CD147/EMMPRIN overexpression and prognosis in cancer: A systematic review and meta-analysis

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CD147/EMMPRIN (extracellular matrix metalloproteinase inducer) plays an important role in tumor progression and a number of studies have suggested that it is an indicator of tumor prognosis. This current meta-analysis systematically reevaluated the predictive potential of CD147/EMMPRIN in various cancers. We searched PubMed and Embase databases to screen the literature. Fixed-effect and random-effect meta-analytical techniques were used to correlate CD147 expression with outcome measures. A total of 53 studies that included 68 datasets were eligible for inclusion in the final analysis. We found a significant association between CD147/EMMPRIN overexpression and adverse tumor outcomes, such as overall survival, disease-specific survival, progression-free survival, metastasis-free survival or recurrence-free survival, irrespective of the model analysis. In addition, CD147/EMMPRIN overexpression predicted a high risk for chemotherapy drugs resistance. CD147/EMMPRIN is a central player in tumor progression and predicts a poor prognosis, including in patients who have received chemo-radiotherapy. Our results provide the evidence that CD147/EMMPRIN could be a potential therapeutic target for cancers.

The incidence of various cancers has been increasing and cancer is the most deadly disease threatening human life. One of the main causes of deaths is the inherent metastatic property of malignant tumors. This poses great difficulty in developing clinical therapeutics. The multi-linked pathological processes of tumor metastasis include: basement membrane degradation, matrix permeability, forward movement of tumor cells including secondary growth, and interaction between tumor cells and host stromal cells. CD147/EMMPRIN, also known as basigin or M6 antigen, has been shown to play an important role in tumor metastasis by stimulating tumor stromal cells to produce matrix metalloproteinases (MMPs) and degrading basement membrane and stroma1.

CD147/EMMPRIN is a member of the immunoglobulin family and is widely expressed in a variety of human tissues and cells1. CD147/EMMPRIN functions to: (1) facilitate secretion of MMP-1, MMP-3, MMP-9 and membrane-type 1-MMP from cancer cells, fibroblasts and endometrial cells, leading to degradation of basement membrane and extracellular matrix, thus promoting tumor proliferation, invasion and metastasis1,2; (2) drive tumor angiogenesis by enhancing MMPs and vascular endothelia growth factor (VEGF) levels in cancer cells and the mesenchyme3; (3) regulate expression and activity of monocarboxylate transporters-1 (MCT-1) and MCT-4, and form complexes on the membrane to transport lactic acid produced by anaerobic glycolysis4; (4) develop chemoresistance in many cancers, probably by mediating activation of phosphatidylinositol 3-hydroxy kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways5–8; and (5) interact with α3β1, α6β1 integrins to

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regulate adhesion with extracellular matrix proteins, collagen, laminin or fibronectin and also promote expression of cyclophilin A to induce cancer cell proliferation. All of these functions are regulated by CD147/EMMPRIN and are summarized in Fig. 1. The outcomes of many of the pathways regulated by CD147 have been associated with the adverse outcomes highlighted in our study.

It is highly upregulated in several malignant tumors. A few recent studies have revealed a conflicting correlation between CD147/EMMPRIN and various outcomes in different cancers. A meta-analysis of the literature published previously suggests that elevated MCT-4 and CD147 expressions are associated with worse prognosis across many cancer types focusing on the aspect of tumor metabolism while the existing evidence lacks statistical power to draw a convincing conclusion. The objective of this updated study was to systematically assemble all the existing CD147 literature, link the data to variable outcomes, perform a comprehensive meta-analysis to predict potential prognostic effects in different cancers, and provide further evidence to establish CD147/EMMPRIN as a key player in tumor progression from a number of perspectives.

**Results**

Our systematic literature search of CD147 and its correlation with different outcomes identified 910 articles. Among these, 836 articles were excluded and only 82 studies satisfied the inclusion eligibility for the meta-analysis. Upon further review of the full text articles, eight additional articles from reference sources were included. An additional 29 studies were excluded due to the following reasons: two articles were reviews; three were duplicate reports; four had insufficient data; four included only a few cases; nine explored the prognostic value of CD147/EMMPRIN in combination with other biomarkers, such as VEGF, MMP-2, CD44s, MCT-1; and seven studies were determined to be too complicated for subgroup analysis. The remaining 53 studies containing 68 datasets that met our inclusion criteria were included in this review (Fig. 2). Among the eligible studies, 33 provided survival information about the correlation of CD147/EMMPRIN expression with tumor prognosis using a multivariate model and 20 presented the same information using a univariate model. The characteristics of these two models are summarized in Tables 1 and 2, respectively.

The 53 eligible studies represented 26 different carcinomas or sarcomas and a median number of 204.5 patients (range, 40–600). CD147/EMMPRIN expression in these studies was mainly detected by immunohistochemistry (IHC). One publication had three groups of subjects from different cancers and was therefore considered as three different studies. Ten publications presented two different prognostic results, while one publication presented three prognostic results. Some studies also investigated the link between CD147/EMMPRIN and chemotherapy or radiation resistance. In terms of clinicopathological variables, most of the studies suggested that increased CD147/EMMPRIN expression correlated significantly with higher clinical grade, tumor size, invasion depth, lymphatic invasion, histological grade, and some additional parameters (Table 3).

**CD147/EMMPRIN and overall survival (OS).** The 44 studies, with data from a total of 5,813 patients, showed that CD147/EMMPRIN expression was associated with worse OS, both in multivariate (meta-hazard...
CD147/EMMPRIN and progression free survival (PFS), metastasis-free survival (MFS) and recurrence-free survival (RFS). Analysis of 19 studies, with a total of 2,472 patients, showed that CD147/EMMPRIN expression was associated with worse PFS/MFS/RFS, both in multivariate (meta-HR = 2.32; 95% CI: 1.67–3.21) and univariate (meta-HR = 2.18; 95% CI: 1.30–3.63) models (Table 3 and Fig. 4A,B). Moreover, the HR estimates derived specifically from the solid tumors by both models showed a similar pattern of association (multivariate: meta-HR = 2.26; 95% CI: 1.61–3.18; univariate: meta-HR = 2.18; 95% CI: 1.30–3.63). Exclusive analysis of non-solid tumors by a multivariate model suggested a significant association (meta-HR = 3.52; 95% CI: 1.18–10.5) (Table 4).

Similarly, the subgroup analysis of tumors stratified by cancer type again demonstrated a significant association between CD147/EMMPRIN overexpression and adverse outcome of PFS/MFS/RFS in breast carcinoma (meta-HR = 2.92; 95% CI: 1.85–4.60), bladder cancer (meta-HR = 2.32; 95% CI: 1.63–3.29), colorectal cancer (meta-HR = 2.14; 95% CI: 1.38–4.26), ovarian cancer (meta-HR = 1.57; 95% CI: 1.23–2.01) and osteosarcoma (meta-HR = 7.83; 95% CI: 3.18–19.27) in the multivariate model. However, an association was only observed in renal cell carcinoma (meta-HR = 1.87; 95% CI: 1.37–2.56) and bladder carcinoma (meta-HR = 2.51; 95% CI: 1.46–4.33), using the univariate model. In contrast, there was no association in gastric carcinoma (meta-HR = 1.33; 95% CI: 0.99–1.80) and lung cancer (meta-HR = 1.16; 95% CI: 0.63–2.12) (Table 4). We also found a similar association of CD147 with the adverse outcome (OS) in many other cancers, such as adenoid cystic carcinoma of salivary glands, esophageal squamous cell carcinoma, prostate cancer, pediatric medulloblastoma, glioblastoma, gallbladder carcinoma, nasopharyngeal carcinoma, tongue squamous cell carcinoma, endometrial cancer, uterine cervical carcinoma, hepatocellular carcinoma, pancreaticobiliary adenocarcinoma, cutaneous squamous cell carcinoma, astrocytomas and soft tissue sarcomas (Supplementary Figure 1A,B).

CD147/EMMPRIN and disease-specific survival (DSS). Quantitative analysis of five different studies, representing 1,031 patients, linked CD147/EMMPRIN overexpression with DSS in four different solid tumors, namely breast cancer, colorectal cancer [24, 41], oral squamous cell carcinomas and cervical cancer. Multivariate model analysis established that CD147/EMMPRIN expression was associated with a worse DSS (meta-HR = 5.81; 95% CI: 4.16–7.46) (Table 4). This pattern was
CD147/EMMPRIN and chemotherapy drug/radiation resistance. Among the included articles, three studies reported risk for CD147/EMMPRIN overexpression and chemotherapy drug resistance, while only one study reported radiation resistance. Quantitative analysis of three articles revealed that positive expression of CD147/EMMPRIN predicted recurrence of drug resistance (meta-OR = 3.89; 95% CI: 2.09–41.30) (Fig. 5B). In

Table 1. Characteristics of studies exploring the relationship between CD147/EMMPRIN expression and tumor prognosis (Multivariate model).

| Author                 | Year | Country         | Cancer type                        | Stage/grade | Number (range) | Median (range) | Follow-up time (range) | Detection method | Cut-off | Outcome |
|------------------------|------|-----------------|------------------------------------|-------------|----------------|------------------|------------------------|-----------------|---------|---------|
| Natalie Reimers-10     | 2004 | Germany         | Breast carcinoma                   | pT1–pT4     | 600            | >50y             | 63m (1–176m)           | TMA/IHC          | ≥1      | DSS     |
| HC Zheng-19            | 2006 | Japan           | Gastric carcinoma                  | 0–IV        | 219            | 66.8y (38–88y)    | 40.4m (0.2m–12.2y)     | TMA/IHC          | ≥5%     | OS      |
| Kazu Ueda-20           | 2006 | Japan           | Endometrial carcinoma              | 1–IV        | 112            | 55.3 ± 11.7      | NA                     | IHC             | score > 2 | RFS     |
| Qing Zhang-21          | 2007 | China           | Hepatocellular carcinoma           | 1–IV        | 111            | 47.47 ± 9.55 (24–66y) | 26m (30–1880d) | IHC             | ≥1%     | RFS     |
| Anne B. Als-5          | 2007 | Denmark         | Bladder cancer                    | T4b, N2–3, M1 | 124          | 62.6y (31–78y)    | 56.5 (19.5–129.8 m)     | IHC             | ≥5%     | OS      |
| Wulf Sienel-22         | 2008 | Germany         | Non-small-cell lung cancer         | T1–T4       | 57             | 60y (37–80y)      | 36 m (4–156)           | IHC             | score ≥ 200 | OS      |
| Xingzhu Ju-23          | 2008 | China           | Cervical Cancer                   | Ib2–Iib     | 75             | 49.7y (21–72y)    | 52m (3–168m)          | IHC             | ≥1%     | DSS     |
| Yu Li-11               | 2009 | China           | Breast carcinoma                  | infiltrating | 106           | NA               | 63.5m (7–170)         | TMA/IHC          | ≥30%    | RFS     |
| Fangfang Liu-12        | 2010 | China           | Breast carcinoma                  | Invading    | 186            | 52.5y (23–85y)    | 64.8m (7–170m)        | IHC             | ≥1%     | OS, DFS |
| Xinjie Yang-24         | 2010 | China           | Adenoid cystic carcinoma of salivary glands | 1–IV        | 72             | NA               | 76.76 ± 37.47 m; (9–178m) | IHC             | ≥5%     | OS      |
| Wei–De Zhong-25        | 2011 | China           | Bladder cancer                    | T1–T4       | 101            | 68.1y (46–82y)    | 36m                     | IHC             | ≥5%     | OS, DFS |
| Tongwei Chu-26         | 2011 | China           | Pediatric Medulloblastoma          | M0–M4       | 56             | Paediatric patients | 5–y                   | IHC             | ≥5%     | OS      |
| Yijun Xue-27           | 2011 | China           | Bladder cancer                    | pT1–pT4     | 108            | 58.3y (31–82y)    | 35.5 m (3–86m)        | TMA/IHC          | ≥1%     | OS      |
| Shaojun Zhu-28         | 2011 | China           | Esophageal Squamous Cell Carcinoma | NA          | 86             | 40–78y           | 4–6 y                   | IHC             | ≥5%     | OS      |
| Weide Zhong-29         | 2011 | China           | Prostate cancer                   | pT2–pT3     | 240            | 61.81 ± 6.54y/61.94 ± 5.83y | NA                     | TMA/IHC          | ≥5%     | MFS, OS |
| Xuecheng Bi-30         | 2012 | China           | Human seminomas                   | pT1–pT4     | 65             | 21.66 ± 10.18y   | 5 y                     | IHC             | ≥5%     | OS      |
| K Boye-31              | 2012 | Norway          | Colorectal cancer                 | 1–III       | 242            | 70y (21–98 y)    | 9.1y (8.2–10.0y)       | IHC             | ≥5%     | MFS, DSS, OS |
| Zhangxuan Shou-32      | 2012 | China           | Gastric Cancer                    | 1–IV        | 436            | 64y (30–91y)     | >5y                     | TMA/IHC          | ≥5%     | OS      |
| Albrecht Stenzinger-33 | 2012 | Germany         | Colorectal cancer                 | 1–IV        | 285            | 66.6y           | NA                     | TMA/IHC          | score > 6 | OS      |
| Shuhua Zhao-13         | 2013 | China           | Ovarian cancer                    | 1–IV        | 146            | 52.8y (26–79y)   | 36m (7–82m)            | IHC             | ≥4      | OS, DFS |
| Ying Liu-34            | 2013 | China           | Breast cancer                     | 1–III       | 189            | NA              | NA                     | IHC             | ≥10%    | OS      |
| Anja Rabien-35         | 2013 | Germany         | Renal cell carcinoma              | pN0/M0      | 181            | 60y (21–86y)      | 112m (0–194m)         | TMA/IHC          | ≥1      | OS      |
| Xiaoyan Xu-36          | 2013 | China           | Non-small lung cancer             | 1–IV        | 136            | 60y (35–82y)     | 28m (1–87m)            | IHC             | ≥1%     | OS      |
| Min Yang-37            | 2013 | China           | Glioblastoma                      | NA          | 206            | 53.6y (14–78y)   | 12.3m (1–60m)          | IHC             | score > 1 | OS      |
| Yang Zhao-14           | 2013 | China           | Ovarian carcinomas                | 1–IV        | 88             | 51.2y (20–81y)   | 52m (1–103m)           | TMA/IHC          | score ≥ 1 | RFS, OS |
| Qiang Lu-17            | 2013 | China           | Osteosarcoma                      | IIA–III     | 55             | 32m (8–72m)      | IHC                     | ≥5%     | OS      |
| Dake Chu-38            | 2014 | China           | Gastric cancer                    | T1–T4       | 223            | NA              | 41.8m (DFS)/58.0m (OS) | IHC             | ≥5%     | OS, DFS |
| Qin Xu-39              | 2014 | China           | Cervical carcinoma                | Ia1–Iib     | 110            | NA              | NA                     | IHC             | ≥10%    | OS, DFS |
| Shu Zhao-40            | 2014 | China           | Breast cancer                     | 1–III       | 127            | 49y (30–68y)     | NA                     | IHC             | ≥10%    | OS, DFS |
| Naohisa Futamura-16    | 2014 | Japan           | Osteosarcoma                      | IIA–IIB     | 53             | 20y (4–57y)      | 72m (8–200m)           | IHC             | score ≥ 1 | OS, DFS |
| Jian Gao-43            | 2014 | China           | Ovarian cancer                    | 1–IV        | 92             | NA              | NA                     | IHC             | ≥5%     | OS      |
| Luis Silva Monteiro-15 | 2014 | Portugal        | Oral squamous cell carcinomas     | 1–IV        | 74             | 62.3 ± 15.3y (25–96y) | 36.45 ± 31.7m        | TMA/IHC          | score > 3 | CSS     |

unchanged even in the subgroup analyses stratified by cancer type. Multivariate model analysis also identified the following associations with DSS: breast carcinoma (meta-HR = 1.70; 95% CI: 1.02–2.84), oral squamous cell carcinoma (meta-HR = 3.89; 95% CI: 1.11–13.71) and colorectal cancer (meta-HR = 2.30; 95% CI: 1.03–5.14). The only cancer for which we did not observe an association was uterine cervical carcinoma (meta-HR = 1.23; 95% CI: 0.52–2.90) (Supplementary Figure 4).
addition, CD147/EMMPRIN overexpression appeared to be linked to high risk of radiation resistance (OR = 13.30; 95% CI: 4.38–40.35) in cervical squamous cell carcinomas, although this is just based on one study (Fig. 5C).

**Heterogeneity analysis.** There was evidence of significant heterogeneity ($I^2 > 50\%$) between OS and PFS studies, but not among DSS studies (Table 4). Therefore, the random-effect model was used in all analyses except for the DSS. For the OS and PFS studies, we conducted a meta-regression analysis using publication year, cancer type, sample size, and country as covariates. All covariates were entered into the meta-regression model simultaneously, and the covariates with the highest $p$ values were omitted one at a time to identify sources of heterogeneity. The meta-regression did not identify any of these covariates as a significant source of heterogeneity for OS studies; however, the covariates with the highest $p$ values were omitted one at a time to identify sources of heterogeneity for PFS studies. For the OS and PFS studies, we conducted a meta-regression analysis using publication year, cancer type, sample size, and country as covariates. All covariates were entered into the meta-regression model simultaneously, and the covariates with the highest $p$ values were omitted one at a time to identify sources of heterogeneity. The meta-regression did not identify any of these covariates as a significant source of heterogeneity for OS studies.

**Sensitivity analysis.** We also performed a sensitivity analysis to evaluate the effects of individual studies on the pooled HR estimates by omitting one study at a time. The HR estimates for the DSS and PFS studies in multivariate, and indicated that cancer type may be the source of heterogeneity for OS studies (Table 4). Therefore, the random-effect model was used in all analyses except for the DSS. For the OS and PFS studies, we conducted a meta-regression analysis using publication year, cancer type, sample size, and country as covariates. All covariates were entered into the meta-regression model simultaneously, and the covariates with the highest $p$ values were omitted one at a time to identify sources of heterogeneity. The meta-regression did not identify any of these covariates as a significant source of heterogeneity for OS studies. Therefore, the random-effect model was used in all analyses except for the DSS. For the OS and PFS studies, we conducted a meta-regression analysis using publication year, cancer type, sample size, and country as covariates. All covariates were entered into the meta-regression model simultaneously, and the covariates with the highest $p$ values were omitted one at a time to identify sources of heterogeneity. The meta-regression did not identify any of these covariates as a significant source of heterogeneity for OS studies.

**Publication bias.** To assess confidence in our study, we performed a publication bias analysis using the funnel plot and Egger’s and Begg’s rank correlation tests. There was no significant publication bias in both models for the DSS and PFS/MFS/RFS groups (Table 4; Fig. 6D–F). In the case of the OS group, the univariate model (Table 4; Fig. 6C) suggested no publication bias, but in the multivariate model, results were inconsistent based on the $p$ value obtained by Begg’s rank test (0.05) and Egger’s test (0.007) (Table 4; Fig. 6A). These test results were nonparametric and therefore the Trim and Fill method was used to further verify this analysis. After filling the deleted studies (square dots), we found no obvious asymmetry in the funnel plot (Fig. 6B). Thus, the HR estimates for the prognostic value of CD147/EMMPRIN were not notably altered (data not shown). This suggests that there was no publication bias even in the OS group in the multivariate model.
| Author          | Cancer type                  | Relative to other factors | Relative to clinicopathologic variables                                                                 |
|-----------------|------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------|
| Natalie Reimers-10 | Breast carcinoma              | ER, PR (inversely)        | High tumor grade, histologically determined mitotic index, tumor size, inversely correlated to age        |
| HC Zheng-19     | Gastric carcinoma            | ki-67, MMP-2, MMP-9, VEGF | Tumour size, depth of invasion, lymphatic invasion, not with lymph node metastasis, UICC staging or differentiation |
| Kazu Ueda-20    | Endometrial carcinoma        | MVD-CD34, MMP-2 in pericancerous, not in cancerous lesions; VEGF | Advanced stage, poorly differentiated carcinoma, lymph node metastasis, lymphatic vessel infiltration, pathological high risk group |
| Qing Zhang-21   | Hepatocellular carcinoma     | MMP-2, MMP-9, VEGF, MVD   | pTNM tumor stages, tumor size and venous invasion, IV stage and large tumor size, preoperative AFP level; not: viral hepatitis, the number of tumor nodules, lymph node metastasis |
| Anne B. Als-5   | Bladder Cancer               |                           | Visceral metastases                                                                                        |
| Wulf Sienel-22  | Non-small-cell lung cancer   | MMP-2 (no), MMP-9 (no)   | Pelvic lymph node metastasis, no correlation with clinical stage and histopathology                         |
| Xingzhu Ju-23   | Cervical Cancer              |                           | Pelvic lymph node metastasis, no correlation with clinical stage and histopathology                         |
| Yu Li-11        | Breast carcinoma             |                           | Pelvic lymph node metastasis, no correlation with clinical stage and histopathology                         |
| Fangfang Liu-12 | Breast carcinoma             | C-erbB-2: ER, PR (inversely) | Histological grade, local recurrence, distant metastasis and tumor mortality                              |
| Xinjie Yang-24  | Adenoid cystic carcinoma of salivary glands | MMP-2, MMP-9, VEGE  | Tumor size, histotypes, clinical stage, perineural invasion, vascular invasion, metastasis                  |
| Wei-De Zhong-25 | Bladder cancer               |                           | Tumor stage and grade, status of carcinoma in situ, tumor recurrence, tumor progression                    |
| Tongwei Chu-26  | Pediatric Medulloblastoma    |                           | Higher metastatic stage, aggressive histopathological type, necrosis, undifferentiated tumor               |
| Yijun Xue-27    | Bladder cancer               |                           | Lymph node status, tumor stage, histologic grade                                                         |
| Shaojun Zhu-28  | Esophageal Squamous Cell Carcinoma | MMP-2, MMP-9, Ki-67 index, MVD | Lymph node metastasis cases, differentiation, depth of tumor invasion                                      |
| Weide Zhong-29  | Prostate cancer              |                           | Gleason score, positive surgical margin status, reduced PSA failure-free survival                          |
| Xuecheng Bi-30  | Human seminomas              | MMP-2                     | advanced T, N and M stage, poor differentiation types                                                    |
| K Boye-31       | Colorectal cancer            | S100A4                    | no associations with any of the clinical or histopathological parameters                                  |
| Zhangxuan Shou-32 | Gastric Cancer              | ADAM17                    | Age, tumor size, location, depth of invasion, TNM stage, Lauren’s classification, vessel invasion, and lymph node and distant metastasis of tumor |
| Albrecht Stenzinger-33 | Colorectal cancer       |                           | Trend correlation with stage, distant metastasis, blood vessel invasion, and Dukes classification          |
| Shuhua Zhao-13  | Ovarian cancer               |                           | Lymph-vascular space involvement, lymph node metastasis                                                  |
| Ying Liu-34     | Breast cancer                |                           | pT stage and Fuhrman grading                                                                             |
| Anja Rabien-35  | Renal cell carcinoma         |                           | Tumor diameter, lymph node status, tumor stage                                                           |
| Xiaoyan Xu-36   | Non-small lung cancer        |                           | Karnofsky performance status (KPS) score                                                                |
| Min Yang-37     | Glioblastoma                | Ki-67                     | FIGO staging, dedifferentiation                                                                          |
| Yang Zhao-14    | Ovarian carcinomas           |                           | Pathological classification, percentage of dead cells                                                     |
| Qiang Lu-17     | Osteosarcoma                 |                           | Invasion, metastasis and TNM stage                                                                       |
| Dane Chu-38     | Gastric cancer               |                           | FIGO clinical stage, lymph node metastasis, parametrum invasion, and differentiation                      |
| Qin Xu-39       | Cervical carcinoma           |                           | FIGO clinical stage, lymph node metastasis, parametrum invasion, and differentiation                      |
| Shu Zhao-40     | Breast cancer                | MMP-9, Ki67               | Lymph node metastasis, high pathological grade, tumor size larger than 2 cm                             |
| Naohisa Futamura-16 | Osteosarcoma               | MT1-MMP                   | Not associated with age, gender, anatomic location, necrosis after neoadjuvant chemotherapy, or surgical stage |
| Jian Gao-43     | Ovarian cancer               | Lewis y antigen           | Drug-resistant                                                                                           |
| Luis Silva Monteiro-15 | Oral squamous cell carcinomas | Ki-67                     | Advanced tumor stages, histological grade                                                              |
| Shaojun Zhu-41  | Hepatocellular carcinoma     |                           | No relationship between differentiation, HBV infection, significantly opposite to cirrhosis               |
| Hai-Gang Li-42  | Hepatocellular carcinoma     | paxillin and syndecan-1 (no) | Not associated with serum AFP level, HBsAg status, presence of microsatellite nodule, tumor size, presence of cirrhosis and necrosis, differentiation, presence of portal vein thrombosis and extra-hepatic metastasis |
| Wen-Chiuang Tsai-43 | Renal cell carcinoma       | fascin                    | Histological grades and clinical stages                                                                 |
| Nobuyuki Hakuma-44 | Non-Small Cell Lung Cancers | fascin                    | Well differentiated, not associated with any of the following variables: age, gender, histology, pT or pN classification, and pathological stage |
| Wen Chiuang Tsai-45 | Pancreatobiliary adenocarcinoma | fascin                    | Histologic grades and clinical stages                                                                    |

Continued
suggest that combination of CD147/EMMPRIN with other factors, especially VEGF, and MMP-2, can predict the prognosis of some cancers. Here, we exclusively studied the role of CD147/EMMPRIN in tumor prognosis. Our meta-analysis revealed that the prognosis in three adverse outcomes was significantly poor in cases with CD147/EMMPRIN overexpression. This was further confirmed in subgroup analyses of tumors stratified by cancer type.

Table 3. Relationship between CD147/EMMPRIN overexpression and clinical and pathological factors.

| Author         | Cancer type                      | Relative to other factors                                      | Relative to clinicopathologic variables                  |
|----------------|----------------------------------|----------------------------------------------------------------|---------------------------------------------------------|
| Wei Wu-46      | Gallbladder carcinoma            | MMP-2                                                           | Nevin stages of tumor tissues, histological differentiated degree, distant metastasis |
| Daniel Buergy-47| Colorectal Cancer                |                                                                  | pT or pN status, metastasis                              |
| Ziming Du-48   | Nasopharyngeal carcinoma         | Cav-1                                                           | Metastasis of the disease                                |
| Zhaodong Han-49| Renal/Bladder/Prostate carcinoma | TNM stages, histological subtypes                               |                                                         |
| H. Z. Zeng-7   | Non-small-cell lung cancer       |                                                                  | No association (overall CD147); (membranous CD147) associated with a poor response to chemotherapy |
| Congfa Huang-9 | Cervical squamous cell carcinoma  | HIF-1α, VEGF-A, VEGF-C, CypA                                    | Recurrence and node metastasis                          |
| Larissa Sweeney-50 | Cutaneous Squamous Cell Carcinoma |                                                                  | Node positive disease                                    |
| Keiichiro Nakamura-51 | Endometrial cancer            |                                                                  | FGIO stage, histology, depth of myometrial invasion, cervical involvement, lymph node metastasis, lymph vascular space involvement, peritoneal cytology |
| Mototaka Sato-52 | Renal cell carcinoma              | anti-CD34                                                       | Pathological T stage, clinical M stage, AJCC stage, Fuhrman grade, microvessel area of immature vessels |
| Wen Chuan Tsai-53 | Astrocytomas                   |                                                                  | WHO grades                                              |
| Qing Yang-54   | Hypopharyngeal Squamous Cell Carcinoma | CD44+6, COX-2                                           | T classification, lymph node metastasis and clinical stage |
| Xinwen Zhong-55| Lung cancer                      | RACK1                                                          | Differentiation, Lymph node metastasis                   |
| Jung-Woo Choi-56 | Urothelial carcinoma of the bladder | MCT1, MCT4                                                | High World Health Organization grade, advanced tumor node metastasis stage, and nonpapillary growth type |
| Xin-Qiong Huang-57 | Cervical squamous cell carcinoma | GLUT-1                                                       | Histopathological grade, Tumor diameter, radiation-resistant |
| Céline Pinheiro-58 | Soft tissue sarcomas     | MCT1, MCT4                                                  | Disease progression                                      |
| Youngbye Kim-59 | Clear cell renal cell carcinoma  |                                                                  | High grade, tumor necrosis, larger tumor size            |

Table 4. Meta-analysis of association between CD147/EMMPRIN expression and tumor prognosis. P* present P for HR, P# present P for I2.
by cancer type. Meanwhile, the predictive role of CD147/EMMPRIN in cervical cancer and hepatocellular carcinoma prognosis has been controversial and its result in cervical carcinoma, endometrial carcinoma,
pancreatobiliary adenocarcinoma and some additional tumors did not consistently reach significance. However, the sample size and studies in our stratified analysis were small, and our findings should be further verified.

CD147/EMMPRIN has been shown to be involved in the regulation of tumor cell invasion, metastasis, angiogenesis, anti-apoptosis, adhesion and facilitation of drug resistance through its association with various proteins, such as MMP-2, MMP-9, Ki-67, VEGF, microvessel density, C-erbB-2, S100A4, a disintegrin and metalloproteinase 17, Lewis y antigen, fascin, caveolin-1, hypoxia inducible factor 1 alpha, cyclophilin.

Figure 5. Qualitative meta-analysis of the association between CD147/EMMPRIN over-expression and disease free survival (DSS) in cancer patients, and to predict easier recurrence of drug resistance. Panel A, represents the association of CD147/EMMPRIN positive expression with worse DSS in multivariate model. Panels B, represents the potential of CD147/EMMPRIN positive expression to predict easier recurrence of drug resistance.

Figure 6. Assessment of publication bias for OS, DSS, and PFS/MFS/RFS studies. Panel (A) depicts the assessment of publication bias for multivariate model studies, by funnel plot analysis, whereas panel (B) shows funnel plot analysis using nonparametric Trim and Fill method. Panel (C) represents the publication bias in univariate model studies. Panel (D) represents the assessment of publication bias for multivariate and univariate model studies, respectively.
A, CD44v6, cyclooxygenase-2, receptor for activated C kinase and metabolism related factors like MCT-1, MCT-4, glucose transporter -1. However, there is some conflicting literature refuting associations with paxillin, syndecan-1, and MMP-2 and MMP-9. In addition, CD147 expression has been proposed to inversely correlate with estrogen and progesterone expression. Furthermore, CD147/EMMPRIN was positively associated with clinicopathological variables in most studies (Table 3). It is speculated that CD147/EMMPRIN interacting with many proteins representing various molecular or biological pathways contributes to malignant progression, eventually causes adverse clinical outcomes.

Previous meta-analyses didn’t explore any significant association between CD147/EMMPRIN and susceptibility of radio-chemotherapy. In the view of more studies are warranted to validate CD147/EMMPRIN association with chemotherapy and radiation resistance prediction. It has been suggested that chemotherapy drugs combined with CD147-targeted therapy may increase the sensitivity of tumor cells to several different chemotherapy drugs, and can result in more effective inhibition of tumor proliferation and recurrence. Our study also established that increased CD147/EMMPRIN expression is linked to high risk of drug resistance and our preliminary analysis linked CD147 to radiation resistance. It follows that CD147/EMMPRIN has been proposed to be an important potential therapeutic target.

The results of the present study must be interpreted with caution due to the presence of substantial heterogeneity. In addition, there were several limitations in this study. First, the composition of the cancer type or stage varied between studies, and the detection and corresponding cut-offs varied. For instance, some studies only included pediatric patients while others included older patients. Also, in non-small-cell lung cancer, CD147/EMMPRIN was associated with poor survival in patients with adenocarcinoma only, but not with squamous cell carcinoma. The scoring criteria were also inconsistent. Second, the follow-up time varied across studies, which may have contributed to the non-homogeneity of prognostic information. Sensitivity analysis results also showed instability within individual articles. Third, this study was based on published articles only and, since negative data are hard to publish, there could be publication bias, which is an inherent limitation of all meta-analyses, irrespective of outcomes from the Egger’s linear regression test and Begg’s rank correlation test.

Conclusion
In summary, this meta-analysis indicated that higher expression of CD147/EMMPRIN potentially may be a prognostic marker for most cancers, and thus can serve as a potential therapeutic target. We further verified that CD147/EMMPRIN had a complex role in tumor progression by crosstalk with numerous factors. However, additional multicenter prospective studies are warranted to confirm these findings, especially in various types of tumors.

Methods
Study identification. We searched PubMed and Embase databases through March 2015 to identify relevant studies for inclusion in our meta-analysis. The following keywords were used in the literature searches; “CD147”, “extracellular matrix metalloproteinase inducer”, “EMMPRIN”, “basigin”, “survival”, “prognosis”, “tumor”, “cancer”, “carcinoma”, “neoplasm”, or their combinations. Eligible articles were selected based on title, abstract and full text. If the same patient cohort was reported in multiple publications, only the most complete and most recent publication was included.

Inclusion and exclusion criteria. Based on the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines, we included studies that met all of the following criteria: (1) written in English; (2) reported quantitative outcomes from prognostic association studies of tumor and CD147/EMMPRIN; (3) described outcomes as overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS), metastasis-free survival (MFS) or recurrence-free survival (RFS), depending upon the study; (4) had a minimum of 40 case numbers describing prognosis; (5) provided a detailed protocol, including the source of raw materials, methodology, quantification methods, and scoring criteria; (6) precisely defined the time-to-event outcome, time to follow-up, and the median follow-up time; and (8) data were presented as the estimated hazard ratios (HRs) with 95% confidence intervals (CIs) or in the case where HRs or 95% CIs were not reported directly, a calculation was used to determine if the conditions of the study were suitable for inclusion. Multivariate analyses were used for statistical analysis biomarkers that had independent prognostic factors for cancers after adjusting for one or more additional standard clinical prognostic variables like age, pathology, stage, grade, lymphatic metastasis or other biological marker variables. Studies were excluded if they were case reports, case-only studies, letters, reviews, reported insufficient data, lacked statistical analysis, combined with other factors, or were duplicate studies. All studies were independently reviewed by two authors, and in a case of conflict a third author resolved the issue after thorough discussion.

Data collection and analysis. We assessed heterogeneity using the Chi² test and I² test. If heterogeneity was present, meta-regression was used to determine the source. We combined data from different trials using a fixed-effect model when there was no significant heterogeneity in populations (I² < 50%) and a random-effect model when there was considerable heterogeneity. If heterogeneity was present, meta-regression was used to determine the source. Variables were synthesized using HR/OR. By convention, an overall HR (OR) > 1 with a 95% CI implied a poor outcome (high risk) for the group with either positive or negative biomarker expression. The high HR value corresponded with poor survival. To evaluate the effects of individual studies on the pooled HR estimates, we performed a sensitivity analysis omitting one study at a time. The statistical significance was set at 0.05. We used funnel plot asymmetry using Egger’s linear regression test and Begg’s rank correlation test to assess the publication bias. If both test results were inconsistent, Nonparametric Trim and Fill method was used to verify the results. A P value of < 0.05 suggested significant publication bias. All statistical analyses were performed using STATA 12.0 (StataCorp, College Station, TX) statistical software.
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