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ORIGINAL RESEARCH

Prognostic values of HE4 expression in patients with cancer: a meta-analysis

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Background: To evaluate the prognostic impact of HE4 expression in patients with cancer.

Materials and methods: We searched the PubMed, Web of Science, Chinese National Knowledge Infrastructure and WangFang databases for publications concerning HE4 expression in patients with cancer. The correlation of HE4 expression level with overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) was analyzed.

Results: In this meta-analysis, 29 studies, with a total of 4,235 patients, were included. Our results showed that HE4 expression was significantly associated with poorer OS (hazard ratio [HR] =2.15, 95% confidence interval [CI] =1.77–2.62, $P<0.001$). Further subgroup analysis found that this correlation was not affected by race (White: HR =1.92, 95% CI =1.53–2.39, $P<0.001$; Asian: HR =2.62, 95% CI =2.06–3.35, $P<0.001$) or tumor types (endometrial cancer: HR =2.91, 95% CI =1.86–4.53, $P<0.001$; ovarian cancer: HR =1.82, 95% CI =1.50–2.22, $P<0.001$; lung cancer: HR =2.31, 95% CI =1.54–3.47, $P<0.001$). Our meta-analysis showed that HE4 overexpression was significantly associated with DFS (HR =2.50, 95% CI =1.86–3.37, $P<0.001$) and PFS (HR =1.27, 95% CI =1.11–1.45, $P=0.001$).

Conclusion: These results suggest that expression of HE4 was associated with a worse prognosis in patients with cancer. HE4 is a potential novel prognostic factor in patients with cancer.

Keywords: HE4, cancer, prognosis, meta-analysis

Introduction

Cancer is a global health problem associated with increasing mortality rates, in spite of advances in diagnostic and therapeutic approaches.[1] Several pathological parameters and specific blood tumor markers have been proposed as predictive prognostic factors in cancer.[2,3] However, the high incidence of cancer-related deaths indicates a need for reliable and efficient biomarkers for patient stratification and treatment selection.

Human epididymis protein 4 (HE4), also known as whey-acidic-protein four-disulfide core protein-2 (WFDC2), is a member of the protease inhibitor family with immune protective effects and is a promising novel cancer biomarker.[4,5] HE4 has been approved by the US Food and Drug Administration as a new tumor marker for the diagnosis of early stage ovarian cancer.[6] Several cancer types[7–9] are associated with HE4 overexpression in the serum and tissues. HE4 overexpression is also associated with cancer progression, and its prognostic value has been investigated in several published studies. However, the results remain controversial, and therefore this meta-analysis was performed to accurately assess the prognostic value of HE4 expression in cancer patients.

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Materials and methods

Search strategy

The research databases PubMed, Web of Science, Chinese National Knowledge Infrastructure and WangFang databases were searched independently by two authors (Cong Dai and Yi Zheng) to obtain all relevant papers published as of August 2017. The following search terms were used: "Human Epididymis Protein 4 or HE4" and "neoplasms or cancer or tumor" and "prognosis." No language restrictions were applied. Furthermore, references within the retrieved relevant articles were screened to identify potentially eligible studies. Disagreements were resolved by iteration, discussion, and consensus between the two authors.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they met the following criteria: 1) studies evaluated the relationship of HE4 expression in patients with cancer with detailed information about overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS); 2) selected cancer cases were pathologically confirmed, and 3) the study provided a hazard ratio (HR) with the corresponding confidence interval (CI), or sufficient data to calculate it. The exclusion criteria were as follows: 1) duplicate publications; 2) animal studies; 3) articles without usable data; 4) reviews, case reports, letters, and conference abstracts without original data.

Data extraction

Two independent reviewers (Cong Dai and Yi Zheng) extracted the details of included studies using a standardized form, and any disagreements were resolved through discussion with a third reviewer (Zhijun Dai). The following information was recorded: first author's surname, year of publication, number of patients, patient source, tumor types, HE4 assessment method, sample, prognostic outcomes, analytical method, and HR with the corresponding 95% CI.

Methodological quality of the studies

Quality assessment of included studies was conducted independently by two authors (Cong Dai and Tian Tian) following the Newcastle–Ottawa Scale (NOS) criteria,[10] and any disagreements were resolved by discussion with a third reviewer (Zhijun Dai). The NOS criteria were scored on the basis of three aspects: 1) subject selection, 2) comparability of subject, and 3) clinical outcome. NOS scores may range from 0 to 9, and a score ≥6 indicates high quality.

Statistical methods

Included studies were divided into three groups on the basis of the parameter that was reported: OS, DFS, and PFS. According to the cutoff values provided by the authors of each study, HE4 expression was designated as "high" or "low." HR and 95% CI were used to assess the association between HE4 expression and OS, DFS, and PFS. HRs obtained from studies were used directly in further analyses. For studies where HR values were not included explicitly, Kaplan–Meier survival curves or other methods were used to derive HRs from available data.[11] Data from the Kaplan–Meier survival curves were read using the Engauge Digitizer version 4.1 software. Heterogeneity among studies was determined by the χ^2 test and Q test. If there was no significant heterogeneity ($I^2 \leq 50\%$ or $P \geq 0.05$), a fixed-effect model was used; if significant heterogeneity was found to exist ($I^2 > 50\%$ or $P < 0.05$), a random-effects model was used. We further conducted subgroup analyses by race, tumor type, sample, method, and HR estimate. Sensitivity analysis was performed by omitting individual studies to examine the reliability of the results. Probable publication bias was assessed by Egger's and Begg's test.[12,13] All P-values were two-sided, and $P < 0.05$ was considered statistically significant. Statistical calculations were performed using STATA 14.0 (StataCorp LLC, College Station, TX, USA).

Results

Search results and study characteristics

A total of 369 articles from the primary literature were searched in PubMed, Web of Science, CNKI, and WangFang databases. References within the retrieved relevant articles had been screened, but there were no more potentially eligible studies. As shown in Figure 1, 340 studies were excluded because they were irrelevant to the analysis or because the primary outcome was insufficient. Finally, 29 available studies were included in this meta-analysis.[7–9,14–39]

The characteristics of the 29 studies are summarized in Table 1. Of the 29 publications, 23 assessed the relationship between HE4 expression and OS, eight studies evaluated the association between HE4 expression and DFS, and eleven evaluated PFS. A total of 4,235 patients from People's Republic of China, the Netherlands, Italy, Denmark, United States of America, France, Australia, Germany, Japan, Canada, Korea, and Sweden were enrolled with sample numbers ranging from 23 to 373. HE4 status in tumors was assessed by various methods: immunohistochemistry (IHC) (6 studies), electrochemiluminescence immunoassay assay (ECLIA) (2 studies), enzyme immu-

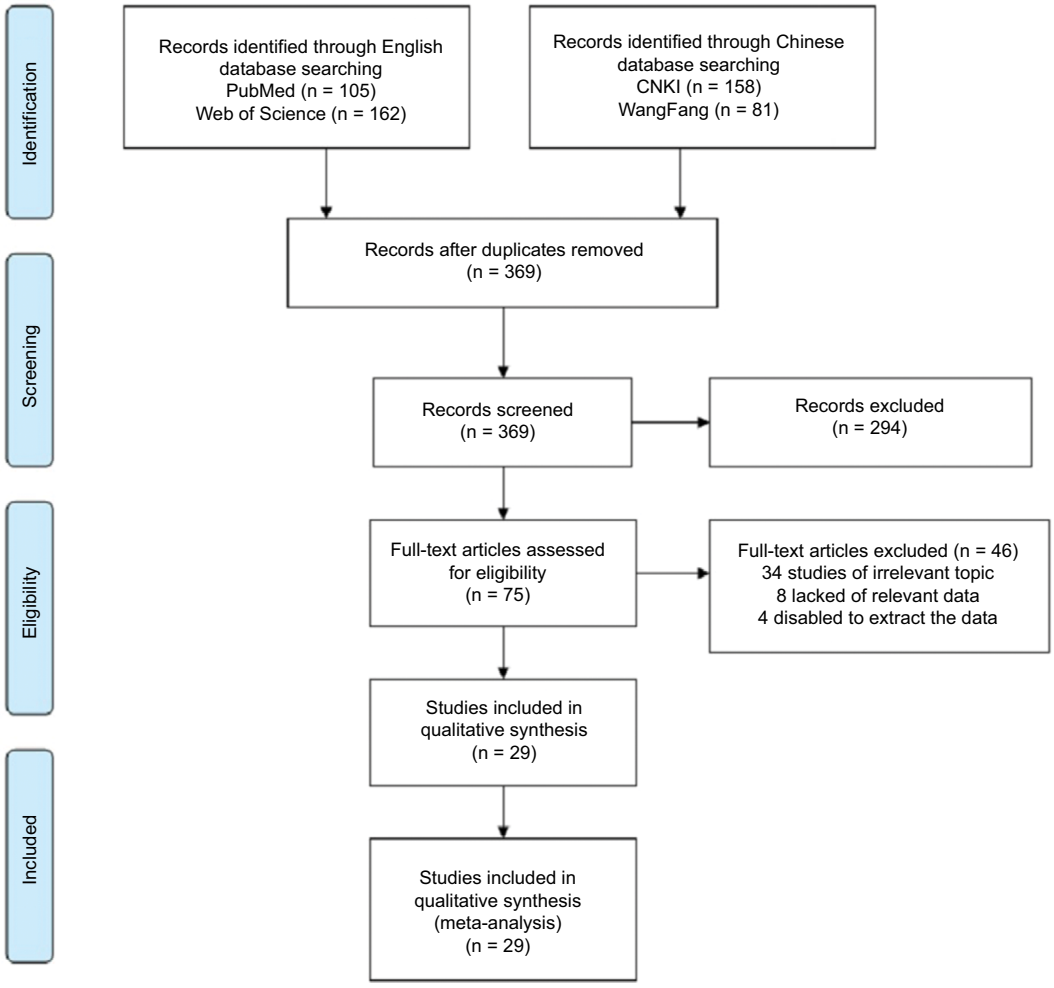

Figure 1 Flowchart of the selection of the studies in the meta-analysis.

noassay assay (EIA) (15 studies), and Chemiluminesent Microparticle Immunoassay (CMIA) (5 studies). Study quality assessment, as per the Newcastle–Ottawa quality assessment scale, yielded scores ranging from 6 to 9, with a mean score of 7.6.

Quantitative synthesis

HE4 expression and OS in cancers

Overall, 23 studies, including 3,564 patients, reported a relationship between OS and HE4 expression level. As heterogeneity among the studies was statistically significant (P=0.001, I^2=55.6%), a random-effects model was used. The pooled HR for OS showed that the overexpression of HE4 was significantly associated with reduced OS in cancers (HR =2.15, 95% CI =1.77–2.62, P<0.001, Table 2 and Figure 2).

We also performed subgroup analysis as per race, tumor type, sample, analysis method, and HR estimate (Table 2). Subgroup analysis showed that the correlation between OS and HE4 expression did not differ by race (White: HR =1.92, 95% CI =1.53–2.39, P<0.001; Asian: HR =2.62, 95% CI =2.06–3.35, P<0.001) and tumor type (endometrial cancer: HR =2.91, 95% CI =1.86–4.53, P<0.001; ovarian cancer: HR =1.82, 95% CI =1.50–2.22, P<0.001; lung cancer: HR =2.31, 95% CI =1.54–3.47, P<0.001). Subgroup analysis, based on pooled data pertaining to sample, method, and HR estimate, also demonstrated that there was a significant association between OS and HE4 expression. Subgroup analysis of HR estimates found no significant heterogeneity (multivariate analysis: I^2=13.4, univariate analysis: I^2=47.8).

Included studies were sequentially removed to investigate whether any single study could have an influence on the pooled results. The results of the sensitivity analyses showed (Figure 3) that there was no influence of any single study on stable pooled HR.

Table 1 Main characteristics of all studies included in the meta-analysis

Study	Year	Patient source	Number of patients	Tumor types	Method	Sample	Cutoff	Outcome	M/U	HR (95% CI)	Quality
Stiekema et al[7]	2017	Netherlands	88	EC	ECLIA	Blood	60 pmol/L for women <40 years, 75 pmol/L for patients between 40 and 60 years of age, and 90 pmol/L for patients >60 years of age	OS DFS	M	7.37 (2.16–25.1) 5.12 (1.54–17.1)	9
Orsaria et al[14]	2016	Italy	105	OC	IHC	Tissue	H-score value >1	OS	M	1.82 (0.81–4)	8
Aarenstrup Karlsen et al[8]	2016	Denmark	198	OC	IHC	Tissue	–	OS PFS	U	1.44 (1.01–2.0) 1.49 (1.06–2.11)	8
Lan et al[15]	2015	People's Republic of China	218	LC	EIA	Blood	20.5 ng/mL	OS	M	3.78 (2.23–7.34)	8
Deng et al[16]	2015	People's Republic of China	65	EC	IHC	Tissue	–	OS	U	2.51 (0.66–9.53)	7
Li et al[17]	2015	People's Republic of China	102	EC	IHC	Tissue	H-score value >2	OS	U	1.85 (0.37–9.28)	6
Lee et al[18]	2015	United States of America	53	OC	–	Tissue	–	OS	U	1.72 (0.87–3.46)	6
Lamy et al[9]	2015	France	346	LC	EIA	Blood	140 pm	OS	U	1.96 (1.53–2.53)	8
Guo et al[19]	2015	United States of America	243	GC	IHC	Tissue	H-score value >1	OS	U	1.62 (1.00–2.62)	7
Lou et al[20]	2014	United States of America	153	LC	EIA	Blood	65–83 pm	OS PFS	U	1.08 (0.87–1.36) 0.95 (0.78–1.17)	6
Jiang et al[21]	2014	People's Republic of China	100	LC	EIA	Blood	7.26 ng/mL	OS	M	3.65 (2.75–11.98)	7
Brennan et al[22]	2014	Australia	373	EC	CMIA	Blood	H-score >75%	DFS	M	2.40 (1.19–4.38)	9
Zhang et al[23]	2014	People's Republic of China	191	LC	EIA	Blood	91.63 pmol/L	OS	M	2.15 (1.49–3.12)	7
Braicu et al[24]	2014	Germany	73	OC	ECLIA	Blood	250 pm	OS	U	3.33 (1.03–10.7)	6
Zheng et al[25]	2013	People's Republic of China	112	OC	EIA	Blood	415.5 pmol/L	OS	U	2.17 (1.11–4.23)	8
Liu et al[26]	2013	People's Republic of China	169	LC	EIA	Blood	83.90 pm	OS	M	2.2 (0.8–5.9)	7
Zanotti et al[27]	2012	Italy	190	EC	CMIA	Blood	51 pm	OS DFS PFS	M	2.78 (1.16–6.63) 2.49 (1.13–5.49) 2.66 (1.10–6.45)	9
Yamashita et al[28]	2012	Japan	74	LC	EIA	Blood	50.3 pm	DFS	U	3.28 (0.57–18.84)	7
Trudel et al[29]	2012	Canada	136	OC	CMIA	Blood	394 pmol/L	OS PFS	M	1.67 (1.08–2.59) 1.32 (0.87–1.99)	9
Mutz-Dehbalaie et al[30]	2012	Austria	183	EC	CMIA	Blood	81 pmol/L	OS DFS	M	2.41 (1.17–4.97) 1.59 (0.82–3.08)	8
Kong et al[31]	2012	Korea	80	OC	EIA	Blood	98.7 pm	PFS	M	1.47 (1.02–2.1)	8
Kalapotharakos et al[32]	2012	Sweden	312	OC	EIA	Blood	405 pm	OS	M	2.02 (1.1–3.8)	9
Hu et al[33]	2012	People's Republic of China	76	OC	EIA	Blood	208 pmol/L	PFS	U	1.72 (0.92–3.21)	6
Steffensen et al[34]	2011	Denmark	139	OC	EIA	Blood	140 pm	OS PFS	M	3.17 (1.41–7.10) 1.77 (1.03–3.04)	9

(*Continued*)

Table 1 (*Continued*)

Study	Year	Patient source	Number of patients	Tumor types	Method	Sample	Cutoff	Outcome	M/U	HR (95% CI)	Quality
Yamashita et al[35]	2011	Japan	137	LC	IHC	Tissue	H-score >75%	OS	M	5.5 (1.8–17.2)	8
								DFS		3.7 (1.7–8.4)	
Paek et al[36]	2011	Korea	45	OC	EIA	Blood	70 pm	PFS	M	2.24 (1.14–6.84)	8
Han et al[37]	2011	United States of America	23	OC	EIA	Blood	74 pm	PFS	U	1.97 (0.61–6.39)	7
Bignotti et al[38]	2011	Italy	153	EC	EIA	Blood	–	OS	U	3.74 (0.43–32.45)	8
								PFS		1.78 (0.30–10.44)	
								DFS		2.43 (0.87–6.77)	
Bandiera et al[39]	2011	Italy	98	OC	CMIA	Blood	43.8 pm	OS	M	3.98 (1.35–11.75)	8
								DFS		2.46 (1.09–5.56)	
								PFS		2.77 (1.12–6.85)	

Abbreviations: M, multivariate analysis; U, univariate analysis; HR, hazard ratio; EC, endometrial cancer; OC, ovarian cancer; LC, lung cancer; GC, gastric cancer; ECLIA, electrochemiluminescence immunoassay assay; IHC, immunohistochemistry; EIA, enzyme immunoassay assay; CMIA, chemiluminescent microparticle immunoassay; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

HE4 expression and DFS in cancers

Eight studies, with a total of 1,296 patients, provided results pertaining to DFS. There was no significant heterogeneity (P=0.757, I^2=0.0%) among the studies, so a fixed-effect model was used to calculate the pooled HR and 95% CI. Our results showed that increased HE4 expression was significantly associated with poorer DFS (HR =2.50, 95% CI =1.86–3.37, P<0.001) (Figure 4).

HE4 expression and PFS in cancers

As shown in Figure 5, there were eleven studies, comprising a total of 1,291 patients, that provided results regarding PFS. The pooled data demonstrated that there was a significant association between HE4 expression and PFS (HR =1.27, 95% CI =1.11–1.45, P=0.001). There was no significant heterogeneity (P=0.070, I^2=41.8%) among the studies, so a fixed-effect model was used.

Publication bias

In this meta-analysis, both the Begg's and the Egger's tests were performed to assess if any publication bias existed in the included studies. Publication bias was observed in studies reporting OS (P=0.051, 0.000) and PFS (P=0.755, 0.003) but not in those reporting DFS (P=0.174, 0.149). The Begg's plots for the effect of HE4 expression level on OS are shown in Figure 6.

Discussion

HE4 is a new tumor biomarker, which has been a subject of intense research in recent years. HE4, originally discovered by Kirchhoff in the human distal epididymal epithelial cells,[40] is located on chromosome 20 at 20q12-13 and contains five exons and four introns.[41] It contains a gene encoding protein domains that have homology with whey acidic protein, by which the product encoded is mainly protease inhibitor.[42] As a member of the protease inhibitor family, it has an inhibitory effect on cell proliferation. Previous studies have reported that HE4 overexpression significantly promotes tumor cell apoptosis and adhesion and inhibits cell proliferation, migration, and invasiveness.[43] Further, Kong et al[44] found in vitro that this antitumor effect may be achieved by regulating the mitogen-activated protein kinase and phosphoinositide 3-kinase/AKT signal transduction pathways. Recently, further studies have been carried out to investigate the association between HE4 overexpression and prognosis in several tumors.[45,46] However, the studies were inconclusive because of small sample sizes and inconsistencies in results. Therefore, to evaluate the relationship between HE4 expression and

Table 2 Main meta-analysis results for OS

Analysis	Number of studies	Number of patients	Model	HR (95% CI)	*P*-value	Heterogeneity	
						I^2 (%)	P-value
OS	23	3,564	Random	2.15 (1.77–2.62)	0.000	55.6	0.001
Race							
White	15	2,470	Random	1.92 (1.53–2.39)	0.000	55.9	0.004
Asian	8	1,094	Fixed	2.62 (2.06–3.35)	0.000	0.0	0.587
Tumor types							
EC	6	781	Fixed	2.91 (1.86–4.53)	0.000	0.0	0.719
OC	9	1,226	Fixed	1.82 (1.50–2.22)	0.000	0.0	0.515
LC	7	1,314	Random	2.31 (1.54–3.47)	0.000	82.4	0.000
GC	1	243	–	1.62 (1.00–2.62)	–	–	–
Sample							
Blood	16	2,661	Random	2.34 (1.82–3.02)	0.000	65.7	0.000
Tissue	7	903	Fixed	1.67 (1.32–2.11)	0.000	0.0	0.488
Method							
ECLIA	2	161	Fixed	4.86 (2.09–11.34)	0.000	0.0	0.358
IHC	6	850	Fixed	1.66 (1.30–2.13)	0.000	8.1	0.365
EIA	10	1,893	Random	2.20 (1.61–3.01)	0.000	73.1	0.000
CMIA	4	607	Fixed	2.10 (1.51–2.91)	0.000	0.0	0.402
HR estimate							
Multivariate analysis	13	2,066	Fixed	2.47 (2.05–2.97)	0.000	13.4	0.310
Univariate analysis	10	1,498	Fixed	1.50 (1.31–1.71)	0.000	47.8	0.045

Abbreviations: HR, hazard ratio; OS, overall survival; EC, endometrial cancer; OC, ovarian cancer; LC, lung cancer; GC, gastric cancer; ECLIA, electrochemiluminescence immunoassay assay; IHC, immunohistochemistry; EIA, enzyme immunoassay assay; CMIA, chemiluminescent microparticle immunoassay.

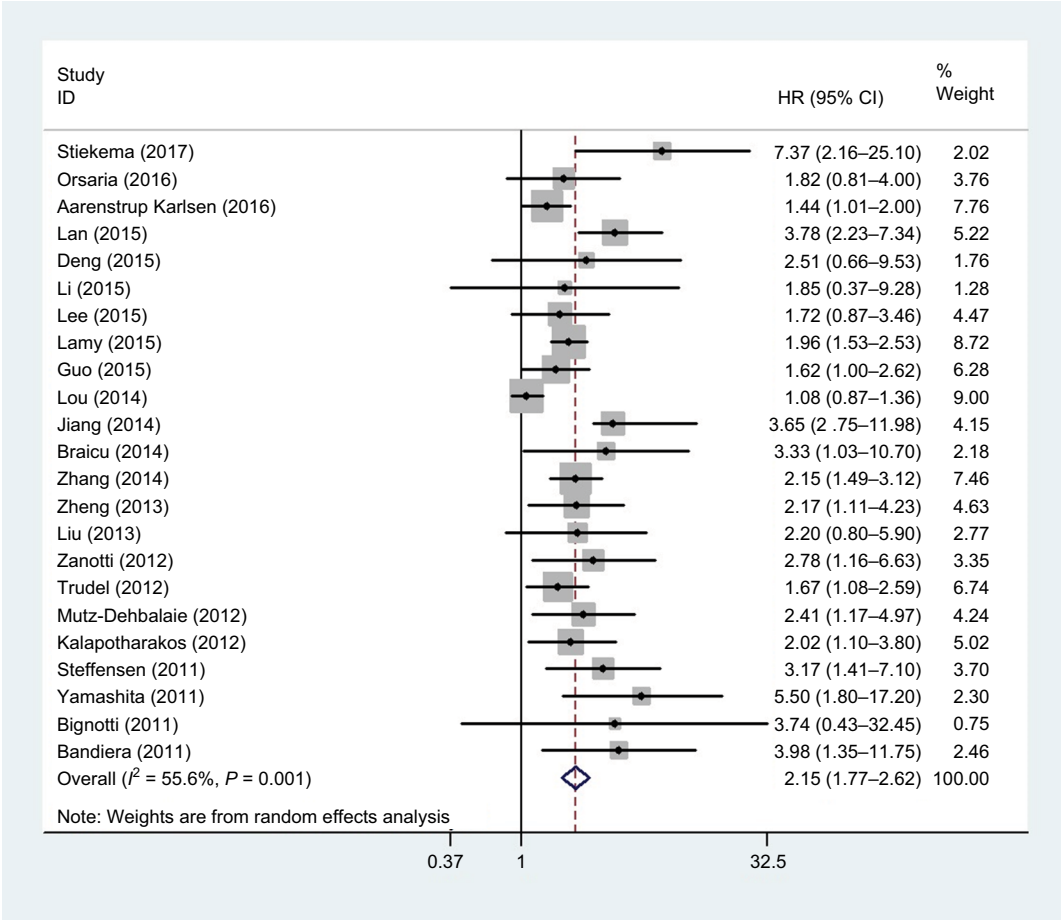

Figure 2 Forest plot of hazard ratio for the association of HE4 expression and overall survival.

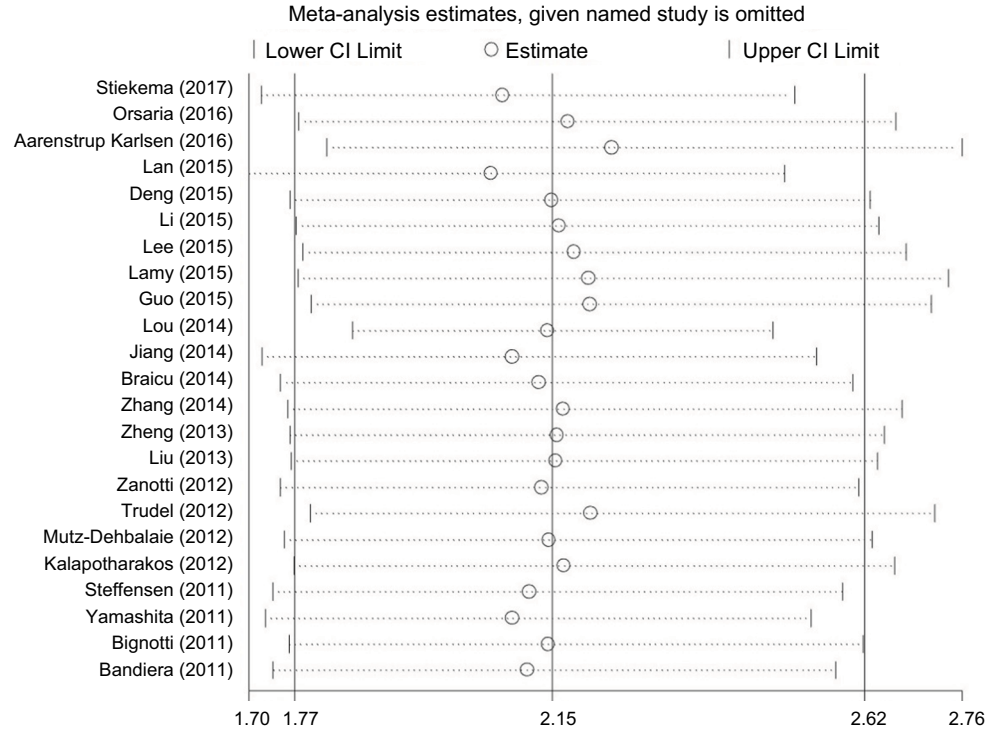

Figure 3 Sensitivity analysis of pooled HRs on the association between HE4 expression and overall survival.

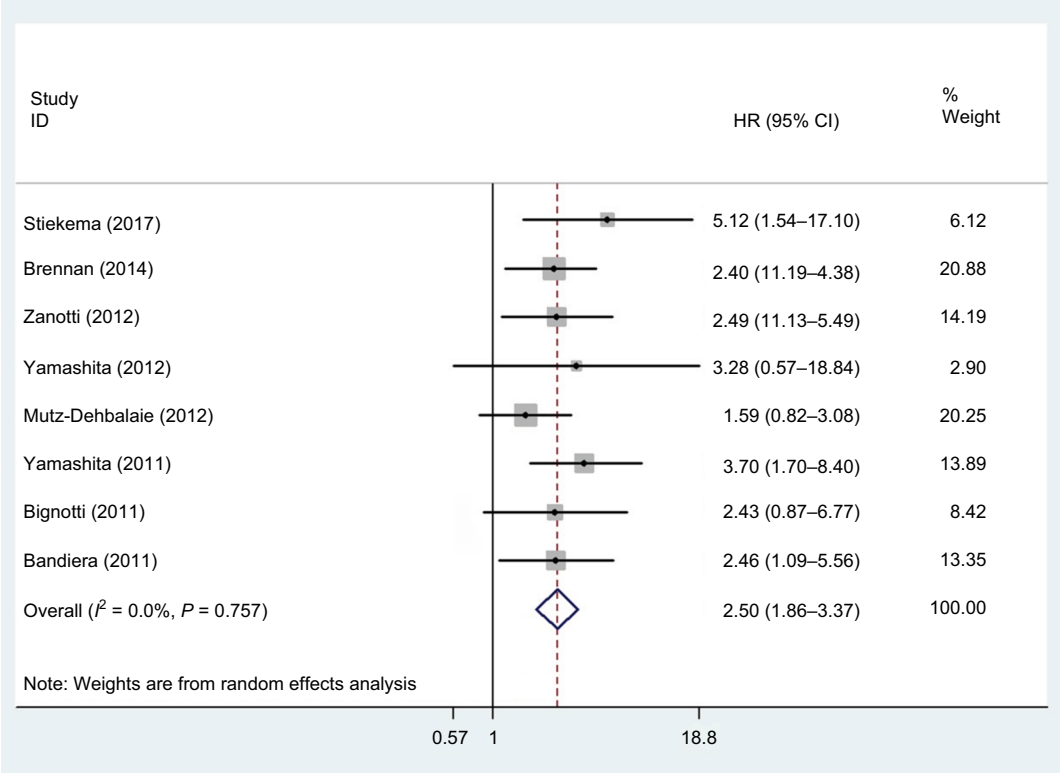

Figure 4 Forest plot of hazard ratio for the association of HE4 expression and disease-free survival.

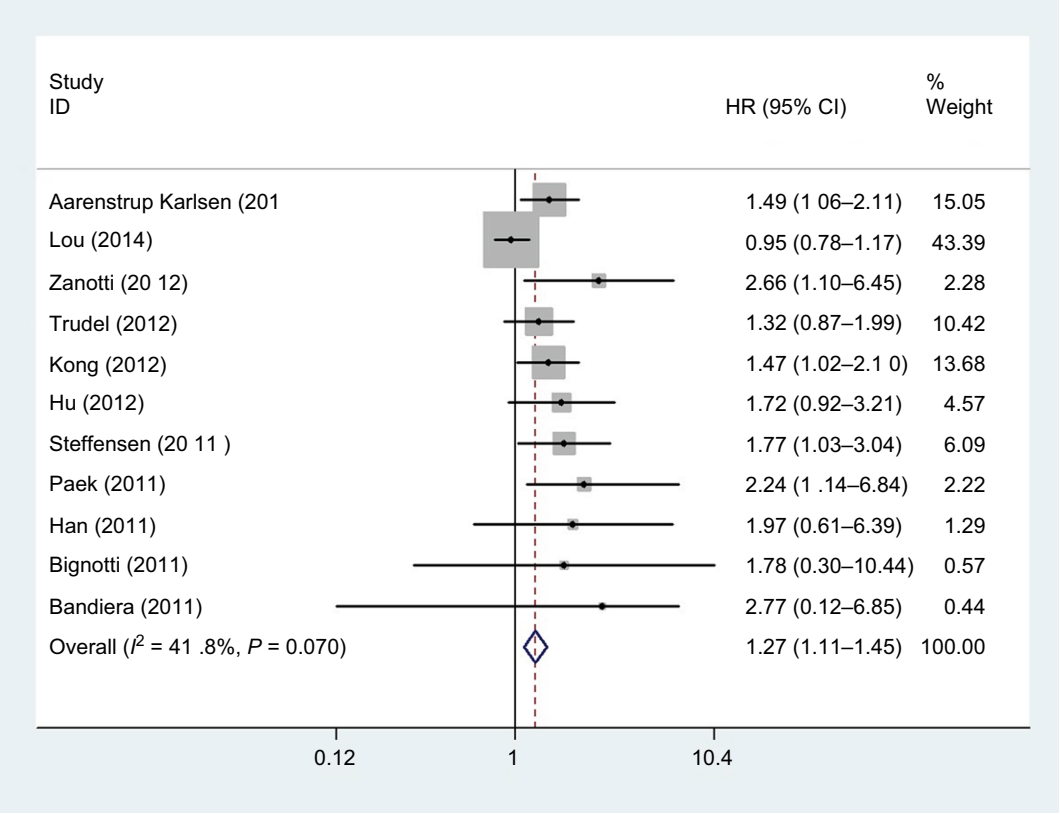

Figure 5 Forest plot of hazard ratio for the association of HE4 expression and progression-free survival.

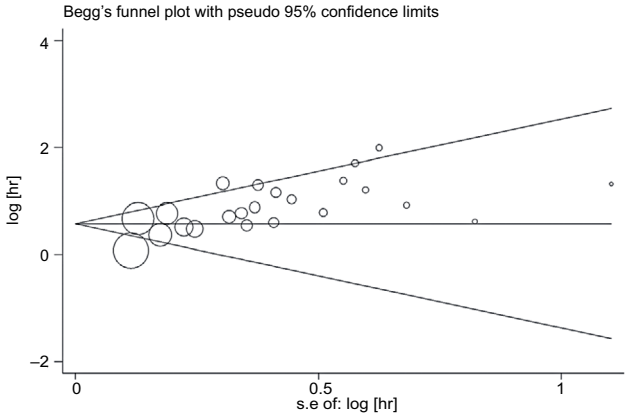

Figure 6 Funnel plots of publication bias for all of the included studies reported with overall survival.

prognosis of cancer patients, we conducted this meta-analysis to mitigate sample size problems of individual studies and enhance the statistical power.

In the present meta-analysis, we analyzed 29 studies, including 3,564 patients, with OS data from 23 studies, DFS data from eight studies, and PFS data from eleven studies. The results indicated that there was no significant difference in the OS, DFS, and PFS outcomes based on HE4 expression status. There was significant heterogeneity in OS across the included studies. In order to ascertain the reason for the heterogeneity, we performed sensitivity analyses, and the results showed that the stable pooled HR was not significantly affected by any individual study. However, subgroup analyses revealed that the heterogeneity may have been due to the HR estimate methods used. Differences in the baseline characteristics of patients and in the HE4 expression cutoff values may have also contributed to the observed heterogeneity. However, for want of relevant data, it was not possible to determine the contribution of each of the above factors to the heterogeneity. In addition, we also found that the correlation between HE4 expression and OS of cancer patients was not affected by race, tumor type, sample source, detection method, or HR estimation method, and we therefore believe that HE4 may serve as a reliable and novel parameter for prognostication and a promising target for anticancer therapy in cancers.

Several previous meta-analyses have been conducted to research the association between HE4 expression and diagnosis and prognosis of cancer patients. For example, Zhong et al[47] identified eight studies that involved 1,412 lung

cancer patients and showed that high serum HE4 level was a marker of poor prognosis in lung cancer patients, particularly in patients of Asian origin. Compared with previous studies, our meta-analysis has several limitations as well as advantages. Our study is the first meta-analysis to review the role of HE4 in the OS, DFS, and PFS in several cancer types. In addition, to ensure the reliability of results, we have increased the number of studies included in the analysis.

Although we made every effort to conduct a comprehensive analysis, our study has several limitations. First, we tried to analyze the association between HE4 expression and prognosis in all cancer types, but the majority of included studies focused on endometrial cancer, ovarian cancer, or lung cancer. Hence, suitably designed larger future studies are needed to confirm our results. Second, when we evaluated the relationship between OS and HE4 expression, there was obvious publication bias, possibly because positive results are more likely to be published than are negative results. Last, the cutoff value for HE4 expression differed between studies, which may have led to heterogeneity. A standardized baseline value to designate positive/high HE4 expression status is thus needed. Meanwhile, the collection time and survival times were not standard, and this may be one of the sources of heterogeneity.

Conclusion

We found that increased expression of HE4 indicated poor survival outcomes in patients with cancer. Therefore, HE4 is a potential novel prognostic factor in cancer patients.

Author contributions

ZD, CD, and JL designed the research. CD, YL, and TT contributed to the literature search. PX, MW, and YD carried out the data extraction. YW, ZZ, and QH contributed to statistical analysis. CD and YZ wrote the manuscript. ZD and CD contributed to revision of the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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