Original Article

Efficacy and Safety of Bevacizumab-Combined Chemotherapy for Advanced and Recurrent Endometrial Cancer: A Systematic Review and Meta-Analysis

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Background: Bevacizumab-combined chemotherapy is a new regimen for advanced/recurrent endometrial cancer.
Aims: This study aimed to evaluate the efficacy and safety of bevacizumab-combined chemotherapy in advanced/recurrent endometrial cancer.
Study design: This is a systematic review and meta-analysis of clinical trials.
Methods: Eligible studies were retrieved form Embase, PubMed, and Cochrane Library. The data of primary outcomes including progression-free and overall survival and secondary outcomes including overall survival, response rate, and adverse events (grade ≥2) were extracted, pooled and used for the meta-analysis to compare the efficacy and safety of bevacizumab-combined chemotherapy versus other treatments in patients with advanced/recurrent endometrial cancer.
Results: Two randomized-controlled and five single arm trials of bevacizumab-combined chemotherapy or bevacizumab single-agent therapy for endometrial cancer were included. Meta-analysis indicated that bevacizumab-combined chemotherapy significantly increased the progression-free survival rate (Hazards ratio, HR=0.82, 95% CI 0.70, 0.97) and overall survival rate (HR=0.83, 95% CI 0.70, 0.98) as compared with chemotherapy alone. The rates of overall, complete, and partial response to bevacizumab-combined chemotherapy were 76%, 22%, and 21%, respectively. The six and 12-month disease-free progression rate after bevacizumab-combined chemotherapy were 79% and 62%, respectively. Anemia (23%), leukopenia (46%), neutropenia (51%), hypertension (16%), and fatigue (24%) were the general adverse events following bevacizumab-combined chemotherapy.
Conclusions: This study suggested that bevacizumab-combined chemotherapy may have a higher

efficacy in improving the overall and progression-free survival in patients with advanced/recurrent endometrial cancers as compared with chemotherapy alone.

Keywords: Chemotherapy, overall survival, randomized controlled trial, single arm trials, systematic review

Endometrial cancer is the most common gynecological tumor and one of the leading causes of cancer-related death in women.[1 2] Patients with advanced (FIGO stage III-IV) or recurrent endometrial cancers always have a dismal prognosis, and the conventional chemotherapy is not ideal for this cohort. Paclitaxel and carboplatin (PC) chemotherapy is a standard therapy for advanced and recurrent endometrial cancer.[3-5] According to recent randomized-controlled trials (RCTs), the combination of PC with bevacizumab showed significant benefits in endometrial cancer.[3 4] Lorusso et al[3] showed that the median overall survival (OS) and progression-free survival (PFS) for patients with advanced or recurrent endometrial cancers receiving PC chemotherapy were 29.7 and 10.5 months, respectively. They indicated the combination of PC plus bevacizumab had a median OS of 40.0 months and a median PFS of 13.7 months. Besides, the PC chemotherapy combined with bevacizumab achieved a higher overall response rate (ORR, 74.4%) compared with PC chemotherapy (53.1%). Aghajanian et al[4] and Rose et al[5] also confirmed the beneficial effect of bevacizumab combined chemotherapy in endometrial cancer.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor-A (VEGF-A), which is expressed in most endometrial cancers especially in advanced types.[6-8] However, the higher incidence of ≥ grade 2 adverse events including hypertension and arterial and venous thrombosis might query the safety of bevacizumab-combined chemotherapy in endometrial cancer.[3 4] Accordingly, the bevacizumab-combined therapy for endometrial cancer is still controversial. We, therefore, performed this systematic review and meta-analysis to analyze the efficacy and safety of bevacizumab-combined therapy of advanced or recurrent endometrial cancers. Single-arm trials or RCTs were included and used for the analysis.

MATERIALS AND METHODS

Ethics statement

This systematic review and meta-analysis was designed and performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols.[9] Neither human samples nor animals were included in this study, and therein ethics committee approval is inapplicable.

Searching strategy

We systematically searched the English publications updated to December 2019in the PubMed, Embase, and the Cochrane library. Publications were searched using the searching terms of 'endometrial cancer', 'Endometrial carcinoma', 'Bevacizumab', and 'Avastin'. The searching strategy was 'endometrial cancer[Title/Abstract]' OR 'endometrial cancer[MeSH Terms]' OR 'Endometrial carcinoma[Title/Abstract]' OR 'Endometrial carcinoma[MeSH Terms]' AND 'Bevacizumab [MeSH Terms]' OR 'Bevacizumab [Title/Abstract]' OR 'Avastin [Title/Abstract]' OR 'Avastin [MeSH Terms]' AND 'randomized controlled trial [MeSH]' OR 'random allocation [MeSH]' OR '[singl* OR doubl* OR trebl* OR tripl*] AND [blind* OR mask*]'.

Inclusion and exclusion criteria for eligible reports

The inclusion criteria were: (1) clinical trials with and without control group design; (2) English articles involving adult patients (aged ≥18 years) with endometrial cancer, without age and ethnicity restriction; (3) patients were treated with chemotherapy combined with bevacizumab; (4) included at

least two outcomes such as OS, PFS, objective response rate (ORR), and adverse events (grade ≥2), among others. Reports were excluded if they were (1) duplicated articles; (2) without the aforementioned outcomes; (3) reviews or case reports.

Outcome measures and data extraction

Full-text articles were retrieved and the title, first author name, publication year, number of patients, age of patients, and outcome data were extracted. The primary outcome was PFS and the secondary outcomes were OS, ORR, complete response rate (CRR), partial response rate (PRP), and adverse events. Outcome data were extracted and assessed independently by two authors (Chen H and Min J).

Evaluation of quality

The 5-point Jadad scoring tool[10] and methodological index for non-randomized studies (MINORS) [11] were used for the assessment of RCTs and nonrandomized studies, respectively. RCTs with scores ≥ 3 and nonrandomized studies with scores ≥ 10 were regarded as high-quality reports; RCTs with scores ≤2 and nonrandomized studies with scores < 10 were considered as low-quality reports. The secondary review was performed in case of doubt. The evidence strength of outcome data was evaluated using the commonly used Cochrane Collaboration Grade Profiler (GradePro) tool (http://ims.cochrane.org). Accordingly, publication bias was assessed for the included reports based on the key elements of bias risk assessment.

Statistical methods

Meta-analysis was performed using the Stata (StataCorp) software (Stata Corporation, CollegeStation, TX; v 15.1) and Revman 5.2. Data heterogeneity was evaluated using the χ^2 test and I^2 statistics, with the threshold of P<0.10. Homogeneity data (I^2<50%) were pooled and analyzed using a fixed-effects model, and heterogeneity data (I^2≥50%) were pooled and analyzed using a random-effects model, respectively. Effect size (ES) or hazard ratio (HR) and 95% confidence intervals (CIs) were calculated for all analyses. The inverse variance and mantel-haenszel method was used for the meta-analysis for continuous and dichotomous variables, respectively. P < 0.05 was considered as apparent difference.

RESULTS

Study identification

We searched 742 studies in databases (including 317 in PubMed, 398 in EMBASE, and 27 in Cochrane library). After removing the duplicates (n=293), 449 articles were titles and abstracts screened by two authors. The remaining 17 studies were full-text screened, and seven articles [3-5 12-15] were finally included in this study according to the inclusion criteria. The flow chart of search strategy followed is shown in **Figure 1**.

Study characteristics

The seven studies included two RCTs [3 4] and five non-RCTs [5 12-15] and 622 patients with advanced and recurrent or persistent endometrial cancers. In the trials published since 2015,[3-5 14] patients were mainly treated with PC chemotherapy combined with bevacizumab, while in that published before 2015 patients were treated with bevacizumab alone[13] or in combination with other cytotoxics including temsirolimus, paclitaxel, 5-Fluorouracil, cyclophosphamide, doxorubicin, and Carboplatin plus docetaxel.[12-15] The outcomes including OS, PFS, ORR, PRR, and/or adverse events (grade ≥2) were reported in all trials (**Table 1**). There was no risk of bias across the included studies (**Figure S1**).

Median PFS and OS

Three studies[3-5] involving 491 patients with advanced endometrial cancers reported the median PFS and OS at > 12 months after therapy. The pooled data of PFS (I^2=0%, P=0.54) and OS (I^2=17%, P=0.31) were homogeneity. Meta-analysis showed there were significant differences in PFS (HR=0.82,

95% CI 0.70, 0.97, p=0.02; **Figure 2A**) and OS (HR=0.83, 95% CI 0.70, 0.98, p=0.03; **Figure 2B**) between patients receiving chemotherapy combined with (n=307) and without bevacizumab (n=184). Aghajanian et al[4] also suggested a significantly increased OS at 36 months in patients treated with PC chemotherapy combined with bevacizumab (n=116; HR=0.71, 92.2% CI 0.55, 0.91), but not in patients treated with ixabepilone-carboplatin chemotherapy combined with bevacizumab (n=118; HR=0.99, 92.2% CI 0.77, 1.23). However, Aghajanian et al[4] showed that there was no significant difference in PFS beween patients receiving PC chemotherapy combined with and without bevacizumab (HR=0.81, 92.2% CI 0.63, 1.02).

Responses rate

The ORR, CRR, and PRR were ranged from 53% to 74.4%,[3 4] 1.9% to 44.7%,[3 12-14] and 11.0% to 40%,[3 5 12-15] respectively, in the included studies. Aghajanian et al[4] indicated the ORRs following bevacizumab-combined chemotherapy were 59% and 53%, and Lorusso et al[3] reported that there was a high ORR of 74.4% in patients receiving bevacizumab-combined chemotherapy. Meta-analysis showed that bevacizumab-combined chemotherapy induced a pooled ORR (three studies, 172/233), CRR (five studies, 43/201), and PRR (six studies, 59/212) of 76% (95% CI 71%, 81%; Fixed-effects model, I^2=0%, P=0.887; **Figure S2A**), 22% (95% CI 9%, 35%; Random-effects model, I^2=93.5%, P<0.001; **Figure S2B)**, and 21% (95% CI 16%, 26%; Fixed-effects model, I^2=49.1%, P=0.080 **Figure S2C**), respectively.

Rate of stable disease and tumor progression

The rates of stable disease and tumor progression in patients with endometrial cancers were ranged from 11.8% to 55.1% [3 5 12 14 15] and 2.9% to 45.5%,[3 5 14 15] respectively. The pooled stable disease (six studies, 73/212) and tumor progression rates (four studies, 9/107) were 33% (95% CI 19%, 47%; Random-effects model, I^2=79.6%, P<0.001; **Figure S3A**) and 7% (95% CI 1%, 17%; Random-effects model, I^2=61.8%, P=0.049; **Figure S3B**), respectively. The non-progression rates of disease at six and 12 months were 79% (95% CI, 68%, 90%; Random-effects model, I^2=89.6%, P<0.001; **Figure S4A**) and 62% (95% CI 57%, 68%; I^2=18.0%, P=0.301; **Figure S4B**), respectively.

Adverse events

The common grade ≥2 adverse events following bevacizumab-combined chemotherapy were anemia (23%, 95% CI 14%, 33%; **Table 2**), leukopenia (46%, 95% CI 26%, 65%), neutropenia (51%, 95% CI 30%, 73%), thrombocytopenia (16%, 95% CI 9%, 23%), hypertension (16%,95% CI 12%, 20%), pain (grade ≥2; 20%, 95% CI 8%, 31%) and fatigue (24%, 95% CI 12%, 36%). The infrequent adverse events were arterial thromboembolic events (1%, 95% CI 0, 2%), nausea (3%, 95% CI 1%, 6%), venous thromboembolic events (8%, 95% CI 5%, 11%), fistulas (3%, 95% CI 1%, 5%), dyspnea (5%, 95% CI 1%, 10%), and hemorrhage (3%, 95% CI 0, 6%; **Table 2**).

DISCUSSION

VEGF factors are important proteins in angiogenesis and nourishing and supplying oxygen to tumors.[7 16] It has been reported that VEGF factors express higher level in metastatic and advanced tumors.[7 8 17 18] Some researchers indicated that the addition of bevacizumab into the standard or conventional chemotherapy strategies improved the survival time in patients with advanced cancers.[3 4] Also, there is a large gap in the ORR between clinical trials, ranging from 13.5% to 82.8%.[3-5] This present meta-analysis of trials (five single-arms and two RCTs) demonstrated that the OS and PFS in patients with advanced/recurrent endometrial cancers were increased by bevacizumab-combined chemotherapy compared with control, with a high ORR of 76% (95% CI 71%, 81%). The rate of grade ≥2 adverse events was relatively high: leukopenia, 46%; neutropenia, 51%; and fatigue, 24%.

VEGF is associated with a higher histological grade, metastasis, and invasion of several malignant cancers.[8 14 19] VEGF-mediated signaling pathways are critical to feature cancer stem cells, tumorigenesis and self-renewal of cancer stem cells.[20] By contrast, anti-VEGF therapy using bevacizumab could reduce the expression level of plasma VEGF [21] and the tumor volume in a preclinical orthotopic mouse model of endometrial cancer.[22] Bevacizumab has been approved for first-line treatment of advanced colorectal cancer in 2004.[23 24] Aghajanian et al[4] enrolled a large cohort of 349 patients assigned into three arms and showed that there was a significant increase in OS at 36 months in patients treated with PC chemotherapy combined with bevacizumab compared to the historical reference arm. Simpkins et al[14] reported that 93% of patients were progression-free at six months after a median treatment period of eight causes. Lorusso et al[3] showed that the addition of bevacizumab to PC chemotherapy improved the OS from 29.7 months to 40.0 months compared with PC chemotherapy (Hazard ratio =0.71, p =0.24). Our meta-analysis involving three trials showed that the OS and PFS at > 12 months were increased significantly by bevacizumab-combined chemotherapy, with an ORR, CRR, and PRR of 76%, 22% and 21%, respectively. The six and 12-month PFS was 79% and 62%, respectively. These findings suggested that bevacizumab-combined chemotherapy may have a high efficacy of in advanced/recurrent endometrial cancer.

The biggest problem related to bevacizumab-combined chemotherapy was the high incidence of grade ≥2 adverse events. Bevacizumab was associated with the high incidences of mild and severe events including bleeding, neutropenia, and non-hematological toxicity like arterial and venous thrombosis and hypertension.[3 4 8] The incidence of adverse events following bevacizumab-combined chemotherapy in the study by Aghajanian et al[4] was 100% in the three groups, and the incidences of grade ≥3 adverse events were 93.7%, 98.2%, and 95.6% in the PC+bevacizumab, PC+temsirolimus, and ixabepilone+carboplatin+bevacizumab group. Lorusso et al[3] reported that patients in PC+bevacizumab group had a higher incidence of grade ≥3 adverse events (n=92) in 53 patients, and patients (n=53) in the control PC chemotherapy group developed 51 grade ≥3 adverse events. Our present study showed the common adverse events after bevacizumab-combined chemotherapy were anemia (23%), leukopenia (46%), neutropenia (51%), thrombocytopenia (16%), hypertension (16%), pain (20%), and fatigue (24%), and adverse events including arterial (1%) and venous thromboembolic events (8%), dyspnea (5%), and hemorrhage (3%) were rare. These findings were in consistent with the results from other studies.[25 26]

Lorusso et al[3] and Aghajanian et al[4] both indicated that the appearance of grade ≥2 or 3 hypertension was higher following the inclusion of bevacizumab compared with control therapies. The rate of hypertension was relatively low and was lower than that in patients with other cancers receiving bevacizumab.[27 28] Shah et al[27] and Zhu et al [28] performed a meta-analysis and showed that the incidence of hypertension was significantly and dose-dependently increased among patients receiving bevacizumab. The reason for the increased incidence of hypertension was unclear and was assumed to be associated with the renin–angiotensin-aldosterone system (RAAS) and the production of angiotensin II derived from renin-mediated conversion.[25] The frequent monitoring of blood pressure is recommended for patients receiving bevacizumab-combined chemotherapy.

Study limitations

Limitations in this study included: (1) various treatment cycles among the included trials; (2) small patient sizes; and (3) non-uniform regimes of bevacizumab-combined chemotherapy. For instance, Aghajanian et al[13] treated 56 patients with 1-8+ cycles of single-agent bevacizumab; Alvarez et al[12] treated 53 patients with 1-19 cycles of bevacizumab combined with temsirolimus; Aghajanian et al[4]

treated 116 patients with PC combined with bevacizumab and 115 patients with ixabepilone+carboplatin combined with bevacizumab for 6-8 cycles; and Lorusso et al [3] treated 54 patients with 6-8 cycles of PC therapy combined with bevacizumab. The efficacy and safety of using bevacizumab as a combined or adjuvant chemotherapy for advanced/recurrent endometrial cancers may be clearer after overcoming these problems.

In conclusion, This present study showed that conventional chemotherapy combined with bevacizumab had a potential efficacy in improving the OS and PFS in patients with advanced/recurrent endometrial cancers. The ORR, CRR, and PRR in patients following bevacizumab-combined chemotherapy were 76%, 22%, and 21%, respectively, with a high incidence of adverse events, including leukopenia, neutropenia, hypertension, and anemia. The six-month and 12-month PFS in patients receiving bevacizumab-combined chemotherapy were 79% and 62%, respectively. This systematic review and meta-analysis of seven clinical trials suggested that bevacizumab-combined chemotherapy may have a higher efficacy in patients with advanced/recurrent endometrial cancer as compared with chemotherapy alone. However, the safety of it is inconclusive.

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Table 1. Demographic characteristics of the included studies

Study	Region	Phase	Design	Patient No. (Com /C)	Age (yr, Com /C)	Interventions		Median OS (mo)	Outcomes	Jadad / MIN ORS
						Com	C			
Lorusso D 2019 [3]	Italy	II	RCT	54/54	63 (28,81)/ 65 (32,80)	Bevacizumab+PC	PC	23.5	OS, PFS, ORR, CPR, PRR, AEs	5
Aghajanian C 2018[4]	USA	II	RCT	116/118/115	62 (36,87)/65 (37,89)/63 (38,82)	Bevacizumab+PC; ixabepilone+carboplatin +bevacizumab	PC+Temsirolimus	36	OS, PFS, ORR, AEs	4
Rose PG 2017 [5]	USA	II	ST	34	62 (32,88)	Bevacizumab+PC	/	56	OS, PFS, ORR, CPR, PRR, AEs	14
Alvarez E 2013 [12]	USA	II	ST	53	63 (35,80)	Bevacizumab+ temsirolimus	/	16.9	OS, PFS, ORR, CPR, PRR, AEs	13
Aghajanian C 2011[13]	USA	II	ST	52	62(32,84)	Bevacizumab	/	10.55	OS, PFS, ORR, CPR, PRR, AEs	14
Simpkins F 2015[14]	USA	II	ST	15	63(32,88)	Bevacizumab+PC	/	58	OS, PFS, ORR, CPR, PRR, AEs	12
Wright JD 2007 [15]	USA	NA	ST	11	57(38,70)	Bevacizumab+cytotoxic	/	15.3	OS, PFS, ORR, PRR, AEs	12

AEs, adverse events; ORR, overall response rate; CPR, complete response rate; PRR, partial response rate; OS, overall survival; PC, paclitaxel + carboplatin; PFS, progression-free survival; RCT, randomized-controlled trial. ST, single-arm trial. NA, not applicable. Com for experiment group (PC combined), and C for control group

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Table 2. The common adverse events in patients with endometrial cancers after bevacizumab combined with chemotherapy.

Adverse events (grade ≥2)	**ES**	**95% CI**	**Model**	I^2	**P**
Anemia	23%	14%, 33%	Random-effects	83.4%	<0.0001
Leukopenia	46%	26%, 65%	Random-effects	85.3%	<0.0001
Neutropenia	51%	30%, 73%	Random-effects	96.4%	<0.0001
Thrombocytopenia	16%	9%, 23%	Random-effects	71.0%	0.002
Hypertension	16%	12%, 20%	Fixed-effects	0	0.899
Pain (grades ≥2)	20%	8%, 31%	Random-effects	72%	0.013
Fatigue	24%	12%, 36%	Fixed-effects	0	0.817
Arterial thromboembolic events	1%	0, 2%	Fixed-effects	0	0.871
Venous thromboembolic events	8%	5%, 11%	Fixed-effects	0	0.999
Fistulas	3%	1%, 5%	Fixed-effects	0	0.770
Dyspnea	5%	1%, 10%	Fixed-effects	41.5%	0.191
Nausea	3%	1%, 6%	Fixed-effects	10.7%	0.345
Hemorrhage	3%	0, 6%	Fixed-effects	0	0.543

ES, effect size. 95% CI, 95% confidential interval. P value indicates the χ^2 test for the data heterogeneity (I^2).

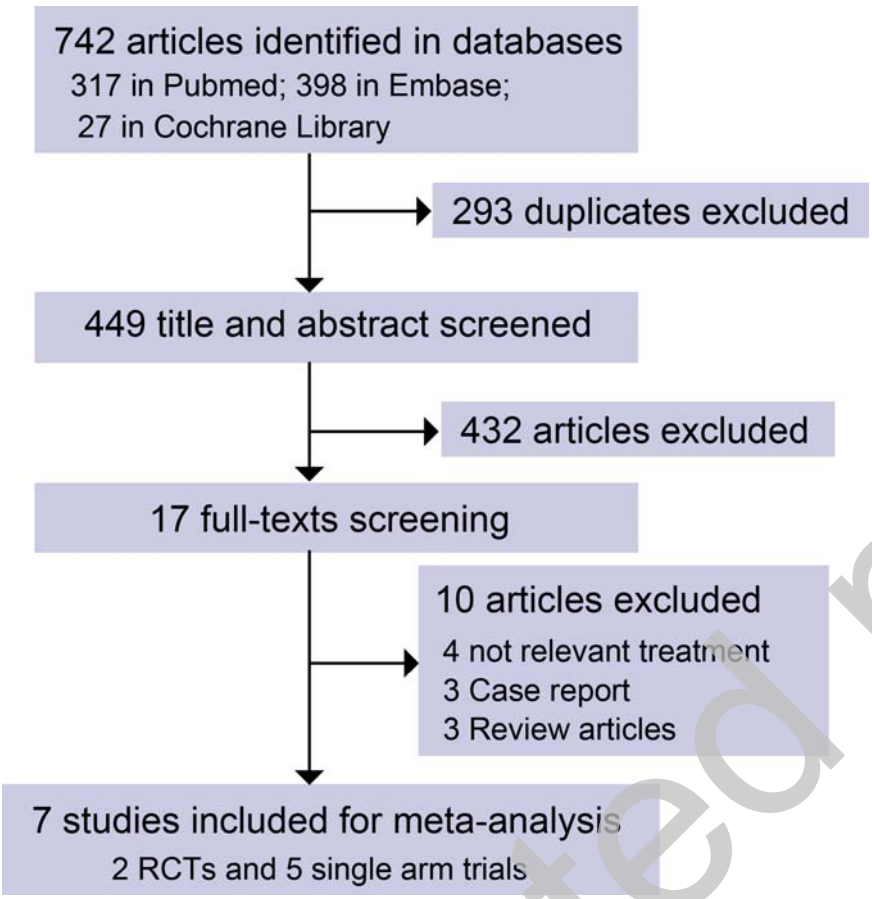


FIG. 1. The PRISMA flow chart of search strategy followed for article search and selection in current study. Seven studies were included in this systematic review, including two randomized-controlled trials (RCTs) and five single-arm trials.

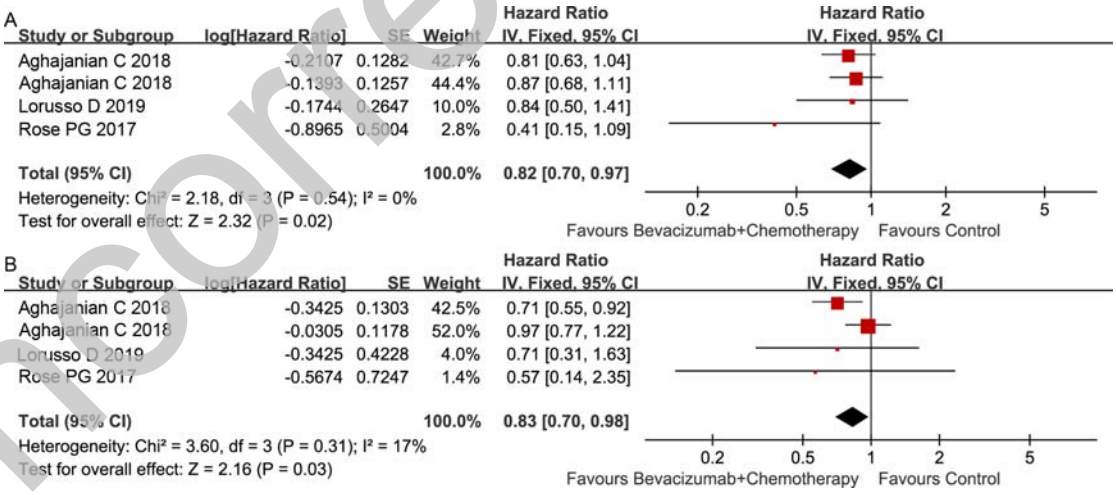


FIG. 2. The forest plot of the pooled median progression-free survival (PFS) and overall survival (OS) in patients treated with bevacizumab-combined chemotherapy. A and B, the forest plot evaluating the efficacy of chemotherapy plus bevacizumab in improving the PFS and OS in patients with endometrial cancers (n=491). SE, standard error. 95% CI, 95% confidence interval. The difference level was calculated using the inverse variance (IV) method.

Supplemental online materials

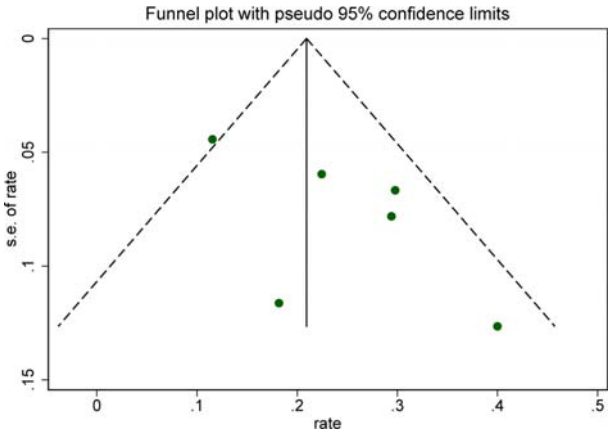


Figure S1. The funnel plot of the risk of bias. Se. standard error.

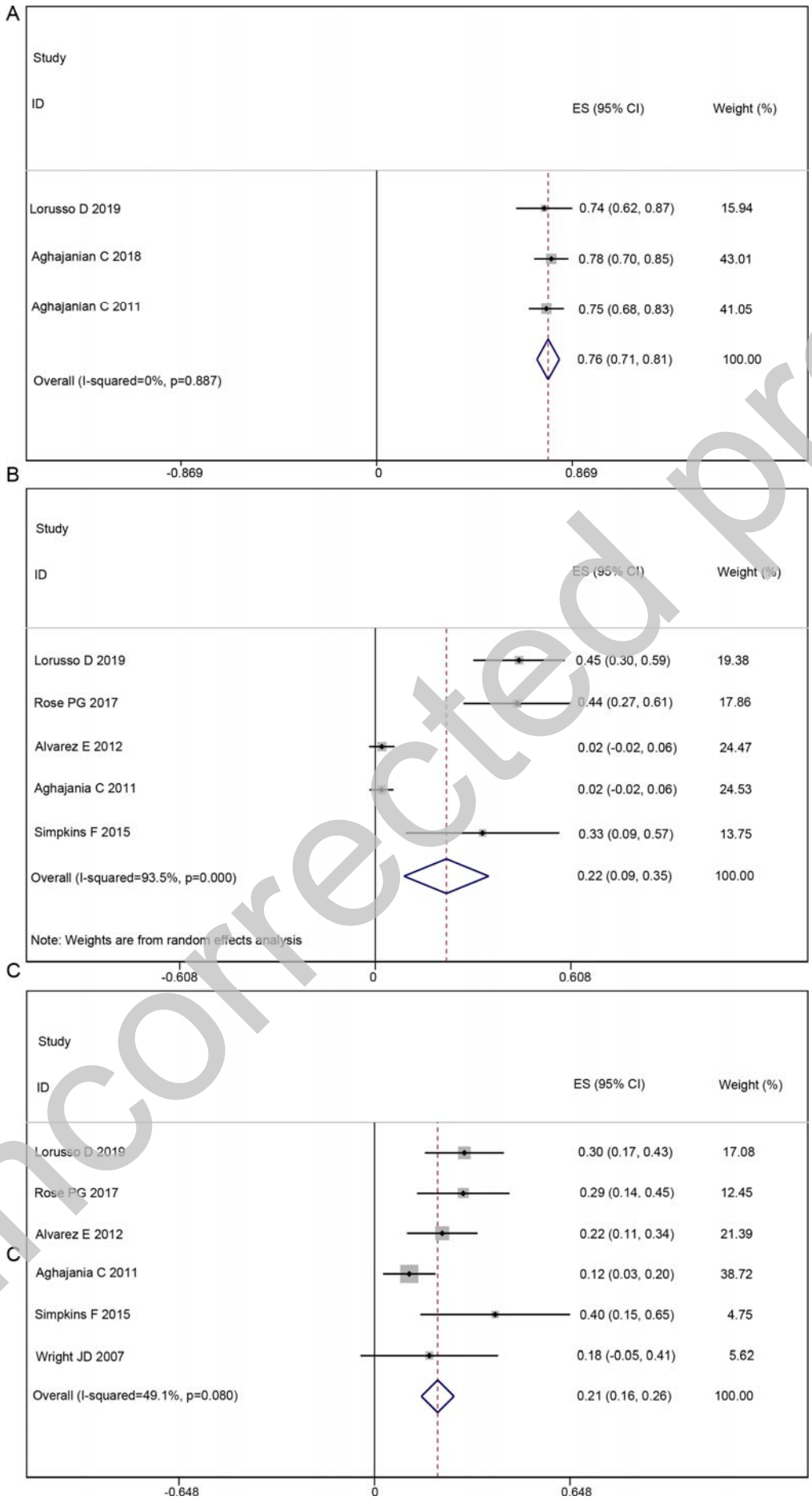
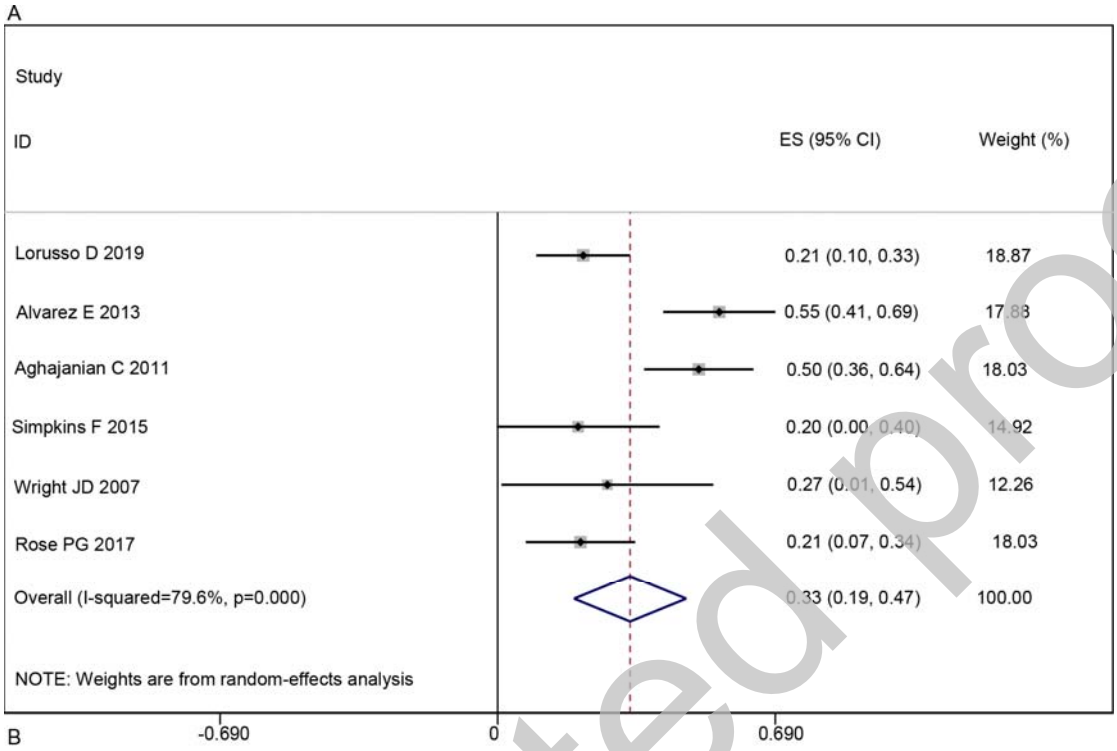


Figure S2. Pooled analysis of the overall response rate (ORR), complete response rate (CRR), and partial response rate (PRR) in endometrial cancer patients treated with bevacizumab-combined chemotherapy.



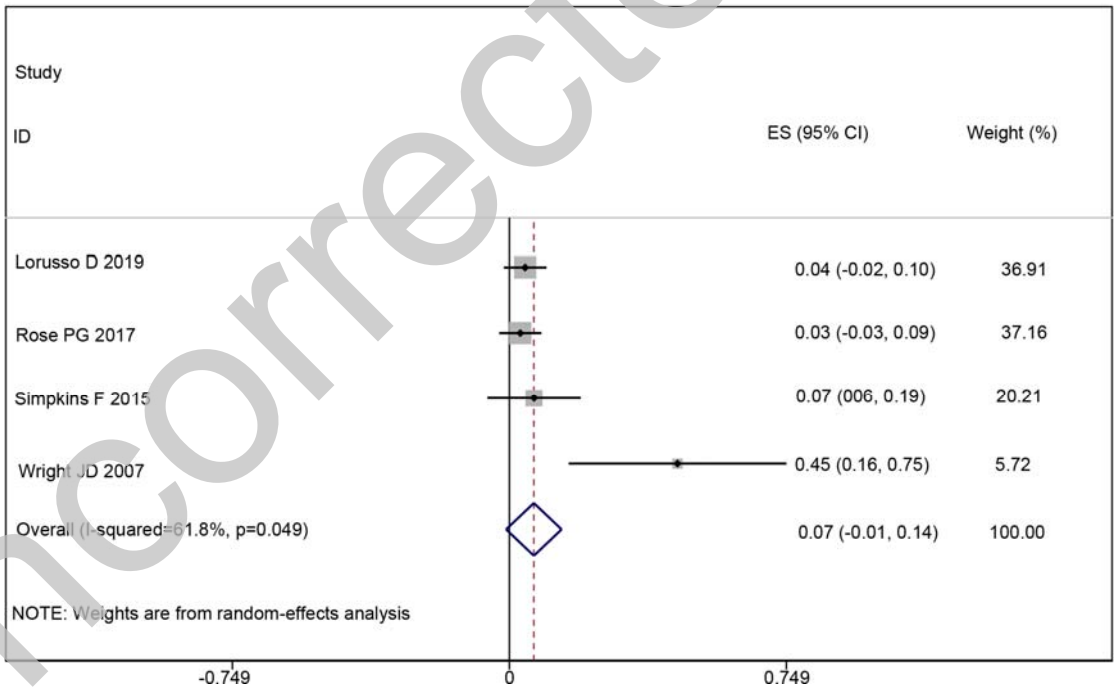


Figure S3. Pooled analysis of the stable disease and tumor progression in endometrial cancer patients treated with bevacizumab-combined chemotherapy.

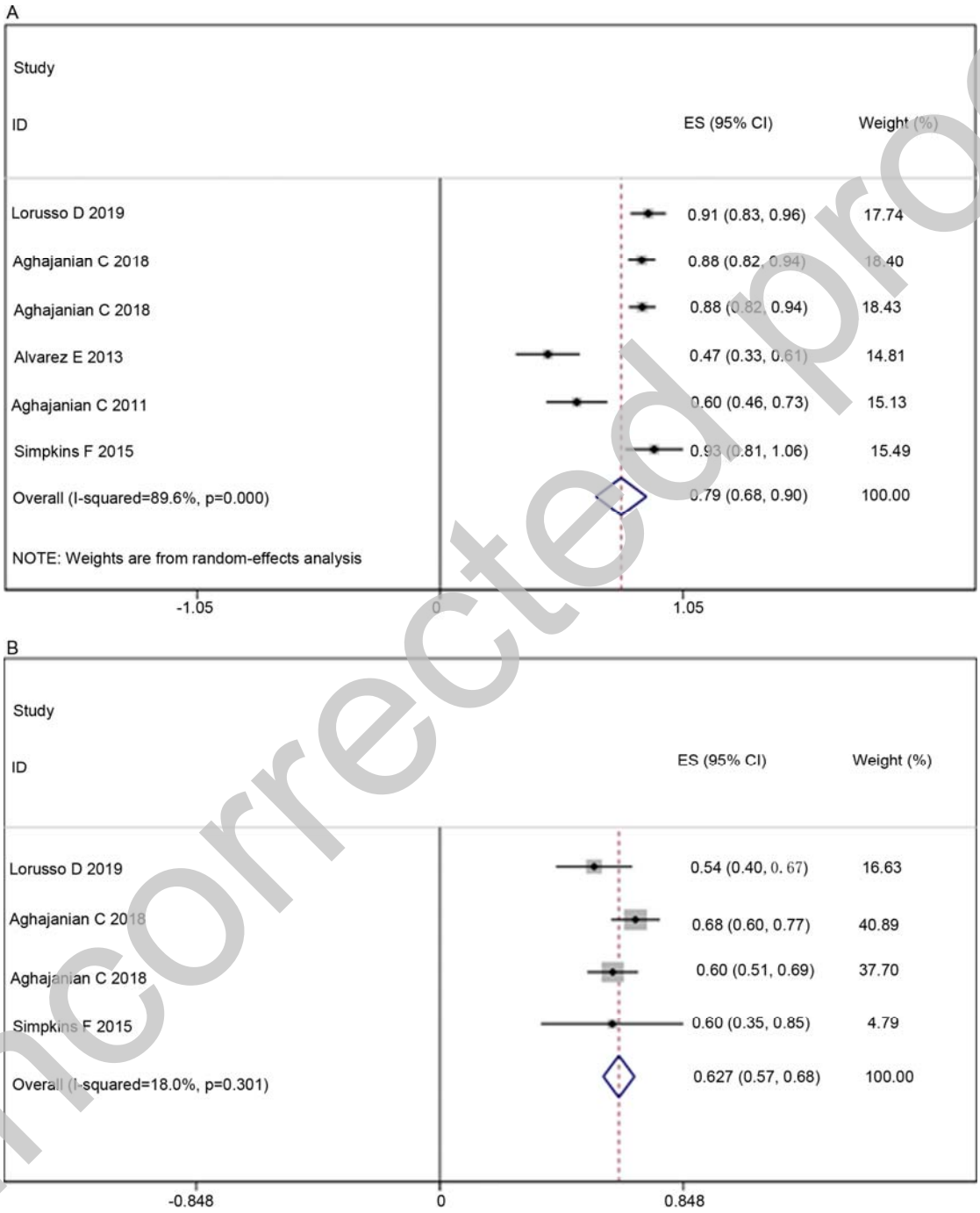


Figure S4. Pooled analysis of the non-progression of disease at six and 12 month in endometrial cancer patients treated with bevacizumab-combined chemotherapy.