Original Article

The association between ephrin receptor-A1 expression and survival in patients with cancer: a meta-analysis

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Background: Ephrin receptor-A1 (EPHA1) participates in various developmental processes by engaging in cell adhesion, migration, and tissue boundary formation. EPHA1 is also associated with cancer progression and poor prognosis. However, the results of individual studies were inconsistent. Therefore, we aimed to systematically evaluate the association between survival and EPHA1 expression in patients with cancer.

Methods: We searched electronic databases including PubMed, Embase, Scopus, and the Cochrane library until February 8, 2022. The pooled hazard ratio (HR) with 95% confidence interval (CI) was calculated to explore the relationship between EPHA1 expression and survival in patients with cancer. Funnel plots and Egger's regression tests were conducted to evaluate publication bias, and sensitivity analysis was performed to determine the reliability of the pooled results.

Results: Eight studies with 1079 cancer patients were enrolled. EPHA1 expression was associated with progression-free survival (PFS) (HR 1.79, 95% CI: 1.49–2.15, P<0.001). EPHA1 expression was also associated with poor overall survival (HR 2.23, 95% CI: 1.42–3.51, P<0.001), higher tumor stage [odds ratio (OR) 1.74, 95% CI: 1.15–2.61, P=0.008], and lymph node metastasis (OR 1.88, 95% CI: 1.24–2.87, P=0.003) in patients with gastric cancer.

Discussion: EPHA1 expression was significantly associated with PFS in patients with cancer.

Keywords: Cancer; ephrin receptor-A1 (EPHA1); meta-analysis; survival

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Introduction

Despite the advances in treatment modalities, the survival of patients with cancer is still poor. For this reason, individualized and targeted therapies have been developed, and research on biomarkers that can predict the prognosis of patients with cancer has been essential. Therefore, researchers have attempted to find molecules participating in cancer pathogenesis (1). Among them, Ephrin receptor was speculated to be a possible key factor in carcinogenesis and a biomarker of tumorigenic processes (1).

The Ephrin receptor was originally found in hepatocellular carcinoma cells in 1987 (2). Ephrin receptor-A1 (EPHA1) is a member of the Ephrin tyrosine kinase receptor family and is a plasma membrane protein (2). EPHA1 participates in various developmental processes by

engaging in cell adhesion, migration, and tissue boundary formation. In addition to these biological functions, EPHA1 is involved in tumor angiogenesis, tumor invasion, and metastasis (2-4). Moreover, studies show that EPHA1 can not only predict the prognosis of patients with cancer but also serve as a target for cancer treatment (3,5-12).

However, the results of individual studies were inconsistent. Therefore, we evaluated the association between survival and EPHA1 expression in patients with cancer. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1367/rc).

Methods

Search strategy

Studies were selected through a literature search performed in PubMed, Embase, Scopus, and the Cochrane library until February 8, 2022, using the following keywords: (EPHA1 or Ephrin receptor-A1) and (cancer, tumor, carcinoma, neoplasm, or malignancy) and (prognostic or predict prognosis, survival, or outcome). A manual search was conducted through the references to related studies.

Inclusion and exclusion criteria

The studies were included in the analysis only if they met the following criteria: (I) EPHA1 expression was assessed in human cancer; (II) the association between survival and EPHA1 expression was evaluated by immunohistochemistry; (III) survival data were provided for the calculation of the hazard ratio (HR) with 95% confidence interval (CI). Studies were excluded if they met the following criteria: (I) duplicate-searched articles; (II) conference abstracts, reviews, and non-English articles.

Data extraction and quality assessment

Each of the two researchers individually reviewed the included studies and collected the following information: first author, publication year, country, cancer type, sample size, sex of patients, follow-up time, survival outcome, and cut-off value of EPHA1 expression. If there was any difference in the information collected, we reached consensus through discussion. Each of the two researchers evaluated the quality of the included studies using the Newcastle-Ottawa Scale. If there was any difference in the information collected, we reached an agreement regarding the quality of the study through discussion.

Statistical analysis

The pooled HR and odds ratio (OR) with 95% CI were calculated to evaluate the prognostic and clinicopathological value of EPHA1 expression. The I^2 value was used to evaluate the heterogeneity among the included studies. If the I^2 value is 50% or more, random-effect model was selected, otherwise, fixed-effect model was applied. Funnel plots and Egger's regression tests were also conducted to show publication bias. Sensitivity analysis was performed to show the reliability of the pooled results. All of the data were analyzed using StataSE12 (Stata, College Station, TX, USA), and it was determined to be statistically significant if the P value was less than 0.05.

Results

Characteristics of the included studies

Of the 135 studies initially searched, eight were adopted for analysis (*Figure 1*). The basic information of the included studies is summarized in *Table 1*. The included studies comprised of 1,079 patients with different cancers including gastric cancer (n=4), epithelial ovarian cancer (n=1), clear cell renal cell carcinoma (n=1), non-small cell lung cancer (n=1), and colorectal cancer (n=1).

Association between EPHA1 expression and overall survival (OS)

The analysis of the association between EPHA1 expression and OS, disease-specific survival, or tumor-specific survival included 7 studies with 814 cancer patients. In this meta-analysis, disease-specific or tumor-specific survival was regarded as OS.

The included studies were evaluated using a random-effects model due to the severe heterogeneity (I^2=80.2%, P<0.001) present among the included studies. The pooled HR for the association between EPHA1 expression and OS was 1.39 (95% CI: 0.79–2.44, P=0.249) (*Figure 2A*). Subgroup analysis revealed that EPHA1 expression was related to poor OS in patients with gastric cancer (HR 2.23,

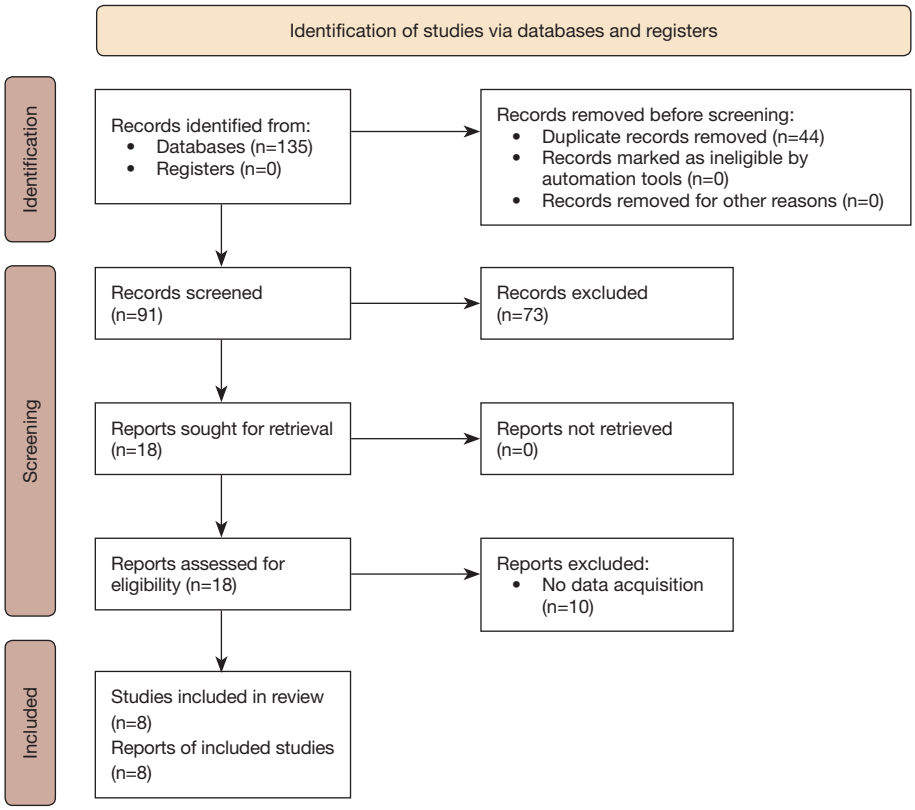

Figure 1 Flow diagram of the study selection process.

95% CI: 1.42–3.51, P<0.001) (*Figure 2B*).

Association between EPHA1 expression and progression-free survival (PFS)

The analysis of the association between EPHA1 expression and PFS, relapse-free survival, or event-free survival included 4 studies with 678 patients with cancer. In this meta-analysis, relapse-free or event-free survival was considered as PFS.

The included studies were assessed using a fixed-effects model due to the low heterogeneity (I^2=0.0%, P=0.584) present among the included studies. The pooled HR was 1.79 (95% CI: 1.49–2.15, P<0.001), indicating that EPHA1 expression is related to the disease progression in cancer patients (*Figure 3A*). Moreover, in the subgroup analysis between cancer types, the gastric cancer group and "others" cancer group still showed significant results (gastric cancer, HR 1.87, 95% CI: 1.53–2.30, P<0.001; Others, HR 1.50, 95% CI: 1.01–2.24, P=0.047) (*Figure 3B*).

Association between EPHA1 expression and clinicopathological factors

When analyzed with various cancers, there were no significant results obtained from the analysis of EPHA1 expression and clinicopathological factors (*Table 2*). However, EPHA1 expression was significantly associated with higher tumor stage (OR 1.74, 95% CI: 1.15–2.61, P=0.008) and lymph node metastasis (OR 1.88, 95% CI: 1.24–2.87, P=0.003) (*Table 3*, *Figure 4A*,*4B*) in gastric cancer.

Publication bias

Funnel plots were created, and the results showed an asymmetric distribution (*Figure 5A*,*5B*). However, Egger's regression test did not show a small-study effect (for OS, P=0.275; for PFS, P=0.501). In addition, we performed filled funnel plots, and the results for OS revealed that the HR was reduced and the range of 95% CI was downgraded (HR 1.05, 95% CI: 0.60–1.82, P=0.867) compared with

Table 1 Basic characteristics of the included studies

Study	Country	Cancer type	Sample size	Sex of patients (male/female)	Study period	Follow-up (months)	Survival outcome	EPHA1 detection	Cut-off value of EPHA1 expression	Survival analysis	NOS
Wang *et al.* (2020)	China	Gastric cancer	57	37/20	2015–2016	Till Oct 2019	OS	IHC	Staining scores with proportion (≥2, 25–50%)	MVA	8
Nagare *et al.* (2020)	India	Epithelial ovarian cancer	101	–	2005–2007	Median 48.8	OS, EFS	IHC	Staining scores with intensity and proportion (≥3)	UVA	7
Inokuchi *et al.* (2018)	Japan	Gastric cancer	114	89/25	2003–2007	Median 60	DSS, RFS	IHC	Staining scores with intensity and proportion (≥3)	MVA	8
Nakagawa *et al.* (2015)	Japan	Gastric cancer	222	168/54	2003–2007	Mean 58.4	RFS	IHC	Staining scores with intensity and proportion (≥4)	MVA	8
Toma *et al.* (2014)	Germany	Clear cell renal cell carcinoma	241	160/81	1993–2006	NA	PFS, TSS, OS	IHC	Weakly and moderately positive	MVA	7
Giaginis *et al.* (2014)	Greece	Non-small cell lung cancer	88	72/16	NA	Mean 25.39	OS	IHC	Staining scores with intensity and proportion (≥3)	UVA	7
Wang *et al.* (2010)	China	Gastric cancer	145	105/40	2002–2006	Median 24	OS	IHC	Staining scores with intensity and proportion (by comparing the scores of tumor tissues and adjacent normal tissues)	SC	7
Dong *et al.* (2009)	China	Colorectal cancer	111	66/45	2004–2006	Median 25	OS	IHC	Staining scores with intensity and percentage (by comparing the scores of tumor tissues and matched normal tissues)	SC	7

EPHA1, ephrin receptor A1; NOS, Newcastle-Ottawa Scale; OS, overall survival; EFS, event-free survival; DSS, disease-specific survival; RFS, relapse-free survival; PFS, progression-free survival; TSS, tumor-specific survival; IHC, immunohistochemistry; MVA, multivariate analysis; UVA, univariate analysis; SC, survival curve; NA, not available.

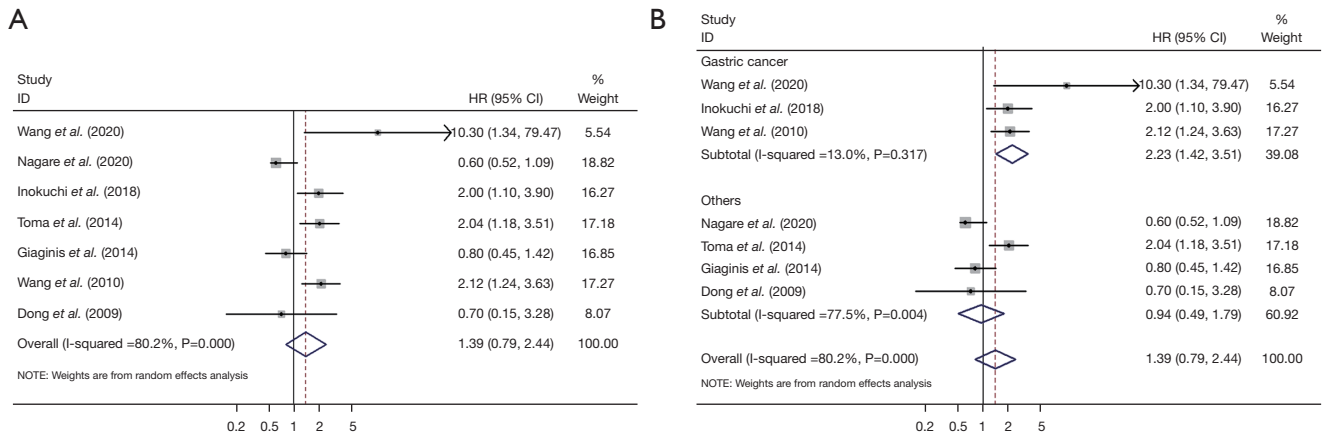

Figure 2 Forest plot of the association between EPHA1 expression and overall survival (A), stratified by cancer type (B). EPHA1, ephrin receptor A1.

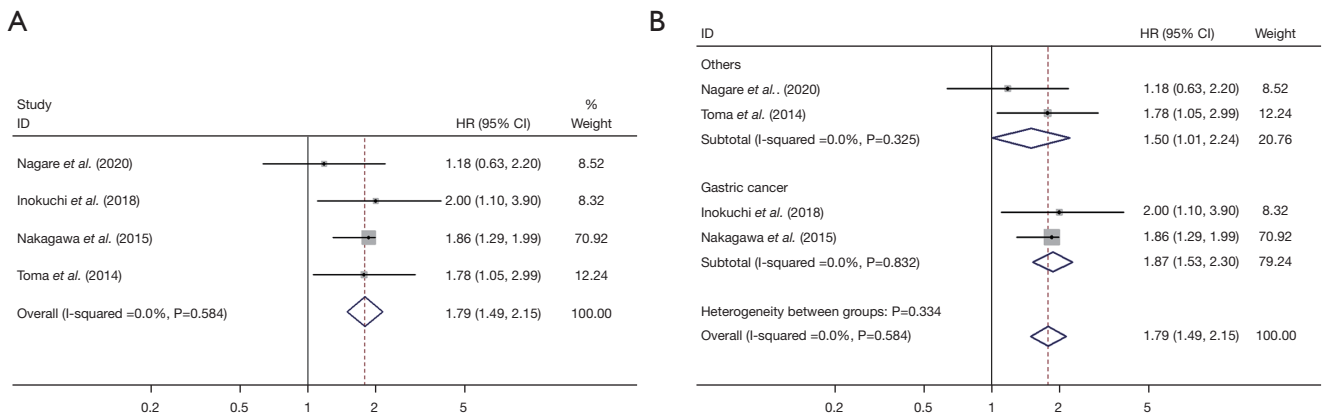

Figure 3 Forest plot for the association between EPHA1 expression and progression-free survival (A), stratified by cancer type (B). EPHA1, ephrin receptor A1.

Table 2 Association between EPHA1 expression and clinicopathological factors in patients with cancer

Characteristic	Number of studies	Number of patients	Pooled OR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Age (old *vs.* young)	6	781	1.17 (0.85–1.62)	0.342	0.0	0.513	Fixed
Sex of patients (male *vs.* female)	5	680	0.95 (0.65–1.39)	0.799	14.7	0.320	Fixed
Tumor grade (high *vs.* low)	7	1022	1.21 (0.63–2.33)	0.561	80.1	<0.001	Random
Tumor stage (high *vs.* low)	6	921	1.16 (0.58–2.33)	0.675	78.1	<0.001	Random
Lymph node metastasis (present *vs.* absent)	6	921	1.28 (0.62–2.65)	0.499	75.2	0.001	Random
TNM stage (high *vs.* low)	4	579	1.85 (0.56–6.09)	0.314	86.6	<0.001	Random

OR, odds ratio; CI, confidence interval; EPHA1, ephrin receptor A1; TNM, tumor-node-metastasis.

Table 3 Association between EPHA1 expression and clinicopathological factors in patients with gastric cancer

Characteristic	Number of studies	Number of patients	Pooled OR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Age (old *vs.* young)	3	481	1.02 (0.69–1.52)	0.917	0.0	0.804	Fixed
Sex of patients (male *vs.* female)	3	481	1.15 (0.74–1.78)	0.539	0.0	0.441	Fixed
Tumor grade (high *vs.* low)	3	481	1.83 (0.80–4.17)	0.153	76.6	0.014	Random
Tumor stage (high *vs.* low)	3	481	1.74 (1.15–2.61)	0.008	35.5	0.212	Fixed
Lymph node metastasis (present *vs.* absent)	3	481	1.88 (1.24–2.87)	0.003	26.8	0.255	Fixed
TNM stage (high *vs.* low)	2	367	4.98 (1.00–24.91)	0.051	82.2	0.018	Random

EPHA1, ephrin receptor A1; OR, odds ratio; CI, confidence interval; TNM, tumor-node-metastasis.

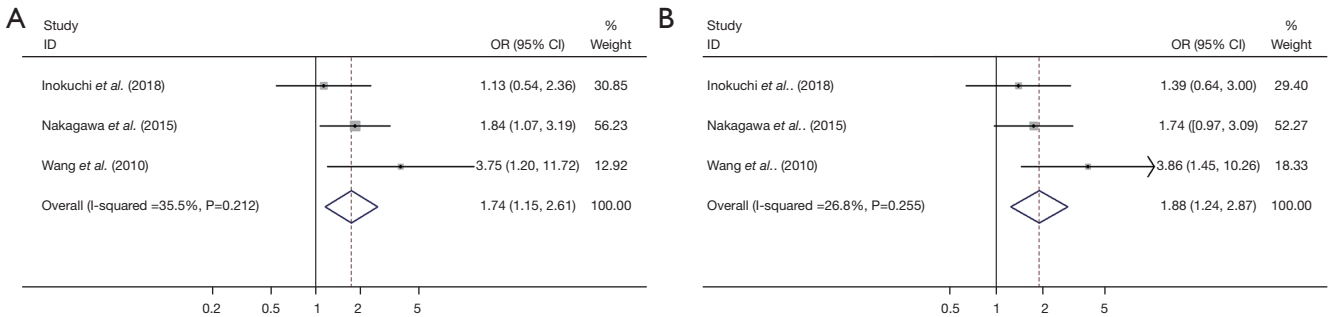

Figure 4 Forest plot for evaluating the association between EPHA1 expression and tumor stage (A) and lymph node metastasis (B) in gastric cancer. EPHA1, ephrin receptor A1.

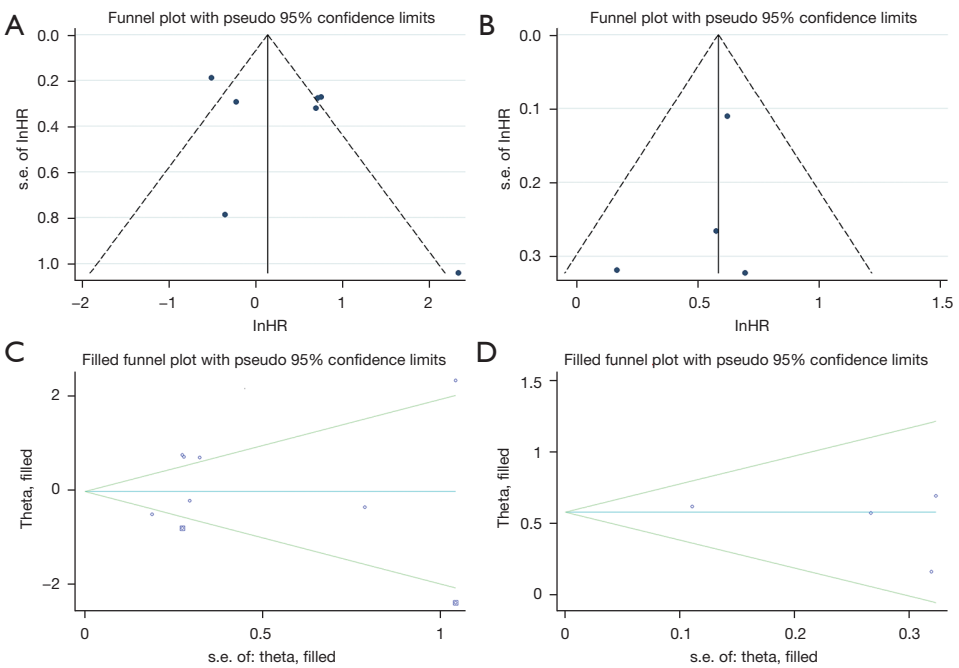

Figure 5 Funnel plot and trim and fill method for the association between EPHA1 expression and overall survival (A,C) and progression-free survival (B,D). EPHA1, ephrin receptor A1.

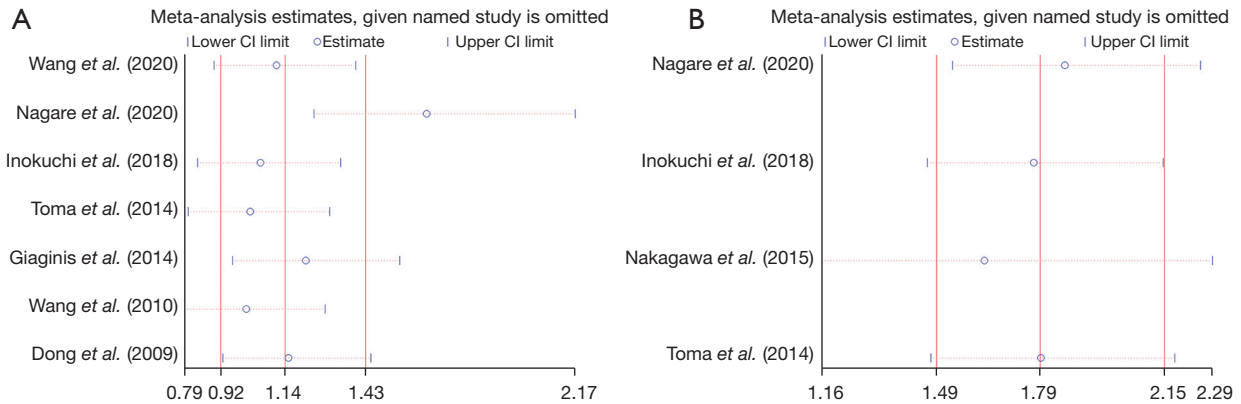

Figure 6 Sensitivity analysis for the association between EPHA1 expression and overall survival (A) and progression-free survival (B). EPHA1, ephrin receptor A1.

the initial pooled results (*Figure 5C*). The results for PFS showed that data did not change (*Figure 5D*).

Sensitivity analysis

For OS, it was confirmed that the study published by Nagare *et al.* (5) had a significant effect on the initial pooled results (HR 1.64, 95% CI: 1.24–2.17) (*Figure 6A*). The pooled results of the sensitivity analysis showed that the HR was decreased and the range of 95% CI was narrowed (HR 1.14, 95% CI: 0.91–1.43) as compared with the initial pooled results (*Figure 6A*).

For PFS, the overall results were the same as the initial pooled results (HR 1.79, 95% CI: 1.49–2.15), although the study published by Nakagawa *et al.* (6) seemed to have an impact (HR 1.63, 95% CI: 1.16–2.29) (*Figure 6B*).

Discussion

EPHA1 is a component of the ephrin receptor, which belongs to the receptor tyrosine kinase family (13). EPHA1 is the first member of the ephrin receptor and it is located on chromosome 7q34 (14). EPHA1 is expressed in various normal tissues such as the intestine, lung, kidney, bladder, and thymus. It is also seen in cancer cells, including colorectal carcinoma, gastric cancer, lung cancer, ovarian carcinoma, renal cell carcinoma, and head and neck squamous cell carcinoma (5-10,12-15). Recent studies have reported that EPHA1 is carcinogenic through interaction with tumor cells as well as interaction with the surrounding tumor microenvironment, and it could also be a potential therapeutic target (10,13,15). Moreover, EPHA1 is known to be closely related to the survival of cancer patients (5-12). Thus, we systematically analyzed the effects of EPHA1 on the survival of cancer patients.

In the present study, we identified eight eligible studies consisting of 1079 patients with cancer to evaluate the association between survival and EPHA1 expression in patients with cancer. Wang *et al.* (10,11) and Inokuchi *et al.* (8) demonstrated that EPHA1 expression was correlated with poor OS in patients with gastric cancer. Toma *et al.* (9) reported the association between EPHA1 expression and unfavorable OS in clear cell renal cell carcinoma. Nagare *et al.* (5), Giaginis *et al.* (7), and Dong *et al.* (12) showed that there was no significant clear link between EPHA1 expression and OS in epithelial ovarian cancer, non-small cell lung cancer, and colorectal cancer, respectively. With respect to PFS, Nagare *et al.* (5), Inokuchi *et al.* (6), Nakagawa *et al.* (6), and Toma *et al.* (9) reported consistent results that EPHA1 expression was closely related to PFS of cancer patients.

In this study, we demonstrated that EPHA1 expression is associated with poor OS in patients with gastric cancer and is related to PFS in patients with cancer. We also found that EPHA1 expression is correlated with higher tumor stage and lymph node metastasis in gastric cancer.

However, this study has a limitation in that the number of small samples and the heterogeneity between the included studies have not been overcome. We hope that further research will be carried out.

In summary, we systematically evaluated the relationship between EPHA1 expression and survival in patients with cancer for the first time. We revealed that EPHA1 expression

was significantly associated with PFS in patients with cancer.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1367/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1367/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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