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Radiomics analysis of transvaginal ultrasound images in threatened preterm labor: A novel approach to high-risk cases

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Abstract

Objective: Radiomics analysis is a technique that extracts numerous quantitative markers related to tumor characters from medical images. This approach is widely used in cancer research to classify cancer grades and predict treatment prognosis. In this study, radiomics analysis of transvaginal ultrasound images was conducted to extract numerical markers associated with preterm labor.

Methods: We enrolled patients admitted to our hospital with a diagnosis of threatened preterm labor or a shortened cervical length from April 2019 to December 2023. Radiomic features were extracted based on the area of the cervix on the transvaginal ultrasound images at admission. The patients were classified into preterm and term using 37 weeks of gestation as the cutoff value. Two-group comparisons were statistically analyzed for clinical variables and extracted radiomic features. Additionally, logistic regression models were developed and predictive importance of variables.

Results: Overall, 51 patients were included in the study, 25 and 26 in the term and preterm groups, respectively. The mean cervical lengths at admission were 16.2 and 18.0 mm in the term and preterm groups, respectively, with no significant differences in the clinical data ($p=0.55$). In contrast, 13 of the 104 radiomic features extracted showed significant differences ($p<0.05$). No variables were statistically significant in the univariate regression analysis. However, "firstorder_ Energy" and "diagnostics_Mask-VolumeNum" differed significantly in the multivariate analysis.

Conclusion: In high-risk cases, radiomic features could be a better predictor than cervical length and clinical variables. Radiomics analysis suggests the possibility of extracting numerical markers associated with preterm delivery from transvaginal ultrasound images.'

Keywords: Radiomics; Preterm labor; Cervical length; Machine learning; Transvaginal ultrasound.

Introduction

Preterm birth is the leading cause of neonatal and child mortality and is associated with an increased risk of long-term neurodevelopmental disorders in surviving infants [1]. Accurate prediction and appropriate risk classification remain substantial challenges in preterm birth management to ensure that those most likely to benefit are treated [2]. Preventive interventions and more intensive prenatal monitoring can be applied in high-risk cases, and unnecessary interventions such as hospitalization can be avoided in low-risk preterm cases. Currently, cervical length measurement using transvaginal ultrasound images is widely used in clinical settings to predict preterm birth [3]. However, there are cases in which short cervical canal length does not result in preterm delivery. Therefore, other techniques of assessing preterm birth risk are desirable for managing preterm birth.

Radiomics analysis is a method of image analysis studied in radiology and developed with the current advances in artificial intelligence (AI) image processing techniques [4]. Radiomics analysis extracts numerous quantitative values strongly associated with cancer diagnosis or prognosis from Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) images. When these quantitative markers are combined with blood examination or patient demographics, a more accurate prediction of postoperative diagnosis or recurrence after treatment can be made [5].

Currently, assessment of the cervix using transvaginal ultrasound is limited to cervical length. However, cervical images could have more quantitative markers associated with preterm labor. Similar to using the cervical length extracted from ultrasound images as a predictor, radiomics analysis can extract more numerical markers related to preterm birth from transvaginal ultrasound images. In this study, we performed radiomics analysis and statistical comparisons between the preterm and term birth groups. We also discussed the valuable radiomic features extracted from transvaginal ultrasound images as essential predictors.

Methods

Study population

We enrolled patients admitted to our institute from April 2019 to December 2023. All patients were hospitalized and treated for threatened preterm labor or shortened cervical length. The inclusion criteria were pregnancies with gestational age <36 weeks requiring hospitalization. To ensure uniformity of ultrasound images for the learning models, only cases whose images were stored on a single device were included, and those whose images were stored on other devices were excluded. Twin pregnancies and cases of premature rupture of membranes were also included in this study. Exclusion criteria were a gestational age >36 weeks at admission and cases in which preterm birth occurred for iatrogenic reasons, such as hypertensive disorders of pregnancy or fetal growth restriction. Placenta previa cases were also excluded, as elective cesarean sections were often performed at 36 weeks due to iatrogenic reasons. Preterm births are defined in this study as births before 36 weeks of pregnancy.

This study was approved by the Institutional Review Board of our institute and conducted in accordance with the Declaration of Helsinki. Due to its retrospective nature, informed consent was waived. The data were anonymized for model training.

Processing ultrasound examination and extraction of radiomics features

Transvaginal ultrasonography was performed using the HITACHI digital ultrasound system Noblus (Aloka; Hitachi Medical Corporation, Kashiwa City, Japan) at 5.0–8.0 MHz to evaluate the cervix. Ultrasound cervical images at admission or within 3 days of admission were collected in JPEG format. Only eligible images that contained the midsagittal plane of the cervical length in the B-mode were considered for analysis. The quality of each image was checked manually by specialized obstetricians with over 10 years of clinical experience.

For segmentation, the obstetrician manually cut the area containing the cervix using polygons with straight sides that were fully connected and formed a closed shape. The area was used as the region of interest (ROI), and radiomic features were extracted. The image processing example is shown in Figure 1. Using the ROI of transvaginal images, we extracted the radiomic features using the "PyRadiomics" package implemented in the Python programming language. All extracted features were normalized for statistical analysis. The study pipeline is shown in Figure 2.

Clinical variables

We used ten clinical variables as follows: (1) age, (2) number of pregnancies (gravity), (3) number of deliveries (parity), (4) number of previous preterm birth, (5) body mass index (BMI), (6) white blood cell count (WBC), (7) hemoglobin (Hb), (8) C-reactive protein (CRP), (9) cervical length at admission, and (10) pregnant gestation of admission. These clinical variables and cervical length were obtained from hospital records upon admission.

Statistical analysis of clinical parameters and radiomic features

We divided the patients into preterm and term groups using 36 weeks gestation as the cutoff value, and performed statistical analysis for the two variables as follows.

1) Statistical comparison between the two groups. Student's t-test and chi-square test were performed for continuous and categorical variables, respectively.

2) Univariate and multivariate regression analysis. Univariate and multivariate regression analyses were performed for the predicted outcomes. The features with a predictive accuracy of >0.5 (defined as the threshold for good predictability) were selected. After features indicating multicollinearity were eliminated using a variance inflation factor (VIF) of >10 as a redundant feature, we constructed regression models using two predictors and evaluated the prediction performance.

Statistical significance was set at $p<0.05$. Since the t-test and chi-square test were conducted for >100 items, the Benjamini–Hochberg correction was performed to correct p-values for multiple testing. The Benjamini–Hochberg correction was considered more appropriate than the Bonferroni correction because the cutoff value for the p-value in the Bonferroni cor-

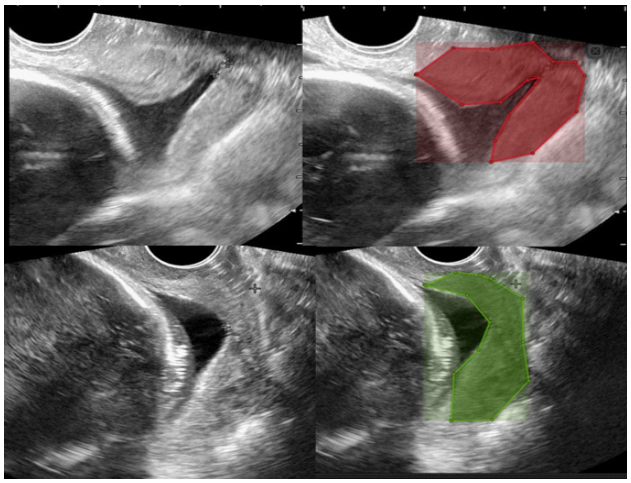

Figure 1: Image processing of transvaginal ultrasound images. We manually cut out the area of the cervix containing the inner and outer uterine os (red and green areas). The cut areas were used and analyzed as the area of the image (ROI: region of interest).

rection was too small to detect significant differences in multivariable studies with >100 variables. The BH (Benjamini–Hochberg) correction was calculated as below.

1) BH-adjusted p(i) = min (1, (m/i)*p(i)) (i = 1, 2, …, m)

2) Final adjusted p(i) = min (BH-adjusted p(i), final adjusted p(i + 1), …, final adjusted p(m))

p(i): p-values sorted in ascending order p(1), p(2), …, p(m)

Statistical analyses were performed using Python (version 3.7). Logistic regression models were implemented using Keras (version 1.2.2) and SKlearn (version 1.0) in Python (version 3.7) as the programming language.

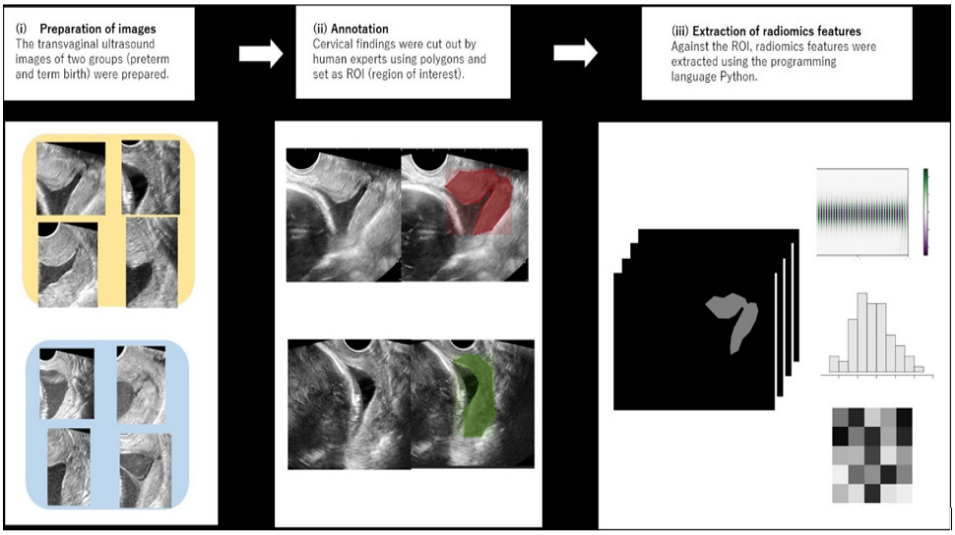

Figure 1: The pipeline of the study.

Results

Patient demographics

Our study included 51 patients, 26 and 25 in the preterm and term groups, respectively (Table 1). The mean age of the patients was 32.2 years, with a mean gravidity of 2.1 pregnancies and mean parity of 0.7 births. The mean frequency of past preterm birth was 0.1 times, and the mean BMI was 22.4 kg/m². Blood examination at admission showed a mean WBC of 9372/µL, Hb level of 11.1 g/dL, and C-reactive protein (CRP) level of 0.78 mg/dL. Additionally, the mean gestational ages at admission and delivery were 26.5 and 35.4 weeks, respectively. The average cervical length at admission was 17.0 mm.

Statistical comparison between the two groups

Regarding the Student's t-test for patient characteristics, the statistical results revealed no significant differences in all clinical variables (Table 2). Although the history of preterm birth and BMI did not show statistically significant differences, they had lower p-values than other variables and might become significant with increasing data size. In addition, the mean gestational age upon admission was older in the preterm group than in the term group (25.5 vs 27.6 weeks) with a slight difference (p=0.097). Mean cervical length was longer in the preterm group than in the term group (16.2 vs 18.0 mm) with no statistical difference (p=0.556). These results indicate that a history of preterm delivery and emaciation, which have traditionally been associated with increased risk, were linked to the likelihood of preterm delivery. However, they also suggest that the predictive value of clinical variables in identifying preterm delivery risk in high-risk populations is limited.

In contrast, among the total 104 radiomic features, 13 were statistically significant (p<0.05; Table 2). Particularly, "firstorder_Entropy" (5716 vs 7763) and "firstorder_Uniformity" (51448 vs 69868) showed significant differences (p<0.01), highlighting the textural differences between the groups.

Univariate and multivariate regression analyses

In the univariate analysis of clinical variables related to preterm birth, a history of preterm birth had the highest odds ratio (OR; OR=4.76, p=0.72), suggesting a strong but insignificant association (Table 3). BMI (OR=0.91, p=0.72) and gestational age at admission (OR=1.12, p=0.72) showed a slight insignificant increase in the OR. Neutral ORs were observed for WBC (OR=1.00, p=0.92) and Hb (OR=1.06, p=0.93). Cervical length

Table 1: Statistical comparision of the variables.

	Variables	n =51
1	Age (years)	32.2 ± 4.9
2	Gravity (times)	2.1 ± 1.1
3	Parity (times)	0.7 ± 0.8
4	History of preterm birth (times)	0.1 ± 0.3
5	Body mass index, BMI (kg/m2)	22.4 ± 4.7
6	White blood cell (WBC) (μ/l)	9372 ± 2681
7	Hemoglobin (Hb) (g/dl)	11.1 ± 0.9
8	C-reactive protein (CRP) (mg/dl)	0.78 ± 1.81
9	Cervical length (mm)	17.0±10.7
10	Pregnant gestation of admission (week)	26.5 ± 4.4
11	Pregnant gestation of labor (week)	35.4 ± 3.9

The numerical values in the table are presented as mean ± standard deviation.

Table 2: Statistical comparision of the variables.

	Clinical variables	Term birth (n=25)	Preterm birth (n=26)	p-value
1	Age (year)	31.6 (18-41)	32.8 (24-44)	0.401
2	Gravity (time)	2.08 (1-4)	2.20 (1-6)	0.706
3	Parity (time)	0.73 (0-2)	0.72 (0-4)	0.962
4	History of preterm birth (time)	0.04 (0-1)	0.16 (0-1)	0.151
5	Body mass index: BMI (kg/m^2)	23.41 (18.2-48.0)	21.59 (17.3-28.0)	0.188
6	White blood cell (WBC) (μ/l)	9250 (5100-15900)	9500 (5700-19700)	0.743
7	Hemoglobin (Hb) (g/dl)	11.1 (9.1-12.7)	11.2 (8.4-12.9)	0.84
8	C-reactive protein (CRP) (mg/dl)	0.97 (0.04-11.1)	0.58 (0.03-3.85)	0.449
9	Cervical length (mm)	16.20 (5.2-35.0)	18.02 (0.0-46.0)	0.552
10	Pregnant gestation of admission (week)	25.54 (17-33)	27.60 (19-35)	0.097
11	Pregnant gestation of labor (week)	37.92 (37-40)	32.92 (24-36)	<0.001
	Radiomic features			
1	Firstorder_Energy	5716 (2558-9572)	7763 (2976-14633)	0.003
2	Firstorder_TotalEnergy	51448 (23022-86154)	69868 (26791-131703)	0.003
3	Glrlm_LongRunLowGrayLevelEmphasis	159 (19-232)	242 (76-725)	0.006
4	Diagnostics_Mask-VolumeNum	3.54 (1-13)	2.04 (1-5)	0.008
5	Glszm_LargeAreaLowGrayLevelEmphasis	159959 (6236-325401)	381041 (80483-1988112)	0.010
6	Glrlm_LongRunEmphasis	635 (71-929)	934 (269-2901)	0.016
7	Glszm_LargeAreaEmphasis	639386 (24650-1301541)	1382755 (304661-7952382)	0.019
8	Glszm_ZonePercentage	0.01 (0.0019-0.024)	0.00 (0.0007-0.0078)	0.020
9	Glrlm_LongRunHighGrayLevelEmphasis	2539 (281-3717)	3699 (269-11604)	0.021
10	Glrlm_RunVariance	264 (40-393)	361 (73-957)	0.025
11	Glszm_LargeAreaHighGrayLevelEmphasis	2557091 (98306-5206102)	5389609 (1168561-31809462)	0.026
12	Glszm_ZoneVariance	574413 (22925-1038372)	1118536 (0.0-6809621)	0.040
13	Gldm_DependenceNonUniformity	2029 (259-2786)	2606 (618-6406)	0.046

The numerical values in the table are presented as the mean (range: minimum–maximum).

Table 3: Regression analysis of each variables.

		Univariate analysis		Multivariate analysis	
	Clinical variables	Odds rate	p-value	Odds rate	p-value
1	Age (year)	1.05	0.91		
2	Gravity (time)	0.98	0.96	0.45	0.61
3	Parity (time)	1.10	0.92	1.44	0.65
4	History of preterm birth (time)	4.76	0.72	10.86	0.56
5	Body mass index: BMI (kg/m2)	0.91	0.72		
6	White blood cell (WBC) (μ/l)	1.00	0.92		
7	Hemoglobin (Hb) (g/dl)	1.06	0.93		

8	C-reactive protein (CRP) (mg/dl)	0.87	0.91	0.86	0.65
9	Cervical length (mm)	1.02	0.91	1.01	0.85
10	Pregnant gestation of admission (week)	1.12	0.72		
		Univariate analysis	**Multivariate analysis**		
	Radiomic features	**Odds rate**	**p-value**	**Odds rate**	**p-value**
1	firstorder_Energy	1.00	0.19	1.00	0.01
2	firstorder_TotalEnergy	1.00	0.19		
3	glrlm_LongRunLowGrayLevelEmphasis	1.01	0.19		
4	diagnostics_Mask-VolumeNum	0.56	0.19	0.40	<0.01
5	glszm_LargeAreaLowGrayLevelEmphasis	1.00	0.26		
6	glrlm_LongRunEmphasis	1.00	0.19		
7	glszm_LargeAreaEmphasis	1.00	0.19		
8	glszm_ZonePercentage	<0.01	0.26		
9	glrlm_LongRunHighGrayLevelEmphasis	1.00	0.24		
10	glrlm_RunVariance	1.01	0.35		
11	glszm_LargeAreaHighGrayLevelEmphasis	1.00	0.19		
12	glszm_ZoneVariance	1.00	0.24	0.69	0.60
13	gldm_DependenceNonUniformity	210.55	0.47		

showed an OR of 1.02 (p=0.91); however, this was statistically insignificant. Analysis of radiomic features showed that "gldm_DependenceNonUniformity" had a markedly high OR of 210.55 (p=0.47), indicating a strong association with the outcome, although it was statistically insignificant. The "diagnostics_Mask-VolumeNum" showed a lower OR of 0.56 (p=0.19), suggesting a decreased likelihood of the outcome.

In the multivariate analysis, both clinical variables and imaging features were assessed. Of the clinical variables, "history of preterm birth" showed a high OR (10.86), but it was statistically insignificant (p=0.56). Regarding imaging features, "firstorder_Energy" and "diagnostics_Mask-VolumeNum" showed significant differences (p=0.01), with ORs of 1.00 and 0.40, respectively. No significant differences were observed for other variables. Since most variables had VIF >10, the results for these variables were not calculated. These high VIF values often indicate multicollinearity between variables, but neither the clinical nor radiomics features showed correlation coefficients >0.7. The small sample size in this study also strongly affected the VIF; therefore, the extent of the effect of collinearity involvement was unclear.

Discussion

This study presented the possibility of radiomic features as measurable image markers that could be a new image assessment of preterm birth risk on transvaginal ultrasonography. Currently, cervical length is the only quantitative indicator of preterm birth risk on transvaginal ultrasonography. Other clinical quantitative evaluation methods are of limited use for preterm birth. Cervical imaging findings may have features attributable to preterm birth, such as textures and softness. Several numerical markers indicative of preterm labor could be extracted from transvaginal ultrasound cervical images. Additionally, our findings suggest that cervical length and blood inflammatory markers may have limited utility in predicting preterm birth in high-risk populations requiring hospitalization. Instead, as traditionally noted, we observed the predictive significance of a history of preterm labor and BMI in both high-risk and general pregnant populations. Thus, quantitative markers that can predict preterm birth are needed to identify the risk of preterm birth accurately. The radiomic feature could be one such marker.

Radiomics analysis is being actively studied in various medical fields to extract the quantitative features of a target region from medical images [5,6]. In particular, in cancer treatment, attempts have been made to extract tumor characteristics using radiomics analysis, such as in lung [7] and breast cancers [8]. These studies have demonstrated the utility of radiomics as a noninvasive approach to predicting tumor characteristics, thereby avoiding unnecessary surgery and complications. In obstetrics, radiomics analysis has mainly been performed using placental MRI images to predict the placenta accreta spectrum (PAS) [9,10]. Stanzione et al. conducted a systematic review of radiomics studies for placental images, including 10 published studies [10]. Four studies were prognostic (focused on either prediction of bleeding volume or treatment required), and six were diagnostic (PAS vs non-PAS classification). Therefore, heterogeneous methodological quality was found among the studies, and more robust investigations were needed.

The strengths of this study are as follows. First, our study used radiomics analysis to evaluate transvaginal ultrasound images. Although most radiomics studies in obstetrics have been performed with MRI images, ultrasound examinations are performed much more frequently than MRI images in clinical practice. Thus, this study will induce future research on radiomics analysis of perinatal ultrasound examinations. Second, by comparing the radiomic features with cervical length, we exhibited that radiomics analysis has better predictive power in high-risk patients requiring hospitalization.

This study had several limitations. First, the data set size was too small, reducing statistical power, making it more difficult to detect true differences between groups. It increases the risk of type II errors, causing less reliable estimates of effect sizes. Additionally, a small sample size may lead to biased or unrepresentative findings.Second, with ultrasound images, image quality varies from examiner to examiner in terms of gain, brightness, etc., making it difficult to maintain data uniformity and reducing study reproducibility. With MRI images, maintaining image uniformity is easier in terms of target site and sequencing. The extracted radiomic features can be easily compared with those of other centers and studies. Third, the manual setting of ROI regions in the cervix requires further investigation. ROI setting is often done based on clinical experience, called "domain

knowledge" in data science. Moreover, in this study, the cervix, including the inner and outer uterine orifices, was sliced with the human eye. However, the possibility of extracting important radiomic features has not yet been fully tested. Further studies are needed to repeat the radiomics analysis in different study designs using other sequences that may reveal more disease-specific markers. Finally, no active machine learning model was created in this study due to the small sample size. Numerical markers extracted from radiomics analysis can be used for risk classification in combination with other numerical markers, such as patient background and blood test data. Prediction of preterm birth by machine learning models allowing a more accurate assessment of preterm birth risk for each case.

Radiomics analysis suggested the possibility of extracting numerical markers associated with preterm birth from transvaginal ultrasound images. In high-risk cases, radiomic features could be better predictors than cervical length and clinical variables. In the future, with sufficient data size, more preterm birth-specific features could be found in cervical images.

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