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Overall survival and progression-free survival with cyclin-dependent kinase 4/6 inhibitors plus endocrine therapy in breast cancer: an updated meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have been recommended as standard therapeutic strategies for hormone receptor-positive (HR+), human epidermal growth factor receptor type 2-negative (Her2-) advanced breast cancer (ABC). While the benefits to progression-free survival (PFS) rates have been confirmed, whether the combination of CDK4/6i and ET leads to overall survival (OS) rate improvements remains controversial. This study aimed to assess the long-term efficacy and safety of CDK4/6i in HR+, Her2- ABC patients and identify a population suitable for treatment with CDK4/6i by subgroup analysis.

MATERIALS AND METHODS: Electronic literature databases (MEDLINE, EMBASE and the Cochrane Library) were searched for relevant randomized controlled trials (rcts) published from Jan 2014 to Jan 2020. In addition, abstracts and presentations from all major conference proceedings were reviewed. All rcts that compared the efficacy and safety of CDK4/6i plus ET with ET alone in HR+, Her2- ABC patients were selected. The pooled analyses of hazard ratios (hrs) for PFS and OS, and risk ratios (rrs) for the objective response rate (ORR) and adverse events (aes) were obtained with the random-effects model.

RESULTS: A total of 6 rcts and 3421 HR+, Her2- ABC patients were enrolled for OS outcome analysis, while all 8 trials and 4580 patients were included for PFS outcome analysis. The pooled hrs for the OS and PFS were 0.76 (95% CI: 0.67–0.84) and 0.55 (95% CI: 0.50–0.59), respectively, and were consistent in the subgroup analysis. Moreover, CDK4/6i meaningfully improved the ORR in both the intention-to-treat population (RR=1.47; 95% CI: 1.29–1.67) and patients with measurable disease (RR=1.47; 95% CI: 1.30–1.67); however, CDK4/6i increased the incidence of grade 3/4 aes (RR=2.69; 95% CI: 2.43–2.97).

CONCLUSIONS: The combination of CDK4/6i and ET was superior to ET alone in terms of OS and PFS regardless of the drugs administered, the treatment line, age distribution, race, PR status, menopausal status, metastasis site and endocrine resistance status.

Key Words:
CDK4/6 inhibitors, Advanced HR+, HER2– breast cancer, Overall survival, Progression-free survival, Meta-analysis.

Introduction

Approximately 70% of patients with advanced breast cancer (ABC) have hormone receptor-positive (HR+) disease[1]. Although endocrine therapy (ET), the standard treatment option for HR+, human epidermal growth factor receptor 2-negative (Her2-) breast cancer patients, has led to an improvement in survival, resistance to ET and subsequent disease progression remain major challenges. The activation of the cyclin D-cyclin dependent kinase 4 and 6 (CDK4/6) signalling axis driven by the oestrogen pathway is an important mechanism of resistance to ET in HR+ patients. Cyclin D and CDK4/6 play important roles in the G1/S phase transition by regulating the phosphorylation state of retinoblastoma tumour suppressor protein (RB). After phosphorylation by CDK4/6, phospho-RB releases transcription factor E2F to initiate the transition from G1 to S phase, which accelerates the progression of the cell cycle[2]. The deregulation of the cyclin D-CDK4/6-RB pathway is a common cause of ET resistance in HR+ breast cancer patients; therefore, this provides a rationale to overcome endocrine resistance by the blockade of this pathway[3,4].

Recently, the results of several clinical trials have established the efficacy of CDK4/6 inhibitors (CDK4/6i), such as palbociclib[5,6], ribociclib[7,8]

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and abemaciclib[9,10], in HR+, Her2- breast cancer patients. In terms of progression-free survival (PFS) outcomes, consistent results were achieved among all available randomized controlled trials (rcts), showing that the addition of CDK4/6i to ET resulted in a significant PFS benefit, regardless of treatment line, menopausal status, metastasis site, and other prespecified factors. Several meta-analyses have been performed to define the efficacy and safety of CDK4/6i plus ET according to PFS outcome data[11-14]. The results showed that CDK4/6i can significantly prolong PFS and improve objective response rates (orrs) among patients with HR+, Her2- ABC. However, regarding overall survival (OS), the results of rcts to date are inconsistent. According to the results of the PALOMA-1[15] and PALOMA-3[16] trials, palbociclib plus ET yielded a statistically nonsignificant trend towards an improvement in OS outcomes among the overall population. In 2019, the results of the MONALEESA-7[17], MONARCH-2[18] and MONALEESA-3[19] trials demonstrated a significant OS benefit associated with CDK4/6i in HR+, Her2- ABC patients.

Therefore, it is important to understand the long-term efficacy of CDK4/6i for the treatment of HR+, Her2- breast cancer patients. We conducted this meta-analysis to better define the efficacy and safety of CDK4/6i in HR+, Her2- ABC patients and aimed to identify a suitable patient population for CDK4/6i therapy through subgroup analysis.

Materials and Methods

Search Criteria

Original articles published from Jan 2014 to Jan 2020 concerning the combined use of CDK4/6i and ET *vs.* Endocrine monotherapy in HR+, Her2- ABC were searched in the MEDLINE, EMBASE and the Cochrane Library databases using the following key terms: 'cyclin-dependent kinase 4 and 6 inhibitor', 'CDK4/6 inhibitor', 'palbociclib', 'ribociclib', 'abemaciclib' and 'breast cancer'. All studies retrieved by this process were considered, and their bibliographies were carefully examined manually to identify further potentially eligible articles. The conference proceedings of the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS) were also searched to identify unpublished studies and updated data. To be included in this meta-analysis, all studies had to meet the following criteria: 1) phase 2 or 3 rcts designed to evaluate the efficacy and safety of CDK4/6i plus ET *vs.* ET alone in HR+, Her2- ABC patients and 2) the hazard ratios (hrs) for the PFS and OS outcomes were reported. Non-randomized prospective studies, retrospective studies, single-arm studies, reviews, meta-analyses and case reports were excluded. Inclusion and exclusion decisions were reached by two investigators after they evaluated the manuscripts. If their views diverged, the differences were resolved through discussion and reaching a consensus between the two investigators or through consultation with a third investigator.

Data Extraction

Data collection and methodological quality assessment followed the Quality of Reporting of Meta-analyses and Cochrane Collaboration guidelines (http://www.cochrane.de). To ensure the quality of the data, two of the authors extracted information carefully and independently from all eligible publications. Any disagreement between these researchers was resolved by discussion until a consensus was reached. After application of the above inclusion criteria, the following data were extracted from each study: study characteristics (i.e., first author, time of recruitment, study design, study phase, number of patients, line of treatment and study drugs), participant characteristics (i.e., age distribution, Eastern Cooperative Oncology Group Performance Status, pathological characteristics and menopausal status), and measured outcome indexes (i.e., hrs with 95% confidence intervals (CIs) for OS and PFS, outcomes, the objective response rate (ORR) and the incidence of adverse events).

Statistical Methods and Analysis

The guidelines recommended by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group were applied during the statistical analyses[20]. For the quantitative aggregation of the effect of CDK4/6i plus ET *vs.* ET alone on OS and PFS outcomes in HR+, Her2- ABC patients, hrs and 95% CIs were combined to obtain the effective value. Subgroup analyses to determine the association between CDK4/6i treatment and prognosis were performed according to the drugs administered, the line of treatment, age distribution, race, ER and PR status, menopausal status, site of metastasis and endocrine resistance status. For noncontinuous variables, orrs

and aes, the risk ratios (rrs) were calculated from the reported data directly by number of events. Statistical analysis was performed with the random-effects model. The estimation of heterogeneity was performed by the chi-square-based Q test and I^2 estimate, and $p<0.05$ or $I^2>50\%$ indicated the presence of heterogeneity, whereas $p>0.05$ or $I^2<50\%$ indicated no heterogeneity. Potential publication bias was tested by Begg's funnel plot[21] and Egger's regression asymmetry test[22]. All statistical analyses were performed using Stata version 15.0 (Stata Corporation, College Station, TX, USA) or RevMan 5.3 (Cochrane Collaboration, London, UK).

Results

Search Results

In total, 565 records were identified in the primary literature search. After the exclusion of 58 duplicate articles and 383 irrelevant publications, 124 were identified as records eligible for the present study. Another 107 articles were excluded as they were laboratory-based studies, reviews and meta-analysis articles, not rcts or subgroup analyses. After these rounds of exclusion, 17 publications about 8 rcts met our criteria for evaluation. The detailed diagram of the selection processes is shown in Figure 1.

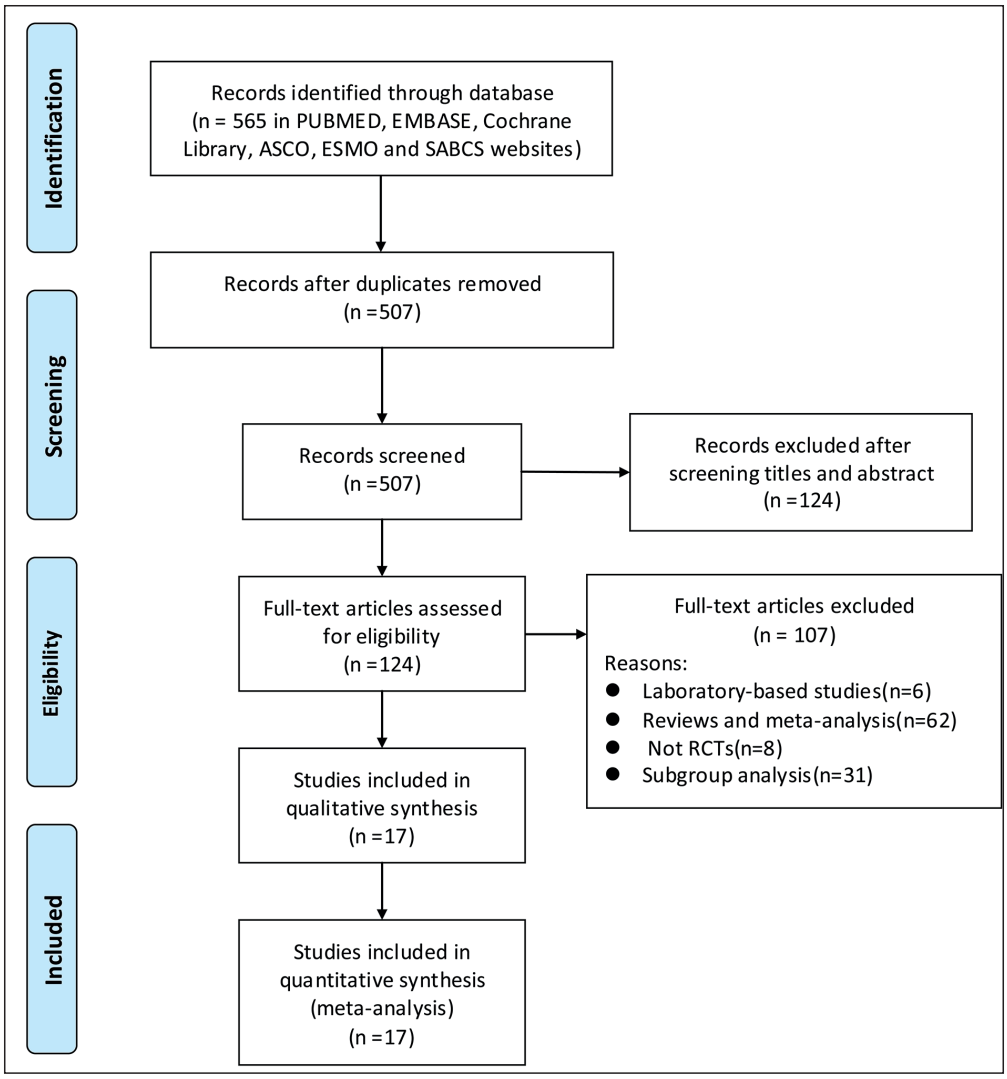

Figure 1. The PRISMA flow chart outlining the study selection process.

Study Characteristics

The main characteristics of the involved studies are summarized in Table I. A total of eight rcts (1 phase 2 and 7 phase 3) and 4580 HR+, Her2- ABC patients were enrolled in this meta-analysis. Of these eight studies included, seven[6-10,16,19] were phase 3 randomized, double-blind, placebo-controlled trials, and one[5] was an open-label phase 2 trial. Five trials[5-8,10] estimated the efficacy and safety of CDK4/6i plus ET in HR+, Her2- ABC patients who had no prior systemic therapy in the advanced setting, two trials[9,16] in patients whose disease progressed during prior ET, and one trial[19] included patients in both settings. All eight rcts were available for the analysis of up-to-date PFS, and six rcts were available for the analysis of OS at the end of the observation period.

Five out of eight trials[5-7,10,19] enrolled only postmenopausal patients, one trial[8] enrolled only pre-, perimenopausal patients, and two trials[9,16] enrolled any menopausal status women. About 20% of the whole study population were Asian, and most patients had ECOG performance status scores of 0 or 1. All breast cancers were histologically HR-positive and Her2-negative, and many patients were ER-positive and PR-positive. The other baseline characteristics of the included population in each clinical trial are summarized in Table II.

OS and PFS Outcomes of the Overall Population

OS results were reported in six of the enrolled studies, involving 3421 patients. The results of five studies were mature, except for the MONALEESA-2 trial. A total of 2030 patients were enrolled in the CDK4/6i plus ET arm and 1391 in the ET alone arm. The pooled data showed that the CDK4/6i plus ET group had a longer OS than those of the endocrine monotherapy group (HR=0.76; 95% CI: 0.67–0.84) (Figure 2A). All 8 rcts enrolling 4580 patients were available for the analysis of up-to-date PFS data. A total of 2802 patients were enrolled in the CDK4/6i plus ET arm and 1778 in the ET alone arm. The addition of CDK4/6i to ET was associated with a statistically significant PFS benefit (HR=0.55; 95% CI: 0.50–0.59) (Figure 2B).

Subgroup Analyses

Subgroup analyses were conducted based on the following stratification factors: type of drug administered, line of treatment, age, race, ER and PR status, menopausal status, metastasis site and ET resistance status. The addition of ribociclib (HR=0.72; 95% CI: 0.60-0.84) and abemaciclib (HR=0.76; 95% CI: 0.59-0.93) to ET resulted in a numerically larger improvement in OS benefits than the addition of palbociclib (HR=0.83; 95% CI: 0.66-1.00). The combination treatment improved OS outcomes in patients with treatment-naïve advanced disease (HR=0.74; 95% CI: 0.61–0.87) and in patients who had received up to one line of prior endocrine therapy for advanced disease (HR=0.77; 95% CI: 0.66–0.88). Consistent treatment effects on OS outcomes were observed in both postmenopausal patients (HR=0.75; 95% CI: 0.66–0.85) and pre-, perimenopausal patients (HR=0.74; 95% CI: 0.56–0.91). Regarding the metastasis site, a numerically larger effect was observed in patients with visceral disease (HR=0.74; 95% CI: 0.58–0.91) compared to the effect on those with non-visceral disease (HR=0.79; 95% CI: 0.56–1.01) or bone-only disease (HR=0.76; 95% CI: 0.50–1.03). The subgroup analysis of patients with primary *vs.* secondary endocrine resistance showed a statistically significant OS benefit in patients with secondary endocrine resistance (HR=0.75; 95% CI: 0.61–0.89) compared to that in patients with primary resistance (HR=0.85; 95% CI: 0.42–1.27). The OS outcomes of several other subgroups are summarized in Figure 3.

Improvements in PFS outcomes were consistent among all subgroups. Three CDK4/6 inhibitors, palbociclib (HR=0.53; 95% CI: 0.45–0.60), ribociclib (HR=0.59; 95% CI: 0.50–0.64), and abemaciclib (HR=0.54; 95% CI: 0.46–0.62), showed similar PFS benefits when combined with ET. The PFS advantage was obtained regardless of whether the treatments were applied as first-line (HR=0.55; 95% CI: 0.49–0.61) or subsequent-line (HR=0.53; 95% CI: 0.46–0.60) therapies. The addition of CDK4/6i to ET showed a numerically larger effect in the Asian population (HR=0.42; 95% CI: 0.33-0.52) than in the non-Asian population (HR=0.56; 95% CI: 0.47-0.64). PR-negative patients (HR=0.43; 95% CI: 0.33-0.53) obtained a greater PFS benefit from the combination treatment than PR-positive patients (HR=0.57; 95% CI: 0.50-0.64). Regarding menopausal status, the PFS advantage was significant in postmenopausal patients (HR=0.55; 95% CI: 0.50–0.60) and pre-, perimenopausal patients (HR=0.52; 95% CI: 0.41–0.62). Analysis by metastasis site indicated consistent PFS benefits for visceral (HR=0.52; 95% CI: 0.45–0.58), nonvisceral (HR=0.48; 95% CI: 0.40–0.56) and bone-only (HR=0.48; 95% CI: 0.38–0.57) metastases. Subgroup analysis by endocrine resistance status indicated consistent PFS improvements among patients with both primary (HR=0.48; 95% CI: 0.34–0.63) and secondary (HR=0.49; 95% CI: 0.35–0.63) ET resistance. The subgroup analyses of PFS outcomes are summarized in Figure 4.

Table I. Main characteristics of the randomized studies included in this meta-analysis.

Clinical trail	Recruitment period	Sample size	Design	Phase	Setting	Arms	PFS	OS	TTC
PALOMA1	2009.12-2012.5	165	Open-label, randomized study	2	1 line	P+L group L group	HR=0.488 95%CI:0.319-0.748	HR=0.897 95%CI:0.623-1.294	NA
PALOMA2	2013.2-2014.7	666	Randomized, double-blind, placebo-controlled study	3	1 line	P+L group L group	HR=0.58 95%CI:0.46-0.72	NA	40.4(34.7-47.3) HR=0.735 29.9(25.6-35.1) 95%CI:0.589-0.917
PALOMA3	2013.10-2014.8	521	Randomized, double-blind, placebo-controlled study	3	2 line	P+F group F group	HR=0.42 95%CI:0.32-0.56	HR=0.81 95%CI:0.64-1.03	17.6(15.2-19.7) HR=0.58 8.8(7.3-12.7) 95%CI:0.47-0.73
MONALEESA2	2014.1-2015.3	668	Randomized, double-blind, placebo-controlled study	3	1 line	R+L group L group	HR=0.56 95%CI:0.43-0.72	HR=0.746 95%CI:0.517-1.078	NA
MONALEESA3	2015.6-2016.6	726	Randomized, double-blind, placebo-controlled study	3	1 & 2 line	R+F group F group	HR=0.587 95%CI:0.488-0.705	HR=0.724 95%CI:0.568-0.924	NR HR=0.696 29.5 95%CI:0.551-0.879
MONALEESA7	2014.12-2016.8	672	Randomized, double-blind, placebo-controlled study	3	1 line	R+T/AI+OFS group T/AI+OFS group	HR=0.55 95%CI:0.44-0.96	HR=0.71 95%CI:0.54-0.95	NA
MONARCH2	2014.8-2015.12	669	Randomized, double-blind, placebo-controlled study	3	2 line	A+F group F group	HR=0.536 95%CI:0.445-0.645	HR=0.757 95%CI:0.606-0.945	50.2 HR=0.625 22.1 95%CI:0.501-0.779
MONARCH3	2014.11-2015.11	493	Randomized, double-blind, placebo-controlled study	3	1 line	A+AI group AI group	HR=0.54 95%CI:0.418-0.698	NA	NA

Notes: *P,* Palbociclib; *L,* Letrozole; *F,* Fulvestrant; *R,* Ribociclib; *T,* Tamoxifen; *AI,* Aromatase Inhibitors; *OFS,* Ovarian function suppression; *A,* Abemaciclib; *PFS,* Progression-free survival; *HR,* Hazard ratio; *CI,* Confidence interval; *OS,* Overall survival; *TTC,* Time to chemotherapy.

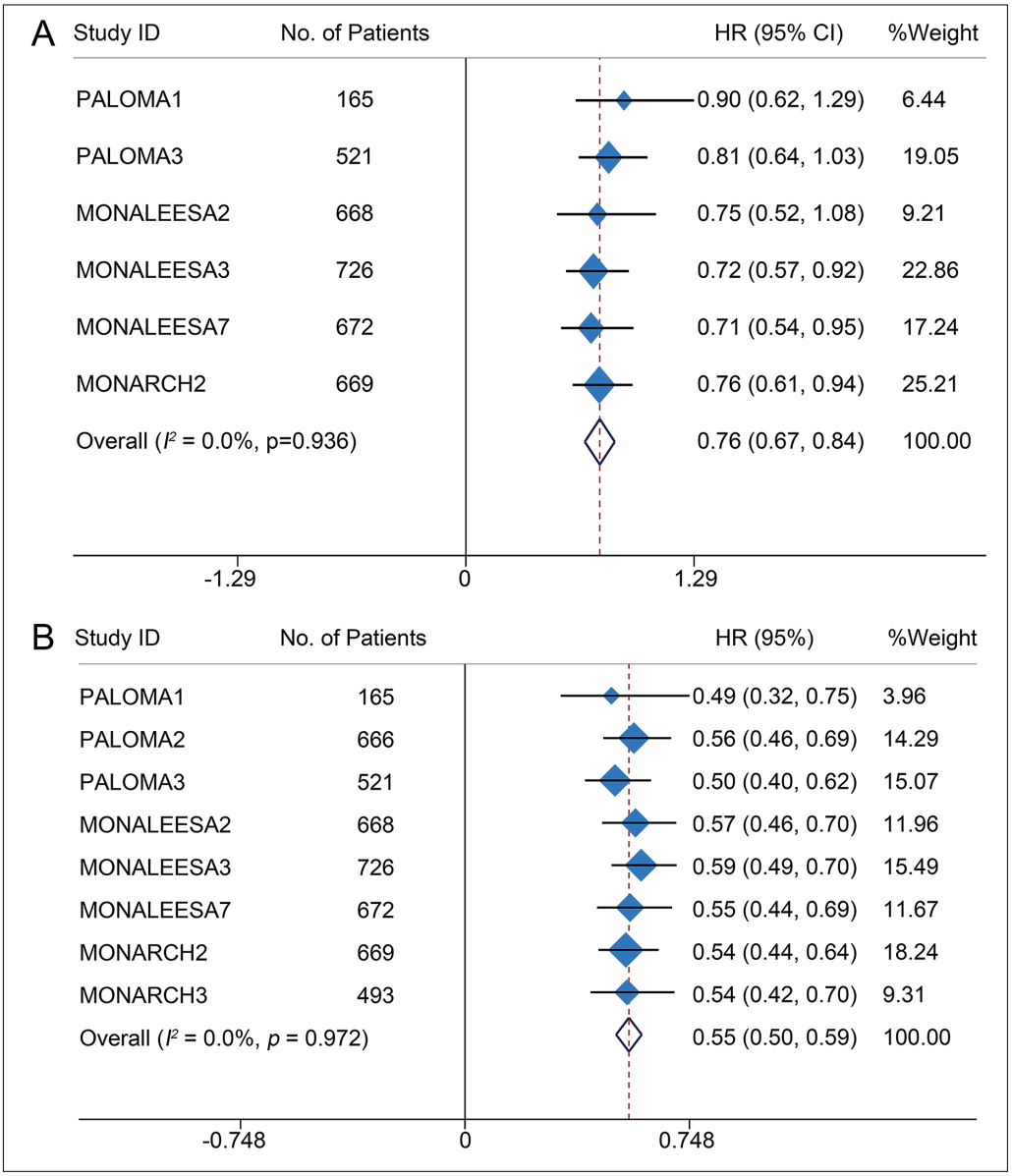

Figure 2. Pooled hazard ratios for overall survival **(A)** and progression-free survival **(B)** of overall population.

ORR

All eight trials included in our study reported ORR events occurring in the intervention and control groups in both the intention-to-treat (ITT) population and the group of patients with measurable disease. In the ITT population, a total of 1045 ORR events occurred in 2802 patients in the CDK4/6i plus ET group, while 464 ORR events occurred in 1778 patients in the ET group. The combination of CDK4/6i and ET significantly improved the ORR compared to that obtained with ET alone (RR=1.47; 95% CI: 1.29–1.67) in the ITT population (Figure 5A). In patients with measurable disease, a total of 1037 ORR events occurred in 2160 patients in the CDK4/6i group, 459 ORR events occurred in 1372 patients in the ET group, and the pooled RR for the ORR was 1.47 (95% CI: 1.30-1.67) (Figure 5B). Subgroup analyses of ORR stratified by the drugs administered were conducted to show the consistency obtained with the three drugs, as shown in Figure 5.

Adverse Events

Seven trials[5-10,16] included in our study reported any G3/4 aes in the intervention and control groups. A total of 1660 out of 2309 patients in the CDK4/6i group developed any G3/4 aes compared

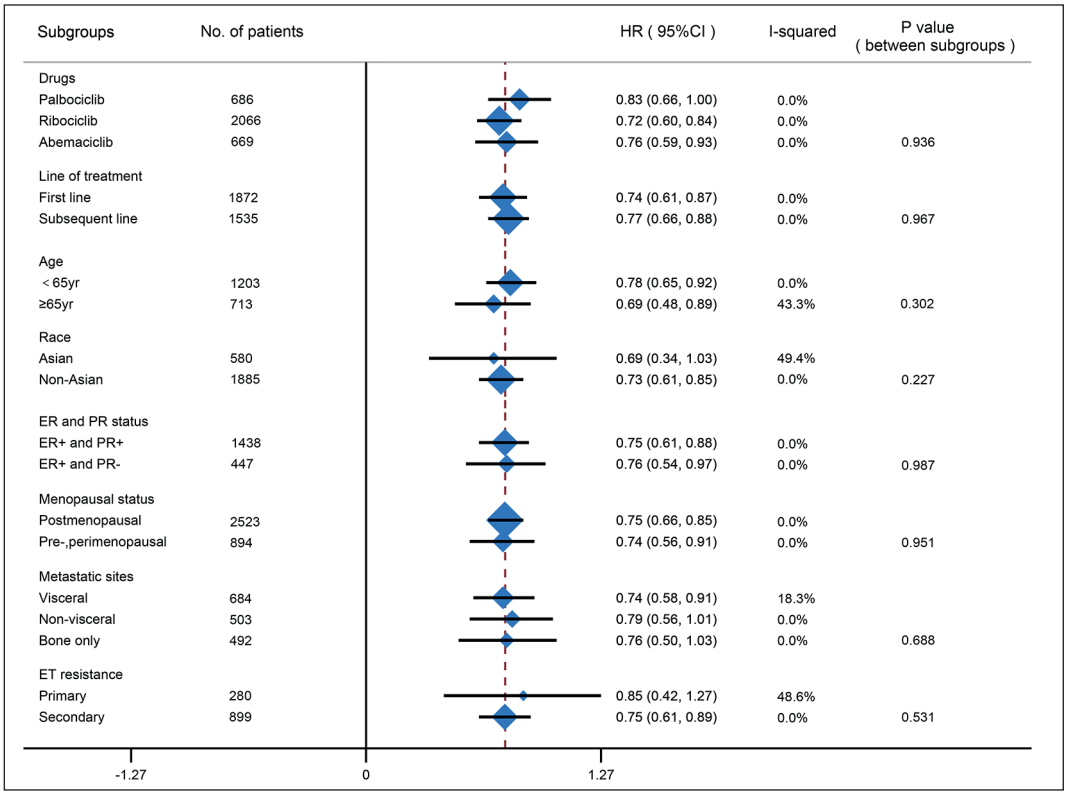

Figure 3. Subgroup analyses of pooled hazard ratios for overall survival.

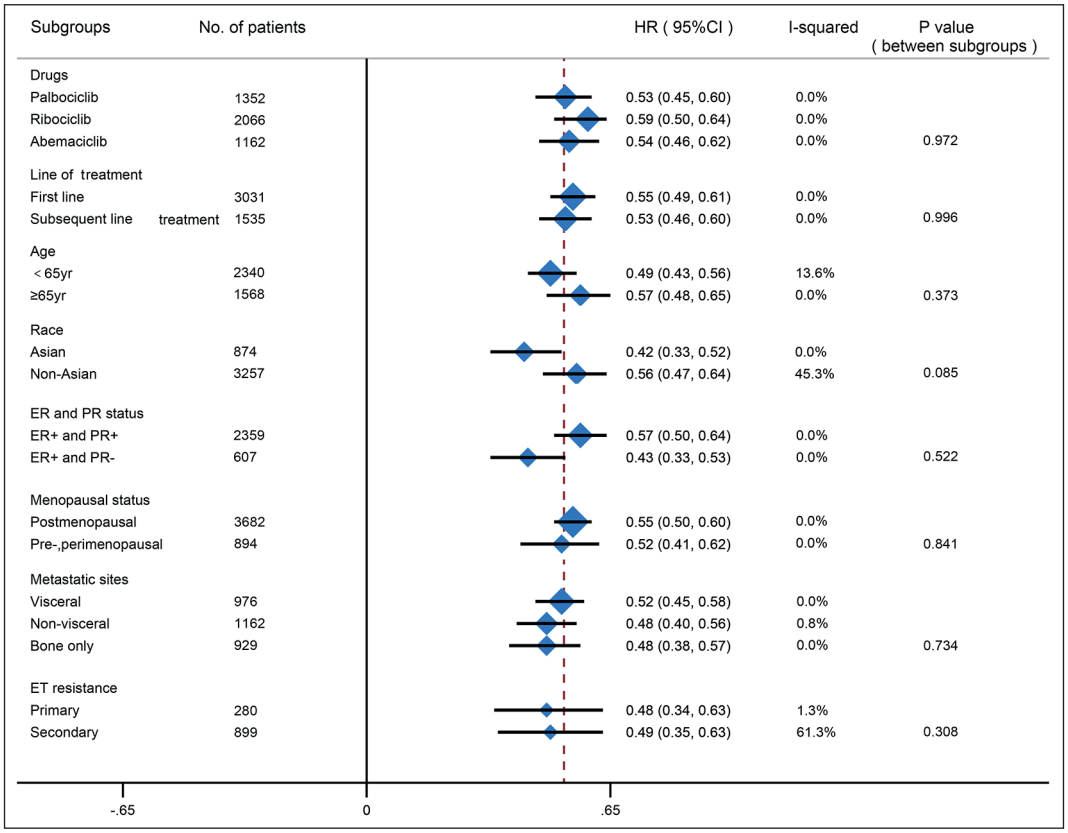

Figure 4. Subgroup analyses of pooled hazard ratios for progression-free survival.

Table II. Baseline characteristics of included population of each clinical trials in this meta-analysis.

	PALOMA1		PALOMA2		PALOMA3		MONALEESA2		MONALEESA3		MONALEESA7		MONARCH2		MONARCH3	
	P+L	L	P+L	L	P+F	F	R+L	L	R+F	F	R+ET	ET	A+F	F	A+AI	AI
	N=84	N=81	N=444	N=222	N=347	N=174	N=334	N=334	N=484	N=242	N=335	N=337	N=446	N=223	N=328	N=165
Age																
Median (range)-yr	63 (54-71)	64 (56-70)	62 (30-89)	61 (28-88)	57 (30-88)	56 (29-80)	62 (23-91)	63 (29-88)	63 (31-89)	63 (34-86)	43 (25-58)	45 (29-58)	59 (32-91)	62 (32-87)	63 (38-87)	63 (32-88)
<65 yr-no. (%)	47 (56.0)	42 (51.9)	263 (59.2)	141 (63.5)	261 (75.2)	131 (75.3)	184 (55.1)	189 (56.6)	258 (53.3)	129 (53.3)					180 (54.9)	91 (55.2)
≥65 yr-no. (%)	37 (44.0)	39 (48.1)	181 (40.8)	81 (36.5)	86 (24.8)	43 (24.7)	150 (44.9)	145 (43.4)	226 (46.7)	113 (46.7)					148 (45.1)	74 (44.8)
Race-no. (%)																
Asian			65 (14.6)	30 (13.5)	74 (21.3)	31 (17.8)	28 (8.4)	23 (6.9)	45 (9.3)	18 (7.4)	99 (29.6)	99 (29.4)	149 (33.4)	65 (29.1)	103 (31.4)	45 (27.3)
Non-asian			379 (85.4)	192 (86.5)	272 (78.4)	142 (81.6)	306 (91.6)	311 (93.1)	424 (87.6)	219 (90.5)	236 (70.4)	238 (70.6)	266 (59.6)	149 (66.8)	197 (60.1)	109 (66.1)
ECOG performance status-no. (%)																
0	46 (54.8)	45 (55.6)	257 (57.9)	102 (45.9)	207 (59.7)	115 (66.1)	205 (61.4)	202 (60.5)	310 (64.0)	158 (65.3)	245 (73.1)	255 (75.7)	264 (59.2)	136 (61.0)	192 (58.5)	104 (63.0)
1 or 2	38 (45.2)	36 (44.4)	187 (42.1)	120 (54.1)	140 (40.3)	59 (33.9)	129 (38.6)	132 (39.5)	173 (35.7)	83 (34.3)	87 (26.0)	79 (23.4)	176 (39.5)	87 (39.0)	136 (41.5)	61 (37.0)
Menopausal status-no. (%)																
Postmenopause	84 (100)	81 (100)	444 (100)	222 (100)	275 (79.3)	138 (79.3)	334 (100)	334 (100)	484 (100)	242 (100)	0	0	371 (83.2)	180 (80.7)	328 (100)	165 (100)
Pre,-perimenopause	0	0	0	0	72 (20.7)	36 (20.7)	0	0	0	0	335 (100)	337 (100)	72 (16.1)	42 (18.8)	0	0
Metastatic site-no. (%)																
Visceral	37 (44.0)	43 (53.1)	214 (48.2)	110 (49.5)	206 (59.4)	105 (60.3)	197 (59.0)	196 (58.7)	293 (60.5)	146 (60.3)	193 (57.6)	188 (55.8)	245 (54.9)	128 (57.4)	172 (52.4)	89 (53.9)
Nonvisceral	47 (56.0)	38 (46.9)	230 (51.8)	112 (50.5)	141 (40.6)	69 (39.7)	137 (41.0)	138 (41.3)	191 (39.5)	96 (39.7)	142 (42.4)	149 (44.2)	201 (45.1)	95 (42.6)	156 (47.6)	76 (46.1)
Bone only	17 (20.2)	12 (14.8)	103 (23.2)	48 (21.6)	75 (21.6%)	36 (20.7%)	69 (20.7)	78 (23.4)	103 (21.3)	51 (21.1)	81 (24.2)	78 (23.1)	123 (27.6)	57 (25.6)	70 (21.3)	39 (23.6)
Prior endocrine therapy -no. (%)																
Yes	27 (32.1)	28 (34.6)	249 (56.1)	126 (56.8)			175 (52.4)	171 (51.2)			127 (37.9)	141 (41.8)			150 (45.7)	80 (48.5)
No	57 (67.9)	53 (65.4)	195 (43.9)	96 (43.2)			159 (47.6)	163 (48.8)			208 (62.1)	196 (58.2)			178 (54.3)	85 (51.5)
Prior chemotherapy-no. (%)																
Yes	34 (40.5)	37 (45.7)	213 (48.0)	109 (49.1)	252 (72.6)	138 (79.3)	146 (43.7)	145 (43.4)			185 (55.2)	185 (54.9)	267 (59.9)	134 (60.1)	125 (38.1)	66 (40.0)
No	50 (59.5)	44 (54.3)	231 (52.0)	113 (50.9)	95 (27.4)	36 (20.7)	188 (56.3)	189 (56.6)			150 (44.8)	152 (45.1)	179 (40.1)	89 (39.0)	203 (61.9)	99 (60.0)
Disease-free interval-no. (%)																
≤12 months	15 (17.9)	14 (17.3)	99 (22.3)	48 (21.6)	11 (3.2)	3 (1.7)	4 (1.2)	10 (3.0)	22 (4.5)	9 (3.7)	23(6.9)	13 (3.9)				
>12 months	25 (29.8)	30 (37.0)	178 (40.1)	93 (41.9)	222 (64.0)	120 (69.0)	216 (64.7)	210 (62.9)	365 (75.4)	190 (78.5)	176 (52.5)	190 (56.4)				
Newly diagnosed disease	44 (52.4)	37 (45.7)	167 (37.6)	81 (36.5)			114 (34.1)	113 (33.8)	97 (20.0)	42 (17.4)	136(40.6)	134 (39.8)				
≤24 months					41 (11.8)	22 (12.6)	18 (5.4)	25 (7.5)								
>24 months					192 (55.3)	101 (58.0)	202 (60.5)	195 (58.4)								
Hormone-receptor status																
ER+ and PR+					238 (68.6)	111 (63.8)	269 (80.5)	277 (82.9)	350 (72.3)	167 (69.0)	290 (86.6)	288 (85.5)	339 (76.0)	171 (76.7)	255 (77.7)	127 (77.0)
ER+ and PR-					91 (26.2)	48 (27.6)	65 (19.5)	57 (17.1)	134 (27.7)	75 (31.0)	45 (13.4)	49 (14.5)	96 (21.5)	44 (19.7)	70 (21.3)	36 (21.8)

Notes: *P,* Palbociclib; *L,* Letrozole; *F,* Fulvestrant; *R,* Ribociclib; *ET,* Endocrine therapy; *A,* Abemaciclib; *AI,* Aromatase Inhibitors; *ECOG,* Eastern Cooperative Oncology Group; *ER,* Estrogen receptor; *PR,* Progesterone receptor

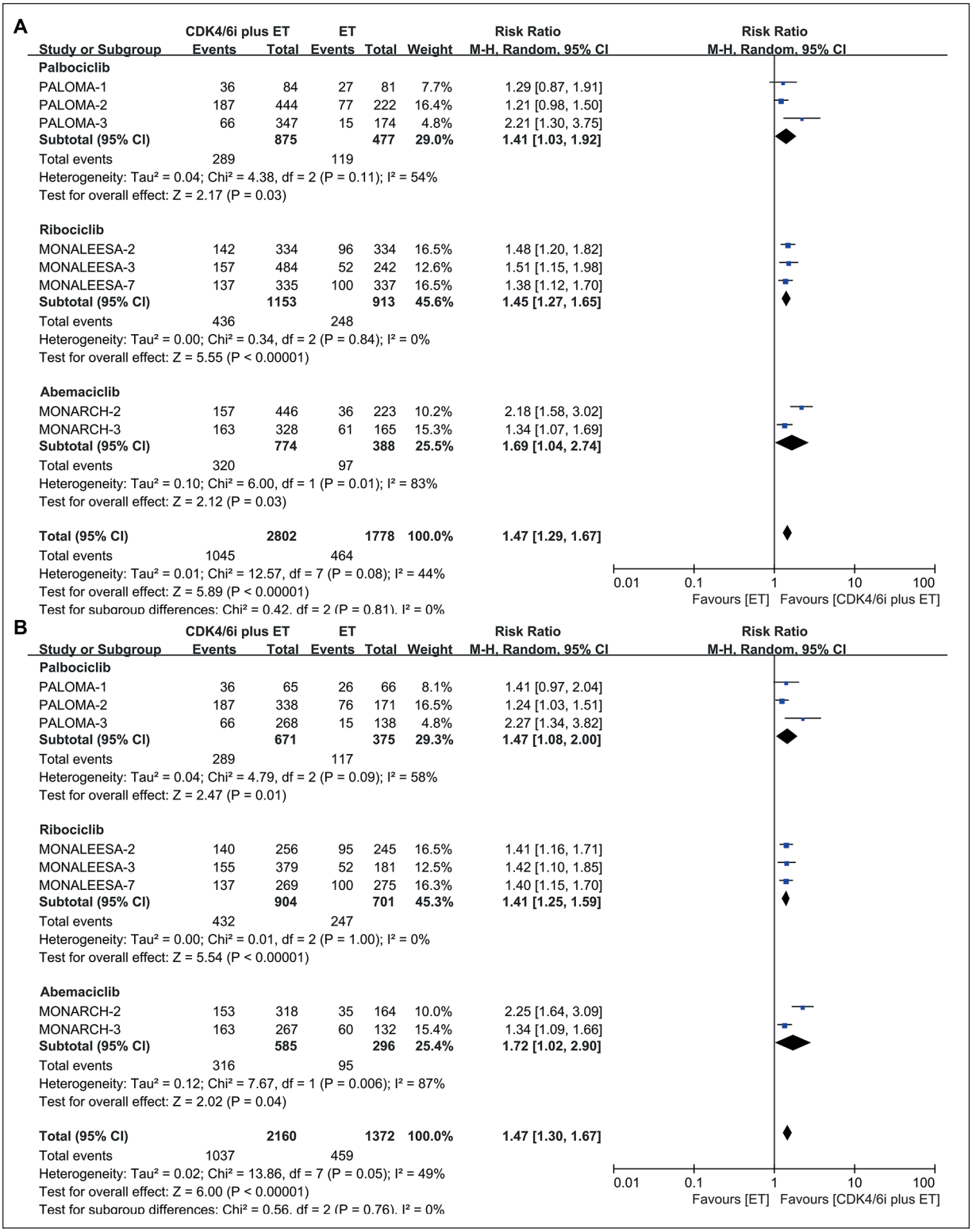

Figure 5. Pooled risk ratios for objective response rates in intention-to-treat population **(A)** and patients with measurable disease **(B)**.

with 416 out of 1522 patients in the ET alone group. The pooled RR was 2.69 (95% CI: 2.43–2.97), indicating a much higher probability of developing G3/4 aes in the CDK4/6i group (Figure 6A).

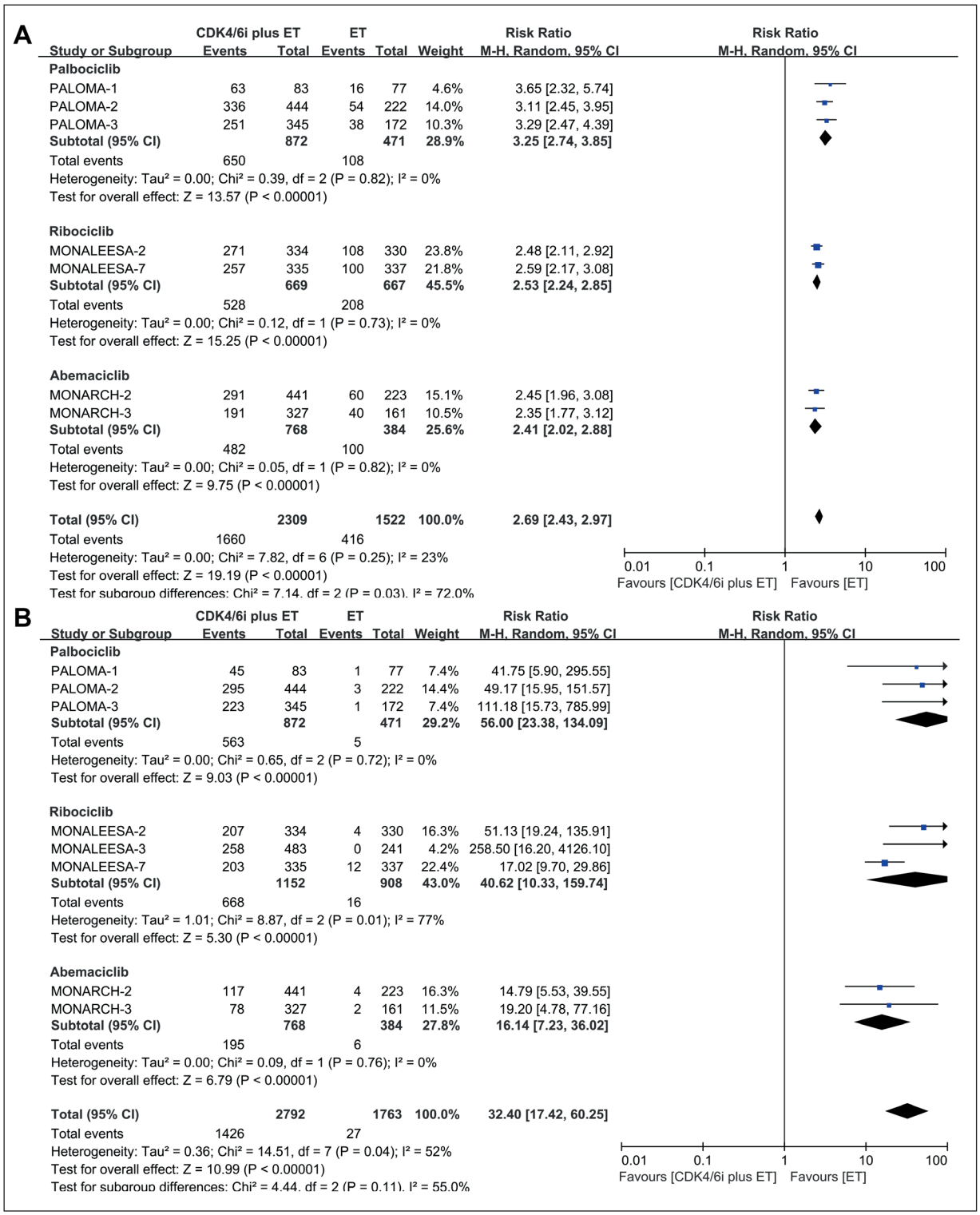

Figure 6. Pooled risk ratios for any grade 3/4 adverse events **(A)** and grade 3/4 neutropenia **(B)**.

The pooled data of G3/4 common aes were extracted from 4555 participants across all eight enrolled trials. The G3/4 haematologic toxicities were increased in the CDK4/6i group compared with those in the ET alone group. For G3/4 neutropenia, the RR was 32.40 (95% CI: 17.42-60.25) (Figure

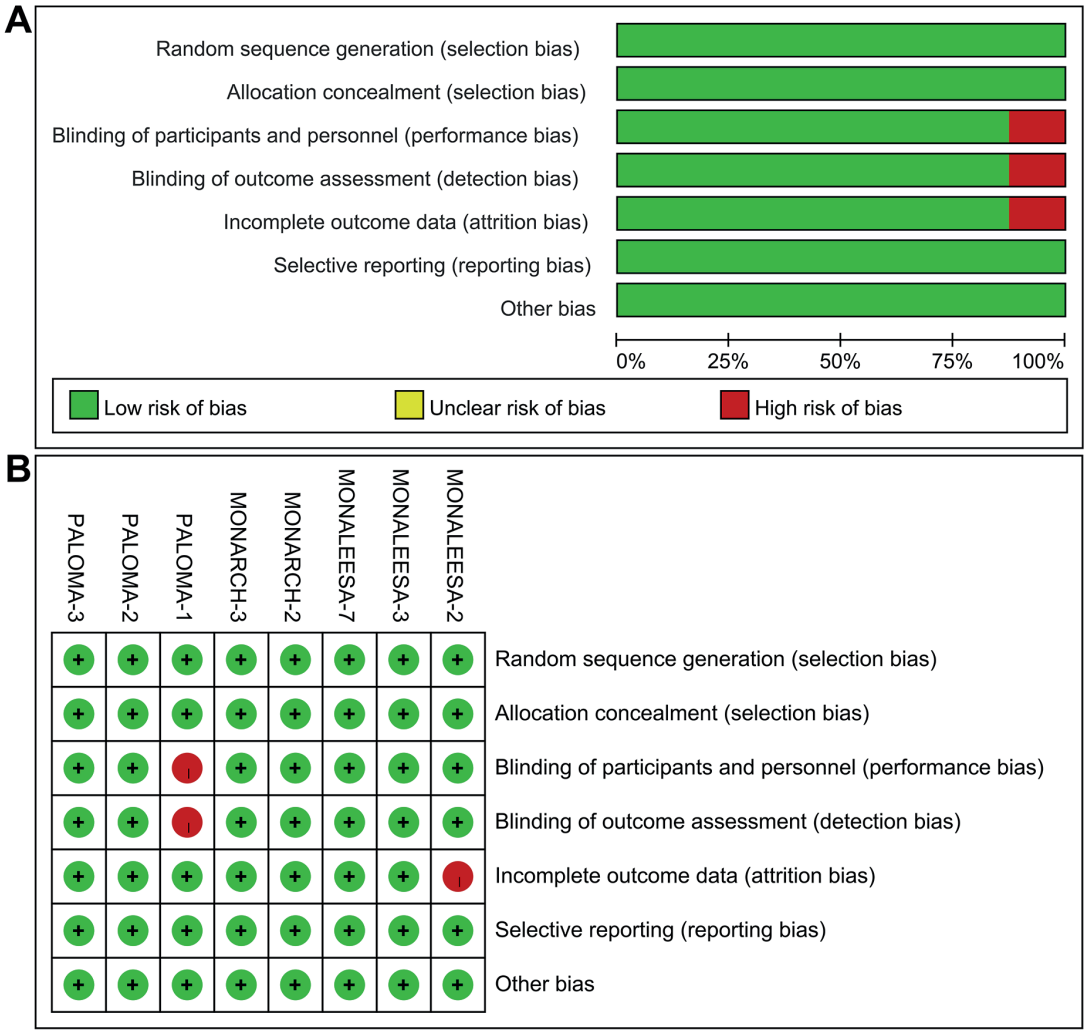

Figure 7. Risk of bias for selected publications.

6B); for G3/4 leucopenia, the RR was 20.96 (95% CI: 11.81-37.22) **(Supplementary Figure 1)**; and for G3/4 anaemia, the RR was 2.42 (95% CI: 1.55-3.77) **(Supplementary Figure 2)**. For G3/4 nonhaematologic toxicity, the RR of G3/4 diarrhoea was 2.88 (95% CI: 1.01-8.22) **(Supplementary Figure 3)**, and the RR of G3/4 fatigue was 3.69 (95% CI: 1.88-7.26) **(Supplementary Figure 4)**, indicating a higher incidence of developing G3/4 diarrhoea and fatigue in the intervention group. Subgroup analyses of G3/4 aes based on the drugs administered showed that the incidence of G3/4 neutropenia was much higher in the palbociclib and ribociclib subgroups (Figure 6B), and the incidence of developing G3/4 diarrhoea was much higher in the abemaciclib subgroup **(Supplementary Figure 3).** The pooled rrs for G3/4 aes are summarized in Table III.

Risk Bias and Publication Bias

The risk of bias assessments is summarized in Figure 7. The enrolled trials were all international, randomized, double-blind, placebo-controlled studies, except for the PALOMA1 study, which was an open-label, phase 2 trial.

Begg's funnel plot and Egger's weighted regression tests were performed to assess publication bias among the selected studies regarding pooled OS, PFS, ORR and G3/4 AE outcomes. Visual inspection of the Begg's funnel plots did not reveal any significant asymmetry, indicating no evidence of substantial publication bias in our pooled analysis, which was further supported by the results of Egger's weighted regression test (t=0.64, p=0.558; t=1.52, p=0.178; t=1.04, p=0.338; t=0.58, p=0.589, respectively) (Figure 8).

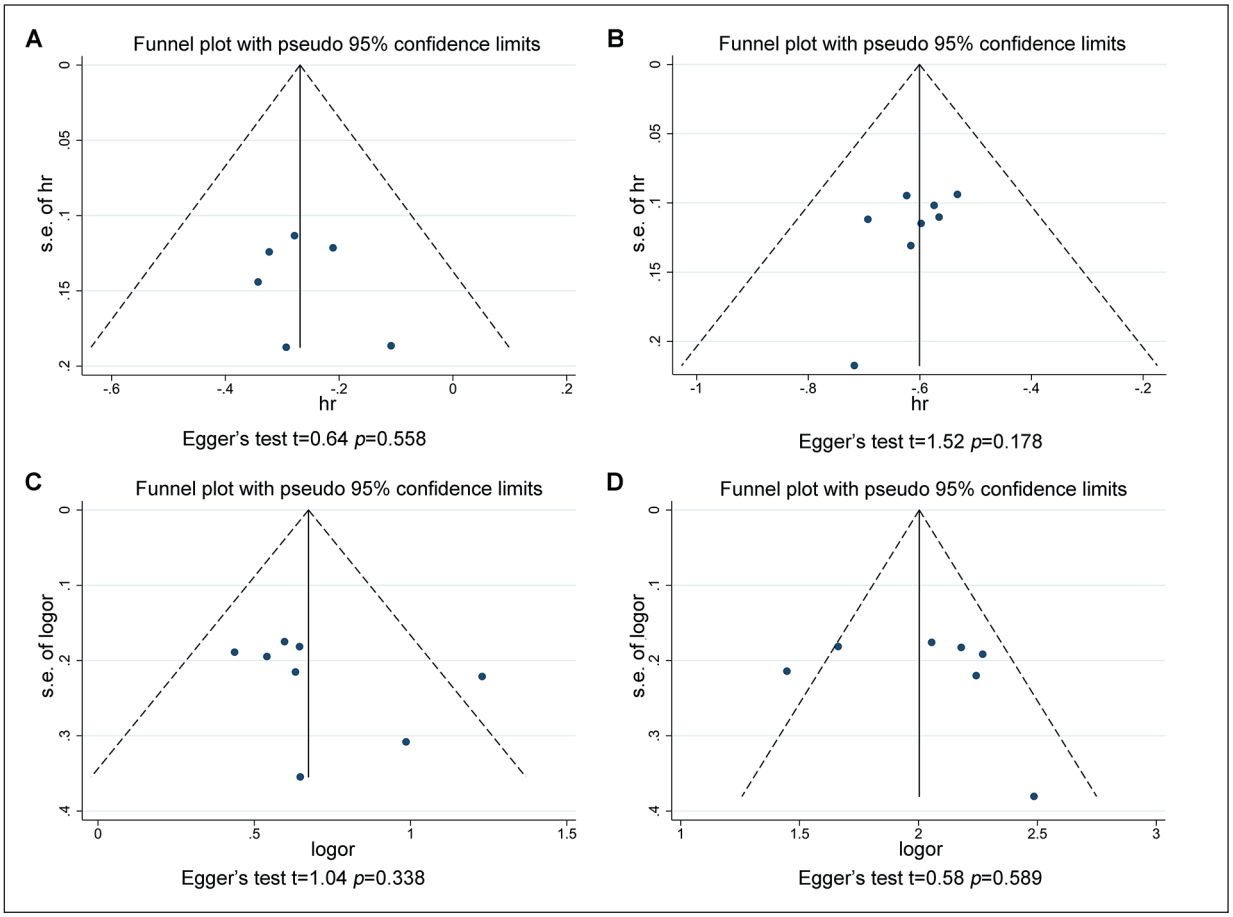

Figure 8. Begg's funnel plot and Egger's test of effect sizes for publication bias of overall survial **(A)**, progression-free survial **(B)**, objective response rates **(C)** and grade 3/4 adverse events **(D)**.

Table III. Grade 3/4 adverse events in advanced breast cancer patients treated with CDK4/6 inhibitors.

G3/4 aes	RR	95% CI	p
Any	2.69	2.43-2.97	<0.001
Neutropenia	32.40	17.42-60.25	<0.001
Leucopenia	20.96	11.81-37.22	<0.001
Anemia	2.42	1.55-3.77	<0.001
Diarrhea	2.88	1.01-8.22	<0.05
Fatigue	3.69	1.88-7.26	<0.001
Nausea	1.39	0.63-3.06	=0.42

Notes: G3/4 aes, Grade 3/4 adverse events; RR, Risk ratio; CI, Confidence interval.

Discussion

The current results of our meta-analysis further confirmed the PFS benefits of CDK4/6i in HR+, Her2- ABC patients. More importantly, the results also revealed that the addition of CDK4/6i to ET was associated with better OS outcomes. In the exploratory analysis of other secondary endpoints, time to chemotherapy (TTC) was also significantly prolonged (Table I). Thus, longer PFS and extended TTC will ultimately translate into marked OS benefits. Consistent with previous meta-analyses, CDK4/6i plus ET meaningfully improved the ORR in both the ITT population and patients with measurable disease. Moreover, the combination treatment increased the inci-

dence of G3/4 aes. Specifically, the incidence of G3/4 neutropenia was increased in the palbociclib and ribociclib subgroups, and the incidence of G3/4 diarrhoea was much higher in the abemaciclib subgroup.

We conducted this meta-analysis due to the inconsistencies in OS outcome data among previous clinical trials. The combination treatment of CDK4/6i and ET did not confer long-term survival improvements in the entire trial group enrolled in the PALOMA-1[15] and PALOMA-3[16] trials. It is worth noting that the OS results of three clinical trials (MONALEESA-7[17], MONARCH-2[18] and MONALEESA-3[19]) reported in 2019 showed that CDK4/6i significantly improved OS outcomes in patients with HR+, Her2- ABC. The MONALEESA-7 trial was the first study to show a significant improvement in OS outcomes with ribociclib plus ET among pre-, perimenopausal breast cancer patients[17]. Recently, the OS results of the MONARCH-2 trial indicated that the addition of abemaciclib to fulvestrant significantly improved OS outcomes in patients whose disease progressed after prior ET regardless of menopausal status[18]. Furthermore, the OS result of the MONALEESA-3 trial revealed that ribociclib plus fulvestrant meaningfully improved OS outcomes in postmenopausal patients who were treatment-naïve or had received up to one line of ET[19]. Our results provide favourable evidence for long-term survival benefits in HR+, Her2- ABC patients receiving combination treatment with CDK4/6i and ET.

Subgroup analyses demonstrated consistent OS and PFS outcome improvements among most subgroups. Although PFS benefits have been achieved with all three CDK4/6 inhibitors, OS benefits have not been obtained with palbociclib to date[15,16]. Our pooled OS results also showed that the palbociclib subgroup gained the smallest benefit from the combination treatment.

Several clinical trials (PALOMA-1[5],2[6]; MONALEESA-2[7],7[8,17]; and MONARCH-3[10]) have established the efficacy of CDK4/6i in HR+, Her2- ABC patients who had no prior systemic therapy for advanced disease. The PALOMA-3[16,23] and MONARCH-2[9,18] trials confirmed the efficacy of CDK4/6i for patients who experienced disease progression or relapse during previous ET. The MONALEESA-3[19,24] trial was the only study involving both patients who were treatment naïve and those who had received up to one line of prior ET for advanced disease. According to our results, the subgroup analysis of PFS and OS outcomes by line of treatment was consistent with those of the overall population, confirming the efficacy of CDK4/6i as first- and subsequent-line therapies.

Analysis by menopausal status indicated consistent PFS and OS benefits for pre-, perimenopausal and postmenopausal patients. In the PALOMA-3 trial, approximately 21% (108/521) of the enrolled patients were pre-, perimenopausal women. In this subgroup, patients benefitted from palbociclib according to the PFS data[23]; however, palbociclib resulted in a longer median OS only among postmenopausal patients[16]. The MONALEESA-7 trial assessed the efficacy of ribociclib in combination with ET plus ovarian suppression with goserelin in pre-, perimenopausal patients. In the MONALEESA-7 trial, adding ribociclib to ET demonstrated a statistically significant benefit in both PFS and OS outcomes[8,17]. The subgroup analysis of menopausal status in the MONARCH-2 trial demonstrated that abemaciclib resulted in significant improvements in both PFS and OS outcomes regardless of menopausal status[9,18]. Our pooled analysis result was consistent with the results of the MONALEESA-7 and MONARCH-2 trials, indicating that pre-, perimenopausal patients with HR+, Her2- ABC derived meaningful improvements in both PFS and OS outcomes from CDK4/6i treatment.

A previous meta-analysis performed by Messina et al[12] showed that CDK4/6i improved PFS outcomes both in the presence and absence of visceral disease. In our study, the PFS benefits of CDK4/6i were maintained in the subgroups of patients with visceral, nonvisceral and bone-only metastases. However, in terms of OS outcomes, a numerically larger effect was observed in patients with visceral metastasis compared with that in those with bone-only metastasis. No statistically significant difference was observed in the nonvisceral metastasis or bone-only metastasis subgroups. These results indicate that CDK4/6i plus ET tend to be an even more effective option for patients with visceral metastases.

The results of the PALOMA-3 trial indicated that the combination treatment with palbociclib and fulvestrant resulted in longer PFS and OS among patients who were sensitive to previous ET[16,23], which is in contrast with the PFS and OS results obtained with abemaciclib and fulvestrant in the MONARCH-2 study. The subgroup analysis of the MONARCH-2 trial showed numerically larger PFS and OS improvements in primary endocrine-resistant patients receiving abemaciclib with fulvestrant[9,18]. Although only the two studies mentioned above could be included in the

subgroup analysis of ET resistance, our pooled results showed consistent PFS improvements among patients with both primary and secondary ET resistance, while a statistically significant OS benefit was only found in secondary ET-resistant patients. The divergent results might be due to the difference in the study eligibility criteria or the potential differential activity of palbociclib and abemaciclib in patients with different endocrine resistance statuses. More prospective studies may be warranted to confirm these observations.

It is important to identify patients who will preferentially benefit from CDK4/6i. Some prespecified subgroups in clinical trials were designed to identify patients who were eligible for treatment with CDK4/6i based on their genomic information. In the PALOMA-1 trial, the subgroup analysis of patients with tumours with amplification of cyclin D, loss of p16, or both failed to confirm the potential of these genetic changes to be used to improve patient selection beyond the use of hormone receptor status alone[5]. In the exploratory analysis of the PALOMA-3, baseline tumour ESR1 and PIK-3CA mutation rates were lower among long-term responders in both the palbociclib group and the placebo group[23]. To date, no specific biomarkers that can effectively predict the efficacy of CDK4/6i have been identified. Additional confirmatory studies to find biomarkers that predict the efficacy of CDK4/6i are necessary.

Although ET with or without targeted therapy should be offered as a standard treatment for HR+, Her2- ABC patients according to international clinical guidelines, the use of chemotherapy is still common, even in the absence of visceral crisis. The Young-PEARL (KCSG-BR15-10) trial was a multicentre, open-label, randomized, phase 2 study comparing the clinical antitumour activity and safety of palbociclib plus ET with single-agent capecitabine chemotherapy in premenopausal patients with HR+, Her2- metastatic breast cancer. This study showed that palbociclib plus exemestane with ovarian function suppression led to significantly longer PFS than capecitabine in HR+, Her2- metastatic breast cancer patients[25]. Several network meta-analyses[26] were also performed to compare hormone therapy with chemotherapy for the treatment of HR+, Her2- ABC due to too few head-to-head rcts. Giuliano et al[26] reported that, in terms of PFS outcomes, no chemotherapy regimen with or without targeted therapy was significantly superior to CDK4/6i plus ET. This indirect evidence supports the treatment of HR+, Her2- ABC with the new combination of targeted agents and ET.

Preclinical studies[27] have revealed that CDK4/6i have potent growth inhibitory activity in two patient groups—those who are hormone receptor-positive and those who have amplified Her2. Thus, it is of substantial interest to evaluate the efficacy of CDK4/6 inhibition in combination with anti-Her2 therapy for HR+, Her2+ breast cancer patients. The results of a multicentre, phase 2, randomized study (monarcher) demonstrated that abemaciclib in combination with fulvestrant and trastuzumab significantly improved PFS and ORR outcomes compared with abemaciclib plus trastuzumab or chemotherapy plus trastuzumab, indicating that CDK4/6i have activity against both HR+, Her2- and HR+, Her2+ ABC[28].

Several limitations of this study should be acknowledged: 1) the absence of OS outcome data from the PALOMA-2 and MONARCH-3 trials; 2) immature OS outcome data from the MONALEESA-2 trial; 3) the unbalanced number of patients included in the different subgroups; and 4) partial data in the subgroup analysis.

Conclusions

Based on the results of the present meta-analysis, we conclude that the combination of CDK4/6i and ET is superior to ET alone in terms of OS and PFS outcomes, irrespective of the drug administered, treatment line, age distribution, race, PR status, menopausal status, site of metastasis and endocrine resistance status. CDK4/6i meaningfully improved the ORR in both the ITT population and patients with measurable disease; however, they also increased the incidence of G3/4 aes. More mature OS results are awaited to consolidate our study.

Data Availability Statement:

All the analyzed data in this meta-analysis were included in the published articles.

Author Contributions

All authors were involved in the concept and design of the study. TQ and GH: drafting the manuscript, data acquisition and management; ZY: statistical analysis; YJ: supervision and critical revision of the manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

This research work is a meta-analysis of published data and does not contain any direct involvement of human participants.

Informed consent

It was unnecessary given this study does not contain any studies with human participants performed by any of the authors.

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