

## RESEARCH ARTICLE

# Lack of Prognostic Value of Human Epidermal Growth Factor-Like Receptor 2 Status in Inflammatory Breast Cancer (IBC): a Meta-analysis

Xiu-Juan Li<sup>1&</sup>, Quan-Bin Zha<sup>2&</sup>, Xin-Yu Xu<sup>3</sup>, Lei Xia<sup>3</sup>, Zhe Zhang<sup>3</sup>, Zhao-Jun Ren<sup>3,4\*</sup>, Jin-Hai Tang<sup>1,4\*</sup>

### Abstract

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer which is more likely to be her-2/neu amplified. While the her-2/neu status has been utilised to predict prognosis, the published data are inconsistent. The present meta-analysis was conducted to determine whether the her-2/neu status predicts outcomes. Papers were selected from the PubMed database based on defined inclusion and exclusion criteria. Parameters such as total patients, follow-up time and outcome statistics (i.e. overall survival (OS), relapse-free survival (RFS) were collected. The analysis included 6 studies with 2,838 IBC patients. The summary hazards ratio (HR) estimating the association of OS with HER-2-positive disease was 0.96 (95% confidence interval (95% CI: 0.85-1.10)), with similar findings for RFS (HR=0.81, 95% CI: 0.61-1.09). No obvious statistical heterogeneity was detected. This meta-analysis suggests that HER-2-positive status is not an independent adverse prognostic factor for survival among IBC patient cases.

**Keywords:** Human epidermal growth factor-like receptor 2 - inflammatory breast cancer - meta-analysis - prognosis

*Asian Pac J Cancer Prev*, 15 (22), 9615-9619

### Introduction

Inflammatory breast cancer (IBC) is the most aggressive form of primary breast cancer with poor 5-year rates of disease-free survival (DFS) and overall survival (OS). Clinically, IBC is characterized by diffuse erythema and edema of the skin of the breast, called 'peau d'orange', with or without associated palpable mass. IBC is a relatively rare form of breast cancer, and chemotherapy plays the primary role in their treatment. Although the survival of patients with IBC has been improved greatly by the use of combined treatment modalities, people with IBC still have far lower survival rates than those with other types of breast cancer. Advances in the treatment of IBC have been hampered by absence of prognostic factors, in part because the rarity of IBC has made it difficult to conduct clinical trials.

Human epidermal growth factor-like receptor 2 (HER2) is a proto-oncogene located on chromosome 17. It is overexpressed in about 30% of breast cancer and is associated with a more aggressive breast cancer phenotype (Slamon et al., 1987). Although studies have reported an increased incidence of HER-2 amplification in patients with IBC, the prognostic significance of HER-2 amplification in this cohort has not been clearly defined,

and due to the rarity of this disease the prognostic impact of HER-2 status on survival outcomes of patients with IBC is not well known (Turpin et al., 2002). Unfortunately, there are limited high quality prospective data and the current publications have not been consistent in their conclusions. We performed a meta-analysis aiming to analyse the existing data to determine if HER-2 status predicts for outcomes in IBC patients.

### Materials and Methods

#### Literature search

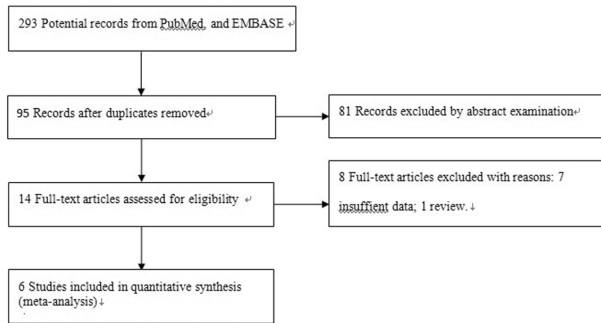
We conducted a systematic literature search of PubMed and EMBASE through April 2013 by using the following key words: Inflammatory breast cancer, human epidermal growth factor-like receptor 2, HER-2, prognosis and survival. References from identified studies were also reviewed. The search was limited to English language. The eligible studies should meet the following criteria: (1) We have restricted our analyses to inflammatory breast cancer. (2) Only original papers evaluating the association between HER-2 status and overall survival (OS), relapse-free survival (RFS) or disease free survival (DFS) were selected. (3) Hazard ratio (HR) for OS, RFS or DFS according to HER-2 status either had to be reported or

<sup>1</sup>Department of General Surgery, <sup>3</sup>Department of Pathology, Jiangsu Cancer Hospital, <sup>4</sup>Department of Pathology, Jiangsu Cancer Hospital, The Affiliated Hospital of Nanjing Medical University, Nanjing, <sup>2</sup>Department of Oncology, Jintan Hospital Affiliated to Jiangsu University, Jintan, Jiangsu, China &Equal contributors \*For correspondence: renzhaojun18@126.com, 673008034@qq.com

**Table 1. Characteristics of the Studies Included in the Meta-analysis**

| Study            | T       | HER-2     | Duration     | No. of   | CT       | TNM     | No. of H- | Survival |
|------------------|---------|-----------|--------------|----------|----------|---------|-----------|----------|
|                  | therapy | detection | of follow-up | Patients | Regimen  | Stage   | positive  | Data     |
| Sawaki et al     | No      | IHC       | 1990-2000    | 46       | A-based  | III     | 23        | OS, DFS  |
| Dawood et al     | No      | IHC+FISH  | Median 35 m  | 179      | AT-based | III     | 68        | OS, RFS  |
| Zell et al       | Yes     | IHC+FISH  | 1999-2007    | 2104     | AT-based | III, IV | 477       | OS       |
| Sutherland et al | Yes     | IHC+FISH  | 1990-2007    | 155      | AT-based | III, IV | 59        | OS, RFS  |
| Li et al         | Yes     | IHC+FISH  | Median 35 m  | 316      | AT-based | III     | 62        | OS, RFS  |
| Chaher et al     | No      | IHC+FISH  | 2005-2009    | 117      | AT-based | III, IV | 20        | OS       |

\*A, Anthracycline; T, taxane; IHC, immunohistochemical; FISH, fluorescent in situ hybridization; m, months; T, Trastuzumab; CT, Chemotherapy; H, HER-2



**Figure 1. Flow Chart of the Selection of Publications Included in the Meta-analysis**

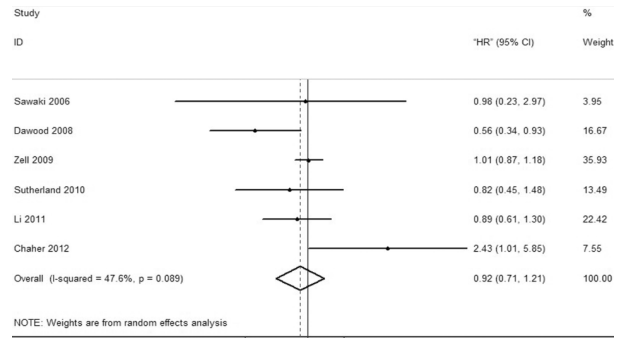
could be calculated from the paper. Furthermore, abstracts were excluded because of insufficient data.

**Data Extraction**

The following data from eligible publications was extracted respectively by two reviewers (Li XJ and Ren ZJ) with a standardized data collection form: first author’s last name, duration of follow-up, sample size, number and of patients with HER-2-positive, disease stage, chemotherapy regimen, inclusion of trastuzumab therapy, the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). When both univariate and multivariate analysis were used to adjust for covariates, only survival data from multivariate analysis were included in our meta-analysis. If HRs and 95% CIs were not provided directly, estimated value was obtained indirectly by using the methods described by Tierney et al (Tierney et al., 2007). Disagreement was resolved by discussion and consensus, and where required through discussion with, or independent extraction by two authors with content expertise (Tang JH and Gong JP).

**Statistical analysis**

Summary statistics of patients with HER-2-positive disease for survival outcome with HRs and 95%CI were calculated using the fixed effect model/Mantel-Haenszel method when there was no significant heterogeneity in the variables amongst studies and the DerSimonian-Laird method (random effect model) when there was significant heterogeneity. Heterogeneity between trials was evaluated by I-squared (I<sup>2</sup>) statistic (Higgins et al., 2003). Statistical heterogeneity was considered significant if *p* value less than 0.10 or I<sup>2</sup>>50%. Publication bias was assessed by Begg’s funnel plots and Egger’s regression test (Begg et al., 1994). Additionally, we also conducted a sensitivity analysis to investigate the influence of a single trial on the overall risk (Tobias et al., 1999). All reported P values were two-sided and P values less than 0.05 were regarded



**Figure 2. Forest Plots of Hazard Ratio (HR) for Overall Survival (OS) from Eligible Studies of IBC with HER-2-positive.** The combined HRs and 95% CIs were calculated using the random-effects model

as statistically significant. Statistical analyses were carried out using STATA 12.0 (Stata Corporation, USA).

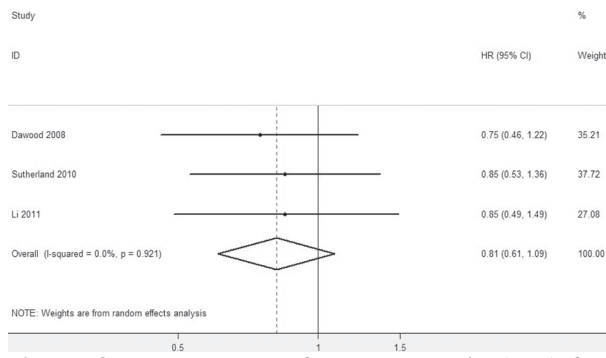
**Results**

**Literature search**

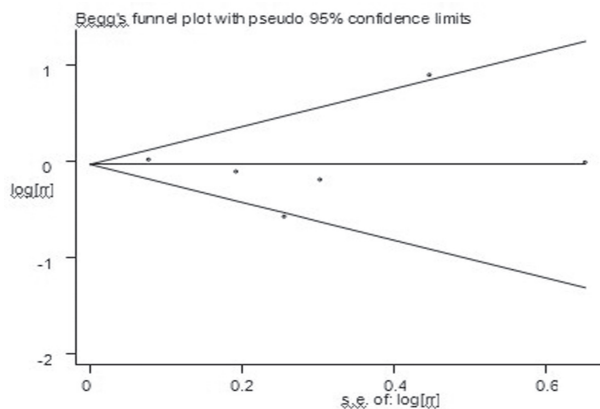
We initially reviewed 293 relevant citations using search strategies as described previously. Of these, the majority were excluded after the first screening based on abstracts, because they were not relevant to our analysis, or the primary outcome was not OS, RFS, or DFS. After full-text review of 14 papers, 7 studies (Low et al., 2004; Panades et al., 2004; Labidi et al., 2008; Mehta et al., 2008; Ellis et al., 2011; Gianni et al., 2012; Rehman et al., 2012) were excluded because of poor data for meta-analysis. Another one study was excluded because it was review (Kim et al., 2006). Finally, 6 studies (Dawood et al., 2008; Zell et al., 2009; Sutherland et al., 2010; Li et al., 2011; Chaher et al., 2012) were included in our meta-analysis. Flow diagram of selecting eligible trials was shown in Figure 1.

**Study Characteristics**

The characteristics of these 6 studies are listed in Table 1. The sample size of the included studies ranged from 46 to 2041 patients. The number of patients with HER-2-positive disease ranged from 20 to 477 patients. HER2 status was determined by fluorescent in situ hybridization (FISH) and immunohistochemical (IHC) analysis in 5 of the 6 eligible studies, and patients were categorized as having HER-2-positive disease if their tumor samples exhibited overexpression (2+) by IHC technique in one study. All systemic therapy delivered typically consisted of an anthracycline and/or taxane with other chemotherapeutic agents, in accordance with



**Figure 3. Forest Plots of Hazard Ratio (HR) for Relapse-free Survival (RFS) from Eligible Studies of IBC with HER-2-positive.** The combined HRs and 95% CIs were calculated using the random-effects model



**Figure 4. Funnel Plot Detect Publication Bias in the Study of Relationship between HER-2 Status and Overall Survival (OS).** The vertical line indicated the pooled estimate of the overall HR, with the sloping lines representing the expected 95%CI for a given SE

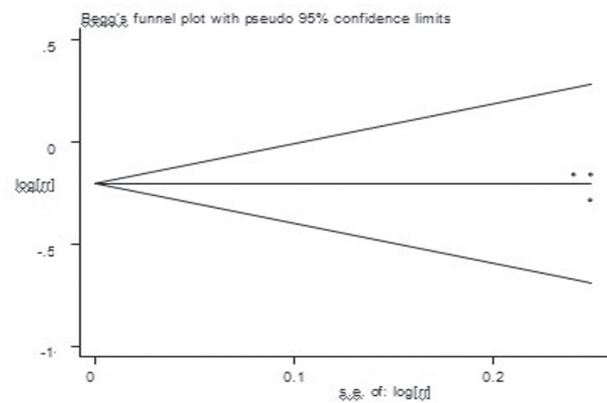
the standard of care for IBC. Detailed information from each trial was listed in Table 1.

#### Meta analysis

Data for OS were available from all 6 studies (Sawaki et al., 2006; Dawood et al., 2008; Zell et al., 2009; Sutherland et al., 2010; Li et al., 2011; Chaher et al., 2012) with 2838 patients reported. The HER-2-positive group was not associated with a statistically significant improvement in OS when compared with the HER-2-negative group (HR=0.96, 95%CI 0.85-1.10;  $I^2=47.6%$ ) (Figure 2) under a random-effect model. RFS was reported in 3 papers [15, 16, 18], including 650 patients with similar findings (HR =0.81, 95%CI: 0.61-1.09;  $I^2=0.0%$ ) (Figure 3). There was only one study which reported DFS. The efficacy of HER-2-positive on the DFS was HR=1.19, (95%CI 0.76-1.84, random-effects model).

#### Publication bias

Visual assessment of the funnel plot did not provide evidence of publication bias for studies (Figure 4 and Figure 5). The Begg rank correlation test and Egger linear regression test also indicated no evidence of publication bias (Begg,  $p=0.851$  for OS; and,  $p=0.602$  for RFS); (Egger's test  $p=0.878$ , for OS; and,  $p=0.833$  for RFS).



**Figure 5. Funnel Plot Detect Publication Bias in the Study of Relationship between HER-2 Status and Relapse-free Survival (RFS).** The vertical line indicated the pooled estimate of the overall HR, with the sloping lines representing the expected 95%CI for a given SE

## Discussion

The clinical researches of IBC are hampered because of the rarity of the disease and the reliance on nonspecific clinical diagnostic criteria to identify cases. IBC is more likely than other breast cancers to be her2/neu amplified (Turpin et al., 2002; Hance et al., 2005). While her2/neu status has been utilised to predict prognosis (Abdul et al., 2013), the published data are inconsistent. Dawood et al. (2005), reported that, IBC patients with HER-2-positive disease had increased OS compared with HER-2-negative disease, presumably because of the use of trastuzumab for their recurrent disease. Sawaki et al. (2006), did not find HER-2 positivity to be a significant prognostic factor in IBC; Zell et al. (2009), also did not observe statistically significant difference in survival outcome for IBC patients with HER-2-positive disease. The present meta-analysis was conducted to determine the her2/neu status predicts for outcomes. Based on the combined data of 6 eligible published studies with 2838 IBC patients, our findings suggest that the summary hazards ratio (HR) estimating the association of OS with HER-2-positive disease was 0.96 (95%CI: 0.85-1.10), with similar findings for RFS (HR=0.81, 95%CI: 0.61-1.09). No obvious statistical heterogeneity was detected (Begg,  $p=0.851$  for OS; and,  $p=0.602$  for RFS); (Egger's test  $p=0.878$ , for OS; and,  $p=0.833$  for RFS). This meta-analysis suggests that HER2+ status is not prognostic for survival among IBC patient cases.

To our knowledge, HER-2 amplification in primary breast cancers was associated with shorter OS and RFS compared with tumors that did not exhibit HER-2 amplification (Slamon et al., 1987). The introduction of a monoclonal antibody, trastuzumab, that targeted the HER-2 receptor, significantly improved survival outcomes in primary breast cancers with HER-2 amplification (Romond et al., 2005).

However, our meta-analysis concluded that HER-2 status was not a significant prognostic factor in patients with IBC, despite the finding that HER-2 amplification is common in this disease. There are several possible explanations for why HER2 is not prognostic for survival

in IBC. Many other molecules may contribute to IBC's aggressive behavior, including chemokine receptors such as CCR7 (Cabioglu et al., 2007), EGFR (Cabioglu et al., 2007), E-cadherin (Colpaert et al., 2003), Rho proteins, and WISP3 (Van Golen et al., 2000; Kleer et al., 2002). Future studies should attempt to identify which molecular target was specific to IBC. It has been reported that an anthracycline-based chemotherapy regimen may be more effective in HER2-positive patients compared with HER2-negative ones because HER2-positive patients often overexpress topoisomerase II, which is the target of anthracyclines (Tanner et al., 2006). It may possibly come to a conclusion that anthracycline-based chemotherapy regimen eliminates HER2 positivity's impact on survival outcome in these HER2-positive patients.

Potential limitations of this study should be considered. First, although most of studies adjusted for a series of key covariates, we still cannot rule out the possible residual confounding variables. Second, it is unknown how many people received trastuzumab and their survival outcome. Third, the total number of included studies and the total sample size were relatively small, which may influence the accuracy of meta-analysis to some extent.

It is thus clear that more specific prognostic and predictive markers, with the subsequent development of novel therapeutic regimens, are needed to individualize treatment and thus improve survival outcomes.

Monoclonal antibody, trastuzumab, is an important variable known to have a favorable prognostic impact in breast cancer, and it calls into question whether trastuzumab may improve survival in these HER2-positive IBC patients. In this meta-analysis, there were 2 included studies without addition trastuzumab to patients with HER-2-positive and other 4 studies restricted their analyses to the period prior to 2005, when trastuzumab became widely used in the adjuvant setting for treatment of breast cancer (Romond et al., 2005). Further studies are warranted to evaluate the effect of trastuzumab on HER2-positive IBC. It is interesting that HER-2 status is not an adverse prognostic factor for survival in IBC patients, and yet trastuzumab may still benefit IBC patients, a finding that needs further research.

In summary, we conclude that HER-2 status is not an independent adverse prognostic factor for survival among IBC patients. The aggressive biology of IBC and other unknown prognostic factors may explain the poor OS for IBC.

## References

- Abdul MNA, Razak ZA, Hussain RM, et al (2013). Quantification of Her-2/Neu gene in breast cancer patients using real time-polymerase chain reaction (Q-PCR) and correlation with immunohistochemistry findings. *Asian Pac J Cancer Prev*, **14**, 1655-9.
- Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.
- Cabioglu N, Gong Y, Islam R (2007). Expression of growth factor and chemokine receptors: new insights in the biology of inflammatory breast cancer. *Ann Oncol*, **18**, 1021-9.
- Chaher N, Arias-Pulido H, Terki N, et al (2012). Molecular and epidemiological characteristics of inflammatory breast cancer in Algerian patients. *Breast Cancer Res Treat*, **131**, 437-44.
- Colpaert CG, Vermeulen PB, Benoy I, et al (2003). Inflammatory breast cancer shows angiogenesis with high endothelial proliferation rate and strong E-cadherin expression. *Br J Cancer*, **88**, 718-25.
- Dawood S, Broglio K, Gong Y, et al (2008). Prognostic Significance of HER-2 Status in women with inflammatory breast cancer. *Cancer*, **112**, 1905-11.
- Ellis GK, Barlow WE, Gralow JR, Hortobagyi GN, et al (2011). Phase III comparison of standard doxorubicin and cyclophosphamide versus weekly doxorubicin and daily oral cyclophosphamide plus granulocyte colony-stimulating factor as neoadjuvant therapy for inflammatory and locally advanced breast cancer: SWOG 0012. *J Clin Oncol*, **29**, 1014-21.
- Gianni L, Pienkowski T, Im YH (2012). Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomized multicentre, open-label, phase 2 trial. *Lancet Oncol*, **13**, 25-32.
- Hance KW, Anderson WF, Devesa SS (2005). Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the national cancer institute. *J Natl Cancer Inst*, **97**, 966-75.
- Higgins JP, Thompson SG, Deeks JJ, et al (2003) Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-60.
- Kim T, Lau J, Erban J (2006). Lack of uniform diagnostic criteria for inflammatory breast cancer limits interpretation of treatment outcomes: a systematic review. *Clinical Breast Cancer*, **7**, 386-95.
- Kleer CG, Zhang Y, Pan Q, et al (2002). WISP3 is a novel tumor suppressor gene of inflammatory breast cancer. *Oncogene*, **21**, 3172-80.
- Labidi SI, Mrad K, Mezlini A, et al (2008). Inflammatory breast cancer in Tunisia in the era of multimodality therapy. *Ann Oncol*, **19**, 473-80.
- Li J, Gonzalez-Angulo AM, Allen PK, et al (2011). Triple-negative subtype predicts poor overall survival and high locoregional relapse in inflammatory breast cancer. *Oncol*, **16**, 1675-83.
- Low JA, Berman AW, Steinberg SM, et al (2004). Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. *J Clin Oncol*, **22**, 4067-74.
- Mehta RS, Schubert T, Kong K (2008). Trastuzumab in inflammatory breast cancer. *Ann Oncol*, **19**, 1815-7.
- Panades M, Olivotto IA, Speers CH, et al (2004). Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. *J Clin Oncol*, **23**, 1941-50.
- Rehman S, Reddy CA, Tendulkar RD (2012). Modern outcomes of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys*, **84**, 619-24.
- Romond EH, Perez EA, Bryant J (2005). Trastuzumab plus adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*, **353**, 1673-84.
- Romond EH, Perez EA, Bryant J, et al (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*, **353**, 1673-84.
- Sawaki M, Ito Y, Akiyama F, et al (2006). High prevalence of HER-2/neu and p53 overexpression in inflammatory breast cancer. *Breast Cancer*, **13**, 172-8.
- Slamon DJ, Clark GM, Wong SG, et al (1987). Human breast cancer: correlation of relapse and survival with amplification



- of the HER-2/neu oncogene. *Science*, **235**, 177-82.
- Sutherland S, Ashley S, Walsh G, et al (2010). Inflammatory breast cancer-the royal marsden hospital experience. *Cancer*, **116**, 2815-20.
- Tanner M, Isola J, Wiklund T (2006). Topoisomerase IIa gene amplification predicts favorable treatment response to tailored and dose-escalated anthracycline-based adjuvant chemotherapy in HER-2/neu-amplified breast cancer: scandinavian breast group trial 9401. *J Clin Oncol*, **24**, 2428-36.
- Tierney JF, Stewart LA, Ghersi D, et al (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, **8**, 16.
- Tobias A (1999). Assessing the influence of a single study in the meta-analysis estimate. *Stata Technical Bulletin*, **8**, 15-27.
- Turpin E, Bieche I, Berthaeau P (2002). The increased incidence of ERBB2 over expression and TP53 mutation in inflammatory breast cancer. *Oncogene*, **21**, 7593-7.
- Van Golen KL, Wu ZF, Qiao XT, et al (2000). RhoC GTPase, a novel transforming oncogene for human mammary epithelial cells that partially recapitulates the inflammatory breast cancer phenotype. *Cancer Res*, **60**, 5832-8.
- Zell JA, Tsang WY, Taylor TH, et al (2009). Prognostic impact of human epidermal growth factor-like receptor 2 and hormone receptor status in inflammatory breast cancer (IBC): analysis of 2,014 IBC patient cases from the California cancer registry. *Breast Cancer Res*, **11**, 9.