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Original Research Article

Effect of the combined use of docetaxel, cisplatin and apatinib mesylate on serum tumor markers and prognosis in advanced ovarian cancer patients

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Abstract

Purpose: *To examine the impact of combining docetaxel and cisplatin injections with apatinib mesylate tablets on serum tumor markers and prognosis of advanced ovarian cancer patients.*
Methods: *A total of 121 advanced ovarian cancer patients admitted to Jiande First People's Hospital, Jiande, China between June 2014 and December 2022 were enrolled in this study. Of these, 59 patients treated solely with docetaxel and cisplatin injections comprised control group while 62 patients who received apatinib mesylate tablets in conjunction with docetaxel and cisplatin injections formed the study group. Serum tumor marker levels, serum vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) levels in peripheral venous blood were evaluated. Furthermore, improvements in ascites, efficacy, incidence of adverse reactions, Karnofsky Performance Status (KPS) scores and quality of life (QoL) scores were recorded. The Kaplan-Meier method was implemented for survival analysis.*
Results: *After chemotherapy, serum tumor markers (CEA, CA199, CA125, CA153), VEGF and MMP-2 significantly decreased from pre-chemotherapy levels. The study group showed greater reduction than control group ($p < 0.05$), and also exhibited superior abdominal effusion treatment efficacy and overall effectiveness ($p < 0.05$). Adverse reactions were rarer in the study group ($p < 0.05$). The study group's KPS and QoL scores after chemotherapy exceeded those of the control group, with regard to baseline improvement ($p < 0.05$). Additionally, the study group had a higher 3-year survival rate ($p < 0.05$).*
Conclusion: *Although docetaxel and cisplatin injections exhibit significant efficacy in managing advanced ovarian cancer, the adjunctive use of apatinib mesylate tablets augments the efficacy and offers superior safety as well, rendering the combination a potential strategy for improved management of advanced ovarian cancer.*

Keywords: *Docetaxel, Cisplatin, Combination therapy, Apatinib mesylate, Ovarian cancer*

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INTRODUCTION

Annually, there is an alarming increase in both the incidence and mortality of primary ovarian cancer, representing a significant fraction of gynecological malignancies. This ailment predominantly affects perimenopausal women, significantly compromising their health [1]. The

insidious nature of ovarian malignancies, originating deep within the pelvis, renders early-stage symptoms inconspicuous. Consequently, by the time symptoms manifest, most patients are already in advanced stages with extensive metastasis, making curative interventions elusive [2]. Patients often exhibit clinical signs such as abdominal and pelvic masses, ascites, abdominal discomfort and cachexia, attributable to the progressive growth of tumor cells [3]. Early detection and intervention can considerably extend the life expectancy of those in the initial stages of ovarian cancer. Although patients with advanced stages can achieve some life prolongation through targeted pharmacotherapy and surgical interventions, their therapeutic outcomes are suboptimal compared to their early-stage counterparts [4].

Chemotherapy remains the cornerstone of ovarian cancer management, primarily aimed at halting cancerous proliferation. However, these drugs, in their bid to suppress malignant cells, inadvertently harm healthy cells, precipitating severe adverse reactions. Such complications have compelled some patients to discontinue treatment, undermining the therapeutic trajectory [5]. This highlights the urgent need for more effective and tolerable therapeutic strategies to both halt the disease progression and enhance the prognosis of ovarian cancer patients.

Docetaxel, a prominent member of the paclitaxel family of antineoplastic agents, acts by modulating microtubule proteins, particularly inhibiting their depolymerization [6]. Cisplatin, a metallic compound, targets cancer cell DNA and its augmented production impedes DNA replication while inflicting structural damage on cancer cell membranes [7]. Apatinib mesylate stands out as a selective anti-angiogenic small-molecule tyrosine kinase inhibitor, curbing enzymatic activity and downstream signaling in vascular endothelial cells, thus manifesting antitumor properties [8]. This research examines the combined efficacy of Docetaxel, Cisplatin and Apatinib Mesylate tablets in managing advanced ovarian cancer, specifically focusing on their impact on patients' serum tumor markers and prognosis.

METHODS

Patient demographics and groupings

The clinical records of 121 patients with advanced ovarian cancer, admitted to Jiande First People's Hospital, Jiande, China between September 2013 and April 2015 were reviewed. Patients were stratified into two cohorts: control group, consisting of 59 patients treated exclusively with docetaxel and cisplatin injection, and study group, which comprised 62 patients who were administered apatinib mesylate tablets in conjunction with the treatment received by control group.

Ethical considerations

This study was conducted following the guidelines of Declaration of Helsinki [9] and approved by the ethics committee of Jiande First People's Hospital, China (approval no.14-LL-20). Signed written informed consent were obtained from the patients and/or guardians.

Inclusion criteria

The included patients were those who were histologically or clinicopathologically diagnosed with advanced ovarian cancer, exhibiting ambiguous masses on imaging [10], and those naive to other chemotherapy or targeted therapeutic protocols.

Exclusion criteria

The study excluded patients falling within the following categories: Coexistence of other malignancies; non-compliance or alteration of the treatment course midway; concurrent severe vital system failure compromising survival; known hypersensitivity to the drugs in question; and a Karnofsky Performance Score (KPS) below 60.

Treatment plan

Control group

Central venous catheter placement was implemented before chemotherapy. The chemotherapy commenced with a 1 h continuous intravenous drip of Docetaxel injection (20 mg per vial; Jiangsu, China) at 75 mg/m^2. Subsequently, ultrasound-guided paracentesis was conducted, introducing a warmed solution (approx. 45 °C) containing 60 mg of cisplatin (30 mg per vial; Jiangsu, China) and 1,800 mL saline via an indwelling catheter. The patient's position was periodically adjusted to guarantee a uniform distribution of this solution. To thwart allergic reactions, dexamethasone (10 mg; Chengdu, China) and promethazine hydrochloride (25 mg; Shanghai, China) were administered intramuscularly 30 minutes preceding docetaxel infusion. Pantoprazole (40 mg per vial; Hangzhou, China) was administered intravenously for gastric protection, and cimetidine (0.2 g per vial; Zhejiang, China) was

administered intravenously for antiemetic purposes before chemotherapy.

Study group

Building on the aforementioned regimen, these patients also received apatinib mesylate tablets (0.425 g/tablet, once daily; Jiangsu, China) following the initial day of chemotherapy. Both cohorts underwent three 21-day chemotherapy cycles.

Evaluation of parameters/indices

Biochemical assays

Preceding testing, patients fasted and subsequently had 5 mL of venous blood drawn. The blood sample was centrifuged at 30 rpm for 10 min to separate plasma. Quantitative assessments of serum carcinoembryonic antigen (CEA), glycoprotein markers (CA199, CA125, CA153), vascular endothelial growth factor (VEGF), and matrix metalloproteinase-9 (MMP-9) levels were conducted via enzyme-linked immunosorbent assays (ELISA), rigorously adhering to the kit manufacturers' instructions.

Ascites amelioration

The clinical efficacy of peritoneal effusion was assessed based on the following standards: Sustained complete absorption of peritoneal fluid for over 4 weeks signifies effectiveness (E); absorption exceeding 50 % and below 50 % were categorized as "improved" (IM) and "ineffective" (IN), respectively; any escalation in peritoneal fluid volume is deemed a deterioration; the overall success rate in peritoneal fluid management is calculated as shown in Eq 1 [11].

$$EF = ((E + IM)/TC)100 \quad \ldots\ldots\ldots \quad (1)$$

where EF = efficacy and TC = total number of cases.

Outcomes

Clinical responses were delineated as *Cured (CR)* when all lesions vanished within 4 weeks with no new lesions; *Effective (PR)* when there's a reduction of less than 50 % from pre-treatment lesions without notable size alteration; *Stabilized (SD)* in the absence of significant size change and appearance of new lesions; *Deterioration (PD)* when lesion dimensions augmented or new lesions emerged. The cumulative efficacy was calculated by utilizing Eq 2 [12].

$$TE = ((CR + PR)/TC)100 \quad \ldots\ldots\ldots \quad (2)$$

where TE = total efficacy and TC = total number of cases.

Adverse reactions

A comparative analysis of the adverse reaction incidence between the two cohorts.

Patient wellness

Utilizing the Karnofsky Functional Status score (KPS) and the Quality of Life (QoL) score, with higher scores correlating to enhanced health and standard of living.

Survival analysis

The 3-year survival rates for both the combined treatment and control groups were analyzed using the Kaplan-Meier method [13].

Follow-up regimen

Post-treatment, patients underwent routine examinations. The follow-up protocol mandated quarterly evaluations in the initial post-treatment year and shifted to biannual reviews for the succeeding years, thus culminating in an aggregate 3-year follow-up period.

Statistical analysis

Statistic Package for Social Science (SPSS), version 19.0 software (Beijing Netnumbers Times Technology Co. Ltd, Beijing, China) was utilized for a rigorous statistical appraisal. Categorical data were analyzed using the Chi-square test. The continuous variables were expressed as mean ± standard deviation (SD) and analyzed using the *t*-test. Independent samples *t*-tests were performed for inter-group comparison. The 3-year survival status of patients was illustrated using the Kaplan-Meier survival curve, with visual representations rendered via GraphPad Prism8 (La Jolla, CA, USA). A *p*-value below 0.05 was indicative of statistical significance.

RESULTS

General patient data

The age, disease duration, BMI, tumor diameter and other clinicopathological data did not show a significant statistical difference between the two groups ($p > 0.05$; Table 1), thus establishing a suitable foundation for the comparative analysis of treatments in this study. Patients in control group were aged 42 – 76 years and averaged

57.45 ± 7.68 years. Their mean disease duration stood at 29.94 ± 7.65 months, with a mean tumor diameter of 8.01 ± 2.17 cm. Study group patients were aged between 43 and 77 years, with a mean age of 57.53 ± 7.84 years. Their mean disease persistence was 30.99 ± 7.63 months, while the mean tumor diameter was 8.15 ± 2.42 cm.

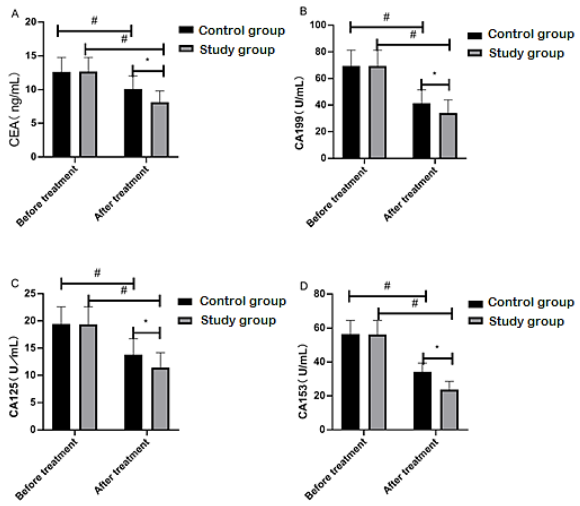

Figure 1: Evaluation of serum tumor marker levels pre- and post-treatment: (A) Post-treatment analysis revealed a decline in serum CEA expression relative to baseline levels, with a more pronounced reduction in study group versus control group. (B) Post-chemotherapy, serum CA199 levels exhibited a decline from baseline, with a more substantial reduction noted in study group relative to the control. (C) A marked decrease in serum CA125 levels was observed post-chemotherapy compared to baseline, with study group presenting a more significant reduction than the control. (D) Serum CA153 levels, post-treatment, declined from their initial levels, with study group showing a greater reduction than control group. ***Note:*** $^{\#}P < 0.05$ vs. before treatment; $^{*}p < 0.05$ vs. control group

Serum tumor marker levels: Pre- and post-chemotherapy cycle treatment

Prior to the initiation of the chemotherapy cycle, no significant differences were observed in the serum tumor markers (CEA, CA199, CA125 and CA153) between the two cohorts ($p > 0.05$). By the cycle's conclusion, all these markers exhibited a decline compared to their baseline values. However, study group demonstrated a more pronounced reduction than control group ($p < 0.05$; Figure 1).

Serum VEGF and MMP-2 Levels: Pre- and post-chemotherapy cycle treatment

Before chemotherapy initiation, the levels of serum VEGF and MMP-2 between the two groups did not differ significantly ($p > 0.05$). Post-treatment, both VEGF and MMP-2 showed reduced levels compared to before treatment, with study group displaying a more significant decrease than control group – a noteworthy distinction ($p < 0.05$; Figure 2).

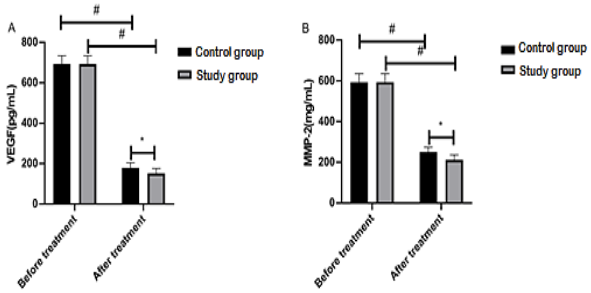

Figure 2: Comparison of Serum VEGF and MMP-2 Levels pre- and post-treatment: (A) After treatment, serum VEGF levels were reduced in both groups compared with before treatment, with the study group exhibiting significantly lower VEGF levels compared with control group. (B) After treatment, serum MMP-2 levels were reduced in both groups compared with before treatment, with the study group exhibiting significantly lower MMP-2 levels compared with control group. ***Note:*** $^{\#}P < 0.05$ vs. before treatment; $^{*}p < 0.05$ vs. control group

Amelioration of ascites

The study group exhibited a significantly enhanced overall efficacy rate in ascites treatment compared to control group ($p < 0.05$; Table 2).

Efficacy

The efficacy of treatment in the study group was higher than that in control group ($p < 0.05$; Table 3).

Incidence of adverse reaction

The total adverse reaction incidence in study group was significantly reduced compared to control group ($p < 0.05$; Table 4).

KPS and QoL score

Initially, the KPS and quality of life (QoL) scores did not reveal any significant disparities between the two patient groups ($p > 0.05$). By the end of the chemotherapy cycle, scores for both the KPS and QoL in study group were notably superior to those in control group. Moreover, post-treatment scores in both groups were enhanced compared to their respective pre-treatment scores ($p < 0.05$). These findings are illustrated in Figure 3.

Table 1: Comparison of general patient data (mean ± SD)

Group	Control group	Study group	χ^2/t	*P*-value
Age (years)	57.45±7.68	57.53±7.84	0.057	0.955
Mean duration of disease (months)	29.94±7.65	30.99±7.63	0.756	0.451
BMI (kg/m^2)	19.23±2.13	19.19±2.08	0.105	0.917
Tumor diameter (cm)	8.01±2.17	8.15±2.42	0.335	0.739
Smoking history (cases)			0.221	0.638
Yes	6 (10.17)	8 (12.90)		
No	53 (89.83)	54 (87.10)		
History of alcohol consumption (cases)			0.043	0.836
Yes	18 (30.51)	20 (32.26)		
No	41 (69.49)	42 (67.74)		
Fertility history (cases)			0.026	0.872
Yes	37 (62.71)	38 (61.29)		
No	22 (37.29)	24 (38.71)		
Abdominal distension and pain (cases)			0.414	0.520
Yes	27 (45.76)	32 (51.62)		
No	32 (54.24)	30 (48.39)		
Menopause (cases)			0.260	0.610
Yes	36 (61.02)	35 (56.45)		
None	23 (38.98)	27 (43.55)		
Degree of differentiation (cases)			0.020	0.888
High/medium differentiation	35 (59.32)	36 (58.06)		
Low differentiation	24 (40.68)	26 (41.94)		
TNM staging (cases)			0.174	0.677
III Stage	33 (55.93)	37 (59.68)		
IV Stage	26 (44.07)	25 (40.32)		
Pathologic staging (cases)			0.515	0.916
Hepatogenic epithelial tumor	33 (55.93)	35 (56.45)		
Sex cord-mesenchymal tumors	4 (6.78)	5 (8.06)		
Ovarian junctional tumor	16 (27.12)	14 (22.58)		
Germ cell tumors	6 (10.17)	8 (12.90)		
Site of metastasis (cases)			2.447	0.294
Pelvic metastasis	41 (69.49)	45 (72.58)		
Liver, kidney and lung metastasis	5 (8.47)	9 (14.52)		
Metastasis to other sites	13 (22.03)	8 (12.90)		

Table 2: Comparison of the improvement of ascites

Group	Control group	Study group	χ^2	*P*-value
Effective	33 (55.93)	37 (59.68)	-	-
Improvement	11 (18.64)	18 (29.03)	-	-
Ineffective	6 (10.17)	4 (6.45)	-	-
Deterioration	9 (15.25)	3 (4.84)	-	-
Overall effective rate of treatment for abdominal cavity effusion	44 (74.58)	55 (88.71)	4.059	0.044

Table 3: Comparison of clinical efficacy

Group	Control group	Study group	X^2	*P*-value
Cured	22 (37.29)	32 (51.62)	-	-
Effective	12 (20.34)	19 (30.65)	-	-
Stable	11 (18.64)	7 (11.29)	-	-
Deterioration	14 (23.73)	4 (6.45)	-	-
Clinical efficacy	34 (57.63)	51 (82.26)	8.775	0.003

Table 4: Comparison of the incidence of adverse reactions

Group	Control group	Study group	X^2	*P*-value
Nausea and vomiting	3 (5.08)	2 (3.23)	-	-
Bleeding	2 (3.39)	0	-	-
Decreased appetite	3 (5.08)	1 (1.61)	-	-
Myelosuppression	2 (3.39)	1 (1.61)	-	-
Hypothermia	1 (1.69)	0	-	-
Incidence of adverse reaction	11 (18.64)	4 (6.45)	4.138	0.042

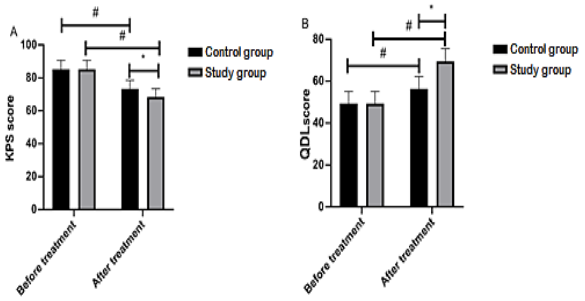

Figure 3: Assessment of KPS and QoL Scores pre- and post-treatment: (A) Post-chemotherapy, KPS scores in study group surpassed those in control group. Scores in both groups improved post-treatment compared to pre-treatment. (B) At the end of the treatment cycle, QoL scores for study group were notably superior to those in control group. Additionally, both groups reflected enhanced QoL scores post-treatment compared to pre-treatment benchmarks. ***Note:*** $^{\#}P < 0.05$ vs. before treatment; $^{*}p < 0.05$ vs. control group

Three-year survival rate

The 3-year overall survival rate in control group, was 28.81 %, which was significantly lower than 43.55 % in study group ($p < 0.05$; Figure 4).

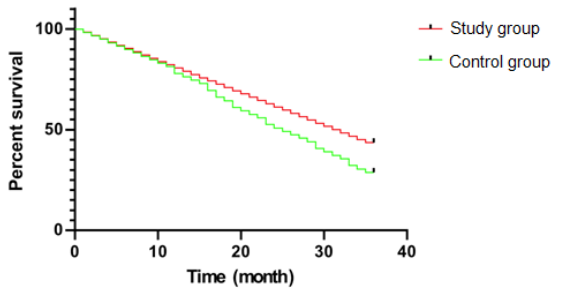

Figure 4: Three-year survival analysis based on treatment modality: Utilizing the Kaplan-Meier method, it was ascertained that the 3-year survival rate for control group (28.81 %) was significantly inferior to that of study group (43.55 %)

DISCUSSION

Ovarian cancer, a predominant malignancy among gynecological tumors, is typically stratified into four stages based on its progression. As the disease advances to its fourth stage, patients' risk to life intensifies, with complete remission becoming increasingly elusive [14]. In surgically addressing advanced ovarian cancer, many patients present with pelvic tumors that implicate the omentum, multifocal tumors in the intestines and mesentery, and are further characterized by diffuse peritoneal carcinomatosis and diaphragmatic engagement [15]. As ovarian cancer progresses, it ushers in intricate organic pathologies, encompassing endocrine perturbations and immune system dysregulation. This functional disequilibrium during the advanced stages exacerbates the proliferation and distant metastasis of cancer cells, thereby amplifying ovarian impairment in affected individuals [16]. Pioneering effective clinical interventions for advanced ovarian cancer stands as a paramount endeavor for medical investigations. Conventional therapeutic strategies frequently face challenges, including tissue resistance, during their administration. Embracing a novel multimodal chemotherapy approach emerges as a pivotal tactic in treating this advanced malignancy. Consequently, this research primarily focuses on exploring the therapeutic potential of Docetaxel, Cisplatin and Apatinib Mesylate tablets in patients with advanced ovarian cancer.

Upon an analysis of the tumor marker expression, the study discerned a decline in serum tumor markers post-chemotherapy, relative to their initial levels. Notably, this decline was more pronounced in study group than in control group. As underscored in existing literature [17], tumor markers serve as pivotal diagnostic criteria, with their fluctuations indicating tumor onset and progression. CA125 and CA199 consistently manifested high expression in ovarian malignancies, while both CEA and CA153 were discernibly elevated across a broader spectrum of malignant tumors, aiding in their diagnosis [18]. Reports highlight the profound diagnostic and therapeutic significance of these four markers in advanced ovarian cancer, underscoring the efficacy of the combined treatment elucidated in this study in managing patient conditions.

Evaluating the comparative levels of serum VEGF and MMP-2 between the groups, a more substantial reduction was noted in study group than in control group. Both groups exhibited significant reductions from their baseline measurements. It has been pointed out that tumor growth and metastasis are contingent upon the angiogenic pathway, with VEGF – a salient growth factor – often observed in heightened levels due to its role in ovarian cancer cell angiogenesis and metastasis [19]. Furthermore, as detailed in other studies, MMP-9 facilitates capillary lumen construction by degrading the vascular basement membrane and collaboratively influencing metastatic VEGF and endothelial cell division, culminating in extensive neovascularization at tumor sites [20]. Given their functions in vascular formation around and within tumor cells, this study's findings infer that

the combined treatment substantially curtails both vascularization and cancer cell proliferation.

Recent insights further reveal that Apatinib mesylate, a targeted anti-angiogenic agent, hinders neovascularization and augments tumor cell responsiveness to platinum-based drugs by inhibiting VEGF and VEGFR-2 binding and curbing tyrosine kinase synthesis [21]. This corroborates this study's observation that the combined approach with Apatinib potentiates angiogenesis inhibition, mitigating disease progression. The therapeutic efficacy assessment showed enhanced outcomes in ascites management, overall treatment effectiveness, reduced adverse reactions and improved quality of life and self-sufficiency in study group compared to the control. Notably, Docetaxel spares normal tissue cells in G0-stage ovarian cancer and, upon evaluation, synergizes well with cisplatin [22]. Alone or in tandem, Apatinib mesylate has showcased efficacy in extending both overall and progression-free survival in advanced ovarian cancer patients post-chemotherapy or following other targeted interventions [23]. The heightened therapeutic outcomes and clinical relevance of this combined modality are in line with literature assertions.

Nonetheless, there is a dearth of prognostic literature regarding this dual chemotherapeutic paradigm with Apatinib. Our study's prognosis reveals that the three-year survival rate of control group markedly lags behind that of study group. In summary, both Docetaxel and cisplatin injections demonstrate commendable clinical efficacy in addressing advanced ovarian cancer. Their combined use with Apatinib Mesylate tablets further augments their effectiveness, with superior safety profiles, making them a promising clinical intervention.

Limitations of this study

Nevertheless, this research is not without its limitations. Ascites, a hallmark of advanced ovarian cancer, bear significant prognostic implications. Understanding and pinpointing these mechanisms is paramount to precisely targeting and eliminating ascites, thereby potentially extending patients' survival durations. This gap underscores a pivotal direction for subsequent investigations.

CONCLUSION

The findings of this study indicate that the drug combination potentially optimizes overall outcomes and prognosis for ovarian cancer patients, predominantly by diminishing angiogenesis and the associated inflammatory cascade in cancer cells. The aim is to refine and optimize treatment regimens for advanced ovarian cancer patients, ensuring not just extended survival but also improved quality of life by alleviating associated discomforts was achieved. Studies to ascertain the specific mechanisms underlying ascites reduction and therapeutic intricacies need to be carried out.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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