Homologous recombination deficiency predicts the response to platinum-based neoadjuvant chemotherapy in early-stage triple-negative breast cancer patients: a systematic review and meta-analysis

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Abstract

Background: Recent studies have shown that homologous recombination deficiency (HRD) may be correlated with the pathological complete response (pCR) rate. This meta-analysis aimed to determine the predictive value of HRD for the pCR rate in patients with triple-negative breast cancer (TNBC) receiving platinum-based neoadjuvant chemotherapy (NCT).

Methods: Published articles were searched in the PubMed, Embase, Medline, Web of Science, and Cochrane databases up to 1 June 2021, and studies reporting the pCR rate for HRD carriers on platinum-based NCT were selected. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined for the pCR rate, clinical response rate, and Grade 3 or higher adverse events (AEs) using the random-effects model. Bias risk was evaluated using the Cochrane Collaboration tool (PROSPERO, registration number CRD42021249874).

Results: Seven studies were eligible. The results showed that HRD carriers had higher pCR rates than non-HRD carriers across all treatment arms (OR = 3.84, 95% CI = [1.93, 7.64], $p = 0.0001$). Among HRD carriers, the pCR rate was higher in patients on platinum-based NCT than in those without platinum exposure (OR = 1.95, 95% CI = [1.17, 3.23], $p = 0.01$). We did not observe marked pCR improvements in non-HRD carriers. Among HRD carriers, the pCR rates in the mutant and wild-type breast cancer susceptibility gene (BRCA) groups did not differ significantly (OR = 2.00, 95% CI = [0.77, 5.23], $p = 0.16$), but HRD carriers with wild-type BRCA had a significant advantage over non-HRD carriers on platinum-based NCT (OR = 3.64, 95% CI = [1.83, 7.21], $p = 0.0002$).

Conclusion: HRD is an effective predictor of increased pCR rates in platinum-based NCT, especially in wild-type BRCA patients. Adding platinum to NCT for non-HRD carriers can increase the incidence of AEs but may not improve the therapeutic effect.

Keywords: homologous recombination deficiency, platinum-based chemotherapy, triple-negative breast cancer

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Introduction

Patients with early stage triple-negative breast cancer (TNBC) who achieve pathological complete response (pCR) show better event-free survival (EFS) and overall survival (OS) than those with residual invasive disease following neoadjuvant chemotherapy (NCT).[1] Although adding platinum to taxane- and anthracycline-based NCT regimens for TNBC patients may improve the pCR rate, it is associated with higher

treatment-related adverse events (AEs).[2–5] Here, we used response predictors to select patients who may benefit from platinum-based chemotherapy.

Deleterious breast cancer susceptibility gene (BRCA) mutations occur in 15–20% of TNBC patients.[6,7] Preclinical data indicate that patients with BRCA mutations are more sensitive to platinum.[8,9] Although this has been confirmed by some clinical studies, others indicate that BRCA mutations do not significantly correlate with benefit from platinum-based chemotherapy.[5,10]

Some sporadic TNBCs without BRCA mutations have the same pathological and molecular characteristics as those bearing BRCA mutations. These tumors can be identified by homologous recombination deficiency (HRD) and are more sensitive to platinum agents, which trigger DNA inter- and intra-strand crosslinks that cannot be repaired by a faulty homologous recombination system.[8] At present, the methods for evaluating HRD include tests from Myriad Genetics and Foundation Medicine. Foundation Medicine tests evaluate HRD by the loss of heterozygosity (LOH), and Myriad Genetics employs a next-generation sequencing-based *in vitro* diagnostic test that assesses the qualitative detection and classification of single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes and determines the genomic instability score, which is an algorithmic measurement of LOH, telomeric allelic imbalance (TAI), and large-scale state transitions (LSTs) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens.[11–15]

Recent studies have explored HRD as a potential biomarker and have shown that HRD may correlate with the pCR rate.[5,16–18] However, whether (a) HRD specifically predicts platinum chemotherapy efficacy or predicts an improvement to the pCR irrespective of treatment regimen; (b) platinum supplementation efficacy differs in HRD carriers with mutant *versus* wild-type BRCA; and (c) adding platinum to NCT for patients without HRD has any curative benefit or only increases AEs have not been clarified. We sought to answer these questions using this meta-analysis, which included all relevant clinical trials.

Materials and methods

Search strategy

This study complied with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19,20] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42021249874).

Two investigators systematically searched eligible studies in the Embase, PubMed, Medline, Web of Science, and Cochrane databases from inception to 1 June 2021. Abstracts from the American Society of Clinical Oncology (ASCO) annual meeting and European Society for Medical Oncology (ESMO) Congress were also reviewed to include any relevant unpublished studies. Articles were searched using the keywords 'breast cancer', 'breast tumor', 'homologous recombination deficiency', 'triple negative breast cancer', 'homologous recombination', 'HRD', 'DNA repair', 'neoadjuvant treatment', 'neoadjuvant chemotherapy', 'preoperative' and 'platinum', 'carboplatin', and 'cisplatin'.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) randomized controlled trial (RCT), single-arm study, or ongoing research with publicly available data; (b) patients with non-metastatic TNBC; (c) patients who received platinum (including carboplatin, cisplatin, or lobaplatin) alone or combined with other agents for NCT; (d) description of the relationship between the therapeutic response and HRD; and (e) available pCR information.

The exclusion criteria were as follows: (a) inclusion of gene mutations not related to HRD or (b) the use of nonhuman models or publication in a non-English language journal.

Data extraction and quality assessment

The eligible literature was reviewed by two researchers who extracted the data onto a standard form in compliance with PRISMA guidelines.[20] The following variables were recorded from each study: first author, year of publication, trial registry number, trial phase, study design, treatment arms, total number of patients, median

age, number of patients who received genetic testing, number of HRD patients, and number of patients who discontinued due to AEs. The risk of bias approach proposed by the Cochrane Collaboration tool was independently used by the two authors to assess the quality of the included trials with regard to various biases, including reporting, attrition, detection, performance, and selection bias,[21] and, for each category, was graded as high, low, or unclear. To ensure that all assessments were formatted consistently throughout the article, we used 'unclear risk of bias' to describe the quality of certain areas in single-arm trials. Any discrepancies in the results were resolved by a third investigator.

The primary outcome was the pCR rate, which is defined as the absence of residual invasive breast cancer, with or without ductal carcinoma *in situ* in the breast and axilla – that is, ypT0/is ypN0. Secondary outcomes included clinical response rates and Grade 3 or higher AEs.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for the pCR rate, the clinical response rate, and Grade 3 or higher AEs were calculated to assess the treatment efficacy and safety in the indicated groups. Due to significant heterogeneity between the included studies, a random-effects model was used for the meta-analysis.[22] The I^2 statistic and Q tests were used to quantify inconsistency levels between studies, with $p < 0.05$ or $I^2 \geqslant 75\%$, indicating statistically significant heterogeneity.[23,24] A sensitivity analysis was performed by sequentially excluding individual studies, assessing the stability of the analysis results, and identifying potential sources of heterogeneity. Subgroup or meta-regression analyses were not performed due to the small number of studies.

Publication bias was evaluated using Egger's test, with $p < 0.05$ indicating statistical significance.[25] Meta-analysis results are presented in classic forest plots. All analyses were performed in R Version 3.6.1 (with meta packages).[26,27]

Results

The systematic literature search yielded 420 records, database searches yielded 351 articles, and ASCO and ESMO annual meetings yielded 69 abstracts. An overview of the literature search and detailed selection process is shown in Figure 1.

After removing duplicates, title and abstract screening of the remaining 356 studies excluded 332 articles because they did not meet the inclusion criteria. Of the remaining 24 articles subjected to a full-text reading, 17 were excluded: one was a review, four were reports on already included RCTs, nine reported BRCA mutations, HRD carriers, or platinum-based regimens, two were ongoing studies and data were unavailable, and one did not provide sufficient data for quantitative synthesis of the pCR rate. The remaining seven studies met our inclusion criteria.[5,16–18,28–30]

Study characteristics

The main characteristics of the included studies are summarized in Table 1. There were two single-arm trials[16,17] and five RCTs.[5,18,28–30] Six studies were phase II trials,[16–18,28–30] and one was a phase III trial.[5] The meta-analysis involved 1387 patients, and the HRD assay was measurable for 1002 patients (72.2%), 691 (49.8%) of whom were confirmed to have HRD. One study (TBCRC030) used cisplatin as a single-agent regimen,[29] while the others used carboplatin in combination with other agents.[5,16–18,28,30] The included studies reported data on the pCR rate, clinical tumor response, and Grade 3 or higher AEs.

Quality assessment

Information on the risk of bias for the included studies is shown in Supplementary Figure S1.

PCR rates

Chemotherapy regimens and pCR. The pCR analysis of TNBC patients with regard to treatment regimens involved five studies (1264 patients).[5,17,18,28,29] The meta-analysis revealed that relative to platinum-free NCT, platinum-based NCT was significantly correlated with a better pCR rate (50.9% *vs* 31.5%, OR = 2.21, 95% CI = [1.46, 3.34], $p = 0.0002$; $I^2 = 50\%$, $p = 0.09$, Figure 2). A sensitivity analysis performed by excluding each study in turn yielded consistent results.

An evaluation of the efficacy of platinum agents in HRD *versus* non-HRD carriers revealed that four studies reported the pCR rate in HRD carriers.[5,18,29,30] A total of 56.7% of the patients achieved a pCR after receiving platinum-based NCT *versus* 39.4% who received platinum-free
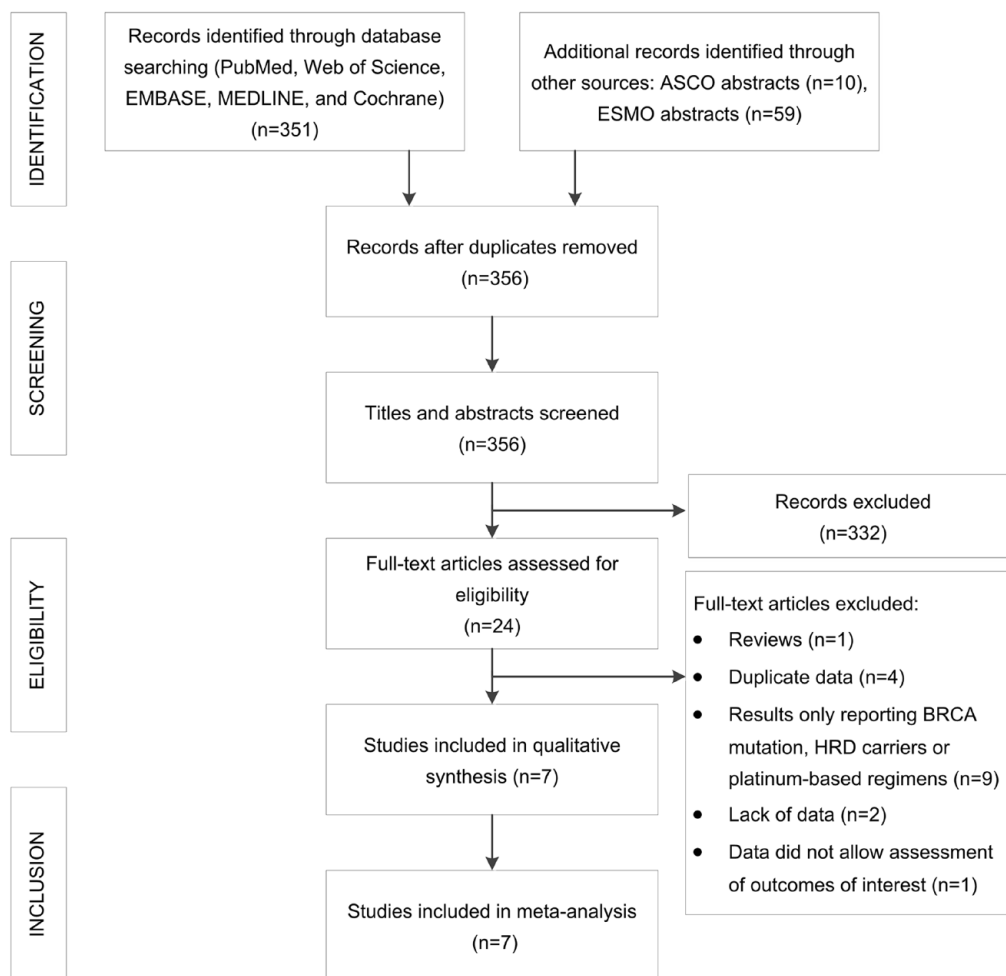
Figure 1. Study flow diagram.
ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

NCT (OR = 1.95, 95% CI = [1.17, 3.23], $p = 0.01$, $I^2 = 36\%$, $p = 0.20$, Figure 2). Three studies reported the pCR rate among non-HRD carriers.[5,18,29] No significant differences were identified between the platinum-based and platinum-free groups (36.5% *vs* 20.5%, OR = 1.82, 95% CI = [0.61, 5.40], $p = 0.28$, $I^2 = 51\%$, $p = 0.13$, Figure 2). Significant publication bias was observed in this subgroup ($p = 0.03$).

HRD and pCR. With regard to the association between HRD and the pCR rate, six studies were included in the analysis (HRD carriers: $N = 614$, non-HRD carriers: $N = 311$).[5,16–18,28,29] HRD was significantly associated with an improved pCR (52.9% *vs* 27.0%, OR = 3.84, 95% CI = [1.93, 7.64], $p = 0.0001$, $I^2 = 68\%$, $p = 0.008$, Figure 3). The funnel plots and Egger's test revealed no significant publication bias ($p = 0.30$).

An analysis of the association between HRD and pCR with regard to different NCT regimens revealed that of the patients on platinum-based NCT,[5,16–18,29] HRD carriers had a significantly better pCR benefit than non-HRD carriers (60.3% *vs* 32.8%, OR = 4.66, 95% CI = [1.85, 11.71], $p = 0.001$, $I^2 = 62\%$, $p = 0.03$, Figure 3). For patients without platinum exposure,[5,18,29] there were no differences in the pCR rate irrespective of HRD (34.3% *vs* 20.5%, OR = 1.89, 95% CI = [0.81, 4.43], $p = 0.14$, $I^2 = 41\%$, $p = 0.18$, Figure 3). No considerable heterogeneity was observed across studies.

A meta-regression was performed to determine whether the associations between HRD and pCR on platinum-based NCT were influenced by companion chemotherapy, such as anthracycline agents.[5,16–18] The results showed that platinum-based NCT combined with anthracycline was a significant factor for

Table 1. Main characteristics of the included studies.

Author (year)	Trial registry number	phase	Study design	Treatment arms	Total no. of pts.	Median age, year (range)	HRD assessment	No. of HRD assay available pts.	Definition of HRD	No. of HRD pts.	No. of discontinuations due to AEs
Kaklamani et al.[16]	NCT01372579	II	Single-arm	• Cb + eribulin	30	52.5 [35–78]	Myriad genetic	26	HRD score ≥42 and/or BRCAm	12	1
Telli et al.[17]	NCT00813956	II	Single-arm	• Gemcitabine + Cb + iniparib	93	48 [26–74]	Foundation medicine	65	HRD-LOH score ≥10 and/or BRCAm	53	5
Loibl et al.[5]	NCT02032277	III	RCT	• TPV • TP + placebo • T + dual placebo	634	50 [41–59]	Myriad genetic	438	HRD score ≥42 and/or BRCAm	294	50
Loibl et al.[18]	NCT01426880	II	RCT	• PM • PMCb	315	48 [21–75]	Myriad genetic	193	HRD score ≥42 and/or BRCAm	136	NA
Mayer et al.[29]	NCT01982448	II	RCT	• Cis • P	139	53 [28–82]	Myriad genetic	104	HRD score ≥33 and/or BRCAm	74	NA
Masuda et al.[28]	UMIN000023162	II	RCT	• P + Cb • Eribulin + Cb • Eribulin + C • Eribulin + capecitabine	99	NA	Myriad genetic	99	HRD score ≥42 and/or BRCAm	45	0
Fasching et al.[30]	NCT02789332	II	RCT	• PO • PCb	77	47 [25–71]	Myriad genetic	77	HRD score ≥42 and/or BRCAm	77	2

AEs, adverse events; BRCAm, BRCA mutation; C, cyclophosphamide; Cb, carboplatin; Cis, cisplatin; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; M, non-pegylated liposomal doxorubicin; NA, not available; NCT, neoadjuvant chemotherapy; O, olaparib; P, paclitaxel; pts., patients; RCT, randomized controlled trial; TPV, paclitaxel + carboplatin + veliparib.
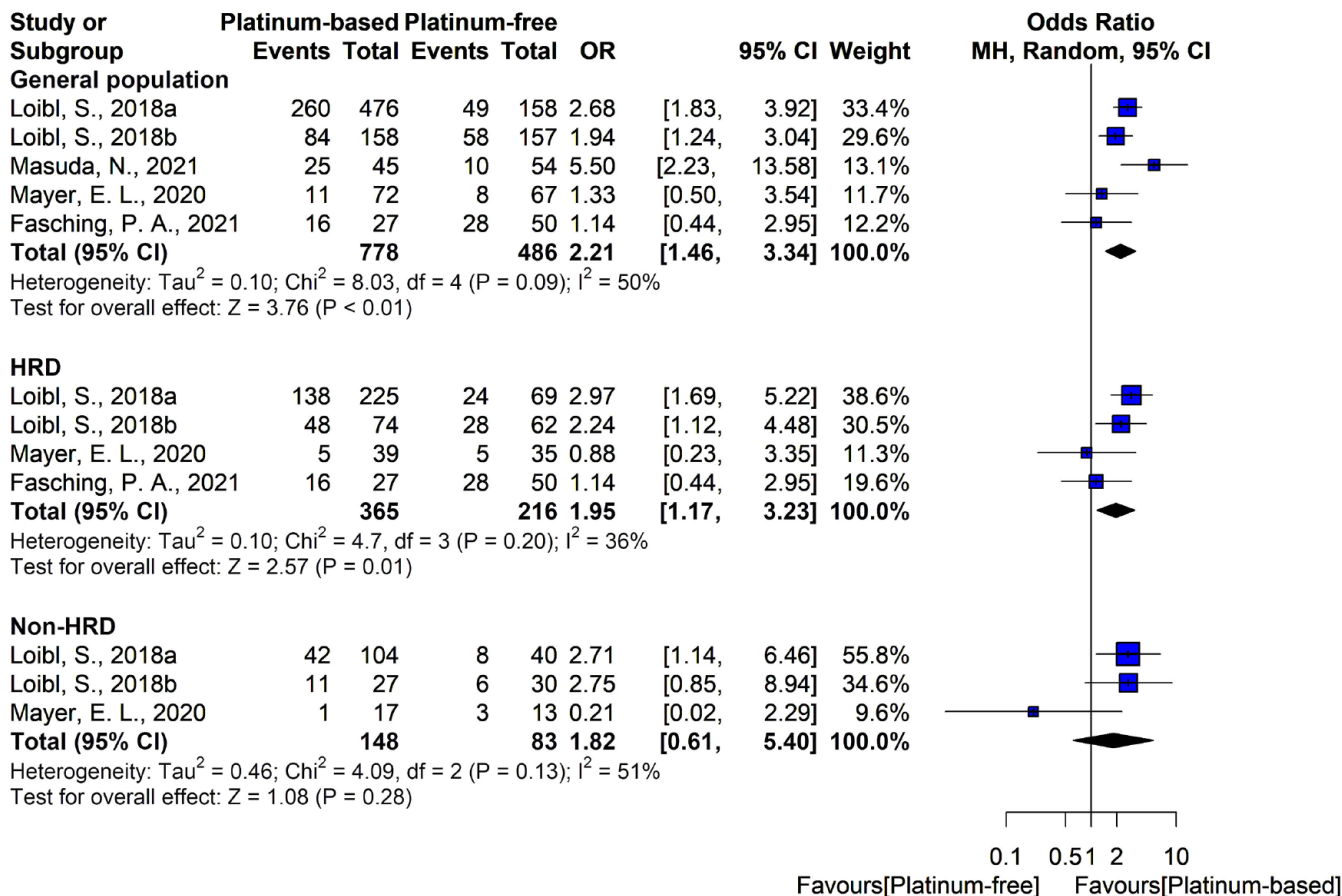
Figure 2. Forest plots of the odds ratios for the pCR rate in platinum-based *versus* platinum-free neoadjuvant chemotherapy in the general population, HRD carriers, and non-HRD carriers.
CI, confidence interval; HRD, homologous recombination deficiency; OR, odds ratio; pCR, pathological complete response.

a poorer association between the predictive value of HRD and the pCR rate among TNBC patients ($p < 0.001$, Supplementary Table 2).

For patients treated with platinum-based NCT, analysis of the pooled data derived from the five eligible studies revealed that HRD carriers with wild-type BRCA had a significant advantage over non-HRD carriers in terms of the pCR rate (56.8% *vs* 32.8%, OR = 3.64, 95% CI = [1.83, 7.21], $p = 0.0002$, Figure 4). Low heterogeneity was observed, with $I^2 = 31\%$ and $p = 0.21$.

BRCA and pCR. Subgroup analysis of the association between BRCA status and the pCR rate among HRD carriers on platinum-based NCT involved five eligible studies.[5,16–18,30] Pooled results revealed no statistically significant differences in the pCR rate in the BRCA mutant (BRCAm) *versus* BRCA wild-type (BRCA-wt) groups (63.0% *vs* 56.6%, OR = 2.00, 95%

CI = [0.77, 5.23], $p = 0.16$, Figure 5). Substantial heterogeneity was detected ($I^2 = 69\%$, $p = 0.01$).

Clinical response rates
An analysis of the clinical response rates based on the treatment regimen included four studies[5,18,28,30] and revealed that relative to platinum-free NCT, platinum-based NCT was correlated with a higher clinical response rate, although not significantly (85.1% *vs* 76.1%, OR = 1.97, 95% CI = [0.91, 4.27], $p = 0.08$). Substantial heterogeneity was detected ($I^2 = 82\%$, $p < 0.01$). Sensitivity analysis revealed that the results were stable. Detailed data on this group of comparisons are shown in Supplementary Figure S2.

AEs
Our analysis revealed a significantly higher incidence of Grade 3 or higher hematologic toxicities among

Study or Subgroup	HRD Events	Total	Non-HRD Events	Total	OR	95% CI	Weight	Odds Ratio MH, Random, 95% CI
General population								
Loibl, S., 2018a	162	294	50	144	2.31	[1.53, 3.49]	29.1%	
Loibl, S., 2018b	76	136	17	57	2.98	[1.54, 5.77]	24.0%	
Masuda, N., 2021	25	45	10	54	5.50	[2.23, 13.58]	19.3%	
Mayer, E. L., 2020	10	74	4	30	1.02	[0.29, 3.53]	13.9%	
Telli, M. L., 2015	43	53	1	12	47.30	[5.46, 410.01]	6.4%	
Kaklamani, V. G., 2015	9	12	2	14	18.00	[2.47, 131.29]	7.3%	
Total (95% CI)		614		311	3.84	[1.93, 7.64]	100.0%	

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 15.57$, df = 5 (P < 0.01); $I^2 = 68\%$
Test for overall effect: Z = 3.83 (P < 0.01)

	HRD Events	Total	Non-HRD Events	Total	OR	95% CI	Weight	
Platinum-based								
Loibl, S., 2018a	138	225	42	104	2.34	[1.46, 3.76]	41.6%	
Loibl, S., 2018b	48	74	11	27	2.69	[1.09, 6.63]	28.8%	
Mayer, E. L., 2020	5	39	1	17	2.35	[0.25, 21.83]	9.1%	
Telli, M. L., 2015	43	53	1	12	47.30	[5.46, 410.01]	9.6%	
Kaklamani, V. G., 2015	9	12	2	14	18.00	[2.47, 131.29]	10.9%	
Total (95% CI)		403		174	4.66	[1.85, 11.71]	100.0%	

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 10.64$, df = 4 (P = 0.03); $I^2 = 62\%$
Test for overall effect: Z = 3.27 (P < 0.01)

	HRD Events	Total	Non-HRD Events	Total	OR	95% CI	Weight	
Platinum-free								
Loibl, S., 2018a	24	69	8	40	2.13	[0.85, 5.35]	41.0%	
Loibl, S., 2018b	28	62	6	30	3.29	[1.18, 9.18]	37.1%	
Mayer, E. L., 2020	5	35	3	13	0.56	[0.11, 2.75]	21.8%	
Total (95% CI)		166		83	1.89	[0.81, 4.43]	100.0%	

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 3.39$, df = 2 (P = 0.18); $I^2 = 41\%$
Test for overall effect: Z = 1.47 (P = 0.14)

0.01 0.1 1 10 100
Favours[Non-HRD] Favours[HRD]

Figure 3. Forest plots of the odds ratios for the pCR rate in HRD *versus* non-HRD in the general population, patients on platinum-based regimens, and patients on platinum-free regimens.
CI, confidence interval; HRD, homologous recombination deficiency; OR, odds ratio; pCR, pathological complete response.
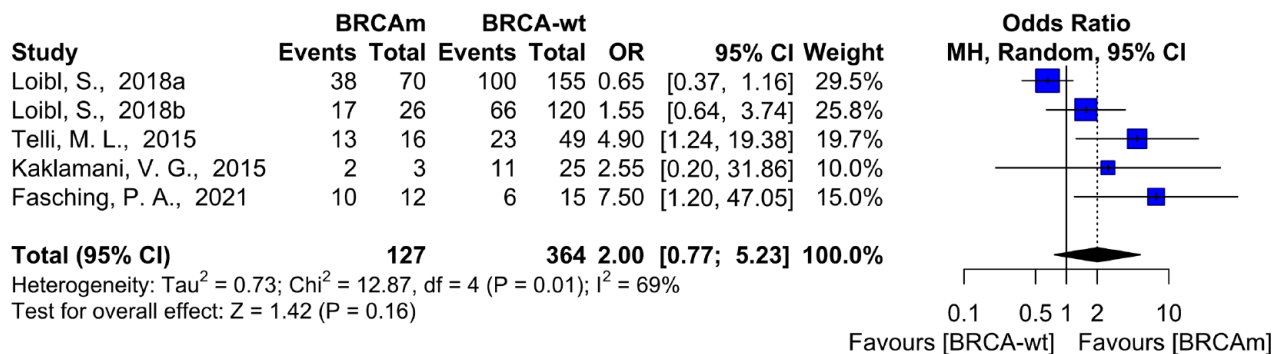
patients receiving platinum-based NCT (anemia: OR = 20.32, 95% CI = [5.48, 75.35], $p < 0.01$; neutropenia: OR = 3.89, 95% CI = [0.93, 16.32], $p = 0.06$; and thrombocytopenia: OR = 10.07, 95% CI = [1.10, 92.03], $p = 0.04$). Grade 3 or higher non-hematologic toxicities were also more frequently observed in patients on platinum-based regimens (nausea: OR = 2.75, 95% CI = [1.44, 5.24], $p < 0.01$; vomiting: OR = 2.57, 95% CI = [1.14, 5.80], $p = 0.02$; and diarrhea: OR = 1.78, 95% CI = [1.13, 2.82], $p = 0.01$). The pooled analysis results for two AEs were statistically nonsignificant (leukopenia: OR = 2.01, 95% CI = [0.44, 9.27], $p = 0.37$; and fatigue: OR = 2.13, 95% CI = [0.36, 12.69], $p = 0.41$). Treatment-related Grade 3 or higher AEs are shown in Figure 6.

Discussion

To our knowledge, this is the first meta-analysis of the association between HRD and the efficacy of platinum-based NCT in early stage TNBC patients. The results showed that platinum-based NCT accounted for significantly improved pCR rates in TNBC patients. Relative to non-HRD carriers, HRD carriers experienced higher pCR rates irrespective of treatment. Further analysis found that HRD carriers derived more clinical benefit from platinum-based NCT than from platinum-free NCT. However, no significant improvement was observed among non-HRD carriers. In addition, our meta-analysis revealed HRD to be an effective predictor of higher pCR rates in platinum-based NCT, especially among wild-type BRCA patients.
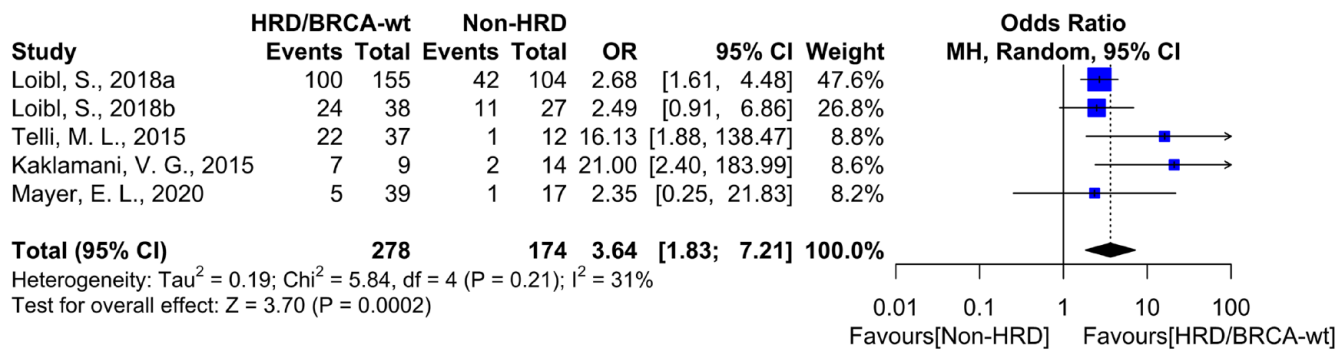
Figure 4. Forest plot of the odds ratios for the pCR rate in HRD/BRCA-wt *versus* non-HRD patients on platinum-based regimens.
BRCA-wt, BRCA wild-type; CI, confidence interval; HRD, homologous recombination deficiency; OR, odds ratio; pCR, pathological complete response.

Figure 5. Forest plots for pCR analyses in patients with HRD receiving platinum-based neoadjuvant chemotherapy, stratified by BRCA status.
pCR, pathological complete response; HRD, homologous recombination deficiency; BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutant; BRCA-wt, BRCA wild-type; CI, confidence interval; OR, odds ratio.
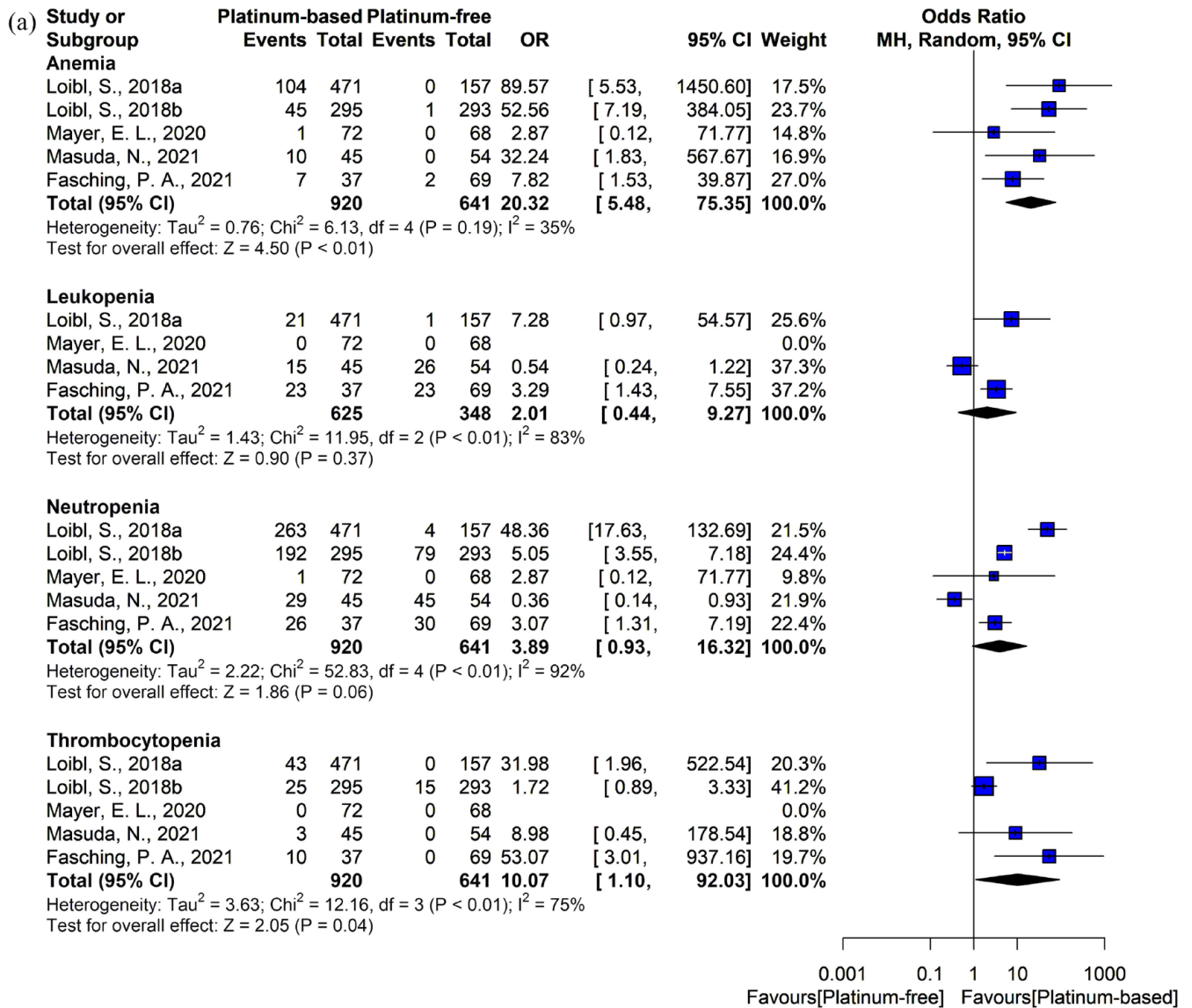
Adding platinum agents to taxane- and anthracycline-based NCT improved the pCR in TNBC patients.[3,4] Consistent with a prior meta-analysis,[31] our data show a significantly increased pCR rate in patients receiving platinum-based NCT (50.9% *vs* 31.5%, $p = 0.0002$).
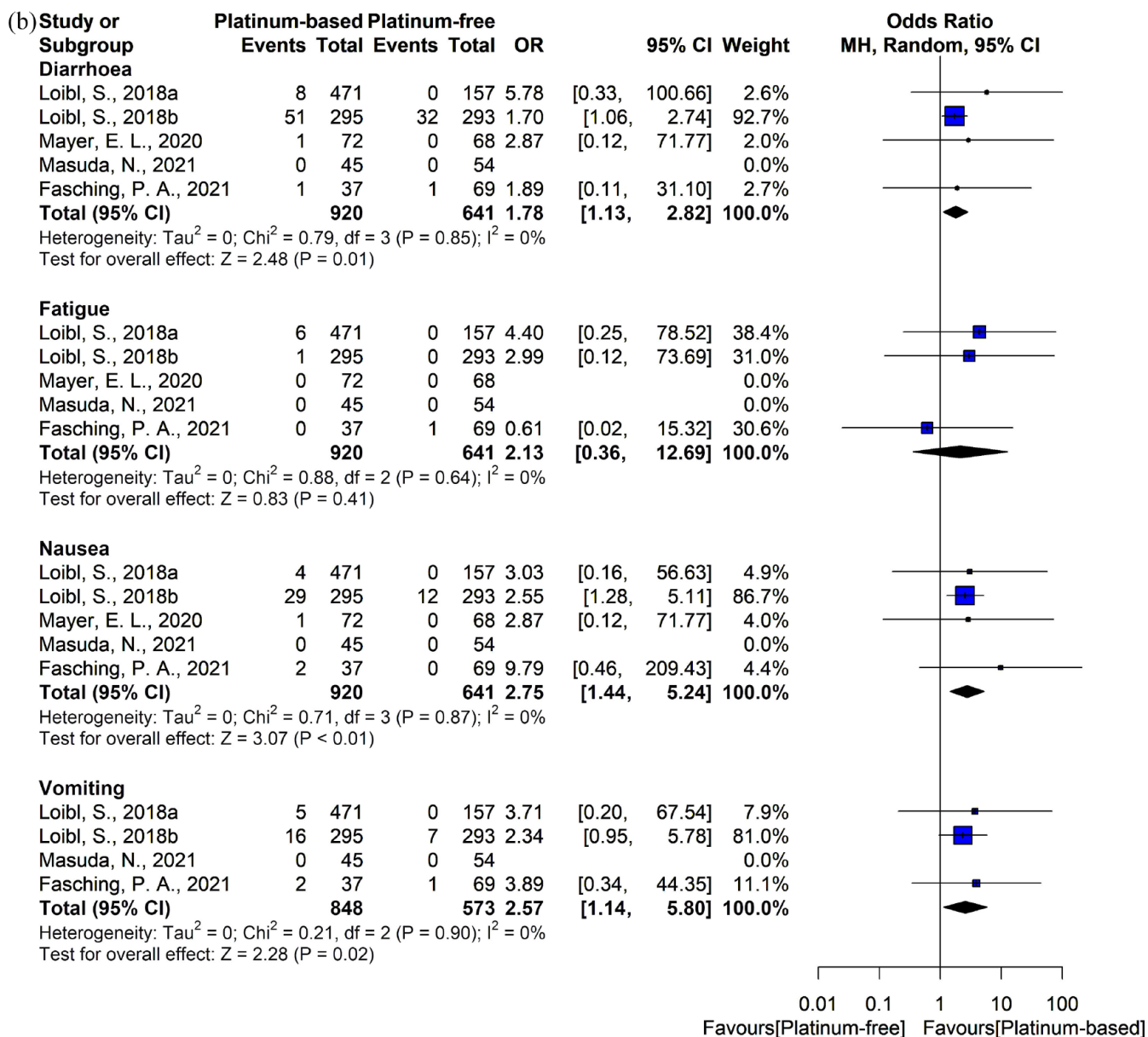
A pooled analysis of the association between HRD and pCR rates revealed a significantly higher pCR rate in HRD carriers than in non-HRD carriers (52.9% *vs* 27.0%, $p = 0.0001$), which is consistent with the findings from two randomized clinical trials. GeparSixto revealed a twofold increase in the pCR rates in HRD carriers relative to non-HRD carriers across all treatment arms (55.9% *vs* 29.8%, $p < 0.01$).[18] Similar observations were reported in the BrighTNess study ($p = 0.0005$).[5]

Next, we analyzed the effects of treatment with platinum agents among HRD *versus* non-HRD carriers and found that among HRD carriers, pCR rates were significantly higher among those receiving platinum-based NCT than among those receiving platinum-free NCT (56.7% *vs* 39.4%, $p = 0.01$), while only a subtle improvement was observed among non-HRD carriers (36.5% *vs* 20.5%, $p = 0.28$). This finding suggests that HRD is a potential predictor of the therapeutic response to platinum-based NCT, which is consistent with the findings from the PrECOG 0105, GeparSixto, and BrighTNess studies.[5,17,32,33] In contrast, the randomized phase II trial TBCRC030 showed no difference in the pCR rate when comparing neoadjuvant single-agent cisplatin patients with paclitaxel in patients with TNBC, regardless of HRD score (13.0% *vs* 14.0%).[29] The reason may lie in the different study designs. TBCRC030 adopted cisplatin or paclitaxel as monotherapy, while GeparSixto and GeparOLA assessed the efficacy of adding carboplatin to taxane- and

(a)

Study or Subgroup	Platinum-based		Platinum-free		OR	95% CI		Weight
	Events	Total	Events	Total				
Anemia								
Loibl, S., 2018a	104	471	0	157	89.57	[5.53,	1450.60]	17.5%
Loibl, S., 2018b	45	295	1	293	52.56	[7.19,	384.05]	23.7%
Mayer, E. L., 2020	1	72	0	68	2.87	[0.12,	71.77]	14.8%
Masuda, N., 2021	10	45	0	54	32.24	[1.83,	567.67]	16.9%
Fasching, P. A., 2021	7	37	2	69	7.82	[1.53,	39.87]	27.0%
Total (95% CI)		920		641	20.32	[5.48,	75.35]	100.0%

Heterogeneity: Tau^2 = 0.76; Chi^2 = 6.13, df = 4 (P = 0.19); I^2 = 35%
Test for overall effect: Z = 4.50 (P < 0.01)

Study or Subgroup	Events	Total	Events	Total	OR	95% CI		Weight
Leukopenia								
Loibl, S., 2018a	21	471	1	157	7.28	[0.97,	54.57]	25.6%
Mayer, E. L., 2020	0	72	0	68				0.0%
Masuda, N., 2021	15	45	26	54	0.54	[0.24,	1.22]	37.3%
Fasching, P. A., 2021	23	37	23	69	3.29	[1.43,	7.55]	37.2%
Total (95% CI)		625		348	2.01	[0.44,	9.27]	100.0%

Heterogeneity: Tau^2 = 1.43; Chi^2 = 11.95, df = 2 (P < 0.01); I^2 = 83%
Test for overall effect: Z = 0.90 (P = 0.37)

Study or Subgroup	Events	Total	Events	Total	OR	95% CI		Weight
Neutropenia								
Loibl, S., 2018a	263	471	4	157	48.36	[17.63,	132.69]	21.5%
Loibl, S., 2018b	192	295	79	293	5.05	[3.55,	7.18]	24.4%
Mayer, E. L., 2020	1	72	0	68	2.87	[0.12,	71.77]	9.8%
Masuda, N., 2021	29	45	45	54	0.36	[0.14,	0.93]	21.9%
Fasching, P. A., 2021	26	37	30	69	3.07	[1.31,	7.19]	22.4%
Total (95% CI)		920		641	3.89	[0.93,	16.32]	100.0%

Heterogeneity: Tau^2 = 2.22; Chi^2 = 52.83, df = 4 (P < 0.01); I^2 = 92%
Test for overall effect: Z = 1.86 (P = 0.06)

Study or Subgroup	Events	Total	Events	Total	OR	95% CI		Weight
Thrombocytopenia								
Loibl, S., 2018a	43	471	0	157	31.98	[1.96,	522.54]	20.3%
Loibl, S., 2018b	25	295	15	293	1.72	[0.89,	3.33]	41.2%
Mayer, E. L., 2020	0	72	0	68				0.0%
Masuda, N., 2021	3	45	0	54	8.98	[0.45,	178.54]	18.8%
Fasching, P. A., 2021	10	37	0	69	53.07	[3.01,	937.16]	19.7%
Total (95% CI)		920		641	10.07	[1.10,	92.03]	100.0%

Heterogeneity: Tau^2 = 3.63; Chi^2 = 12.16, df = 3 (P < 0.01); I^2 = 75%
Test for overall effect: Z = 2.05 (P = 0.04)

Odds Ratio
MH, Random, 95% CI

0.001   0.1   1   10   1000
Favours[Platinum-free]   Favours[Platinum-based]

(b)

Figure 6. Forest plot of the odds ratios for Grade 3 or higher adverse events in platinum-based *versus* platinum-free neoadjuvant chemotherapy: (a) hematological toxicities and (b) nonhematological toxicities.
CI, confidence interval; OR, odds ratio.

anthracycline-based regimens.[18,34] In addition, in TBCRC030, 36.7% of patients with inadequate clinical responses crossed over to alternative pre-operative chemotherapy rather than continuing on the initial regimen. Hence, it is possible that a combination with other DNA-damaging agents may mask the potential benefits of adding a platinum agent to NCT.

A subgroup analysis for determining whether BRCA status correlated with the clinical response

to NCT among HRD carriers found that those who received platinum-based NCT had similar pCR rates, whether they were BRCAm or BRCA-wt (63.0% *vs* 56.6%, $p = 0.16$). Although previous studies have suggested that BRCA mutations can predict the efficacy of platinum-based regimens,[35] large RCTs and systematic retrospective analyses have obtained findings similar to ours,[10,36–38] suggesting that TNBC patients with BRCA mutations do not derive additional benefits from adding platinum agents to NCT. BRCA

genes are critical in the homologous recombination repair of double-strand DNA breaks, although HRD may also occur in BRCA-wt patients *via* a variety of mechanisms related to other mutations involved in HRD,[39] which may enhance tumor sensitivity to DNA-damaging agents, such as platinum agents.

Another important finding of this meta-analysis was that the ability of HRD to predict the outcome of platinum-based chemotherapy was affected by the combination of anthracycline agents; in addition, the heterogeneity was lower among BRCA wild-type, HRD-carrying patients. In the carboplatin-free groups in the BrighTNess and GeparSixto trials, patients with BRCA mutations had a higher pCR rate than patients with the BRCA wild-type.[5,10] This finding may be the result of a better treatment response of BRCA mutation carriers to the chemotherapy drugs used, such as anthracycline, in the carboplatin-free group. Anthracycline plays an antitumor role by mediating the breaking of single-stranded and double-stranded DNA.[40] Therefore, it seems reasonable for BRCA mutation carriers to obtain a higher response rate under anthracycline treatment. For patients with BRCA mutations, carboplatin cannot further improve the pCR rate when based on anthracycline chemotherapy. The same results were also observed in the TBCRC031 trial. Among the BRCA mutation carriers, cisplatin did not show a higher pCR rate than doxorubicin + cyclophosphamide.[41] On the other hand, the results of the TNT trial confirmed that the high response rate of BRCA mutation carriers may not be related to docetaxel.[35] In some trials without anthracycline, BRCA status was still a strong predictor of carboplatin efficacy,[17] which may explain the correlation between BRCA status and carboplatin efficacy in ovarian cancer, which is treated with paclitaxel combined with platinum-based chemotherapy rather than anthracycline.[42] Therefore, HRD can identify patients who truly need platinum drugs, that is, those with BRCA wild-type but HRD tumors. These results may suggest that anthracycline-based chemotherapy is sufficient for BRCA mutation carriers and that non-HRD carriers will not benefit from the added carboplatin. HRD is an attractive aspect for a clinically useful test, as it could be used to screen patients who cannot benefit from carboplatin, and the adverse reactions caused by the use of platinum can be reduced.

In addition, in our meta-analysis, the incidence of Grade 3 or higher AEs, such as anemia, neutropenia, thrombocytopenia, nausea, vomiting, and diarrhea, often increased with platinum-based regimens, which is consistent with previous studies.

This study has certain limitations. First, aggregated data were obtained from published articles instead of individual patient data. Second, most studies did not report subgroup analysis data on the association between HRD and platinum-based NCT with regard to age, chemotherapy dosage, and treatment duration. Third, given the insufficient sample size in the subgroup analysis, the results should be interpreted with caution. Currently, available data on the assessment of the survival benefits of NCT based on HRD are limited. Our study is the first to determine the association between HRD and the clinical benefit of NCT. However, more prospective clinical trials are needed to validate the predictive and prognostic value of HRD.

In conclusion, HRD is an effective predictor of the pCR rate in platinum-based NCT, especially in BRCA wild-type patients. Adding platinum to NCT for non-HRD carriers can increase the incidence of AEs but may not improve the therapeutic effect.

Author contribution(s)

Liulu Zhang: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft.

Yuanqi Chen: Formal analysis; Methodology; Project administration; Writing – original draft.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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