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# A systematic review and meta-analysis of *BRCA1/2* mutation for predicting the effect of platinum-based chemotherapy in triple-negative breast cancer

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ABSTRACT

*Introduction:* Platinum-based chemotherapy (PBC) remains the mainstay of treatments for triple-negative breast cancer (TNBC). TNBC is a heterogeneous group, the issue of whether *BRCA1/2* mutation carriers have a particular sensitivity to platinum agents is inconclusive. We conducted a meta-analysis to explore the relationship between *BRCA1/2* mutation and PBC susceptibility in individuals with TNBC, aiming to gain more information on the size of the benefit of PBC in *BRCA1/2* mutation carriers.

*Materials and methods:* All studies applying PBC with a subgroup of BRCA1/2 status were included. All endpoints, including pCR and RCB in the neoadjuvant phase, DFS in the adjuvant phase, ORR, PFS, and OS in the advanced phase, were assessed using HRs and 95% CI.

*Results:* From the 22 studies included, there were 2158 patients with TNBC, with 392 (18%) bearing the *BRCA1/2* gene mutation. Based on 13 studies applying neoadjuvant PBC, we discovered that *BRCA1/2* mutation was substantially associated with a 17.6% increased pCR rate (HR 1.32, 95% CI 1.17–1.49, $p < 0.00001$; $I^2 = 51\%$). Same result was observed in RCB0/I index (HR 1.38, 95% CI 1.08–1.76, $P = 0.009$; $I^2 = 0\%$). The meta-analysis of 6 trials addressing advanced therapy revealed that ORR rates were significantly higher in patients with *BRCA1/2* mutation (HR 1.91, 95% CI 1.48–2.47, $p < 0.00001$; $I^2 = 32\%$), as well as PFS(HR 1.13, 95% CI 0.81–1.57, $P = 0.47$; $I^2 = 0\%$) and OS (HR 1.89, 95% CI 1.22–2.92, $P = 0.004$; $I^2 = 0\%$).

*Conclusion:* According to our meta-analysis of 22 trials in TNBC, *BRCA1/2* mutation carriers were significantly more sensitive to PBC regimens, especially in neoadjuvant and advanced therapy.

## 1. Introduction

Triple-negative breast cancer (lacking the estrogen/progesterone receptor and the human epidermal growth factor receptor 2) accounts for 10%–20% of all breast cancers. A large number of clinical studies have shown TNBC is more frequent in young groups with larger tumor size, higher rate of histological stage III, higher positive lymph node rate and higher recurrence rate than other types of breast cancer, and more prone to lung, liver and brain metastasis [1,2]. Cytotoxic chemotherapy, such as a platinum-contained regimen, remains the mainstay of treatment for TNBC despite the promise of new targeted and biologic agents. TNBC is a heterogeneous group, and the identification of additional molecular biomarkers to predict response to specific chemotherapy is required to further improve treatment strategies with the current menu of chemotherapy. Therefore, the discovery of *BRCA1/2* mutation seems to offer a new therapeutic opportunity for TNBC.

Patients with TNBC had a substantially higher proportion of *BRCA1/2* mutation (15–20%) than other breast cancer subtypes [3]. *BRCA1/2*, a tumor suppressor gene, is a susceptibility gene for breast cancer. Homologous recombination repair (HRR) is an important pathway for cells to repair double strand break (DSB). *BRCA1/2* is essential in HRR, its encoding protein involves in a variety of cell life processes, including

*Abbreviations:* pCR, Pathological complete response; RCB, Residual cancer burden; DFS, Disease-free survival; ORR, Objective remission rate; PFS, Progression-free survival; OS, Overall survival; HRs, Hazard ratios; 95% CI, 95% confidence intervals.

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DNA damage repair, gene transcription regulation, and cell cycle regulation [4]. *BRCA1/2* mutant (*BRCA1/2*-mut) cells typically have defective DNA repair and genome-wide instability, as well as an early start, high grade, and aggressive clinicopathological profile [5]. Olaparib, a PARP inhibitor, kills tumor cells with *BRCA1/2*-mut by synthesizing lethal effects. The results of OlympiAD [6], a Phase III trial, revealed that Olaparib monotherapy could provide statistically significant and clinically meaningful PFS benefits to HER2-negative metastasis breast cancer patients with *BRCA1/2*-mut. The ORR rate of the Olaparib group was 59.9%. Recently, researchers have suggested that PBC is also effective in patients with *BRCA1/2* mutations [7]. Subgroup analysis of the TNT study [8] showed that carboplatin group's ORR rate achieved 68% in advanced patients with TNBC carrying *BRCA1/2* mutation. Perhaps, TNBC patients with *BRCA1/2*-mut benefit more from PBC.

Platinum and its derivatives, a group of cytotoxic DNA-damaging agents, destroy the tumor cells by inducing DNA strand breaks. They can also eliminate tumor cells by triggering oxidative stress, affecting the regulation of microRNAs and phosphorylating protein kinase C [9–11]. It is acknowledged that the *BRCA1/2*-mut cells with DNA repair deficiencies are sensitive to DNA damage agents [12]. Therefore, the relationship between *BRCA1/2* mutation and platinum sensitivity in patients with TNBC has emerged as a critical research concern. Our primary aim was to investigate whether platinum-contained chemotherapy can provide additional benefits to TNBC *BRCA1/2* mutation carriers. Thus, we did a systematic review and meta-analysis of RCTs to investigate the prognosis difference between TNBC patients with or without *BRCA1/2* mutation receiving PBC. Our study provides a meaningful result, that shows *BRCA1/2* mutation was more sensitive to platinum-containing chemotherapy regimens.

## 2. Material and methods

### 2.1. Search strategy and study identification

A comprehensive literature search of Pubmed, Medline, and Cochrane found RCTs that were acceptable between January 2000 and March 2022, with no language constraints. The following keywords were used in the search strategy: "triple-negative breast cancer," "platinum," "carboplatin," "cisplatin," and"*BRCA1/2*" (Supplementary Table 1). To identify more relevant tests, references were systematically searched. Two authors (JXM, WKN) conducted the systematic literature search separately, and any differences were addressed by a discussion with the third author (XLZ). The protocol was submitted in the PROSPERO database (CRD42022331023, available from https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=331023). The systematic review and meta-analysis were designed and conducted in accordance with to the Cochrane Handbook for Systematic Reviews of Interventions [13]. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14].

### 2.2. Selection criteria

Studies must fulfill all of the following inclusion criteria to be considered for inclusion in this meta-analysis: (1) patients with triple-negative breast cancer; (2) RCTs involving *BRCA1/2* mutation and wild-type cohorts; (3) intervention regimens should include PBC; and (4) endpoint data has been published. Exclusion criteria included: (1) studies that classified patients based on *BRCA1/2* expression levels or methylation rather than *BRCA1/2* mutation; (2) studies that classified patients based on other homologous recombination repairs (HRR) mutations; and (3) case reports.

### 2.3. Data extraction

The following information was retrieved separately by two authors in the *BRCA1/2* mutation and wild-type arms: author/trial name, year of publication, country, stages, outcomes, treatment arms, number of patients. Disagreements were addressed via consensus. Data were extracted and reported as a single trial when several publications for the same trial were located.

### 2.4. Assessment of bias risk

Two authors independently assessed the risk of bias for each included study using the Cochrane Collaboration tool. Disagreements were addressed with the assistance of the third author. We evaluated the following using the Cochrane risk of bias tool: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants, personnel, and outcome assessment (performance bias and detection bias); (4) incomplete outcome data (attrition bias); and (5) selective reporting data (reporting bias).

### 2.5. Statistical analysis

The trial results were separated into three sections: neoadjuvant phase outcomes of pCR and RCB, adjuvant phase outcomes of DFS, and advanced phase outcomes of ORR, PFS, and OS. HRs and 95% CIs were estimated for each outcome in the *BRCA1/2*-mut TNBC group against the *BRCA1/2*-wt group. HR $> 1$ implies that the *BRCA1/2* mutation is a platinum-sensitive factor that can confer survival advantages. To compare the differences in outcomes between the two groups, the chi-square test was performed. To show our findings, we chose a woodland tract. The p-value of 0.05 was thought to be statistically significant. To validate homogeneity, the Higgins $I^2$ index was computed. When $I^2$ was more than 50%, the random-effects model (DerSimonian and Laird technique) was employed; otherwise, the fixed-effects model (Mantel-Haenszel method) was used. In addition, funnel plots were performed to analyze bias and optimize the sensitivity analysis. The program Review Manager was used to conduct the meta-analysis (RevMan, version 5.3; Stata version 16).

## 3. Results

### 3.1. Study selection and characteristics

There was a total of 427 records found. After deleting duplicate entries, irrelevant themes, review articles, reviews, and study methods, we included 199 research. After screening the title and abstract, there are only 39 publications were left for full-text review. After excluding 17 publications based on full-text analysis, 22 studies [8,15–35] remained for qualitative and quantitative analysis, containing 18% (392/2158) of patients with a *BRCA1/2* mutation. To further understand the significance of *BRCA1/2*, 22 trials were separated into three phases: neoadjuvant, adjuvant, and progressed. Fig. 1 shows the flow diagram of the selection strategy. Tables 1–3 summarizes the major features of the studies covered.

### 3.2. Platinum-containing neoadjuvant regimen leads to higher pCR and RCB rates in patients with BRCA1/2 mutation TNBC

To investigate the relationship between platinum-contained neoadjuvant treatment and *BRCA1/2* mutation in TNBC, we analyzed the data from 13 RCTs. Their sample sizes vary from 28 to 476 for a total of 1321 individuals, 269 (20.4%) of whom have a *BRCA1/2* mutation. The pCR rate was regarded as the evaluation index. Overall, all 13 studies suggest pCR rates, with 669 patients (50.6%) receiving pCR (Fig. 2A). In the *BRCA1/2* mutation and wild-type groups, pCR was attained in 64.7% (174/269) and 47.1% (495/1052) of the patients, respectively (HR 1.32, 95% CI 1.17–1.49, $p < 0.00001$; $I^2 = 51\%$). RCB outcomes were also reported by PrECOG0105, Yuan2020, and NCT01372579 (Fig. 2B). RCB has been proven to be an independent prognostic factor for distant recurrence-free survival in patients with early breast cancer

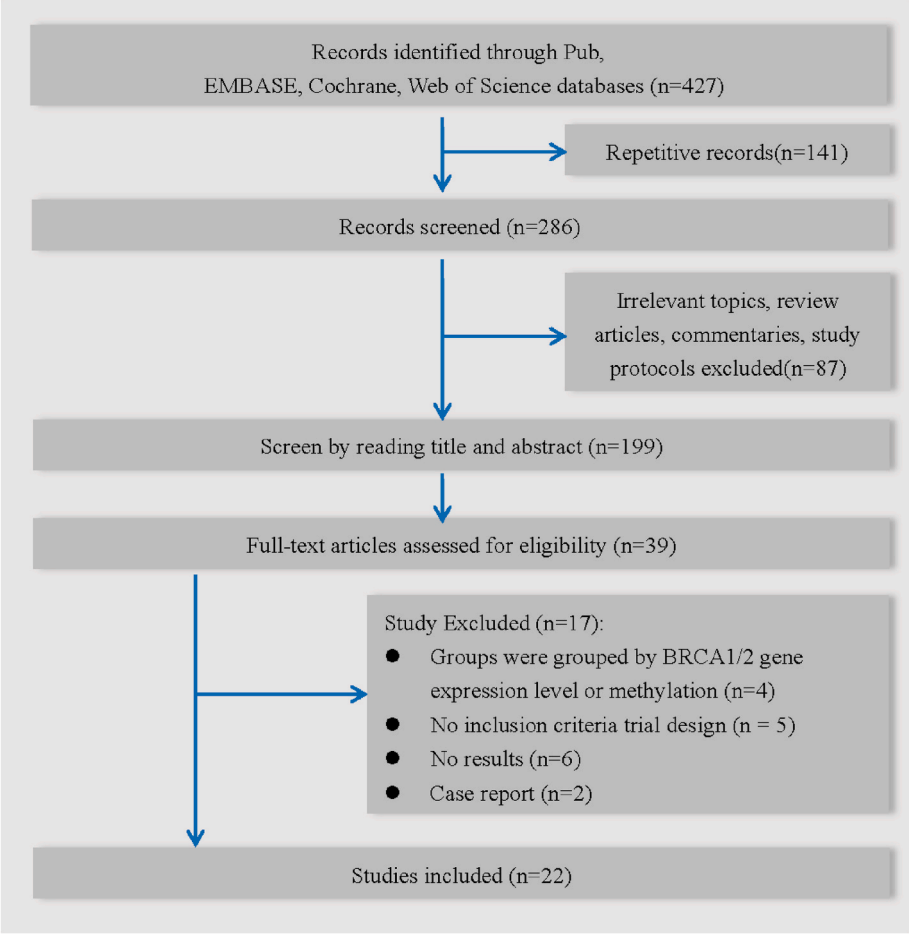


**Fig. 1.** Flow diagram of the selection strategy.

(RCB0 represents full pathological response; RCBI represents minimum residual illness; RCBII represents moderate residual disease, and RCBIII represents substantial residual disease.). RCB0/I was considered a favorable pathological response. In the three investigations, 85/162 instances (52.5%) reached RCB0/I, with 76.7% (23/30) and 47.0% (62/132) cases in the *BRCA1/2* mutation and wild-type groups, respectively (HR 1.38, 95% CI 1.08–1.76, P = 0.009, $I^2$ = 0%).

In addition, except for Silver 2010 and TBCRC030, which used cisplatin alone, all studies employed carboplatin in conjunction with other chemotherapy regimens (anthracycline, paclitaxel, eribulin, and PARP inhibitors). Thus, we performed separate analyses in the cisplatin monotherapy group and platinum combination group. In the cisplatin monotherapy group, patients with *BRCA1/2*-mut TNBC achieve a 37.5% pCR benefit than patients with *BRCA1/2*-wt TNBC(9.5%) (HR 4.29, 95% CI 1.78–10.34, p = 0.001; $I^2$ = 0%) (Fig. 2C). In platinum combination group, patients with BRCA1/2-mut TNBC achieve 65.5% pCR benefit than patients with *BRCA1/2*-wt TNBC (50.8%) (HR 1.37, 95% CI 1.15–1.63, p = 0.0004; $I^2$ = 43%) (Fig. 2D). Together, early TNBC patients with *BRCA1/2*-mut are shown to have a large additional benefit from the platinum-contained neoadjuvant regimen.

### 3.3. In patients with BRCA1/2 mutation TNBC, a platinum-containing adjuvant treatment fails to provide a prolonged DFS survival benefit

Only 3 adjuvant stage trials who use carboplatin as the only PBC agent pass eligibility criteria, involving a total of 317 patients (Supplementary Figure 1). The survival benefit of the *BRCA1/2* mutant or the wild-type group is comparable (HR 1.10, 95%CI 0.82–1.46, P = 0.53, $I^2$ = 43%). Thus, our results failed to prove that *BRCA1/2* mutation can provide an additional benefit to patients with TNBC from adjuvant platinum-containing chemotherapy. In addition, NCT01150513 reported OS outcome. The result showed that OS had no significant differences in TP with mutation group (n = 12) and wild-type group (n = 62) (P value > 0.05).

### 3.4. Platinum-containing advanced treatment regimen improves ORR rates and survival benefits in patients with TNBC carrying BRCA1/2 mutation

A total of 6 advanced-stage trials were included in the analysis. The TNT trial used carboplatin monotherapy, whereas other studies combined carboplatin or cisplatin with additional treatments. The number of instances in the sample ranged from 40 to 153. There were 467 patients in all, with 70 (15%) having *BRCA1/2* mutation. The overall ORR of patients with advanced TNBC who received PBC was 41.8% (195/467), 67.1% (47/70) in the *BRCA1/2* mutation group, and 37.3% (148/397) in the wild-type group (HR 1.91, 95% CI 1.48–2.47, P < 0.00001; $I^2$ = 32%) (Fig. 3A). All 6 studies compared PFS in the *BRCA1/2* mutant group (n = 70) to the *BRCA1/2* wild-type group (n = 397). The median PFS varies from 2.8 to 14.9 months. Our findings revealed a substantial difference in PFS between individuals with the *BRCA1/2* mutation and those with the wild-type gene (HR 1.13, 95% CI 0.81–1.57, p = 0.47; $I^2$ = 0%) (Fig. 3B). Moreover, 5 studies found a greater OS advantage in *BRCA1/2* mutant advanced patients with TNBC (HR 1.89, 95% CI 1.22–2.92, P = 0.004; $I^2$ = 0%) (Fig. 3C). Therefore, *BRCA*1/2-mut may bring more objective tumor responses and improve long-term survival in patients with advanced TNBC.

**Table 1**
Baseline characteristics of neoadjuvant studies. P: paclitaxel; Cb: carboplatin; E: epirubicin; C: cyclophosphamide; Ola: olaparib; A: doxorubicin; D: docetaxel; Gem: gemcitabine; nab-P: nab-paclitaxel.

| Author/Trial | Year | Country | Stage | Outcomes | Treatment arm | Number of cases | | pCR rate | | RCB0/I |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *BRCA1/2*-mut | *BRCA1/2*-wt | *BRCA1/2*-mut | *BRCA1/2*-wt | mut/wt |
| BrighTNess | 2018 | 15 countries | II-III | pCR | **Platinum-contained chemotherapy I:** P (80 mg/m$^2$ weekly for 12 weeks) + Cb (AUC 6, every 21 days, for four cycles) + veliparib (50 mg) orally twice a day; **Platinum-contained chemotherapy II:** P (80 mg/m$^2$ weekly for 12 weeks) + Cb (AUC 6, every 3 weeks, for four cycles) + veliparib placebo; **Platinum-free chemotherapy:** P (80 mg/m$^2$ weekly for 12 weeks) + Cb placebo + veliparib placebo. | 70 | 406 | 54.29% | 54.68% | na |
| BSMO | 2019 | Belgium | II-III | pCR | P (80 mg/m$^2$, weekly) + Cb(AUC 2, weekly for 12 weeks), followed by bi-weekly E (90 mg/m$^2$) + C (600 mg/m$^2$) for four cycles. | 9 | 42 | 77.78% | 52.38% | na |
| GeparOLA | 2020 | Germany | I-III | pCR | **Platinum-free chemotherapy:** P (80 mg/m$^2$ weekly) + Ola(100 mg twice daily for 12 weeks); **Platinum-contained chemotherapy:** P (80 mg/m$^2$ weekly) + Cb(AUC 2, weekly for 12 weeks); both followed by EC. | 20 | 16 | 60.00% | 37.50% | na |
| GeparSixto | 2014 | Germany | II-III | pCR,DFS | **Platinum-contained chemotherapy:** P (80 mg/m$^2$) + non–pegylated liposomal doxorubicin (20 mg/m$^2$) weekly for 18 weeks + bevacizumab (15 mg/kg every 3 weeks)+ Cb(AUC 5, once every week for 18 weeks); **Platinum-free chemotherapy:** P (80 mg/m$^2$) + non–pegylated liposomal doxorubicin (20 mg/m$^2$) weekly for 18 weeks + bevacizumab (15 mg/kg every 3 weeks). | 26 | 120 | 65.38% | 45.00% | na |
| NCT01372579 | 2015 | USA | II-III | pCR,RCB | Cb(AUC 6, every 3 weeks) + eribulin (1.4 mg/m$^2$, day 1,8 every 3 weeks) for four cycles. | 3 | 27 | 100.00% | 77.78% | 1.14 (0.75,1.74) |
| NeoSTOP | 2020 | USA | I-III | pCR | **Platinum-contained chemotherapy I**: P (80 mg/m$^2$, weekly for 12 weeks) + Cb(AUC 6, every 3 weeks for four cycles) followed by A (60 mg/m$^2$) + C (600 mg/m$^2$) every 14 days for four cycles; **Platinum-contained chemotherapy II**: Cb(AUC 6)+ D (75 mg/m$^2$) every 3 weeks for six cycles. | 17 | 65 | 76.47% | 49.23% | na |
| PrECOG 0105 | 2015 | USA | I-III | pCR,RCB | Gem (1000 mg/m$^2$;day1,8) + Cb(AUC 2, day1,8) + iniparib (5.6 mg/kg; days 1,4,8,11) every 3 weeks for four cycles. | 16 | 61 | 56.25% | 32.79% | 1.48 (1.01,2.15) |
| Sharma 2017 | 2017 | USA, Spanish | I-III | pCR,RCB | **DCb** : Cb(AUC 6)+ D (75 mg/m$^2$) every 21 days for 4–6 cycles. | 27 | 133 | 59.26% | 40.60% | na |
| Sliver 2010 | 2010 | USA | II-III | pCR | Cisplatin 75 mg/m$^2$ every 3 weeks for 4 cycles. | 2 | 26 | 100.00% | 15.38% | na |
| TBCRC030 | 2020 | USA | I-III | pCR | **Platinum-contained chemotherapy:** Cisplatin 75 mg/m$^2$ every 3 weeks for 4 cycles; **Platinum-free chemotherapy:** P 80mg/m2 weekly for 12 weeks. | 6 | 69 | 16.67% | 7.25% | na |
| Yuan2020 | 2020 | USA | II-III | pCR,RCB | Cb(AUC 6, every 4 weeks for 4 cycles) + nab-P (100 mg/m$^2$, weekly for 16 weeks). | 11 | 44 | 72.73% | 45.45% | 1.60 (0.98,2.60) |
| Holanek2021 | 2021 | Czech | II-III | pCR | **Platinum-contained chemotherapy I** : Cisplatin alone(75 mg/m$^2$, every 3 weeks for 3–4 cycles) **Platinum-contained chemotherapy II:** P (80 mg/m$^2$, weekly) + Cb (AUC 1.5–2 for 12 cycles). | 48 | 20 | 81.25% | 20.00% | na |
| Sella 2018 | 2018 | Israel | I-III | pCR | A (60 mg/m$^2$for 4 cycles) + C (600 mg/m$^2$ every 2 weeks followed by 12 cycles) followed by P (80 mg/m$^2$ weekly) + Cb(AUC 1.5) for 12 cycles. | 14 | 23 | 64.30% | 44.80% | na |

### 3.5. Bias risk assessment and sensitivity analysis

The funnel plot showed good homogeneity of the included studies (Supplementary Figure 2). Supplementary Figure 3 shows the bias risk assessment for included studies, and our study has no substantial bias. We performed a sensitivity analysis on all indicators, and excluded them each individually. The results revealed that no one piece of literature seemed significant for the research, so our findings were credible (Supplementary Figure 4).

## 4. Discussion

Platinum has certain clinical efficacy in the treatment of TNBC, which can lead to DNA damage to tumor cells. Platinum directly acts on DNA, forms adduct with DNA, restricts the unwinding of DNA, and inhibits the replication of DNA. This is the main mechanism of the antitumor action of platinum [36]. This process mainly occurs in the G2 phase of mitosis [37]. Like other antitumor drugs, platinum drugs inhibit DNA replication in a non-specific way. Tumor cells are more sensitive to platinum because it has fast DNA synthesis. However, there are few predicting biomarkers of platinum sensitivity. *BRCA1/2* is a key

**Table 2**
Baseline characteristics of adjuvant studies. P: paclitaxel; Cb: carboplatin; E: epirubicin; C: cyclophosphamide; F: fluorouracil; D: docetaxel.

| Author/Trial | Year | Country | Stage | Outcomes | Treatment arm | Number of cases | | DFS(HRs, 95% Cl) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *BRCA1/2*-mut | *BRCA1/2*-wt | mut/wt |
| PATTERN | 2020 | China | I-III | DFS | **Platinum-contained chemotherapy I:**P (80 mg/m$^2$), + Cb(AUC 2) every 4 weeks for 6 cycles; **Platinum-contained chemotherapy II:** CEF-T: C (500 mg/m$^2$, E 100 mg/m$^2$ + F 500 mg/m$^2$ every 3 weeks for 3 cycles) followed by D (100 mg/m$^2$, every 3 weeks for 3 cycles). | 34 | 235 | 0.73 (0.25,2.13) |
| Vollebergh | 2010 | Netherlands | III | DFS | **Platinum-free chemotherapy: Conventional chemotherapy** (5*FEC: 5-fluorouracil 500 mg/m$^2$, epirubicin 90 mg/m$^2$, cyclophosphamide 500 mg/m$^2$); **Platinum-contained chemotherapy: HD-PB chemotherapy** (4*FEC, followed by 1*CTC: cyclophosphamide 6000 mg/m$^2$, thiotepa 480 mg/m$^2$ and carboplatin 1600 mg/m$^2$). | 7 | 20 | 1.43 (0.48,4.23) |
| NCT01150513 | 2022 | China | I-III | DFS,OS | **Platinum-contained chemotherapy:** D (75 mg/m$^2$) or P (175 mg/m$^2$)+ carboplatin (AUC 5) every 3 weeks; **Platinum-free chemotherapy:** E (90 mg/m$^2$)+ C (600 mg/m$^2$) followed by D (75 mg/m$^2$) or P (175 mg/m$^2$) every 3 weeks. | 12 | 62 | 0.49 (0.04,6.00) |

**Table 3**
Baseline characteristics of advanced studies. Cb: carboplatin; D: docetaxel; DDP: Cisplatin; Gem: gemcitabine.

| Author/Trial | Year | Country | Stage | Outcomes | Treatment arm | Number of cases | | ORR (HRs, 95% Cl) | PFS(HRs, 95% Cl) | OS(HRs, 95% Cl) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *BRCA1/2*-mut | *BRCA1/2*-wt | mut/wt | mut/wt | mut/wt |
| TNT | 2019 | K | na | ORR,PFS, OS | **Platinum-contained chemotherapy:** Cb (AUC 6, day 1 3-weekly for 6 cycles); **Platinum-free chemotherapy:** D (100 mg/m$^2$, day 1 3-weekly for 6 cycles). | 25 | 128 | 2.42 (1.64,3.56) | 0.97 (0.55,3.36) | 1.73 (0.52,5.76) |
| CBCSG006 | 2015 | China | na | ORR,PFS, OS | **Platinum-contained chemotherapy**: DDP (75 mg/m$^2$) + Gem (1250 mg/m$^2$) every 3 weeks; **Platinum-free chemotherapy**:GT | 6 | 62 | 1.36 (0.90,2.05) | 2.26 (0.74,6.90) | na |
| TBCRC009 | 2015 | USA | na | ORR,PFS, OS | DDP (75 mg/m$^2$) or Cb(AUC 6) every 3 weeks | 11 | 66 | 2.77 (1.34,5.73) | 1.03 (0.53,2.00) | 1.86 (0.88,3.93) |
| Wang 2020 | 2020 | China | I-III | PFS,OS | **Platinum-contained chemotherapy:** platinum-based chemotherapy **Platinum-free chemotherapy**: Non-platinum-based chemotherapy | 7 | 37 | 2.44 (1.43,4.15) | 0.84 (0.21,3.36) | 2.47 (0.67,9.11) |
| Roodler2016 | 2016 | USA | na | ORR,PFS | veliparib (300 mg, Bid for 14 days) + DDP (75 mg/m$^2$, day 1) + vinorelbine (25 mg/m$^2$;days 1,8) every 3 weeks for 6–10 cycles, followed by veliparib monotherapy. | 14 | 26 | 1.86 (0.89,3.87) | 0.91 (0.35,2.37) | 1.23 (0.47,3.22) |
| Galland2022 | 2022 | France | na | ORR,PFS, OS | platinum-based chemotherapy | 7 | 78 | 1.39 (0.83,2.33) | 1.63 (0.70,3.80) | 2.67 (1.04,6.86) |

gene of HRR. The repair function of *BRCA1/2*-mut cells is not perfect. *BRCA1/2* mutation can fail DNA double-strand break repair [38]. Tumor cells with *BRCA1/2* mutation lack the function of homologous recombination repair. While platinum act directly on DNA to impede DNA replication. Therefore, *BRCA1/2* mutation has the potential to act as a sensitizer of platinum. Patients with TNBC had a substantially high proportion of *BRCA1/2* mutation. The mutation rate of *BRCA1/2* in overall breast cancer was 5.3% in the Chinese cohort, with the highest prevalence of 11.2% in TNBC [39]. In our analysis, the incidence of *BRCA1/2* mutation in patients with TNBC was 18% (392/2158). To the best of our knowledge, this is the first and broadest meta-analysis to examine the role of *BRCA1/2* in patients with TNBC receiving PBC. In this meta-analysis, we found that platinum-based regimens achieved a greater additional benefit in the *BRCA 1/2*-mut group than in the *BRCA 1/2*-wt group.

In our meta-analysis, the results of 13 neoadjuvant trials supported our hypothesis, with a 17.6% increase in pCR rate in patients with *BRCA1/2*-mut TNBC compared to *BRCA1/2*-wt TNBC (HR 1.32, 95% CI 1.17–1.49, $p < 0.00001$; $I^2 = 51\%$). However, in a meta-analysis of 96 *BRCA1/2*-mut patients, Poggio et al. [40] discovered that carboplatin was not related to an increased pCR rate (OR 1.17, 95%CI 0.51–2.67, P = 0.711). We considered no solid conclusions can be drawn in this regard because of the limited number of *BRCA1/2*-mut patients (N = 96). Then, we investigated RCB results and discovered that *BRCA1/2* mutation enhanced the rate of reaching RCB0/1 by 29.7% (HR 1.38, 95%CI 1.08–1.76, P = 0.009; $I^2 = 0\%$). Six advanced-stage trials also supported our hypothesis with a greater ORR rate in *BRCA1/2*-mut patients (HR 1.91, 95% CI 1.48–2.47, $P < 0.00001$; $I^2 = 32\%$). The findings of the analysis for survival outcomes revealed that the *BRCA1/2* mutation promoted OS (HR 1.89, 95% CI 1.22–2.92, P = 0.004; $I^2 = 0\%$) and PFS (HR 1.13, 95% CI 0.81–1.57, P = 0.47; $I^2 = 0\%$) benefits. In Fig. 3, TNT and TBCRC009 showed comparable PFS improvements between patients with *BRCA1/2*-mut TNBC and *BRCA1/2*-wt TNBC, and we contributed this outcome to "the high rate of crossover" and "relatively rapid subsequent disease progression in carriers and the presence of a subset of noncarriers who exhibited durable responses", respectively. The latter is also known as "BRCAness". BRCAness appears in 40–50% of spontaneous patients with TNBC who do not have *BRCA1/2* mutation but have *BRCA1/2* pathway malfunction [41]. Thus, the advantages of PBC may outweigh *BRCA1/2* mutation, we look forward to more prospective clinical trials focusing on this issue. In conclusion, early and advanced patients with *BRCA1/2*-mut TNBC can achieve greater

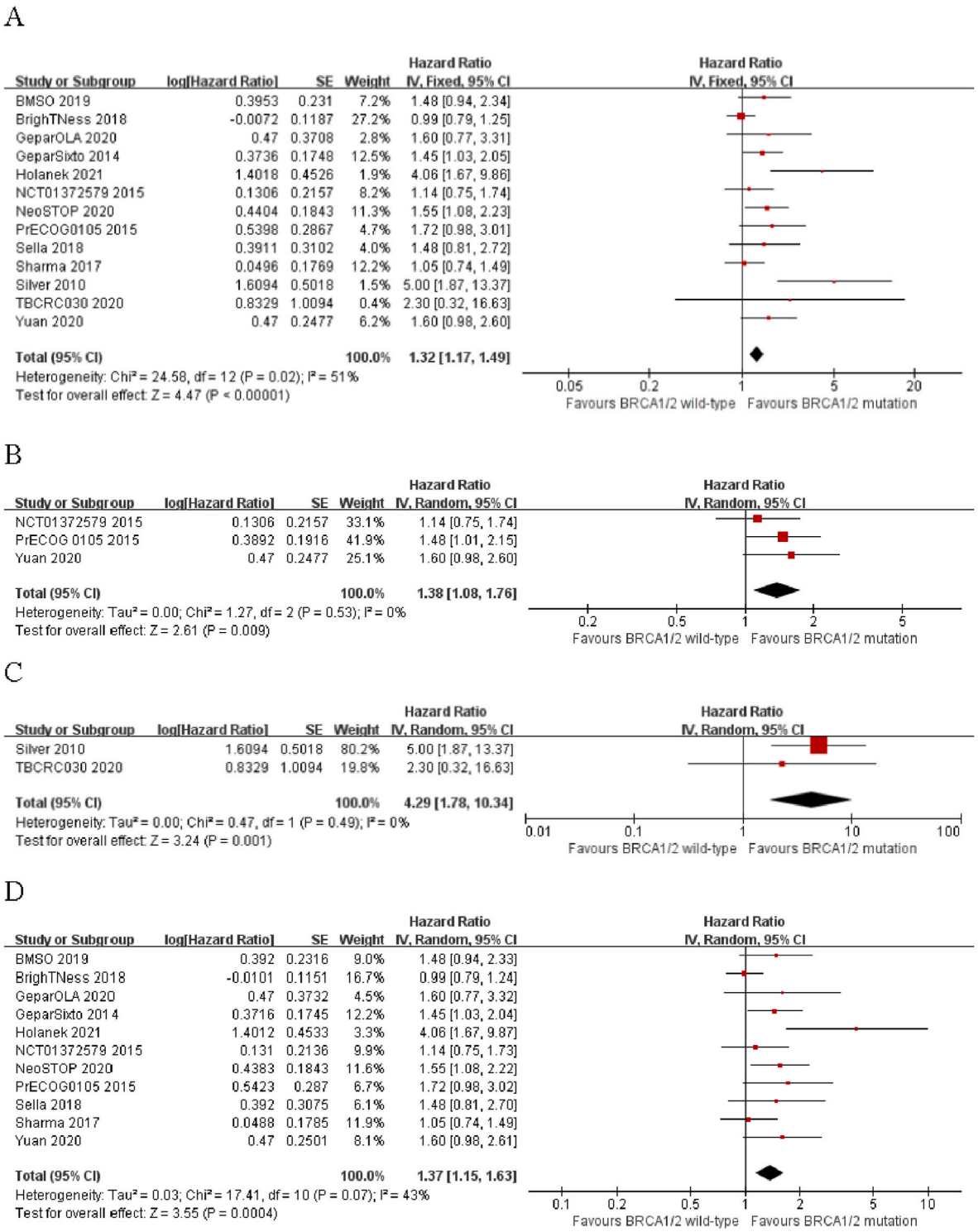


**Fig. 2.** Platinum-containing neoadjuvant regimen leads to higher pCR and RCB rates in patients with TNBC with *BRCA1/2* mutation. A = pCR in platinum-containing neoadjuvant regimen, B = RCB0/I in platinum-containing neoadjuvant regimen, C = pCR in cisplatin monotherapy group, D = pCR in platinum combination group. pCR: pathological complete response; RCB: residual cancer burden.

objective tumor remission with a platinum-based regimen. And what's even more exciting is that we've shown a longer long-term survival in advanced patients with *BRCA1/2*-mut TNBC.

However, the analysis of studies with platinum-containing adjuvant treatment did not support our hypothesis. Adjuvant chemotherapy based on anthracycline paclitaxel is still the mainstay treatment for TNBC. Only three studies met the criteria, and the results reveal no significant differences (HR 1.10, 95%CI 0.82–1.46, P = 0.53, $I^2$ = 43%). Because of the limited number of studies, our findings do not provide a strong evidence-based rationale for recommending platinum-based adjuvant treatment for *BRCA1/2*-mut patients with TNBC. In addition, the race of patients, tumor stage, and drug combination regimen were different, resulting in significant differences in results. By further analysis, we found an 8.94% increase in the incidence of DFS events in patients with *BRCA1/2*-mut TNBC compared to *BRCA1/2*-wt TNBC. In addition, a 10-year OS outcome was reported in NCT01150513. There

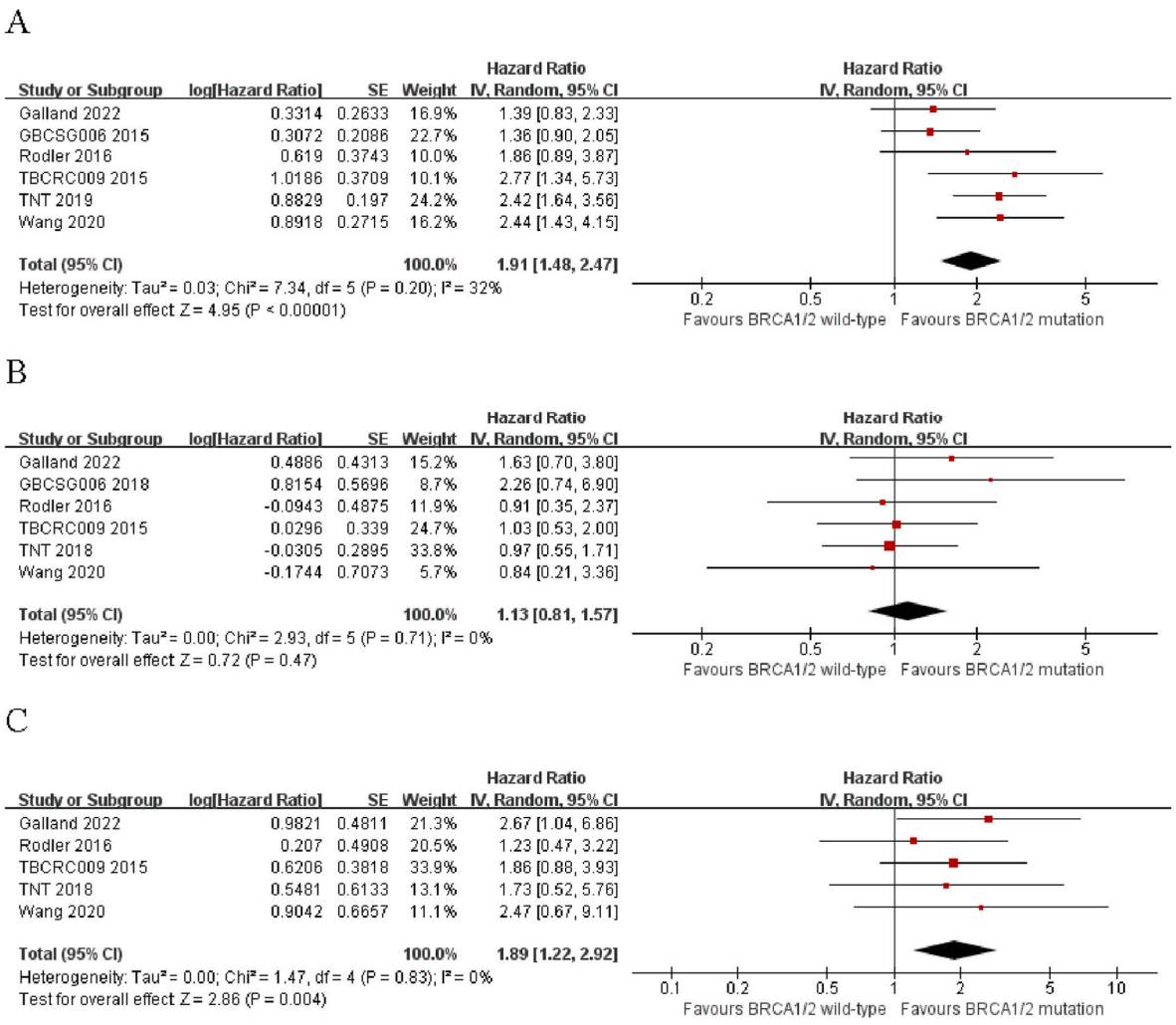


**Fig. 3.** Platinum-containing advanced treatment regimen improves ORR rates and survival benefits in patients with TNBC carrying *BRCA1/2* mutation. A = ORR in platinum-containing advanced treatment regimen, B=PFS in platinum-containing advanced treatment regimen. C=OS in advanced treatment regimen. ORR: objective remission rate; PFS: progression-free survival; OS: overall survival.

were 7 (27.0%) patients with *BRCA1/2*-mut TNBC who achieved long-term survival at 10 years and 8 (16.3%) patients with *BRCA1/2*-wt TNBC. These impressive OS results provide a basis for platinum-based adjuvant chemotherapy. We are delighted to see additional significant clinical trials that will provide fresh information on this issue. Besides *BRCA1/2*, other genes involved in homologous recombination repairs, such as ATM, RAD51, and BRIP1 [42] are required to be explored in the future.

## 5. Limitations

The majority of the trials we included were subgroups of larger clinical studies, which might add bias to our meta-analysis. Furthermore, the definitions of outcomes, treatment regimens, and assessment criteria are not similar among these included researches, which may contribute to bias but not considerable variance.

## 6. Conclusion

It is acknowledged that TNBC is characterized by significant biological heterogeneity. Therefore, it is essential to continually refine the subtype, screen the superior population, and optimize treatment options for prolonging the survival of patients with TNBC. When mechanism-related biomarkers are available, such as *BRCA1/2*, specialized chemotherapy administered to a certain group might be deemed "targeted" treatment. Based on our meta-analysis of 22 trials, platinum-based treatment is efficacious in patients with *BRCA1/2*-mut TNBC, the addition of platinum provides a significant added benefit, especially neoadjuvant and advanced stage. Other confounding factors need to be addressed in future prospective studies.

## Author contributions

**XMJ** designed the study. **XMJ**, **KNW** and **LZX** conduct the systematic literature search. **XMJ**, **KNW** and **NL** conduct the data analysis and interpretation. **XMJ** and **KNW** analyze the statistics and wrote the manuscript. **ZWZ** and ML revised the manuscript.

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## Date availability statement

All data generated or analyzed during this study are included in this published article and referenced articles are listed in the References section.

## Ethical approval

This study involved a meta-analysis; thus, no ethical approval or informed consent was required.

## Consent to participate

This study involved a meta-analysis; thus, no medical informed consent was required.

## Consent for publication

This study involved a meta-analysis; thus, no informed consent was required.

## Declaration of competing interest

The authors confirm that this article content involves no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.08.012.

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