Prediction model development of preterm birth using time series technology based machine learning

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Abstract

Background: Globally, the trends of preterm birth rate have been increasing over time. Ultrasonography cervical length assessment is considered to be the most effective screening method, however, universal cervical length screening in the whole population remains controversial because of the cost budget.

Objective: In this work, obstetric data are used to analyze and assess the risk of preterm birth. The purpose is to screen high-risk groups of preterm birth in the early and second trimester of pregnancy, and targeted cervical screening is more in line with health economics.

Methods: This study attempts to use continuous electronic medical records(EMRs) data of pregnant women to construct a preterm birth predicting classifier based on long short-term memory (LSTM) networks. The clinical data were collected from 5187 Chinese pregnant women with natural vaginal delivery, including more than 25,000 obstetric EMRs during the early trimester to 28 weeks of gestation. The area under ROC curve, accuracy, sensitivity and specificity were used to assess the performance of prediction model.

Results: Compared with traditional cross-sectional study, LSTM model in time series study has better overall prediction ability, which has a lower misdiagnosis rate with the same detection rate, and the accuracy was 0.739, sensitivity was 0.407, specificity was 0.982, and AUC was 0.651. Feature importance identification indicated that blood pressure, blood glucose, lipids, uric acid and other metabolic factors were the important factors related to preterm birth.

Conclusions: The results of this study are helpful to the formulation of guidelines for the prevention and treatment of preterm birth, and it can assist the clinicians to make correct decisions during the obstetric examinations. For the preterm birth prediction scenario, time series model has certain advantages.

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Original Paper

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Keywords: preterm birth prediction; temporal data mining; electronic medical records; pregnant healthcare

Introduction

Preterm birth, occurring before 37 weeks of completed gestation, is the primary cause of neonatal death and disability, and affects the long-term health of newborns [1,2]. According to the global action report on preterm birth of WHO, there were about 15 million premature infants born in the

world every year, with an incidence rate of 5% - 18%, of which 1 million premature infants died [3]. China is the most populous country in the world, with the implementation of the two-child policy, the average childbearing age of pregnant women has increased, and the incidence rate of preterm birth was also on the rise [4-6]. Compared with full-term infants, premature infants have adverse effects on the health and safety of pregnant women and fetuses, for example, the incidence rate of congenital malformation, SGA and nervous system diseases increased because of immature organs [7-9]. Therefore, early prediction of preterm birth and preventive measures have a great significance to reduce mortality and improve the survival rate of preterm infants [10-11].

Despite the serious clinical consequences, there are currently no effective early screening methods for preterm birth. It is generally considered that ultrasonography cervical length assessment is the most effective screening method [11,12], however, universal cervical length screening in the whole population remains controversial because of the cost budget [13,14]. In fact, cervical screening is not popular in China, and only for pregnant women with cervical insufficiency [15]. Fetal fibronectin (fFN) is an extracellular matrix glycoprotein which has also been extensively studied to predict preterm birth, but this method has high specificity and low detection rate [16]. In addition, other biomarkers (inflammatory factors, serum proteomics, genetic factors and etc.) associate with preterm birth [17], but their best performance is limited to a subset of all cases, few studies have demonstrated clinically sufficient properties.

Recently, machine learning algorithms, which can solve the nonlinear relationship among multi-dimensional variables, have been shown to be effective in the prediction of obstetric diseases [18,39]. ML based on time series technology has been recognized as a promising method for diagnosing obstetric diseases and shown to predict diseases with higher accuracy than conventional methods [19]. Electronic medical records (EMRs) are rich in temporal characteristics, and EMRs are scalable and readily available for disease-risk modeling [20]. Therefore, EMRs data can be combined with socio-demographic factors to comprehensively model disease risk using time series technology.

The specific aims of this study were to develop models using ML based on time series technology to predict Preterm birth using EHRs data and compare the performance of the models developed from conventional ML and time series model.

Methods

Setting and study population

The data were collected from the Hangzhou Women’s Hospital (Hangzhou Maternity and Child Health Care Hospital), Hangzhou, Zhejiang Province, China between 2017 and 2020. The study design was approved by the local Ethical and Research Committees (written permission with approval NO. 2019-02-2). All medical procedures were performed in accordance with relevant guidelines and regulations. The informed consent requirement for this study was waived by the board because the researcher only accessed the database for analysis purposes, and all patient data were de-identified. The authors declare that they have no conflicts of interest.

This study included 25000+ pregnant women who received antenatal care at Hangzhou Women’s Hospital and eventually delivered naturally through vagina. Those pregnant women would not be enrolled if they had any of the following exclusion criteria: multiple pregnancy, assisted reproduction, severe cardio cerebrovascular complications/comorbidity, cervical cerclage was performed during pregnancy. Pregnant women were included who had their first pregnancy test before 12 gestational weeks. According to the guidelines for prenatal examination [21], the hospital of the research group suggests that pregnant women should have a monthly outpatient examination

before 28 weeks of gestation. Figure 1 showed the filtering and processing flow chart of the study population. Some women were excluded owing to failing to get the data or implausible pregnancy outcomes, and data from the remaining 5187 were available for analyses.

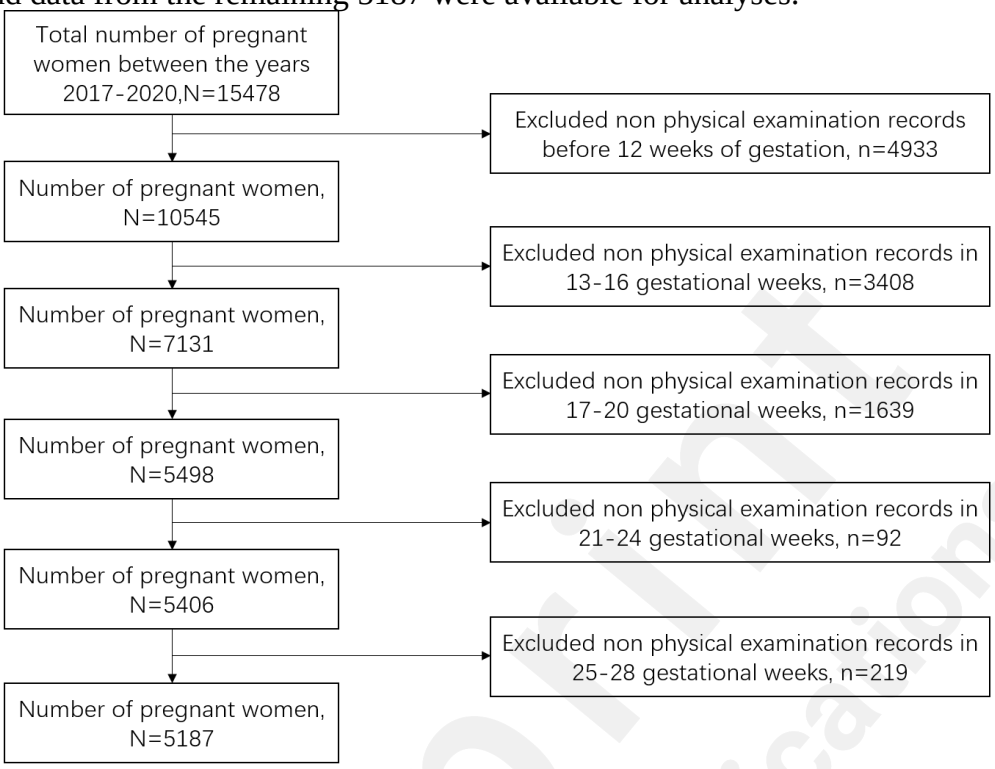

Figure 1. Flow chart of the inclusion of study participants

Clinical measurements and data collection

Demographic, physical examination, ultrasound records and laboratory data during the antenatal period were retrieved from the EMRs. At registration for pregnancy, the information on maternal demographic characteristics (e.g. age, education, occupation), anthropometrics (e.g. body weight, height, blood pressure), and clinical history (e.g. parity, disease history) were recorded. As shown in Table 1, pregnancy data were obtained for each individual repeatedly from the first pregnancy test to the pregnancy test between 25-28 weeks. The clinical data included age, weight, Uterine height, abdominal circumference, blood pressure and ultrasonic examination report. Laboratory tests (e.g. blood routine examination and blood biochemistry examination including blood lipids, glucose, etc.) were undertaken at 24 weeks of gestation.

Table1 Data source description

Gestational age	12 weeks before	13-16 weeks	17-20 weeks	21-24 weeks	25-28 weeks
check item	examination1	examination2	examination3	examination4	examination5
	ultrasonic1	ultrasonic2	ultrasonic3	ultrasonic4	ultrasonic5
	-	-	-	-	laboratory

Participants were asked to wear light clothing when measuring height and weight and BMI was calculated as body weight in kilograms divided by squared body height in meters. Sitting blood pressure was examined after at least 10 mins of break, using standard mercury sphygmomanometers with patients and with the right arm held at heart level. Maternal venous blood samples were drawn in the morning after an overnight fast of ≥8 h.

Model design

Based on the above-mentioned features, two kinds of machine learning models were constructed to predict the preterm birth. One is the early prediction model based on Table 1 in each cross-sectional, extreme gradient boosting (XGB) combined with decision trees was employed to established prediction models. XGB is an improvement of gradient lifting algorithm, which has been widely used in the field of obstetric auxiliary diagnosis [22].

The other is to predict premature birth using temporal prediction techniques. Short term memory network (LSTM, long short term memory) is a kind of time cyclic neural network, which is suitable for processing and predicting the events with relatively long intervals and delays in the time series [23]. LSTM can avoid the gradient disappearance of conventional RNN, and has been widely used in the field of disease diagnosis [24].

LSTM realizes information protection and control through three control gates, namely input gate, forgetting gate and output gate. The key of LSTM is the unit state. LSTM unit judges whether the output of the previous time step is useful, and only useful information is saved, the rest is forgotten at the forget gate. Equations (1) through (5) represent the parameter update process, where σ represents the sigmoid function, h_{t-1} represents the output of the LSTM at the previous time step, and h_t represents the current output. *i*, *f*, and o are respectively represented as input gate, forgetting gate and output gate in LSTM unit. Equation (4) represents the process of the state transition of the memory unit, where c_t is the state of the memory unit at the current time step. The current state is calculated by the previous time step state, c_{t-1} and the result of the forget gate and the input gate of the current time LSTM unit.

$$i_t = \sigma\left(W_{xi} x_t + W_{hi} h_{t-1} + b_i\right) \tag{1}$$

$$f_t = \sigma\left(W_{xf} x_t + W_{hf} h_{t-1} + b_f\right) \tag{2}$$

$$o_t = \sigma\left(W_{Xo} x_t + W_{ho} h_{t-1} + b_o\right) \tag{3}$$

$$C_t = f_t c_{t-1} + i_t \tanh\left(W_{xc} x_t + W_{hc} h_{t-1} + b_c\right) \tag{4}$$

$$h_t = o_t \tanh\left(c_t\right) \tag{5}$$

The parameters of these prediction models were determined by grid search and the models were validated with 5-fold cross-validation. The 5-fold cross-validation splits the training dataset into two sections, where 80% of the dataset is used for training and the remaining 20% is used for testing. Table2 shows the values of the parameters for two models. Simultaneously, the incidence rate of preterm birth is about 5%, in situations where there was imbalanced class data combined with unequal error costs, oversampling is used to balance the dataset to get true performance values for the classifier.

Table 2. Summary of parameter values in each model

Models	Parameters	Values
XGB	Learning rate	0.01
	N_estimators	200
	Min_samples_leaf	4
	Min_samples_split	3
	Max_depth	2

LSTM	Loss function	CrossEntropy
	Num_layers	2
	Optimizer	Adam
	Hidden_size	130
	Input size	65
	Learning rate	0.001
	Batch-size	256
	Epochs	20

Model evaluation

The characteristics were compared between the preterm birth and no preterm birth groups. Statistical tests were two-sided and all p-values <0.05 were considered statistically significant. All analyses were performed using the statistical software SPSS22.0.

The prediction performance was considered as an important factor to evaluate the proposed model. In this paper, the receiver operating characteristic curve and area under the curve were used to evaluate the model's ability to predict preterm birth. In addition, the evaluation indicators of the confusion matrix, including accuracy, sensitivity and specificity, were used to analyze the relationship between the actual values and the predicted values for the risk of preterm birth.

$$Accuracy = (TN + TP)/(TN + TP + FN + FP) \tag{6}$$

$$Sensitivity = TP/(TP + FN) \tag{7}$$

$$Specificity = TN/(TN + FP) \tag{8}$$

where, TP = True Positive, FP = False Positive, TN =True Negative, FN = False Negative.

Feature importance reflects the contribution each variable makes in classifying preterm birth, which explains the results of the model decision. In this study, feature importance of XGB was calculated by the sum of the decrease in error when split by a variable [25]. For LSTM model, Feature Ablation (FA) provides feature importance at a given time step to each input feature [26], which computes attribution as the difference in output after replacing each feature with a baseline, the more the area under ROC curve decreases, the more important the feature is.

Results

General characteristics of the study participants

The dataset used in the paper comes from a hospital in the eastern part of China, which includes a large amount of data such as the maternal ultrasound records, prenatal examination reports, laboratory data and so on. Of the 5187 pregnant women enrolled in the present study, 4966 cases had full term delivery. The remaining 221 cases had preterm birth. The general characteristics of the participants are presented in Table 3. Table 4 summarizes the clinical characteristics of the study subjects at second trimester (25-28 weeks).

Model performance

Based on the above-mentioned features in Table 3 and Table 4, two machine learning models were constructed to predict the preterm birth. XGB model was used for cross-sectional research, and

LSTM model was used for time-series research. Using the optimal parameters for each model, the predictive models were corroborated via a test set which was derived from the training dataset by 5-fold cross-validation. The accuracy, sensitivity, specificity and AUC of models for predicting preterm birth are shown in Table 5, which were used to compare the performances of these two models in the identical testing dataset. Notably, the LSTM model in time-series research has the best overall prediction ability, the accuracy, sensitivity, specificity and AUC were 0.739, 0.407, 0.982 and 0.651, respectively. Furthermore, with the progress of pregnancy, the model performance gradually improved. The overall performance of the model is the best in the last cross-sectional, the overall accuracy was 0.689, sensitivity was 0.407, specificity was 0.979, and AUC was 0.601.

Table 3. General characteristics of the study population (n=5187)

Characteristics	**mean (SD)**
Age, years	29.63(3.52)
Pre-pregnancy weight, kg	53.65(8.15)
Height, cm	161.45(4.84)
Pre-pregnancy BMI, kg/m2	20.57(2.92)
Parity, number of times	0.26(0.46)
Gravidity, number of times	1.71(0.98)
Pre-pregnancy SBP, mmHg	106.12(13.02)
Pre-pregnancy DBP, mmHg	67.29(9.31)
Number of preterm births in reproductive history, Parity, number of times	0.003(0.05)
Menarche, years	13.47(1.22)
Period, days	6.07(3.03)
Cycle, days	29.55(7.06)

Based on the validation result for the training dataset, an independent testing dataset was used for predicting preterm birth. The matrices and ROC curve for the predictive models in that testing dataset are shown in Figure. 2. Compared with cross-sectional research, LSTM model has a lower misdiagnosis rate with the same detection rate. High specificity can exclude more true negative samples to save the cost of screening.

Table 4. Clinical characteristics and laboratory parameters at second trimester.

Characteristics	**No preterm birth (n=4966)**	**Preterm birth (n=221)**	**P**
General characteristics			

Age, years	29.61(3.49)	30.14(3.64)	<0.05
Pre-pregnancy weight, kg	53.92(7.16)	53.74(8.12)	0.31
Pre-pregnancy sbp, mmHg	106.70(10.45)	106.19(11.98)	0.48
Pre-pregnancy dbp, mmHg	67.65(7.96)	67.47(7.41)	0.53
Physical data			
Gestational age, Week	26.02(1.17)	26.09(1.19)	0.73
Pulse rate	77.63(7.27)	77.32(6.82)	0.56
Maternal weight at pregnancy, kg	61.16(7.28)	60.39(8.29)	0.29
SBP, mmHg	111.42(10.62)	113.19(11.24)	<0.05
DBP, mmHg	65.29(7.78)	66.09(8.20)	<0.05
Uterine Height, cm	24.48(1.82)	24.02(2.28)	0.45
Mother abdominal circumference, cm	88.76(5.45)	86.98(8.33)	0.45
Ultrasonic data			
Biparietal diameter, cm	6.70(0.23)	6.84(0.48)	0.05
Head circumference, cm	24.60(0.76)	25.02(1.47)	0.13
Femur length, cm	4.83(0.17)	4.93(0.34)	0.06
Fetal abdominal circumference, cm	22.18(0.86)	22.94(1.45)	<0.05
Laboratory data			
Triglyceride	2.15(0.78)	2.25(0.79)	<0.05
Total bile acid	2.22(1.75)	2.17(1.52)	0.43
Uric acid	244.05(49.69)	246.05(49.60)	0.12
Platelet	209.12(45.24)	212.26(46.10)	0.11
Fasting blood glucose	4.35(0.38)	4.40(0.46)	<0.05
TotalCholestero	6.23(1.01)	6.19(1.07)	0.28
Activated partial thromboplastin timme	26.25(2.97)	26.26(3.31)	0.75
Fibrinogen	3.77(0.63)	3.85(0.64)	<0.05
Hemoglobin	115.96(8.44)	116.79(8.61)	<0.05

Table 5 Prediction average results of different methods after 5-fold CV.

	cross-sectional					time series
	12 weeks before	13-16	17-20	21-24	25-28	
ROC	0.532	0.558	0.516	0.568	0.601	0.651
sensitivity	0.286	0.365	0.362	0.387	0.407	0.407
Specificity	0.974	0.978	0.977	0.977	0.979	0.982
accuracy	0.525	0.574	0.584	0.622	0.689	0.739

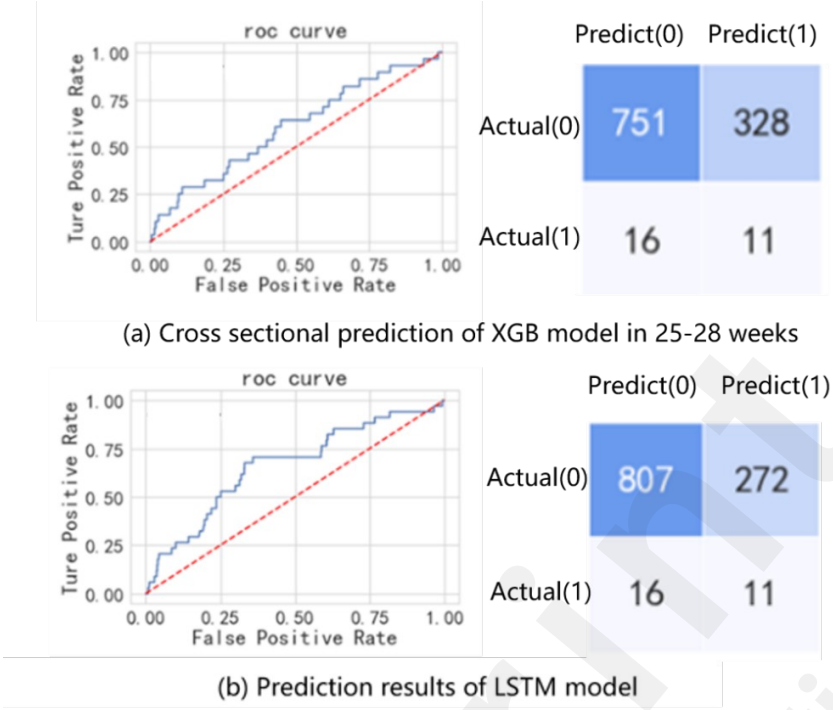

Figure 2 Receiver operating characteristic curves and confusion matrix of prediction models

Model performance

The identification of feature importance based on XGB and LSTM is shown in Fig 3. Feature importance of XGB was calculated by the sum of the decrease in error when split by a variable, which reflects the contribution each variable makes in classifying. The maternal age was the most important variable to predict preterm birth, followed by triglyceride, total bile acid, systolic pressure during pregnancy, fundal height, uric acid, platelet and pre-pregnancy weight. In addition, as illustrated in the above section, LSTM model in time-series research achieved the best performance, and feature ablation provides feature importance at a given time series input feature. The importance of features is evaluated according to the degree of AUC decline. The results indicate that the AUC decrease rate of systolic blood pressure was 2%, which was the most important time series feature, followed by fetal abdominal circumference, head circumference and maternal weigh.

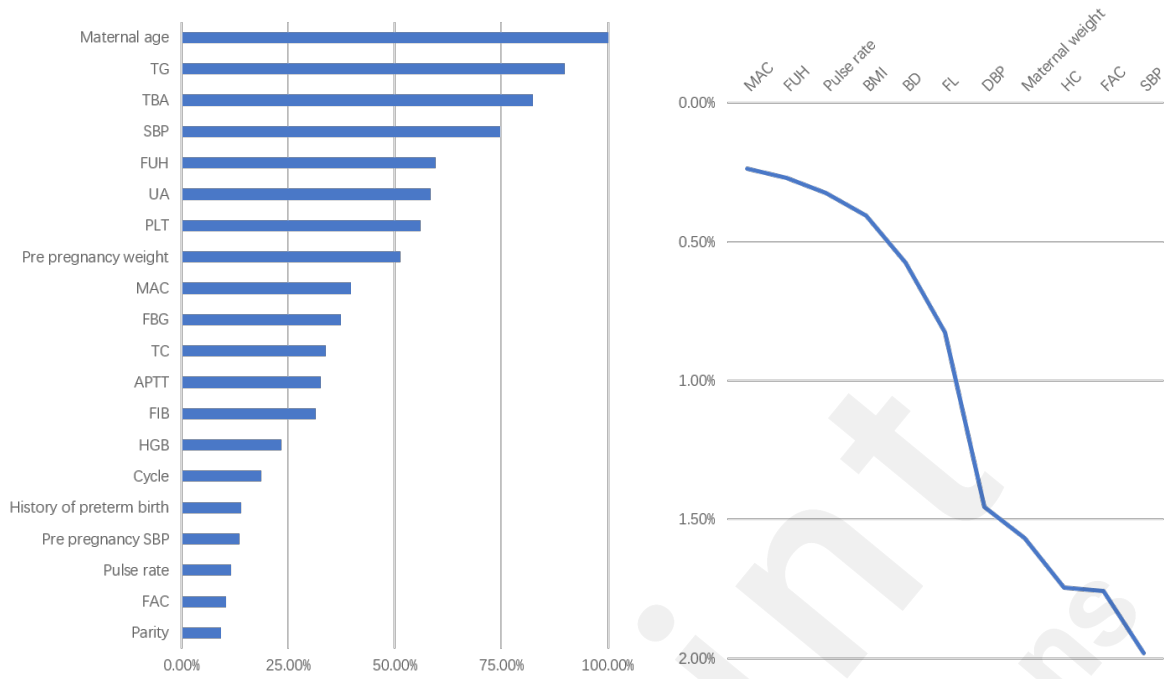

Figure 3 Importance of the variable.

Discussion

Principal Findings

It is obvious that premature birth is an increasingly serious problem. In this study, five pregnancy test records in the early and middle trimester of pregnancy were selected to construct a time series model to predict preterm delivery. Compared with the traditional ML model, the use of time series model improves the prediction performance of preterm birth. In addition, influential variables for predicting preterm birth were delineated.

The early prediction of preterm birth has always been a challenging subject. In this study, the input index of traditional prediction model research is usually a special test item or a combination of tests, which aims to find new markers with high contribution to preterm birth prediction, and most of these studies have not been clinically verified [11,17,27]. Many studies have tried to effectively predict preterm birth, which would lead to its early detection and prompt management. Cervical screening, fetal fibronectin or their combined detection can effectively predict preterm birth [12-14,16,28]. However, there are still flaws in the forecast. For asymptomatic women, the performance of the fetal fibronectin test was too low to be clinically relevant [29]. Many studies have believed that cervical status is an independent risk factor for preterm birth, In the 2014 edition of clinical diagnosis and treatment guidelines for preterm delivery, it is recommended that cervical length < 25 mm measured by transvaginal ultrasound before 24 weeks is a prediction method for high-risk patients [30]. In fact, cervical examination is still controversial in the general screening of the whole population. Some studies advocate that dynamic cervical examination can be carried out regardless of high-risk and low-risk pregnant women [31,32]. But more studies do not recommend or oppose large-scale cervical screening, and the potential reasons include but are not limited to the material cost, the time required, the lack of unified standards and the professional training of laboratory personnel [13,14,33-36], which may be lead to the cost accounting that does not conform to health economics. In this study, the prediction model in this study effectively predicts the early development of preterm labor by using demographic factors and prenatal laboratory data, and the data is easy to obtain in routine clinical practice. Therefore, the prediction model of preterm birth proposed in this study can be used

as a practical screening method for preterm birth in the first and second trimester of pregnancy.

The traditional preterm birth prediction model is based on a single indicator or combined detection of indicators, and Logistic regression is the most commonly used model in a cross-sectional study of early pregnancy. However, the etiological mechanism of preterm birth is elusive, the nonlinear interaction between risk factors is also complex, and the structure of traditional statistical model is so simple that it is difficult to meet the pre demand. Therefore, the machine learning model based on the routine diagnosis and treatment data of EMRs has been applied to the prediction of preterm birth. For example, Koivu et al built a prediction model based on artificial neural network and gradient enhanced decision tree algorithm in New York public data set, and the AUC of preterm birth is about 0.64 [37]. Abraham used the high-risk factors in electronic medical records to build the prediction model, the AUC is about 0.59 [38].

The above-mentioned prediction models ignored the effect of time-dependent factors. The time series analysis and prediction method predicts the future development according to the past change trend, and highlights the role of time factors in the prediction. Previous studies have reported that time series model performs well in the field of obstetrics, such as fetal weight [39], postpartum hemorrhage [40]and so on. Compared with other medical time queues, the 280 day gestational cycle is relatively fixed, and pregnant women have higher compliance to obstetric outpatient examination [41]. Therefore, the time series model mining time series characteristics during pregnancy has more potential.

Some new factors were found to affect the prediction of preterm birth. Parameters that have been traditionally reported to be related to delivery date such as age, pre pregnancy weight, history of preterm birth and menstrual cycle were also determined to be influential factors in preterm birth prediction [1,42]. Interestingly, blood pressure, blood glucose, lipids, uric acid and other metabolic factors are also the most important factors related with preterm birth. Although not thoroughly investigated, the relationship between metabolic risk factors and preterm birth has been preliminarily recognized in several previous studies [43,44]. In a recent observational study of 5535 deliveries, pregnant women with a cluster of metabolic risk factors during the early pregnancy were more likely to have preterm birth [45]. The metabolic reaction during pregnancy is to meet the needs of fetal growth, however, excessive amplification of metabolic stress reaction can also lead to the occurrence of some pathological pregnancy [46]. Despite the controversy, metabolic levels during pregnancy have been noticed in preterm birth patients.

Limitations

This study also has several limitations. First, the laboratory examination of pregnant women was completed in their respective communities before 20 weeks of gestation, which could not be included in the analysis due to the difference of test standards. In addition, there is recall bias in pre pregnancy characteristics, and most of the included women are primipara, so the contribution of preterm birth history to the model is limited. Second, the performance of the model still needs to be improved, although LSTM has great potential. Nonetheless, considering this prediction model is a baseline model based on conventional data, and the model can continue to add biochemical and / or biophysical markers to obtain better screening performance. In addition, advanced maternal age is a clear confounding factor [47], and stratified analysis by age will be considered in the follow-up study. Third, the study is a possible selection bias due to the single-center study. The prediction model has not been widely used in clinical practice, which accuracy and practicality should be verified in prospective studies with larger samples.

Conclusions

Globally, the trends of preterm birth rate have been increasing over time. Ultrasonography cervical length assessment is considered to be the most effective screening method, however, universal cervical length screening in the whole population remains controversial because of the cost budget. In this work, we analyzed obstetric medical data based on time-series machine learning and evaluated the risk of preterm birth. Our study can screen high-risk groups of preterm birth in the early and middle trimester of pregnancy, and targeted cervical screening is more in line with health economics. Compared with the existing research, time series model has certain advantages.

Authors' Contributions

YW and YZ were responsible for the study design. WH extracted the data. YW completed the relevant experiments. YW, WH, SL and YZ provided feedback on analyses and interpretation of results. YZ, YW, ZY wrote this paper. All authors read and approved the final manuscript.

Conflicts of Interest

none declared.

Abbreviations

EMR: electronic medical records
LSTM: long short-term memory
fFN: Fetal fibronectin
XGB: extreme gradient boosting
RNN: recurrent neural network
FA: Feature Ablation

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