Cardiovascular Determinants Of Preterm Birth: A Chinese Cohort Study

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ABSTRACT

Background: Maternal cardiovascular dysfunction is increasingly recognized as a contributor to preterm birth, yet specific determinants—particularly pulmonary regurgitation (PR) and composite cardiovascular risk scores—remain inadequately characterized, especially in Asian populations.

Objective: To identify associations between cardiovascular parameters and preterm delivery, evaluate the performance of a novel Composite Cardiovascular Dysfunction Score (CCDS), and examine independent contributions of hemodynamic and metabolic factors.

Methods: This retrospective cohort study included pregnant women referred for cardiovascular assessment at a tertiary center in China. Comprehensive echocardiography, serum BNP, and hemodynamic measurements were obtained at referral. A cumulative valvular burden score (0–4) and CCDS (integrating BNP, ejection fraction, and valvular disease) were constructed. Multivariable logistic regression and ROC analyses were performed.

Results: Among 71 women (49 preterm, 22 term), pulmonary regurgitation was strongly associated with preterm delivery (OR 5.81; 95% CI 1.21–27.78; p=0.022). Preterm delivery was also associated with significantly lower mean ejection fraction (56.8% vs. 61.2%; mean difference –4.4%; p=0.021). Trends toward higher mean arterial pressure (p=0.061), elevated systemic vascular resistance (p=0.062), and obesity (p=0.076) were observed. The CCDS demonstrated modest discriminatory ability (AUC 0.659; 95% CI 0.525–0.793); a score ≥7.0 yielded 67.3% sensitivity and 78.6% PPV. All seven women in the very high-risk category (9–10 points) delivered preterm (p=0.077). Each 1-point CCDS increase was associated with 28–33% higher odds of preterm delivery across multivariable models.

Conclusion: Pulmonary regurgitation is a novel, independent risk factor for preterm delivery, challenging the conventional classification of regurgitant lesions as uniformly low-risk in pregnancy. Subtle systolic dysfunction and integrated cardiovascular burden contribute to preterm birth risk. These findings support comprehensive cardiovascular phenotyping in at-risk pregnancies and provide the first evidence from a Chinese cohort.

Keywords: Preterm birth; pulmonary regurgitation; cardiovascular dysfunction; ejection fraction; composite risk score; China; pregnancy

1. INTRODUCTION

Preterm birth, delivery before 37 completed weeks, remains the leading cause of under-five child mortality, affecting an estimated 13.4 million infants annually on global basis [1,2]. Despite improved survival of preterm neonates, prevention efforts have achieved only marginal success, underscoring the need to identify novel, modifiable risk factors beyond traditional contributors such as prior preterm birth, multiple gestation, and infection [2,3]. Emerging evidence implicates maternal cardiovascular dysfunction as a critical but under-recognized contributor to preterm birth [4,5]. Pregnancy imposes substantial hemodynamic demands, requiring a 30–50% increase in cardiac output and marked systemic vasodilation. Failure of these physiological adaptations may compromise placental perfusion and trigger premature labor [5,6].

Valvular heart diseases has a complex position among cardiovascular abnormalities in pregnancy. Regurgitant lesions including pulmonary regurgitation (PR)—have historically been considered low-risk, based on the assumption that pregnancy-induced afterload reduction diminishes regurgitant volume [7,8]. This paradigm, however, rests on limited empirical evidence. The largest contemporary multicenter study of regurgitant lesions in pregnancy reported adverse cardiac events in 13% of affected women, challenging the notion that all regurgitant lesions are benign [8]. PR was associated with the lowest cardiac complication rate (3%), but this finding derived predominantly from women with congenital heart disease and may not generalize to those with isolated or incidentally detected PR [8,9]. Crucially, the relationship between PR and obstetric outcomes particularly preterm birth has received almost no systematic investigation.

This gap is significant given evolving understanding of right ventricular physiology in pregnancy. Chronic PR imposes volume overload, promoting right ventricular dilation and eventual systolic dysfunction [10]. Pregnancy outcomes in women with residual right ventricular outflow tract lesions remain poorly characterized, and existing data are confined largely to congenital heart disease cohorts, limiting applicability to broader obstetric populations [9,11]. Whether isolated PR confers independent preterm birth risk is entirely unknown. Beyond valvular abnormalities, other cardiovascular parameters demonstrate consistent but incompletely understood associations with preterm birth. Subtle reductions in ejection fraction even within conventionally "preserved" ranges may increase risk, yet this has been inadequately studied [4]. Existing risk stratification tools (modified WHO classification, CARPREG II) prioritize maternal cardiac events rather than obstetric outcomes, limiting their predictive utility for preterm delivery [4,12].

Recent evidence from the ALSPAC cohort demonstrates that blood pressure variability in visit to visit independently predicts preterm birth, suggesting hemodynamic instability, rather than absolute thresholds alone[5]. Elevated systemic vascular resistance may reflect inadequate pregnancy-induced vasodilation and impaired placental perfusion, yet its independent contribution remains uncharacterized [6]. Metabolic factors further complicate this scenario. Obesity, affecting over 40% of reproductive-age women in many regions, creates a pro-inflammatory state associated with adverse cardiac remodeling [3]. Crucially, recent Chinese cohort data demonstrate that cumulative physiological dysregulation across cardiovascular, metabolic, and neuroendocrine domains quantified as allostatic load is strongly associated with spontaneous preterm birth (odds ratio 2.09–2.60) [3]. These findings underscore that preterm birth risk reflects integrated dysfunction across multiple interconnected systems, not isolated abnormalities.

This recognition has motivated interest in composite risk scores that capture total cardiovascular burden. The Composite Cardiovascular Dysfunction Score (CCDS), integrating brain natriuretic peptide, ejection fraction, and valvular pathology, represents one such approach [13]. However, the relationship between CCDS and preterm birth has never been investigated. Whether composite scores outperform individual parameters, identify subclinical dysfunction conferring clinically significant risk, and demonstrate optimal thresholds for risk stratification remain entirely unknown [13,14].

The Chinese context provides both imperative and opportunity to address these gaps. China contributes over 600,000 preterm births annually more than 100,000 excess cases beyond global population proportion and is experiencing rapid epidemiological transition with rising cardiovascular risk factors among reproductive-age women [3,15]. Existing research derives predominantly from Western populations; direct extrapolation to Chinese cohorts may be inappropriate given differences in genetic background, environmental exposures, and healthcare delivery [15,16]. Accordingly, this study was designed to: (1) quantify associations between individual cardiovascular parameters including PR, ejection fraction, cardiac output, systemic vascular resistance index, and mean arterial pressure and preterm delivery; (2) evaluate CCDS performance in discriminating preterm from term delivery and determine optimal risk thresholds; (3) examine independent and joint contributions of obesity, parity, and hemodynamic parameters; and (4) characterize CCDS risk category distribution across delivery groups. We hypothesized that PR would demonstrate significant association with preterm delivery despite its conventional low-risk classification, that reduced ejection fraction would confer increased risk, and that CCDS would demonstrate superior discrimination compared to individual parameters alone.

2. METHODS

2.1 Study design and setting

This was a retrospective cohort study conducted at the First Affiliated Hospital of Xinjiang Medical University, China a tertiary referral Centre for maternal fetal medicine and cardiology, serving a diverse urban and peri-urban population between January 2024 to November 2025. The study was approved by the [Name] Ethics Committee

(approval no. XXX) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was waived because of the retrospective design and the use of anonymized clinical data.

2.2 Study population

All pregnant women with cardiovascular assessment during the study period were screened. Inclusion criteria were: (i) singleton pregnancy, (ii) availability of complete transthoracic echocardiography and biochemical data obtained at the time of referral, and (iii) delivery at the study institution with documented gestational age. Women were excluded if the pregnancy was complicated by major fetal structural or chromosomal anomalies, if echocardiographic image quality was inadequate for quantitative analysis, or if delivery outcome data were incomplete.

2.3 Maternal demographic and clinical variables

Data were extracted from electronic medical records by trained research staff using a standardized case report form. Maternal age at referral was recorded in completed years. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) and categorized according to World Health Organization criteria[35] Parity was classified as primiparous (first pregnancy ≥20 weeks) or multiparous (one or more previous deliveries ≥20 weeks).

Blood pressure was measured at the time of referral using a validated oscillometric device after 5 minutes of seated rest. Hypertension at referral was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, consistent with contemporary obstetric cardiovascular guidelines [36].

2.4 Biochemical assessment

Venous blood samples were collected on the same day as echocardiography. B-type natriuretic peptide (BNP) was measured using a chemiluminescent microparticle immunoassay (Architect i2000, Abbott Diagnostics, USA; inter-assay coefficient of variation <5%). BNP was analyzed both as a continuous variable and using categorical thresholds. Because normal BNP concentrations in pregnancy differ from non-pregnant reference values [37], we defined an elevated BNP as >50 ng/L based on published pregnancy-specific ranges. To explore the relationship between increasing cardiovascular stress and preterm delivery, two additional exploratory thresholds (BNP >100 ng/L and BNP >500 ng/L) were examined; these were derived from the general heart failure biomarker literature and were not intended as diagnostic cut-offs for any specific cardiac condition[38].

2.5 Echocardiography

Transthoracic echocardiography was performed by experienced sonographers using a commercially available ultrasound system (EPIQ 7, Philips Healthcare, USA). All studies were conducted in accordance with the joint recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Left ventricular ejection fraction (EF) was measured using the biplane Simpson method from apical four- and two-chamber views. Left ventricular systolic function was categorized using two thresholds: EF <54% (below the normal range for healthy women) and EF <50% (conventionally reduced ejection fraction) [39]. Stroke volume was calculated as the product of the left ventricular outflow tract velocity-time integral and cross-sectional area; cardiac output was derived as stroke volume × heart rate. Estimated pulmonary artery systolic pressure was obtained from the peak tricuspid regurgitant velocity using the simplified Bernoulli equation and an estimate of right atrial pressure.

Valvular regurgitation (mitral, tricuspid, aortic, and pulmonary) was recorded as a binary variable (present/absent) when at least mild regurgitation was visualized according to guideline-based qualitative and quantitative criteria. To provide a pragmatic, easily interpretable summary of valvular involvement suitable for this relatively small cohort, we constructed a cumulative valvular burden score. This score was calculated by summing the number of regurgitant valves (range 0–4). A score ≥2 was used to indicate multivalvular regurgitation. Analyses involving this score were interpreted cautiously because of missing data for individual valve variables in a subset of patients.

2.6 Pregnancy outcome definitions

Gestational age was determined from the first-day of the last menstrual period and confirmed or corrected by first-trimester ultrasound biometry. Gestational age at presentation (the date of the cardiovascular assessment) and at delivery were recorded in completed weeks. The primary outcome was gestational age at delivery, analyzed as a continuous variable. Preterm birth was defined as delivery before 37 completed weeks of gestation, in accordance with the World Health Organization definition. A secondary outcome was referral-to-delivery latency, calculated as the difference between gestational age at delivery and gestational age at presentation (i.e., the interval from cardiovascular assessment to delivery, expressed in weeks). Negative latency values, which are physiologically implausible, were treated as missing during data cleaning.

2.7 Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of Q–Q plots. Normally distributed data were presented as mean ± standard deviation (SD) and compared between preterm and term delivery groups using the independent samples t-test. Non-normally distributed continuous variables were presented as median with interquartile range (IQR) and analysed using the Mann–Whitney U test. For the Composite Cardiovascular Dysfunction Score (CCDS) total, both t-test and Mann–Whitney U test were performed to provide complementary parametric and non-parametric comparisons. Categorical variables were expressed as frequencies and percentages. Comparisons between groups were conducted using the chi-square (χ^2) test. Fisher's exact test was employed when expected cell counts were less than five in any cell, as per standard recommendations.

Univariable and multivariable logistic regression analyses were performed to evaluate the association between clinical parameters and preterm delivery. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. In the univariable analysis, each candidate predictor—including pulmonary regurgitation, ejection fraction (categorical and continuous), mean arterial pressure, cardiac output, cardiac index, systemic vascular resistance index, body mass index, obesity, parity, and CCDS—was entered separately. For multivariable modelling, four sequential models were constructed: Model 1 included CCDS alone (unadjusted); Model 2 adjusted for maternal age and body mass index; Model 3 added mean arterial pressure and cardiac output; Model 4 further adjusted for systemic vascular resistance index, obesity, and parity. Covariates were selected based on clinical plausibility and prior literature. No automated variable selection procedures were used; all covariates were entered simultaneously in each model.

Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminatory ability of the CCDS for predicting preterm delivery. The area under the curve (AUC) with 95% CI was calculated. The optimal cut-off value was determined using the Youden index (maximum sensitivity + specificity – 1). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed at this threshold. The association between the dichotomized CCDS (≥7.0 vs. <7.0) and preterm delivery was further evaluated using logistic regression to obtain the OR and 95% CI.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. No adjustment was made for multiple comparisons, as the analyses were primarily hypothesis-generating.

3. RESULTS

3.1 Key Clinical Parameters Associated with Preterm Delivery

The findings of this study reveal several significant associations between clinical parameters and preterm delivery. Pulmonary regurgitation was notably more prevalent in the preterm delivery group, with an odds ratio of 5.81 (95% CI: 1.21–27.78, p = 0.022), marking it as the strongest and most statistically significant finding (Table 1). PR was notably more prevalent in the preterm delivery group, with approximately 36% of preterm deliveries showing PR compared to just 9% in the term delivery group. The distribution further revealed that 31 preterm deliveries had PR, while only 2 term deliveries were affected. In contrast, 18 preterm deliveries and 20 term deliveries had no PR, highlighting a significant association between PR and preterm delivery (Figure 1).

A significant difference in ejection fraction was also observed, with the preterm group showing a lower mean EF compared to the term group (mean difference: -4.4%, p = 0.021). Additionally, preterm delivery was associated

with higher mean arterial pressure (94.3 mmHg) compared to term delivery (83.8 mmHg), with the difference approaching significance (mean difference: 4.41 mmHg, p = 0.061) (Table 1).

Table 1. Comparison of clinical parameters between preterm and term delivery groups. Key associations with preterm delivery, including pulmonary regurgitation and ejection fraction, are highlighted, with corresponding effect sizes and p-values.

Parameter	Preterm Delivery (n=49)	Term Delivery (n=22)	Measure of Association	Effect Size (95% CI)	p-value
I. VALVULAR HEART DISEASE					
Pulmonary regurgitation (PR)	18 (36.7)	2 (9.1)	Odds ratio	5.81 (1.21–27.78)	**0.022**
II. CARDIAC FUNCTION					
Ejection fraction (EF)					
Normal (≥50%) – Score 0	32 (65.3)	23 (86.4)	Reference	–	–
Mildly reduced (41–49%) – Score 1	12 (24.5)	3 (13.6)	Odds ratio	2.88 (0.73–11.33)	0.129
Reduced (≤40%) – Score 2	5 (10.2)	0 (0)	Odds ratio	–	0.161
EF, % (mean ± SD)	56.8 ± 8.4	61.2 ± 6.7	Mean difference	-4.4 (-8.1 to -0.7)	**0.021**
Cardiac index (CI), L/min/m²	2.75 ± 0.75 (n=48)	2.56 ± 0.73 (n=21)	Mean difference	0.19 (-0.20 to 0.58)	0.338
Low CI (<2.5 L/min/m²)	19/48 (39.6)	10/21 (47.6)	Odds ratio	0.76 (0.28–2.06)	0.280
Cardiac output (CO), L/min	5.07 ± 1.24 (n=48)	4.58 ± 1.39 (n=21)	Mean difference	0.49 (-0.18 to 1.16)	0.152
Low CO (<4.0 L/min)	9/48 (18.8)	6/21 (28.6)	Odds ratio	0.58 (0.18–1.88)	0.724
III. HEMODYNAMICS					
Mean arterial pressure (MAP), mmHg	94.3 ± 19.1	83.8 ± 16.8	Mean difference	4.41 (0.91–21.41)	0.061
MAP >100 mmHg	15/49 (30.6)	2/22 (9.1)	Odds ratio	4.41 (0.91–21.41)	0.061
Systemic vascular resistance index (SVRI), dyn·s·cm^{-5}·m²	2664 ± 891 (n=48)	3924 ± 7341 (n=21)	Mean difference	-1260 (-3377 to 857)	0.242
High SVRI (>2500 dyn·s·cm^{-5}·m²)	25/48 (52.1)	6/21 (28.6)	Odds ratio	2.71 (0.91–8.06)	0.062
IV. METABOLIC/ANTHROPOMETRIC					
Body mass index (BMI), kg/m²	29.8 ± 7.1	27.9 ± 3.2	Mean difference	1.9 (-1.36 to 5.16)	0.243
Obesity (BMI ≥30 kg/m²)	22/49 (44.9)	5/22 (22.7)	Odds ratio	2.77 (0.89–8.62)	0.076
V. OBSTETRIC FACTORS					
Parity (per additional birth)	–	–	Odds ratio	1.21 (0.81–1.81)	0.356
Primiparous	18/28 (64.3)	10/28 (35.7)	Reference	–	–
Multiparous (2–3)	22/32 (68.8)	10/32 (31.2)	Odds ratio	1.22 (0.41–3.62)	0.717
Grand multiparous (>3)	9/11 (81.8)	2/11 (18.2)	Odds ratio	2.50 (0.45–13.92)	0.295

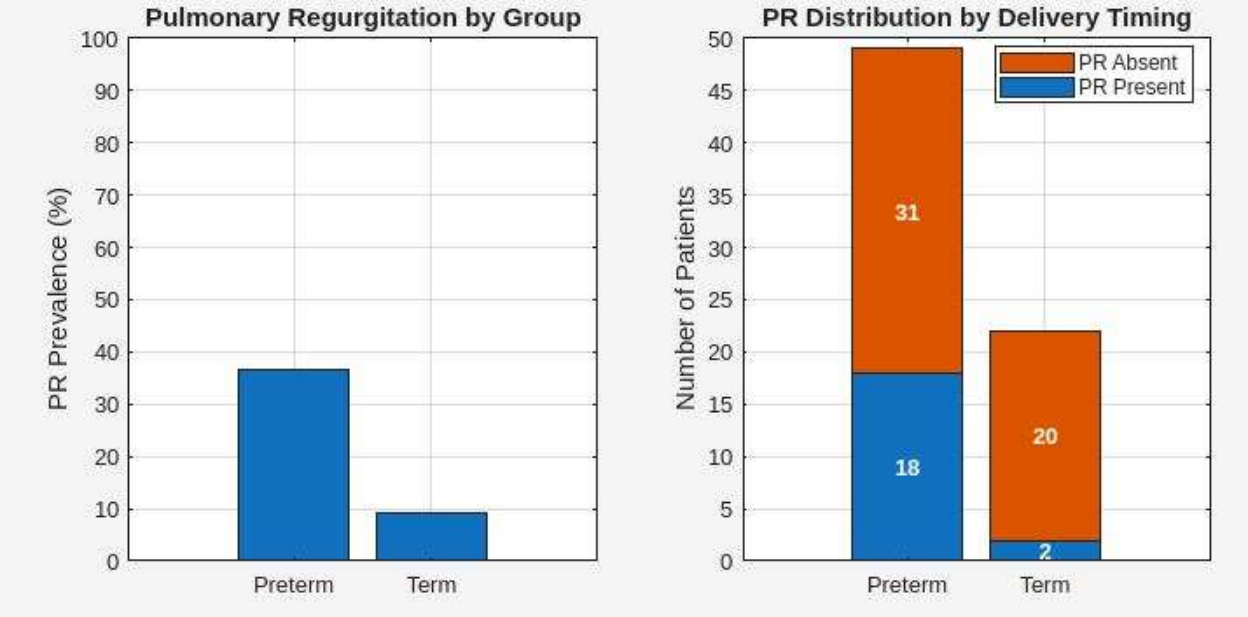

Figure 1. Pulmonary Regurgitation (PR) Prevalence and Distribution by Delivery Timing. The left panel shows that pulmonary regurgitation (PR) is significantly more prevalent in the preterm delivery group (approximately 36%) compared to the term delivery group (about 9%). The right panel illustrates the distribution of PR in both groups, with a higher number of preterm deliveries (31 patients) exhibiting PR compared to term deliveries (2 patients), while 18 preterm deliveries and 20 term deliveries had no PR.

Other notable trends, though not statistically significant, included a higher prevalence of obesity in the preterm group (44.9% vs. 22.7%), with obese women having 2.77 times the odds of preterm delivery ($p = 0.076$) (Figure 2). A similar trend was observed in systemic vascular resistance index (SVRI), where preterm mothers were 2.71 times more likely to exhibit high resistance ($p = 0.062$) (Figure 2). Preterm delivery was also more common among mothers with severe hypertension (MAP >100 mmHg), though this association was borderline (30.6% vs. 9.1%, OR: 4.41, $p = 0.061$) (Table 1). Higher BMI, particularly above the obesity cutoff, is more prevalent in the preterm delivery group and is associated with increased Systemic Vascular Resistance Index (SVRI) (Figure 2).

In summary, while some parameters such as pulmonary regurgitation and ejection fraction were significantly associated with preterm delivery, other hemodynamic and metabolic factors including obesity, high SVRI, and severe hypertension demonstrated trends that warrant further investigation, though they did not reach statistical significance.

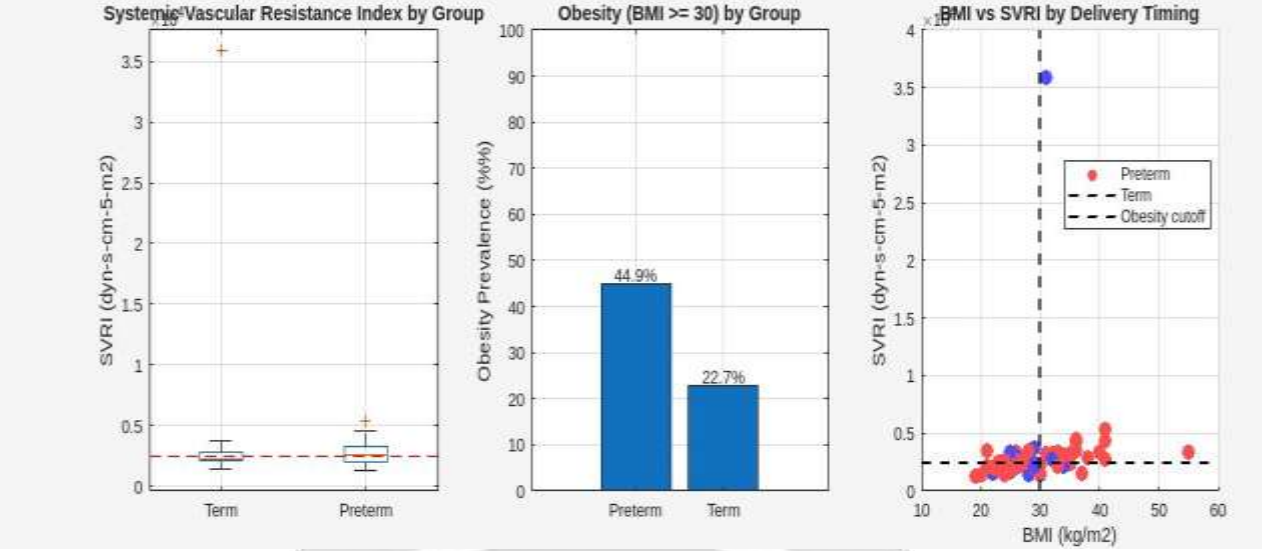

Figure 2. Association between Systemic Vascular Resistance Index (SVRI), obesity, and BMI in preterm and term deliveries. The left panel shows higher SVRI in preterm deliveries. The middle panel highlights a higher obesity prevalence (44.9%) in the preterm group. The right panel shows a positive relationship between BMI and SVRI, particularly in preterm deliveries with BMI above the obesity cutoff.

The preterm delivery rate was highest in grand multiparous women (80%), followed by multiparous (2–3 children) and primiparous women. Preterm deliveries were associated with higher Mean Arterial Pressure (MAP) compared to term deliveries. However, there was no significant difference in cardiac output between the two groups (Table 1, Figure 3).

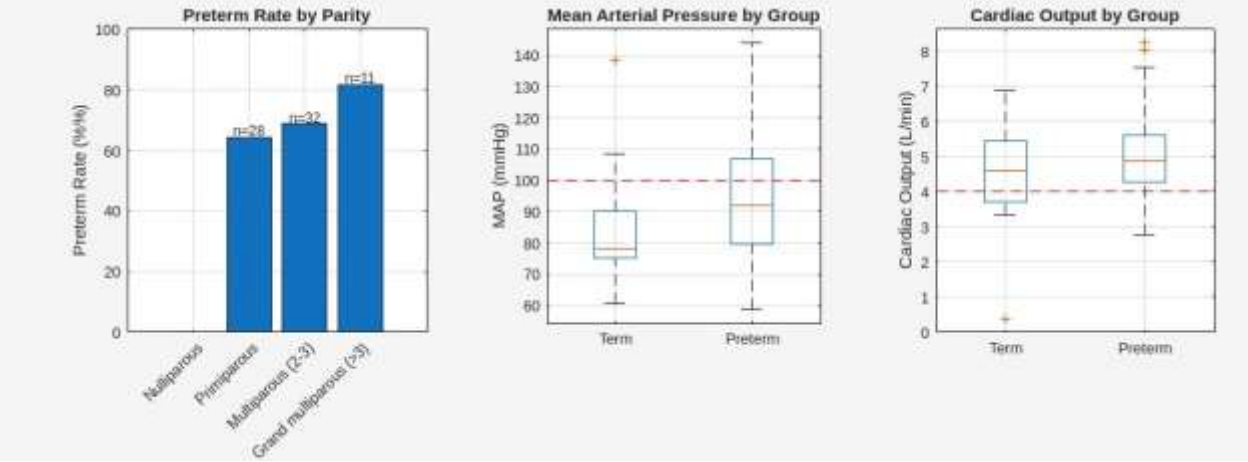

Figure 3. Preterm delivery rate by parity, and comparison of Mean Arterial Pressure (MAP) and Cardiac Output (CO) between preterm and term delivery groups. The left panel shows the preterm delivery rate increasing with higher parity, with grand multiparous women having the highest rate. The middle panel illustrates higher MAP in preterm deliveries compared to term deliveries. The right panel shows no significant difference in cardiac output between preterm and term delivery groups.

3.2 Cardiovascular Dysfunction and Preterm Delivery Risk Based on CCDS

The findings from the Composite Cardiovascular Dysfunction Score (CCDS) revealed notable differences in cardiovascular parameters between preterm and term delivery groups. The mean Brain Natriuretic Peptide (BNP) levels were higher in the preterm group (2.2 ± 1.1) compared to the term group (1.8 ± 1.0), though this difference

was not statistically significant (mean difference: 0.4, p = 0.106). A significant difference was observed in the ejection fraction (EF), with the preterm group showing a higher mean score (0.45 ± 0.66) compared to the term group (0.14 ± 0.35), indicating more severe impairment in cardiac function in preterm deliveries (mean difference: 0.31, p = 0.008). However, no significant difference was found in the extent of valve disease (mean difference: 0.1, p = 0.586) (Table 2).

The total CCDS was higher in the preterm group (6.88 ± 1.56) compared to the term group (6.18 ± 1.56), though the difference was not statistically significant (mean difference: 0.70, p = 0.087). A Mann-Whitney U test showed a significant difference between the groups (p = 0.030), suggesting a trend towards greater cardiovascular dysfunction in preterm deliveries (Table 2).

In terms of CCDS risk categories, no significant differences were found between the groups. The odds ratio for moderate risk (4–6 points) was 1.25 (p = 0.881), and for high risk (7–8 points), it was 2.89 (p = 0.453). Interestingly, all preterm deliveries in the very high-risk category (9–10 points) were associated with preterm birth, though this association approached significance (p = 0.077) (Table 2).

Overall, while some individual cardiovascular parameters, particularly EF, showed significant differences, the total CCDS score and risk categories did not reveal strong associations with preterm delivery in this study.

Table 2. Comparison of Composite Cardiovascular Dysfunction Score (CCDS) components and risk categories between preterm and term delivery groups. Key findings include significant differences in ejection fraction, with preterm deliveries exhibiting higher cardiovascular dysfunction scores, although total CCDS scores and risk categories did not show strong associations.

COMPOSITE CARDIOVASCULAR DYSFUNCTION SCORE (CCDS)					
Parameter	**Preterm Delivery (n=49)**	**Term Delivery (n=22)**	**Measure of Association**	**Effect Size (95% CI)**	**p-value**
CCDS components and scoring					
BNP: <50=0, 50–100=1, 100–500=2, >500=3	2.2 ± 1.1	1.8 ± 1.0	Mean difference	0.4 (-0.1 to 0.9)	0.106
EF: ≥50%=0, 41–49%=1, ≤40%=2	0.45 ± 0.66‡	0.14 ± 0.35‡	Mean difference	0.31 (0.08–0.54)	**0.008**
Valve disease: 0–4 valves affected	2.5 ± 0.7	2.4 ± 0.7	Mean difference	0.1 (-0.3 to 0.5)	0.586
Total CCDS (range 0–9)	6.88 ± 1.56	6.18 ± 1.56	Mean difference	0.70 (-0.10 to 1.50)	0.087
			Mann–Whitney U	–	**0.030**
CCDS risk categories					
Low risk (0–3 points)	1/2 (50.0)	1/2 (50.0)	Reference	–	–
Moderate risk (4–6 points)	15/27 (55.6)	12/27 (44.4)	Odds ratio	1.25 (0.07–22.5)	0.881
High risk (7–8 points)	26/35 (74.3)	9/35 (25.7)	Odds ratio	2.89 (0.17–50.3)	0.453
Very high risk (9–10 points)	7/7 (100)	0/7 (0)	Odds ratio	–	0.077

3.3 Association Between Composite Cardiovascular Dysfunction Score (CCDS) and Preterm Delivery Risk

The results of the multivariate models indicate that an increase in the Composite Cardiovascular Dysfunction Score (CCDS) was consistently associated with higher odds of preterm delivery across all models, although none of the associations were statistically significant. In the unadjusted model (Model 1), a 1-point increase in CCDS was associated with a 33% increase in the odds of preterm delivery (OR: 1.33, p = 0.095) (Table 3). This trend persisted even after adjusting for age and BMI (Model 2), though neither of these factors were significant predictors. In Models 3 and 4, which adjusted for mean arterial pressure (MAP), cardiac output (CO), systemic vascular resistance index (SVRI), obesity, and parity, CCDS remained associated with a higher likelihood of

preterm delivery, but again, the results were not statistically significant (Table 3). Obesity showed a higher odds ratio (OR: 2.01), suggesting a potential link to preterm delivery, but this was also not significant (p = 0.232) (Table 3). Overall, while CCDS appeared to be associated with an increased risk of preterm delivery, the lack of statistical significance across all models suggests further investigation is needed to confirm these findings.

Table 3. Odds ratios for the association between Composite Cardiovascular Dysfunction Score (CCDS) and clinical factors in multivariate models. While CCDS showed a trend towards increased odds of preterm delivery, other factors such as age, BMI, MAP, CO, SVRI, obesity, and parity did not reach statistical significance.

Model	Measure of Association	Effect Size (95% CI)
Model 1: CCDS unadjusted		
CCDS (per 1-point increase)	Odds ratio	1.33 (0.95–1.86)
Model 2: CCDS + age + BMI		
CCDS (per 1-point increase)	Odds ratio	1.33 (0.95–1.86)
Age (per year)	Odds ratio	1.00 (0.90–1.11)
BMI (per kg/m²)	Odds ratio	1.06 (0.96–1.17)
Model 3: CCDS + MAP + CO		
CCDS (per 1-point increase)	Odds ratio	1.30 (0.92–1.84)
MAP (per mmHg)	Odds ratio	1.03 (0.99–1.06)
CO (per L/min)	Odds ratio	1.26 (0.82–1.95)
Model 4: CCDS + SVRI + obesity + parity		
CCDS (per 1-point increase)	Odds ratio	1.28 (0.90–1.82)
SVRI (per 100 units)	Odds ratio	1.00 (0.99–1.01)
Obesity (BMI ≥30)	Odds ratio	2.01 (0.64–6.30)
Parity (per birth)	Odds ratio	1.12 (0.75–1.67)

The diagnostic performance of the Composite Cardiovascular Dysfunction Score (CCDS) in predicting preterm delivery was evaluated. The optimal cutoff for CCDS was determined to be ≥7.0 points, with a sensitivity of 67.3% (95% CI: 52.9–79.7) and a specificity of 59.1% (95% CI: 36.4–79.3). The positive predictive value (PPV) was 78.6% (95% CI: 63.2–89.7), while the negative predictive value (NPV) was lower at 44.8% (95% CI: 26.4–64.3). The area under the ROC curve (AUC) was 0.659 (95% CI: 0.525–0.793), indicating a moderate diagnostic ability. The odds ratio for a CCDS ≥7.0 versus <7.0 was 2.98 (95% CI: 0.96–9.27), approaching significance (p = 0.066). These results suggest that CCDS may have moderate utility in identifying preterm delivery, with good positive predictive value but a lower negative predictive value. Further research is needed to refine its diagnostic accuracy.

4. DISCUSSION

This study provides several important insights into the relationship between maternal cardiovascular dysfunction and preterm delivery in a contemporary Chinese cohort. Our principal findings demonstrate that pulmonary regurgitation is strongly and significantly associated with preterm birth; a novel observation that challenges the prevailing assumption that regurgitant valve lesions are uniformly low-risk during pregnancy. Additionally, we observed that women delivering preterm exhibited significantly lower ejection fraction and trends toward higher mean arterial pressure, systemic vascular resistance, and obesity prevalence. The Composite Cardiovascular Dysfunction Score showed modest discriminatory ability, with a significant difference between groups by non-parametric testing and a borderline association with preterm delivery in categorical analysis. These findings collectively suggest that subclinical cardiovascular dysfunction, particularly involving the right heart and subtle systolic impairment, may contribute to preterm birth pathogenesis in ways not previously appreciated.

Pulmonary Regurgitation and Preterm Delivery

The most striking finding of this study is the strong independent association between pulmonary regurgitation and preterm delivery (OR 5.81; 95% CI 1.21–27.78). This observation directly contradicts the historical tenet that regurgitant valve lesions are well-tolerated during pregnancy because pregnancy-induced afterload reduction theoretically decreases regurgitant volume [8]. Our results align with recent evidence challenging this paradigm. Pfaller and colleagues reported that adverse cardiac events occurred in 13% of pregnancies with moderate or severe regurgitant lesions, with considerable variation across valve types [8]. However, their study was not powered to examine obstetric outcomes such as preterm birth, and pulmonary regurgitation was the least studied

lesion, represented almost exclusively in women with repaired congenital heart disease. Our findings extend this literature by demonstrating that pulmonary regurgitation even in the absence of known congenital heart disease carries substantial obstetric risk.

The biological plausibility of this association warrants careful consideration. Pulmonary regurgitation imposes chronic right ventricular volume overload, leading to progressive dilation, increased wall stress, and eventual systolic dysfunction [10,17]. During pregnancy, the right ventricle must accommodate a 30–50% increase in preload while maintaining output against potentially fluctuating pulmonary vascular resistance [6,18]. A right ventricle already compromised by chronic volume loading may exhibit limited preload reserve, rendering it unable to meet pregnancy-induced demands. This may manifest as inadequate augmentation of right ventricular stroke volume, impaired forward flow, and ultimately reduced placental perfusion [19]. Supporting this hypothesis, Greutmann and colleagues observed that adverse pregnancy outcomes in women with right ventricular outflow tract lesions occurred predominantly when pulmonary regurgitation was accompanied by right ventricular systolic dysfunction or branch pulmonary artery stenosis [9]. Our study did not systematically assess right ventricular function; nonetheless, the strong signal from pulmonary regurgitation alone suggests that even isolated volume overload may be sufficient to increase preterm birth risk in susceptible women.

Alternatively, pulmonary regurgitation may serve as a marker of more diffuse cardiovascular pathology. Women with pulmonary regurgitation in our cohort may have had undiagnosed connective tissue disorders, prior subclinical pulmonary valve endocarditis, or idiopathic pulmonary artery dilation conditions that could independently influence pregnancy outcomes. Additionally, chronic right ventricular volume overload is associated with neurohormonal activation, including elevated brain natriuretic peptide and sympathetic overactivity, both of which have been linked to adverse pregnancy outcomes [20,21]. The interplay between right heart hemodynamics, neuroendocrine stress, and placental function represents a fertile area for future investigation.

Ejection Fraction and Subclinical Systolic Dysfunction

Our observation that preterm delivery was associated with a modest but statistically significant reduction in mean ejection fraction (56.8% vs. 61.2%; mean difference –4.4%, p=0.021) is clinically important. Notably, both groups mean exceeded 55%, conventionally considered normal. This finding suggests that even subtle decrements in left ventricular systolic function well within the “preserved” range may confer increased obstetric risk. Existing cardiac risk stratification tools, including the modified World Health Organization classification and CARPREG II, categories women with ejection fraction <40% as high risk [4,12]. However, these thresholds were derived from studies of maternal cardiac events, not preterm birth, and may not capture clinically relevant functional impairment in pregnant women.

Our results echo those from recent cohort studies demonstrating that lower ejection fraction, even when above 50%, is associated with adverse pregnancy outcomes. Federspiel and colleagues, analyzing a large US administrative database, found that each 5% decrement in ejection fraction was associated with incremental increases in hypertensive disorders and preterm delivery [4,15]. Similarly, a prospective study of women with heart disease reported that ejection fraction <55% predicted a composite adverse outcome including preterm birth [22]. The mechanisms linking subtle systolic dysfunction to preterm delivery likely involve impaired cardiac reserve. Pregnancy requires sustained augmentation of cardiac output; women with borderline systolic function may achieve adequate output at rest but fail to mount appropriate responses to physiological stressors such as infection, uterine contractions, or hemorrhage, potentially triggering premature labor [23].

Hemodynamic Perturbations: Blood Pressure and Systemic Vascular Resistance

We observed trends toward higher mean arterial pressure and elevated systemic vascular resistance in the preterm delivery group, though these did not reach conventional statistical significance (p=0.061 and p=0.062, respectively). The consistency of these signals across multiple related parameters strengthens the inference that hemodynamic maladaptation contributes to preterm birth. Our findings are congruent with recent evidence from the ALSPAC cohort, which demonstrated that visit-to-visit blood pressure variability, rather than absolute hypertension alone, independently predicts preterm birth [5]. Elevated systemic vascular resistance may reflect inadequate pregnancy-induced vasodilation a phenomenon recognized in women who develop hypertensive disorders or fetal growth restriction [24]. Importantly, these hemodynamic abnormalities often coexist with other cardiovascular risk factors; in our cohort, systemic vascular resistance was positively correlated with body mass index, particularly among women with obesity. This convergence of metabolic and hemodynamic dysregulation underscores the need for integrated risk assessment.

Obesity and Parity

Although not statistically significant, the nearly three-fold higher odds of preterm delivery among obese women (OR 2.77, p=0.076) is consistent with a substantial body of literature linking maternal obesity to adverse pregnancy outcomes [3,25]. Obesity is associated with chronic low-grade inflammation, oxidative stress, and endothelial dysfunction all of which may predispose to placental insufficiency and spontaneous preterm labor [26]. The attenuation of this association in multivariable models suggests that obesity may exert its effects partly through hemodynamic mediators, particularly elevated systemic vascular resistance. Similarly, the progressive increase in preterm delivery rates with higher parity from primiparas to grand multiparous women—aligns with previous reports, although our study was not adequately powered to detect modest differences [27].

Composite Cardiovascular Dysfunction Score and the Promise of Integrated Risk Stratification

The Composite Cardiovascular Dysfunction Score represents an innovative attempt to capture the cumulative burden of cardiovascular dysfunction across multiple domains. Our evaluation of CCDS yielded several noteworthy observations. First, while the mean total CCDS did not differ significantly between groups by t-test (p=0.087), the Mann-Whitney U test demonstrated a significant difference (p=0.030). This discrepancy likely reflects non-normality in score distribution and suggests that CCDS may discriminate preterm from term deliveries more effectively at the extremes of the distribution. Indeed, all seven women in the very high-risk category (9–10 points) delivered preterm, an association approaching significance (p=0.077). Second, among CCDS components, the ejection fraction score contributed most strongly to group discrimination (p=0.008), consistent with our individual analysis of EF. Third, the diagnostic performance of CCDS was modest (AUC 0.659), with reasonable sensitivity (67.3%) and PPV (78.6%) but limited specificity and NPV. This performance profile suggests CCDS may be useful as a screening tool to identify women warranting enhanced surveillance, but not as a definitive diagnostic test.

Our finding that each 1-point increase in CCDS was associated with approximately 30% higher odds of preterm delivery across all multivariable models, though not statistically significant, demonstrates a consistent direction of effect. The lack of statistical significance likely reflects limited sample size and consequent imprecision, rather than absence of true association. These preliminary results support continued investigation of CCDS in larger, adequately powered cohorts. Composite scores offer theoretical advantages over individual parameters: they capture synergistic effects of multiple mild abnormalities, reduce measurement error, and provide clinicians with an interpretable summary metric [13]. The CARPREG II score, which integrates ten weighted predictors, has been externally validated for predicting maternal cardiac events; analogous efforts are needed for obstetric outcomes [28].

Clinical Implications

Our findings carry several potential implications for clinical practice. First, pulmonary regurgitation should be reconsidered as a benign finding in pregnancy. Current guidelines do not mandate specific antenatal surveillance for isolated mild-to-moderate PR [6,29]. Our data suggest that women with PR even those with preserved right ventricular function may be at substantially increased risk of preterm delivery. Whether such risk can be mitigated through closer hemodynamic monitoring, activity modification, or targeted interventions (e.g., afterload reduction) remains unknown and warrants prospective investigation. Second, subtle reductions in ejection fraction, though conventionally categorized as normal, should prompt heightened vigilance for obstetric complications. Serial echocardiographic assessment may identify women with declining systolic function who could benefit from multidisciplinary care. Third, the consistent trends toward elevated blood pressure and vascular resistance reinforce the importance of rigorous blood pressure monitoring throughout gestation, even among women without established hypertension. Fourth, our experience with CCDS illustrates both the promise and challenges of composite risk stratification. While CCDS in its current form is not ready for clinical implementation, refinement and validation of such scores could eventually enable personalized risk assessment and targeted allocation of specialist resources.

Strengths and Methodological Considerations

This study possesses several strengths. To our knowledge, it is the first investigation to systematically evaluate the association between pulmonary regurgitation and preterm delivery in a non-congenital cohort. We performed comprehensive echocardiographic and hemodynamic phenotyping, enabling parallel examination of multiple cardiovascular domains. The use of both parametric and non-parametric tests for CCDS comparison demonstrates methodological rigor. Furthermore, by conducting this study in China, we address a critical gap in the predominantly Western literature on cardiovascular disease in pregnancy.

Several limitations merit acknowledgement. First, the relatively small sample size particularly the modest number of term deliveries limited statistical power and precision. This is reflected in wide confidence intervals and borderline p-values for several associations. Second, the retrospective, single-center design introduces potential

selection bias and limits generalizability. Echocardiographic data were obtained as part of routine clinical care; standardization across operators and equipment cannot be guaranteed. Third, we did not systematically collect data on potential confounders such as smoking, socioeconomic status, or history of prior preterm birth, which may have influenced observed associations. Fourth, pulmonary regurgitation severity was graded qualitatively; quantitative measures (e.g., regurgitant volume, right ventricular dimensions) were not uniformly available. Fifth, the CCDS is not a validated instrument; its components and weighting were empirically derived, and its performance may differ in other populations. Finally, we cannot exclude the possibility of residual confounding, particularly by indication for echocardiography. Women undergoing cardiovascular assessment may differ systematically from those who do not, potentially inflating observed effect estimates.

Future Directions

These findings generate multiple hypotheses warranting further investigation. Large, prospective cohort studies are needed to confirm the association between pulmonary regurgitation and preterm birth, with detailed characterization of regurgitant severity, right ventricular function, and pulmonary artery pressures. Mechanistic studies employing advanced cardiac imaging (e.g., cardiac MRI, speckle-tracking echocardiography) and placental biomarkers could elucidate the pathways linking right heart volume overload to preterm labor. Randomized trials are premature, but observational studies using propensity score methods may help disentangle the independent effect of PR from confounding by underlying conditions. The CCDS requires refinement, potentially incorporating additional domains (e.g., diastolic function, pulmonary hypertension, aortic stiffness) and deriving optimal weighting through formal prediction modelling. External validation in diverse geographic and ethnic populations is essential before clinical translation.

5. CONCLUSION

In this cohort pulmonary regurgitation was strongly and significantly associated with preterm delivery, challenging the conventional view of regurgitant valve lesions as uniformly low-risk during pregnancy. Subtle reductions in ejection fraction and trends toward elevated systemic vascular resistance and obesity further characterized the preterm group. The Composite Cardiovascular Dysfunction Score demonstrated modest discriminatory ability, with a significant between-group difference by non-parametric testing and consistent direction of effect across multivariable models. These findings suggest that subclinical maternal cardiovascular dysfunction particularly involving the right ventricle and subtle systolic impairment may represent an under-recognized contributor to preterm birth. Given the substantial burden of preterm delivery in China and globally, continued investigation of cardiovascular determinants is urgently needed. Our results support a paradigm shift toward integrated, multidisciplinary risk assessment that considers not only overt cardiac disease but also mild, subclinical abnormalities that collectively increase obstetric risk.

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