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Original Article

Risk factors of necrotizing enterocolitis-related mortality and patient survival: a preliminary prospective study

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Abstract

Background Necrotizing enterocolitis (NEC) is a prematurity-related complication of the gastrointestinal tract that affects 3-15% of preterm infants. Due to its atypical signs and symptoms, NEC is often diagnosed late, leading to mortality and morbidity.
Objective To describe the incidence, characteristics, and survival rate of preterm infants with NEC in the Neonatal Unit of Dr. Cipto Mangunkusumo Hospital.
Methods This prospective cohort study was conducted on preterm infants born in Dr. Cipto Mangunkusumo Hospital in 2019 who had NEC Bell stage 2 or higher. Subjects were recruited consecutively. The NEC was classified into either early-onset (<14 days of life) or late-onset (≥14 days of life). We identified the risk factors of mortality and survival using multiple Cox regression.
Results Within the study period, 55/639 preterm infants born in Dr. Cipto Mangunkusumo Hospital were diagnosed with NEC. Mean gestational age was 31.16 (SD 2.63) weeks and mean birth weight was 1,378.12 (SD 438.26) grams. The median age at NEC diagnosis was 6 (range 0-24) days. The most common symptoms were gastrointestinal bleeding (29.09%) and abdominal distension (29.09%). Plain abdominal radiographs showed dilated bowels in 92.72%, thickened intestinal walls in 83.63%, and pneumatosis intestinalis in 61.81% of subjects. Positive blood cultures were found in 63.63% of subjects, with *Staphylococcus epidermidis* and *Klebsiella pneumoniae* being the predominant organisms. Median survival was 27 days and 31 days for infants born at <32 weeks and ≥32 weeks gestational age, respectively (P=0.37). Median survival was 27 and 28 days in infants with early-onset and late-onset NEC, respectively (P=0.07), and 23 and 28 days in infants with birth weight of <1,000 grams and ≥1,000 grams, respectively (P=0.14).
Conclusion The incidence of NEC among preterm infants born in Dr. Cipto Mangunkusumo Hospital in 2019 was 8.6%. The survival rate of infants with NEC was 27.27%. Early-onset and late-onset NEC have similar mortality rates. **[Paediatr Indones. 2022;62:186-91 DOI: 10.14238/pi62.3.2022.186-91**].

Keywords: *necrotizing enterocolitis; preterm; gastrointestinal tract; survival rate; risk factor*

Necrotizing enterocolitis (NEC) commonly affects preterm infants in the neonatal intensive care unit (NICU). The incidence of NEC in developed countries varies from 2-7% in infants with a gestational age of <32 weeks, and 5-22% in infants with birth weight of <1,000 grams. Previous studies have shown that 11% of infants with a birth weight <750 grams develop NEC.[1] Of all NEC cases, 20-40% of infants require further surgical management, including laparotomy and bowel resection.[1] Other NEC-related issues, such as short bowel syndrome, cholestasis-related parenteral nutrition, and impaired growth and development, also contribute to extended length of stay and hospital charges.[1]

Prematurity is a primary risk factor of NEC, particularly for infants receiving enteral nutrition who were born at <34 weeks gestational age. The incidence falls to less than 10% in full-term infants. In developed countries, the incidence of NEC (Bell

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stage II and III) in preterm infants is associated with gestational age, birth weight, and the patient's geographical location.[2,3] The incidence of NEC in infants born at <28 weeks gestational age was lowest in Japan (2%) and highest in Australia, Canada, and Italy (7-9%).[2] The reported incidence of NEC in neonates born at a gestational age of 28-31 weeks was also lowest in Japan (0.2%), while iin other developed countries it varies around 2-3%. Similarly, NEC in very low birth weight (VLBW) infants also varied in incidence from 2% in Japan to 6-7% in the USA and 9% in Poland.[2-4] The differences in incidence rates between countries showed that different factors affect the development of NEC, including the environment, dietary patterns, and genetic tendencies.[2-4]

The diagnosis and disease progression of NEC is often difficult to predict, resulting in late management. Suspicions of NEC in a neonate would further affect medical management in providing enteral feeding, hence, NEC-related characteristics and survival data are needed to improve the diagnosis of NEC. We aimed to describe the incidence, characteristics, and survival of preterm infants diagnosed with NEC in the Perinatology Division of Dr. Cipto Mangunkusumo Hospital (CMH).

Methods

This prospective cohort study was conducted in the NICU of CMH, a tertiary referral hospital in Indonesia with a well-established neonatal unit. We included preterm infants born in CMH who were diagnosed with NEC and admitted to the NICU between January to December 2019. We excluded infants with multiple congenital anomalies and syndromes.

A NEC diagnosis was based on the modified Bell criteria,[5] which includes clinical signs and symptoms, such as abdominal distension, vomiting, orogastric tube (OGT) residue, and the presence of at least one radiologic abnormality, such as pneumatosis intestinalis, gas in the portal vein, or pneumoperitoneum.[5] Only infants with Bell stage 2 or above were included in this study. Based on the onset of symptoms, we divided NEC into two categories: early-onset NEC, which occurs in infants <14 days of age, and late-onset NEC, which occurs in infants ≥14 days of age.[6]

We collected the infants' demographic data, which included gestational age, method of delivery, APGAR score, birth weight, age and clinical symptoms at diagnosis, radiologic findings, and mortality. Descriptive analysis was conducted on the subjects' basic characteristics. Bivariate and multivariate survival analysis was conducted using multiple Cox regression to compute hazard ratio (HR) and 95% confidence interval. Risk factors with $P<0.2$ on bivariate analysis were entered in the multivariate analysis. The HR was considered statistically significant if its confidence interval did not include 1. Data analysis was done using *STATA v. 14* software. This study was approved by the Medical Research Ethics Committee of the Universitas Indonesia Medical School, as part of an ongoing prospective cohort observed since 2019.

Results

During the study period, 55/639 (8.6%) premature infants were diagnosed with NEC. The mean gestational age of subjects was 31.16 (SD 2.63) weeks, with the youngest born at 26 weeks. Subjects' mean birth weight was 1,378.12 (SD 438.26) grams; the lowest birth weight was 720 grams. Subject characteristics are shown in **Table 1**. Early-onset NEC was diagnosed in 46 infants and late-onset NEC in 9 infants . The mortality rate of infants with NEC in this study was 72.73%.

Median age at NEC diagnosis was 6 days (range 0 to 24 days). The most common clinical manifestations were gastrointestinal bleeding (29.09%), abdominal distension (29.09%), vomiting (12.7%), and desaturation (7.27%), as shown in **Table 2**. **Table 3** shows the radiologic workup results, which were remarkable for dilated bowels (92.72%), intestinal wall thickening (83.63%), pneumatosis intestinalis (61.81%), and foamy appearance (40.00%). Of all subjects, 35 (63.63%) had sepsis, as confirmed by positive blood culture. Culture results were predominantly *Staphylococcus epidermidis* (28.57%), followed by *Klebsiella pneumoniae* (25.71%) and *Acinetobacter sp.* (14.38%) (**Table 4**).

Median survival was not significantly different between infants with gestational age of <32 weeks *vs.* ≥32 weeks (27 *vs.* 31 days, log-rank P=0.37) (**Figure 1**) and between those with birth weight of <1,000 grams *vs.* ≥1,000 grams (23 *vs.* 28 days, log-rank P=0.14) (**Figure 2**). However, median survival was significantly

Table 1. Demographic characteristics of preterm infants with NEC at CMH in 2019

Characteristics	(N=55)
Gestational age, days	
Mean (SD)	31.16 (2.63)
Median (range)	31 (26-36)
Birth weight, grams	
Mean (SD)	1,378.12 (438.26)
Median (range)	1,365 (720-2470)
Cesarean section, n (%)	38 (69.09)
History of resuscitation, n (%)	
PPV during resuscitation	24 (43.63)
Intubation upon resuscitation	16 (29.09)
Median age at NEC diagnosis (range), days	6 (0-24)
Onset of NEC, n (%)	
Early-onset	46 (83.64)
Late-onset	9 (16.36)
NEC-related mortality, n (%)	40 (72.73)

Table 2. Clinical symptoms of preterm infants with NEC at CMH in 2019 (N=55)

Clinical symptoms	n(%)
Gastrointestinal bleeding	16 (29.09)
Abdominal distention	16 (29.09)
Vomiting	7 (12.72)
Gastric residue	2 (3.63)
Temperature instability	2 (3.63)
Decreased bowel sounds	2 (3.63)
Apnea	2 (3.63)
Others (discoloration, lethargy)	2 (3.63)

Table 3. Radiological imaging of preterm infants with NEC at CMH in 2019 (N=55)

Clinical symptoms	n(%)
Gastric and intestinal dilatation	51(97.72)
Intestinal wall thickening	46 (83.63)
Pneumatosis intestinalis	34 (61.81)
Foamy appearance	22 (40.00)
Abdominal cloaking	11 (20.00)
Pneumoperitoneum	7 (12.72)
Air fluid level	1 (1.81)

Table 4. Blood cultures of preterm infants with NEC at CMH in 2019

Blood culture results	(N=35)
Staphylococcus epidermidis	10 (28.57)
Klebsiella pneumoniae	9 (25.71)
Acinetobacter sp.	5 (14.38)
Staphylococcus aureus	2 (5.71)
Enterobacter cloacae	2 (5.71)
Staphylococcus saprophyticus	2 (5.71)
Enterococcus faecalis	1 (2.85)
Streptococcus alfanemoliticus	1 (2.85)
Enterobacter coli	1 (2.85)
Pseudomonas aeruginosa	1 (2.85)
Pantoea sp.	1 (2.85)

lower in early-onset compared to late-onset NEC (27 *vs.* 28 days, log-rank P=0.07) (**Figure 3**).

Bivariate analysis revealed that intubation upon resuscitation, onset of NEC, and birth weight had the lowest P values compared to the other risk factors (**Table 5**) and were therefore entered in the multivariate analysis. On multivariate analysis, however, neither variable were significantly associated with mortality (**Table 6**).

Discussion

Our subjects had higher mean gestational age and birth weight than infants with NEC in other studies. A study found that 27% of infants with NEC had very low birth weight (VLBW) or <1,000 grams,[7] while only 12/55 (22%) of our subjects had VLBW.[7] This difference might have been due to the low survival rate in our neonatal unit for infants weighing <1,000 grams, due to the limited capability in our hospital. From January to mid-2020, survival of extremely preterm infants in CMH increased from 12.22% to 13.80% due to better management of preterm infants, but this occurred after the time of our study.

Nutrition guidelines for preterm infants were revised in 2020 to recommend commencing enteral feeding in preterm infants as soon as the infants were stable. This revision may have caused the NEC incidence increase in the extremely preterm group, from 0.46% in 2019 to 4.40% in 2020. Moreover, the incidence of NEC was lower iin the late preterm group, which was likely due to better management in preterm infants. We commenced a new feeding protocol in 2018 which supported early enteral feeding in preterm infants, which may explain the improvement

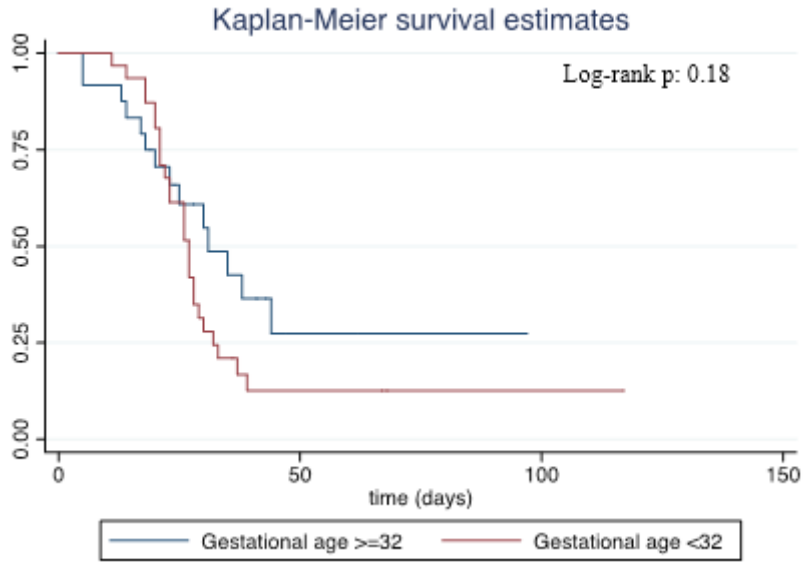

Figure 1. Survival curve of preterm infants with NEC based on gestational age group

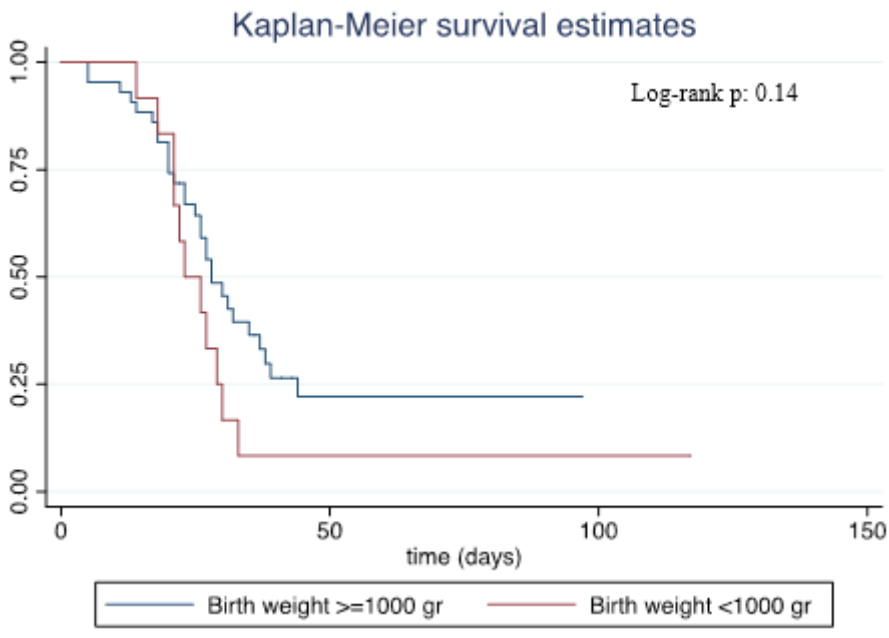

Figure 2. Survival curve of preterm infants with NEC based on birthweight group

in late preterm infants. However, the incidence of NEC decreased from 16.64% in 2018 to 8.6% in 2019.

The incidence of NEC in CMH was higher (8.6%) than that in several studies, such as that of Battersby *et al*.[2] who reported an incidence of 2-7%. Another study reported that an exclusively human milk diet through 33 weeks post-menstrual age may reduce the incidence of NEC associated with enteral feeding.[8] The prevalence of exclusive breastfeeding in preterm infants in CMH was still very low, mostly due to lack of breast milk and complications of preterm infants. Instead, we commenced predominant breastfeeding, targeting at

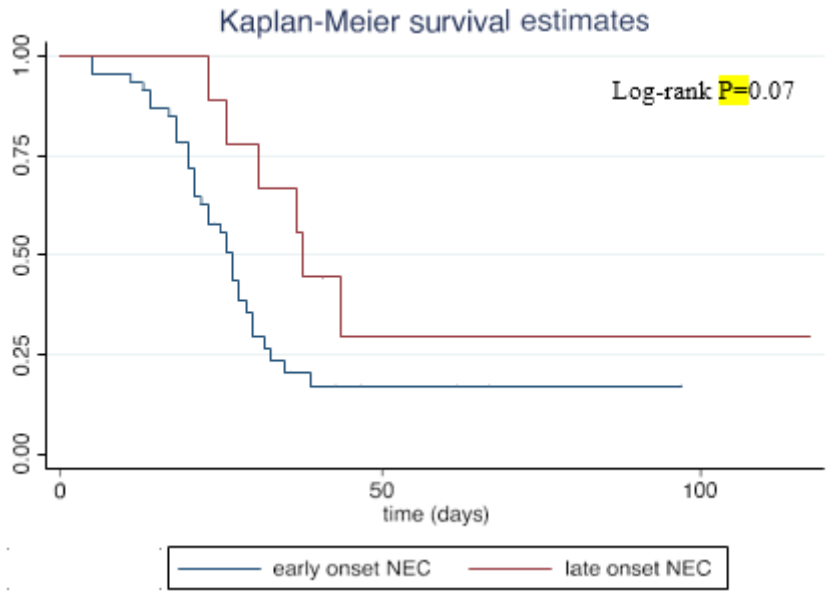

Figure 3. Survival curve of preterm infants with NEC based on NEC onset group

Table 5. Risk factors of NEC related to infant survival (Bivariate analysis)

Survival	Risk Factors		HR (95% CI)	P value
	Yes n=15	No n=40		
Gestational age			1.54 (0.80 to 2.97)	0.19
<32 weeks	5 (9.09)	26 (47.27)		
≥32 weeks	10 (18.18)	14 (25.45)		
Birth weight			1.65 (0.82 to 3.34)	0.15
<1000 gram	1(1.81)	11 (20.00)		
≥1000 gram	14(25.45)	29 (52.72)		
Positive-pressure ventilation on resuscitation			1.27 (0.68 to 2.36)	0.45
Yes	4 (7.27)	20 (36.36)		
No	11 (20.00)	20 (36.36)		
Intubation on resuscitaion			1.75 (0.91 to 3.34)	0.08
Yes	1 (1.81)	15 (27.27)		
No	14 (25.45)	25 (45.45)		
Onset NEC			0.45 (0.19 to 1.10)	0.08
Early	12 (21.81)	34 (61.81)		
Late	3 (5.45)	6 (10.90)		

Table 6. Multivariate analysis of risk factors related to NEC infant mortality

Risk factors	Adjusted HR (95%CI)	P value
Birth weight <1,000 gr	1.48 (0.71 to 3.10)	0.28
Late-onset NEC	0.42 (0.17 to 1.04)	0.06
Intubation upon resuscitation	1.65 (0.84 to 3.24)	0.14

least 65% human milk from the total enteral feeding.

The immaturity of the gastrointestinal tract may increase the colonization of pathogenic bacteria. *Staphyloccocus epidermidis* was found as the predominant pathogen of sepsis in preterm infants.[9] A strong association was found between these species and

inflammation-related neonatal morbidities such as NEC.[9] A previous study showed that NEC incidence in extremely preterm infants with *S. epidermidis* was nearly two times higher than in non-sepsis infants.[9]

The establishment of a NEC diagnosis before infants were 14 days old was linked to a higher risk of mortality.[5] We noted that the median infant age upon NEC diagnosis was at day 6 of life. Most infants in our study (83.63%) suffered from early-onset NEC. Risk factors of early-onset NEC were associated with greater gestational age and vaginal delivery.[6] However, in our study, multivariate logistic regression showed that extremely low birth weight, late-onset NEC, and intubation on resuscitation were not significantly associated with NEC. A study found that early-onset NEC was characterized by higher rate of stage III NEC compared to late-onset NEC.[5]

In our study, we had very few subjects with late-onset NEC. More subjects are needed to further investigate factors influencing the survival of infants with early-onset and late-onset NEC. Preterm infants who had NEC also need to be followed-up until later childhood, to evaluate whether the occurrence of NEC in early life had an impact on long-term outcomes in growth and development.

In conclusion, in 2019, the overall incidence of NEC in CMH was higher than that reported by other centers and networks. Mean gestational age of infants with NEC was 31.16 (SD 2.63) weeks and mean birth weight was 1,378.12 (SD 438,26) grams. Early-onset NEC was the most frequent type, presenting at median age of 6 days. The most common clinical symptoms were gastrointestinal bleeding and abdominal distension, while radiologic findings showed dilated and intestinal wall thickening. Predominant organisms on blood cultures were *Staphylococcus epidermidis* and *Klebsiella pneumoniae*. Future studies with a larger sample size are required to understand the etiology and risk factors of NEC.

Conflict of interest

None declared.

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