The Prognostic and Clinicopathological Significance of LASP1 Expression in Cancer Patients: Systematic Review and Meta-Analysis

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Abstract

Background

Many cancer researchers have investigated the prognostic significance of LASP1 for survival of patients with various types of cancer. Nevertheless, the role LASP1 palyed in cancer prognosis remains unknown. In consequence, we carried out this study in order to comprehensively analyze the prognostic value of LASP1 in cancer patients.

Methods

A systematical research was conducted in electronic databases, such as PubMed, Embase and Web of Science. Eighteen studies meeting the inclusion criteria were enrolled. Overall survival (OS), recurrence-free survival (RFS) and various clinicopathological parameters were used as the endpoints in this study.

Results

A total of 2023 cancer patients from eighteen studies were finally enrolled into our meta-analysis. The results revealed that the cancer patients with high expression of LASP1 exhibited shorter OS (HR = 2.04, 95%CI = 1.77–2.34, P < 0.01) and RFS (HR = 2.11, 95%CI = 1.51–2.95, P < 0.01) than those with low expression of LASP1, and patients whose tumors expressed high LASP1 had shorter OS in lung cancer (HR = 2.20, 95%CI = 1.45–3.36, P < 0.01) and gastric cancer (HR = 1.64, 95%CI = 1.14–2.36, P < 0.01) respectively. Furthermore, the cancer patients whose tumors expressed high LASP1 were apparently associated with advanced TNM stage (OR = 2.92, 2.27–3.76, P < 0.01), earlier lymph node metastasis (OR = 2.69, 1.62–4.45, P < 0.01), advanced T classification (OR = 2.17, 1.48–3.18, P < 0.01) and earlier distant metastasis (OR = 2.56, 1.03–6.35, P = 0.04) when compared to those whose tumors expressed low LASP1.

Conclusions

Our study showed that the high LASP1 expression might be an undesirable predictor for patients with various types of cancers in the aspect of OS, RFS, TNM stage, lymph node metastasis, T classification and distant metastasis, and the high LASP1 expression might be an undesirable predictor for lung cancer patients and gastric cancer patients. Therefore, the expression of LASP1 might be utilized as a novel indicator in judging the prognosis of cancer patients, especially in lung cancer and gastric cancer.

Background

Carcinoma is currently one of the primary causes of death in humans. In 2020, there might be 1,806,590 new cancer cases and 606,520 cancer deaths in the United States [1]. Treatment of cancer patients will certainly increase the financial burden on families and society. With the continuous innovation of medical technology, the level of diagnosis and treatment for cancer patients has been improved significantly, but the long-term prognosis of various cancer patients is still not optimistic [2]. Therefore, it is of great importance to find appropriate biomarkers that can predict the prognosis of cancer patients.

MLN50 gene was firstly identified in a cDNA library of metastatic lymph nodes from breast carcinoma [3]. MLN encodes a protein which contains an N-terminal LIM domain, followed by two actin-binding sites and a C-terminal SRC homology SH3 domain [4]. Therefore MLN50 was also known as LIM and SH3 domain protein 1 (LASP1). Due to the particularity of the LASP1 structure, it played a crucial role in wound healing, inflammation, angiogenesis, and atherosclerosis [5]. Furthermore, majority of studies have demonstrated that LASP1 performed important roles in regulation of proliferation, apoptosis, invasion and metastasis of cancer [6–8]. The prognostic significance of LASP1 in patients with different types of cancer has been investigated by many cancer researchers. Nevertheless, these studies reported inconsistent results [9–11]. For instance, a study that enrolled 91 pancreatic cancer patients indicated there was significant correlation between LASP1 expression and lymph node metastasis of cancer (P = 0.001) [11]. Grunewald et al [10] observed similar result by analyzing 83 breast carcinoma patients (P = 0.007). However, no significant correlation between LASP1 expression and lymph node metastasis was found in breast cancer (P = 0.2) [9]. Now that the prognostic value of LASP1 in cancer patients remains unclear, this study was conducted to analyze the clinicopathological significance and prognostic value of LASP1 in patients suffering from various cancers.

Method

This study was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [12].

Literature search

PubMed, Embase, and Web of Science were thoroughly searched to identify relevant English articles published up to January 03, 2021. The following terms were used in the comprehensive search strategies: “LASP1 or LIM and SH3 domain protein 1” and “carcinoma or cancer or tumor or neoplasm”, with language restricted in English. Manual search was carefully performed on the references of retrieved articles to search other relevant articles.

Inclusion and exclusion criteria

The following was the eligible criteria: (1) cohort studies were conducted in cancer patients and the diagnosis of cancer was confirmed by histopathology; (2) studies in which the prognostic value of LASP1 in cancer patients was focused on; (3) studies in which the overall survival (OS), recurrence-free survival (RFS) or other clinicopathological parameters was or were reported; (4) studies with sufficient data. The following was the exclusion criteria: (1) duplicate studies, review, abstract or letters; (2) basic research or animal studies; (3) Non-English studies or studies with insufficient data.

Data extraction and quality evaluation

Two authors independently extracted relevant data from original studies. The following information was extracted from the eligible studies: first author’s name, year of publication, country where the study was carried out, type of cancer, number of patients, detection methods, cut-off value for LASP1 overexpression, prognostic parameters (e.g., OS or RFS), clinicopathological parameters (e.g., age, gender, TNM stage, histological grade, lymph node metastasis, tumor size, T classification, distant metastasis). Several of the eligible studies provided the HR and its corresponding 95% confidence interval (CI), so we extracted this information from original studies directly. Other studies did not directly report such information, so we calculated it from a Kaplan–Meier survival curve using Engauge Digitizer version 5.3 [13]. In addition, we used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of included studies [14].

Statistical analysis

The statistical analysis was performed using Review Manager 5.3 (Cochrane Collaboration, London, UK) and Stata15.0 software. HRs and its 95% CIs were calculated to assess the prognostic significance of LASP1 expression in cancer patients. ORs and its 95% CIs were calculated to assess the association between LASP1 expression and clinicopathological parameters. The heterogeneity among studies was assessed using the I2 statistic. When the statistic of I2 was greater than 50%, we considered that the heterogeneity among the included studies was statistically significant, and a random-effect model was used to pool the data under this condition. Otherwise, a fixed-effect model was selected to pool the data. We used Begg’s and Egger’s tests to assess publication bias, and sensitivity analysis was used to assess the stability of results. A two-tailed p value < 0.05 was considered statistically significant.

Results

Literature search

As shown in Fig. 1, a total of 534 articles were initially retrieved through the search strategy mentioned above. After excluding duplicate publications, a number of 180 articles left. By screening of title and abstract on the 180 articles, 4 review and 3 abstracts were excluded. According to the inclusion and exclusion criterion, 18 articles were finally included.

Study characteristics

A total of 2023 cancer patients from 18 included studies concerning LASP1 were included in this study [9–11, 15–29]. The sample size in these studies ranged from 32 to 216. The publication year of LASP1 ranged from 2007 to 2020. The level of LASP1 expression in 17studies was detected by IHC, and one study reported the level of LASP1 expression detected by quantitative real-time PCR (qRT-PCR). The included studies were performed in Asia, Europe and North America, and majority of these studies were conducted in China. Among the 18 eligible studies, 16 studies reported OS [9, 11, 15–27, 29], 2 studies reported RFS [20, 28], and 13 studies reported clinicopathological parameters [9–11, 15–20, 22, 23, 27, 29]. The included articles varied in their detection regions of LASP1 expression and the cut-off value for LASP1 positive, which might have an effect on the positive rate of LASP1 overexpression. The quality score in 17studies differs from 6 to 9 based on the NOS. One study only reported Kaplan-Meier survival analysis of 149 glioblastoma patients from TCGA, so we can’t evaluate the quality of this study. The baseline characteristics of eligible studies are listed in Table 1.

Table 1
Characteristics of studies included in the meta-analysis

Reference	First auther	year	country	Type of cancer	Number of patients	method	Cut-off	LASP1 positve (%)	outcome	NOS
11	Zhao et al	2015	China	pancreatic cancer	91	IHC	>=4	58/91(64%)	OS	9
15	Zhang et al	2017	China	non-small-cell lung cancer	109	IHC	>=4	55/109(50%)	OS	9
16	Gao et al	2018	China	nasopharyngeal carcinoma	210	IHC	>=4	92/210(44%)	OS	9
17	Li et al	2016	China	gallbladder cancer	81	IHC	>=3	37/81(64%)	OS	6
18	Zheng et al	2014	China	gastric cancer	126	IHC	>=4	72/126(46%)	OS	9
19	Zheng et al	2016	China	non-small cell lung cancer	132	IHC	>=4	81/132(61%)	OS	9
20	Yang et al	2014	China	clear cell renal cell cancer	216	IHC	> 10%	92/216(43%)	OS/RFS	8
21	Zhong et al	2018	China	glioblastoma	149	NR	NR	75/149(50%)	OS	-
22	Wang et al	2013	China	hepatocellular carcinoma	144	IHC	>=2	84/144(58%)	OS	9
23	Li et al	2017	China	gastric cancer	84	qRT-PCR	NR	39/84(46%)	OS	9
9	Frietsch et al	2010	Germany	breast cancer	177	IHC	> 10%	56/177(32%)	OS	6
10	Grunewald et al	2007	Germany	breast carcinoma	83	IHC	> 5	46/83(55%)	-	7
24	Zhao et al	2010	China	colorectal cancer	126	IHC	>=2	41/126(33%)	OS	7
25	Fahrmann et al	2016	USA	lung adenocarcinoma	32	IHC	NR	NR	OS	6
26	Sato et al	2017	Japan	bladder cancer	48	IHC	> 50%	33/48(69%)	OS	7
27	Traenka et al	2010	Germany	medulloblastoma	207	IHC	NR	107/207(52%)	OS	9
28	Subramaniyan et al	2020	USA	triple-negative breast cancer	112	NR	NR	NR	RFS	7
29	Zhang et al	2016	China	cholangiocarcinoma	40	IHC	>=3	22/40(55%)	OS	8

Notes: NR: not reported

Relationship between LASP1 expression and OS

Sixteen studies containing 2072 patients with various types of cancer were utilized to calculate a pooled HR and its 95% CI for OS. As shown in Fig. 2, because of no heterogeneity (I2 = 0%), a fixed-effect model was utilized. The result indicated that patients whose tumors expressed high LASP1 exhibited a poorer OS than those whose tumors expressed low LASP1 (HR = 2.04, 95%CI = 1.77–2.34, P < 0.01). The sensitivity analysis was performed to confirm the robustness of this result (Fig. 3A). Begg's funnel plot analysis showed an asymmetrical distribution (Fig. 3B), and Egger's test indicated that there was obvious publication bias in OS (P < 0.05). Tow studies reported OS of lung cancer, and the result showed that lung cancer patients whose tumors expressed high LASP1 exhibited a poorer OS than those whose tumors expressed low LASP1 (HR = 2.20, 95%CI = 1.45–3.36, P < 0.01, Fig. 4A). Similarly, Tow studies reported OS of gastric cancer, and the result revealed that gastric cancer patients whose tumors expressed high LASP1 exhibited a poorer OS than those whose tumors expressed low LASP1 (HR = 1.64, 95%CI = 1.14–2.36, P < 0.01, Fig. 4B). The sensitivity analysis was not performed and publication bias was not assessed because of small sample size.

Relationship between LASP1 expression and RFS

Tow studies containing 328 cancer patients were utilized to calculate a pooled HR and its 95% CI for RFS. As shown in Fig. 4C, because of no heterogeneity (I2 = 0%), a fixed-effect model was utilized. The result indicated that when compared to the cancer patients with low LASP1 expression, those with high LASP1 expression had significantly poorer RFS (HR = 2.11, 95%CI = 1.51–2.95, P < 0.01). The sensitivity analysis was not performed and publication bias was not assessed because of same reason previously mentioned.

Association of LASP1 expression with clinicopathological parameters

Thirteen literatures were enrolled into the meta-analysis for clinicopathological parameters. As shown in Table 2, high LASP1 expression was significantly correlated with advanced TNM stage (P < 0.01, Fig.S1), earlier lymph node metastasis (P < 0.01, Fig.S2), advanced T classification (P < 0.01, Fig.S3), and earlier distant metastasis (P = 0.04, Fig.S4). However, the expression of LASP1 had no connection with age (P = 0.70, Fig.S5), gender (P = 0.89, Fig.S6), tumor size (P = 0.05, Fig.S7), and histological grade (P = 0.58, Fig.S8).

Table 2
The meta-analysis of clinicopathological parameters

Clinicopathological parameter	Included studies	OR(95% CI)	P	I^2	Model
TNM stage (Ⅲ/Ⅳ versus Ⅰ/Ⅱ)	9	2.92(2.27–3.76)	< 0.01	28%	Fixed
Lymph node metastasis (yes versus no)	9	2.69(1.62–4.45)	< 0.01	68%	Random
T classification (T3-T4 versus T1-T2)	4	2.17(1.48–3.18)	< 0.01	29%	Fixed
Distant metastasis (yes versus no)	4	2.56(1.03–6.35)	0.04	60%	Random
Age (old versus young)	9	1.05(0.83–1.32)	0.70	0	Fixed
Gender (male versus female)	10	1.02(0.81–1.28)	0.89	17%	Fixed
Tumor size (large versus small)	7	1.97(1.01–3.86)	0.05	79%	Random
Histological grade (well/moderate versus poor)	9	1.17(0.67–2.05)	0.58	71%	Random

Discussion

In recent years, LASP1 has been widely concerned by researchers due to its important role in tumorigenesis. Some publications have reported the prognostic significance of LASP1 in cancer patients, but controversial results were found in terms of disease parameters such as lymph node metastasis of cancer. To explore the prognostic significance of LASP1 expression in cancer patients, this study was carried out.

To the best of our knowledge, this is the first meta-analysis to focus on the prognostic value and clinicopathological significance of LASP1 expression in cancer patients. Survival data of 1,940 cancer patients from 17 eligible studies were systematically analyzed. We found that LASP1 overexpression was a significant prognostic factor for poor OS and RFS of solid tumors. Tow studies on lung cancer reported the association between LASP1 expression and OS. To explore the association between LASP1 expression and prognosis of lung cancer patients, we conducted the meta-analysis of OS in lung cancer patients. Our result showed that lung cancer patients whose tumors expressed high LASP1 had a poor prognosis. Similar result was obtained in gastric cancer patients. Furthermore, our meta-analysis found that the high LASP1 expression was obviously associated more advanced TNM stage and T classification, earlier lymph node metastasis and distant metastasis. The aforementioned findings highlighted that the overexpression of LASP1 was potentially utilized to predict poor prognosis in patients with various types of cancer, especially in lung cancer and gastric cancer.

Plenty of studies have reported that the abnormal expression of certain proteins played an important role in the occurrence and development of tumors [30–32]. The relationship between LASP1 expression and the prognosis of human cancers has been explored by many cancer researchers, however the mechanisms underlying the role of LASP1 remain indistinct. A study reported that LASP1 expression was higher in colorectal cancer (CRC) tissue of advanced stages, and the overexpression of LASP1 promoted proliferation, migration and tumorigenesis of CRC cell through Hippo signaling and Nanog mediated EMT [33]. In addition, other researchers demonstrated that LASP1 played an important role in viability and migration of bladder cancer cell by regulating microRNAs [34]. Nishikawa et al found that miRNA-218, a tumor-suppressive microRNA, inhibited prostate cancer cell migration and invasion by interacting with LASP1 [35]. Similarly, Li et al found that miRNA-133b inhibited proliferation, invasion and migration via regulating LASP1 in hepatocarcinoma cells [36]. So far, the mechanisms underlying the prognostic significance of LASP1 in cancers have been investigated by a few researchers. Hence, the prognostic value of LASP1 in cancers should be investigated by conducting more basic researches.

Of course, there are several limitations in this meta-analysis. Firstly, the cutoff value used to determine LASP1 positivity varied among the studies included in our meta-analysis. Secondly, the HR and its 95% CI of OS in certain studies were indirectly calculated from survival curve, which could influence the result. However, many similar studies utilized this method [37, 38]. Thirdly, our meta-analysis was limited to studies published in English. Last but not least, all the included studies were cohort in design, which maybe compromise the validity of this study.

Conclusions

In conclusion, our study showed that the high LASP1 expression might be an undesirable predictor for patients with various types of cancers in the aspect of OS, RFS, TNM stage, lymph node metastasis, T classification and distant metastasis, and the high LASP1 expression might be an undesirable predictor for lung cancer patients and gastric cancer patients. Therefore, the expression of LASP1 might be utilized as a novel indicator in judging the prognosis of cancer patients, especially in lung cancer and gastric cancer. More multi-center clinical investigations should be conducted to certify our findings.

Abbreviations

LASP1
LIM and SH3 domain protein 1; OS:overall survival; RFS:recurrence-free survival; CI:Confidence interval; NOS:Newcastle-Ottawa Scale; TNM:Tumor, Lymph Node, Metastasis

Declarations

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Authors' contributions

JL: formal analysis and writing original draft; YZ: and HM: formal analysis; YL and FH: data acquisition; XL: software; JW: methodology; ZH: supervision; YH: writing review & editing.

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Availability of data and materials

The datasets used during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present meta-analysis does not contain any studies with human participants performed by any of the authors. Therefore, no ethical approval is required.

Consent for publication

Not applicable.

Competing interests

The author reports no conflicts of interest in this work.

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Supplementary Figure Legends

Fig.**S1**. Forest plot for the association between LASP1 expression and TNM stage

Fig.**S2**. Forest plot for the association between LASP1 expression and lymph node metastasis

Fig.**S3**. Forest plot for the association between LASP1 expression and T classification

Fig.**S4**. Forest plot for the association between LASP1 expression and distant metastasis

Fig.**S5**. Forest plot for the association between LASP1 expression and age

Fig.**S6**. Forest plot for the association between LASP1 expression and gender

Fig.**S7**. Forest plot for the association between LASP1 expression and tumor size

Fig.**S8**. Forest plot for the association between LASP1 expression and histological grade

Figures

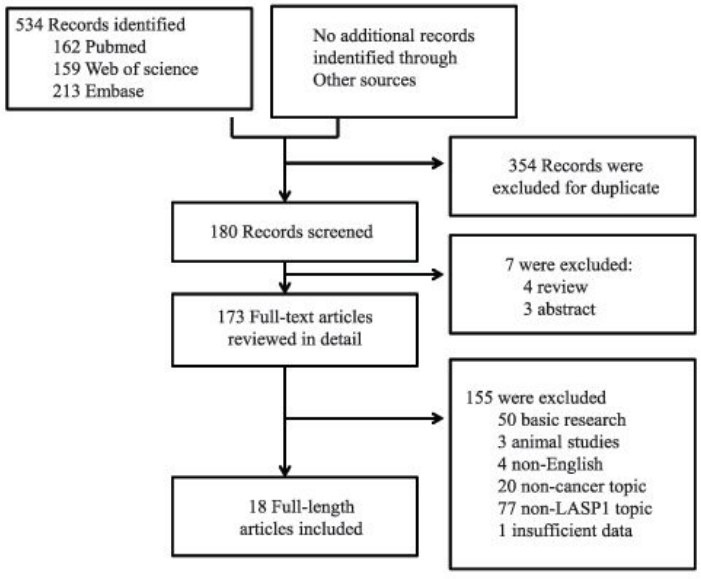

Figure 1

Flow diagram of study selection

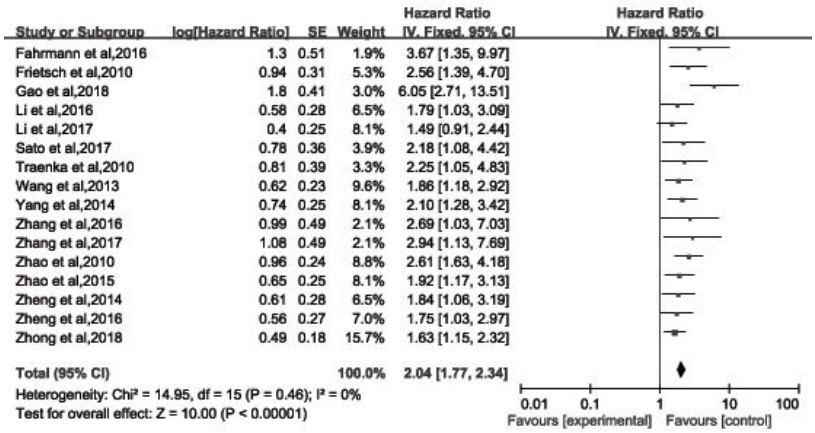

Figure 2

Forest plot for the association between LASP1 expression and OS in various cancer patients

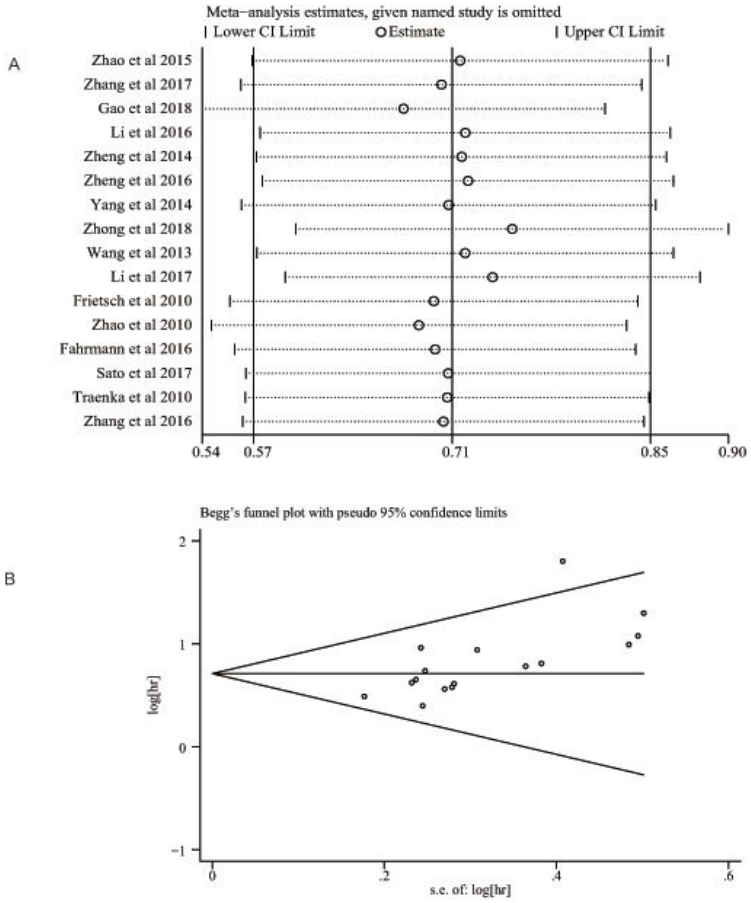

Figure 3

Sensitivity analysis of studies evaluating the relationship between LASP1 expression and OS in various cancer patients (A) and Begg's funnel plot to evaluate the publication bias of LASP1 expression and OS in various cancer patients (B)

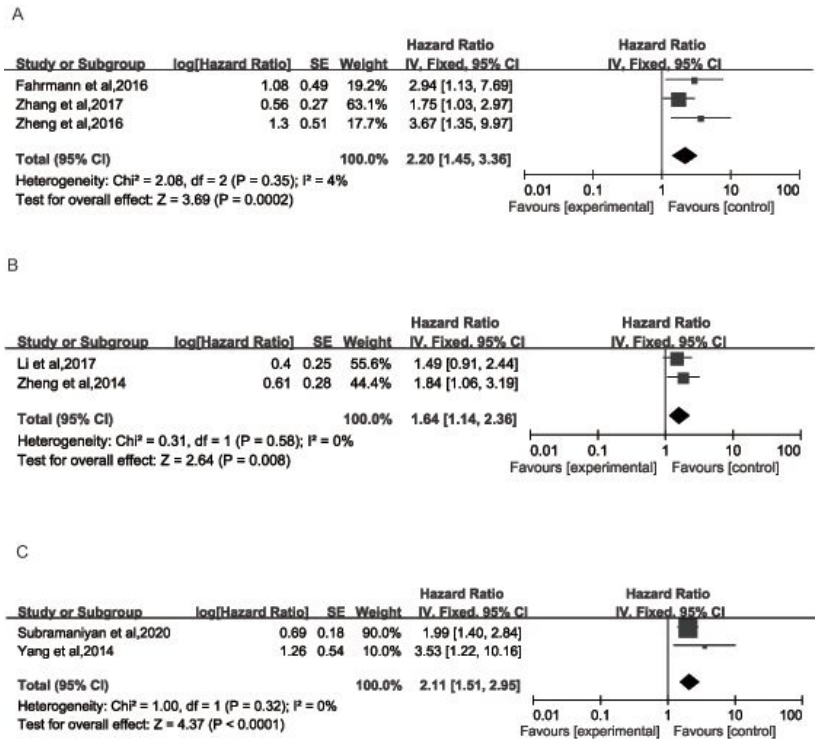

Figure 4

Forest plot for the association between LASP1 expression and OS in lung cancer patients (A), forest plot for the association between LASP1 expression and OS in gastric cancer patients (B) and forest plot for the association between LASP1 expression and RFS in different cancer patients (C)

Supplementary Files

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- Fig.S1.eps
- Fig.S2.eps
- Fig.S3.eps
- Fig.S4.eps
- Fig.S5.eps
- Fig.S6.eps
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- Fig.S8.eps