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The prognostic values of estrogen receptor alpha and beta in patients with gastroesophageal cancer

A meta-analysis

Dongyun Zhang, MD[a,*], Jianwei Ku, MD[b], Yingjie Yi, MM[c], Junhui Zhang, MM[d], Rongzhi Liu, MM[a], Nianya Tang, MM[a]

Abstract

Background: Published studies have investigated the prognostic roles of estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) in gastroesophageal cancer patients with the controversial results. The aim of the study was to systematically evaluate the impacts of ERα and ERβ on the overall survival (OS) in patients.

Method: Relevant eligible studies were extracted from PubMed, Embase, Web of Science, CNKI and Wanfang databases (from the start date to November 2018) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. HR (hazard ratio) with 95% confidence intervals (CIs) were used to assess the prognostic values of ERα and ERβ for OS in patients.

Results: High ERα expression was associated with poor OS (HR = 1.58, 95% CI = 1.29–1.94, $P < .001$) and ERβ with better OS (HR = 0.56, 95% CI = 0.37–0.83, $P = .004$) in gastroesophageal cancer. Furthermore, unfavorable OS was found in Chinese gastroesophageal patients with higher ERα expression (HR = 1.57, 95% CI = 1.25–1.96, $P < .001$) and better OS with higher ERβ expression (HR = 0.51, 95% CI = 0.31–0.83, $P < .01$) in our subgroup analysis. Meanwhile, worse OS was found in esophageal squamous cell carcinoma (ESCC) patients with high ERα expression (HR = 1.74, 95% CI = 1.33–2.26, $P < .001$), and favorable OS in ESCC with ERβ overexpression (HR = 0.40, 95% CI = 0.31–0.52, $P < .001$). Besides, high ERα expression was associated with lower tumor differentiation in ESCC (OR = 1.64; 95% CI = 1.02–2.64, $P = .04$) and ERβ was linked with better tumor differentiation in gastric adenocarcinoma (GCA) (OR = 0.49; 95% CI = 0.26–0.94, $P = .03$).

Conclusions: ERα and ERβ might serve as potential prognostic biomarkers for gastroesophageal cancer patients. ERα overexpression predicted poor OS and lower tumor differentiation, and ERβ suggested favorable OS and better tumor differentiation. Further related studies should be performed to test these results.

Abbreviations: 95% CIs = 95% confidence intervals, CNKI = China National Knowledge Infrastructure, ERα = estrogen receptor alpha, ERβ = estrogen receptor beta, ESCC = esophageal squamous cell carcinoma, GCA = gastric adenocarcinoma, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, OR = odds ratios, OS = overall survival.

Keywords: estrogen receptor, gastroesophageal cancer, meta-analysis, overall survival

1. Introduction

Gastroesophageal cancer, consists of stomach and esophagus cancers, is one of the most common and leading reasons of tumor related mortality worldwide.[1] Globally, esophageal cancer ranks eighth for cancer incidence and sixth for cancer death, while gastric cancer ranks fourth and second, respectively.[2] Clinically, many patients have locally advanced of metastasis at the diagnosis time, and some patients develop recurrence after treatment.[3] The late detection and rapid progression may be responsible for the higher mortality and lower survival rate following diagnosis. Therefore, the novel treatments and reliable biomarkers are urgent needed for the predictive and prognosis of gastroesophageal cancer patients.

Estrogen performs biological function, including cell growth and differentiation, by binding to their nuclear hormone receptors subtypes i.e., estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ).[4] Several previous studies have reported that estrogen receptor is more than a predictive marker but a prognosis biomarker in cancer with the controversy results.[5–11] Tadahiro et al[5] and our group[6] reported that ERα-positive/ERβ-negative expressions indicate poor overall survival (OS) in patients with

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[a] Department of Basic Medicine, [b] The Second Affiliated Hospital of Nanyang Medical College, [c] Department of Book Cataloguing, [d] Department of Traditional Chinese Medicine, Nanyang Medical College, Nanyang, Henan, China.

[*] Correspondence: Dongyun Zhang, Department of Basic Medicine, Nanyang Medical College, Nanyang, Henan 473061, China (e-mail: zhangdy79@126.com).

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esophageal cancer, especially in esophageal squamous cell carcinoma (ESCC) patients. And it is the same result in gastric adenocarcinoma (GCA) reported by Xu et al.[7] Whereas, Dong et al[8] and Masashi et al[10] suggested that downregulation of ERα and upregulation of ERβ may indicate unfavorable prognosis of ESCC. We performed a comprehensive systematic review and meta-analysis to better understand and evaluate the prognostic values of ERα and ERβ in gastroesophageal cancer, which will be further facilitate the identification of novel therapeutic strategies.

2. Methods

The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Furthermore, the study was conducted by reviewing the published papers, thus, the patients' informed consent and the ethical approval were not supplied.

2.1. Publication searching

The eligible studies published in PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases were searched using the following subject heading terms and keywords (gastroesophageal neoplasm OR gastroesophageal cancer OR esophageal neoplasm OR esophageal cancer OR stomach neoplasms OR gastric neoplasm) AND (estrogen receptors OR estrogen nuclear receptor OR estrogen receptor type I OR estrogen receptor type II) AND (prognosis OR survival OR outcome). The specific strategy for the databases was presented in the Supplementary material 1, http://links.lww.com/MD/D363. Additionally, the reference lists of the relevant studies were also manually screened for potentially eligible studies. The displayed language was limited to English and Chinese.

2.2. Inclusion and exclusion criteria

Inclusion criterions for this meta-analysis were: full text available with cross-sectional study, cohort study or case-control study in gastroesophageal cancer; detection of ER expression in primary tissue samples; OS and/or clincopathological features were investigated; the sufficient relevant data or higher dots per inch of K–M survival curves were available to calculate hazard ratio (HR). Besides, the exclusion standards were: cell or animal studies; case report or review; conference abstracts or comments; no sufficient data.

2.3. Data extraction and quality assessment

Two investigators (Jianwei Ku and Yingjie Yi) independently extracted the data from included studies and the disagreement pointes were resolved by consensus. The following details were extracted: first author name, publication year, patient origin, type of cancer, detection method, number of patients, clinicopathological parameters, effect size, and so on. One study can be evaluated from 3 aspects of selection, comparability, and exposure by the Newcastle–Ottawa Scale (NOS).[12] A maximum of 1 star can be awarded to an article for selection or exposure, and 2 stars for comparability. Thus, 1 study with above to 6 stars was usually considered to be high-quality study.

2.4. Statistical analysis

All statistical analyzes were conducted using the RevMan5.2 and STATA software (version 12.0, STATA Corporation, College Station, TX, USA). 95% confidence intervals (CIs) with Hazard ratio (HR) and/or odds ratios (OR) were combined to evaluate the prognostic and clinicopathologic values. For studies that only offered Kaplan–Meier curves, Engauge Digitizer (version 4.1) was performed to extract the survival data and calculate the estimated HR and 95% CIs according to Tierney method.[13] Heterogeneity was assessed using Cochrane Q test and I^2 measurement.[14] $P < .1$ or $I^2 > 50\%$ indicate a significant heterogeneity. If heterogeneity existed, a random effect model was applied.[15] And if not, the fixed effect model.[16] Sensitivity analysis was performed to further explore the stability of the pooled results. Begg[17] and Egger[18] tests were deemed to quantitatively evaluate the extent of publication bias with P value of less than .05.

3. Results

3.1. literature research and characteristics

A total of 319 articles were identified by electronic search and 36 articles were excluded because of duplication. After reading the titles and abstracts, 207 articles were excluded. 76 possible full texts were carefully reviewed. Finally, a total of 7 eligible publications with 11 retrospective cohort studies involving 1874 patients were included for in-depth quantitative analysis.[5–11] The detailed flow chart was presented in Figure 1. These included literatures published from 2010 to 2017, and the sample sizes ranged from 83 to 866. One literature were from Korea,[11] 2 literatures were from Japan[5,10] and 4 literatures were from China.[6–9] The cancer types of the included studies were ESCC and GCA. Of these 7 articles with 11 studies, 1 article with 2 OS studies was not involved clinicopathologic parameters,[8] other 6 articles with 9 OS studies based on tissue sample to explore the prognostic and clinicopathologic values.[5–7,9–11] The survival index of OS was conducted in all studies. The expressions of ERα and ERβ were measured by immunohistochemistry. The features of included studies were presented in Table 1.

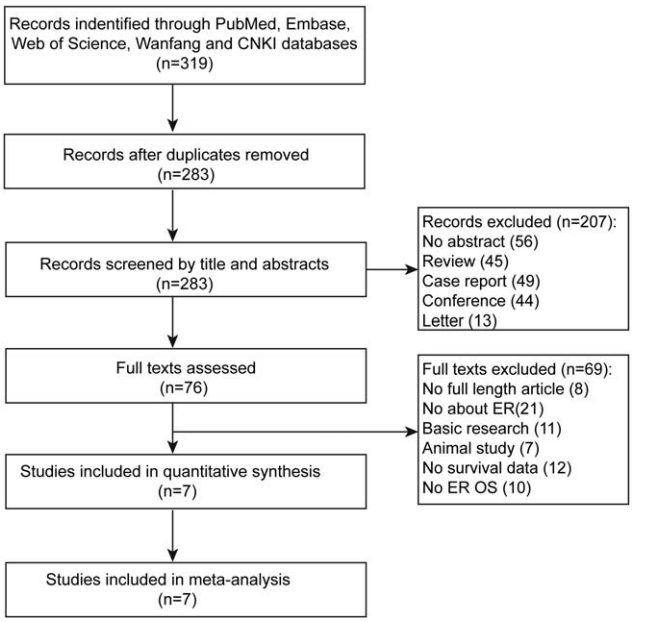

Figure 1. Flow diagram of selection studies.

Table 1

The characteristics of included studies.

First author	Year	Origin	Type of cancer	Sample size	Detection Method	ERα positive (%)	ERβ positive (%)	clinicopathology parameters	Effect size	NOS score
Dong J	2013	China	ESCC	89	IHC	21 (23.6)	87 (97.8)	NR	OS	7
Gan L	2012	China	GCA	866	IHC	848 (97.9)	823 (95.0)	A,B,C,D,E	OS	7
Masashi Z	2012	Japan	ESCC	90	IHC	35 (38.9)	NR	A,B,C,D,E	OS	6
Ryu WS	2012	Korea	GCA	148	IHC	NR	67 (45.3)	A,B,C	OS	7
Tadahiro N	2007	Japan	ESCC	83	IHC	47 (56.6)	21 (25.3)	A,B,C,D,E	OS	7
Xu CY	2010	China	GCA	211	IHC	48 (22.7)	104 (49.3)	A,C,E	OS	8
Zhang DY	2017	China	ESCC	387	IHC	219 (76.3)	208 (53.7)	B,C,D,E,F	OS	8

A = gender, B = tumor invasion depth, C = lymph node metastasis, D = TNM stage, E = tumor differentiation, ESCC = esophageal squamous cell carcinoma, F = tumor location, GCA = gastric adenocarcinoma, IHC = immunohistochemistry, NOS = Newcastle–Ottawa Scale, NR = not reported, OS = overall survival, OS = overall survival.

3.2. Overexpression of ERα and ERβ with prognostic value

All of 6 OS studies concentrated ERα investigation in gastroesophageal cancer,[5–10] 4 studies provided OS for ESCC and 2 studies for GCA. A fixed effect model was used to calculate the pooled HR and 95% CI due to the low heterogeneity ($P = .090$, $I^2 = 48\%$). The result showed that higher ERα expression was associated with poor OS (HR = 1.58, 95% CI = 1.29–1.94, $P < .001$) (Fig. 2A). Additionally, other 5 OS studies reported the prognosis impact of ERβ in gastroesophageal cancer.[5–7,9,11] The pooled HR for OS was 0.56 (95% CI = 0.37–0.83, $P = .004$) with high heterogeneity ($I^2 = 72\%$, $P = .007$) (Fig. 2B).

Subsequently, we conducted subgroup analysis to explore the potential heterogeneity sources. Firstly, subgroup analysis based on geographic area was conducted. Unfavorable OS was found in Chinese gastroesophageal cancer patients with higher ERα expression (HR = 1.57, 95% CI = 1.25–1.96, $P < .001$) and better OS with higher ERβ expression (HR = 0.51, 95% CI = 0.31–0.83, $P = .007$) (Fig. 3A, B). It did not remained statistically significance for patients derived from no-China (Japan and Korea) area irrespective of patients with ERα (HR = 1.73, 95% CI = 0.67–4.44, $P = .26$) or ERβ expression (HR = 0.71; 95% CI = 0.29–1.73, $P = .45$) (Fig. 3C, D).

Additionally, subgroup analysis of OS was also performed based on ESCC and GCA. the pooled HR estimate for OS was 1.74 (95% CI = 1.33–2.26, $P < .001$) for ESCC patients and 1.51 (95% CI = 0.83–2.76, $P = .18$) for GCA patients with higher ERα expression (Fig. 4A, C). Subgroup analysis also suggested the better OS with higher ERβ expression (HR = 0.40, 95% CI = 0.31–0.52, $P < .001$) in ESCC, not in GCA patients (HR = 0.69, 95% CI = 0.41–1.17, $P = .17$) (Fig. 4B, D).

3.3. Overexpression of ERα and ERβ with clinicopathologic parameters

In present study, 1874 tissue samples were collected to detect the expression levels of ERα and ERβ in gastroesophageal cancer. The average expression rates of ERα and ERβ were 70.6%, 67.8% in all studies, respectively. The associations between ERα and ERβ with clinicopathologic parameters including gender, tumor invasion depth, lymph node metastasis, TNM stage, and

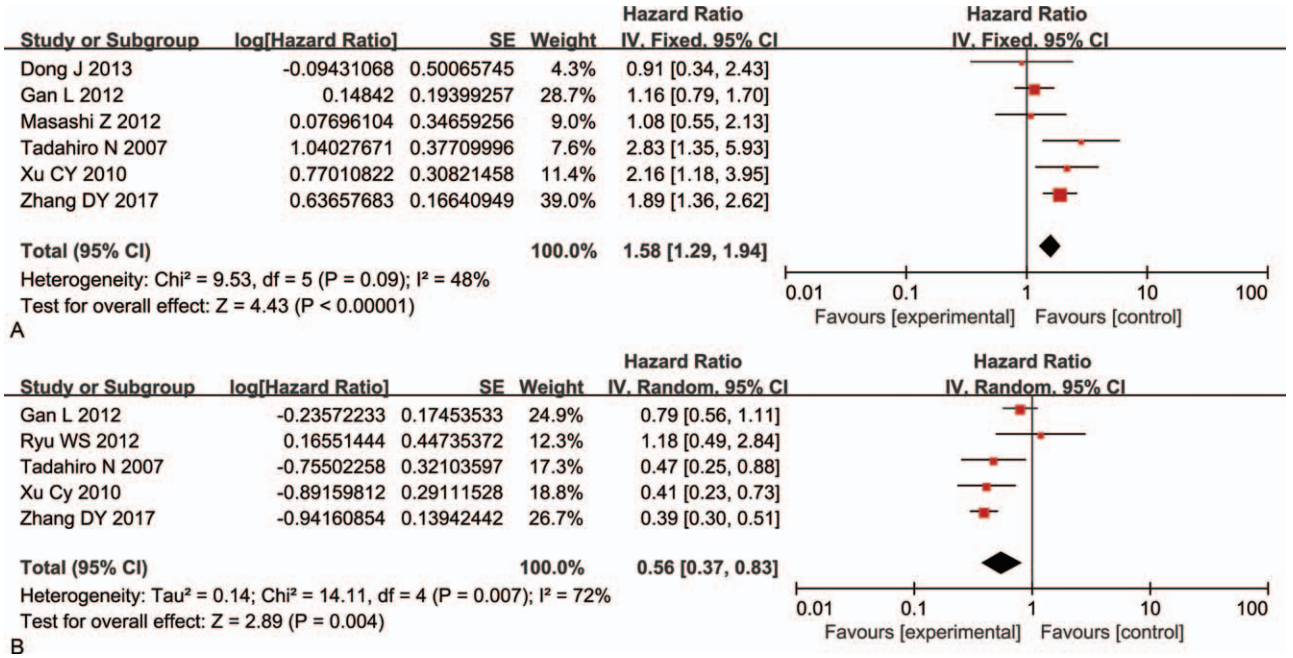

Figure 2. The forest plots for the prognostic values of tissue ERα (A) and ERβ (B) on OS in gastroesophageal cancer patients.

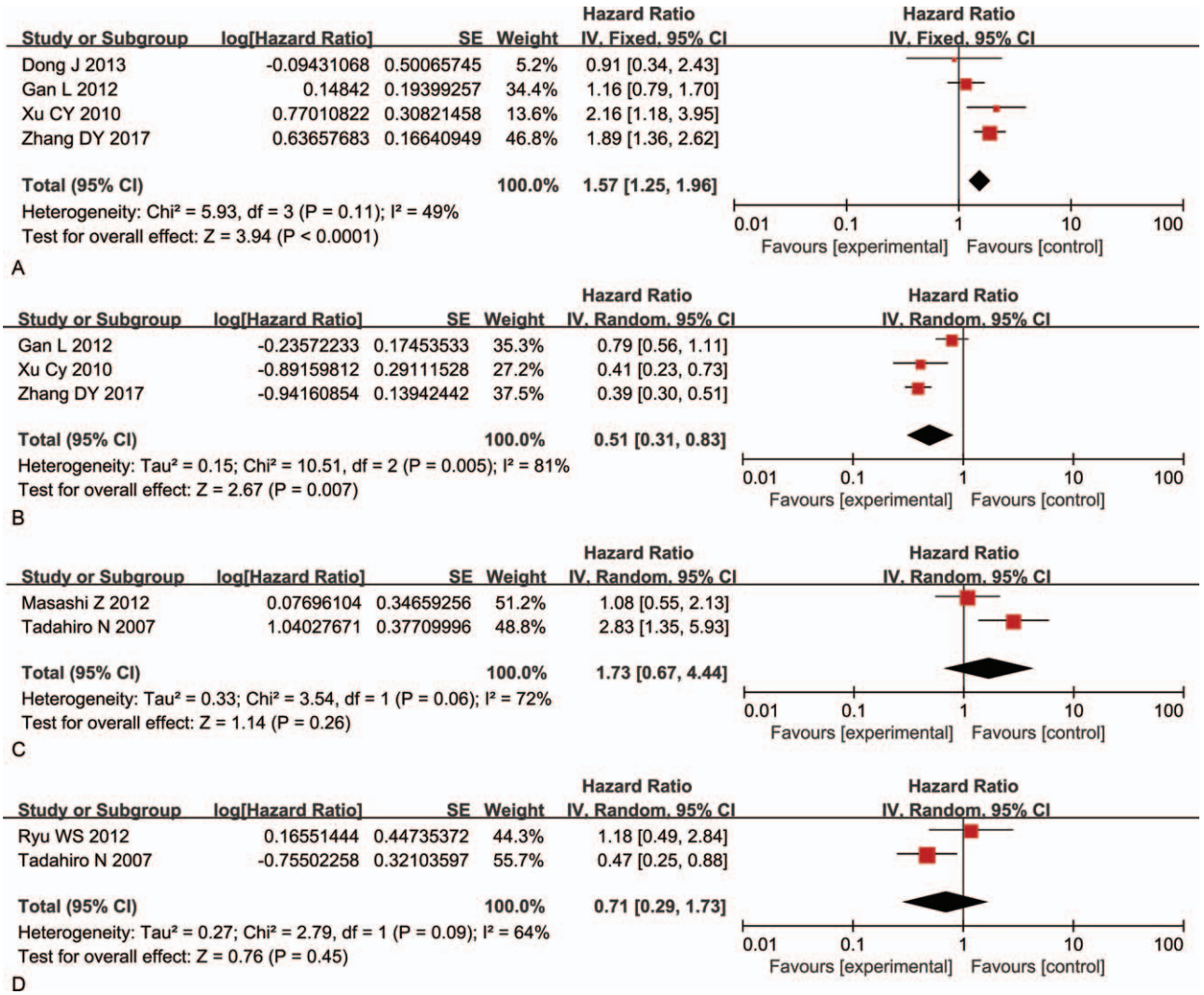

Figure 3. The forest plots for the prognostic values of tissue ERα and ERβ in patients form China (A, B) and non-China (C, D).

tumor differentiation were studied based on ESCC and GCA. Higher ERα expression was linked with tumor low and/or undifferentiation in ESCC (OR = 1.64, 95% CI = 1.02–2.64, $P = .04$). Two studies with 1034 tissues revealed a statistically correlations between high ERβ expression and better tumor differentiation in GCA (OR = 0.49, 95% CI = 0.26–0.94, $P = .03$). No significant association was revealed in other clinicopathologic features (Table 2).

3.4. Publication bias and sensitivity analysis

No obvious asymmetry was presented through the visual assessment of the Begg funnel plots (Fig. 5). Egger test also failed to find the significant bias. Sensitivity analysis was conducted to justify the influence of individual study on the synthetic results of OS. The pooled HR was stable after omitting 1 study each time (Fig. 6).

4. Discussion

The present study included 7 eligible articles with 11 cohort studies and a total of 1874 patients. This was the 1st meta-analysis to estimate the prognostic values of ERα and ERβ in gastroesophageal cancer. Our results revealed that high ERα expression was correlated with worse prognosis whereas ERβ with better OS. ERα overexpression in cancer tissues suggested poor OS and lower tumor differentiation for patients. Furthermore, based on tissue samples from cancer patients, the correlation between higher expression of ERβ and better OS and well tumor differentiation was also statistically significance.

ERα is largely associated with poor prognosis in breast, prostate, ovarian, and endometrial cancer.[19] Studies in ERα knock-out mice found that ERα is required for the onset of mammary tumor development and prostate cancer progression.[20–22] ERβ activation reduces proliferation[23] and angiogenesis in ER-positive breast cancer cell lines and tumor formation in mice.[24] Our results showed that ERα and ERβ expression were also linked with OS in gastroesophageal cancer. One previous study in our laboratory found that ESCC patients with ERα negative (−)/ERβ positive (+) have a better OS than those with ERα (+)/ERβ(+) and ERα (+)/ERβ(-) expression.[6] The role of ERβ in tumor suppression is highly dependent on the co-expression of ERα.[25] ERα and ERβ share 96% homology in the DNA-binding region and 59% in the ligand-binding

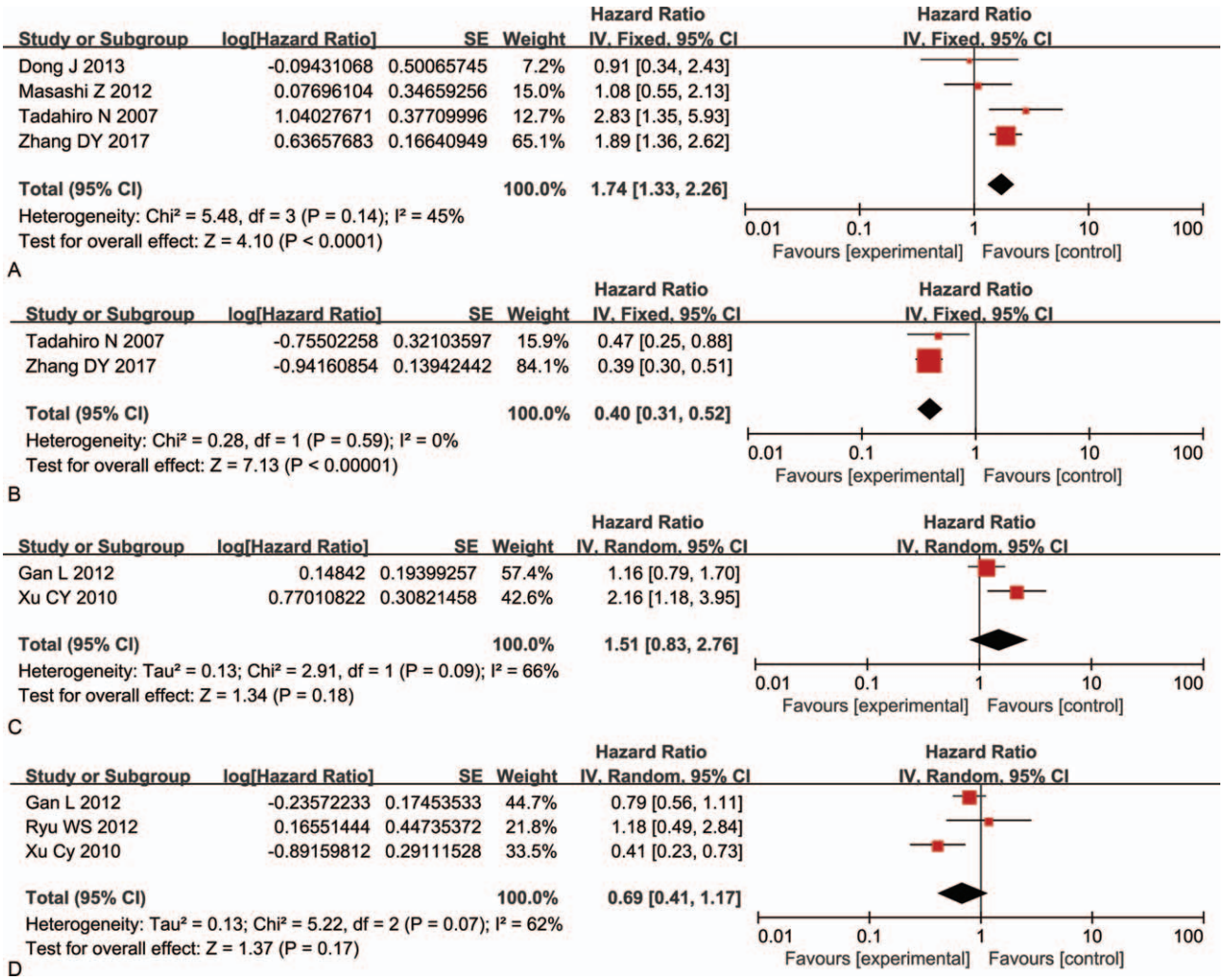

Figure 4. The forest plots for the prognostic values of tissue ERα and ERβ in ESCC (A, B) and GCA (C, D).

Table 2

Subgroup analysis: the association of ERα and ERβ expression with clinicopathologic parameters.

Subgroup type	Variables	No. study	OR (95% CI)	Z, *P* (OR)	Heterogeneity (I^2, *P* bias)	Pooling model
ERα						
ESCC	Gender (male /female)	2	3.77 (0.41–34.69)	1.17, 0.24	67%, .08	RE
	T stage (T3 + T4/T1 + T2)	3	0.65 (0.22–1.95)	0.77, 0.44	84%, .002	RE
	N (positive/negative)	3	0.87 (0.20–3.69)	0.19, 0.85	90%, <.0001	RE
	TNM (III + IV/I + II)	3	1.45 (0.75–2.80)	1.10, 0.27	37%, .20	FE
	differentiation (poor/well)	3	1.64 (1.02–2.64)	2.04, 0.04*	0%, .36	FE
GCA	Gender (male /female)	2	1.16 (0.79–1.71)	0.74, 0.46	0%, .67	FE
	T (T3 + T4/T1 + T2)	1	0.39 (0.26–0.60)	4.36, 0.0001*	NR	NR
	N (positive/negative)	2	0.52 (0.11–2.42)	0.83, 0.40	93%, .0001	RE
	TNM (III + IV/I + II)	1	0.30 (0.20–0.47)	5.41, 0.0001*	NR	NR
	differentiation (poor/well)	2	0.68 (0.10–4.84)	0.39, 0.70	92%, .0003	RE
ERβ						
ESCC	Gender (male /female)	1	0.26 (0.05–1.28)	1.65, 0.10	NR	NR
	T stage (T3 + T4/T1 + T2)	2	1.02 (0.67–1.54)	0.08, 0.94	22%, .26	FE
	N (positive/negative)	2	0.78 (0.53–1.15)	1.24, 0.21	0%, .93	FE
	TNM (III + IV/I + II)	2	1.09 (0.42–2.86)	0.18, 0.86	0%, .82	FE
	differentiation (poor/well)	2	0.45 (0.11–1.82)	1.12, 0.26	61%, .11	RE
GCA	Gender (male /female)	3	1.27 (0.93–1.72)	1.52, 0.13	0%, .76	FE
	T stage (T3 + T4/T1 + T2)	2	0.54 (0.15–1.96)	0.93, 0.35	89%, .003	RE
	N (positive/negative)	3	0.91 (0.67–1.22)	0.52, 0.64	33%, .23	FE
	TNM (III + IV/I + II)	1	0.90 (0.54–1.47)	0.43, 0.66	NR	NR
	differentiation (poor/well)	2	0.49 (0.26–0.94)	2.16, 0.03*	0%, .55	FE

* statistical significance.

CI = confidence interval, FE = fixed effect model, N = lymph node metastasis, OR = odds ratio, RE = random effect model, T = tumor invasion depth.

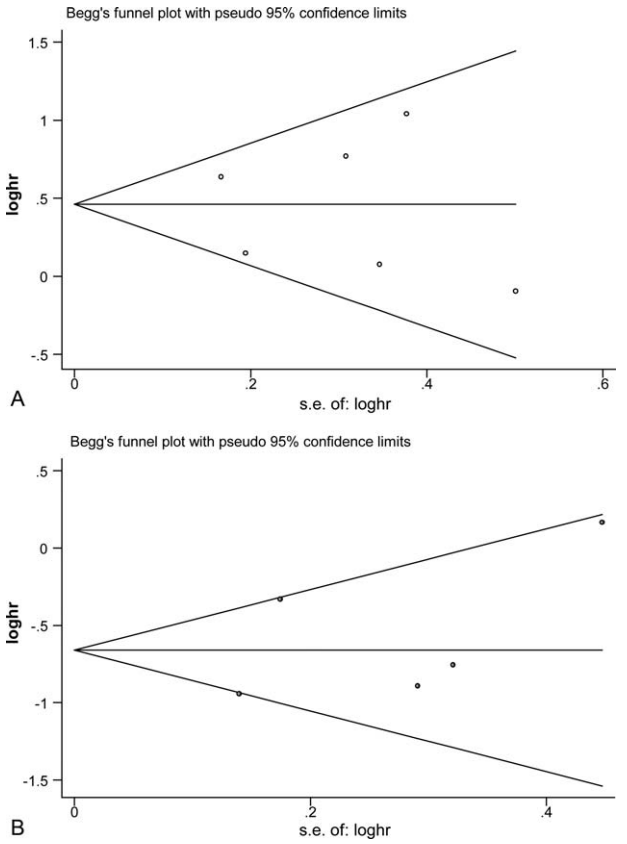

Figure 5. Begg's funnel plot for publication bias of included studies with ERα (A) and ERβ (B).

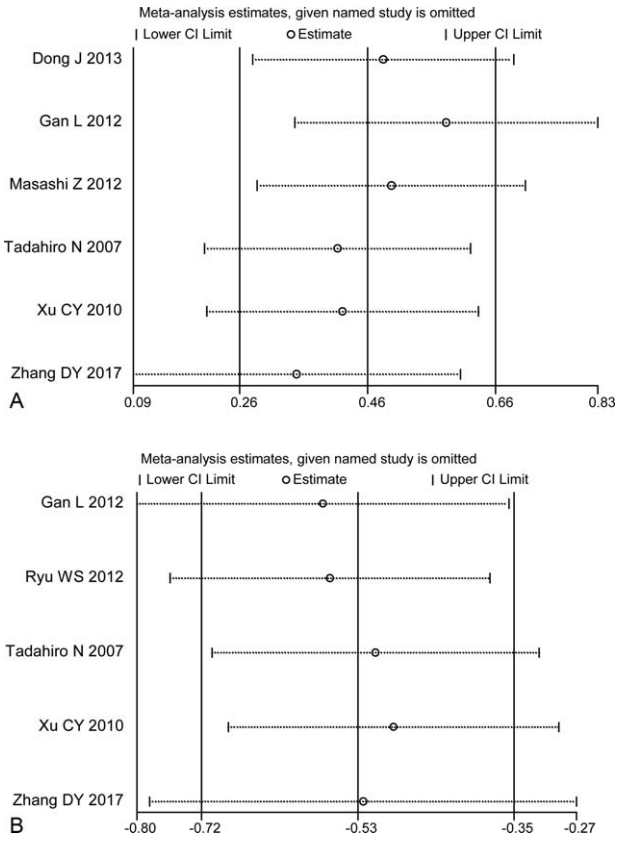

Figure 6. Sensitivity analysis for assessing the influence of individual study for OS in 6 eligible studies related to ERα (A) and 5 studies related to ERβ expression (B).

region.[26,27] However, cell-specific expression patterns of alternatively spliced receptor isoforms play a role in mediating the diverse responsiveness to ligand binding.[28,29] ERβ activation is proliferative in ERα(−) cancers,[30,31] and ERβ is tumor suppressive in ERα positive breast cancer.[32,33]

Subgroup analysis also displayed that ERα was largely associated with unfavorable OS and ERβ with better OS in Chinese patients, which was consistent with the results of overall analysis. No significant associations of ERα and ERβ with OS were observed in non-China patients (Japan and Korea). The results suggested that ethnicity might account for the heterogeneity sources. Another possible reasons may be due to the fact that most of patients were mainly from China, and there were only 17.1% (321/1874) non-Chinese patients which results in the selection bias. Further related research should be conducted in other regions.

Although the present study revealed that the overexpression of ERα and ERβ were linked with prognosis and tumor differentiation for gastroesophageal cancer patients, there were some limitations in the meta analysis. First of all, the quality of included studies is with selection bias due to the deletion of some unqualified literatures. Secondly, the screening of language is only English and Chinese, which could not represent the whole population. Finally, the publication bias could not be completely eliminated due to some unpublished studies with negative or null results.

In conclusion, ERα and ERβ in tissues are tumor biomarkers with prognostic and clinicopathologic values for gastroesophageal cancer, and ERα overexpression predicted poor prognosis, lower tumor differentiation and ERβ expression suggested better prognosis and better tumor differentiation. More related research is required to testify these results.

Author contributions

Data curation: Dongyun Zhang, Jianwei Ku, Yingjie Yi, Nianya Tang.
Formal analysis: Junhui Zhang, Rongzhi Liu.
Investigation: Junhui Zhang.
Methodology: Jianwei Ku, Yingjie Yi, Nianya Tang.
Project administration: Dongyun Zhang.
Resources: Jianwei Ku, Rongzhi Liu.
Software: Yingjie Yi, Junhui Zhang.
Supervision: Dongyun Zhang.
Writing – original draft: Dongyun Zhang.
Writing – review & editing: Dongyun Zhang, Jianwei Ku, Rongzhi Liu, Nianya Tang.

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