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Prognostic value of visfatin in various human malignancies: A systematic review and meta-analysis

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ABSTRACT

Although numerous studies have shown that visfatin is linked to several cancers, its prognostic value is still unclear. This first comprehensive meta-analysis was performed to evaluate the prognostic effect of visfatin in cancer patients. A systematic search was conducted for relevant studies in health-related electronic databases up to May 2019. The pooled hazard ratios (HRs) and ORs with 95% confidence intervals (CIs) for total and stratified analyses were calculated to demonstrate the prognostic value of visfatin expression level in cancer patients. Heterogeneity and publication bias were also investigated. A total of 14 eligible studies with 1616 patients were included in the current meta-analysis. Pooling results revealed that, high visfatin expression was significantly associated with poorer overall survival (OS) (HR = 2.43, 95% CI 1.64–3.62, P < 0.001). Elevated visfatin level was also correlated with positive lymph node metastasis (OR = 2.45, 95% CI 1.43–4.17, P ≤ 0.001), positive distance metastasis (OR = 2014, 95% CI 1.25–3.69, P ≤ 0.001), advanced tumor stage (OR = 3.01, 95% CI 1.91–7.72, P ≤ 0.001), and larger tumor size (OR = 1.99, 95% CI 1.49–2.69, P ≤ 0.001). Our meta-results indicates that altered visfatin expression is a potential indicator of poor clinical outcomes in tumor patients, suggesting that high visfatin expression may serve as a potential biomarker of poor prognosis and metastasis in cancers.

1. Introduction

Although the mortality of cancer has dropped in the past two decades, it is still the biggest human health problem. According to WHO, cancer as the second leading cause of death, has been responsible for an estimated 9.6 million deaths in 2018 [1]. Lack of valid and reliable markers for early detection of cancer has been associated with reduced survival rate. Developing new specific biomarkers is necessary to increase the efficiency of early detection and treatment of cancers.

Evidences have revealed that obesity and overweight are associated with different types of malignancy such as colorectal, pancreatic, renal, prostate, breast, endometrial, thyroid and esophageal cancers [2]. However, the mechanisms underlying the association between obesity and cancer are not fully elucidated. The relationship between obesity and cancer seems to be due to disturbances in adipocytokines, insulin metabolism, and sex hormones as well as inflammation [3]. Adipocytokines as small peptide hormonal growth factors secreted by adipocytes are important mediators of metabolic regulation [4]. Adipocytokines have shown modified expressions that may attribute obesity to cancer [3]. Altered serum levels of some adipocytokines including adiponectin, leptin, visfatin, and omentin have been reported in various cancers due to their multidirectional metabolic functions [5–8].

Visfatin or nicotinamide phosphorybosiltransferase (NAMPT) or pre-B-cell-enhancing factor has been shown to be involved in different cancers as it plays important roles in the synthesis of cellular nicotinamide adenine dinucleotide (NAD+), regulation of cellular growth, angiogenesis, and apoptosis in mammalian cells [9–11].

Visfatin overexpression has been reported in colorectal, gastric, breast, prostate, pancreatic, and esophageal cancers [12–17]. In addition, a recent meta-analysis have revealed a significant association

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between high circulating visfatin (eNampt) levels and increased risk of various cancers [7]. Nevertheless, a consensus on the prognostic value of visfatin in various cancers is yet to be done. In this meta-analysis, all relevant published evidences are systematically pooled to elucidate the prognostic significance of visfatin (both intracellular and extracellular) in different tumors.

2. Methods

2.1. Literature search strategy and study selection

An electronic literature search of databases including Medline, Web of sciences, Embase, and Scopus was conducted for English publications up to May/2019. The search terms included "visfatin", "NAMPT", "PBEF", "Visfatin/NAMPT", "Visfatin/PBEF", "nicotinamide phosphoribosyltransferase", "pre-B-cell colony-enhancing factor 1 (PBEF1)", "NAmPRTase" "cancer", "carcinoma", "neoplasm", "tumor" and "prognosis or prognostic or survival or outcome" or their equivalents were used individually or/and in various combinations to retrieve the relevant literatures. We increased the integrity and accuracy of the search process by manually screening the reference lists for the included articles to explore potential studies.

2.2. Inclusion and exclusion criteria

The studies were considered eligible if they met all of the following inclusion criteria: proven diagnosis of solid tumor in human; evaluation of visfatin expression both in serum/plasma or tissue; any study investigating the relationship between visfatin expression and survival; having sufficient data for estimation of hazard ratio (HR) and their corresponding 95% confidence intervals (CI). Articles with the following criteria were excluded: review or laboratory articles; case studies; letters; articles describing the survival outcome of other indicators; and unpublished studies. In the case of articles by the same author using the same patients, only the most recent or complete study was included.

2.3. Data extraction and quality assessment

Two authors (MM and HMM) independently performed data extraction from all eligible publications. Briefly, the following information was extracted from each study: first author's surname, publication year, country of origin, cancer type, study design, source of visfatin (serum or tissue), visfatin detection assay, number of cases and controls, tumor stage, visfatin overexpression cutoff value, prognostic outcomes of interest, analytical method, and HR with its 95% CI. Regarding the quality assessment, two investigators (AM and HMM) independently assessed and scored the included studies according to the Newcastle-Ottawa Scale (NOS). Any disagreements were resolved through discussion with a third investigator (AA).

2.4. Statistical analysis

High and low visfatin expression was defined according to the arbitrary cutoff values provided by the literature. The impact of visfatin over expression on prognosis of solid tumors was estimated by pooled hazard ratios (for overall survival (OS)) or odds ratios (for clinicopathological outcomes) (HRs or ORs) and 95% CI. Crude values were directly used when HRs were reported in the original studies; otherwise, the values were calculated using Kaplan–Meier curves according to the methods described by Parmar [18], Williamson et al [19], and Tierney et al [20]. Statistical heterogeneity between the studies was quantified using Cochran's Q test and Higgins I-squared statistics. Heterogeneity was defined as $P < 0.05$ or $I^2 > 50\%$. In case of significant heterogeneity, the random effect model was selected to combine the data; otherwise, fixed effect model was used. Poor outcome for visfatin over expression was considered when the HR was > 1 and the 95% CI did not include 1. Subgroup, sensitivity, and Galbraith plot analyses were performed to explore the source of heterogeneity. Publication bias was investigated through visual assessment of the asymmetry of an inverted funnel plot. The Begg's and Egger's tests were also conducted to quantitatively support the publication bias. All analyses were performed using the Comprehensive Meta-Analysis software. A P-value < 0.05 was considered as statistically significant.

3. Results

3.1. Literature search

The detailed process of screening, identification, and selection of the eligible articles is presented in Fig. 1. Based on the inclusion and exclusion criteria, a total of 438 studies were retrieved in the initial search. After screening titles and abstracts, 378 articles were excluded as basic research, animal studies, reviews, conference abstracts,

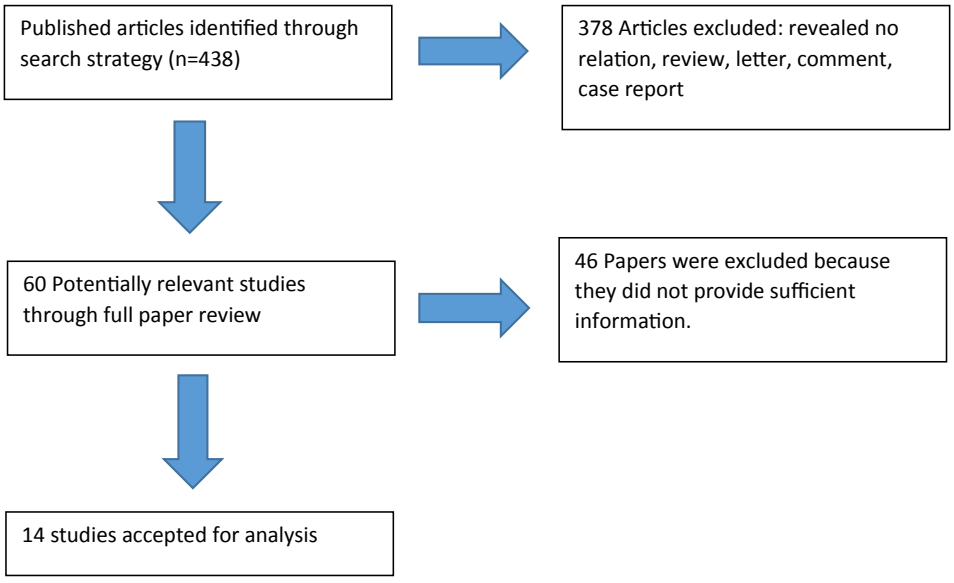

Fig. 1. Flow diagram of the study selection.

Table 1
Basic characteristics of the included studies.

Study/year	Age (High/Low)	Country	Tumor type	Histological grade (High/Low)	Tumor size (High/Low)	Sample size (n)	Male (High/Low) Female (High/Low)	TNM Stage (High/Low)	Specimen	Cut-off value	Visfatin expression						Survival analysis	HR (95% CI) (High/Low)	Method	References
											High (n)			Low (n)						
											Total	LNM	DM	Total	LNM	DM				
Zhou, 2018	≤50 19/25 > 50 21/18	China	Breast cancer	I/II 28/34 III 12/9	< 2 12/25 ≥2 28/18	83	Female	I/II 26/37 III/IV 14/6	Tissue	a total staining score of 3	40	16	–	43	7	–	UA MA	3.13 (1.27-7.73) 0.53 (0.17-1.59)	IHC	[21]
Cymbaluk-Ploska, 2018	NA	Poland	EC	–	–	62	–	–	Serum	20.7 ng/ml	–	–	–	–	–	–	UA	0.97 (0.36–2.74)	EIA	[22]
Li H, 2017	< 60 23/27 ≥60 41/25	China	EJA	G1 & G2 33/25 G3& G4 31/27	–	116	39/31 25/21	I/II 20/44 III/IV 44/8	Tissue	a total staining score of 4	64	51	–	52	13	–	UA MA	6.78 (1.81–25.33) 3.00 (1.03–8.69)	IHC	[17]
Sun, 2017	< 60 42/62 > 60 12/19	China	HCC	–	< 3cm 22/56 ≥3cm 32/25	135	51/67 3/14	I, II 21/49 III, IV 33/32	Serum	1.403	54	–	–	81	–	–	UA	#1.84 (0.96–1.90)	ELISA	[23]
Zhu Y, 2016	≤50 13/10 > 50 13/12	China	Breast cancer	–	≤2 cm 10/9 > 2 cm 16/13	48	Female	0-II 18/20 III-IV 8/2	Tissue	The final staining index	26	11	–	22	6	–	–	–	IHC	[24]
Yang J, 2016	≤60 10/6 > 60 52/19	China	CRC	–	≤10 cm3 21/8 > 10 cm3 41/17	87	34/12 28/13	–	Tissue	a total staining score	53	41	–	25	13	–	UA	* 1.37 (0.48–4.0)	IHC	[25]
Ke, 2015	< 65 20/17 ≥65 40/28	Taiwan	UC	Low 13/21 High 47/24	–	105	30/20 30/25	I/II 28/36 III/IV 32/9	Tissue	Stained cell < 50%	60	–	–	45	–	–	UA DSS MA	9.04 (2.10–38.88) 5.74 (1.27–25.98)	IHC	[26]
Lv, 2015	< 60 9/8 ≥60 26/14	China	CRC	–	< 5 22/12 ≥ 5 13/10	57	16/10 19/10	I/II 19/10 III/IV 16/12	Tissue	Staining index	35	14	–	22	9	–	–	–	IHC	[27]
Lu, 2014	< 60 59/82 ≥ 60 51/70	China	GC	–	< 5 66/116 ≥ 5 44/36	262	66/90 44/62	I-II 31/76 III-IV 79/76	Plasma	Mean value (78.4 ng/mL)	110	91	42	152	89	34	UA MA	3.77 (2.35–5.195) 2.97 (1.87–5.20)	EIA	[28]
Zhang K, 2014	≤64 33/24 > 64 32/42	China	BC	Low 32/28 High 33/38	–	131	55/52 10/14	–	Serum	Median level (14.74 ng/mL)	65	9	–	66	11	–	UA MA	0.79 (0.31–2.01) 0.94 (0.37–2.39)	ELIZA	[29]
Li XY, 2014	≥45 116 ≤45 132	China	Breast cancer	Low 136 High 112	< 2 cm 137 ≥2 cm 111	248	–	I–II 175 III–IV 73	Serum	65.6 ng/mL	–	–	–	–	–	–	UA MA	3.01 (1.741–5.193) 2.91 (1.64–5.03)	EIA	[30]
Tian, 2013	< 50 7/17	China	EC	Low 50/50	–	126	–	I–II 44/57	Tissue		61	9	–	65	7	–			IHC	[31]

(*continued on next page*)

Table 1 (*continued*)

Study/year	Age (High/Low)	Country	Tumor type	Histological grade (High/Low)	Tumor size (High/Low)	Sample size (n)	Male (High/Low) Female (High/Low)	TNM Stage (High/Low)	Specimen	Cut-off value	Visfatin expression					Survival analysis	HR (95% CI) (High/Low)	Method	References
											High (n)			Low (n)					
											Total	LNM	DM	Total	LNM DM				
	≥ 50 52/48			High 6/9				III–IV 17/8		a total staining score of 3						UA	1.12 (0.24–5.26)1.78		
Lee, 2011	≤ 50 24/32 > 50 26/23	Taiwan	Breast cancer	I/II 33/41 III 17/14	< 2 17/31 ≥ 2 33/24	105	Female	I/II 36/47 III/IV 14/8	Tissue	a total staining score of 3	50	16	–	55	9 –	UA MA	5.73 (1.92–17.14) 4.11 (1.15–14.70)	IHC	[32]
Reddy, 2008	–	India	GBM	–	–	51	–	–	Tissue	50% cell positivity	31	–	–	20	– –	UA MA	1.33 (0.11–15.6) 1.75 (0.21–14.9)	IHC	[33]

EC: endometrial cancer, EJA:esophagogastric junction adenocarcinoma, CRC: colorectal cancer, HCC: hepatocellular carcinoma, UC:urothelial carcinoma, GC: gastric cancer, BC:bladder cancer, GBM: glioblastoma, UA:univariate analysis, MA: multivariate analysis, IHC: immunohistochemistry, EIA: enzyme immunoassay, ELIZA: enzyme-linked immunosorbent assays.

meta-analysis, letters, case reports, or expert opinions. Then, the remaining 60 articles were subjected to full-text evaluation. Of these, 46 articles were excluded due to insufficient data to estimate HR or OR for quantitative analysis. Finally, a total of 14 eligible articles with 1616 patients were included in the current meta-analysis [17,21–33].

3.2. Study characteristics

The general characteristics of the selected studies are summarized in Table 1. All studies were published between 2008 and 2018. In the included 14 studies, 10 studies were conducted in China [17,21,23–25,27–31], two in Taiwan [26,32], one in Poland [22], and one in India [33]. Nine different types of cancer including two endometrial cancers (EC), one esophagogastric junction adenocarcinoma (EJA), one hepatocellular carcinoma (HCC), two colorectal cancers (CRC), one urothelial carcinoma (UC), one gastric cancer (GC), one bladder cancer (BC), four breast cancers, and one glioblastoma (GBM) were evaluated in this meta-analysis. Visfatin expression levels were measured either in serum or tumor specimens.

The cut-off values for high or low visfatin expression levels varied throughout the different studies. Regarding the HR estimations, the HR values were directly reported from seven studies, while, for five studies, the HRs were calculated through data reading from Kaplan-Meier survival curves. However, two studies had reported no data regarding the OS. Moreover, nine articles provided data regarding the association between visfatin expression and lymph node metastasis (LNM), one article reported distance metastasis (DM), nine articles reported TNM stage, six articles reported tumor histological grade, and seven studies reported tumor size. Ten articles with NOS scores greater than five were considered as high quality studies.

3.3. Association between visfatin level and OS in cancers

A cumulative meta-analysis was performed to assess the relationship between the visfatin expression level and OS. As for survival analysis, nine out of fourteen studies had reported the OS outcomes both in univariate and multivariate models, while three studies reported HR in only univariate model. Data from 12 studies with 1511 patients reporting HR in univariate model, were compiled to evaluate the impact of visfatin on survival rate. Due to a significant heterogeneity among the studies (I^2 = 53.43, P = 0.014) the random effects model was applied. The pooled HR indicated that high visfatin expression levels were significantly associated with poor OS compared with the low visfatin expression (HR = 2.43, 95% CI 1.64–3.62, P < 0.001) (Fig. 2).

Considering the significant heterogeneity, subgroup analysis was also performed according to the cancer type (digestive or non-digestive), sample size, specimen type (serum or tumor type), and study quality. Stratified analysis based on the cancer type revealed a significant association between high visfatin level and poor OS both in digestive (HR = 2.72, 95% CI 1.51–4.88, P < 0.001) and non-digestive cancers (HR = 2.25, 95% CI 1.26–4.02, P = 0.006) (Table 2) (Fig. 2). In subgroup analysis according to sample size, no significant association was observed for high visfatin level and patient survival in studies < 100 cases (HR = 1.66, 95% CI 0.939–2.49, P = 0.081) (Table 2). However, high visfatin level was significantly associated with poor OS in eight studies with sample size ≥100 (HR = 2.85, 95% CI 1.77–4.61, P < 0.001) (Table 2). In addition, high visfatin expression was significantly related to poor OS in both groups using serum (HR = 1.95, 95% CI 1.12–3.38, P < 0.019) or tissue (HR = 3.22, 95% CI 1.78–5.84, P < 0.001) (Table 2) as visfatin sources. Also, meta-analysis on the study quality subgroups indicated that high visfatin expression was associated with poor OS in only high quality studies (HR = 2.57, 95% CI 1.98–3.33, P < 0.001; fixed effects) (Table 2).

Moreover, cumulative meta-analysis was also performed to determine the association of visfatin expression with OS outcome in

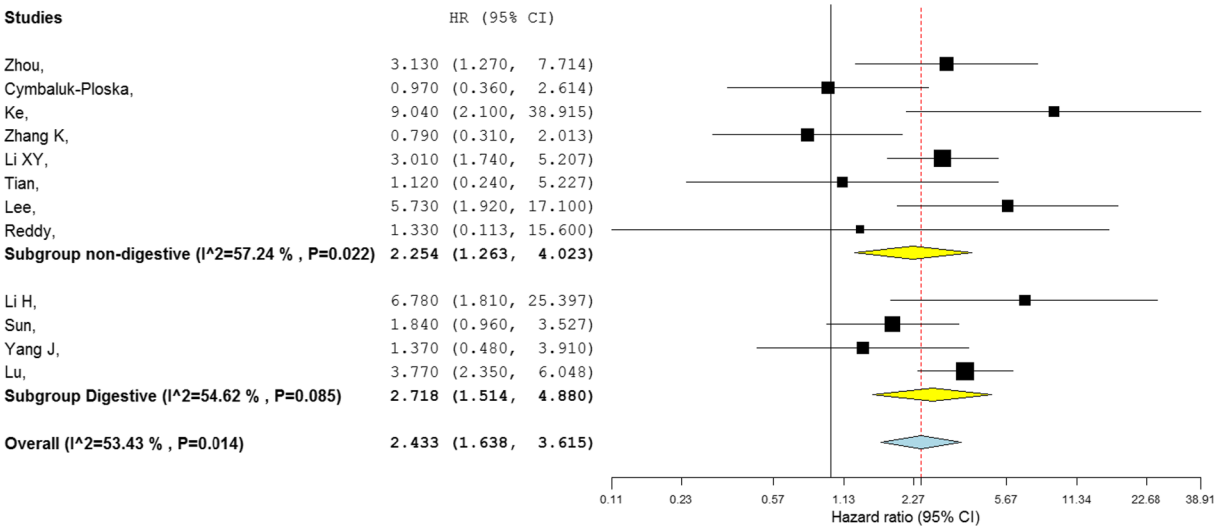

Fig. 2. Forest plot showing the association between OS and visfatinexpression inoverall and based on different cancer types.

Table 2
Stratified analyses of pooled hazard ratios for overall survival.

Categories		Studies (n)	No. of patients	Test of association		Heterogeneity		
				Pooled HR (95% CI)	*P*-value	I^2 (%)	*P*-value	Model
Univariate Survival Analysis								
Overall survival (OS)		12	1511	2.43 (1.64–3.62)	< 0.001	53.43	0.014	R
Cancer Type	Digestive system	4	600	2.72 (1.51–4.88)	< 0.001	54.62	0.085	R
	Others	8	911	2.25 (1.26–4.02)	0.006	57.24	0.023	R
Sample size	< 100	4	283	1.66 (0.939–2.94)	0.081	5.86	0.939	F
	> 100	8	1228	2.85 (1.77–4.61)	< 0.001	59.72	0.015	R
Tumor specimen	Serum	5	838	1.94 (1.12–3.38)	< 0.001	70.22	0.009	R
	Tissue	7	673	3.22 (1.78–5.84)	< 0.001	33.73	0.171	F
Quality score	> 5	9	1228	2.57 (1.98–3.33)	< 0.001	46.63	0.059	F
	≤5	3	283	3.63 (0.815–16.18)	0.091	76.68	0.014	R
Multivariate Survival Analysis								
Overall survival (OS)		9	1227	2.13 (1.46–3.12)	< 0.001	49.92	0.043	R
Cancer Type	Digestive system	2	378	2.98 (1.95–4.55)	< 0.001	0	0.987	F
	Others	7	849	1.87 (1.14–3.06)	0.013	53.02	0.047	R
Sample size	< 100	2	134	0.689 (0.25–1.88)	0.467	0	0.334	F
	> 100	7	1093	2.27 (1.81–2.85)	< 0.001	39.41	0.129	F
Tumor specimen	Serum	3	641	2.27 (1.28–4.03)	0.005	60.17	0.081	R
	Tissue	6	586	1.87 (1.39–2.52)	0.001	45.35	0.103	F
Quality score	> 5	7	1006	1.94 (1.27–2.95)	0.002	56.63	0.032	R
	≤5	2	221	3.73 (1.56–8.92)	0.003	0	0.492	F

HR: hazard ratio; CI: confidence interval; R: random effect model; F: fixed effect model.

multivariate model, from nine studies with 1227 patients. The pooling results showed a significant relationship between the high visfatin level and unfavorable OS, indicating an independent relationship between visfatin and cancer prognosis (HR = 2.13, 95% CI 1.46–3.12, P < 0.001) (Table 2). In stratified analysis based on cancer type, sample size, specimen type, and study quality, meta-results indicated a significant association of elevated visfatin level with poor OS in all subgroups except for studies with sample sizes less than 100 cases (HR = 0.689, 95% CI 0.25–1.88, P = 0.467) (Table 2).

3.4. Association between visfatin and clinicopathological characteristics

A meta-analysis was performed to assess the association between visfatinexpression level and clinicopathological characteristics. The pooled ORs and 95% CIs of all outcomes including LNM, DM, tumor histological grade, tumor size, TNM stage, age, and gender are presented in Table 3. Briefly, nine studies with 1015 patients, one study with 262 patients, six studies with 666 patients, seven studies with 777 patients, nine studies with 1037 patients, eleven studies with 1255 patients, and seven studies with 893 patients provided data for assessing the relationship between visfatin expression and LNM, DM, tumor histological grade, tumor size, TNM stage, age and gender of patients, respectively. As shown in Table 3, the pooling results indicated a significant association of elevated visfatin expression with positive LNM (OR = 2.45, 95% CI 1.43–4.17, P ≤ 0.001, random-effect) (Fig. 3), positive DM (OR = 2014, 95% CI 1.25–3.69, P ≤ 0.001), advanced TNM stage (OR = 3.01, 95% CI 1.91–7.72, P ≤ 0.001, random-effect), and larger tumor size (OR = 1.99, 95% CI 1.49–2.69, P ≤ 0.001, fixed-effect). However, the pooling results indicated that the over expression of visfatin was not associated with tumor differentiation (OR = 1.37, 95% CI 0.79–2.38, P = 0.262, random-effect), age (OR = 1.99, 95% CI 0.95–1.62, P = 0.130, fixed-effect) and gender (OR = 0.84, 95% CI 0.63–1.12, P = 1.262, fixed-effect) of patients.

3.5. Sensitivity analysis and publication bias

Galbraith plot analysis was carried out to detect the outlier studies as the potential sources of heterogeneity. For the pooling OS and other

Table 3
Meta-analysis of the association between visfatin expression and clinicopathological characteristics.

Stratified analysis	Studies (n)	No. of patients	Test of association		Heterogeneity		
			Pooled OR (95% CI)	*P*-value	I^2 (%)	*P*-value	Model
Gender (male vs. female)[a]	7	893	0.84 (0.63–1.12)	0.232	0.00	0.630	F
Age (High vs. Low)	11	1255	1.99 (0.95–1.52)	0.130	4.44	0.401	F
Tumor size (large vs. small)	7	777	1.99 (1.49–2.69)	< 0.001	40.69	0.120	F
Histological grade (Poorly and others vs. well and moderately)	6	666	1.37 (0.79–2.38)	0.262	61.70	0.023	R
LNM (yes vs. no)	9	1015	2.45 (1.43–4.17)	< 0.001	65.34	0.003	R
DM (yes vs. no)[b]	1	262	2.14 (1.25–3.69)	< 0.001	NA	NA	NA
TNM stage (III + IV vs. I + II)	9	1037	3.01 (1.91–4.72)	< 0.001	55.70	0.021	R

CI: confidence interval; LNM: lymphatic node metastasis; DM: distant metastasis; NA: not applicable; TNM: tumour-node-metastasis.
[b] The heterogeneity is not applicable, for there is only one study reported data about DM.
[a] Three studies about breast cancer was not involved because there were only female patients in the studies.

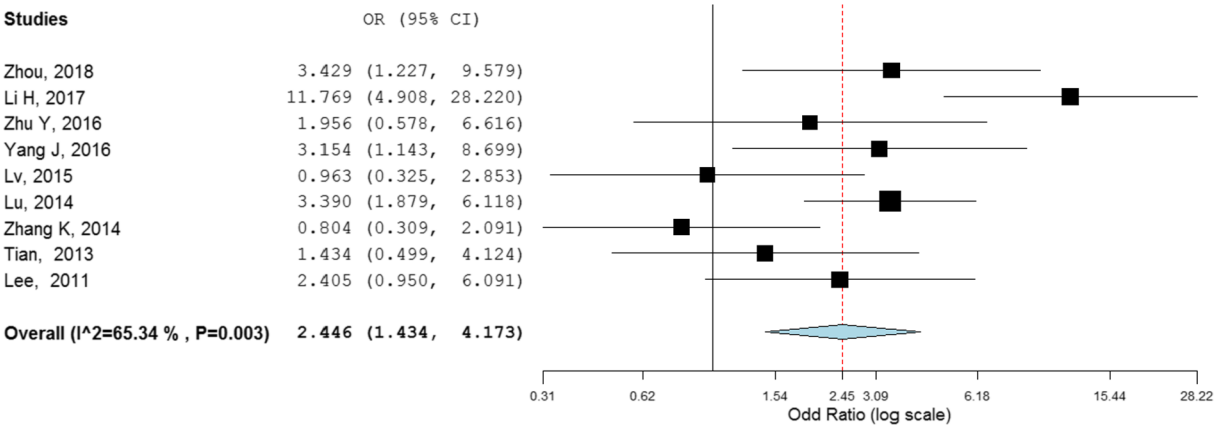

Fig. 3. Forest plot showing the association between LNM and visfatin expression in different cancer types.

ORs analysis, no specific study was detected as the outliers and possible major contributors to the moderate available heterogeneity (Fig. 4). Moreover, sensitivity analysis assessing the effect of each study on the overall results of meta-analysis, revealed that sequential deletion of any single study did not significantly change the direction of the HRs and ORs, indicating the stability and robustness of the pooled results (Fig. 5).

The Begg's funnel plot and Egger's tests were also conducted to detect the publication bias for the present meta-analysis. The visual inspection of funnel plots and Egger's test results for OS showed that there was no significant publication bias across the included studies (Fig. 6). However, the Egger's test results for ORs of visfatin over expression on the LNM and TNM of patients in nine studies indicated a significant publication biases (Egger's test, P < 0.0.001).

4. Discussion

Although there have been great advances in cancer prevention and treatment during the past decades, many cancers cannot be cured yet due to the lack of effective biomarkers for early detection and subsequent efficient treatment at the terminal stages. Currently, increasing evidence supports the association between adipocytokines and cancer risk. Several studies have reported altered visfatin expression (both in mRNA and protein levels) in various types of cancer [31,34–36]. Increasing evidence has shown that visfatin may affect many aspects of cancer cells and regulate angiogenesis, proliferation, metastasis, and drug resistance. Hence, it may be used as a potential prognostic marker and therapeutic target for cancer metastasis and progression, providing impetus for further investigations.

Visfatin regulates cancer cell proliferation by several mechanisms. For example, it has been shown to induce exogenous gastric cancer cell

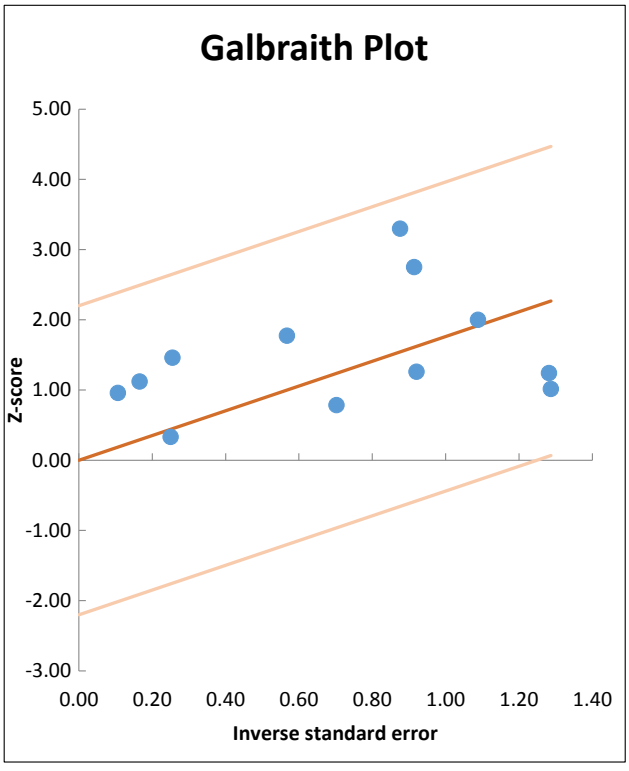

Fig. 4. Galbraith plots of the association between visfatin expression and OS in different cancer types.

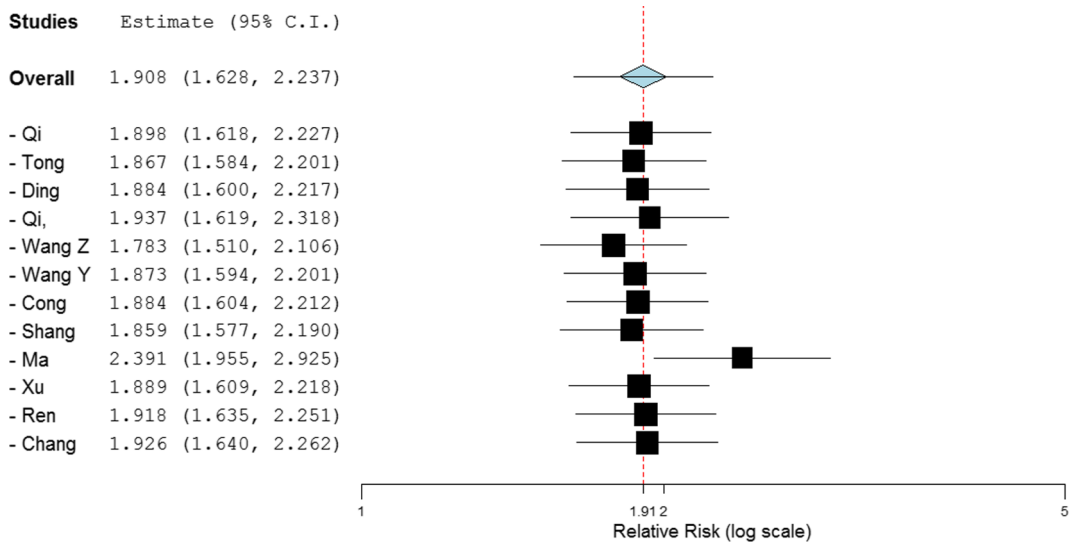

Fig. 5. The sensitivity analysis for the meta-analysis of OS in tumor patients.

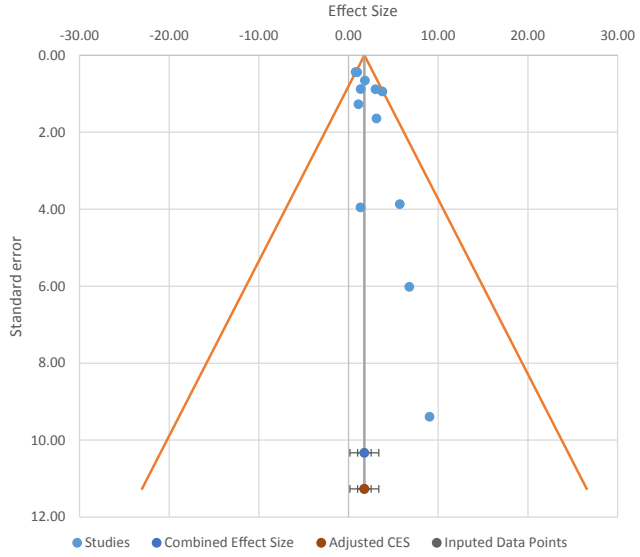

Fig. 6. Funnel plot analysis of potential publication bias for meta-analysis.

proliferation and increase hTERT (human telomerase catalytic subunit) gene expression as well as prostate cancer cell proliferation [9,34]. Visfatin promotes proliferation via the E2F2/SIRT1 axis in melanoma cells and upregulates Notch1 and activates NF- B pathway in breast tumor, [37,38]. It can also increase the cell proliferation via promoting G1/S phase progression through the PI3K/Akt and MAPK/ERK1/2 signaling pathways [39].

Visfatin also, causes metastasis in cancers by several mechanisms. Visfatin has been shown to stimulate the epithelial–mesenchymal transition (EMT) in breast cancer cells by inducing fibroblast-like morphology, striking reduction in E-cadherin expression, and a consistent upregulation of N-cadherin, vimentin, and ZEB1 [40]. Visfatin can upregulate Snail in CRC cells by activating Akt/GSK-3β/β-catenin signaling [25]. In osteosarcoma cells, visfatin, upregulates MMP-2 and fibronectin expression through the NF- B/IL-6 signaling pathway [41].

Visfatin regulates cancer cell angiogenesis by several mechanism. In breast cancer, visfatin induces the expression of the matrix metalloproteinase (MMP)-2, MMP-9, and vascular endothelial growth factor (VEGF) genes, suggesting it's potential role in breast cancer metastasis and angiogenesis [42]. Upregulation of thromboxane synthase mediates visfatin-induced interleukin-8 expression and angiogenic activity in endothelial cells [43].

Recent studies have suggested that visfatin affects cancer drug resistance. Visfatin mediates doxorubicin resistance in human non–small-cell lung cancer (NSCLC) via Akt-mediated upregulation of ATP Binding Cassette Subfamily C Member 1 (ABCC1) [44]. It also impacts chemotherapy in patients with colorectal cancer (CRC) and serves as a prognostic indicator for a poor response to chemotherapy [45]. Suppression of vistatin signaling can sensitize glioblastoma to temozolomide treatment via activation of the ROS/JNK signaling pathway [46]. Higher visfatin mRNA levels in bortezomib-resistant myeloma patients was correlated with poor overall survival. Therefore, inhibition of visfatin through intracellular NAD^+ depletion enhances bortezomib-induced anti-myeloma activity [47].

Visfatin can act as a tumor promoting cytokine by increasing proliferation and angiogenesis, decreasing apoptosis, and promoting epithelial-to-mesenchymal transition (EMT). Visfatin activates human leukocytes and induces cytokine production such as IL-1beta, TNF-alpha, and IL-6. It also increases the surface expression of co-stimulatory molecules CD54, CD40, and CD80, indicating a proinflammatory role for visfatin [48]. Signaling pathways such as PI3K, ERK1/2, p38 MAPK, JNK, AKT, STAT3, NF-κB can contribute to activation of downstream target gene transcription induced by visfatin, which leads to over-expression of proinflammatory cytokines, resulting in higher survival of tumor cells [49].

In our previous study, we demonstrated a direct association between high circulating visfatin levels and the risk of cancers, suggesting its potential role as a biomarker for early detection of cancers [7]. However, the prognostic role of visfatin expression level was yet to be clarified in different solid tumors. This comprehensive meta-analysis was performed to evaluate the prognostic value of visfatin expression (intercellular or extracellular) levels in different tumors. In addition its potential association with the main tumor clinicopathological features including LNM, DM, and clinical stage, as important indicators of predicting prognosis has also been examined.

Our meta-data revealed that high visfatin expression was an indicator for advanced disease and poor prognosis with statistical significance for OS (HR = 2.43, 95% CI 1.64–3.62, P < 0.001). Combining HRs from Cox multivariate analyses also resulted in a poorer OS in patients with higher visfatin level, indicating the probable role of

visfatin in the prognosis of cancer patients. Furthermore, visfatin over expression was also remarkably correlated with LNM, DM, advanced TNM stage, and larger tumor size in different malignancies. Meta-results from subgroup analyses according to the cancer type, sample size, specimen type, and study quality, indicated the significant detrimental effect of visfatin level on the OS in almost all subgroups. In general, the pooled data illustrated that high visfatin expression may represent a significant prognostic factor for survival outcomes and provides a new benchmark in predicting the metastasis and progression of cancer.

Certain limitations must be considered when interpreting the conclusions in this meta-analysis. Foremost, all included studies were only published in English, which may lead to a limited generalizability and some footprint for selection bias. Second, the existence of some degree of heterogeneity among studies might influence the results of this study. However, a random effect model was used to minimize the effect of the heterogeneity. Third, lack of a consistent standard for visfatin expression cut-off values can enhance the heterogeneity. Finally, different post- surgery treatment protocols and follow-up times in various studies may affect the survival outcomes and lead to some heterogeneity.

5. Conclusions

In conclusion, the present meta-analysis indicates a significant association of visfatin over expression with LNM, DM, advanced TNM stage, larger tumor size, and poor OS in different malignancies. Our findings support visfatin overexpression as a promising potential biomarker to predict poor prognosis in cancer patients.

CRediT authorship contribution statement

Masoumeh Mohammadi: Data curation, Formal analysis, and writing-original draft. **Ali Moradi:** Formal analysis, writing-original draft, Writing-review editing. **Javad Farhadi:** Investigation, Data curation, and writing-original draft. **Abolfazl Akbari:** Data curation, Validation, Writing-original draft. **Shokoufeh Pourmandi:** Data curation, Formal analysis. **Hassan Mehrad-Majd:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Writing-review editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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