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Original Article

Prognostic significance of placenta growth factor expression in patients with multiple cancers: a meta-analysis

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Abstract: Background: Placenta growth factor (PLGF) is a member of the vascular endothelial growth factor (VEGF) family which is associated with the progression and metastasis of cancer. However, whether it can be used to predict prognosis in multiple cancer is still inconsistent. Methods: A meta-analysis was performed by searching electronic databases updated to December 2014. Eligible studies which evaluated the relationship between PLGF expression level and survival of patients with multiple cancers were conducted. Overall survival (OS), progression-free survival (PFS), hazard ratio (HR), and 95% confidence intervals (CI) were calculated. Results: Nineteen studies with a variety of cancers were included for the meta-analysis. Combined HR suggested that high expression of PLGF significantly associated with a poor OS (HR=1.69, 95% CI, 1.32-2.16), and PFS (HR=1.8, 95% CI, 1.33-2.44) in patients with different cancers. Moreover, a subgroup analysis based on cancer type demonstrated that high expression level of PLGF predict poor OS in both digestive system carcinoma (HR=1.63, 95% CI, 1.21-2.19; I^2=80.7%, P<0.001) and respiratory system tumor (HR=1.75, 95% CI, 1.28-2.41; I^2=0.0%, P=0.394). For PFS, the similar result was found in respiratory system tumor (HR=1.64, 95% CI, 1.23-2.19; I^2=0.0%, P=0.807), but not in digestive system carcinoma (HR=1.81, 95% CI, 0.93-3.52; I^2=80.2%, P<0.001). Conclusion: Our meta-analysis demonstrates that PLGF might be regarded as a poor prognostic fact for multiple cancers. More large-scale and well-designed studies are still needed to strengthen our findings.

Keywords: Multiple cancers, placenta growth factor, prognosis, meta-analysis

Introduction

Angiogenesis is essential to multiple tumor's growth, progression and metastasis [1] and is tightly regulated by numerous angiogenic factors [2]. Of the known angiogenic factors, Placenta growth factor (PLGF), as a number of the vascular endothelial growth factor (VEGF) family, has been established as a very potent inducer of tumor angiogenesis which can stimulate endothelial cell growth, migration, and amplification, and vascular permeability [3-6]. It is worth to note that the expression of PLGF is undetectable in majority of human tissues under healthy conditions, but in pathological conditions, it is highly expressed in several cell types, such as vascular endothelial cells, smooth muscle cells, keratin cells, hematopoietic stem cells, retinal pigment epithelial cells and various tumor cells [7]. Besides, PLGF selectively binds to Flt-1 which can regulate the contribution of monocyte and macrophages to lymphangiogenesis and angiogenesis [8, 9].

Numerous of evidence suggests that PLGF levels in tumor tissue and/or serum correlated with tumor stage, metastasis, vascularity, recurrence, and survival in various human tumors [10-14]. Lots of clinical studies demonstrate that the expression of PLGF upregulated in various cancer, such as colorectal, hepatocellular, renal and others, and the high PLGF levels are significantly associated with poor prognosis [11, 12, 15, 16]. Nevertheless, some research demonstrated that the PLGF mRNA down regulated or undetectable in several tumors. Moreover, anti-PLGF antibodies as anti-angiogenic therapies in mouse models, and

constituted a functionally relevant mechanism of inhibited the growth and metastasis of tumor in some pre-clinical model. Thus, it is necessary to establish whether PLGF expression is a prognostic biomarker in human cancer. Here, we performed a meta-analysis of published studies to evaluate whether PLGF overexpression may be a prognostic biomarker for survival in multiple cancers.

Material and methods

Search strategy

We searched the relevant studies form the electronic literature database of PubMed to include in our meta-analysis. Our search identified relevant articles up to December 2014, and limited to studies conducted on human theme. Search terms included: ("placental growth factor", or "PLGF"), and ("cancer", OR "carcinoma", OR "sarcoma"), and ("prognostic", OR "survival", "mortality"). The reference of the included studies was manually examined to complete the search.

Inclusion and exclusion criteria

Studies included in this meta-analysis had to meeting the following criteria: 1) they were clinical trials study on human who suffer from cancer. 2) They had to investigating the association between the expression levels of PLGF and survival provided by information of OS, or PFS. 3) Hazard ratio (HR) and their corresponding 95% CI estimated by the sufficient data. The criteria used to exclude of studies were: 1) reviews, letters and repeated literature; 2) the clinical trials about the new drug of anti-angiogenesis.

Data extraction and quality assessment

The following information was carefully extracted from studies using a purpose-designed from: first author, publication year, study population, source of control, different ethnicities were categorized as Asian and non-Asian, Due to the more types of cancer and a relatively small sample size, we classified four types according to the human body system, like digestive system carcinoma, respiratory system tumor and others (hematological cancer, nervous system tumors, urinary genital system tumor), study population, methods of detecting PLGF, specimens, outcomes, and HR estimates with corresponding 95% CI for PLGF which extracted from the most completely adjusted one. If the HRs and their 95% weren't given explicitly, we calculated it from survival information using methods proposed by Parmar et al. [17]. In order to ensure the quality of our meta-analysis, we excluded the studies which without these points. Systematically evaluated was conducted by us according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology [18, 19].

Statistical analysis

HR with 95% confidence intervals (CIs) was used to estimate the strength association strength between PLGF and cancer survival. Heterogeneity was tested by the Q test which was considered statistically significant when P values <0.01 and inconsistency index I^2 statistic which take values between 0% and 100% (I^2<25%: low heterogeneity; I^2=25%-50%: medium heterogeneity; I^2=50%-75%: high heterogeneity; I^2=75%-100%: respectively heterogeneity). According to the heterogeneity of studies, it considered to be significant when P<0.01 or I^2>50%, the random effects model (based on Der Simonian and Laird method) or fixed effects model (based on Mantel-Haenszel method) was used for meta-analysis [20, 21]. By convention, poor survival for high expression level of PLGF was considered when reported HR >1. What's more, if the 95% CI didn't overlap 1, the impact of PLGF on survival of multiple cancers was considered with statistical significance. Robustness of the results of meta-analysis was tested through the sensitivity analyses. Subgroup analyses were performed based on cancer types, ethnicities and detection methods to investigate the value of PLGF for multiple cancers.

The publication bias was evaluated by using the methods of Begg's and of Egger's [22, 23]. A P<0.05 was considered as statistically significant publication bias. All of the calculations were performed by Review Manager 5.2 (RevMan version 5.2; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA version 12.0 (Stata Corporation, College Station, TX).

Results

Characteristics of studies

Nineteen eligible studies [12-15, 24-39], including 2,528 cases of a variety of cancer patients,

Table 1. Main characteristic and results of the eligible studies

First author-year	Cancer	Country	N	Specimen source	Methods	survival analysis method	HR estimation	HR (95% CI)
Chang YT-2008	Pancreatic Cancer	China	92	Serum	ELISA	Kaplan-Meier analysis	Given	OS 0.98 (0.94-1.00)
Chen CN-2004	gastric cancer	China	79	Tissue	Others	Kaplan-Meier analysis	Calculate	OS 1.46 (0.99-2.15)
Cheng SJ-2010	oral squamous cell carcinoma	China	100	Tissue	IHC	Multivariate Cox analysis	Given	OS 4.28 (1.53-20.56)
Cheng SJ-2013	oral squamous cell carcinoma	China	63	Tissue	PCR	Multivariate Cox analysis	Given	PFS 7.28 (3.57-18.27)
Sanmartín E-2013	Non-small Cell Lung Cancer	Spain	175	Tissue	PCR	Kaplan-Meier analysis	Calculate	OS 1.46 (0.93-2.34)
								PFS 1.59 (1.08-2.34)
Maae E-2012	breast cancer	Denmark	229	Tissue	Others	Multivariate Cox analysis	Given	PFS 1.94 (1.08-3.48)
Pompeo E-2009	Malignant pleural mesothelioma	Italy	27	Tissue	IHC	Kaplan-Meier analysis	Calculate	OS 1.82 (1.08-3.07)
								PFS 1.71 (1.11-2.66)
Hilfenhaus G-2013	neuroendocrine tumors (NETs)	Germany	87	Serum	Others	Kaplan-Meier analysis	Given	OS 2.35 (1.08-5.10)
								PFS 4.87 (1.18-20.13)
Ho MC-2007	hepatocellular carcinoma	China	71	Tissue	PCR	Kaplan-Meier analysis	Calculate	PFS 2.06 (0.15-27.5)
Coenegrachts L-2013	endometrial carcinomas	Belgium	128	Tissue	PCR	Kaplan-Meier analysis	Calculate	OS 1.24 (0.51-3.03)
								PFS 0.95 (0.44-2.02)
Rahbari NN-2011	colorectal liver metastases	Germany	107	Serum	ELISA	Multivariate Cox analysis	Given	PFS 0.26 (0.08-0.81)
Rahbari NN-2011	pancreatic cancer	Germany	67	Serum	ELISA	Multivariate Cox analysis	Given	OS 0.87 (0.35-2.12)
Kemik Ö-2012	colorectal cancer	Turkey	158	Serum	ELISA	Multivariate Cox analysis	Given	OS 3.00 (1.53-6.21)
Sujka-Kordowska P-2012	ALL	Poland	264	BM	IHC	Kaplan-Meier analysis	Calculate	PFS 2.12 (1.08-4.16)
Nagaoka S-2010	hepatocellular carcinoma	Japan	78	Serum	ELISA	Kaplan-Meier analysis	Given	OS 1.36 (0.91-2.03)
Sung CY-2012	colorectal cancer	Korea	83	Tissue	IHC	Kaplan-Meier analysis	Calculate	OS 2.17 (1.01-4.65)
Wei SC-2009	colorectal cancer	China	86	Serum	ELISA	Multivariate Cox analysis	Given	OS 3.20 (1.01-10.10)
			71					PFS 2.46 (1.27-4.78)
Xu HX-2010	hepatocellular carcinoma	China	394	Tissue	IHC	Kaplan-Meier analysis	Calculate	OS 1.58 (1.22-2.04)
								PFS 1.43 (1.10-1.87)
			102			Multivariate Cox analysis	Given	OS 2.05 (1.09-3.85)
								PFS 1.95 (1.03-3.69)
Zhang LJ-2005	non-Small cell Lung cancer	China	91	Tissue	IHC	Multivariate Cox analysis	Given	OS 2.74 (1.27-6.10)

Note: N, number of patients; IHC, immunohistochemistry; ELISA, Enzyme-linked immunosorbent assay; RT-PCR, reverse transcription-polymerase chain reaction; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression free survival; BM, bone marrow.

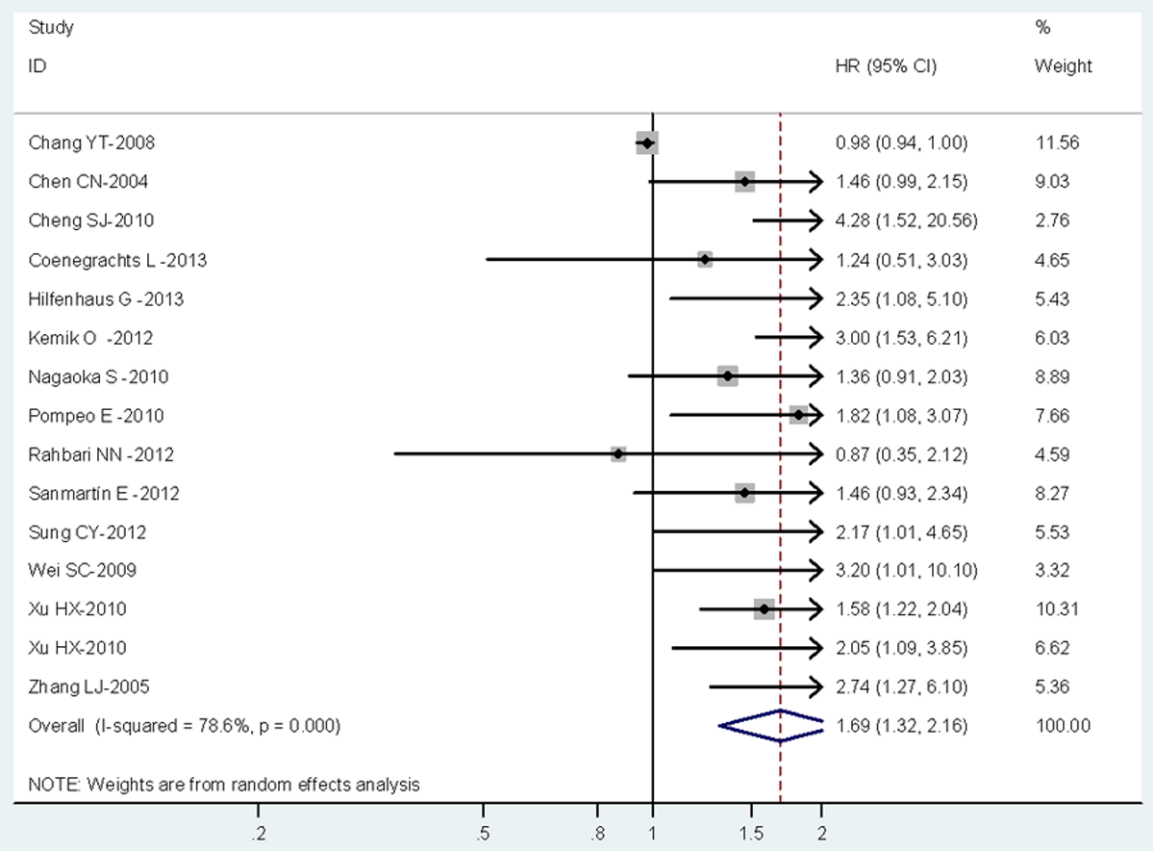

Figure 1. Meta-analysis (forest plot) of 15 included studies evaluation PLGF in Overall survival.

were included in our meta-analysis. The baseline data and other details were presented in **Table 1**. Specimens of 11 studies were collected from tumor tissue, 7 studies used serum specimens, and 1 studies used bone marrow (BM). The eligible studies were conducted in ten countries (China, Spain Germany, Belgium, Denmark, Korea, Italy, Turkey, Poland, Japan). Among them, 10 studies were performed in Asian, and the remaining 9 studies were non-Asian. 6 studies used Enzyme-linked immunosorbent assay (ELISA) to detect the expression of PLGF; 6 studies applied immunohistochemistry (IHC); 4 studies used quantitative real-time PCR (qRT-PCR) and three studies applied other methods (enzyme immunoassay, Luminex System and Roche-Elecsys).

The prognostic value of PLGF status for survival in patients with several cancers (Non-small Cell Lung Cancer, hepatocellular carcinoma (HCC), pancreatic cancer, endometrial carcinomas, colorectal cancer, hepatocellular carcinoma, neuroendocrine tumors (NETs), breast cancer, oral squamous cell carcinoma (OSCC), gastric cancer, Pancreatic Cancer, Malignant pleural mesothelioma, acute lymphoblastic leukaemia (ALL) were reported among the studies. Due to the more types of cancer and a relatively small sample size, we classified four types according to the human body system, like digestive system carcinoma, respiratory system tumor and others (hematological cancer, nervous system tumors, urinary genital system tumor). The HR estimation of 12 studies was directly reported, while others calculated using the information given by authors. Of the 19 studies, 14 studies offered OS, and 11 studies offered PFS.

Meta-analysis

The combined HR of 15 included studies including 1747 cancer patients showed that high PLGF level was associated with poor overall survival (HR=1.69, 95% CI, 1.32-2.16). Furthermore, there was significant heterogeneity among the studies (I^2=78.6%, *P*=0.000), as shown in **Figure 1**. As for PFS, the pooled HR of

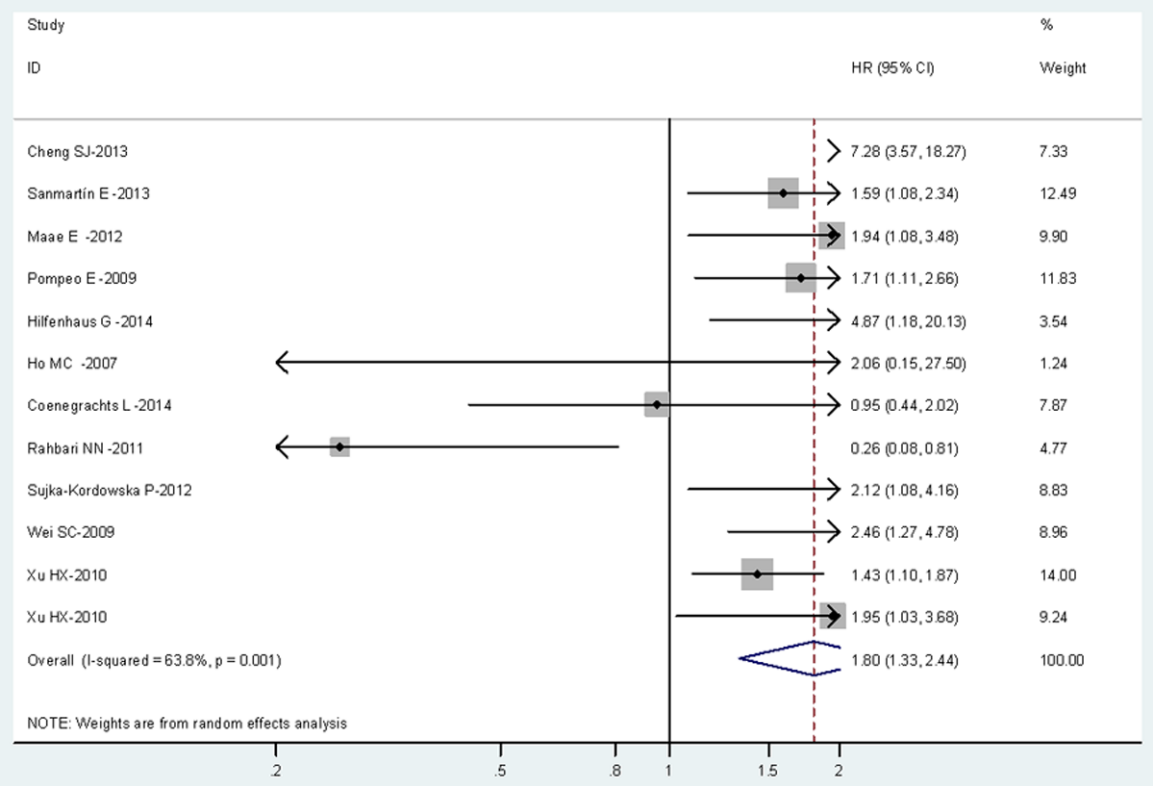

Figure 2. Meta-analysis (forest plot) of 12 included studies evaluation PLGF in Progression-Free Survival.

12 eligible studies including 1678 cancer patients was 1.8 (95% CI, 1.33-2.44), which suggests that high PLGF level represent an indicator of poor prognosis for multiple cancer, and significant heterogeneity was found between studies (I^2=63.8%, *P*=0.001), as shown in **Figure 2**.

Tumor type analysis

Analysis by tumor type was performed in **Table 2**. It showed high expression of PLGF was associated with poor OS in digestive system carcinoma (HR=1.63, 95% CI, 1.21-2.19), and significant heterogeneity was observed in studies (I^2=80.7%, *P*<0.001). But not obvious associated with poor PFS in those cancer patients (HR=1.81, 95% CI, 0.93-3.52; I^2=80.2%, *P*<0.001). In respiratory system tumor, the similar result found high expression of PLGF predicted poor OS (HR=1.75, 95% CI, 1.28-2.41) without heterogeneity (I^2=0.0%, *P*=0.394) and PFS (HR=1.64, 95% CI, 1.23-2.19) without heterogeneity (I^2=0.0%, *P*=0.807) either. In other system cancers, it also suggest a poor PFS (HR=1.79, 95% CI, 1.24-2.59; I^2=38.6%, *P*=0.181).

Other subgroup analysis

We performed other subgroup analysis on ethnicity, high expression of PLGF associate with poor OS either in Asian patients (HR=1.68, 95% CI, 1.23-2.28, *P*=0.001; I^2=81.6%, *P*<0.001) or non-Asian patients (HR=1.70, 95% CI, 1.31-2.21, *P*<0.001; I^2=20.4%, *P*=0.279). Moreover, the same founding for the PFS in Asian patients (HR=2.44, 95% CI, 1.35-4.39, *P*=0.003; I^2=73.4%, *P*=0.005) and non-Asian patients (HR=1.50, 95% CI, 1.02-2.22, *P*=0.040; I^2=59.5%, *P*=0.022). Studies detected by IHC found high expression of PLGF indicated worse OS (HR=1.79, 95% CI, 1.47-2.19, *P*=0.000; I^2=0.0%, *P*=0.525) and PFS (HR=1.59, 95% CI, 1.30-1.95, *P*=0.000; I^2=0.0%, *P*=0.615). However, in studied which detected by ELISA or PCR, the combined HR didn't show obvious association between high expression of PLGF and survival. Then, other subgroup analysis including sources of specimen and survival analysis method were performed, all of them suggested that high PLGF level was an indicator of poor prognosis for multiple cancer. As shown in **Table 2**.

Table 2. Meta-analysis: HRs value of OS and PFS in overall and subgroups of multiple cancer according to study design

	Subgroup	No. of cases	No. of studies	Pooled HR (95% CI)	*P*-value	Heterogeneity	
						I^2 (%)	*P*-value
OS	Overall	1747	15	1.69 (1.32-2.16)	<0.001	78.6	<0.001
	Tumor type						
	Digestive system carcinoma	1239	10	1.63 (1.21-2.19)	0.001	80.7	<0.001
	Respiratory system tumor	293	3	1.75 (1.28-2.41)	0.001	0.0	0.394
	Others	215	2	1.78 (0.99-3.20)	0.053	11.1	0.289
	Ethnicity						
	Asian patients	1105	9	1.68 (1.23-2.28)	0.001	81.6	<0.001
	non-Asian patients	642	6	1.70 (1.31-2.21)	<0.001	20.4	0.279
	Detection methodl						
	IHC	797	6	1.79 (1.47-2.19)	<0.001	0.0	0.525
	ELSIA	481	5	1.45 (0.93-2.25)	0.104	75.6	0.003
	qRT-PCR	303	2	1.41 (0.94-2.12)	0.100	0.0	0.750
	Others	166	2	1.61 (1.13-2.27)	0.007	13.5	0.282
	Survival analysis method						
	Kaplan-Meier analysis	1143	9	1.46 (1.14-1.89)	0.003	77.8	<0.001
	Multivariate Cox analysis	604	6	2.29 (1.63-3.21)	<0.001	23.5	0.257
	Specimen source						
	Serum	568	6	1.56 (1.02-2.40)	0.042	76.4	0.001
	Tissue	1179	9	1.67 (1.42-1.96)	<0.001	0.0	0.661
PFS	Overall	1678	12	1.80 (1.33-2.44)	<0.001	63.8	<0.001
	Tumor type						
	Tumor type	808	6	1.81 (0.93-3.52)	0.079	80.2	<0.001
	Respiratory system tumor	202	2	1.64 (1.23-2.19)	0.001	0.0	0.807
	Others	668	4	1.79 (1.24-2.59)	0.002	38.6	0.181
	Ethnicity						
	Asian patients	701	5	2.44 (1.35-4.39)	0.003	73.4	0.005
	non-Asian patients	977	7	1.50 (1.02-2.22)	0.040	59.5	0.022
	Detection method						
	IHC	787	4	1.59 (1.30-1.95)	<0.001	0.0	0.615
	ELSIA	178	2	0.84 (0.09-7.60)	0.879	90.8	0.001
	qRT-PCR	437	4	2.15 (0.87-5.29)	0.096	79.1	0.002
	Others	276	2	2.22 (1.29-3.81)	0.004	27.7	0.240
	Survival analysis method						
	Kaplan-Meier analysis	1059	6	1.52 (1.27-1.82)	<0.001	0.0	0.703
	Multivariate Cox analysis	619	6	2.14 (1.06-4.33)	0.033	78.2	<0.001
	Specimen source						
	Serum	225	3	1.45 (0.30-7.02)	0.646	85.1	0.001
	Tissue	1189	8	1.81 (1.34-2.44)	<0.001	57.5	0.021
	BM	264	1	2.12 (1.08-4.16)	0.029	-	-

Publication bias

At last, the Publication bias of our meta-analysis was performed by Begg's funnel plot and Egger's test. 12 studies evaluating PFS of patients with multiple cancer yield a Begg's and Egger's test which score of P=0.304 and P=0.519 respectively. Meanwhile according to the funnel plot (**Figure 3**), there were no publication biases. However, for evaluating high

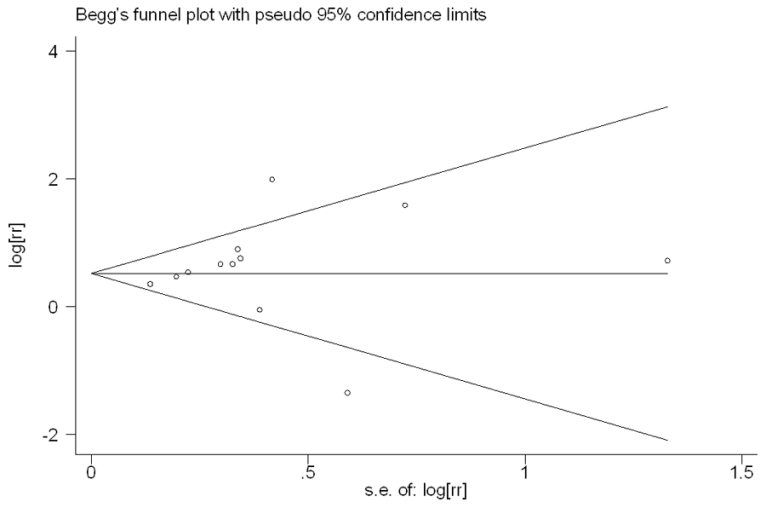

Figure 3. Funnel plot of the 12 evaluable studies assessing PLGF in multiple cancer for progression-free survival.

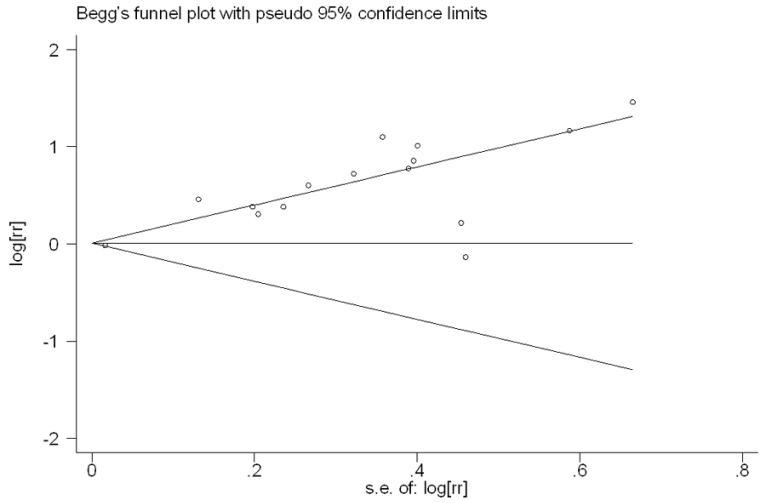

Figure 4. Funnel plot of the 15 evaluable studies assessing PLGF in multiple cancer for overall survival.

PLGF level on OS of patients in 16 studies, publication biases was found (Begg's test P=1.0 and Egger's test P<0.001) (**Figure 4**).

Discussion

Although various pre-clinical models and clinical studies have been conducted, the role of PLGF in tumor growth and tumor angiogenesis is still controversial [40]. Moreover, increasing clinical settings have been demonstrated the relationship between expression of PLGF and prognosis for multiple cancers. Here, we performed the first meta-analysis by collected complete articles and pooled the prognostic value to explore the association between PLGF and cancer prognosis.

In present meta-analysis, included 19 studies with 2528 cases, were identified and analyzed. The results shown that PLGF over-expression is a poor prognostic factor in multiple cancers with statistical significance for OS (HR=1.69, 95% CI, 1.32-2.16), and PFS (HR=1.8, 95% CI, 1.33-2.44). According to the different of tumor type, ethnicity, detection and survival analysis method, and specimen source, we conducted the subgroup analysis. For tumor type, the analysis indicated a statistically significant detrimental effect of PLGF on OS in digestive and respiratory systems carcinomas. Furthermore, high PLGF expression also significantly related with worse PFS in respiratory system carcinoma and others, but not on PFS in digestive respiratory system carcinoma. Several studies have confirmed that PLGF was high expressed in digestive and respiratory systems cancers [28, 35]. Further studies showed that inhibiting the production of PLGF in NSCLC can reduce the activity of tumor cells [41]. Thus, PLGF may be used as a prognostic marker and therapeutic target for those two systems carcinomas.

Furthermore, there are several limitations for our analysis. (1) Non-English literature was included in our meta-analysis which leads to lose some potential important survival data; meanwhile there might be selection bias. (2) Different detection methods (IHC, ELISA, RT-PCR or others) were used to detect the expression of PLGF in multiple cancers. (3) The sources of specimen were different from tis-

sue, serum or bone marrow in different studies. (4) No consistent standard for cut-off values in our eligible studies. All of above might cause clinical and statistical heterogeneity. Moreover, the HRs itself may source of heterogeneity owing to the methodology for calculating from unreported articles. In order to decrease the influence of this heterogeneity, we used a random effects model and performed subgroup analysis. However, due to the number of studies of each tumor type especially in the other system type and the patient cases of subgroup were limited, we still need more researches to analyze the value of PLGF expression in multiple cancers. Although our results demonstrated that high PLGF expression is poor prognostic factor for OS and PFS in cancer patients, we could not identify it as an independent prognostic fact of all the tumors. On the contrary, in the Rahbari NN et al. 2011 study, we found the low levels of circulating PLGF predicted a poor recurrence-free survival [34].

Publication bias is a major concern for all forms of meta-analysis [42]. The present analysis only included the published studies; we did not search for unpublished. Nevertheless, most of those published articles with a positive results; the negative results are often rejected or not even given in the articles. And part of the results was based on unadjusted HRs which may cause serious confounding bias. Under those possibility of publication bias, our meta-analysis could not completely exclude bias although no publication bias for OS was indicated. Much less, a publication bias for PFS. All of those affect the prognosis. As a result, it is necessary to flexibly regard these results.

To sum up, due to the heterogeneity, biases, and other limitations our paper is imperfect, but it is worth noting that PLGF is a candidate prognostic biomarker. The present meta-analysis demonstrated that PLGF over-expression is associated with poor outcome in multiple cancers. To strengthen our findings, more large-scale and well-designed studies need to further investigate the associations of PLGF with survival of multiple cancers.

In conclusion, we demonstrated that PLGF over-expression is significantly associated with poor overall survival and progression-free survival, especially in respiratory and digestive system carcinoma. High expression of PLGF may predict poor prognosis in different cancer. At the same time, the target of PLGF could become an effective target for anticancer therapy.

Disclosure of conflict of interest

None.

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