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Original Article

Placental pathologic score 1-2 subclinical abnormalities and early neonatal clinical indicators in term infants: a retrospective study

Xinwu Mao[1], Fanbin Ye[1], Haidi Chang[1], Xiaowen Zhang[1], Tingting Cheng[2]

[1]Department of Pathology, The First Affiliated Hospital of Lishui University, Lishui People's Hospital, Lishui 323000, Zhejiang, China; [2]Department of Obstetrics, The First Affiliated Hospital of Lishui University, Lishui People's Hospital, Lishui 323000, Zhejiang, China

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Abstract: Objective: To explore the association between placental pathology scores of 1-2 and early neonatal clinical indicators, and evaluate the independent predictive effect of such abnormalities on composite adverse outcomes. Methods: This single-center retrospective case-control study enrolled 125 term singleton live births that underwent placental pathologic examination. Based on Amsterdam Consensus scoring criteria, neonates were assigned to abnormal (score 1-2, n = 63) or control (score 0, n = 62) groups. Neonatal clinical indicators within 7 days postpartum were compared between groups, followed by multivariate logistic regression and receiver operating characteristic (ROC) curve analyses. Results: Baseline maternal and neonatal characteristics were balanced across the two groups (all P>0.05). The abnormal group exhibited a markedly higher composite adverse outcome rate (50.8% vs. 19.4%, P<0.001), lower umbilical artery pH (7.25±0.07 vs. 7.31±0.05, P<0.001), a higher acidosis rate (19.0% vs. 0.0%, P<0.001), lower 1-h blood glucose (3.18±0.65 vs. 3.48±0.67 mmol/L, P = 0.012), and elevated C-reactive protein (CRP) levels (8.94±7.42 vs. 3.61±2.78 mg/L, P<0.001) alongside a higher proportion of CRP >10 mg/L (34.9% vs. 4.8%, P<0.001). No significant intergroup differences were observed in the incidence of clinical hypoglycemia (19.0% vs. 11.3%, P = 0.338) or intravenous antibiotic administration (3.2% vs. 4.8%, P = 0.680). Multivariate logistic regression confirmed that placental subclinical abnormalities constituted an independent risk factor for composite adverse outcome (adjusted OR = 3.779, 95% CI: 1.499-9.529, P = 0.005). The area under the ROC curve was 0.672. Conclusions: Placental pathology scores of 1-2 are independently associated with neonatal acidosis and elevated inflammatory markers in term neonates, and correlate with a nearly fourfold increased risk of composite adverse outcome. Mild placental subclinical abnormalities should be integrated into routine neonatal risk assessment to optimize perinatal transitional care.

Keywords: Placental pathology, subclinical placental abnormality, term neonates, composite adverse outcome

Introduction

The placenta is a core maternal-fetal interface organ during pregnancy, performing physiologic functions including gas exchange, nutrient transport, metabolic waste clearance, hormone synthesis, and immune barrier formation [1]. Placental morphologic alterations sensitively reflect intrauterine environmental perturbations, and placental pathologic examination is widely recognized as the "black box decoder" for unexplained adverse pregnancy outcomes [2, 3]. Robust clinical studies have clarified causal links between severe placental lesions and adverse perinatal outcomes: grade III chorioamnionitis accompanied by fetal inflammatory response syndrome is an independent risk factor for preterm birth, early-onset neonatal sepsis and periventricular white matter injury; extensive maternal vascular malperfusion (MVM, including large-scale placental infarction and decidual arteriopathy) correlates strongly with fetal growth restriction and stillbirth risk elevation [4]; severe fetal vascular malperfusion (FVM, including large-vessel thromboembolism and extensive avascular villi) is closely linked to intrapartum fetal distress, neonatal hypoxic-ischemic encephalopathy and long-term neurodevelopmental impairment [5]. These high-grade lesions have been incorpo-

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rated into international placental pathological reporting standards defined by the Amsterdam Consensus and are now standard components of perinatal multidisciplinary case review [6].

However, routine placental pathologic reviews identify far more mild focal lesions than severe ones. Typical examples include grade I-II maternal-limited acute chorioamnionitis (subchorionic neutrophil infiltration without fetal vessel involvement), MVM limited to isolated decidual vascular lesions or micro-infarctions occupying <5% of placental parenchyma, and FVM presenting with focal villous avascularity [7]. Per the Amsterdam working group semi-quantitative scoring framework, these lesions receive total scores of 1-2 and are categorized as subclinical or mild, meaning they meet neither clinical chorioamnionitis diagnostic criteria nor thresholds for high-grade pathologic lesions [8, 9]. Lacking overt maternal clinical symptoms, such pathologic reports are frequently overlooked during obstetric-neonatal handover, and affected neonates rarely receive targeted enhanced monitoring or follow-up [10].

Nonetheless, pathophysiologic evidence indicates that mild placental lesions are not biologically inert. Intrauterine adverse exposures exert dose-dependent fetal impacts: even low-grade intrauterine inflammation drives transplacental transfer of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), which activate fetal innate immunity and disrupt fetal hypothalamic-pituitary-adrenal axis function and peripheral glucose homeostasis [11, 12]. Human observational and animal studies have verified that asymptomatic intrauterine inflammation induces fetal oxidative stress, impairs peripheral insulin sensitivity, and weakens postnatal glucose counterregulation [13]. Similarly, mild placental vascular malperfusion, despite not causing measurable fetal growth restriction, depletes fetal acid-base buffering reserves, rendering neonates susceptible to metabolic acidosis during delivery and postnatal transitional adaptation [14]. Chronic villous hypoxia secondary to mild MVM and FVM also stimulates excessive erythropoietin secretion, which indirectly alters neonatal bilirubin clearance pathways [15]. Collectively, these mechanisms suggest that mild placental lesions can trigger quantifiable physiologic abnormalities in early postnatal life rather than remaining truly subclinical.

Three critical research gaps remain regarding mild placental lesions and term neonatal outcome. First, most prior studies adopted clinical diagnostic indicators rather than standardized pathologic scoring for exposure grouping, failing to differentiate asymptomatic subclinical lesions from symptomatic mild lesions [16]. Second, nearly all studies using Amsterdam pathologic scoring focused exclusively on preterm cohorts, with minimal systematic analysis for term neonates [17]. Third, existing outcome assessments were limited to single-dimensional indicators (either inflammatory or neuroimaging markers), lacking multi-parameter evaluation of neonatal transitional physiology [18]. Notably, no case-controlled studies based on Amsterdam placental scoring have been reported in Chinese term neonatal populations to date.

Based on these gaps, this single-center retrospective case-control study adopted Amsterdam semi-quantitative scoring as the grouping standard, comparing term neonates with placental scores of 1-2 and 0 across six outcome domains: umbilical acid-base balance, postnatal glucose metabolism, inflammatory biomarkers, Apgar scores, and respiratory adaptation, healthcare resource utilization, and composite adverse outcomes. We aimed to address three research questions: (1) Are 1-2 point subclinical placental lesions associated with disrupted early physiologic indicators in term neonates? (2) Do such associations remain independent of confounding obstetric variables including prolonged premature rupture of membranes (PROM) and meconium-stained amniotic fluid? (3) What is the predictive efficacy of 1-2 point placental abnormalities for composite adverse neonatal outcomes? We hypothesized that subthreshold mild placental lesions induce multisystem physiologic perturbations in term neonates and independently increase composite adverse outcome risk.

Materials and methods

Research design

This study was a single-center retrospective case-control study approved by the Ethics Committee of Lishui People's Hospital. All study procedures complied with the 2013 revised Declaration of Helsinki.

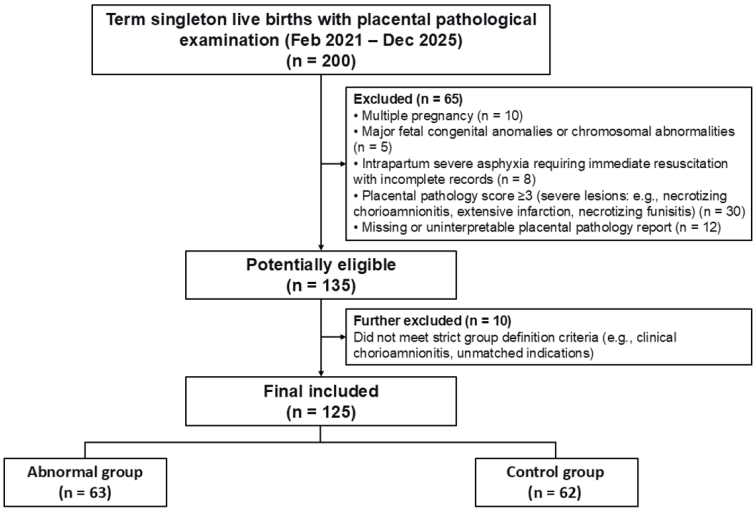

Figure 1. Study flow chart.

Research subjects

We retrospectively screened electronic medical records for all term deliveries (February 2021 to December 2025) with routine placental pathologic examination at the obstetric department. Eligible neonates were stratified into the abnormal group (placental score 1-2) and control group (placental score 0). Inclusion criteria: singleton live birth with gestational age ≥37 weeks; abnormal group: no clinical chorioamnionitis (maternal intrapartum temperature <38°C, no uterine tenderness or purulent amniotic fluid) and no pre-existing severe gestational hypertensive disorder or gestational diabetes mellitus; control group: unremarkable placental pathology, with placental submission indications matched to the abnormal group (including PROM >18 hours, meconium-stained amniotic fluid, suspected fetal distress or intrauterine infection). Exclusion criteria: multiple gestation, major fetal congenital malformations or chromosomal anomalies, severe intrapartum asphyxia requiring immediate neonatal resuscitation, incomplete medical documentation, placental score ≥3, and illegible or missing pathologic reports. A total of 125 neonates were enrolled, including 63 in the abnormal group and 62 in the control group (**Figure 1**).

Placental pathologic assessment and scoring method

All placental specimens underwent standardized gross and histological assessment by board-certified hospital pathologists. Per Amsterdam Placental Working Group guidelines, three lesion subtypes were scored semi-quantitatively:

Acute inflammatory response (maternal and fetal): 0 = absent; 1 = grade I (isolated subchorionic inflammation or umbilical phlebitis); 2 = grade II (chorioamnionitis or umbilical arteritis); 3 = grade III (necrotizing chorioamnionitis or necrotizing funisitis).

MVM: 0 = absent; 1 = decidual arteriopathy or accelerated villous maturation, infarction area <5% of placental parenchyma; 2 = multiple micro-infarctions or 5%-10% intervillous fibrin deposition; 3 = large-scale infarction or diffuse decidual atherosclerosis.

FVM: 0 = absent; 1 = focal villous avascularity; 2 = multifocal villous avascularity; 3 = diffuse villous fibrosis.

In this study, subclinical placental abnormality was defined as a cumulative lesion score of 1-2 with no concurrent maternal or intrapartum infectious symptoms.

Data collection

Maternal baseline data retrieved: maternal age, gravidity, parity, gestational age, delivery mode, PROM duration, amniotic fluid grade, intrapartum maternal fever, intrapartum pharmacologic interventions, and indications for placental pathological submission.

Neonatal early postnatal indicators (within 7 days): birth weight, birth weight percentile, 1- and 5-minute Apgar scores, umbilical artery blood gas (pH, base excess), 1- and 2-hour postnatal capillary blood glucose, 12-24-hour peripheral blood white blood cell count (WBC) and neutrophil percentage, high-sensitivity CRP, respiratory adverse events (grunting, tachypnea, oxygen supplementation or mechanical ventilation), NICU admission, length of stay, intravenous antibiotic use, phototherapy, tube feeding requirements, and peak serum bilirubin.

Clinical interpretation of indicators

Umbilical artery pH and base excess reflect intrapartum fetal acid-base status; an umbilical artery pH <7.20 is associated with increased risks of neonatal encephalopathy and multi-organ dysfunction [19]. Capillary blood glucose <2.6 mmol/L is the internationally accepted threshold for clinically significant transitional hypoglycemia requiring intervention [20]. CRP, WBC and neutrophil percentage are first-line intrauterine inflammatory biomarkers; CRP >10 mg/L has high negative predictive value for early-onset neonatal sepsis [21]. A 5-minute Apgar score ≤7 indicates transient neonatal physiologic depression and predicts short-term neurological risk [22]. NICU admission, antibiotic administration, phototherapy, tube feeding, and prolonged hospitalization serve as surrogate markers of neonatal illness severity and healthcare resource consumption.

Outcome definition

Primary outcome: early composite adverse neonatal outcome, defined as any one of the following: 5-minute Apgar score ≤7, umbilical artery pH <7.20, intervention-requiring hypoglycemia (blood glucose <2.6 mmol/L), unplanned NICU admission, or confirmed early-onset neonatal infection/sepsis.

Secondary outcomes: individual abnormal biomarker rates, respiratory distress incidence, NICU admission rate, antibiotic/phototherapy/tube feeding utilization rate, and neonatal length of hospital stay.

Inter-observer reliability

To validate scoring reproducibility, 35 randomly selected placental slides (28% of total specimens) were independently re-evaluated by a second blinded pathologist with no access to original scores or clinical data. Two-way random-effects intraclass correlation coefficient (ICC) was calculated for dichotomized total scores (0 vs. 1-2). Weighted Cohen's kappa was used to assess inter-rater agreement for individual lesion subtype scores.

Statistical analysis

All analyses were performed using SPSS 26.0 and Python 3.9. Continuous variables were first tested for normality by the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation and compared using Welch's t-test; non-normal data were presented as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables were reported as counts (percentages) and compared using the χ^2 test or Fisher's exact test for cell counts with expected frequencies <5.

Multivariate logistic regression was constructed with composite adverse outcome as the dependent variable. Confounders incorporated included placental grouping, gestational age, delivery mode, PROM duration, and amniotic fluid grade. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were calculated. ROC curves were plotted to assess the predictive performance of placental scoring for composite adverse outcomes. A two-tailed P<0.05 was defined as significant.

Results

General information and baseline characteristics

Maternal age, gravidity, parity, cesarean delivery rate, intrapartum medication use, neonatal birth weight and birth weight percentile z-score showed no significant intergroup differences (all P>0.05). Two obstetric confounding factors differed significantly: the abnormal group had longer mean PROM duration (8.54±7.63 h vs. 3.03±2.83 h, P<0.001) and higher mean amniotic fluid contamination grade (1.22±1.10 vs. 0.37±0.73, P<0.001). Placental submission indications also differed: the abnormal group was submitted primarily for prolonged PROM (33.3%) and meconium-stained amniotic fluid (19.0%), while the control group had a higher proportion of non-specific indications (37.1% vs. 11.1%, P = 0.001). Inter-rater reliability was excellent: dichotomized score ICC = 0.92 (95% CI: 0.85-0.96), and weighted kappa values for individual lesions ranged from 0.79 to 0.88, indicating substantial to perfect agreement (**Table 1**).

Main outcomes and secondary outcomes

The composite adverse outcome rate was significantly higher in the abnormal group (50.8% vs. 19.4%, P<0.001) (**Figure 2**; **Table 2**).

Table 1. Baseline characteristics of the study population

Characteristic	Abnormal Group (n = 63)	Control Group (n = 62)	Shapiro-Wilk P	U/t/χ^2	*P* value
Age (years)	28.14±3.68	29.26±3.54	0.029	1645.000†	0.127
Gravidity	2.71±1.41	2.82±1.43	<0.001	1867.000†	0.664
Parity	1.40±1.45	1.39±1.21	<0.001	1880.500†	0.713
Gestational age (weeks)	39.00±1.07	39.61±0.93	0.192	-3.450‡	<0.001
PROM duration (h)	8.54±7.63	3.03±2.83	<0.001	3038.500†	<0.001
Amniotic fluid (grade)	1.22±1.10	0.37±0.73	<0.001	2825.000†	<0.001
Birth weight (g)	3237.81±392.75	3390.75±467.45	0.142	-1.979‡	0.050
Birth weight percentile	57.98±20.46	58.09±19.42	0.008	1935.500†	0.933
Cesarean section	20 (31.7%)	15 (24.2%)	-	0.549§	0.459
Intrapartum medication	36 (57.1%)	36 (58.1%)	-	0.000§	1.000
Indication for placental examination					
PROM >18 h	21 (33.3%)	15 (24.2%)	-	0.866§	0.352
Other	7 (11.1%)	23 (37.1%)	-	10.187§	0.001
Meconium-stained fluid	12 (19.0%)	13 (21.0%)	-	0.002§	0.964
Fetal distress	13 (20.6%)	9 (14.5%)	-	0.440§	0.507
Suspected infection	10 (15.9%)	2 (3.2%)	-	4.394§	0.036

Data are mean ± SD or n (%). † Mann-Whitney U test statistic (U). ‡ Welch's t-test statistic (t). § Chi-square test statistic (χ^2). Shapiro-Wilk *P* value is the minimum of the two groups; normally distributed data were analyzed with t-test, non-normally distributed with Mann-Whitney U test. Abbreviation: PROM, premature rupture of membranes; SD, standard deviation.

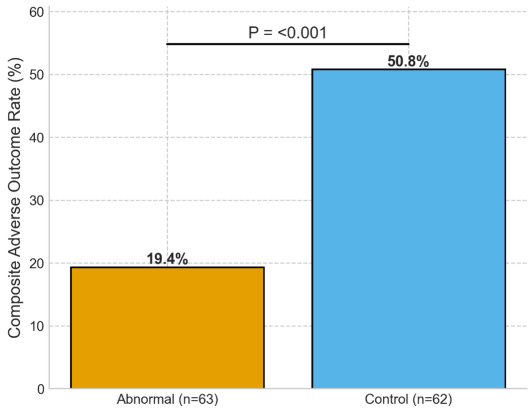

Figure 2. Comparison of the incidence of composite adverse neonatal outcome between the abnormal and control groups.

For umbilical arterial blood gas, the abnormal group had lower mean umbilical artery pH (7.25±0.07 vs. 7.31±0.05, P<0.001) and more negative base excess (-3.66±2.46 mmol/L vs. -2.23±2.18 mmol/L, P<0.001), indicating mild metabolic acidosis. All acidosis cases (pH <7.20) occurred in the abnormal group (19.0%, n = 12), with zero cases in the control group (P<0.001, **Figure 3**; **Table 2**).

Postnatal capillary glucose was significantly lower in the abnormal group at both 1 hour (3.18±0.65 mmol/L vs. 3.48±0.67 mmol/L, P = 0.012) and 2 hours (3.39±0.71 mmol/L vs. 3.68±0.67 mmol/L, P = 0.020). However, the incidence of intervention-requiring hypoglycemia (<2.6 mmol/L) showed no intergroup difference (19.0% vs. 11.3%, P = 0.338, **Figure 4**; **Table 2**).

All inflammatory biomarkers were elevated in the abnormal group: CRP (8.94±7.42 vs. 3.61±2.78 mg/L, P<0.001), WBC (17.09±4.44×10^9/L vs. 14.58±4.89×10^9/L, P = 0.003), and neutrophil percentage (0.59±0.13 vs. 0.48±0.09, P<0.001). The proportion of neonates with CRP >10 mg/L was seven times higher in the abnormal group (34.9% vs. 4.8%, P<0.001, **Figure 5**; **Table 2**).

No significant differences were detected in 1-minute (8.30±1.19 vs. 8.66±0.72, P = 0.143) or 5-minute Apgar scores (9.54±0.86 vs. 9.31±1.05, P = 0.187), nor in the rate of 5-minute Apgar scores ≤7 (3.2% vs. 8.1%, P = 0.273, **Figure 6**; **Table 2**).

Neonatal hospitalization metrics showed no intergroup differences in length of stay (4.03±2.13 vs. 3.91±1.61 days, P = 0.943), intravenous antibiotic use (3.2% vs. 4.8%, P = 0.680), NICU admission rate (19.0% vs. 9.7%, P =

Table 2. Early neonatal clinical indicators and hospitalization outcomes

Outcome	Abnormal Group (n = 63)	Control Group (n = 62)	Shapiro-Wilk P	U/t/χ^2	*P* value
Apgar score 1 min	8.30±1.19	8.66±0.72	<0.001	1702.500†	0.143
Apgar score 5 min	9.54±0.86	9.31±1.05	<0.001	2183.500†	0.187
Umbilical artery pH	7.25±0.07	7.31±0.05	0.256	-6.049‡	<0.001
Base excess (mmol/L)	-3.66±2.46	-2.23±2.18	0.038	1256.000†	<0.001
1-h blood glucose (mmol/L)	3.18±0.65	3.48±0.67	0.730	-2.542‡	0.012
2-h blood glucose (mmol/L)	3.39±0.71	3.68±0.67	0.791	-2.351‡	0.020
CRP (mg/L)	8.94±7.42	3.61±2.78	<0.001	2892.500†	<0.001
WBC (×10^9/L)	17.09±4.44	14.58±4.89	0.177	3.002‡	0.003
Neutrophil proportion	0.59±0.13	0.48±0.09	0.118	5.497‡	<0.001
Peak bilirubin (μmol/L)	210.15±43.45	199.79±36.08	0.724	1.451‡	0.149
Length of stay (days)	4.03±2.13	3.91±1.61	0.010	1968.000†	0.943
Umbilical artery pH <7.20	12 (19.0%)	0 (0.0%)	-	10.961§	<0.001
Hypoglycemia (<2.6 mmol/L)	12 (19.0%)	7 (11.3%)	-	0.919§	0.338
CRP >10 mg/L	22 (34.9%)	3 (4.8%)	-	15.843§	<0.001
Apgar 5 min ≤7	2 (3.2%)	5 (8.1%)	-	-¶	0.273
Composite adverse outcome	32 (50.8%)	12 (19.4%)	-	12.197§	<0.001
Respiratory distress	12 (19.0%)	4 (6.5%)	-	3.385§	0.066
NICU admission	12 (19.0%)	6 (9.7%)	-	1.531§	0.216
Intravenous antibiotics	2 (3.2%)	3 (4.8%)	-	-¶	0.680
Phototherapy	12 (19.0%)	6 (9.7%)	-	1.531§	0.216
Tube feeding	6 (9.5%)	2 (3.2%)	-	-¶	0.273
Neonatal infection/sepsis	8 (12.7%)	1 (1.6%)	-	-¶	0.033

Data are mean ± SD or n (%). † Mann-Whitney U statistic (U). ‡ Welch's t-test statistic (t). § Chi-square test statistic (χ^2). ¶ Fisher's exact test (no statistic reported). Shapiro-Wilk *P* value as in **Table 1**. Hypoglycemia defined as blood glucose <2.6 mmol/L requiring treatment. Abbreviation: CRP, C-reactive protein; WBC, white blood cell count; BG, blood glucose; BE, base excess; NICU, neonatal intensive care unit; SD, standard deviation.

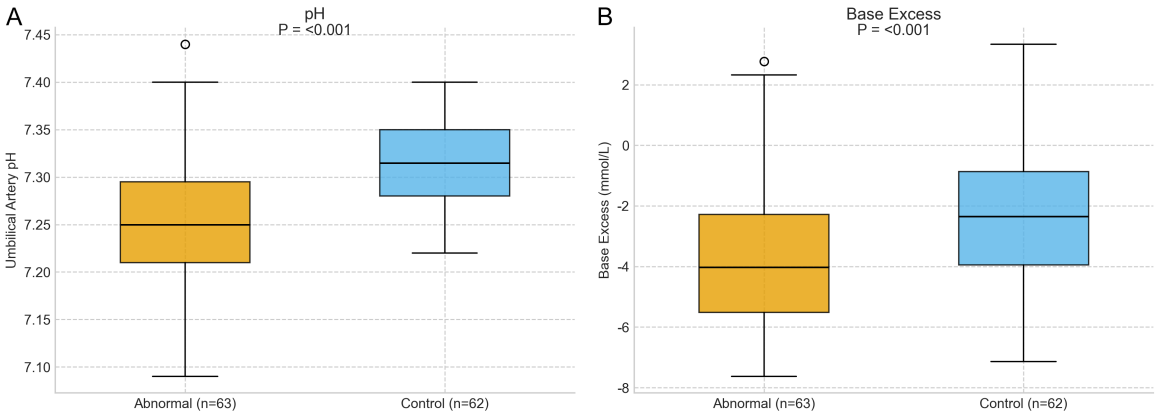

Figure 3. Umbilical artery blood gas values. Box plots show medians (horizontal lines), interquartile ranges (boxes), and ranges (whiskers). A. pH. B. base excess (mmol/L). *P* values were calculated using Welch's t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data, based on Shapiro-Wilk normality test. Abbreviation: BE, base excess; pH, potential of hydrogen.

0.216), respiratory distress incidence (19.0% vs. 6.5%, P = 0.066) or peak bilirubin (210.15± 43.45 vs. 199.79±36.08 μmol/L, P = 0.149, **Figure 7**; **Table 2**).

Multivariate Logistic regression analysis

After adjusting for gestational age, cesarean delivery, intrapartum medication, birth weight,

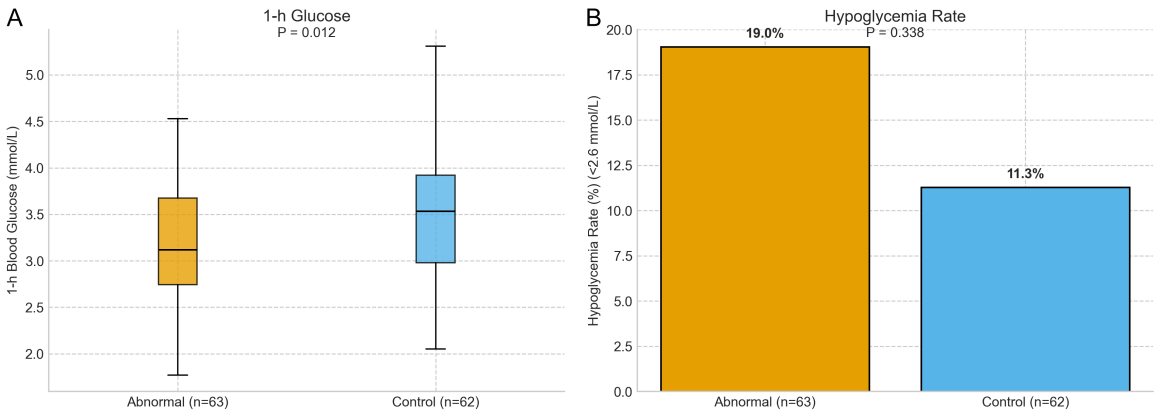

Figure 4. Early neonatal blood glucose. (A) Box plot of 1-h glucose (mmol/L). (B) Hypoglycemia rate (<2.6 mmol/L). *P* value in (B) from chi-square test. Abbreviation: BG, blood glucose.

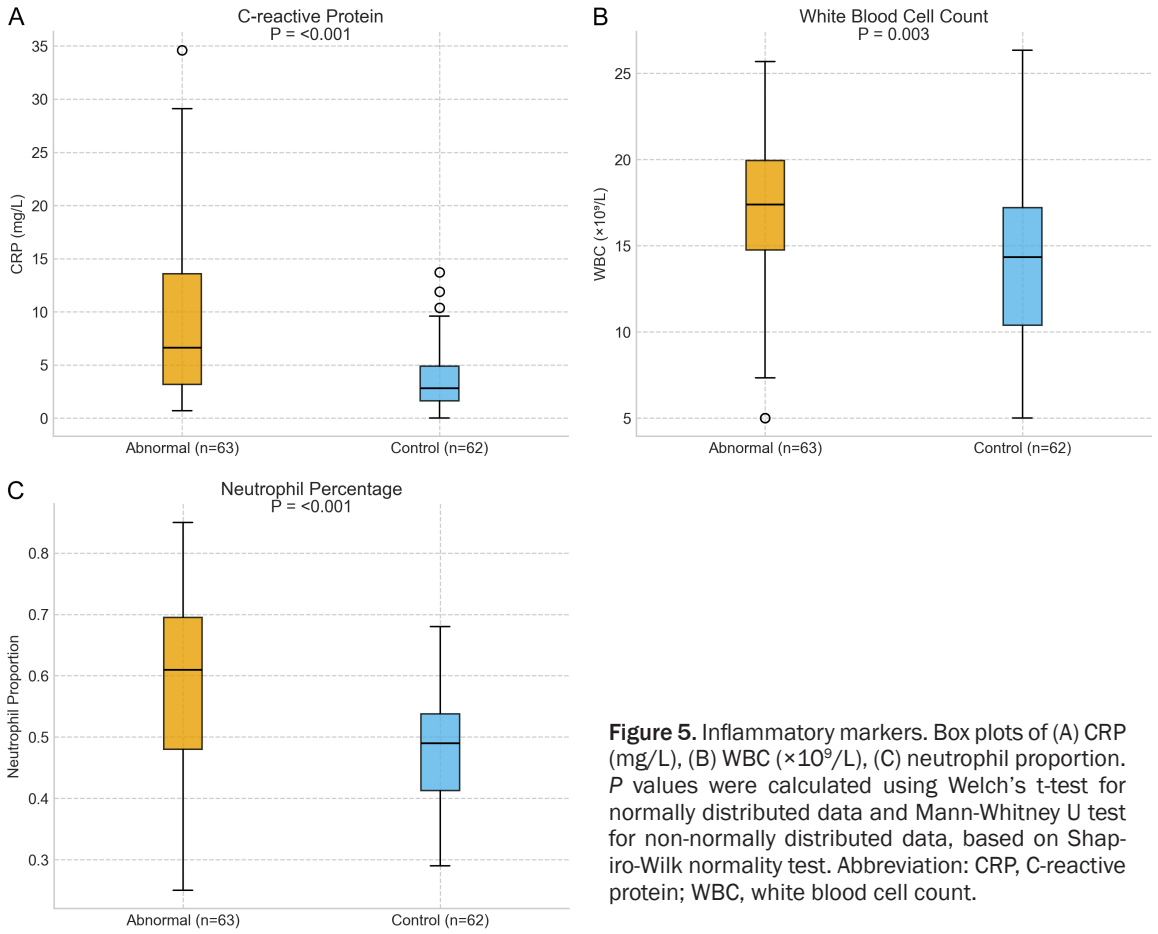

Figure 5. Inflammatory markers. Box plots of (A) CRP (mg/L), (B) WBC (×10^9/L), (C) neutrophil proportion. *P* values were calculated using Welch's t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data, based on Shapiro-Wilk normality test. Abbreviation: CRP, C-reactive protein; WBC, white blood cell count.

prolonged PROM and amniotic fluid grade, multivariate regression confirmed that 1-2 point placental abnormalities independently increased composite adverse outcome risk (aOR = 3.779, 95% CI: 1.499-9.529, P = 0.005). Higher amniotic fluid contamination grade was also an independent risk factor (OR = 1.564, 95% CI: 1.022-2.395, P = 0.039). Prolonged PROM showed a marginally non-significant protective trend (OR = 0.114, 95% CI: 0.012-1.086, P = 0.059). All other covariates had no statistical significance (**Table 3**; **Figure 8**). Subgroup analysis for individual composite outcome components showed a high odds ratio for neonatal

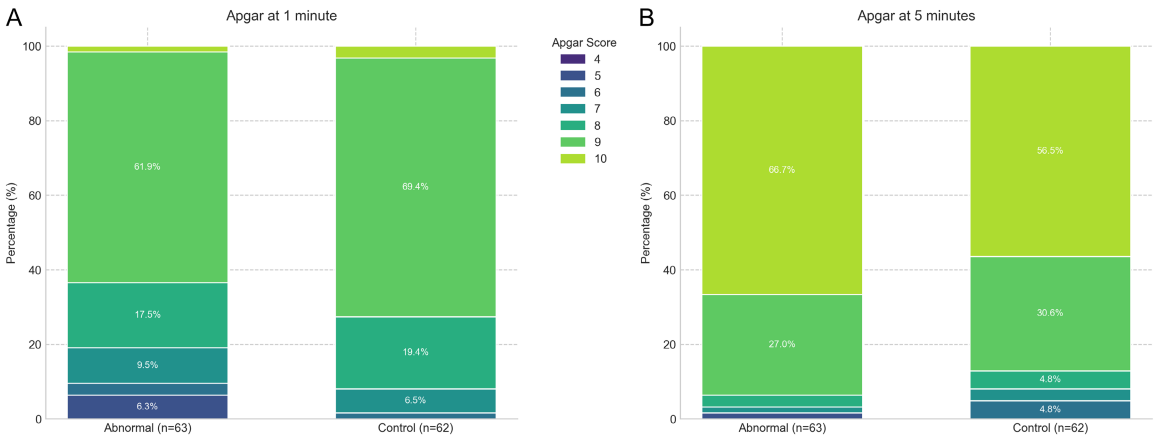

Figure 6. Apgar score distribution. Stacked bars show percentage of infants with each score (4-10) at (A) 1 min and (B) 5 min. Colors represent Apgar values as shown in the legend. Abbreviation: Apgar, Apgar score.

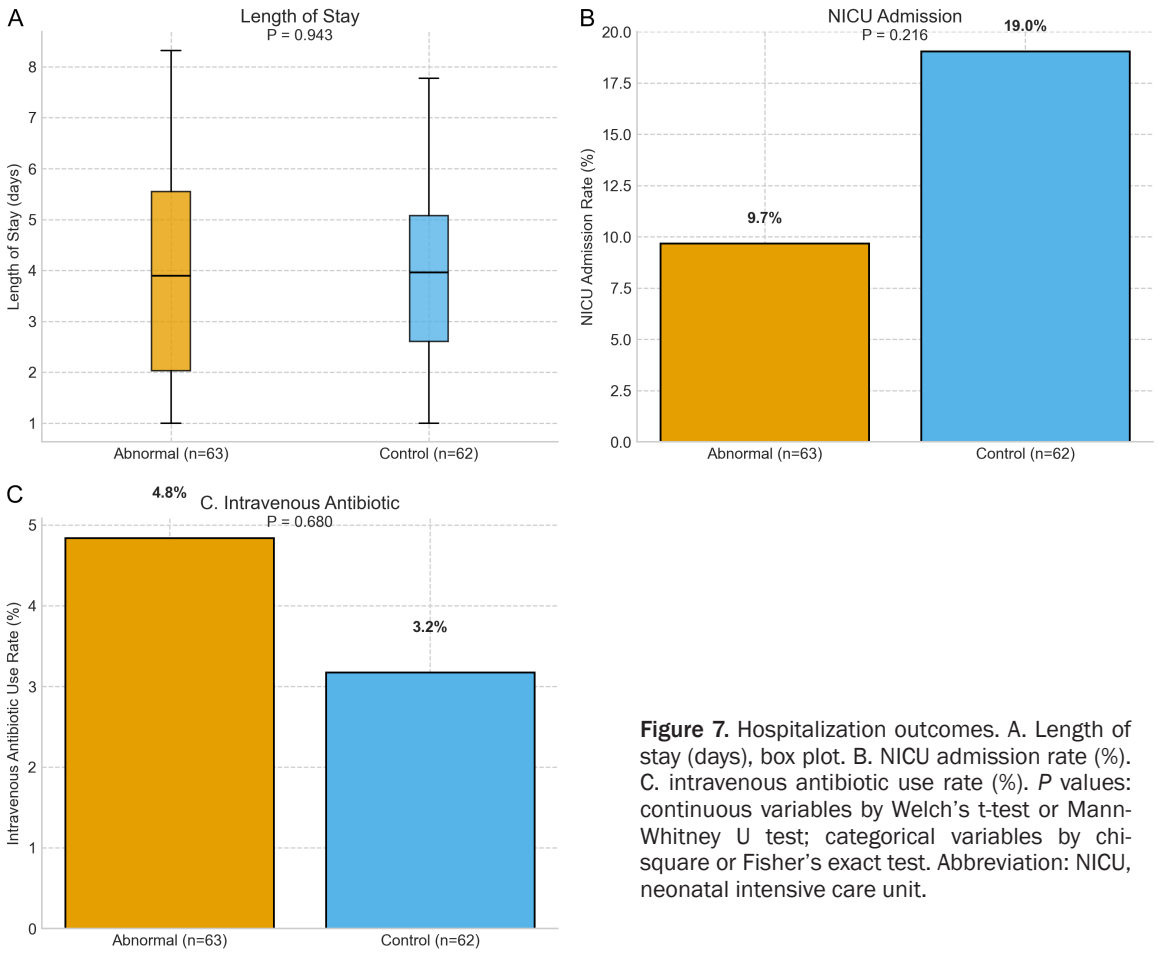

Figure 7. Hospitalization outcomes. A. Length of stay (days), box plot. B. NICU admission rate (%). C. intravenous antibiotic use rate (%). *P* values: continuous variables by Welch's t-test or Mann-Whitney U test; categorical variables by chi-square or Fisher's exact test. Abbreviation: NICU, neonatal intensive care unit.

infection in the abnormal group (OR = 7.264), though the wide confidence interval rendered the result non-significant (95% CI: 0.728-72.526, P = 0.091, Table S1).

ROC curve analysis

Using placental grouping as the sole predictive variable, the AUC for composite adverse out-

Table 3. Multivariate logistic regression analysis for composite adverse outcome

Variable	Coefficient (β)	Std. error	Wald z	Odds ratio (OR)	95% CI	*P* value
Group (Abnormal vs. Control)	1.329	0.472	2.817	3.779	[1.499, 9.529]	0.005
Gestational age	-0.054	0.212	-0.253	0.948	[0.625, 1.437]	0.800
Cesarean section	-0.479	0.489	-0.979	0.620	[0.238, 1.616]	0.328
Intrapartum medication	0.041	0.438	0.093	1.042	[0.441, 2.460]	0.926
Birth weight (g)	0.000	0.000	0.009	1.000	[0.999, 1.001]	0.993
PROM >18 h	-2.174	1.152	-1.888	0.114	[0.012, 1.086]	0.059
Amniotic fluid grade	0.448	0.217	2.059	1.564	[1.022, 2.395]	0.039

Model adjusted for all variables listed. PROM >18 h: premature rupture of membranes lasting >18 hours. Abbreviation: OR, odds ratio; CI, confidence interval; PROM, premature rupture of membranes.

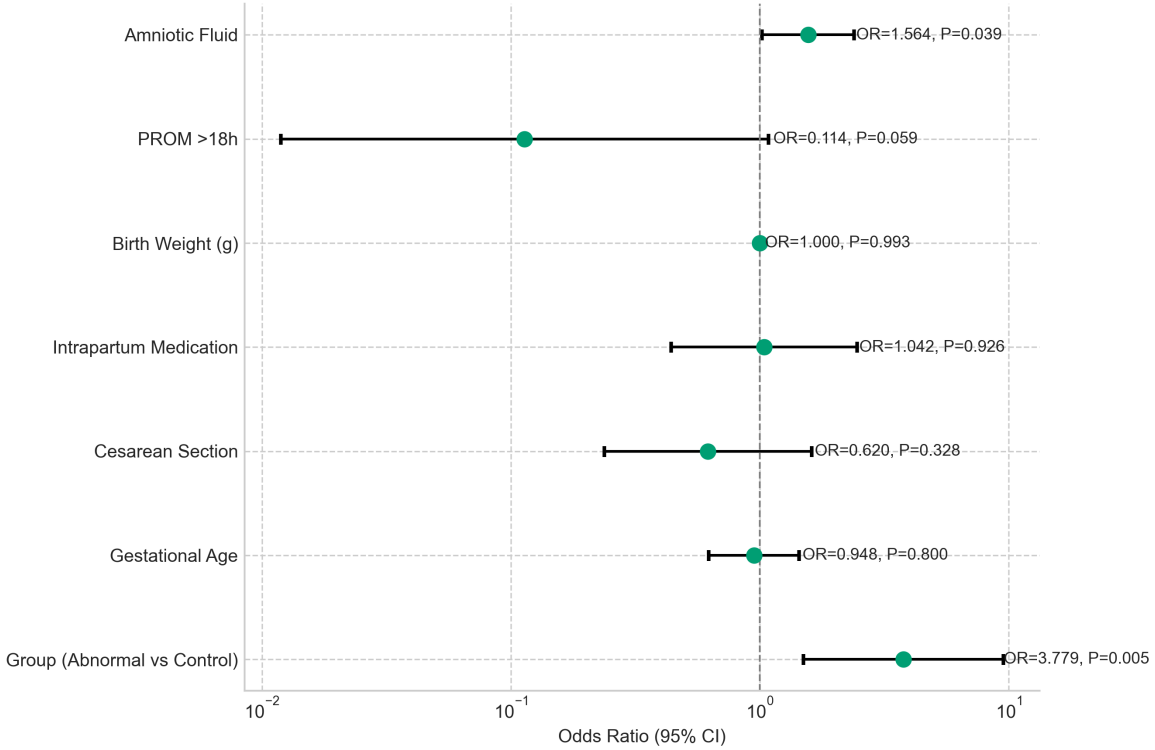

Figure 8. Forest plot of multivariate logistic regression. Squares represent adjusted odds ratios, horizontal lines 95% confidence intervals. The vertical dashed line indicates OR = 1. Model adjusted for gestational age, cesarean section, intrapartum medication, birth weight, PROM >18 h, and amniotic fluid grade. Abbreviation: OR, odds ratio; CI, confidence interval.

comes was 0.672 (**Figure 9**), indicating weak standalone discriminative ability for clinical risk stratification.

Discussion

This retrospective analysis of 125 term singleton neonates demonstrated that 1-2 point subclinical placental abnormalities independently increased composite adverse neonatal outcome risk by nearly fourfold. Affected neonates presented with significant umbilical arterial acidosis and systemic inflammatory activation, with no measurable differences in clinical hypoglycemia, antibiotic use, or NICU admission. Contrary to our preliminary hypothesis, mild glucose suppression did not translate to clinical hypoglycemia, indicating graded physiologic effects of placental lesions rather than uniform multi-system impairment.

Mild placental inflammatory lesions impair trophoblast respiratory transport function and induce chronic sub-lethal fetal hypoxia, which

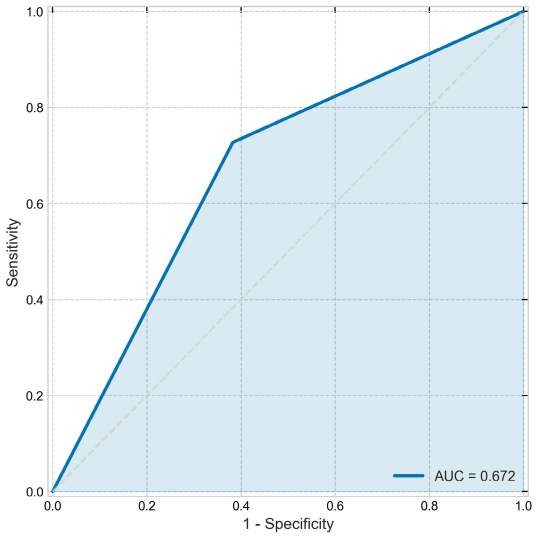

Figure 9. ROC curve for placental score predicting composite adverse outcome. AUC = 0.672. Abbreviation: ROC, receiver operating characteristic; AUC, area under the curve.

accounts for the observed metabolic acidosis [23, 24]. The absence of clinical hypoglycemia is consistent with existing literature confirming robust glucose counterregulation in term neonates compared with preterm cohorts, which can compensate for mild inflammatory-induced insulin resistance [25-27].

Elevated fetal peripheral inflammatory biomarkers despite maternal-limited grade I-II chorioamnionitis verifies that low-grade maternal intrauterine inflammation triggers fetal systemic inflammatory responses through transplacental cytokine cascades, even without direct fetal vessel inflammation [28-31]. This finding aligns with Døllner et al.'s cohort study, which confirmed asymptomatic intrauterine inflammation upregulates fetal pro-inflammatory cytokines without culture-proven neonatal sepsis [32].

Our results are consistent with large-scale term placental cohort studies. Zemtsov et al. reported MVM lesions correlated with umbilical acidosis in term neonates [33]. Loverro et al. linked all three placental lesion subtypes to low Apgar scores and severe acidosis [34]. For term deliveries complicated by intraamniotic infection, Bosco et al. demonstrated that acute funisitis (fetal inflammatory response) was independently associated with neonatal sepsis, low 5-minute Apgar score, and NICU admission [35]. Sahni et al. found asymptomatic chorioamnionitis correlated with elevated neonatal CRP [36]. Unlike prior studies focusing on preterm populations or ungraded histologic chorioamnionitis [6, 9], our study excluded symptomatic maternal infection and adopted standardized Amsterdam scoring, filling the evidence gap for low-risk term neonates.

The modest ROC AUC of 0.672 indicates placental scoring cannot serve as a standalone screening tool. Combining placental scores with umbilical blood gas and early CRP data will improve clinical risk stratification accuracy. Non-significant differences in healthcare utilization indicators are attributable to three factors: small lesion effect size, limited sample statistical power, and heterogeneous clinical postnatal observation practices [37].

Clinically, we recommend enhanced 24-hour postnatal monitoring of blood glucose and inflammatory biomarkers for neonates with 1-2 point placental abnormalities, alongside strict adherence to antibiotic administration guidelines to avoid unnecessary antimicrobial overuse [38]. Such neonates should also be prioritized for long-term neurodevelopmental and metabolic follow-up.

Study limitations are listed in hierarchical order: first, single-center retrospective design with limited sample size; second, pathologist-dependent scoring despite excellent inter-rater reliability; third, unmeasured confounders including intrapartum opioid exposure and early feeding patterns; fourth, unweighted composite outcome definition lacking risk stratification for individual adverse events; fifth, only 7-day short-term outcome assessment with no long-term developmental follow-up. Accordingly, conclusions are limited exclusively to early postnatal transitional physiology and cannot be extrapolated to childhood neurodevelopmental or metabolic outcomes.

Translational implications include the need for integrated placental biobanking and pediatric health registry linkage in future prospective cohorts to explore lifelong impacts of subclinical placental lesions.

Conclusion

1-2 point subclinical placental abnormalities were independently associated with early

umbilical arterial acidosis and subclinical systemic inflammation in term neonates, with a nearly fourfold increase in composite adverse outcome risk. Placental semi-quantitative scoring should be integrated into routine neonatal early risk assessment to individualize postnatal transitional monitoring protocols. Given the lack of long-term pediatric follow-up data, findings are restricted to short-term neonatal outcomes and require validation via large-scale multicenter prospective cohorts with extended developmental follow-up.

Disclosure of conflict of interest

None.

Address correspondence to: Tingting Cheng, Department of Obstetrics, The First Affiliated Hospital of Lishui University, Lishui People's Hospital, No. 1188 Liyang Street, Yanquan Street, Liandu District, Lishui 323000, Zhejiang, China. Tel: +86-18957097763; E-mail: 18957097763@163.com

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Table S1. Component analysis of the composite adverse outcome (univariate or multivariate as indicated)

Component	OR (Abnormal vs. Control)	95% CI	*P* value
Apgar 5 min ≤7	0.374*	[0.070, 2.004]	0.251
Umbilical pH <7.20	Inf†	-	<0.001
Hypoglycemia <2.6 mmol/L	1.849*	[0.675, 5.061]	0.232
NICU admission	2.196*	[0.768, 6.281]	0.142
Neonatal infection	7.264	[0.728, 72.526]	0.091

*Univariate logistic regression (unadjusted for covariates). † Inf indicates that no event occurred in the control group; the *P* value is from Fisher's exact test. Abbreviation: OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit.