Int J Clin Exp Med 2015;8(6):8686-8697
www.ijcem.com /ISSN:1940-5901/IJCEM0008108

Original Article

Overexpression of estrogen receptor beta is a prognostic marker in non-small cell lung cancer: a meta-analysis

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Received March 17, 2015; Accepted June 3, 2015; Epub June 15, 2015; Published June 30, 2015

Abstract: Background: Expression of estrogen receptor beta (ERβ) is a potentially interesting prognostic marker and therapeutic target in non-small cell lung cancer (NSCLC). Although the expression of ERβ has been reported to correlate with better prognosis of NSCLC in most literatures, some controversies still exist. Since the limited patient numbers within independent studies, here we performed a meta-analysis to clarify the correlations between ERβ expression and prognosis in NSCLC. Materials and methods: We performed a final analysis of 2279 patients from 14 evaluable studies for Prognostic Value of overexpression ERβ (up to October 2014). Data from eligible studies were extracted and included into meta-analysis using a random effects model. Studies were pooled. Summary hazard ratios (HR) were calculated. Results: Our study shows that the pooled hazard ratio (HR) of overexpression ERβ for overall survival in NSCLC was 0.78 [95% confidence interval (CI): 0.62-0.98] by univariate analysis and 1.06 (95% CI: 0.70-1.61) by multivariate analysis. Pooled HR in American and Japan was 1.09 (95% CI: 0.95-1.25, *P*=0.239) from 6 studies reported, however, pooled HR was 0.57 (95% CI: 0.46-0.70) outside of American and Japan from 8 studies reported. Pooled HR was 0.75 (95% CI: 0.60-0.94) from 6 studies reported for N-ERβ and 0.76 (95% CI: 0.51-1.12) from 6 Studies reported for C-ERβ. Conclusion: Our results suggested ERβ was significant associated with good overall survival in patients with NSCLC on univariate analysis but not multivariate analysis. ERβ expression is a good prognostic outcome outside of American and Japan. Overexpression of N-ERβ NSCLC patients had better survival. Large prospective studies are now needed to confirm the clinical utility of ERβ as an independent prognostic marker.

Keywords: Estrogen receptor beta (ERβ), non-small cell lung cancer (NSCLC), prognosis, meta-analysis, hazard ratio

Introduction

Lung cancer is the leading cause of cancer-related deaths among males and the second leading cause among females worldwide [1, 2]. In the developing world, the lung cancer epidemic is still spreading and is suspected to have a major impact on public health throughout the coming decades. Clinicians face many difficulties in the management of lung cancer patients. First, few clinical factors are useful for assessing individual prognosis which are insufficient to predict the evolution of each patient. In this scene, it is of high priority to find tumor markers able to identify a subset of patients with prognosis in order to apply an earlier therapy that may have impact on survival. Second, patient survival has been shown to be mainly dependent on the stage of the disease diagnosed, being the rate of incidence practically equal to the rate of death when NSCLC is diagnosed at advanced stages. Growing evidence suggesting that gender and hormonal status may influence the susceptibility and progression of lung cancer [3]. In this regard, some epidemiologic data indicate that women have a higher risk of lung adenocarcinoma compared to men [4]. Many studies have demonstrated that estrogens (ERS) and estrogen signaling play a significant role not only in normal lung

development but also in lung cancer pathophysiology [5, 6]. There is increasing evidence to suggest that estrogens may contribute to the proliferation of lung carcinoma cells [5-7]. In addition to known hormone responsive tissues, ERβ are expressed in normal lung and NSCLC cells [8-11] [Ramchandran, 2009 #5]. The effect of abnormalities expression of ERβ has been investigated for NSCLC by using univariate or multivariate analysis, however, the prognosis value of ERβ overexpression in NSCLC is still controversial mainly because of the limited patient numbers of independent reports. Based on the discordant results obtained by numbers of studies, we conducted this meta-analysis to quantify the prognostic impact of ERβ expression on overall survival among NSCLC patients.

Materials and methods

Literature search

A literature search via PubMed, EMBASE and CNKI (China National Knowledge Infrastructure) databases was conducted to search articles that evaluated the role of ERβ in NSCLC. The keywords and text words were used as follows: (1) estrogen receptor beta or ERβ, and (2) non-small cell lung cancer or NSCLC or lung cancer or lung carcinoma or carcinoma of lung and (3) outcome or survival or prognosis.

Study selection

All languages were included, and all eligible articles that examined the association between the expression of ERβ and overall survival were gathered. However, the papers which only have abstracts were excluded because of insufficient data for meta-analysis. Therefore, we first read the titles of the publications and the abstracts to find exactly those articles that examined the relationship between ERβ and overall survival (OS) in NSCLC patients. After the abstracts met these conditions, the full texts were analyzed and included into our meta-analysis according to the following criteria: (1) an original paper; (2) expression levels of ERβ were compared to patient's overall survival; (3) expression of the proteins were evaluated in tumor tissues by immunohistochemistry (IHC) analysis; (4) studies that reported a hazard ratio (HR) and confidence interval (CI) or could be calculated from the sufficient data; (5) if the same group of patients were used to analyze more than once, the most complete research was selected for our study. The major exclusion criteria were (1) reviews, non-original articles, abstracts and letters; (2) non-ERβ or NSCLC; (3) duplication of a previous publication.

Data extraction

Two reviewers (Zhuang Luo and Rong-rong Wu) independently checked all articles and extracted data in separate databases. The following information was collected from each study: first author's name, type of ERβ, year of publication, ethnicity, sample size, laboratory methodology, cut-off value, and HR with 95% CI. Disagreements were resolved through discussion among the authors.

Statistical analysis

The intensity of relationship between the expression levels of ERβ and overall survival were described as HRs. Overexpression of ERβ indicated good prognosis in patients with NSCLC if HR > 1 with the 95% CI did not overlap 1. From some published papers, HR and 95% CI could be directly obtained by using univariate or multivariate survival analysis. Otherwise, HR and 95% CI were calculated by Kaplan-Meier survival curves using the software Engauge Digitizer Version 4.1 (http://digitizer.sourceforge.net/) and the method presented by Parmar et al. before [12, 13] [Zhang, 2013 #15; Parmar, 1998 #16]. Then, extracted data were utilized to reconstruct the HR and its variance (GraphPad Software, Inc, La Jolla, CA, USA).

The pooled HR corresponding to the 95% CI was used to assess the prognostic value of ERβ in patients. Statistical heterogeneity was tested by Cochrane's Q test (Chi-squared test; Chi^2) and inconsistency (I^2) [14, 15]. If there was no obvious heterogeneity, the fixed-effects model (Mantel-Haenszel method) was used to estimate the pooled HR; otherwise, the random-effects model (DerSimonian and Laid method) was used [13]. We assessed the possibility of publication bias using a funnel plot and tested it with Egger's test [16]. A *P* value less than 0.05 was considered statistically significant. STATA 12.0 (STATA Corp., College, TX) was used to perform statistical analysis.

Results

Seventy-two, 10, 58 articles were retrieved from PubMed, EMBASE and CNKI electronic

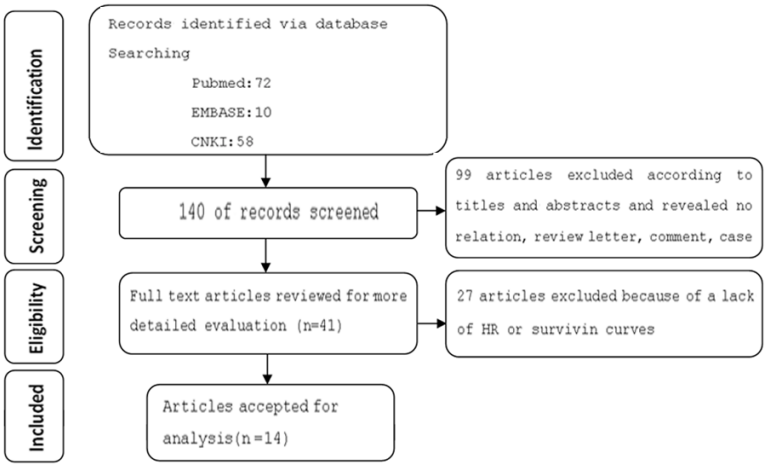


Figure 1. Flow chart summarizing the literature search and study selection.

database according to our defined keywords and text words, respectively (**Figure 1**). Then, via careful reading the abstracts, 41 researches that focused on the association between the expression of ERβ and survival were included in our full-text review process. After reading the full-text researches, 27 papers had to be excluded because data were not extractable or could not provide enough information about overall survival. As a result, 14 eligible studies were included in this meta-analysis. Fourteen studies including 2279 cases were available for our meta-analysis [9, 17-29]. Among all the included studies, the individual Characteristics and results of eligible prognostic studies evaluating surviving are summarized in **Table 1**.

We evaluated whether ERβ expression levels were associated with the overall survival in patients with NSCLC. Of the 14 trials evaluable for systematic review, 14 and 7 could be included in meta-analysis by univariate and multivariate analysis effect of ERβ on overall survival due to sufficient data to estimate the HR and 95% CI. The relationship between ERβ expression and NSCLC prognosis is illustrated in **Figure 2**. Fourteen studies (including a total of 2279 patients) that demonstrated the association of ERβ expression and OS rate were obtained from the published information. According to univariate analysis of ERβ expression and OS rate in fourteen studies (including a total of 2279 patients), with a pooled HR of 0.78 (95% CI: 0.62-0.98, $P = 0.030$, $I^2 = 71.3\%$, random-effect). According to multivariate analysis of ERβ expression and OS rate in seven studies (including a total of 1320 patients), with a pooled HR of 1.06 (95% CI: 0.70-1.61, $P = 0.792$, $I^2 = 86.3\%$, random-effect).

Summarized univariate HR of subgroup analyses for ERβ on NSCLC survival in the **Figures 3** and **4**. When grouped according to the area, pooled HR in American and Japan was 1.09 (95% CI: 0.95-1.25, $P = 0.239$, $I^2 = 45.4\%$, random-effect) from 6 studies reported (including a total of 1301 patients). Although pooled HR outside of American and Japan, was 0.57 (95% CI: 0.46-0.70, $P = 0.239$, $I^2 = 0.0\%$, random-effect) from 8 studies reported (including a total of 978 patients). In the subgroup analysis according to antibody type of ERβ the combined HR was were 0.75 (95% CI: 0.60-0.94, $P = 0.011$, $I^2 = 26.0\%$, random-effect) from 6 studies reported (including a total of 1186 patients) for nuclear estrogen receptor β (N-ERβ) and 0.76 (95% CI: 0.51-1.12, $P = 0.162$, $I^2 = 75.9\%$, random-effect) from 6 studies reported (including 1093 patients in total) for cytoplasmic estrogen receptor β (C-ERβ).

Publication bias statistics were determined by the method of Begg's test (**Figure 5**) between ERβ expression and NSCLC prognosis. The association between ERβ expression and the OS in NSCLC patients had no significant publication bias existed (All $P > 0.05$). In all studies, no funnel plot asymmetry was found Sensitivity analysis was performed to investigate the effect of every study on the overall meta-analysis by omitting one study each time, and the omission of any study made no significant difference, demonstrating that our results were statistically reliable.

Discussion

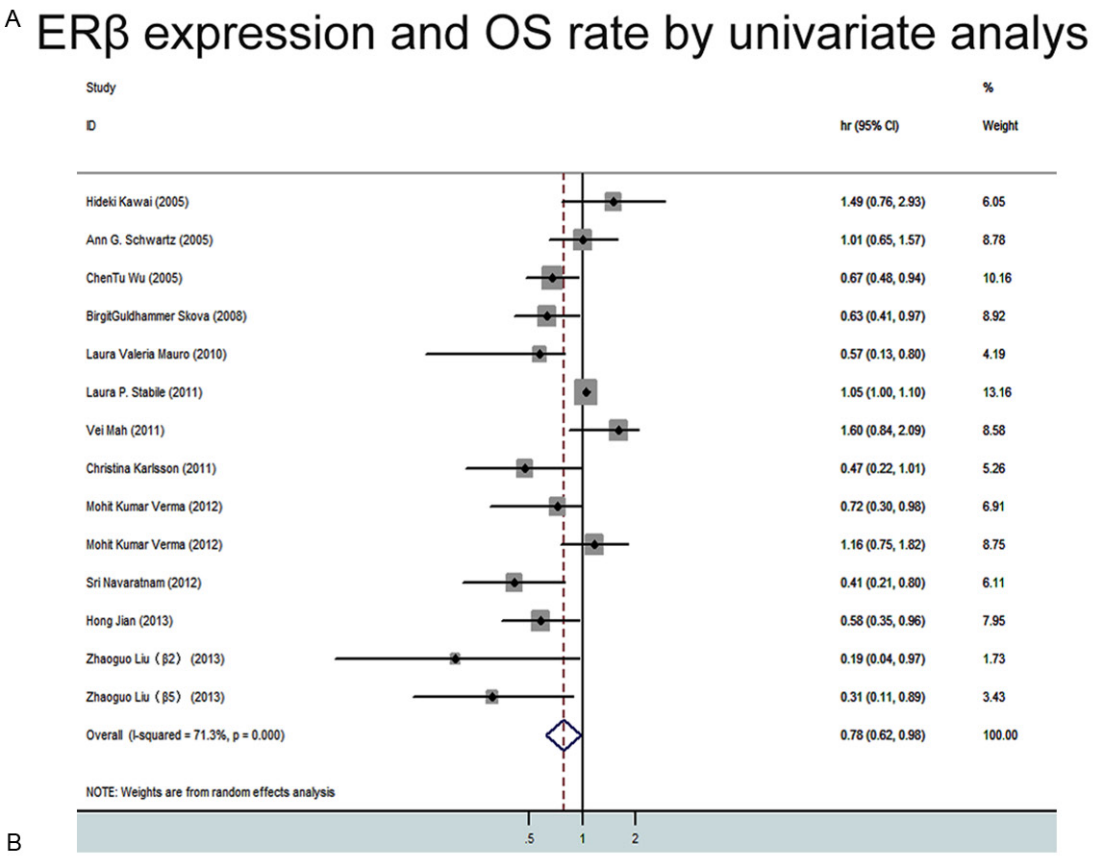
Although there have been a number of studies investigating the expression of ERβ in NSCLC [18, 30], the results remain inconclusive, and the relationship between ERβ expression and prognosis remains unclear. For procuring a reasonable conclusion, we combined 2279 patients from 14 evaluable studies for prognostic value to perform this meta-analysis. Our

Table 1. Individual Characteristics and results of eligible prognostic studies evaluating survival

First Author	ERβ type	Year	Ethnicity	Case	Method	Follow up time (months)	Cutt off value	Univariate HR AND 95% CI		Mutivariate HR AND 95% CI		Smoking Y/N	SCC/ADC/others
Hideki Kawai	N-ERβ	2005	Japan	132	IHC	60	≥5 score	1.49	0.76-2.93	1.9	1.1-3.4	71/61	28/102/2
Ann G. Schwartz	N-ERβ	2005	American	278	IHC	50	≥10%	1.01	0.65-1.57	NA	NA	247/30	13/231/35
Chentu Wu	N-ERβ	2005	Taiwan	301	IHC	180	≥50%	0.672	0.48-0.95	0.719	0.50-1.03	290/11	90/194/17
Birgit Guldhammer Skova	N-ERβ	2008	Denmark	104	IHC	180	≥10%	0.63	0.41-0.97	0.77	0.59-0.98	NA	56/40/8
Laura Valeria Mauro	N-ERβ	2010	Argentina	58	IHC	120	≥10%	0.57	0.13-0.8	NA	NA	41/16	18/33/6
Laura P. Stabile	C-ERβ1	2011	American	183	IHC	55	>7 score	1.05	1.0-1.1	1.67	1.14-2.14	157/26	62/103/18
Vei Mah	C-ERβ	2011	American	377	IHC	120	>3 score	1.6	0.84-2.09	2.17	1.46-3.21	330/47	93/226/58
Christina Karlsson	C-ERβ2	2011	Sweden	68	IHC	60	>30%	0.47	0.22-1.01	NA	NA	42/13	0/68/0
Mohitkumar Verma	N-ERβ	2012	Japan	169	IHC	140	>10%	0.721	0.3-0.98	NA	NA	NA	36/129/4
Mohitkumar Verma	C-ERβ	2012	Japan	162	IHC	140	≥10%	1.16	0.75-1.82	NA	NA	NA	38/40/4
Sri Navaratnam	C-ERβ1	2012	Canada	79	IHC	36	>60 score	0.41	0.21-0.80	0.4	0.20-0.79	NA	NA
Hong Jian	N-ERβ	2013	China	144	IHC	50	≥10%	0.58	0.35-0.96	0.819	0.43-1.56	0/144	24/109/11
Zhaoguo Liu	C-ERβ2	2013	China	112	IHC	40	>3 score	0.19	0.04-0.97	NA	NA	52/60	54/58/0
Zhaoguo Liu	C-ERβ5	2013	China	112	IHC	40	>3 score	0.31	0.11-0.89	NA	NA	52/60	54/58/0

Abbreviation: P/N, positive expression/negative expression; IHC, immunohistochemistry; SCC, squamous cell carcinoma; ADC, adenocarcinoma; HR, hazard ratio; NA, no available or no applicable; Smoking Y/N, smoking/no smoking.

A



B

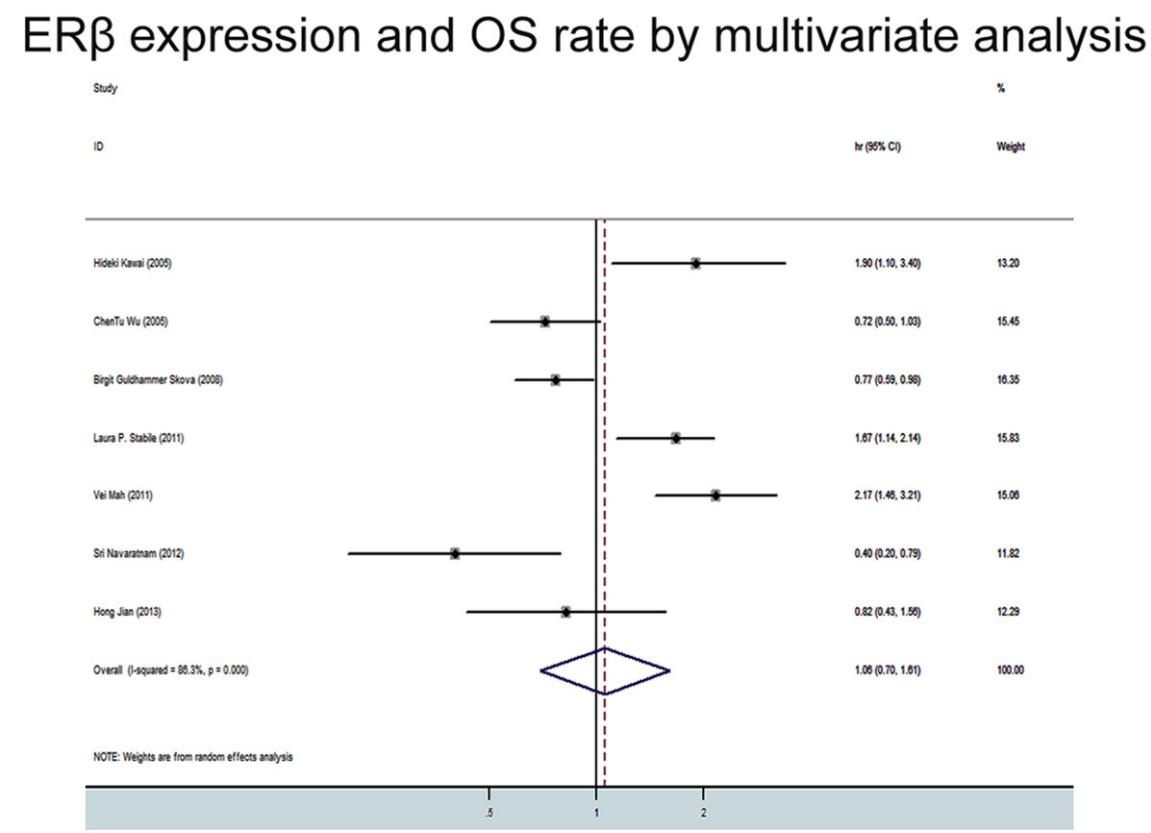
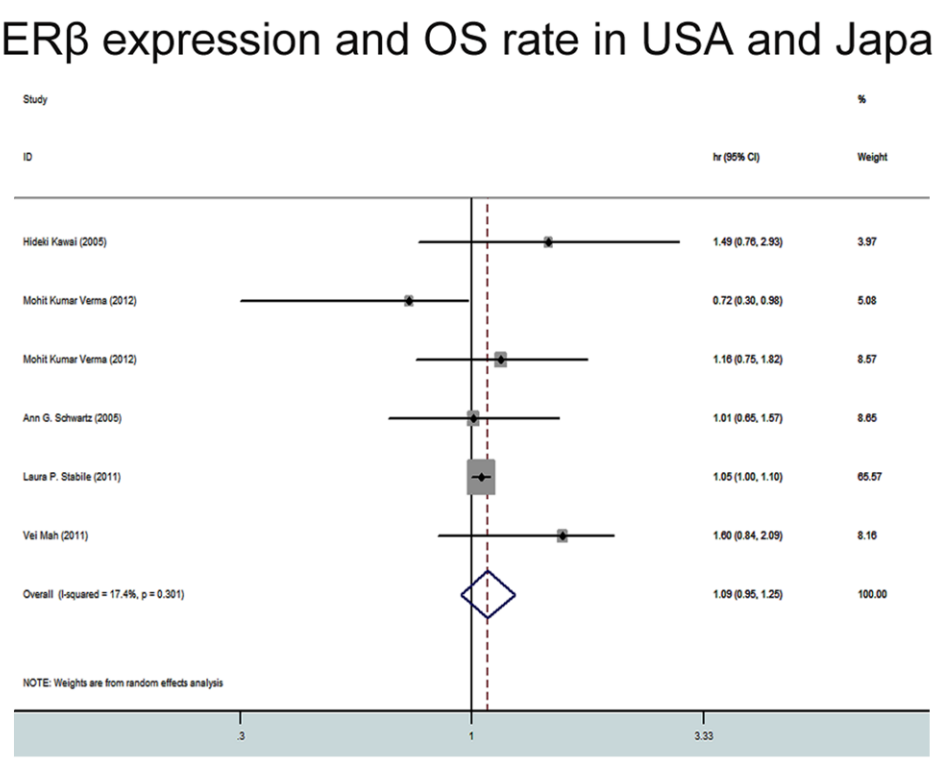


Figure 2. Forest plot showing the combined relative HR from the random-effects model for overall survival by univariate and multivariate analysis such as (A), ERβ expression and OS rate by univariate analysis (B), ERβ expression and OS rate by multivariate analysis.

A



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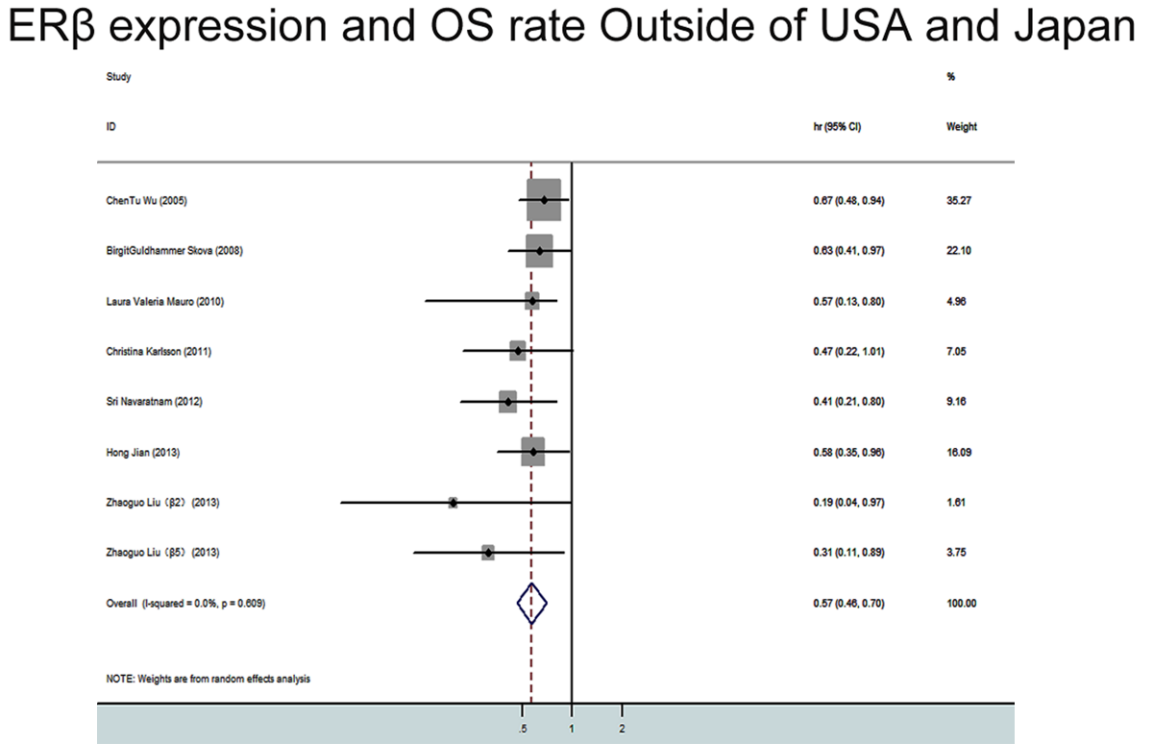
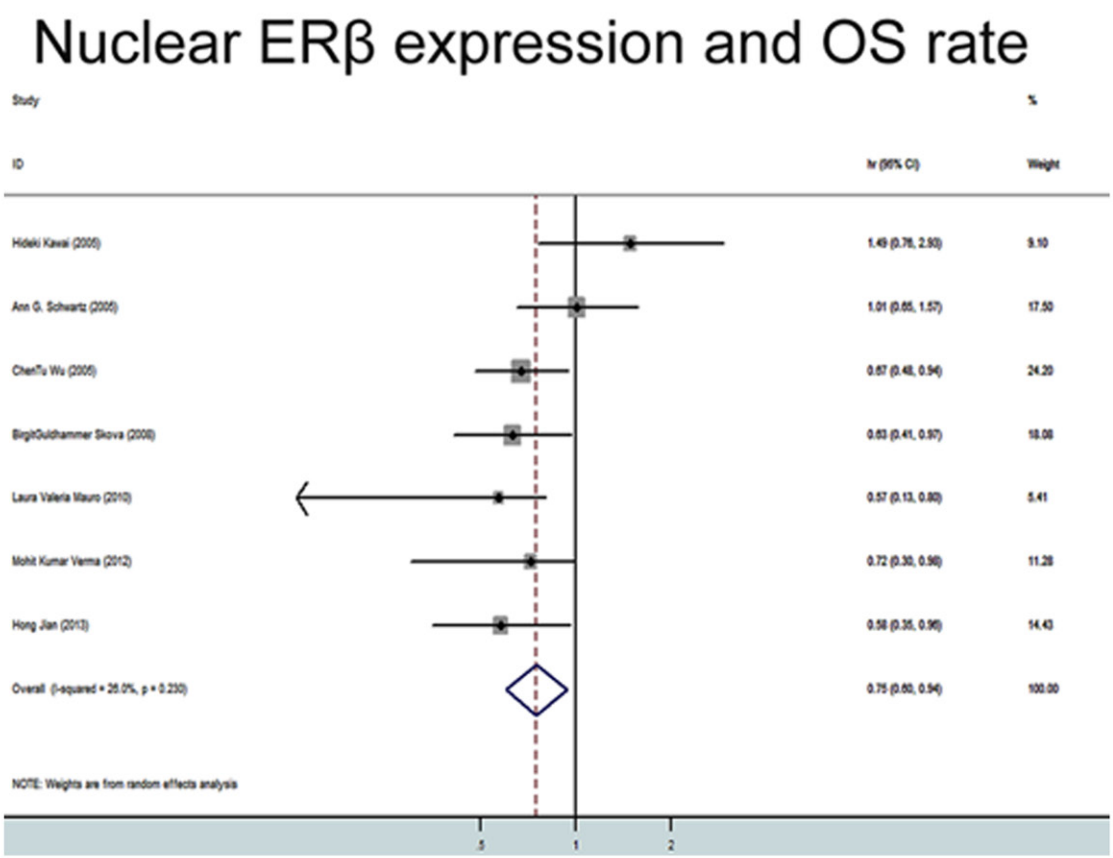


Figure 3. Forest plot showing the combined relative HR from the random-effects model for overall survival in subgroup analyses according to district by univariate analysis such as (A), ERβ expression and OS rate in American and Japan (B), ERβ expression and OS rate outside of American and Japan.

results suggested ERβ was significant associated with good overall survival in patients with NSCLC on univariate analysis but not multivariate analysis. In subgroup analyses we found

A


Nuclear ERβ expression and OS rate
Study
ID
hr (95% CI)
%
Weight
Hideki Kawai (2005)
1.49 (0.76, 2.93)
9.10
Ann G. Schwartz (2005)
1.01 (0.65, 1.57)
17.50
ChenTu Wu (2005)
0.67 (0.48, 0.94)
24.20
BirgitGuldhammer Skova (2008)
0.63 (0.41, 0.97)
18.08
Laura Valeria Mauro (2010)
0.57 (0.13, 0.80)
5.41
Mohit Kumar Verma (2012)
0.72 (0.30, 0.98)
11.28
Hong Jian (2013)
0.58 (0.35, 0.96)
14.43
Overall (I-squared = 26.0%, p = 0.230)
0.75 (0.60, 0.94)
100.00
NOTE: Weights are from random effects analysis
.5
1
2

B

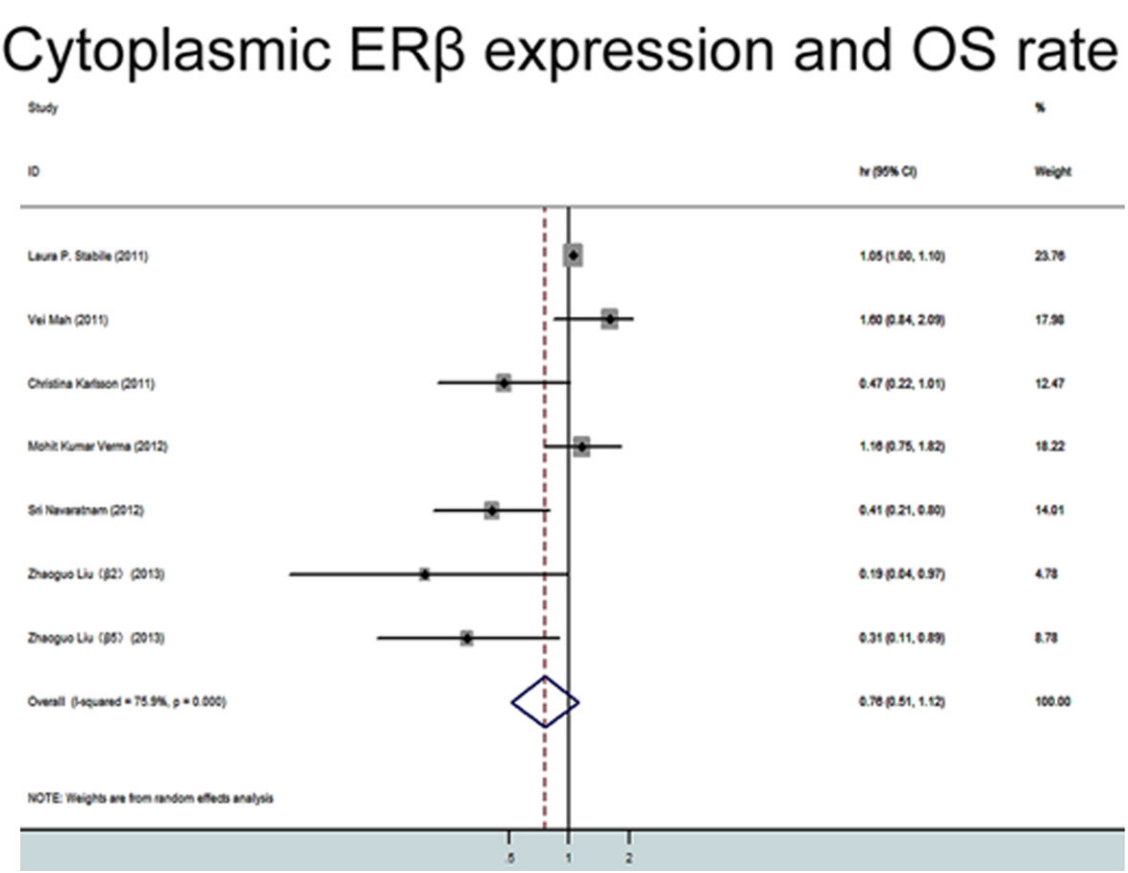

Cytoplasmic ERβ expression and OS rate
Study
ID
hr (95% CI)
%
Weight
Laura P. Stabile (2011)
1.05 (1.00, 1.10)
23.76
Vei Mah (2011)
1.60 (0.84, 2.09)
17.96
Christina Karlsson (2011)
0.47 (0.22, 1.01)
12.47
Mohit Kumar Verma (2012)
1.16 (0.75, 1.82)
18.22
Sri Navaratnam (2012)
0.41 (0.21, 0.80)
14.01
Zhaoguo Liu (β2) (2013)
0.19 (0.04, 0.97)
4.78
Zhaoguo Liu (β5) (2013)
0.31 (0.11, 0.89)
8.78
Overall (I-squared = 75.9%, p = 0.000)
0.76 (0.51, 1.12)
100.00
NOTE: Weights are from random effects analysis
.5
1
2

Figure 4. Forest plot showing the combined relative HR from the random-effects model for overall survival in subgroup analyses according to antibody type of ERβ by univariate analysis such as (A), N-ERβ expression and OS rate (B), C-ERβ expression and OS rate.

that ERβ expression was a good prognostic outcome outside of American and Japan, however, ERβ expression maybe is a poor prognostic outcome in American and Japan.

Recently conflicting reports were published where in one report it was demonstrated that neither C-ERβ nor N-ERβ was a predictor of survival in NSCLC patients [23]. Whereas in the other reports C-ERβ was demonstrated as an important predictor of poorer survival in NSCLC patients [17, 18]. There are reports of N-ERβ as a positive prognostic factor for lung cancer [9, 21, 24, 28, 31]. The status of N-ERβ was reported to be associated with better clinical outcome among NSCLC patients [9, 28]. This is in contrast with both in vitro and in vivo studies in NSCLC cell lines demonstrating tumor promoting features of ERβ particularly through a non-genomic pathway via C-ERβ [32, 33]. We also have collected the information about the relationship between the N-ERβ and c-ERβ expression and OS. Survival of meta-analysis reveals over-expression of N-ERβ NSCLC patients had better survival. However, C-ERβ expression did not predict survival.

There are few therapeutic options available for NSCLC patients. Previous studies had suggested that hormone therapy may be a useful new strategy for the treatment of NSCLC [8]. The absence of ERβ expression was each associated with poor prognosis. In particular, the absence of ERβ was found to be an important indicator that could serve as a marker identifying patients at high risk even at an early clinical stage I [34]. Previous studies support the selection of ERβ as possible prognosis biomarkers. It is nowadays accepted that estrogens are relevant in the homeostasis of the lung and may have a role in initiating and maintaining the growth of NSCLC [35].

Extensive evidence has showed that estrogens and ERs played important roles in tumor progression. Steroid hormones can modulate physiological cellular functions and modulate tumor progression among the key molecules. They are mediated by specific receptors, which regulates the expression of genes involved in cell proliferation, apoptosis, invasion, metastasis and angiogenesis [36]. There are two estrogen receptors, including ERα and ERß. They can induce different biological responses, regulating gene expression in classical and non-classical ways [37]. Estrogens and ERs play important roles in regulating differentiation and growth of various tissues by acting through potentially two different ligand-activated mechanisms. One mechanism involves binding of a ligand to ERα or ERβ nuclear receptors that stimulates a conformational change in the receptor, inducing an alteration of transcription through binding to the estrogen-response element or to transcription factors in the promoter regions of target genes [38]. Unlike ERα or ERβ has been shown to decrease overall transcriptional activity, but can also function as a transcriptional activator at increased estradiol levels [39]. Research shows that estradiol promotes an association between ERβ and GRIP1/TIF2 co-activators that regulates gene expression and promotes cell growth in NSCLC cell lines [40]. Cross-talk between ERs and growth factor receptor–mediated pathways in the plasma membrane is a potential second mechanism [41]. A study by Yu et al. [42] about cell growth of pulmonary lymphangioleiomyomatosis cells via ERα and ERβ mechanisms indicate that estradiol and tamoxifen citrate stimulate both genomic events, through increased expression of c-myc, and nongenomic events, through rapid cytoplasmic activation of p44/42 mitogen-activated protein kinase. In addition, functional interactions between ERβ and epidermal growth factor receptor have been proved [43]. An epidermal growth factor receptor–dependent induction of phospho-p44/p42 mitogen-activated protein kinase was reported in response to estrogen in NSCLC cell lines expressing ERβ. Epidermal growth factor receptor protein is up-regulated in response to antiestrogens and down-regulated by estrogen in these same cell lines also reported by Stabile et al [43].

ERs are concentrated in caveolae and lipid rafts, regions highly enriched with critical signaling molecules as EGFR and HER2 [44], and growth factor signaling pathways can be activated by membrane-initiated steroid signaling activity [45, 46]. Thus, in tumor progression, estrogens could be acting as a dominant factor by activating multiple pathways important in

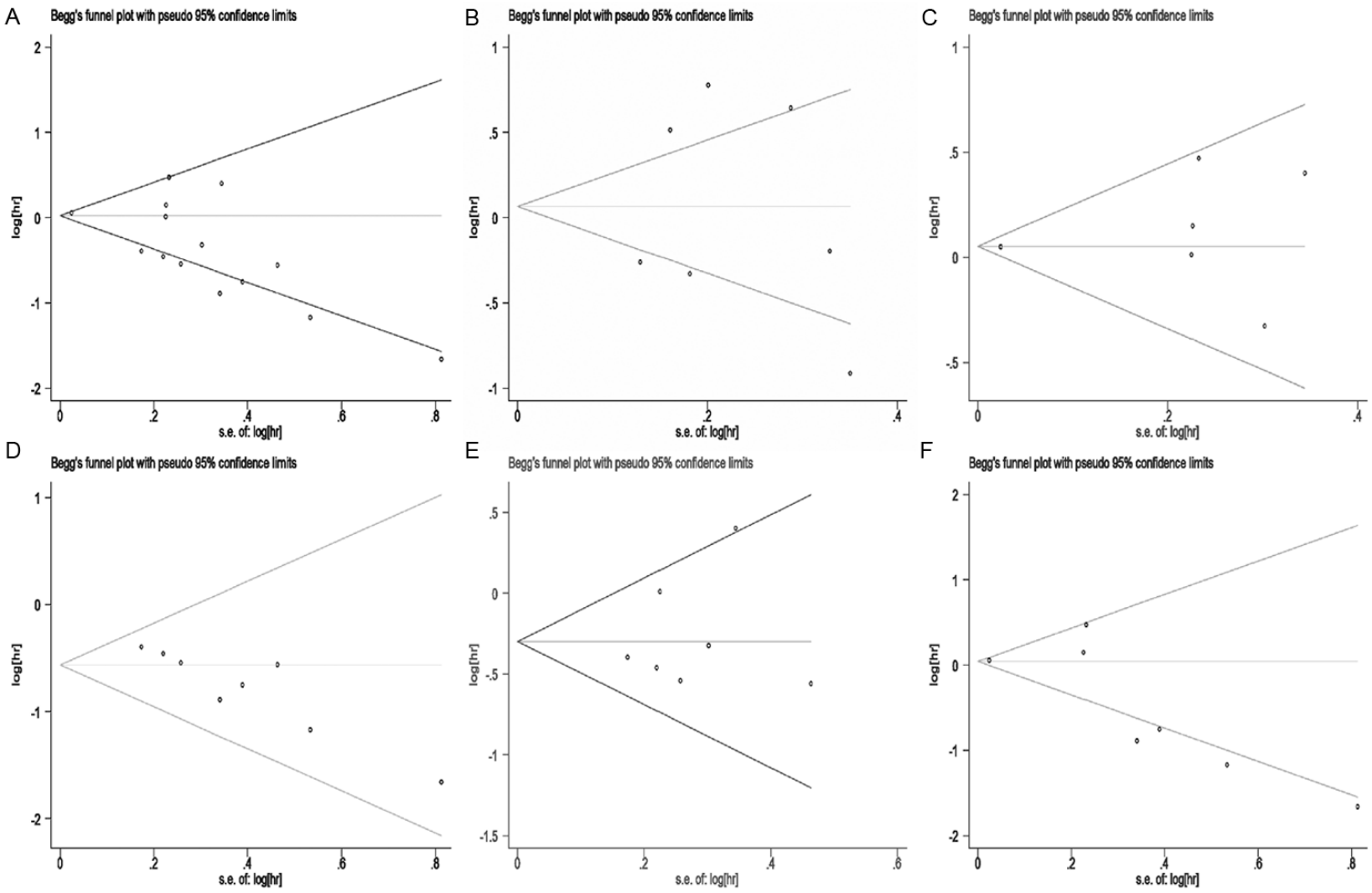


Figure 5. Begg's test results of overall survival rate such as (A), ERβ expression and OS rate by univariate analysis (B), ERβ expression and OS rate by multivariate analysis (C), ERβ expression and OS rate in American and Japan (D), ERβ expression and OS rate outside of American and Japan (E), N-ERβ expression and OS rate (F), C-ERβ expression and OS rate (All $P > 0.05$).

some tumors. In addition, EGFR and IGFR (insulin growth factor receptor) can also activated ERs by crosstalk with via receptor phosphorylation [47]. Studies have provided evidence about a functional interaction between ER and EGFR pathways in NSCLC tissues [47, 48]. In this sense, it was proved that the combined targeting of EGFR and ER showed higher antiproliferative effects than those obtained independently in NSCLC cells [43].

Although we performed a comprehensive analysis of the association between overall survival and ERβ expression, there were several limitations that should be considered in our meta-analysis. First, Only English and Chinese studies were included in this analysis, which may cause language bias. Second, the risks calculated in our meta-analysis may be an overestimate due to publication bias. Some eligible studies were excluded from this meta-analysis because they lacked sufficient data on survival; negative or small-sample studies may be less likely to be published. Third, another potential source of bias is related to the method used to extrapolate the HR. HR was extracted from the data included in the article directly or calculated from the survival curves. Actually, the method of extrapolating HR from survival curves seems to be less reliable because this strategy did not completely eliminate inaccuracy in the extracted survival rates. Furthermore, we also think that different objects included in these studies have different impact on overall survival, so this factor should be taken into consideration. Therefore, more meticulous research should be conducted. Finally, the heterogeneity could be explained by the fact that differences in antibodies used for staining, different criteria for defining stain positivity, and different patient demographics such as tumor stage, histological subtype, and adjuvant treatment. These differing results in these 2279 patients NSCLC may be partially attributed to technique of detecting ERβ is not comparable among the studies. Nevertheless, no publication bias was detected using Begg's test ($P > 0.05$), indicating that the statistics obtained approximate the actual results. Sensitivity analysis was also conducted to investigate the influence of a single study on the overall meta-analysis by omitting one study at a time, and the omission of any study made no significant difference, suggesting that our results were statistically reliable.

In summary, despite of the limitations listed above, the present study showed overexpression of ERβ was significant associated with good overall survival in patients with NSCLC on univariate analysis but not multivariate analysis. However, more prospective clinical studies are needed to explore the prognostic value of ERβ in NSCLC. Overexpression of N-ERβ NSCLC patients had better survival, but C-ERβ expression did not predict survival. ERβ expression is a good prognostic outcome outside of American and Japan, however, ERβ expression maybe is a poor prognostic outcome in American and Japan. Large prospective studies are now needed to confirm the clinical utility of ERβ as an independent prognostic marker.

Acknowledgements

The research was supported by grants from the National Natural Science Foundation of China (81372504, 81241068, 81201851), Chinese Postdoctoral Science Foundation (2013M542281) and the Application of Infrastructure Program from the Department of Science and Technology, Sichuan Province, China (2013JY0012).

Disclosure of conflict of interest

None.

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