Research Square

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Histologic Chorioamnionitis and Neonatal Outcomes in Preterm Infants: A Gestational Age- and Birth Weight-Matched Cohort Study

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Research Article

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Abstract

Background

Histologic chorioamnionitis (HCA) is frequently implicated in adverse neonatal outcomes, but most evidence derives from unmatched comparisons in which gestational age (GA) — the dominant determinant of prematurity-related morbidity — acts as a powerful confounder. We evaluated neonatal outcomes of HCA-exposed preterm infants in a cohort matched for GA and birth weight (BW).

Methods

In this single-center retrospective matched cohort study (January 2018–December 2024), 83 preterm infants with histologically confirmed HCA were compared with 88 non-HCA controls matched for GA and BW. Short-term outcomes (intraventricular hemorrhage [IVH], bronchopulmonary dysplasia [BPD], respiratory distress syndrome [RDS], clinical sepsis, necrotizing enterocolitis [NEC], retinopathy of prematurity [ROP], and mortality), respiratory support trajectories, and serial maternal and neonatal inflammatory markers were compared. Adjusted odds ratios (aORs) were estimated by logistic regression controlling for GA and BW.

Results

Groups were well matched (GA 32.6 ± 2.7 vs 32.5 ± 2.6 weeks, P = 0.708; BW 1847 ± 660 vs 1805 ± 623 g, P = 0.714). The HCA group had higher rates of premature rupture of membranes (59.0% vs 20.5%, P < 0.001), vaginal delivery (45.8% vs 13.6%, P < 0.001), and antenatal antibiotic exposure (42.2% vs 22.7%, P = 0.009), confirming exposure validity. After adjustment, HCA was not associated with clinical sepsis, RDS, NEC, ROP, BPD of any grade or moderate-to-severe BPD, pulmonary surfactant use, duration of respiratory support, length of stay, or mortality. Unexpectedly, HCA was inversely associated with IVH of any grade (23.0% vs 42.1%; aOR 0.38, 95% CI 0.17–0.83, P = 0.015); the association strengthened in an extended model additionally adjusting for delivery mode, antenatal corticosteroids, and fetal distress (aOR 0.28, 95% CI 0.11–0.71, P = 0.007), and was confined to infants born at ≥ 32 weeks (6.7% vs 31.8%; OR 0.15, 95% CI 0.04–0.58, P = 0.003). All IVH in the HCA group was grade I–II. Maternal pre-delivery leukocytosis and neutrophilia, and neonatal day-0 leukocyte and neutrophil responses, were significantly more pronounced in the HCA group, whereas C-reactive protein did not differ at any time point.

Conclusions

In a GA- and BW-matched preterm cohort, HCA exposure produced a measurable maternal–neonatal inflammatory response without worsening conventional short-term outcomes, and was associated with a substantially lower risk of IVH, particularly among infants born at ≥ 32 weeks. The relationship between

intrauterine inflammation and neonatal brain injury warrants re-examination in prospective cohorts with histologic staging.

Background

Chorioamnionitis — inflammation of the chorion, amnion, and placenta — is a frequent antecedent of preterm birth. Histologic chorioamnionitis (HCA), defined by neutrophilic infiltration of the fetal membranes and/or chorionic plate, is present in a substantial proportion of spontaneous preterm deliveries and is regarded as the pathologic gold standard for diagnosing intrauterine infection or inflammation [1, 2]. Because HCA reflects the intrauterine environment to which the fetus is exposed, its association with neonatal morbidity has been studied extensively.

HCA has been linked to early-onset sepsis, bronchopulmonary dysplasia (BPD), and brain injury in preterm infants [3–6], and chorioamnionitis has been associated with cerebral palsy in meta-analysis [7]. However, the evidence is inconsistent. Meta-analyses have repeatedly shown that chorioamnionitis-exposed infants are born approximately one week earlier and with lower birth weight than unexposed infants [5, 6], and analyses restricted to studies with comparable gestational ages, or using adjusted data, often show attenuated or absent associations — for BPD as well as for intraventricular hemorrhage (IVH) [5, 6]. Gestational age (GA) and birth weight (BW) are by far the strongest determinants of nearly every outcome of prematurity, yet relatively few clinical studies have matched or fully adjusted for them, leaving the independent contribution of intrauterine inflammation uncertain.

The relationship between chorioamnionitis and IVH is particularly controversial. A 2018 systematic review and meta-analysis reported that chorioamnionitis was associated with an increased risk of IVH in unadjusted analyses, whereas pooling of adjusted data — especially for histologic chorioamnionitis — rendered the association non-significant [6]. Conversely, intrauterine inflammation may induce fetal organ maturation ("inflammatory preconditioning"): experimental and clinical observations suggest that antenatal inflammatory exposure can accelerate lung maturation and modulate cerebrovascular vulnerability, potentially reducing certain complications while increasing others [8, 9]. Whether such maturation-dependent effects extend to the germinal matrix vasculature of moderately preterm infants is unknown.

We therefore conducted a single-center, retrospective cohort study in which preterm infants exposed to histologically confirmed HCA were matched to non-exposed controls on GA and BW, the two dominant confounders. We compared short-term neonatal outcomes, respiratory support trajectories, and serial maternal and neonatal inflammatory markers between groups, with IVH designated a priori as the primary outcome of interest.

Methods

Study design and population

This retrospective matched cohort study was conducted at The First Affiliated Hospital of Xi'an Jiaotong University, a tertiary referral center in northwest China. We identified all preterm infants (< 37 weeks of gestation) born between 1 January 2018 and 31 December 2024 whose placentas underwent routine histopathologic examination. Infants whose placentas showed histologic evidence of acute chorioamnionitis (neutrophilic infiltration of the chorionic plate and/or fetal membranes) constituted the HCA group (n = 83). A control group of preterm infants without histologic chorioamnionitis (n = 88) was selected from the same period by frequency matching on GA and BW; balance of the matching variables was verified by comparing their distributions between groups (Table 1). Matching was performed at the group (distributional) level rather than by one-to-one pairing, which accounts for the unequal group sizes (83 vs 88). Infants with major congenital anomalies or chromosomal abnormalities were excluded. No a priori sample size calculation was performed; all eligible preterm infants with histologically confirmed HCA during the study period were included. The study was approved by the institutional ethics committee (approval number XJTU1AF2024LSYY-124); the requirement for individual informed consent was waived because of the retrospective design.

Table 1
Baseline and peripartum characteristics

Characteristic	HCA group (n = 83)	Control group (n = 88)	P value
Gestational age, weeks	32.6 ± 2.7	32.5 ± 2.6	0.708
Birth weight, g	1847 ± 660	1805 ± 623	0.714
Maternal age, years	31 [27–34]	32 [29–35]	0.086
Male sex, n (%)	47 (56.6)	40 (45.5)	0.169
Vaginal delivery, n (%)	38 (45.8)	12 (13.6)	< 0.001
Premature rupture of membranes, n (%)	49 (59.0)	18 (20.5)	< 0.001
Rupture-to-delivery interval, h	2 [0–31] (mean 33.6)	0 [0–0] (mean 8.3)	< 0.001
Antenatal corticosteroids, n (%)	79 (95.2)	78 (88.6)	0.164
Antenatal antibiotics, n (%)	35 (42.2)	20 (22.7)	0.009
Maternal intrapartum fever, n (%)	4 (4.8)	1 (1.2)	0.208
Fetal distress, n (%)	36 (43.4)	26 (29.5)	0.080
Meconium-stained amniotic fluid (any grade), n (%)	12 (14.5)	15 (17.0)	0.203*
Apgar score 1 min	9 [8–10]	9 [8–10]	0.958
Apgar score 5 min	10 [9–10]	9.5 [9–10]	0.407
Birth length, cm	43 [39.5–47]	42.5 [39–45]	0.366
Head circumference, cm	29 [27–32]	30 [27.9–31.1]	0.805

*Data are mean ± SD, median [IQR], or n (%). Continuous variables were compared with the Mann–Whitney U test and categorical variables with the chi-square or Fisher exact test. *P value across all four contamination grades (0–III). Meconium-stained fluid of any grade = grades I–III combined. Maternal intrapartum fever data were unavailable for 3 control infants (denominator 85).*

Definitions and outcomes

HCA was diagnosed exclusively by placental histopathology; histologic staging and grading and the presence of funisitis were not systematically recorded during the study period and are acknowledged as unavailable. Clinical sepsis was defined as a clinical diagnosis of sepsis made by the attending neonatologist together with elevation of blood infection markers. Culture-proven sepsis was defined as a positive blood or other clinical culture; cultures were not obtained in 34 infants (18 HCA, 16 control). Respiratory distress syndrome (RDS) was diagnosed clinically from respiratory distress with typical

radiographic findings requiring oxygen or ventilatory support. Necrotizing enterocolitis (NEC) was defined as Bell stage II or higher. Retinopathy of prematurity (ROP) screening and cranial ultrasonography were performed according to institutional screening criteria; cranial ultrasonography was available for 150 infants (74 HCA, 76 control) and ROP screening for 85 infants (37 HCA, 48 control), and analyses of IVH and ROP are based on infants with available examinations. IVH was graded I–IV by cranial ultrasound and analyzed as any grade (I–IV) and severe (III–IV). BPD was defined and graded according to the need for supplemental oxygen and/or respiratory support at 36 weeks of postmenstrual age [10]. Respiratory support mode (invasive ventilation, non-invasive ventilation, supplemental oxygen, or none) was recorded at days 0, 1, 2, 3, 5, 7, 10, 14, and 28 of life.

Inflammatory markers

Maternal complete blood counts and (high-sensitivity) C-reactive protein (CRP) were obtained before and after delivery. Neonatal white blood cell count (WBC), absolute neutrophil count, neutrophil percentage, platelet count, and CRP were measured on days 0–5 of life as clinically indicated.

Statistical analysis

Continuous variables are summarized as median [interquartile range] or mean ± standard deviation and were compared with the Mann–Whitney U test; categorical variables were compared with the chi-square test or Fisher exact test as appropriate. For binary neonatal outcomes we computed crude odds ratios (ORs) and adjusted ORs (aORs) from logistic regression controlling for GA and BW. For the IVH finding we additionally fitted an extended model adjusting for GA, BW, mode of delivery, antenatal corticosteroid exposure, and fetal distress, and performed a GA-stratified analysis (< 32 vs ≥ 32 weeks). All tests were two-sided and $P < 0.05$ was considered statistically significant. Analyses were performed with Python 3.12 (Python Software Foundation) using the pandas, SciPy, and statsmodels libraries [13–16]. This study is reported in accordance with the STROBE statement for observational studies.

Results

Baseline and peripartum characteristics

The final cohort comprised 83 HCA-exposed and 88 non-exposed preterm infants. Matching was successful: GA (32.6 ± 2.7 vs 32.5 ± 2.6 weeks, $P = 0.708$), BW (1847 ± 660 vs 1805 ± 623 g, $P = 0.714$), sex distribution, Apgar scores, and anthropometrics did not differ between groups (Table 1). As expected for histologically verified exposure, the HCA group had significantly higher rates of premature rupture of membranes (59.0% vs 20.5%; OR 5.60, $P < 0.001$), longer rupture-to-delivery intervals (median 2 [0–31] vs 0 [0–0] h; mean 33.6 vs 8.3 h, $P < 0.001$), more vaginal deliveries (45.8% vs 13.6%; OR 5.35, $P < 0.001$), and more antenatal antibiotic use (42.2% vs 22.7%; OR 2.48, $P = 0.009$). Antenatal corticosteroid coverage was high in both groups (95.2% vs 88.6%, $P = 0.164$). Maternal intrapartum fever was numerically more frequent with HCA (4.8% vs 1.2%, $P = 0.208$).

Maternal and neonatal inflammatory markers

Maternal pre-delivery WBC (median 11.2 vs 9.1 × 10^9/L, P < 0.001), neutrophil percentage (81.6% vs 76.6%, P < 0.001), and absolute neutrophil count (9.1 vs 7.0 × 10^9/L, P < 0.001) were significantly higher in the HCA group, and pre-delivery high-sensitivity CRP showed a smaller but significant elevation (P = 0.040); post-delivery values no longer differed (Table 3). Neonatal day-0 WBC (median 10.0 vs 7.0 × 10^9/L, P < 0.001) and neutrophil percentage (P = 0.009) were likewise elevated in HCA-exposed infants, with a recurrent difference in WBC at day 5 (P = 0.016; Fig. 1). CRP did not differ between groups at any neonatal time point. These trajectories corroborate a genuine maternal–fetal inflammatory activation in the HCA group, albeit one that was not accompanied by worse clinical outcomes.

Neonatal outcomes

After matching, conventional short-term outcomes did not differ significantly between groups (Table 2). Rates of clinical sepsis (66.3% vs 70.5%; aOR 0.87, 95% CI 0.38–1.98), RDS (60.5% vs 72.7%; aOR 0.44, 95% CI 0.18–1.12), NEC (3.7% vs 1.1%; aOR 3.36, 95% CI 0.33–34.16), abnormal ROP screening (18.9% vs 10.4%; aOR 1.85, 95% CI 0.49–6.95), BPD of any grade (37.3% vs 34.5%; aOR 1.65, 95% CI 0.56–4.86), moderate-to-severe BPD (12.0% vs 5.7%; aOR 2.61, 95% CI 0.80–8.57), pulmonary surfactant use (41.0% vs 48.9%; aOR 0.59, 95% CI 0.25–1.42), and mortality (3.6% vs 1.1%; aOR 3.24, 95% CI 0.32–32.35) were comparable. Culture-proven sepsis was rare and equally frequent in the two groups (3.6% vs 3.4%). Two of the three deaths in the HCA group occurred after redirection of intensive care following parental decision, and the two in-hospital deaths (one per group) were both extremely preterm, very-low-birth-weight infants. Durations of invasive ventilation, non-invasive ventilation, supplemental oxygen, and hospital stay were also similar, and the longitudinal distribution of respiratory support modes from day 0 to day 28 of life was visually nearly superimposable between groups (Fig. 2).

Table 2
Neonatal outcomes

Outcome	HCA group	Control group	Crude OR (95% CI), P	Adjusted OR (95% CI)†, P
Intraventricular hemorrhage, any grade, n (%)	17/74 (23.0)	32/76 (42.1)	0.41 (0.20–0.83), 0.015	0.38 (0.17–0.83), 0.015
— IVH in infants ≥ 32 weeks, n (%)	3/45 (6.7)	14/44 (31.8)	0.15 (0.04–0.58), 0.003	—
— IVH in infants < 32 weeks, n (%)	14/29 (48.3)	18/32 (56.2)	0.73 (0.26–1.99), 0.612	—
Severe IVH (grade III–IV), n (%)	0/74 (0)	1/76 (1.3)	0.34 (0.01–8.43), 1.000	—
Clinical sepsis, n (%)	55/83 (66.3)	62/88 (70.5)	0.82 (0.44–1.55), 0.622	0.87 (0.38–1.98), 0.731
Culture-proven sepsis, n (%)	3/83 (3.6)	3/88 (3.4)	1.06 (0.21–5.42), 1.000	1.19 (0.19–7.46), 0.855
Respiratory distress syndrome, n (%)	49/81 (60.5)	64/88 (72.7)	0.57 (0.30–1.07), 0.104	0.44 (0.18–1.12), 0.085
Necrotizing enterocolitis, n (%)	3/82 (3.7)	1/88 (1.1)	3.30 (0.34–32.36), 0.354	3.36 (0.33–34.16), 0.306
Abnormal ROP screening, n (%)	7/37 (18.9)	5/48 (10.4)	2.01 (0.58–6.93), 0.350	1.85 (0.49–6.95), 0.362
Bronchopulmonary dysplasia, any grade, n (%)	31/83 (37.3)	30/87 (34.5)	1.13 (0.61–2.12), 0.750	1.65 (0.56–4.86), 0.361
Moderate-to-severe BPD, n (%)	10/83 (12.0)	5/87 (5.7)	2.25 (0.74–6.89), 0.181	2.61 (0.80–8.57), 0.113
Pulmonary surfactant use, n (%)	34/83 (41.0)	43/88 (48.9)	0.73 (0.40–1.31), 0.357	0.59 (0.25–1.42), 0.240
Neonatal fever, n (%)	16/83 (19.3)	12/88 (13.6)	1.51 (0.67–3.42), 0.409	1.61 (0.69–3.76), 0.268
Hyperbilirubinemia, n (%)	79/82 (96.3)	83/88 (94.3)	1.59 (0.41–6.14), 0.721	2.15 (0.44–10.45), 0.344
Death, n (%)	3/83 (3.6)	1/88 (1.1)	3.26 (0.33–32.02), 0.356	3.24 (0.32–32.35), 0.317

OR, odds ratio; CI, confidence interval; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia. Percentages are computed among infants with the outcome assessable; denominators are shown. Crude associations were tested with the Fisher exact test. †Logistic regression adjusted for gestational age and birth weight. Culture-proven sepsis required a positive blood or other clinical culture (not obtained in 18 HCA and 16 control infants; percentages use full-group denominators). IVH and ROP rows use denominators of infants with available examinations. ‡Mann–Whitney U test P value.

Outcome	HCA group	Control group	Crude OR (95% CI), P	Adjusted OR (95% CI)†, P
Invasive ventilation, days	0.4 [0–2]	1 [0–2]	—	0.875‡
Non-invasive ventilation, days	3 [1–24]	5 [0.75–18.8]	—	0.981‡
Supplemental oxygen, days	5 [0–13]	5 [0.5–11]	—	0.795‡
Length of hospital stay, days	18 [9–39.5]	23 [13.8–41]	—	0.262‡

OR, odds ratio; CI, confidence interval; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia. Percentages are computed among infants with the outcome assessable; denominators are shown. Crude associations were tested with the Fisher exact test. †Logistic regression adjusted for gestational age and birth weight. Culture-proven sepsis required a positive blood or other clinical culture (not obtained in 18 HCA and 16 control infants; percentages use full-group denominators). IVH and ROP rows use denominators of infants with available examinations. ‡Mann–Whitney U test P value.

Table 3
Maternal and neonatal inflammatory markers

Marker	HCA group	Control group	P value
Maternal pre-delivery			
WBC, ×10⁹/L	11.2 [9.2–13.9]	9.1 [7.4–10.7]	< 0.001
Neutrophils, %	81.6 [75.3–85.4]	76.6 [69.5–81.3]	< 0.001
Absolute neutrophils, ×10⁹/L	9.1 [7.1–11.5]	7.0 [5.3–8.4]	< 0.001
hs-CRP, mg/L	8.7 [3.0–10.0]	3.6 [1.3–6.0]	0.040
Platelets, ×10⁹/L	204.5 [152–253]	200 [159.5–244]	0.941
Maternal post-delivery			
WBC, ×10⁹/L	12.9 [10.6–16.3]	13.1 [10.8–15.9]	0.859
Neutrophils, %	83.7 [75.7–88.4]	84.5 [79.3–86.9]	0.967
Neonatal day 0			
WBC, ×10⁹/L	10.0 [6.9–14.9]	7.0 [5.6–10.4]	< 0.001
Neutrophils, %	56.6 [48.8–68.1]	52.9 [39.2–61.2]	0.009
CRP, mg/L	10.0 [10.0–10.0]	10.0 [10.0–10.0]	0.426
Neonatal day 5			
WBC, ×10⁹/L	11.9 [8.4–15.2]	8.9 [7.8–10.5]	0.016
Neutrophils, %	45.3 [34.1–53.1]	39.5 [31.4–46.7]	0.174
CRP, mg/L	10.0 [10.0–10.0]	10.0 [10.0–10.0]	0.747

Data are median [IQR]; groups were compared with the Mann–Whitney U test. Sample sizes vary by time point because tests were performed as clinically indicated (day 0: n = 83/88; day 5: n = 42/58; maternal pre-delivery WBC: n = 80/83; hs-CRP pre-delivery: n = 35/16). Neonatal CRP values at the lower reporting limit (10 mg/L) predominated at all time points. Complete day-by-day trajectories are shown in Fig. 1.

Intraventricular hemorrhage: an inverse association

In contrast to the null findings above, among infants with available cranial ultrasonography (74 HCA, 76 control), IVH of any grade was significantly less frequent in the HCA group (23.0% [17/74] vs 42.1% [32/76]; crude OR 0.41, 95% CI 0.20–0.83, P = 0.015). The association persisted after adjustment for GA and BW (aOR 0.38, 95% CI 0.17–0.83, P = 0.015) and strengthened in the extended model additionally controlling for delivery mode, antenatal corticosteroids, and fetal distress (aOR 0.28, 95% CI 0.11–0.71, P = 0.007); the estimate was essentially unchanged after additional adjustment for antenatal antibiotic

exposure (aOR 0.28, 95% CI 0.11–0.70). Stratification by GA showed that the inverse association was concentrated among infants born at ≥ 32 weeks (6.7% vs 31.8%; OR 0.15, 95% CI 0.04–0.58, P = 0.003), with no significant difference below 32 weeks (OR 0.73, 95% CI 0.26–1.99, P = 0.612; Fig. 3). Severe (grade III–IV) IVH was rare: no case occurred among examined infants in the HCA group and one case (1.3%) occurred in the control group. All IVH in HCA-exposed infants was grade I–II.

Discussion

In this GA- and BW-matched cohort of 171 preterm infants, histologically confirmed chorioamnionitis was associated with clear evidence of maternal and neonatal inflammatory activation, yet not with worse short-term neonatal outcomes — and, unexpectedly, was associated with a markedly lower risk of IVH. The inverse association was robust to adjustment, stronger in an extended model, and confined to infants born at ≥ 32 weeks of gestation, in whom the odds of IVH were reduced by more than 80%.

Our null findings for BPD, RDS, sepsis, NEC, and ROP contrast with large meta-analyses reporting adverse associations [3–6] and with population-based studies reporting increased neonatal respiratory morbidity after chorioamnionitis [11], but are concordant with a recurring observation in that literature: chorioamnionitis-exposed infants are systematically born earlier and smaller, and associations weaken or disappear in analyses that adequately handle GA [5, 6]. For BPD, meta-regression attributed most of the between-study variance in effect size to differences in GA and RDS risk, and studies without significant GA differences found no association [5]. Our design removes this confounding by matching rather than regression alone. The high antenatal corticosteroid coverage (> 88% in both groups) may additionally have equalized pulmonary outcomes. The trend toward less RDS in the HCA group (aOR 0.44, P = 0.085) is reminiscent of the "early-protection, late-damage" (Watterberg) hypothesis, in which intrauterine inflammation accelerates lung maturation while promoting later injury [5, 8]; in our matched, steroid-covered cohort, neither arm of that hypothesis reached significance.

The IVH finding runs counter to the 2018 meta-analysis, which reported increased IVH risk with chorioamnionitis [6]. Notably, however, that meta-analysis also found that pooled adjusted data — particularly for histologic chorioamnionitis — no longer showed a significant association, and that funisitis added no further risk [6]. Few included studies matched on GA and BW, and more recent work linking histologic chorioamnionitis to MRI-defined brain abnormalities in very preterm infants was likewise unmatched [12]. Our results extend this uncertainty in an unexpected direction and are biologically conceivable: antenatal inflammatory exposure can induce fetal "preconditioning", and the germinal matrix vasculature undergoes maturation-dependent changes in fragility across the early third trimester [8, 9]. The restriction of the protective signal to infants ≥ 32 weeks, and the absence of any severe IVH among HCA-exposed infants, are compatible with a maturation-dependent window in which inflammatory preconditioning could stabilize the cerebral microvasculature or modulate hemodynamic responses at birth. This interpretation remains speculative; alternatively, residual differences in perinatal management (more vaginal deliveries and antenatal antibiotics in the HCA group) or selection of which mothers reach histologic diagnosis could contribute, although the extended model argues against

delivery mode as an explanation, and additional adjustment for antenatal antibiotics left the association essentially unchanged.

Clinically, our data caution against treating histologic chorioamnionitis per se as a marker of poor neonatal prognosis when GA and BW are taken into account. The dissociation between systemic inflammatory markers (elevated WBC and neutrophils without CRP elevation) and clinical outcomes also suggests that routine leukocyte-based screening in HCA-exposed moderately preterm infants may generate more alarm than actionable information; serial rather than single measurements, and integration with clinical signs, appear more informative (Fig. 1).

Strengths of this study include histologic confirmation of exposure in all cases, strict matching on the two dominant confounders, and longitudinal rather than single-point inflammatory marker data. Limitations must be emphasized: the retrospective single-center design; the modest sample size, which leaves wide confidence intervals for infrequent outcomes such as NEC and mortality and limits the ROP subgroup; cranial ultrasonography and ROP screening were not performed in all infants (150/171 and 85/171, respectively), so selection bias in the IVH and ROP analyses cannot be excluded; the large number of comparisons without formal multiplicity adjustment, so that the findings should be regarded as exploratory; the lack of histologic staging, grading, and funisitis assessment, precluding analysis of the fetal inflammatory response; low culture positivity, so infectious versus sterile inflammation could not be distinguished; and the possibility of residual confounding by unmeasured factors (e.g., latency antibiotics, cord blood gases, placental pathology beyond HCA). The IVH association, although robust in our data, arose among multiple outcomes and should be regarded as hypothesis-generating until replicated in prospective cohorts with full placental phenotyping.

Conclusions

In a gestational age- and birth weight-matched preterm cohort, exposure to histologic chorioamnionitis produced measurable maternal–neonatal inflammatory activation without worsening conventional short-term outcomes, and was associated with a significantly lower risk of intraventricular hemorrhage, concentrated among infants born at ≥ 32 weeks. Histologic chorioamnionitis alone should not be interpreted as an indicator of adverse neonatal prognosis. Prospective studies incorporating placental staging and fetal inflammatory response are needed to verify the unexpected inverse association with IVH and to clarify the underlying mechanisms.

Abbreviations

HCA
histologic chorioamnionitis
IVH
intraventricular hemorrhage
BPD

bronchopulmonary dysplasia
RDS
respiratory distress syndrome
NEC
necrotizing enterocolitis
ROP
retinopathy of prematurity
GA
gestational age
BW
birth weight
OR
odds ratio
aOR
adjusted odds ratio
CI
confidence interval
WBC
white blood cell count
CRP
C-reactive protein
PROM
premature rupture of membranes.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (approval number XJTU1AF2024LSYY-124). The requirement for individual informed consent was waived because of the retrospective design. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. The manuscript does not contain any individual person's data in any form (including individual details, images or videos).

Availability of data and materials

The dataset(s) supporting the conclusions of this article is(are) included within the article and its additional file (Additional file 1: de-identified participant-level dataset). De-identified data are additionally

available from the corresponding author on reasonable request, subject to institutional ethics requirements.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Furong Cao: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft;

Fei Wang: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft;

Mi Xiao: Data curation, Project administration;

Wanyan Zhang: Data curation, Investigation;

Zhen Tian: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing;

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Figures

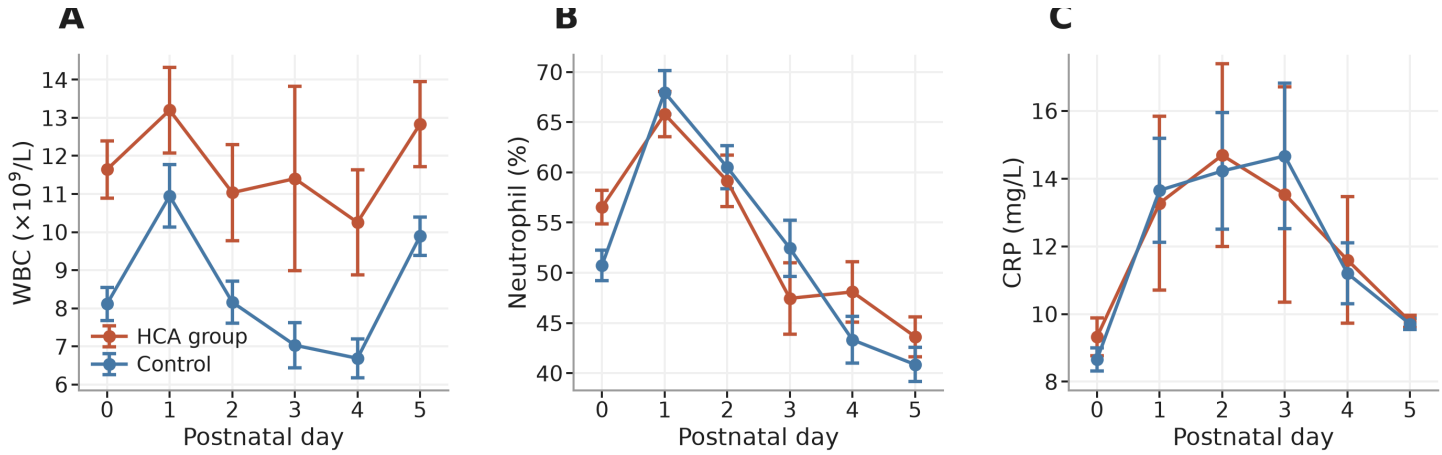


Figure 1

Serial neonatal inflammatory markers in HCA-exposed and control preterm infants. White blood cell count, neutrophil percentage, and C-reactive protein from day 0 to day 5 of life, comparing HCA-exposed (red) and control (blue) infants. Points and error bars represent medians and interquartile ranges; asterisks denote time points with $P < 0.05$ (Mann–Whitney U test). HCA, histologic chorioamnionitis.

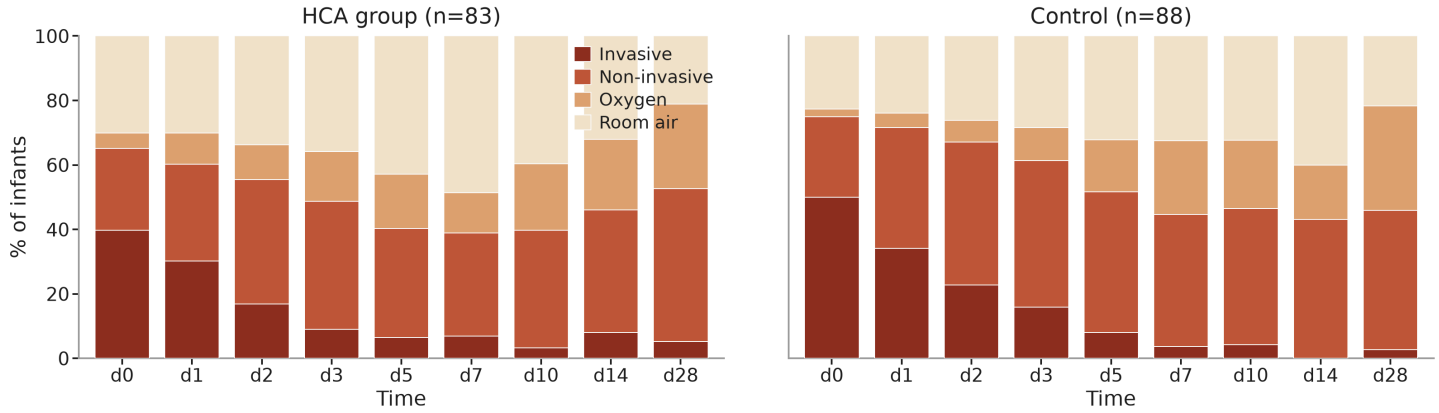


Figure 2

Evolution of respiratory support modes from day 0 to day 28 of life. Stacked bars show the percentage of infants in the HCA (left panel) and control (right panel) groups receiving invasive ventilation, non-invasive ventilation, supplemental oxygen, or no support at each time point. HCA, histologic chorioamnionitis.

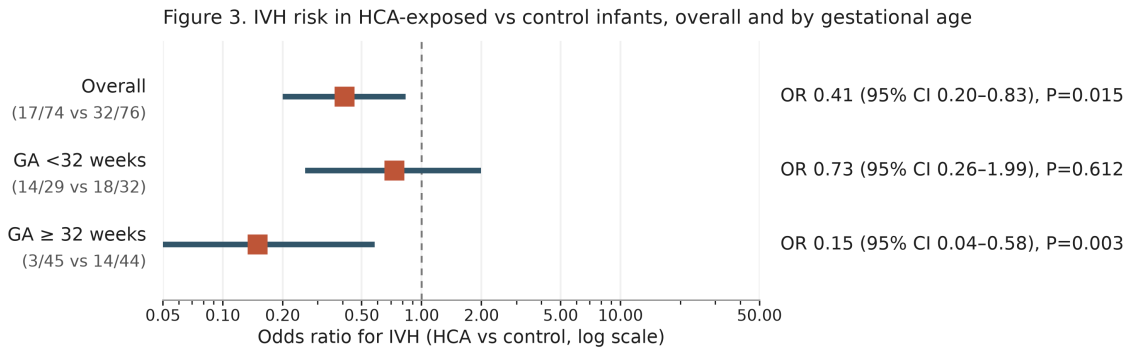


Figure 3

Association between histologic chorioamnionitis and intraventricular hemorrhage. Odds ratios (squares) with 95% confidence intervals (horizontal lines) on a log scale, overall and stratified by gestational age; the dashed vertical line indicates OR = 1. OR, odds ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 4Additionalfile1dataset.xlsx
- 5Additionalfile2STROBEchecklist.pdf