

Maternal Risk Factors and Short-Term Clinical Outcomes of Different Small Vulnerable Newborn (SVN) Phenotypes: A Retrospective Cohort Study of 998 Cases

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Abstract

Background

Traditional perinatal risk assessment relies on isolated indicators such as preterm birth, low birth weight (LBW), and small-for-gestational-age (SGA) status. The 2023 Lancet Small Vulnerable Newborn (SVN) framework integrates these overlapping vulnerabilities. This study examined maternal inflammatory and placental ischemic pathways across distinct SVN phenotypes and their associations with postnatal mechanical ventilation.

Methods

This retrospective cohort included 998 high-risk neonates admitted to a tertiary NICU. Infants were classified into five mutually exclusive SVN phenotypes: pure preterm (n = 278), preterm + LBW (n = 425), preterm + LBW+SGA ("Three-in-One"; n = 122), term + LBW (n = 145), and term+normal-weight + SGA (n = 28). Continuous variables were analyzed using Welch's ANOVA or Kruskal-Wallis tests. Independent predictors were assessed using multivariable logistic regression with variance inflation factor evaluation.

Result

Preterm + LBW was the most common phenotype (42.6%). Chorioamnionitis and premature rupture of membranes were most frequent in this group, occurring in 63.8% and 37.2% of infants, respectively. In contrast, the "Three-in-One" phenotype was strongly associated with placental ischemic markers. Maternal preeclampsia and umbilical artery absent end-diastolic velocity independently predicted this phenotype, with adjusted odds ratios of 3.828 and 6.692, respectively. Postnatally, preterm + LBW infants required substantially more CPAP support than term + LBW infants. Maternal chorioamnionitis independently predicted mechanical ventilation, whereas term + LBW status was associated with lower ventilation risk. The predictive models showed modest discrimination, with Area Under the Curve (AUC) values of 0.663 and 0.684.

Conclusions

Distinct SVN phenotypes were associated with different maternal risk pathways and respiratory outcomes, supporting phenotype-based perinatal risk stratification.

Summary Box

What is already known on this topic

1. The Small Vulnerable Newborn (SVN) framework integrates preterm birth, low birth weight, and small-for-gestational-age to better stratify neonatal risk profiles.
2. Overlapping clinical phenotypes face significantly higher mortality, but specific maternal pathogenetic pathways driving distinct SVN configurations remain poorly quantified.

What this study adds

1. Intrauterine infection independently drives preterm low birth weight, while severe maternal placental ischemia and umbilical artery AEDV uniquely trigger the critical "Three-in-One" phenotype.
2. Postnatal respiratory support risks decouple absolute birth weight from gestational age, showing term low-weight infants require drastically less mechanical ventilation than preterm peers.

How this study might affect research, practice or policy

1. Perinatal care should transition from isolated weight metrics to multi-parameter antenatal tracking of vascular and inflammatory pathways to predict specific SVN configurations.
2. Phenotype-driven postnatal triage will optimize neonatal intensive care unit resource allocation and improve targeted interventions for vulnerable infants globally.

Introduction

Every year, tens of millions of neonates are born either too small or too early, presenting a monumental challenge to global public health^[1–5]. These infants contribute disproportionately to neonatal mortality, short-term intensive care utilization, and long-term neurodevelopmental or metabolic sequelae. In traditional clinical practice, obstetricians and neonatologists have conventionally utilized single-dimensional metrics—such as "preterm birth" (gestational age < 37 weeks), "low birth weight (LBW)" (birth weight < 2500 g), and "small-for-gestational-age (SGA)" (birth weight < 10th percentile)—to identify high-risk infants^[1–2,6–9]. However, these distinct definitions overlap significantly in clinical scenarios, and an isolated metric fails to reflect the underlying heterogeneous pathophysiology or provide accurate risk stratification.

To address this paradigm limitation, the 2023 The Lancet series introduced the unifying concept of the "Small Vulnerable Newborn (SVN)"^[6, 10–12]. The SVN framework integrates preterm birth, LBW, and SGA into a single comprehensive grid, defining mutually exclusive overlapping phenotypes. Accumulating international consensus indicates that infants with combined vulnerabilities—specifically those who are simultaneously preterm, low birth weight, and growth-restricted—suffer from exponentially higher mortality rates than those meeting only a single criterion^[1–6,10–12]. Nonetheless, quantitative large-scale clinical data mapping how specific maternal risk pathways differentiate these overlapping SVN phenotypes remains scarce, particularly regarding how maternal intrauterine infections versus placental vascular ischemic conditions shape distinct newborn archetypes.

Utilizing a comprehensive perinatal database of 998 high-risk mother-infant pairs from our tertiary care facility, this study aims to characterize the clinical distribution of distinct SVN phenotypes. Furthermore, we seek to elucidate the etiological "dual-pathway" split, distinguishing the "infection/inflammation pathway" (typified by chorioamnionitis and premature rupture of membranes) from the "vascular/placental ischemia pathway" (typified by preeclampsia and absent end-diastolic velocity). Finally, we contrast the requirements for advanced postnatal respiratory support and early morbidities across these phenotypes to establish data-driven support for precision perinatal triaging.

Materials and Methods

Study Design and Population

This study was a single-center, retrospective cohort analysis of mother-infant pairs admitted to the Neonatal Intensive Care Unit (NICU) at Wuxi Maternity and Child Health Care Hospital, China. The study period spanned from January 2024 to December 2025. Medical records were consecutively screened. The analytic cohort was restricted to infants admitted to the NICU within 24 hours of birth who fulfilled at least one SVN criterion (preterm birth, LBW, or SGA) and had complete obstetric and neonatal records. Infants admitted only because of maternal high-risk pregnancy complications but not meeting any SVN criterion were not included in the final phenotypic analysis. Exclusion criteria comprised major congenital or chromosomal anomalies and records with missing critical birth weight, gestational age, growth-percentile, or diagnostic values. A total of 998 mother-infant pairs were included.

Definition of Mutually Exclusive SVN Phenotypes

Based on combinations of gestational age, birth weight, and growth percentiles, all infants were partitioned into five mutually exclusive clinical groups. Preterm birth was defined as gestational age < 37 weeks, LBW as birth weight < 2500 g, and SGA as birth weight below the 10th percentile for gestational age and sex according to the birth-weight-for-gestational-age reference routinely used in our hospital:

Group 1 (Pure Preterm)

Gestational age < 37 weeks, birth weight $\geq$ 2500g, and non-SGA.

Group 2 (Preterm + LBW)

Gestational age < 37 weeks, birth weight < 2500g, and non-SGA.

Group 3 (Preterm + LBW+SGA / "Three-in-One")

Gestational age < 37 weeks, birth weight < 2500 g, and birth weight < 10th percentile for gestational age.

Group 4 (Term + LBW)

Gestational age ≥ 37 weeks, birth weight < 2500 g, but non-SGA.

Group 5 (Term+Normal Weight + SGA)

Gestational age ≥ 37 weeks, birth weight ≥ 2500 g, but birth weight < 10 th percentile for gestational age.

Data Extraction and Clinical Covariates

Obstetric and neonatal parameters were double-extracted from electronic health systems. Maternal risk factors were categorized into two main mechanistic pathways: (1) Infection/Inflammation Pathway: chorioamnionitis (Grade 1 and Grade 2), premature rupture of membranes (PROM), peripartum fever, and Group B Streptococcus (GBS) positivity; (2) Vascular/Placental Ischemia Pathway: preeclampsia, gestational hypertension (GH), fetal growth restriction (FGR), and umbilical artery absent end-diastolic velocity (AEDV)^[7–9,13–18]. Gestational diabetes mellitus (GDM) was tracked as a metabolic covariate. Neonatal short-term variables included birth weight (g), Apgar scores, fetal distress, postnatal respiratory support modalities (mechanical ventilation and CPAP), phototherapy, and primary diagnoses including congenital pneumonia, neonatal respiratory failure, neonatal sepsis, and structural delays (atrial septal defect [ASD] or patent ductus arteriosus [PDA]).

Diagnostic and Clinical Criteria

The clinical and pathological diagnoses utilized in this cohort study were established according to prespecified clinical criteria and relevant international guidelines or consensus statements^[7–9,13–19]. Chorioamnionitis was identified from obstetric clinical records and/or placental pathological reports. PROM was defined as rupture of membranes before the onset of labor. Preeclampsia, gestational hypertension, GDM, FGR, and umbilical artery AEDV were diagnosed according to contemporaneous obstetric criteria and Doppler ultrasound assessment. Neonatal respiratory outcomes were defined according to NICU treatment records: CPAP support referred to non-invasive continuous positive airway pressure after admission, and mechanical ventilation referred to invasive ventilation via endotracheal intubation. Congenital pneumonia, neonatal respiratory failure, neonatal sepsis, and ASD/PDA findings were recorded according to discharge diagnoses and echocardiographic reports. All definitions were applied consistently throughout data extraction.

Statistical Analysis

Continuous variables were first assessed for normality using the Shapiro-Wilk test and for homogeneity of variance using Levene's test. Because birth weight showed non-homogeneity of variance ($p < 0.0001$), multi-group mean comparisons were performed using Welch's ANOVA, followed by Games-Howell post-hoc pairwise tests. Neonatal Apgar scores, representing ordinal/skewed data, were expressed as median and interquartile range [Median (IQR)] and compared across groups using the non-parametric Kruskal-Wallis H test. Categorical data were expressed as frequencies and percentages and analyzed

using the Pearson Chi-square test; for sparse cells with expected counts below 5, such as umbilical artery AEDV, Fisher's exact test was used. To determine independent maternal predictors of the compound "Three-in-One" phenotype (Group 3), a multivariable logistic regression model was constructed using prespecified antenatal covariates. A secondary multivariable model was fitted to evaluate factors associated with neonatal mechanical ventilation, including SVN phenotype and selected maternal risk factors; Group 1 was used as the reference category for phenotype comparisons. Multicollinearity among independent predictors was evaluated using the Variance Inflation Factor (VIF), with $VIF < 5$ considered acceptable. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed. Statistical significance was defined as two-tailed $P < 0.05$. Analyses were performed using SPSS 26.0 and Python 3.9 modules.

Results

Cohort Distribution and Baseline Characteristic

A total of 998 high-risk neonates were partitioned into five mutually exclusive SVN phenotypes. Group 2 constituted the largest phenotypic subset in this NICU cohort, encompassing 425 cases (42.6%), followed by Group 1 with 278 cases (27.9%) and Group 4 with 145 cases (14.5%). Group 3 accounted for 122 cases (12.2%), while Group 5 was the least frequent configuration (2.8%). Demographic and peripartum metrics differed across groups. The primipara rate was highest in Group 5 (96.4%, $p = 0.0024$). Cesarean delivery was most frequent in Group 3 (89.3%), exceeding that in Group 5 (42.9%, $p < 0.0001$). Neonatal admission weight differed significantly across groups ($p < 0.0001$), with Group 3 having the lowest mean birth weight (1734.02 ± 403.20 g). Non-parametric analysis of Apgar scores showed significant inter-group differences, with lower scores clustered within the preterm low-weight groups (Group 2 and Group 3, $p < 0.0001$), indicating higher delivery-room resuscitation needs. (Table 1)

Table 1

Demographic and Clinical Baseline Characteristics Across Mutually Exclusive Small Vulnerable Newborn (SVN) Phenotypes (N = 998)

Baseline Characteristics	Group 1 (n = 278, 27.9%)	Group 2 (n = 425, 42.6%)	Group 3 (n = 122, 12.2%)	Group 4 (n = 145, 14.5%)	Group 5 (n = 28, 2.8%)	p Value
Singleton pregnancy	206(74.1%)	298(70.1%)	83(68.0%)	101(69.7%)	28(100.0%)	0.0091
Primiparous mother	187(67.3%)	299(70.4%)	92(75.4%)	115 (79.3%)	27(96.4%)	0.0024
Cesarean delivery	221(79.5%)	340(80.0%)	109(89.3%)	101(69.7%)	12(42.9%)	< 0.0001
Birth weight (g)	2807.95 ± 277.41	1981.86 ± 442.02	1734.02 ± 403.20	2259.93 ± 246.69	2593.21 ± 80.53	< 0.0001
Birth Apgar score	10 (10, 10)	10 (9, 10)	10 (9, 10)	10 (10, 10)	10 (10, 10)	< 0.0001

Maternal Peripartum Complications and Etiological Divergence Across SVN Phenotypes

Cross-tabulation of maternal obstetric complications showed distinct distributions of intrauterine infection/inflammation markers and chronic placental ischemia markers across the five mutually exclusive SVN configurations. The infection/inflammation pattern was most frequent in Group 2, which had the highest prevalence of total maternal chorioamnionitis (63.8%, 271/425) and PROM (37.2%, 158/425) across all groups ($p < 0.0001$). Maternal preeclampsia was more frequent in Group 3 (38.5%, 47/122) than in Group 1 (11.9%) and Group 2 (11.5%) ($p < 0.0001$). AEDV, a marker of severe placental vascular resistance, was concentrated in Group 3 (8.2%, 10/122) and absent in the term groups ($p < 0.0001$). Metabolic and transient distress markers, including gestational diabetes mellitus ($p = 0.0515$) and clinical fetal distress ($p = 0.2540$), did not differ significantly among cohorts.(Table 2)

Table 2
Maternal Peripartum Complications and Etiological Divergence Across SVN Phenotypes

Indicators	Group 1 (n = 278)	Group 2 (n = 425)	Group 3 (n = 122)	Group 4 (n = 145)	Group 5 (n = 28)	p Value
Chorioamnionitis	116 (41.7%)	271 (63.8%)	70 (57.4%)	51 (35.2%)	11 (39.3%)	< 0.0001
PROM	86 (30.9%)	158 (37.2%)	23 (18.9%)	24 (16.6%)	8 (28.6%)	< 0.0001
Preeclampsia	33 (11.9%)	49 (11.5%)	47 (38.5%)	21 (14.5%)	5 (17.9%)	< 0.0001
Umbilical Artery AEDV	0 (0.0%)	5 (1.2%)	10 (8.2%)	0 (0.0%)	0 (0.0%)	< 0.0001
Fetal Growth Restriction	1 (0.4%)	15 (3.5%)	43 (35.2%)	52 (35.9%)	0 (0.0%)	< 0.0001
Gestational Hypertension	15 (5.4%)	19 (4.5%)	9 (7.4%)	10 (6.9%)	1 (3.6%)	0.6507
Gestational Diabetes	74 (26.6%)	97 (22.8%)	24 (19.7%)	25 (17.2%)	2 (7.1%)	0.0515
Fetal Distress	20 (7.2%)	28 (6.6%)	6 (4.9%)	15 (10.3%)	4 (14.3%)	0.2540

Postnatal Respiratory Support Trajectories and Neonatal Morbidities

Post-birth therapeutic interventions and early neonatal outcomes appeared to correspond more closely to gestational maturity than to absolute birth weight alone. A clear difference in respiratory support was identified between Group 2 and Group 4. Despite both groups having birth weight deficits (mean: 1981.86g vs. 2259.93g), infants in Group 2 more frequently required non-invasive continuous positive airway pressure (CPAP) support (49.9%, 212/425), whereas Group 4 term infants rarely required CPAP (0.7%, 1/145; $p < 0.0001$). Invasive mechanical ventilation was most frequent in Group 2 (15.8%) and Group 5 (14.3%), with significant inter-group heterogeneity ($p = 0.0002$). Congenital pneumonia was more common in Group 2 (24.5%) and Group 5 (32.1%) ($p = 0.0004$), accompanied by differences in clinical respiratory failure ($p = 0.0001$). Kruskal-Wallis H testing showed significant differences in Apgar scores across groups, with lower scores clustered within the preterm cohorts (Group 2 and Group 3, $p < 0.0001$). Echocardiographic ASD/PDA findings were frequent across all high-risk NICU subgroups (86.0-92.6%) but did not differ significantly between groups ($p = 0.1303$) .(Table 3)

Table 3
Postnatal Respiratory Support Trajectories and Neonatal Morbidities

Indicators	Group 1 (n = 278)	Group 2 (n = 425)	Group 3 (n = 122)	Group 4 (n = 145)	Group 5 (n = 28)	p Value
Mechanical Ventilation	27 (9.7%)	67 (15.8%)	9 (7.4%)	4 (2.8%)	4 (14.3%)	0.0002
CPAP Support	5 (1.8%)	212 (49.9%)	53 (43.4%)	1 (0.7%)	0 (0.0%)	< 0.0001
Phototherapy	247 (88.8%)	407 (95.8%)	118 (96.7%)	119 (82.1%)	24 (85.7%)	< 0.0001
Congenital Pneumonia	35 (12.6%)	104 (24.5%)	24 (19.7%)	21 (14.5%)	9 (32.1%)	0.0004
Respiratory Failure	23 (8.3%)	59 (13.9%)	8 (6.6%)	2 (1.4%)	4 (14.3%)	0.0001
ASD / PDA Structural Delay	239 (86.0%)	368 (86.6%)	113 (92.6%)	134 (92.4%)	25 (89.3%)	0.1303
Birth Weight	2807.9 ± 277.4	1981.9 ± 442.0	1734.0 ± 403.2	2259.9 ± 246.7	2593.2 ± 80.5	< 0.0001
Birth Apgar Score	10 (10, 10)	10 (9, 10)	10 (9, 10)	10 (10, 10)	10 (10, 10)	< 0.0001

Multivariable Logistic Regression Analysis of Antenatal Determinants for the "Three-in-One" SVN Phenotype

Before fitting the multivariable logistic regression model for the compound "Three-in-One" configuration, collinearity diagnostics were evaluated. The Variance Inflation Factor (VIF) values for all antenatal covariates were below the prespecified threshold of 5.0 (PROM: 1.081; preeclampsia: 1.120; umbilical artery AEDV: 1.044; gestational hypertension: 1.003; gestational diabetes mellitus: 1.007; overall chorioamnionitis: 1.081), indicating no severe multicollinearity. After mutual adjustment, maternal preeclampsia was independently associated with Group 3 status (aOR = 3.828, 95%CI: 2.407–6.086; $p < 0.0001$). Umbilical artery AEDV also showed a strong independent association with this phenotype (aOR = 6.692, 95%CI: 2.080–21.535; $p = 0.0014$). In contrast, markers representing the acute intrauterine infection/inflammation pathway were not statistically significant after multivariable adjustment. Neither maternal overall chorioamnionitis (aOR = 1.355, 95%CI: 0.902–2.034; $p = 0.1434$) nor premature rupture of membranes (aOR = 0.783, 95%CI: 0.469–1.309; $p = 0.3513$) emerged as independent predictors of Group 3 status. Similarly, gestational diabetes mellitus ($p = 0.4590$) and gestational hypertension ($p = 0.1588$) showed no independent association with the compound phenotype. These findings suggest that the overlapping "Three-in-One" SVN phenotype was more closely associated with maternal-fetal vascular disease and placental insufficiency than with acute inflammatory markers in this cohort.(Table 4)

Table 4
Multivariable Logistic Regression Analysis of Antenatal Determinants for the "Three-in-One" SVN Phenotype

Maternal Variables	Beta Coefficient	Standard Error (SE)	p Value	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)
Preeclampsia	1.342	0.236	< 0.0001	3.828	[2.407, 6.086]
Absent End-Diastolic Velocity (AEDV)	1.901	0.596	0.0014	6.692	[2.080, 21.535]
Chorioamnionitis (Overall)	0.304	0.208	0.1434	1.355	[0.902, 2.034]
Premature Rupture of Membranes	-0.244	0.262	0.3513	0.783	[0.469, 1.309]
Gestational Hypertension	0.556	0.394	0.1588	1.743	[0.805, 3.775]
Gestational Diabetes Mellitus	-0.185	0.251	0.4590	0.831	[0.509, 1.357]

Multivariable Logistic Regression Analysis of Independent Predictors for Postnatal Neonatal Mechanical Ventilation Support

To evaluate clinical and obstetric factors associated with advanced respiratory intervention, a secondary multivariable logistic regression model was constructed with postnatal invasive mechanical ventilation (ventilation support = 1, none = 0) as the dependent variable. Group 1 was designated as the reference category for evaluating the associations of other SVN phenotypes and maternal intrapartum conditions with ventilation requirement. Maternal chorioamnionitis was independently associated with neonatal mechanical ventilation (aOR = 2.627, 95%CI: 1.660–4.157; $p < 0.0001$). Using the pure preterm group (Group 1) as the reference, infants in Group 4 showed significantly lower odds of mechanical ventilation (aOR = 0.271, 95%CI: 0.093–0.796; $p = 0.0176$). This finding suggests that gestational maturity may partly mitigate acute respiratory risk despite low birth weight. In contrast, Group 2 ($p = 0.1501$) and Group 3 ($p = 0.2151$) did not differ significantly from Group 1 in ventilation odds. Maternal preeclampsia ($p = 0.5504$) and gestational diabetes mellitus ($p = 0.5771$) were not independently associated with postnatal mechanical ventilation in this model.(Table 5)

Table 5

Multivariable Logistic Regression Analysis of Independent Predictors for Postnatal Neonatal Mechanical Ventilation Support

Predictive Variables	Beta Coefficient	Standard Error (SE)	P Value	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)
Maternal Chorioamnionitis	0.966	0.234	< 0.0001	2.627	[1.660, 4.157]
Group 4 (Term + LBW)	-1.304	0.549	0.0176	0.271	[0.093, 0.796]
Group 2 (Preterm + LBW)	0.357	0.248	0.1501	1.430	[0.879, 2.327]
Group 3 (Three-in-One)	-0.521	0.420	0.2151	0.594	[0.261, 1.353]
Group 5 (Term Normal Weight SGA)	0.441	0.585	0.4513	1.555	[0.493, 4.904]
Maternal Preeclampsia	0.182	0.304	0.5504	1.199	[0.661, 2.178]
Maternal Gestational Diabetes	-0.139	0.250	0.5771	0.870	[0.532, 1.421]

Discriminative Performance and Validation of the Predictive Models

To evaluate the discriminative performance of the two multivariable logistic regression models, Receiver Operating Characteristic (ROC) curve analysis was performed, and the respective AUC metrics were computed (Fig. 1).

Model 1, constructed using maternal peripartum clinical covariates (preeclampsia, umbilical artery AEDV, chorioamnionitis, PROM, GDM, and gestational hypertension) to identify the compound "Three-in-One" SVN phenotype (Group 3), showed modest discriminative performance with an AUC of 0.663. This suggests that antenatal clinical variables may help identify infants at increased risk of this phenotype, although the model requires external validation before clinical application.

Model 2, which integrated SVN phenotypic classification with maternal intrapartum risk factors to evaluate the likelihood of invasive mechanical ventilation, achieved an AUC of 0.684. This indicates limited-to-moderate discrimination and suggests potential value for early risk stratification, but further calibration analysis and validation in independent cohorts are needed before the model can be used for clinical decision-making.

Discussion

The present retrospective cohort study of 998 high-risk neonates provides clinical data supporting the usefulness of the 2023 Lancet SVN framework in a NICU population^[6, 10–12]. By partitioning infants into five mutually exclusive phenotypic configurations based on gestational maturity, birth weight, and growth percentiles, we observed distinct maternal risk-factor patterns across SVN phenotypes. Specifically, an intrauterine infection/inflammation pattern was more closely associated with preterm LBW, whereas a vascular/placental ischemia pattern was more closely associated with the compound "Three-in-One" configuration. In addition, the respiratory-support model suggested that gestational maturity may influence acute respiratory risk independently of birth weight category.

The Intrauterine Infection/Inflammation Pathway Driving Preterm LBW

A major finding of our study is that maternal chorioamnionitis (63.8%) and PROM (37.2%) were most frequent in Group 2 (Preterm + LBW) ($p < 0.0001$). From a pathogenetic standpoint, ascending microbial invasion or sterile intrauterine inflammation may activate maternal-fetal inflammatory responses and pro-inflammatory cytokine cascades—including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α)—at the chorioamniotic interface^[13–15]. This inflammatory cascade may stimulate local prostaglandin synthesis, cervical ripening, and myometrial contractions, culminating in spontaneous or medically indicated preterm delivery. Because fetal growth restriction was not present in Group 2 by definition, the birth weight deficit in this group likely reflects shortened gestational duration rather than SGA-related growth impairment. For infants tracking along this inflammatory pathway, prenatal prevention and management may prioritize infection screening, PROM latency management, and timely obstetric-neonatal coordination^[12–14].

The Chronic Placental Ischemic Pathway Cultivating the "Three-in-One" Phenotype

In contrast to the infection/inflammation pattern, Group 3 (Three-in-One: Preterm + LBW + SGA) was more strongly associated with markers of maternal-fetal vascular disease. In our multivariable model, maternal preeclampsia and umbilical artery AEDV were independently associated with this compound phenotype, with aORs of 3.828 and 6.692, respectively. Pathologically, defective trophoblast invasion and impaired spiral artery remodeling during early placentation can result in high-resistance, low-perfusion placental structures. Under chronic ischemic stress, fetal adaptive hemodynamic responses may preserve cerebral perfusion at the expense of somatic and visceral growth, clinically manifesting as FGR/SGA. When placental vascular impedance progresses, as reflected by AEDV, or maternal disease severity increases, medically indicated preterm delivery may be required for maternal-fetal safety. The compound "Three-in-One" phenotype may therefore reflect a combined burden of chronic growth impairment and preterm delivery.^[7–9, 16–18] In this cohort, chorioamnionitis and PROM were not independently associated with Group 3 after adjustment ($p > 0.05$), supporting etiological separation between this phenotype and the acute inflammatory pathway.

Gestational Maturity and Postnatal Pulmotoxicity of Intrauterine Inflammation

From a neonatological perspective, our ventilation model (Model 2, AUC = 0.684) suggests that gestational maturity may be more relevant than absolute birth weight alone for short-term respiratory support. Although infants in Group 4 (Term + LBW) and Group 2 (Preterm + LBW) both had birth weight deficits, Group 4 status was associated with lower odds of mechanical ventilation (aOR = 0.271, $P = 0.0176$) compared with pure preterm infants. This finding is biologically plausible because pulmonary competence depends on gestational-age-related alveolar and surfactant maturation^[19–25]. Conversely, maternal chorioamnionitis was independently associated with mechanical ventilation (aOR = 2.627, $P < 0.0001$). Intrauterine exposure to inflammation may contribute to fetal lung injury, congenital pneumonia, and respiratory failure. Among preterm configurations (Groups 1, 2, and 3), respiratory risk appeared to be driven mainly by prematurity and inflammatory exposure rather than by birth weight category alone.

Strengths and Limitations

Several limitations of the present study should be acknowledged. First, as a retrospective cohort derived from a single tertiary academic medical center, our sample is susceptible to selection bias and reflects a high-risk NICU population rather than the general birth population. Second, the relatively small size of Group 5 ($n = 28$) may limit statistical power and produce unstable estimates for this subgroup. Third, the high frequency of echocardiographic ASD/PDA findings across all subsets may reflect local screening practices and should be interpreted cautiously; future studies should distinguish physiological transitional findings from clinically significant structural disease. Fourth, the predictive models showed only modest to limited-to-moderate discrimination and were not externally validated or calibrated. Finally, the current analysis was constrained to short-term peripartum outcomes during the immediate NICU hospitalization phase. Prospective, multi-center studies with longitudinal follow-up are needed to determine how mutually exclusive SVN phenotypes relate to catch-up growth, metabolic programming, and neurodevelopmental outcomes.

Conclusion

In conclusion, the 2023 Lancet SVN framework provides a useful multi-dimensional approach for describing distinct maternal risk-factor patterns and short-term respiratory trajectories in high-risk neonates. Maternal intrauterine inflammation (the chorioamnionitis-PROM pathway) was more closely associated with preterm low birth weight configurations and with postnatal mechanical ventilation. In contrast, maternal-fetal vascular disease (the preeclampsia-AEDV pathway) was independently associated with the combined "Three-in-One" phenotype. These findings support moving beyond isolated birth weight or gestational age criteria toward phenotype-informed perinatal risk stratification, while further external validation is needed before clinical prediction models can be implemented.

Abbreviations

SVN: Small Vulnerable Newborn

LBW: Low Birth Weight

SGA: Small for Gestational Age

NICU: Neonatal Intensive Care Unit

PROM: Premature Rupture of Membranes

GDM: Gestational Diabetes Mellitus

AEDV: Absent End-Diastolic Velocity

CPAP: Continuous Positive Airway Pressure

ASD: Atrial Septal Defect

PDA: Patent Ductus Arteriosus

GBS: Group B Streptococcus

FGR: Fetal Growth Restriction

GH: Gestational Hypertension

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of [*Wuxi Maternity and Child Health Care Hospital*] (Approval No. [YLSL2026-082]). The requirement for informed consent was waived due to the retrospective nature of the study, and patient data were anonymized. The committee waived the requirement for informed consent from parents or legal guardians of all minor participants (all <16 years), as the study used only anonymized, routinely collected medical data and posed no additional risk.

Consent for publication

not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

Z.F., X.C., X.Z., M.J. and S.J. designed and conducted experiments, collected and analyzed the data, and wrote the original manuscript. X.D., and H.R.provided knowledge insights and critical discussion on this project. All authors have made critical revisions to the important knowledge content in the manuscript and have read and approved the final version.

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Figures

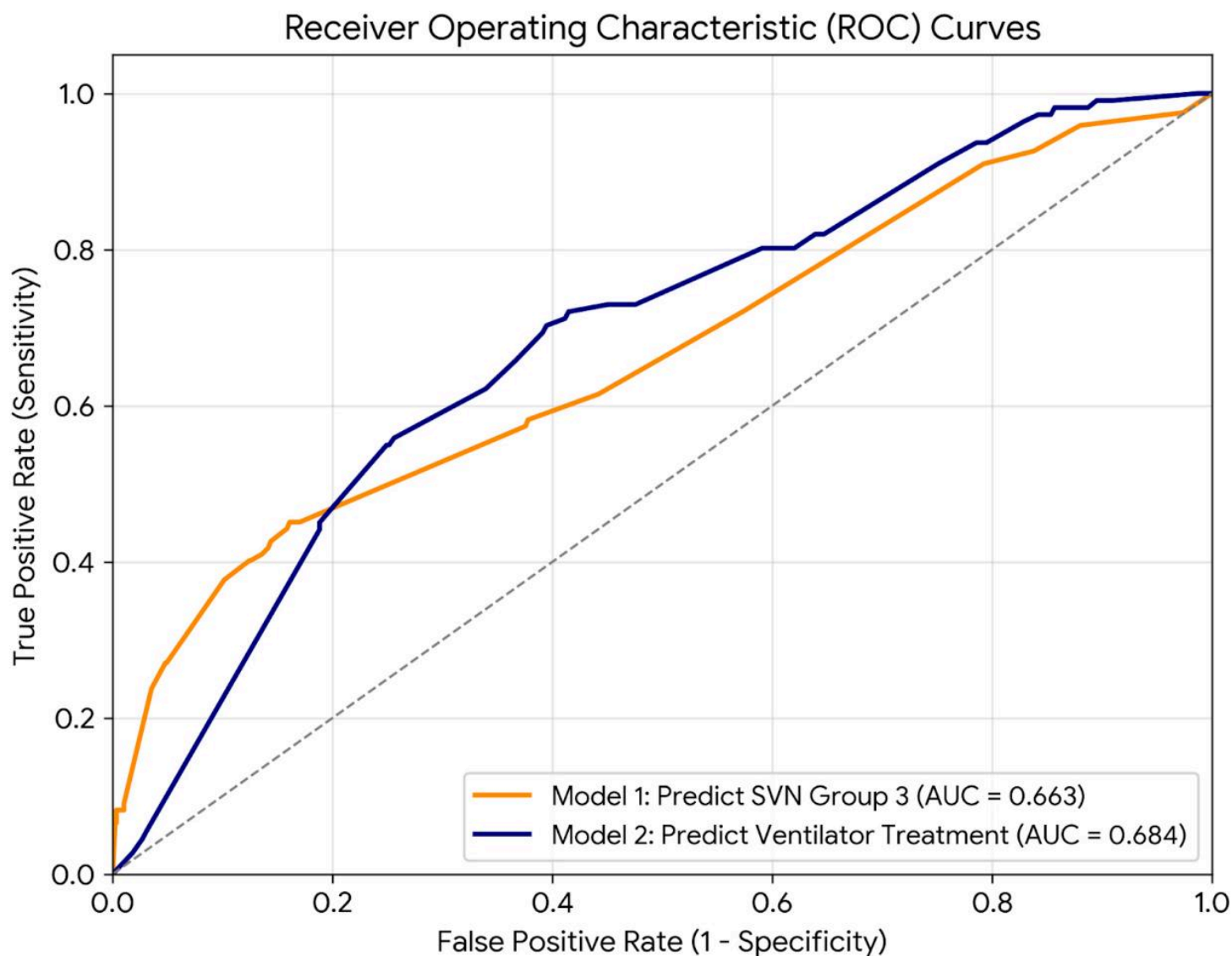


Figure 1

ROC curves evaluating the discriminative performance of the derived multivariable logistic regression predictive models (N = 998).

Model 1 showed modest discrimination for the "Three-in-One" SVN phenotype (AUC=0.663), whereas Model 2 showed limited-to-moderate discrimination for postnatal mechanical ventilation (AUC=0.684). The dashed line indicates a non-informative model (AUC=0.50). AUC, Area Under the Curve; SVN, Small Vulnerable Newborn.

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