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Overexpression of macrophage-colony stimulating factor-1 receptor as a prognostic factor for survival in cancer

A systematic review and meta-analysis

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Abstract

Background: The relation between the expression of macrophage-colony stimulating factor-1 receptor (CSF-1R) and prognosis of cancer patients has been evaluated in multiple studies, but the results remain controversial. We, therefore, performed a meta-analysis and systematic review to figure out the role of CSF-1R in the prognosis of patients with cancer.

Methods: Several databases were searched, including Web of Science, PubMed, and EMBASE. All human studies were published as full text. The Newcastle–Ottawa risk of bias scale was applied to evaluate the research. We extracted hazard ratios (HRs) with 95% confidence interval (95% CI) which assessed progression-free survival (PFS) and overall survival (OS) in order to assess the impacts of CSF-1R on the prognosis of cancer patients.

Results: A total of 12 citations were identified, with studies including 2260 patients in different cancer types that met the eligibility criteria. It was suggested in a pooled analysis that the over-expression of CSF-1R was significantly related to worse PFS (HR: 1.68; $P < .001$, 1.25–2.10, 95% CI) and also poorer OS (HR=1.28; $P < .001$, 1.03–1.54, 95% CI). Analysis in subgroups indicated over-expressed CSF-1R was significantly associated with worse OS in hematological malignancy (HR=2.29; $P < .001$, 1.49–3.09, 95% CI; model of fixed-effects; $I^2 = 0.0\%$, $P < .001$). Sensitivity analysis suggested that there was no study influencing the stability of the results.

Conclusions: The overexpression of CSF-1R was significantly predictive of worse prognosis in those who suffer from different kinds of malignancies, particularly in hematological malignancy, which indicates that it might be a potential biomarker of prognosis in cancer survival and a potential molecular target in the treatment of malignant tumors.

Abbreviations: CI = confidence interval, CSF-1R = macrophage-colony stimulating factor-1 receptor, HRs = hazard ratios, OS = overall survival, PFS = progression-free survival.

Keywords: cancer, macrophage-colony stimulating factor-1 receptor, meta-analysis, prognosis biomarker, survival

1. Introduction

Based on GLOBOCAN, there are estimated to be approximately 18.1 million newly-emerging cases of malignant tumors (17.0 million cases without non-melanoma skin malignancies) and a total of 9.6 million deaths from cancer (9.5 million cases without non-melanoma skin malignancies) in 2018.[1] The number of cancer cases is increasing, but some patients cannot benefit from treatments such as chemotherapy, radiotherapy or surgery. Moreover, biotherapies and targeted medicines are increasingly coming into use. However, the number of patients the patients who can apply for these methods are still limited. Overall survival of most tumors is still very poor.[2] Thus, the discover of biomarkers for prognosis would be valuable in the clinic to guide individualized treatment and improve unfavorable prognosis.[3]

Macrophage-colony stimulating factor-1 receptor (CSF-1R) belongs to the family of type III RTK. CSF-1R consists of a single transmembrane domain, an intracellular cleaved kinase domain, and 5 immunoglobulin-like extracellular domains in the ligand-connected part. The molecule originates from the encoding of c-fms, a proto-oncogene, and is considered to be the main regulatory factor of the immune system.[4–9] Recently, it was proven by clinical research that the abnormally high expression of CSF-1R in tumor tissues was closely associated with cancer recurrence, tumor metastasis and worse prognosis, including nasopharyngeal carcinoma,[10] lung cancer,[11] breast Cancer,[12,13] classical Hodgkin lymphoma,[14–17] soft tissue sarcomas,[18] ovarian carcinoma,[19,20] colorectal adenocarcinoma,[21] prostatic carcinoma,[22] clear cell renal cell carcinoma,[23,24]

cervical cancer,[25] gastric cancer,[26] endometrial adenocarcinomas,[27] pancreatic cancer,[28] etc. CSF-1R has been show to play an important role in various diseases, which has promoted the development of CSF-1R inhibitor used in clinic.[29–33] Nevertheless, the significance of CSF-1R overexpression in prognosis for the survival rate among multiple cancer types remains controversial. Hence, we performed a meta-analysis and studies-based systematic review to evaluate the connection between expression of CSF-1R and cancer prognosis, thus promoting the development of CSF-1R in cancer treatment.

2. Methods

We followed the Meta-Analyses (PRISMA) recommendations in our meta-analysis and Preferred Reporting Items in carrying out Systematic Reviews.[34] Ethical review was not required since our manuscript is metaanalysis.

2.1. Searching methods and criteria for selection

The studies were searched in the databases from Embase, Web of Science, and PubMed. We performed serial searching for non-English and English articles (from October 25, 2017 to April 31, 2019). The key words we set were listed as follows: Boolean logic was applied with search terms such as "CSF-1R," "CSF1R," "colony stimulating factor 1 receptor," "survival," and "prognosis." We also used controlled vocabularies to recognize synonyms (e.g., Medical Subject Heading terms). No restrictions were set on the language, status, or publication date for any study. According to the reference lists, the extra concerned publications were also annually searched. Two authors (Huaqing MO, and Zenan Chen) independently searched the database.

2.2. Criteria of exclusion and inclusion

The criteria listed below were strictly followed in selecting the studies qualified to be included in the meta-analysis, studies could be selected only when they contained information regarding the criteria below:

1. Expression of CSF-1R in malignant tumors.
2. Exploration of the connection between survival outcome and CSF-1R expression levels, with the parameters including PFS, disease-free survival (DFS) or OS.
3. Provision of adequate information to estimate the 95% confidence interval (CI) and hazard ratio (HR).
4. Studies containing the fullest information when multiple studies were in coincident time periods or cohorts.

   The criteria for exclusion included:

1. Reproductive publications.
2. Letters, meetings, reviews, case reports, and nonhuman trials.
3. Studies with small sample sizes (less than 40 subjects).

   All the studies initially identified have been independently assessed in terms of abstracts and/or titles by 2 investigators, and the unrelated studies were excluded. Afterwards, we obtained the full texts of the studies which met all the inclusion criteria. Consensuses were carried out to resolve any different opinions on eligibility.

2.3. Data extraction methods and validity evaluation

The required data were independently obtained by 2 researchers from all studies; we extracted the last names of the 1st author,

publication year, country of origin, cancer types, the number of patients, study type, sample size, cutoff value, follow-up time, gender of patients, method to detect CSF-1R, stage of tumor, outcomes, and 95% CI and HR of the over-expressed CSF-1R group patients and control group compared with the group of low CSF-1R expression for DFS, OS and PFS. If HRs were absent in the studies, authors were contacted to provide additional data or raw information was applied to extract the survival data (curves of Kaplan–Meier) via the Engauge Digitizer 4.1. The data of the survival information have been calculated by Tierney method.[35] If HRs in both univariate analysis and multivariate were available, only the latter was used.

2.4. Study quality

According to the quality assessment scale of Newcastle–Ottawa (NOS), each study's quality was independently and systematically assessed by 2 reviewers.[36] Scores of 9 or 0 were considered as the highest or the poorest quality, respectively. High quality was defined as a study with a score of no less than 6. If there were disagreements in quality assessment and data collection, a consensus was applied by involving another author (Lv).

2.5. Statistical analysis

Studies with both cancerous patients' prognosis and CSF-1R expression were described using the 95% CIs and the pooled HRs. Data were obtained to calculate the HRs specific to the studies. Hazard ratios effect on assessment was calculated as the weighted mean value. If the HR was greater than 1, the overexpression of CSF-1R was considered to be significantly related to worse prognosis in patients with cancer. Heterogeneity was investigated between research with I^2 statistical data and Cochrane Q statistical data, and classified as high, moderate, or low according to the I^2 statistical data of 75%, 50%, or 25%, separately, based on the techniques proposed by Higgins and his colleagues.[37] The publication bias of the research was assessed with Egger test and Begg test; a P value >.05 indicated no potential publication bias, based on which a model of random effect might be utilized. On the other hand, we also needed a fixed-effect model. We performed subgroup analyses with regards to the country of origin, cancer type, and study type. The analysis of sensitivity has been completed by omitting every single study in order to test the robustness of our findings. To assess whether the analysis of complete cases brought in bias, the correlation between the covariate and HR was calculated. We applied univariate preselection of covariates to decrease covariates number. Covariates were chosen with $\alpha = 0.05$ as the cutoff point. Stata SE (version 12.0) was applied in all the statistical analyses and management. P value <.05 suggested statistically significant.

3. Results study

3.1. Characteristics

A flow chart showing the search process of studies is presented in Figure 1. According to the searching strategy, a total of 1882 references were retrieved. After we comprehensively screened the publication types, titles, overall text, and abstracts, 30 articles contained an analysis of the association of CSF-1R expression with outcomes in those who suffered from multiple types of cancer. Five studies that detected CSF-1R not in tumor tissues
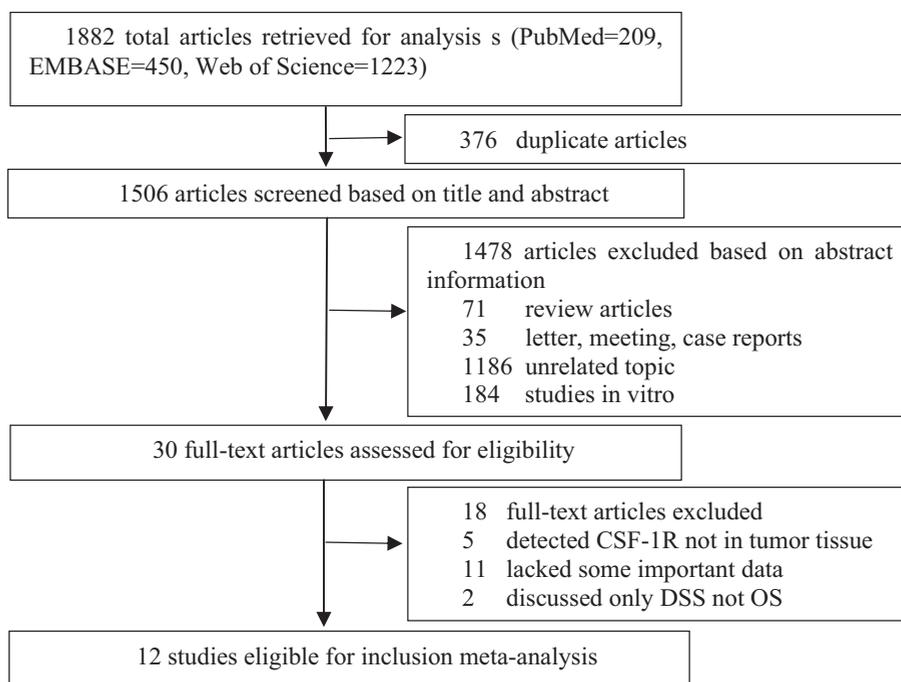
Figure 1. Flow chart showing study searches and literature selection.

were excluded. Eleven studies that lacked important data were removed. Furthermore, 2 articles were excluded from meta-analyses because only DSS (not OS) survival outcomes were discussed, but these were included in the systematic review. If multiple outcomes appeared in 1 study, the outcomes were treated as different researches. Ultimately, the meta-analysis included 13 studies which were chosen from 12 articles[10–12,14–20,26,38] published between 1997 and 2018, encompassing 2260 patients, with sample sizes ranging from 45 to 510 subjects (Table 1). In total, 12 studies had qualified information in OS analysis, and 4 studies reported HRs for PFS. We quantitatively synthesized the outcomes of prognosis, containing PFS and OS in this meta-analysis. Detailed information about the studies we

included has been collated in Table 1. Figure 2 presents how different cancer varieties are distributed in the patients and studies.

3.2. Quality assessment

Among 13 studies, 5 were prospective cohort research studies, whereas 8 were retrospective. Four studies did not have definite loss rates. Interpretation criteria of CSF-1R expression were not well defined in 2 studies. Furthermore, the follow-up has not been clearly explained in 3 studies. The results of quality evaluation of the 13 qualified studies are shown in Table 1. The results revealed that NOS scores were not less than 6, with an average of 7. Larger

Table 1

Major features of all research involved in this meta-analysis.

Study	Country	Cancer	Sample size	Type	Median age (month, range)	Stage	CSF-1R (±) NO	Cut-off	Multivariate analysis	HR and 95% CI	Study quality (NOS score)
Jia[37]	China	HCC	105	Pro	51 (18-75)	TNM I–III	(53/52)	IRS>1	NO	SC	8
Kluger[12]	USA	Breast	301	Pro	NA	NA	(114/187)	IRS>1	Yes	Report	6
Kluger[12]	USA	Breast	280	Pro	NA	NA	(189/91)	IRS>1	Yes	Report	6
Martín[14]	Spain	cHL	249	Re	NA	TNM II–IV	(105/144)	IHC≥27.5%	Yes	Report	6
Okugawa[26]	Japan	Gastric	148	Pro	67 (18–90)	TNM I–IV	(73/75)	NA	NO	Report	7
Sorbye[18]	Norway Russia	STS	249	Re	55 (0–91)	FNCLCC1,2,3	(191/38)	IHC≥10%	NO	SC	8
Steidl[15]	British	cHL	132	Re	43 (16–77)	TNM I–IV	(63/69)	ISH	NO	SC	7
Wang[17]	China	cHL	45	Re	24 (7–72)	Ann Arbor I–IV	(18/27)	IHC≥30%	Yes	Report	8
Yoo[11]	South Korea	NSCLC	510	Pro	NA	TNM I–III	NA	NA	Yes	Report	6
Wang[16]	China	cHL	86	Re	NA	Ann Arbor I–IV	(37/49)	IHC≥30%	NO	Report	7
Toy[19]	USA	EOC	47	Re	NA	TNM II–IV	NA	H scor≥200	NO	SC	8
Huang[10]	China	NPC	56	Re	47 (28–76)	TNM I–IV	(41/15)	IHC≥30%	Yes	Report	7
Chambers[20]	America	EOC	108	Re	NA	TNM I/II/IIIA	NA	H scor≥200	Yes	Report	8

cHL = classic Hodgkin lymphoma, EOC = epithelial ovarian carcinoma, H score = immunohistochemistry H score, HCC = hepatocellular carcinoma, HR = hazard ratio, IHC = Study immunohistochemistry, IRS = immunoreactivity score, ISH = mRNA in situ hybridization, N = not available, NPC = nasopharyngeal carcinoma, NSCLC = non-small cell lung cancer, Pro = prospective, Re = retrospective, SC = survival curve, STS = soft tissue sarcomas.
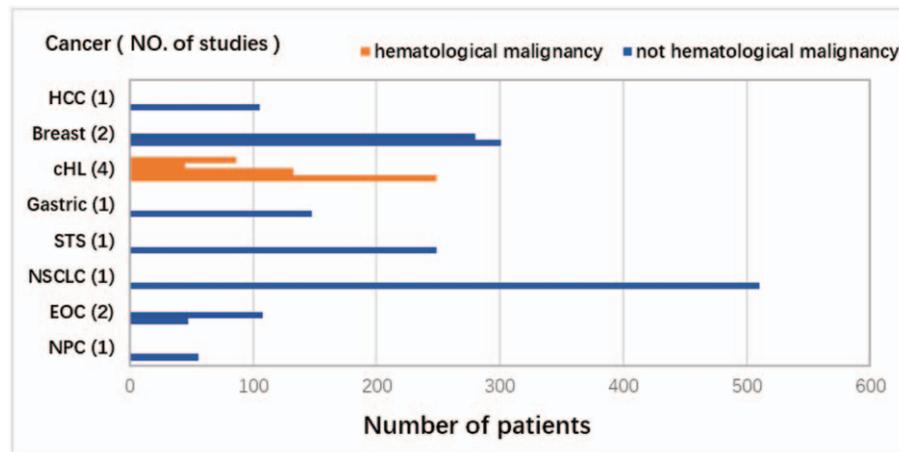
Figure 2. Types of tumors that are distributed in patients and studies. cHL = classic Hodgkin lymphoma, EOC = epithelial ovarian carcinoma, HCC = hepatocellular carcinoma, NPC = nasopharyngeal carcinoma, NSCLC = non-small cell lung cancer, STS = soft tissue sarcomas.

values indicated a preferable method. Therefore, the resulting analysis adopted all of the qualified studies.

3.3. Results of meta-analysis

3.3.1. Over-expression of CSF-1R was associated with poorer OS. Table 2 shows the most important results of our meta-analysis. Because homogeneity tests proved significant statistical heterogeneity ($I^2 = 56\%$) among studies in the OS, the model of random effects has been used to obtain the pooled HRs. According to the statistic results, CSF-1R overexpression correlation with a worse OS in those who had cancer, and the pooled HR was HR = 1.28; $P < .001$, 1.03 to 1.54, 95% CI (Fig. 3).

3.3.2. Over-expression of CSF-1R was associated with worse PFS. Four articles revealed data regarding the relationship of PFS and CSF-1R. In the meta-analysis applying the model of random effects, the results suggested that increased CSF-1R was significantly related to shorter PFS (HR: 1.68; $P < .001$, 1.25–2.10, 95% CI) and no significant heterogeneity ($I^2 = 0.0\%$) (Fig. 4).

3.3.3. Subgroup analyses and meta-regression analysis. To investigate the heterogeneity of these articles, subgroup

analysis was performed according to 3 essential features; type of cancer, ethnicity, and type of study. Subgroup analysis indicated that over-expression of CSF-1R was significantly correlated with poorer OS in hematological cancer with no heterogeneity ($P < .001$, HR = 2.29, 95% CI 1.49–3.09; model of fixed effects; $I^2 = 0.0\%$). In epidemiological research, differences in ethnicity was considered as an important source for bias. It was found that the CSF-1R overexpression was remarkably related to worse OS among the research in Caucasians ($P < .001$, HR = 1.43, 95% CI 1.06–1.78; random-effect model; $I^2 = 59.0\%$) (Fig. 5). In addition, we carried out subgroup analysis in both retrospective studies and prospective cohorts, and the results showed that the correlation between high expression of CSF-1R and worse OS was statistically significant, but with remarkable statistical heterogeneity in retrospective studies ($P < .001$, HR = 1.64, 95% CI 1.08–2.12; model of random-effect; $I^2 = 60.1\%$). Related covariates were preselected by applying univariate analyses of meta-regression for covariates mentioned above, which indicated that heterogeneity of effect size among studies could be expounded by cancer type ($P = .019$, 95% CI 0.06–0.63), resulting in a total explained variance of 61% (Fig. 6). This suggests the regression graph of cancer type in the

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Table 2

Results of subgroup analysis of OS prognosis and CSF-1R expression in patients with cancers.

Variable	No. of studies	No. of patients	Model	Outcome (OS)		Heterogeneity	
				HR (95% CI)	P value	I^2 (%)	P
All	12	2260	R	1.28 (1.03–1.54)	<.001	56%	.009
Cancer type							
Hematological malignancy	4	512	F	1.29 (1.49–3.09)	<.001	0.0%	.696
Non hematological malignancy	8	1748	R	1.17 (0.93–1.40)	<.001	53.8%	.034
Ethnicity							
Asian	5	894	R	1.11 (0.72–1.50)	<.001	53.0%	.074
Caucasian	7	1366	R	1.43 (1.06–1.78)	<.001	59.0%	.023
Study type							
Prospective	5	1344	R	1.12 (0.84–1.40)	<.001	55.0%	.064
Retrospective	7	916	R	1.64 (1.08–2.20)	<.001	60.1%	.020

F = model of fixed effects, OS = overall survival, R = model of random effects.
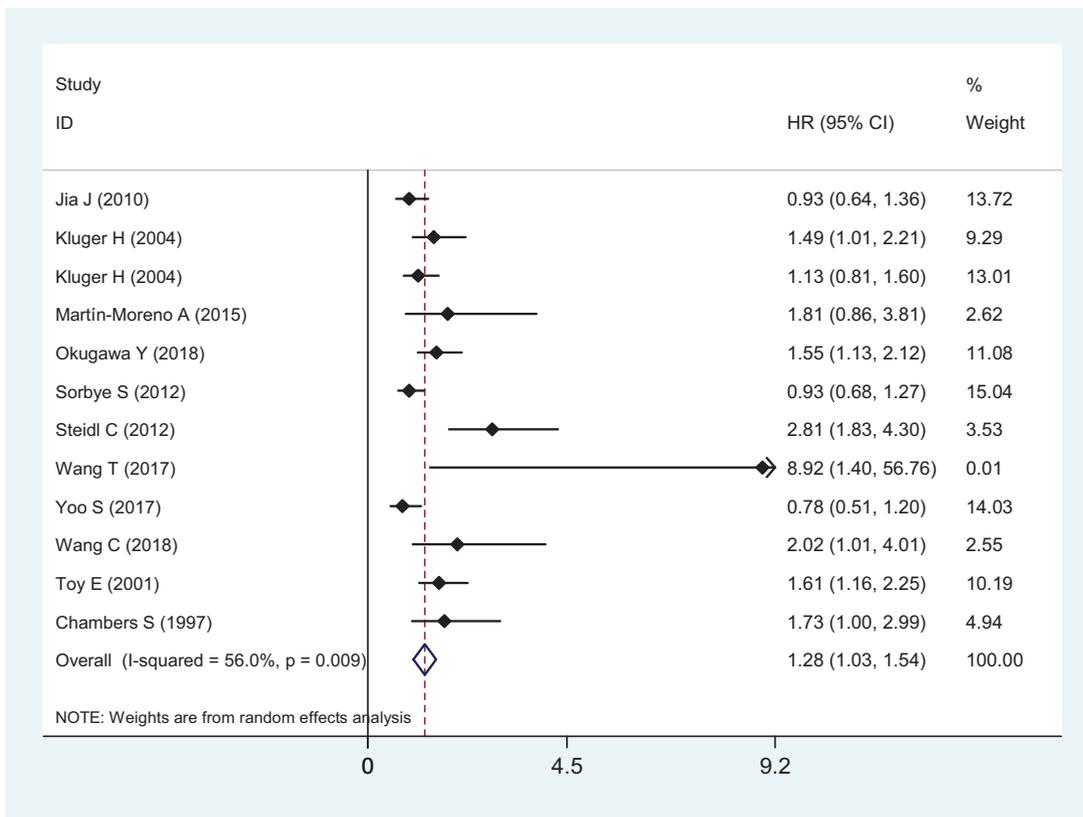
Figure 3. Forest graph of the 95% CI and pooled HR of OS prognosis and CSF-1R over-expression.
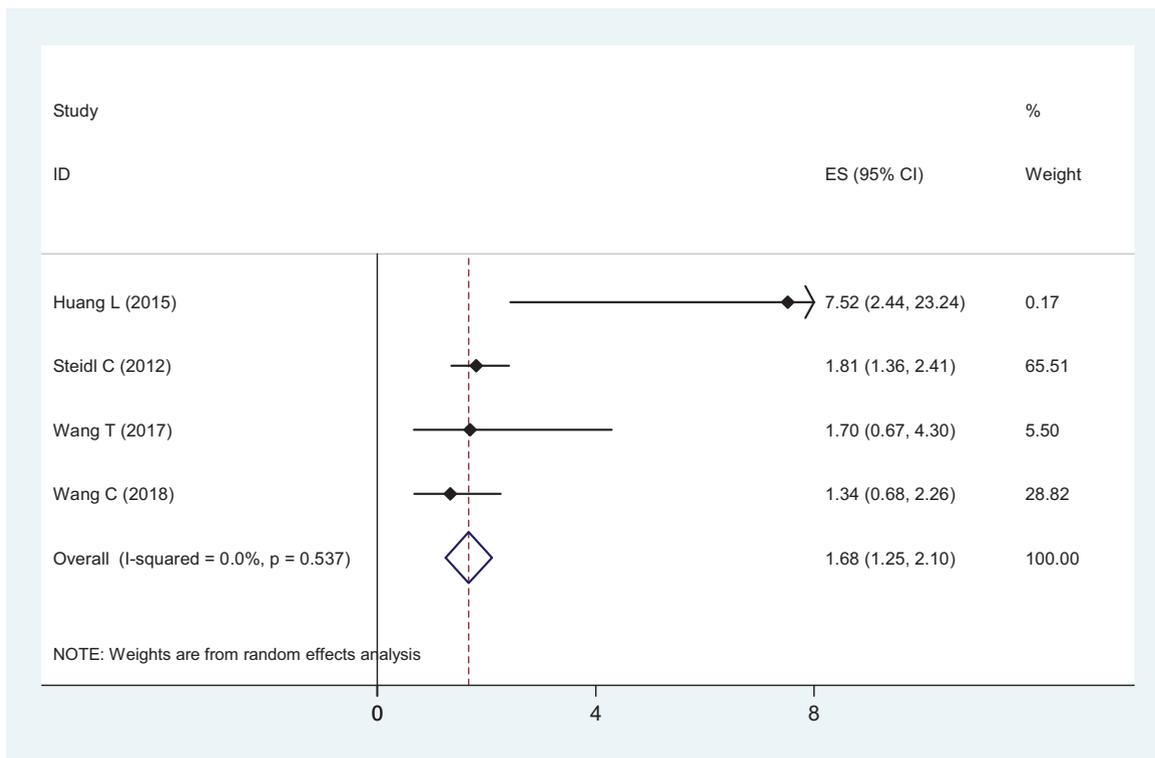
Figure 4. Forest graph of 95% CI and pooled the HR of over-expressed CSF-1R and PFS prognosis.
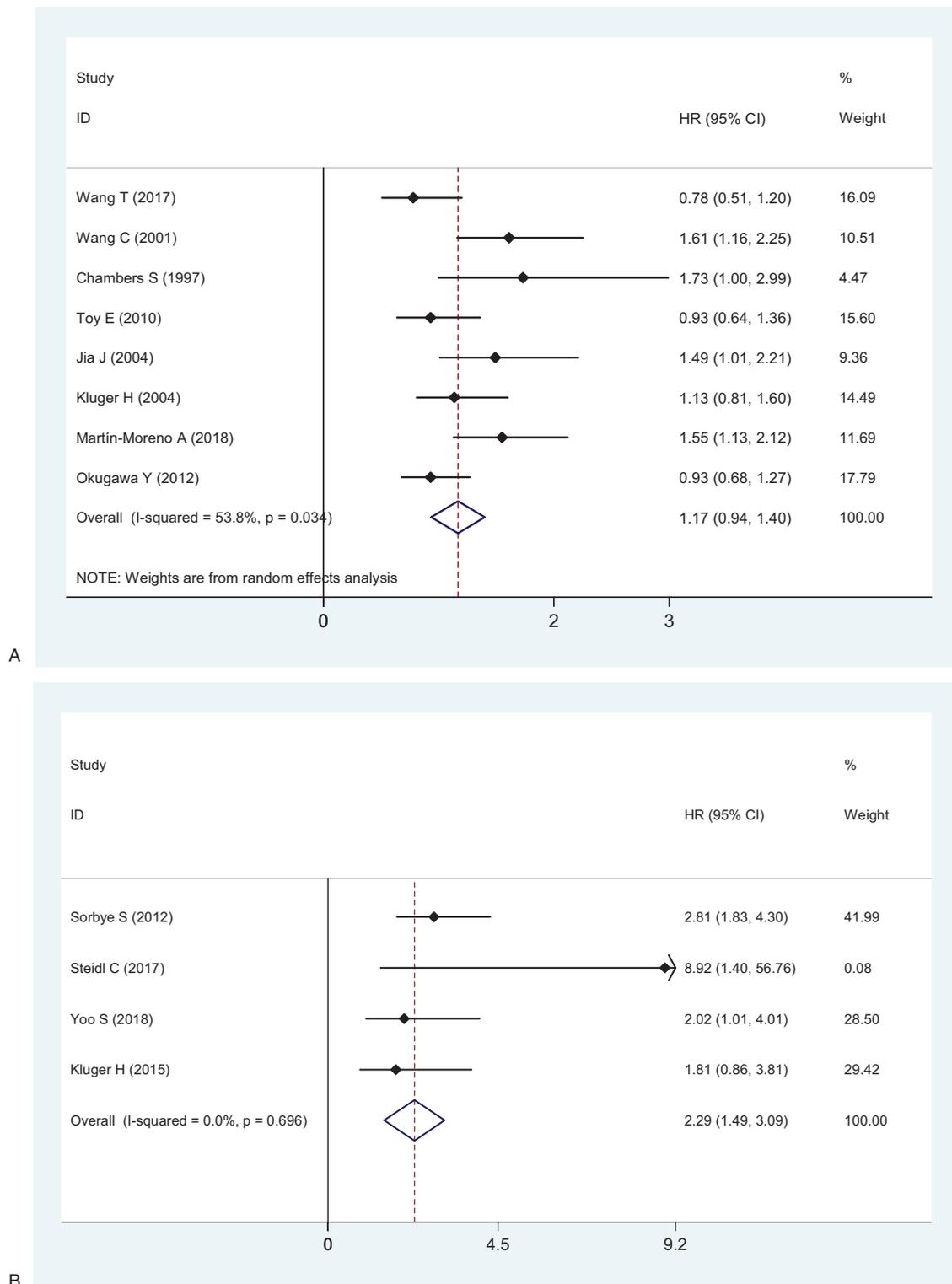
Figure 5. Forest graphs of articles evaluating HR of over-expressed CSF-1R in hematological malignancy (A) and non hematological malignancy (B).
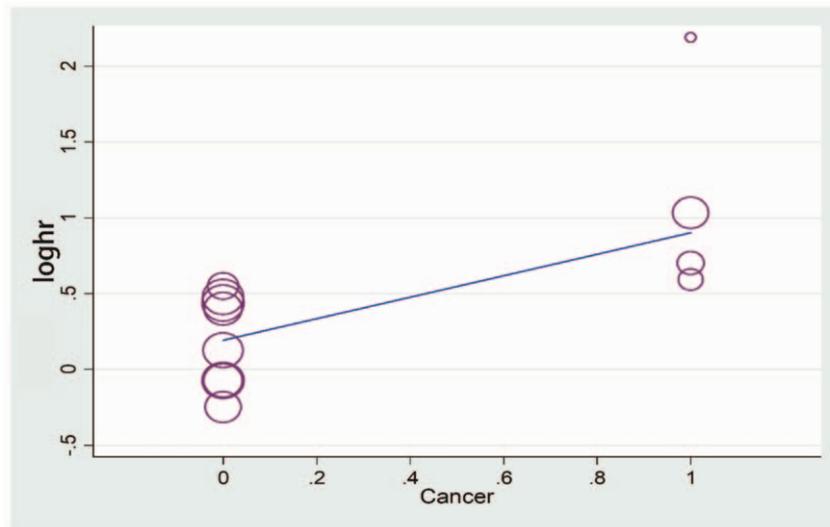
Figure 6. Meta-regression analysis association between Cancer type and the articles evaluating the HR of over-expressed CSF-1R in malignant tumors. Plotting features are proportional to the weight of the study.

research evaluating the HR of CSF-1R over-expression in malignancies.

3.4. Sensitivity analysis

Sensitivity analyses were carried out by sequentially deleting any single study to determine the influence of every individual article. The result of all meta-analytic conclusions was based on this testing (Fig. 7).

3.5. Bias of publication

The evaluation of bias of publication for OS was carried out using Egger test and Begg funnel plot. Underlying bias of publication

was revealed by visually inspecting the Begg funnel plots (OS, $P=.134$ in Egger test, $P=.244$ in Begg test) (Fig. 8). Therefore, the results of in our meta-analysis were shown to be reliable.

4. Discussion

As far as we know, there has been no meta-analysis assessing the relationship between CSF-1R expression and survival rates of cancer patients. Our results indicate that over-expression of CSF-1R was remarkably correlated with a shorter PFS and a worse OS in patients with cancer. Besides the overall assessment, subgroup analyses have been performed with regard to cancer type, ethnicity and study type. Moreover, subgroup analysis indicated high CSF-1R expression was significantly correlated with poorer
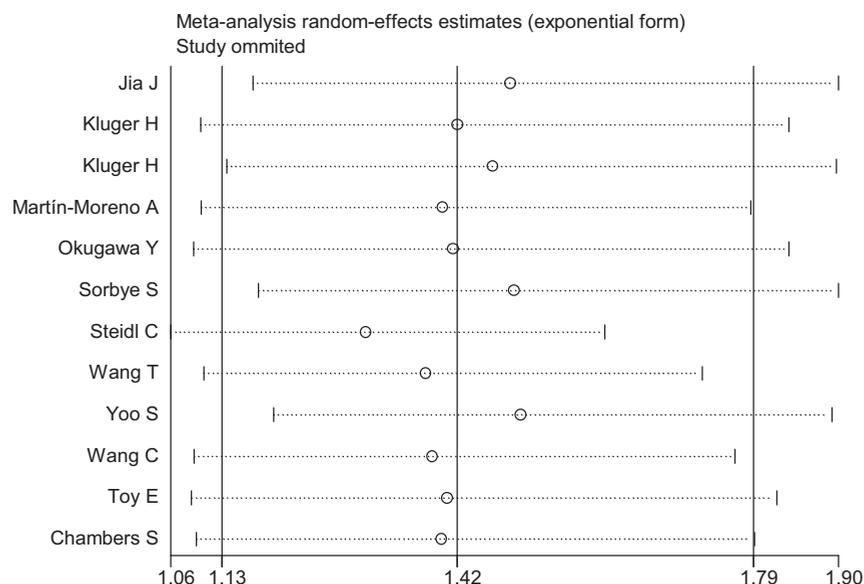
Figure 7. Sensitivity analysis for meta-analysis CSF-1R.
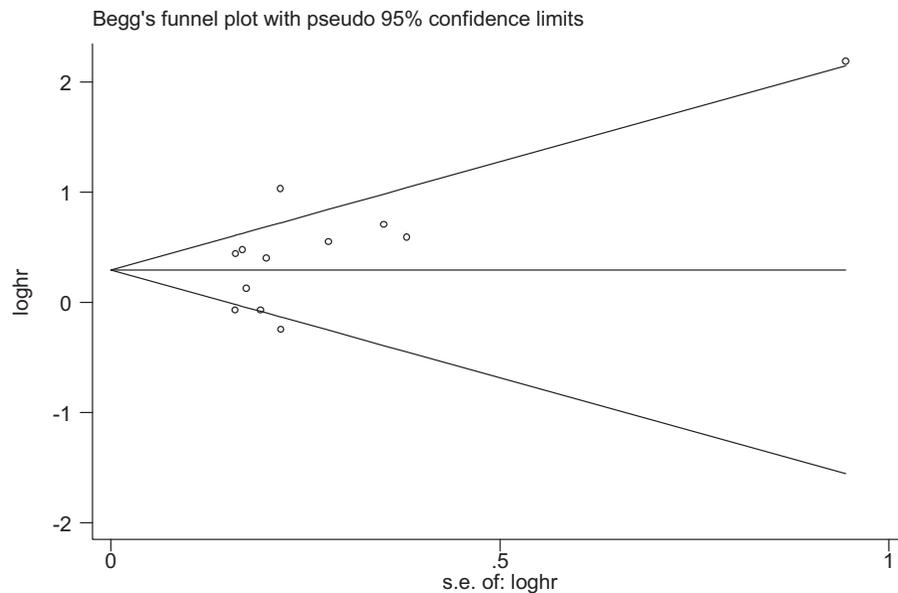
Figure 8. Funnel graphs of Begg test of OS prognosis and over-expressed CSF-1R.

OS in hematological malignancies. The relationship between CSF-1R over-expression and survival was significant according to the subgroup of Caucasian and Retrospective. We considered that the meta-analysis heterogeneity was mostly because of the difference in types of analysis, tumor types, and patients. Differences may also result from differences in therapies for different types of tumor, multiple mechanisms, and signaling pathways. Furthermore, all of the cut-off values were presented in the research, which could result in heterogeneity because of the lack of unified standards. The analysis of sensitivity and tests' outcomes of publication bias also provided proof to our results. In summary, the results revealed that the relationship between the expression of CSF-1R and cancerous patients' prognosis was remarkable. Therefore, CSF-1R may be a possible biomarker of prognosis for those who suffer from cancer.

The possible underlying mechanisms may involve CSF-1R signaling, which binds to its ligand and induces CSF-1R chain dimerization, leading to cross-tyrosine phosphorylation and the direct relationship between signaling molecules and their receptors via the phosphotyrosine-binding domains.[39,40] Activation triggers the Ras-Raf-MEK1/2-ERK1/2 axis[41,42] and/or PI3K-PDK1-AKT intracellular pathway,[4] contributing to the pathway signaling cascade and resulting in proliferation of tumor cells, differentiation processes,[43] angiogenesis, adhesion, and migration.[8,43–45] Besides, in the tumor microenvironment, the oncogenic potential of CSF-1R arises from autocrine and/or paracrine signaling between CSF-1R (+) tumor-associated macrophages (TAMs) and CSF-1–secreting cancer cells,[46,47] which promotes tumor cell proliferation, mediates immune suppression and promotes metastatic dissemination.[48,49] Many studies have shown that CSF-1R plays an important role in cancer prognosis by changing the biological behavior of tumors.

Inhibition of CSF-1R interactions was confirmed to have an effect on suppressing tumor angiogenesis processes, metastasis, invasion, migration, and growth of cancer cells.[50–53] Monoclonal antibodies and various inhibitors targeting CSF-1R are currently in clinical development.[54–56] Some inhibitors of CSF-

1R/c-FMS like Imatinib and PLX3397 were applied in the therapeutic treatment of cHL cancer patients.[52,57,58] In preclinical studies, small-molecule inhibitors directed against CSF-1R in combination with immunotherapy with checkpoint inhibitors have been reported to inhibit the TAMs and Foxp3 regulatory T cells.[59] This combination approach facilitates antigen presentation and augments T cell activation within the tumor microenvironment.[60] Moreover, it has been demonstrated that an immunosuppressive tumor microenvironment mediated by CSF-1/CSF-1R may limit the antitumor activity of checkpoint blockade and lead to low response rates in preclinical models.[61] There is also some evidence that CSF-1/CSF-1R blockade decreases the immune suppressive signals mediated by tumor-associated macrophages might up-regulate PD-L1, rendering previously immune resistant or escaped tumors sensitive to checkpoint inhibition, chemo-and radiotherapy, and cellular therapies to improve antitumor responses in patients.[62,63] Consequently, CSF-1R-targeting agents can be applied as promising therapies for malignant tumors.[61,64,65]

It is of vital importance to understand the limitations of this meta-analysis. Firstly, some of the HRs have been obtained from the Kaplan–Meier curve as we could not acquire the direct survival information, which might possibly influence the results. Secondly, due to the utilization of multiple detecting measures, there may be differences in survival rates, types of antibodies, cut-off levels, and ratios of over-expressed CSF-1R in the studies qualified for inclusion. Every factor mentioned above may result in high heterogeneity. Lastly, the retrospective design of 4 included articles (Table 1) could result in possible recall bias. Because of the limitations in the current analysis, we should further perform more excellent large-scale tumor research.

5. Conclusions

This meta-analysis included all the research, and it was indicated that over-expression of CSF-1R was correlated with poor prognosis according to PFS and OS in multiple kinds of cancer,

suggesting that over-expression of CSF-1R could be applied as a worse prognosis biomarker for cancer and may potentially become an important molecule target in cancer treatment. Additional studies regarding CSF-1R are warranted, since the current analysis has only sparse data.

Author contributions

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Writing – review & editing: Huaqing Mo, Yanrong Hao.

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