WEP Warwick Evans Publishing

International Journal of Public Health and Medical Research

ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online) | Volume 6, Number 2, Year 2026
DOI: https://doi.org/10.62051/ijphmr.v6n2.04
Journal homepage: https://wepub.org/index.php/IJPHMR/index

Determination of Optimal Detection Time Window and Error Analysis for Male Fetal Non-Invasive Prenatal Testing Based on K-Means Clustering and Particle Swarm Optimization

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ABSTRACT

To address the issue that unreasonable timing of non-invasive prenatal testing (NIPT) increases detection risks, this study constructed a risk optimization model to determine the optimal NIPT time window for male fetuses. Taking gestational age and BMI as optimization variables, the study integrated the time-related risk from exponential fitting and the accuracy-related risk from density estimation, determined weights using the Analytic Hierarchy Process (AHP), and further established a total risk function. Pregnant women were divided into four groups by BMI via K-means clustering, and the Particle Swarm Optimization (PSO) algorithm was employed to solve the model. The results showed that: the optimal gestational ages corresponding to BMI ranges [26.6, 30.2), [30.2, 33.8), [33.8, 37.5), and [37.5, 46.9] were 11.85 weeks, 13.22 weeks, 15.78 weeks, and 19.33 weeks, respectively, indicating that the higher the BMI, the later the optimal detection time. Finally, an analysis of ±5% and ±10% concentration errors revealed that negative errors delay the optimal time point and reduce risks, while positive errors advance the time point and increase risks—with the high BMI groups being more significantly affected. This study provides a basis for personalized clinical testing.

KEYWORDS

NIPT; Risk Optimization; K-Means Clustering; PSO; Detection Time Window

1. INTRODUCTION

Non-invasive Prenatal Testing (NIPT) has become a core method for fetal chromosomal aneuploidy screening due to its non-invasiveness, high accuracy, and wide applicability across gestational ages. For male fetuses, the detection accuracy of NIPT is highly reliable only when the Y-chromosome concentration is ≥4%. In clinical practice, the Y-chromosome concentration is closely correlated with the gestational age and Body Mass Index (BMI) of pregnant women. However, there are significant individual differences in BMI among different pregnant women, and the current mode of a unified testing time point is difficult to meet the needs of special populations such as those with high BMI. Meanwhile, the timing of detecting fetal abnormalities directly affects the risk level: detection before 12 weeks of gestation is associated with a low risk, between 13 and 27 weeks with a high risk, and after 28 weeks with an extremely high risk [1-2]. Therefore, early implementation of NIPT in clinical practice is necessary to avoid the narrowing of the treatment window.

Scholars at home and abroad have conducted relevant research on this research direction: DEVINE O et al. [3] addressed the insufficient detection sensitivity of NIPT in pregnant women with high BMI by adopting a customized whole-genome sequencing workflow, which effectively improved the detection performance of samples with low cell-free fetal DNA (cffDNA) concentration and reduced

clinical residual risk. Zhang L et al. [4] systematically analyzed the factors associated with NIPT detection failure, confirming that maternal BMI shows a significant negative correlation with fetal free DNA concentration—the detection failure rate in the high BMI group can be as high as 24.3%—and clarifying that BMI is a core factor restricting the clinical application of NIPT. CHEN L et al. [5] reviewed the progress of artificial intelligence (AI) applications in NIPT, proposing that deep learning and computational genomics technologies can significantly improve detection precision and effectively reduce the false positive rate. Although existing studies have focused on the impact of BMI on NIPT and explored timing optimization methods, the personalized adaptation for male fetal populations and the analysis of the impact of detection errors still need to be improved.

Focusing on the problem that the unified testing time point in non-invasive prenatal testing (NIPT) for male fetuses is difficult to adapt to individual BMI differences, leading to increased detection risks, this study uses clinical data mainly from the high BMI population as samples. Through BMI clustering grouping and risk quantification modeling, the optimal NIPT testing time points for different BMI groups are determined to achieve the comprehensive minimization of time risk and accuracy risk. Meanwhile, the impact of Y-chromosome concentration detection errors on the results is analyzed, providing scientific support for the clinical development of personalized and precise NIPT testing protocols.

2. MATERIALS AND METHODS

2.1. Data Source

The data of this study were obtained from the open-source website (https://www.mcm.edu.cn). To address the research question, the sample data was processed as follows:

(1) Regarding chromosomal abnormalities (i.e., presence of chromosomal aneuploidy), normal chromosomes were coded as one, and abnormal chromosomes as zero.

(2) For fetal health status, healthy fetuses were coded as one, and unhealthy fetuses as 0.

(3) For diagnostic errors: if a sample had normal chromosomes (coded as one) with a healthy fetus (coded as one), or abnormal chromosomes (coded as zero) with an unhealthy fetus (coded as zero), the diagnosis was considered accurate (coded as zero); if a sample had normal chromosomes (coded as one) with an unhealthy fetus (coded as zero), or abnormal chromosomes (coded as zero) with a healthy fetus (coded as one), the diagnosis was deemed erroneous (coded as one).

2.2. Research Methods

For the construction of the risk model, considering that both timing and diagnostic accuracy affect risk, this study adopted a three-step approach to establish the comprehensive risk model: first, constructing a timing risk model; second, developing an accuracy risk model; third, determining the weights of the two risk factors using the Analytic Hierarchy Process (AHP), integrating them to form the comprehensive risk model, and defining the comprehensive risk function as the objective optimization function (i.e., minimizing the comprehensive risk function). Subsequently, constraint conditions were identified based on clinical practice research. Samples with different Body Mass Index (BMI) values were subjected to K-means clustering analysis, and the optimal number of clusters (K=4) was determined using the elbow method. On this basis, the Particle Swarm Optimization (PSO) algorithm was applied to optimize the objective function for the clustered samples, and result visualization was generated. Finally, the impact of error verification on the results was analyzed.

3. ESTABLISHMENT AND SOLUTION OF THE MODEL

3.1. Construction of the Temporal Risk Model

In clinical practice, when fetal chromosomal abnormalities are screened and identified using NIPT technology, diagnostic testing is required to clarify the specific type and severity of the chromosomal abnormalities [6]. When fetal chromosomal abnormalities are confirmed, effective treatment for chromosomal disorders cannot be provided with the current medical standards, so pregnant women can only choose between two options: termination of pregnancy or "close prenatal monitoring + postnatal intervention". However, risks such as massive hemorrhage, infection, and cervical adhesion may occur during the termination of pregnancy. Among these, massive hemorrhage is one of the most typical and dangerous complications during termination of pregnancy. Its incidence directly reflects the risk level of termination of pregnancy and is highly correlated with core risk factors such as gestational age, making it one of the key indicators for clinical evaluation of the safety of termination of pregnancy. Therefore, this study uses the incidence of massive hemorrhage as the main indicator to characterize the potential temporal risk function. In contrast, "close prenatal monitoring + postnatal intervention" has no impact on the risk model and will not be considered.

Therefore, the model assumptions for the construction of the temporal risk model are as follows: when fetal chromosomal abnormalities are detected using NIPT technology, it is assumed that termination of pregnancy is performed immediately, and the incidence of its most typical and dangerous complication—massive hemorrhage—is adopted as the indicator to measure temporal risk. Data on the incidence of massive hemorrhage and pregnant women's gestational age were obtained by reviewing relevant literature, which showed that the risk of termination of pregnancy for pregnant women increases exponentially with the increase in gestational age [7]. As shown in Figure 1, the fitting curve of the incidence of massive hemorrhage against gestational age is presented. Therefore, an exponential function was used to fit and standardize the functional relationship between the incidence of massive hemorrhage and gestational age, and this function was defined as the temporal risk function:

$$h(t) = 1.88 \times 10^{-4} \cdot e^{4.04 \times 10^{-1} t} + 3.16 \times 10^{0} \quad (1)$$

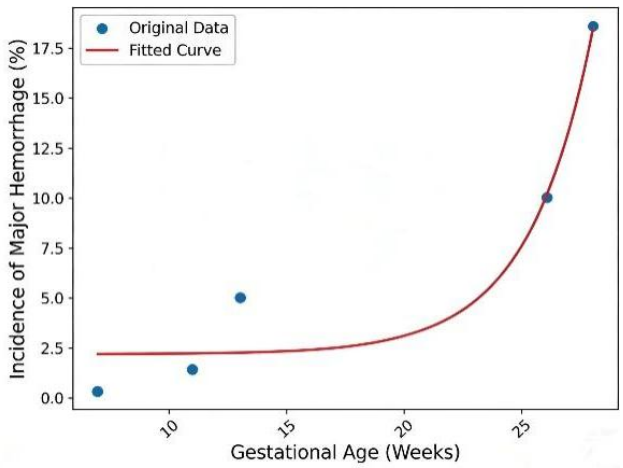

Figure 1. Fitting Curve of the Incidence of Massive Hemorrhage

3.2. Construction of the Accuracy Risk Model

As documented in the literature, the results of NIPT are basically accurate when the Y-chromosome concentration in male fetuses reaches or exceeds 4%, indicating a certain correlation between the Y-chromosome concentration in male fetuses and detection errors [8]. For the Accuracy Risk Function, this study first plotted two density distribution histograms of Y-chromosome concentration—one

with detection errors and the other without detection errors—then fitted the histograms using kernel density estimation curves [9]. Finally, a kernel density estimation function for Y-chromosome concentration was obtained. Using Bayes' theorem, the probability function of detection errors occurring under different Y-chromosome concentrations was calculated, which is defined as the Accuracy Risk Function. As shown in Figure 2, the kernel density estimation fitting curve for Y-chromosome concentration (both with and without detection errors) is illustrated, the abscissa represents the concentration of Y chromosome, and the ordinate represents the sample size.

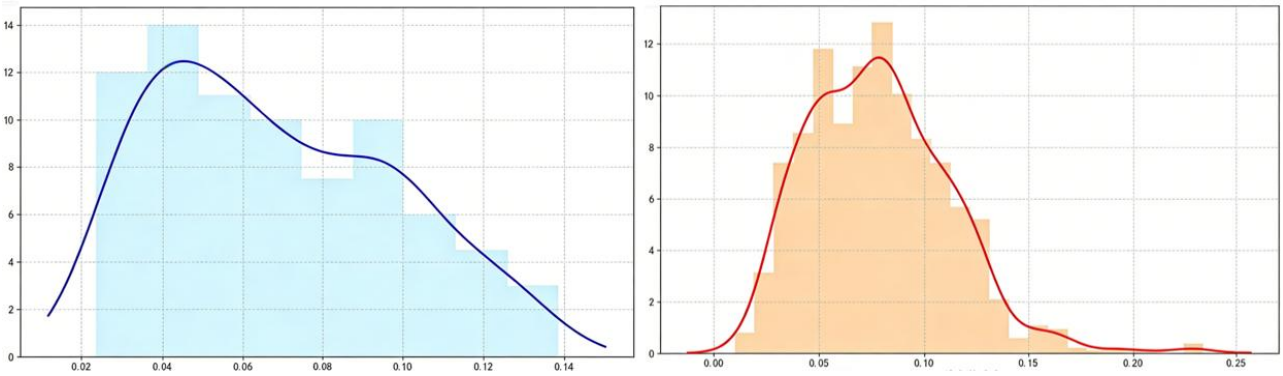

Figure 2. Kernel Density Estimation Fitting Curve

Based on the mathematical principle of kernel density estimation, we first divided the samples into two categories: samples with detection errors and samples without detection errors, where the number of samples with detection errors was n_1=156 and that of samples without detection errors was n_2=925. Subsequently, we constructed the sample kernel density $f(y)_1$ for incorrect detection (i.e., with detection errors) and the sample kernel density $f(y)_2$ for correct detection (i.e., without detection errors) with respect to the Y-chromosome concentration y, h is the bandwidth, σ is the sample standard deviation, and IQR (Interquartile Range) is the interquartile range.

$$f_1(y) = \frac{1}{n_1 \cdot h_1} \cdot \sum_{i=1}^{n_1} \left[\frac{1}{\sqrt{2\pi}} \cdot \exp\left(-\frac{(y-y_i)^2}{2 \cdot h_1^2} \right) \right] \tag{2}$$

$$f_2(y) = \frac{1}{n_2 \cdot h_2} \cdot \sum_{j=1}^{n_2} \left[\frac{1}{\sqrt{2\pi}} \cdot \exp\left(-\frac{(y-y_j)^2}{2 \cdot h_2^2} \right) \right] \tag{3}$$

$$h = 1.06 \cdot \min(\sigma, IQR/1.34) \cdot n^{-1/5} \tag{4}$$

Using Bayes' theorem, the probability function of incorrect detection can be derived as follows:

$$G(y) = \frac{f_1(y)\ h_1 n_1}{f_1(y) h_1 n_1 + f_2(y) h_2 n_2} \tag{5}$$

Substitute the functional relationship of the Y-chromosome concentration y with respect to gestational age (t) and BMI (B):

$$y = -4.331B + 1.090t + 0.040(Bt) + 5.598 \tag{6}$$

We can then obtain the Accuracy Risk Function $G(B, t)$.

3.3. Construction of the Comprehensive Risk Model

This study defines the Comprehensive Risk Function as:

$$F(B,t) = \omega_1 h(t) + \omega_2 G(B,t) \tag{7}$$

The Analytic Hierarchy Process (AHP) is adopted to determine the weights of Accuracy Risk and Temporal Risk: $\omega_1 = 0.75,\ \omega_2 = 0.25$.

3.4. Solution of the Comprehensive Risk Model

Clarification of Constraints:

(1) $10 \le t \le 25$ (gestational age, weeks)

(2) Constraint on Y-chromosome concentration: $y(t,B) \ge 0.04$

(3) Constraint on BMI range: $20 \le B \le 50$ (Body Mass Index, kg/m²)

As shown in Figure 3, K-Means Clustering for BMI Interval Division: The elbow method was used to determine the optimal K value as four. After performing K-Means clustering, at the 7th iteration, ε≈0.114, and the centroids barely moved, indicating stable clustering. Consequently, the BMI was divided into four intervals: [26.6, 30.2), [30.2, 33.8), [33.8, 37.5), and [37.5, 46.9].

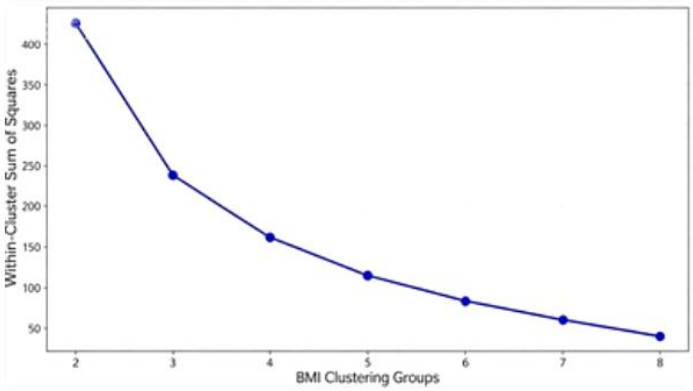

Figure 3. Elbow Plot

Particle Swarm Optimization (PSO) for Solution: The samples were divided into four groups based on BMI, and the mean BMI value of each group was calculated to fix the BMI parameter, rendering B a constant in the comprehensive risk function $F(B,t)$. Subsequently, with gestational age t as the sole variable, the Particle Swarm Optimization (PSO) algorithm was adopted to optimize the comprehensive risk function, aiming to achieve the global minimum of $F(B,t)$. In Figure 4, the abscissa represents the BMI interval groups of pregnant women, and the ordinate represents the optimal detection weeks corresponding to each group; specifically, the optimal detection weeks at the mean BMI values of the intervals [26.6, 30.2), [30.2, 33.8), [33.8, 37.5), and [37.5, 46.9] are 11.85 weeks, 13.22 weeks, 15.78 weeks, and 19.33 weeks, respectively.

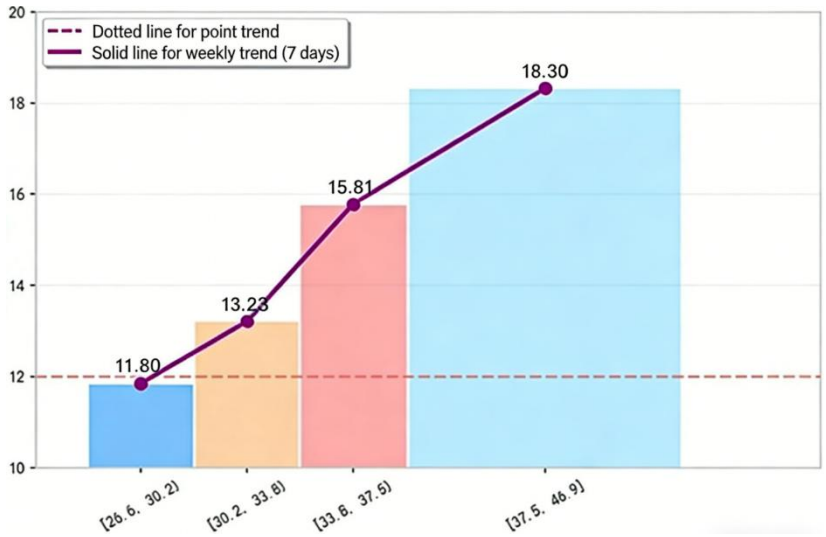

Figure 4. Results of Optimal NIPT Detection Time Points

3.5. Impact of Detection Errors on the Results

When analyzing the impact of detection errors on the results, the analysis mainly covers two aspects: the optimal NIPT detection time points and potential risks. In the field of biomedical testing, ±5% is classified as mild error and ±10% as moderate error—these are common error magnitudes in clinical NIPT concentration detection, capable of covering most error scenarios caused by instrument precision, sample processing, and other factors [10]. Therefore, these four error values were selected to simulate changes in the optimal NIPT detection time points when errors occur in Y-chromosome concentration detection. An analysis was conducted by combining the Y-chromosome concentration detection error magnitudes (-10%, -5%, 5%, and 10%) with different BMI intervals:

When the detection error is negative (i.e., the detected Y-chromosome concentration is lower than the actual value), the optimal NIPT detection time point shows a delayed trend. Specifically, when the error magnitude is -10%, the delay in the optimal time point for the BMI interval group [37.5, 46.9] reaches 2.66 weeks; when the error magnitude is -5%, the delay in the optimal time point for this interval group is 1.33 weeks. Further research found that as the BMI interval increases from [26.6, 30.2) to [37.5, 46.9] and the absolute value of the error increases from 5% to 10%, the delay in the optimal NIPT detection time point shows an increasing trend.

When the detection error is positive (i.e., the detected Y-chromosome concentration is higher than the actual value), the optimal NIPT detection time point shows an advanced trend. Specifically, when the error magnitude is 10%, the advancement of the optimal time point for the BMI interval group [37.5, 46.9] reaches 2.66 weeks; when the error magnitude is 5%, the advancement of the optimal time point for this interval group is 1.33 weeks. Similarly, as the BMI interval increases and the error magnitude increases from 5% to 10%, the advancement of the optimal NIPT detection time point also shows an increasing trend.

4. CONCLUSIONS

Through risk quantification modeling, clustering grouping, and intelligent algorithm optimization, this study determined the optimal non-invasive prenatal testing (NIPT) timing for pregnant women carrying male fetuses with different body mass index (BMI) values. It verified the positive correlation between BMI and detection risk, and clarified the regularity of how different detection errors influence the optimal testing timing. The proposed scheme in this study can reduce the detection risk of NIPT, improve the level of personalized medical care, provide more accurate decision support for fetal chromosomal abnormality screening, and safeguard maternal and infant health. Future research

can integrate more clinical indicators to optimize the risk model, thereby further enhancing the precision of timing selection.

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