

Preplanned Studies

Associations Between Longitudinal Antenatal Hematological Indicators and Risk of Patent Ductus Arteriosus in Newborns — Beijing, China, 2011–2025

Xiaoqian Jia^{1,2,3,&}; Pengbo Yuan^{4,&}; Jufen Liu^{1,2,3}; Zhiwen Li^{1,2,3}; Yuan Wei^{4,#}; Tianchen Wu^{1,3,#}

Summary

What is already known about this topic?

Patent ductus arteriosus (PDA) is closely associated with prematurity. Maternal conditions may increase offspring cardiac risk. However, antenatal hematological evidence remains limited.

What is added by this report?

Among 68,945 singleton live births, 945 were diagnosed with PDA. After false discovery rate correction, trimester-specific indicators, particularly prothrombin time and thrombin time, were found to be associated with PDA risk. The patterns differed by preterm birth, hypertensive disorders of pregnancy, gestational diabetes mellitus, and conception mode.

What are the implications for public health practice?

Routine maternal hematological indicators may provide preliminary evidence for further investigation of perinatal risk markers and may help identify pregnancies and newborns who may benefit from closer cardiovascular surveillance.

ABSTRACT

Introduction: This study aimed to examine whether longitudinal antenatal hematological indicators are associated with the risk of patent ductus arteriosus (PDA) in neonates.

Methods: A retrospective cohort study was conducted using electronic medical records from the Peking University Third Hospital, including 68,945 singleton live births between December 2011 and June 2025. Routine prenatal hematological, inflammatory, and coagulation-related indicators were summarized by trimester and standardized before analysis. Logistic regression models were used to estimate adjusted odds ratios (ORs) for PDA per 1-SD increase in each indicator, with false discovery rate correction (FDR) for multiple testing. Stratified analyses were conducted

by preterm birth, hypertensive disorders of pregnancy, gestational diabetes mellitus, and conception mode.

Results: Among 68,945 neonates, 945 (1.37%) were diagnosed with PDA. The preterm birth rate (61.69% *vs.* 8.12%) and NICU (Neonatal intensive care unit) admission rate (80.11% *vs.* 4.47%) were higher in the PDA group than in the non-PDA group. After FDR correction, longitudinal antenatal hematological profiles differed between neonates with and without PDA, with mean platelet volume (MPV) consistently and activated partial thromboplastin time (APTT) inversely associated with PDA across gestation. In the third trimester, each 1-SD increase in MPV and prothrombin time (PT) was associated with higher odds of PDA {adjusted ORs of 1.12 [95% confidence interval (CI): 1.05–1.20] and 1.25 (95% CI: 1.19–1.31), respectively}, whereas each 1-SD increase in APTT was associated with lower odds (adjusted OR, 0.81; 95% CI: 0.75–0.88).

Conclusion: Trimester-specific prenatal hematological indicators were associated with neonatal PDA risk, with distinct patterns between term and preterm births and across maternal subgroups. Routinely collected antenatal laboratory data may help characterize PDA-related perinatal risk and warrant further evaluation in future risk prediction research.

Patent ductus arteriosus (PDA) is a common cardiovascular condition in neonates and represents an important adverse outcome within the spectrum of congenital heart disease, particularly among preterm infants (1–4). Although prematurity is the dominant risk factor, maternal hypertensive disorders, diabetes, and the use of assisted reproductive technologies (ART) have also been associated with an increased cardiac risk (4–7). Routine prenatal hematological indicators may reflect maternal inflammatory, hemostatic, and metabolic status. However, their

interpretation requires consideration of physiological changes during gestation (8).

Evidence remains limited regarding whether longitudinal antenatal hematological indicators are associated with neonatal PDA risk. Therefore, this study assessed trimester-specific associations between routinely measured prenatal hematological, inflammatory, and coagulation-related indicators and neonatal PDA using stratified analyses by preterm birth, hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM), and conception mode.

This retrospective cohort study used electronic medical record data from the Peking University Third Hospital. Singleton pregnancies resulting in live births between December 2011 and June 2025 were eligible for inclusion. Maternal prenatal laboratory results, obstetric characteristics, disease diagnoses, delivery information, and neonatal outcomes were obtained from the hospital information system. All diagnoses were identified from medical records using the ICD-10 codes, with PDA identified using code Q25.001. The primary outcome was the occurrence of PDA among live-born infants. Maternal blood tests were treated as longitudinal measurements, and each participant underwent at least three blood examinations during pregnancy at early, mid, and late gestation. The Peking University Third Hospital Medical Science Research Ethics Committee approved this study (IRB00006761-M20250060).

Maternal hematological exposures included complete blood count markers, coagulation-related markers, and inflammatory markers measured during pregnancy. Hematology results were linked to gestational age at sampling and categorized as first trimester (≤ 12 weeks), second trimester (13–27 weeks), and third trimester (≥ 28 weeks). For trimester-specific analyses, repeated measurements within the same trimester were summarized using the within-person median for each marker. These trimester-specific marker values were standardized prior to modeling.

Potential confounders included pre-pregnancy body mass index (BMI), gestational weight gain, maternal age, parity, ART, gestational age at delivery, HDP, and GDM. Pregnancy and neonatal outcomes were compared between the PDA and non-PDA groups, including delivery method, gestational age at delivery, preterm birth (< 37 weeks), birth weight, birth length, infant sex, neonatal intensive care unit (NICU) admission, and respiratory distress syndrome, and were further classified as small-for-gestational-age,

appropriate-for-gestational-age, or large-for-gestational-age based on Chinese reference standards (9).

Categorical variables were summarized as numbers and percentages and compared using Pearson's chi-square test. Normally distributed continuous variables were presented as means and standard deviations and compared using *t*-test, whereas non-normally distributed variables were presented as medians and interquartile ranges and compared using the Wilcoxon rank-sum test. To characterize longitudinal changes in maternal blood parameters across gestation, mixed-effects models with restricted cubic splines for gestational age were fitted for each biomarker, with participant-level random effects used to account for repeated measurements. Differences in trajectories between the PDA and non-PDA groups were evaluated using likelihood ratio tests. To quantify the associations during clinically relevant periods, logistic regression models were fitted separately for the first, second, and third trimesters. For each marker, the results were reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs) per 1-SD increase, with each marker being standardized before regression analysis by subtracting its mean and dividing by its standard deviation in the analytic sample. Multivariable models were adjusted for the confounders listed above. Stratified analyses were performed within strata defined by preterm birth, HDP, GDM, and use of ART. As multiple markers were tested, false discovery rate (FDR) correction was applied to analyses across all tested hematological indicators within the three trimesters. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) and R (version 4.5.2, R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a *P* value < 0.05 was considered statistically significant.

As shown in Table 1, among 68,945 eligible participants, 945 neonates were diagnosed with PDA (1.37%) and 68,000 served as controls. Compared with controls, neonates with PDA were more often born to mothers with higher pre-pregnancy BMI [23.12 ± 3.67 *vs.* 22.06 ± 3.28], lower gestational weight gain [11.39 ± 4.89 *vs.* 12.90 ± 4.49], and older maternal age [33.80 ± 4.17 *vs.* 33.09 ± 3.93 years, all $P < 0.01$]. Advanced maternal age, multiparity, and ART conception were also more frequent in the PDA group than in controls [37.99% (359/945) *vs.* 30.59% (20,803/68,000); 36.72% (347/945) *vs.* 26.91% (18,301/68,000); and 13.86% (131/945) *vs.* 11.31%

TABLE 1. Comparison of baseline characteristics between groups.

Characteristics	All (N=68,945)	PDA group, n (%) (N=945)	Non-PDA group, n (%) (N=68,000)	P
Pre-pregnancy BMI (kg/m ²)	22.08±3.29	23.12±3.67	22.06±3.28	<0.01*
Gestational weight gain (kg)	12.88±4.50	11.39±4.89	12.90±4.49	<0.01*
Maternal age (years)	33.10±3.93	33.80±4.17	33.09±3.93	<0.01*
Advanced maternal age				
No	47,783	586 (62.01)	47,197 (69.41)	<0.01 [†]
Yes	21,162	359 (37.99)	20,803 (30.59)	
Parity				
Primipara	50,297	598 (63.28)	49,699 (73.09)	<0.01 [†]
Multipara	18,648	347 (36.72)	18,301 (26.91)	
Assisted reproductive technology				
No	61,125	814 (86.14)	60,311 (88.69)	0.01 [†]
Yes	7,820	131 (13.86)	7,689 (11.31)	
Hypertensive disorders of pregnancy				
No	61,092	637 (67.41)	60,455 (88.9)	<0.01 [†]
Yes	7,853	308 (32.59)	7,545 (11.10)	
Preeclampsia				
No	64,738	695 (73.54)	64,043 (94.18)	<0.01 [†]
Yes	4,207	250 (26.46)	3,957 (5.82)	
Gestational diabetes mellitus				
No	52,570	679 (71.85)	51,891 (76.31)	<0.01 [†]
Yes	16,375	266 (28.15)	16,109 (23.69)	
Delivery method				
Cesarean delivery	28,551	612 (64.76)	27,939 (41.09)	<0.01 [†]
Vaginal delivery	40,394	333 (35.24)	40,061 (58.91)	
Gestational age at delivery (week)	38.93±1.93	35.12±3.78	38.98±1.84	<0.01*
Preterm birth				
No	62,843	362 (38.31)	62,481 (91.88)	<0.01 [†]
Yes	6,102	583 (61.69)	5,519 (8.12)	
Birth weight (g)	3,231.55±526.19	2,412.23±912.36	3,242.94±509.62	<0.01*
Appropriate for gestational age	55,055	685 (72.49)	54,370 (79.96)	<0.01 [†]
Large for gestational age	9,540	156 (16.51)	9,384 (13.8)	
Small for gestational age	4,350	104 (11.01)	4,246 (6.24)	
Birth length (cm)	49.14±2.58	44.74±5.17	49.20±2.47	<0.01*
Gender				
Boys	35,782	487 (51.53)	35,295 (51.9)	0.82 [†]
Girls	33,163	458 (48.47)	32,705 (48.1)	
NICU admission				
No	65,147	188 (19.89)	64,959 (95.53)	<0.01 [†]
Yes	3,798	757 (80.11)	3,041 (4.47)	
Respiratory distress syndrome				
No	68,177	572 (60.53)	67,605 (99.42)	<0.01 [†]
Yes	768	373 (39.47)	395 (0.58)	

Abbreviation: BMI=body mass index; NICU=neonatal intensive care unit; PDA=patent ductus arteriosus.

* Continuous variables are presented as means and standard deviations, and between-group differences were assessed using *t*-tests.[†] Categorical variables are presented as numbers and percentages, and between-group differences were assessed using Pearson chi-square tests.

(7,689/68,000), respectively]. Pregnancy complications were more frequent in mothers of neonates with PDA than in controls. HDP occurred in 32.59% (308/945) *vs.* 11.10% (7,545/68,000, $P<0.01$), and preeclampsia in 26.46% (250/945) *vs.* 5.82% (3,957/68,000, $P<0.01$). GDM was also higher in the PDA group

[28.15% (266/945) *vs.* 23.69% (16,109/68,000), $P<0.01$]. Compared with controls, neonates with PDA had a lower gestational age at delivery, lower birth weight, higher rates of preterm birth and cesarean delivery, greater proportions of small- and large-for-gestational-age infants, while the distribution of fetal

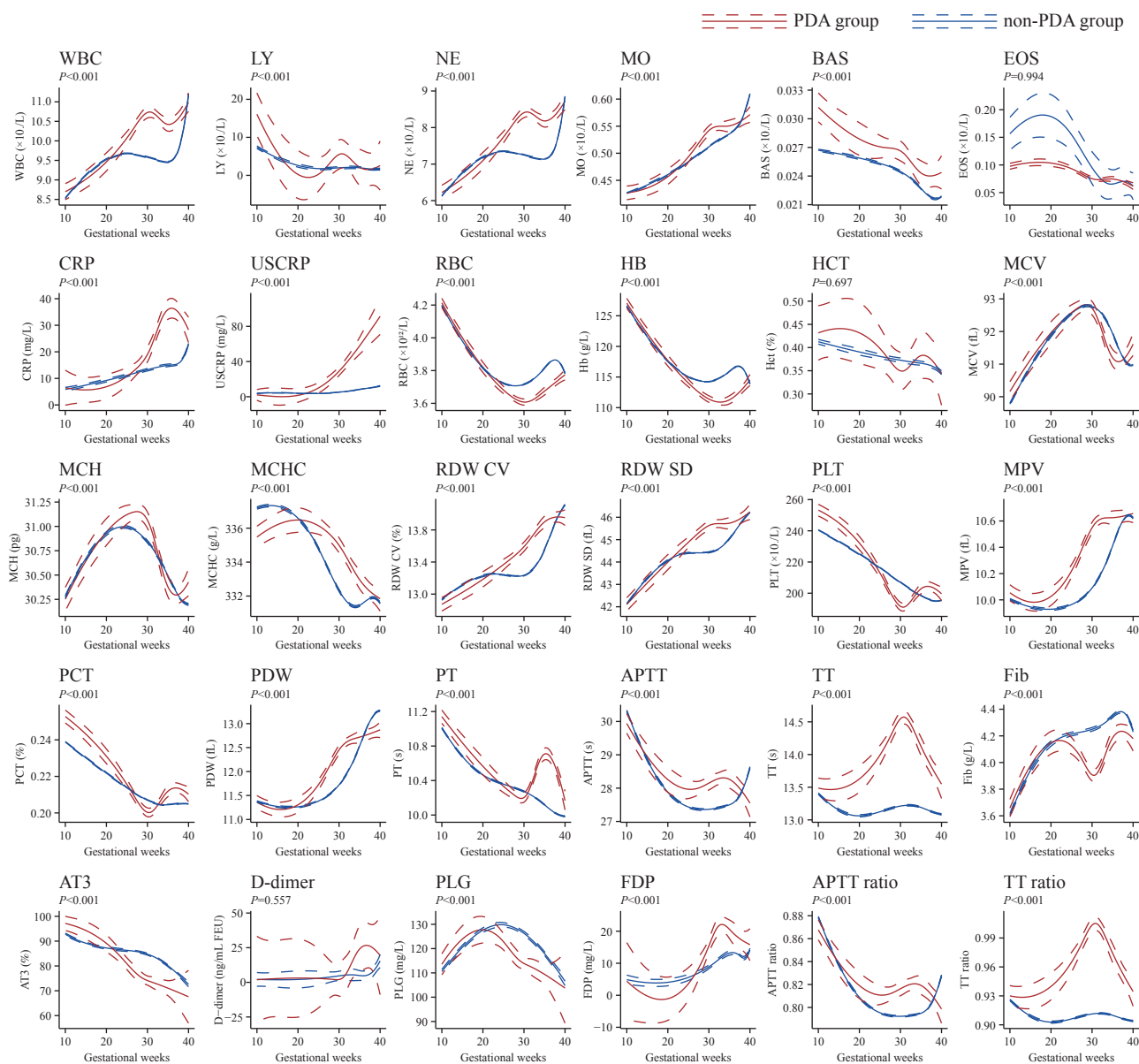


FIGURE 1. Comparison of hematologic test trajectories between the PDA and non-PDA groups.

Note: P values indicate FDR-adjusted P -values.

Abbreviation: WBC=white blood cell; LY=lymphocyte; NE=neutrophil; MO=monocyte; BAS=basophil; EOS=eosinophil; CRP=C-reactive protein; USCRP=Ultra-sensitive C-reactive protein; RBC=red blood cell; HB=hemoglobin; HCT=hematocrit; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; RDW CV=red cell distribution width coefficient of variation; RDW SD=red cell distribution width standard deviation; PLT=platelet; MPV=mean platelet volume; PCT=plateletcrit; PDW=platelet distribution width; PT=prothrombin time; APTT=activated partial thromboplastin time; TT=thrombin time; Fib=fibrinogen; AT3=antithrombin III; PLG=plasminogen; FDP=fibrin degradation products; APTT ratio=activated partial thromboplastin time ratio; TT ratio=thrombin time ratio.

sex was similar between groups. They also showed higher rates of NICU admission and respiratory distress syndrome.

As shown in Figure 1, most indicators showed significantly different pregnancy trajectories between the PDA and non-PDA groups after FDR correction, including white blood cell count and differentials* (WBC, LY, NE, MO, and BAS), red-cell indices† (RBC, HB, MCV, MCH, MCHC, RDW CV, and RDW SD), platelet indices§ (PLT, MPV, PCT, and PDW), coagulation-related markers¶ (PT, APTT, TT, Fib, AT3, PLG, FDP, APTT ratio, and TT ratio), and C-Reactive Protein (CRP)/Ultra-Sensitive CRP (USCRP) ($P<0.001$). In contrast, eosinophil (EOS), hematocrit (HCT), and D-dimer levels did not show significant group-level trajectory differences in the supplied trajectory figure ($P=0.994$, $P=0.697$, and $P=0.557$, respectively).

As shown in Figure 2, after FDR correction, significant associations were concentrated in the selected coagulation-, inflammatory-, and erythrocyte-related indicators. In the overall population, higher ORs were observed for BAS in the first and third trimesters, MPV in all three trimesters, PT in the first and third trimesters, and TT/TT ratio in the second and third trimesters. The third-trimester CRP levels also reached significance. In contrast, lower ORs were observed for first-trimester MCHC; second-trimester NE, APTT, and APTT ratio; and third-trimester RBC, HB, HCT, APTT, Fib, AT3, and APTT ratio. Preterm birth stratification showed distinct patterns. Among term births, significant positive associations were mainly observed for BAS, PT, TT, and TT ratio, with additional signals for CRP and MCV, whereas inverse associations were observed for MCHC, MO, APTT, and APTT ratio. Among preterm births, significant associations were confined to the third trimester; MPV, PT, TT, and TT ratio showed higher ORs, whereas RBC, HB, HCT, APTT, Fib, and APTT ratio showed lower ORs. Among women without HDP or GDM, the pattern generally resembled that observed in the overall population, characterized by positive associations for BAS and PT/TT/TT ratio and inverse associations for APTT/APTT ratio and selected erythrocyte-related markers. Among women with

HDP, significant associations were restricted to the third trimester and included the MPV, APTT, TT, FDP, APTT ratio, and TT ratio. Similarly, among women with GDM, only third-trimester associations remained significant, including higher ORs for MPV, PT, and TT and lower ORs for APTT, AT3, and APTT ratio. Natural conceptions closely mirrored the overall pattern. In assisted reproductive pregnancies, significant associations were fewer and confined to the third trimester, involving higher ORs for MPV, PDW, TT, and TT ratio and lower ORs for RBC, HB, HCT, APTT, and APTT ratio.

DISCUSSION

In this large retrospective cohort study, longitudinal antenatal hematological indicators showed trimester- and subgroup-specific associations with neonatal PDA risk. The most consistent FDR-significant findings involved coagulation markers, with PT, TT, and TT ratio generally showing positive associations, and APTT and APTT ratio showing inverse associations. MPV was positively associated with PDA across the three trimesters, whereas inverse erythrocyte-related associations, particularly for RBC, HB, and HCT, were observed mainly in late pregnancy. Subgroup analyses revealed further heterogeneity, with significant findings among preterm births. Women with HDP or GDM were largely concentrated in the third trimester. These findings suggest that routinely collected antenatal hematological profiles may provide complementary information for PDA risk assessment and targeted perinatal surveillance, although further validation is required before clinical application.

The associations of PT, TT, and TT ratio with higher PDA risk were consistently observed across the overall population and multiple strata. APTT and APTT ratio assess the intrinsic and common coagulation pathways, whereas TT and TT ratio reflect terminal fibrin formation. Thus, their opposite associations may reflect different aspects of maternal hemostasis rather than inconsistent findings. However, these maternal coagulation markers do not directly measure fetal ductal physiology, and the underlying mechanisms remain unclear. As ductal closure is

* WBC=white blood cell; LY=lymphocyte; NE=neutrophil; MO=monocyte; BAS=basophil.

† RBC=red blood cell; HB=hemoglobin; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; RDW CV=red cell distribution width coefficient of variation; RDW SD=red cell distribution width standard deviation.

§ PLT=platelet; MPV=mean platelet volume; PCT=plateletcrit; PDW=platelet distribution width.

¶ PT=prothrombin time; APTT=activated partial thromboplastin time; TT=thrombin time; Fib=Fibrinogen; AT3=antithrombin III; PLG=plasminogen; FDP=fibrin degradation products; APTT ratio=activated partial thromboplastin time ratio; TT ratio=thrombin time ratio.

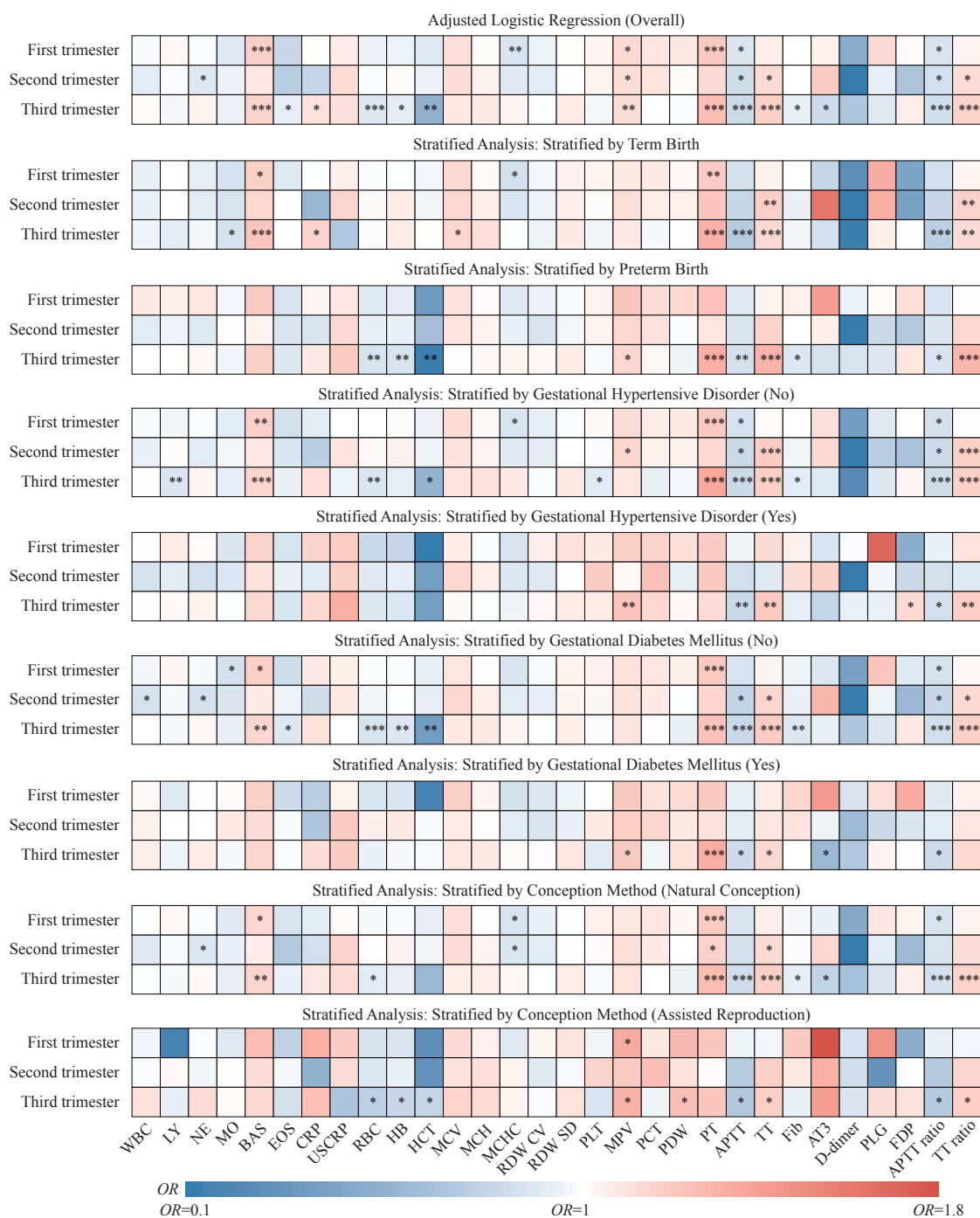


FIGURE 2. Trimester-specific associations of prenatal hematological indicators with neonatal patent ductus arteriosus risk: Overall and stratified analyses.

Note: Colors represent adjusted ORs on the original scale for PDA per 1-SD increase in each prenatal indicator.

Abbreviation: WBC=white blood cell; LY=lymphocyte; NE=neutrophil; MO=monocyte; BAS=basophil; EOS=eosinophil; CRP=C-reactive protein; USCRP=ultra-sensitive C-reactive protein; RBC=red blood cell; HB=hemoglobin; HCT=hematocrit; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; RDW CV=red cell distribution width coefficient of variation; RDW SD=red cell distribution width standard deviation; PLT=platelet; MPV=mean platelet volume; PCT=plateletcrit; PDW=platelet distribution width; PT=prothrombin time; APTT=activated partial thromboplastin time; TT=thrombin time; Fib=Fibrinogen; AT3=antithrombin III; PLG=plasminogen; FDP=fibrin degradation products; APTT ratio=activated partial thromboplastin time ratio; TT ratio=thrombin time ratio.

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$.

regulated by oxygen tension, prostaglandins, nitric oxide, platelet activity, and vascular remodeling (3–4,10), the observed associations may reflect broader maternal conditions related to postnatal ductal adaptation.

Preterm birth stratification suggested heterogeneity, with term births showing a broader pattern across gestation, whereas associations among preterm births were confined to the third trimester. Because prematurity influences PDA and may have different roles in the causal pathway, we additionally examined models without adjustment for gestational age, which yielded similar results. In preterm births, higher coagulation- and platelet-related indicators were inversely associated with RBC, HB, and HCT levels. These findings may indicate differences by prematurity status, although residual confounding factors related to preterm birth and their causes cannot be excluded. This erythrocyte-related pattern may reflect hemodilution or altered maternal-placental-fetal oxygen transport. This interpretation is biologically plausible because oxygen tension is central to postnatal ductal constriction (3); however, maternal erythrocyte indices do not measure fetal oxygenation.

The inflammatory findings were selective. BAS was positively associated with PDA risk across multiple strata, whereas CRP level was significant only in the overall and term birth analyses. This selective pattern is consistent with the mixed findings of previous studies, although experimental evidence suggests that inflammatory stimulation may delay ductal closure through nitric oxide-related mechanisms (11–13). HDP, GDM, and ART were associated with distinct marker profiles. The findings in HDP and GDM were confined to the third trimester, whereas those in ART pregnancies were fewer and predominantly observed in late pregnancy. These differences may reflect smaller subgroup sample sizes, altered baseline laboratory distributions, or distinct vascular–metabolic profiles associated with hypertension, diabetes, and ART pregnancies (5–7).

This study has several strengths, including its large obstetric cohort, longitudinal prenatal laboratory data, trimester-specific modeling, FDR correction, and clinically relevant stratified analyses. However, as all data were obtained from a single hospital, the study population's medical characteristics, prenatal examination protocols, and neonatal diagnostic and treatment practices may have been center-specific, limiting the racial and regional generalizability of our findings. In addition, unmeasured clinical factors, such

as infection, medication use, nutritional status, and differences in neonatal cardiac screening, may have influenced the observed associations. Future multicenter studies are needed to validate these findings and assess their generalizability.

Conflicts of interest: No conflicts of interest.

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Corresponding authors: Yuan Wei, weiyuan@bjmu.edu.cn; Tianchen Wu, wtc17@pku.edu.cn.

¹ Institute of Reproductive and Child Health/National Health Commission Key Laboratory of Reproductive Health, School of Public Health/Department of Obstetrics and Gynecology, Third Hospital, Peking University, Beijing, China; ² Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China; ³ State Key Laboratory of Female Fertility Promotion, Peking University, Beijing, China; ⁴ National Centre for Healthcare Quality Management in Obstetrics, Beijing, China.

[✉] Joint first authors.

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