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ORIGINAL RESEARCH

Analysis of Risk Factors and Prediction Model of Chromosomal Abnormalities in Embryos from Patients with Missed Miscarriage

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Purpose: To study the chromosome distribution characteristics in embryos of patients with missed miscarriage and analyze the risk factors of embryonic chromosomal abnormalities.

Methods: Clinical data were collected from 216 hospitalised patients diagnosed with missed miscarriages who successfully underwent embryo chromosomal analysis at the Urumqi Maternal and Child Health Hospital between January 2022 and August 2024. The distribution of embryonic chromosomes was investigated, and risk factors for chromosomal abnormalities were identified using multivariate logistic regression analysis. Based on the above-described results, a nomogram prediction model was established and validated. The receiver operating characteristic curve was plotted, the area under the curve (AUC) was calculated, and the calibration curve and clinical decision curve were plotted to verify the model discrimination, calibration, and clinical practicability.

Results: Our results showed that the rate of chromosomal abnormalities in patients with missed miscarriages was 66.67%; among these, trisomy 16 (45, X) and triploidy were the most common numerical abnormalities, while deletions were the predominant structural abnormality. Being underweight or overweight, insufficient or deficient in 25-hydroxyvitamin D, and having elevated thyroid-stimulating hormone levels were identified as risk factors for developing embryonic chromosomal abnormalities ($P<0.05$). Based on the above results, a nomogram prediction model was constructed with an AUC of 0.887 (95% CI: 0.833~0.940). The *Hosmer–Lemeshown* goodness-of-fit test indicated a good fit ($\chi^2 = 11.452$, $p = 0.177$) and the calibration and clinical decision curve results suggested good calibration degree and clinical practicability.

Conclusion: Chromosomal abnormalities are the main causes of missed miscarriages, with trisomy 16 and Turner syndrome being the most common among these. A close correlation between weight in women and embryonic chromosomal abnormalities was observed. Vitamin D deficiency or insufficiency and elevated thyroid-stimulating hormone levels may also contribute to increased risk of chromosomal abnormalities in embryos.

Keywords: miscarriage, chromosomal aberrations, body mass index, thyroid, vitamin D

Introduction

A missed miscarriage is a type of spontaneous abortion in which the embryo or fetus dies or stops developing, but remains in the uterine cavity instead of being expelled naturally in a timely manner.[1,2] This condition accounts for 10–20% of spontaneous abortions.[1,3] The cause of this condition is complex, and it is often diagnosed using ultrasonography.[4] Missed miscarriages are related to factors such as chromosomal, physiological, anatomical, endocrine function, and immunological abnormalities.[5] Research has found that women who are overweight or obese (BMI > 24 kg/m^2) have an increased risk of missed miscarriage.[1] Vitamin D deficiency is also closely

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associated with the occurrence of missed miscarriage.[6] Through a retrospective study, Fang et al[7] identified thyroid dysfunction and low vitamin D levels as potential risk factors for missed miscarriage. Furthermore, their model analysis revealed that the synergistic effects of these factors may increase the risk of missed miscarriage. Despite ongoing research, in nearly half of missed miscarriages, the cause remains unclear.[8] Currently, most studies indicate that chromosomal abnormalities in embryos are the most common cause of spontaneous abortion, accounting for over 50% of all miscarriages.[9–11] Nearly 50–70% of chorionic villi samples can be used to detect chromosomal abnormalities.[12] The most common abnormality found (with an incidence rate of up to 90%) is an abnormal number of chromosomes, as compared to structural chromosomal abnormalities which have an incidence rate of 6%.[10,12] Investigating the risk factors for chromosomal abnormalities in patients with missed miscarriages can help alleviate physical and emotional distress, reduce financial burden, lower the rate of recurrent miscarriages, and ultimately improve fertility rates.

Therefore, in this study, the chromosomal results of 216 patients with missed miscarriages from the Urumqi Maternal and Child Health Hospital were retrospectively analyzed to explore the distribution of embryonic chromosomes and the associated risk factors for chromosomal abnormalities, thereby provide a scientific reference for clinical prevention and treatment.

Materials and Methods

Participants

A total of 216 patients diagnosed with missed miscarriages who were admitted to Urumqi Maternal and Child Health Hospital from January 1, 2022 to August 30, 2024 and successfully underwent chromosomal microarray analysis (CMA) were enrolled. Based on the results of the chromosomal analysis, the research participants were divided into normal and abnormal groups. (a) Inclusion criteria: (1) Diagnosis of missed miscarriage or embryonic arrest using ultrasound. (2) Patients and their family members who signed an informed consent form for medical abortion or uterine evacuation surgery, as well as a sample retention consent form. (b) Exclusion criteria: (1) Previous clear analysis of the chromosomal karyotype of one or both spouses with abnormalities. (2) Patients who had a miscarriage caused by abnormalities in the reproductive tract anatomy. (3) Contaminated tissue.

Detection Method

(1) First, 25 mg of chorionic villus tissue was collected, rinsed with physiological saline to remove residual blood, and separated from other tissues. Simultaneously collected maternal peripheral blood as a control for subsequent contamination testing. Subsequently, deoxyribonucleic acid (DNA) was extracted and adjusted to a concentration of 50 ng/μL. After NspI enzyme digestion, common primers were ligated, and the DNA fragments were amplified to 150–2000 bp using polymerase chain reaction (PCR). DNA fragments (25–125 bp) were purified, labelled, placed on a chip for hybridization for 16–18 h, scanned, and analyzed after washing and dyeing. (2) Affymetrix chips were used for single nucleotide polymorphism and copy number variant (CNV) detection. All operations strictly followed the experimental procedures described by Affymetrix Corporation.

Data Analysis

Chromosome analysis suite software was used to process the results, and the analysis was conducted according to the 2011 American College of Medical Genetics standards and guidelines for the interpretation of microarray CNV results.[13] Test results were compared with data from the DECIPHER, DGV, Genes-NCBI, and 0MIM databases.

Clinical Data

The clinical data obtained for the research participants included age, height, weight, birth history, previous natural miscarriage frequency, 25-hydroxyvitamin D levels, and thyroid-stimulating hormone levels.

Statistical Analysis

Data processing and statistical analysis were conducted using the Statistical Package for the Social Sciences (version 25.0). The quantitative data did not conform to a normal distribution; the median (25th percentile and 75th percentile)

[M (P25, P75)] was used to represent data, and the non-parametric rank sum test was used for comparisons between groups. Count data were described as the number of cases (n) and percentages (%), and comparisons between groups were performed using the Chi-square test or Fisher's exact probability method. A multivariate logistic regression model was used for stepwise regression analysis. Furthermore, based on the meaningful indicators in multivariate logistic regression, a nomogram prediction model was constructed through the R4.4.2 related software package. The bootstrap method was used for the internal verification of the model. The receiver operating characteristic curve (ROC) was plotted to determine the area under the curve (AUC) and the 95% confidence interval (CI) to verify the discrimination level of the model. Calibration curve (CC) and decision curve analysis (DCA) curve were plotted to verify model calibration and clinical utility. The test level was $\alpha = 0.05$, using two-sided test. The differences were considered statistically significant at P-values of $p < 0.05$.

Results

Distribution of Embryo Chromosomal Abnormalities in Patients with Missed Miscarriage

Among the 216 patients with missed miscarriages, 144 had abnormal chromosomal results, with an incidence of 66.67%. Of these, a total of 135 cases had abnormal chromosome numbers, with an incidence rate of 62.50% (135/216), including trisomy (66.67%), (45, X) (17.78%) and triploidy (6.67%). Trisomy 16 was the predominant chromosomal abnormality, with an incidence of 26.67%. Nine cases of structural chromosomal abnormalities were detected by CMA, with an incidence rate of 4.17% (9/216); the most common structural chromosomal abnormality was deletion (77.78%), as shown in Figures 1 and 2.

Univariate Analysis of Embryonic Chromosomal Abnormality-Associated Risk Factors

Univariate analyses of age, body mass index (BMI), live birth history, number of previous spontaneous abortions, and 25-hydroxyvitamin D and thyroid-stimulating hormone levels between the two groups were performed. The results showed that there were significant differences in the rates of chromosomal abnormalities related to age, BMI, 25-hydroxy vitamin D levels, and thyroid-stimulating hormone levels (P<0.05), as shown in Table 1.

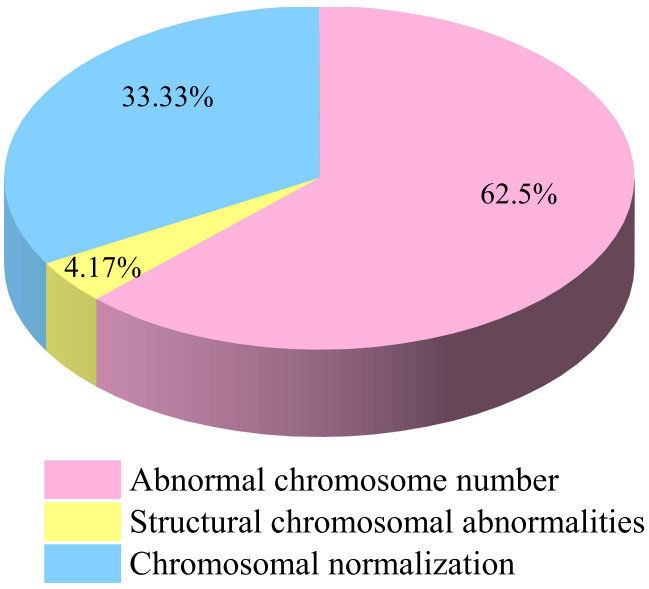

Figure 1 Distribution of all chromosomal abnormalities.

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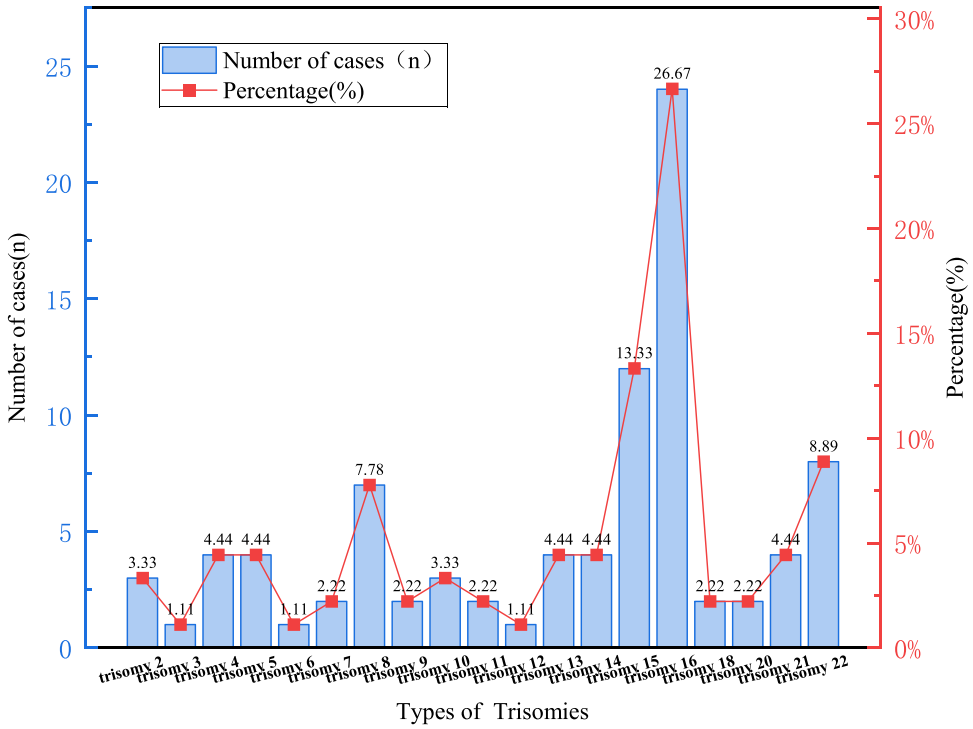

Figure 2 Distribution of different types of chromosomal trisomy.

Multivariate Analysis of Embryonic Chromosomal Abnormality-Associated Risk Factors

Statistically significant indices in the univariate analysis were assigned (Table 2) and included in the multivariate logistic regression model for analysis. The results showed that being underweight or overweight, 25-hydroxyvitamin D insufficiency

Table 1 Univariate Analysis of Risk Factors Related to Chromosomal Abnormalities

	Normal Group	Exception Group	Chromosomal Abnormality Rate (%)	Z/χ^2	*P*
Age (years)				8.064	0.005
≤30	39	49	55.68		
>30	33	95	74.22		
BMI (kg/m^2)				17.060[a]	0.001
Underweight (<18.5)	2	12	85.71		
Normal (18.5–23.9)	59	77	56.62		
Overweight (24–27.9)	9	39	81.25		
Obese (28)	2	16	88.89		
Obstetric history				1.117	0.324
Yes	14	20	58.82		
No	58	124	68.13		
Previous natural miscarriage frequency				0.164	0.685
No	46	96	67.61		
≥1	26	48	64.86		
25 Hydroxyvitamin D (ng/mL)				90.300	<0.001
Normal (30–100)	38	3	7.32		
Insufficient (>20 to <30)	15	21	58.33		
Deficient (≤20)	19	120	86.33		
Thyroid-stimulating hormone (mIU/L)	1.58 (1.31, 1.90)	2.29 (1.60, 3.37)		−5.095	<0.001

Note: [a]Exact Fisher method.
Abbreviation: BMI, body mass index.

Table 2 Chromosome Abnormality-Related Risk Factor Coding Table

Factors	Variable Name	Code Explanation
Chromosome results	Y	0 = "Normal", 1 = "Exception"
Age	X1	0 = "≤30", 1 = ">30"
BMI	X2	0 = "Normal", 1 = "Underweight", 2 = "Overweight", 3 = "Obese"
25 Hydroxyvitamin D	X3	0 = "Normal", 1 = "Insufficient", 2 = "Lack"

Abbreviation: BMI, body mass index.

Table 3 Logistic Regression Analysis of Risk Factors Related to Chromosomal Abnormalities

Factors	*B*	*SE*	*Wald*χ^2	*P*	*OR*	95% CI	
						Lower Limit	Upper Limit
Age	0.505	0.416	1.472	0.225	1.657	0.733	3.744
BMI			8.964	0.030			
Underweight	2.347	1.183	3.935	0.047	10.457	1.029	106.326
Overweight	1.252	0.570	4.828	0.028	3.499	1.145	10.693
Obese	1.118	0.848	1.735	0.188	3.057	0.580	16.127
25 Hydroxyvitamin D			37.424	<0.001			
Insufficient	3.011	0.816	13.622	<0.001	20.309	4.104	100.493
Deficient	4.432	0.768	33.288	<0.001	84.115	18.663	379.113
Thyroid-stimulating hormone	0.577	0.180	9.565	0.002	1.746	1.226	2.486
Constant	−4.528	0.888	26.008	<0.001	0.011		

Abbreviation: BMI, body mass index.

or deficiency, and having elevated thyroid-stimulating hormone levels were risk factors for developing chromosomal abnormalities in embryos (P<0.05; Table 3).

Nomogram Prediction Model Construction

Based on the results of the multi-factor logistic regression analysis, factors with statistical significances ($p < 0.05$) included BMI, 25-hydroxyvitamin D, and thyroid-stimulating hormone as nomogram model construction predictors. The above-mentioned factors were scored individually, and the total score was calculated by accumulating the individual scores of each factor to observe the probability corresponding to the total score. The nomogram model in this study revealed that the thyroid-stimulating hormone score accounted for a substantial proportion, followed successively by those of the 25-hydroxyvitamin D and BMI (Figure 3).

Nomogram Prediction Model Validation

The area under the ROC of the model was 0.887 (95% CI: 0.833~0.940), indicating that the model displayed a good discrimination degree (Figure 4). The Hosmer–Lemeshow goodness of fit test yielded $\chi^2 = 11.452$, $p = 0.177$, indicating a good calibration level. The results of calibration and clinical decision curves suggest that the calibration degree and clinical practicability of the model are good (Figure 5). A clinical decision curve was drawn to assess the clinical utility of the model. The red line represents the net benefit of the model in chromosomal abnormality-related risk prediction in embryos of patients with missed miscarriage. The gray line, slope, and black line represent that all patients triggered the intervention, the net benefit, and that none of the patients had triggered the intervention with a net benefit of zero, respectively. The results indicated that the red line was higher than the gray and black lines, indicating that the model exhibited strong clinical practicability (Figure 6).

Discussion

Chromosomal abnormalities in embryos are the primary cause of miscarriages, leading to adverse outcomes in nearly 50% of pregnancies.[14] All patients with missed miscarriage in this study underwent CNV testing. This technology can detect deletions

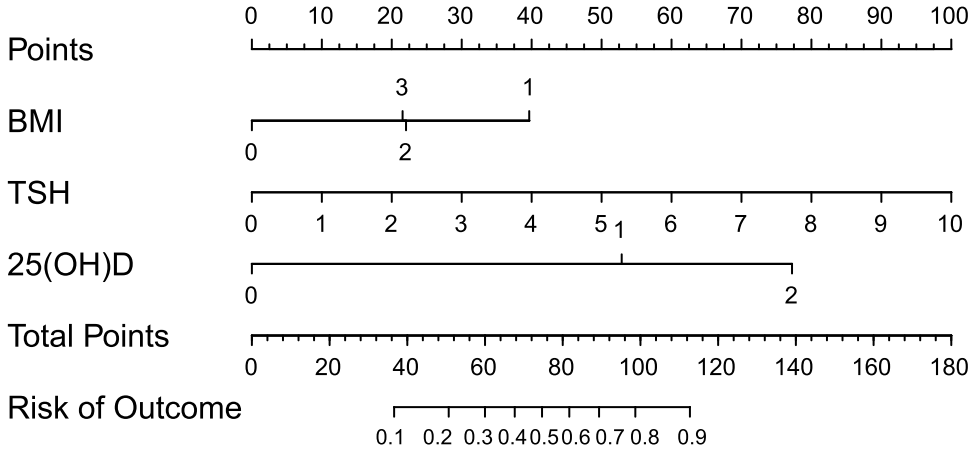

Figure 3 Nomogram model of risk factors associated with chromosomal abnormalities in embryos.

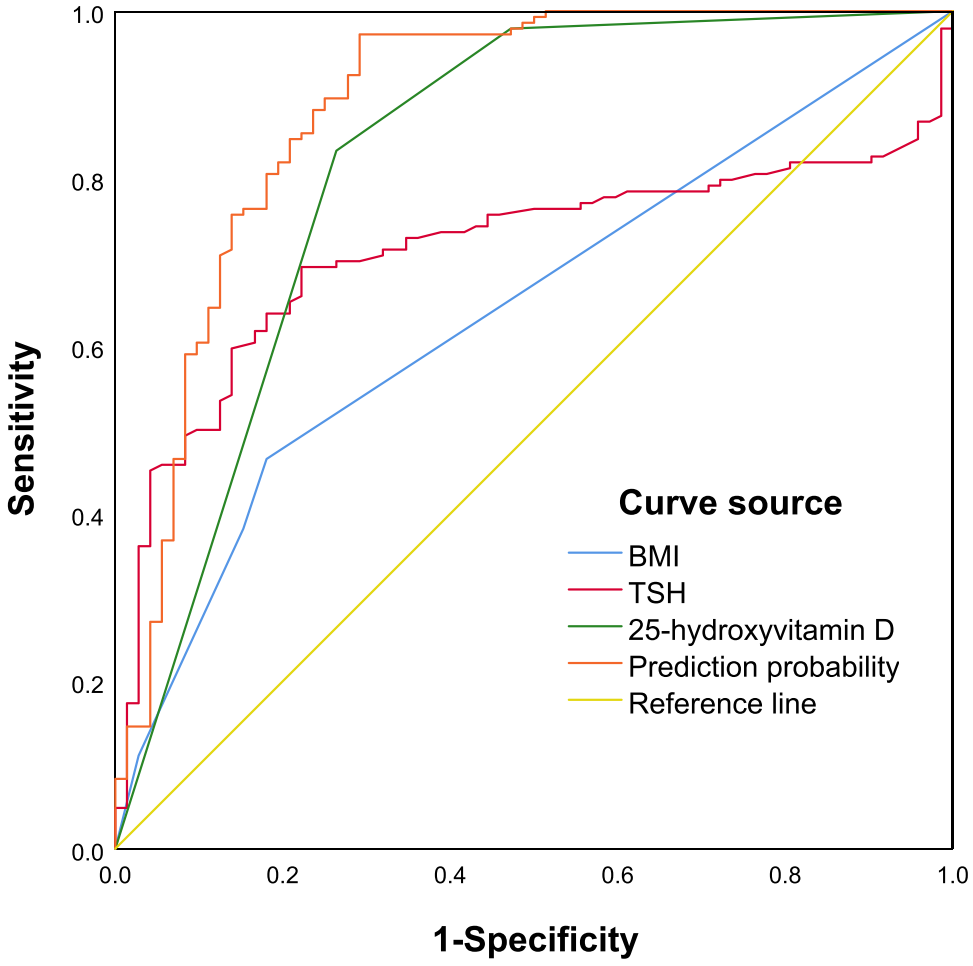

Figure 4 Single-variable ROC and overall ROC.

or duplications of chromosomal segments beyond traditional methods, specifying their size and location. The incidence of chromosomal abnormalities in patients with missed miscarriages in this study was 66.67%, which is consistent with the 66.80% reported by Qin et al,[15] and higher than the 56.40% reported by Lei et al.[16] Notably, Lei et al[16] used next-generation sequencing-based short tandem repeat detection in combination with low-pass CNV sequencing, a novel approach that

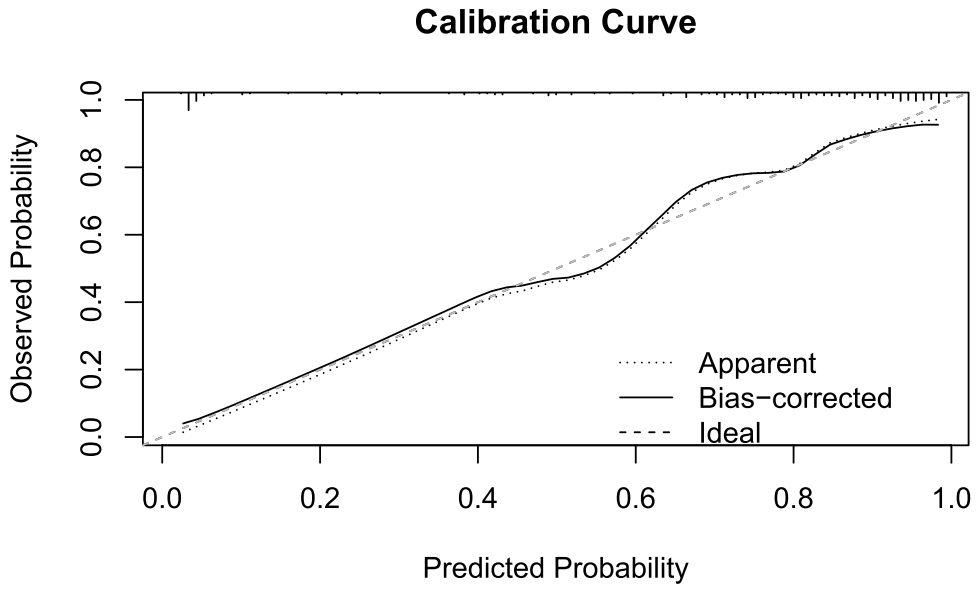

Figure 5 Calibration curve of the nomogram prediction model.

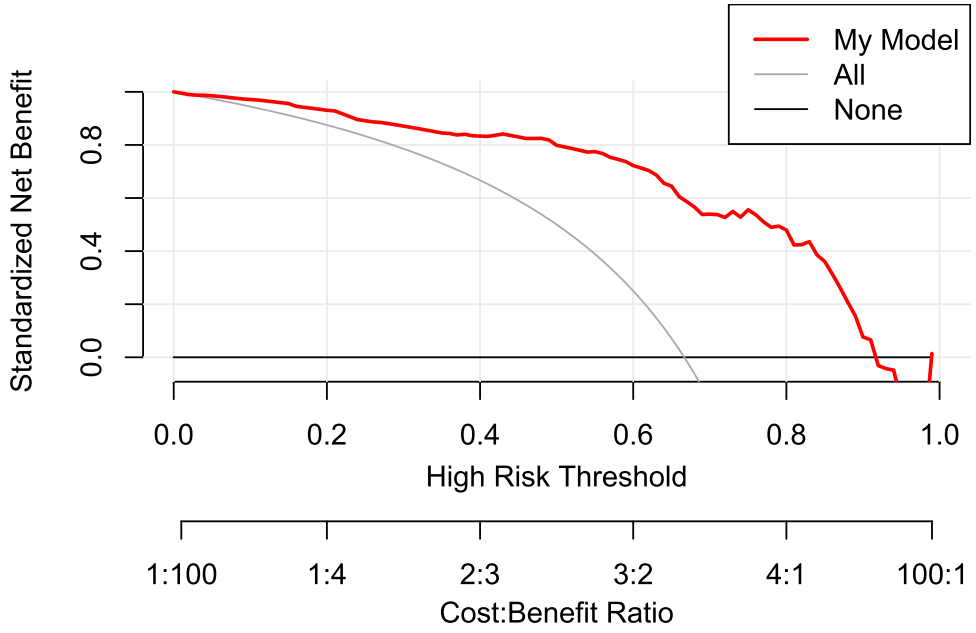

Figure 6 DCA curve of the nomogram prediction model.

enhances the detection rate of chromosomal abnormalities and identifies the parental origins of abnormal chromosomes. However, not all patients with missed miscarriages at our center underwent chromosomal examination, despite chromosomal abnormalities being a significant cause of miscarriages.

Embryonic chromosomal abnormalities include numerical and structural abnormalities, with numerical abnormalities being more common. The occurrence of aneuploidy may be related to meiosis during germ cell formation, in which the non-disjunction of homologous chromosomes leads to differences in the number of chromosomes in embryos.[14] Zhu et al[17] found that trisomy 16 was the predominant abnormality found in a sample of 1355 aborted tissues, which is consistent with the results of this study. In addition, we found that patients with a history of previous spontaneous abortions had similar detection rates for chromosomal abnormalities. Patients with missed miscarriages may have

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chromosomal abnormalities regardless of whether they have experienced one or multiple spontaneous abortions in the past. Therefore, chromosomal examination is recommended for such patients to guide future pregnancy planning and management.

The impact of age on pregnancy has long been a focal point in medical research. A longitudinal missed miscarriage study revealed that for every additional year of a woman's age, the risk of embryonic chromosomal abnormalities increases by approximately 14%, while the risk of miscarriage rises by 15%.[1] Women exhibit peak fertility between the ages of 20 and 30. As age advances, the quantity of eggs gradually diminishes and egg quality progressively declines, leading to a corresponding increase in miscarriage risk.[18] In this study, the chromosomal abnormality rate among women over 30 reached 74.22%. Unfortunately, due to sample size limitations, we were unable to further establish an association between advanced maternal age and chromosomal abnormalities in patients with missed miscarriage. Nevertheless, the adverse effects of advanced maternal age on chromosomal integrity cannot be overlooked. Research indicates that mitochondria are critically important for both oocyte and embryo development, and mitochondrial function has been demonstrated to be closely associated with pregnancy outcomes.[19] With advancing age, female oocyte quality declines, the microenvironment undergoes alterations, and oxidative stress levels increase. This leads to abnormalities in oocyte mitochondrial coding, subsequently disrupting meiosis and resulting in pregnancy failure.[19]

Additionally, body mass index (BMI) is closely associated with pregnancy outcomes. In recent years, multiple studies have confirmed that overweight or obesity constitutes an independent risk factor for missed miscarriage,[2,20] yet its impact on chromosomal abnormalities remains underreported. Therefore, investigating the influence of BMI on chromosomal abnormalities is crucial for guiding subsequent pregnancies and improving global female fertility rates. In 2004, the World Health Organization (WHO) established the following BMI standards: obesity as a BMI $\geq$ 30 kg/m^2 and overweight as a BMI between 25.0–29.9 kg/m^2.[21] However, influenced by geographical environment and dietary habits, Asian populations exhibit higher rates of diabetes and cardiovascular disease even at BMIs below 25 kg/m^2. Consequently, the WHO recommends applying stricter standards to Asian populations.[21] As all subjects in this study were from China, the Chinese criteria were adopted herein. In this study, compared to women of normal weight, overweight women exhibited a more than threefold increased risk of embryonic chromosomal abnormalities. This may be related to impaired oocyte quality caused by chromosomal mechanisms.[22] Tang et al[23] demonstrated through mouse experiments that maternal obesity can induce meiotic defects in oocytes, leading to abnormal chromosomal recombination. Furthermore, elevated levels of oxidative stress markers in the follicular fluid environment of women with high BMI can impair mitochondrial function in oocytes. As the primary energy source for oocyte development and accurate chromosome segregation, mitochondrial dysfunction leads to insufficient energy supply, thereby triggering chromosomal segregation errors.[24] Concurrently, being underweight or overweight may induce ovulation issues, impairing oocyte development capacity and reducing endometrial receptivity.[25] Therefore, maintaining a healthy weight plays a crucial role in preventing missed miscarriages caused by embryonic chromosomal abnormalities.

Recently, the role of vitamin D in female reproduction has attracted considerable attention in research. Although the exact mechanisms underlying its effects remain unclear, the potential immune-regulatory and potent anti-inflammatory effects of vitamin D cannot be overlooked. Maternal vitamin D deficiency may lead to decreased maternal immune function, thereby affecting reproductive disorders and increasing the risk of spontaneous miscarriage.[26–28] In this study, the prevalence of chromosomal abnormalities in the embryos of females with 25-hydroxyvitamin D insufficiency and deficiency was 58.33% and 86.33%, respectively. Therefore, vitamin D deficiency was correlated with an increased proportion of embryonic chromosomal abnormalities, which is consistent with the findings of Du et al.[26] Vitamin D may be involved in human cell proliferation and differentiation. Notably, vitamin D deficiency or insufficiency may lead to a decrease in follicle quality during fertilization, improper separation during meiosis, or other abnormalities, resulting in an increased occurrence of embryonic chromosomal abnormalities.[26,29]

Thyroid disease is common among women of childbearing age. Elevated thyroid-stimulating hormone is associated with an increased risk of spontaneous abortion[30–32] and is thought to be associated with thyroid dysfunction or potential disruption of immune tolerance.[33] Previous studies found a correlation between TGAb, TPOAb, and X chromosome monomers in the chorionic tissues of patients who had experienced a missed miscarriage.[34] However, there have been no reports of a correlation between TSH levels and embryonic chromosomal abnormalities in missed miscarriages. In the

present study, women with excessively high TSH levels were more likely to develop embryonic chromosomal abnormalities, which may be related to telomere shortening due to TSH. Telomeres are regions of repeating nucleotide sequences at the ends of chromosomes that prevent chromosomes from fusing to ensure complete replication.[35] This was also confirmed by Ohadi et al,[36] who found that TSH levels in the neonatal cord blood were inversely correlated with relative telomere length. Thus, women should be encouraged to adjust their TSH levels during pregnancy to support a healthy pregnancy.

In recent years, the nomogram model has been widely used for disease and survival prediction. For disease risk prediction, the model is mostly used through logistic or Cox regression analyses and cumulative score. The analysis results are visualized, representing a relevant value for clinical guidance. In this study, meaningful factors were screened by multifactorial logistic analysis, based on which the prediction model was constructed, and the model was validated by drawing ROC, calibration, and DCA curves. The results indicated that the line length of each index in the model could clearly reflect its different contribution rate and individualized risk assessment. The area under the ROC curve was 0.887, suggesting that the model displayed a better differentiation. The Hosmer–Lemeshown goodness-of-fit test yielded $\chi^2 = 11.452$ and $p = 0.177$, indicating a good calibration. The results of the clinical decision curve showed that the net clinical benefit rate of the patients was higher than the two extreme modalities, suggesting good clinical utility for the predictive model.

This was a single-center, small-sample, retrospective study. Therefore, because of time limitations, limited economic resources, and limited public awareness, only hospitalized patients with missed miscarriages were included in the study. In addition, no clinical data such as age, BMI, or sperm counts, were collected from the male partners, and this may contribute to bias. In the future, collaborative, multicenter, and long-term prospective studies should be conducted to further explore the relevant risk factors and mechanisms of chromosomal abnormalities in patients with missed miscarriage. This will provide better guidance for clinical genetic counselling and early intervention, ultimately improving women's reproductive health and increasing fertility.

In summary, embryonic chromosomal abnormalities are a strong risk factor for missed miscarriage, and trisomy (45, X), triploidy, and trisomy 16 are the predominant abnormalities. There was a close correlation between female weight status and the rate of embryonic chromosomal abnormalities. Vitamin D deficiency or insufficiency and elevated TSH levels may increase the occurrence of foetal chromosomal abnormalities. The nomogram model constructed based on the above-described influencing factors could effectively predict the risk of chromosomal abnormality in embryos, thereby providing a reference for clinical prevention and treatment.

Abbreviations

BMI, body mass index; CMA, chromosomal microarray analysis; CNV, copy number variant; TSH, thyroid stimulating hormone.

Data Sharing Statement

The data supporting this article are available from the corresponding author on reasonable request.

Ethics Approval

This study was reviewed and approved by the Medical Ethics Committee of Urumqi Maternal and Child Health Hospital (Ethics Approval No. XJFYLL2024010; 8th January, 2024), following the ethical principles of the Declaration of Helsinki on medical research. Written informed consent was obtained from all participants.

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Disclosure

The authors declare no conflicts of interest in this work.

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