**RESEARCH ARTICLE** 

# The prognostic and clinicopathologic characteristics of CD147 and esophagus cancer: A meta-analysis

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### Abstract

#### Objective

The prognostic significance of CD147 expression in esophageal cancer patients remains controversial. Using a meta-analysis, we investigated the prognostic and clinicopathologic characteristics of CD147 in esophageal cancer.

#### Methods

A comprehensive literature search of the PubMed (1966–2016), EMBASE (1980–2016), Cochrane Library (1996–2016), Web of Science (1945–2016), China National Knowledge Infrastructure (1982–2016), and Wanfang databases (1988–2016) was performed to identify studies of all esophageal cancer subtypes. Correlations between CD147 expression and survival outcomes and clinicopathological features were analyzed using meta-analysis methods.

#### Results

Seventeen studies were included. High CD147 expression reduced the 3-year survival rate (OR = 3.26, 95% CI = (1.53, 6.93), p = 0.02) and 5-year survival rate(OR = 4.35, 95% CI = (2.13, 8.90), p < 0.0001). High CD147 expression reduced overall survival in esophageal cancer (HR = 1.60, 95% CI = (1.19, 2.15), p = 0.02). Additionally, higher CD147 expression was detected in esophageal cancer tissues than noncancerous tissues (OR = 9.45, 95% CI = (5.39, 16.59), p < 0.00001), normal tissues (OR = 12.73, 95% CI = (3.49, 46.46), p = 0.0001), para-carcinoma tissues (OR = 12.80, 95% CI = (6.57, 24.92), p < 0.00001), and hyperplastic tissues (OR = 3.27, 95% CI = (1.47, 7.29), p = 0.004). CD147 expression was associated with TNM stage (OR = 3.66, 95% CI = (2.20, 6.09), p < 0.00001), tumor depth (OR = 7.97, 95% CI = (4.13, 15.38), p < 0.00001), and lymph node status (OR = 5.14, 95% CI = (2.03, 13.01), p = 0.0005), but not with tumor differentiation, age, or sex.



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#### Conclusion

Our meta-analysis suggests that CD147 is an efficient prognostic factor in esophageal cancer. High CD147 expression in patients with esophageal cancer was associated with worse survival outcomes and common clinicopathological indicators of poor prognosis.

#### Introduction

Esophagus cancer (EC) is a malignant disease with the eighth incidence rate and the sixth mortality rate wordwide [1, 2]. The prognosis of EC is unfavorable, largely due to its unapparent symptom at the early stage and tumor infiltration and metastasis which makes it hard to completely remove the tumor by surgery [3]. Therefore, it is with great significance to study the molecular mechanism in the development, invasion and metastasis of EC. Up to now, it is proved that the expression of some molecules, such as NF-kappaB, MIF, CXCR4 and EGFR, are related to the treatment or the prognosis of EC[4-6].

CD147, also named extracellular matrix (ECM) metalloproteinase inducer, is a molecule highly expressed on the surface of cancer cells and promotes the secretion of matrix metalloproteinases (MMPs) from fibroblasts, degrading the matrix of cancer cell and thus facilitating the invasion and metastasis of cancer[7, 8]. Numerous papers showed that CD147 plays an important role in different sorts of cancer, including bladder cancer, prostate cancer, ovarian cancer, glioma, and esophageal cancer is also one of them[9-14].

Although evidence exists that CD147 is an important factor implicated in clinicopathological features and the prognosis of EC. Some conflicting results have been reported. Wan and Wu [15] reported the CD147 expression wasn't associated with overall survival (OS), which contradictory with Zhu et al[16]. Some studies found that CD147 high Expression might be related to advanced clinical stage and lymph node metastasis[15, 17]. But other studies reported that there was no significant difference between CD147 and clinical stage and lymph node metastasis[17, 18]. Moreover, there are also arguments about relationship of the CD147 high expression with invasive depth, histological differentiation[16, 18–20].

This controversial issue could be results of differences in sample sizes and other factors, such as the criteria of the CD147 high expression, and unfortunately evidence-based confirmation by large-scale clinical trials is still lacking. Therefore, we conducted this meta-analysis to quantitatively inspect the relationship between CD147 and clinicopathological features and survival of EC patients.

#### Methods and materials

#### Search strategy

We searched PubMed (1966–2016), EMBASE (1980–2016), the Cochrane Library (1996–2016), Web of Science (1945–2016), China National Knowledge Infrastructure (1982–2016), and the WanFang databases (1988–2016). The studies were restricted to humans, but not restricted by date, language, or publication status. The following combined search term was used:(Esophageal <u>Cancer, esophageal carcinoma, esophageal neoplasms, carcinoma of esophagus, esophageal</u> tumor, <u>Malignant Neoplasm of Oesophagus</u>) AND (CD147, (extracellular AND matrix AND metalloproteinase AND inducer), extracellular MMP inducer, EMMPRIN, BSG) to identify relevant papers addressing all subtypes of esophageal cancer. We combined the term appropriately with MeSH Terms and used an appropriate adjustment for different databases. Details of the search strategies can be found in <u>S1 File</u>.

#### Criteria for including studies

- 1. Published or unpublished case control study or cohort study in English or Chinese with the full text available;
- 2. All cases had survival or clinical pathological characteristic data, without radiotherapy or chemotherapy or biological therapy before sampling;
- 3. Diagnosis of esophagus cancer was proven by pathological methods;
- 4. Studies of CD147 expression based on primary esophagus cancer tissues, rather than serum or any other kinds of indirect specimen were included;
- 5. The best quality study was retained for dealing duplicated studies.

#### Criteria for excluding studies

- 1. Cell or animal studies, case reports, letters, reviews;
- 2. The standard of pathological diagnosis was not clear.

#### Assessment of included studies

The Newcastle-Ottawa quality assessment scale of case control studies (NOS)[21] was adopted to assess the quality of included studies, which has three categories (selection, comparability, and exposure) and eight items. The quality assessment values ranged from 0 to 9 stars. Studies scored more than 6 stars was included for our analysis.

#### Statistical analysis

Records were independently scanned by two authors to exclude apparent irrelevant studies. Then, full text were independently reviewed by two authors, and controversial opinions about whether to include specific study were resolved by discussion. Data was extracted independently by two authors: Hui Li and Chunxiang Jiang. Excel was designed according to the Cochrane manual to extract data and the survival data from the Kaplan-Meier curve was obtained by using Engauge Digitizer software. The software Revman 5.3 and Stata 13.0 were applied to analyze the data. Results were showed with odds ratios (OR) or HR (hazard ratio) and 95% confidence intervals (95% CI). Fixed-effects model was adopted when there was no evidence of significant heterogeneity (p > 0.1 and  $I^2 < 50\%$ ); otherwise, random-effects model was used. If possible, heterogeneity was explored and subgroup analyses were performed. All p values were 2-sided, and p < 0.05 was considered significant.

Sensitivity analysis was also performed to evaluate the influence of individual study on the final effect if the parameter has more than two data sets, and different model was used for no more than two data sets.

Begg's test was used to assess publication bias (p < 0.05 was considered statistically significant). If publication bias was confirmed, a trim-and-fill method developed by Duval and Tweedie[22] was implemented to adjust for this bias. Then, we replicated the funnel plot with their "missing" counterparts around the adjusted summary estimate.

#### Results

#### Literature search

The literature searches revealed 64 studies, of which 21 studies were excluded owing to duplication. After reading the titles and abstracts, 20 studies were excluded. The full-length texts of 23 candidate studies were carefully reviewed (animal studies [n = 5]; review and meta-analysis [n = 2]; no control group [n = 2]). Finally, 17 trials were included in the quantitative analysis (Fig 1). Only Huang et al.[7] reported CD147 expression in type II/III adenocarcinoma of the esophagogastric junction (Type II/III AEGs). An association between CD147 and esophageal squamous cell carcinoma (ESCC) was reported in 16 studies.

#### Qualitative assessment

Study quality was assessed using the Newcastle–Ottawa quality assessment scale; scores ranged from 7 to 8 (with a mean of 7.35), and higher values indicated better methodology. The quality assessment results are shown in <u>S1 Table</u> and detailed information for this analysis is provided in <u>Table 1</u>.

#### CD147 and survival analysis

**CD147 expression and overall survival.** We analyzed the relationship between CD147 expression and overall survival in EC patients based on the results of two studies[9, 15]. Wan and Wu[15] used Kaplan–Meier survival curves and Zhu et al.[9] used Cox regression analyses. In both studies, high CD147 expression was related to poor OS. As shown in Fig 2A, the data did notexhibit heterogeneity (p = 0.23,  $I^2 = 30.1\%$ ), and the fixed effects model showed thatthe combined HR was 1.60 (95% CI = (1.19, 2.15), p = 0.02).

**Impact of CD147 on 3-year** <u>survival rate</u> of EC. Two reports [7, 15] including a total of 154 patients reported an association between CD147 expression and the <u>3-year survival rate</u>. Huang et al. [7] detected CD147 expression in Type II/III AEGs, and Wan and Wu[15] observed CD147 expression in ESCC. Without heterogeneity (p = 0.61,  $I^2 = 0\%$ ), a fixed-effects model showed that high CD147 expression (57.95%) was statistically significantly associated with a lower <u>3-year survival rate</u> than that of low expression (81.82%) (OR = 3.26, 95% CI = (1.53, 6.93), p = 0.02) (Fig 2B).

**Impact of CD147 on the 5-**<u>year survival rate of EC.</u> The association between CD147 and the 5-year survival rate of EC was reported in two studies [7, <u>15</u>]. Both Huang et al. [7] (OR = 4.0, 95% CI = (1.46, 10.95)) and Wan and Wu[<u>15</u>] (OR = 4.75, 95% CI = (1.72, 13.13)) showed that high CD147 expression is statistically significantly associated with a lower 5-year survival rate. Without heterogeneity (p = 0.81,  $I^2 = 0\%$ ), a significant difference in the 5<u>-year survival rate</u> was detected between groups with high CD147 expression (29.55%) and low CD147 expression (62.12%) assuming a fixed-effects model (OR = 4.35, 95% CI = (2.13, 8.90), p < 0.0001) (Fig 2C).

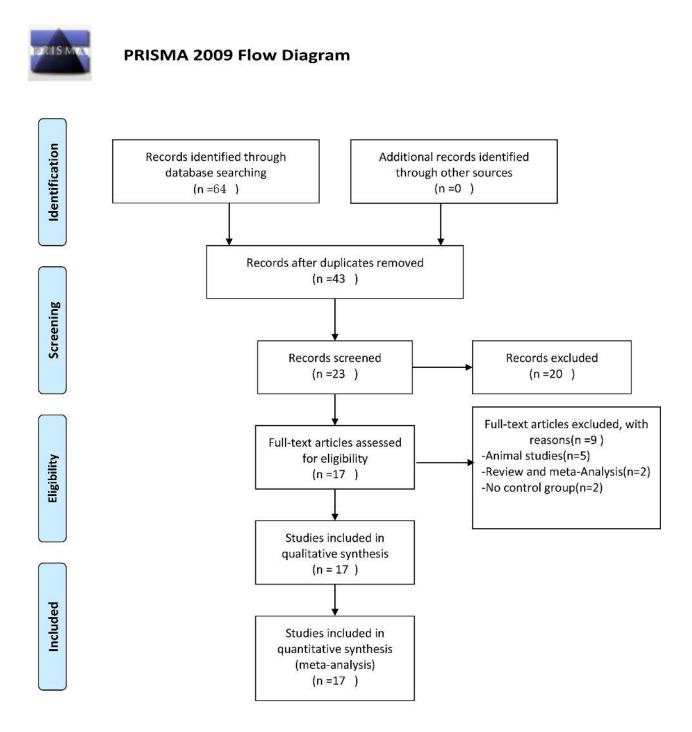
**CD147 expression and disease-free survival (DFS).** Ishibashi et al.[17] reported an association between CD147 and DFS. The <u>risk</u> was 1.5 times higher for the high CD147 expression group than the low CD147 expression group (HR = 4.6, 95% CI = 1.55, 13.4), p = 0.006). The pooled HR for DFS showed that high expression of CD147 reduced DFS in EC.

#### CD147 expression in different EC tissues

**CD147** in esophageal cancer and noncancerous tissues. CD147 expression in esophageal cancer and noncancerous tissues was investigated in 14 studies [7, 15, 17–20, 23–30] including 1544 patients. With significant heterogeneity (p < 0.00001,  $I^2 = 77\%$ ), a random-effects model showed that CD147 expression in esophageal cancer (72.83%) was higher than that in noncancerous tissues (29.19%) (OR = 9.45, 95% CI = (5.39, 16.59), p < 0.00001) (Fig 3A).

**CD147** in esophageal cancer and normal esophageal tissues. Five trials[<u>18</u>, <u>20</u>, <u>24</u>, <u>29</u>, <u>30</u>] reported the expression of CD147 in esophageal cancer tissues and normal esophageal cancer tissues, including 302 esophageal cancer tissues and 91 normal esophageal cancer tissues.





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Fig 1. Flowchart of selection of studies for inclusion in meta-analysis. A total of 64 studies were identified, and 21 studies were excluded because of duplication. After reading the titles and abstracts, 20 studies were excluded. 23 possible full text studies were carefully reviewed (animal studies [n = 5]; review and meta-analysis [n = 2]; no control group [n = 2]). Finally, 17 trials were included for quantitative analysis.

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With significant heterogeneity (p = 0.02,  $I^2$  = 66%), a random-effects model showed that CD147 expression was higher inesophageal cancer tissues (78.48%) than in normal tissues (28.57%) (OR = 12.73, 95%CI = (3.49, 46.46), p = 0.0001) (Fig 3B).

**CD147** in esophageal cancer and para-carcinoma tissues. Eleven trials [7, 15, 17–19, 23, 25–28, 30] investigated the expression of CD147 in esophageal cancer tissues and para-carcinoma tissues, including 700 esophageal cancer tissues and 539 para-carcinoma tissues. A random-effects model showed that CD147 expression was higher in esophageal cancer tissues (71.29%) than in para-carcinoma tissues (17.63%) (OR = 12.80, 95% CI = (6.57, 24.92), p < 0.00001) with significant heterogeneity (p < 0.0001,  $I^2 = 75\%$ ) (Fig 3C).

**CD147** in esophageal cancer and hyperplastic tissues. Three trials [17, 18, 29] reported the expression of CD147 in esophageal cancer tissues and hyperplastic tissues, including 273 esophageal cancer tissues and adjacent hyperplastic tissues. A random-effects model showed a difference in the rate of high CD147 expression between the two groups (OR = 3.27, 95% CI = (1.47, 7.29), p = 0.004) with heterogeneity ( $I^2$  = 59%, p = 0.09) (Fig 3D).

#### Correlation of CD147 with clinicopathological parameters

**Correlation between CD147 and TNM stage of esophageal cancer tissues.** TNM stage is an international standard for tumor staging. TNM stage I–II has a better prognosis than TNM stage III–IV in EC. The association between CD147 and TNM stage was investigated in five studies[7, 15, 18, 23, 29]. A fixed-effects model wasused without heterogeneity (p = 0.13,  $I^2 = 44\%$ ); it

First Author	Year	Origin	Median age	sample size	CD147 distribution	Type of cancer	Counting method	Definition of CD147 positive	NOS score
Yoshio Ishibashi	2004	Japan	61	101	-	ESCC	-	No staining, partial staining, and diffuse and strong staining	8
Zhao JH	2004	China	54.6	70	M and C	ESCC	A and B	>0% or weak intensity	7
Cheng, M. F	2006	Taiwan	62.5	41	M and C	ESCC	A and B	>0% or weak intensity	7
Zhang HZ	2006	China	58	85	М	ESCC	В	Brown	7
Xiong SongBai	2007	China	55.6	57	M and C	ESCC	A and B	>0% or weak intensity	7
Xie L	2008	China	53.2	87	M and C	ESCC	A and B	>5% or weak intensity	7
Qi Bo	2008	China	58.2	52	С	ESCC	A and B	>0% or weak intensity	8
Ma Guang	2009	China	59.5	70	M and C	ESCC	A and B	A+B>3	8
Chen JX	2009	China	42	50	M and C	ESCC	A and B	>10% or weak intensity	7
Liu HaiMing	2010	China	-	19	M and C	ESCC	A	>10%	7
Xiao XiangZhi	2011	China	50	60	M and C	ESCC	A and B	A2*B>1	7
Zhu ShaoJun	2011	China	-	108	M and C	ESCC	A	>5%	7
Xiong LN	2011	China	-	40	M and C	ESCC	A	>5%	8
Zhu, S	2011	China	-	86	M and C	ESCC	A	>5%	7
Wan, Y	2012	China	58.8	80	М	ESCC	A and B	A3*B≥5	8
Li ChangXiu	2013	China	63.4	60	M and C	ESCC	A and B	A4*B≥5	7
Huang, L	2015	China	62.2	74	M and C	Type II/III AEGs	A and B	A3*B≥3	8

Table 1. Characteristics of eligible studies.

Positive cell percentage (A). A1:0 point for positive cell percentage  $\leq 25\%$ ;1 point for 26%-50%; 2 points for 51%-75%;3 points for>75%. A2: point for positive cell percentage  $\leq 5\%$ ;1 point for 5%-25%,26%-50%;3 points for >50%. A3:0 point for positive cell percentage  $\leq 5\%$ , 1 point for 6%-25%, 2 points for 26%-50%, 3 points for 51%-75%, and 4 points for >75%. A4: point for positive cell percentage < 1%;1 point for1%-10%; 2 points for11%-50%;3 points for  $\geq 51\%$ . Staining intensity (B):0 point for basically no coloration, 1 point for light yellow, 2 points for pale brown, and 3 points for dark brown. M:Membrane, C:Cytoplasm. ESCC:esophageal squamous cell carcinoma. Type II/III AEGs:type II/III adenocarcinoma of esophagogastric junction.

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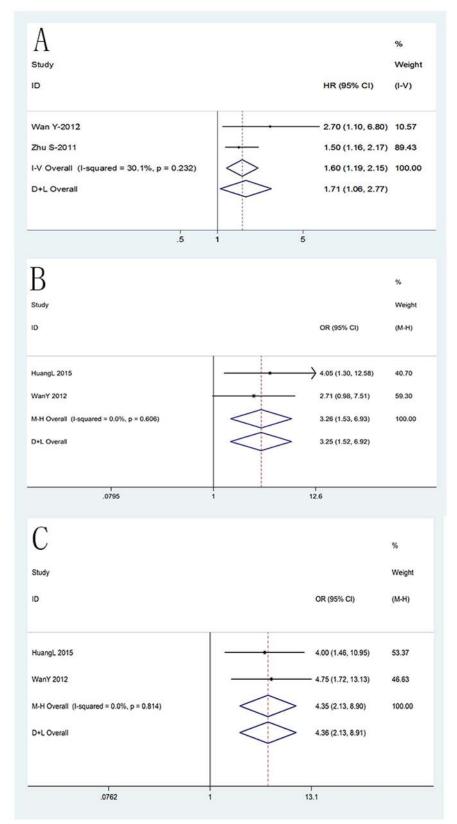


Fig 2. Survival analysis forest plot. The squares and horizontal lines correspond to the study- specific OR and 95%CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds

represent the pooled OR and 95% CI. The solid vertical line is at the null value (OR = 1). **A** The relationship between CD147 expression and overall survival. CD147 expression was associated with overall survival (HR = 1.60, 95% CI = (1.19, 2.15), p = 0.02). **B** The relationship between CD147 expression and 3-year survival rate. CD147 expression was associated with 3-year survival rate (OR = 3.26, 95% CI = (1.53, 6.93), p = 0.02). **C** The relationship between CD147 expression and 5-year survival rate. CD147 expression was associated with 3-year survival rate. CD147 expression was associated with 5-year survival rate (OR = 4.35, 95% CI = (2.13, 8.90), p < 0.0001).

https://doi.org/10.1371/journal.pone.0180271.g002

indicated a significant difference between the TNM stage III–IV group (83.87%) and TNM stage I–II group (59.17%) (OR = 3.66, 95% CI = (2.20, 6.09), p < 0.00001) (Fig 4A).

**CD147 with invasive depth of esophageal cancer tissues.** Nine studies [15, 16, 18–20, 26–28, 31] including 622 tissue samples investigated the relationship between CD147 expression and depth of tumor invasion. With significant heterogeneity (p = 0.07,  $I^2 = 45\%$ ), a random-effects model showed a significant difference between the pt3/pt4 group (79.44%) and pt1/pt2 group (34.71%) (OR = 7.97, 95% CI = (4.13, 15.38), p < 0.00001) (Fig 4B).

**CD147 with lymph node metastasis of esophageal cancer tissues.** Prognosis is often not good when esophageal cancer patients develop lymph node metastasis; accordingly, it is very important to identify indicators of metastasis at an early stage. Thirteen studies [7, 15, 16, 18–20, 23, 25–29, 31] that examined metastasis were included. With significant heterogeneity (p < 0.00001,  $I^2 = 83\%$ ), a random-effects model showed a significant difference between the lymph node metastasis group (82.58%) and the non-metastasis group (58.86%) (OR = 5.14, 95% CI = (2.03, 13.01), p = 0.0005) (Fig 4C).

**CD147 with differentiation of esophageal cancer tissues.** The association between CD147 and histological differentiation was investigated in ten studies [7, 15, 16, 18, 20, 23, 26, 28, 30, 31]. With significant heterogeneity (p = 0.0009,  $I^2 = 68\%$ ), a random-effects model showed no difference between 234 poorly differentiated tissues (76.50%) and 471 moderately to well differentiated tissues (67.52%) (OR = 1.57, 95% CI = (0.79, 3.12), p = 0.19) (Fig 4D).

**CD147** with age and sex of esophageal cancer tissues. Seven [7, 9, 15, 16, 23, 26, 28] and eight studies [7, 9, 15, 16, 18, 23, 26, 28] reported the relationship of CD147 expression with age and sex, respectively. Heterogeneity was not observed in the analysis of CD147 expression with respect to age (p = 0.61,  $I^2 = 0\%$ ) and sex (p = 0.62,  $I^2 = 0\%$ ); therefore, a fixed-effect model was used. The results showed that CD147 was not associated with age (OR = 1.05, 95% CI = (0.72, 1.53), p = 0.79) (Fig 4E) or sex (OR = 0.70, 95% CI = (0.47, 1.04), p = 0.07) (Fig 4F).

#### Sensitivity analysis and publication bias

A sensitivity analysis was performed to evaluate the stability of the results. As the survival analysis included fewer than three data sets, a different model was used or the sensitivity analysis, i.e., a random effect model. The results indicated stability, as shown in <u>Table 2</u>.

We excluded studies one-by-one for the sensitivity test for parameters with more than 3 data sets. The sensitivity analysis (<u>S1 Fig</u> and <u>S2 File</u>) showed that all parameters are stable, except for EC vs. hyperplastic tissues and poorly vs. middle to well differentiated states (<u>Table 3</u>). For publication bias, we used Begg's test (<u>S2 Fig</u> and <u>S3 File</u>). Only two parameters (EC vs. noncancerous and lymph node metastasis group) showed publication bias (<u>Table 3</u>). We then used a trim-and-fill method, as described in the Materials and Methods, after omitting studies with small sample sizes. The pooled analysis results were the same as the original results based on all studies.

#### Discussion

CD147 is a 55-kDa molecule found on the surface of tumor cells. It can stimulate the expression of MMPs, which facilitate the invasiveness of cancer cells [17, 32]. The correlation between

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	esophagua d	ancer	hyperplastic	tissue		Odds Ratio	Od	ds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Ra	ndom, 95% Cl
Xie L2008	73	87	11	20	28.6%	4.27 [1.49, 12.19]		
Yoshiolshibashi 2004	70	101	56	101	43.7%	1.81 [1.02, 3.23]		
Zhang HZ 2006	68	85	7	18	27.7%	6.29 [2.12, 18.63]		
Total (95% CI)		273		139	100.0%	3.27 [1.47, 7.29]		-
Total events	211		74					
Heterogeneity: Tau <sup>2</sup> = 0	0.30; Chi <sup>2</sup> = 4.8	9, df = 2 (	(P = 0.09); I <sup>2</sup> =	59%				1 10 100
Test for overall effect: 2	Z = 2.90 (P = 0.	004)					0.01 0.1 Favours [experimenta	1 10 100 I] Favours [control]

#### В

	esophagus o	ancer	normal ti	issue		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	CI M-H, Random, 95% CI
ChengMF 2006	30	41	0	16	12.5%	87.52 [4.84, 1581.25]	]
LiuHaiMing 2010	12	19	3	20	22.6%	9.71 [2.08, 45.37]	n – – – – – – – – – – – – – – – – – – –
MaGuang 2009	54	70	0	10	12.5%	69.36 [3.85, 1248.08]	j
Xie L2008	73	87	20	30	28.2%	2.61 [1.01, 6.74]	]
Zhang HZ 2006	68	85	3	15	24.2%	16.00 [4.06, 63.11]	1
Total (95% CI)		302		91	100.0%	12.73 [3.49, 46.46]	
Total events	237		26				
Heterogeneity: Tau <sup>2</sup> =	1.31; Chi <sup>2</sup> = 11	.83, df =	4 (P = 0.02	2); l² = 6	6%		
Test for overall effect:			•				0.01 0.1 1 10 100 Favours [experimental] Favours [control]

#### С

	esophagus o	cancer	para-esophagus	cancer		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C		M-H	I. Random, 95	% CI	
ChengMF 2006	30	41	5	41	9.4%	19.64 [6.14, 62.82]					- 18 <sub>10</sub>
ChenJX 2009	45	50	1	10	5.2%	81.00 [8.43, 778.70]				10	
HuangL 2015	42	74	2	20	7.8%	11.81 [2.55, 54.64]			-		
LiChangXiu 2013	40	60	9	40	10.6%	6.89 [2.76, 17.22]				• •	
QiBo2008	42	52	10	52	10.3%	17.64 [6.65, 46.78]				•	-
WanY 2012	46	80	20	80	11.7%	4.06 [2.07, 7.95]			271		
KiaoXiangZhi 2011	48	60	8	60	10.3%	26.00 [9.79, 69.06]					
XiongLiNa 2011	31	40	10	40	10.0%	10.33 [3.69, 28.97]					
XiongSongBai 2007	37	57	10 5	57	9.9%	19.24 [6.62, 55.91]					
Yoshiolshibashi 2004	70	101	0	101	3.9%	454.33 [27.35, 7547.92]					$\rightarrow$
Zhang HZ 2006	68	85	25	38	10.9%	2.08 [0.88, 4.89]					
Total (95% CI)		700		539	100.0%	12.80 [6.57, 24.92]				-	
Total events	499		95								
Heterogeneity: Tau <sup>2</sup> = (	0.88; Chi <sup>2</sup> = 39.	97, df = 1	10 (P < 0.0001); 12 =	75%						10	400
Test for overall effect: 2	Z = 7.50 (P < 0.	00001)	er rene en				0.01 Fa	0.1 vours [experin	1 iental] Favou	10 rs [control]	100

#### D

	esophagus o	cancer	Noncancer	tissue		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
ChengMF 2006	30	41	5	57	7.2%	28.36 [8.99, 89.46]	
ChenJX 2009	45	50	1	10	3.9%	81.00 [8.43, 778.70]	· · · · · · · · · · · · · · · · · · ·
HuangL 2015	42	74	2	20	5.8%	11.81 [2.55, 54.64]	
LiChangXiu 2013	40	60	9	40	8.1%	6.89 [2.76, 17.22]	
LiuHaiMing 2010	12	19	3	20	5.8%	9.71 [2.08, 45.37]	
MaGuang 2009	54	70	0	10	2.8%	69.36 [3.85, 1248.08]	
QiBo2008	42	52	10	52	7.9%	17.64 [6.65, 46.78]	· · · · · · · · · · · · · · · · · · ·
WanY 2012	46	80	20	80	9.0%	4.06 [2.07, 7.95]	
XiaoXiangZhi 2011	48	60	8	60	7.9%	26.00 [9.79, 69.06]	
Xie L2008	73	87	31	50	8.5%	3.20 [1.42, 7.17]	
XiongLiNa 2011	31	40	10	40	7.6%	10.33 [3.69, 28.97]	
XiongSongBai 2007	37	57	5	57	7.5%	19.24 [6.62, 55.91]	
Yoshiolshibashi 2004	70	101	56	101	9.3%	1.81 [1.02, 3.23]	
Zhang HZ 2006	68	85	35	71	8.9%	4.11 [2.03, 8.34]	
Total (95% Cl)		876		668	100.0%	9.45 [5.39, 16.59]	•
Total events	638		195				
Heterogeneity: Tau <sup>2</sup> = (	0.80; Chi <sup>2</sup> = 56.	37, df = 1	3 (P < 0.0000	1); l <sup>2</sup> = 7	7%		
Test for overall effect: 2			1992	83894 - 194 1			0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Fig 3. Forest plots of CD147 expression and different tissues. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds

represent the pooled OR and 95% CI. The solid vertical line is at the null value (OR = 1). **A** CD147 positive expression between cancer and noncancer tissues. Significant difference was found between cancer and noncancer tissues (OR = 9.45, 95% CI = (5.39, 16.59), p < 0.00001). **B** CD147 positive expression between cancer and normal tissues. Significant difference was found between cancer and normal tissues (OR = 12.73, 95% CI = (3.49, 46.46), p = 0.0001). **C** CD147 positive expression between cancer and para-carcinoma tissues. Significant difference was found between cancer and para-carcinoma tissues (OR = 12.80, 95% CI = (6.57, 24.92), p < 0.00001). **D** CD147 positive expression between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues. Significant difference was found between cancer and hyperplastic tissues.

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CD147 expression and EC has been investigated extensively. However, the clinical relevance of CD147 remains controversial. Sample size, as a strong predictor in epidemiological studies, may play an important role in resolving this controversy. In the current meta-analysis, we pooled data from 17 studies and demonstrated a remarkable association between CD147 expression and EC. We evaluated the association between CD147 in cancer and other tissues. Based on our results, we concluded that high CD147 expression was significantly associated with malignant tissues.

CD147 stimulates adjacent interstitial normal cells to produce MMPs[<u>33</u>]. MMPs are proteases known to degrade the ECM[<u>34</u>]. Thus, carcinoma cells can interact with adjacent normal cells to produce MMPs via CD147 on their surface, and, in turn, invade lymphatic tissue and blood vessels and penetrate the ECM to reach adjacent organs, with the help of MMPs. Tumor invasion and metastasis are a major barrier to cancer treatment and a main cause of death[<u>35</u>]. The basement membrane and ECM form a histological barrier that can prevent the progression of malignant tumors, and its degradation facilitates tumor progression.

Efforts were made to conduct a comprehensive analysis, but some limitations need to be acknowledged. First, despite our efforts, we did not obtain unpublished data; therefore, the data included in the analyses were from only published data. However, most of the parameters showed no publication bias according to Begg's test, with the exception of two indicators (EC vs. Noncancerous and lymph node metastasis). We obtained a stable result when studies with small sample sizes were removed. Second, only 4 studies [7, 9, 15, 17] including 341 patients reported survival data. Wan and Wu[15] and Zhu et al. [9] focused on overall survival and Ishibashi et al. [17] considered disease-free survival. Wan and Wu[15] and Huang et al. [7] reported impact of CD147 on the 3-year survival rate and 5-year survival rate. Accordingly, the small sample size is a limitation. Fortunately, we obtained stable results among models in a test of the sensitivity. Last,16 studies reported an association between high CD147 expression and ESCC; therefore, our results were particularly representative of ESCC. Further studies of adenocarcinoma of the esophagus are required to verify these results. However, Huang et al. [7] also showed that high CD147 expression in Type II/III AEGs was significantly associated with cancer tissue types (esophageal cancer versus noncancerous tissues (OR = 11.81, 95%CI =(2.55, 54.64)), poor 3-year survival (OR = 4.05, 95% CI = (1.30, 12.58)), poor 5-year survival (OR = 4.00, 95% CI = (1.46, 10.95)), TNM stage (OR = 4.11, 95% CI = (1.52, 11.14)), lymph node metastasis (OR = 4.40, 95% CI = (1.64, 11.78)), and histological differentiation (OR =3.30,95% CI = (1.21, 9.00)). Furthermore, the sensitivity analysis showed that the study of Huang et al.<sup>[7]</sup> had no influence on the results.

To our knowledge, this meta-analysis is the first study to systematically estimate the association between CD147 expression and the risk of EC and its clinicopathological parameters. Early diagnosis and early treatment are fundamental approaches to improve prognosis[36]. Our results indicated that high CD147 was significantly associated with EC tissues, supporting the notion that CD147 could potentially be applied as a clinical marker for the early diagnosis of EC. We demonstrated that high CD147 expression strongly predicted a poorer TNM stage, invasion depth, lymph node metastasis, and a worse survival rate in patients with EC. In

12 05 01 0000000000000000000000000000000					Weight	M-H, Fixe			М-	H. Fixed.	95% CI		
HuangL 2015	32	46	10	28	23.9%	4.11 [1.5							
WanY 2012 XiaoXiangZhi 2011	31 26	38 28	15 22	42 32	18.6% 9.2%	7.97 [2.8				1			
Xie L2008	63	68	15	19	10.9%	3.36 [0.8				-	- 41		
Zhang HZ 2006	30	37	38	48	39.5%		38, 3.31]			-			
		100000		200		202020					-		
Total (95% CI) Total events	182	217	100	169	100.0%	3.66 [2.	20, 6.09]				-		
Heterogeneity: Chi <sup>2</sup> :		4(P = 0)		44%				H	- ti	-		des.	
Test for overall effec								0.01 Favou	0.1 Irs [experim	1 ental] Fi		10 Introi]	1
В													
D	pt3/pt	4	pt1/pt2	2		Odds Ra	atio			Odds R	atio		
Study or Subgroup	Events	Total I	Events	Total		I-H. Rando	m. 95% C	1	M-H		n. 95% CI	1	
LiChangXiu 2013	35	41	5	19	12.5%		28, 62.31]				20-		
MaGuang 2009 QiBo2008	51 29	59 40	3	11	10.9%		71, 77.88] 80, 34.73]				_	2	
WanY 2012	38	56	8	24	16.1%		53. 11.68)				-		
XiongLiNa 2011	28	31	3	9	8.7%	18.67 [3.0							
XiongSongBai 2007	37	54	0	3	4.0%	15.00 [0.7				- 1		0	
Zhang HZ 2006	62 50	77 58	8	8	9.5%		0.25, 7.52]		-		S		_
ZhaoJH 2004 ZhuSheoJun 2011	50 68	56 87	3 11	14 21	10.8%	30.56 [6.6 3.25 [1	u, 141.38] [.20, 8.81]			-		2	
			10001									- 1.15	
Total (95% Cl)	1 m	501		121	100.0%	7.97 [4.1	13, 15.38]						
Total events Heterogeneity: Tau <sup>a</sup>	398 - 0.43: Chiž	= 14 52	42 df = 8 /0	= 0.03	9-12 = A592			L		_			_
Test for overall effect				- 0.07	j. i = 4078			0.01 Eavo	D.1 urs (experim	1 Entell F	avours Inc	10 ntroll	1
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ChenJX 2009	26	1	26	19	2	4 4.9%	14.85 [0.7	8, 286.62]					-
HuangL 2015 JiChangXiu 2013	28 34		38 36	14 6	3		4.40 [1. 51.00 [9.3	.84, 11.78]					_
MaGuang 2009	30	- 3	34	24	3	6 8.4%	3.75[1.	07, 13.12]					_
QiBo2008 WanY 2012	11 13		15 39	4	3		22.69 [4.8	H, 106.34] 0.04, 0.34]					
KisoXiangZhi 2011	28		31	20	2	8 80%	4.20 [1.	01, 17.50]			-		
Kie L2008 XionaLiNe 2011	32 29		35 33	35 2	5	282% 769%	5,18[1.	.39, 19.35] 9, 126.72]				· .	
XiongSongBel 2007	14		15	23	4	2 6.5%	11.57 [1.	39, 96,14]			-		
Zhang HZ 2006 ZhaoJH 2004	33 32		40 33	35	4		1.35	0,46, 3.95] 10, 197.89]			1.2		_
ZhuShaoJun 2011	36		44	43	5			0.87. 5.55]					
Total (95% Cl)		41	19		47	4 100.0%	5.14 (2)	03, 13.01]					
Totel events Heterogeneity: Tau <sup>e</sup> = 2.2	346			279			8100000	98.8399 <b>*</b>	. D			8 - AN	
										1000 000		10	
Test for overall effect: Z =	= 3.46 (P = 0.0	005)							Favours [e		Favoura		
risaritor overall effect. Z =	= 3.46 (P = 0.0	005)							Favours [e		i] Fevoura		
D			middle to		Resentioned		Odde P	atio :	Favours [e	xperimente			
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D Study of Subaroup CheryM 2006 Humpl, 2015 LichargXU 2013 Manr 2010 Humpl, 2016 2009 2009 2010 2010 2019 2009 2010 2010 2019 2010 2019 2010 2019 2010 2019 2010 2019 E Study of Subgroup Humpl, 2015 LichargXU 2013	Events           11           22           23           12           24           26           9           17           23           24           26           10           9           17           23           20           21           22           24           26           170           9           17           23           24           25           26           27           28           29           20           210 (P = 0 1           advanc           16           29	tisted         Total           12         30           28         8           13         5           16         17           21         30           224         30           6, or = 9 (         9)           33         33           44         44	(P = 0.000) youn <u>Events</u> 26 11	o well di venta 18 20 17 42 22 20 27 59 38 58 318 318 318 318 318 41 41 16	Toti 2 4 3 5 4 2 4 6 4 4 7 7 47 8% 47 8%	el Weinht 9 59% 4 114% 9 4 114% 9 81% 4 94% 4 94% 9 114% 5 99% 9 114% 9 100% 9 110% 1 100.0% 0 110% 1 100.0% 0 0dds R: M-H. Fixed 0.54 [0.1] 0.68 [0.1]	M-H, Rands 5.79 (0 3.30 ( 7.87 [1 0.86 ( 4.21 (1 1.00 ( 0.86 ( 0.71 ( 1.53 ( 1.29 () 1.57 () 1.57 () 1.57 () 1.57 () 1.57 () 2.57 () 2	om. 95% CI 65, 51.50] 1.21, 9.00] 93, 30.42] 0.23, 3.15] 53, 11.59] 0.28, 3.61] 0.28, 2.87] 0.05, 0.56] 0.44, 5.41] 0.48, 3.44]	D.01 B. Favours [e	odds Ra	de Ratio Indom. 95%	[contro]	-
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D Bludy or Subaroup Chengki 2006 than 2012 2019 July 2006 than 2012 2019 July 2006 than 2012 2019 July 2016 2019 July 2018 2019 July 2018 2019 July 2018 E Study or Subgroup Huangl_2015 LichangXu 2013 WanY 2012 XiaoXiang2n 2011 XiaoXiaoXiang2n 2011 XiaoXiaoXiaoXiaoXi Total (95% CI) Total (95% CI)	Poorty different 11 22 23 12 24 26 0 0 9 179 80, CN* = 28.1 179 80, CN* = 28.1 130 (P = 0.1 16 29 20 20 20 20 33 38 178 = 4.50, cf = t t Z = 0.26 (t) male		(P = 0.0002 youn 266 266 26 17 31 41 41 178 8.61); I <sup>2</sup> =	9 well di 18 17 17 22 20 27 59 38 58 318 9; P=6 9 9 9 9 9 10 1 10 10 1 59 265 0%	Toto 2 4 3 5 4 4 4 4 4 4 4 6 4 4 7 8 7 8 8 8 8 8 8 8 22,7 8 8 22,7 8 8 22,7 10,4% 10,4% 10,0%	Weight         9         59%           9         59%         4           4         9.4%         9.4%           4         9.4%         9.4%           4         9.4%         9.6%           9         11.4%         4           4         9.6%         9           9         11.4%         9           9         10.5%         9           0.64%         9         10.0%           0         0.44%         9           0         0.45%         0           0.64%         0         0.65%           0.64%         0         0.65%           0.64%         0         0.65%           0.64%         0         0.65%           0.64%         0         0.65%           0.65%         0         0.65%           0.65%         0         0.65%           0.65%         0         0.65%           0.65%         0         0.65%	H:H.Band 578 [0 3.30 [0 3.421 [1 1.00 [1 1.52] 1.57 [0 1.57 [0 1.57 [1 1.57 [0 1.57 [1 1.57 [1	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056, 056 004, 354, 354 005, 056, 056 004, 354, 056 005, 056	D.01 B. Favours (e M- 0.1 rs (experime	Odds Ra Attal France	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		
D     Budy or Suboroup     CheryM 2006     turnup(2015     ClargXV 2015     Mary 2012     Xano X 2012     Total (955 C)     Total (955 C)     Total (955 C)     Total (955 C)	Poorty different 11 22 23 12 24 26 0 0 9 179 80, CN* = 28.1 179 80, CN* = 28.1 130 (P = 0.1 16 29 20 20 20 20 33 38 178 = 4.50, cf = t t Z = 0.26 (t) male	Total           12           30           28           18           17           35           18           17           35           16           30           234           234           33           44           36           27           27           45           49           260           6 (P = 0, 75)           6 (P = 0, 75)	(P = 0.0000 <u>youns</u> 26 11 26 26 26 26 17 31 41 178 8.51); I <sup>2</sup> =	o well di venta 18 20 17 22 20 27 59 318 318 9 <b>Total</b> 41 16 45 30 41 16 45 30 41 265 30 41 265 9 <b>2</b> 56 56 56 56 56 56 56 56 56 56	Toto 2 4 3 5 4 4 4 4 4 4 4 6 4 4 7 8 7 8 8 8 8 8 8 8 22,7 8 8 22,7 8 8 22,7 10,4% 10,4% 10,0%	Weight         8         59%           8         59%         9           4         114%         9 94%           4         9.4%         9.4%           4         9.4%         9.4%           5         9.9%         11.4%           4         9.0%         11.0%           9         11.4%         9.00%           9         11.0%         1.00%           9         11.0%         1.00%           9         11.0%         0.54 [0.7]           0.54 [0.7]         0.58 [0.7]         0.58 [0.7]           0.52 [0.7]         1.52 [0.7]         1.52 [0.7]           0.0dds R:         M-H. Fixed         0.0dds R:	H:H.Band 578 [0 3.30 [0 3.421 [1 1.00 [1 1.52] 1.57 [0 1.57 [0 1.57 [1 1.57 [0 1.57 [1 1.57 [1	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056, 056 004, 354, 354 005, 056, 056 004, 354, 056 005, 056	D.01 B. Favours (e M- 0.1 rs (experime	Odds R4 1 aperimental Odds R4 1 aperimental 1 fr	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		
D      Budy or Suboroup      Chargk or Suboroup      Chargk 2006     turnul, 2015     LChargk 2007     turnul, 2015     LChargk 2014     KongSangka 2007     turnul, 2016     tradi 2008     turnul, 2016     tradi 2008     turnul, 2016     Total (2015; CI)     Total (2016; CI)     Total (2016; CI)     Total (2016; CI)     Total (2016; CI)     Total (2012; CI)     LChargk 2012; 2013	poorty difference           Events           11           22           23           12           24           26           0           9           179           800, CNF = 28.1           = 1.30 (P = 0.1           16           29           20           20           20           20           20           20           20           20           20           20           33           178           = 4.50, cf = 1           TZ           male           Events           32           25	stiated           12           300           28           31           32           41           33           34           35           44           36           42           27           49           260           6 (P = 0, 79)           7           10           10           11           12           12           12           13           260           10           11           12           12           13           14           36           15           16           17           18           19           10           10           10           10           10           10           10           10           10           10           10           11           12           13 <td>(P = 0.0002 Events 266 261 17 31 4 .61); (P = )) formal Events 10 15</td> <td>9 weil di 20 18 20 17 42 22 20 27 9 33 18 318 318 319 41 16 45 330 41 59 265 0% e Total 18 42 20 07 9 9 9 26 7 9 9 26 20 27 9 36 20 20 20 20 20 20 20 20 20 20</td> <td>Toto 2 2 4 3 3 5 4 4 4 4 4 7 4 7 4 7 8 8 8 8 8 8 8 8 8 8</td> <td>Weight         8         59%           9         59%         9           4         114%         4           4         9.4%         9.8%           9         11.4%         6           4         9.4%         9.8%           9         11.4%         6           5         9.9%         1           9         10.0%         9           9         10.0%         9           1         100.0%         9           0.54 [0:0         0.68 [0:0           0.58 [0:0]         1.52 [0:1           1.05 [0:7         0.68 [0:2           0.44%         9.9%           1.05 [0:7         0.68 [0:2           0.68 [0:2         1.52 [0:1           1.52 [0:7         0.58 [0:2           0.45 [0:7 [0:2         0.77 [0:2</td> <td>H-H. Bandy 578 [0] 3.30 [7.87 [1] 0.86 [1] 1.32 [1] 1.57 [0] 1.57 [0] 1.57 [1] 1.57 [1] 1.57</td> <td>m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056, 056 004, 354, 354 005, 056, 056 004, 354, 056 005, 056</td> <td>D.01 0. Favours (e M- 0.1 rs (experime</td> <td>Odds Ra Attal France</td> <td>de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4</td> <td></td> <td>0</td>	(P = 0.0002 Events 266 261 17 31 4 .61); (P = )) formal Events 10 15	9 weil di 20 18 20 17 42 22 20 27 9 33 18 318 318 319 41 16 45 330 41 59 265 0% e Total 18 42 20 07 9 9 9 26 7 9 9 26 20 27 9 36 20 20 20 20 20 20 20 20 20 20	Toto 2 2 4 3 3 5 4 4 4 4 4 7 4 7 4 7 8 8 8 8 8 8 8 8 8 8	Weight         8         59%           9         59%         9           4         114%         4           4         9.4%         9.8%           9         11.4%         6           4         9.4%         9.8%           9         11.4%         6           5         9.9%         1           9         10.0%         9           9         10.0%         9           1         100.0%         9           0.54 [0:0         0.68 [0:0           0.58 [0:0]         1.52 [0:1           1.05 [0:7         0.68 [0:2           0.44%         9.9%           1.05 [0:7         0.68 [0:2           0.68 [0:2         1.52 [0:1           1.52 [0:7         0.58 [0:2           0.45 [0:7 [0:2         0.77 [0:2	H-H. Bandy 578 [0] 3.30 [7.87 [1] 0.86 [1] 1.32 [1] 1.57 [0] 1.57 [0] 1.57 [1] 1.57	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056, 056 004, 354, 354 005, 056, 056 004, 354, 056 005, 056	D.01 0. Favours (e M- 0.1 rs (experime	Odds Ra Attal France	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		0
D     Study or Subarrou     ChergMP 2006     terrup(2005     LichargXu 2013     Mark 2006     WanY 2012     XiaoXiang2n 2014     XiaoXiang2n 2014     Zixoshaular 2014     Total events     LichargXu 2013     XiaoXiang2n 2014     Zixoshaular 2014     Total events     Hearogonaly: rup = 0.1     Zixoshaular 2014     Zixos	advanc           Events           11           22           23           14           24           24           24           24           26           9           179           20. Ch* = 28.1           130 (P = 0.1           20           20           20           20           20           20           20           20           33           38           178           = 4.50, cf = 1           t Z = 0.26 (t           male           Events.           25           33	stiated Total 12 12 12 12 12 12 12 12 12 12	Events (₽ = 0.0002 266 11 266 17 31 41 41 178 8.61);  ₽ = 9) 10 15 13 13	a well di venta 18 20 17 42 22 20 27 58 318 56 56 56 56 56 56 56 56 56 56	Toto 2 2 4 3 5 4 4 2 2 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4	Weinht         9         5.9%           9         5.9%         4           4         9.4%         9.4%           4         9.4%         9.4%           4         9.4%         9.6%           4         1.03%         9           5         9.9%         1.14%           4         9.4%         9.60%           3         1.04%         9           9         1.12%         1           0         0.45%         0.5%           0.54 (0.0         0.86 [0.0         0.27 [0.1.86 [0.0           0.26 [0.3         1.52 [0.0         1.65 [0.7           0.4045 R:         M-H. Fixed         1.07 [0.3           1.05 [0.7         0.90 [0.1         1.06 [0.7	H-H. Bands 5779 (0 5779 (0 7.87 (1 0.046 ( 1.151 ( 1.151 ( 1.151 ( 1.157 (1 1.157 (1	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056, 056 004, 354, 354 005, 056, 056 004, 354, 056 005, 056	D.01 0. Favours (e M- 0.1 rs (experime	Odds Ra Attal France	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		
D      Study or Subarroup     CheryM 2006     thorp M 2007     thorp M 200	Poorly difference Events 11 22 23 12 24 26 10 17 23 179 40, CN* = 28, 1 179 40, CN* = 28, 1 179 40, CN* = 28, 1 179 40, CN* = 28, 1 179 20 20 20 20 20 20 20 20 20 20	stated           12           12           12           12           12           12           12           12           12           12           12           12           11           12           11           12           12           11           12           12           12           12           12           12           130           14           15           16           17           18           18           17           18           18           18           18           18           18           18           18           18           18           18           18           18           18           18           18           18           18           18	(P = 0.3000 Events 266 267 267 267 266 267 267 267 267 267	9 well di renta 18 20 17 42 22 20 27 9 38 56 56 56 56 56 56 56 56 56 56	Toto 2 4 3 3 5 4 4 4 4 4 4 6 4 4 7 8 7 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	Weight         8         59%           9         59%         4           9         59%         4         94%           4         94%         94%         94%           4         94%         94%         94%           9         114%         60%         1           1         103%         9         114%           2         140%         9         100%           1         100.8%         11.3%         1           0.54 (0.0         0.86 (0.3)         0.47 (0.4%)         0.86 (0.3)           0.58 (0.3)         0.48 (0.3)         0.48 (0.3)         0.48 (0.3)           1.52 (0.0)         1.52 (0.3)         1.52 (0.3)         0.50 (0.3)           0.60 (0.4)         1.52 (0.3)         0.50 (0.3)         1.05 (0.7)	H-H. Bandy 578 [0 3.30 [0 4.21 [1 1.00 [1 1.52] 1.53 [1 1.53 [1 1.55 [1]] 1.55 [1 1.55 [1]] 1.	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056 024, 354, 354 005, 056 024, 354 024, 354 024, 354 024, 354 024, 354 024, 354 025, 056 025, 0	D.01 0. Favours (e M- 0.1 rs (experime	Odds Ra Attal France	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		0
D     Study or Subarrou     ChergMP 2006     terrup(2005     LichargXu 2013     Mark 2006     WanY 2012     XiaoXiang2n 2014     XiaoXiang2n 2014     Zixoshaular 2014     Total events     LichargXu 2013     XiaoXiang2n 2014     Zixoshaular 2014     Total events     Hearogonaly: rup = 0.1     Zixoshaular 2014     Zixos	advanc           Events           11           22           23           14           24           24           24           24           26           9           179           20. Ch* = 28.1           130 (P = 0.1           20           20           20           20           20           20           20           20           33           38           178           = 4.50, cf = 1           t Z = 0.26 (t           male           Events.           25           33	stiated Total 12 12 12 12 12 12 12 12 12 12	Events (₽ = 0.0002 266 11 266 17 31 41 41 178 8.61);  ₽ = 9) 10 15 13 13	a well di venta 18 20 17 42 22 20 27 58 318 56 56 56 56 56 56 56 56 56 56	Toto 2 2 4 3 5 4 4 2 2 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4	Weight         8         59%           9         59%         4           4         9.4%         9.4%           4         9.4%         9.4%           4         9.4%         9.6%           4         1.4%         9.6%           4         1.03%         9           9         1.00.9%         9           0.00%         9         10.0%           1         100.0%         9           0.54 (0.0)         0.58 [0.0)         0.58 [0.1]           0.58 [0.2]         1.52 [0.4]         1.05 [0.7]           1.05 [0.7]         1.05 [0.7]         1.05 [0.7]           0.44 [1.07 [0.1]         1.00 [0.2]         1.05 [0.7]           0.04ds R.         M-H. Fixed         1.07 [0.2]           0.05 [0.1]         1.05 [0.7]         1.06 [0.2]	H-H. Bands 5779 (0 5779 (0 7.87 (1 0.046 ( 1.151 ( 1.151 ( 1.151 ( 1.157 (1 1.157 (1	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056 024, 354, 354 005, 056 024, 354 024, 354 024, 354 024, 354 024, 354 024, 354 025, 056 025, 0	D.01 0. Favours (e M- 0.1 rs (experime	Odds Ra Attal France	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		
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D         Image: Contemport of the second secon	poorly differents           11           22           23           12           24           20           10           9           179           80, CM* = 28.1           130 (P = 0.1           16           20           20           20           20           20           20           20           20           20           20           33           36           178           = 4,50, eff =           t Z = 0.26 (I           male           Events           22           33           178           = 4,50, eff =           t Z = 0.26 (I           male           25           33           18           29           20           21	stated           12           12           12           12           12           12           12           12           13           33           44           36, or = 1+           43           36           27           45           47           260           6 (P = 0, 0P)           P = 0.75           6           7           7           7           7           7           7           7           7           7           7           7           7           7           7           7           7           7           7           8           7           7           7           8           7           7           8           7           7           7           8	(P = 0.4000 Events 206 11 206 17 31 41 41 41 178 8-01; I <sup>a</sup> = 9) femal 5 13 30 8 30 8 15	o well di venta 19 20 17 42 20 37 59 37 59 265 0% e Total 18 27 59 37 41 16 33 30 0 41 15 20 27 59 37 41 16 27 59 37 41 16 27 59 37 41 16 27 59 37 41 16 59 265 265 265 265 27 59 37 41 16 27 59 37 41 16 59 265 265 265 265 265 265 265 265	Toto 2 2 4 3 5 4 4 3 5 4 4 2 2 4 4 3 5 4 4 2 2 4 4 3 5 4 4 2 2 4 4 3 5 4 4 2 2 4 4 3 5 4 4 2 2 4 4 3 5 4 4 2 2 4 4 5 4 4 2 2 4 4 5 4 4 2 2 4 4 5 4 4 2 2 4 4 5 4 4 2 2 4 4 5 4 4 2 2 4 4 4 5 4 4 4 7 7 8 8 8 8 8 8 8 8 8 8 8 8 8	Weight         9         59%           9         59%         4           9         59%         4         94%           4         94%         94%         9           4         94%         93%         9         10.0%           9         11.4%         9         10.0%         9           9         11.4%         9         9.0%         1           9         10.0%         9         11.5%         9           0.54 (0.1         0.65 (0.1         0.57 [0.1         0.58 [0.2           0.54 (0.1         0.86 [0.1         0.52 [0.1         1.52 [0.1           1.05 [0.7         1.05 [0.7         1.05 [0.7           Odds R:         MH. Fixer         0.90 [0.2         1.05 [0.7           0.50 [0.1         0.90 [0.2         0.90 [0.2         1.06 [0.1           0.50 [0.1         0.50 [0.1         0.50 [0.1         1.27 [10.2	MH: Bands 578 [0] 578 [0] 3.30 [0] 4.21 [1] 1.00 [1] 1.21 [1] 1.22 [1] 1.57 [0] 1.57 [0] 1.57 [0] 1.57 [1] 1.57	m. 935, c1 121, 600 023, 351, 023 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 351, 159 024, 354, 354 005, 056 024, 354, 354 005, 056 024, 354 024, 354 024, 354 024, 354 024, 354 024, 354 025, 056 025, 0	D.01 0. Favours (e M- 0.1 rs (experime	Odds Ra Attal France	de Ratio ndom 2555 4 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4		
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Fig 4. Forest plots of CD147 expression and the clinicopathological features of patients with esophagus cancer. The squares and horizontal lines correspond to the study- specific OR and 95% CI. The

area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled OR and 95% CI. The solid vertical line is at the null value (OR = 1). **A** The relationship between CD147 expression and TNM staging. CD147 expression was associated with TNM staging of esophagus cancer (OR = 3.66, 95%CI = (2.20, 6.09), p < 0.00001). **B** The relationship between CD147 expression and tumor depth. CD147 expression was associated with tumor depth (OR = 7.97, 95%CI = (4.13, 15.38), p < 0.00001). **C** The relationship between CD147 expression and status of lymph node.CD147 expression was associated with status of lymph node (OR = 5.14, 95%CI = (2.03, 13.01), p = 0.0005). **D** The relationship between CD147 expression and status of lymph node (OR = 1.57, 95%CI = (0.79, 3.12), p = 0.19). **E** The relationship between CD147 expression and age.CD147 expression wasn't associated with age (OR = 1.05, 95%CI = (0.72, 1.53), p = 0.79). **F** The relationship between CD147 expression and sex.CD147 expression wasn't associated with sex (OR = 0.70, 95%CI = (0.47, 1.04), p = 0.07).

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	Sample number	Fixed model	Random model	Heterogeneity	Publication bias(p value)
3-year survival rate	154	OR = 3.26, 95% CI = (1.53, 6.93)	OR = 3.25,95% CI = (1.52, 6.92)	<i>l</i> <sup>2</sup> = 0.0%, p = 0.606	1.000
5-year survival rate	154	OR = 4.35, 95% CI = (2.13, 8.90)	OR = 4.35, 95% CI = (2.13, 8.90)	<i>l</i> <sup>2</sup> = 0.0%, p = 0.814	1.000
Overall survival	166	HR = 1.60, 95% CI = (1.19, 2.15)	HR = 1.71, 95% CI = (1.06, 2.77)	<i>P</i> = 30.1%, p = 0.233	1.000

#### Table 2. Summary of the sensitivity analysis of parameters with less than 3 data sets.

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#### Table 3. Summary of sensitivity analysis of parameters with more than 2 data sets.

	<b>OR Fluctuation</b>	95%CI Fluctuation	Publication bias (p value)		
CD 147 Expression among different tissu	IE				
EC VS noncancer	8.55~10.73	4.87~19.43	0.024		
EC vs normal tissue	9.27~18.43	2.37~90.29	1.000		
EC vs para-EC	10.82~15.24	5.83~30.30	0.074		
EC vs hyperplastic tissue	2.48~5.14	0.93~10.95	0.296		
CD 147 Expression with clinicopathologi	ic characteristics				
TNM I/II vs TNM III/IV	2.80~5.31	1.94~9.59	1.000		
pt3/pt4 VS pt1/pt2	6.64~9.46	3.54~19.26	0.536		
LNM vs LNUM	4.22~6.50	1.74~16.32	0.016		
Poorly vs middle to well differentiated	1.33~2.01	0.67~3.55	0.721		
Advance VS Young	0.95~1.08	0.63~1.82	1.000		
Male vs Female	0.64~0.80	0.41~1.18	0.902		

Note: p < 0.05, exist Publication Bias; EC means esophagus cancer; LNM means lymph node metastasis; LUNM means lymph node unmetastasis.

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conclusion, CD147 was an important molecule for the diagnosis and estimating the prognosis of patients with EC. Further studies using additional putative EC surface markers in combination with CD147 are required to evaluate their potential use in predicting patient outcomes.

#### **Supporting information**

S1 Table. NOS score. (DOCX)S1 File. Searching strategy. (DOCX) S2 File. Sensitivity analysis plot legend. (DOCX)
S3 File. Begg's plot legend. (DOCX)
S4 File. PRISMA 2009 checklist. (DOC)
S1 Fig. Sensitivity analysis plot. (TIF)
S2 Fig. Begg's plot. (TIF)

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