Meta-analysis of Clinical Efficacy of Metformin Combined with Chemotherapy in the Treatment of Ovarian Cancer

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Abstract: Objective — To systematically evaluate the clinical efficacy of metformin combined with chemotherapy in the treatment of patients with ovarian cancer. Methods — Methods: Search Pubmed, Embase, Web of science, Cochrane Library database, and screen the literature of randomized controlled trials and cohort studies of metformin combined with chemotherapy in the treatment of ovarian cancer, and use Revman5.2 software to conduct meta-analysis to compare metformin combined with chemotherapy (experimental Group) or chemotherapy alone (control group) for the treatment of ovarian cancer. Results — A total of 389 articles were retrieved, and 4 cohort studies and 2 randomized controlled trials were screened and included, involving 2010 patients with ovarian cancer. Compared with the control group, the overall survival rate of metformin combined with chemotherapy in patients with ovarian cancer (HR=0.55, 95% confidence interval 0.34-0.89, P=0.01, I^2=36%), progression-free survival rate (HR=0.43, The 95% confidence interval 0.20-0.96, P=0.04, I^2=42%) and disease-free survival rate (HR=0.24, 95% confidence interval 0.11-0.50, P=0.0001) were significantly better than the control group. Conclusion — Metformin combined with chemotherapy can significantly improve the therapeutic effect of patients with ovarian cancer.

***Keywords*:** metformin, ovarian cancer, chemotherapy, survival rate

Ovarian cancer is one of the most common malignancies of the female reproductive system and the fifth most common cause of cancer death in women worldwide[1]. Ovarian cancer is characterized with extremely poor prognosis, with 151,900 deaths a year worldwide[2]. First-line treatment for ovarian cancer includes complete reduction surgery and platinum-based chemotherapy[3]. Patients with ovarian cancer will undergo multiple chemotherapy as a consequence of recurrence, and the tumor-free survival period after each chemotherapy is gradually shortened from platinum/paclitaxel sensitivity to platinum/paclitaxel resistance. Therefore, chemotherapy drug resistance is one of the main reasons for treatment failure in ovarian cancer patients[4,5].

Therefore, there is a need to develop new therapies for ovarian cancer to overcome acquired resistance of ovarian cancer cells or to reduce the side effects of platinum-based/paclitaxel therapies. Metformin is a small molecule found naturally in plants[6], which has been used to treat type 2 diabetes for more than 40 years. In 2001, antitumor effects were first identified in mammals[7]. Numerous clinical trials are currently under way in various types of solid tumors to demonstrate the anticancer effects of metformin[10]. This meta-analysis is adopted in this paper to analyze the efficacy of metformin combined with chemotherapy in the treatment of ovarian cancer.

1. Data and methods

1.1 Literature retrieval strategy

We systematically searched Pubmed, Embase, Web of science, Cochane library for all published articles up to November 2020. Pubmed subject search "#1 Metformin", subject or keyword search "#2 metformin" or "glucophage", "#3 (#1 OR #2), subject search "#4 Ovarian Neoplasms", title or key Word search "#5 ovar* and (cancer* or carcinom* or neoplasm* or tumor* or tumor* or malignan*)" "#6 (#5 OR #4), #7 (#3 AND #6). We also searched for originally published articles by references cited in the study and relevant review articles. The language of final included articles is limited to English.

1.2 Inclusion criteria

The inclusion criteria of this study were as follows: (1) Type of literature study: Cohort study and randomized controlled study were selected. (2) Research subjects: Patients with ovarian cancer certified with microanatomy. (3) Intervention measures: The conventional chemotherapy and metformin method is adopted in the experimental group, while the control

group was treated with conventional chemotherapy. (4) Main outcome indicators: Overall survival, progression-free survival.

1.3 Literature exclusion criteria:

Exclusion criteria for this study were as follows: (1) Randomized controlled trials that covered patients with other cancers are involved in the research subjects; (2) Literature types include news, manuscript, review, text notice, conference report, system evaluation plan and literature that are repeatedly published and fails to be downloaded in full.

1.4 Literature screening and data extraction

Two researchers conducted screening for the retrieved literature in an independent manner based on the screening process. By reading the titles and abstracts of the literature, the literature irrelevant to our research objectives were excluded by us. By reading the full text in detail, eligible studies that meet the inclusion and exclusion criteria are included. Besides, relevant literature data was extracted by the structured form[8], which specifically include: the first author, year of publication, the country, the total number of samples, the number of experimental samples, the number of control samples, age, follow-up time, research type, treatment methods and treatment outcome — overall survival (OS), progression-free survival (PFS) and disease free survival (DFS), etc.

1.5 Evaluation on literature quality

The Newcastle-Ottawa Scale (NOS) scoring method was adopted for evaluation of the literature quality of the included cohort studies, and the bias risk assessment Table recommended by Cochrane was used to evaluate the literature quality of the included RCTS.

1.6 Statistical analysis

The effect of metformin and chemotherapy on ovarian cancer survival (overall survival, progression-free survival, disease-free survival) was calculated using HR of individuals with 95% CIs in each included study. I^2 statistical magnitude was utilized to test the heterogeneity of the study. I^2 values of 25%, 50% and 75% were considered as with heterogeneity at low, medium and high level, respectively[9]. If I^2>50% was analyzed by random effects model, and I^2<50% was analyzed by fixed effects model. Publication bias was assessed by Egger's small-scale study effect test[10]. All statistical analyses were performed using Review Manager 5.2. $P < 0.05$ was defined as the significance level.

2. Results

2.1 Process for literature screening and results

The flow chart of literature search research selected is shown in Figure 1. A total of 389 articles were retrieved based on the established search strategy. After abstracts or full texts were screened, four retrospective cohort studies and two randomized controlled trials (11-16) were selected.

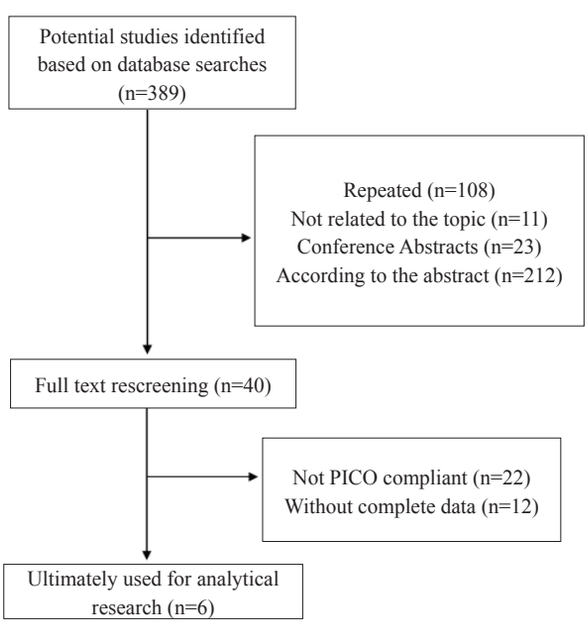

Figure 1. Flow chart of inclusion literature screening

2.2 Basic characteristics and quality assessment of inclusion studies

The studies included in this study entail four cohort studies and two randomized controlled studies, ranging from 2012 to 2020 with follow-up of 6 to 63 months. The number of samples of the included studies range from 44 to 737. The basic characteristics of the inclusion studies are shown in Table 1. The risk assessment results of bias in included cohort studies are shown in Table 2, and the risk assessment results of characteristic bias in randomized controlled studies are shown in Figure 2. The quality assessment results of all studies are shown in Table 2 and Figure 2. All the studies were rated six to eight stars, indicating that they were acceptable.

Table 1. Characteristics of inclusion studies

Inclusion study	Research Country	Number of Samples of Experimental Group	Number of Samples of Control Group	AAge	Follow-up time	Research design	Therapy scheme	Result indicator
Kuo Chang Wen[11] (2020)	America	32	705	None	5 Years	cohort studies	Metformin + chemotherapy VS chemotherapy	OS
Shan-Bing Wang[12] (2017)	China	70	497	86.5±7.4/ 60.4±6.4	6 Months	cohort studies	Metformin + chemotherapy VS chemotherapy	PFS/OS
Sanjeev Kumar[13] (2013)	America	61	178	62 ± 11/ 61 ± 11	T: 3.7 Years; C: 4.3 Years	cohort studies	Metformin + chemotherapy VS chemotherapy	OS
Iris L. Romero[14] (2012)	America	16	325	89.5±11/ 67±9	63 Months	cohort studies	Metformin + chemotherapy VS chemotherapy	PFS
Bahareh Hamedi[15] (2018)	Italy	41	41	30-80	4 Years	RCT	Metformin + chemotherapy VS chemotherapy	DFS
Hong Sun[16] (2019)	Germany	20	24	53.55 ± 9.20 /52.88 ± 8.77	18-24 Weeks	RCT	Metformin + chemotherapy VS chemotherapy	PFS/DFS

Table 2. Bias risk assessment results of included cohort studies

Inclusion studies	Exposure of the representativeness of the cohort	The choice of the unexposed	Determination of exposure	Adjustment for confounding factors	Assessment result	Adequate follow-up time	Appropriate follow-up	Data integrity	Scores (0-9)
Kuo Chang Wen	1	1	1	1	1	1	1	0	7
Shan-Bing Wang	1	1	1	1	1	0	1	1	7
Sanjeev Kumar	0	1	1	1	1	1	1	1	7
Iris L. Romero	1	1	1	1	1	1	1	1	8

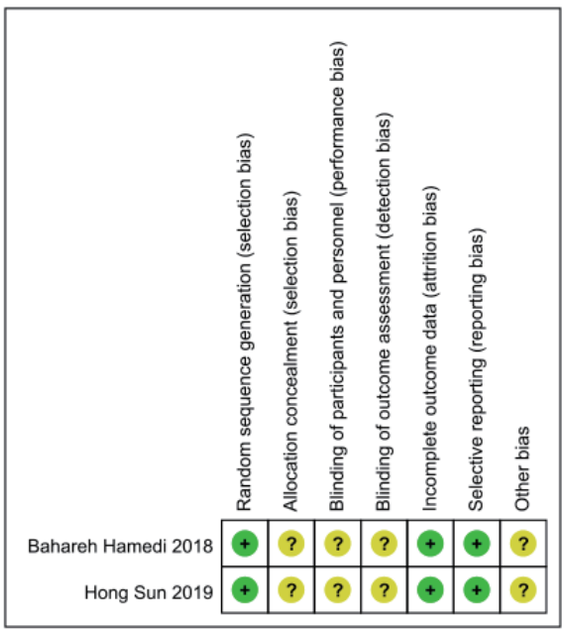

Figure 2. Bias risk assessment results for inclusion in randomized controlled studies

(Note: question mark indicates uncertain risk, plus sign indicates low risk)

2.3 Results of meta-analysis

2.3.1 Effect of metformin and chemotherapy on overall survival rate (OS) of ovarian cancer

OS of ovarian cancer patients treated with metformin and chemotherapy was reported in three studies, and fixed-effect model results suggested that metformin and chemotherapy significantly improved OS in ovarian cancer patients compared with chemotherapy alone (HR=0.55, 95% confidence interval 0.34-0.89, P=0.01, I^2= 36%), as shown in Figure 3.

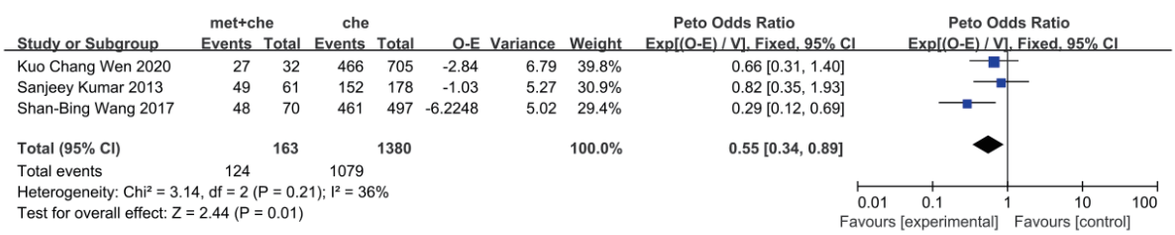

Figure 3. Forest plot of overall survival in patients with ovarian cancer treated with metformin combined with chemotherapy

2.3.2 Effect of metformin and chemotherapy on progression-free survival rate of ovarian cancer

PFS was released in two studies on treatment of patients with metformin and chemotherapy for patients with ovarian cancer, and fixed-effect model results indicated that the treatment method of application of metformin and chemotherapy significantly increased progression-free survival in ovarian cancer patients compared with chemotherapy alone (HR=0.43, 95% confidence interval 0.20-0.96, P=0.04, I^2=42%), as shown in Figure 4.

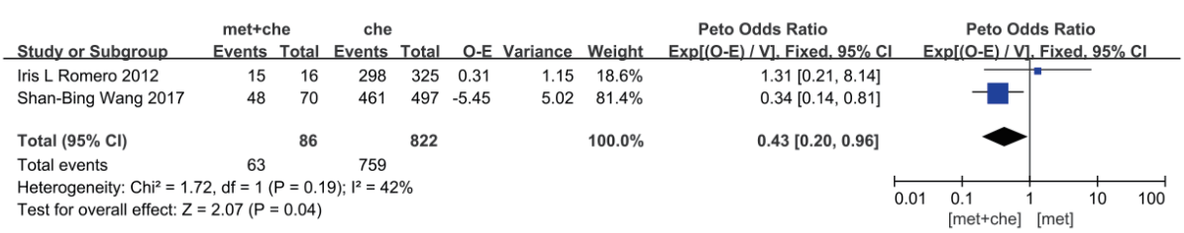

Figure 4. Forest plot of progression-free survival in patients with ovarian cancer treated with metformin and chemotherapy

2.3.3 Effect of treatment method of metformin and chemotherapy on disease-free survival rate of ovarian cancer

The disease-free survival of of patients with ovarian cancer who were treated with metformin and chemotherapy is researched in 2 randomized controlled trials, and the heterogeneity result showed that there is heterogeneity between the two studies (P = 0.05, I^2 = 74%).Through the random effects model analysis, the results indicate that the therapy of metformin and chemotherapy can significantly increases the disease free survival rate of patients with ovarian cancer (HR = 0.24, 95% confidence interval 0.11-0.50, P=0.0001), as shown in Figure 5.

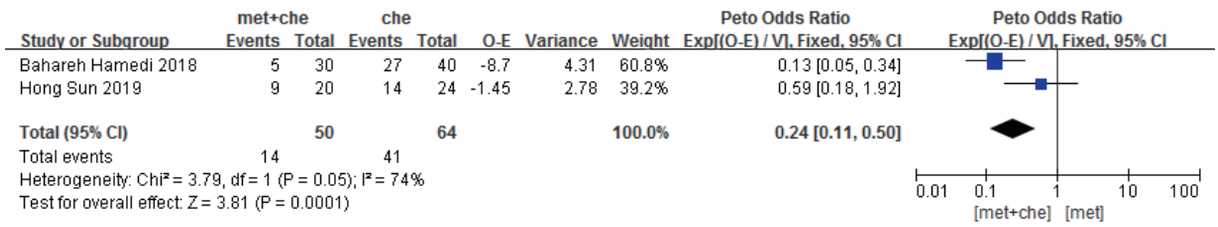

Figure 5. Forest plot of the association between metformin and chemotherapy and disease-free survival in ovarian cancer

3. Discussion

In this meta-analysis, HR of OS, PFS, and DFS and 95% of the feasible intervals were calculated, indicating that the therapy of metformin and chemotherapy was superior to chemotherapy alone in patients with ovarian cancer,which proved to with statistically significant differences. Metformin and chemotherapy based therapy can be adopted to significantly improve overall survival and progression-free survival. This is consistent with epidemiological studies,that is,metformin is capable of significantly reducing the risk of cancer in patients with type 2 diabetes[17-20]. Hepatic gluconeogenesis, protein synthesis and cancer cell proliferation can be inhibited through AMPK activation and inhibition of mTOR signaling pathway[21,22], which may be the molecular mechanism by which metformin can significantly improve the prognosis of cancer patients.

However, there are the following problems in this paper as follows: First, only 2 randomized controlled trials and 4 cohort studies in this study proved to be eligible with the requirements, and the inherent weakness of retrospective cohort design may lead to selection bias. Second, in most studies, different treatments for cancer and other important factors related to prognosis, such as adverse events and safety outcomes, were characterized with incompleteness, as a result,adverse events caused by therapy of metformin and chemotherapy failed to be studied in this study. In addition, different histopathological subtypes and clinical grading and staging failed to be studied in some studies. In conclusion, our present study provides preliminary evidence that the therapy of metformin and chemotherapy is capable of improving survival in patients with ovarian cancer, but more well-designed studies can possibly be required for confirmation.

Acknowledgments

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References

[1] Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[J]. *Ann Oncol*, 2013; 24 Suppl 6: vi24-32.

[2] Torre LA, Bray V, Siegel RL, et al. Global cancer statistics[J]. *CA Cancer J Clin*, 2015; 65(3): 87-108.

[3] Liang WF, Wang LJ, Li H, et al. The added value of CA125 normalization before interval debulking surgery to the chemotherapy response score for the prognostication of ovarian cancer patients receiving neoadjuvant chemotherapy for advanced disease [J]. *J Cancer*, 2021; 12(3): 946-953.

[4] Shen Xiameng, Lv Weiguo. Study on the role of exosomes in chemotherapy resistance of ovarian cancer patients [J]. *Journal of Zhejiang University*, 2019; 48(1): 116-120.

[5] Raja FA, Counsell N, Colombo N, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data[J]. *Ann Oncol*, 2013; 24(12): 3028-34.

[6] Block KI, Gyllenhaal C, Lowe L, et al. Designing a broad-spectrum integrative approach for cancer prevention and treatment[J]. *Semin Cancer Biol*, 2015; 35 Suppl(Suppl): S276-s304.

[7] Schneider MB, Matsuzaki H, Haorah J, et al. Prevention of pancreatic cancer induction in hamsters by metformin[J]. *Gastroenterology*, 2001; 120(5): 1263-70.

[8] Kobayashi Y, Banno K, Kunitomi H, et al. Current state and outlook for drug repositioning anticipated in the field of ovarian cancer[J]. *Journal of Gynecologic Oncology*, 2019; 30(1): 1-13.
[9] Higgins JP, Thompson SG.Quantifying heterogeneity in a meta-analysis[J]. *Stat Med*, 2002; 21(11): 1539-58.
[10] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test[J]. *Bmj*, 1997; 315(7109): 629-34.
[11] Wen KC, Sung PL, Wu ATH, et al. Neoadjuvant metformin added to conventional chemotherapy synergizes anti-proliferative effects in ovarian cancer[J]. *J Ovarian Res*, 2020; 13(1): 95.
[12] Wang SB, Lei KJ, Liu JP, al. Continuous use of metformin can improve survival in type 2 diabetic patients with ovarian cancer: A retrospective study[J]. *Medicine (Baltimore)*, 2017; 96(29): e7605.
[13] Kumar SA, Meuter, Thapa P, et al. Metformin intake is associated with better survival in ovarian cancer: a case-control study[J]. *Cancer*, 2013; 119(3): 555-62.
[14] 14 Romero IL, McCormick A, McEwen KA, et al. Relationship of type II diabetes and metformin use to ovarian cancer progression, survival, and chemosensitivity[J]. *Obstet Gynecol*, 2012; 119(1): 61-7.
[15] Hamedi B, Khalili A, Roozmeh S, et al. Combination of Metformin and Chemotherapy Decreases the Recurrence Rates of Epithelial Ovarian Cancers: A Randomized Clinical Trial[J]. *International Journal of Cancer Management*, 2018; 11(7): 1-7.
[16] Zheng Y, Zhu J, Zhang H, et al. Metformin plus first-line chemotherapy versus chemotherapy alone in the treatment of epithelial ovarian cancer: a prospective open-label pilot trial[J]. *Cancer Chemother Pharmacol*, 2019; 84(6): 1349-1357.
[17] Zhang ZJ, Zheng ZJ, Kan H, et al. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis[J]. *Diabetes Care*, 2011; 34(10): 2323-8.
[18] Zhang ZJ, Zheng ZJ, Shi R, et al. Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis[J]. J *Clin Endocrinol Metab*, 2012; 97(7): 2347-53.
[19] Zhang ZJ, Bi Y, Li S, et al. Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis[J]. *Am J Epidemiol*, 2014; 180(1): 11-4.
[20] Zhang ZJ. Metformin and Reduced Risk of Cancer in the Hong Kong Diabetes Registry: Real Effect or Immortal Time Bias?[J]. *J Gen Intern Med*, 2019; 34(7): 1154-1157.
[21] Zhang F, Chen H, Du J, et al. Anticancer Activity of Metformin, an Antidiabetic Drug, Against Ovarian Cancer Cells Involves Inhibition of Cysteine-Rich 61 (Cyr61)/Akt/Mammalian Target of Rapamycin (mTOR) Signaling Pathway [J]. *Med Sci Monit*, 2018; 24: 6093-6101.
[22] Zheng Y, Zhu J, Zhang H, et al. Metformin inhibits ovarian cancer growth and migration in vitro and in vivo by enhancing cisplatin cytotoxicity[J]. *Am J Transl Res*, 2018; 10(10): 3086-3098.