to evaluate the publication bias for OS. The Begg's and Egger's plots are shown in Fig. 4, and the P-values of Begg's and Egger's test were 0.072 and 0.064, respectively. These results suggested that there was no significant publication bias in the meta-analysis.

3.2.4. *Sensitivity analysis*

As presented in Fig. 5, the pooled HR was not obviously affected after omitting any individual study.

3.3. *GAPLINC expression level in different cancer types*

In order to understand the expression level of GAPLINC in different cancer types, the GEPIA was used to analyze the expression patterns of GAPLINC in different cancer types, one-way ANOVA was used for differential expression analysis. The results indicated that the expression of GAPLINC was higher in the tumor tissues than the corresponding normal tissues in colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), pancreatic adenocarcinoma (PAAD), skin cutaneous melanoma (SKCM) and uterine carcinosarcoma (UCS) (Fig. 6).

3.4. *Validation of the prognostic value of GAPLINC in human tumors*

The TCGA datasets using GEPIA were applied for the validation of the prognostic significance of GAPLINC expression in human tumors. As shown in Fig. 7, a total of 9502 patients were grouped into high or low categories according to median expression of GAPLINC. These results confirmed that the high expression of GAPLINC was significantly associated with poor prognosis in various malignancies.

4. Discussion

Recently, novel prognostic markers have attracted much attention. Accumulating evidence has shown that lncRNAs are associated with tumorigenesis and progression [28–30]. GAPLINC, which located in the human chromosome 18p11.31 [27], is a novel identified lncRNA. Multiple studies have reported that abnormal expression of lncRNA GAPLINC was associated with poor clinical outcomes and GAPLINC could play the role of potential prognostic biomarker across a variety of cancers. However, there was no consensus on the prognostic value of

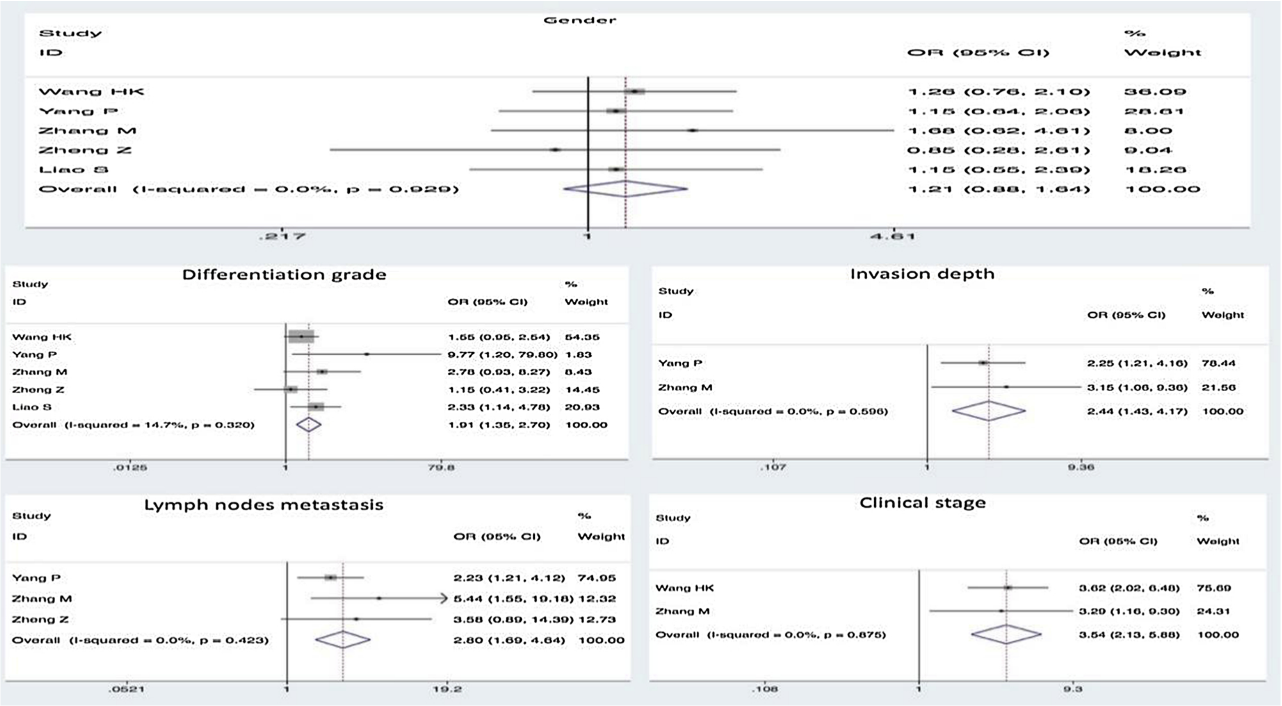

Fig. 3. Forest plot describing the relationship between increased GAPLINC expression and clinicopathological features.

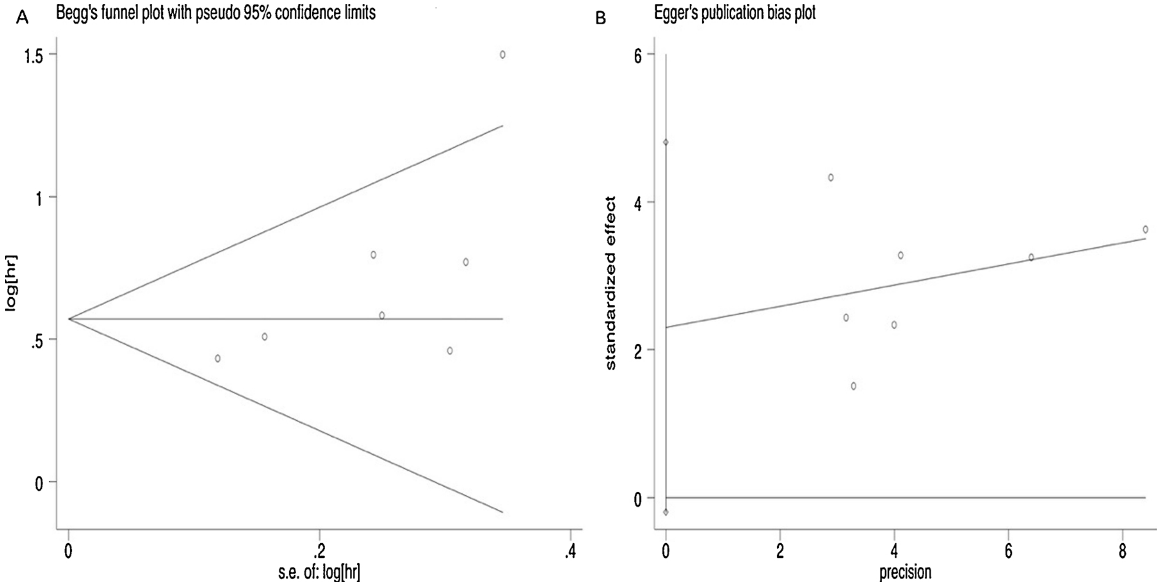

Fig. 4. Begg's funnel plot (A) and Egger's plot (B) of publication bias for OS.

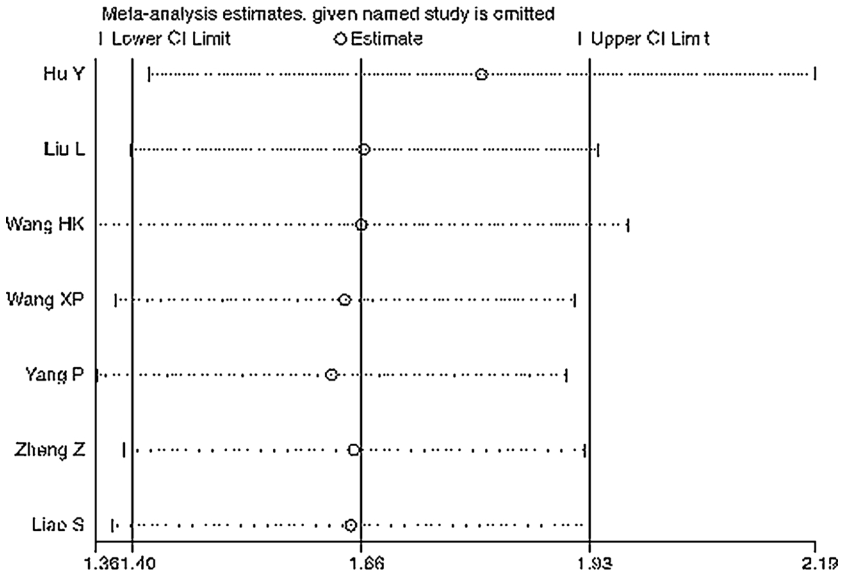

Fig. 5. Sensitivity analysis of the association between GAPLINC expression and OS.

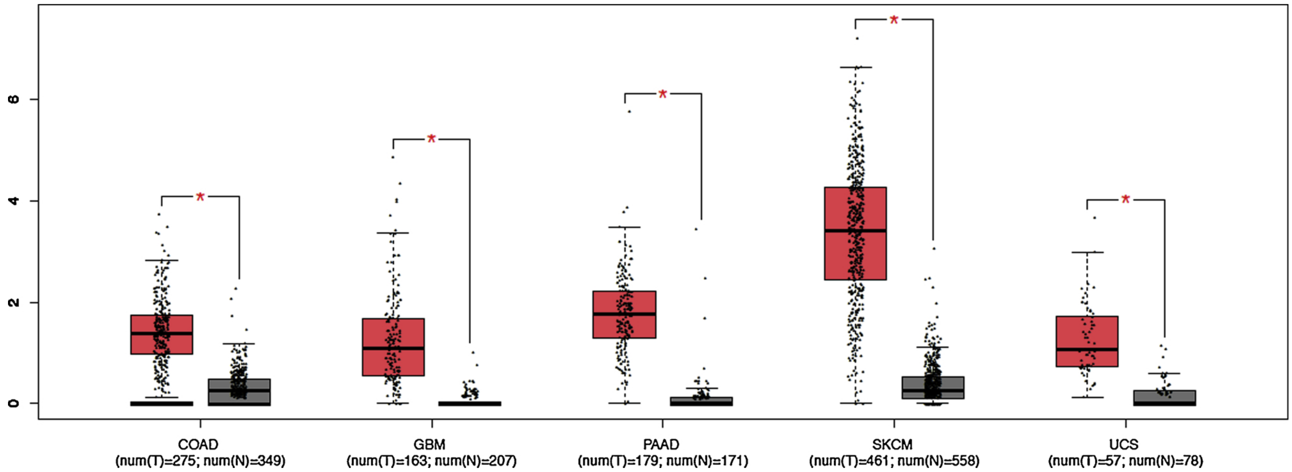

Fig. 6. The expression levels of GAPLINC in five different kinds of cancer tissues and normal tissues. "*"$|\text{Log2FC}| > 0.6$ and $p < 0.01$.

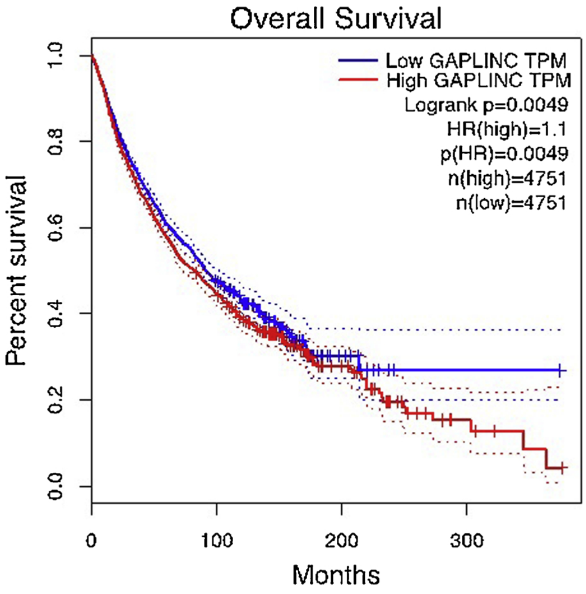

Fig. 7. Survival curves of GAPLINC in all kinds of cancers from TCGA dataset (n = 9502).

GAPLINC in solid malignant tumors, so we gathered all published GAPLINC-related papers to conduct this meta-analysis.

As a novel cancer-related lncRNA, GAPLINC was predicted to contain MREs in the promoter region by database of transcriptional start sites [17]. It was highly expressed in gastric cancer tissues, via regulating CD44 as a molecular decoy for miR211-3p, GAPLINC affects biologically invasiveness of gastric cancer and associated with poor prognosis of gastric cancer [17]. Diao et al [31] demonstrated that lncRNA GAPLINC enhanced gastric cancer cell proliferation and cell cycle progression of GC by promoting the expression of MAPK1. Through binding with PTB-associated splicing factor (PSF) and non-POU-domain-containing octamer-binding (NONO) protein, GAPLINC could promote colorectal cancer invasion partly by promoting the expression of SNAI2 [25]. Zhang et al [19] reported that GAPLINC had a positive effect on CRC proliferation and metastasis. In bladder cancer, knockdown the expression of GAPLINC inhibited cell proliferation, colony formation, migration, and invasion, resulted in more tumor cells arresting at G1 phase [26], and GAPLINC also had similar biological functions in hepatocellular carcinoma [20].

As far as we know, our work is the first meta-analysis that comprehensively assessed the prognostic and clinicopathological significance of GAPLINC in human cancers. A total of eight cohort studies including 943 patients were included in the current meta-analysis. The final results indicated that high expression of GAPLINC in tissue was significantly related to unfavorable clinical outcomes in patients with various types of cancers. The cancer patients with increased GAPLINC had a shorter OS when compared with the group with low GAPLINC (HR = 1.66, 95%CI: 1.40–1.93, $p < 0.001$). The relationships of high expression of GAPLINC in clinicopathological features were also analyzed in this meta-analysis. The combined data suggested that increased GAPLINC expression was associated with higher tumor grade, positive lymph node metastasis, deeper tumor invasion, and advanced clinical stage, the pooled ORs were 1.91 (95%CI: 1.35–2.70, $p < 0.001$), 2.80 (95%CI: 1.69–4.64, $p < 0.001$), and 2.44 (95%CI: 1.43–4.17, $p = 0.001$), 3.54 (95%CI: 2.13–5.88, $p < 0.001$), respectively.

However, this present meta-analysis has several limitations. First, only English articles were included in the current meta-analysis, and the total sample size of those studies was relatively small. Second, all patients included were from China, this might limit the global spread of our conclusion. Third, some HRs and the corresponding 95% CIs were estimated from Kaplan-Meier survival curves, which may lead to numerical inaccuracy. Fourth, scholars preferred to report positive results rather than negative results, this might lead to some negative data missing. Finally, the cut-off values of high expression of GAPLINC in tissue were various among all included studies.

In conclusion, this meta-analysis showed overexpression of GAPLINC was significantly associated with poor prognosis in various cancers, and it might serve as a promising prognostic biomarker. Due to the limitations, higher quality studies with larger sample size are further required to conduct and confirm the prognostic value of GAPLINC in cancers.

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Conflicts of interest

The authors declared no conflicts of interest.

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No.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.03.016.

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