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Research Paper

Pathologic and prognostic impacts of *FGFR2* amplification in gastric cancer: a meta-analysis and systemic review

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Abstract

Fibroblast growth factor receptor-2 (*FGFR2*) gene is amplified in up to 15% of patients with gastric cancer (GC). However, the prognostic significance of *FGFR2* amplification has been controversial. This meta-analysis was conducted to evaluate the clinicopathological impacts of *FGFR2* amplification in patients with GC. We performed a systematic computerized search of the electronic databases of PubMed, PMC, EMBASE, Web of Science, and Google Scholar and selected studies assessing the correlation of *FGFR2* amplification with pathologic features and/or prognosis in gastric adenocarcinoma. From eight studies, 2,377 patients were included in the pooled analysis of odds ratios (ORs) with 95% confidence intervals (CIs) for pathologic findings and hazard ratios (HRs) with 95% CIs for overall survival. *FGFR2* amplification was significantly associated with LN metastasis (OR = 3.93, 95% CI: 2.22-6.96, p < 0.00001) and poorly differentiated adenocarcinoma (OR = 2.36, 95% CI: 1.03-5.39, p = 0.04). In addition, patients with GC harboring *FGFR2* amplification showed significantly worse survival (HR = 2.09, 95% CI: 1.68-2.59, p < 0.00001), compared with patients with *FGFR2*-unamplified GC. In conclusion, this meta-analysis indicates that *FGFR2* amplification is an adverse prognostic factor in patients with GC.

Key words: *FGFR2* amplification; gastric cancer; prognosis; meta-analysis; review

Introduction

Despite a steady decline in incidence, gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1,2]. Radical surgery with or without perioperative or adjuvant treatment offers a potential chance of cure for patients with early-stage disease. However, a considerable number of patients present with advanced disease at the time of diagnosis. Moreover, more than 60% of the patients who received complete resection with curative intent develop recurrence within five years after surgery [3,4]. For patients with recurrent or metastatic diseases, systemic chemotherapy with best supportive care can prolong median overall survival (OS) from 3-4 months to approximately 10-13 months [5,6]. The combination of trastuzumab with chemotherapy in patients with HER2-positive advanced GC and the addition of ramucirumab to taxane as second-line therapy in non-selective patients with advanced GC demonstrated modest survival benefits [7,8]. Despite the introduction of new molecular targeted agents, however, the five-year survival rate is still less than 10%; therefore, there is a critical need to identify novel therapeutic targets in order to develop more efficacious targeted agents.

The fibroblast growth factors (FGF) pathway has recently emerged as a potential therapeutic target in several types of human cancers including GC [9-12]. The FGF signaling pathway regulates a variety of cellular functions including cell proliferation,

migration, and differentiation [12,13]. The *FGFR2* gene is located on chromosome 10q26 and functions as FGF receptor (FGFR). The genetic alterations of *FGFR2* reportedly enhance downstream signaling and are associated with cancer development and progression [13-15]. In preclinical models of GC, *FGFR2* amplification was associated with increased proliferation and survival of tumor cells and conferred sensitivity to selective molecular agents targeting this pathway [9, 16]. Therefore, *FGFR2* amplification has been proposed as a potential treatment target and predictive biomarker for small molecule tyrosine kinase inhibitors (TKIs) or monoclonal antibodies to FGFR2 [9-11,17].

FGFR2 amplification has been reported in up to 15% of patients with GC [18-26]. Several clinical studies investigated the clinicopathological features of *FGFR2*-amplified GC and found that *FGFR2* amplification was correlated with lymphatic invasion [19,24] or worse prognosis [19-21,24]. However, the data are limited with a small number of patients with *FGFR2*-amplified GC, and other studies have failed to demonstrate the prognostic role of *FGFR2* amplification as an independent predictor in patients with advanced GC [23,26]. Therefore, we performed a meta-analysis to evaluate the pathologic and prognostic impacts of *FGFR2* amplification in patients with GC.

Materials and Methods

Publication search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. We searched the electronic databases of PubMed, PMC, EMBASE, Web of Science, and Google Scholar (up to December 2018) to identify studies assessing the correlation of *FGFR2* amplification with pathologic features and/or prognosis in gastric adenocarcinoma. The search used following keywords variably combined: "fibroblast growth factor receptor 2" or "FGFR2" AND "gastric cancer" or "stomach cancer".

Inclusion criteria

Eligible studies should meet the following inclusion criteria: (i) clinical trials and prospective or retrospective cohort studies investigating the correlation of *FGFR2* amplification with pathologic features and/or overall survival (OS) in patients with gastric adenocarcinoma, including adenocarcinoma of the esophago-gastric junction; (ii) the use of adequate detection methods including fluorescence *in situ* hybridization (FISH) or real-time quantitative polymerase chain reaction (qPCR); (iii) results providing sufficient data for odds ratio (OR) with 95% confidence intervals (CI) for pathologic findings or hazard ratio (HR) along with 95% CI for OS; (iv) publication only in peer-reviewed journals; and (v) articles written in English. If the articles did not accord with any of these inclusion criteria, they would be excluded from the analysis.

Data extraction

All eligible studies were independently selected by two researchers (Kim HS and Jang HJ). The following data were extracted: first author, year of publication, country, study period, sample size, stage, detecting methods and cut-off values for *FGFR2* amplification, data for estimating ORs with their 95% CIs for pathologic features [tumor depth, lymph node (LN) metastasis, and differentiation], and HR with its 95% CI for OS. If studies included cohorts of different ethnic populations, the data were collected separately to be recognized as independent results. When both univariate and multivariate analysis were performed to get the HR for survival, the data from multivariate analysis were extracted preferentially.

Quality assessment

The methodological quality of included studies was scored based on the Newcastle-Ottawa System (NOS) [28]. The scores range from 0 to 9 and studies with a score ≥ 6 were considered to be high quality.

Statistical analysis

The survival outcomes were expressed as time-to-event HRs with 95% CI. The strength of the correlation of pathological features was shown as ORs with 95% CIs. These statistical values were derived directly from the primary publications. When papers did not provide the ORs and HRs with their 95% CIs, the Engauge Digitizer was used to estimate them from the available data and Kaplan-Meier curves, respectively. The RevMan version 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) was utilized to combine the ORs or HRs along with their 95% CIs. The heterogeneity across studies was estimated by the Q statistics and I^2 inconsistency test. The Mantel–Haenszel method (fixed-effect model) was used for pooling homogeneous outcomes ($p \geq 0.1$ and $I^2 \leq 50\%$), and the DerSimonian–Laird method (random-effects model) was selected when significant heterogeneity was observed ($p < 0.1$ or $I^2 > 50\%$).

Outcomes are provided as forest plots with diamonds representing the estimate of the pooled effect. The line of no effect is number one for binary outcomes, which depicts statistical significance if not crossed by the diamond [29]. The OR or HR > 1.0 implies worse pathological features or survival for patients with *FGFR2* amplified GC.

Publication bias was visually evaluated by the funnel plots and then quantified by the Begg's test and Egger's test [30,31]. Two-sided p was considered statistically significant if it was less than 0.05.

Results

Results of search

A total of 162 potentially relevant articles were initially found, but 142 of them were excluded after careful screening of the titles and abstracts. Of the remaining 20 potentially eligible studies, 12 were further excluded by the inclusion criteria. Finally, 8 studies were included in the meta-analysis [19-26]. Figure 1 shows the search flow diagram of this meta-analysis.

Characteristics of the included studies

Table 1 summarizes the main characteristics and pathological findings of the eight included studies. The studies were performed retrospectively and published between 2012 and 2017. Two studies [23,26] involved only patients who had received chemotherapy for advanced or metastatic GC. The studies were conducted mostly in Asian populations (from Korea, Japan, China, and Singapore), and one consisted of 3 cohorts from the United Kingdom (UK), China, and Korea [24]. The NOS scores were more than 7 in all the studies, indicating a good methodological quality.

FISH or real-time qPCR was used to detect *FGFR2* amplification. Most studies using FISH adopted *FGFR2*/CEP10 ≥2 as cut-off for *FGFR2* amplification [19-24]. Frequencies of *FGFR2* amplification in the included studies ranged from 1.8% [21] to 15% [25], depending on the technique used and the cut-point for positivity. Three studies reported *FGFR2* amplification as a potential adverse prognostic factor [19-21]. In the study with 3 cohorts, *FGFR2* amplification showed a significant prognostic role only in the UK cohort [24]. However, the remaining four studies failed to observe statistically significant impact of *FGFR2* amplification on survival in the univariate [22, 25] or multivariate analysis [23, 26].

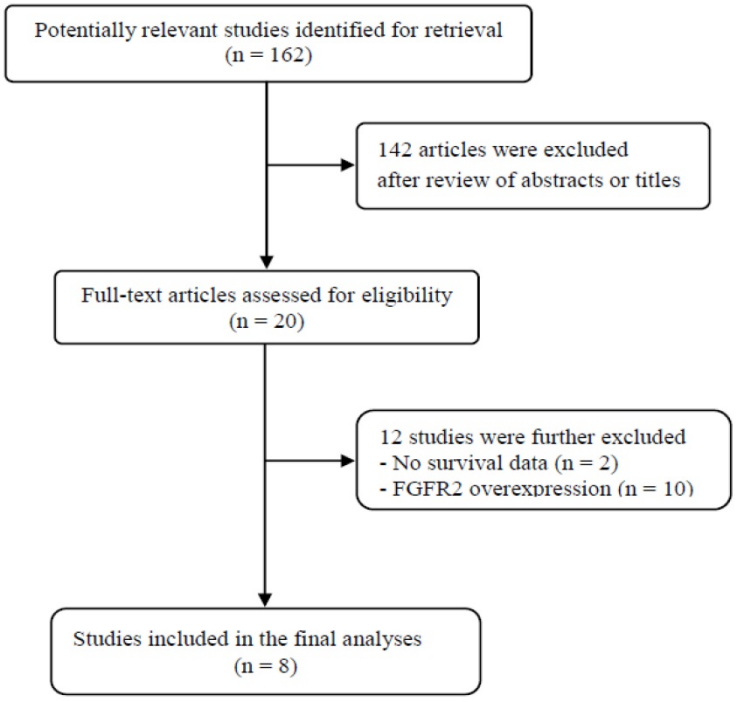

Figure 1. Flow diagram of search process

Impact of *FGFR2* amplification on pathologic features

From five studies [19,20,22,24,15], 1,818 patients were included in the pooling of ORs with 95% CIs for the depth of tumor invasion (pT). There was no significant heterogeneity among studies ($X^2 = 2.72$, $p = 0.61$, $I^2 = 0\%$). *FGFR2* amplification was not significantly associated with tumor invasion (pT3-4) (OR = 1.36, 95% CI: 0.90-2.05, p = 0.14, fixed-effect model) (Figure 2A).

From five studies [19,22-25], 1,612 patients were analyzed for the impact of *FGFR2* amplification on the LN metastasis. There was no substantial heterogeneity across the studies ($X^2 = 4.77$, $p = 0.31$, $I^2 = 16\%$). Compared with tumors without *FGFR2* amplification, *FGFR2*-amplified GCs exhibited higher rate of LN metastasis (OR = 3.93, 95% CI: 2.22-6.96, p < 0.00001, fixed-effect model) (Figure 2B).

From five studies [19,22,24-26], 1,878 patients were included in combining the ORs for tumor differentiation. The random-effects model was selected for pooling heterogeneous outcomes ($X^2 = 9.34$, $p = 0.05$, $I^2 = 57\%$). *FGFR2* amplification were significantly associated with differentiation (poorly differentiated or undifferentiated adenocarcinoma) in GCs (OR = 2.36, 95% CI: 1.03-5.39, p = 0.04) (Figure 2C).

Impact of *FGFR2* amplification on survival

From the eight studies, a total of 2,377 patients were included in the meta-analysis of HRs for OS. Compared with patients with *FGFR2*-unamplified GC, patients with GC harboring *FGFR2* amplification showed significantly worse survival (HR = 2.09, 95% CI: 1.68-2.59, p < 0.00001) (Figure 3A). The fixed-effect model was used because there was no significant heterogeneity among studies ($X^2 = 4.31$, $p = 0.89$, $I^2 = 0\%$).

Table 1. Summary of the eight included studies

First author (year) [ref.]	Country	No. of pts	Inclusion period	TNM stage	Methods	Cut-off	*FGFR2* amplification (%)	Tumor depth (pT3-4) (yes : no)	LN metastasis (yes : no)	Differentiation (PD or UD) (yes : no)	NOS score
Jung (2012) [19]	Korea	313	2004	I-IV	FISH	FGFR2/CEP10 > 2	14 (4.5%)	10 (71%) : 159 (53%) p = 0.032	12 (86%) : 168 (56%) p = 0.038	9 (64%) : 160 (54%) p = 0.452	8
Matsumoto (2012) [20]	Japan	267	1996-2006	I-IV	RT-qPCR or FISH	≥ 5 copies or FGFR2/CEP10 ≥ 2	11 (4.1%)	11 (100%) : 198 (77%) p = 0.16	NA	NA	8
Betts (2014) [21]	UK	171	1995-2004	I-IV	FISH	FGFR2/CEN10 ≥ 2	3 (1.8%)	NA	NA	NA	8
Das (2014) [22]	Singapore	137	1997-2012	I-IV	FISH	FGFR2/CEN10 ≥ 2	10 (7.3%)	4 (50%) : 42 (46%)	7 (88%) : 67 (73%)	8 (89%) : 58 (64%)	7
Shoji (2015) [23]	Japan	61	2005-2013	IV	FISH	FGFR2/CEP10 > 2 or tight gene clusters in > 10% of tumor cells	7 (11.5%)	NA	7 (100%) : 31 (57%) p = 0.04	NA	7
Su (2014) [24]	China, Korea, UK	197 356 408	2007-2010 1996 1970-2004	I-IV	FISH	FGFR2/CEP10 ≥ 2 or gene clusters in > 10% of tumor cells	9 (4.6%) 15 (4.2%) 30 (7.4%)	29 (54%) : 475 (52%) p = 0.567	50 (93%) : 602 (66%) p = 0.000012	43 (80%) : 525 (58%) p = 0.0176	8
Tokunaga (2016) [25]	Japan	140	2000-2014	I-IV	RT-qPCR	> 3 copies	21 (15%)	13 (62%) : 63 (53%) p = 0.689	12 (57%) : 53 (45%) p = 0.286	4 (19%) : 39 (33%) p = 0.305	7
Seo (2017) [26]	Korea	327	2006-2014	IIIB-IV	RT-qPCR	≥ 8 copies	16 (4.9%)	NA	NA	14 (88%) : 190 (62%) p = 0.041	8

FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; RT-qPCR, real-time quantitative polymerase chain reaction; pts, patients; PD, poor differentiation; UD, undifferentiation; NOS, Newcastle-Ottawa System; NA, not available.

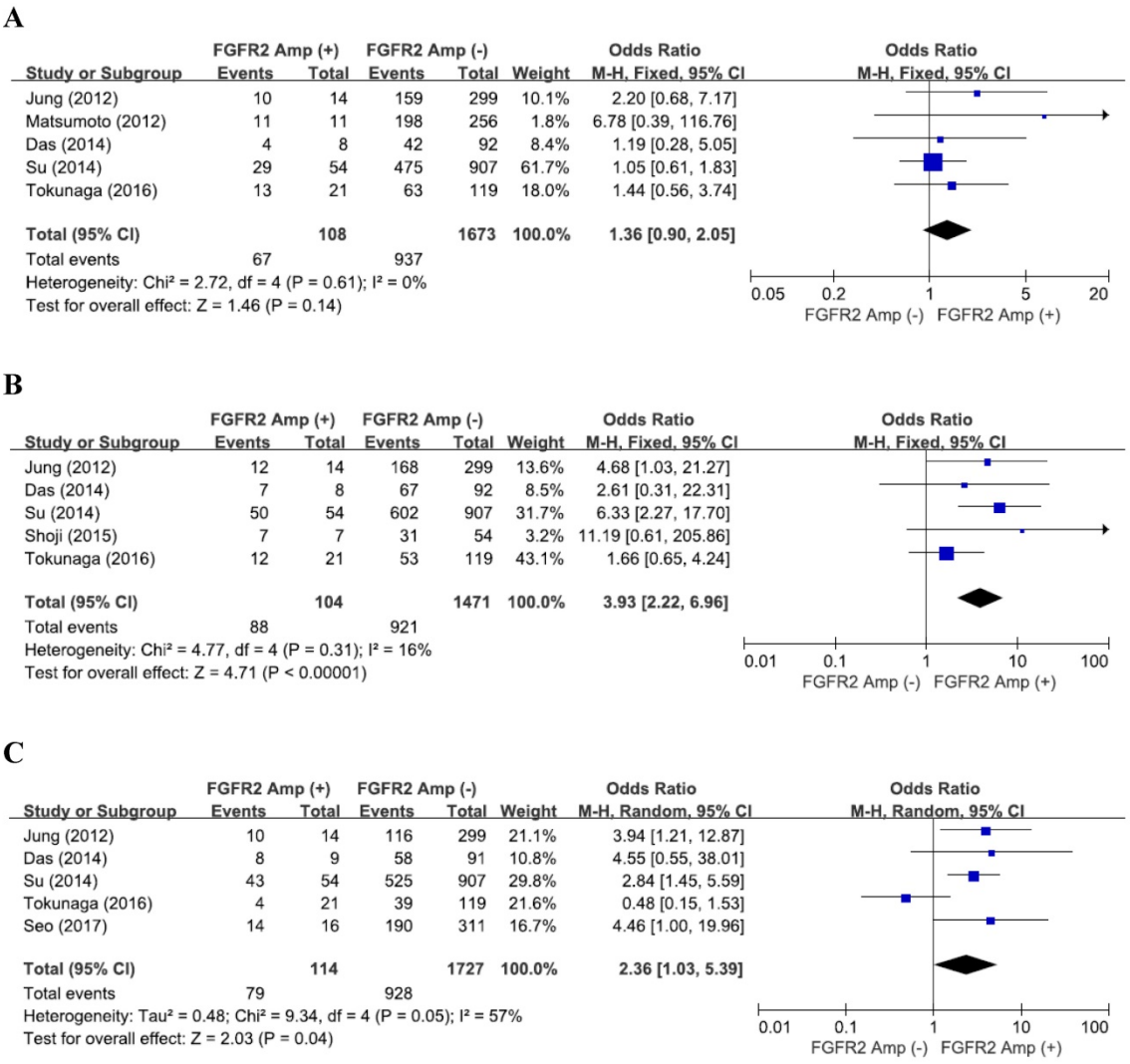

Figure 2. Forest plots of odds ratios for pT3-4 (A), LN metastasis (B), and differentiation (C). *FGFR2* amplification is significantly associated with LN metastasis and differentiation.

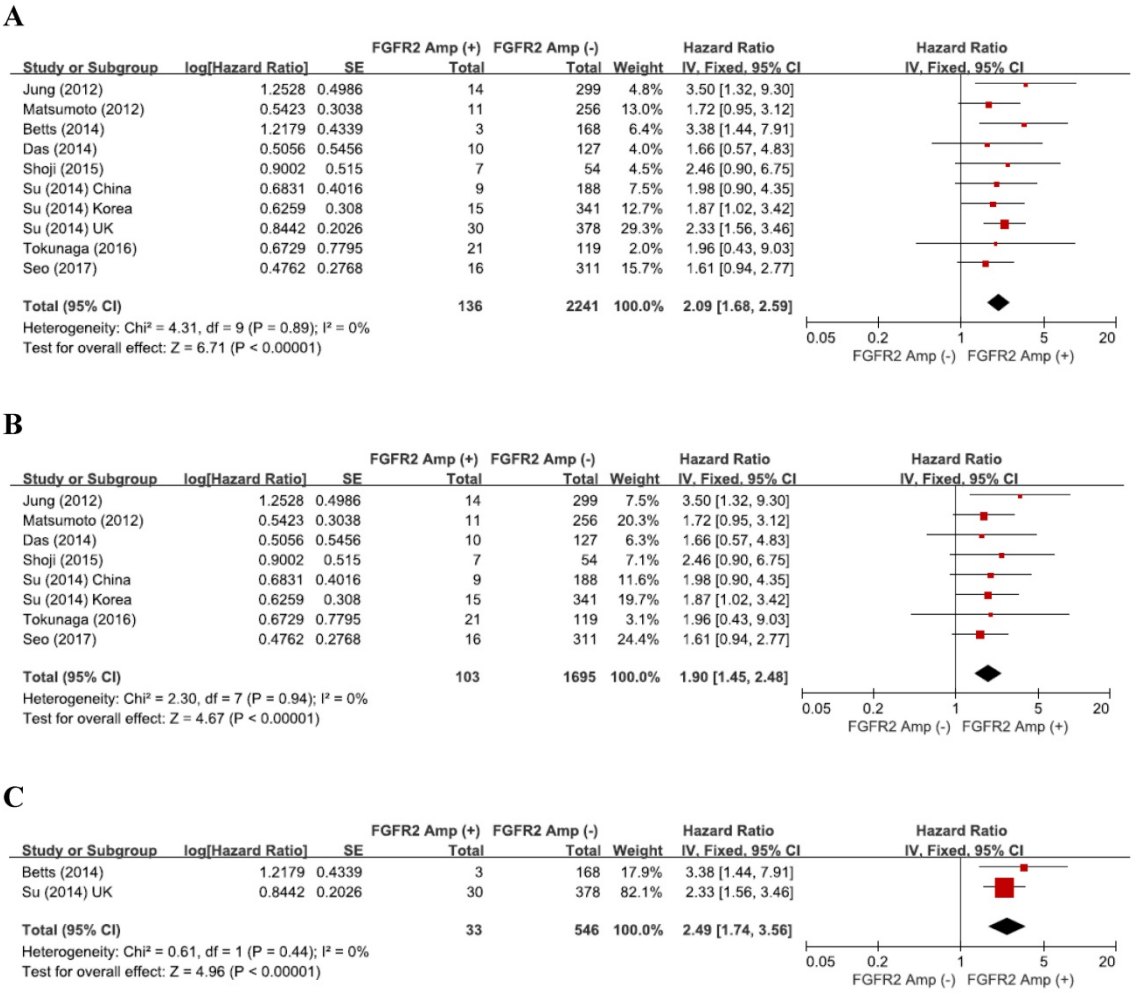

Figure 3. Forest plots of hazard ratios for survival: (A) overall, (B) Asian, and (C) European (UK). *FGFR2* amplification was significantly associated with worse survival, regardless of ethnicity.

The subgroup-analysis according to the ethnicity showed that there was a significant correlation between *FGFR2* amplification and survival in both Asian (HR = 1.90, 95% CI: 1.45–2.48, p < 0.00001, fixed-effect model, Figure 3B) and European patients (HR = 2.49, 95% CI: 1.74–3.56, p < 0.00001, fixed-effect model, Figure 3C).

Publication bias

We did not perform publication bias tests for pathologic findings because a small number of studies were included in the analyses. Begg's funnel plot and Egger's test indicated no evidence of substantial publication bias for OS (Begg's p = 0.210, Egger's p = 0.620) (Figure 4).

Discussion

The FGFR signaling pathway has recently emerged as a potential molecular target for the treatment of advanced GC. However, the prognostic impact of *FGFR2* amplification is still controversial. In the current meta-analysis, we evaluated the pathologic and prognostic significance of *FGFR2* amplification in patients with GC. To our knowledge, this is the first meta-analysis to provide an in-depth analysis of *FGFR2* amplification in relation with prognosis of patients only with GC.

The FGF/FGFR signaling pathway has been involved in tumorigenesis and progression in human cancers including multiple myeloma, cancers of the stomach, breast, bladder, prostate, and endometrium [32]. Mechanisms for genetic alteration of *FGFR2* include gene amplification, mutations, gene fusions, or receptor overexpression. In GC, FGFR2 protein by immunohistochemistry is overexpressed in up to 40%. Although *FGFR2* amplification is significantly associated with FGFR2 overexpression [25], *FGFR2* gene is amplified rarely in GCs [33]. In the included studies of this meta-analysis, frequencies of *FGFR2* amplification varied from 1.8% [21] to 15% [25]. Notably, various laboratory methods, such as real-time qPCR, FISH, chromogenic or silver *in situ* hybridization, can be used for assessing *FGFR2* amplification. Although FISH has been most

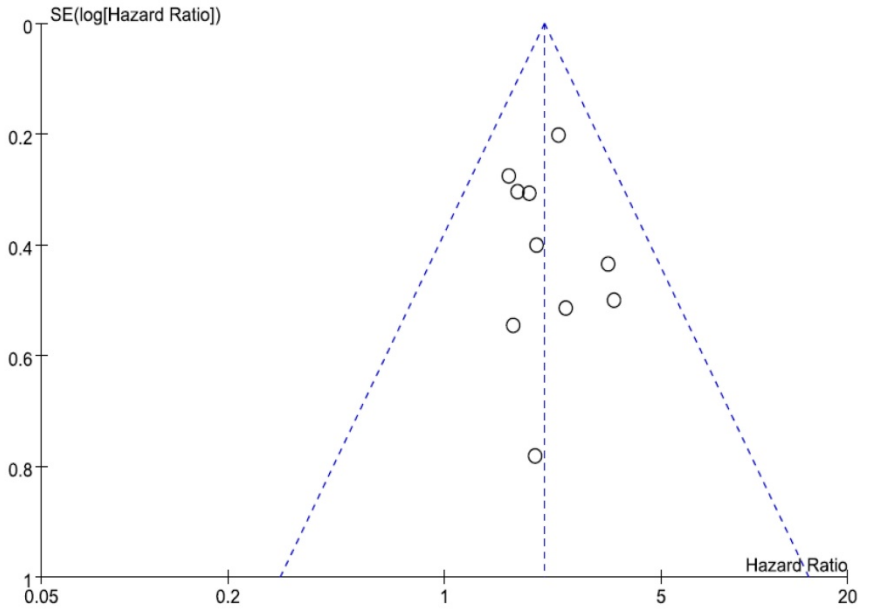

Figure 4. Funnel plot for publication bias regarding overall survival. The symmetry indicated no evidence of substantial publication bias.

commonly used, there is no consensus for the cut-off criteria to define *FGFR2* amplification [33]. These differences in methodology may be the cause of the large range heterogeneity of *FGFR2* positivity and the discrepancies in the prognostic role of *FGFR2* amplification among studies.

The clinical significance of *FGFR2* amplification or receptor overexpression has been investigated in multiple cancers [18-26,33,34]. However, their prognostic impacts in patients with GC remains controversial, as existing studies reported conflicting results with a small number of patients. There are three published papers of meta-analysis which evaluated the prognostic roles of *FGFR2* gene amplification or receptor overexpression in human cancers [33-35]. Chang *et al.* conducted the first meta-analysis to evaluate the prognostic value of *FGFR* (*FGFR1* and *FGFR2*) gene amplification in patients with different types of cancer [33]. Their results revealed that OS was significantly worse among patients with *FGFR1* or *FGFR2* amplification. The subgroup analysis indicated that *FGFR2* amplification was associated with worse survival in patients with GC (HR = 2.27, 95% CI: 1.73-3.00). However, the subgroup analysis used only 3 studies, including one published in abstract from [36]. Liu *et al.* conducted a meta-analysis to examine the prognostic role of FGFR2 protein expression in human cancers and suggested that FGFR2 overexpression was correlated with decreased survival in most solid tumors [34]. However, they pooled together the studies evaluating the prognostic significance of not only receptor overexpression but also *FGFR2* amplification (without separation between protein overexpression and gene amplification). Recently we published the results of the meta-analysis assessing the clinicopathological significance of FGFR2 overexpression in patients only with GC [35]. Tumors showing high FGFR2 expression revealed deeper invasion (pT3-4) (OR = 2.63, 95% CI: 1.70-4.06, p < 0.0001), higher rate of LN metastasis (OR = 1.87, 95% CI: 1.31-2.67, p < 0.0001), and more advanced stage (III-IV) (OR = 1.78, 95% CI: 1.07-2.96, p = 0.03). In addition, patients with FGFR2-overexpressed GC showed worse survival, compared to patients with FGFR2-low tumor (HR = 1.40, 95% CI: 1.25-1.58, p < 0.00001) [35].

In the current study, we systematically evaluated pathological findings and survival data of 2,377 patients from the eight studies assessing *FGFR2* gene amplification in GC samples [19-26]. *FGFR2* amplification failed to show a significant correlation with tumor depth (OR = 1.36, 95% CI: 0.90-2.05, p = 0.14). However, *FGFR2* amplification was significantly associated with LN metastasis (OR = 3.93, 95% CI: 2.22-6.96, p < 0.00001) and poorly differentiated or undifferentiated adenocarcinoma (OR = 2.36, 95% CI: 1.03-5.39, p = 0.04). In addition, patients with *FGFR2*-amplified GC showed significantly worse survival (HR = 2.09, 95% CI: 1.68-2.59, p < 0.00001). In the study with three cohorts (UK, Chinese, and Korean) by Su *et al.* [24], whereas *FGFR2* amplification and polysomy were associated with poor OS in the Korean (1.83 vs. 6.17 years, p = 0.0073) and UK cohorts (0.45 vs. 1.9 years, p < 0.0001), *FGFR2* amplification was an independent marker of poor survival only in the UK cohort (HR = 2.33, 95% CI: 1.56-3.46, p = 0.0002). In our study, however, the subgroup analysis according to the ethnicity revealed that the relationship between *FGFR2* amplification and poor survival was significant in both Asian (HR = 1.90, 95% CI: 1.45-2.48, p < 0.00001) and European (patients from UK) (HR = 2.49, 95% CI: 1.74-3.56, p < 0.00001). These results indicate that *FGFR2* amplification is a potential biomarker of poor prognosis in GC.

There has been a strong rationale for the development of FGFR2 inhibitors in solid tumors [9-12,16,33-35]. GC cell lines harboring *FGFR2* amplification are highly sensitive to FGFR2 inhibitors

in preclinical models [9]. Therefore, *FGFR2* amplification has attracted significant interest as a therapeutic target for *FGFR2*-amplified GC. Although several FGFR TKIs has been under active investigation, only AZ4547 has demonstrated encouraging signs of efficacy among patients with *FGFR2*-amplifed GC so far [37]. AZD4547 is a selective FGFR-1, 2, 3 TKI that has a potent anti-tumor activity [9,38]. AZD4547 induced rapid tumor regression in two *in vivo* models (SNU16 and SGC083) of GC possessing *FGFR2* amplification [9]. In the randomized phase II SHINE study, however, AZD4547 failed to significant improve progression-free survival versus paclitaxel in patients with advanced GC harboring *FGFR2* polysomy or gene amplification [39]. In addition, exploratory biomarker analyses revealed marked intratumoral heterogeneity of *FGFR2* amplification and poor concordance between amplification/polysomy and FGFR2 mRNA expression. Therefore, the potential usefulness of *FGFR2* amplification as a predictive factor for response to FGFR2 targeting therapy remains to be investigated in GC. The mechanisms that cause primary or acquired resistance to FGFR2 inhibitors in GC are unknown. One possible explanation is that other receptor tyrosine kinases (RTKs) can restore the activation of key intracellular signaling pathways despite inhibition of oncogenic kinase, leading to resistance [40]. Actually Chang *et al.* demonstrated that several RTKs, including EGFR, HER3, and MET, activation contributed to AZ4547 hyposensitivity in *FGFR2*-amplified GC cells [41]. In addition, combination of AZ4547 and cetuximab (EGFR monoclonal antibody) showed synergic growth inhibition both *in vitro* and *in vivo*. These results may provide a rationale for a combination strategy with agents targeting FGFR2 and other resistance-enriched RTKs.

Our study has several inherent limitations. First, the included studies showed considerable differences in the detection methods and cut-off criteria for *FGFR2* amplification, tumor stage, treatment, and other demographic or clinicopathological data. Second, the studies were retrospectively performed and therefore might carry the biases of the retrospective design. Finally, the heterogeneity observed among studies could not be completely interpreted although the random-effects model was selected in pooling ORs for differentiation.

In conclusion, this meta-analysis and systemic review summarized the existing data on *FGFR2* amplification and clinical outcomes in patients with GC. The results suggest that *FGFR2* amplification is an adverse prognostic factor in GC. However, large prospective studies using standardized methods based on the homogeneous populations are warranted to validate the prognostic value of *FGFR2* amplification in patients with GC. In addition, the potential usefulness of *FGFR2* amplification as a predictive biomarker for response to FGFR2 inhibitors remains to be investigated.

Competing Interests

The authors have declared that no competing interest exists.

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