

Newborn risk factors of necrotizing enterocolitis in developing countries: A literature review

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Abstract

Necrotizing enterocolitis (NEC) is the most prevalent multifactorial gastrointestinal emergency and a leading cause of mortality amongst preterm neonate admitted to the neonatal intensive care unit. The disease progress rapidly once clinical signs are present thus increasing the likelihood of death. Identifying major risk factors associated with this disease can help determine who is most at risk and be given targeted early preventive action to increase survival rate. The purpose of this literature review is to provide a comprehensive NEC neonatal risk factor mapping for neonates in developing countries. By incorporating and elaborating upon existing research findings, this review aims to offer an extensive analysis of this crucial health problem.

Keywords: Risk Factors; Newborn; Necrotizing Enterocolitis; Developing Countries

1. Introduction

Necrotizing enterocolitis (NEC) is a critical gastrointestinal disease that predominantly affects neonates. While the exact etiology of NEC remains unclear, this disease is characterized by inflammation and necrosis of the intestinal tissue, leading to severe complications and a significant risk of mortality in affected infants. The disease course of NEC typically involves an acute phase, during which clinical symptoms progress rapidly, followed by a chronic phase, marked by the potential development of long-term complications such as strictures and short bowel syndrome. [1] Early symptoms of NEC are often nonspecific and can mimic other neonatal conditions. Clinical manifestations may include abdominal distension, bilious vomiting, bloody stools, and signs of systemic illness like temperature instability and lethargy. In some cases, neonates may exhibit signs of sepsis, further complicating the diagnostic process. [2] To aid in the timely identification of NEC, clinicians commonly utilize radiographic findings, such as pneumatosis intestinalis and portal venous gas, as well as laboratory tests to assess for elevated inflammatory markers.

Despite advances in neonatal care, NEC continues to pose a considerable challenge, particularly in developing countries where limited access to specialized healthcare facilities and resources exacerbates the burden of the disease. Early diagnosis and prompt intervention are crucial for improving outcomes, and understanding the risk factors associated with NEC in neonates is essential for devising effective preventive and therapeutic strategies. This literature review aims to comprehensively explore the existing research on NEC in neonates, particularly in the context of developing countries, to map the risk factors contributing to its occurrence that will guide early diagnosis and targeted interventions to improve neonatal outcomes.

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2. Review

2.1. Risk Factors of Necrotizing Enterocolitis in Developing Countries

Necrotizing enterocolitis remains as one of the major contributors of neonatal death in preemies. Despite its importance and the efforts of various organizations, there is a lack of comprehensive risk factors data on premature newborns in developing countries.

2.1.1. Brazil

A retrospective study was done by França et al, 2020 in the Neonatal and Pediatric Intensive Care Clinical Hospital of the Federal University of Triângulo Mineiro Brazil. Using a case-control design evaluating 154 medical records from January 2010 to June 2017, 61% of preterm developed NEC and further classified based on gestational age and birth weight. [3] Newborns with NEC received longer hospital stays. Prolonged length of hospitalization is linked to a higher prevalence of NEC associated comorbidities, causing longer hospital care as a result of disease severity. [4] Another study reported shorter hospital stay was correlated to this disease due to increased neonatal death with NEC. [5] Other notable variable was longer duration of nutritional parenteral use. Parenteral nutrition is essential for disease treatment as a mean to suspend enteral feedings for a couple of days as per disease progression. Therefore, parenteral nutrition offers the nutritional needs for the healing process of the impaired bowel function while allowing balance of energy and nutrients after birth. [6]

Previous study reveals a mean of 28 days as a time of parenteral nutrition in preterm neonates with NEC and was positively linked with the more advanced NEC stages. [7] Though, this kind of long-term feeding is correlated to gastrointestinal atrophy, potentially causing structural and functional reduction of the organ, liver injury and impairment, sepsis, and increased possibility of complications. [8] Longer antibiotic consumption was also seen in NEC cases. Prolong antibiotic exposure in preterm neonates treated at NICU may elevate the risk of developing NEC, which can give rise to abnormal bowel colonization. Such exposure may decrease the neonatal microbiota biodiversity, interrupt beneficial gut flora colonization, and can induce pathogenic proliferation and antibiotic-resistant organisms. [9]

Findings in this study also shows artificial formula to have a notable relation with NEC. Bovine based milk formula lacks carbohydrates leading to possibly selecting pathogenic microorganisms, namely enterobacteria. Hence, the excessive pathogenic bacterial growth response to this action may lead to NEC. Breast milk components have a protective role that can lower inflammation process and pathogenic microorganism invasion in the intestine. [10] Furthermore, there was a positive association between disease stages, gestational age, and birth weight. [3] One study revealed that NEC occurrence lessens with increasing gestational age and is more prevalent in very low birth weight neonates. [11] Thus, NEC cases may be lower with increasing birth weight and gestational, however if it arises in these newborns, it will pose a sequence of greater morbidity, leading to more advanced degree of NEC.

2.1.2. Ethiopia

In Ethiopia, a retrospective cross-sectional study was done at selected public hospitals in Addis Ababa by Mekonnen et al. A total of 350 patients data were collected consisting of those of preterm and low birth weight admitted to the NICU from January 2019 to January 2020. NEC incidence in low birth weight and enteral fed newborns included in this study was 89 newborns (25.4%). This study reveals a different pattern between the possibility of developing NEC amongst gestational age subgroups. Neonates with ≤ 28 weeks gestational age were 3.94 times more likely to acquire NEC than those compared to > 34 weeks gestational age. [12] This finding was in accordance with a previous systematic review which stated that low gestational age was a notable prognostic factors for NEC. [13] Birth weight remains the predominant risk factor for NEC. Low birth weight may indicate a problem related to nutrition since nutrition highly influence the maturation of the neonatal immune system. [14] This study reported newborn with birthweight of 1000-1499 g had 2.29 times more possibility to have NEC compared to newborns with 1500-2499 g birthweight. [12] Newborns with ≤ 3 APGAR score had 2.34 times higher chances to develop NEC when compared to newborns with ≥ 7 APGAR score. [12] Another retrospective case-control study also shows result of neonates with NEC had a substantially higher occurrence of APGAR score < 7 at 1 and 5 minutes when compared to the control group. [15] In conclusion, worsening of APGAR score was a predictor for NEC. The probability of acquiring NEC among mixed milk-fed newborns were 3.58 times higher than breastfed newborns. [12] During the first week neonates should be breastfed exclusively to decrease NEC prevalence. A retrospective analysis also described breast milk should be the diet of choice in preterm newborns. [16] Breast feeding in neonate is linked with lower NEC cases.

An institution based cross-sectional study collected 288 data of preterm neonates treated at NICU of Gurage Zone public hospitals, Southwest Ethiopia from June 2019 to June 2021. This study reveals the NEC prevalence was 28 neonates (9.7%). [17] Birth weight was a significant factor for the development of NEC. Low birth weight elevates neonatal morbidity and mortality diagnosed with NEC. [18] Newborns with birth weight <1500 gm were 7.33 times had higher possibility to acquire NEC compared to those with a birth weight of 2500 gm–4000. [17] Trophic feeding initiation was linked with a higher risk to develop NEC. Suspending trophic feeding was associated with less NEC cases and NEC related death.[19] Findings in this study describes neonates who started trophic feeding had 5.89 times more likely to acquire NEC. Length of hospitalization was notably linked with NEC contributing of 3.28 times higher chances of acquiring NEC compared to neonates with less than a week length of stay in this study.

Another retrospective follow-up study was done at the NICU of Felege Hiwot comprehensive specialized hospital (FHCSH), BahirDar, Ethiopia. This study involves 747 low birth weight and preemies with a gestational age of more than 28 weeks hospitalized from 1 January 2017 to 30 December 2019. The overall prevalence rate of NEC among low birth weight and preemies was 6.8%. Newborns with gestational age between 28 and 32 weeks was 3.59 times higher chances of developing NEC than that of term newborns, and newborns with birth weight less than 1,000 g were 5.45 times more likely to have NEC compared to newborns weighing between 1,500 and 2,500 g. [20] The immaturity of the gastrointestinal tract in premature newborns increases the susceptibility to infection possibly leading to NEC. [21]

2.1.3. China

Su et al. conducted a meta-analysis from various databases with a total of 48 case control studies and 4 cohort studies. Findings from this meta-analysis reported that low birth weight was a risk factor for the development of NEC. This may be as a result of the intestinal immaturity and slow bowel movements in low-birth-weight preemies, food residues are prone to accumulate thus fermented, creating a prime environment for bacteria to grow, leading to an overgrowth of bacteria colonization. Other reason might be due to immature intestinal microbiota of low-birth-weight preemies, direct interaction with pathogenic bacteria will induce inflammation related mucosal injury, potentially progressing to NEC. [22] Breast milk is well-known as the safest natural food for infants and neonates. It contains the antibodies and nutrients required for organ development particularly antibodies that can support neonatal immune systems, suppress inflammatory responses, and accelerate damaged intestinal mucosa healing process. Breast milk has a lower osmotic pressure than formula, which can reduce the food's osmotic load and decrease the influence on intestinal function, decreasing the likelihood of NEC. This meta-analysis also reveals that premature neonates was a risk factor for NEC. Due to the defective enteric nervous system development and insufficient small intestine peristaltic regulator, preterm neonates are more likely to experience extreme bacteria overgrowth and gas deposition following food fermentation and is highly susceptible to NEC. [22]

A cohort study conducted by Qian et al collected 1167 cases of NEC from 95 participating NICUs across China. The prevalence rate reported in this study was of 2.50% and 4.53% in low birth weight (birth weight <2500 g) and very low birth weight (birth weight <1500 g) neonates, respectively. Study findings also shows stage 1, 2 and 3 of NEC prevalence were 51.1%, 30.3% and 18.6% of cases respectively. Total mortality cases in NEC stage 2 and 3 of this study was 41.7%. Thus, this cohort study concludes a higher death rate in low-birth-weight preemies with NEC amongst the Chinese population, specifically in very low birth weight neonates. We establish exceptional risk factors for death from NEC based on the birth weight subgroups. In very low birth weight neonates, the critical risk factors for death were small for gestation and stage 3 NEC. Whereas in moderate low birth weight neonates (birth weight 1500- 2499 g), sepsis during hospital care and stage 3 NEC were discovered as significant risk factors contributing to death rate.[23]

3. Conclusion

In summary, the research findings conducted in several developing countries, including Ethiopia, Brazil, and China produce valuable insights and further understanding in newborn risk factors of necrotizing enterocolitis. These research findings consistently reported high death rates. Factors such as low birth weight, preterm delivery, small gestational age, initiation of formula-based trophic feeding, duration of hospitalization, low APGAR score, as well as prolong antibiotic exposure, contribute to an increased risk of NEC related morbidity and mortality observed in these patients.

The findings also emphasize the importance of early risk factor detection and immediate treatment intervention to improve patient survival and reduce NEC related morbidity and mortality. Further investigation and exploration are required to improve our understanding of necrotizing enterocolitis in newborn, specifically in developing countries, where limited data exists. Healthcare providers can work towards enhancing outcomes and reducing the burden of NEC disease among newborns in developing countries by tackling the issues related to timely diagnosis and treatment.

Compliance with ethical standards

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Disclosure of Conflict of interest

There was no conflict of interest.

References

- [1] Cuna, A., George, L., & Sampath, V. Genetic predisposition to necrotizing enterocolitis in premature infants: Current knowledge, challenges, and future directions. *Seminars in fetal & neonatal medicine*. 2018; 23(6), 387–393.
- [2] Afzal, B., Elberson, V., McLaughlin, C., et al. Early onset necrotizing enterocolitis (NEC) in premature twins. *Journal of neonatal-perinatal medicine*. 2017; 10(1), 109–112.
- [3] França, A.M.N. de, Contim, D., Borges, L.G.S, et al. Clinical and epidemiological characterization of newborns with necrotizing enterocolitis. *ABCS Health Sci*. 2022; 47:e022206.
- [4] Cotten CM, Oh W, McDonald S, et al. Prolonged hospital stay for extremely premature infants. *J. Perinatol*. 2005; 25(10), 650-5.
- [5] March MI, Gupta M, Modest AM, et al. Maternal risk factors for neonatal necrotizing enterocolitis. *J Matern Fetal Neonatal Med*. 2015; 28(11), 1285-90.
- [6] Oliveira ND, Miyoshi MH. Avanços em enterocolite necrosante. *J Pediatr*. 2005; 81(1), 16-22.
- [7] Sangild PT, Thymann T, Schmidt M, et al. Invited review: the preterm pig as a model in pediatric gastroenterology. *J Animal Sci*. 2013; 91(10), 4713-29.
- [8] Jain AK, Stoll B, Burrin DG, et al. Enteral bile acid treatment improves parenteral nutrition-related liver disease and intestinal mucosal atrophy in neonatal pigs. *Am J Physiol Gastrointest Liver Physiol*. 2012; 302(2), 218-24.
- [9] Wang Y, Hoenig JD, Malin KJ, et al. 16S rRNA gene-based analysis of fecal microbiota from preterm infants with and without necrotizing enterocolitis. *ISME J*. 2009; 3(8), 944-54.
- [10] Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol*. 2016; 36(3), 216-20.
- [11] Nair, J., Longendyke, R., & Lakshminrusimha, S. Necrotizing Enterocolitis in Moderate Preterm Infants. *BioMed research international*. 2018; 4126245.
- [12] Mekonnen, S. M., Bekele, D. M., Fenta, F. A., et al. The Prevalence of Necrotizing Enterocolitis and Associated Factors Among Enteral Fed Preterm and Low Birth Weight Neonates Admitted in Selected Public Hospitals in Addis Ababa, Ethiopia: A Cross-sectional Study. *Global pediatric health*. 2021; 8, 2333794X211019695.
- [13] Samuels, N., van de Graaf, R. A., de Jonge, R. C. J., et al. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. *BMC pediatrics*. 2017; 17(1), 105.
- [14] Derienzo, C., Smith, P. B., Tanaka, D., et al. Feeding practices and other risk factors for developing transfusion-associated necrotizing enterocolitis. *Early human development*. 2014; 90(5), 237–240.
- [15] Martinez-Tallo, E., Claire, N., & Bancalari, E. Necrotizing enterocolitis in full-term or near-term infants: risk factors. *Biology of the neonate*. 1997; 71(5), 292–298.
- [16] Chowning, R., Radmacher, P., Lewis, S., et al. A retrospective analysis of the effect of human milk on prevention of necrotizing enterocolitis and postnatal growth. *Journal of perinatology: official journal of the California Perinatal Association*. 2016; 36(3), 221–224.
- [17] Chekole Temere, B., Aynalem Mewahegn, A., Tefera Zewudie, B., et al. Necrotizing Enterocolitis and Its Predictors Among Preterm Neonates Admitted in Neonatal Intensive Care Units of Gurage Zone Public Hospitals, Southwest Ethiopia, 2021. *Pediatric health, medicine and therapeutics*. 2022; 13, 95–102.

- [18] Rose, A. T., & Patel, R. M. A critical analysis of risk factors for necrotizing enterocolitis. *Seminars in fetal & neonatal medicine*. 2018; 23(6), 374–379.
- [19] Masoli, D., Dominguez, A., Tapia, J. L., et al. Enteral Feeding and Necrotizing Enterocolitis: Does Time of First Feeds and Rate of Advancement Matter?. *Journal of pediatric gastroenterology and nutrition*. 2021; 72(5), 763–768.
- [20] Alene, T., Feleke, M. G., Yeshambel, A., et al. Time to occurrence of necrotizing enterocolitis and its predictors among low birth weight neonates admitted at neonatal intensive care unit of felege hiwot compressive specialized hospital BahirDar, Ethiopia, 2021: A retrospective follow-up study. *Frontiers in pediatrics*. 2022; 10, 959631.
- [21] Hsueh, W., Caplan, M. S., Tan, X., MacKendrick, W., et al. Necrotizing enterocolitis of the newborn: pathogenetic concepts in perspective. *Pediatric and developmental pathology: the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*. 1998; 1(1), 2–16.
- [22] Su Y, Xu R-H, Guo L-Y, et al. Risk factors for necrotizing enterocolitis in neonates: A meta-analysis. *Frontiers in pediatrics*. 2023; 10, 1079894.
- [23] Qian T, Zhang R, Zhu L, et al. Necrotizing enterocolitis in low birth weight infants in China: Mortality risk factors expressed by birth weight categories. *Pediatrics & Neonatology*. 2017; 58 (6): 509-515.