Factors Associated With Macrophage Migration Inhibitory Factor in Neonates: a Pilot Study

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Research note

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Abstract

Objective: The study was to conduct an investigation of associated factor with macrophage migration inhibitory factor (MIF) in neonates.

Results: MIF was measured by Enzyme-linked Immunosorbent Assay (ELISA) using sera obtained from sick neonates on the median postnatal 2.0nd day. Clinical details were reviewed from medical record and grouped into preterm and near or full-term neonates based on 34 weeks of gestation at birth. Statistical analyses were performed between MIF concentration and clinical factors. In total, 77 neonates consisted of preterm (n = 42) and term neonates (n = 35) were included. The median value of plasma MIF was higher in preterm neonates (7,037.6 pg/mL, IQR: 3,285.2-12,267.4) than in the others (3,968.8 pg/mL, IQR: 2,566.4-6,995.2, *P* = 0.013). Among 42 preterm neonates, those with necrotizing enterocolitis (NEC) in later had higher MIF concentration (12,170.9 pg/mL, IQR: 8,353.3-23,537.7, n = 9) compared with the others without NEC (5,189.6 pg/mL, IQR: 3,220.2-9,097.9, n = 33, *P* = 0.016). Associated factors of higher MIF in neonates were preterm neonates and NEC.

Introduction

Macrophage migration inhibitory factor (MIF) is the potent inflammatory cytokine and exists in the blood with a low concentration in healthy adults [1, 2]. Preformed MIF exists already in cytoplasm and rapidly releases into the blood in response to microbial, proliferative and hypoxic stimuli [3, 4]. It has been studied in sepsis, cancer, autoimmune, and metabolic diseases in adults [4]. In neonates, the plasma level of MIF is higher than in adults and a higher level of MIF can play a major role in innate immune response [5]. However, there has been a small number of study of MIF in preterm neonates until now. Preterm neonates have higher susceptibility to infection than full-term neonates due to detrimental effect of immaturity of the organ and immune system [6, 7]. However, vulnerability of preterm neonates to infection is not confined to the immature immune system or organs, and it is unclear how the set point of the immune system is regulated [8]. In addition to vulnerability to infection, preterm neonates are susceptible to respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), or bronchopulmonary dysplasia (BPD). Though immaturity could be the main factor, a number of immune or inflammatory responses could work as a part of pathogenesis in the various diseases of preterm neonate. On the aspect of different diseases and microbial susceptibility between preterm and term neonates, we hypothesized that MIF of preterm neonates would be different from that in term neonates and the difference of MIF might associate with the development of prematurity-associated diseases.

Methods

1. Subjects and blood samples

Clinical data and blood samples of 77 neonates with parental consents were obtained from Biobank of Korea. Major congenital anomalies or chromosomal abnormalities were excluded. The subjects were

classified into 2 groups as neonates prematurely born at ≤ 34 (n = 42) and the others born after 34 weeks of gestation (n = 35). Clinical information was reviewed as follows.

1. Obstetric problems were reviewed under following definitions; prolonged rupture of membrane (PROM) as leakage of amniotic fluid over 18 hours prior to giving birth; maternal hypertensive disease as underlying essential hypertension, or pregnancy-induced hypertension, preeclampsia, eclampsia, or abruption of placenta caused by hypertension; preterm labor pain as pain caused by uterine contraction which occurred before 37 weeks of gestation and could not be controlled by medication; prenatal steroid as injection of betamethasone to mother prior to giving birth.
2. Perinatal clinical factors were reviewed including gestational age (GA) at birth, birth weight (BW), sex, Apgar score at 5-minute (5'-AS), and delivery method.
3. Postnatal clinical factors were investigated as following definitions; RDS as ground glass opacity in both lungs on chest X-ray with respiratory difficulties; patent ductus arteriosus (PDA) as an existence of hemodynamically significant shunt from aorta to pulmonary artery on echocardiography [9]; intraventricular hemorrhage (IVH) as intraventricular or intracerebral hemorrhage on ultrasonography of the brain [10]; Sepsis as positive result of culture from blood, urine, cerebrospinal fluid or other bodily fluid; NEC as stage ≥ 2 of modified Bell's classification [11]; BPD as a pulmonary condition which supplemental oxygen was necessary at 36 weeks of gestation or postnatal 28 days [12]; laboratory findings were reviewed on the day of sample collection by the Biobank of Korea.

After clinical laboratory tests from neonate with the 2nd day of life (range: 1–9), remnant blood was collected and stored at -80℃ till analysis.

2. Plasma MIF

Plasma MIF was measured by an enzyme-linked immunosorbent assay (ELISA) using a human MIF ELISA kit (LSBio, Seattle WA, US). The concentration was compared between preterm and term neonates. Comparisons of clinical characteristics were performed to investigate associating factor with MIF among 77 neonates. And then, MIF was statistically analyzed according to the presence of prematurity-related diseases such as RDS, PDA, IVH, NEC or BPD among the 42 preterm neonates.

3. Statistical analyses

Variables were reported as median and interquartile range (IQR), or number and percentage. Comparisons according to clinical factors were performed using Mann-Whitney U test or Fisher's exact test. The non-parametric Spearman test was used for assessment of correlation between continuous variables and the authors excluded one of them when the coefficient was more than 0.7. To investigate an associating factor with MIF in neonates, multivariate regression analysis was done among statistically significant factors on univariate comparisons. The *P*-value was set as < 0.05. Statistical analyses were performed using SPSS Statistics 25.0 (IBM, NY, US).

Results

1. Clinical characteristics of included neonates

A total of 77 neonates with $34^{6/7}$ weeks of gestation and weighed 2,340 g were included. Among them, 42 were born at 33 weeks of gestation (IQR: 31.9–34.3) and weighed 2,075 g (IQR: 1,690-2,270). Two prematurely born infants died after 5 and 12 months after birth because of sepsis and pneumonia, respectively. Clinical characteristics were described between the 2 groups at Table 1. The prenatal factors, sex, 5`-AS and breast milk feeding were not statistically different between the 2 groups. RDS, PDA, IVH, sepsis, NEC and hospital duration were significantly different between the 2 groups.

Table 1
Clinical characteristics of preterm and near or full-term neonates

Variables, n (%) or median (IQR)	Preterm neonates (N = 42)	Near or Full-Term neonates (N = 35)	*P* value
Prenatal Clinical characteristics			
Obstetric problems	33 (78.6)	30 (85.7)	0.556
PROM	11 (33.3)	12 (40.0)	
Maternal hypertensive disease	8 (24.2)	6 (20.0)	
Preterm labor pain	5 (15.2)	4 (13.3)	
Others	9 (27.3)	8 (26.7)	
Use of prenatal steroid	16 (38.1)	11 (32.4)	0.638
Multiple gestations	5 (11.9)	3 (8.6)	0.721
Vaginal delivery	15 (35.7)	12 (34.3)	1.0
Postnatal Clinical characteristics			
Gestation at birth, weeks	33.4 (31.9–34.3)	38.1 (37.0–39.0)	< 0.001
Birth weight, g	2,075.0 (1,690.0–2,270.0)	2,720.0 (2,430.0–3,150.0)	< 0.001
Female	17 (40.5)	16 (45.7)	0.653
5`-AS	9 (8–10)	9 (8–10)	0.202
Breast milk	13 (31.7)	12 (34.3)	1.0
RDS	23 (54.8)	2 (5.7)	< 0.001
PDA	14 (33.3)	0	< 0.001
IVH	7 (17.1)	2 (8.0)	0.464
Sepsis	12 (28.6)	2 (5.7)	0.016

Prolonged rupture of membrane (PROM) meant rupture of membrane over 18 hours before delivery. Maternal hypertensive disease included pregnancy-induced hypertension, preeclampsia, eclampsia, or abruption of placenta caused by hypertension or essential hypertension. Preterm labor pain meant labor pain occurred before 37 weeks of gestation, which could not be controlled by tocolytic agents. Others included oligohydramnios, polyhydramnios, meconium stained amniotic fluid, etc. Prenatal steroid meant use of betamethasone to mother before delivery. Definition of multiple gestations was two or more fetuses in a gestation. Sepsis was defined as late onset sepsis with a positive result of culture from blood, urine or cerebral fluid. *P* values were obtained using Mann-Whitney U or Fisher's exact test. Abbreviations; PROM, prolonged rupture of membrane; 5`-AS, Apgar Score at 5-minute; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

Variables, n (%) or median (IQR)	Preterm neonates (N = 42)	Near or Full-Term neonates (N = 35)	*P* value
NEC	9 (21.4)	0	0.003
BPD	4 (9.5)	0	0.121
Hospital stays, days	22.0 (14.0–41.0)	7.0 (5.0–10.0)	< 0.001
Mortality	2 (4.8)	0	0.498
Laboratory findings on the day of sample collection			
Nutrophils/uL	4,387.3 (3,043.8-7282.4)	6,034.0 (3,696.6-9,605.3)	0.054
Lymphocytes/uL	2,995.9 (2,506.5-3,955.1)	3,500.6 (2,592.8-4,806.7)	0.373
Monocytes /uL	849.0 (650.4-1,101.5)	975.1 (675.0–1,333.7)	0.331
C-reactive protein (mg/L)	0.6 (0.2, 1.2)	0.3 (0.1, 0.9)	0.501

Prolonged rupture of membrane (PROM) meant rupture of membrane over 18 hours before delivery. Maternal hypertensive disease included pregnancy-induced hypertension, preeclampsia, eclampsia, or abruption of placenta caused by hypertension or essential hypertension. Preterm labor pain meant labor pain occurred before 37 weeks of gestation, which could not be controlled by tocolytic agents. Others included oligohydramnios, polyhydramnios, meconium stained amniotic fluid, etc. Prenatal steroid meant use of betamethasone to mother before delivery. Definition of multiple gestations was two or more fetuses in a gestation. Sepsis was defined as late onset sepsis with a positive result of culture from blood, urine or cerebral fluid. *P* values were obtained using Mann-Whitney U or Fisher's exact test. Abbreviations; PROM, prolonged rupture of membrane; 5`-AS, Apgar Score at 5-minute; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

2. Plasma MIF and clinical factors

The median plasma MIF concentration was 4,534.1 pg/mL (IQR: 2,945.0–9,160.5), in total. MIF was not significantly different according to perinatal factors such as obstetric problems, use of prenatal steroid, number of gestation, delivery method, sex or feeding formula (Fig. 1). And it was not correlated with postnatal day (range: 1 to 9 days after birth, r = -0.101, P = 0.383). MIF was higher in preterm neonates (7,037.6 pg/mL, IQR: 3,285.2–12,267.4) than in term neonates (3,968.8 pg/mL, IQR: 2,566.4-6,995.2, P = 0.013, Fig. 1).

Among 42 preterm neonates, MIF was not statistically different according to RDS, PDA, IVH, sepsis or BPD. However, MIF was higher in NEC (n = 9, 12,170.9 pg/mL, IQR: 8,353.27-23,537.7) than in no NEC (n = 33, 5,189.6 pg/mL, IQR: 3,220.2-9,097.9, P = 0.016, Fig. 2) among 42 preterm neonates. When multivariate logistic regression analysis was performed among statistically significant clinical factors on univariate analyses to compensate the inter-current effect, high MIF concentration was associated with preterm neonates (4,177.41 ± 1,564.96 pg/mL, P = 0.009) and development of NEC (6,471.35 ± 2,258.25 pg/mL, P

= 0.005). BW was not considered as one of associating factors with MIF due to the high coefficient with GA at birth (r = 0.846, P < 0.001).

3. Plasma MIF and laboratory findings

To investigate whether MIF could be associated with laboratory findings, specific cell type and inflammatory marker were reviewed and statistical compared (Table 1). The number of neutrophil, lymphocyte, or monocyte using Beckman Coulter DxH 800 (Beckman Coulter, CA, US) was not significantly different between the 2 groups. Plasma MIF showed a weakly negative correlation with monocytes (r = -0.256, P = 0.024).

Discussion

MIF is a proinflammatory cytokine and plays a role in modulating diverse immune responses. It has been studied in diverse diseases in adults including sepsis, autoimmune disease, cancer and so on [4, 13, 14]. However, a few studies on the role of MIF in neonates have been reported and the clinical significance has been unclear. Recently, Roger et al reported that plasma MIF in healthy neonates was 10-fold higher than in adults, and MIF obtained from cord blood was lower in preterm neonates than in term [3]. Regarding to preterm birth, elevated MIF in cord blood and lower MIF in amniotic fluid were reported previously [15, 16]. In this study, MIF in preterm neonates was about 2-fold higher than that of term neonates (P = 0.013, Fig. 1). The previous reports had studied MIF from cord blood and amniotic fluid [3, 5, 15, 16], but we studied MIF in peripheral venous blood from the 2nd day-old neonates with diverse clinical conditions. In this study, higher MIF of preterm than term neonates was not associated with perinatal factors including obstetric problems, use of prenatal steroid, multi-gestation, mode of delivery, sex, or 5'-AS (Fig. 1). Although there was no statistically significant difference according to RDS, PDA, and IVH among preterm neonates (Fig. 2), unstable early clinical condition in preterm neonates compared to term neonates might affect to high MIF concentration in this study. There have been a few studies on the role of MIF in RDS and BPD [3, 17, 18]. It was emphasized that MIF could promote lung development, provoke hypoxia-induced lung injury in mice, and develop BPD [3, 17–19]. Apart from the previous studies, we found no significant difference in plasma MIF according to RDS or BPD among 42 preterm neonates (Fig. 2). The differences from the previous studies might be caused by different samples of cord blood or tracheal aspirates [3, 17], character or number of inclusions [3, 18], and species of mouse or human [17, 19]. Since BPD could be developed in preterm infants caused by multifactorial factors including arrest of lung development, mechanical trauma, oxygen toxicity, infection, inflammation, and presence of PDA, some limitation might exist for prediction of BPD based on MIF level in the early period of preterm neonate [20]. Although there have been many reports of MIF in sepsis in adults, the role of MIF in neonatal sepsis has been unclear. Roger et al. reported MIF can play a role in sustaining the innate immune response of neonate [5]. In our result, plasma MIF of neonates with sepsis was higher than those without sepsis but was not significantly different (median 8,180.65 pg/mL, IQR 3,871.28-13,110.33 vs. 5,379.14 pg/mL, IQR 3,044.88-11,810.20, P = 0.252). Further study with larger number of inclusions would be necessary.

MIF in preterm neonates who experienced NEC in later was noted at about 2-fold higher than that of preterm without NEC in this study, albeit small number of patients with NEC (n = 9, Fig. 2). NEC is a systemic devastating disease in prematurely born infants not confined to intestine [21]. Although the survival rate of preterm neonates has been increased, mortality or complication caused by NEC has not been decreased. The main risk factors of NEC are shown to be prematurity, bacterial colonization and formula feeds, which can disturb the inflammatory balance that consequently leads to bowel necrosis and systemic catastrophic state [22],[23]. However, the pathogeneses of NEC are still unclear. Recently, activation of Toll-like receptor 4 (TLR4) signaling has been focused on pathogenesis of NEC [24–26]. MIF could modulate a host immune response by regulating the expression of TLR4 to lipopolysaccharides in NEC [13, 27]. On the aspect of activation of pro-inflammatory response and TLR4 signaling in NEC, the authors tentatively suggested that MIF could play a role on the initiation of NEC and high MIF concentration of preterm neonate in the early postnatal period could be related with occurrence of NEC in later.

In the present study, MIF was negatively correlated with monocyte count (r = -0.256, P = 0.024). Neonatal monocyte can play phagocytic function and kill bacteria intracellularly, but their ability of signal amplification and cytokine production are significantly reduced, compared to monocyte in adult [28]. The weakly negative correlation between MIF and monocytes in this study might reflect reduced neonatal monocyte function and secretion of MIF from various cells other than monocyte, indirectly [4].

The authors found plasma MIF was higher in preterm neonates than in term during transitional period, and reviewed clinical characteristics in detail and tried to investigate clinical factors associated with MIF, unlike the previous reports [4, 15, 17, 19, 20, 29]. By comparing the concentration of MIF according to each prematurity-associated disease, higher MIF level in early postnatal period was statistically significant with the occurrence of NEC in later among preterm neonates. Further prospective research regarding the role of MIF in preterm neonates would be warranted.

Limitations

Retrospective and exploratory nature with small number of inclusions was the first. The second, we could not obtain additional MIF in neonates with NEC when the disease occurred. Hence, the change of MIF before and after NEC was not available. The third, since the remnant blood after clinical laboratory tests were used, more detailed investigation of specific neonatal immune cells using flow cytometry could not be performed because of insufficient amount of blood.

List Of Abbreviations

MIF, macrophage migration inhibitory factor; ELISA, Enzyme-linked Immunosorbent Assay; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; PROM, prolonged rupture of membrane; GA, gestational age at birth; BW, birth weight; 5’-AS, Apgar score at 5-

minute; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; IQR, interquartile range; TLR4, Toll-like receptor 4

Declarations

Ethics approval and consent to participate:

The study was reviewed and approved by the Institutional Review Board of our Hospital (GNUH 2018-06-007) in accordance with the Declaration of Helsinki.

Consent to publish:

The authors stated the consent for publication and attach the individual consent form with detail and image as supplementary material.

Availability of data and materials:

The datasets generated and analysed during the current study is available in the 'MIF_neonate_BMC.sav' as supplementary material.

Competing interests:

There was no potential competing interest to be declared by the authors.

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Authors' Contributions:

Ji Sook Park: Designing and conducting the study, and drafting the manuscript

Jin Su Jun: Conducting the study

Ji-Hyun Seo: Presenting the study

Jae Young Lim, Chan-Hoo Park, Hyang Ok Woo: Collecting data

Hee-Shang Youn: Interpreting data

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Figures

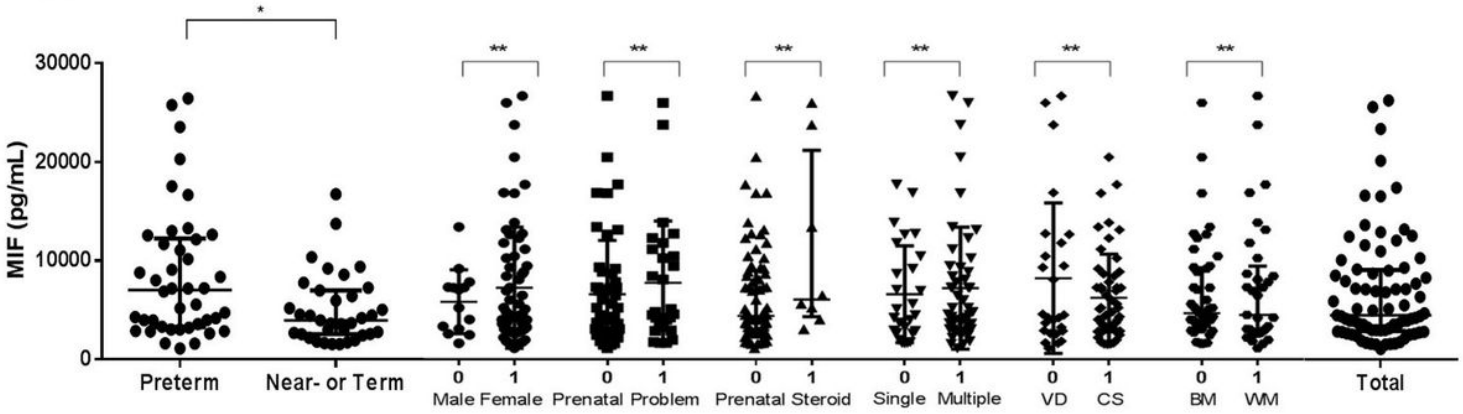

Figure 1

Comparisons of the plasma level of macrophage migration inhibitory factor (MIF) according to the perinatal variables among total 77 neonates. Data were presented as median with interquartile range. * P = 0.009 and ** P >0.05 were obtained by Mann-Whitney U test according to each clinical variable. Abbreviations: VD, vaginal delivery; CS, Cesarian section; BM, breast milk; WM, formula whole milk

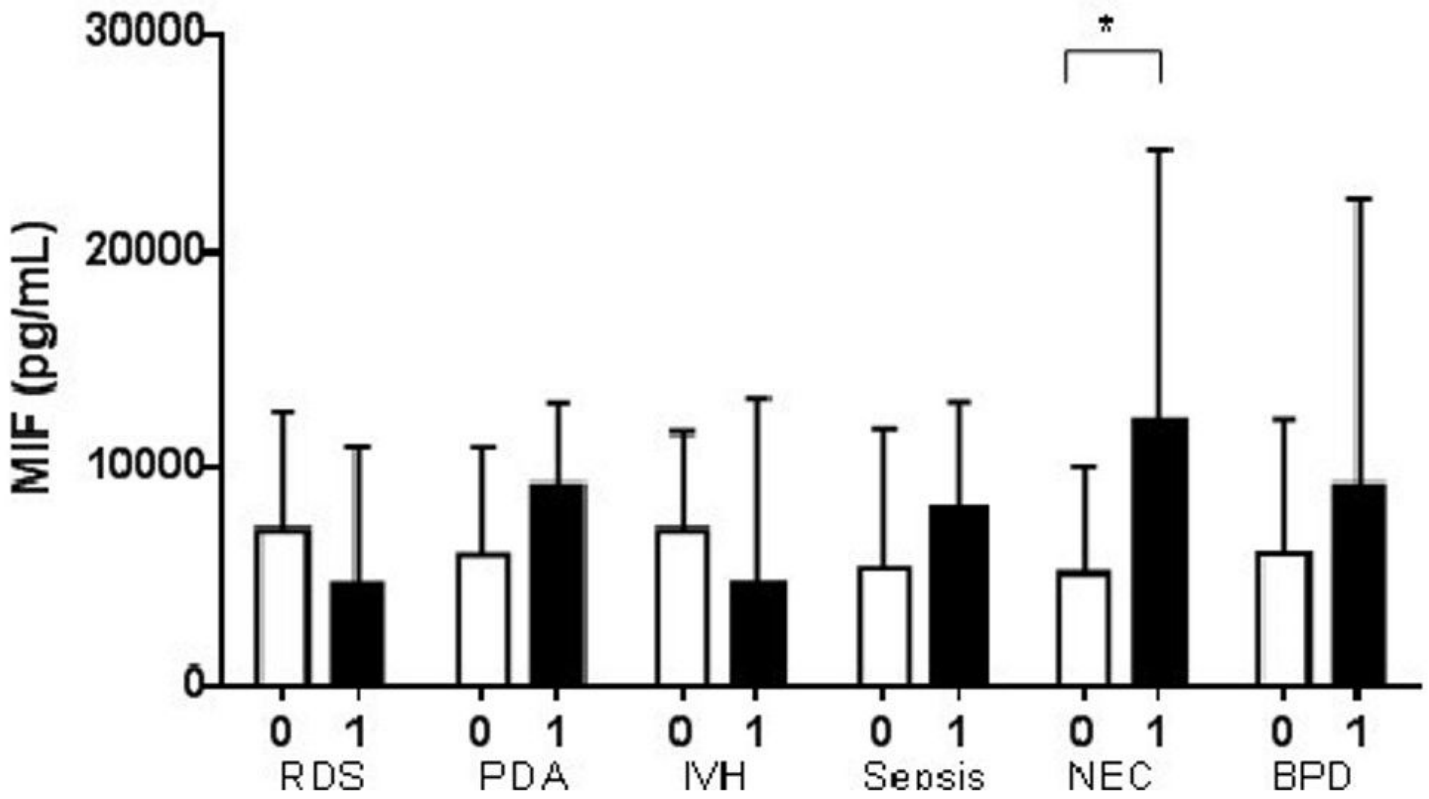

Figure 2

Macrophage migration inhibitory factor according to prematurity-associated disease among 42 preterm neonates born at ≤34 weeks of gestation. Zero (0) on X axis meant preterm neonates without disease, and 1 on X axis meant preterm neonates with disease. Data represented as median with interquartile range and * P=0.016 was obtained by Mann-Whitney U test according to NEC. Abbreviations: RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; N. jaundice, neonatal jaundice that required phototherapy; Sepsis, late onset sepsis; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

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