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Efficacy and Safety of PARP Inhibitors in Advanced or Metastatic Triple-negative Breast Cancer: A Systematic Review and Meta-analysis

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Abstract

Background

Poly (ADP-ribose) polymerase (PARP) inhibitors have shown promising results in metastatic triple-negative breast cancers (TNBC). We performed a systematic review and meta-analysis to evaluate the efficacy and safety of this drug in patients with advanced or metastatic TNBC.

Methods

On August 2020, we searched all published phase II/III clinical studies of PARP inhibitors in advanced/metastatic TNBC patients. Data were extracted independently by two authors and analyzed using Review Manager software version 5.3. End points included overall response rate (ORR), progression-free survival (PFS) and adverse events.

Results

Ten clinical trials were identified, with a total of 1495 patients included. Pooled analyses showed that the addition of PARP inhibitors could provide a significant improvement of ORR (risk ratio [RR]=2.00, 95% confidence interval [CI]: 1.14–3.50, p=0.02) and PFS (hazard ratio [HR]=0.68, 95 %CI: 0.59-0.77, p<0.0001) compared to chemotherapy in the whole population. In subgroup analysis, *BRCA* mutated patients have a higher objective response to PARP inhibitor, with a RR of 2.85 (95%CI: 1.34–6.06, p=0.007) compared to *BRCA* wild-type patients. However, no significant differences in ORR were observed between homologous recombination deficiency (HRD) positive and non-HRD subgroup (RR=1.82, 95%CI: 0.81–4.08, p=0.14). Hematologic toxicities were common adverse events of PARP inhibitors.

Conclusions

PARP inhibitors are an effective option for the treatment of advanced or metastatic TNBC patients. *BRCA* mutated patients could derive more benefits from PARP inhibitors when compared to *BRCA* wild-type patients. In clinical application, hematological toxicity related to PARP inhibitors should be monitored regularly.

Background

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer, accounting for 15 to 20% of all cases of breast cancer.(1, 2) Cytotoxic chemotherapy is currently the mainstay of treatment for TNBC due to lacking expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2.(3) Unfortunately, TNBC is frequently resistant to chemotherapy and eventually evolves lethal metastatic disease, with a median survival of approximately 1 year.(4, 5) Notably, more than one-third of TNBC patients will have distant metastases,(6) and no standard of care therapy exists for metastatic TNBC (mTNBC) patients.(7) Therefore, development of new therapeutic approach for patients with mTNBC are urgently needed.

With the advancement of genomics analysis, new druggable targets are being identified, which may contribute to broadening the novel therapeutic scenario for mTNBC. Among patients with TNBC, about 10–30% cases present with *BRCA1* or *BRCA2* gene mutations.(8, 9) On the other hand, approximately 70% of *BRCA1*-mutated breast cancers are triple negative phenotype.(10) *BRCA1* and *BRCA2* genes are involved in the homologous recombination repair (HRR) pathway and responsible to repair DNA double-strand breaks. HRR pathway also contains many other genes such as *ATM, PALB2, RAD51, CDK12, CHK1/2*. Alterations on these genes can lead to homologous recombination deficiency (HRD). Poly (ADP-ribose) polymerase (PARP) is an important enzyme in the repair of DNA single-strand breaks.(11, 12) Thus, inactivation of PARP in tumors with HRD will increase genomic instability, ultimately result in cell death. Preclinical studies have shown that cancer cells with functional *BRCA1* or *BRCA2* mutation are sensitive to PARP inhibition,(13) providing a strong rationale for treating mTNBC with PARP inhibitors.

There are currently several PARP inhibitors being tested in clinical trials for mTNBC patients. Based on the promising results observed in clinical trials, olaparib has been approved by the Food and Drug Administration (FDA) for the treatment of patients with germline *BRCA*-mutated, HER2-negative metastatic breast cancer.(14, 15) Whereas, several clinical trials suggested that PARP inhibitors also conferred a survival benefit in metastatic TNBC patients irrespective of *BRCA* status.(16, 17) Thus, in this systematic review and meta-analysis, we aimed to comprehensively evaluate the efficacy and safety of PARP inhibitors in advanced or

metastatic TNBC based on available clinical trial results. We also explored biomarkers to identify the subgroups of patients who could most benefit from PARP inhibitors.

Methods

Search strategy

On August 2020, A systematic literature search was performed by two independent reviewers through PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.(18) The search terms are as following: ((“Poly(ADP-ribose) Polymerase inhibitors” OR “PARP inhibitors”) OR “Olaparib” OR “rucaparib” OR “talazoparib” OR “veliparib” OR “niraparib” OR “iniparib”) AND (“breast”) AND (“randomized controlled trial” OR “clinical trial”).

Inclusion and exclusion criteria

Inclusion criteria: (1) Phase II and Phase III clinical trials evaluating the efficacy of PARP inhibitor as single-agent or in combination with other anticancer drugs in patients with advanced or metastatic TNBC were considered for inclusion. (2) The eligible studies mentioned objective response rate (ORR), progression-free survival (PFS), overall survival (OS) or safety outcomes. (3) Only English-language articles were included.

Exclusion criteria: (1) Phase I clinical trial, case reports, editorials, review articles, retrospective studies were excluded; (2) Single-arm studies that did not report *BRCA* or HRD status were not included. (3) Clinical trials focused on neoadjuvant therapy. (4) Finally, for the continuously updated and published follow-up data, the latest results were considered for analysis. The selected studies were identified based on inclusion and exclusion criteria by two independent reviewers (X. Liu and K. Wu).

Data extraction

Two authors (Xu. Liu and K. Wu) independently extracted data from eligible studies included in the meta-analysis. The following data was included: first author's information, year of publication, study design, trial phase, ClinicalTrial.gov Number, sample size, *BRCA* or HRD status, type of intervention/control, efficacy results (ORR and PFS) and numbers of adverse events (AEs) in each arm. If the PFS was only represented by Kaplan-Meier curve, the Engauge digitizer 4.1 software was used to digitize and extract the data (only in one study(19)).

Risk of bias assessment

The potential risks of bias in the selected studies was independently assessed by two reviewers (Xu. Liu and K. Wu), using the Cochrane Risk of bias tool, which included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other possible sources of bias. The risk of bias was graded as high, low or unclear risk. Disagreement was resolved through consensus or a third reviewer (X.R. Zhong).

Study objectives

The objectives of this study were to compare the antitumor efficacy and safety between the PARP inhibitor group and the chemotherapy group. The primary outcomes of this meta-analysis were ORR and PFS, AEs were the secondary outcomes. We also performed exploratory subgroup analyses to investigate treatment activity of PARP inhibitors in the *BRCA* mutated vs *BRCA* wild-type group, and HRD group vs non-HRD group.

Statistical analysis

The hazard ratio (HR) with its 95% confidence interval (CI) was calculated to compare the PFS. The risk ratios (RR) and 95% CI was calculated to measure the ORR and AEs. A two-sided p value < 0.05 was considered statistically significant. The statistical heterogeneity was assessed using the I^2 statistic and chi-squared tests. When heterogeneity was observed (I^2 value > 50% and p value < 0.05), a random effects model was applied; otherwise a fixed effect model was used. Funnel plot was used to detect potential publication bias. All statistical analyses were performed using Review Manager software version 5.3.

Results

Study selection and characteristics

After the electronic databases searches, a total of 2689 records were initially retrieved (Fig. 1). After removing duplicates and screening titles and abstracts, only 27 full-text articles were further assessed for their eligibility based on inclusion/exclusion criteria. After full-text review, 17 published articles were excluded for the following reasons: 5 articles did not report the related outcomes of this study population; five studies reported the results from the same population; 4 were clinical trials for neoadjuvant therapy in TNBC; two single-arm studies did not report HRD or *BRCA* mutation status; one single-arm study only reported *BRCA* mutation. Ultimately, 10 clinical trials were included for final pooled analysis, including 7 randomized controlled trials(14, 16, 17, 19–22) and 3 single-arm studies.(23–25) For BROCADE study,(21) they randomly set up two comparison groups: veliparib with carboplatin/paclitaxel versus placebo plus carboplatin/paclitaxel, and veliparib plus temozolomide versus placebo plus carboplatin/paclitaxel, we only evaluated veliparib plus carboplatin/paclitaxel versus placebo plus carboplatin/paclitaxel in order to avoid statistical influences on research weights.

The main features of the selected studies and enrolled patients were summarized in Table 1. All clinical trials reported the antitumor efficacy of PARP inhibitors in patients with advanced or metastatic TNBC, ranging from 21 to 519 patients per study. Globally, a total of 1495 patients were included in the meta-analysis, of whom 735 patients harbored somatic or germline *BRCA1/2* mutations.

Table 1
Characteristics of the selected studies.

Study (Year)	Study Name (NCT number)	Phase	Study design	Treatment	Total no. of TNBC patients	No.of *BRCA*mut patients	No.of *BRCA*wt patients	No.of HRD patients
Gelmon et al. (2011)	NCT00679783	II	Single-arm	Olaparib	21	5	16	NA
O'Shaughnessy et al. (2011)	NCT00540358	II	RCT	Iniparibs + gemcitabine and carboplatin vs gemcitabine and carboplatin	123	NA	NA	NA
O'Shaughnessy et al. (2014)	NCT00938652	III	RCT	Iniparibs + gemcitabine and carboplatin vs gemcitabine and carboplatin	519	NA	NA	NA
Kummar et al. (2016)	NCT01306032	II	RCT	Veliparib + cyclophosphamide vs cyclophosphamide	45	7	4	NA
Robson et al. (2017)	OlympiAD NCT02000622	III	RCT	Olaparib vs standard therapy	150	150	0	NA
Litton et al. (2018)	EMBRACA NCT01945775	III	RCT	Talazoparib vs standard single-agent therapy	190	190	0	NA
Han et al. (2018)	BROCADE NCT01506609	II	RCT	Veliparib + carboplatin/paclitaxel vs placebo + carboplatin/paclitaxel	120	120	0	NA
Vinayak et al. (2019)	TOPACIO NCT02657889	II	Single-arm	Niraparib + pembrolizumab	55	15	27	20
Shimomura et al. (2019)	EO UMIN000018721	II	Single-arm	Olaparib + Eribulin	29	5	24	9
Diéras et al. (2020)	BROCADE3 NCT02163694	III	RCT	Veliparib + carboplatin-paclitaxel vs placebo + carboplatin/paclitaxel	243	243	0	NA

NCT ClinicalTrials.gov identifier, TNBC Triple-negative breast cancer, *BRCA*mut *BRCA* mutation, *BRCA*wt *BRCA* wild type, HRD homologous recombination deficiency.

Efficacy of PARP inhibitors in advanced/metastatic TNBC

PARP inhibitors vs control

To evaluate the effect of PARP inhibitors on the patients with advanced/metastatic TNBC, we first conducted a pooled analysis comparing the antitumor efficacy between the PARP inhibitor group and the chemotherapy group. Seven randomized controlled trials were pooled into the analysis of ORR or PFS,(14, 16, 17, 19–22) which included 778 advanced/metastatic TNBC patients who received PARP inhibitors (Olaparib, iniparibs, veliparib or talazoparib) and 568 participants who were administered with chemotherapies. In the whole population, the pooled RR showed that PARP inhibitor treatment significantly improved the incidence of achieving ORR compared to chemotherapy (RR = 2.00, 95% CI: 1.14–3.50, p = 0.02) (Fig. 2a). The pooled analysis for PFS indicated that the PARP inhibitor group had a better PFS when compared with the chemotherapy group (HR = 0.68, 95% CI: 0.59–0.77, p < 0.0001) (Fig. 3a).

With regard to the clinical benefit of PARP inhibitors in patients with *BRCA* mutation, four randomized controlled trials were eligible for the analysis of ORR or PFS.(14, 20–22) The studies above showed that compared with chemotherapy, the PARP inhibitor

treatment significantly improved ORR (RR = 3.63, 95% CI: 2.18–6.05, p < 0.0001) (Fig. 2b), and PFS (HR = 0.61, 95% CI: 0.50–0.74, p < 0.0001) in the germline/somatic *BRCA* mutated patients (Fig. 3b).

Three clinical trials focused on the efficacy of PARP inhibitors in advanced or metastatic TNBC irrespective of *BRCA* or HRD status,(16, 17, 19) we performed a pooled analysis in this unselected population. Results showed that no significant difference in terms of the ORR was observed between the PARP inhibitor group and the chemotherapy group (RR = 1.22, 95% CI: 0.99–1.52, p = 0.07) (Fig. 2c). However, PARP inhibitors had significant improvements in PFS (HR = 0.74, 95% CI: 0.62–0.89, p = 0.001) (Fig. 3c).

Subgroup analysis of the efficacy of PARP inhibitors

BRCA mutated vs BRCA wild-type

To further compare the efficacy of PARP inhibitors in the *BRCA* mutated and *BRCA* wild-type populations, we subsequently conducted an exploratory analysis directly comparing these two groups. Three studies mentioned ORR in two subgroups and were incorporated into this analysis.(23–25) Subgroup analysis demonstrated that PARP inhibitors could provide a significant improvement in ORR to the *BRCA* mutated patients in comparison to the *BRCA* wild-type patients, with a RR of 2.85 (95% CI: 1.34–6.06, p = 0.007) (Fig. 4a).

HRD vs non-HRD

It is still unclear whether, in addition to *BRCA* mutations, HRD status can be used as a biomarker to predict PARP inhibitors sensitivity in the advanced/metastatic TNBC setting. Therefore, we performed subgroup analyses of the HRD positive group vs. the non-HRD group to address this question. Two articles were eligible for this analysis, and only ORR data was available in two studies with less statistical power.(24, 25) Interestingly, there were not significant differences in ORR when comparing the HRD positive subgroup to the non-HRD subgroup (RR = 1.82, 95% CI: 0.81–4.08, p = 0.14) (Fig. 4b).

Adverse events of PARP inhibitor

In this study, seven randomized controlled trials that reported AEs were used to risk analysis. The comparative safety profile in terms of AEs of interest was shown in Table 2. On the whole, the results showed that the incidence of AEs in the PARP inhibitor group was similar to that in the chemotherapy group, regardless of any grade AEs (98.94% vs. 98.98%, RR = 1.00, 95% CI: 0.99–1.01, p = 0.66), and grade ≥ 3 AEs (76.32% vs. 79.68%, RR = 0.97, 95% CI: 0.88–1.07, p = 0.54). Notably, PARP inhibitor weakly increased the overall risk to suffer serious AEs compared with chemotherapy (26.88% vs. 24.57%, RR = 1.18, 95% CI: 1.00–1.38, p = 0.05). In PARP inhibitor group, for any grade events, the five most common AEs were nausea (64.00%), neutropenia (60.30%), thrombocytopenia (59.20%), anemia (59.17%) and fatigue (51.70%); and for grade ≥ 3 AEs, they were neutropenia (47.03%), thrombocytopenia (30.32%), anemia (27.56%), leukopenia (14.78%) and fatigue (5.13%). The pooled data showed that compared with the chemotherapy group, the PARP inhibitor group had an increased incidence of AEs in terms of grade ≥ 3 thrombocytopenia (p < 0.001), any grade nausea (p < 0.001) and any grade vomiting (p = 0.04).

Table 2
Summary of the adverse events (AEs).

Adverse events	No. of studies	Adverse events/total patients (%)		RR	95%CI	P value
		PARP inhibitors	Control treatment			
Any grade adverse events	6	1311/1325 (98.94)	779/787(98.98)	1.00	0.99–1.01	0.66
Grade ≥ 3 adverse events	6	809/1060 (76.32)	541/679 (79.68)	0.97	0.88–1.07	0.54
Any grade neutropenia	6	799/1325 (60.30)	533/787 (67.73)	0.90	0.78–1.03	0.12
Grade ≥ 3 neutropenia	7	633/1346 (47.03)	430/805 (53.42)	0.85	0.69–1.05	0.13
Any grade anemia	6	784/1325 (59.17)	407/787 (51.72)	1.22	0.97–1.54	0.09
Grade ≥ 3 anemia	7	371/1346 (27.56)	158/805 (19.63)	1.52	0.86–2.67	0.15
Any grade thrombocytopenia	5	663/1120 (59.20)	359/696 (51.58)	1.19	0.99–1.43	0.06
Grade ≥ 3 thrombocytopenia	6	346/1141 (30.32)	149/714 (20.87)	1.50	1.26–1.77	< 0.001
Any grade leukopenia	6	346/1325 (26.11)	209/787 (26.56)	0.95	0.82–1.10	0.51
Grade ≥ 3 leukopenia	7	199/1346 (14.78)	121/805 (15.03)	1.00	0.81–1.22	0.98
Any grade fatigue	6	685/1325 (51.70)	415/787 (52.73)	1.05	0.97–1.14	0.22
Grade ≥ 3 fatigue	6	68/1325 (5.13)	44/787 (5.59)	1.04	0.72–1.51	0.83
Any grade nausea	6	848/1325 (64.00)	439/787 (55.78)	1.17	1.09–1.26	< 0.001
Grade ≥ 3 nausea	6	30/1325 (2.26)	21/787 (2.67)	0.87	0.49–1.55	0.64
Any grade constipation	5	406/1120 (36.25)	245/696 (35.20)	1.12	0.99–1.27	0.08
Grade ≥ 3 constipation	5	6/1120 (0.54)	3/696 (0.43)	1.19	0.35–4.06	0.78
Any grade vomiting	6	424/1325 (32.00)	224/787 (28.46)	1.16	1.01–1.33	0.04
Grade ≥ 3 vomiting	6	32/1325 (2.42)	11/787 (1.40)	1.69	0.87–3.29	0.12
Any grade diarrhea	6	394/1325 (29.74)	214/787 (27.19)	1.08	0.94–1.24	0.29
Grade ≥ 3 diarrhea	6	32/1325 (2.42)	22/787 (2.80)	0.82	0.49–1.37	0.44
Any grade decreased appetite	4	215/1013 (21.22)	105/484 (21.69)	0.99	0.80–1.21	0.89
Grade ≥ 3 decreased appetite	4	7/1013 (0.69)	2/484 (0.41)	1.49	0.36–6.13	0.58

Quality of included studies

The 'Risk of bias graph' revealed that this meta-analysis had moderate risk of selection bias, because 3 out of 10 clinical trials were single-arm studies (Supplementary Fig. 1). We performed the funnel plots to detect the publication bias, the results suggested that there was a relatively low risk publication bias (Supplementary Fig. 2).

Discussion

The results of this study highlight that compared with chemotherapy, PARP inhibitors can safely and significantly improve the ORR and PFS in patients with advanced/metastatic TNBC. Furthermore, exploratory analysis showed that the *BRCA* mutated patients could derive more benefits from PARP inhibitors compared with *BRCA* wild-type patients. However, we did not observe any difference in tumor control between HRD positive patients and non-HRD patients. Based on those recent clinical evidences, *BRCA* mutation, rather than HRD status, can be used as a predictive biomarker for response to PARP inhibitors in the advanced/metastatic TNBC setting.

Preclinical studies showed that PARP inhibitors have greater efficacy in *BRCA*-deficient cells when compared with wild-type cells.(26, 27) In the clinical setting, a proof-of-concept trial by Tutt showed that PARP inhibition treatment has a favourable therapeutic index in *BRCA*-mutated advanced breast cancer patients.(28) Based on these results, over the past years, several clinical trials have been conducted and are currently evaluating the role of different PARP inhibitors in this population. Specifically, olaparib has been approved in *BRCA*-mutated HER2-negative metastatic breast cancer patients as the first targeted therapy based on the results of the OlympiAD study.(14) In view of this meta-analysis, our conclusion also confirmed that patients with *BRCA* mutations might be prime candidates for PARP inhibition treatment. However, our analysis also found that PARP inhibitors could provide significant improvement in PFS for unselected patients, regardless of *BRCA* mutational status. Similarly, in the phase II and III clinical trials for metastatic TNBC patients irrespective of *BRCA* status,(16, 17) the gain in PFS was obtained in the PARP inhibition group compared with the chemotherapy group. In addition, those with *BRCA* mutation account for only a small proportion of breast cancer patient.(29) Hence, only using *BRCA* status as a predictive biomarker for PARP inhibitors sensitivity is insufficient and may miss many potential responders.

The major question for oncologists is how to go about practically selecting advanced/metastatic TNBC patients who will benefit from PARP inhibitor therapy? Following large-scale sequence analysis, besides *BRCA1/2* gene, many other HRD-mutation genes (*ATM*, *CHK1/2*, and *PTEN*) were found to be correlated with PARP inhibition sensitivity, and could be utilized as alternative biomarkers for identifying vulnerable population.(30–32) In clinical situations, HRD status has a good predictive power for the benefits of PARP inhibitors in several cancer types, like ovarian cancer, prostate cancer, and gastric cancer.(33) However, in this study, we did not observe any improvement in ORR for HRD positive patients compared with HRD negative patients. It should be noted that there were only two relevant studies in this subgroup analysis with small sample size, which has less statistical power and is difficult to draw strong conclusions. In the future, more clinical trials are needed to evaluate the predictive value of HRD in the TNBC setting, and explore new biomarkers for determining optimal patients who are more likely to benefit from PARP inhibitors.

As PARP inhibitors has gradually been approved for clinical applications worldwide, the evaluation of safety and tolerance of PARP inhibitors in patients is very of value and indispensable. Our pooled analysis of 1346 advanced/metastatic breast cancer patients treated with PARP inhibitors from seven randomized controlled trials showed that the three most common AEs of grade 3 and above were neutropenia (47.03%), thrombocytopenia (30.32%), and anemia (27.56%), suggesting the risks of hematologic toxicities caused by PARP inhibition treatment are more common and serious. Similarly, a meta-analysis of eight clinical trials also found that olaparib could significantly increase the risk of severe neutropenia in cancer patients.(34) This may be because PARP inhibitor not only can interfere with DNA repair in cancer cells, but also may interfere with rapidly dividing blood cells, thus leading to myelosuppression. Notably, our meta-analysis showed that the PARP inhibitors did not increase the incidence of grade $\geq$ 3 AEs except for the risk of thrombocytopenia when compared with chemotherapy. Overall, PARP inhibitors seem to be generally safe and tolerable for advanced/metastatic breast cancer patients, but the high risk of PARP inhibitor-related hematologic toxicities is a trouble that cannot be ignored and should be considered in clinical application.

There are several limitations in the present meta-analysis. First, the potential bias of this study included heterogenous inclusion criteria, patients and treatment schedule in the included trials, for example, age, race, disease status, and interventional arm, these confounding variables were not stratified properly and incorporated into the meta-analysis. In addition, there are few comparative studies on the efficacy of PARP inhibitors between HRD-positive patients and HRD-negative patients, which makes it difficult to fully assess the benefit of PARP inhibitors based on patients' HRD status. Therefore, it is warranted to conduct randomized controlled trials with longer clinical follow-up in the future.

Conclusions

Our findings confirm that the addition of PARP inhibitor is a more effective, well tolerable and useful treatment in advanced/metastatic TNBC patients when compared with chemotherapy. We also support the view that *BRCA* status can be used as a predictive biomarker for PARP inhibitor sensitivity to guide clinical decision-making. However, the predictive value of HRD status still needs further evaluation in future studies. Hematologic toxicities are common adverse events, thus regular hematological monitoring is warranted for patients treated with PARP inhibitors.

Abbreviations

AEs: adverse events; CI: confidence interval; FDA: Food and Drug Administration; HR: hazard ratio; HRD: homologous recombination deficiency; HRR: homologous recombination repair; ORR: overall response rate; PARP: Poly (ADP-ribose) polymerase; PFS: progression-free survival; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; RR: risk ratio; TNBC: triple-negative breast cancer

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XL, KW, and XRZ conceived and designed the analysis; XL, and KW collected the data; XL, KW, and DZ analyzed the data; and CXL, YF, XL, and HZ interpreted the data. All authors were involved in the drafting, critical review, and approval of the final manuscript and the decision to submit for publication.

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Figures

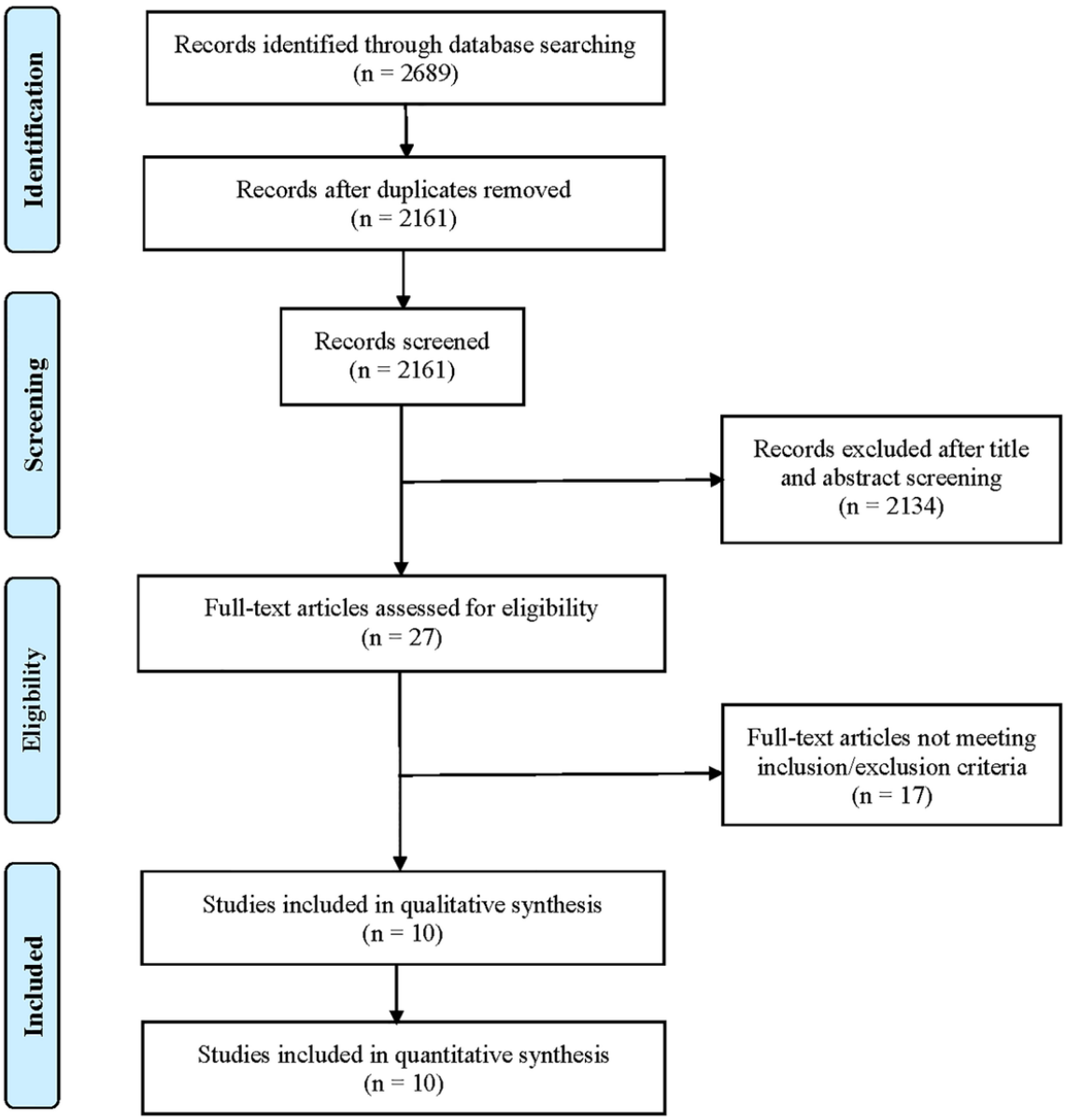


Figure 1

Flow diagram of study inclusion and exclusion.

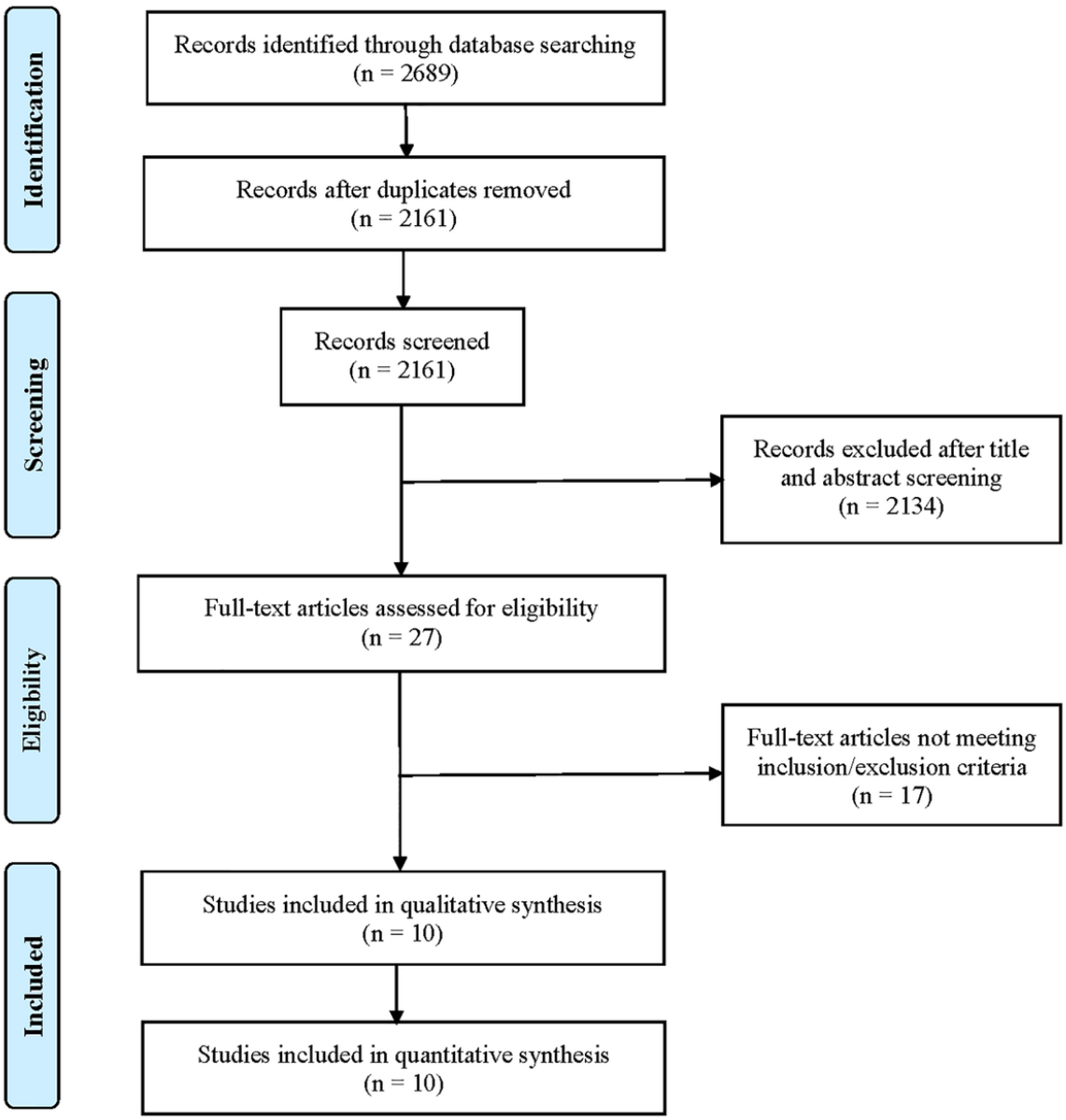
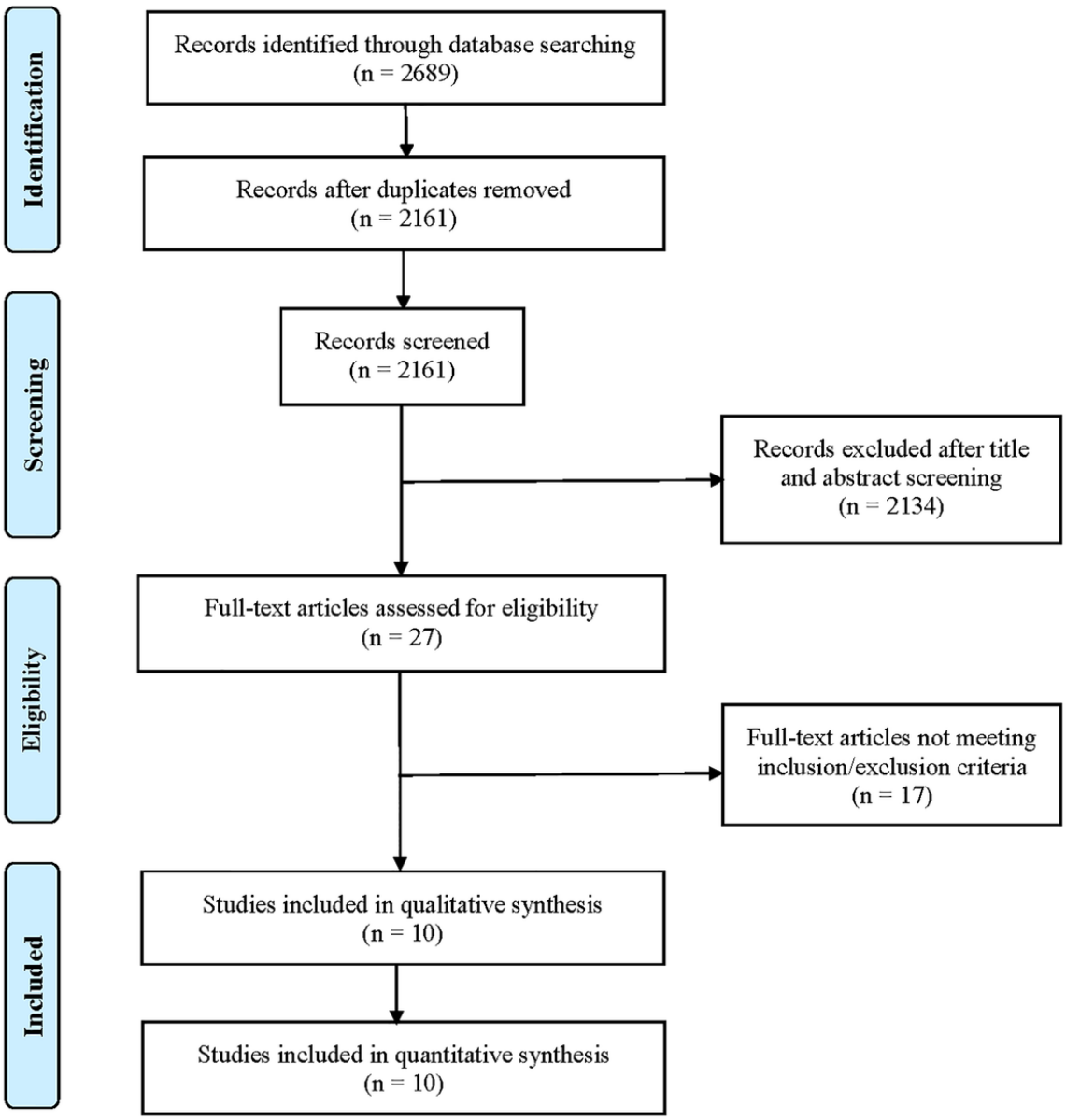


Figure 1

Flow diagram of study inclusion and exclusion.



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Flow diagram of study inclusion and exclusion.

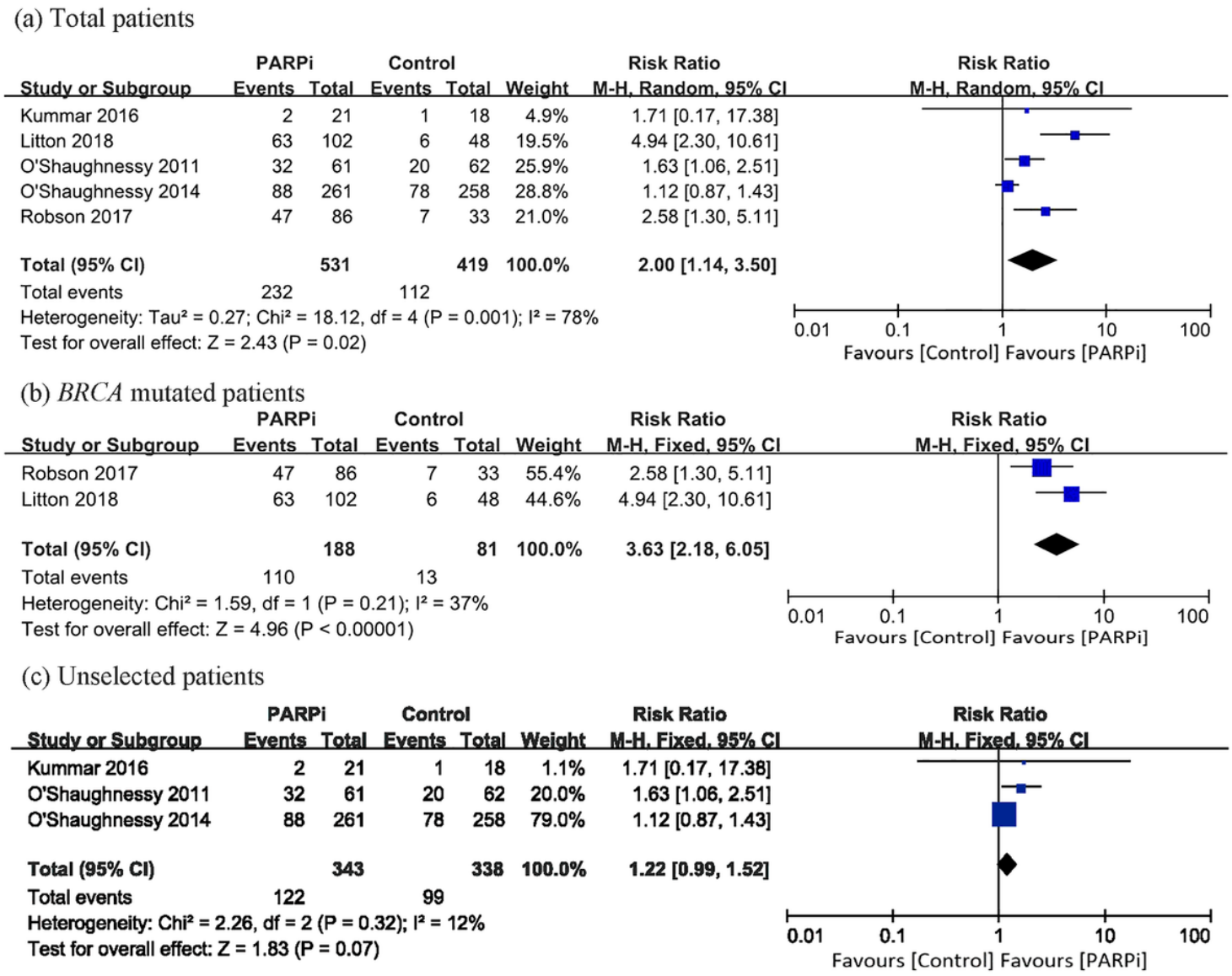
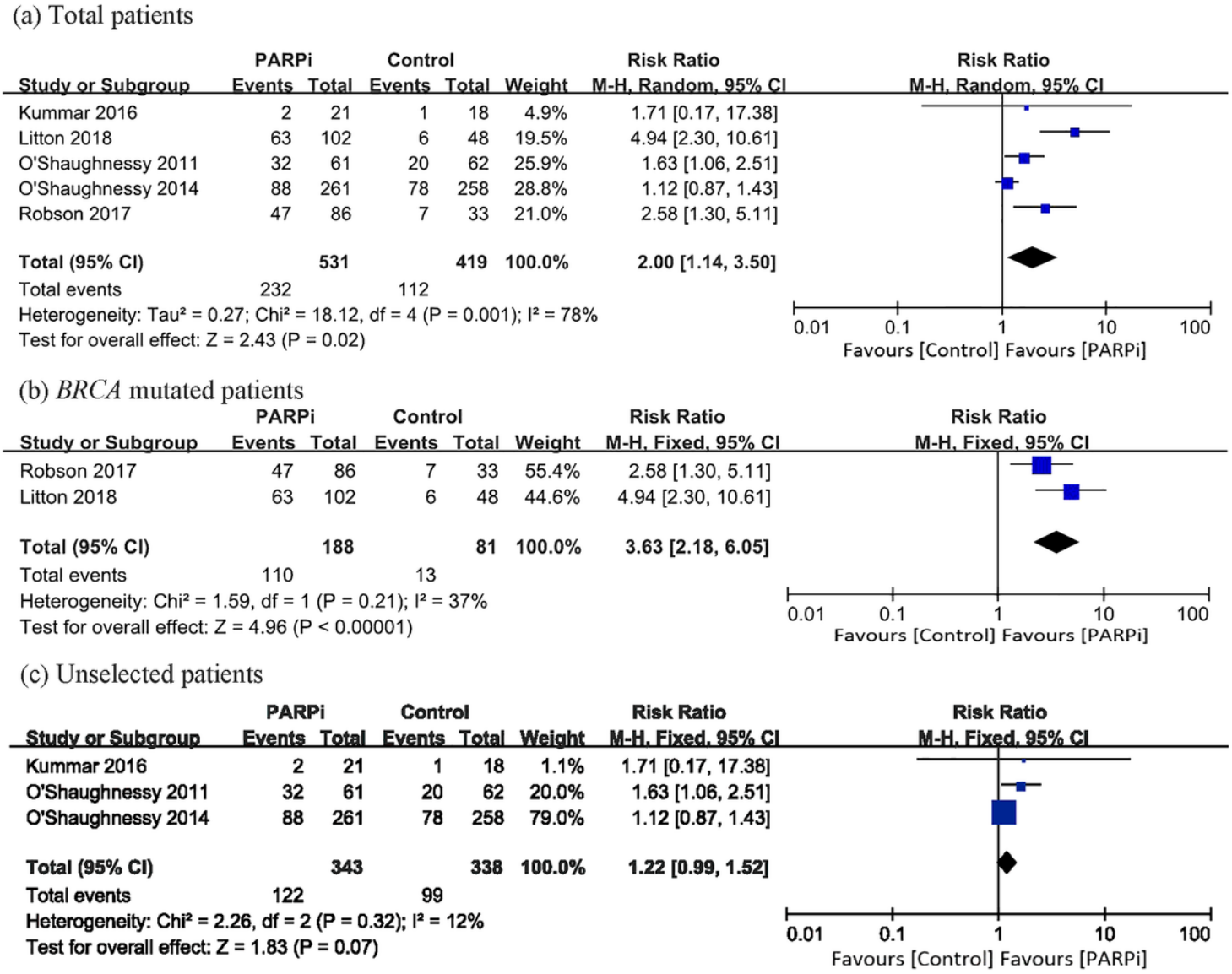


Figure 2

Forest plots of pooled analyses for PARP inhibitors vs control treatment on objective response rate in: (a) total patients, (b) BRCA mutated patients, (c) unselected patients.



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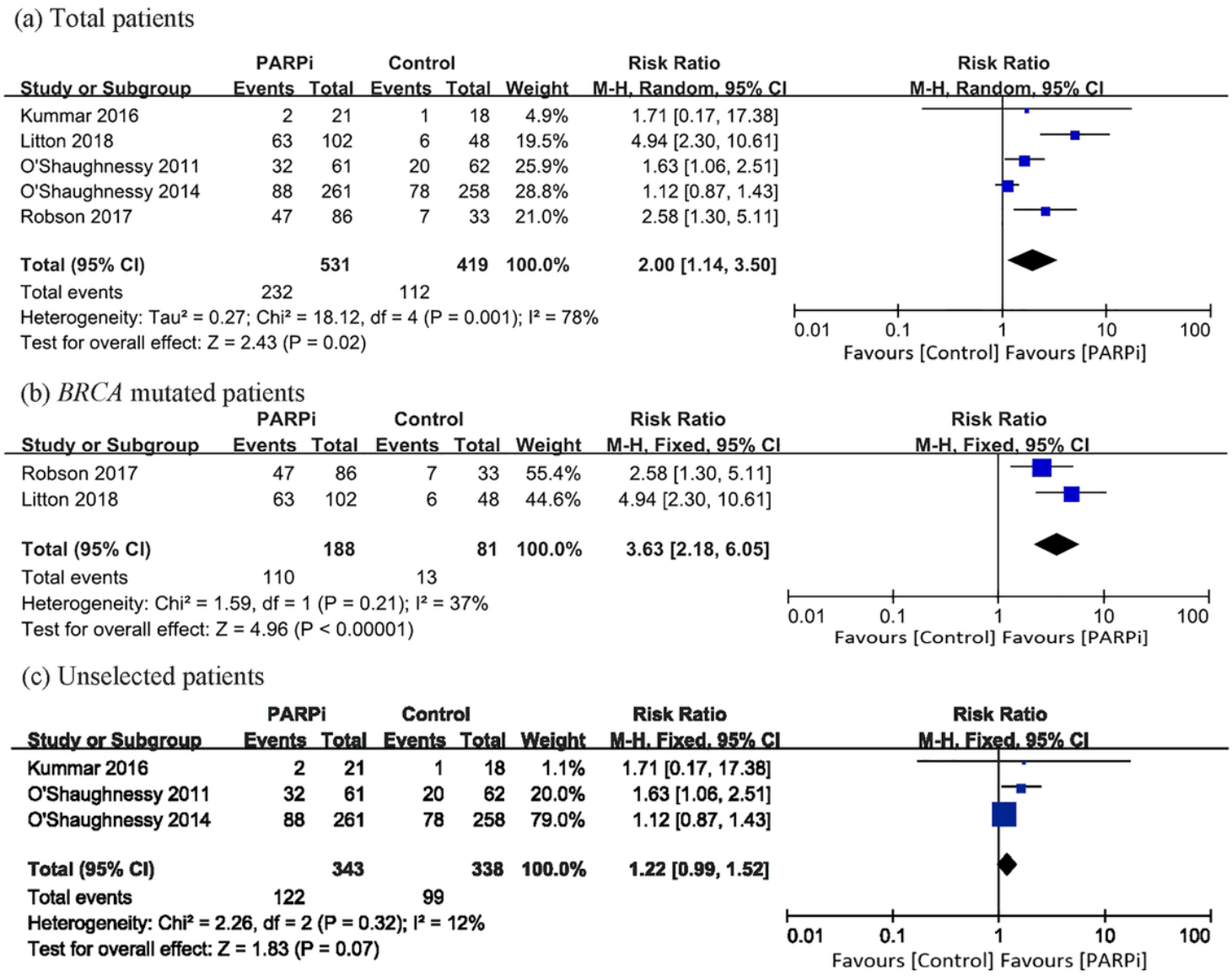

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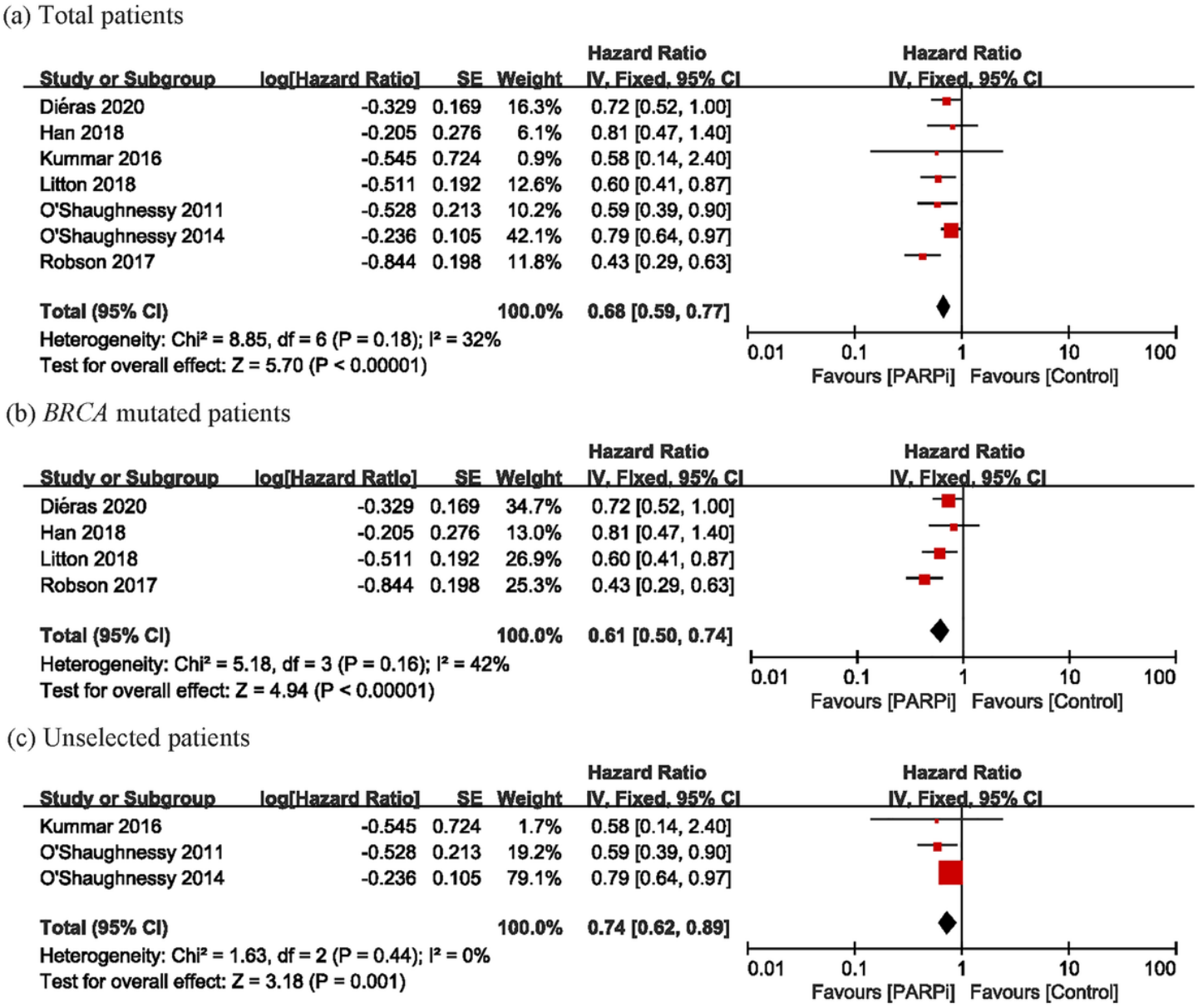
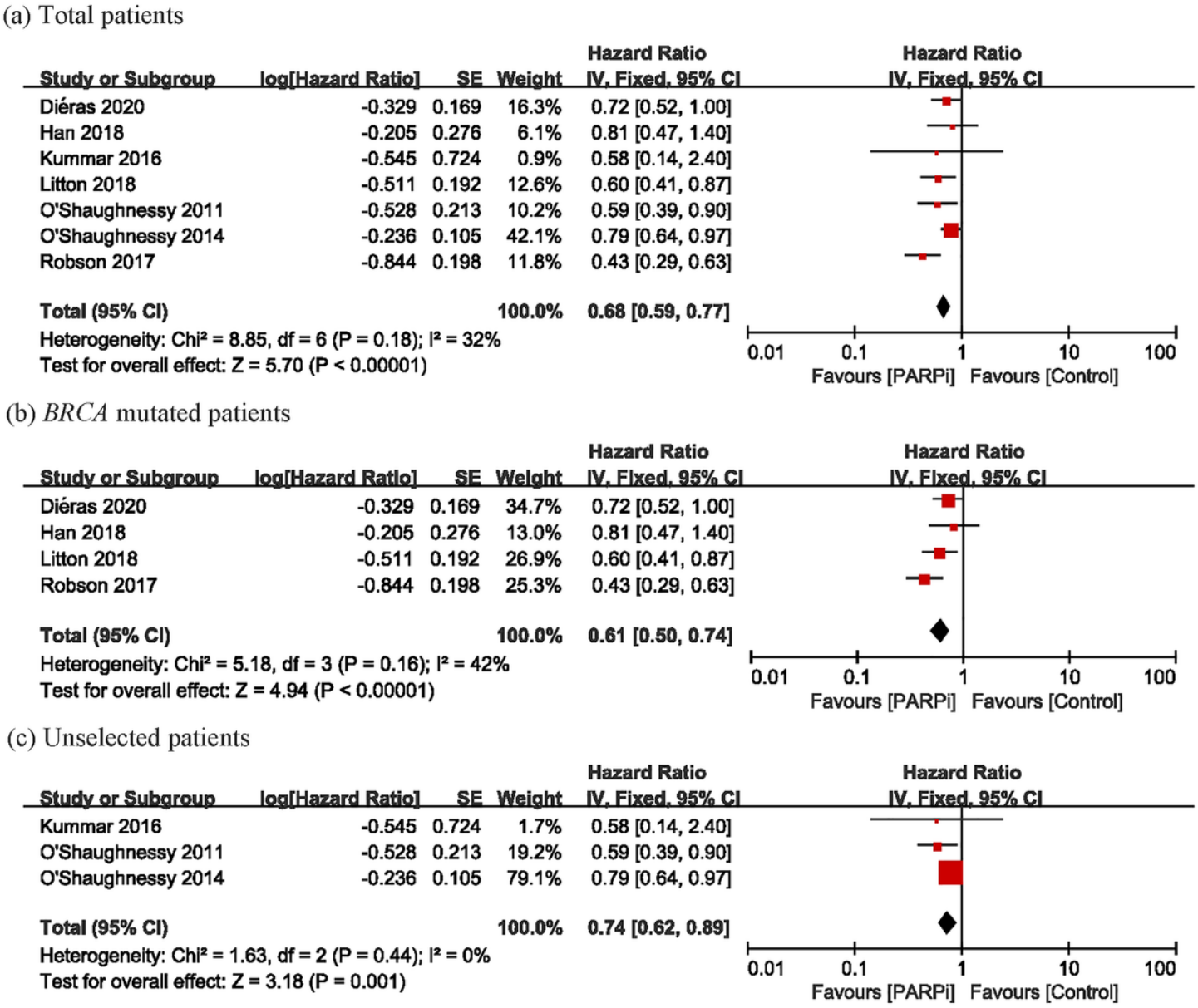


Figure 3

Forest plots of pooled analyses for PARP inhibitors vs control treatment on progression-free survival in: (a) total patients, (b) BRCA mutated patients, (c) unselected patients.



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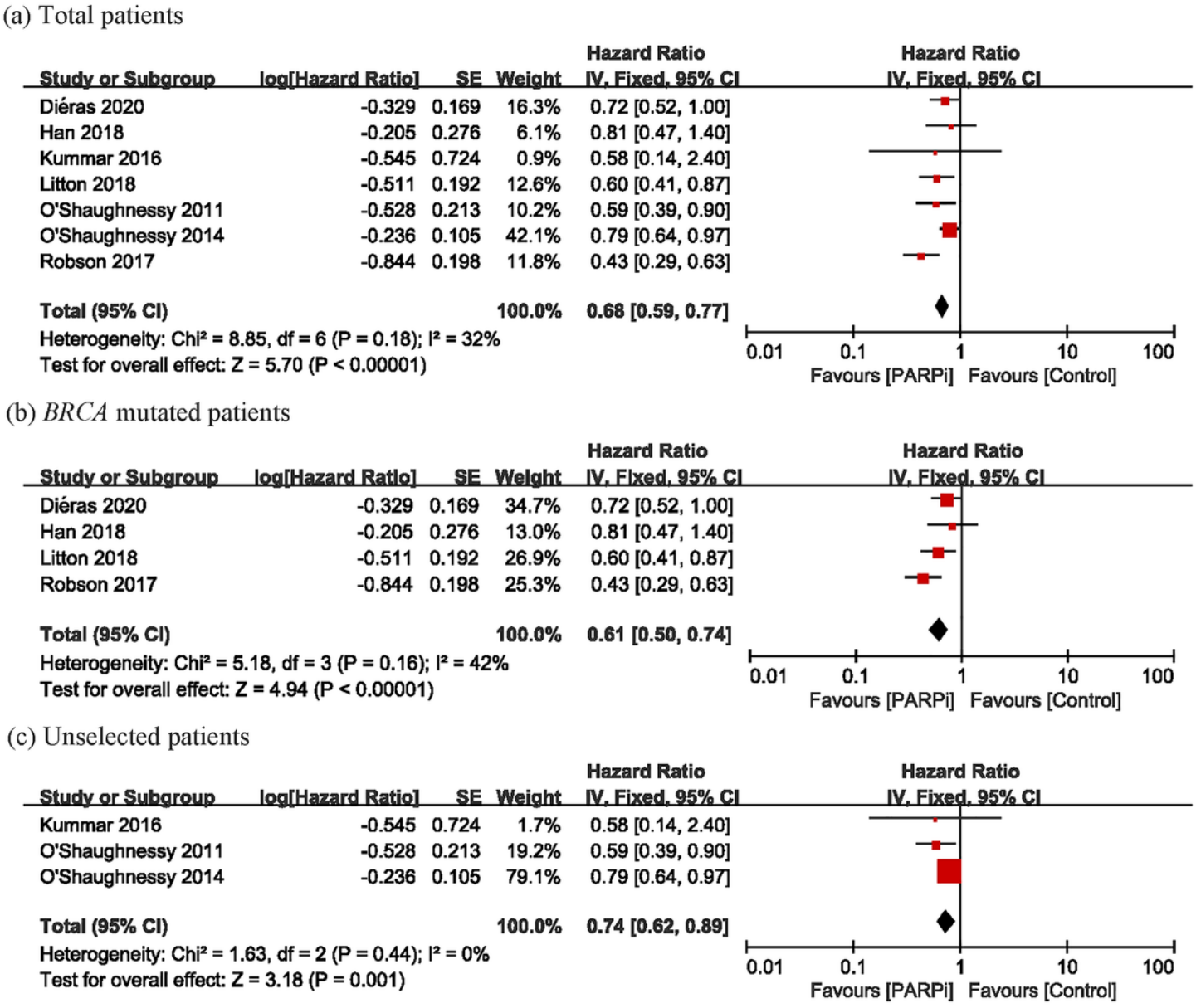

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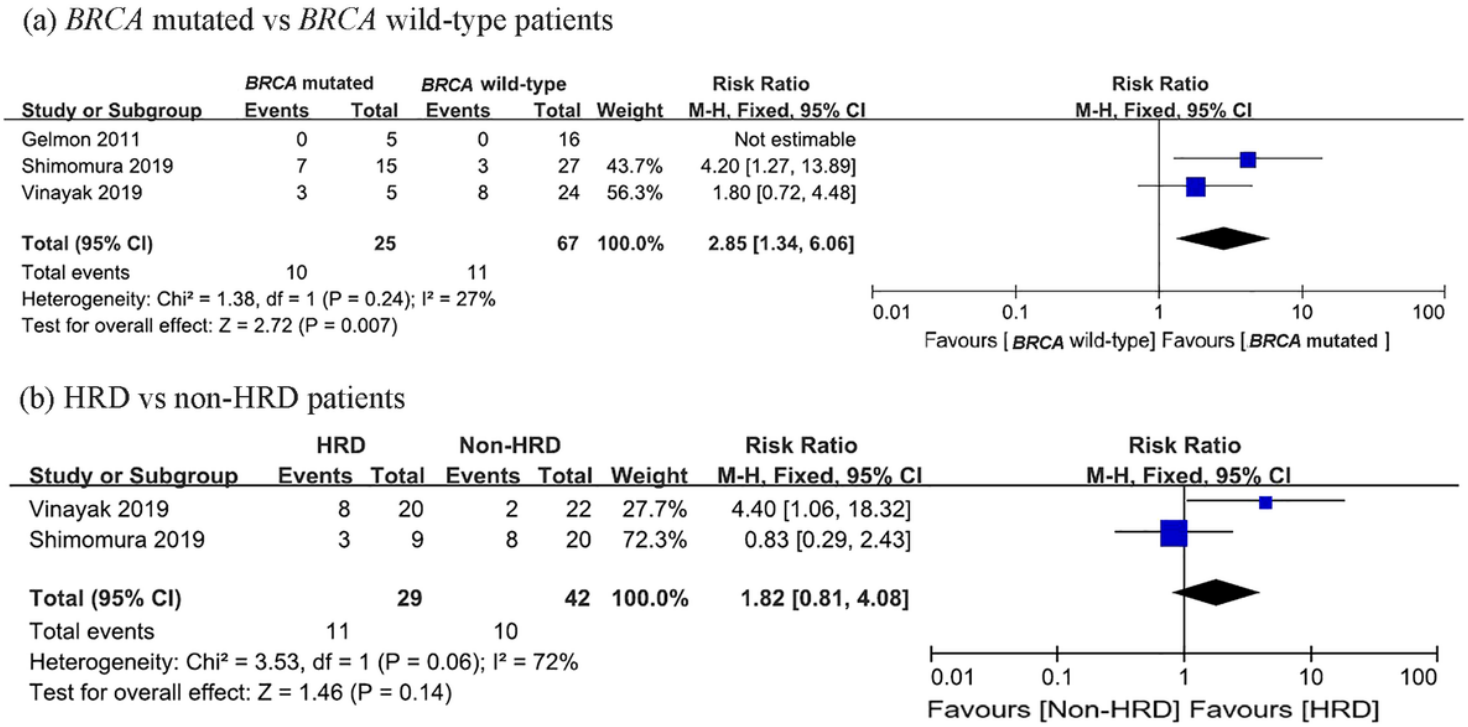


Figure 4

Forest plots of pooled analyses for the effect of PARP inhibitors on ORR in: (a) BRCA mutated vs BRCA wild-type patients, (b) HRD vs non-HRD patients. Abbreviation: ORR, overall response rate; HRD, homologous recombination deficiency.

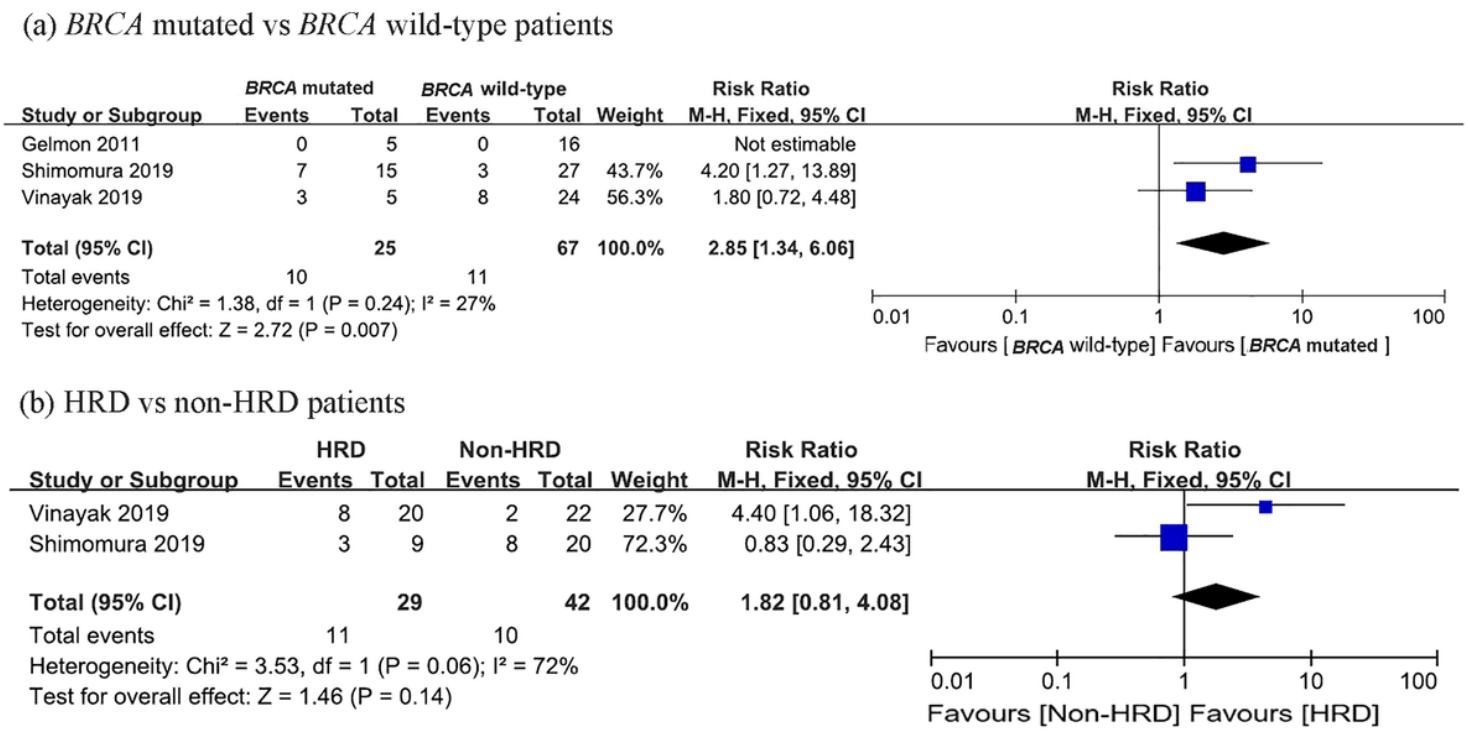
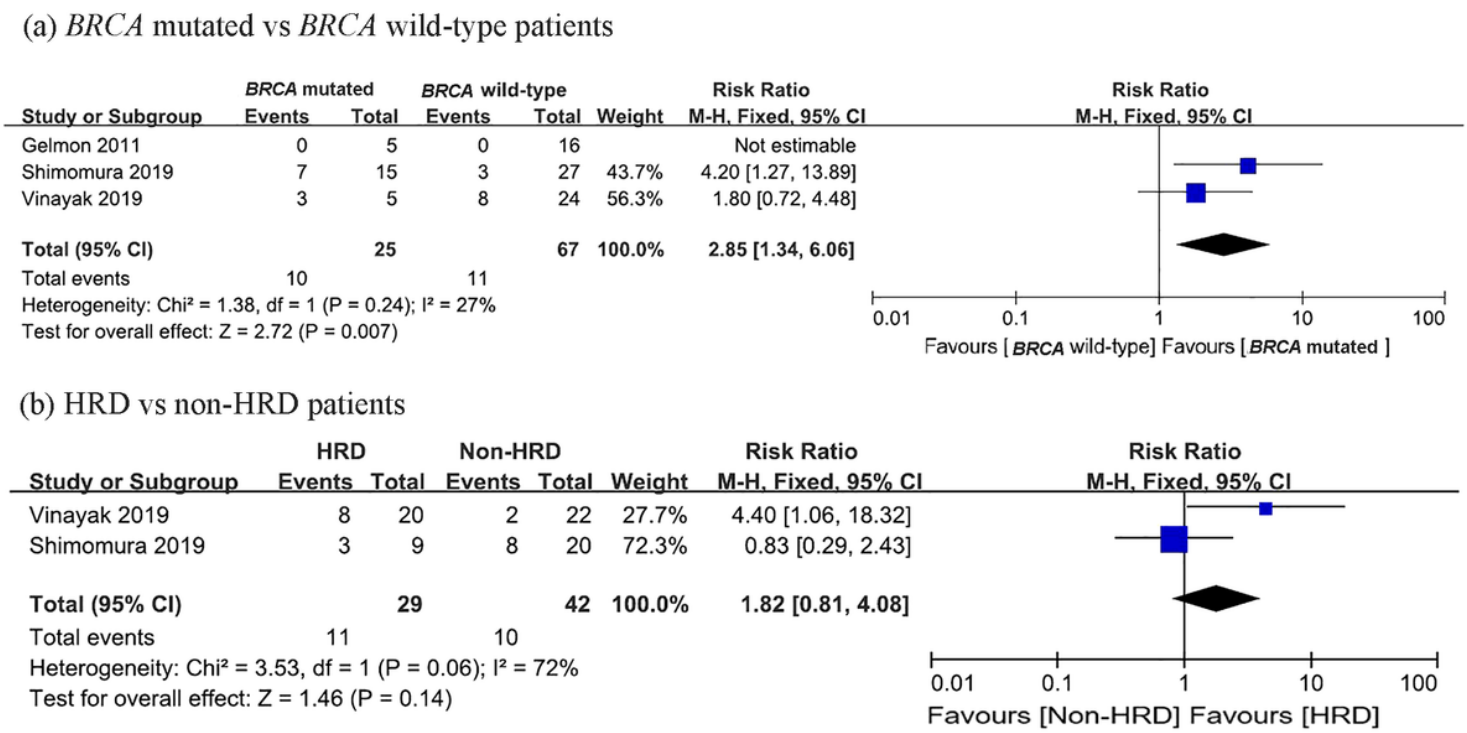

(a) BRCA mutated vs BRCA wild-type patients
BRCA mutated
BRCA wild-type
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Gelmon 2011 0 5 0 16 Not estimable
Shimomura 2019 7 15 3 27 43.7% 4.20 [1.27, 13.89]
Vinayak 2019 3 5 8 24 56.3% 1.80 [0.72, 4.48]
Total (95% CI) 25 67 100.0% 2.85 [1.34, 6.06]
Total events 10 11
Heterogeneity: Chi² = 1.38, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 2.72 (P = 0.007)
0.01 0.1 1 10 100
Favours [BRCA wild-type] Favours [BRCA mutated]
(b) HRD vs non-HRD patients
HRD
Non-HRD
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Vinayak 2019 8 20 2 22 27.7% 4.40 [1.06, 18.32]
Shimomura 2019 3 9 8 20 72.3% 0.83 [0.29, 2.43]
Total (95% CI) 29 42 100.0% 1.82 [0.81, 4.08]
Total events 11 10
Heterogeneity: Chi² = 3.53, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.46 (P = 0.14)
0.01 0.1 1 10 100
Favours [Non-HRD] Favours [HRD]

Figure 4

Forest plots of pooled analyses for the effect of PARP inhibitors on ORR in: (a) BRCA mutated vs BRCA wild-type patients, (b) HRD vs non-HRD patients. Abbreviation: ORR, overall response rate; HRD, homologous recombination deficiency.



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Forest plots of pooled analyses for the effect of PARP inhibitors on ORR in: (a) BRCA mutated vs BRCA wild-type patients, (b) HRD vs non-HRD patients. Abbreviation: ORR, overall response rate; HRD, homologous recombination deficiency.

Supplementary Files

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