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Research Article

Predictive Factors for Surgery in Preterm Neonates with Necrotizing Enterocolitis: A Retrospective Cohort Study

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Abstract

Objectives: Necrotizing enterocolitis (NEC) is a severe neonatal condition. This study aimed to assess predictive factors for surgical treatment in preterm neonates with NEC in a Tunisian center.

Methods: We present a retrospective study including all neonates treated for NEC between January 01, 2010 and March 31, 2022.

Results: Within the study period, 102 patients were included, with an overall survival of 47%. Most of our patients were male (64.7%), with low birth weight or less (100%), 5-min Apgar score ≥8 (79.4%), and Bell's stage II (66.7%). Multivariate logistic analyses demonstrated that gestational age <30 weeks (p=0.002, odds ratio [OR]=4.544), birth weight <1000 g (p=0.001, OR=5.750), NEC onset <7 days (p<0.001, OR=5.667), not being breastfed (p=0.019, OR=3.026), and C-reactive protein level >20 mg/L (p=0.020, OR=2.942) were associated with the need for surgical treatment in neonates with NEC.

Conclusion: Our findings would be helpful in refining treatment modalities for better disease outcomes.

Keywords: Bell's staging criteria, breastfeeding, C-reactive protein, Necrotizing enterocolitis, surgery

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Necrotizing enterocolitis (NEC) is a serious neonatal condition.[1] In the absence of reliable epidemiologic data, the true incidence of NEC remains to be unknown. This incidence varies from 2% to 17% in preterm infants.[2] The etiopathogenesis of NEC is complex, and several factors have been incriminated in the pathogenesis of this condition, including genetic factors, highly immune-reactive intestinal mucosa, abnormal microbial colonization, and the immaturity of the intestine.[3,4] During the last three decades, there has been significant progress in neonatal intensive care with an increased incidence of prematurity. This has led to an increase in the incidence of NEC.[2] Many therapeutic strategies have been developed to prevent NEC, including breastfeeding, prenatal glucocorticoid administration, and probiotic supplementation. However, this condition is still common in neonatal intensive care units.[5-8]

Many researchers have studied the correlation between perinatal, clinical, and laboratory factors and the clinical deterioration of neonates with NEC, ultimately requiring surgical management. However, these factors did not find widespread use due to conflicting results.[9-12] Moreover, most studies regarding NEC management are from high-income countries. Our study aimed to assess predictive factors for surgical treatment in preterm neonates with NEC in a Tunisian center.

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Methods

Subjects and NEC Staging

In the present study, we included all neonates treated for NEC between January 01, 2010 and March 31, 2022. Data were collected retrospectively using the patients' medical records. The diagnosis and staging of NEC were defined using modified Bell's staging classification.[13] The exclusion criteria included incomplete medical records, gestational age ≥37 weeks, and Bell's stage I (suspected NEC). This study was approved by the ethical committee of the University of Sfax, Tunisia (HCH/022/1123).

NEC Management in Our Institution

All neonates with suspected or confirmed NEC receive the same medical management in our institution. Medical treatment includes withholding feeds, parenteral nutrition, nasogastric tube placement for gut decompression, IV fluid resuscitation, and IV antibiotics with activity against Gram-negative, Gram-positive, and anaerobic bacteria. In our practice, a combination of three antibiotics is given in accordance with the guidelines of the Surgical Infection Society and the Infectious Diseases Society of America.[14] This combination includes gentamicin, ampicillin, and metronidazole or cefotaxime, ampicillin, and metronidazole. Vancomycin is prescribed instead of ampicillin if ampicillin-resistant infection or methicillin-resistant Staphylococcus aureus is suspected.

Inotropic support and intubation may be necessary for hemodynamically unstable neonates. Thereafter, close monitoring and possible correction of electrolyte and glucose levels are ensured. Serial complete blood counts are conducted to detect thrombocytopenia and anemia. Serial abdominal examinations and radiographs are performed to assess for disease progression and to detect intestinal perforation early. In our practice, oral feeding is initiated when the following three criteria are met: gastric residue <1 mL/kg/day, absence of bilious gastric residue, and presence of intestinal sounds.

Surgery is indicated in patients with pneumoperitoneum on abdominal X-ray and those with clinical deterioration, including worsening abdominal findings, hemodynamic instability, the requirement of inotropes, and declining laboratory values. In our institution, laparotomy is the gold standard approach for patients needing surgical management. However, in high risk neonates, we insert a peritoneal drain through a percutaneous approach as a temporary measure to delay laparotomy.

Predictive Factors for Surgery

The following predictive factors were evaluated: sex, mode of delivery, birth weight, gestational age, 1-min Apgar score, 5-min Apgar score, NEC onset, mechanic ventilation exposure, mechanic ventilation duration, parenteral feeding duration, C-reactive protein (CRP) level, hemoglobin level, white blood cell (WBC) count, and platelet count.

Bias

We trained and coached local investigators to minimize selection bias. We tried to include all patients with NEC using the X-ray and ultrasound databases.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics package, version 21. We used chi-square tests and Student's t-tests to compare categorical variables and continuous variables, respectively. The univariate analysis enabled us to identify factors associated with surgical NEC. Statistically significant variables were included in the multivariate analysis. A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

One hundred forty-six neonates were treated for NEC during the study period. Three neonates with missing data in the medical records, 13 neonates with gestational age ≥37 weeks, and 28 neonates with Bell's stage I were excluded from the study, with 102 patients remaining for analysis.

The 102 patients were divided into two groups. The surgical NEC group included 25 (24.5%) neonates, and the medical NEC group comprised 77 (75.5%) neonates. Most of our patients were male (64.7%), with low birth weight or less (100%), 5-min Apgar score ≥8 (79.4%), and Bell's stage II (66.7%). The mortality rate was 53% (Table 1).

Univariate Analysis of Deceased Versus Survivor Groups

Outcomes of the univariate analysis showed that patients in the surgical NEC group had lower gestational age, lower birth weight, earlier onset of NEC, and higher CRP level than those in the medical NEC group. There was no correlation between the need for surgical management and 1-min Apgar score, 5-min Apgar score, mechanic ventilation duration, parenteral feeding duration, WBC count, platelet count, and hemoglobin level (Table 2).

Multivariate Analysis of Deceased Versus Survivor Groups

Multivariate logistic regression analysis showed that gestational age <30 weeks (p=0.002, odds ratio [OR] =4.544), birth weight <1000 g (p=0.001, OR=5.750), NEC onset <7 days (p<0.001, OR=5.667), not being breastfed (p=0.019,

Table 1. Baseline characteristics of neonates with NEC in our institution

Characteristics	n (%)
Sex	
Male	66 (64.7)
Female	36 (35.3)
5-min Apgar score	
<8	21 (20.6)
≥8	81 (79.4)
Birth weight (g)	
Normal birth weight (≥2500)	0 (0)
Low birth weight (<2500)	38 (37.2)
Very low birth weight (<1500)	46 (45.1)
Extremely low birth weight (<1000)	18 (17.7)
Platelet count (/mm^3)	
Thrombocytosis (>350,000)	12 (11.8)
Normal (≥150,000–350,000)	51 (50)
Moderate thrombocytopenia (<150,000)	17 (16.7)
Severe thrombocytopenia	22 (21.5)
NEC staging	
IIA	51 (50)
IIB	17 (16.7)
IIIA	13 (12.7)
IIIB	21 (20.6)
Type of treatment	
Conservative	77 (75.5)
Operative	25 (24.5)
Decreased	
Yes	54 (53)
No	48 (47)

OR=3.026), and CRP level >20 mg/L (p=0.020, OR=2.942) were associated with the need for surgical treatment in neonates with NEC (Table 3).

Discussion

NEC is the most common severe gastrointestinal condition in preterm infants. It is associated with a significant risk of death and long-term morbidity in survivors.[14] In our study, we included only preterm infants with NEC. Increasing evidence indicates that NEC in full-term neonates is different from that in preterm newborns.[15, 16]

Identifying predictive factors for progression to surgery in patients with NEC is important. In our daily practice, the absence of a clear pneumoperitoneum on an abdominal X-ray makes it challenging to decide if the patient needs a surgical intervention. According to Kosloske[17], physical signs, such as abdominal wall erythema and a fixed abdominal mass, are reliable criteria for intestinal necrosis. Kosloske[17] also recommended the use of portal venous gas as a strong predictive factor for surgery. However, in their study including 194 neonates with NEC, Sharma et al.[18] concluded that surgery should not be based on portal venous gas alone because half of these infants survive without the need for surgery. Diez et al.[19] proposed a simple clinicoradiological scoring system to determine the timing of surgery in infants with NEC. This score is based on three criteria: pathological findings on abdominal ultrasound, red blood cell transfusion, and cardiac disease.

In our study, the mortality rate of 53% was similar for the surgical and medical NEC groups. Although El Hassani et al.[12] reported a significantly lower survival rate in patients with surgical NEC, Cho et al.[20] found no correlation between the type of treatment and outcomes in patients with NEC.

NEC remains to be a significant cause of mortality despite the progress made in managing this disease in both medical and surgical components. The mortality rates of NEC are highly variable, ranging from 11% to 58.9%.[20]

Table 2. Univariate analysis of surgical vs. medical NEC groups

	Surgical NEC Group (n=25)	Medical NEC Group (n=77)	p*
Gestational age (weeks), median [IQR]	29.6 [28.1-31.5]	32.2 [29.6-32.5]	0.006
Birth weight (g), median [IQR]	1300 [835-1450]	1450 [1080-1800]	0.008
1-min Apgar, mean (SD)	5.1 (2)	4.7 (1.9)	0.369
5-min Apgar, mean (SD)	7.6 (1.3)	7.5 (1)	0.564
NEC onset (days), median [IQR])	6 [5-7]	9 [6-22]	<0.001
Mechanic ventilation (days), median [IQR]	3 [1-12]	3 [2-5]	0.634
Parenteral feeding duration (days), median [IQR]	10 [7-14]	10 [5-15]	0.832
WBC Count** (× 109/ L), median [IQR]	15.5 [5.8-20.7]	9.2 [3.8-18]	0.102
Hemoglobin** (mmol/L), mean (SD)	12.1 (4.4)	11.8 (3.6)	0.807
Platelet count** (×109/L), median [IQR]	225 [100-381]	155 [124-245]	0.251
CRP** (mg/L), median [IQR]	20 [9-99]	7 [2-45]	0.017

IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; * p Value has been bolded if p < 0.05; ** At disease presentation.

Table 3. Multivariate analysis of surgical vs. medical NEC groups

	Surgical NEC Group (n=25)	Medical NEC Group (n=77)	p*	Odds Ratio
Gender male, n (%)	15 (60)	51 (66.2)	0.571	-
Gestational age<30 weeks, n (%)	12 (48)	13 (16.9)	0.002	4.544
Birth weight <1000 g, n (%)	10 (40)	8 (10.4)	0.001	5.750
Vaginal delivery, n (%)	8 (32)	28 (36.4)	0.692	-
NEC onset < 7 days, n (%)	17 (68)	21 (27.3)	<0.001	5.667
Mechanic ventilation exposure, n (%)	16 (64)	37 (48)	0.165	-
Not being breastfed, n (%)	12 (48)	18 (23.4)	0.019	3.026
CRP > 20 mg/L	15 (60)	26 (33.8)	0.020	2.942
Mortality in hospital	15 (60)	39 (50.6)	0.416	-

* p Value and Odds ratio have been bolded if p < 0.05.

This study showed that patients with medical NEC had higher birth weight and gestational age. Our study is consistent with the literature. Many authors have identified low gestational and low birth weight as being associated not only with NEC incidence, severity, and mortality but also with long-term neurodevelopmental impairment in survivors.[14, 21-25]

Our study showed that NEC onset <7 days was associated with the need for surgical management in patients with NEC. Several studies have assessed the relationship between time of onset of NEC symptoms and aggravation of the disease requiring surgical treatment. Most of these studies have found that earlier onset of NEC was strongly associated with the surgical stage of this disease.[12, 26, 27] El Hassani et al.[12] suggested that intestinal maturation, occurring gradually after birth, reduces the risk of advanced NEC in premature infants. In accordance with these findings, Saleem et al.[28] demonstrated that the maturation of the intestinal barrier in these infants depends on gestational age and postnatal age.

Interestingly, patients not being breastfed had a threefold higher risk of surgery than that receiving breast milk alone or in combination. Many authors highlighted the role of breast milk in preventing many prematurity conditions, including NEC, retinopathy of prematurity, bronchopulmonary dysplasia, and sepsis.[29,30] Providing human milk in neonatal intensive care units also has strong economic benefits.[30] In accordance with these findings, Furman et al.[29] demonstrated that the beneficial effect of breast milk exists not only in exclusive feeding but also in partial feeding.

In a prospective study including 926 infants, Lucas et al.[31] compared formula-fed babies with breastfed babies. They found that the risk of developing NEC was 6–10 times lower in patients receiving breast milk alone. Sullivan et al.[32] performed a multicenter trial including 207 premature neonates. They demonstrated that neonates receiving formula-feeding products had a significantly higher incidence of NEC and surgical NEC than those receiving exclusive breast milk feeding.

Breast milk contains a wide diversity of bioactive substances involved in intestinal maturation, regulation of intestinal cell proliferation and differentiation, immune homeostasis, and infant growth.[33] It has been demonstrated that these components, including immune cells, cytokines, immunoglobulins, and growth factors, pass into the breast milk and are transferred to the infant.[34] The absence of these bioactive substances and the presence of foreign bovine proteins can disrupt the intestinal epithelial barrier leading to inflammation, immune disorders, and microbiota dysbiosis. Intestinal dysbiosis, which is an alteration of the composition of the intestinal flora, is a crucial determinant of the progression of NEC.[35]

The correlation between NEC and several breast milk components still needs more research. Several trials have been conducted on integrating some breast milk components, such as probiotics, in premature infants have been carried out. These studies aimed to prevent NEC incidence and severity, usually leading to surgical treatment. The results of this research are promising.[36]

Our study revealed that CRP >20 mg/L is predictive for surgical management in neonates with NEC. In the study of El Hassani et al.[12] including 73 preterm infants with NEC, no correlation between CRP level and need for surgery was found. However, most authors highlighted the role of high CRP level, which reflects the magnitude of systemic inflammation, as a risk factor for surgery in infants with NEC.[20,37,38] In patients with NEC, CRP plays an important role not only in the therapeutic decision but also in predicting pre- and posttherapeutic complications.[39] In a recent study including 191 neonates with nonperforated NEC, Mohd Amin et

al.[40] found that high CRP/albumin ratio (>3) is strongly associated with surgery and mortality.

Our study is one of the few works performed in low-income countries investigating predictive factors for surgery in preterm neonates with NEC. These predictive factors would be helpful to develop and validate a management score, accurately dividing patients into four categories (low, intermediate, high, and very high risk of surgery). Such a score would be of great interest in clinical practice and research. However, our study has some limitations. The first one was the retrospective nature of the study. Therefore, it was possible to have some bias and errors in data extraction. The second limitation was the monocentric nature of this study. Consequently, we believe that further prospective studies would be of great value in validating the identified predictive factors.

Conclusion

Our study showed that birth weight <1000 g, gestational age <30 weeks, NEC onset <7 days, not being breastfed, and CRP level >20 mg/L were predictive factors for surgical treatment in neonates with NEC. These factors would be helpful to refine treatment modalities for better disease outcomes. However, further prospective multicenter cohort studies with a consensual definition of NEC are needed to validate these factors.

Disclosures

Ethics Committee Approval: This study was approved by the ethical committee of the University of Sfax, Tunisia (HCH/022/1123).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.Z., A.B.H.; Design – M.Z., H.B.A.; Supervision – M.Z., R.M.; Materials – N.B.S.; Data collection &/or processing – N.K., O.G.; Analysis and/or interpretation – M.Z., H.B.A.; Literature search – M.Z., N.B.S.; Writing – M.Z.; Critical review – R.M.

References

1. Zozaya C, García González I, Avila-Alvarez A, Oikonomopoulou N, Sánchez Tamayo T, Salguero E, et al. Incidence, treatment, and outcome trends of necrotizing enterocolitis in preterm infants: A multicenter cohort study. Front Pediatr 2020;8:188.
2. Alsaied A, Islam N, Thalib L. Global incidence of necrotizing enterocolitis: A systematic review and meta-analysis. BMC Pediatr 2020;20:344. [CrossRef]
3. Ginglen JG, Butki N. Necrotizing enterocolitis. [Updated 2021 Aug 13]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK513357/. Accessed Dec 19, 2022.
4. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med 2011;364:255–64. [CrossRef]
5. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2014;4:CD005496. [CrossRef]
6. Good M, Sodhi CP, Hackam DJ. Evidence-based feeding strategies before and after the development of necrotizing enterocolitis. Expert Rev Clin Immunol 2014;10:875–84.
7. Halac E, Halac J, Bégué EF, Casañas JM, Indiveri DR, Petit JF, et al. Prenatal and postnatal corticosteroid therapy to prevent neonatal necrotizing enterocolitis: a controlled trial. J Pediatr 1990;117:132–8. [CrossRef]
8. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics 2010;125:921–30. [CrossRef]
9. Bhatt D, Travers C, Patel RM, Shinnick J, Arps K, Keene S, et al. Predicting mortality or intestinal failure in infants with surgical necrotizing enterocolitis. J Pediatr 2017;191:22–7.e3.
10. Markel TA, Engelstad H, Poindexter BB. Predicting disease severity of necrotizing enterocolitis: how to identify infants for future novel therapies. J Clin Neonatol 2014;3:1–9. [CrossRef]
11. Srinivasjois R, Nathan E, Doherty D, Patole S. Prediction of progression of definite necrotising enterocolitis to need for surgery or death in preterm neonates. J Matern Fetal Neonatal Med 2010;23:695–700. [CrossRef]
12. El Manouni El Hassani S, Niemarkt HJ, Derikx JPM, Berkhout DJC, Ballón AE, de Graaf M, et al. Predictive factors for surgical treatment in preterm neonates with necrotizing enterocolitis: A multicenter case-control study. Eur J Pediatr 2021;180:617–25. [CrossRef]
13. Patel RM, Ferguson J, McElroy SJ, Khashu M, Caplan MS. Defining necrotizing enterocolitis: current difficulties and future opportunities. Pediatr Res 2020;88:10–5. [CrossRef]
14. Qian T, Zhang R, Zhu L, Shi P, Yang J, Yang CY, et al; Chinese Collaborative Study Group for Neonatal Necrotizing Enterocolitis. Necrotizing enterocolitis in low birth weight infants in China: Mortality risk factors expressed by birth weight categories. Pediatr Neonatol 2017;58:509–15.
15. Kinstlinger N, Fink A, Gordon S, Levin TL, Friedmann P, Nafday S, et al. Is necrotizing enterocolitis the same disease in term and preterm infants? J Pediatr Surg 2021;56:1370–4.
16. Frid G, Reppucci M, Lum T, Paul M, Seiden H, Coakley BA. Comparison of necrotizing enterocolitis in pre-mature infants vs. term-born infants with congenital heart disease. Front Pediatr 2021;9:802607. [CrossRef]
17. Kosloske AM. Indications for operation in necrotizing enterocolitis revisited. J Pediatr Surg 1994;29:663–6. [CrossRef]
18. Sharma R, Tepas JJ 3rd, Hudak ML, Wludyka PS, Mollitt DL, Garrison RD, et al. Portal venous gas and surgical outcome of neonatal necrotizing enterocolitis. J Pediatr Surg 2005;40:371–6.
19. Diez S, Bell LE, Moosmann J, Weiss C, Müller H, Besendörfer

M. Prediction of high bell stages of necrotizing enterocolitis using a mathematic formula for risk determination. Children (Basel) 2022;9:604. [CrossRef]
20. Cho A, Ko D, Youn J, Yang HB, Kim HY. Characteristics of surgical necrotizing enterocolitis: is it different from medical necrotizing enterocolitis? a single-center retrospective study. Children (Basel) 2021;8:1148.
21. Siahaan ESED, Adriansyah W, Sasmita AP, Fauzi AR, Dwihantoro A, Gunadi. Outcomes and prognostic factors for survival of neonates with necrotizing enterocolitis. Front Pediatr 2021;9:744504. [CrossRef]
22. Rose AT, Patel RM. A critical analysis of risk factors for necrotizing enterocolitis. Semin Fetal Neonatal Med 2018;23:374–9.
23. Mara K, Clark R, Carey WA. Necrotizing enterocolitis in very low birth weight neonates: A natural history study. Am J Perinatol 2022 Sep 16. doi: 10.1055/a-1851-1692. [Epub ahead of print]. [CrossRef]
24. Jones IH, Hall NJ. Contemporary outcomes for infants with necrotizing enterocolitis-a systematic review. J Pediatr 2020;220:86–92.e3.
25. Wadhawan R, Oh W, Hintz SR, Blakely ML, Das A, Bell EF, et al; NICHD Neonatal Research Network. Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis. J Perinatol 2014;34:64–70. [CrossRef]
26. Duci M, Fascetti-Leon F, Erculiani M, Priante E, Cavicchiolo ME, Verlato G, et al. Neonatal independent predictors of severe NEC. Pediatr Surg Int 2018;34:663–9.
27. Liu Y, Qiao L, Wu X, Jiang Z, Hao X. Predictive factors for the surgical treatment of necrotizing enterocolitis in preterm infants: A single-center retrospective study. BMC Pediatr 2022;22:9.
28. Saleem B, Okogbule-Wonodi AC, Fasano A, Magder LS, Ravel J, Kapoor S, et al. Intestinal barrier maturation in very low birthweight infants: Relationship to feeding and antibiotic exposure. J Pediatr 2017;183:31–6.e1. [CrossRef]
29. Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. Arch Pediatr Adolesc Med 2003;157:66–71.
30. Johnson TJ, Patel AL, Bigger HR, Engstrom JL, Meier PP. Economic benefits and costs of human milk feedings: a strategy to reduce the risk of prematurity-related morbidities in very-low-birth-weight infants. Adv Nutr 2014;5:207–12.
31. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet 1990;336,1519–23. [CrossRef]
32. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010;156:562–7.e1 [CrossRef]
33. Patel AL, Kim JH. Human milk and necrotizing enterocolitis. Semin Pediatr Surg 2018;27:34–8.
34. Nolan LS, Parks OB, Good M. A review of the immunomodulating components of maternal breast milk and protection against necrotizing enterocolitis. Nutrients 2019;12:14.
35. Altobelli E, Angeletti PM, Verrotti A, Petrocelli R. The impact of human milk on necrotizing enterocolitis: a systematic review and meta-analysis. Nutrients 2020;12:1322. [CrossRef]
36. Beghetti I, Panizza D, Lenzi J, Gori D, Martini S, Corvaglia L, et al. Probiotics for preventing necrotizing enterocolitis in preterm infants: a network meta-analysis. Nutrients 2021;13:192.
37. Yu L, Liu C, Du Q, Ma L. Predictive factors for surgical intervention in neonates with necrotizing enterocolitis: A retrospective study. Front Surg 2022;9:889321. [CrossRef]
38. Ibrohim IS, Pratama HA, Fauzi AR, Iskandar K, Agustriani N. Association between prognostic factors and the clinical deterioration of preterm neonates with necrotizing enterocolitis. Sci Rep 2022;12:13911.
39. Gaudin A, Farnoux C, Bonnard A, Alison M, Maury L, Biran V, et al. Necrotizing enterocolitis (NEC) and the risk of intestinal stricture: the value of C-reactive protein. PloS One 2013;8:e76858. [CrossRef]
40. Mohd Amin AT, Zaki RA, Friedmacher F, Sharif SP. C-reactive protein/albumin ratio is a prognostic indicator for predicting surgical intervention and mortality in neonates with necrotizing enterocolitis. Pediatr Surg Int 2021;37:881–6.