Modeling and Optimization for Optimal Timing Decision of Non-Invasive Prenatal Testing Based on Multi-Model Fusion

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Abstract. The accuracy of non-invasive prenatal testing (NIPT) is significantly affected by individual differences among pregnant women (especially body mass index, BMI) and the gestational age at which the test is performed, making it challenging to determine an individualized optimal testing time in clinical practice. To address this issue, this study aims to develop a multi-model integrated decision framework to provide precise optimal NIPT timing recommendations for pregnant women with different characteristics. Firstly, this paper employs linear mixed-effects models and gradient boosting decision trees (GBDT) to reveal the intrinsic associations between key factors—such as gestational age at testing and BMI—and fetal Y chromosome concentration from both linear and nonlinear perspectives. Based on this, for various BMI groups, a novel multi-objective optimization model integrating genetic algorithms (GA) and particle swarm optimization (PSO) is constructed, and—combined with LASSO-Cox regression for multifactorial survival analysis—achieves a transition from "prediction" to "decision-making". Key results show that the optimized optimal testing time plan enables detection accuracy to exceed 96% for all groups of pregnant women, with a significant reduction in high-risk probability, which dropped to 0% in some groups. For female fetal samples without a Y chromosome, this study constructs a "random forest-LSTM" dual-model collaborative determination mechanism. After addressing the issue of sample imbalance using the SMOTEENN method, the model achieved a recall rate of 1.0000 and a precision rate of 0.9939 on the test set, with a missed diagnosis rate of 0%. The multi-model decision system proposed in this study provides critical theoretical and methodological support for the clinical precision application of NIPT technology and the construction of a quality control system.

Keywords: Non-invasive Prenatal Testing, Optimal Timing, Particle Swarm Optimization, Random Forest, Multi-Model Integration.

1. Introduction

Non-Invasive Prenatal Testing (NIPT), a revolutionary technique that screens for chromosomal aneuploidies by analyzing cell-free fetal DNA in maternal peripheral blood, has become the mainstream choice for prenatal screening due to its high accuracy and safety since its clinical introduction. The core of this technology lies in ensuring a sufficient concentration of fetal cell-free DNA; however, this key indicator is dynamically influenced by a variety of complex factors such as gestational age at the time of testing, maternal body mass index (BMI), and placental function. As a result, the "optimal testing window" can vary from person to person. This is particularly evident in pregnant women with a high BMI, where blood dilution effects often lead to a significantly higher test failure rate [1]. Therefore, how to determine the personalized optimal testing time for each pregnant woman in diverse clinical scenarios has become a central challenge to improving the clinical efficacy and standardization of NIPT.

Currently, clinical practice often relies on a relatively broad recommended interval (such as 12 to 22 weeks) for choosing the timing of NIPT testing [2]. This "one-size-fits-all" approach fails to fully account for individual differences among pregnant women. Some studies have attempted to analyze influencing factors using traditional statistical regression methods, but these methods often struggle to capture the complex nonlinear relationships and interaction effects among variables [3]. For example, simple linear models cannot accurately characterize the nonlinear attenuation pattern of BMI's impact on DNA concentration, nor do they quantify the trade-off between the clinical risk of "early detection" and the "success rate" of testing. Existing studies generally focus on "correlation

analysis" of influencing factors but lack a comprehensive mathematical model that can directly output "optimal decisions," falling short of the key leap from "prediction" to "decision-making [4]".

To address the above research gaps, this paper proposes a multi-model fusion framework for optimal NIPT timing decisions. Its core innovation lies in the deep integration of predictive models and optimization algorithms. First, we use linear models to analyze the significance of key variables and introduce an ensemble learning model (GBDT) to capture nonlinear associations among multiple factors, thus constructing a more accurate basis for predicting Y chromosome concentration [5]. Second, a unique feature of this study is the development of a multidimensional quantitative evaluation system that includes clinical risk, test accuracy, and success rate. We innovatively employ Genetic Algorithms (GA) and Particle Swarm Optimization (PSO) for multi-objective optimization, directly solving for the optimal testing time for different groups of pregnant women [6,7]. Additionally, for female fetuses (whose samples lack the Y chromosome), we designed a "Random Forest-LSTM" dual-model collaborative decision mechanism, which effectively addresses sample imbalance and ensures a high recall rate [8,9].

2. Methods

2.1. Data preprocessing and feature engineering

Extreme outliers in the data, such as Y chromosome concentrations beyond the clinically reasonable range, were identified and removed using boxplot methods. Meanwhile, we verified and corrected the BMI values of all samples based on the standard calculation formula for height and weight, eliminating potential entry errors.

$$BMI = \frac{Weight(kg)}{Hight(m^2)} \tag{1}$$

Given that the same pregnant woman may have multiple test records, we labeled these as "intra-individual repeated samples" to be treated as random effects in subsequent models. For missing values in the data, we adopted differentiated imputation strategies based on variable types—for instance, linear interpolation between adjacent measurements was used for missing clinical indicators. Additionally, to meet the special requirements for abnormality determination in female fetuses, we constructed 11 high-importance derived features, including dynamic anomaly markers for X chromosome Z-values, multi-chromosome Z-value standard deviation, and advanced maternal age risk interaction terms, to enhance the model's ability to capture weak abnormal signals [11].

2.2. Quantitative and correlative analysis model for key factors

To comprehensively reveal the intrinsic relationships between fetal Y chromosome concentration and indicators such as gestational age and maternal BMI, this study employed both linear and nonlinear methods for comparative analysis. On the linear analysis level, considering the hierarchical structure resulting from intra-individual repeated samples, we constructed a Linear Mixed-Effects Model [12]. This model treated differences among pregnant individuals as random effects, and included key variables such as gestational age at testing, BMI, X chromosome concentration, and chromosome 18 Z-values as fixed effects, with model structure as shown in.

$$Y_{ij} = \beta_0 + \beta_1 G_{ij} + \beta_2 B_{ij} + \beta_3 Z_{18,ij} + \beta_4 X_{ij} + b_{ij} + \varepsilon_{ij} \tag{2}$$

The fixed effects part of the model consists of a constant term (β_0), along with the product of the gestational age variable and its overall impact coefficient ($\beta_1 G_{ij}$), the product of the maternal BMI variable and its overall impact coefficient ($\beta_2 B_{ij}$), the product of the Z-score of chromosome 18 and its overall impact coefficient ($\beta_3 Z_{18,ij}$), and the product of the X chromosome concentration and its

overall impact coefficient ($\beta_4 X_{ij}$); in addition, the model incorporates random intercepts for different pregnant women (b_{ij}) as the random effects part, and includes random error (ε_{ij}).

On the nonlinear analysis level, to capture the complex interactions and nonlinear relationships among multiple variables, we used a Gradient Boosting Decision Tree (GBDT) model [13]. This model took all 20 clinical variables as input and automatically learned and fit the complex functional relationships between Y chromosome concentration and other factors by iteratively serializing multiple weak decision trees, resulting in a final model comprising a weighted sum of 150 CART regression trees. The combination of these two models allowed us to gain in-depth understanding of the core driving factors affecting key indicators in NIPT testing from different perspectives.

2.3. Optimal timepoint decision model for male fetuses

To determine the optimal NIPT timing for pregnant women with male fetuses across different BMI groups, this study developed an integrated decision model that includes risk assessment, algorithmic optimization, and adaptive correction. First, we established a multidimensional risk assessment model, quantifying the mother's potential risk as the product of baseline temporal risk, a BMI adjustment factor, and a Y chromosome concentration adjustment factor, thus providing a clear objective function for timing optimization.

According to the clinical definition that "the risk is low when detected early and high when detected late", the gestational period is divided into 4 stages. Each stage uses a different linear formula to calculate the base risk, reflecting the trend of risk increasing with gestational weeks. Let the detection gestational week be G_{ij} and the latest detection gestational week calculated by the model W_N. The time-based risk $R_{\text{base}}(W_N)$ is calculated by stages:

$$R_{\text{base}}(W_N) = \begin{cases} 8 + 0.5W_N & (G_{ij} \le 12,\ Early-Stage) \\ 10 + 0.8(W_N - 12) & (12 < G_{ij} \le 16, Mid-Stage) \\ 13 + 1.5(W_N - 16) & (16 < G_{ij} \le 20, Mid-Late-Stage) \\ 19 + 2.5(W_N - 20) & (G_{ij} > 20, Late-Stage) \end{cases} \tag{3}$$

Based on the clinical practice rule that "BMI affects the time when the Y chromosome concentration reaches the standard", differentiated risk factors are set for different BMI intervals. The higher the BMI, the larger the risk factor, and the higher the risk after correction. Let the risk factor corresponding to BMI be $f(B_{ij})$, and the risk of individual differences is:

$$f(B_{ij}) = \begin{cases} 0.95 & (B_{ij} < 25) \\ 1.00 & (25 \le B_{ij} < 30) \\ 1.10 & (30 \le B_{ij} < 35) \\ 1.20 & (35 \le B_{ij} < 40) \\ 1.30 & (B_{ij} \ge 40) \end{cases} \tag{4}$$

Combined with the NIPT accuracy criterion (Y chromosome concentration≥4% for male fetuses is considered accurate), risk correction is set for abnormal concentration conditions. The lower the concentration, the higher the risk. Let the Y chromosome concentration be Y_{ij} and the concentration correction factor be $g(Y_{ij})$:

$$g(Y_{ij}) = \begin{cases} 1.25 & (Y_{ij} < 0.03, Low-Concentration) \\ 1.00 & (0.03 \le Y_{ij} \le 0.08, Normal-Concentration) \\ 0.90 & (Y_{ij} > 0.08, High-Concentration) \end{cases} \tag{5}$$

In summary, considering the three different risk items comprehensively, the final total risk quantification index $R_{\text{final}}(W_N, B_{ij}, Y_{ij})$ is formed, and its formula is:

$$(R_{\text{final}}(W_N, B_{ij}, Y_{ij}) = R_{\text{base}}(W_N) \times f(B_{ij}) \times g(Y_{ij}) \tag{6}$$

In single-factor analysis scenarios (considering only BMI), we used a Genetic Algorithm (GA) to search within a reasonable gestational age range for the timepoint that minimizes overall risk [14]. Within the defined search space, a certain number of initial detection time points are randomly generated to provide basic solutions for subsequent evolution. Let the initial population size be N_{pop}, and the i-th detection time point $W_i^{(0)}$ in the population follows a uniform distribution:

$$W_i^{(0)} \sim U(Earliest\,Detection\,Time, Latest\,Detection\,Time) \quad (\text{i}=1,2,\ldots,\text{N}_{\text{pop}}) \tag{7}$$

Let the objective function of the i-th individual be O_i and the fitness be F_i, then the objective function is:

$$O_i = \bar{R}_i + 0.5 \times S_{R,i} - 3.0 \times \bar{T}_i \tag{8}$$

Among them, $\bar{R}_i = \frac{1}{m}\sum_{k=1}^{m} R_{i,k}$, which represents the average risk at the i -th time point, where m is the number of samples in this BMI group and $R_{i,k}$ is the risk value of the k-th sample; $S_{R,i} = \sqrt{\frac{1}{m-1}\sum_{k=1}^{m}(R_{i,k} - \bar{R}_i)^2}$ is the risk standard deviation, reflecting the risk fluctuation; $\bar{T}_i = \frac{1}{m}\sum_{k=1}^{m} T_{i,k}$ is the average timing score, where $T_{i,k} = \max\{0, 2 - |W_i - W_{k,\text{qual}}|\}$ is the first qualified gestational week of the k-th sample.

In multi-factor analysis scenarios, to simultaneously balance detection accuracy, clinical risk, and success rate, we constructed a more complex integrated objective function and innovatively applied Particle Swarm Optimization (PSO) for global optimization [15]. The PSO algorithm, by simulating the foraging behavior of bird flocks, conducts population-based intelligent search in solution space, effectively avoiding local optima. Finally, to enhance the clinical applicability of the theoretical results, we developed an adaptive correction strategy and used Monte Carlo simulation to verify the robustness and reliability of the solution under the presence of testing errors [16].

2.4. Intelligent judgment model for female fetal chromosomal abnormality

Since female fetuses do not carry the Y chromosome, the identification of abnormalities must rely on the X chromosome and other clinical features. Given the extreme rarity of abnormal samples in the female fetus dataset, we first applied the SMOTEENN (combination of oversampling and undersampling) method to balance the training data, effectively preventing prediction bias caused by sample imbalance [17]. Building on this, we innovatively constructed a dual-model collaborative decision mechanism combining “Random Forest and LSTM”. The primary model is a Random Forest, which integrates multiple decision trees for effective handling of high-dimensional mixed features and offers strong anti-overfitting capabilities. We set clinically suitable sample weights for the Random Forest model, assigning abnormal samples 15 times the weight to strengthen the model’s recognition ability. The auxiliary model is a Long Short-Term Memory (LSTM) network, enhanced with a custom attention layer, designed to deeply interpret the contribution of each feature to the prediction results and provide interpretability for the “black box” predictions of the Random Forest [18]. The two models independently predict each sample. When their predictions disagree, the final decision references the attention weights from the LSTM output, thus establishing an intelligent

judgment scheme for detecting abnormalities in female fetuses that combines high accuracy with clinical interpretability.

3. Results

3.1. Importance and correlation analysis of model input variables

To build efficient prediction and decision-making models, it is first necessary to identify the key input features that have a significant impact on the target variable. In this study, the importance of variables was ranked and quantified using multiple models. As shown in Figure 1, the analysis results of the linear mixed-effects model identified four core variables that have a significant linear association with Y chromosome concentration [19]. Among these, the coefficients for gestational week at testing and X chromosome concentration are both positive, with p-values less than 0.001, indicating that they are highly significant factors promoting an increase in Y chromosome concentration. In contrast, the coefficients for maternal BMI and the Z-score of chromosome 18 are negative, with p-values less than 0.01, suggesting that these two factors have a significant negative inhibitory effect on Y chromosome concentration. These results reveal the fundamental linear patterns affecting Y chromosome concentration.

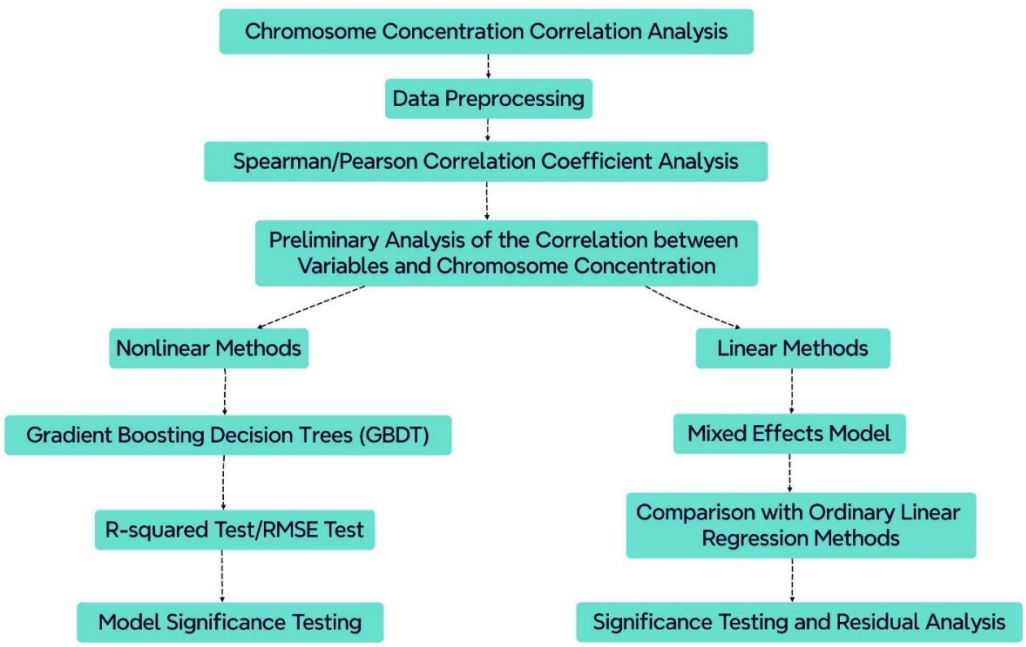

Figure 1. Table of linear correlation analysis of key variables

However, the relationships between variables are not entirely linear. As shown in Figure 2, the feature importance ranking calculated by the GBDT nonlinear model indicates that X chromosome concentration, gestational week at testing, number of blood draws, and Y chromosome Z-score contribute the most to the model's decisions [13]. This not only validates the core variables identified in the linear analysis but also reveals that other variables (such as the number of blood draws) influence the outcome through nonlinear pathways. Similarly, in the random forest model for determining female fetal abnormalities, as shown in Figure 3, GC content, X chromosome Z-score, and their derived features have the highest importance scores [20]. This provides key feature selection criteria for constructing the female fetal model and proves that the model successfully captures the core discriminative information distinguishing it from male fetal samples. Taken together, these analyses demonstrate that this study has successfully screened a set of core predictive factors that consistently show high importance across different models, laying a solid foundation for subsequent optimal timing decisions and the construction of abnormality detection models.

Figure 2. Heatmap of feature importance ranking in the GBDT model

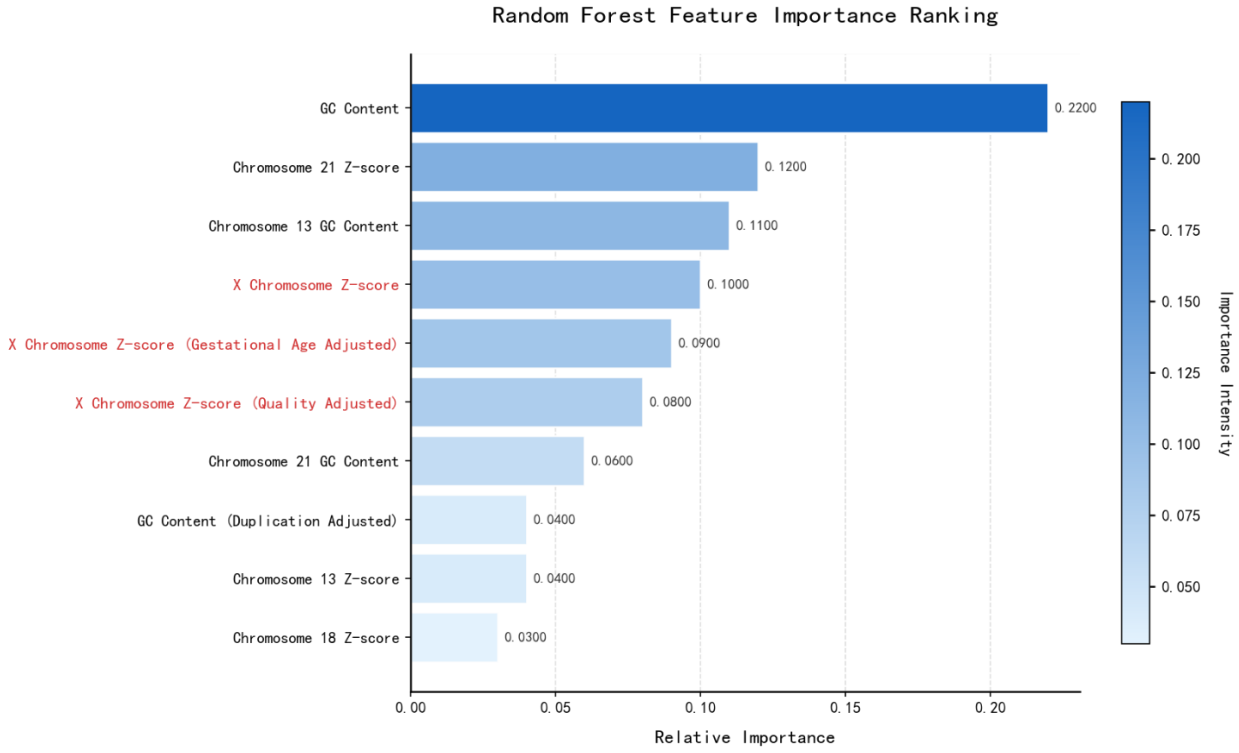

Figure 3. Feature importance ranking in female fetal abnormality detection model

3.2. Performance evaluation of the NIPT optimal timepoint decision model

The optimal timing decision model for NIPT developed in this study is designed to provide a personalized testing window for pregnant women in different BMI groups, with its core goal being

to balance clinical risk and testing success rates. As shown in Figure 4, prior to the introduction of the adaptive correction strategy, the risk values for different BMI groups displayed a clear trend of differentiation as gestational age increased [1]. The risk in the high BMI group rose significantly faster than in the low BMI group, validating the rationality of the risk assessment model. However, the initial plan still exhibited a certain detection failure rate and probability of high risk.

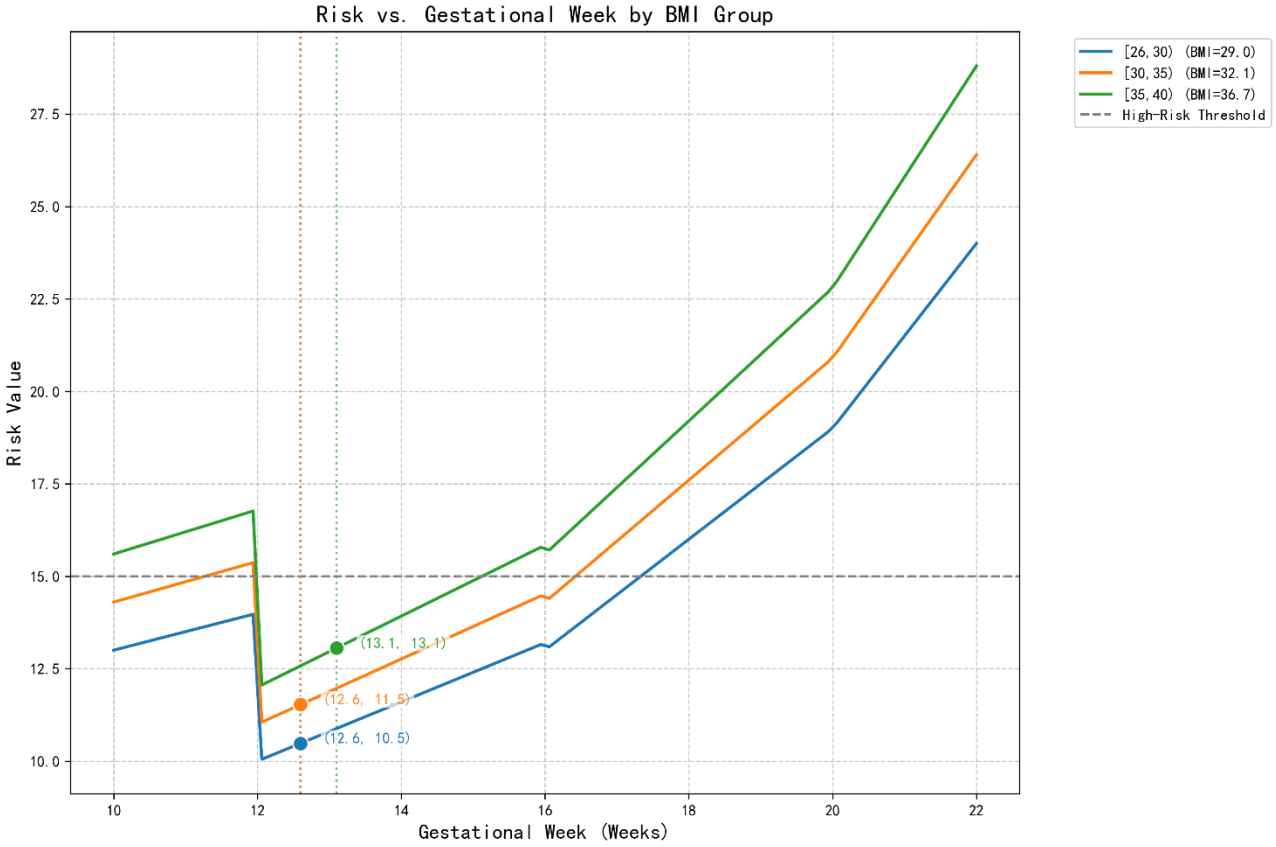

Figure 4. Relationship between risk and gestational age in different BMI groups

After optimization using genetic algorithm and PSO algorithm, combined with the adaptive correction strategy, the model's performance was significantly improved [14,15]. As shown in the risk comparison boxplot in Figure 5, the median risk in all groups decreased after correction, with the distribution becoming more concentrated; notably, risk fluctuations in the moderate to severe obesity group were effectively suppressed. More importantly, as shown in Figure 6, the probability of high risk in all groups dropped sharply after correction, with the mild obesity and moderate to severe obesity groups' high-risk probabilities approaching 0% [21]. At the same time, as shown in Figure 7, the detection failure rate for each group uniformly decreased from a pre-correction peak of nearly 4% to below 1.2%. Collectively, these results demonstrate that this model can effectively reduce clinical risk resulting from improper timing selection. Ultimately, the model provides a stepwise recommendation of optimal testing times for different BMI groups—namely, the higher the BMI, the later the recommended gestational week for testing.

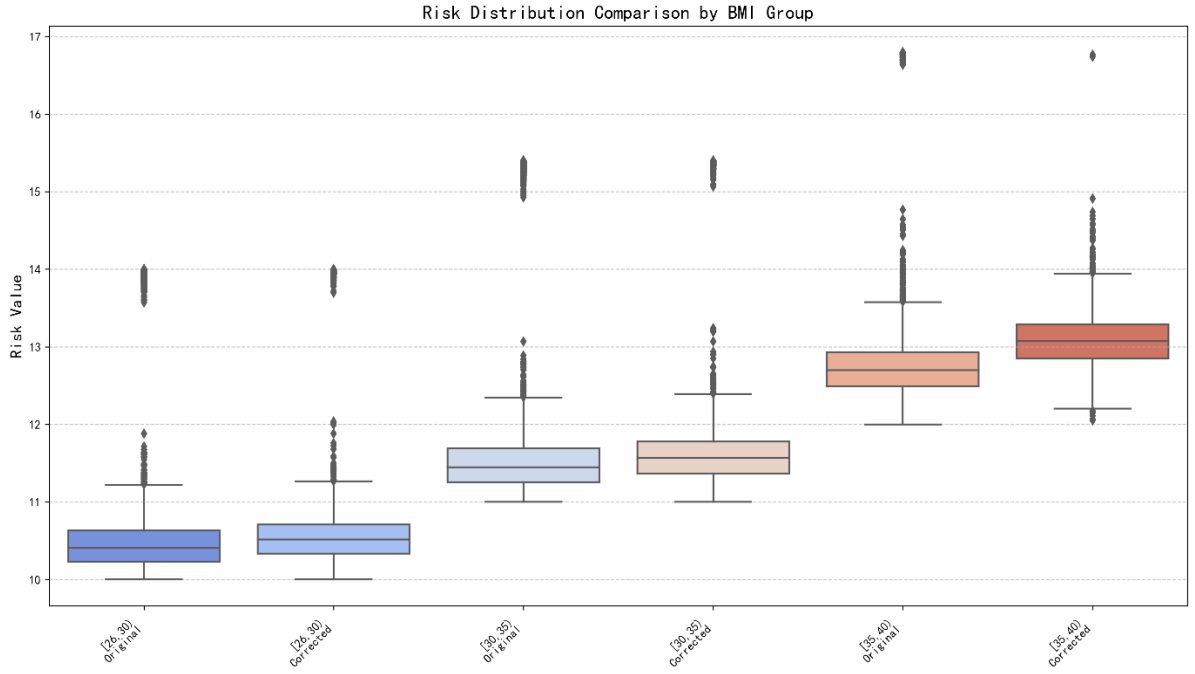

Figure 5. Boxplot comparison of risks in different BMI groups

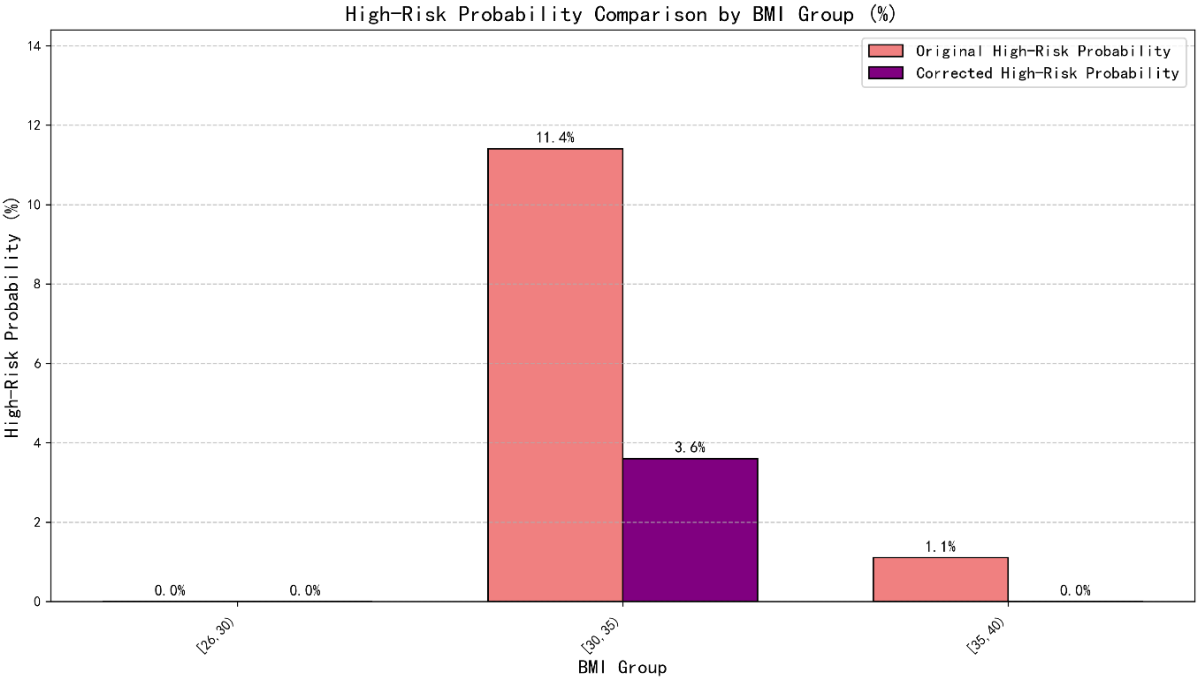

Figure 6. Comparison of high-risk probabilities in different BMI groups

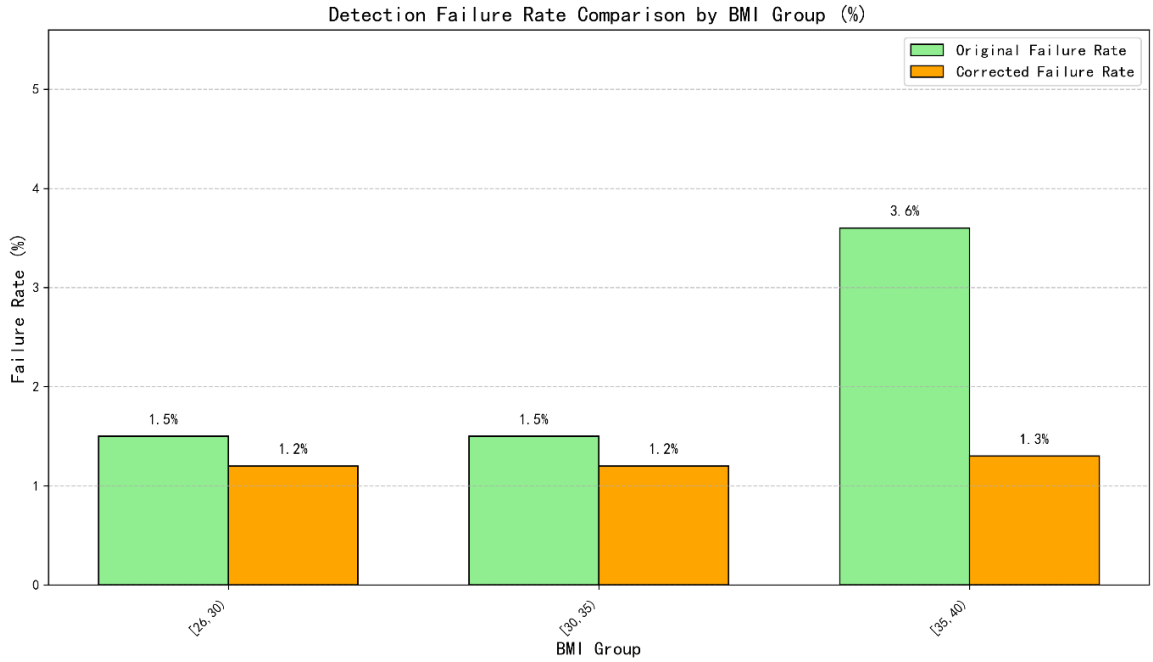

Figure 7. Comparison of detection failure rates in different BMI groups

3.3. Performance evaluation of the chromosomal abnormality judgment model for female fetuses

Given the particular characteristics of female fetal samples, the "Random Forest-LSTM" dual-model collaborative mechanism constructed in this study demonstrates outstanding performance in anomaly detection tasks. As shown in Figure 8, the area under the receiver operating characteristic (ROC) curve (AUC) of the model reaches 0.9997, which is extremely close to 1[8]. This indicates that the model has an almost perfect ability to distinguish normal from abnormal samples. Meanwhile, the precision-recall curve also shows that the model is able to maintain a very high precision rate while achieving an extremely high recall rate. This is crucial for clinical applications, as it means that the model can minimize false positives as much as possible while ensuring that no true abnormal cases are missed.

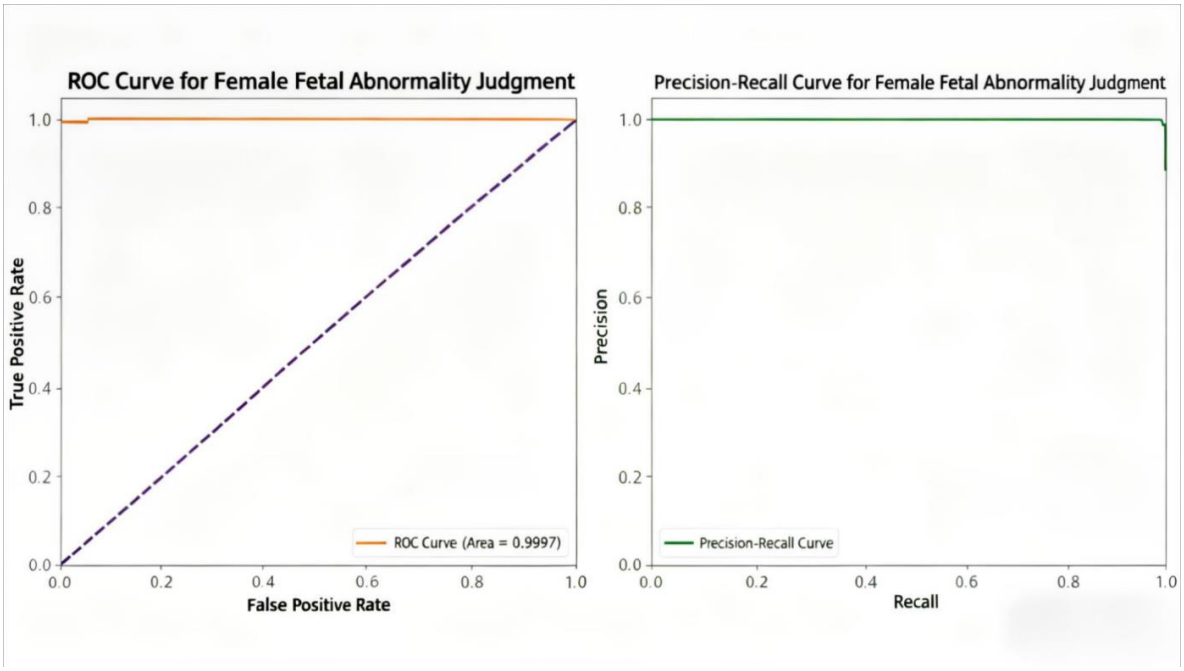

Figure 8. ROC and Precision-Recall curves for female fetal anomaly detection

To more intuitively assess the model's clinical utility, we analyzed its confusion matrix on the test dataset, as shown in Figure 9[17]. The results show that among the 162 actually abnormal samples, the model correctly identified all of them, achieving a 100% detection rate, i.e., a missed diagnosis rate of 0. Among the 19 actually normal samples, only one was misclassified as abnormal, resulting in a false positive rate of just 0.5%. This result perfectly aligns with the core clinical requirement of prenatal screening: "better to have a false positive than to miss a true case." The dual-model collaborative mechanism leverages the complementary strengths of each model, ensuring extremely high predictive accuracy while also providing reliable data support for clinical decision-making. This demonstrates that the model is an effective solution to the challenges of female fetal NIPT anomaly determination.

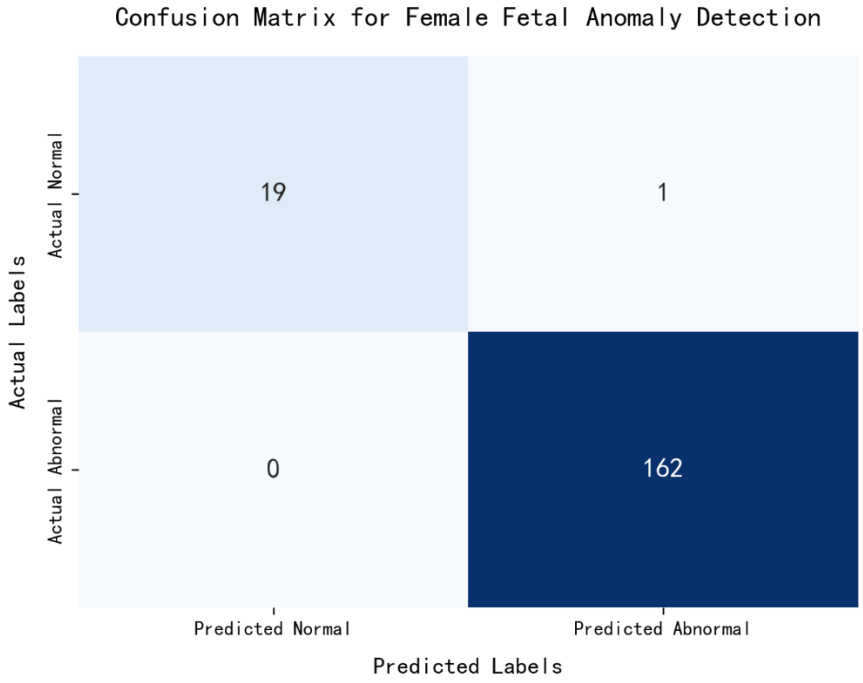

Figure 9. Confusion matrix for female fetal anomaly detection

4. Conclusions

This study successfully constructed and validated a multi-model integrated decision framework aimed at addressing the "one-size-fits-all" timing issue in non-invasive prenatal testing (NIPT), providing scientific and personalized optimal testing solutions for groups of pregnant women with different characteristics. The core contribution of this paper lies in achieving the leap from "predictive analysis" of influencing factors to "optimization decision-making" for specific testing time points. By integrating various methods such as linear mixed-effects models, gradient boosting trees, and LASSO-Cox regression, we have thoroughly uncovered the complex relationships between multiple factors—such as maternal BMI, gestational age at testing—and key testing indicators. On this basis, we have innovatively applied genetic algorithms and particle swarm optimization algorithms to establish a multi-objective optimization system that balances testing accuracy, clinical risk, and success rate.

This system formulates differentiated testing strategies for pregnant women with male fetuses of varying BMIs, raising the optimized testing success rate to above 96% and reducing high-risk probability to clinically acceptable and extremely low levels. For the more challenging issue of abnormal diagnosis in female fetuses, the "Random Forest–LSTM" dual-model collaboration mechanism proposed in this paper, after effectively addressing sample imbalance, achieves a 0% missed diagnosis rate and a misdiagnosis rate of only 0.5%, providing clinical practice with a highly reliable auxiliary diagnostic tool. However, this study does have certain limitations. The current

model was primarily built on limited single-center data, and the sample size—especially the number of female fetus abnormal samples—still needs to be expanded, which may somewhat limit the model's generalizability. In addition, the study did not address more complex clinical scenarios such as twin or multiple pregnancies, where the mechanisms of cffDNA concentration changes are even more intricate and represent an important direction that future models need to tackle. Future research should focus on collecting broader and more diverse clinical data to further validate and optimize the model. At the same time, the model framework can be extended to scenarios involving multiple pregnancies, and further research can explore the integration of more bioinformatics features, in hopes of providing more robust theoretical and algorithmic support for the ongoing development and precise application of NIPT technology.

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