

The Associations and Causal Relationships of Ovarian Cancer - Construction of a Prediction Model

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Purpose: To explore the risk and protective factors for developing ovarian cancer and construct a risk prediction model.

Methods: Information related to patients diagnosed with ovarian cancer on the electronic medical record data platform of three tertiary hospitals in Guangdong Province from May 2018 to September 2023 was collected as the case group. Patients with non-ovarian cancer who attended the clinic during the same period were included in the control group. Logistic regression analysis was used to screen the independent variables and explore the factors associated with the development of ovarian cancer. An ovarian cancer risk prediction model was constructed using a decision tree C4.5 algorithm. The ROC and calibration curves were plotted, and the model was validated.

Results: Logistic regression analysis identified independent risk and protective factors for ovarian cancer. The sample size was divided into training and test sets in a ratio of 7:3 for model construction and validation. The AUC of the training and test sets of the decision tree model were 0.961 (95% CI:0.944–0.978) and 0.902 (95% CI:0.840–0.964), respectively, and the optimal cut-off values and their coordinates were 0.532 (0.091, 0.957), and 0.474 (0.159, 0.842) respectively. The accuracies of the training and test sets were 93.3% and 84.2%, respectively, and their sensitivities were 95.7% and 84.2%, respectively.

Conclusion: The constructed ovarian cancer risk prediction model has good predictive ability, which is conducive to improving the efficiency of early warning of ovarian cancer in high-risk groups.

Keywords: ovarian cancer, incidence factors, decision tree model, risk prediction

Introduction

Ovarian cancer (OC) is a common malignant tumor of the female reproductive system, ranking 3rd among gynecological malignancies.¹ 90% of ovarian cancers are of an epithelial cell type and comprise multiple histologic types, with various specific molecular changes, clinical behaviors, and treatment outcomes. The remaining 10% are non-epithelial ovarian cancers, which include mainly germ cell tumors, sex cord-stromal tumors, and some sporadic tumors such as small cell carcinomas. Germ cell tumors are the most common ovarian neoplasms in women up to 30 years of age, and most of the patients are diagnosed with early-stage disease (60–70%).² There are approximately 200,000 new cases of ovarian cancer globally every year, with a mortality rate as high as 125,000 cases/year. Interestingly, the prevalence of asymptomatic ovarian masses has risen alongside the widespread use of prenatal ultrasonography. Approximately 5% of ovarian tumors complicating pregnancies, are malignant, contributing to the global increase in new cases of ovarian cancer. Currently, surgical intervention is indicated for an ovarian mass > 6 cm in diameter or when symptomatic.³ Incidence trends differ

between countries and regions;⁴ the incidence rate of ovarian cancer in developed countries is decreasing by 2.8% annually on average.⁵ In China, however, the incidence of ovarian cancer is increasing, and the number of new cases and deaths from ovarian cancer is expected to more than triple between 2019 and 2049.⁶ Survey data from Shanghai, China, show that the incidence of ovarian cancer is increasing at a rate of 1.8% annually, and the annual mortality rate is expected to increase by 0.6%.⁷ The onset of ovarian cancer is insidious, with atypical initial symptoms, making detection by patients or diagnosis by doctors difficult. Over 50% of patients are diagnosed at advanced stages,⁸ often miss the best time for intervention,^{9,10} and the 3-year survival rate is lower than 30%.¹¹ The prevention and treatment of ovarian cancer have become major social and public health issues.

There are two types of epithelial ovarian cancer. Type I epithelial ovarian cancers are relatively indolent and genetically stable tumors that typically arise from recognizable precursor lesions, such as endometriosis or borderline tumors with low malignant potential. In contrast, type II epithelial ovarian cancers are thought to be biologically aggressive tumors from the outset, with a propensity for metastasis from small-volume primary lesions. High-grade serous carcinoma, the most common type of epithelial ovarian cancer, accounting for approximately 75% of epithelial ovarian cancers, develops according to the type II pathway and present p53 and BRCA mutations.¹² The development of ovarian cancer may be associated with hormone use, disease, reproduction, lifestyle, family history, and genetic factors.¹³ Effective screening tools are lacking because the cause of the disease remains unclear. For people at a high risk of ovarian cancer, multimodal screening (blood test for CA 125 combined with transvaginal ultrasound) has been shown to detect ovarian cancer earlier. However, it has not reduced the overall mortality rate of ovarian cancer and can lead to overmedication and complications.¹⁴ Currently, CA 125 and HE4 are the only approved biomarkers for epithelial ovarian cancer. However, they are inadequate for early detection.

Multivariate index assays have been developed to mitigate the limitations of single serum biomarkers, particularly during the pre-surgical evaluation of adnexal masses. The Risk of malignancy algorithm (ROMA) integrates menopausal status, CA 125, and HE4 concentrations to diagnose women with pelvic masses. miRNAs (microRNAs) may have remarkable potential in various aspects of epithelial ovarian cancer prediction. However, further research is warranted regarding its characterization as a biomarker. In particular, before miRNAs can be utilized as reliable biomarkers for clinical use, the steps involved in processing samples must be standardized, and the platforms for detecting miRNA in tumors and blood must be refined.¹⁵ For the general population, it is even more challenging to perform multimodal screening because of medical, economic, social, and cultural factors and limited clinical promotion. Currently, scientific management, early warning of high-risk groups, and promotion of healthy lifestyle choices are among the best ways to prevent ovarian cancer.

Therefore, a deeper understanding of ovarian cancer and the search for possible risk and protective factors for developing it is essential for its prevention. Currently, in China, there is a lack of accurate prediction models for the risk of developing ovarian cancer based on individuals' easily accessible information. In this study, we explored new risks and evaluated known protective factors for ovarian cancer incidence through retrospective analysis. We constructed a relevant prediction model based on a machine-learning approach, providing a reference for early warning of this disease and clinical decision-making.

Materials and Methods

Objectives of the Study

This was a retrospective study, and data were obtained from the electronic medical record data platforms of three tertiary hospitals in Guangzhou City. Data were collected from 67 hospitalized ovarian cancer patients on these platforms from May 2018 to September 2023, forming the ovarian cancer case group and 567 patients in the non-ovarian cancer control group. The inclusion criteria for the case group were: 1) age ≥ 18 years; 2) hospitalized surgical patients diagnosed with ovarian cancer by histopathology, without preoperative chemotherapy, radiation therapy, and immunotherapy; and 3) complete case information. The exclusion criteria were concurrent malignant tumors of other organs or tissues and other serious systemic diseases (abnormalities of liver and kidney functions, blood diseases, infections, and inflammation). The inclusion criteria for the control group were members of the general population who

had undergone physical examinations or consultations during the same period. The research department collected the data used in this study; it has standardized protocols and principles to follow to prevent the leakage of patient personal information. The study complied with medical ethics standards and was reviewed by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (review approval number: ZE2023-291). When the patient agreed to be hospitalized, the doctor signed an admission notice after informing them of their condition. There is an entry in the patient's bill of rights, which states that the patient's disease-related information will be entered into an electronic data information platform. When medical research requires it, relevant data may be retrieved for statistical analysis while ensuring patient confidentiality. Owing to the retrospective nature of this study, an ethical review was conducted based on informed consent.

Research Methodology

In accordance with previous publications and other related studies, each patient's dataset included general information (age, education, height, weight, BMI, occupation, blood type, marital status, ethnicity, family history, history of previous illnesses, and medication use), menstrual status (age at menarche, age at menopause, regular menstruation in the past, dysmenorrhea, and others), pregnancy (number of pregnancies and births, age at first pregnancy, and age at first childbirth), and lifestyle (contraceptive methods, history of smoking, alcohol consumption, coffee consumption, bowel movements, and experience of adverse life events), excluding more than 30% of the missing important medical history data.

Quality Control

Study participants were strictly selected according to the inclusion and exclusion criteria to reduce selection bias. Two experienced researchers extracted and output data from the medical history records of the hospital's HIS medical record information management system. We further supplemented the partial data for each medical record using statistical software to ensure data integrity. Subsequently, we entered the data using the Epidata tool to double-check, and correct logic errors. Ensure the reliability of the sample in the end.

Statistical Methods

SPSS 23.0 and R 4.2.3 statistical packages were used for statistical analysis. Logistic regression analysis was used to screen the independent variables and statistically analyze the relevant factors, with $P < 0.05$ considered statistically significant. Seventy percent of the cases in the dataset were randomly selected as the training set for modeling, and the remaining 30% were used as the test set. The ovarian cancer risk prediction model was constructed based on the decision tree C4.5 algorithm, and receiver operating characteristic (ROC) and calibration curves were plotted for both the training and test sets to assess the differentiation and calibration of the model.

Results

Sample Size

The sample size was calculated using the PASS 15.0 software. The sample size was calculated by selecting the allowable error and overall standard deviation based on the data from previous studies and considering 20% of invalid questionnaires.

Logistic Regression Analysis of Risk Factors for Ovarian Cancer

According to the logistic regression analysis of the influencing factors that may be associated with ovarian cancer in the reported literature at home and abroad, a family history of oncologic disease, being unmarried, having uterine fibroids, the number of abortions, and having received hormone replacement therapy (HRT) were independent risk factors for developing ovarian cancer; occupation as a farmer, and irregular menstruation were protective factors for ovarian cancer (Table 1).

Table 1 Ovarian Cancer Risk Factors - Logistic Regression Analysis

variable	Beta	se	t	P
Career-Farmer	-1.938	0.725	-2.674	0.008
Family history-oncological disease	1.751	0.655	2.672	0.008
Marital status-unmarried	3.513	1.348	2.606	0.009
Previous irregular menstruation	-1.544	0.666	-2.318	0.020
Uterine fibroids	0.966	0.437	2.214	0.027
Induced abortion number	2.814	1.396	2.015	0.044
Hormone replacement therapy	1.465	0.748	1.959	0.050

Construction of Decision Tree Model

The samples were divided into training and test sets in a ratio of 7:3. Because of the imbalance between the case and control groups (67 vs 567), the samples were re-divided in the training set using an under-sampling method at a case-to-control ratio of 1:2 to train the model and entire training set. Fifteen variables were screened using logistic regression and used to construct a decision tree model using the C4.5 algorithm. The relevant factors of the input node include occupation, blood type, number of cesarean sections, number of induced abortions, marital status, family history, age at menarche, menopause history, cumulative menstrual years, regularity of menstruation, number of natural abortions, contraceptive methods, history of uterine fibroids, and whether hormone replacement therapy had been used. The factors included in the model were menopausal status, presence of uterine fibroids, use of hormone replacement therapy, career, number of pregnancies, family history, number of induced abortions, and blood group. The results showed that menopause was the root node of the decision tree, and several sub-variables, such as uterine fibroids, hormone replacement therapy, occupation, and pregnancy frequency, subsequently entered the decision tree as sub-nodes. (Figure 1)

Validation of the Decision Tree Prediction Model

ROC Curve

The AUC of the training and test sets of the decision tree model were 0.961 (95% CI:0.944–0.978) and 0.902 (95% CI:0.840–0.964), respectively, and the optimal truncation values and their coordinates were 0.532 (0.091, 0.957) and 0.474 (0.159, 0.842), respectively. The accuracies of the training and test sets were 93.3% and 84.2%, respectively, and

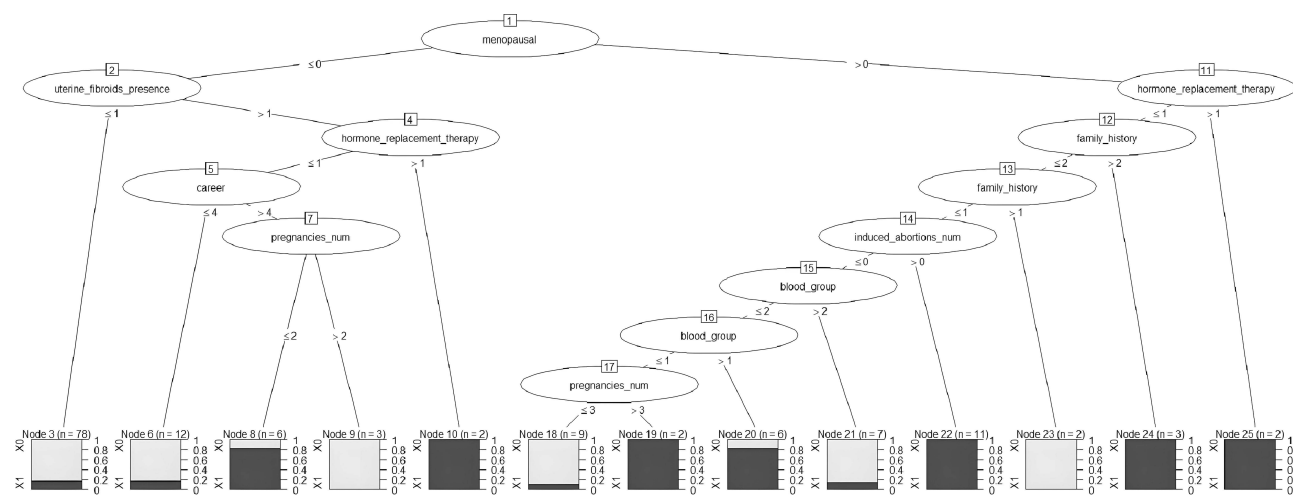


Figure 1 Decision tree model of risk factors for ovarian cancer.

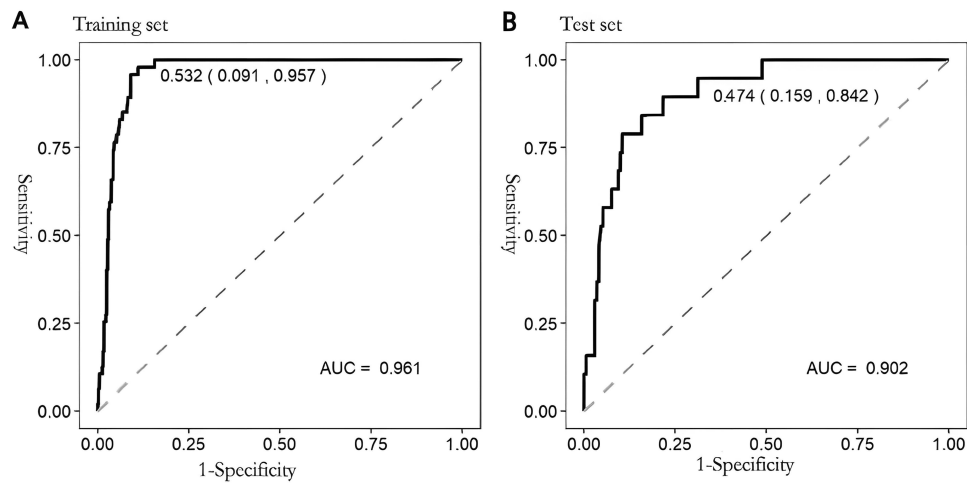


Figure 2 ROC curves ((A) Training set; (B) Test set).

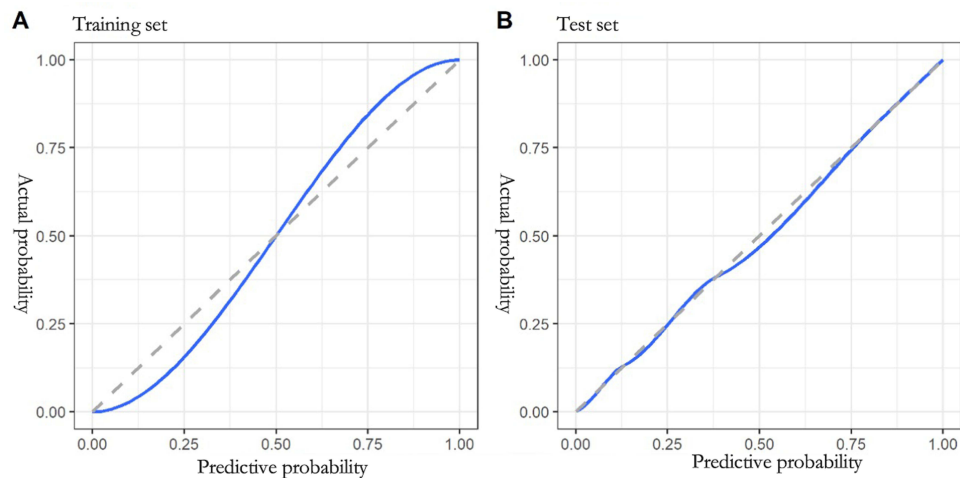


Figure 3 Calibration curves ((A) Training set; (B) Test set).

the sensitivities were 95.7% and 84.2%, respectively, suggesting that the model predicted the risk of ovarian cancer with reasonable discrimination (Figure 2).

Calibration Curves

The calibration curve graphs show that the calibration curves of the training and test sets fit well and deviate less from the ideal curve, indicating that the calibration of the model constructed in this study was good (Figure 3).

Discussion

Ovarian cancer risk factors are among the most challenging issues for researchers and gynecologists. In addition to well-known genetic factors,¹⁶ gynecologic and lifestyle-related risk factors have also been identified.¹⁷ In the past decade, cost-effective strategies for early detection and prevention of OC in the general population have been investigated. Public health strategies for OC prevention and early treatment are paramount to improving disease outcomes.¹⁸ However, many patients in general populations are not diagnosed early due to ineffective screening tools and treatment programs. Prophylaxis is effective at reducing OC incidence and mortality.

Furthermore, the literature suggests a clear economic benefit of prophylactic measures within high-risk groups. The cost of treatment per patient with OC remains the highest among all cancer types. For example, the average initial cost in

the first year can amount to around USD 80,000, whereas the final year cost may increase to USD 100,000.¹⁹ In this study, we retrospectively analyzed the influencing factors and clinical data of patients with ovarian cancer in three hospitals in Guangzhou City over the past five years. Logistic regression analysis showed that seven variables were significantly associated with ovarian cancer, of which two were protective factors and five were risk factors. A family history of oncological disease, being unmarried, a history of uterine fibroids, having a number of abortions, and a history of hormone replacement therapy were risk factors for developing ovarian cancer. Simultaneously, previous irregular menstruation and occupation as a farmer were protective factors for its occurrence. The construction of risk factor prediction models is expected to improve the efficiency of prevention and early diagnosis and reduce the incidence and mortality of ovarian cancer.²⁰

The present study found that previous irregular menstruation was a protective factor against ovarian cancer, which is inconsistent with the results of a prospective cohort study by Cirillo et al.²¹ Furthermore, Nash et al²² showed that the relationship between menstrual cycle characteristics and the risk of epithelial ovarian cancer varies by race. The difference between the results of this study and those of other studies may be related to the sample included; the control group had a sample of non-ovarian cancer patients who were hospitalized in the gynecology department during the same period, where most of the diagnoses were abnormal uterine bleeding, uterine fibroids, and ovarian cysts. Patients with abnormal uterine bleeding and fibroids tend to have previous clinical manifestations of irregular menstruation. It is also possible that the incidence of ovarian cancer is reduced because patients with menstrual abnormalities receive early outpatient treatment and interventions to improve their lifestyle.

Previous studies¹⁷ found that sedentary work is a risk factor for ovarian cancer. Chang²³ reviewed the relationship between shift work and the risk of ovarian cancer. However, no study has predicted the risk of ovarian cancer for a particular occupation. A study in China²⁴ showed that women working as dry cleaners, telephone operators, porters, painters, and printing factories had an increased risk of ovarian cancer compared to women working in other occupations, which may be because their occupations are often exposed to organic dust and aromatic chemicals. In the present study, occupation as a farmer was found to be a protective factor against ovarian cancer development, which may be related to the living environment and mental and psychological state of farmers living in rural areas, where industrialization is relatively light and environmental conditions are comparatively good. Wenhua's study²⁴ showed that environmental factors affect ovarian cancer risk. In some industrialized and developed areas, the incidence of ovarian cancer is higher, which is possibly associated with increased environmental carcinogens due to industrial pollution. This may also be related to farmers being generally less educated and mentally stressed. Some studies have shown that women with higher education have more work and mental stress and a higher risk of ovarian cancer.

Epidemiological investigations²⁵ have shown that a family history of breast, cervical, and ovarian cancer is a risk factor for ovarian cancer, and this study further confirms this finding. Moreover, other studies^{26,27} have shown that most ovarian cancer patients have mutations in the hereditary breast and ovarian cancer susceptibility genes, BRCA1 and BRCA2. Unmarried women who have never been pregnant have an increased risk of ovarian cancer due to ovarian epithelial stimulation caused by persistent ovulation, which induces malignant transformation of epithelial cells.²⁸ In the present study, a history of uterine fibroids was a risk factor for ovarian cancer. Park et al and Herreros-Villanueva et al^{29,30} showed no association with ovarian cancer in women with a history of uterine fibroids or ovarian cysts, but a history of endometriosis was associated with ovarian cancer (OR 1.78; 95% CI 1.09–2.90). These findings may have been related to the study population. However, the risk of ovarian cancer associated with previous uterine fibroids requires further investigation. This study found that abortion is also a risk factor for ovarian cancer, probably because abortion is prone to gynecological inflammation and infertility, which is in line with the findings of Chi et al³¹ who emphasized that the risk of ovarian cancer in women with more than one abortion is 4.199 times higher than that in women with less than one abortion. Sung et al³² showed that spontaneous abortion was negatively associated with Clear Cell (CLC) ovarian cancer. Still, they indicated that induced abortion is an important protective factor when considering the overall incidence of epithelial ovarian cancer. Reid et al³³ found that hormone replacement therapy increases the risk of ovarian cancer, especially in patients with more than five years of life, in line with the results of the present study and those of Sung et al.³²

Studies on ovarian cancer risk factors have focused on European and North American countries, probably because of the low incidence of ovarian cancer in Asian populations. Most studies have focused on risk factors and model construction for postoperative recurrence and complications, with few risk assessment models.³⁴ For example, Wang et al³⁵ constructed an advanced risk assessment model involving an optimal combination of 9 pathways and one clinical factor. Lee et al³⁶ constructed a multifactorial risk prediction model for epithelial duct ovarian cancer that could facilitate stratification, especially with specificity in women with cancer or a dominant family history of intermediate-risk and high-risk causative variants.

The decision tree model constructed in this study for the risk of developing ovarian cancer incorporated 15 variables: menopausal status, previous uterine fibroids, hormone replacement therapy, occupation, number of pregnancies, family history, number of abortions, and blood type. An AUC of 0.5–0.7 indicates a low diagnostic value, and the model had an AUC of 0.961 in the training set and 0.902 in the testing set, indicating the model's good differentiation ability. The higher sensitivity of the decision tree model reflects the model's capacity to predict the risk of ovarian cancer better and accurately differentiate between high-risk and low-risk groups. This model has high accuracy and good generalizability, which can help clinicians and community workers quickly and accurately identify high-risk groups to perform targeted interventions and health management. Furthermore, it can help patients understand their lifestyles and habits, improve their knowledge of ovarian cancer risk factors, and establish the concepts of prevention and "comprehensive risk intervention" to form better living habits¹⁷ and positive medical behaviors.

Conclusions

In summary, ovarian cancer is detected late and has a poor prognosis. Therefore, there is an urgent need to identify high-risk groups and implement interventions as early as possible. The relevant factors identified in this study and the prediction model constructed based on the decision tree can be used by community service centres for the assessment and health education of the population. The clinical staff can also use them to identify high-risk patients, conduct early interventions, to reduce the morbidity rate caused by poor lifestyles and gynecological disorders, and improve patient prognosis.

This was a retrospective analysis of ovarian cancer cases in the last five years conducted in three hospitals, with an unbalanced sample size due to the varying completeness of clinical data collected from electronic case records in different hospitals. The influencing factors included in the text are based on the domestic and international literature. However, some patients were excluded because of missing data or unavailable risk factors, which may have affected the model's efficacy. The case data in this study were recorded over a significant period, and further prospective studies are required to verify the model's reliability.

In future, we will incorporate studies with sub-levels, multiple hospitals, and larger sample sizes to refine the model or use other models for further research.

Abbreviations

OC, Ovarian cancer; ROMA, Risk of malignancy algorithm; miRNAs, microRNAs; ROC, receiver operating characteristic; HRT, hormone replacement therapy; CLC, Clear Cell.

Data Sharing Statement

The datasets generated and analyzed in the present study are available from the corresponding author Jinguo Zhai upon reasonable request.

Ethics Approval and Consent to Participate

The study complied with medical ethics standards and was reviewed by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (review approval number: ZE2023-291). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Acknowledgments

Yulan Guan and Jinguo Zhao are the co-corresponding authors. The paper has been edited and proofread by Medjaden Inc.

Disclosure

The authors report no conflicts of interest in this work.

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