

# E-cadherin expression and prognosis of head and neck squamous cell carcinoma: evidence from 19 published investigations

Xusheng Ren<sup>1,2</sup>Jianning Wang<sup>2</sup>Xuefen Lin<sup>1,3</sup>Xuxia Wang<sup>1,3</sup>

<sup>1</sup>Department of Oral and Maxillofacial Surgery, Stomatological Hospital of Shandong University, <sup>2</sup>Department of Oral and Maxillofacial Surgery, Jinan Stomatological Hospital, <sup>3</sup>Shandong Province Key Laboratory of Oral Tissue Regeneration, Stomatological Hospital of Shandong University, Jinan, Shandong Province, People's Republic of China

**Objective:** The objective of this study was to review the published literature and investigate whether E-cadherin gene is a prognostic factor in head and neck squamous cell carcinoma by conducting a meta-analysis.

**Methods:** Studies were identified from the databases Embase, Medline, and Cochrane Library by using the keywords “E-cadherin gene” and “head and neck cancer”. Overall survival (OS) and disease-free survival (DFS) were the primary outcome measurements.

**Results:** Our literature review identified 1,458 articles; 19 studies with a total number of 2,012 cases were eligible for inclusion in the meta-analysis. The hazard ratio (HR) for OS of patients with decreased expression of E-cadherin gene was 0.57 (95% CI = 0.37, 0.89;  $P=0.000$ ). However, statistical heterogeneity was unacceptably high ( $I^2=74.5\%$ ,  $P=0.000$ ). After sensitivity analysis, heterogeneity became acceptable, and the effect measure was still significant ( $I^2=7.0\%$ ; HR = 0.52; 95% CI = 0.40, 0.66;  $P=0.000$ ). The HR for DFS was 0.53 (95% CI = 0.42, 0.67;  $P=0.000$ ).

**Conclusion:** This meta-analysis showed clear evidence that high E-cadherin gene expression is a positive prognostic factor of head and neck squamous cell carcinoma, resulting in better OS and DFS. However, this conclusion must be interpreted with caution due to a few limitations.

**Keywords:** E-cadherin gene, prognosis, head and neck squamous cell carcinoma, immunohistochemistry

## Introduction

Head and neck squamous cell carcinoma (HNSCC) is the most common cancer in the world and accounts for ~3% of all cancer cases.<sup>1,2</sup> Although significant advancements have been made in prevention, diagnostics, and treatment strategies for HNSCC, the survival rates in patients with progressive or metastatic disease have remained poor over the last 20 years.<sup>3–5</sup> Prognostic markers remain the basis for early detection and accurate survival evaluation for oral squamous cell carcinoma patients.

Numerous studies suggest that E-cadherin gene is a predictor of oral squamous cell carcinoma prognosis.<sup>6–24</sup> E-cadherin is a 120 kDa transmembrane glycoprotein that mediates homotypic  $\text{Ca}^{2+}$ -dependent intercellular adhesion in dissimilar epithelia. Moreover, E-cadherin is a pivotal factor for managing cell-to-cell adhesion in epithelial tissues.<sup>25</sup> At present, downregulation or aberrant expression of E-cadherin gene is associated with cancer invasion and poor prognosis in various carcinomas, including HNSCC. In addition, a multitude of existing studies have investigated the effect of E-cadherin gene on prognosis in HNSCC. However, E-cadherin gene has no consistent prognostic value for HNSCC. Additionally, most of the published literature includes

Correspondence: Xuxia Wang  
Stomatological Hospital of Shandong University, No 44 Wen Hua Xi Lu Road, Jinan 250012, Shandong Province, People's Republic of China  
Email [wxx@sdu.edu.cn](mailto:wxx@sdu.edu.cn)

studies that are small in size,<sup>8,18–20</sup> heterogeneous,<sup>14,19,22</sup> and conflicting in their results.<sup>17,19,22,23</sup> Thus, we performed a meta-analysis to systematically estimate the value of E-cadherin gene as a prognostic factor in HNSCC.

## Methods

### Literature search

A literature search was performed using Embase, Medline, and Cochrane Library. The database was searched with the following keywords (and/or MeSH words): E-cadherin gene, tongue cancer (squamous cell carcinoma), buccal cancer (squamous cell carcinoma), oral cancer (squamous cell carcinoma), mouth cancer (squamous cell carcinoma), tonsil cancer (squamous cell carcinoma), oropharynx cancer (squamous cell carcinoma), hypopharynx cancer (squamous cell carcinoma), nasopharynx cancer (squamous cell carcinoma), larynx cancer (squamous cell carcinoma), neck cancer (squamous cell carcinoma), and head and neck cancer (squamous cell carcinoma). Reference lists within the relevant articles were used as potentially eligible sources.

### Inclusion criteria

Studies were included if they met all the following inclusion criteria: a) patients were diagnosed with HNSCC and biopsy confirmed (no age limit); b) focused on the evaluation of E-cadherin gene expression in primary tumor and the correlation between E-cadherin gene expression and survival outcomes; and c) outcome indicators included overall survival (OS) or disease-free survival (DFS).

### Exclusion criteria

Studies were excluded if they met any of the following exclusion criteria: a) no clear follow-up and survival analysis or could not provide sufficient data required for prognostic estimation of patients; b) no use of immunohistochemistry to assess the expression of E-cadherin gene; c) case reports, comments, letters to the author, reviews, and meta-analyses; and d) were not written in English.

### Quality assessment and data analysis

The quality and risk of bias of all the included trials were assessed independently by two reviewers, Xusheng Ren and Jianning Wang, based on the Cochrane Handbook for Systematic Reviews of Interventions. Assessment of risk of bias was evaluated as “low risk of bias,” “unclear risk of bias,” or “high risk of bias” in each part, with notes explaining the specific reasons for each assessment in the risk of bias table. Any contradictions in opinion were resolved by discussion.

We extracted data from the eligible studies using an extraction form (Review Manager 5.3). We attempted to contact study authors for relevant missing or unclear data. We also attempted to contact the authors to confirm whether the study was duplicated or if there was any doubt whether the studies shared the same patients. We excluded studies that did not meet the inclusion criteria in terms of study design. One reviewer extracted the data, which was checked by another reviewer, and all conflicts were resolved by discussion.

### Statistical analysis

All individual outcomes were pooled using Stata 12.0. The hazard ratio (HR) and its 95% confidence interval (CI) were used for meta-analysis of OS or DFS. We performed a random-effects model to merge HR when the heterogeneity was acceptable ( $I^2 < 50\%$ ) and a fixed-effects model when the heterogeneity was unacceptable ( $I^2 \geq 50\%$ ). Statistical heterogeneity, which is the variation in results between studies, was assessed using the chi-square distributed Q statistic. Subgroup analyses and sensitivity analyses were performed when the heterogeneity was unacceptable.

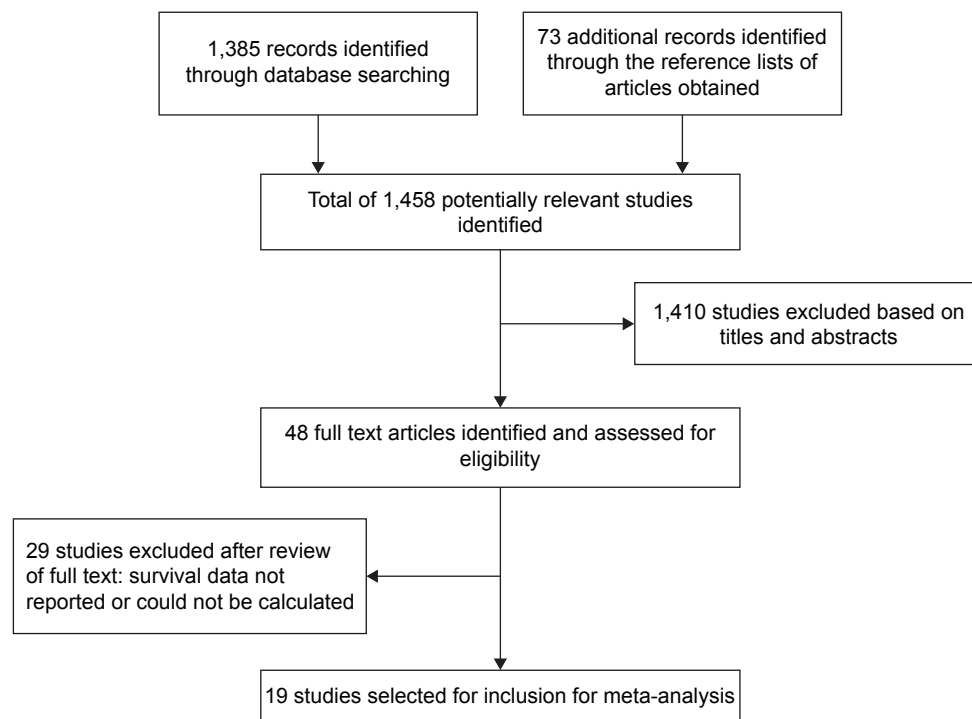
## Results

### Search findings

Our literature review identified 1,458 articles, including 1,385 articles from Medline, Embase, and Cochrane Library and 73 articles from the reference lists of articles obtained. A total of 1,410 articles were excluded after reviewing the titles and abstracts. The remaining 48 articles were further evaluated for eligibility and another 29 articles were eventually excluded. Figure 1 shows the flowchart of literature retrieval and lists the reasons for their exclusion. Nineteen studies with a total number of 2,012 cases were eligible for inclusion in the meta-analysis. Seven studies had data for both OS and DFS, nine studies had data only for OS, and three studies had data only for DFS. We could get all the needed data from these 19 studies and did not need to contact the authors.

### Study characteristics and treatment

As shown in Table 1, in these 19 studies, there were ten studies<sup>6,10,12,16,17,19,20,22–24</sup> that reported only using surgery. Six studies<sup>8,9,11,13,15,18</sup> reported that all the patients were treated with surgery and some patients were treated with radiotherapy. Two studies<sup>7,13</sup> reported that all the patients were treated with surgery and some patients were treated with radiotherapy and/or chemotherapy. Only one study<sup>20</sup> reported that all the patients were treated with surgery and some patients were treated with chemotherapy.



**Figure 1** A flow diagram of literature search.

## Methodology assessment of E-cadherin gene expression

The detection method of E-cadherin gene was immunohistochemistry, and all studies except the study by Psyrri et al<sup>9</sup> provided immunohistochemistry staining figures.

## Meta-analysis

### E-cadherin gene expression and OS

In this meta-analysis, there were seven studies<sup>7,9,10,19,20,23,24</sup> that provided HR values and 95% CI. Therefore, we directly utilized them for the evaluation of E-cadherin gene expression and OS. There were another nine studies<sup>6,8,12–18</sup> from which the HR values and their corresponding 95% CI could be calculated according to the data provided by the investigators.<sup>26</sup> There was significant heterogeneity between each study ( $I^2=74.5\%$ ,  $P=0.000$ ). The HR for OS was 0.57 (95% CI=0.37, 0.89;  $P=0.000$ ). However, statistical heterogeneity was unacceptably high, driven by one study.<sup>22</sup> When this study was excluded, heterogeneity became acceptable, and the effect measure was still significant ( $I^2=7.0\%$ ; HR=0.52; 95% CI=0.40, 0.66;  $P=0.000$ ; Figure 2).

### E-cadherin gene expression and DFS

In this meta-analysis, there were five studies<sup>7,9,11,15,21</sup> that provided HR values and 95% CI. Therefore, we directly utilized them for the evaluation of E-cadherin gene expression

and DFS. There were another five studies<sup>12,13,17,18,20</sup> from which the HR values and their corresponding 95% CI could be calculated according to the data provided by the authors. There was no significant heterogeneity between each study ( $I^2=0.0\%$ ,  $P=0.860$ ). The HR for DFS was 0.53 (95% CI=0.42, 0.67;  $P=0.000$ ; Figure 3).

### Publication bias analysis

Publication bias of this meta-analysis was analyzed by the use of Stata 12.0 software. According to the funnel plots (Figures 4 and 5), there was an asymmetry, either visually or from Begg's test (OS:  $P=0.753$ ; DFS:  $P=0.210$ ). This indicates that there was no obvious publication bias and the result of the study was stable and credible.

## Discussion

Numerous studies have reported that E-cadherin gene is a predictor for cancer prognosis.<sup>27–30</sup> The low expression of E-cadherin gene is a characteristic of loss of epithelial cell adhesion, which has been correlated with the phenotypic changes of increased invasiveness and motility of cancer cells. Some studies have shown that high expression of E-cadherin gene is associated with good prognosis in many epithelial cancers.<sup>29,30</sup> However, the prognostic value of E-cadherin gene in patients with HNSCC is still controversial. Some studies<sup>8,10,15,23</sup> report that high E-cadherin gene expression is

**Table I** The features of included studies

Author	Year	Country	Size of study	Tumor locations	Tumor stage	Treatment	Data of OS or DFS
da Silva et al <sup>6</sup>	2015	Brazil	102	OSCC	I–IV	Surgery	OS (DSS)
Ahmed et al <sup>7</sup>	2014	Egypt	75	LSCC	I–IV	Surgery, radiotherapy, and chemotherapy	OS and DFS
Pectasides et al <sup>8</sup>	2014	USA	67	HNSCC	I–IV	Surgery and radiotherapy	DFS (PFS)
Psyrrri et al <sup>9</sup>	2014	Greece	289	LSCC	I–IVa	Surgery and radiotherapy	OS and DFS
Fan et al <sup>10</sup>	2013	Taiwan	112	OSCC	In situ–IV	Surgery	OS
Kaur et al <sup>11</sup>	2013	India	72	OSCC	I–IVa	Surgery and radiotherapy	DFS
Imajyo et al <sup>12</sup>	2012	Japan	152	OSCC	NA	Surgery	OS and DFS
Li et al <sup>13</sup>	2012	People's Republic of China	64	LSCC	I–IV	Surgery and radiotherapy	OS and DFS
Ukpo et al <sup>14</sup>	2012	USA	154	Oropharyngeal SCC	I–IV	Surgery, radiotherapy, and chemotherapy	OS
Zhao et al <sup>15</sup>	2012	People's Republic of China	98	OSCC	I–IV	Surgery and radiotherapy	OS and DFS
Liu et al <sup>16</sup>	2010	People's Republic of China	83	OSCC	I–IV	Surgery	OS
Zou et al <sup>17</sup>	2010	People's Republic of China	150	LSCC	I–IV	Surgery	DFS
Diniz-Freitas et al <sup>18</sup>	2006	Spain	47	OSCC	I–IV	Surgery and radiotherapy	OS and DFS
Hung et al <sup>19</sup>	2006	People's Republic of China	45	OSCC	III–IV	Surgery	OS
Kurtz et al <sup>20</sup>	2006	USA	45	HNSCC	I–IV	Surgery	OS and DFS
Ueda et al <sup>21</sup>	2006	Japan	131	OSCC	I–IV	Surgery and chemotherapy	DFS
Bosch et al <sup>22</sup>	2005	Germany	151	HNSCC	I–IV	Surgery	OS
Lim et al <sup>23</sup>	2005	South Korea	84	OSCC	I–IV	Surgery	OS
Nakanishi et al <sup>24</sup>	2004	Japan	91	OTSCC	II–IV	Surgery	OS

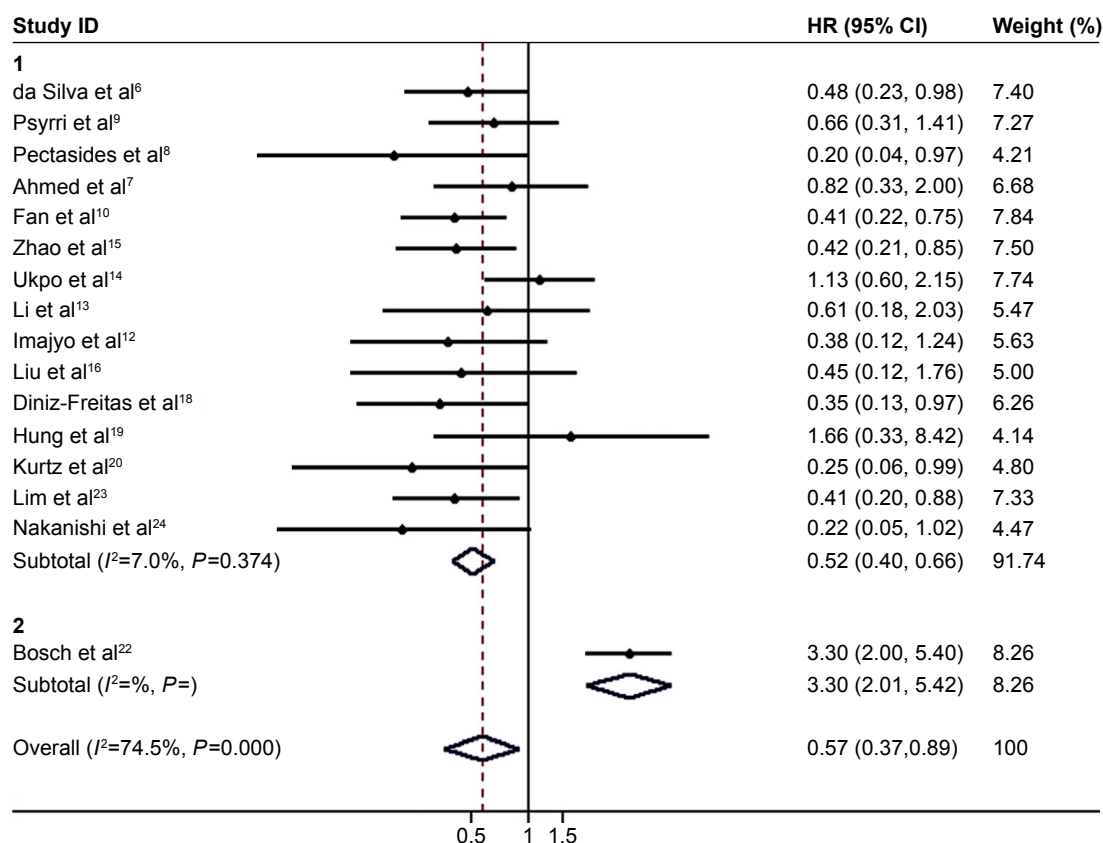
**Abbreviations:** OS, overall survival; DFS, disease-free survival; OSCC, oral squamous cell carcinoma; DSS, disease-specific survival; LSCC, laryngeal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; PFS, progression-free survival; SCC, squamous cell carcinoma; OTSCC, oral tongue squamous cell carcinoma; NA, not available.

a positive prognostic factor of HNSCC and exhibits better OS or DFS. The reports of Diniz-Freitas et al<sup>18</sup> and Kurtz et al<sup>20</sup> were also in line with the findings mentioned above. However, Bosch et al<sup>22</sup> showed that low E-cadherin gene expression is a positive prognostic factor of HNSCC. In addition, many scholars harbored the idea that E-cadherin gene expression was not an independent prognostic factor of HNSCC. Moreover, most studies included in this meta-analysis<sup>6,7,9,11–14,16,17,19,21,24</sup> also reported that E-cadherin gene expression was not significantly associated with OS or DFS. The aim of this meta-analysis was retrospective analysis of published literatures to assess the prognostic value of E-cadherin gene expression in patients with HNSCC.

In the present study, we selected 19 studies that were clear regarding not only diagnostic criteria but also inclusion criteria and exclusion criteria. OS and DFS were the primary outcome measures. HR values and their corresponding

95% CIs were the statistical indicators to evaluate the impact of E-cadherin gene expression on prognosis of patients with HNSCC.

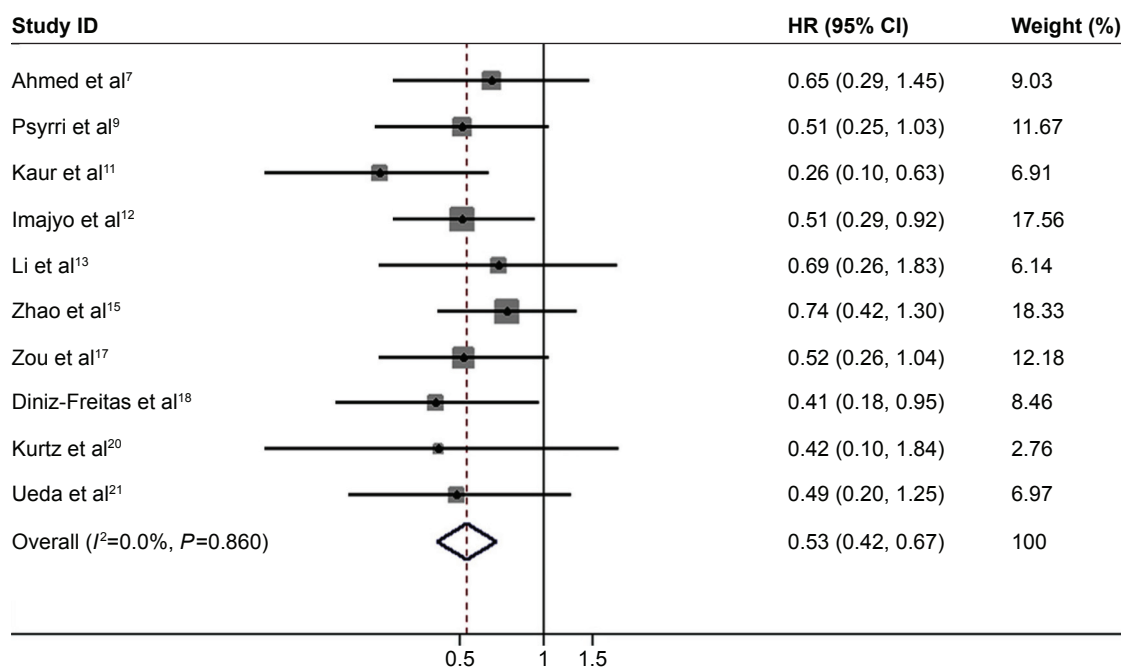
This meta-analysis confirmed that high E-cadherin gene expression was significantly associated with favorable OS. The HR for OS was 0.57 (95% CI = 0.37, 0.89). However, statistical heterogeneity was obvious, driven by one study.<sup>22</sup> After sensitivity analysis, heterogeneity became acceptable, and the effect measure was still significant (HR = 0.52; 95% CI = 0.40, 0.66). Differences in immunohistochemical scoring criteria may have contributed to the large heterogeneity between the study by Bosch et al and other included studies. As is known to all, it would make more sense to run a meta-analysis per individual anatomic site rather than lumping together sites that are known for heterogeneity in molecular signature, different standard of care, and different outcomes. Furthermore, the standard of care and outcome



**Figure 2** A forest plot for overall survival.

**Notes:** The difference between the two groups was significant (HR =0.57; 95% CI =0.37, 0.89;  $P=0.000$ ). However, there was great statistical heterogeneity ( $I^2=74.5\%$ ,  $P=0.000$ ). After sensitivity analysis, heterogeneity became acceptable ( $I^2=7.0\%$ ) and the effect measure remained significant (HR =0.52; 95% CI =0.40, 0.66;  $P=0.000$ ). “1” means after sensitivity analysis and “1+2” means before sensitivity analysis. Weights are from random effects analysis.

**Abbreviations:** HR, hazard ratio; CI, confidence interval.

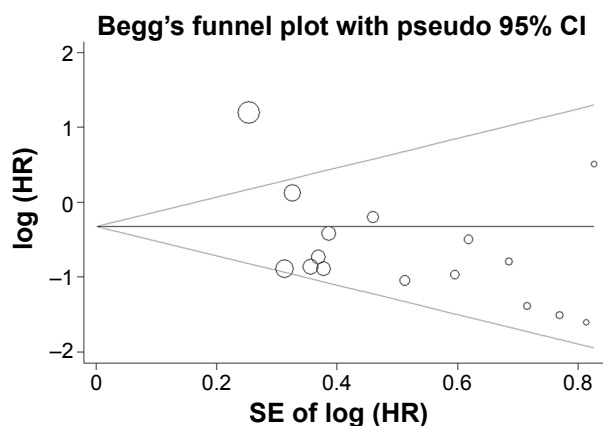


**Figure 3** A forest plot for overall survival.

**Note:** The difference between the high E-cadherin group and the low E-cadherin group was significant (HR =0.53; 95% CI =0.42, 0.67;  $P=0.000$ ) and the heterogeneity was acceptable ( $I^2=0.0\%$ ,  $P=0.860$ ).

**Abbreviations:** HR, hazard ratio; CI, confidence interval.





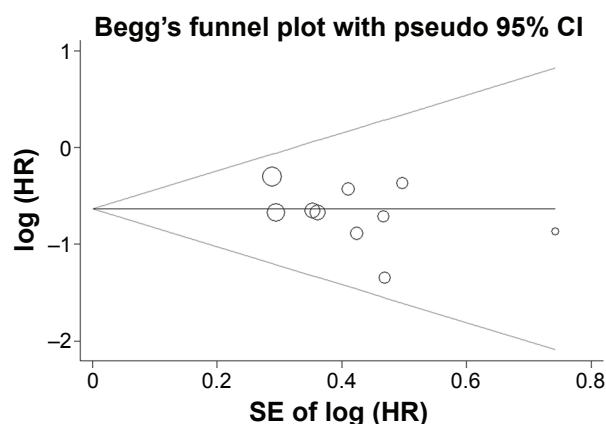
**Figure 4** A funnel plot of meta-analysis of overall survival.

**Note:** According to the funnel plot, there is an asymmetry.

**Abbreviations:** HR, hazard ratio; SE, standard error; CI, confidence interval.

vary dramatically according to the HNSCC stage; thus, meta-analysis per early versus advanced stage carcinomas would have been much more valuable. Because this study had impeccable protocol and strict inclusion criteria, we did not have the above problems. Moreover, this meta-analysis also confirmed that high E-cadherin gene expression was significantly associated with improved DFS. The HR for DFS was 0.53 (95% CI = 0.42, 0.67).

Although a meta-analysis was previously published<sup>29</sup> that had a similar theme as our study, it was published 3 years ago and therefore did not include over half of the studies included in our meta-analysis. Compared with the study by Zhao et al, we analyzed more outcome measures and included more information than the previous meta-analysis. In addition, based on our judgment, the data extraction and statistical analysis of this meta-analysis by Zhao et al had some small flaws.



**Figure 5** A funnel plot of meta-analysis of disease-free survival.

**Note:** According to the funnel plot, there is an asymmetry.

**Abbreviations:** HR, hazard ratio; SE, standard error; CI, confidence interval.

Every meta-analysis, including our own, has its internal limitations.<sup>31</sup> First, all the included studies were retrospective studies, rather than prospective. Additionally, some of these included studies did not provide the HR values and the 95% CI. We could not directly utilize them for the evaluation of E-cadherin gene expression and OS, and had to calculate HR values and their 95% CI according to the data provided by the researchers. Owing to various reasons, the results may have deviated slightly. Also, there was obvious heterogeneity among these studies. Additionally, selective reporting of individual research also limited this meta-analysis. Owing to various reasons, obtaining all data for a complete review of E-cadherin gene in HNSCC is impossible. To resolve these problems, we calculated HR values and their 95% CI according to reported methods.<sup>26</sup> This allowed us to increase the sample size for this study and make the findings more reliable. All these factors might affect the outcomes measured and might have influenced the findings. More studies with better designed criteria are required to further confirm our results.

## Conclusion

In conclusion, this meta-analysis showed clear evidence that high E-cadherin gene expression is a positive prognostic factor of HNSCC and is associated with better OS and DFS. However, some limitations weakened the power of this meta-analysis, and the conclusions should be interpreted with caution.

## Disclosure

The authors report no conflicts of interest in this work.

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