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Original Article

The prognostic value of neuropilin-1 in various cancers: a meta-analysis

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Abstract: Some studies have indicated a correlation between neuropilin-1 (NRP-1) and the progression of many malignant cancers, and the level of NRP-1 expression can be considered as a potential prognostic biomarker for cancers. We conducted a meta-analysis to provide more sufficient evidence that NRP-1 overexpression is associated with unfavorable outcomes in patients with several types of cancers. Eligible studies were searched in the Web of Science and PubMed databases between 1987 and 2015. We analyzed the data from published papers and calculated the hazard ratios (HRs) and 95% confidence intervals (95% CIs) using STATA 12.0 software with the Mantel-Haenszel fixed- or random-effect model. 15 studies with 2049 patients were included in this meta-analysis; NRP-1 overexpression was found in 59.54% of the cases. Our results indicated that NRP-1 overexpression was associated with unfavorable overall survival (HR = 1.91; 95% CI = 1.59-2.28; P < 0.001) and disease-free survival/relapse-free survival (HR = 3.35; 95% CI = 1.39-3.52; P = 0.01) in all cancer patients. Subgroup analyses showed that elevated NRP-1 was a positive prognostic biomarker in patients with NSCLC (HR = 2.06; 95% CI = 1.30-3.26; P = 0.002) and acute myeloid leukemia (HR = 2.38; 95% CI = 1.48-3.84; P < 0.001), but not in patients with colon cancer (HR = 1.24; 95% CI = 0.31-4.96; P = 0.76). The present meta-analysis suggested that increased NRP-1 could be an unfavorable prognostic factor in many human cancers.

Keywords: Neuropilin-1, cancer, meta-analysis, prognosis, hazard ratio

Introduction

Cancer is one of the important causes of death and a major public health problem worldwide [1]. Although cancer patients have experienced an increased survival rate during the past decades, newer diagnostic methods with greater sensitivity and specificity are necessary for the precise detection and prognosis of cancer [2]. Researchers and clinicians in tumor fields have attempted to identify new biomarkers to predict disease progression, patient survival, and drug or surgical treatment response. However, there are insufficient predictors for use with different clinical cancer settings, and therefore, more predictive biomarkers for determining the prognosis of various cancers are urgently needed.

Neuropilin-1 (NRP-1), a member of the neuropilin family, is a 120- to 130-kDa non-tyrosine kinase transmembrane protein that plays an important role in neural development, angiogenesis, immunity, and cancer [3]. NRP-1 was identified as a co-receptor for several growth factors including VEGF and EGF, which helps ligands bind to receptors, enhances ligand signaling, and increases tumor angiogenesis and growth [4]. During the past decades, many researchers have evaluated the association between NRP-1 expression and patient outcomes with malignancies including glioma [5], pancreatic cancer [6], gastric cancer [7], colon cancer [8, 9], breast cancer [10, 11], non-small cell lung cancer (NSCLC) [12], and acute myeloid leukemia (AML) [13]. However, the relationship between NRP-1 expression and clinical outcomes in various cancers remains controversial because of inconsistent results.

Herein, we will present a meta-analysis that evaluated the impact of NRP-1 overexpression

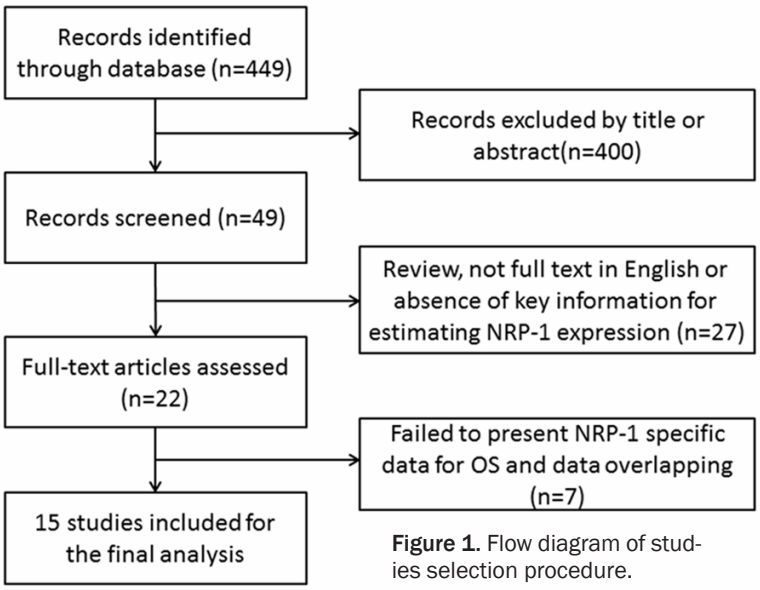

Figure 1. Flow diagram of studies selection procedure.

in the clinical outcomes of cancer patients based on 15 studies.

Methods

Identification and selection of studies

The Web of Science and PubMed databases were searched for studies that evaluated NRP-1 expression levels and overall survival (OS) or disease-free survival/relapse-free survival (DFS/RFS) in patients with various cancers between 1987 and 2015. Studies were selected using the following search terms: NRP-1, CD304, BDCA-4, neuropilin-1, VEGF165R, cancer, and tumor. We identified a total of 449 studies. Additionally, we attempted to find unpublished data by searching Google, Baidu, and Wikipedia, but no additional studies were appropriate for inclusion.

Inclusion and exclusion criteria

The inclusion criteria to select literature were as follows [14]: (1) Studies of NRP-1 expression in human cancers, rather than other animals; (2) Articles on the association of NRP-1 expression and patient prognosis; (3) English-language publications; and (4) Provision of sufficient information to allow the estimation of hazard ratios (HR) and 95% confidence intervals (95% CI).

The exclusion criteria were as follows: (1) letters, reviews, case reports, and conference abstracts without original data; (2) non-English language articles; and (3) articles from which HR or 95% CI data could not be extracted.

Data collection process

Two colleagues (Heng Zhang and Chunxia He) independently extracted data from eligible studies. The following information was extracted: first author's name; year of publication; country and race of the study population; number of patients; cancer type; detection method; and the percentage of overexpression. The two reviewers checked the data again and discussed the data if the results differed, so as to reach a consensus. A third author was invited to the discussion if the two primary authors could not reach an agreement. Two investigators (Heng Zhang and Shuo Han) assessed the study quality independently according to the Newcastle-Ottawa quality assessment scale.

Statistical analysis

The impact of NRP-1 expression on patient survival (OS, DFS/RFS) was estimated using pooled HRs and their 95% CIs which were extracted from each included study according to the methods described by Parmar [15]. Statistical analyses were performed using STATA version 12.0 software (Stata Corporation, Collage Station, Texas, USA). Estimates of HRs were weighted and pooled using the Mantel-Haenszel fixed- or random-effect model. We assessed heterogeneity by calculating I^2 for each analysis, where an I^2 of $\geq$ 50% represented substantial heterogeneity. Begg's and Egger's tests were used to estimate the potential risk of publication bias. All statistical experiments were two-sided, and statistical significance was defined as a P value of < 0.05.

Results

Description of studies

The flow chart in **Figure 1** summarizes the selection method for the literature search. We selected a total of 15 studies that assessed

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

Study	Year	Country	Ethnicity	Number	Cancer type	Methods	NRP-1 overexpression	Quality scores
Ben [26]	2015	China	Asian	172	PDAC	IHC	51.74%	7
Cheng [20]	2014	China	Asian	139	Bladder cancer	IHC	56.12%	7
Chu [21]	2014	China	Asian	60	OSCC	IHC	71.67%	7
Zhu [27]	2014	China	Asian	166	OS	WB	77.11%	7
Zhao [13]	2014	China	Asian	87	AML	WB	NR	5
Ding [17]	2014	China	Asian	40	NSCLC	IHC	55.00%	7
Xu [24]	2013	China	Asian	266	NPC	IHC	66.17%	7
Song [25]	2012	China	Asian	43	Tongue cancer	IHC	30.23%	7
Ghosh [23]	2008	USA	Caucasian	642	Breast cancer	IHC	61.99%	6
Hong [12]	2007	Taiwan	Asian	60	NSCLC	RT-PCR	50.00%	7
Kamiya [18]	2006	Japan	Asian	54	Colon Cancer	RT-PCR	77.78%	6
Ochiumi [8]	2006	Japan	Asian	146	Colon Cancer	RT-PCR	65.07%	7
Kreuter [19]	2006	Germany	Caucasian	69	AML	IHC	55.07%	7
Osada [22]	2004	Japan	Asian	37	Glioma	RT-PCR	56.76%	6
Kawakami [16]	2002	Japan	Asian	68	NSCLC	RT-PCR	58.82%	6

NRP-1 neuropilin-1, *PDAC* pancreatic ductal adenocarcinoma, *OSCC* Oral squamous cell carcinoma, *OS* Osteosarcoma cancer, *AML* Acute myeloid leukemia, *NSCLC* non-small cell lung cancer, *NPC* Nasopharyngeal carcinoma, *IHC* immunohistochemistry, *WB* western blot, *RT-PCR* real time-polymerase chain reaction, *NR* no report.

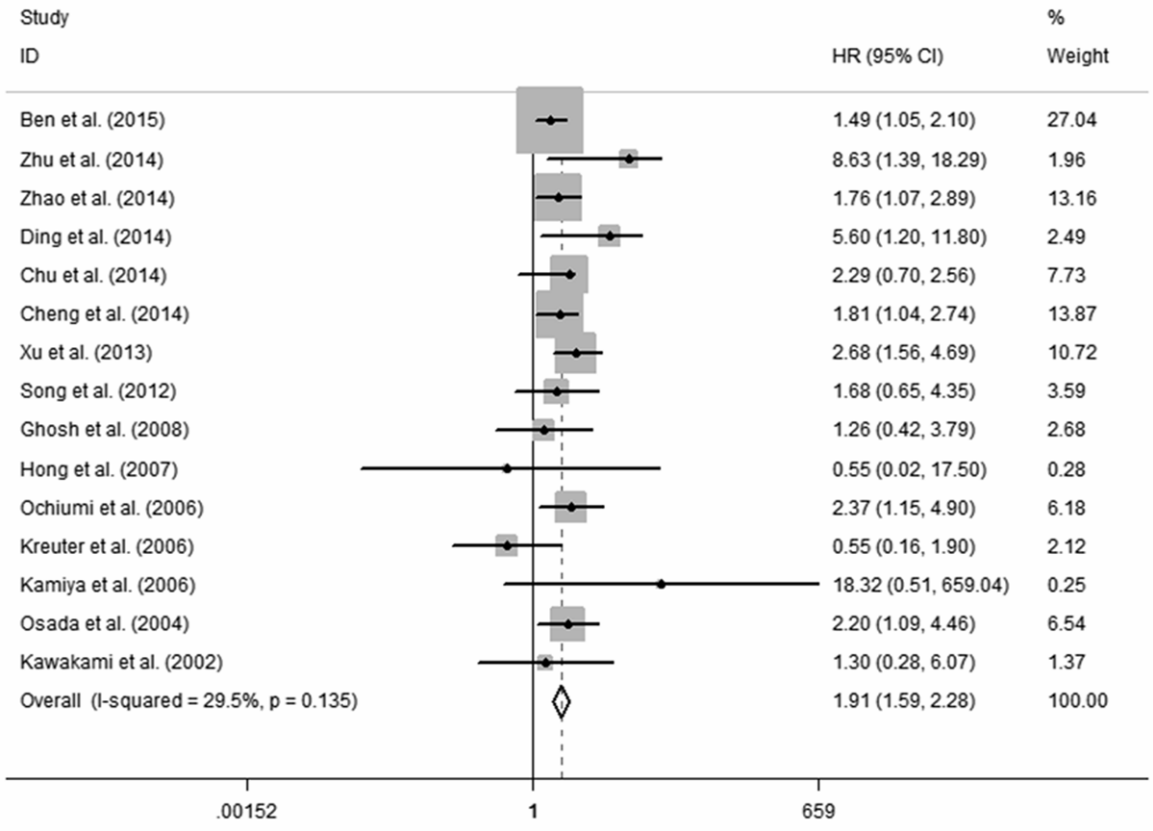

Figure 2. Forrest plot showed hazard ratio (HR) for the association of neuropilin-1 expression with overall survival (OS) in patients with various cancers. Results of individual and summary HRs estimates and 95% CIs of each study are shown.

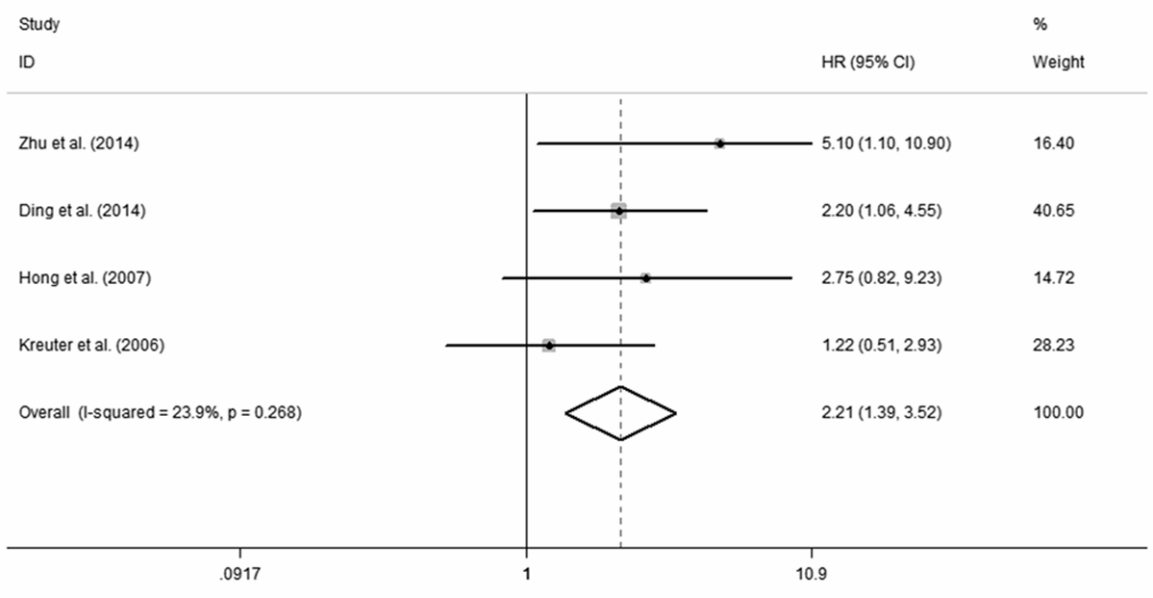

Figure 3. Forrest plot showed hazard ratio (HR) for the association of neuropilin-1 expression with disease-free survival/progression-free survival (DFS/RFS) in patients with various cancers. Results of individual and summary HRs estimates and 95% CIs of each study are shown.

NRP-1 expression and OS involving various cancers. The characteristics and quality levels of the studies included in this review are shown in **Table 1**. For seven studies, three evaluated NSCLC [12, 16, 17]; two assessed colon cancer [8, 18]; and two assessed AML [13, 19]. Further, eight studies evaluated the following (one study for each cancer type): bladder cancer [20], oral squamous cell carcinoma [21], glioma [22], breast cancer [23], nasopharyngeal carcinoma [24], tongue cancer [25], pancreatic ductal adenocarcinoma [26], and osteosarcoma [27]. The studies included a total of 2049 patients, and the size of the median trial sample was 136.6 patients. Among the studies, the median NRP-1 expression was 59.54%. Oral carcinoma, colon cancer, and osteosarcoma had a maximum level of NRP-1 expression (> 70% of tumors). The level of overexpression was 30% in tongue cancer and 50%-60% in other cancer types.

Association of NRP-1 with survival

The pooled analysis of the 15 studies indicated that NRP-1 overexpression was associated with unfavorable overall survival (HR = 1.91; 95% CI = 1.59-2.28; P < 0.001; **Figure 2**) in all cancer patients. A corresponding result was found for DFS/RFS in five studies (OR for death = 2.21; 95% CI = 1.39-3.52; P = 0.01; **Figure 3**). Based on a subgroup analysis for NSCLC, there was a significant association between NRP-1 overexpression and overall survival in NSCLC (HR = 2.06; 95% CI = 1.30-3.26; P = 0.002; **Figure 4**), and increased NRP-1 expression was associated with overall survival in AML (HR = 2.38; 95% CI = 1.48-3.84; P < 0.001; **Figure 4**). However, as compared with normal NRP-1 expression, the pooled analyses for two studies involving colon cancer showed that increased NRP-1 expression was not associated with a poor outcome (HR = 1.24; 95% CI = 0.31-4.96; P = 0.76; **Figure 4**). As shown in **Table 2**, we also performed subgroup analyses for ethnicity (included Asian and Caucasian), sample size, detection methods of immunohistochemistry (IHC), real time-polymerase chain reaction (RT-PCR), and western blot (WB), and percentage of increased NRP-1, but none altered the significant prognostic impact of upregulated NRP-1 expression.

Publication bias

Begg's and Egger's tests were performed to assess publication bias in the studies. As shown in **Table 2**, no publication bias was detected in any comparison, except for a subgroup sample size of ≥ 100 (P = 0.02 and P < 0.001 using Begg's and Egger's tests, respectively).

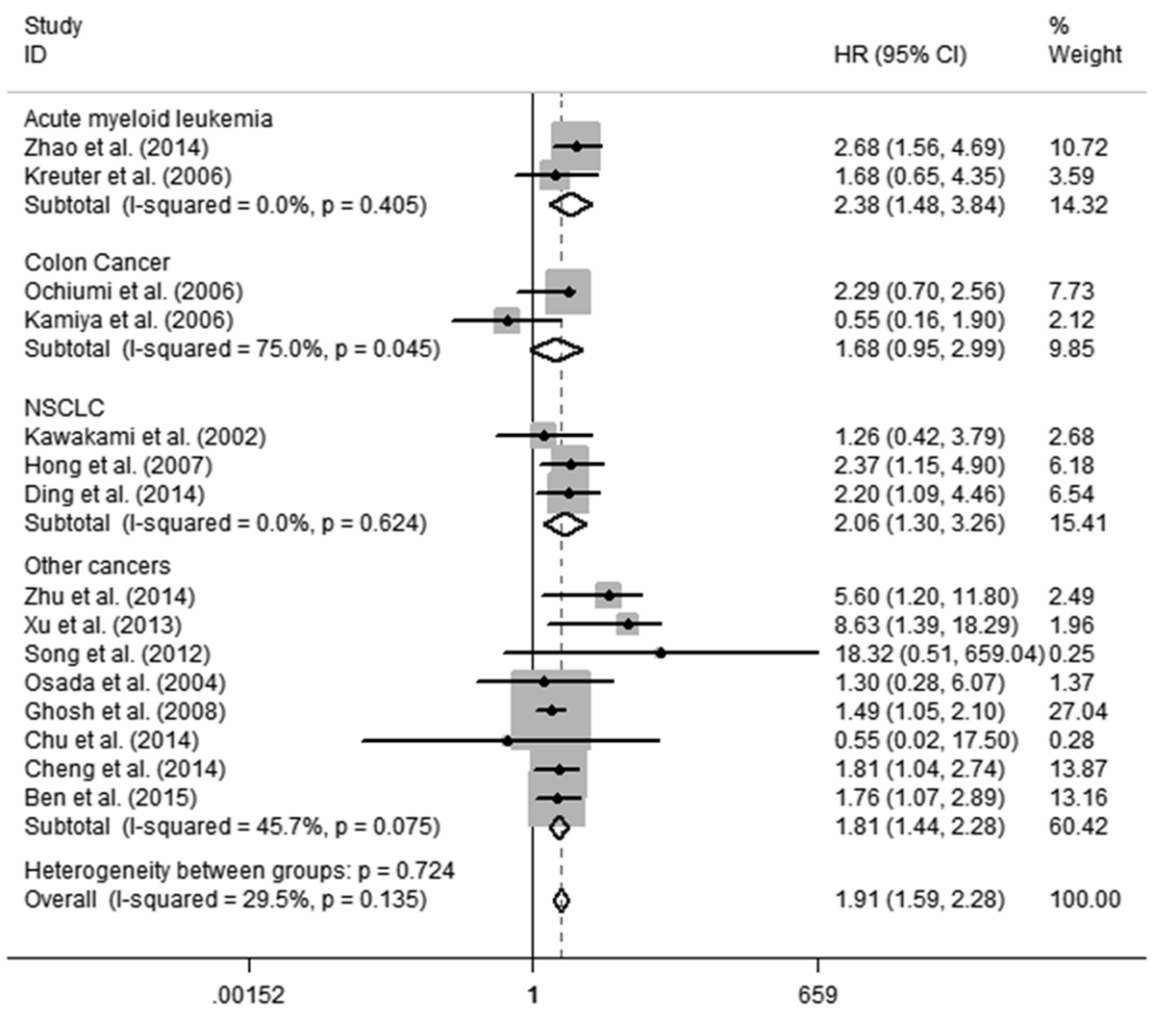

Figure 4. Subgroup analysis of hazard ratio (HR) for the association of neuropilin-1 expression with overall survival (OS) in patients in different cancers. Results of individual and summary HRs estimates and 95% CIs of each study are shown.

Discussion

NRP-1 is a transmembrane glycoprotein that plays a key role in angiogenesis, neural development, tumor growth, and metastasis [3]. NRP-1 was characterized as a regulator of nervous system development when it was identified, acting as a semaphorin co-receptor and regulating the collapse of the axon growth cone during embryonic development [28, 29]. NRP-1, which is a co-receptor of VEGF165, specifically increases the interaction between VEGF165 and VEGFR-2 to enhance cell migration and angiogenesis in HUVEC [30]. NRP-1 is expressed in vascular arteries during embryonic development [31], and NRP-1 knockout mice have completely disorganized vascular networks, thus they do not survive past the embryonic stage (E12.5-13.5). NRP-1 overexpression is significantly associated with poor outcomes in various cancers such as NSCLC, AML, and osteosarcoma. However, some reports demonstrated differing results, with no significant association between NRP-1 and the outcomes of cancer patients. For these inconsistent results, we conducted this meta-analysis to better understand the relationship between NRP-1 expression and the outcomes of various cancers.

To our knowledge, this is the first meta-analysis that focused on the association between NRP-1 levels and patient outcomes. The present meta-analysis included 15 studies and 2049

Table 2. Meta-analysis of neuropilin-1 expression and overall survival (OS) in patients with various cancers

Analysis	Number of studies (No. of patients)	Pooled OR (95% CI)	Z	P	Model	Heterogeneity		Publication bias	
						I^2 (%)	P_{het}	Begg's *P*	Egger's *P*
OS	15 (2049)	1.91 (1.59, 2.28)	7.02	< 0.001	F	29.50%	0.14	0.77	0.39
DFS/RFS	4 (335)	2.21 (1.39, 3.52)	3.35	0.01	F	23.90%	0.27	0.73	0.46
Subgroup 1: ethnicities									
Asian	13 (1338)	2.11 (1.70, 2.62)	6.77	< 0.001	F	29.30%	0.15	0.95	0.52
Caucasian	2 (711)	1.51 (1.09, 2.09)	2.49	0.013	F	0.00%	0.82	1.00	-
Subgroup 2: cancer types									
NSCLC	3 (168)	2.06 (1.30, 3.26)	3.08	0.002	F	0.00%	0.62	1.00	0.14
Colon cancer	2 (200)	1.24 (0.31, 4.96)	0.31	0.76	R	75.00%	0.05	1.00	-
AML	2 (156)	2.38 (1.48, 3.84)	3.57	< 0.001	F	0.00%	0.41	1.00	-
Other cancers	8 (1525)	2.11 (1.41, 3.16)	3.64	< 0.001	R	45.70%	0.08	0.71	0.17
Subgroup 3: methods									
IHC	8 (1431)	1.77 (1.42, 2.21)	5.09	< 0.001	F	24.20%	0.24	0.39	0.16
RT-PCR	5 (365)	1.77 (1.18, 2.64)	2.78	0.005	F	22.80%	0.27	0.22	0.10
WB	2 (253)	3.08 (1.88, 5.06)	4.44	< 0.001	F	22.90%	0.26	1.00	-
Subgroup 4: sample sizes									
≥ 100	6 (1531)	2.16 (1.49, 3.13)	4.07	< 0.001	R	54.80%	0.05	0.02	< 0.001
< 100	9 (518)	1.99 (1.46, 2.71)	4.34	< 0.001	F	7.90%	0.37	0.25	0.34
Subgroup 5: percentage of increased NRP-1									
≥ 60%	8 (1334)	2.18 (1.12, 4.26)	2.29	0.022	R	67.00%	0.01	0.71	0.60
< 60%	6 (628)	1.87 (1.43, 2.42)	4.68	< 0.001	F	0.00%	0.88	1.00	0.48

NRP-1 neuropilin-1, *HR* hazard ratio, *CI* confidence interval, *IHC* immunohistochemistry, *NSCLC* non-small cell lung cancer, *RT-PCR* real time-polymerase chain reaction, *F* fix-effect model, *R* random-effect model, *OS* overall survival, *WB* western blot, P_{het} P for Heterogeneity, I^2 I-squared (variation in ES attributable to heterogeneity), *AML* acute myeloid leukemia, *DFS/RFS* disease-free survival/relapse-free survival.

patients for a systematic analysis, indicating that an increased NRP-1 level was significantly associated with poor OS and DFS/RFS in cancer patients. Different races, detection methods, sample sizes, and percentage of increased NRP-1 did not affect the result that NRP-1 overexpression was significantly associated with poor prognosis in cancer patients. The subgroup analysis results showed that an increased NRP-1 level predicted poor OS in cancer patients with NSCLC and AML, but not with colon cancer.

Limitations of this meta-analysis can be divided into three groups. First, as this was a systematic review and literature-based analysis, the possibility for publication bias might exist, as predominantly negative results were not exposed. Second, the 15 studies utilized three methods to evaluate NRP-1 expression because no accepted or validated method exists. Therefore, substantial heterogeneity could exist that might not be considered in our fixed-effects modeling.

In conclusion, our meta-analysis of 15 studies showed that NRP-1 overexpression is associated with a poor outcome in patients with particular cancer types and suggests that NRP-1 overexpression could be a useful prognostic biomarker for cancer patients.

Disclosure of conflict of interest

None.

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