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Research Paper

Prognostic Values of LAPTM4B-35 in Human Cancer: A Meta-analysis

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Abstract

Background: Lysosome-associated protein transmembrane-4β-35(LAPTM4B-35) has been observed overexpressed in multiple malignant tumors. However, the prognostic value of LAPTM4B-35 remains controversial. Therefore, we conducted a meta-analysis to evaluate the prognostic value of LAPTM4B-35 in human cancers.

Methods: The relevant publications were obtained by systematically searching the PubMed, Web of Science, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for the prognosis value of LAPTM4B-35 for cancer patient.

Results: Our result suggest that LAPTM4B-35 overexpression is significantly associated with poor overall survival (OS) (HR = 2.49, 95% CI = 1.87–3.32, $p < 0.001$), disease-free survival (DFS) (HR = 2.43, 95% CI = 1.35–4.35, $p = 0.003$), and progression-free survival (PFS) (HR = 4.12, 95% CI = 2.30–7.37, $p < 0.001$). Moreover, subgroup analysis revealed significant association with poor OS in lung (HR = 2.05, 95% CI = 1.37–3.06, $p < 0.001$), gastric carcinoma (HR = 1.88, 95% CI = 1.01–3.50, $p < 0.047$) and ovarian cancer (HR = 4.94, 95% CI = 1.44–16.94, $p = 0.011$).

Conclusion: LAPTM4B-35 may be a novel predictive biomarker and a potential target for treatment.

Key words: LAPTM4B-35, cancer, prognosis, meta-analysis

Introduction

Cancer is one of the leading causes of death in the world. According to the most recent global cancer statistics, in 2017, there were 1,688,780 newly diagnosed cancer cases and 600,920 cancer-related deaths in the United States[1]. It is generally believed that highly specific biomarkers could be helpful to cancer diagnosis. However, many biomarkers are not specific enough for cancers. Therefore, it is important to find new biomarkers for cancer diagnosis.

As a member of the mammalian 4-tetra-transmembrane spanning protein superfamily, lysosome-associated protein transmembrane-4β-35 (LAPTM4B-35) was firstly found in hepatocellular carcinoma[2]. The LAPTM4B-35 is rich in proline at the N- and C-termini while *LAPTM4B-35*consisting of seven exons and six introns which locate on chromosome 8g22[3]. Previous studies have shown that LAPTM4B-35 is upregulated in many types of cancer, including breast [4, 5], lung [6, 7], gastric [8], pancreatic [9], colorectal [10], ovarian [11,12], and

hepatocellular cancer[13]. LAPTM4B-35 is a novel oncoprotein that decreases apoptosis, promotes progression and metastasis, and induces tumor angiogenesis [14]. Moreover, it can induce multidrug resistance by activating PI3K/AKT signaling pathway [15, 16].

Multiple studies have shown that LAPTM4B-35 expression is associated with cancer prognosis [4, 6, 17]. However, most studies just focused on the association between LAPTM4B-35 and single cancer. In this article, we conducted a meta-analysis to assess the association between LAPTM4B-35 and multiple cancer.

Materials and Methods

Identification of eligible studies

Eligible studies which were published before March 2018, were selected from the PubMed, Web of Science, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases. The search phrases "cancer or carcinoma or tumor or neoplasm", "LAPTM4B or Lysosome-associated protein transmembrane-4β", "LAPTM4B-35 or Lysosome-associated protein transmembrane-4β-35", and "prognosis or survival" were used. All references were screened to ensure relevant studies were included.

Inclusion and exclusion criteria

The included studies followed the criteria: (1) the source and size of the study population were clearly described, (2) a clear pathological diagnosis of cancer was mentioned, (3) the association with overall survival (OS), disease-free survival (DFS) or progression-free survival (PFS) in cancer patient were declared, (4) hazard ratios (HRs) with 95% confidence intervals (CIs) or survival curves were contained in the study. The excluded studies were classified into categories including: (1) duplicate studies, (2) case reports, reviews, letters, or meta-analyses, (3) no available data, or (4) the experiment was done with organisms other than humans.

Data extraction

Two investigators (Linghui Zhou and Cong Dai) independent performed data extraction. Discussions were held with senior investigators until a consensus was reached to eliminate differences. For each study, the following information was extracted: first author, year of publication, the source of patients, study size, types of specimens, method of detection, types of cancer, LAPTM4B-35 expression, median follow-up, prognostic outcome, analysis method, and HRs with 95% CIs.

Quality assessment

We adopt the Newcastle-Ottawa Scale (NOS) scoring criteria to evaluate the quality of each study[18]. A study with a score of 0–5 was considered a low-quality study and that with a score of 6–9 was considered a high-quality study. Two investigators (Linghui Zhou and Cong Dai) performed independent quality assessments.

Statistical methods

The association between LAPTM4B-35 and patient prognosis was assessed based on pooled HRs and the corresponding 95% CIs. The HR and corresponding 95% CIs were acquired directly from the study or calculated based on Kaplan-Meier survival curves (by Engauge Digitizer version 4.1) [19]. The chi-square-based Q statistic was conducted to evaluate heterogeneity among the studies. In cases where $p < 0.10$ or $I^2 > 50$, the random effects model was used to assess the pooled HRs[20].Otherwise, the fixed effects model was used. Subgroup analyses were conducted based on the cancer type and analysis method[21]. We used Begg's test, Egger's test, and Begg's funnel plot to evaluate publication bias[22, 23]. If $p > 0.05$ and the funnel plots were symmetrical, it means no publication bias. Additionally, sensitivity analysis was calculated by omitting each study in turn. All the data analysis was performed by Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study Characteristics

After searching the PubMed, Web of Science, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases, we obtained 160 different articles without duplication. As shown in Figure 1, after reviewing the title and abstract, 133 studies were excluded. The full text of the remaining 27 articles was analyzed, which excluded another 7 articles. After these analyses, there were 20 eligible studies remained[4-14, 17, 24-31].

The main characteristics of the 20 studies are shown in Table 1**.** All the studies evaluated the association between LAPTM4B-35 and OS in cancer patients. In addition, 7 studies assessed the relationship between LAPTM4B-35 and PFS, and 8 studies assessed the link between LAPTM4B-35 and DFS. Together, the studies assessed 3,274 cancer patients from China, USA, and Japan. The number of patients per study ranged from 39 to 652. The abundance of LAPTM4B-35 was quantified by immunohistochemistry (IHC) staining. The 20 studies analyzed many types of cancer, including pancreatic, ovarian, lung, hepatocellular, glioblastoma, gastric, endometrial,

colorectal, cervical, breast, and bladder cancer.

Association between LAPTM4B-35 and OS in cancer patients

The 20 studies assessed the association between LAPTM4B-35 and OS in cancer patients. Due to significant heterogeneity (p < 0.001, I^2 = 59.2%), we used the random effects model to pool the HRs (Table 2). As shown in Figure 2, LAPTM4B-35 over-expression was significantly associated with poorer OS (HR = 2.49, 95% CI = 1.87–3.32, p < 0.001). Moreover, subgroup analyses by type of cancer revealed a significant association with poorer OS in patients with lung (HR = 2.05, 95% CI = 1.37–3.06, p < 0.001), gastric carcinoma (HR = 1.88, 95% CI = 1.01–3.50, p < 0.047) and ovarian cancer (HR = 4.94, 95% CI = 1.44–16.94, p = 0.011) (Figure 3).

Association between LAPTM4B-35 and DFS PFS in cancer patients

Seven of the twenty studies assessed the link between LAPTM4B-35 and PFS in cancer patients. Because of significant heterogeneity (p < 0.001, I^2 = 75.9%), the random effects model was employed to pool the HRs (Table 2). The results suggest that LAPTM4B-35 overexpression was significantly associated with poor PFS (HR = 4.12, 95% CI = 2.30–7.37, p < 0.001) (Figure 4). In addition, eight studies evaluated the association between LAPTM4B-35 and DFS in cancer patients. Heterogeneity analysis also showed significant heterogeneity (p = 0.047, I^2 = 50.8%) (Table 2), so the random-effects model was used to pool the HRs. The pooled data indicated that LAPTM4B-35 over-expression was significantly related to poor DFS (HR = 2.43, 95% CI = 1.35–4.35, p = 0.003) (Figure 5).

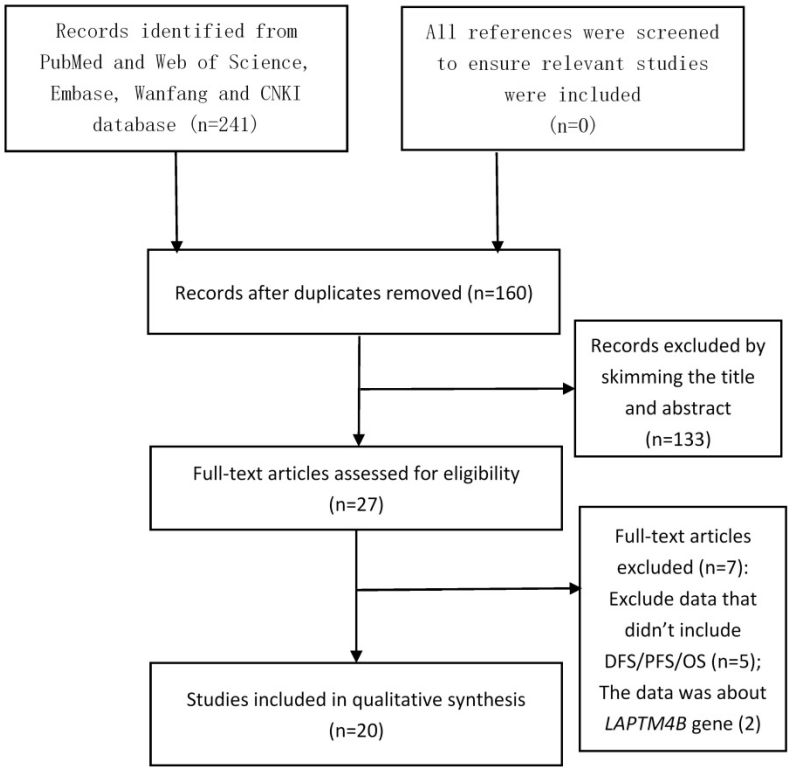

Figure 1. The flow diagram of the meta-analysis. CNKI: China National Knowledge Infrastructure.

Sensitivity analyses

To evaluate the stability of the meta-analysis, we conducted sensitivity analyses by removing each study in turn. As shown in Figure 6, the meta-analysis is reliable and no individual study skewed the pooled HRs values of OS, PFS, or DFS.

Publication bias

We used Begg's and Egger's tests to evaluate publication bias of the eligible studies. No publication bias was observed for OS (p = 0.381, 0.159), PFS (p = 0.072, 0.069), or DFS (p = 0.266, 0.370). Additionally, the funnel plots were symmetrical (Figure 7).

Discussion

Many studies have shown that the levels of LAPTM4B-35 are significantly upregulated in multiple cancer. Moreover, a study conducted by Li *et al.* suggested that the overexpression of LAPTM4B-35 could induce multidrug resistance, which could be eliminated by knockdown of LAPTM4B-35 expression [16]. These findings indicate that LAPTM4B-35 is a potential predictive biomarker for many types of cancers, as well as a promising target for knockdown by iRNA to decrease drug resistance.

Our meta-analysis, with 20 studies and 3,274 cancer patients, suggests that LAPTM4B-35 overexpression is significantly associated with poor OS, DFS, and PFS. Moreover, subgroup analysis showed a significant association with poor OS in lung, gastric and ovarian cancer. There were an insufficient number of studies in the meta-analysis to determine if there is a significant association between LAPTM4B-35 and other types of cancer, so the results should be interpreted carefully. Subgroup analysis suggests that the analysis method may lead to significant heterogeneity in the meta-analysis. The results of the sensitivity analysis prove that the meta-analysis is reliable. No publication bias was detected by either the Begg's or the Egger's test.

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

First author	Year	Patient source	Number of patient	Method	Specimen	Tumor types	expression (%)	Median(range) Follow-up(month)	Outcome	M/ U	HR(95%CI)	NOS
Zhang	2017	China	102	IHC	tissue	BDC	45.1	—	OS	M	6.439(2.67-15.531)	6
Zhang	2017	China	102	IHC	tissue	BDC	45.1	—	PFS	M	20.631(5.574-76.36)	6
Zhang	2014	China	652	IHC	tissue	GC	72.23	—	OS	M	3.055(1.739-5.382)	6
Zhang	2012	China	98	IHC	tissue	PC	78.6	15 (3 - 65)	OS	U	2.03(0.75-5352)	6
Yin	2011	China	113	IHC	tissue	OC	70.8	—	OS	M	20.611(5.916-71.808)	8
Yin	2012	China	102	IHC	tissue	OC	75.49	—	OS	M	2.644(1.439-4.858)	8
Yin	2011	China	113	IHC	tissue	OC	70.8	—	PFS	M	17.852(6.31-50.52)	8
Yin	2012	China	102	IHC	tissue	OC	75.49	—	PFS	M	2.489(1.388-4.461)	8
Yang	2010	China	35	IHC	tissue	HC	57.14	16 (4 - 36)	DFS	M	2(0.29-13.87)	6
Yang	2010	China	71	IHC	tissue	HC	71.83	36 (3 - 93)	DFS	U	2.79(0.73-10.61)	6
Yang	2010	China	35	IHC	tissue	HC	57.14	16 (4 - 36)	OS	M	1.89(0.24-14.67)	6
Yang	2010	China	71	IHC	tissue	HC	71.83	36 (3 - 93)	OS	U	2.87(0.69-11.96)	6
Yang	2008	China	85	IHC	tissue	OC	63.53	—	OS	U	2.68(0.76-9.41)	6
Yang	2008	China	85	IHC	tissue	OC	63.53	—	PFS	U	3.55(1.6-7.86)	6
Xiao	2013	China	194	IHC	tissue	BC	74.74	62 (9 - 74)	DFS	M	1.42(0.34-5.95)	8
Xiao	2013	China	194	IHC	tissue	BC	74.74	61 (9 - 74)	OS	M	1.38(0.17-11.01)	8
Tang	2014	China	186	IHC	tissue	LC	69.35	—	DFS	M	1.52(0.97-2.39)	8
Tang	2014	China	186	IHC	tissue	LC	69.35	—	OS	M	1.31(0.73-2.37)	8
Qiao	2015	China	88	IHC	tissue	LC	50	66	DFS	U	3.802(1.737-7.632)	8
Qiao	2015	China	88	IHC	tissue	LC	50	66	OS	U	4.16(1.964-7.893)	8
Meng	2011	China	113	IHC	tissue	CC	72.57	64 (14-78)	DFS	M	1.07(0.15-7.64)	6
Meng	2011	China	113	IHC	tissue	CC	72.57	64 (14-78)	OS	M	0.96(0.18-5.22)	6
Meng	2010	China	165	IHC	tissue	EC	70.91	70 (9-78)	DFS	M	0.79(0.1-6.12)	9
Meng	2010	China	165	IHC	tissue	EC	70.91	70 (9-78)	OS	M	1.42(0.29-6.9)	9
Maki b	2015	America	123	IHC	tissue	LC	37.4	—	OS	M	1.64(0.85-3.18)	6
Maki a	2015	America	245	IHC	tissue	LC	47.4	—	OS	M	1.53(0.96-2.41)	6
Liu	2015	China	148	IHC	tissue	GC	89.19	—	OS	M	1.54(0.45-5.27)	6
Li	2017	China	110	IHC	tissue	BC	56.36	49 (10–67)	OS	M	1.49(0.78-2.86)	9
Li	2017	China	110	IHC	tissue	BC	56.36	50 (10–67)	PFS	M	1.48(0.78-2.97)	9
Kong	2016	China	107	IHC	tissue	LC	50.47	64.5	OS	M	2.879(1.621-4.318)	7
Kong	2016	China	107	IHC	tissue	LC	50.47	64.5	PFS	M	2.75(1.911-4.607)	7
Kang	2012	China	136	IHC	tissue	CRC	21.15	—	DFS	M	11.674(3.562-38.263)	6
Kang	2012	China	136	IHC	tissue	CRC	37.38	—	OS	M	22.774(5.287-98.091)	6
Dong	2017	Japan	39	IHC	tissue	G	56.41	12.5	OS	U	3.52(1.3-9.57)	8
Dong	2017	Japan	39	IHC	tissue	G	56.41	5.13	PFS	U	4.18(1.5-11.64)	8
Cheng	2015	China	240	IHC	tissue	GC	71.52	26.2 (2.4–119.0)	OS	U	1.32(0.83-2.09)	8

Abbreviations: CI :confidence interval; BDC: Bladder Cancer; BC: Breast Cancer; CC: Cervical Carcinoma; CRC: Colorectal Carcinoma; EC: Endometrial Carcinoma; GC: Gastric Carcinoma; G: Glioblastoma; HC: Hepatocellular Carcinoma; LC: Lung Cancer; OC: Ovarian Carcinoma; PC: Pancreatic Carcinoma; NOS: Newcastle–Ottawa Scale; M: multivariate; U: univariate; OS: overall survival, DFS: disease-free survival; PFS: progression-free-survival; IHC: immunohistochemistry. a, b: different studies in the same article. expression (%): Percentage of patients with high expression LAPTM4B-35 in total patients. -: data is not available.

Table 2. Main meta-analysis results

Analysis	No of studies	Model	HR (95% CI)	P-value	Heterogeneity	
					I^2 (%)	P-value
OS	20	Random	2.49(1.87-3.32)	<0.001	59.20%	<0.001
Tumor types						
LC	5	Random	2.05(1.37-3.06)	<0.001	60.10%	0.04
OC	3	Random	4.94(1.44-16.94)	0.011	77.00%	0.013
GC	3	Random	1.88(1.01-3.50)	0.047	61.2%	0.076
HR estimate						
M	14	Random	2.53(1.75-3.65)	<0.001	64.90%	<0.001
U	6	Fixed	2.11(1.53-2.89)	<0.001	44.20%	0.111
DFS	8	Random	2.43(1.35-4.35)	0.003	50.80%	0.047
PFS	7	Random	4.12(2.30-7.37)	<0.001	75.90%	<0.001

Abbreviations: CI, confidence interval; LC: Lung Cancer; OC: Ovarian Carcinoma; HR, hazard ratio; M: multivariate; U: univariate; OS, overall survival; DFS: disease-free survival; PFS: progression-free-survival. GC: Gastric Carcinoma

A meta-analysis of the association between LAPTM4B-35 expression and cancer prognosis has not been previously reported other than two meta-analyses of the *LAPTM4B* polymorphism [32, 33]. Therefore, we conducted this meta-analysis to assess the prognostic and predictive values of LAPTM4B-35 in many types of human cancer.

Although our meta-analysis provided strong evidence that LAPTM4B-35 overexpression was significantly associated with poor prognosis, there were some limitations. First, some of the studies used did not include the survival data. Thus, we had to obtain the HRs indirectly using the Kaplan-Meier survival curves, which could influence the accuracy of data. In addition, significant heterogeneity was observed in our study and subgroup analysis suggests that the analysis method may contribute to the significant heterogeneity in the meta-analysis. Due to lack of data about age, sex, diet, living environment, smoking, family inheritance, we could not find the exact source of heterogeneity. In addition, we could not verify the conclusions about cancer types other than lung and ovarian cancer due to limited numbers of studies. Therefore, more studies on the prognosis of

patients with other cancers are indispensable to confirm our conclusions.

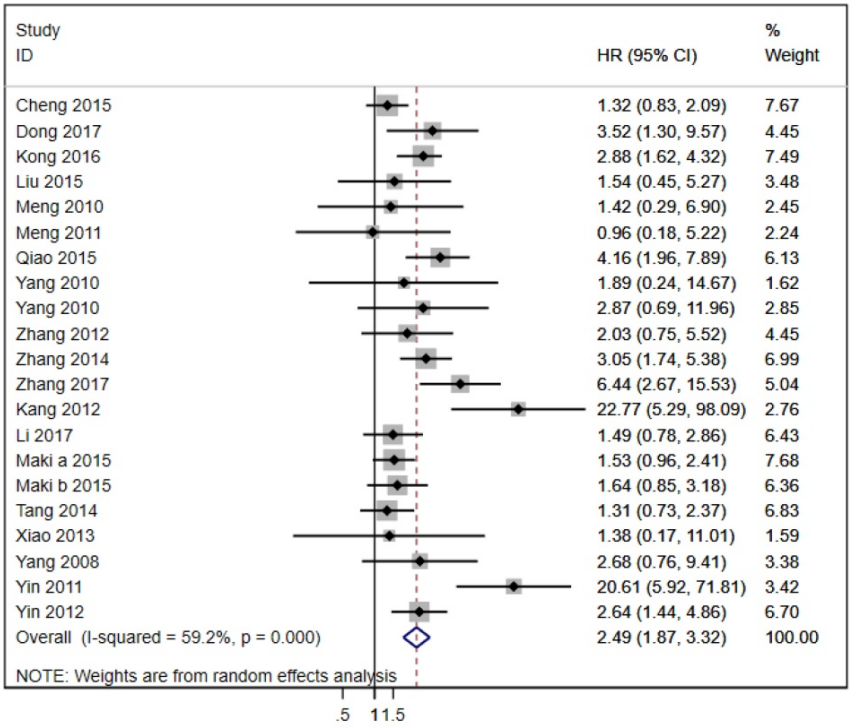

Figure 2. Forest plot of HR for the association of LAPTM4B-35 overexpression and OS. CI: confidence interval; HR: hazard ratio; OS: overall survival.

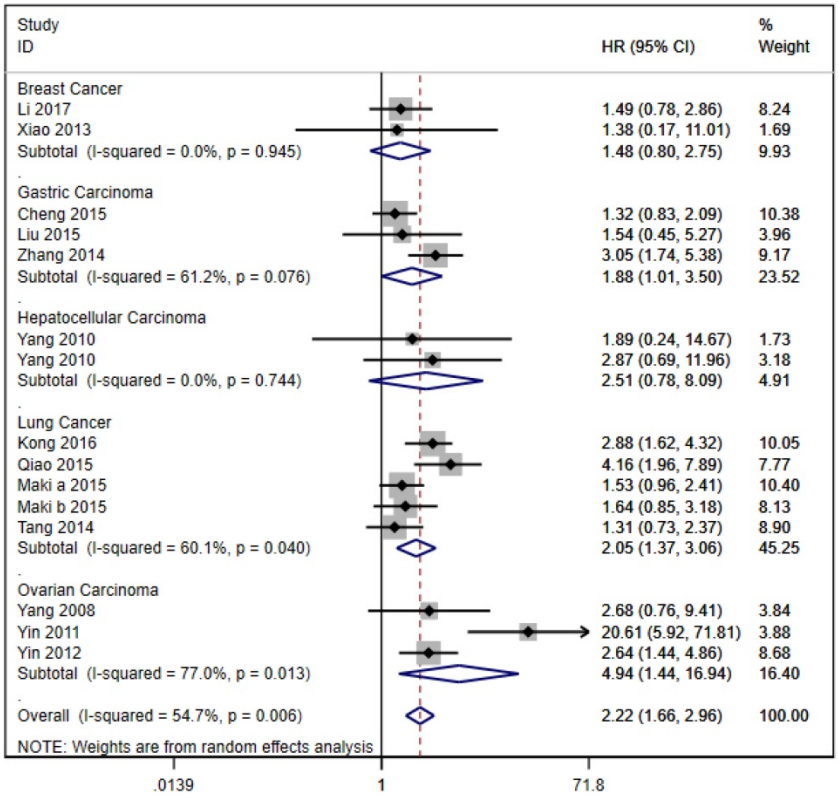

Figure 3. Stratified analysis based on cancer types for the association between LAPTM4B-35 overexpression and OS. CI: confidence interval; HR: hazard ratio; OS: overall survival.

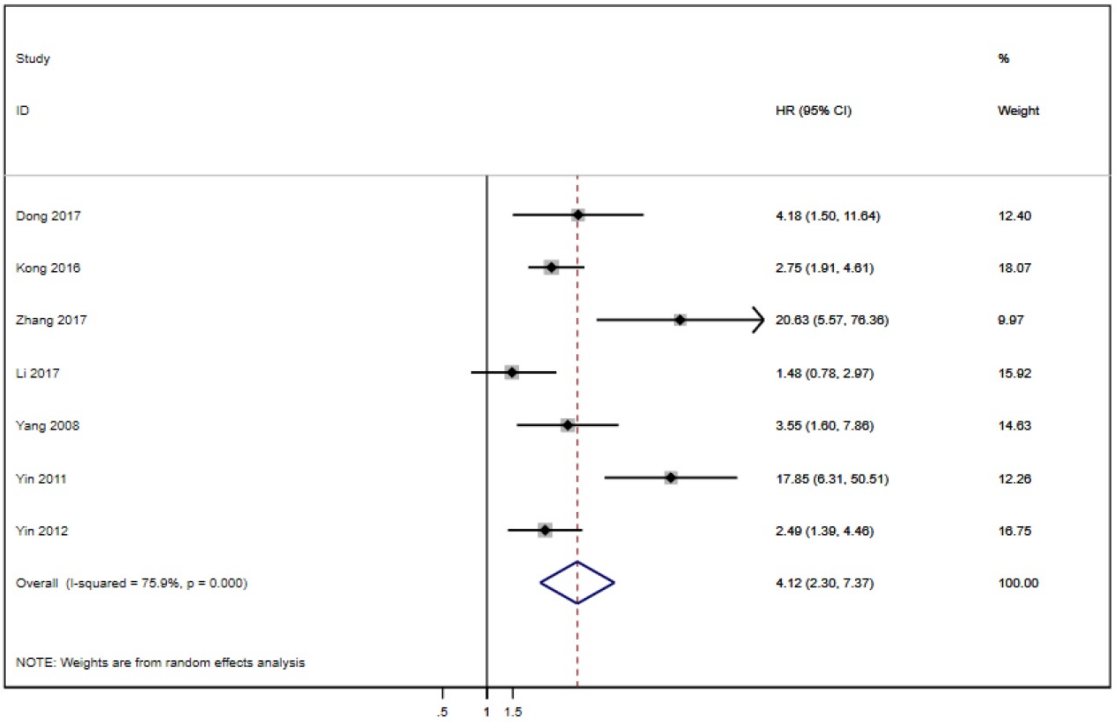

Figure 4. Forest plot of HR for the association of LAPTM4B-35 overexpression and PFS. CI: confidence interval; HR: hazard ratio; OS: overall survival.

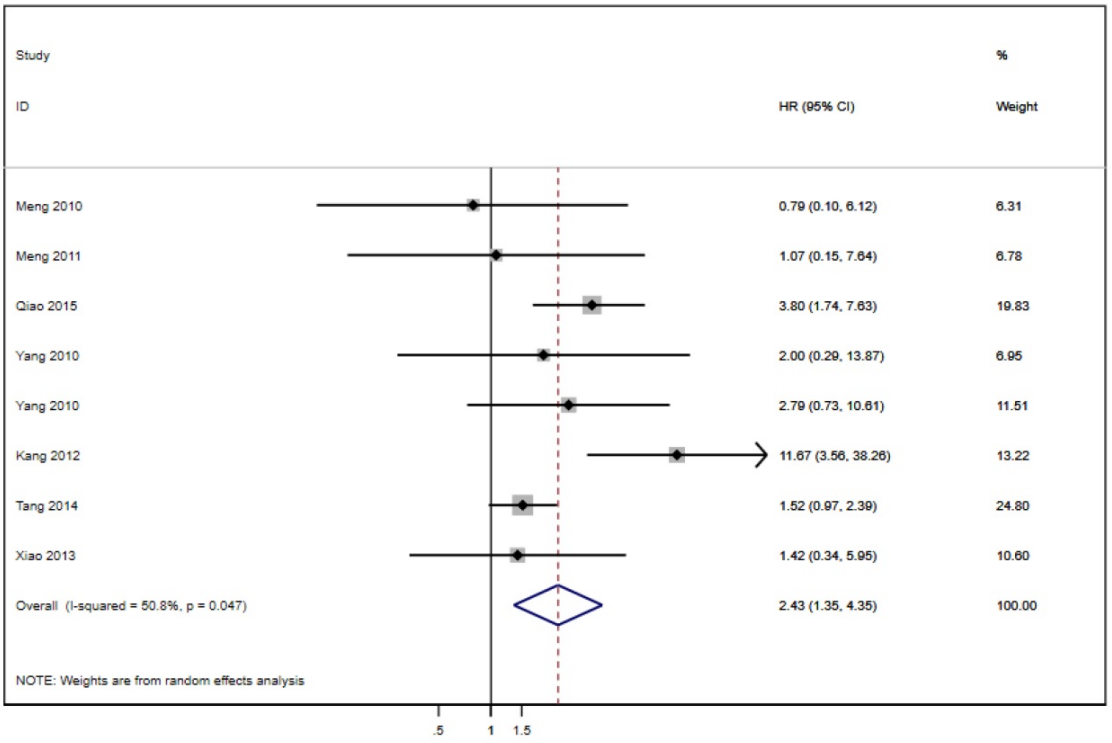

Figure 5. Forest plot of HR for the association of LAPTM4B-35 overexpression and DFS. CI: confidence interval; HR: hazard ratio; OS: overall survival.

Conclusion

Overall, our study showed that the overexpression of LAPTM4B-35 is significantly associated with poor prognosis. As such, LAPTM4B-35 may be a new prognostic marker for many types of cancer. Due to the limitations, our results should be interpreted with caution. And further clinical studies on the prognosis of patients with many types of cancers are necessary to verify our conclusion.

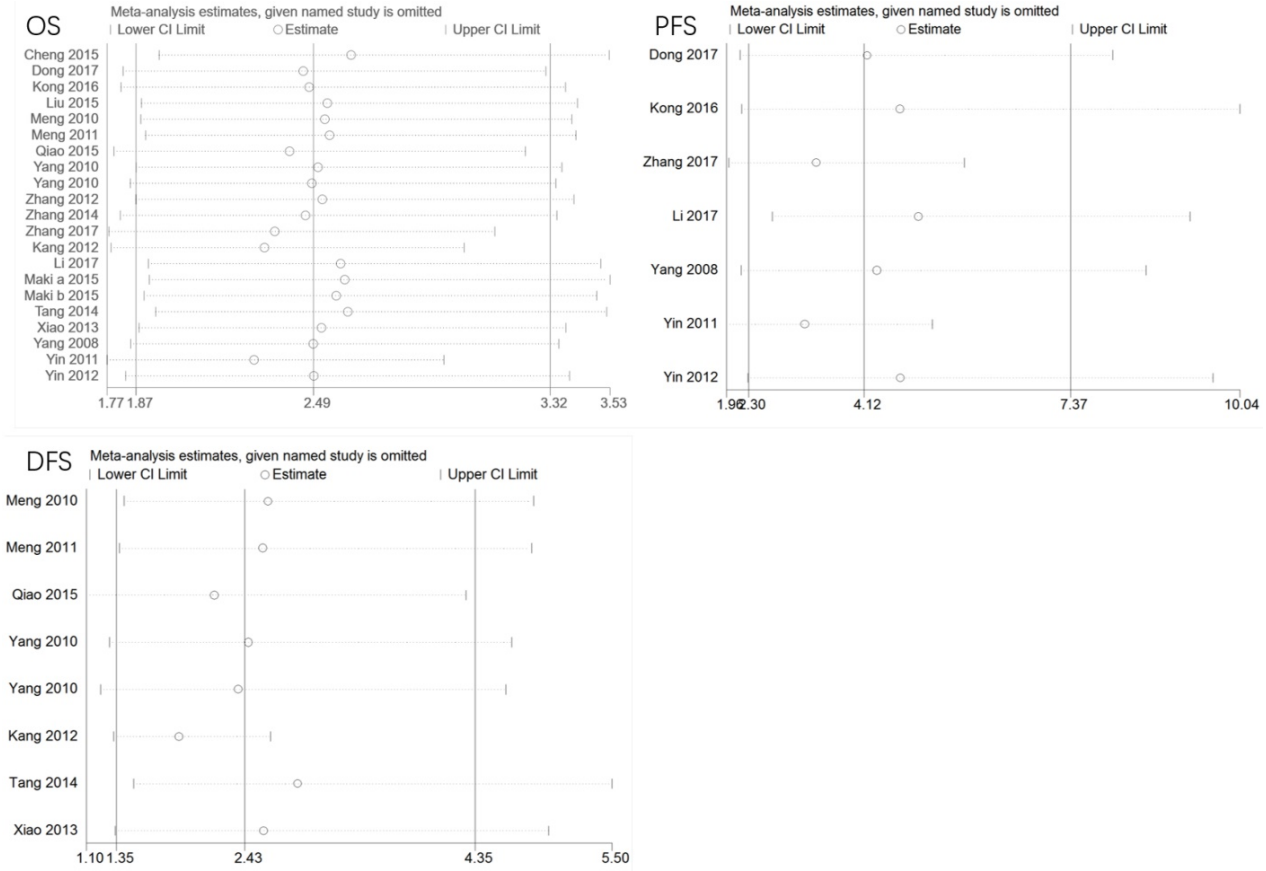

Figure 6. Sensitivity analysis of pooled HRs on the association between LAPTM4B-35 expression and OS/PFS/DFS. CI: confidence interval; HR: hazard ratio; OS: overall survival. DFS: disease-free survival; PFS: progression-free survival.

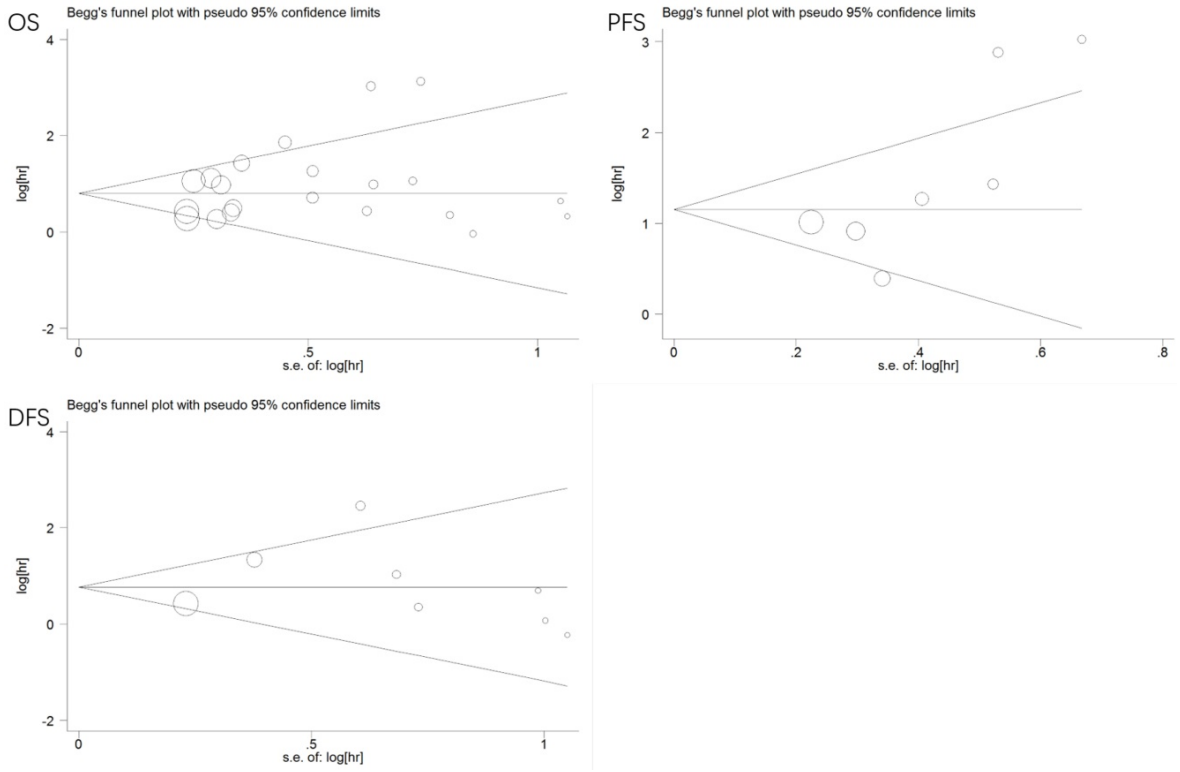

Figure 7. Funnel plots of publication bias for all the included studies reported with OS/PFS/DFS. CI: confidence interval; HR: hazard ratio; OS: overall survival. DFS: disease-free survival; PFS: progression-free survival.

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Author Contributions

L.-H. Z., C.D. and T.T. are contributed equally to this work. Z.-J.D. designed the study. L.-H.Z., C.D. and T.T. wrote the main manuscript text, M.W., S.L and Y.-J.D. performed figures and tables, P.X., Q.H., Y.W., T.-L.Y. and W.-G.Z. reviewed the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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