A XGBoost predictive model of reproductive outcomes in patients following hysteroscopic adhesiolysis

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Research Article

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Abstract

Background

Infertility is the primary clinical symptom and reason for visiting patients with intrauterine adhesions (IUAs). Exploring the factors influencing the prognosis of IUAs and establishing a predictive model for reproductive outcomes after hysteroscopic adhesiolysis (HA) are extremely important for the selection of clinical treatment and prognostic assessment.

Methods

The clinical informations of 369 individuals diagnosed with and treated for IUAs were obtained from the Intrauterine Adhesion Multicenter Prospective Clinical Database (IUADB, NCT05381376) and randomly divided into the training and validation cohorts. A univariate analysis was performed to identify relevant clinical indicators, followed by a least absolute shrinkage and selection operator (LASSO) regression for regularization and SHapley Additive exPlanation (SHAP) for extreme gradient boosting (XGBoost) predictive model visualization. Finally, receiver operating characteristic (ROC) curves were constructed to assess the model’s efficiency.

Results

Univariate analysis and LASSO regression demonstrated that 12 clinical indicators were significantly associated with postoperative reproductive outcomes in IUAs patients. SHAP visualization indicated that postoperative fallopian tube ostia, blood supply, uterine cavity shape and age had the highest significance. The area under the ROC curve (AUC) of the XGBoost model in the training and validation cohorts was 0.987 (95% CI 0.9787–0.996) and 0.9851 (95% CI 0.9668-1), respectively. These values were significantly higher than those of the American Fertility Society (AFS) classification, the Chinese Society for Gynaecological Endoscopy (CSGE) classification and endometrial thickness (all P< 0.01).

Conclusions

The XGBoost model had higher accuracy in predicting postoperative reproductive outcomes in IUAs patients. Clinically, our model may be useful for managing and categorizing IUAs and determining optimal action to aid in pregnancy.

Trial registration:

The study was an observational cohort study, and the data were obtained from the Chinese Uterine Adhesion Database (ClinicalTrials.gov; NCT05381376; 19/05/2022).
Background

Intrauterine adhesions are characterized by partial or total adhesions of the myometrium resulting from fibrous scar repair after injury to the basal layer of the endometrium[1, 2]. The incidence of IUAs is increasing yearly due to an increase in artificial abortion and hysteroscopy use, seriously impacting the female reproductive physiology and mental health[1]. Hysteroscopic adhesiolysis is the standard procedure for treating IUAs in patients with infertility, recurrent miscarriages, and hypomenorrhea[3]. HA can separate and remove scar tissues, recover the anatomical uterine cavity shape, protect the residual endometrium and restore fertility. However, the rate of postoperative adhesion reformation is as high as 62.5%[4], with a conception rate of only 22.5%-33.3%[3, 5, 6]. Thus, a clinical conundrum exists on how to successfully decrease adhesion reformation and improve reproductive prognosis.

Numerous researchers have been working on creating classification systems for fertility quantification to solve this issue. The AFS classification[7], the European Society for Gynaecological Endoscopy (ESGE) classification[8] and the CSGE classification[3] offer objective and quantitative evaluations. These classification systems are mainly applied to assess the degree of adhesion and guide treatment but are inadequate as tools for selecting conception strategies and predicting reproductive outcomes[9]. Moreover, there is a lack of evaluation systems for postoperative fertility recovery, which is presently relying on the endometrial thickness measured using transvaginal ultrasonography. Despite transvaginal ultrasonography's high sensitivity (99%), the specificity only stands at 3%[10]. As a result, further exploration of an optimal classification system is needed.

Machine learning is a hotspot in the field of data analysis and has been widely used in medicine and related fields[11]. LASSO regression is a compression estimation technique that filtrates all variable coefficients using penalized regression to exclude relatively insignificant independent variables from the model.[12]. Clinically, it aids in choosing important defining characteristics related to disease development, progression, and prognosis. XGBoost is an integrative machine learning algorithm based on decision trees with gradient boosting as the framework. It can automatically calculate the importance of traits in the model, quickly and accurately obtain predictive information that can guide clinical decisions[10]. The introduction of machine learning in the field of reproduction can effectively improve the value of postoperative reproductive outcome assessment. To date, no studies have focused on the predictive value of the XGBoost model in reproductive outcomes after HA.

Herein, univariate analysis and LASSO regression were used to select significant clinical indicators as predictor variables, with follow-up reproductive outcomes as the outcome variable. In addition, a predictive model was constructed and validated by XGBoost to assist with patient counseling and management.

Methods

Participants
Data for this study were obtained from the Intrauterine Adhesion Multicenter Prospective Clinical Database (19/05/2022; NCT05381376) from the establishment of enrollment (December 2018) to December 2019. The inclusion criteria were as follows: (1) Women diagnosed with IUAs and underwent HA; (2) Patients with a wish to have children who are also infertile or who frequently miscarry (more than two spontaneous abortions); (3) Patients aged 20–45 years old; (4) Patients without gynecological endocrine disorders (e.g. PCOS) and AMH > 1ng/ml; (5) Patients with signed informed consent. The exclusion criteria were as follows: (1) Patients with significant cardiovascular or respiratory abnormalities in addition to pregnancy contraindications, such as those related to estrogen and progestin use; (2) Patients with additional underlying causes of infertility, such as uterine malformations, endocrine disorders, etc. (3) Patients’ spouses who have infertility related issues, such as abnormal semen. Bipolar energies of 320 W and 160 W were used for the cutting and coagulation powers, respectively. A needle electrode was used to separate the adhesions and a ring electrode was used to remove scar tissue and restore the normal uterine cavity. In addition, all patients in our study received three sequential cycles of hormone therapy following surgery[13]. This study was approved by the China Ethics Committee of Registering Clinical Trials (ethics review document number: ChiECRCT20220180).

Data collection and pre-processing

This study extracted and analyzed clinical information of patients from the IUADB, including age, symptom duration, reduction of menstrual blood flow, age at menarche, menstrual volume, gravidity, parity, missed abortion, artificial abortion, spontaneous abortion, uterine volume, endometrial thickness, Body Mass Index (BMI), fallopian tube ostia (preoperative and postoperative), extent of cavity involved, type of adhesions, AFS classification, CSGE classification (the description of CSGE see Supplementary Table 1 for details), postoperative isolation procedures and comorbidities. Reproductive outcomes were acquired through medical records and telephone call follow-up of at least 2 years after the intervention. Endpoints collected for our study were ongoing pregnancy[14]. Variables with more than 70% missing values were excluded because of potential bias.

Model development and evaluation
All patients were randomly divided into the training and validation cohorts in an 80% / 20% random split, which has been wildly used in various clinical model constructions. The model was developed and initially evaluated in the training cohort, and the model efficiency was validated using the validation cohort. The Train_TEST_Split package (in Python version 3.8.8) was used to ensure randomization. Moreover, based on our baseline statistics, the baseline characteristics of the patients were consistent in both groups.

First, logistic regression was utilized to calculate the odds ratio (OR) value and 95% confidential interval (95% CI), and univariate analysis was performed to screen out significant clinical indicators\[15\]. LASSO regression of clinical indicators was performed using the GLMnet package (R version 3.6.2) to avoid overfitting. Clinical indicators included in the predictive model analysis were selected by the lambda value with the smallest standard error. Then the risk model was established based on LASSO regression.

The XGBoost machine learning model was constructed using the Python package XGBoost. The clinical indicators in each module were weighted to evaluate their applicability in the machine learning model. These models were visualized using the Python package SHAP. Lastly, to test the predictive model efficiency, the PROC package in R (version 3.6.2) was utilized to determine the significance of the AUC using the Z test.

Statistical analyses

R statistical software version 3.6.2 was used for all statistical analyses. When the percentage of missing data was less than 10%, multiple imputations (MICES package in R, version 3.6.2) were used to impute missing values. All statistical tests were two-tailed, and differences were considered statistically significant at \( P < 0.05 \).

Results

Participants

Herein, data related to HA patients were collected from 695 cases. A total of 326 cases were excluded using the pre-designed exclusion criteria, and 369 cases were included in the final analysis, with 295 cases in the training cohort and 74 cases in the validation cohort (Fig. 1). The IUAs data base patient information were completed in Supplementary Table 2.

Univariate analysis for clinical indicators selection

The relationship between clinical indicators and reproductive outcomes was analyzed by univariate analysis, and a total of 16 indicators with a significant effect on fertility were selected (all \( P < 0.05 \)). These indicators include age(OR = 0.930 (95% CI 0.883–0.978), spontaneous abortion (OR = 0.511 (95% CI 0.262–0.890)), CSGE classification (OR = 0.884 (95% CI 0.821 – 0.948)), (OR = 31.500 (95% CI 13.458 –
postoperative endometrial thickness (OR = 3.079 (95% CI 2.195 – 4.522)) and blood supply (OR = 0.335 (95% CI 0.219 – 0.498)) etc. (Supplementary Fig. 1).

**LASSO regression for independent factors selection**

LASSO regression was performed on the 16 selected clinical indicators. The results revealed that the Lambda values had the smallest standard deviations when four variables that could lead to overfitting of the model (mixed type, AFS classification, CSGE classification and combined with adenomyosis) were excluded (Fig. 2A). Therefore, these 12 independent clinical indicators were included as predictor variables for the subsequent analysis (Fig. 2B).

**Risk model establishment based on logistic regression**

Through establishing the risk model, we found that in the 12 clinical indicators, blood supply, uterine cavity shape, extent of cavity involved, uterine volume, spontaneous abortion, age at menarche and age, were high-risk factors for infertility. While postoperative endometrial thickness, postoperative fallopian tube ostia, increase in menstrual blood flow, preoperative fallopian tube ostia, and preoperative endometrial thickness were beneficial factors for pregnancy (Fig. 3).

**SHAP for XGBoost model visualization**

Using a machine learning algorithm (XGBoost) to assess the predictive capability of the module for fertility, the weight of each clinical indicator can be visualized. Postoperative fallopian tube ostia was the most significant indicator influencing fertility in patients following HA, followed by blood supply, uterine cavity shape, age, uterine volume and preoperative endometrial thickness (Supplementary Fig. 2). Collectively, these results revealed that the indicators above have great applicability in model construction.

**ROC curves for model efficiency validation**

Next, ROC curves were used to determine each classification system's predictive value for reproductive outcomes. In the training cohort, the XGBoost model had the highest AUC with a value of 0.987 (95% CI 0.9787–0.996), which was significantly higher than other models (all \( P < 0.01 \)). This was followed by endometrial thickness with 0.6979 (95% CI 0.6511–0.7447), CSGE classification with 0.6262 (95% CI 0.5626–0.6897), and AFS classification with 0.4303 (95% CI 0.367–0.4937) (Fig. 4A). In the validation cohort, the XGBoost model had the highest AUC with a value of 0.9851 (95% CI 0.9668-1), which was markedly higher compared to other models (all \( P < 0.01 \)). However, there was no significant difference in the AUC value of AFS classification, CSGE classification and endometrial thickness (all \( P > 0.05 \)) (Fig. 4B). A sample of 116 from the positive group and 179 from the negative group achieved 100% power using a two-sided Z-test with a significance level of 0.050 for the training cohort. The validation cohort also achieved 100% power.

**Discussion**
Infertility is the most common clinical symptom and reason for visiting patients with IUAs[1]. While treatment options continue to improve, effective fertility restoration remains challenging for gynecologists. This study focused first on selecting the significant clinical indicators that affect fertility using LASSO regression, and second, on constructing an XGBoost model to predict postoperative reproductive outcomes in IUAs patients.

In this study, we found that the XGBoost predictive model outperformed the AFS, CSGE classifications and endometrial thickness, as shown by our ROC curves. Previous studies have also compared the predictive value of various classification systems for live birth rate in IUAs patients following HA. The AUCs of AFS, ESGE, March, Nasr and CSGE classification systems were 0.663, 0.681, 0.653, 0.748 and 0.684, respectively[9]. Importantly these values were lower than the XGBoost model established in this study. Additionally, the advantages inherent in machine learning include the ability to capture complex nonlinear relationships and to focus more on misclassification observations, especially when the sample size is large enough. These results demonstrated the predicate power of this model for postoperative reproductive outcomes.

Postoperative evaluation, especially the use of sonohysterographic and hysteroscopy, is essential for comparing differences before and after treatment and developing postoperative comprehensive management strategies[16]. Existing literature reports used multiple IUAs classification systems, such as the AFS, ESGE and CSGE classifications, but no classification system has been adopted internationally[3]. The AFS classification defined the severities of IUAs as mild, moderate or severe based on a combined evaluation of hysteroscopic findings and the menstrual pattern[7]. The CSGE classification added fallopian tube ostia status, endometrial thickness (late proliferation), previous pregnancy history, and curettage to the AFS and ESGE classifications[3]. Although these classifications have shown the potential to predict live birth following HA, they only have a limited degree of predictive power[9].

It is well known that IUAs have a high recurrence rate following HA, especially in high-risk patients, especially those with severe adhesions[17]. Therefore, postoperative clinical indicators are crucial for predicting reproductive outcomes. The XGBoost predictive model could become an important reference for guiding pregnancy and assisting treatment following HA since the model was established to incorporate preoperative and postoperative clinical indicators. Patients with a high possibility of pregnancy predicted by the XGBoost model may attempt natural conception or artificial insemination. In contrast, patients at high risk of infertility predicted by the XGBoost model would be advised to undergo a series of treatments, including keeping the fallopian tubes clear, restoring the anatomical morphology of the uterine cavity, treating symptoms such as pain and hypermenorrhea, promoting endometrial regeneration, before attempting conception [3, 18, 19].

Then we focused on selecting the significant clinical indicators that affect postoperative pregnancy and live birth rates in IUAs patients. Instead of constructing the XGBoost model by univariate analysis to obtain significant variables, the LASSO regression was first applied to calculate each variable's
contribution and interactions in the overall model. A total of 12 factors strongly associated with the reproductive outcomes of HA were included and were found to be quantitatively and qualitatively superior to the AFS and CSGE classifications. Of these, postoperative fallopian tube ostia, blood supply, uterine cavity shape, age and uterine volume had the greatest impact, consistent with previous studies[20–22]. Zhao et al.[21] found that age, IUAs severity, increased postoperative menstrual flow and HA procedures are the dominant factors affecting reproductive outcomes, indicating that they could be used to predict IUAs prognosis. Moreover, Sun et al.[22] found that age, gestation pattern, the number of visible fallopian tube ostia and the AFS classification are significantly correlated with the live birth rate.

Age is the primary factor affecting fertility, with fertility declining with age, in line with previous research[23]. After the age of 35, female fertility declines rapidly, and the re-pregnancy rate is relatively low after symptomatic treatment[23]. The duration of the symptoms also impacts the prognosis; the longer secondary infertility persists, the more challenging it is for the reproductive system to recover. Repeated abortions and curettage damage to the basal layer of the endometrium are the general causes of IUAs[19, 24]. A prospective study indicated that the incidence of IUAs following only one abortion was 16.3%, 14% following two abortions and 32% following three or more spontaneous abortions[25]. Even though attention was paid to endometrium protection intraoperative and measures were taken to endometrial regeneration postoperation, the basal layer of the endometrium was hard to repair, and the residual endometrium areas were small, resulting in difficulty in fertilized egg implantation[1, 19]. Frequent uterine manipulations are also essential factors that lead to inflammatory narrowing of the fallopian tubes. The visibility of the fallopian tube ostia affects the fusion of the sperm and egg, affecting the natural conception outcome[26]. The prevalence of tubal abnormalities in IUAs patients is as high as 67.39%[26, 27]. Many tubal infections have no obvious symptoms and are easily missed resulting in untimely treatment which could lead to obstruction and secondary infertility.

Nevertheless, in both natural and assisted reproduction, the uterine cavity shape and the endometrial receptivity are the critical factors for fertilization and zygote implantation. Animal experiments found that mechanical injury to the uterus leads to abnormal uterine cavity shape and endometrial trauma, resulting in a thinner endometrium[28]. Late proliferative endometrial thickness and in vitro fertilization (IVF) success show a positive linear association[29]. The minimum endometrial thickness and volume associated with subsequent IVF outcomes were 6.9 mm and 1.59 mL, respectively[30]. Clinical pregnancy rate and live birth rate may achieve their optimal level when endometrial thickness ≥ 12 mm[29]. Transvaginal ultrasonography was previously used to evaluate the endometrial thickness in women with IUAs indicating substantially thinner endometrium compared to normal menstruating women[31]. Importantly, a significant improvement in endometrial thickness was observed after HA[32]. However, Malhotra et al.[33] analyzed endometrial thickness and doppler flow in IUAs patients and found that although the endometrial thickness improved, the vascularity did not. This indicates that even if surgery could improve the uterine anatomy, a normal endometrial function is not guaranteed. Meanwhile, studies also indicated that endometrial pattern, thickness, and changes were not good predictors of clinical pregnancy[34]. Therefore, the capacity to predict reproductive outcomes from endometrial thickness alone is limited.
The IUAs severity was negatively correlated with the prognosis of patients. Compared to women without IUAs, reproductive outcomes of women with IUAs, even mild, remain inferior, let alone patients with moderate and severe IUAs[35]. Roy et al.[6] found that the conception rate was 58% in mild IUAs compared to 30% in moderate and 33.3% in severe cases. The greater the extent of cavity involved and the more dense the type of adhesions, the less active the endometrial area and the worse the reproductive outcomes[36]. In patients with IUAs, the intraoperative risk is higher and more challenging, the incidence of postoperative recurrence is considerable, and the risk of obstetric complications such as spontaneous abortion, premature labor, placenta implantation, and placenta previa is significantly higher [37, 38].

Previous studies have evaluated reproductive outcomes after HA with an early pregnancy loss rate of 17.7%, ectopic pregnancy rate of 4.2%, mid-trimester miscarriage rate of 11.5%, cervical insufficiency rate of 12.5%, postpartum hemorrhage of 7.9%, adherent placenta rate of 4.3% and placenta accrete rate of 10.1%[35, 38].

Moreover, there was no significant correlation between preoperative menstrual pattern and postoperative pregnancy outcome since the actual extent of cavity involved may not be consistent with the symptoms. The postoperative menstrual pattern is important in determining reproductive outcomes because it can reflect the endometrial function. In individuals with improved menstrual patterns, the likelihood of conception was reported to be 44.3%, compared to only 10% in women who continued to experience amenorrhea after HA[6].

Nevertheless, the sample size was suggested to satisfy the test power of the experiment. However, we believe that further expansion of the sample size and further validation of the model are warranted. We will refine this further in a subsequent study. In this study, we extensively included gravidity, parity, menstrual patterns and other clinical indicators for analysis, including various pre- and post-operative characteristics. However, we did not took into consideration all the clinical variables which have impact on post operative results and subsequently in reproductive outcome. This will be incorporated into our improvement plans for future studies with larger samples.

Conclusions

This is the first time that an XGBoost model based on clinical data can be used in reproductive medicine to predict postoperative reproductive outcomes. The XGBoost predictive model is a unique innovative and objective reproductive ability assessment system that includes 12 pregnancy-related clinical indicators. It can help stratify and manage patients with IUAs to adopt individualized pregnancy support strategies, thus improving efficiency and reducing costs.

Abbreviations

IUAs: intrauterine adhesions; HA: hysteroscopic adhesiolysis; LASSO: least absolute shrinkage and selection operator; SHAP: SHapley Additive explanation; XGBoost: xtreme gradient boosting; ROC: receiver
operating characteristic; AUC: area under the ROC curve; AFS: American Fertility Society; CSGE: Chinese Society for Gynaecological Endoscopy; ESGE: European Society for Gynaecological Endoscopy.

**Declarations**

Ethics approval and consent to participate

This study involving human participants were reviewed and approved by the China Ethics Committee of Registering Clinical Trials (ethics review document number: ChiECRCT20220180). All the steps/ methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Yazhu Li, the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted; Hua Duan, the conception and design of the study, revising it critically for important intellectual content, administrative support, final approval of the version to be submitted; Sha Wang, provision of study materials, drafting the article, final approval of the version to be submitted. All authors contributed to the article and approved the submitted version.

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This manuscript has been 'spell checked' and 'grammar checked' by Home for researchers editorial team.

Authors’ information
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40,000 Cycles Among Five Reproductive Centers in China. *Front Endocrinol (Lausanne)* 2021, 12:788706.


**Figures**
Figure 1

Patient inclusion and data processing flow chart. LASSO = last absolute shrinkage and selection operator; XGBoost = extreme gradient boosting; ROC = receiver operating characteristic.
Figure 2

LASSO regression to select predictor variables. A Distribution of LASSO coefficients for 16 clinical indicators in patients with IUAs. A coefficient profile plot was generated against the log (lambda) sequence. (B) Selection of the optimal parameter (lambda) in the LASSO model for eutopic and normal endometrium. LASSO = least absolute shrinkage and selection operator.
Figure 3

The predictive values of 12 clinical indicators, and the risk model were established based on logistic regression to predict postoperative fertility.
Figure 4

ROC curves and AUCs of different predictive models. (A) training cohort (B) validation cohort. ROC = receiver operating characteristic; AUC = area under the receiver operating characteristic curve.

Supplementary Files

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- SupplementaryTable1.docx
- SupplementaryTable2.docx