# *Original Article* Construction and validation of a novel nomogram for predicting spontaneous preterm birth in patients with gestational diabetes mellitus

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Abstract: Objective: To explore the influencing factors of spontaneous preterm birth (sPTB) in patients with gestational diabetes mellitus (GDM) and construct a nomogram model. Methods: A retrospective analysis was conducted on the clinical data of 289 GDM patients who gave birth at Yangzhou University Affiliated Hospital from January 2021 to December 2022. The patients were divided into the sPTB (n = 52) and non-sPTB (n = 237) groups based on whether sPTB occurred. Logistic multivariate analysis was used to explore the influencing factors of sPTB in GDM patients and construct a nomogram model. The predictive performance of the nomogram model was evaluated using ROC curves and calibration curves in internal validation. Additionally, 62 GDM patients who visited Yangzhou University Affiliated Hospital from January 2023 to June 2023 were retrospectively selected for external validation of the prediction model. Results: Logistic analysis showed that maternal age ≥30 years, pre-pregnancy BMI ≥26.3 kg/m<sup>2</sup>, history of spontaneous abortion, premature rupture of membranes, and oral glucose tolerance test (OGTT) fasting blood glucose ≥5.1 mmol/L were independent risk factors for sPTB in GDM patients (all P<0.05). In internal validation, the AUC value of the model's ROC curve was 0.901, and in external validation, the AUC value was 0.939. The calibration curve showed that the predicted probability was consistent with the actual probability. In addition, the sensitivity, specificity, and accuracy of the model in external validation were 84.21%, 81.40%, and 82.26%, respectively. Conclusion: Maternal age ≥30 years, pre-pregnancy BMI ≥26.3 kg/m<sup>2</sup>, history of spontaneous abortion, premature rupture of membranes, and OGTT fasting blood glucose ≥5.1 mmol/L are independent risk factors for sPTB in GDM patients. The nomogram model based on these risk factors has high discrimination and accuracy in predicting sPTB in GDM patients.

Keywords: Gestational diabetes mellitus, spontaneous preterm birth, logistic regression analysis, nomogram model

#### **Introduction**

Gestational diabetes mellitus (GDM) is a condition characterized by abnormal glucose metabolism first detected during pregnancy [1]. This condition is associated with an increased risk of metabolic disorders in both pregnant women and their babies, as well as adverse outcomes such as spontaneous preterm labor and fetal developmental abnormalities. These issues significantly impact the health of both mother and child [2]. Premature birth is the leading cause of neonatal mortality, with approximately 70% attributed to spontaneous preterm birth (sPTB) [3]. Research indicates that women with GDM have a significantly higher incidence of sPTB, up to 20%, thereby substantially elevating the risk of adverse pregnancy outcomes [4].

Furthermore, premature birth not only adversely affects perinatal outcomes but also imposes increased burdens on families and society. Therefore, preventing and treating sPTB in GDM patients is crucial to improving pregnancy outcomes and reducing the incidence of sPTB.

sPTB is a complex pregnancy outcome influenced by multiple factors. Genetic factors play a significant role, with specific genetic variations associated with an increased risk of PTB [5]. Maternal health status is another important factor, with complications such as hypertension and kidney disease being associated with an increased risk of PTB in GDM patients [6]. Additionally, pregnancy-related infections and inflammation are key factors promoting PTB, potentially increasing risk by inducing inflam-

matory responses and altering the cervical environment [7]. Environmental factors, including socio-economic status, residential environment, and occupational exposure, also significantly impact the risk of sPTB. For example, women exposed to high stress, adverse living conditions, or harmful chemicals over a long period have a higher risk of PTB [8]. Lifestyle factors, such as diet, weight management, and exercise habits, also play an essential role in preventing PTB. An unbalanced diet and excessive weight gain can increase the risk of PTB [9]. Women with a history of PTB are at a higher risk of experiencing PTB again [10]. Cervical abnormalities, such as cervical shortening or insufficiency, are also significant factors leading to spontaneous PTB [11]. Finally, psychosocial factors such as psychological stress, anxiety, and depression in pregnant women are associated with an increased risk of PTB, potentially by affecting hormone levels and immune system function [12].

In summary, sPTB is a complex pathological process involving multiple factors and pathways, necessitating comprehensive consideration for effective prevention and intervention. Currently, the prediction of sPTB in GDM patients mainly relies on clinical indicators and biochemical tests, which have limited sensitivity and specificity. With the development of big data and artificial intelligence, medical prediction models have become more accurate and efficient. The nomogram, as a visual prediction model, has been widely used in the risk assessment of various diseases. Nomograms can comprehensively analyze multiple variables, thereby promoting personalized healthcare and assisting in clinical decision-making [13]. Based on this, our study analyzes the risk factors affecting sPTB in GDM patients and constructs a nomogram prediction model to make reasonable predictions. Additionally, clinical validation is conducted to provide theoretical guidance for improving pregnancy outcomes in GDM patients.

# Materials and methods

# *General information*

This study was approved by the Ethics Committee of The Affiliated Hospital of Yangzhou University. A retrospective analysis was conducted on the clinical data of 289 patients with GDM who gave birth at The

Affiliated Hospital of Yangzhou University between January 2021 and December 2022. The patients were categorized into two groups based on the occurrence of sPTB: a sPTB group  $(n = 52)$  and a non-sPTB group  $(n = 237)$ .

The sample size calculation method was as follows: According to reports, the incidence of PTB in GDM patients is 25%. Assuming the same incidence in this study, it is expected to include 6 variables in a multivariate regression model, and the sample size was calculated using the empirical method (EPV). When EPV =  $10$ , the required number of GDM patients is 10 × 6/0.25 = 240. Considering a dropout rate of about 20% and the specific situation of mothers with GDM admitted to our hospital, a final sample size of 289 cases was included.

Inclusion criteria: (1) Diagnosis of GDM in accordance with the guidelines for the diagnosis and treatment of hyperglycemia during pregnancy [14]; (2) Meeting the diagnostic criteria of sPTB in the "Guidelines for the Diagnosis and Treatment of PTB" [15]: 28 to 37 weeks of gestation, regular uterine contractions, accompanied by cervical canal shortening ≥80% and cervical dilation.

Exclusion criteria: (1) Incomplete clinical data; (2) Presence of infectious diseases; (3) Complications with heart, liver, or kidney dysfunction; (4) Iatrogenic PTB.

Furthermore, 62 GDM patients who met the criteria at the Affiliated Hospital of Yangzhou University from January 2023 to June 2023 were selected for clinical validation of the prediction model (Figure 1).

# *Data collection*

Data collected included gestational age, prepregnancy body mass index (BMI), education level, gestational age at delivery, gravidity, parity, age of menarche, history of cesarean section, lower reproductive tract infection, history of spontaneous abortion, family history of diabetes, premature rupture of membranes (PROM), hypertension, and oral glucose tolerance test (OGTT) fasting blood glucose levels.

# *Statistical analysis*

Data were analyzed using SPSS 27.0 and R 4.2.1 software. The factors affecting spontaneous preterm birth in GDM patients were ana-



Figure 1. Flow chart of sample inclusion and exclusion.

lyzed using univariate analysis. Categorical data were expressed as frequencies and analyzed using the Chi-square test. Continuous data were represented as means and standard deviations and analyzed using the independent sample t-test. A P-value of <0.05 was considered statistically significant. The receiver operating characteristic (ROC) curve for a single continuous variable was obtained using Med-Calc software, and the area under the curve (AUC) and the optimal cutoff value were calculated. Logistic regression analysis was used to identify independent risk factors for sPTB in GDM patients. R software was used to create a nomogram of predictive factors, illustrating the

proportion of factors affecting sPTB in GDM patients. ROC and calibration curves were used to validate the predictive ability of the model.

# Results

# *Comparison of clinical data*

Among the 289 patients, there were 52 sPTB and 237 non-sPTB. In the sPTB group, the mean maternal age was 33.52±3.84 years, the mean pre-pregnancy BMI was 26.73±3.37 kg/m<sup>2</sup>, 24 cases (46.15%) had a history of cesarean section, 22 cases (42.31%) had a history of spontaneous abortion, and 28 cases (53.85%) experienced PROM. Additionally, 18 cases (34.62%) had OGTT fasting blood glucose ≥5.1 mmol/L.

In the non-sPTB group, the mean maternal age was 28.47±3.30 years, the mean pre-pregnancy BMI was  $24.36 \pm 1.57$  kg/m<sup>2</sup>, 74 cases (31.22%) had a history of cesarean section, 50 cases (21.10%) had a history of spontaneous abortion, 70 cases (29.54%) experienced PROM, and 41 cases (17.30%) had OGTT fasting blood glucose levels ≥5.1 mmol/L. The proportions of maternal age,

pre-pregnancy BMI, history of cesarean section, history of spontaneous abortion, PROM, and OGTT fasting blood glucose levels ≥5.1 mmol/L were significantly higher in the preterm birth group than in the non-sPTB group (all P<0.05), as shown in Table 1.

# *ROC curve analysis of correlated variables*

The ROC curve analysis was conducted on three statistically significant continuous variables: maternal age, pre-pregnancy BMI, and gestational week at delivery. ROC curves were obtained using MedCalc software, and the AUC and optimal cutoff values were calculated. The AUC for maternal age, pre-pregnancy BMI, and

Index	Non-spontaneous preterm birth group ( $n = 237$ )	Spontaneous preterm birth ( $n = 52$ )		P
Gestational age (years)	28.47±3.30	33.52±3.84		< 0.001
Pre-pregnancy BMI	24.36±1.57 26.73±3.37		8.795	< 0.001
Degree of education			0.517	0.472
College or below	101 (42.62) 25 (48.08)			
College or above	136 (57.38)	27 (51.92)		
Pregnant times (times)	$2.63 \pm 0.98$ $2.63 \pm 0.99$		0.039	0.969
Production times (times)	$1.51 \pm 0.76$ $1.62 \pm 0.87$		0.840	0.401
Age at menarche (years)	$13.71 \pm 1.09$ $13.62 \pm 1.01$		0.591	0.555
History of cesarean section			4.242	0.039
Yes	74 (31.22)	24 (46.15)		
No	163 (68.78)	28 (53.85)		
Lower genital tract infections			1.378	0.240
Yes	93 (39.24)	25 (48.08)		
No	144 (60.76)	27 (51.92)		
History of spontaneous abortion			10.256	0.001
Yes	50(21.10)	22 (42.31)		
<b>No</b>	187 (78.90)	30 (57.69)		
Family history of diabetes			0.537	0.464
Yes	40 (16.88)	11(21.15)		
<b>No</b>	197 (83.12)	41 (78.85)		
Premature rupture of membranes			11.245	< 0.001
Yes	70 (29.54)	28 (53.85)		
<b>No</b>	167 (70.46)	24 (46.15)		
Combined hypertension			2.717	0.099
Yes	33 (13.92)	12 (23.08)		
<b>No</b>	204 (86.08)	40 (76.92)		
OGTT fasting blood glucose (mmol/L)			7.870	0.005
$\geq 5.1$	41 (17.30)	18 (34.62)		
5.1	196 (82.70)	34 (65.38)		
OGTT 1 h blood glucose (mmol/L)			0.896	0.344
$\geq$ 10	115 (48.52)	29 (55.77)		
< 10	122 (51.48)	23 (44.23)		
OGTT 2 h blood glucose (mmol/L)			0.560	0.454
$\geq 8.5$	96 (40.51)	24 (46.15)		
< 8.5	141 (59.49)	28 (53.85)		

Table 1. Comparison of the clinical data between the groups

Note: BMI: body mass index; OGTT: Glucose tolerance test.





Note: BMI: body mass index.

gestational week at delivery were 0.847 and 0.783, with optimal cutoff values of 30 and

26.3, respectively, as shown in Table 2 and Figure 2.



Figure 2. ROC curves for relevant variables. Note: BMI: body mass index.

#### *Multivariate logistic analysis*

Multivariate logistic regression analysis was employed to investigate the factors influencing sPTB in patients with GDM. Variables included in the analysis were maternal age, pre-pregnancy BMI, gestational week at delivery, history of cesarean section, history of spontaneous abortion, PROM, and OGTT fasting blood glucose. The variable assignments are shown in Table 3. Logistic regression analysis showed that maternal age (≥30 years), pre-pregnancy BMI (≥26.3 kg/m2), history of cesarean section, history of spontaneous abortion, PROM, and OGTT fasting blood glucose (≥5.1 mmol/L) were independent risk factors for spontaneous preterm birth in GDM patients (all P<0.05), as demonstrated in Table 4.

# *Construction of nomogram prediction model*

A nomogram was constructed using maternal age, pre-pregnancy BMI, gestational age at delivery, history of cesarean section, history of spontaneous abortion, PROM, and fasting plasma glucose during OGTT as predictors. The logistic regression equation was: Logit  $(P)$  = 2.840 × gestational age + 32.902 × pre-pregnancy BMI +  $1.739 \times$  history of spontaneous abortion  $+ 1.589 \times PROM + 1.498 \times OGTT$  fasting blood-glucose - 5.978, as demonstrated in Figure 3, by mapping each clinical feature of the patient to the upper scale, the corresponding score can be obtained, and the total score can be calculated. The total score can then be mapped to the lower scale to determine the probability of sPTB.

#### *Validation of nomogram prediction models*

The nomogram was evaluated using both a training set and a validation set for discrimination and calibration. The results showed that the AUC value of the ROC curve in the training set was 0.901, and in the validation set, it was 0.939, indicating that the nomogram had good discrimination (Figure 4). The calibration curve was used to assess the model's calibration accuracy. When the predicted probability closely aligns with the actual probability, the dashed line will closely follow the reference line. The results showed that the predicted probability closely aligned with the actual probability, indicating that the nomogram had good calibration (Figure 5).

# *Clinical validation of a nomogram prediction model for sPTB in patients with GDM*

A total of 62 GDM patients who met the criteria at The Affiliated Hospital of Yangzhou University from January 2023 to June 2023 were retrospectively selected for clinical validation of the prediction model. The results showed that the sensitivity was 84.21% (16/19), the specificity was 81.40% (35/43), and the accuracy was 82.26% ((16+35)/62). See Table 5 for details.

# **Discussion**

PTB is one of the most complex and critical challenges in obstetrics, with sPTB being the most common type. In China, the incidence of PTB ranges from 5% to 15%, with premature infants often prone to respiratory distress syndrome, sepsis, and other conditions [16]. sPTB not only increases the medical burden during pregnancy but also raises maternal and infant morbidity and mortality rates [17]. Therefore, investigating and assessing the potential risk factors associated with spontaneous preterm labor in patients with GDM is crucial for developing effective management strategies.

This study analyzed the clinical data of 289 GDM patients. The results indicated that maternal age (≥30 years), pre-pregnancy BMI (≥26.3 kg/m<sup>2</sup>), history of cesarean section, history of spontaneous abortion, PROM, and OGTT fasting blood glucose (≥5.1 mmol/L) were independent risk factors for spontaneous preterm





Note: BMI: body mass index; OGTT: Glucose tolerance test.

delivery in GDM patients. These findings enhance clinicians' understanding of the risk of PTB in GDM patients and provide a basis for early intervention.

Advanced maternal age has multifaceted effects on the risk of spontaneous abortion in GDM patients [18]. Biologically, advanced age may be associated with changes such as decreased ovarian reserve and reduced egg quality, increasing the risk of spontaneous abortion. Zhu et al. [19] noted that as age increases, the quality and quantity of follicles decline, directly affecting fertility and pregnancy outcomes. Genetically and epigenetically, age-related accumulation of genetic damage and epigenetic changes may impair embryo growth, raising the risk of miscarriage. Kordowitzki et al. [20] found that with increasing maternal age, fertilized eggs exhibited lower quality and developmental ability, increasing the risk of adverse pregnancy outcomes due to aneuploidy, oxidative stress, and other factors.

From a metabolic and endocrine perspective, advanced maternal age may alter metabolic and endocrine systems, affecting placental function and fetal development, and thereby increasing the risk of miscarriage in GDM patients. GDM itself poses challenges of insulin resistance and glucose metabolism disorders. Aging-associated endocrine changes can exacerbate these issues, leading to hormonal imbalances that impair placental nutrition and oxygen supply, thus increasing the risk of miscarriage [21]. Clinically, special attention should be given to older GDM patients with regular prenatal monitoring to detect issues early and implement preventive interventions to reduce adverse pregnancy outcomes.

Current studies have shown that an increase in pre-pregnancy BMI elevates the incidence of GDM in pregnant women, leading to higher rates of macrosomia and large-for-gestational-age infants. Additionally, it may induce pregnancy complications such as difficult labor, postpartum hemorrhage, and PTB [22]. This study found a significant association between maternal sPTB risk and increased pre-pregnancy BMI. Higher BMI may affect

pregnancy outcomes through various biological mechanisms.

Firstly, high BMI is associated with increased insulin resistance, which can lead to an imbalance in glucose metabolism, affecting placental function and fetal development [23]. Secondly, obesity-related chronic low-grade inflammation may damage placental formation, increasing the risk of PTB [24]. Additionally, alterations in hormone levels, particularly sex hormones and other pregnancy-related hormones, may be influenced by increased BMI, affecting uterine stability and the maintenance of pregnancy [25].

Increased mechanical pressure due to high BMI may place additional stress on the uterus and pelvis, impacting placental blood supply [26]. Vascular changes, including endothelial dysfunction and vascular inflammation, may also result from obesity, affecting uterine spiral artery remodeling and placental blood supply [27]. Lian et al. [28] found that, compared to mothers with normal pre-pregnancy BMI, those with low or high pre-pregnancy BMI had a significantly increased risk of PTB. Mayo et al. [29], in a large sample study involving 2,645,950 parturients, showed that compared to women of the same race/ethnicity with a BMI of 26 kg/m<sup>2</sup>, those with a BMI of 28 kg/m<sup>2</sup> had a significantly higher risk of sPTB.

Overall, increased pre-pregnancy BMI contributes to a higher incidence of GDM and PTB through various mechanisms. This emphasizes the importance of pregnancy weight management and a healthy lifestyle to prevent adverse pregnancy outcomes. Strengthening preconception care services, early intervention, and actively guiding women to control their prepregnancy BMI within a reasonable range are

Variables of interest	B	SE	Wald	0R	P	95% CI
Age of Pregnancy	2.840	0.543	27.387	17.118	< 0.001	5.909-49.590
Pre-pregnancy BMI	2.902	0.505	32.989	18.214	< 0.001	6.766-49.035
History of cesarean section	0.575	0.440	1.708	1.778	0.191	0.750-4.214
History of spontaneous abortion	1.739	0.523	11.050	5.694	< 0.001	2.042-15.881
Premature rupture of membranes	1.589	0.464	11.716	4.900	< 0.001	1.972-12.173
OGTT fasting blood glucose	1.498	0.500	8.983	4.473	0.003	1.679-11.913
constant	$-5.978$	0.761	61.676		۰	

Table 4. Multivariate logistic-analysis of factors affecting spontaneous preterm birth in patients with GDM

Note: BMI: body mass index; OGTT: Glucose tolerance test; GDM: gestational diabetes mellitus.



Figure 3. Nomogram prediction model for SPTB in women with GDM. Note: BMI: body mass index; PROM: premature rupture of membranes; GDM: gestational diabetes mellitus; OGTT: Glucose tolerance test.

recommended to maintain fetal weight at a normal level.

In this study, pregnant women with GDM and a history of miscarriage had a significantly increased risk of sPTB compared to those without such a history. This risk increase may be associated with various pathophysiological mechanisms related to GDM. Firstly, spontaneous abortion may alter the endometrial environment, affecting embryo implantation and placental development, which can be further exacerbated by GDM [30]. Secondly, a history of abortion can be related to vascular endothelial dysfunction, affecting uterine blood flow, with GDM potentially increasing the risk of vascular complications, leading to insufficient blood flow to the placenta [31]. Additionally, GDM can cause hormonal imbalances that affect progesterone production, and women with a history of miscarriage may already have hormonal regulation issues, combining to increase the risk of PTB [32].

Research by Yu et al. [33] showed that women with a history of abortion had a significantly increased likelihood of PTB before 37 and 34 weeks of gestation. PROM, a common perinatal complication, has an incidence of about 10% [34]. PROM is mainly related to intrauterine infection, and the hyperglycemic state in pregnant women with GDM can lead to vaginal dysbiosis, causing infections that increase the risk of sPTB and related perinatal complications [35]. In mothers with GDM, insulin resistance and hyperglycemia can lead to

increased inflammatory mediators, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), which can affect the structure and function of membranes, making them more prone to rupture [36, 37]. At the same time, the increased sugar content in the amniotic fluid of women with GDM may provide a favorable environment for bacterial growth, increasing the risk of infection, which is a common cause of PROM. Additionally, pregnant women with GDM may have abnormal immune regulation, affecting their ability to defend against infections and regulate the fetal immune system. This can lead to an imbalance in the local immune response of the fetal membranes, promoting inflammatory responses and tissue damage, thereby increasing the risk of PROM [38]. Once PROM occurs, the infection and inflammatory response may be further exacerbated, leading to cervical ripening and the production of contractions, which are direct factors promoting PTB. Therefore, PROM and GDM together may significantly increase the risk of sPTB through mechanisms such as inflammation, infection, and abnormal immune regulation.



Figure 4. ROC Curves of Spontaneous preterm birth in GDM patients. (A) ROC of the training set and (B) ROC of the validation set. Note: GDM: gestational diabetes mellitus.



Figure 5. Calibration evaluation curves of the nomogram prediction model for spontaneous preterm delivery in GDM patients. A. Calibration curve of the training set; B. Calibration curve of validation set. Note: GDM: gestational diabetes mellitus.





Some studies have found that fasting blood glucose levels in pregnant women with GDM are elevated, but the correlation between sPTB and blood glucose levels in GDM patients has not been widely reported [39]. OGTT fasting plasma glucose ≥5.1 mmol/L is an independent risk factor for sPTB in GDM patients. The reason for this may be that increased fasting blood glucose in OGTT is closely related to insulin resistance, necessitating insulin treatment. However, pregnant women with GDM often find it difficult to accept insulin treatment, resulting in poor compliance and eventually leading to pregnancy complications, thereby increasing the risk of spontaneous preterm delivery and other complications [40].

The above research results and analysis indicate that sPTB in mothers with GDM is influenced by multiple factors, with complex interactions and influencing mechanisms among them. Due to the interdependence and interweaving of these factors, focusing on a single factor often fails to fully capture the risk of sPTB in mothers with GDM. Therefore, predicting the risk of sPTB from a single-factor perspective may overlook the influence of other potential factors, thereby reducing the accuracy and reliability of the prediction. For instance, solely considering advanced age without addressing gestational blood glucose control, or solely focusing on past medical history while neglecting lifestyle factors, could lead to incomplete risk assessment.

To enhance prediction accuracy, a multifactorial comprehensive evaluation method is essential. The nomogram prediction model, a visual statistical tool, offers numerous clinical advantages over simply quantifying risk factors or using complex traditional digital models. It integrates numerical probabilities with clinically relevant variables, enabling rapid risk prediction through auxiliary lines and straightforward summation calculations [41]. In this study, a nomogram prediction model was constructed based on gestational age, pre-pregnancy BMI, history of spontaneous abortion, PROM, and OGTT fasting blood glucose, achieving AUC values of 0.901 and 0.939, indicating excellent predictive performance. Furthermore, the calibration curve of the model approaches the ideal curve, reinforcing its reliability.

Clinical validation of the model demonstrated high sensitivity (84.21%), specificity (81.40%), and accuracy (82.26%), underscoring its practical utility. These findings highlight the constructed prediction model as a reliable and objective tool, offering valuable insights into the occurrence of spontaneous PTB in mothers with GDM.

This study introduces several innovations. Firstly, it incorporates OGTT blood sugar and other related factors alongside common predictors of adverse pregnancy outcomes in GDM, presenting novel variables. Secondly, beyond merely evaluating factors influencing GDM sPTB using the nomogram prediction model, this study validates its performance through clinical studies. However, limitations include a small sample size due to study time constraints, potentially impacting the findings. Future research should expand sample sizes through prolonged data collection to enhance result reliability.

In conclusion, this study constructs a nomogram to identify influencing factors of sPTB in GDM patients, facilitating targeted interventions for high-risk individuals to ensure their safety. Findings indicate that maternal age ≥30 years, pre-pregnancy BMI ≥26.3 kg/m2, history of spontaneous abortion, PROM, and OGTT fasting blood glucose ≥5.1 mmol/L independently contribute to sPTB in GDM patients. The nomogram model utilizing these risk factors demonstrates high discrimination and accuracy in predicting sPTB in GDM patients.

# Disclosure of conflict of interest

# None.

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