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Research

Assessment of the efficacy and safety of anlotinib for the treatment of recurrent epithelial ovarian cancer

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Abstract

Objective The current research aims to evaluate the efficacy and safety of anlotinib, an orally administered small-molecular tyrosine kinase inhibitor (TKI), in the treatment of recurrent epithelial ovarian cancer (EOC).

Methods Patients with recurrent EOC subjected to treatment with anlotinib in Fourth Hospital of Hebei Medical University from 2020 to 2022 were included. The evaluation involved a thorough review of medical records, focusing on parameters such as the objective response rate (ORR), disease control rate (DCR), survival outcomes, and safety profile.

Results This study recorded 51 patients, with 26 patients undergoing anlotinib monotherapy. The median progression-free survival (PFS) was 4.0 months, whereas the median overall survival (OS) was not reached. Seven cases underwent a combined treatment of anlotinib with chemotherapy. Among them, two patients achieved partial response (PR), two were categorized as stable disease (SD), and three were identified as having progressive disease (PD). The ORR and DCR were 28.5% (2/7) and 57.1% (4/7), respectively. Additionally, 18 cases received anlotinib maintenance therapy, and the median PFS and the median OS were 7.0 months and 25.5 months, respectively. The most prevalent adverse effects included fatigue (38.6%), hypertension (27.3%), nausea and vomiting (25.0%) and hand-foot syndrome (25.0%).

Conclusion Anlotinib demonstrated mild efficacy in the treatment of recurrent EOC, whether employed as monotherapy, chemotherapy-combined therapy, or maintenance therapy. The safety profile was proven manageable and well-tolerated, suggesting that anlotinib may emerge as a viable and novel treatment option for recurrent EOC.

Keywords Anlotinib · Recurrent epithelial ovarian cancer · ORR · DCR · Survival

1 Introduction

Ovarian cancer (OC) ranks among the most prevalent gynecologic malignancies. In accordance with the comprehensive global cancer statistics of 2020, the incidence of this disease is significant, with 313,959 newly diagnosed cases and 207,252 reported fatalities annually on a global scale. This underscores the considerable impact of OC on public health, necessitating a comprehensive understanding and proactive approach to addressing its challenges [1, 2]. Epithelial ovarian cancer (EOC) is the most common subtype which represents about 85–90% cases. Due to the lack of symptoms, most of the patients were diagnosed in advanced stage. Surgery and chemotherapy are the standard treatment of EOC [3]. Despite advancements in surgery and chemotherapy, recurrence is a prevalent outcome following the initial treatment.

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Recent years have witnessed numerous clinical studies exploring the potential use of targeted therapeutic agents and immunotherapy to enhance the survival outcomes of EOC. However, prognosis remains dismal for recurring cases [4–7]. Therefore, there is a pressing need to explore more effective therapeutic strategies for recurrent EOC.

Typically, recurrent patients are categorized into two groups based on the treatment-free interval (TFI): platinum-sensitive cases (relapse greater than or equal to six months since last platinum agent) or platinum-resistant cases (relapse less than six months since last platinum agent). In platinum-sensitive cases, chemotherapy incorporating platinum continues to be the preferred approach, whereas platinum-free chemotherapy is selected for platinum-resistant cases. Despite these strategies, a majority of patients ultimately experience recurrence and progression, largely attributed to platinum resistance, a prominent factor driving the advancement of OC. Furthermore, the available repertoire of chemotherapeutics remains limited.

Anlotinib, a novel tyrosine kinase inhibitor, demonstrates its selectivity by specifically targeting a multitude of receptor kinases that play pivotal roles in various aspects of tumor development, including proliferation, vasculature formation, and the intricacies of the tumor microenvironment. Existing studies have highlighted its anti-tumor effects in various cancers [8–10]. However, limited research has been dedicated to its application in the treatment of recurrent EOC. This study aims to present findings on the efficacy and safety of anlotinib as a therapeutic approach for patients with recurrent EOC.

2 Materials and methods

2.1 Patients

The approval of this research was granted by the ethics committee of the Fourth Hospital of Hebei Medical University. In terms of research types, this study was a retrospective observational study. Inclusion criteria encompassed all patients treated with anlotinib from March 2020 to April 2022, excluding those receiving treatment for less than two cycles. Enrolled patients were diagnosed with recurrent EOC, classified as either platinum-resistant or platinum-sensitive. Comprehensive clinical data and follow-up data were acquired for all patients, including age, Eastern Cooperative Oncology Group (ECOG) performance status before treatment, histological type, FIGO stage, and prior therapy preceding the use of anlotinib.

2.2 Therapeutic methods

Anlotinib hydrochloride is recommended at a dosage of 12 mg per dose, administered once daily orally before breakfast. Patients are advised to maintain continuous medication for two weeks, followed by a one-week medication pause, constituting a complete course of treatment lasting 21 days. Treatment is continued until disease progression or the occurrence of intolerable adverse reactions. In the event of a missed dose within the medication period and confirmation that the time until the next scheduled dose is less than 12 h, no further supplementation will be provided.

2.3 Observational outcomes

The clinical efficacy was determined utilizing Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, employing indicators such as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was calculated as: $ORR = (CR + PR)/(\text{total cases}) \times 100\%$, and disease control rate $(DCR) = (CR + PR + SD)/(\text{total cases}) \times 100\%$.

Adverse reactions were recorded and assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 during the follow-up period. Progression-free survival (PFS) and overall survival (OS) were documented through follow-up visits. PFS was defined as the time from initiation of anlotinib until disease progression or death, while OS referred to the time from initiation of anlotinib administration to death for any cause.

2.4 Statistical analysis

Statistical analysis was performed utilizing Statistical Product and Service Solutions (SPSS) 25.0 (IBM, Armonk, NY, USA). Measurement data were presented as medians and ranges. Enumeration data were presented as percentages (%) and assessed using the chi-square test for comparisons between the two groups. The Kaplan–Meier method was utilized to generate the survival curve. $P < 0.05$ was deemed as a statistically significant value.

3 Results

3.1 Patients' baseline features

The research comprised a cohort of 51 patients, the median age was 58 (IQR 53–65) years. The pathological and clinical characteristics of the patients are detailed in Table 1. Before the initiation of anlotinib, the cohort had undergone a median

Table 1 Baseline characteristics in 51 patients

Characteristic of patients	N (%)
Age, years	
Median age (range)	58(34–74)
≤ 58	27
>58	24
Histology	
Serous	48(94.1)
Mucinous	1(1.9)
Clear cell	1(1.9)
Mixed serous and mucinous	1(1.9)
Figo stage	
I–II	10(19.6)
III–IV	41(84.3)
BRCA status	
BRCAm	2(3.9)
BRCAwt	11(21.5)
Unknown	38(74.5)
Recurrence type	
Platinum-sensitive	9(17.6)
Platinum-resistant	42(82.4)
Previous lines of chemotherapy	
1	24(47.0)
2	19(37.2)
3	7(13.7)
4	1(1.9)
Prior bevacizumab therapy	
Yes	18(35.2)
No	33(64.7)
Prior PARP inhibitor	
yes	7(13.7)
NO	44(8.2)
Therapeutic schedule	
Anlotinib monotherapy	26(51.0)
Anlotinib plus chemotherapy	7(13.7)
Maintenance therapy	18(35.3)

BRCAm, breast cancer susceptibility gene mutation; BRCAwt, breast cancer susceptibility gene wild type

Fig. 1 Efficacy of anlotinib for the treatment of recurrent EOC. **A** Efficacy of Anlotinib monotherapy. **B** Efficacy of Anlotinib combined with chemotherapy. **C**, **D** Kaplan-Meier curves of PFS and OS in Anlotinib monotherapy group and Anlotinib combined with chemotherapy group. Comparison between monotherapy and combination therapy was also shown. **E**, **F** Kaplan-Meier curves of PFS and OS in group of Arotinib for maintenance therapy. **G** Kaplan-Meier curves of PFS in subgroup analysis. **H** Kaplan-Meier curves of OS in subgroup analysis. PFS, progression-free survival; OS, Overall survival; Bev, bevacizumab

of 2 prior treatment regimens, with the range extending from 1 to 4 previous regimens. The study also investigated the status of recurrence, the utilization of bevacizumab, and the use of PARP inhibitors. As of October 2023, all patients were followed up for a period ranging from 4 to 40 months. Among them, 26 platinum resistant patients received anlotinib monotherapy, 7 underwent combined treatment with anlotinib and chemotherapy, and 18 received anlotinib as maintenance therapy.

3.2 Efficacy

3.2.1 Anlotinib monotherapy

Among 26 patients of anlotinib monotherapy, there were 0 cases of CR, 4 cases of PR, 16 cases of SD and 6 cases of PD. ORR and DCR were 15.4% (4/26) and 76.9% (20/26) respectively (Fig. 1A).The median PFS was 4.0 months and the median OS was not reached (Fig. 1C, D).

A subgroup analysis was performed to assess the effect of previous bevacizumab use (Fig. 1G, H). The results indicated no notable variation in PFS between the two subgroups ($P=0.54$). However, patients without prior bevacizumab therapy demonstrated superior OS outcomes ($P<0.0001$).

3.2.2 Anlotinib combined with chemotherapy

In the cohort of 7 patients who received anlotinib combined with chemotherapy, all cases were characterized as platinum-resistant. Among them, two patients achieved PR, two were classified as SD, and the remaining was identified as having PD. The ORR and DCR were 28.5% (2/7) and 57.1% (4/7), respectively (Fig. 1B). The median PFS was 4.0 months and the median OS was 31.5 months (Fig. 1C, D). No significant differences in PFS ($P=0.28$) and OS ($P=0.55$) were observed compared to the monotherapy group receiving anlotinib.

3.2.3 Anlotinib for maintenance therapy

Out of the total, 18 patients underwent maintenance therapy with anlotinib. Within this group, nine cases were classified as platinum-resistant, and the remaining nine as platinum-sensitive. Subsequent follow-up evaluations were performed for these patients, with the duration of medication ranging from 4 to 29 months. The median PFS and median OS were determined to be 7.0 months and 25.5 months, respectively. Survival curves were generated utilizing the Kaplan–Meier method (Fig. 1E, F).

3.3 Complications

A total of 44 patients including monotherapy group and maintenance treatment group were included in the investigation of complications (Table 2). The observed adverse reactions primarily encompassed fatigue, hypertension, hand and foot syndrome, nausea and vomiting, thrombocytopenia, transaminase elevation, proteinuria, pain, and leucopenia, mostly in grade I–II. Notably, grade III adverse reactions primarily encompassed hypertension in 2 cases (4.5%), hand and foot syndrome in 1 case, pain in 1 case (2.3%), and leukopenia in 1 case (2.3%). In one case (2.3%), severe thrombocytopenia led to treatment interruption after five cycles. Importantly, no grade IV adverse reactions or deaths associated with adverse reactions were noted.

4 Discussion

EOC stands as the second most prevalent cause of death among all gynecological cancers [1]. The primary treatment approach involves surgical cytoreduction to achieve R0 status, followed by adjuvant chemotherapy [11]. Despite this initial intervention, the majority of women with advanced EOC encounter multiple episodes of recurrent disease,

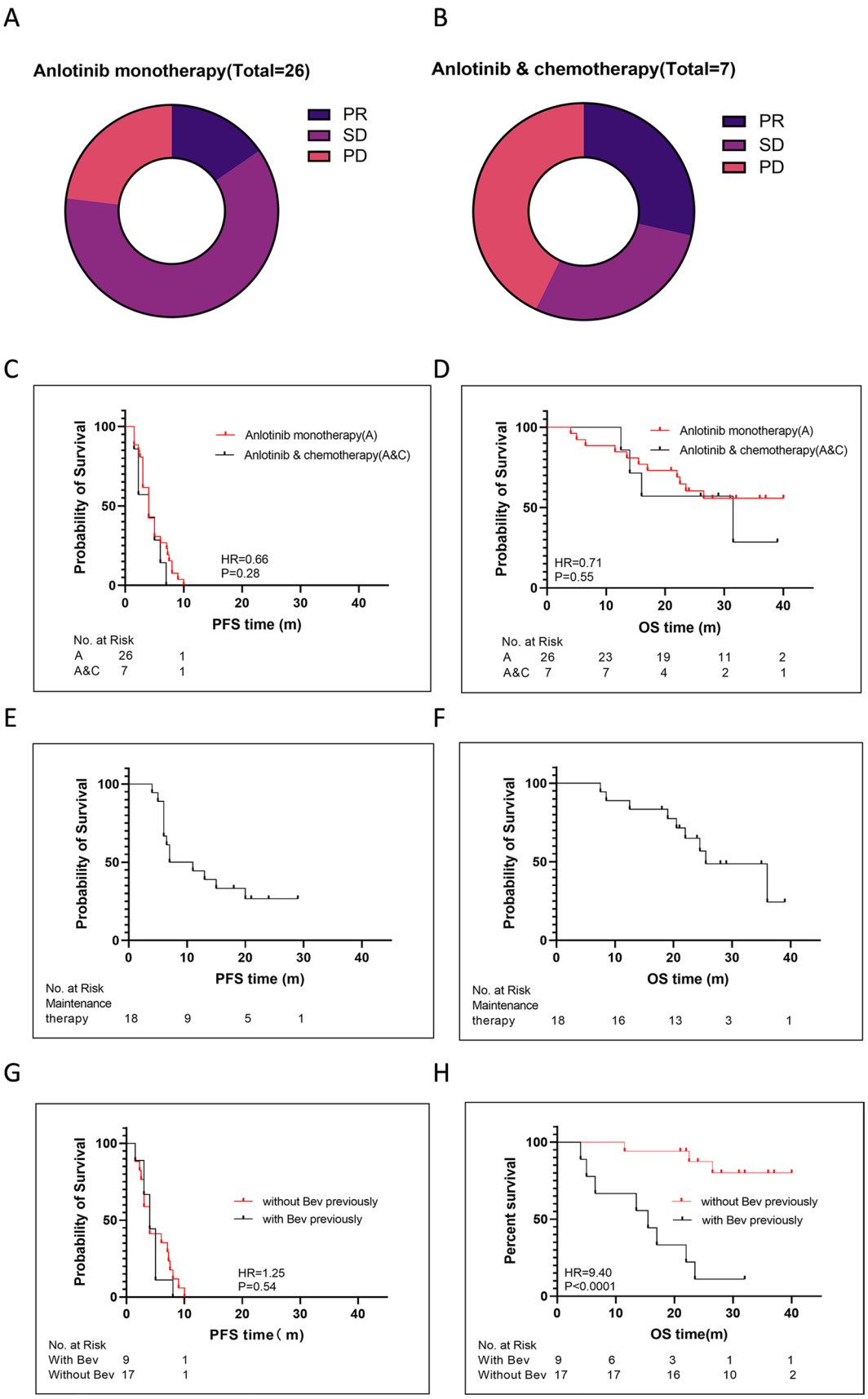
A
Anlotinib monotherapy(Total=26)
PR
SD
PD
B
Anlotinib & chemotherapy(Total=7)
PR
SD
PD
C
Probability of Survival
Anlotinib monotherapy(A)
Anlotinib & chemotherapy(A&C)
HR=0.66
P=0.28
PFS time (m)
No. at Risk
A 26 1
A&C 7 1
D
Probability of Survival
Anlotinib monotherapy(A)
Anlotinib & chemotherapy(A&C)
HR=0.71
P=0.55
OS time (m)
No. at Risk
A 26 23 19 11 2
A&C 7 7 4 2 1
E
Probability of Survival
PFS time (m)
No. at Risk
Maintenance therapy 18 9 5 1
F
Probability of Survival
OS time (m)
No. at Risk
Maintenance therapy 18 16 13 3 1
G
Probability of Survival
without Bev previously
with Bev previously
HR=1.25
P=0.54
PFS time (m)
No. at Risk
With Bev 9 1
Without Bev 17 1
H
Percent survival
without Bev previously
with Bev previously
HR=9.40
P<0.0001
OS time(m)
No. at Risk
With Bev 9 6 3 1 1
Without Bev 17 17 16 10 2

Table 2 Main adverse reactions of the studied patients (n = 44)

	Grade I-II N (%)	Grade III N (%)	Grade IV N (%)	Total N (%)
Fatigue	17(38.6)	0	0	17(38.6)
Hypertension	10(22.7)	2(4.5)	0	12(27.3)
Hand and foot syndrome	8(18.2)	1(2.3)	0	9(20.5)
Nausea and vomiting	11(25.0)	0	0	11(25.0)
Thrombocytopenia	5(11.4)	1(2.3)	0	6(13.6)
Transaminase elevation	6(13.6)	0	0	6(13.6)
Proteinuria	4(9.1)	0	0	4(9.1)
Pain	6(13.6)	1(2.3)	0	7(15.9)
Diarrhea	3(6.8)	0	0	3(6.8)
Leukopenia	6(13.6)	1(2.3)	0	7(15.9)
Anemia	3(6.8)	0	0	3(6.8)
Skin diseases	4(9.1)	0	0	4(9.1)

each characterized by progressively shorter disease-free intervals. The treatment option for recurrent disease is contingent upon the platinum-free interval. Typically, platinum-based chemotherapy is considered appropriate for patients experiencing platinum-sensitive recurrence. Conversely, for those with platinum-resistant recurrence, non-platinum-based agents are favored. Examples include docetaxel, liposomal doxorubicin, oral etoposide, and gemcitabine, among others. Literature reports suggest that the RR for these agents falls within the 10–15% range, and the OS for platinum-resistant cases hovers around 12 months. Despite various therapeutic options, the prognosis of recurrent patients remains unsatisfactory [12].

In recent years, there has been a growing emphasis on angiogenesis [13, 14]. Anlotinib, functioning as an anti-angiogenic agent, exhibits a broad spectrum of inhibitory effects targeting key receptors, including fibroblast growth factor receptor 1–4 (FGFR1-4), vascular endothelial growth factor receptors 2/3(VEGFR2/3), and platelet-derived growth factor receptors a/b (PDGFR a/b) [15]. A previous study has demonstrated that anlotinib possesses the capability to impede the proliferation of OC cells. This inhibition is achieved by inducing G2/M phase arrest and promoting apoptosis, both in vivo and in vitro [16]. Within this study, 26 patients experiencing platinum resistance were administered anlotinib monotherapy. The ORR stood at 15.4%, the DCR reached 76.9%, and the median PFS was recorded at 4.0 months. This outcome is particularly notable when compared to other second-line or posterior-line therapies. Significantly, for patients with platinum resistance, anlotinib monotherapy exhibited the potential to extend the platinum-free interval and enhance the disease response rate to platinum. Therefore, anlotinib monotherapy may be an alternative agent for platinum-resistance cases. Notably, a subgroup analysis investigating prior bevacizumab use was conducted, revealing no significant variation in PFS between the two subgroups. However, an intriguing observation was made: OS was notably superior in patients without prior bevacizumab therapy. While the precise mechanism remains elusive, resistance to anti-angiogenic therapy, a common challenge in cancer treatment, might contribute to this outcome according to existing literature [17]. It is imperative, however, to validate these findings through large-scale prospective studies.

Research has demonstrated that the combination of cytotoxic drugs with bevacizumab, a commonly employed anti-angiogenic agent in OC, leads to heightened tumor responses [18–20]. In osteosarcoma, a comprehensive exploration employed a varied array of in vitro and in vivo models representative of human osteosarcoma. This comprehensive approach was applied to assess the multifaceted effectiveness of anlotinib, encompassing its anti-proliferative, anti-angiogenic, and anti-metastasis properties. The findings obtained from these investigations demonstrated that anlotinib not only exhibited a capacity to impede tumor growth but also significantly increased the chemo-sensitivity of osteosarcoma [21]. In this study, 7 patients received anlotinib combined with chemotherapy. As a result, the ORR was 28.5% (2/7) and the DCR were 57.1% (4/7). Whether anlotinib has a sensitization effect in chemotherapy for ovarian cancer, and what was the mechanism is not clear. Further research is needed.

Maintenance therapy plays a crucial role in the comprehensive treatment of OC. Despite various maintenance therapies explored for recurrent EOC, the FDA has granted approval solely to PARP inhibitors, namely niraparib, rucaparib, and olaparib. Bevacizumab, although investigated in trials such as GOG 218 and NCT02022917, has yielded inconclusive evidence of benefit in maintenance. Similarly, in ICON7, there was no discernible evidence of benefit in PFS or OS in

first-line maintenance, except for a subset of high-risk patients [22, 23]. Very few patients in the high-risk subset in ICON7 received bevacizumab in recurrent settings, and hence its use in maintenance in recurrent EOC is not known [24].

In 2022, the FDA restricted the second-line maintenance indication for niraparib exclusively to patients with gBRCAm. Subsequently, in 2023, the FDA withdrew indications for olaparib for the entire population based on the potentially serious risks leading to increased mortalityin patients without BRCA mutations. This limitation implies that patients with recurrent EOC lacking gBRCAm face a scarcity of options for maintenance therapy. Within this study, 18 patients with recurrent EOC received maintenance therapy with anlotinib following either CR or PR. The outcomes revealed a median PFS of 7.0 months and a median OS of 25.5 months. Notably, the observations of this study underscored the manageable and tolerable safety profile of anlotinib throughout the treatment, with the longest course of medication extending to 29 months. However, to substantiate these findings and establish broader applicability, additional prospective studies are imperative to validate the effectiveness and safety of anlotinib as a maintenance therapy option for recurrent EOC.

It is noteworthy that 94% of patients in this study presented with a pathological type of serous cancer. Further investigation is warranted to ascertain whether anlotinib demonstrates comparable efficacy in addressing other subtypes of ovarian cancer.

5 Limitations

Potential limitations exist within this study. Primarily, it is retrospective in nature, lacking a corresponding control group for comparison. Secondly, the study sample size is relatively small, necessitating future investigations with larger cohorts. Nevertheless, the findings of this study offer genuine and trustworthy insights through comprehensive follow-up and analysis, thereby providing a foundation for prospective research endeavors.

6 Conclusion

This study reports on the treatment outcomes of anlotinib in patients with recurrent EOC. The findings reveal that anlotinib demonstrates promise in various treatment modalities, including monotherapy, chemotherapy-combined therapy, or maintenance therapy. With its encouraging efficacy and tolerable safety profile, anlotinib may emerge as a potential therapeutic option for clinicians aiming to provide benefits to patients with recurrent EOC.

Author contributions Zhengmao Zhang designed the study and performed the experiments. Aili Zhai, Kaiyun Qin, Xin Zhou and Yu Yu collected the data. Ying He analyzed the data and prepared the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability The data set supporting the results of this article are included within the article.

Code availability None.

Declarations

Ethics approval and consent to participate This study was reviewed and approved by the ethics committee of the Fourth Hospital of Hebei Medical University (2020166). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its later amendments. The patients provided their written informed consent.

Competing interests These authors declare that they have no competing interest in this work.

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