# The Clinical Significance and Prognostic Value of HER2 Expression in Bladder Cancer: a Systematic Review and Meta-analysis

**Kai Gan**
Southeast University
**Yue Gao**
Southeast University
**KuangZheng Liu**
Southeast University
**Bin Xu**
Southeast University
**Ming Chen** ( mingchen0712@126.com )
Southeast University https://orcid.org/0000-0002-3572-6886

**Research**

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# Abstract

**Objective**: Human Epidermal Growth Factor Receptor 2 (HER2) is highly expressed in a variety of tumors and associated with patients' prognosis, but its role in bladder cancer remains unclear. We conducted this meta-analysis to explore the clinical significance and prognostic value of HER2 in bladder cancer and its potentiality as an immunotherapy target.

**Methods:** PubMed was searched for studies published between January 1, 2000 and January 1, 2020. The odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (95%CIs) were used to investigate the relationship between HER2 and bladder cancer. UALCAN website was used to obtain TCGA (The cancer genome atlas) database.

**Results:** Our study includes 14 articles, 1398 patients. HER2 expression was significantly higher in bladder cancer than in normal tissues. Our meta-analysis results did not reveal any effect of gender on the expression of HER2 levels in bladder cancer patients. However, HER2 expression in male patients was significantly higher than that in women according to TCGA databases. HER2 expression was also associated with carcinoma in situ, multifocal tumors, large tumor size, high tumor stage and grade, lymph node metastases, risk of recurrence and progression, low recurrence-free survival (RFS) rate. HER2 expression status had no effect on overall survival.

**Conclusions:** Our meta-analysis showed that HER2 expression was related to pathological malignancy and poor prognosis in bladder cancer which indicated that it could be used as an effective biomarker and therapeutic target.


# Introduction

Bladder cancer is the ninth most common malignancy worldwide, accounting for the seventh highest incidence of cancer in men [1]. In 2019, American men died of bladder cancer accounted for 4% of all cancer deaths, and the mortality rate ranked eighth [2]. The most recent data showed that in 2020, bladder cancer is the sixth most common cancer in the United States, behind malignancies such as lung, prostate, breast, colon and lymphoma cancer [3].

Approximately 70% of bladder cancer patients who was newly diagnosed are divided as non-muscle invasive bladder cancer (NMIBC), furthermore, after complete transurethral resection of the bladder tumor or even secondary surgery, 33% of these patients would also progress to muscle invasive bladder cancer (MIBC) [4]. In previous studies, specific biomarkers of bladder cancer such as NUMA1 and CFHR1 in urine have been reported [5]. However, specific pathologic markers related to bladder cancer are still lacking, so that we need better relevant markers to assess the risk and prediction of cancer progression in bladder cancer.

It has been shown that HER2 expression was involved in cell growth, survival and migration [6]. Moreover, it has been extensively studied as a tumor therapeutic target and it is considered to act as a very

important prognostic and therapeutic marker for breast cancer [7, 8]. In addition, HER2 has also been studied in esophageal and gastric cancers [9, 10]. In recent years, there have been report on biomarker research related to bladder cancer, including HER2 molecule [11]. Other studies have reached similar conclusions. One study indicated that HER2 expression was associated with poor prognosis [12]. In another study, the authors claimed that HER2 could be used as a putative therapeutic target in bladder cancer especially NMIBC [13].

Thus, HER2 could be considered as a useful biomarker for clinical prediction. In recent years, there were several new articles about this subject on publication. We thought it was necessary to write a meta-analysis for further exploring the significance of HER2 expression in bladder cancer.

## Materials And Methods

# Search strategy

This meta-analysis was performed following the convention of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. An electronic search of databases from PubMed from January 2000 to January 2020 was conducted. According to the PICO framework (population, intervention, comparison, results), we used specific terms including "HER2", "bladder cancer", “prognosis”, “clinical significance” to search target literature. The search was restricted to English language articles only. Two authors independently screened the title and abstract of each article and reviewed the full text. The eligibility of each article was evaluated. If there was a disagreement, the third author would join the discussion and decide whether we should include that literature.

# Inclusion criteria

Full texts of these studies were read carefully to determine whether the articles met the following inclusion criteria: (1) The study must focus on patients diagnosed with bladder cancer; (2) HER2 expression was detected by immunohistochemistry (IHC). The expression level of HER2 must be clear. Referring to the "ASCO/CAP Guidelines Consensus on Breast Cancer HER2 Detection" which was jointly issued by American Society of Clinical Oncology (ASCO) and the American College of Pathology (CAP) on December 11, 2006, if more than 10% of tumor cells show membrane staining, we call it “positive”. Otherwise, we call it “negative”. (3) Containing patient information, tumor classification, staging and prognosis related conditions.

# Exclusion criteria

The exclusion criteria were set as follow: (1) The study was a review article, case report, letter, comment, conference abstract. (2) Patients were included in another study.

# Data extraction

The extracted data for each study included first author’s name, publication year, proportion of cells with stained cell membrane after IHC, number of including cases, the median or mean age of patients, the

percent of male patients, the median or mean Follow-up, type of bladder cancer, outcome (Table 1).

# Study quality assessment

In the quality evaluation, we used the Newcastle - Ottawa Quality Assessment Scale (NOS) to evaluate the quality of the included literature. The NOS scale covers three key areas, including selection, comparability, and exposure/results. Studies with a score of seven or above are considered to be high quality on this rating scale. The results indicated that the quality of literatures we selected was not low (Table 2).

# Statistical analysis

We used the Stata 15.0 software for data analysis. For dichotomous variables including gender and percentage of carcinoma in situ (CIS), multifocal tumors, tumor size, stage, grade, lymph node metastases and lymph vascular invasion, the odds ratio (OR) and 95% confidence interval (CI) were adopted. For comparison of time related prognostic information which contained recurrence, progression and recurrence-free survival (RFS), hazard ratio (HR) and 95% CI were applied [14]. All statistical tests were two-sided, and a $P$ value < 0.05 was considered statistical significance. Forest plots showed the results of research analysis and publication bias was visually evaluated using funnel plot. The heterogeneity was assessed by $I^2$ statistics, and funnel plots were used to test publication bias. As noted by the Cochrane Handbook [15], when heterogeneity was less than 40%, fixed effect model was recommended for Meta-analysis. Otherwise, random effect model should be used. We access HER2 expression in bladder cancer and survival analysis data of TCGA database from UALCAN (http://ualcan.path.uab.edu/index.html). This is an effective cancer data analysis website, mainly based on the TCGA database.

# Results

### Search Results

The search strategy retrieved 80 unique citations, of which 58 were excluded after the first screening based on abstracts and titles, leaving 22 for full article review. Finally, we included 14 articles, 1398 patients for our study. A study selection flowchart is presented in Fig. 1.

### Comparison of gender difference among patients

The results showed that the gender difference in patients with disparate HER2 positive rates was not statistically significant (OR = 1.04; 95% CI:0.76–1.42; p = 0.80) [16–18, 22, 23, 27–29] (Fig. 2a).

### Oncology-related features

We found that HER2 positive rate was high in both CIS (OR = 0.62; 95% CI:0.42–0.92; p = 0.02) [16, 17, 22, 23, 25, 26, 29] (Fig. 2b) and multifocal tumors (OR = 0.45; 95% CI:0.30–0.68; p < 0.01) [16, 22, 25, 26, 29] (Fig. 2c). HER2 expression was also associated with large tumor size(> 3 cm) (OR = 0.40; 95% CI:0.26–0.63; p < 0.01) [16, 20, 23, 26, 29] (Fig. 2d). In the HER2 positive tumors, the proportion of Ta stage was

significantly lower than that in the negative tumors (OR = 2.52;95%CI:1,58–4.01; p < 0.01) [16, 18, 19, 22, 29] (Fig. 3a). Furthermore, HER2 expression was linked with high tumor grade (OR = 0.23; 95% CI:0.15–0.35; p < 0.01) [16–20, 23, 25–29] (Fig. 3b) and lymph node metastases (OR = 0.52; 95% CI:0.38–0.71; p < 0.01) [17, 18, 22, 27, 28] (Fig. 3c). But the expression level of HER2 was not associated with lymph vascular invasion (OR = 0.11; 95% CI:0.00–3.05; p = 0.19) [17, 26] (Fig. 3d).

### Comparison of prognosis

Patients with high expression of HER2 had a greater risk of tumor recurrence (HR = 0.76; 95% CI:0.63–0.92; p < 0.01) [16–17, 20–22, 24–26, 29] (Fig. 4a) and progression(HR = 0.31; 95% CI:0.18–0.54;p < 0.01) [16, 20–22, 24–26, 29](Fig. 4b) than those with low expression of HER2. HER2 expression was associated with a low 2-year recurrence-free survival (RFS) rate (HR = 1.31; 95% CI:1.01–1.70; p = 0.04) [16–19] (Fig. 4c). Progression, recurrence and survival conditions have different impact between MIBC and NMIBC cohorts, so we did subgroup analysis in NMIBC patients. The results were as follows: recurrence (HR = 0.77; 95% CI:0.61–0.97; p = 0.02) [16, 20–22, 25, 26, 29] (Fig. 4d); 2-year recurrence-free survival (RFS) (HR = 1.22;95%CI:0.87–1.71; p = 0.25) [16, 19] (Fig. 4e).

### TCGA database analysis results

HER2 expression in bladder cancer tissues was significantly higher than that in normal tissues(P < 0.01) (Fig. 5a). HER2 expression in male patients was significantly higher than that in women(P < 0.01) (Fig. 5b). There was no significant difference on overall survival between the high expression group and the low expression group(P = 0.63) (Fig. 5c).

### Publication bias

Funnel plot was used to detect publication bias, as shown in Fig. 6. Evidence showed that funnel plots for each group were symmetrical, with no significant risk of bias. This result suggested that the results of this meta-analysis were reliable.

## Discussion

Our study focused on the relationship of HER2 expression in bladder cancer between oncological characteristics and patient prognosis. We included 14 articles, 1398 patients for our study. We also used the TCGA database for analysis.

Based on the TCGA data analysis chart we obtained from UALCAN, we learned that HER2 expression in bladder cancer was significantly higher than in normal tissues. This has been confirmed by previous study [13]. Our result indicated that there was no difference in HER2 gene expression between men and women. However, TCGA data suggested that HER2 was significantly less expressed in tumor tissues of female patients than that in males. Due to the conflicting results, variances in HER2 expression among bladder cancer patients of different sexes remain unclear. After consulting relevant literatures, we speculated that the differential expression of HER2 in genders might be related to androgen receptor (AR).

The AR signaling pathway has been shown to promote tumor development and progression, which may account for some of the gender differences in bladder cancer [30]. Zheng *et al*. claimed that AR activation upregulated the expression of HER2 in bladder cancer cells [31]. It has been proved that inhibiting AR pathway can successfully control the occurrence and development of bladder cancer, and can be synergistic with cisplatin chemotherapy regimen [32]. These results of our own research and previous studies indicate that AR related pathway regulates HER2 expression in bladder cancer cells.

Our results showed that HER2 tended to be highly expressed in CIS and multifocal tumors. Previous studies have reached similar conclusions [17, 29]. CIS is a flat, noninvasive urothelial carcinoma with a high probability of progression. And CIS are usually multifocal, the incidence of muscle infiltration in CIS is significantly higher than that of Ta and T1 bladder cancer [33, 34]. Multifocal CIS of the Upper Tract is associated with high risk of bladder cancer recurrence [35]. We conclude that overexpression of HER2 in bladder cancer often appears in CIS and multifocal tumors and predicts a high risk of tumor recurrence.

As described earlier in this paper, HER2 is significantly associated with tumor size, grade, and stage. A previous study has reached the same conclusion [36]. All we can say is that HER2 expression status correlates with bladder cancer grade and stage. The details of relevant mechanism need to be confirmed in further study. We also found that HER2 expression was associated with lymph node metastasis. A former study has indicated that the probability of positive expression of HER2 is significantly higher in lymph node metastases than in primary bladder cancer [37].

We also found that HER2 expression was associated with tumor recurrence, progression, and poor RFS in patients with bladder cancer. A recent study has also shown that HER2 expression in bladder cancer cells is associated with tumor recurrence [38]. Similar findings have been previously reported in the past. They said HER2 expression was associated with disease aggressiveness and poor outcome of bladder cancer [39]. The results of subgroup analysis were consistent. However, we found that HER2 expression did not affect RFS in NMIBC. TCGA data analysis indicated that HER2 expression was not associated with overall survival in bladder cancer patients.

The idea of HER2 as a possible therapeutic target for bladder cancer was raised early [27, 40]. Nagasawa *et al*. found that TAK-165(a potent inhibitor of HER2) significantly inhibited the growth of bladder cancer cell. It may be a hopeful agent for bladder [41]. Tsai *et al*. constructed a HER2-targeted, envelope-modified retroviral vector which carried the interleukin (IL)-12 gene for the treatment of bladder cancer [42]. It has also been shown that epidermal growth factor receptor (EGFR) TKI (tyrosine kinase inhibitors) blocked both radiation-activated EGFR and HER2 signaling and inhibited the growth of bladder cancer cells in vitro and vivo [43]. T-DM1, a drug consisting of the HER2 antibody trastuzumab in combination with a cytotoxic agent, has been indicated to be superior to trastuzumab alone in breast cancer by Hayashi *et al* [44]. There were also recent study pointing to EGF - anthrax toxin conjugates as a new approach in the fight against bladder cancer [45]. A number of other HER2 related therapeutic targets in addition to the EGFR-related inhibitor were found. For example, indoleamine 2, 3-dioxygenase and programmed death ligand-1 have been proved to be effective relevant therapeutic targets about HER2 [38].

Except for those specific targeted drugs mentioned above, other researches focusing on the mechanism of HER2 - mediated cancer have also opened the door to new drug development. We've already mentioned AR-related pathways in the previous paragraphs according to other articles [31.32]. Similar studies have been conducted in other types of tumors. Mika *et al*. found the SORLA-dependent molecular pathway in HER2-driven cancers [46]. Yoshihisa *et al*. suggested that syn-miR-143 down-regulated the expression of HER2 through silencing DEAD/H-box RNA helicase 6 (DDX6) in HER2-positive gastric cancer cells [47]. The mechanism of HER2 in bladder cancer still needs to be further explored.

There were limitations in our study. First, we only searched PubMed database, the number of included literatures is not big enough. Second, the search was restricted to English language articles, we may have missed some documents written in other languages. Finally, the literatures we included measured HER2 expression by IHC. It has been suggested that the results of IHC and fluorescence in situ hybridization (FISH) were not completely consistent when detecting HER2 expression in bladder cancer [48, 49]. A combination of FISH assays is needed for further research in the future.

# Conclusion

Expression of HER2 is higher in bladder cancer tissues than in normal tissues. HER2 is highly expressed in CIS and multifocal tumors. HER2 expression is also associated with large tumor size, high tumor stage and grade, lymph node metastasis, risk of progression and recurrence. HER2 expression has no effect on the lymph vascular invasion and overall survival of bladder cancer patients. The effect of gender on HER2 expression remains unclear. Overall, patients with high HER2 expression bladder cancer usually have a shorter recurrence-free survival. However, in NMIBC, this finding needs to be further validated.

# Abbreviations

HER2: Human Epidermal Growth Factor Receptor 2; OR: odds ratio; HR: hazard ratio; TCGA: The cancer genome atlas; RFS: recurrence-free survival; NMIBC: non-muscle invasive bladder cancer; MIBC: muscle invasive bladder cancer; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PICO: population, intervention, comparison, results; IHC: immunohistochemistry; ASCO: American Society of Clinical Oncology; CAP: American College of Pathology; NOS: Newcastle - Ottawa Quality Assessment Scale; CIS: Carcinoma in situ; AR: androgen receptor; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitors; DDX6: DEAD/H-box RNA helicase 6; FISH: fluorescence in situ hybridization.

# Declarations


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Not applicable.


### Authors' contributions

Kai Gan, Yue Gao and Kuangzheng Liu conceived the idea of the study, did the literature search and selected the studies. Kai Gan and Yue Gao extracted the relevant information. All Authors wrote the manuscript together, read and approved the final version of the manuscript.


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### Availability of data and materials

All data generated in this study is included in the article.

### Ethical Approval

Ethical Approval is not applicable for this article.

### Consent for publication

All authors have given their consent for publication.

### Competing interests

The authors declare that they have no competing interests.

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# Tables

Due to technical limitations, table 1 & 2 docx are only available as a download in the Supplemental Files section.

# Figures

Fig.1

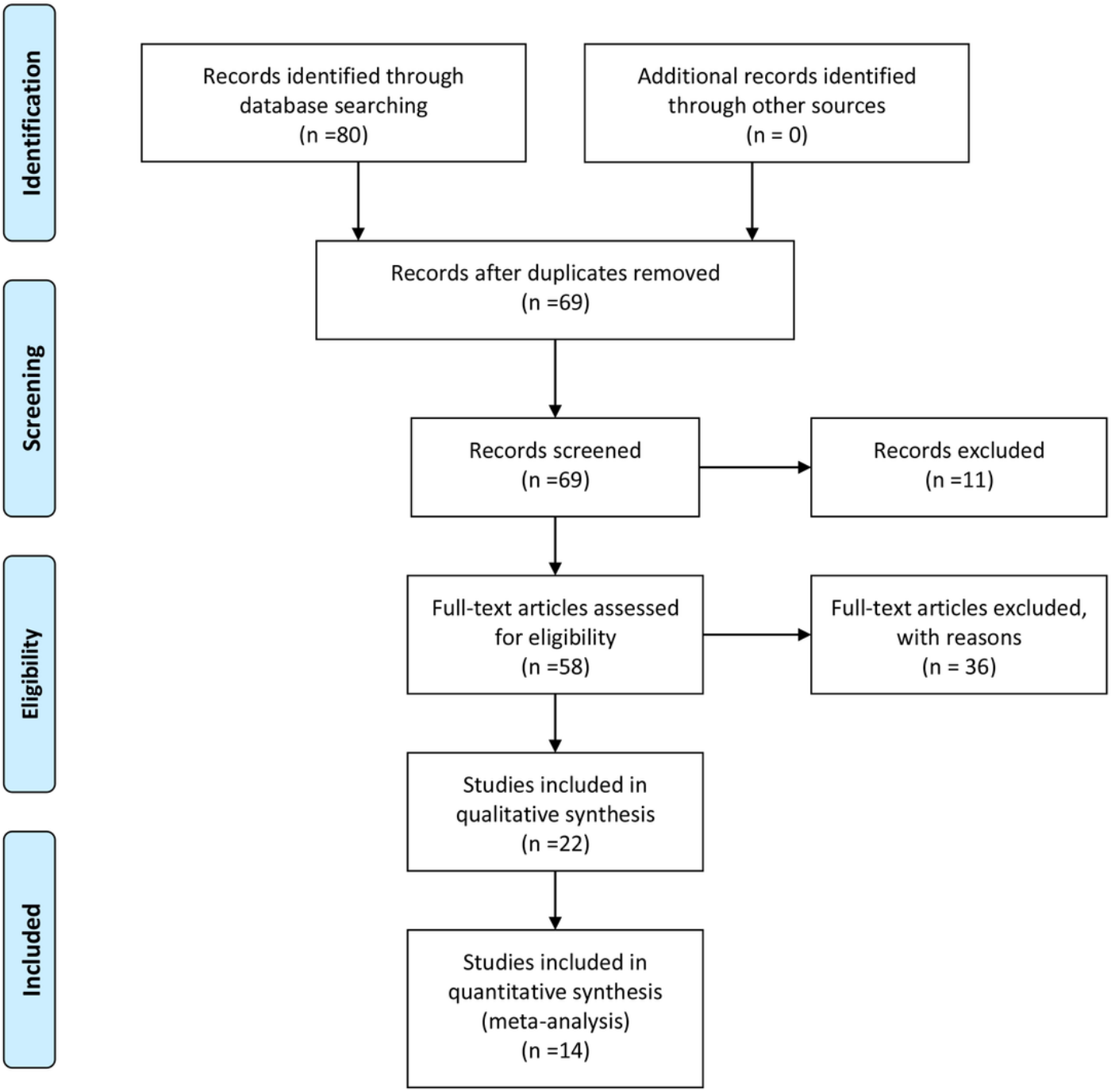
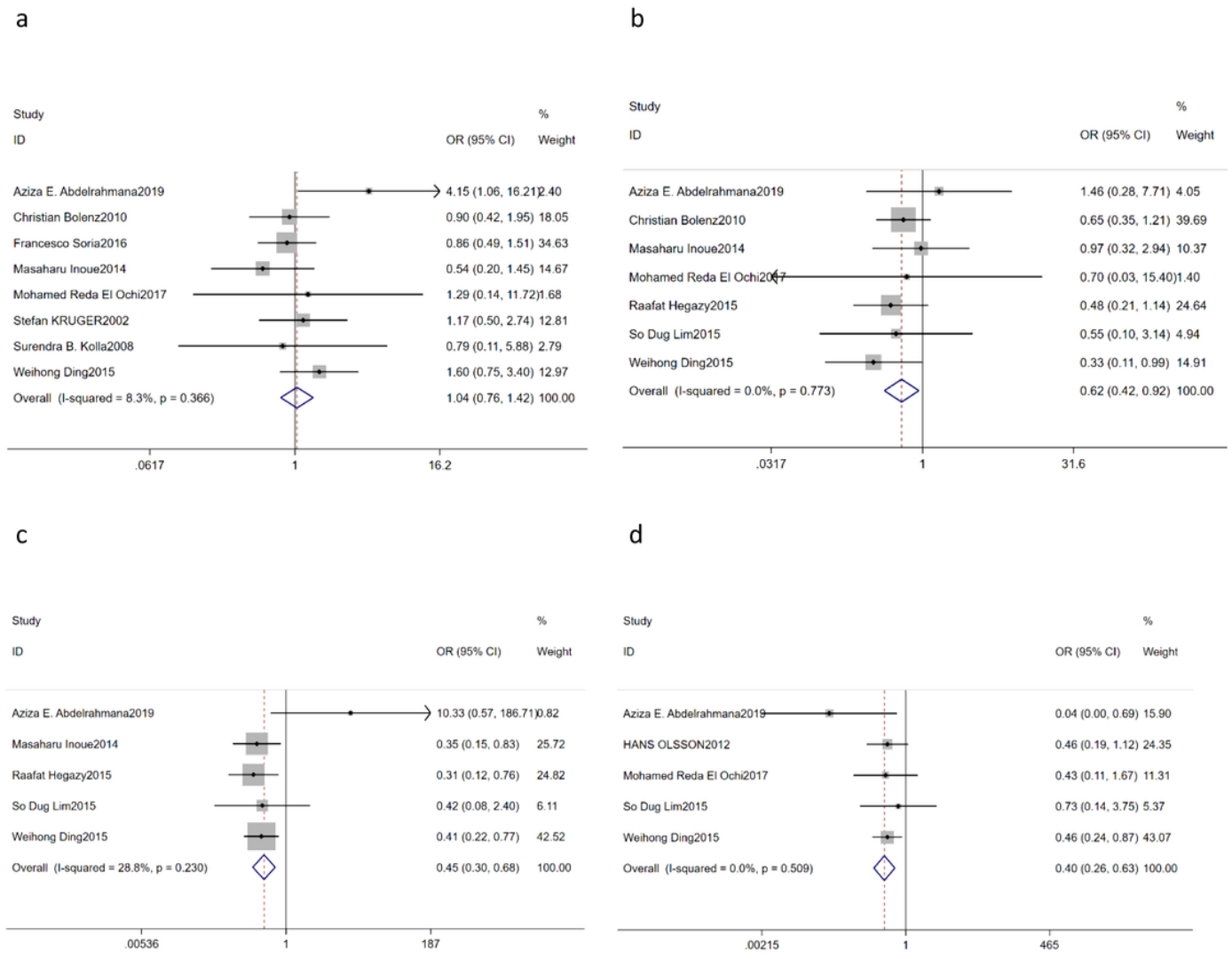



**Figure 1**

Study selection flowchart

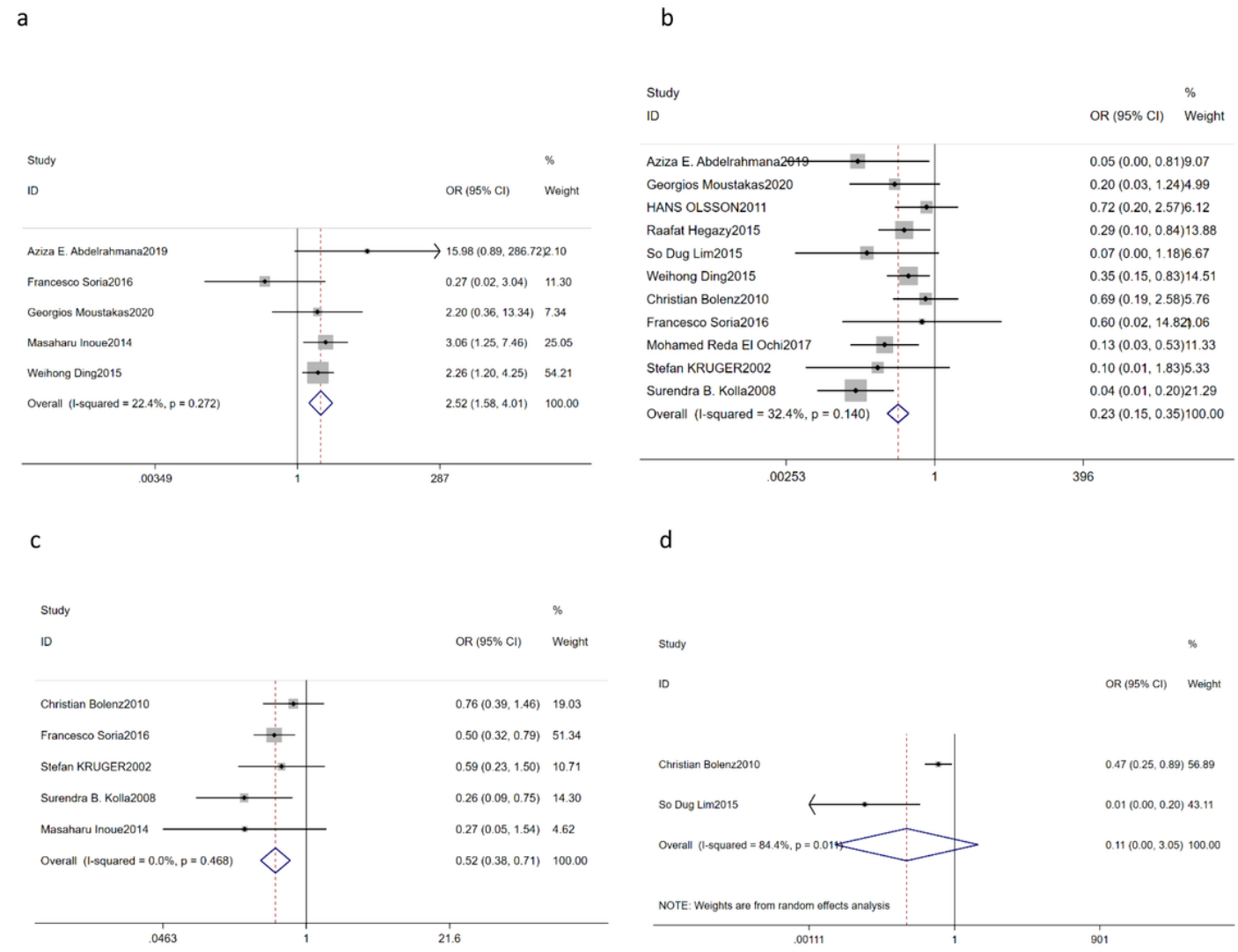
Fig.2




## Figure 2

Forest plots describing the correction of HER2 expression with gender(a), carcinoma in situ(b), multifocal tumors(c) and large tumor size(d).

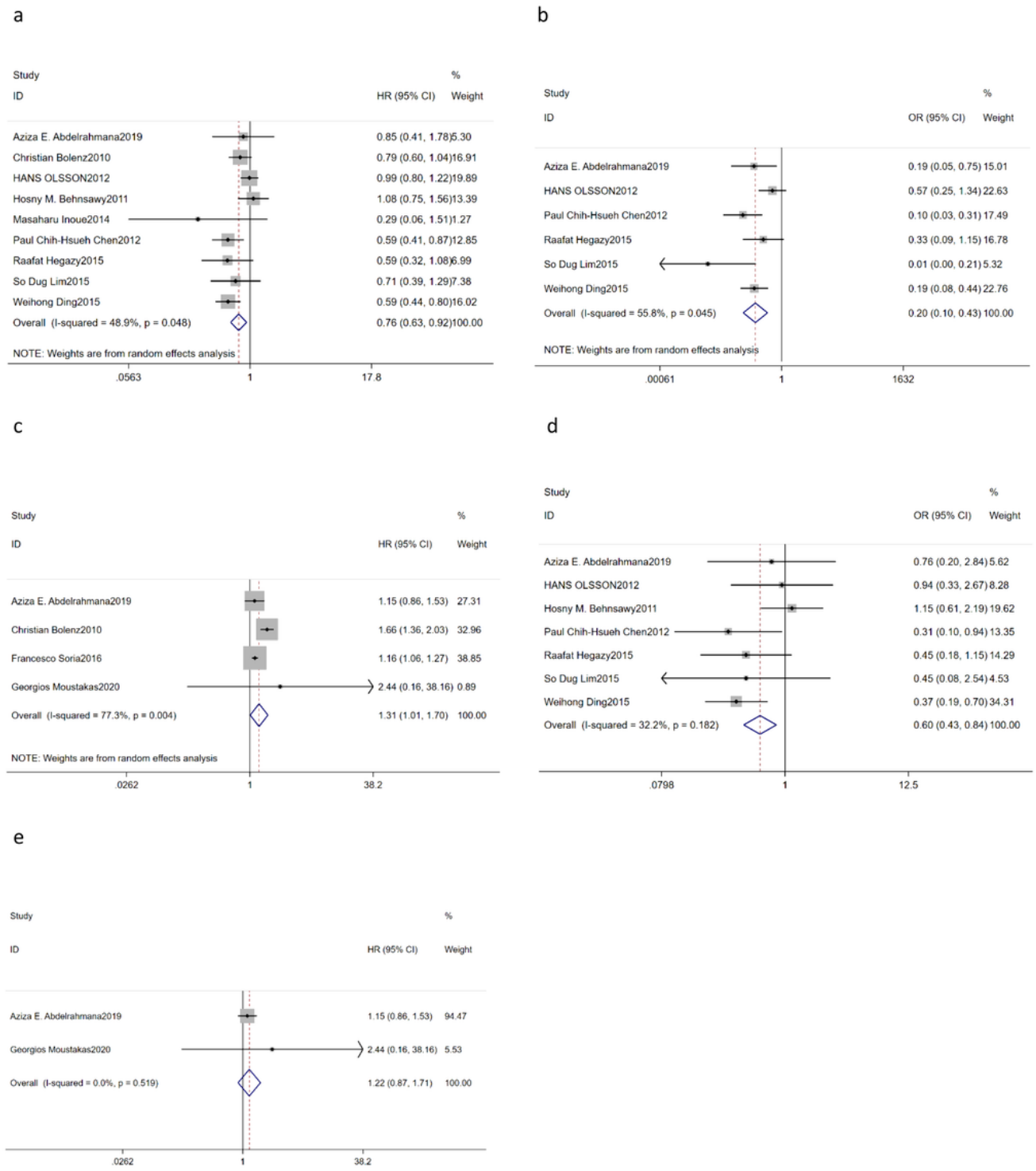
Fig.3




## Figure 3

Forest plots describing the correction of HER2 expression with stage(a), grade(b), lymph node metastases(c) and lymph vascular invasion(d).

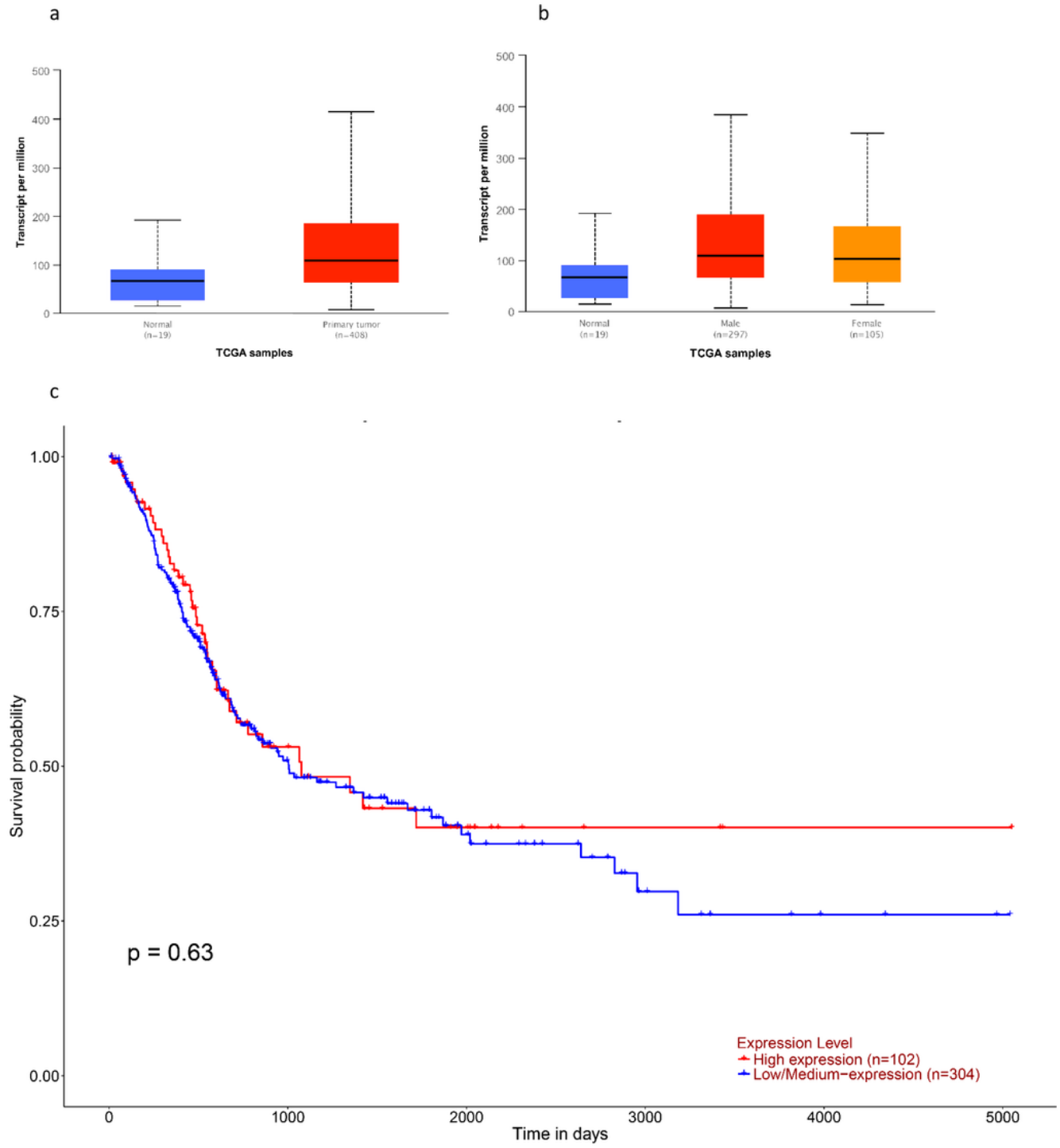
Fig.4




## Figure 4

Forest plots describing the correction of HER2 expression with recurrence(a), progression(b), 2-year recurrence-free survival (RFS)(c), recurrence in NMIBC(d), 2-year recurrence-free survival in NMIBC(e).

Fig.5




## Figure 5

TCGA analysis of differences about HER2 expression between cancer and normal tissues(a), male and female(b). Survival conditions were also compared(c).

Fig.6

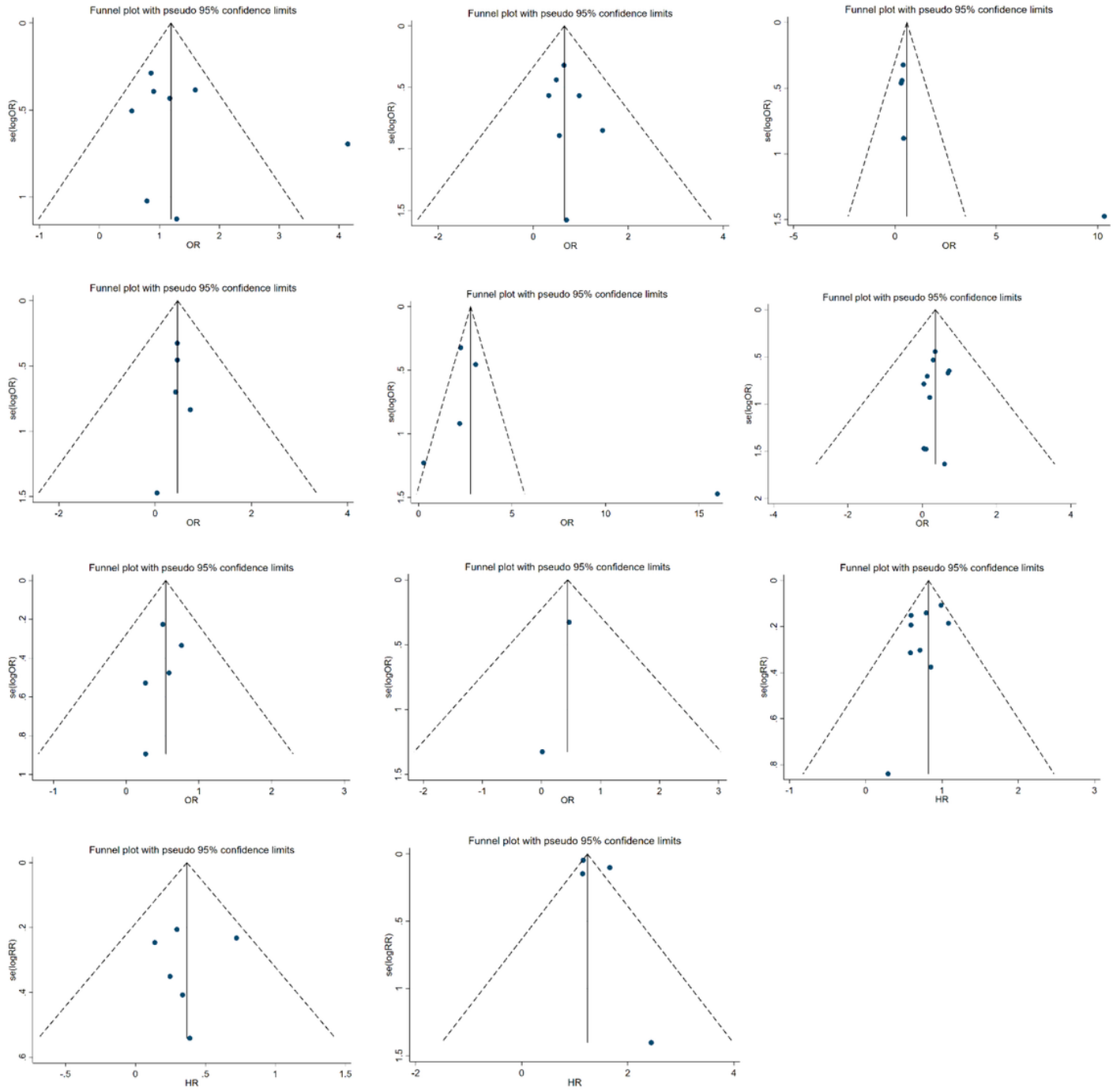



**Figure 6**

Funnel plots of meta analysis.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.docx

- table2.docx