中國醫藥大學臨床醫學研究所碩士論文

論文題目

# 尿液中 β2- microglobulin 濃度與早產兒在新生兒期併發症之相關

# Urinary β2- microglobulin Concentration and Neonatal Complications in Premature Infants

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# 目錄

# 尿液中 β2-microglobulin 濃度與早產兒併發症

**目的**　探討尿中 β2-microglobulin (β2-MG) 濃度升高與早產兒併發症之相關

**方法**　共 75 位出生體重小於 1500 公克之早產兒，在出生後 48 小時及 28 天收集尿液，以免疫物質分析法分析尿中 β2-MG 濃度，同時測尿中 creatinine 來做 β2-MG 分泌的校正。

**結果**　整體死亡率為 8% 統計分析尿中 β2-MG 濃度升高與腦室旁白質軟化、壞死性腸炎及慢性肺病變有正相關，但與呼吸窘迫症、有症狀之開放動脈導管、肺出血、腦室出血、敗血症或早產兒視網膜病變無正相關。

**結論**　在早期尿中 β2-MG 濃度升高且在出生後 28 天仍持續高的早產兒易產生腦室旁白質軟化、壞死性腸炎及慢性肺病變。

**關鍵詞**

尿中 β2-microglobulin，新生兒併發症，胎兒發炎反應，早產兒

***Objectives.*** To investigate the correlations between the elevated urinary $\beta_2$-MG and the risk of development of neonatal complications.

***Methods.*** Seventy-five very low birth weight (<1500 g) premature infants were enrolled. Urinary $\beta_2$-MG was measured with immunometric assay within 48 hours and at 28 days of age. Simultaneous urinary creatinine (Cr) was measured and used for the normalization of $\beta_2$-MG excretion.

***Results.*** The mortality rate was 8% (6/75). Multivariate logistic regression analysis showed that there were positive association of elevated urinary $\beta_2$-MG with periventricular leukomalacia (PVL) (OR 1.25, 95% CI 1.02-1.63 for 48 hrs; OR 1.18, 95% CI 1.09-1.42 for 28 days ), necrotizing enterocolitis (NEC) (OR 1.12, 95% CI 1.02-1.24 for 48 hrs; OR 1.32, 95% CI 1.06-1.84 for 28 days ), and chronic lung disease (CLD) (OR 1.92, 95% CI 1.24-2.13 for 48 hrs; OR 1.61, 95% CI 1.39-1.94 for 28 days ). **N**o similar association was found in respiratory distress syndrome, symptomatic PDA, pulmonary hemorrhage, intraventricular hemorrhage, sepsis or retinopathy of prematurity.

***Conclusions.*** Urinary $\beta_2$-MG was significantly higher at early life and

sustained higher thereafter at least until 28 days of age in premature infants who developed PVL, NEC or CLD than in those who did not.

**Key words:** $Beta_2$-microglobulin, Fetal inflammatory response, Neonatal complications, Premature infant

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# INTRODUCTION

Gomez et al proposed that fetal inflammatory response syndrome (FIRS) determined by inflammatory cytokine elevations in fetal blood is a risk factor for the severe neonatal morbidity [1,2]. Understanding occurrence and magnitude of a fetal inflammatory response is important because it contributes to short- and long-term complications in premature infants [3]. The presence of clinical or histologic chorioamnionitis elevated levels of amniotic fluid proinflammatory cytokines, and elevated fetal and neonatal plasma cytokine levels have all been associated with an increased risk for neonatal morbidity[13-15]. In particular, these include central nervous system morbidity: periventricular leukomalacia (PVL) and cerebral palsy[15-17].

During the past decade, our understanding of the pathogenesis of chronic lung disease(CLD) and bronchopulmoanry dysplasia(BPD) has expanded considerably. The principal risk factors which have clearly been identified are lung immaturity, oxygen toxicity, prenatal and nosocomial infections as well as increased pulmonary blood flow secondary to a patent ductus arteriosus[1]. In addition, there is a new

category of preterm infants with CLD who initially had minimal or absent signs of RDS but who subsequently developed oxygen dependency and ventilatory needs within 14 days. Most likely, these infants have been exposed to chorioamnionitis or early postnatal pulmonary or systemic infection [34]. Fetal exposure to proinflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-8, was clearly identified as a risk factor for BPD [13-15]. In addition elevated levels of IL-6 in fetal cord blood at birth, indicating a fetal inflammatory response, were shown to be an independent risk factor for the development of CLD.

$\beta_2$-microglobulin, a cytokine-induced protein, may be used as a clinical marker of systemic inflammation. This protein is the light chain of the class 1 major histocompatibilary antigens, a 100 amino acid protein with a molecular weight of 11800 daltons. During the inflammatory process, interferon-γ (IFN-γ) stimulates $\beta_2$-microglobulin synthesis and increased plasma levels [4,5]. Urinary $\beta_2$-MG levels increase when plasma levels rise above a renal tubular reabsorption threshold [6,7]. The aim of this study is to measure neonatal urinary $\beta_2$-MG concentration and to rate correlation between elevated $\beta_2$-MG and risk of subsequent neonatal complications: e.g., respiratory distress

syndrome (RDS), symptomatic patent ductus arteriosus (S-PDA), pulmonary and/or intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), chronic lung disease (CLD), and retinopathy of prematurity (ROP) in premature infants.

## MATERIALS AND METHODS

Very low birth weight (VLBW) premature infants with birth weight less than 1500 gm admitted to neonatal intensive care unit of China Medical University Hospital were enrolled after written informed parental consent was obtained. The study was approved by the hospital's Institutional Review Board. Infants with congenital anomaly were excluded. Postnatal steroids were not administered to the infants during the study period. Measurements of the urinary $\beta_2$-MG concentration were performed within 48 hours after birth and at 28 days of age. The urine sample was collected by using urinary bag. Only fresh urine collected within one hour and then stored at -20°C was examined, turbid urine or urine with blood discarded. Urinary $\beta_2$-MG concentration was measured by using immunometric assay with Immulite 2000 (DPC, USA). Simultaneous levels of creatinine (Cr) were analyzed via creatinine picrate reaction and used for normalization of $\beta_2$-MG excretion (μg/gCr).

The diagnosis of RDS required the presence of respiratory grunting and retracting, increased need for oxygen and diagnostic radiographic and laboratory finding in the absence of evidence for other causes of

respiratory disease. Chest X-ray showed Bomsel Grade 2 or over, and surfactant was given. S-PDA was proven by echocardiogram and indomethacin or surgical ligation required. IVH was defined as Grade 2 or over, proven by brain sonogram. PVL was diagnosed by positive finding of cystic change in periventricular white matter on brain sonogram. NEC was diagnosed in the presence of abdominal distension and feeding intolerance for at least 24 hours(vomiting or increased gastric residual) with clear radiologic evidence of pneumatosis intestinalis, perforation, meconium plug syndrome, or definite surgical. CLD was defined as a supplemental oxygen requirement 28 days after birth with symptoms of persistent respiratory distress and chest radiograph showing characteristic appearance. ROP was defined as Stage 3 change and required laser therapy. Correlation between these complications and clinical intrauterine infection were also investigated. Sepsis was diagnosed with a positive blood culture or CSF culture. Clinical intrauterine infection was considered when maternal fever>37.8’C or premature rupture of membrane was associated with signs and symptoms of intrauterine inflammation (i.e., foul-smelling

discharge, uterine tenderness), laboratory evidence of maternal leukocytosis (WBC >15000 cells/$mm^3$) or positive culture results [8].

The values were shown as mean ± SD. Yates-corrected *chi*-square was used to analyze correlation between complications and intrauterine infection. The Wilcoxon Rank Sum test was used to correlate neonatal complications with gestational age (GA), birth weight (BW), or urinary $\beta_2$-MG concentration. Multivariate logistic regression analysis evaluated linkage among neonatal complications, GA, BW and urinary $\beta_2$-MG concentration. Odds ratios (OR) and 95% confidence intervals (CI) were used to qualify degree of association. The statistical package SPSS for Windows was used, with *p* value of less than 0.05 considered significant.

## RESULTS

There were 75 consequent VLBW infants enrolled, the mortality rate was 8% (6/75). Demographic data and prevalence rate of various neonatal complications are summarized in Table 1. The mean GA and BW were significantly lower in infants who developed RDS, pulmonary hemorrhage, IVH, NEC, CLD and sepsis. There was no significant difference in prevalence of use of aminoglicosides and diuretics like furoxemide between infants with and without the above complications, nor in mean Apgar scores at 1-5 minutes.

Values of urinary $\beta_2$-MG (μg/gCr) within 48 hours significantly differ between infants with and without PVL (11256 ± 8057 vs. 3022 ± 2439, $p < 0.05$), with and without NEC (12105 ± 28537 vs. 1715 ± 4087, $p < 0.05$), and with and without CLD (5450 ± 8708 vs. 1948 ± 2798, $p < 0.05$). Values of urinary $\beta_2$-MG at 28 days of age differ markedly between infants with and without PVL (3056 ± 2565 vs. 595 ± 791, $p < 0.05$), with and without NEC (1317 ± 1147 vs. 540 ± 722, $p < 0.01$), and with and without CLD (953 ± 963 vs. 454 ± 638, $p < 0.05$). There is no difference in $\beta_2$-MG 48 hours and 28 days after birth between infants

with or without RDS, S-PDA, pulmonary hemorrhage, IVH, sepsis, or ROP (Table 2).

The independent risk factors for the development of neonatal complications were analyzed by multivariate logistic regression analysis, using backward elimination. Elevated $\beta_2$-MG positively correlated, both 48 hours and at 28 days after birth, with PVL (OR 1.25 , 95% CI 1.02-1.63 for 48 hrs; OR 1.18 , 95% CI 1.09-1.42 for 28 days), NEC (OR 1.12, 95% CI 1.02-1.24 for 48 hrs; OR 1.32 , 95% CI 1.06-1.84 for 28 days), and CLD (OR 1.92, 95% CI 1.24-2.13 for 48 hrs; OR 1.61, 95% CI 1.39-1.94 for 28 days), as shown in Table 3.

Prevalence ratios of solitary presence of RDS and PDA were 28.3% (13/46) and 31.3% (15/48), respectively. There was strong association of complicated PDA with RDS (33/46, 71.7%). Among all complications studied in this study, when RDS and PDA were excluded, prevalence of solitary presence of complication was tallied as follows: pulmonary hemorrhage 56% (5/9), IVH 58.3% (5/12), PVL 0%, NEC 22.2% (2/9), CLD 13% (3/23) and ROP 0%. Five infants had combined complications with NEC, PVL and CLD; twenty showed clinical intrauterine infection (26.7%).

Association of clinical intrauterine infection with various neonatal complications is summarized in Table 4. The presence of intrauterine infection was associated with a significant increase in the rate of CLD, PVL and NEC.

## DISCUSSION

Preterm birth is one of the key factors that affect perinatal prognosis. Maternal cervical and intrauterine infection and inflammation may have a primary causative role in a fraction of cases of preterm birth and preterm rupture of membranes [9]. Evidence from many sources links preterm birth to symptomatic and subclinical infections [3, 10]. In 1993, Leviton described intrauterine infection activating the fetal production of proinflammatory cytokines that, in turn, contribute to perinatal damage [11]. The systemic FIRS is a condition, usually subclinical and characterized by fetal immune system activation resulting in variable-intensity elaboration of numerous proinflammatory cytokines. Accumulating evidence tying FIRS to perinatal morbidity and death, independent of its association with premature birth [1], has led to speculation that the condition itself likely plays a role in perinatal multiple organ damage [12-17]. $\beta_2$-MG is a cytokine-induced low molecular weight protein. In inflammation, IFN-$\gamma$, derived from activated lymphocytes, is known to raise $\beta_2$-MG in the plasma, and then urinary $\beta_2$-MG levels rise when plasma levels are above the renal tubular reabsorption threshold [18]. Urine sample collection is safer and easier,

measurement of urinary $\beta_2$-MG less costly than that of cytokines to identify fetuses developing some previous fetal inflammatory response.

Our results revealed no significant difference in urinary $\beta_2$-MG between infants with and without RDS, PDA, pulmonary hemorrhage, IVH and ROP, what with these complications more closely related to immaturity than inflammatory response. Previous studies including ours reported intrauterine infection tending towards higher incidence of CLD but lower risk of RDS [3, 19, 20]. After the era of surfactant replacement therapy in infants with RDS, the incidence of PDA complicated with RDS has climbed [21-23]. Our data revealed a definite connection between complicated PDA and RDS rates (33/46, 71.7%). Based on prior studies, FIRS is usually accompanied by multiple complications [1-3]; among neonatal complications in this study, when RDS and PDA were excluded, pulmonary hemorrhage and IVH had higher rates of solitary presence. This implies that these complications are more related to the structural immaturity and less with previous systemic fetal inflammatory response. Studies reported positive correlation between fetal inflammatory response and IVH [24, 25], which differed from our results, along with no positive correlation between fetal inflammatory response

and PDA, and complicated pulmonary hemorrhage [26, 27]. Nor was there positive correlation between fetal inflammatory response and ROP as reported in a previous study [3].

Our results revealed urinary $\beta_2$-MG concentration significantly higher in early life and remaining higher thereafter at least until 28 days of age in premature infants with NEC, PVL or CLD. This implies that these specific complications of premature infants may be induced by previous fetal inflammatory response. Previous studies also reported possible correlation between fetal inflammatory response and PVL and the subsequent development of cerebral palsy [13-17, 28], plus correlation with CLD [3, 12, 29, 30]. One study reported the similar correlation between fetal inflammatory response and NEC [28], while another did not [3].

There was a higher rate of combined presence among NEC, PVL and CLD. There was also a significantly higher prevalence of associated clinical intrauterine infection in infants with NEC, PVL and CLD (Table 4). This implies that prolonged inflammatory status might be the crucial mechanism inducing multiple organ damage. Our results of sustained higher urinary $\beta_2$-MG concentration since early life until 28 days of age

in premature infants with these complications might reflect a fetal inflammatory response. Although the mean GA was significantly lower in infants who developed NEC, CLD and sepsis than in those who did not, the factor of lower GA may not completely contribute to these complications, because $\beta_2$-MG is reabsorbed in proximal tubular cells by a complex endocytotic process, which is not fully developed in premature infants until GA of 35~36weeks, and there is no significant difference in the urinary excretion of $\beta_2$-MG by the weeks prior to 36 weeks GA [6]. $\beta_2$-MG ,in contrast with creatinine, it dose not cross the placenta. Urinary $\beta_2$-MG may reflect endogenous production of $\beta_2$-MG in newborns, assuming that their renal function is immature and may be further compromised by various conditions, such as prematruity, asphyxia, sepsis, respiratory distress, or circulatory disturbance[31]. Hypoxia and hypoperfusion in these conditions frequently injure the proximal tubules. They contribute to increased urinary $\beta_2$-MG[32]. Moreover, reabsorption of $\beta_2$-MG by the proximal tubules may be reduced in drug-induced nephrotoxicity or with diuretics. In our study, all the premature infants less than 1500gm required intensive care because of prematurity, RDS, and /or asphyxia, and some received diuretics or antibiotics[33]. We did

not excluded infants such as these from this study. These infants were eligible for this study if they voided urine before 48 hours of age and survived after 28 days of life. Their conditions and laboratory data were not life-threatening. There was no significant difference in prevalence of use of aminoglicosides and diuretics such as furoxemide and in the mean Apgar scores at 1-5 minutes between infants with and without the above complications. Nishimaki et al. found that elevated urinary $\beta_2$-MG value in premature infants with chronic lung disease decreased approximately 40% after steroid therapy〔29〕. This change also infers that inflammation may be sufficient to elevated urinary $\beta_2$-MG values.

One of the limitations in our study is that we didn't demonstrate a level of urinary $\beta_2$-MG, below which morbidity did not occur. However, each study in the literature defines a different cutoff for elevated urinary $\beta_2$-MG in the evaluation of risk for morbidity. This is probably due to the kit used. Another limitation is that we measured urinary $\beta_2$-MG levels in neonatal urine but did not determine inflammatory cytokines (INF-α, IL-6, and IL-8) in amniotic fluid, blood, or bronchoalveolar lavage fluid.

## Conclusion

Although our study of urinary $\beta_2$-MG provides a convenient means to assess presence of fetal systemic inflammation and the risks of inflammation-related neonatal complications, to exclude the possibility of elevated $\beta_2$-MG simply reflecting underlying proximal tubular dysfunction resulting from prematurity per se, further study to demonstrate abnormal serum levels of $\beta_2$-MG in association with elevated urinary $\beta_2$-MG is warranted.

**Table 1.** The demographic data and neonatal complications of all infants

| Infants with /without | GA (wk) | | BW (g) | |
|---|---|---|---|---|
| **Complications** | **Mean ± SD** | ***p*** | **Mean ± SD** | ***p*** |
| Total infants (n=75) | 28.1 ± 2.5 | | 1049 ± 293 | |
| RDS (n=46) | 27.1 ± 2.4 | < 0.0001 | 997 ± 3044 | 0.0003 |
| RDS (-) | 29.5 ± 1.9 | | 1247 ± 197 | |
| S-PDA (n=48) | 27.7 ± 2.5 | 0.089 | 1052 ± 298 | 0.155 |
| S-PDA (-) | 28.7 ± 2.4 | | 1168 ± 274 | |
| Pul hemor (n=9) | 25.1 ± 2.4 | 0.003 | 763 ± 329 | 0.005 |
| Pul hemor (-) | 28.5 ± 2.3 | | 1139 ± 260 | |
| IVH (n=12) | 25.8 ± 2.0 | 0.0004 | 917 ± 245 | 0.012 |
| IVH (-) | 28.5 ± 2.4 | | 1128 ± 291 | |
| PVL (n=5) | 26.6 ± 2.6 | 0.371 | 949 ± 357 | 0.531 |
| PVL (-) | 28.2 ± 2.5 | | 1104 ± 286 | |
| NEC (n=9) | 26.3 ± 1.8 | 0.023 | 824 ± 159 | 0.004 |
| NEC (-) | 28.3 ± 2.5 | | 1131 ± 289 | |
| Sepsis (n=17) | 25.5 ± 2.1 | < 0.0001 | 818 ± 273 | 0.0001 |
| Sepsis (-) | 28.8 ± 2.1 | | 1175 ± 248 | |
| CLD (n=23) | 26.8 ± 2.2 | < 0.0001 | 956 ± 305 | 0.003 |
| CLD (-) | 29.2 ± 1.9 | | 1202 ± 231 | |
| ROP (n=4) | 27.8 ± 2.5 | 0.615 | 1090 ± 197 | 0.581 |
| ROP (-) | 28.5 ± 2.2 | | 1132 ± 282 | |

Wilcoxon Rank Sums test. *p* value means when each complication compared with its paired control. RDS, respiratory distress syndrome; S-PDA, symptomatic patent ductus arteriosus; Pul hemor, pulmonary hemorrhage; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC,

necrotizing enterocolitis; CLD, chronic lung disease; ROP, retinopathy of prematurity.

**Table 2.** The urinary $\beta_2$-MG of all infants with and without neonatal complications

| **Complications** | **urinary $\beta_2$-MG <48 hours (μg/gCr)** | | **urinary $\beta_2$-MG at 28 days (μg/gCr)** | |
|---|---|---|---|---|
| | **Mean ± SD** | ***p*** | **Mean ± SD** | ***p*** |
| Total infants (n=75) | 3014 ± 10818 | | 638 ± 803 | |
| RDS (n=46) | 2431 ± 5065 | 0.12 | 809 ± 961 | 0.054 |
| RDS (-) | 3930 ± 16397 | | 336 ± 302 | |
| S-PDA (n=48) | 3166 ± 13020 | 0.67 | 567 ± 726 | 0.81 |
| S-PDA (-) | 2760 ± 6010 | | 711± 919 | |
| Pul hemor (n=9) | 3251± 4315 | 0.89 | 293 ± 279 | 0.45 |
| Pul hemor (-) | 2985 ± 11457 | | 649 ± 825 | |
| IVH (n=12) | 1656 ± 1038 | 0.31 | 945 ± 1179 | 0.41 |
| IVH (-) | 3259 ± 11808 | | 570 ± 725 | |
| PVL (n=5) | 11256 ± 8057 | 0.03 | 3056 ± 2565 | 0.001 |
| PVL (-) | 3022 ± 2439 | | 595 ± 791 | |
| NEC (n=9) | 12105 ± 28537 | 0.049 | 1317 ± 1147 | 0.03 |
| NEC (-) | 1715 ± 4087 | | 540 ± 722 | |
| Sepsis (n=17) | 3247 ± 4250 | 0.87 | 926 ± 1027 | 0.34 |
| Sepsis (-) | 2947 ± 12157 | | 557 ± 742 | |
| CLD (n=23) | 5450 ± 8708 | 0.04 | 953 ± 963 | 0.042 |
| CLD (-) | 1948 ± 2798 | | 454 ± 638 | |
| ROP (n=4) | 3540 ± 6025 | 0.99 | 1080 ±1279 | 0.26 |

| | | |
|---|---|---|
| ROP (-) | 2878 ± 11480 | 601 ±756 |

Wilcoxon Rank Sums test. *p* value means when each complication compared with its paired control.

Table 3. The association among neonatal complications, urinary $\beta_2$-MG, GA and BW by multivariate logistic regression analysis

| complication | Urinary β2-MG<48hours (μg/gCr) | | | Urinary β2-MG<48hours at 28 days(μg/gCr) | | | GA(week) | | | BW(g) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | p | OR | 95%CI | p | OR | 95%CI | p | OR | 95%CI | p |
| **RDS** | 1.0 | 0.9-1.0 | 0.15 | 1.01 | 0.93-1.11 | 0.79 | 0.65 | 0.44-0.95 | 0.02 | 0.86 | 0.64-1.17 | 0.34 |
| **S-PDA** | 1.0 | 1.0-1.01 | 0.97 | 0.95 | 0.88-1.02 | 0.17 | 0.91 | 0.66-1.26 | 0.57 | 0.93 | 0.71-1.23 | 0.62 |
| **Pul hemor** | 1.0 | 0.98-1.01 | 0.67 | 0.88 | 0.7-1.1 | 0.25 | 0.68 | 0.39-1.2 | 0.18 | 0.79 | 0.5-1.25 | 0.31 |
| **IVH** | 0.97 | 0.94-1.01 | 0.15 | 0.95 | 0.85-1.07 | 0.41 | 0.39 | 0.2-0.76 | 0.006 | 1.31 | 0.82-2.08 | 0.25 |
| **PVL** | 1.25 | 1.02-1.63 | 0.015 | 1.18 | 1.09-1.42 | 0.026 | 0.9 | 0.47-1.73 | 0.74 | 0.96 | 0.55-1.67 | 0.88 |
| **NEC** | 1.12 | 1.02-1.24 | 0.018 | 1.32 | 1.06-1.84 | 0.015 | 1.07 | 0.67-1.71 | 0.76 | 0.68 | 0.45-1.02 | 0.06 |
| **Sepsis** | 1.01 | 0.98-1.03 | 0.64 | 1.01 | 0.91-1.12 | 0.87 | 0.63 | 0.39-1.02 | 0.06 | 0.83 | 0.57-1.21 | 0.33 |
| **CLD** | 1.92 | 1.24-2.13 | 0.02 | 1.61 | 1.39-1.94 | 0.024 | 0.63 | 0.41-0.96 | 0.031 | 0.94 | 0.69-1.28 | 0.68 |
| **ROP** | 1.02 | 0.99-1.04 | 0.17 | 1.07 | 0.96-1.19 | 0.23 | 0.92 | 0.43-1.96 | 0.82 | 1.0 | 0.53-1.89 | 0.99 |

The odds ratio is the factor by which various complication increases for elevated urinary $\beta_2$-MG, decreased GA and BW. RDS, respiratory distress syndrome; S-PDA, symptomatic patent ductus arteriosus; Pul hemor, pulmonary hemorrhage; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; CLD, chronic lung disease; ROP, retinopathy of prematurity.

**Table 4.** The prevalence of infants with neonatal complications associated with clinical intrauterine infection

| **Infants with Complications** | **Clinical intrauterine infection (n=20)** | *p* |
|---|---|---|
| | Number of infants (percentage) | |
| RDS ≥ Gr 2 (n=46) | 13 (28.3%) | 0.9 |
| S-PDA (n=48) | 14 (29.2%) | 0.7 |
| Pul hemor (n=9) | 1 (11%) | 0.47 |
| IVH ≥ Gr 2 (n=12) | 3 (25%) | 1.0 |
| PVL (n=5) | 4 (80%) | 0.023 |
| NEC (n=9) | 6 (66.7%) | 0.013 |
| Sepsis (n=17) | 4 (23.5%) | 0.98 |
| CLD (n=23) | 14 (60.9%) | 0.0001 |

Yates-corrected chi-square test. RDS, respiratory distress syndrome; S-PDA, symptomatic patent ductus arteriosus; Pul hemor, pulmonary hemorrhage; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; CLD, chronic lung disease; ROP, retinopathy of prematurity.

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