Zhang *et al.*
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Serum calcium level at 32 weeks of gestation could be applied as a predictor of preterm delivery: a retrospective study

Jingjing Zhang[1†], Chong Fan[1†], Chenyang Xu[1†], Yuhan Zhang[1], Jingyan Liu[1], Chunxiu Zhou[1*], Shanwu Feng[1*] and Yuru Fan[1*]

Abstract

Preterm delivery (PTD) is associated with severe adverse maternal and neonatal outcomes and higher medical costs. Therefore, PTD warrants more attention. However, predicting PTD remains a challenge for researchers. This study aimed to investigate potential prenatal predictors of PTD. We retrospectively recruited pregnant women who experienced either PTD or term delivery (TD) and underwent laboratory examinations at 32 weeks of gestation. We compared the test results between the two groups and performed logistic regression analysis and receiver operating characteristic (ROC) curve analysis to identify risk factors and predictive factors for PTD. Our investigation revealed that the PTD cohort exhibited statistically significant elevations in lymphocyte count, mean corpuscular hemoglobin concentration, calcium, uric acid, alkaline phosphatase, triglycerides, and total bile acids. Conversely, the PTD group demonstrated statistically significant reductions in mean corpuscular volume, homocysteine, neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), neutrophils to (white blood cells–neutrophils) ratio (dNLR), and (neutrophils × monocytes) to lymphocyte ratio (SIRI). The ROC curve analysis revealed that calcium had an area under the curve (AUC) of 0.705, with a cut-off value of 2.215. Logistic regression analysis showed that premature rupture of membranes was an independent risk factor for PTD. Our study demonstrated that serum calcium levels, NLR, dNLR, and other laboratory tests conducted at 32 weeks of gestation can serve as predictors for PTD. Furthermore, we identified premature rupture of membranes as a risk factor for PTD.

Keywords Preterm delivery, Calcium, Biomarker, Predictor, Neutrophil to lymphocyte ratio (NLR)

Introduction

Preterm delivery (PTD), affecting 5–18% of pregnancies, is defined as delivery occurring before 37 weeks of gestation [1]. It is estimated that nearly 11% of newborns worldwide are born preterm and 35% of neonatal deaths are related to PTD [2]. Furthermore, complications associated with PTD are the second leading cause of death among children under 5 years old [2]. Additionally, PTD poses long-term health risks for mothers, including an increased risk of hypertension, diabetes, hyperlipidemia, and other diseases in subsequent years [3, 4]. As for preterm infants, PTD can lead to various complications, such as neonatal neurodevelopmental

†Jingjing Zhang, Chong Fan, and Chenyang Xu contributed equally to this work.

*Correspondence:
Chunxiu Zhou
1340362367@qq.com
Shanwu Feng
shanwufeng@163.com
Yuru Fan
fyr1899@njmu.edu.cn
[1] Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital, Nanjing 210004, Jiangsu, China

problems, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, feeding difficulties, visual and hearing problems, as well as learning difficulties [4, 5]. Given the adverse outcomes of PTD for both mothers and neonates, it is crucial to predict PTD prior to delivery. However, there is currently no standardized protocol for predicting PTD [4]. Several studies have indicated that amniotic fluid sludge and cervical length, as assessed through ultrasound examinations, show promise in predicting PTD [6, 7]. Nonetheless, ultrasound measurements are constrained by the expertise of the examiner. Therefore, there is an imperative need to develop objective measurements to overcome this limitation.

Previous research has identified several risk factors associated with PTD, such as Black or African American ethnicity, urinary or genital tract infection, amphetamine exposure, single umbilical artery, maternal personality and sleep disorders, a history of vacuum aspiration, lower gestational weight gain, and a shorter interval between pregnancies following a miscarriage [4, 8]. Recently, a growing body of literature has further elucidated the link between PTD and infectious factors. Richardson et al. indicated that approximately half of all PTD cases were associated with infection [9], with intrauterine infection accounting for forty percent of PTD cases [10]. Meanwhile, certain blood tests can serve as effective indicators of infection due to their convenience and accuracy. For instance, Tascini et al. demonstrated the utility of white blood cell count as a predictor of bacterial infection [11]. Additionally, Russell CD et al. emphasized the significance of peripheral blood leukocyte ratios, such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), in infectious diseases [12]. Qu et al. identified abnormal liver and kidney function indices as predictors of the severity of coronavirus disease 2019 [13]. These studies collectively underscore the potential of blood tests in predicting both infection and PTD.

In this work, we obtained and analyzed basic information and laboratory test results of women with and without PTD at 32 weeks of gestation. The objective was to compare the characteristics of these two groups and identify potential biomarkers that could be used to forecast PTD. Moreover, we also noticed changes in calcium levels among pregnant women [14–16]. However, the relationship between PTD and serum calcium remains ambiguous. Therefore, we have carried out extensive research and in-depth discussions on this topic in order to provide a reference for clinical practice. The successful outcomes of this research have the potential to enable the early prediction of PTD, thereby reducing the societal burden associated with this condition.

Methods

Study design

The present study was approved by the Medical Ethics Committee of Nanjing Women and Children's Healthcare Hospital. A retrospective data collection was performed on pregnant women who experienced either PTD or term delivery (TD). These participants underwent a complete blood count, as well as hepatic and renal function tests, at 32 weeks of gestation. By analyzing the test results between the PTD and TD groups, we aimed to identify both the risk factors and predictive factors associated with PTD. This was accomplished through the utilization of logistic regression analysis and the construction of receiver operating characteristic (ROC) curves.

Study populations

All pregnant women included in this study were randomly selected from the hospital information system of Nanjing Women and Children's Healthcare Hospital. The PTD group comprised 100 pregnant women who delivered between 32 and 37 weeks of gestation (less than 37 weeks). The TD group consisted of 100 pregnant women who delivered after 37 weeks of gestation (over 37 weeks). All participants underwent a complete blood count and hepatic and renal function tests at 32 weeks of gestation. These tests are routine prenatal examinations performed at 32 weeks, allowing for timely interventions to prevent preterm birth or prolong the gestation period if abnormalities are detected.

The following exclusion criteria were applied: women younger than 18 or older than 49 years of age who were pregnant, those who had undergone a cesarean section, exhibited cervical incompetence or had undergone cervical cerclage, those with twin pregnancies, and those suffering from serious diseases of other organ systems.

Data collection

Age, gravidity, parity, weeks of gestation, body mass index (BMI), complete blood count at 32 weeks of gestation, hepatic and renal function tests at 32 weeks of gestation, and primary pre-delivery diagnosis of pregnant women were recorded. Subsequently, we calculated the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), the ratio of neutrophils to (white blood cells−neutrophils) (dNLR), and the ratio of (neutrophils × monocytes) to lymphocyte (SIRI). Besides, the birth weight and the sex of newborns were also recorded for the final analysis.

Statistical analysis

The data analysis for this study was performed using IBM SPSS Statistics® 25.0 (Armonk, NY, USA: IBM Corp.) [17]. To assess the differences between groups for quantitative data, Student *t*-test was employed, following tests for normal distribution and homogeneity of variance. For qualitative data, non-parametric tests were utilized to determine group disparities.

In order to identify the risk factors associated with PTD, logistic regression analysis was conducted. Additionally, ROC curve analysis was employed to explore the diagnostic indicators for preterm birth. The significance level was set at $P < 0.05$, indicating that any observed results with a *p*-value less than 0.05 were considered statistically significant.

Results

Population characteristics

The basic clinical characteristics of the two groups were compared and summarized in Table 1. The average gestational age at delivery in the PTD group was 35.7 ± 1.3 weeks, significantly lower than in the TD group (39.6 ± 0.8 weeks, $P < 0.0001$). Correspondingly, the birth weight of newborns in the PTD group (2683.7 ± 396.6 g) was significantly lower than that in the TD group (3394.5 ± 322.0 g, $P < 0.0001$). No significant differences were observed in other basic characteristics between the two groups. The average age of pregnant women in the PTD group was 31.2 ± 3.5 years, and in the TD group, it was 30.5 ± 3.4 years ($P = 0.155$). The preterm birth population had an average gravidity of 2.1 ± 1.2 and parity of 0.5 ± 0.6, while the term birth population had an average gravidity of 2.1 ± 1.1 ($P = 0.814$) and parity of 0.5 ± 0.5 ($P = 0.729$). Furthermore, the BMI was 24.8 ± 3.3 kg/m^2 in the PTD group and 25.2 ± 2.5 kg/m^2 in the term group, showing no statistically significant difference ($P = 0.131$). Additionally, there was no significant difference in the gender of newborns, with 37% female newborns in the PTD and 50% female newborns in the TD group ($P = 0.064$).

Table 1 Clinical characteristics of the PTD and TD group

	PTD ($n = 100$)	TD ($n = 100$)	*P*
Age (years)	31.2 ± 3.5	30.5 ± 3.4	0.155
Gravidity (number)	2.1 ± 1.2	2.1 ± 1.1	0.814
Parity (number)	0.5 ± 0.6	0.5 ± 0.5	0.729
Gestational age at delivery (weeks)	35.7 ± 1.3	39.6 ± 0.8	**< 0.0001**
BMI (kg/m^2)	24.8 ± 3.3	25.2 ± 2.5	0.131
Birth weight (g)	2683.7 ± 396.6	3394.5 ± 322.0	**< 0.0001**
Birth gender (female/male)	37/63	50/50	0.064

PTD preterm delivery, *TD* term delivery

Comparison of the laboratory test between the PTD and TD groups

The laboratory tests, including complete blood cell and hepatic and renal function tests, were compared between two groups at 32 weeks of gestation (Table 2). The results demonstrated that differences existed in lymphocyte count, mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), uric acid (UA), alkaline phosphatase (ALP), triglyceride (TG), total bile acid (TBA), homocysteine, NLR, MLR, dNLR, and SIRI among all the laboratory tests between two groups. Specifically, in terms of complete blood cell analysis, in the PTD group, lymphocyte count and MCHC were significantly higher than those in the TD group ($P < 0.05$), but MCV was significantly lower than that in the TD group ($P < 0.05$). Regarding the hepatic and renal function tests, calcium (Ca), UA, ALP, TG, and TBA were all remarkably increased in the PTD group ($P < 0.05$). However, homocysteine was significantly decreased in the PTD group ($P < 0.05$). Additionally, the converted ratios,

Table 2 Comparison of laboratory test between the PTD and TD group

	PTD ($n = 100$)	TD ($n = 100$)	*P*
WBC (× 10^9/L)	9.4 ± 2.1	9.4 ± 2.0	0.921
PLT (× 10^9/L)	217.8 ± 49.2	206.3 ± 50.9	0.105
Neu (× 10^9/L)	6.8 ± 1.8	7.0 ± 1.7	0.404
Lym (× 10^9/L)	1.9 ± 0.5	1.7 ± 0.4	**0.002**
Mon (× 10^9/L)	0.5 ± 0.2	0.6 ± 0.2	0.804
MCHC (g/L)	325.5 ± 8.8	322.4 ± 10.6	**0.010**
MCV (fL)	91.7 ± 5.3	92.6 ± 5.3	**0.049**
Ca (mmol/L)	2.2 ± 0.1	2.3 ± 0.1	**< 0.0001**
UA (μmol/L)	260.4 ± 70.7	238.7 ± 56.1	**0.036**
ALP (U/L)	116.1 ± 46.5	103.5 ± 31.5	**0.049**
TG (mmol/L)	3.1 ± 1.2	2.8 ± 1.1	**0.038**
TBA (μmol/L)	2.3 ± 1.4	2.1 ± 1.4	**0.015**
HCY (μmol/L)	5.2 ± 0.9	5.6 ± 0.9	**0.011**
NLR	3.8 ± 1.2	4.3 ± 1.3	**0.003**
MLR	0.3 ± 0.1	0.3 ± 0.1	**0.010**
PLR	120.2 ± 35.3	124.9 ± 33.9	0.316
dNLR	2.7 ± 0.8	3.0 ± 0.8	**0.007**
SIRI	2.1 ± 1.0	2.4 ± 1.0	**0.043**

WBC white blood cell, *PLT* platelets, *Neu* neutrophil count, *Lym* lymphocyte count, *Mon* monocyte count, *MCHC* mean corpuscular hemoglobin concentration, *MCV* mean corpuscular volume, *Ca* calcium, *UA* uric acid, *ALP* alkaline phosphatase, *TG* triglyceride, *TBA* total bile acid, *HCY* homocysteine, *NLR* neutrophil to lymphocyte ratio, *MLR* monocyte to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *dNLR* neutrophils / (white blood cells – neutrophils), *SIRI* (neutrophils × monocytes)/lymphocyte ratio

including NLR, MLR, dNLR, and SIRI, were found to be significantly decreased in the PTD group.

ROC analysis for the diagnosis of PTD in pregnant women

ROC curve analysis was conducted to assess the diagnostic value of the laboratory test results at 32 weeks of gestation in differentiating between preterm delivery and term delivery populations (Table 3). All the area under the curve (AUC) values of the laboratory test results at 32 weeks of gestation that showed statistically difference were significant. The better performing index was Ca (AUC = 0.705, 95% CI 0.302–0.457, $P < 0.0001$), and a sensitivity and specificity of 79% and 51%, respectively. For the other indexes, the AUC was 0.621 (95% CI 0.543–0.698, $P = 0.003$) for lymphocyte count, 0.605 for MCHC (95% CI 0.526–0.683, $P = 0.010$), 0.581 for MCV (95% CI 0.501–0.660, $P = 0.049$), 0.586 for UA (95% CI 0.501–0.660, $P = 0.036$), 0.580 for ALP (95% CI 0.501–0.660, $P = 0.049$), 0.585 for TG (95% CI 0.505–0.664, $P = 0.038$), 0.600 for TBA (95% CI 0.521–0.678, $P = 0.015$), 0.604 for HCY (95% CI 0.526–0.682, $P = 0.011$), 0.623 for NLR (95% CI 0.545–0.700, $P = 0.003$), 0.605 for MLR (95% CI 0.527–0.683, $P = 0.010$), 0.610 for dNLR (95% CI 0.532–0.688, $P = 0.007$); 0.583 for SIRI (95% CI 0.504–0.662, $P = 0.040$).

Logistic regression analysis for diagnosis of PTD in pregnant women

To investigate the risk factors associated with PTD, we conducted a chi-square test for primary prenatal diagnoses, encompassing gestational diabetes mellitus, gestational hypertension, anemia in pregnancy, nuchal encirclements of the umbilical cord, premature rupture of membranes (PROM), twin pregnancy, chorioamnionitis, uterine myoma, and scarred uterus, between the two groups (Table 4). The results revealed that the incidence of PROM (76% vs. 22%, $P < 0.0001$) and uterine myoma (11% vs. 2%, $P < 0.010$) in the PTD group was significantly higher compared to those in the TD group. Furthermore, we conducted a logistic regression analysis (Table 5). The analysis indicated that pregnant women who experienced PROM were at independent risk for preterm delivery ($P < 0.0001$), with a calculated odds ratio (OR) value of 10.563 (95% CI 5.359–20.820). However, the OR value for uterine myoma was 0.463 (95% CI 0.072–2.959, $P = 0.415$), indicating a non-significant association with preterm delivery.

Discussion

PTD is a significant obstetric complication that poses risks to both the mother and newborn [18]. Globally, approximately 15 million babies are born prematurely each year [19]. However, the development of effective predictive tools for PTD remains limited. In the present study, we identified PROM as a risk factor for PTD. Additionally, our findings suggest that the level of serum calcium at 32 weeks of gestation may serve as a potential predictive marker for PTD. Furthermore, parameters such as NLR, MLR, dNLR, and SIRI also exhibited potential predictive value for PTD. This research marks a promising step towards developing a predictive method for PTD, which can ultimately contribute to prolonging

Table 3 The results of ROC analysis for the diagnosis of PTD

	AUC	95% CI	*P*	Cut-off	Sensitivity	Specificity
Lym ($\times 10^9$/L)	0.621	0.543–0.698	**0.003**	1.43	78%	17%
MCHC (g/L)	0.605	0.526–0.683	**0.010**	328.5	27%	64%
MCV (fL)	0.581	0.501–0.660	**0.049**	92.95	56%	64%
Ca (mmol/L)	0.705	0.302–0.457	**< 0.0001**	2.215	79%	51%
UA (μmol/L)	0.586	0.036–0.507	**0.036**	207.95	75%	25%
ALP (U/L)	0.580	0.501–0.660	**0.049**	79.45	80%	22%
TG (mmol/L)	0.585	0.505–0.664	**0.038**	2.06	76%	19%
TBA (μmol/L)	0.600	0.521–0.678	**0.015**	1.495	81%	38%
HCY (μmol/L)	0.604	0.526–0.682	**0.011**	5.28	62%	56%
NLR	0.623	0.545–0.700	**0.003**	3.70	62%	54%
MLR	0.605	0.527–0.683	**0.010**	0.29	67%	51%
dNLR	0.610	0.532–0.688	**0.007**	2.72	61%	55%
SIRI	0.583	0.504–0.662	**0.040**	1.88	64%	51%

ROC receiver operator characteristic, *Lym* lymphocyte count, *Mon* monocyte count, *MCHC* mean corpuscular hemoglobin concentration, *MCV* mean corpuscular volume, *Ca* calcium, *UA* uric acid, *ALP* alkaline phosphatase, *TG* triglyceride, *TBA* total bile acid, *HCY* homocysteine, *NLR* neutrophil to lymphocyte ratio, *MLR* monocyte to lymphocyte ratio, *dNLR* neutrophils / (white blood cells – neutrophils), *SIRI* (neutrophils × monocytes)/lymphocyte ratio

Table 4 Obstetric characteristics of the PTD and TD group

	PTD ($n=100$)	TD ($n=100$)	*P*
GDM			0.744
Yes	26	24	
No	74	76	
Gestational hypertension			0.516
Yes	6	4	
No	94	96	
Anemia in pregnancy			0.256
Yes	42	50	
No	58	50	
NEUC			0.061
Yes	23	35	
No	77	65	
PROM			**< 0.0001**
Yes	76	22	
No	24	78	
Twin pregnancy			0.059
Yes	5	0	
No	95	100	
Chorioamnionitis			0.152
Yes	9	4	
No	91	96	
Uterine myoma			**0.010**
Yes	11	2	
No	89	98	
Scarred uterus			0.059
Yes	5	0	
No	95	100	

PTD preterm delivery, *TD* term delivery, *GDM* gestational diabetes mellitus, *NEUC* nuchal encirclements of umbilical cord, *PROM* premature rupture of membranes

Table 5 Logistic regression analysis for diagnosis of PTD

	β	*P*	OR	95% CI
PROM	2.357	**< 0.0001**	10.563	5.359–20.820
Uterine myoma	− 0.773	0.415	0.463	0.072–2.959

PROM premature rupture of membranes

gestational weeks and improving outcomes for both mothers and newborns.

PROM is defined as the rupture of the amniotic membranes before the onset of labor. It is estimated that about fifty percent of pregnant women with PROM will deliver within a week [20]. Additionally, PROM is responsible for 25–30% of all preterm delivery cases [21]. Previous studies have consistently associated PROM with an increased risk of PTD, and our research further supports this finding [22]. PROM can lead to intrauterine infection, which in turn triggers the production of inflammatory mediators such as interleukin-6 (IL-6), IL-8, and other inflammatory molecules [23]. This inflammatory response may play a role in the initiation of labor. Furthermore, the decrease in amniotic fluid and fetal distress caused by PROM may lead doctors to undertake medical interventions in advance [24]. However, further comprehensive investigations into the pathogenic mechanisms underlying PROM and its association with PTD are still warranted.

In the present study, we observed a significant reduction in serum calcium concentration in the PTD group compared to the TD group ($P<0.05$). Subsequent ROC analysis displayed that the AUC of Ca was 0.705 (95% CI: 0.302–0.457, sensitivity: 79%, specificity: 51%). These findings suggest that measuring serum calcium levels at 32 weeks of gestation prior to labor may serve as a potential predictive biomarker for PTD. Moreover, 2.215 mmol/L was considered the optimal cut-off value of serum calcium in our results. Previous studies have demonstrated that calcium supplementation is significantly associated with reduced risk of PTD (OR = 0.72, 95% CI: 0.60–0.87, $P=0.001$) [25]. Furthermore, calcium supplementation during pregnancy can help maintain normal vasodilation [26]. Thus, we speculate that PTD may occur following fetal ischemia and hypoxia, which could be triggered by vasoconstriction in the vascular smooth muscle cells of pregnant women due to calcium deficiency [26]. Calcium deficiency may also contribute to increased myometrial contractility through changes in muscle cell tone, potentially initiating PTD [27]. Additionally, lower serum calcium levels have been associated with preeclampsia and other obstetric complications, which further increase the risk of preterm delivery [28]. It is important to note that the pathogenic mechanisms underlying preterm delivery are complex, and further research is needed to gain a deeper understanding of these processes.

The exploration of biomarkers in order to predict diseases has always been a research hotspot. Biomarkers such as NLR, PLR, and MLR have been extensively studied as potential indicators for various diseases, including pulmonary diseases [29], gastric cancer [30], immune diseases [31], sepsis [32], viral infection, and other diseases [33]. Accumulating research has associated PTD with infection and inflammation [34]. Given this connection, we aimed to investigate the association between PTD and these biomarkers. In our study, we observed that NLR, dNLR, and SIRI in the PTD group were all significantly lower than those in the TD group ($P<0.05$). Subsequent ROC analysis suggested that NLR and dNLR might have prognostic value for PTD, with cut-off values of 3.70 and 2.72, respectively. Our results further enrich the predictive framework for PTD.

Indeed, while our study has made significant contributions to the prediction of PTD, there are some limitations that should be acknowledged. Firstly, the population included in our study consisted exclusively of Asians, which may limit the generalizability of our findings to other populations. Nevertheless, our study provides valuable insights for future research focused on the prediction of PTD and expands the current body of knowledge regarding PTD prediction. Secondly, our data collection was confined to laboratory tests obtained at 32 weeks of gestation. Although our study may capture the majority of PTD cases, some preterm births occur before this gestational period [35]. Thirdly, as a retrospective study, this research has inherent limitations in design, leading to potential information bias. Additionally, there are challenges in controlling for confounding factors. Therefore, more large-scale multicenter prospective clinical studies are needed in the future to validate the results of this study. Overall, while our study has shed light on the prediction of PTD, further research incorporating diverse populations and exploring earlier predictors is essential to enhance the accuracy and clinical utility of these predictive models.

Conclusion

In summary, our study has identified several potential predictive factors for PTD, including serum calcium concentration, NLR, and dNLR measured at 32 weeks of gestation. These findings offer promising avenues for reducing the burden of PTD and improving maternal and neonatal health outcomes. Furthermore, our study reaffirmed the association between PROM and an increased risk of PTD, consistent with previous research. Understanding the role of PROM in PTD provides valuable insights for identifying high-risk pregnancies and enabling timely interventions. However, more comprehensive study designs and prospective clinical cohort studies are required to validate and refine the predictive models for PTD. Such research efforts will help in developing more accurate and reliable methods for identifying individuals at high risk of PTD and implementing appropriate preventive and management strategies.

Author contributions

Jingjing Zhang, Chong Fan, and Chenyang Xu drafted the article and analyzed the data. Yuhan Zhang prepared tables. Jingyan Liu collected the data. Chunxiu Zhou conceived the experiments and reviewed the drafts. Shanwu Feng and Yuru Fan conceived and designed the experiments, and also reviewed the drafts.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Nanjing Women and Children's Healthcare Hospital (ref. number 2020 KY-035).

Competing interests

The authors declare no competing interests.

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