Review

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Prognostic value of HE4 in patients with ovarian cancer

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Keywords: HE4; meta-analysis; ovarian cancer; prognosis.**Abstract**

Background: There is no consensus in the medical community about the prognostic role of preoperative serum levels of human epididymis protein 4 (HE4) in ovarian cancer (OC). The purpose of this meta-analysis was to establish whether preoperative serum levels of HE4 are associated with OC prognosis.

Content: Eligible studies were searched for in PubMed, ClinicalTrials.gov, CNKI and Wanfang Med Online. We performed a meta-analysis of 1315 OC cases from 14 published articles.

Summary: Our meta-analysis demonstrated that high HE4 was associated with poor overall survival (OS) (random effects model, hazard ratio [HR]=1.91, 95% confidence interval [CI]=1.40–2.614, $p<0.0001$; $I^2=52\%$, $p=0.04$) and; progression-free survival (PFS) (random effects model, HR=1.38, 95% CI=1.13–1.69, $p=0.002$; $I^2=85\%$, $p<0.00001$). However, subgroup analysis showed that high HE4 was not associated with poor OS (fixed effects model, HR=1.86, 95% CI=0.89–3.89, $p=0.1$; $I^2=34\%$, $p=0.22$) or PFS (random effects model, HR=1.34, 95% CI=0.95–1.88, $p=0.1$; $I^2=69\%$, $p=0.007$) for studies including only Asian populations.

Outlook: In conclusion, this meta-analysis shows that high HE4 was associated with poor OC OS and PFS overall. However, the association of high HE4 with poor OS and PFS was not observed for Asians. Large-scale, multi-center investigations should be performed.

Introduction

Epithelial ovarian cancer (EOC) is the fourth most common cause of female cancer death and the leading cause of death from gynecologic cancer in the developed world [1], with over 22,440 new cases and 14,080 deaths in the United States in 2017 [2]. Even with numerous efforts to improve surgical techniques and with carefully designed chemotherapy programs, the 5-year survival rate remains 10%–30% [3–6]. The poor rate of survival and the high rate of lethality are primarily due to late detection and rapid progression [3–6]. Therefore, there is an urgent need to find reliable predictive biomarkers of patients' prognosis and to develop novel therapeutic strategies [6].

Carbohydrate antigen 125 (CA125) levels are widely used for the diagnosis of ovarian cancer (OC). Unfortunately, because of its high false-positive and false-negative rates, CA125 has a limited value for prognosis. The human epididymis protein 4 (HE4) is located on chromosome 20q12-13; HE4 is encoded by the WFDC2 gene, which is one of several WAP domain-coding genes within that chromosomal region [7, 8]. HE4 is highly expressed in different types of OC, especially in serous and endometrioid cancers [9]. HE4 has been used in EOC diagnosis [10]. In 2008, HE4 was the first biomarker since CA125 to be approved by the FDA for monitoring patients with OC for disease recurrence [11]. In particular, the combination of HE4 and CA125 (ROMA algorithm) has been recommended for differential diagnosis of OC in patients with pelvic masses [12].

However, there is no consensus in the medical community about the prognostic role of preoperative serum levels of HE4 in OC. Some studies have evaluated the role of HE4 as a prognostic factor of OC [8, 13–25], but the experimental results remain inconclusive. A few previous studies have been limited by their relatively small patient populations. To systematically evaluate the potential of preoperative serum levels of HE4 as a biomarker for the prognostic prediction of OC, we conducted a meta-analysis.

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Materials and methods

Search and selection process

We performed this meta-analysis by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Checklist S1) [26].

We searched the PubMed database, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI) database and Wanfang Med Online, using combinations of the following keywords: (“HE4” or “human epididymis secretory protein E4” or “human epididymis protein 4”) and (“tumor” or “cancer” or “carcinoma” or “neoplasm” or “malignancy”) and (“ovarian” or “ovary”) and (“survival” or “outcome” “prognosis” or “prognostic” or “mortality”) from January 1, 2000, to May 20, 2017. Two authors, Yan and Li, independently examined the retrieved references to assess their appropriateness for inclusion in this meta-analysis. In addition, we investigated all of the relevant literature cited in the articles and reviews.

Selection criteria and quality score assessment

Studies were required to meet the following criteria: (a) the association of HE4 with the prognostic value in OC should be described; (b) the studies reported survival outcomes (overall survival [OS], progression-free

survival [PFS] or disease-free survival [DFS]) with HR and 95% CI or survival curves; and (c) the studies were published in the English literature or Chinese literature. The exclusion criteria were no sufficient data for obtaining hazard ratio (HR) and 95% confidence interval (CI).

All studies were independently evaluated by the two authors (Yan and Li) according to a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE [27, 28]. The key points of the current checklist include the following: (a) clear definition of the study population and origin of country; (b) clear definition of the association of HE4 with the prognostic value in OC; (c) clear definition of the study design; (d) clear definition of the outcome assessment; (e) clear definition of the measurement of HE4; (f) clear definition of the cutoff of HE4; and (g) sufficient period of follow-up. The 14 studies included mentioned all seven points [27, 28]. A flow diagram of the study selection process is presented in Figure 1.

Data extraction

The data of the eligible studies were independently extracted according to the prespecified criteria by the two authors (Yan and Li). Inconsistencies in data extraction were resolved by joint review and consensus. All of the necessary information, if available, was extracted from each study, including first author, publication year, period of patient recruitment, country, institution of the patients, ethnicity, cancer type, case no., HE4 high no., HE4 low no., sample type, test methods, reagent brand, age (years), cutoff values and follow-up (Table 1). In addition, the HRs of HE4 expression for OS, PFS or DFS and 95% CIs were extracted (Table 2). If the HRs and 95% CIs were not directly available, we calculated HRs and their 95% CIs from survival curves by the methods reported by Tierney et al. [29, 30].

Statistical analysis

Pooled HRs and 95% CIs were used to evaluate the association of HE4 with OC prognosis. The multivariate Cox model was the most appropriate method for OS and PFS, but a univariate Cox model was chosen when the multivariate Cox model was not available. We calculated HRs and their 95% CIs from survival curves using a univariate Cox model. An observed HR of more than one indicated a poorer prognosis for patients with high HE4 than for those with low HE4. A heterogeneity test of pooled HR was calculated using Cochran's Q test and Higgins

Figure 1: Study flowchart outlining the selection of the studies included in the meta-analysis.

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

First author	Year	Recruitment period of patients	Country	Study site	Ethnicity	Cancer type	No. of cases	No. with high HE4	No. with low HE4	Test methods	Age, years	Cutoff values	Follow-up, months
Aarenstrup Karlisen M [17]	2016	2004.09–2010.01	Denmark	Danish Gynecologic Cancer Database	Caucasian	EOC	198	NA	NA	CMA (Abbott Diagnostics)	64 (30–88)	Continuous, log base 2 transformed	88.6
Bandiera E [24]	2011	2003–2010	Italy	The University of Brescia	Caucasian	EOC	98	49	49	CMA (Abbott Diagnostics)	NA	Median	85
Braicu EI [18]	2014	2006.02–2009.04	Germany	Charite' Medical University Berlin	Caucasian	EOC	73	NA	NA	ELISA (Fujirebio Diagnostics)	53 (21–77)	250 pmol/L	57
Chudecka-Glaz A [20]	2012	2006–2008	Poland	Pomeranian Medical University	Caucasian	EOC	39	NA	NA	ELISA (Fujirebio Diagnostics)	53.6 (32–79)	150 pmol/L	60
Dong N [25]	2014	2006.02–2010.02	China	Yingkou Central Hospital	Asian	EOC	100	NA	NA	ELISA (CanAg Diagnostics)	53.5 ± 10.24	2080 pmol/L	50
Hu S [14]	2012	2008.02–2009.04	China	Cancer Hospital Chinese Academy of Medical Sciences	Asian	EOC	76	38	38	ELISA (CanAg Diagnostics)	58 (17–88)	208 pmol/L (median)	50
Kalapocharakos G [19]	2012	1993–2009	Sweden	The Department of Obstetrics and Gynecology in Lund	Caucasian	EOC	85	43	42	ELISA (Fujirebio Diagnostics)	63.1 (31–87)	40.5 pmol/L (median)	203
Kong SY [23]	2012	2003–2007	Korea	Tumor Bank of National Cancer Center	Asian	EOC	80	40	40	ELISA (Fujirebio Diagnostics)	56 (26–78)	98.7 pg/mL (median)	56
Li L [13]	2013	2007.08–2009.06	China	Shengjing Hospital of China Medical University	Asian	EOC	70	35	35	ELISA (CanAg Diagnostics)	57 (20–78)	205.6 pmol/L (median)	49
Paek J [22]	2011	NA	Korea	Yonsei University College of Medicine	Asian	EOC	45	33	15	ELISA (Fujirebio Diagnostics)	51.1 ± 10.72	70 pmol/L	55
Steffensen KD [21]	2011	2005.10–2010.03	Denmark	Vejle Hospital	Caucasian	EOC	139	69 or 70	69 or 70	ELISA (Fujirebio Diagnostics)	64 (32–84)	Median	39.6 (median)
Trudel D [8]	2012	1998.01–2006.12	Canada	The University Hospital Center of Quebec	Caucasian	OC	136	68	68	CMA (Abbott Diagnostics)	61.9 ± 11.1	394 pmol/L (median)	144
Zhang F [15]	2016	2012.01–2015.01	China	The Affiliated Hospital of Inner Mongolia Medical University	Asian	EOC	64	39	25	ELISA (CanAg Diagnostics)	41.9 ± 10.8	205.6 pmol/L	32
Zheng H [16]	2013	2004–2010	China	Beijing Cancer Hospital	Asian	EOC	112	56	56	ELISA (CanAg Diagnostics)	55.9 ± 10.6	415.5 pmol/L (median)	88

NA, not available; CanAg Diagnostics was the subsidiary of Fujirebio Diagnostics in China. HE4, human epididymis protein 4; OC, ovarian cancer; EOC, epithelial ovarian cancer.

Table 2: Prognostic role of HE4 in ovarian cancer in the eligible studies.

First author	Year	OS			PFS		
		HR	95% CI	p-Value	HR estimate	HR	HR estimate
Aarenstrup Karlisen M [17]	2016	1.3	1.19–1.42	<0.001	Univariate Cox	1.34	Univariate Cox
Bandiera E [24]	2011	3.98	1.35–11.75	0.012	Multivariate Cox	2.77	Multivariate Cox
Braicu EI [18]	2014	3.33	1.03–10.7	0.044	Multivariate Cox	NA	NA
Chudecka-Glaz A [20]	2012	2.27	0.67–7.73	<0.05	Kaplan-Meier curves	1.43	Kaplan-Meier curves
Dong N [25]	2014	NA	NA	NA	NA	1.61	Kaplan-Meier Curves
Hu S [14]	2012	NA	NA	NA	NA	1.001	Univariate Cox
Kalapocharakos G [19]	2012	2.02	1.1–3.8	0.02	Multivariate Cox	NA	NA
Kong SY [23]	2014	NA	NA	NA	NA	1.47	Multivariate Cox
Li L [13]	2013	NA	NA	NA	NA	7.14	Multivariate logistic
Paek J [22]	2011	0.69	0.12–3.89	0.63	Kaplan-Meier curves and log-rank	0.89	Kaplan-Meier curves and log-rank
Steffensen KD [21]	2011	3.17	1.41–7.10	0.005	Multivariate Cox	1.77	Multivariate Cox
Trudel D [8]	2012	1.67	1.08–2.59	0.0191	Multivariate Cox	1.32	Multivariate Cox
Zhang F [15]	2016	NA	NA	NA	NA	1.11	Kaplan-Meier curves
Zheng H [16]	2013	2.31	1.02–5.22	0.044	Multivariate Cox	NA	NA

NA, not available. HE4, human epididymis protein 4; HRs, hazard ratios; CIs, confidence intervals; OS, overall survival; PFS, progression-free survival.

I² statistic [31]. If the heterogeneity was significant, a random effects model was used; otherwise, a fixed effects model was chosen [32, 33]. In addition, a sensitivity analysis was performed by omitting each study. Furthermore, subgroup analysis stratified by ethnicity, HR estimate method and test methods was also performed. Publication bias was examined using a funnel plot. The degree of asymmetry was estimated by Egger’s test ($p < 0.05$ was considered to indicate significant publication bias) [34, 35]. The statistical analyses were performed using Review Manager statistical software (RevMan version 5.0.17.0; The Nordic Cochrane Center, Rigs Hospitalet, Copenhagen, Denmark) and STATA software (version 11.2; Stata Corporation, College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

Results

Search results

Through the article search, we found 59 articles. We excluded 28 because the studies were irrelevant. We also excluded 12 articles because no data were available (HR and 95% CI), no data were also calculated from survival curves or the data were of low quality. Five articles were excluded because of a lack of preoperative serum samples.

A total of 14 articles [8, 13–25] published from 2011 to 2016 with 1315 patients satisfied the criteria for the meta-analysis. The flowchart of the study is shown in Figure 1. There were nine articles [8, 17–24] published in English and five articles [13–16, 25] published in Chinese.

Characteristics of studies

The characteristics of the 14 studies are summarized in Tables 1 and 2. The subjects in seven of the studies were Asian [13–16, 22, 23, 25], and the subjects in the other studies were Caucasian [8, 17–21, 24]. Most of the patients in these studies were diagnosed with EOC with different tumor types. The sample type in 14 studies was preoperative serum; 9 studies [8, 16–22, 24] were conducted to investigate OS, and 11 studies [8, 13–15, 17, 20–25] were performed to analyze PFS. HE4 levels were tested by ELISA in 11 studies [13–16, 18–23, 25] and by CMIA in three studies [8, 17, 24].

OS

PFS

Figure 2: Forest plot summary of the HRs and 95% CIs for the association between HE4 and ovarian cancer prognosis.

Meta-analysis

The meta-analysis results regarding HE4 are shown in Figure 2. Our meta-analysis demonstrated that high HE4 was associated with poor OS (random effects model, $HR=1.91$, 95% $CI=1.40-2.614$, $p<0.0001$; $I^2=52\%$, $p=0.04$) and poor PFS (random effects model, $HR=1.38$, 95% $CI=1.13-1.69$, $p=0.002$; $I^2=85\%$, $p<0.00001$).

Furthermore, a subgroup analysis stratified by ethnicity, HR estimate method and test methods was also performed (Table 3). The associations of high HE4 with poor OS (random effects model, $HR=1.96$, 95% $CI=1.39-2.77$, $p=0.0001$; $I^2=58\%$, $p=0.03$) and poor PFS (fixed effects model, $HR=1.36$, 95% $CI=1.25-1.48$, $p<0.00001$; $I^2=0\%$, $p=0.49$) were observed for studies including only Caucasian patients. However, the associations of high HE4 with poor OS (fixed effects model, $HR=1.86$, 95% $CI=0.89-3.89$, $p=0.1$; $I^2=34\%$, $p=0.22$) and poor PFS (random effects model, $HR=1.34$, 95% $CI=0.95-1.88$, $p=0.1$; $I^2=69\%$,

$p=0.007$) were not observed for studies including only Asian patients.

Subsequently, the association of high HE4 with poor OS was observed for studies using multivariate Cox and univariate Cox analyses ($HR=2.16$, 95% $CI=1.63-2.87$, $p<0.00001$; $I^2=0\%$, $p=0.55$ and $HR=1.3$, 95% $CI=1.19-1.42$, $p<0.00001$; $I^2=0\%$, $p=0.54$, respectively) both with fixed effects models. There was no association between high HE4 and poor PFS for studies using univariate Cox analysis (random effects model, $HR=1.2$, 95% $CI=0.95-1.51$, $p=0.13$; $I^2=89\%$, $p<0.00001$). There was an association between high HE4 and poor PFS in studies using a multivariate Cox model (fixed effects model, $HR=1.61$, 95% $CI=1.27-2.02$, $p<0.0001$; $I^2=46\%$, $p=0.12$).

The association of high HE4 with poor OS was observed, both with fixed effects models, when HE4 was measured by CMIA and ELISA ($HR=1.32$, 95% $CI=1.21-1.44$, $p<0.00001$; $I^2=62\%$, $p=0.07$ and $HR=2.31$, 95% $CI=1.59-3.34$, $p<0.00001$; $I^2=0\%$, $p=0.7$, respectively).

Table 3: Subgroup analysis of pooled HR for ovarian cancer patients with HE4.

Outcome	Subgroup	Studies	Pooled HR	95% CI	p-Value	Model ^a	Heterogeneity I ² , %	p-Value
OS	Ethnicity	7	1.96	1.39–2.77	0.0001	Random effects	58	0.03
	Caucasian							
	Asian	2	1.86	0.89–3.89	0.101	Fixed effects	34	0.22
	HR estimate							
	Univariate Cox	3	1.3	1.19–1.42	<0.00001	Fixed effects	0	0.54
	Multivariate Cox	6	2.16	1.63–2.87	<0.00001	Fixed effects	0	0.55
PFS	Test methods							
	CMIA	3	1.32	1.21–1.44	<0.00001	Fixed effects	62	0.07
	ELISA	6	2.31	1.59–3.34	<0.00001	Fixed effects	0	0.7
	Ethnicity							
	Caucasian	5	1.36	1.25–1.48	<0.00001	Fixed effects	0	0.49
	Asian	6	1.34	0.95–1.88	0.108	Random effects	69	0.007
	HR estimate							
	Univariate Cox	6	1.2	0.95–1.51	0.131	Random effects	89	<0.00001
	Multivariate Cox	5	1.61	1.27–2.02	<0.0001	Fixed effects	46	0.118
	Test methods							
	CMIA	3	1.35	1.24–1.47	<0.00001	Fixed effects	19	0.289
	ELISA	6	1.39	1.03–1.88	0.029	Random effects	66	0.004

HE4, human epididymis protein 4; HRs, hazard ratios; OS, overall survival; PFS, progression-free survival.

There was an association between high HE4 with poor PFS when HE4 was measured by CMIA (fixed effects model, HR=1.35, 95% CI=1.24–1.47, $p<0.00001$; $I^2=19\%$, $p=0.29$). There was no association between high HE4 with poor PFS when HE4 was measured by ELISA (random effects model, HR=1.39, 95% CI=1.03–1.88, $p=0.03$; $I^2=66\%$, $p=0.004$).

Sensitivity analysis and publication bias

A statistical significant heterogeneity was found among studies evaluating the association between HE4 and both OS and PFS ($p=0.04$ and $p<0.00001$, respectively). Therefore, a random effects model was applied to assess the pooled HR and its 95% CI. A sensitivity analysis was carried out by sequential omission of individual studies. The pooled HRs of OS and DFS were not significantly changed, suggesting the robustness of the results.

We checked the publication bias using both Begg’s funnel plot and Egger’s test. The shapes of the two Begg’s funnel plots for all studies showed no obvious asymmetry (Figure 3). Egger’s test of all studies showed no significant publication bias for OS or PFS (data not shown).

Discussion

HE4 is highly expressed in OC [9]. HE4 has been used in OC diagnosis. A combination of HE4 and CA125, as well as ultrasound imaging, has been used to diagnose EOC, but there are no satisfactory molecular markers for the prognostic prediction of OC in clinical practice. Some studies have begun to explore the prognostic role of HE4 for OC [8, 13–25, 36]; however, results have been inconsistent. The aim of this study was to conduct a systematic review to evaluate the accuracy of serum HE4 as a prognostic biomarker for OC, a disease with high mortality.

Scaletta et al. [37] reviewed that serum HE4 seems to have a promising role in the prediction of clinical and surgical outcomes. We completed the meta-analysis to further calculate preoperative serum levels of HE4 as a marker for OC prognosis. This meta-analysis shows that high HE4 was associated with poor prognosis in the studies evaluated. HE4 was a probable effective biomarker for OC prognosis.

Of the 14 included studies, 4 [20, 22, 25, 38] did not have directly available HR and 95% CI values; thus, we calculated the HRs and their 95% CIs from the survival curves. The HRs from the survival curves were generated using a univariate Cox model, and there was also a study

Figure 3: Begg's funnel plot of HE4 and ovarian cancer prognosis for all 14 studies.

in which the HRs and their 95% CI were based on a univariate Cox model [17]. Therefore, there were studies based on both a univariate Cox model and a multivariate Cox model. Perhaps this result was the one of the reasons contributing to the heterogeneity in the meta-analysis. The subgroup analysis showed that there was no heterogeneity in the evaluations of OS based on multivariate Cox and univariate Cox models. However, the heterogeneity was significant for PFS assessed by univariate Cox analysis, suggesting that the HR estimation methods were important and that these methods may have affected the result.

There were two ethnicities (Caucasian and Asian) in the 14 studies included in the meta-analysis. The association of high HE4 with poor OS and poor PFS was observed only for Caucasians. Ethnicity probably contributed to this difference in association. In general, multicenter studies can provide more valuable conclusions than single-center studies [33]. Although high HE4 was associated with poor OC prognosis, the larger sample studies of HE4 and OC prognosis should be done. Multicenter studies are sure more valuable. For some molecular markers for diagnosis and prognosis, there are differences between

different ethnic group and region. Large-scale, single-center studies are also valuable. This type of stratification was one of the differences between this study and others [33].

The cutoff used in the 14 studies were very different. The median values of the seven studies were regarded as cutoff values. Did the differences of HE4 in the studies affect the HE4 and OC prognosis? It needs to be studied further. In addition, the role for HE4 in cell growth and OC progression was rarely studied. It should also be studied to better understand HE4 and OC.

This meta-analysis has objectively and systematically calculated the association between preoperative serum levels of HE4 and OC prognosis. The current studies have shown that HE4 was a probable effective biomarker for OC prognosis. However, more large-scale, multicenter investigations should be performed to testify the clinically applicable value of HE4.

In the past years, a wide spectrum of serological biomarkers for OC diagnosis and prognosis has been investigated. In addition to HE4, circulating micro-RNAs have also shown the potential clinical utility. However, a perfect and reliable biomarker (stable, highly specific and sensitive, inexpensive) is currently unavailable [39, 40]. These molecules are needed to verify diagnostic performance and have great potential.

In conclusion, this meta-analysis shows that high HE4 was generally associated with OC, poor OS and PFS. HE4 was a probable effective biomarker for OC prognosis. However, the associations of high HE4 with poor OS and poor PFS were not observed for Asians. Larger scale and different ethnic investigations should be performed.

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