Single hormone receptor-positive breast cancer patients experienced poor survival outcomes: a systematic review and meta-analysis

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Received: 12 March 2019 / Accepted: 28 May 2019 / Published online: 20 June 2019
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Abstract

Background The prognostic and clinical significance of single hormone receptor expression in breast cancer has not been clearly established. The goal of this study was to conduct a meta-analysis to compare the clinical outcomes of patients with ER+PR− tumours and ER−PR+ tumours to those of patients with ER+PR+ tumours.

Methods A systematic review of the literature was conducted to identify studies that compared the clinical outcome of patients with ER+PR− tumours or ER−PR+ tumours with those of patients with ER+PR+ tumours. A total of 18 studies met the inclusion criteria and included 217,485 women. Standard methods for meta-analysis were used, including fixed-effect models.

Results Patients with ER+PR− tumours or ER−PR+ tumours had significantly worse DFS (HR 1.60, 95% CI 1.44–1.77 and HR 2.27, 95% CI 1.67–3.09), BCSS (HR 1.43, 95% CI 1.33–1.53 and HR 1.82, 95% CI 1.68–1.98) and OS (HR 1.38, 95% CI 1.28–1.47 and HR 1.48, 95% CI 1.17–1.89) than those of patients with ER+PR+ tumours. In subgroup analyses, patients who had ER+PR− tumours experienced a higher risk of recurrence than patients with ER+PR+ tumours in the HER2− (HR 1.57, 95% CI 1.32–1.87), LN − (HR 2.07, 95% CI 1.44–2.86) and endocrine therapy (HR 1.65, 95% CI 1.45–1.89) subgroup. Patients who had HER2− and ER−PR+ tumours had an increased risk of recurrence compared with patients who had HER2− and ER+PR+ tumours (HR 3.10, 95% CI 1.92–5.10).

Conclusions Among patients with hormone receptor-positive breast cancer, patients with either ER+PR− tumours or ER−PR+ tumours have a higher risk of recurrence and a shorter survival time than those with ER+PR+ tumours. Patients with both types of breast cancer need additional or better treatments.

Keywords Breast cancer · Hormone receptor positive · Estrogen receptor · Progesterone receptor · Disease-free survival · Overall survival · Breast cancer-specific survival

Introduction

Breast cancer (BC) has been known to be an endocrine-related cancer since Beatson demonstrated that tumours regressed after oophorectomy in advanced breast cancer patients [1]. Jensen et al. then found that there are a large number of estrogen receptor (ER)-positive and progesterone receptor (PR)-positive tumours in breast cancer patients, and there was a possibility that these receptors contribute to the progression of BC. Currently, endocrine therapy plays an important role in the comprehensive treatment of breast cancer. The status of estrogen receptor (ER) and progesterone receptor (PR) expression is commonly used to direct the treatment strategies for BC patients because of their predictive value in prognosis and endocrine therapy (ET) responsiveness.
It is commonly accepted that ER+ and PR+ BC require ET. The ER status is now widely considered to be the most important predictive factor for determining the optimal therapeutics for BC patients and patients with ER+ tumours show a trend towards increased survival [2, 3]. However, routinely evaluating the PR status to guide treatment options and recognizing it as an independent predictive factor remain controversial [4, 5]. Olivotto claimed that treatment decisions in ER+ patients will not be affected by the PR results [6]. However, studies have shown that the absence of PR expression has a powerful prognostic value in ER+ breast cancer patients, emphasizing the importance of re-evaluating PR status as a biological marker for poor prognosis [7]. The clinicopathological characteristics and prognosis of ER−PR+ tumours are not well known due to the small number of patients with this type of disease. The ER−PR+ group is reported to be only 1–5% of all breast cancer patients. Whether the ER−PR+ phenotype is a unique biological entity is still debatable and remains poorly understood. Patients with ER−PR+ tumours seem to fall short of the expectations for survival after systemic therapy, and tamoxifen does not reduce recurrence in patients with ER-negative tumours [8].

In this systematic review and meta-analysis, we evaluated the different clinical outcomes among the single hormone receptor-positive phenotypes (ER+PR− and ER−PR+ tumours) and the double hormone receptor-positive phenotype (ER+PR+ tumours), especially after ET. We included overall survival (OS), BC-specific survival (BCSS) and disease-free survival (DFS). Our aim was to identify which patients tend to benefit from ET and to determine whether any additional value was provided by the double-positive hormone receptor-positive phenotype in hormone receptor-positive BC. As a result, we will be able to perform better management of BC patients according to their different ER and PR expression patterns.

Methods

Data sources and search strategy

We identified potentially relevant studies by systematically searching Google Scholar and using the following combination of key words: ER+/PR− and breast cancer and survival; ER positive/PR negative and breast cancer and survival; ER−/PR+ and breast cancer and survival; and ER negative/PR positive and breast cancer and survival. The COCHRANE database search strategy used the terms "breast cancer", "estrogen receptor", "progesterone receptor", "positive", "negative", "endocrine therapy" and "prognosis". PUBMED was searched with the terms "breast neoplasms", "estrogen receptor", "progesterone receptor", "positive", "negative", "endocrine therapy", "endocrine therapy" and "prognosis". The last search was performed in January 2017.

Study selection

We included studies that compared the survival between ER+PR+ BC and ER−PR+ BC or ER+PR− BC patients. The following three inclusion criteria were applied to the studies that were retrieved: (1) all patients having hormone receptor-positive breast cancer (positive for estrogen receptor, progesterone receptor or both); (2) clear description of the status of the ER and PR; and (3) quantified DFS, OS or BCSS by effective measures such as hazard ratios (HRs) or relative risks (RRs). For articles based on the same population, only the least informative article was excluded, and the most recently published article was enrolled in the study. Articles not in English or Chinese were excluded (Fig. 1).

Data extraction

From each study, we extracted the name of the first author, date of publication, number of patients reported, years that the patients were recruited, follow-up time, hormone receptor status, status of the lymph nodes, location where the study was performed, the main treatment and hazard ratios (HRs) or relative risks (RRs). For articles based on the same population, only the least informative article was excluded, and the most recently published article was enrolled in the study. Articles not in English or Chinese were excluded (Fig. 1).

Statistical analysis

The hazard ratios (HRs) with their corresponding 95% CIs were used to assess the difference in survival between the single hormone receptor-positive phenotype and the double hormone receptor-positive phenotype, according to the methods described by Parmar et al. [9]. The RR was considered the HR. When the HR of an event in the control arm versus the experiment arm was reported, we obtained the HR of the research arm versus the control arm by calculating the reciprocal of the HR, i.e. 1/HR and the associated CI [10]. An HR > 1 implied worse survival, favouring single hormone receptor-positive patients. A fixed-effect model was used for our main results.

The heterogeneity of the included studies was evaluated with the $I^2$ statistic [11, 12]. The $I^2$ values > 50% indicated the presence of significant heterogeneity between studies. The subgroup analysis was based on ET, lymph node (LN)-negative status and human epidermal growth factor receptor 2 (HER2)-negative status. We used funnel plot analyses and the trim and fill method to investigate the publication bias [13, 14]. A quality assessment was performed for each of the acceptable studies using the Newcastle–Ottawa scale [15].
All analyses were conducted with Stata software (version 12.0), with \( p \) values less than 0.05 considered significant.

Results

The systematic search finally identified 22 original studies, including 217,485 patients that met the inclusion criteria. All included studies were retrospective and cohort observational studies.

Table 1 provides a detailed summary of the baseline characteristics. Sixteen studies compared the prognosis of patients with ER+PR− tumours versus ER+PR+ tumours, of which 12 studies reported OS, 11 reported DFS and 4 reported BCSS. Twelve studies compared the prognosis of patients with ER−PR+ tumours versus ER+PR+ tumours. Among these studies, five reported OS, seven reported DFS and four reported BCSS. Most articles were published after 2003, except for the one that was published in 1996. Thirteen studies had a sample size of more than 500 patients. Two studies recognized \( \geq 10\% \) of tumour cells with nuclear staining as the cutoff for ER/PR positivity. Most studies used a cutoff of \( \geq 1\% \) to define ER/PR positivity. Two studies did not provide clear criteria for ER/PR positivity. Most patients received treatment according to the local standards.

ER+/PR− tumours versus ER+/PR+ tumours

Eleven studies compared the prognosis of patients with ER+PR− tumours versus patients with ER+PR+ tumours using DFS. The meta-analysis showed a significantly increased risk of recurrence in patients with ER+PR− tumours than in patients with ER+PR+ tumours \((I^2 = 0\%, \text{ meta-analytic HR } 1.60, 95\% \text{ CI } 1.44–77)\) (Fig. 2a). There was no significant heterogeneity among the 11 studies \((p = 0.718)\). When the analysis was limited to the nine
Table 1 The characteristics of the included studies

| References          | Year | Country | Recruitment | Follow-up | Age | Subjects | Cutoff (ER, PR) | Clinical stages | Pathology | Surgery | NOS |
|---------------------|------|---------|-------------|-----------|-----|----------|----------------|-----------------|-----------|---------|-----|
| Rakha et al. [16]   | 2007 | UK      | 1986–1998   | 108 m     | NA  | 333      | 1%, 1%         | I–III           | IBC       | 100%    | 6   |
| Ma et al. [17]      | 2016 | China   | 2008–2010   | 59 m      | 52  | 318      | 1%, 20%        | I–III           | IBC       | 100% (MRM) | 4 |
| Chen et al. [18]    | 2015 | China   | 2006–2009   | 72 m      | 49  | 229      | NA             | I–III           | IBC       | 100% (MRM) | 4 |
| Bal et al. [19]     | 2015 | Turkey  | 1984–2011   | 170 m     | 51  | 400      | 1%, 1%         | I–III           | IDC, ILC, others | 100% (92% MRM + 6% BCS + 2% others) | 5 |
| Purdie et al. [7]   | 2013 | UK      | 2000–2004   | 100 m     | NA  | 860      | 1%, 1%         | NA              | IBC       | 100% (43% BCS + 57% M) | 5 |
| Yu et al. [20]      | 2015 | China   | 2008–2011   | 37 m      | NA  | 1720     | NA             | I–III           | IDC       | 100% (BCS+M) | 6 |
| America             |      |         | 49 m        | 55        | 427 | 1%, 1%   | NA             | I–III           | IBC       | 100%    | 6   |
| America             | 2010–2013 |           | 11 m        | 61        | 51,240 | 1%, 1% | NA             | NA             | NA        | NA      | 6   |
| Itoh et al. [21]    | 2013 | America | NA          | 49.8      | 243 | 1%, 1%   | NA             | NA             | NA        | NA      | 5   |
| Cancelllo et al. [22]| 2012 | Italy   | 1997–2005   | NA        | NA  | 4010     | 1%, 1%         | I–III           | IBC       | 100% (80.8% BCS + 19.2% M) | 4 |
| Park et al. [23]    | 2013 | Korea   | 1996–2006   | 49.3 m    | 49.1| 1180     | 1%, 1%         | I–III           | IBC       | 100% (31.9% BCS + 68.1% M) | 4 |
| Korea               | 1996–2006 |         | 49.2 m      | 49.2      | 9916 | 1%, 1%   | I–III           | IBC       | 100%    | 4   |
| Bae et al. [24]     | 2015 | Korea   | 2003–2013   | 45 m      | 47  | 5084     | AS > 2         | I–III           | IDC       | 100%    | 6   |
| Ng et al. [25]      | 2014 | Malaysia| 2003–2008   | NA        | 53  | 1251     | 10%, 10%       | I–IV            | NA        | NA      | 5   |
| Li et al. [26]      | 2016 | China   | 2005–2010   | 41 m      | 47  | 250      | 1%, 1%         | I–IV            | NA        | 100% (63.6% M + 36.4% BCS) | 6 |
| Shen et al. [27]    | 2015 | America | 1997–2013   | NA        | 57.1| 4037     | 1%, 1%         | NA              | IBC       | NA      | 5   |
| Poorolajal et al. [28]| 2016 | Iran    | 1998–2013   | NA        | 48.59| 692      | NA             | I–IV           | IDC, DCIS, LCIS, ILC | 100% (BCS + MRA) | 5 |
| Tovey et al. [29]   | 2005 | UK      | 1980–1999   | 77.4 m    | NA  | 387      | 10%, 10%       | NA              | IBC       | NA      | 5   |
| Dunnwald et al. [30]| 2007 | America | 1990–2001   | NA        | 123,245| NA     | I–IV           | IBC       | NA      | 4   |
| Keshgegian et al. [31]| 1996 | America | NA          | 41 m      | NA  | 194      | 10 fmol/mg     | NA              | IBC       | NA      | 5   |
| Bardou et al. [32]  | 2003 | America | 1970–1998   | 53 m      | 65  | 1581     | 3 fmol/mg, 5 fmol/mg | NA        | NA      | 100% (86.2% M + 13.8% MRM) | 6 |

ER estrogen receptor, PR progesterone receptor, NA not available, IBC invasive breast cancer, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, DCIS ductal carcinoma in situ, LCIS lobular carcinoma in situ, BCS breast-conserving surgery, MRM modified radical mastectomy, M mastectomy, NOS Newcastle–Ottawa Scale
studies in which all patients received endocrine therapy, there was a significantly higher increased risk of recurrence in patients with ER+PR− tumours than in patients with ER+PR+ tumours ($I^2 = 0\%$, meta-analytic HR 1.65, 95% CI 1.45–89) (Fig. 2b). The subgroup analysis based on HER2-negative status is shown in Fig. 2c. The pooled HR from the combined analysis was 1.57 (95% CI, 1.32–1.87), which suggests that patients with ER+PR− tumours have an increased risk of recurrence compared with that of patients with ER+PR+ tumours. In the lymph node-negative subgroup analysis, there was significantly more recurrence in patients with ER+PR− tumours than in those with ER+PR+ tumours ($I^2 = 0\%$, meta-analytic HR 2.03, 95% CI 1.44–86) (Fig. 2d).

OS was reported in ten studies. We pooled the data from those studies and found that ER+PR+ tumours were associated with a significantly better OS ($I^2 = 30.6\%$, meta-analytic HR 1.38, 95% CI 1.28–1.47) (Fig. 3a).

The association between ER+PR− tumours versus ER+PR+ tumours and death from BC was reported in four studies. The patients with ER+PR− tumours were 43% more likely to die from BC than those with ER+PR+ tumours (95% CI 1.33–1.53) (Fig. 3b).

The funnel plots indicated the existence of a publication bias. The trim and fill showed that four of the studies did not change the results significantly. This suggests that systematic bias did not significantly contribute to our results (Supplementary Figure 1A, 1B, 1C).

**ER−/PR+ tumours versus ER+/PR+ tumours**

Six studies explored the outcome discrepancies in DFS between patients with ER−PR+ tumours and those with ER+PR+ tumours. The pooled effect was statistically significant, with the pooled HR being 2.27 (95% CI 1.67–3.09) (Fig. 4a). This indicated that patients with ER−PR+ tumours have an increased risk of recurrence compared to patients with ER+PR+ tumours ($I^2 = 18.8\%$, meta-analytic HR 2.27, 95% CI 1.67–3.09) (Fig. 4a). Subgroup analyses focusing on patients receiving ET found no difference in outcome between patients with the two types of tumours (HR 1.31, 95% CI 0.71–2.42) (Fig. 4b). Subgroup analysis for patients with HER2-negative tumours showed that the HR was significantly increased in ER−PR+ tumours compared to ER+PR+ tumours (HR 3.10, 95% CI 1.92–5.10) (Fig. 4c).

The pooled hazard ratio was 1.48 (95% CI 1.17–1.89) (Fig. 5a), indicating that ER−PR+ tumours were associated with a worse OS than ER+PR+ tumours.

We also found that the risk of death from BC was significantly elevated in patients with ER−PR+ tumours compared to ER+PR+ tumours (HR 1.82, 95% CI 1.68–1.98) (Fig. 5b).

No indication of publication bias was found based on the funnel plots (Supplementary Figure 2A, 2B, 2C).

### Discussion

This meta-analysis demonstrates that patients with ER+PR− and ER−PR+ tumours may have outcomes that are unsatisfactory compared to those of breast cancer patients with ER+PR+ tumours who receive ET. We observed that patients with ER+PR+ tumours had significantly less recurrence and significantly superior survival compared to patients with ER+PR− tumours. Similar results were obtained for all subgroups within these groups. Previous studies have reported that ER+PR− tumours are more likely to have higher levels of HER2 than those with ER+PR+ tumours, and the absence of PR may be a surrogate marker of aberrant growth factor signalling, which could contribute to tamoxifen resistance [33, 34]. Unfortunately, only one study reported the HR between ER+PR+ HER2− tumours and ER+PR− HER2− tumours, with an HR of 1.58. However, in the HER2− subgroup analysis, our data show that ER+PR− tumours have a similarly high risk, with an HR of 1.57. This indicates that patients with ER+PR− tumours have a worse prognosis, even if they are HER2 negative, which also supports the hypothesis that PR expression is an independent prognostic factor in breast cancer.

Several researchers have reported that ER+PR− tumours respond poorly to endocrine treatment [34, 35]. A slightly higher risk of recurrence was found in our results for ER+PR− tumours than for ER+PR+ tumours in the subgroup in which all patients received ET. These results again indicate a worse outcome for patients with ER+PR− tumours than for patients with ER+PR+ tumours. However, patients with this type of tumour can still benefit from endocrine therapy, and it is essential that patients with this type of tumour receive endocrine therapy. A meta-analysis of individual early breast cancer patient data containing 20 trials of adjuvant tamoxifen versus no adjuvant tamoxifen found that the reduction in recurrence at 15 years in ER+PR− patients seemed higher than that in ER+PR+ patients [36]. That is, ET strongly delayed relapse and improved survival of ER+PR− patients. In addition, ER+PR− tumours are originally aggressive and have a higher background risk of recurrence without treatment. As has been seen in some research findings, aromatase inhibitors and fulvestrant have much better treatment effects than tamoxifen in ER+PR− patients [37, 38]. Perhaps more aggressive ET, such as ovarian function suppression or ablation, and additional adjuvant chemotherapy could be considered to improve the poor prognosis of ER+PR− patients.

The earliest theory to explain the development of this subset of breast cancer patients was that nonfunctional ER failed to stimulate PR production and finally led to the absence of estrogen, generating ER+PR− breast cancer [39, 40].
Fig. 2  

a Meta-analysis results for DFS in ER+/PR− tumours compared with ER+/PR+ tumours.  
b All patients received endocrine therapy subgroup analysis results for DFS in ER+/PR− tumours compared with ER+/PR+ tumours.  
c HER2-negative subgroup analysis results for DFS in ER+/PR− tumours compared with ER+/PR+ tumours.  
d Lymph node-negative subgroup analysis results for DFS in ER+/PR− tumours compared with ER+/PR+ tumours.
Actually, more than one mechanism can result in this phenotype and the reduced response to ET. Experimental data have implied that growth factor signalling mediates PR down-regulation through the activation of the PI3K–Akt–mam-malian target of rapamycin (mTOR) pathway [35]. Additionally, growth factors potentiate non-classical ER signalling, such as membrane-initiated steroid signalling (MISS) or other non-classical molecular pathways of signalling [41]. Molecular cross talk occurs between membranous ER and the growth factor signalling pathway; at the same time, the PR protein levels are down-regulated [42]. All of these molecular mechanisms promote tumour progression and lead to resistance to tamoxifen. However, these pathways do not completely account for the earlier recurrence and the relative unresponsiveness to ET of ER+PR− tumours, and additional mechanisms remain to be discovered.

As our data show, this phenomenon becomes more significant in the lymph node-negative subgroup, with a pooled hazard ratio (HR) of 2.03. Only one study reported DFS for a lymph node-positive subgroup, with a hazard ratio (HR) of 1.841. A possible explanation is that lymph node-positive patients likely received more active management, such as radiotherapy and adjuvant chemotherapy. These results again demonstrate the higher risk of recurrence in ER+PR− tumours without treatment. These results also indicate that even in lymph node-negative breast cancer, which is believed to be less invasive, ER+PR− patients need more treatment than ER+PR+ patients.

In regard to ER−PR+ tumours, it remains unclear whether these tumours represent an established subtype. Some researchers have suggested that the ER−PR+ phenotype is a reproducible biologic subtype, but others have argued that it may represent a technical artefact [27, 43, 44]. A recent study reported that in a series of repeated immunohistochemistry analyses, using a new cutoff, the phenotype of only 36.7% of previously diagnosed ER−PR+ tumours remained stable [45]. Significantly, almost all studies have shown that ER−PR+ tumours are biologically distinct from ER+PR− tumours and have a poor clinical outcome [46, 47]. Consistent with previous findings, our data also show that ER−PR+ tumours are associated with a higher risk of recurrence and shorter survival than ER+PR+ tumours. Especially for DFS, the risk is increased by more than two times for the ER−PR+ group compared to the ER+PR+ group. No significant difference was seen in DFS between the subgroups of the endocrine treated patients, but we think this result is due to the small sample size.

The HER2− subgroup displayed a higher risk differential between patients with ER−PR+ tumours and ER+PR+ tumours. The risk of recurrence increased the most with ER−PR+ HER2− tumours compared with ER+PR+ tumours, indicating that ER−PR+HER2− tumours behaved aggressively and that these patients have the worst clinical outcome of the hormone receptor-positive BC patients. Yu et al. suggested that the group of ER−PR+ HER2− molecular subtype breast cancer patients consists of a majority of basal-like tumours and a minority of luminal-like tumours [20]. Hefti found a trend towards low levels of PR in ER− breast cancer tumours [48]. An increasing body of evidence has shown that patients with ER−PR+ tumours share similar survival outcomes with ER−PR− BC patients. In addition, ER−PR+ tumour patients usually receive more adjuvant chemotherapy, which probably leads to an underestimation of the hazard ratio between ER−PR+ tumours and ER+PR+ tumours. Using current immunohistochemical technology, some patients will continue to be diagnosed with ER−PR+ tumours, although the number is low. It is important to recognize the high invasiveness and worse prognosis associated with ER−PR+ tumours compared to double hormone receptor-positive tumours.

A patient-level meta-analysis of randomized trials reported no apparent effect on recurrence at 5 years with tamoxifen treatment versus no adjuvant tamoxifen treatment in ER-low PR-positive disease [36]. This suggests that ER−PR+ tumours do not respond to endocrine therapy. Hammond et al. recommended repeated testing using
another tissue sample to eliminate false-negative ER assay results in patients who are likely to benefit from endocrine treatment [49]. Nevertheless, this benefit may be negligible. Hence, optional targeted therapeutic intervention for this type of tumour should be encouraged to achieve improved clinical outcome.

Moreover, three studies that were included in our analysis compared the outcome of patients with ER+/PR− tumours and ER−PR+ tumours. Unfortunately, none of these studies found a significant difference in DFS between the two phenotypes, probably due to the small number of ER−PR+ tumours and the short follow-up period. Therefore, we did not combine the available data from those studies. However, patients with ER−PR+ tumours have a higher risk of recurrence events than ER+/PR− tumour patients when both groups are compared with ER+/PR+ tumour patients. From this result, we can infer that the survival of patients with
ER−PR+ tumours will be worse than that of patients with ER+PR− tumours.

Our review and meta-analysis have several limitations. Despite a comprehensive literature search, the possibility of missing relevant studies cannot be ignored. Although we attempted to conduct a comprehensive systematic review and meta-analysis on this topic, the sample size of patients with ER−PR+ tumours was still small. A few studies used different levels of ER and PR expression for statistical analysis. Moreover, the difference between ER+PR− tumours and ER−PR+ tumours versus ER+PR+ has not been extensively studied in different clinical situations, such as HER2 positivity, LN positivity, with or without chemotherapy, and menopausal state. However, none of the studies that we reviewed provided any evidence to support the hypothesis that the risk of recurrence of ER+PR− tumours or of ER−PR+ tumours was lower than that of ER+PR+ tumours, although some outcomes did not show a statistically significant difference. Another limitation is the possibility of publication bias in the literature, and most of the studies we reviewed were not prospective studies. Thus, we should interpret the results reported here with caution.

We conclude that in hormone receptor-positive breast cancer, even lymph node- and HER2-negative tumours, ER+PR− tumours and ER−PR+ tumours are associated with a poor prognosis even with ET. The loss of either ER
or PR helps to identify high-risk hormone receptor-positive BC patients. These two types of tumours require a more aggressive therapeutic strategy. To improve the survival of patients with these two types of tumours, further investigations focusing on the most appropriate endocrine therapy strategy or the development of targeted agents that can benefit these patients warrant investigation.

Author contributions FF, NW, YL and CW conceived and wrote the protocol of the study. NW, YL and PY performed the search, assessed the references for inclusion and extracted data from the studies. LC performed the statistical calculation. NW produced the manuscript, which was critically revised by FF and YL.

Funding sources/sponsors This work was supported by the National Nature Science Foundation (Grant number 81302320), National Key Clinical Specialty Construction Program (Grant number 201030404#), Sci-Tech Key Program of Fujian Province (2013Y0040 and 2016J01549) and Medical Elite Cultivation Program of Fujian, P.R.C. (2013-ZQN-ZD-12).

Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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