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Necrotizing Enterocolitis among Very Low Birthweight Neonates: A Systematic Review and Meta-Analysis

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Objective: Necrotizing enterocolitis (NEC) is a critical gastrointestinal disorder that primarily affects very low birthweight (VLBW) neonates. Enhancing neonatal care requires a thorough understanding of the incidence, risk factors, and outcomes associated with NEC. This systematic review and meta-analysis aim to consolidate and analyze existing literature to provide a comprehensive overview of NEC among VLBW neonates.

Methods: A systematic search of relevant studies was conducted, resulting in the inclusion of 15 studies encompassing a total of 259,500 infants from diverse populations and regions. Pooled estimates of NEC incidence were calculated using a random-effects model. Additionally, factors contributing to NEC incidence and their consistency across studies were explored.

Results: The meta-analysis yielded a pooled estimate of NEC incidence among VLBW neonates at approximately 6.62% (95% CI: 5.33% to 7.90%). Notably, significant heterogeneity was observed among the included studies (I^2 = 100%), reflecting the multifaceted nature of NEC. Qualitative data synthesis revealed that lower birth weight, gestational age, maternal age, intrapartum antibiotics, racial disparities, chorioamnionitis, healthcare-associated sepsis, and antenatal steroids were consistently associated with NEC risk, aligning with existing literature.

Conclusion: This systematic review and meta-analysis provide a comprehensive overview of NEC among VLBW neonates, underscoring the imperative for evidence-based interventions aimed at reducing NEC incidence and improving outcomes for this vulnerable population. Insight into the intricate complexities of NEC and its associated risk factors is crucial for guiding clinical practice and informing future research endeavors

Key words: low-birthweight Neonates; necrotizing enterocolitis; meta-analysis; systemic review.

Introduction:

Background

Necrotizing enterocolitis (NEC) stands as a formidable challenge within neonatal care, predominantly impacting premature and very low birth weight (VLBW) infants [1,2]., thus representing a critical concern in neonatal intensive care units (NICUs) globally. This severe gastrointestinal ailment is characterized by inflammation and necrosis of the intestinal tissue, often leading to life-threatening complications [3,4].

NEC typically emerges within the initial weeks of life, frequently without clear forewarning [5]. While the precise etiology of NEC remains intricate and multifaceted, extensive research has identified several risk factors. Noteworthy among these factors are low birth weight, prematurity, and inadequate prenatal nutritional support [6,7].

The immature gastrointestinal tract of preterm infants, combined with a fragile immune system, predisposes them to NEC. Additionally, factors such as formula feeding, enteral feeding advancement, and bacterial colonization of the gut have been implicated in NEC pathogenesis [8].

The clinical presentation of NEC can vary, ranging from mild cases with localized intestinal inflammation to severe cases with extensive tissue necrosis and systemic complications [9,10]. Infants with NEC often presented with symptoms such as abdominal distension, feeding intolerance, bloody stools, and signs of sepsis. The severity of NEC necessitates prompt diagnosis and intervention, as delayed treatment can lead to bowel perforation, sepsis, multi-organ failure, and death [11].

Mitigating the incidence of NEC and enhancing outcomes in affected infants represent paramount objectives in neonatal medicine. Diverse strategies have been instituted to diminish the risk of NEC, including the encouragement of human milk feeding, probiotic utilization, and meticulous administration of enteral feeding regimens [12]. Nonetheless, the variability in NEC prevalence and outcomes observed across different regions and populations underscores the insufficiency of a uniform approach that called (one-size-fits-all approach) [10,13].

Study objectives:

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This systematic review and meta-analysis endeavour to enhance our comprehension of NEC by consolidating data from a multitude of studies conducted in different countries and populations. Through comprehensive analysis of NEC incidence, risk factors, and outcomes across varied settings and populations, this study aims to identify patterns, variances, and determinants that contribute to the heterogeneity in NEC epidemiology.

Study Rationale:

Understanding the variations in NEC incidence and outcomes is crucial for tailoring prevention and management strategies to specific populations. This underscores the necessity for further research to investigate emerging risk factors, interventions, and disparities in care. Ultimately, the goal is to mitigate the burden of NEC and improve the outcomes of vulnerable very low birthweight (VLBW) infants through evidence-based and region-specific approaches to neonatal care.

Methodology

Search Strategy and Data Sources

A systematic and comprehensive literature search was conducted to identify relevant studies. The exploration encompassed a range of electronic databases, including PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, Scopus, and Google Scholar. The search encompassed all available literature from the inception of these databases until January 2024.The search strategy employed a combination of Medical Subject Headings (MeSH) terms, keywords, and Boolean operators, focusing on studies concerning NEC, VLBW neonates, and pertinent risk factors.

The search was designed to be broad to capture all potentially eligible studies, and it was adapted to the syntax and requirements of each database. Throughout the study, established guidelines for conducting systematic reviews and meta-analyses, specifically the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), were followed. These guidelines were implemented to uphold transparency and rigor in the research process.

Eligibility criteria

The selection process for eligible studies involved utilizing searching software such as Web of Science, PubMed, Embase, and Ovid. These studies exclusively included peer-reviewed journals containing original research articles conducted on human neonates that reported NEC incidence or provided data from which incidence could be calculated. The focus was primarily on VLBW neonates, with a birth weight below 1500 grams, or studies that included a subgroup analysis specifically for this population. Moreover, studies that were published in languages other than English, case reports, case series, review articles, conference abstracts, or editorial comments, were excluded. Additionally, studies that did not report NEC incidence or provide sufficient data for calculation, or those that exclusively focused on populations other than VLBW neonates, were also excluded from the analysis

Literature screening and data extraction

Two independent reviewers conducted the initial screening of titles and abstracts to identify potentially relevant studies. Full-text articles of the selected studies were then retrieved and reviewed for eligibility based on the inclusion and exclusion criteria. Discrepancies in study selection were resolved through discussion and consensus.

Data extraction was performed independently by the same two reviewers using a standardized data extraction form. Extracted data included study characteristics (e.g., authors, publication year, study location), study design, population characteristics, NEC incidence, and relevant risk factors or outcomes. Any discrepancies or disagreements were resolved through discussion and consensus.

Data Synthesis and Statistical Analysis

The statistical analysis in this meta-analysis was performed using Stata 16.0 software (Stata Corp LLC, TX, USA). The incidence of necrotizing enterocolitis (NEC) in very low birth-weight infants was assessed using a Forest plot. Each study's sensitivity and specificity values, along with their corresponding 95% confidence intervals (CI), were compared. The studies on NEC were represented by different shapes, with a summary point indicated by a dot surrounded by the 95% CI. Pooled estimates of NEC incidence were calculated using a random-effects model, taking into consideration the anticipated heterogeneity among the studies. The degree of heterogeneity among the studies was assessed using the I^2 statistic, and publication bias was evaluated using funnel plots.

Results

Search Results

After an extensive search and thorough screening of 1072 records, we identified and included a total of 15 relevant studies in our systematic review and meta-analysis. These studies comprised 259,500 infants and encompassed a wide range of geographic locations, spanning Sweden, Saudi Arabia, the United States, Malaysia, the United Arab Emirates, India, China, Belgium, Poland, Australia, and Korea. The studies included various populations, primarily focusing on VLBW neonates and, in some instances, all live births or critically ill infants. The study durations ranged from 1987 to 2015, collectively providing a comprehensive overview of the incidence and factors associated with NEC among neonates. The study selection is detailed in Figure 1.

Characteristics of the Included Studies

Table 1 summarizes the key characteristics of the 15 studies included in our analysis. Each study offers insights into the incidence, risk factors, and outcomes related to NEC among different populations. Notably, the studies vary in terms of their focus, ranging from examining NEC in all live births to specifically studying VLBW infants or critically ill neonates. The diverse geographical locations of the studies provide insights into the global prevalence of NEC.

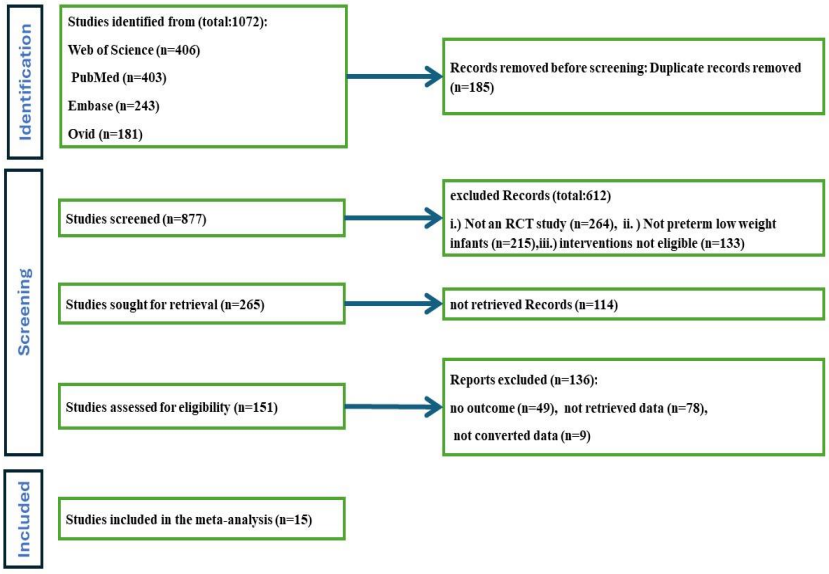

Figure 1 Prisma flow chart shows the literature search and screening results.

Table 1: Characters of the included studies (n=15).

Study	Country	Population type	Study duration	Findings	NEC Cases	Total population included in our data synthesis	Incidence of NEC	Ref.
Ahle et al., 2013	Sweden	All live births	1987–2009	Incidence of NEC has increased in Sweden during the last decades. An association with the concurrent dramatically improved early survival seems likely.	473	17,608	2.69%	[13]
Al-Hazzani et al., 2011	Saudi Arabia	VLBW infants (501-1500 g)	2006-2008	The incidence of NEC in VLBW infants in Saudi Arabia is comparable to international data.	14	186	7.53%	[14]
Boghossian et al., 2018	United States	Large for gestational age infants	2006-2014	Being born LGA was associated with lower risks for all the examined outcomes except for early onset sepsis and severe intraventricular haemorrhage.	10376	138869	7.47%	[15]
Boo et al., 2012	Malaysia	VLBW infants (<1500 g)	2007	Risk factors for NEC include maternal age, birth weight, surfactant therapy, congenital pneumonia, and indomethacin therapy for the closure of PDA. Intrapartum antibiotics were associated with a reduced risk of developing NEC.	222	3601	6.16%	[16]
Chedid et al., 2008	UAE	VLBW infants (501-1500 g)	2004–2006	The incidence of NEC in very low birth weight infants (VLBWI) in a developing country is lower than in developed countries.	10	173	5.78%	[17]
Fanaroff et al., 2003	US	VLBW infants (501-1500 g)	87/88, 93/94,99/2000	Necrotizing enterocolitis (NEC) is a major cause of morbidity and mortality in VLBW infants. The incidence of NEC has not changed significantly over time.	786	12,628	6.22%	[18]
Holman et al., 2006	United States	Hospitalized neonates	2000	The rate of NEC hospitalizations was highest among non-Hispanic Black neonates. The median hospital length of stay was 49 days. The in-hospital fatality rate was 15.2%.	2554	58,810	4.34%	[19]

Study	Country	Population type	Study duration	Findings	NEC Cases	Total population included in our data synthesis	Incidence of NEC	Ref.
Llanos et al., 2002	United States	All live births	1991-1998	The highest incidence of NEC occurred among infants weighing 750–1000 g at birth and declined with increasing birthweight. The urban county had a 1.53 times higher risk of NEC than rural counties. The overall incidence of NEC for non-Hispanic blacks was significantly greater than that for non-Hispanic whites (2.2 vs. 0.5 cases per 1000 live births, P = 0.00).	70	1425	4.91%	[20]
Narang et al., 1993	India	VLBW infants (501-1500 g)	1986–1990	The incidence of NEC is higher in VLBW infants and in preterm infants of gestational age less than 32 weeks. The mortality rate from NEC is higher in VLBW infants and in infants with severe birth asphyxia.	33	2200	1.50%	[21]
Qian et al., 2017	China	Low birth weight infants (<2500 g)	2011	Risk factors for NEC-associated mortality in VLBW infants include small for gestation age and stage 3 NEC. Risk factors for NEC-associated mortality in LBW infants include sepsis during hospitalization and stage 3 NEC.	221	8727	2.53%	[22]
Stoll et al., 2010	United States	Extremely preterm infants	2003-2007	High rates of morbidity among survivors continue to be observed, including respiratory distress syndrome (93%), patent ductus arteriosus (46%), severe intraventricular hemorrhage (16%), necrotizing enterocolitis (11%), and late-onset sepsis (36%).	937	8515	11.00%	[23]
Verstraete et al., 2016	Belgium	All critically ill infants	2002–2011	Healthcare-associated sepsis (HAS) is a risk factor for mortality in VLBW infants, especially those with gastrointestinal diseases such as NEC.	158	973	16.24%	[24]
Wojkowska-Mach et al., 2014	Poland	VLBW infants (<1500 g)	2009	Risk factors for NEC include VLBW and chorioamnionitis. There was no relationship between the consumption of antibiotics in neonates with NEC and positive results of microbiological testing indicating sepsis accompanying NEC or gut colonization with pathogens.	79	910	8.68%	[25]
Wong et al., 2013	Australia	Very premature infants (<29 weeks gestational age)	1998–2004	Exposure to a complete course of antenatal steroids is associated with a lower incidence of NEC.	199	2549	7.81%	[26]
Youn et al., 2015	Korea	VLBW infants	2013-2014	NEC was related to lower gestational age and birth weight (P < 0.001). Multivariate logistic regression analysis demonstrated that NEC was consistently related to hypotension within one week after birth (OR 2.0, 95% CI 1.0-3.9).	149	2326	6.41%	[27]

Incidence of NEC

The pooled estimate of NEC incidence among VLBW neonates, as depicted in Figure 2, was approximately 6.62% (95% CI: 5.33% to 7.90%). This estimate was derived from a random-effects model, given the significant heterogeneity observed among the included studies (I^2 = 100%).

The individual study findings contributed to this overall estimate. Notably, Ahle et al [13] reported an incidence of 2.69% in Sweden, while Al-Hazzani et al [14] found an incidence of 7.53% among VLBW neonates in Saudi Arabia. The study by Stoll et al [23] in the United States reported a notably higher incidence of 11.00%. These variations in incidence highlight the influence of geographic and population-specific factors on NEC rates.

Heterogeneity and Publication Bias

The substantial heterogeneity observed among the included studies (I^2 = 100%) indicates the presence of variations in NEC incidence that cannot be solely attributed to chance. This heterogeneity may be influenced by geographic factors, differences in study populations, and variations in data collection and reporting.

Publication bias, which can skew the results of a meta-analysis, was assessed using funnel plots. Figure 3 displays a funnel plot demonstrating a symmetrical distribution, suggesting that publication bias was not a significant concern in this meta-analysis.

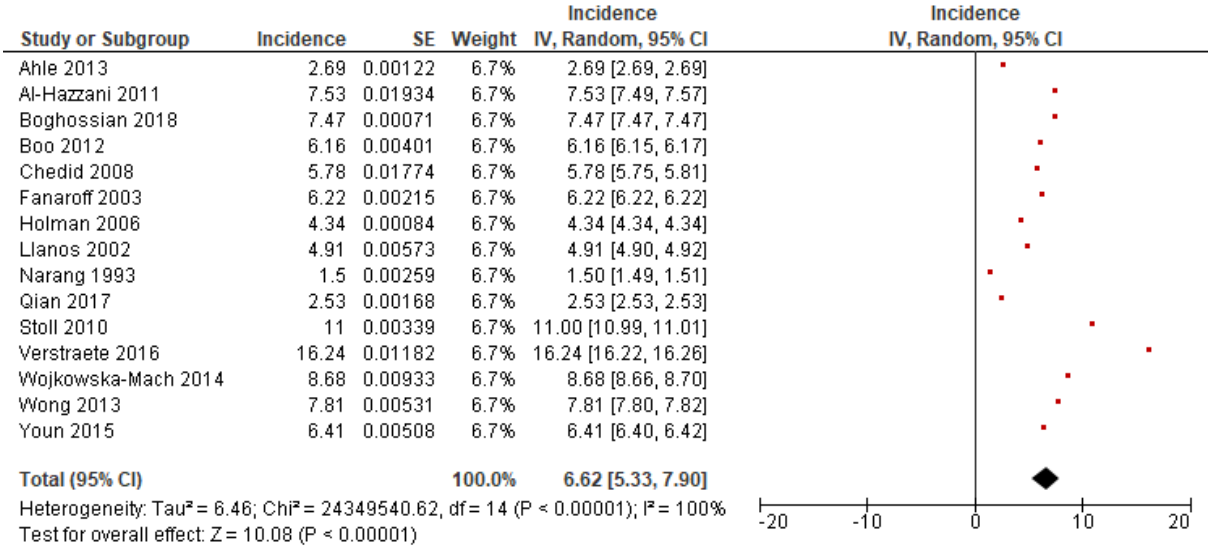

Figure 2: Forest plot of the incidence of NEC among very low birth-weight infants.

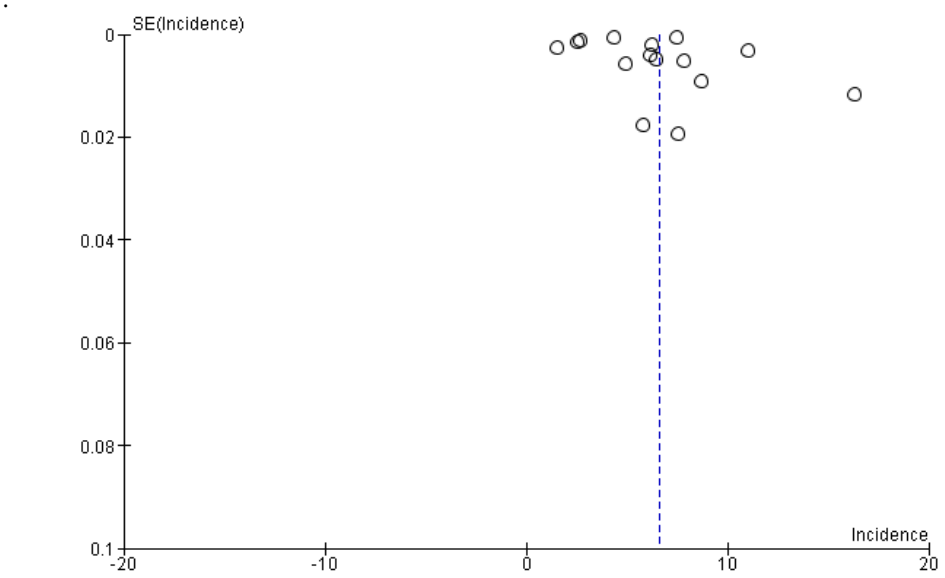

Figure 3: Funnel plot for assessment of publication bias.

Discussion

Necrotizing enterocolitis (NEC) remains a significant concern in neonatal care, particularly among VLBW infants [3]. This systemic review analysed 15 high-quality diverse studies conducted in different countries involved a total of 259,500 infants with low bodyweight.

The pooled estimate of NEC incidence among VLBW neonates in this meta-analysis was 6.62%, with a 95% confidence interval ranging from 5.33% to 7.90%. This estimate highlights the substantial burden of NEC in this vulnerable population. However, it's essential to acknowledge the substantial heterogeneity observed among the included studies, as indicated by the high I^2

value of 100%. This heterogeneity underscores the need to consider the variations in study characteristics, populations, and methodologies across the diverse set of studies[28].

The observed heterogeneity may be attributed to several factors. First, the geographical diversity of the studies, spanning countries from Sweden to Saudi Arabia, the United States to India, reflects regional variations in NEC incidence and risk factors. Such variations may be influenced by differences in healthcare practices, antenatal care, and socioeconomic factors. where, Al-Hazzani et al. [14] found NEC incidence in Saudi Arabia to be comparable to international data, while Chedid et al. [17] reported lower NEC rates in the United Arab Emirates, emphasizing the role of regional disparities and may be reflected to other factors especially varied healthcare practices, socioeconomic status, and population characteristics [29,30]

Furthermore, the variations in population types studied contribute to heterogeneity. Some studies focused on specific subpopulations, such as large-for-gestational-age infants [15] or extremely preterm infants [23]. These distinctions highlight that NEC risk factors and outcomes may differ among neonatal subgroups, reinforcing the importance of tailored prevention and management approaches.

The temporal diversity of the studies, spanning several decades, also plays a role in heterogeneity. The evolving landscape of neonatal care and advancements in medical technology over time may have influenced NEC incidence rates. Fanaroff *et al*. [18] noted a relatively stable NEC incidence over time in the United States, suggesting that despite medical progress, NEC remains a persistent concern.

In terms of risk factors, the included studies collectively emphasize the multifactorial nature of NEC. Factors such as birthweight, gestational age, maternal age, antibiotic therapy, and antenatal steroids emerged as significant contributors to NEC risk. Notably, studies like Boo et al. [16] and Wong et al. [26] underscored the impact of antenatal interventions, highlighting the potential for preventive strategies in reducing NEC incidence.

Disparities in NEC incidence and outcomes were also evident among different racial and ethnic groups, as demonstrated by Llanos et al. [20] and Holman et al. [19]. These findings underscore the importance of addressing health disparities in neonatal care to ensure equitable outcomes for all infants.

The variations in findings among the included studies reinforce the need for tailored NEC prevention and management strategies. Clinicians must consider regional, population-specific, and temporal factors when developing care protocols. Additionally, the high heterogeneity observed underscores the complexity of NEC and the challenges in conducting standardized research in this field. Future studies should aim to minimize heterogeneity through standardized definitions, data collection methods, and reporting.

Conclusion

In conclusion, this meta-analysis consolidates and analyzes data from diverse populations, providing a comprehensive overview of NEC incidence and associated risk factors among VLBW neonates. To further advance our understanding of NEC, future research should explore emerging risk factors and interventions while addressing the methodological challenges associated with studying this complex neonatal condition. Ultimately, improving NEC outcomes requires a holistic, multidisciplinary approach that considers the diverse factors contributing to its occurrence and severity.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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