Cardiogenic Necrotizing Enterocolitis: A Clinically Distinct Entity from Classical Necrotizing Enterocolitis

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Abstract

Aim The main purpose of this study was to investigate if necrotizing enterocolitis (NEC) has a different presentation and outcome in patients with congenital heart defect (CHD) (cardiogenic NEC) from those without (classical NEC).

Materials and Methods A systematic review of the literature on the characteristics of infants with NEC and CHD was performed by three independent investigators using a defined strategy (PubMed, Cochrane, Embase, and Web of Science). A meta-analysis was conducted on studies comparing NEC in infants with CHD and non-CHD infants using RevMan 5.3.

Results Systematic review: Of 7,291 abstracts screened, 126 full-text articles were analyzed and 51 studies were included. NEC had an incidence of 5.1% in CHD infants (7,728/151,046, range 0–24%) and 0.8% in non-CHD infants (26,430/3,256,891, range 0.1–8.9%; $p < 0.0001$). In very low birth weight infants, NEC occurred in 6.3% of CHD patients (6,361/100,454pts) and in 8.9% of non-CHD (23,201/257,794pts; $p < 0.0001$). In CHD cases, NEC occurred before cardiac surgery in 48% cases and surgery for NEC was required in 31% infants (2,037/6,683). Meta-analysis: In eight comparative studies, the incidence of NEC was higher in CHD infants (6%, 768/13,145) than in infants with no CHD (0.9%, 32,625/3,354,323pts; $p < 0.00001$, odds ratio [OR] 1.84, 95% confidence interval [CI] 1.7–1.9). The overall mortality was higher in infants with CHD and NEC (38%, 243/640) than in those without CHD (27%, 6651/24810; $p < 0.00001$, OR 3.4, 95% CI 2.8–4.1).

Conclusion This is the first evidence-based study showing that infants with cardiogenic NEC have different demographics and outcomes than those with classical NEC. The risk of developing NEC and the mortality rate are higher among infants with CHD than in those without. Conversely, the need for intestinal surgery is lower in babies with cardiogenic NEC than in those with classical NEC. Further studies are needed to establish preventative and management interventions that are specific to infants with or at risk of developing cardiogenic NEC.

Keywords
- necrotizing enterocolitis
- meta-analysis
- systematic review
- congenital heart defect
- neonates

Introduction

Necrotizing enterocolitis (NEC) remains one of the most severe gastrointestinal emergency conditions in the neonatal period, with high morbidity and mortality rates.[1,2] Most cases of NEC occur in preterm infants, and indeed prematurity has been consideredas a major risk factor for the developmentof NEC.[3,4] Nonetheless, 7 to 20% of all cases of NEC occur in term infants,[2,5,6] where the major risk factor is the presence of a congenital heart defect (CHD).[6-10] In this population of infants with CHD, the pathophysiology of NEC is different from that of preterm infants, since NEC develops as a result of mesenteric hypoperfusion secondary to an underlying cardiac lesion. The mesenteric hypoperfusion phenomenon is thought to be secondary to a diastolic steal and flow reversal in the abdominal aorta that are characteristic of CHD,[10,11] to a low cardiac output state,[12] and to a compensatory mechanism of hypoxia like the "diving reflex."[13]

Although the number of infants affected by cardiogenic NEC is substantial, most of the literature focuses on the management of the classical form of NEC, with only few studies differentiating cardiogenic NEC from classical NEC. As a result, in the clinical practice the management of infants with cardiogenic NEC and the counseling of their parents are not tailored to this population of infants, but are adopted from those with classical NEC. The aim of the present study was to analyze the existing literature to establish whether infants affected by cardiogenic NEC have different presentation and outcome from those with classical NEC.

Materials and Methods

Both the systematic reviewand the meta-analysis were drafted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] Two different health librarians were involved at the Gerstein Science Information Centre (Universityof Toronto, ON, Canada) and the Bibl@Ud'A (University of Chieti-Pescara, Italy).

Systematic Review

The present study was registered on PROSPERO—international prospective register of systematic reviews.[15] A systematic review of the literature was made using a defined search strategy. Three investigators (E.S., G.L., and S.C.) independently searched scientific databases (PubMed, Medline, Cochrane Collaboration, Embase, and Web of Science) using a combination of keywords (►Table 1). MeSH headings and terms used were "Necrotizing enterocolitis," "Necrotizing enterocolitis AND (Congenital heart defect OR heart defect)," and "Cardiogenic necrotizing enterocolitis" (►Supplementary Material A, available in the online version). Case reports, opinion articles, experimental studies, and case series with less than 10 patients were excluded. All gray literature publications (i.e., reports, theses, conference proceedings, bibliographies, commercial documentations, and official documents not published commercially) were excluded. The full text of the potentially eligible studies was retrieved and independently assessed for eligibility by the same three investigators. Any disagreement between the investigators over the eligibility of a specific study was resolved through the discussion with a fourth author (AZ).

Table 1 Inclusion criteria of systematic review

Publication	
Language	Any
Date	After 1950
Subject	Human studies
Study type	Retrospective
	Prospective
	Case control
	Cohort
Excluded	Case reports
	Case series
	Letters
	Editorials
	Gray literature
Keywords	Necrotizing enterocolitis
	Congenital heart disease
	Heart disease
	Cardiogenic necrotizing enterocolitis
	Infants
	Neonates
	Newborn

Meta-Analysis

Only studies comparing classical NEC (NEC in non-CHD infants) *versus* cardiogenic NEC (NEC in CHD infants) were included. Outcome measures included patient demographics (gestational age, birth weight, and the age at NEC onset/diagnosis), NEC incidence in all patients as well as in very low birth weight (VLBW) infants, NEC location in the intestine, and the mortality rate. The meta-analysis was conducted with RevMan 5.3,[16] using the random-effects model to produce risk ratio for categorical variables and mean differences (MD) for continuous variables, along with 95% confidence intervals (CI). We produced I^2 values to assess homogeneity and quantify the dispersion of effect sizes. Publication biases were assessed using the funnel plot method.

Data were compared using Fisher's exact test and expressed as mean standard deviation (SD). When median and range were reported, mean SD were estimated, as previously reported.[17]

Quality Assessment

Risks of bias for individual studies were assessed in duplicate (by ES and GL) using the methodological index for nonrandomized studies (MINORS).[18] Differences between the two reviewers (ES and GL) were resolved through consensus and

discussion with another author (AZ). The total score for this 12-item instrument ranges between 0 and 24 points, with a validated "gold standard" cut-off of 19.8.[18] Two authors (SC and AZ) independently evaluated the present systematic reviews and meta-analysis using A Measurement Toll to Assess Systematic Reviews (AMSTAR).[19] The PRISMA checklist of our study was then completed.[14]

Results

Systematic Review

Of 7,291 abstracts screened, 126 full-text articles were thoroughly examined, and 51 studies met our inclusion criteria (►Fig. 1). Selected articles included 3,413,657 infants, with 156,766 (4.6%) CHD infants and 3,256,891 (95.4%) non-CHD infants.[8,11,12,20-67] The incidence of cardiogenic NEC was 5.1% (7,728/151,046 CHD infants, range 0–23.7%), whereas that of classical NEC was 0.8% (26,430/3,256,891 non-CHD infants, range 0.1–8.9%; $p < 0.0001$). In VLBW infants, cardiogenic NEC occurred in 6.3% (6,361/100,454) CHD infants and classical NEC in 8.9% of patients (23,201/257,794 non-CHD infants; $p < 0.0001$). In CHD cases, NEC occurred before cardiac surgery in 48% of cases (120/248 patients). A surgical procedure to treat NEC was required in 31% of infants with cardiogenic NEC (2,037/6,683 patients) and in 66% of infants with classical NEC (21/32 patients; $p < 0.0001$).

Meta-Analysis

Of 21 comparative studies,[11,12,21,22,26,30,32–34,42,45,47,50,51,53,55 57,63,64,68,69] only eight papers reported results of NEC in CHD infants *versus* NEC in non-CHD patients (►Table 2).[26,33,45,51,53 55,63,64] Five of the eight studies were retrospective,[26,33,45,55,63] and only three were cohort studies with data prospectively collected.[51,53,64] The incidence of cardiogenic NEC was significantly higher (5.8%, 768/13,145 CHD infants) than that of classical NEC (0.9%, 32,625/3,354,323 infants with non-CHD; $p < 0.00001$, odds ratio [OR] 1.84, 95% CI 1.7–1.9; ►Fig. 2). Two studies reported detailed demographics in both groups of patients.[33,45] Gestational age was higher in infants with cardiogenic NEC (32.3 2.4 weeks) in comparison with those with classical NEC (28.9 1.3 weeks; $p < 0.001$, MD 2.10, 95% CI 0.9–3.3; ►Fig. 3). Similarly, the birth weight was higher in infants with cardiogenic NEC (1798 436 g) in comparison with those with classical NEC (1309 185 g; $p < 0.00001$, MD 747.67, 95% CI 643.6–851.8; ►Fig. 4). Moreover, infants with cardiogenic NEC were older when NEC occurred (54.2 20.1 days) in comparison with those with classical NEC (22.6 2.3 days; $p < 0.00001$, MD 21.41, 95% CI 17.0–25.8; ►Fig. 5).

Onlyone studyanalyzed thelocation of NEC in the intestine, which was found not to be different between infants with cardiogenic NEC and those with classical NEC.[45] In both groups, the predominant location was the small intestine (cardiogenic NEC¼ 31% versus classical NEC¼ 33%; p ¼ ns).

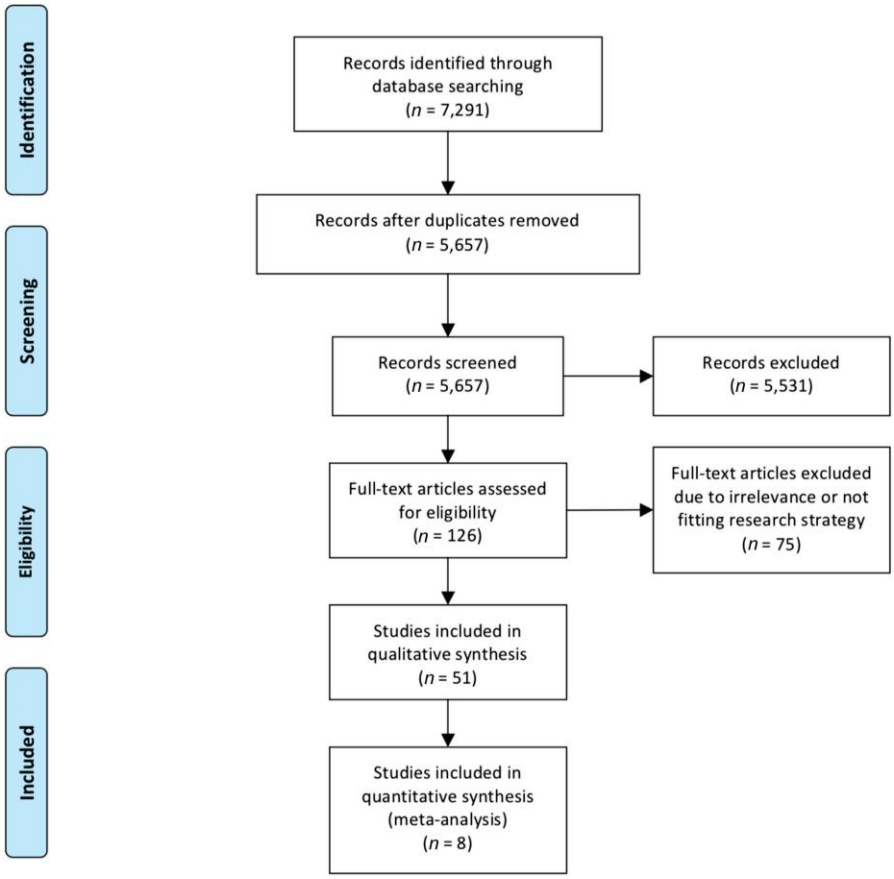

Fig. 1 Diagram of workflow in the systematic review and meta-analysis.

Table 2 Comparative studies included in the meta-analysis

Author	Year of publication	Type of study	Incidence NEC (%)		Mortality NEC (%)	
			CHD infants	Non-CHD infants	CHD infants	Non-CHD infants
Dees et al[26]	2000	Retrospective study	19/201 (9.4)	597/10476 (5.7)		
Pickard et al[33]	2009	Retrospective cohort study			6/76 (7.9)	18/126 (14.3)
Cozzi et al[45]	2013	Retrospective cohort study			13/18 (72.2)	43/147 (29.2)
Bain et al[51]	2015	Prospective cohort study	338/3940 (8.6)	6108/98523 (6.2)		
Motta et al[55]	2015	Retrospective cohort study	9/170 (5.3)	109/4508 (2.4)		
Fisher et al[53]	2015	Prospective cohort study	253/1931 (13.1)	23201/257794 (8.9)	139/253 (54.9)	6496/23201 (27.9)
Steurer et al[63]	2017	Retrospective cohort study	149/6903 (2.2)	2610/2983022 (0.09)		
Velazco et al[64]	2017	Prospective cohort study			85/293 (29.0)	94/1336 (7.0)

Abbreviations: CHD, congenital heart defect; NEC, necrotizing enterocolitis.

The large intestine was the affected area in 22% infants with cardiogenic NEC and in 8% infants with classical NEC (p ¼ ns), whereas the ileocecal junction was affected in 5% of infants with cardiogenic NEC and 14% of those with classical NEC (p ¼ ns). Moreover, NEC was multifocal in 5% of infants with CHD and in 19% of non-CHD infants (p ¼ ns).

The mortality rate of infants with cardiogenic NEC was higher (38%, 243/640 patients) than that of infants with classical NEC (27%, 6651/24810 patients; $p < 0.00001$, OR 3.4, 95% CI 2.8–4.1; ►Fig. 6).

Discussion

This is the first evidence-based study showing that infants with cardiogenic NEC have different demographics and outcome than those with classical NEC. To date, only a few studies have been published on infants with NEC and CHD, and there are no prospective observational reports or randomized controlled trials on this topic. Whiletherehas been agreat focus on strategies for the prevention and treatment of classical NEC, a very few studies have included the population of infants with cardiogenic NEC in their analysis.[34,56,58,62,70,71]

The first noticeable difference between infants with cardiogenic NEC and those with classical NEC is the incidence of the disease in these two populations. In our study, the incidence of NEC within a population of infants with CHD is much higher than that ofclassical NEC within a broader population of infants. Although there have been many population-based studies looking at the incidence of classical NEC, we are not aware of any epidemiology study that has investigated the incidence of cardiogenic NEC within a CHD population. It has well been documented that the incidence ofclassical NEC has a great degree of variabilityamong different countries.[72] To date, it is unknown whether such variability in NEC incidence is encountered also within the population of infants with CHD. It has been speculated that the variability of classical NEC is due to several environmental and possibly genetic factors that make some babies more susceptible than others to develop the disease. Given that the main causative factor of cardiogenic NEC is the presence of a CHD, it would not be a surprise to observe less variability in the incidence of this form of NEC across countries.

Although the pathophysiology of classical NEC is not completely understood, there are several risk factors that have

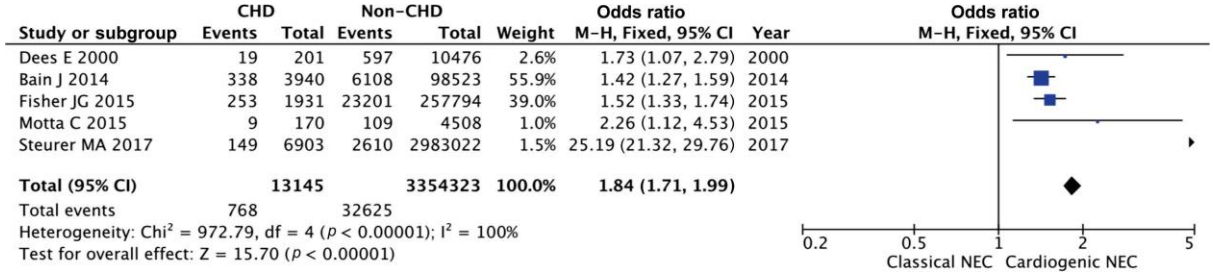

Fig. 2 Forest plot comparison of the incidence of cardiogenic necrotizing enterocolitis (NEC) (NEC in congenital heart defect [CHD] patients) versus classical NEC (NEC in non-CHD). CI, confidence interval.

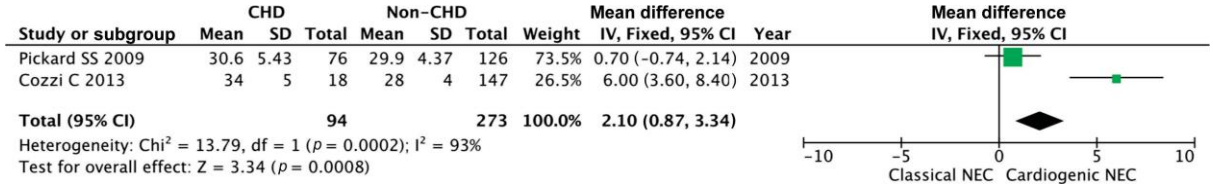

Fig. 3 Forest CHD, congenital heart defect; CI, confidence interval; SD, standard deviation.

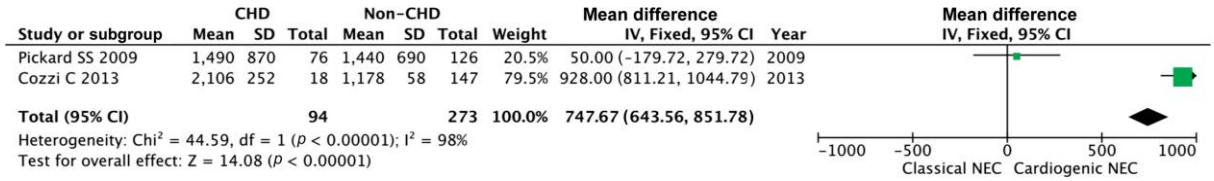

Fig. 4 Forest plot comparison of birth weight in cardiogenic necrotizing enterocolitis (NEC) versus classical NEC. CHD, congenital heart defect; CI, confidence interval; SD, standard deviation.

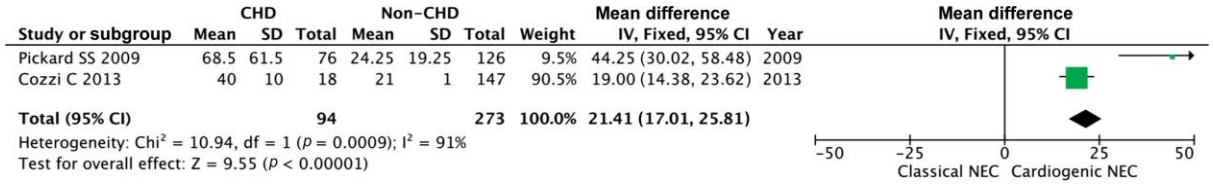

Fig. 5 Forest plot comparison of the age when necrotizing enterocolitis (NEC) occurred in cardiogenic NEC versus classical NEC. CHD, congenital heart defect; CI, confidence interval; SD, standard deviation.

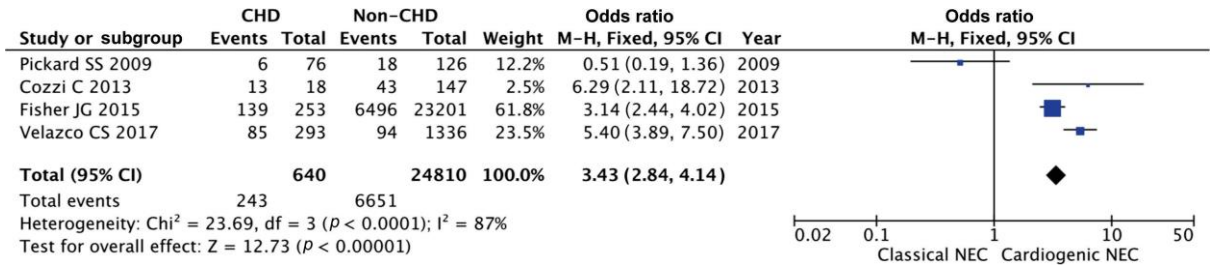

Fig. 6 Forest plot comparison of mortality rate in infants with cardiogenic necrotizing enterocolitis (NEC) versus patients with classical NEC. CHD, congenital heart defect; CI, confidence interval.

been described as commonly present in almost all infants with classical NEC; these include prematurity, low birth weight, hypoxia, and formula feeding.[70] Conversely, in infants with CHD, NEC has a cardiogenic cause that results in mesenteric hypoperfusion, bowel ischemia, and in some cases bowel perforation. In our study, the demographics of the two populations of infants are substantially different from one another, and somehow reflect the different causes of NEC. In fact, infants with CHD had a higher gestational age and greater birth weight in comparison with non-CHD infants. Moreover, the proportion of infants born with VLBW was smaller in the CHD population compared with the population of infants with classical NEC. Thesefindings confirm our hypothesis that these two populations are distinct. On the one hand, in infants with classical NEC, the prematurity, the smaller size, and the immaturity of the immune system make the intestine vulnerable to NEC development. On the other hand, infants with cardiogenic NEC are bigger, older, and possibly have a more mature immune system; however, the associated CHD makes their intestine vulnerable to mesenteric hypoperfusion and hypoxic injury.[10-13]

Many studies have previously reported an earlier onset of NEC in term or near-term infants compared with the preterm population.[6,73-76] Conversely, in our analysis, we found that infants with CHD that develop NEC were older in comparison with those without CHD. This is in keeping with another study, where the authors reported that term patients with a late diagnosis (after 7 days of life) of NEC were more likely to present a concomitant diagnosis of CHD.[77]

In our study, half of the infants with CHD developed NEC prior to cardiac surgery and half following cardiac surgery. The pathogenesis of NEC in these two groups of infants can be explained by the fragility of their intestine in different phases of life. On the one hand, the infants that developed NEC prior to cardiac surgery may have had a decrease in bowel perfusion secondary to the underlying CHD.[10-13] On the other hand, the infants that developed NEC following cardiac surgery may have been exposed to a surgical stress that may have

precipitated the hypoxic gut injury. During cardiac surgery, especially if a heart-lung bypass machine is required, hypothermia is generally induced to reduce the tissue metabolic needs to protect vital organs like the brain, the kidneys, and the heart.[78,79] Uncontrolled hypothermia may be one of the possible causes of gut damage, which may induce a decrease in intestinal mucosal blood flow.[44,80] Furthermore, some infants undergoing surgery may develop a systemic inflammatory response syndrome that may further contribute to the increased susceptibility of the gastrointestinal tract in the postoperative period.[44,81] It has also been reported that cardiopulmonary bypass may affect the intestinal barrier both morphologically and functionally,[82] by altering the gut permeability, which may be another cause of increased susceptibility of the intestine to NEC development after a cardiac procedure.[83]

In our study, the proportion of infants with cardiogenic NEC that required surgical intervention was much smaller than that of infants with classical NEC. This is an interesting finding that may correlate with the differences in the severity of bowel damage in these two populations of infants. It has already been reported that infants with cardiogenic NEC respond well to the conservative management with intravenous antibiotic and bowel rest. In fact, it has been reported that infants with CHD have a lower risk of developing morbidity, like intestinal perforation, stricture, and short bowel syndrome, after NEC diagnosis, compared with infants with classical NEC.[33,42] Although the proportion of infants with classical NEC undergoing surgery may be overestimated in our analysis as it comprises only a retrospective study, it is not surprising that babies, who are mostly premature, have a more fragile intestine that more easily perforates and demands surgical repair.

In our analysis, we did not find any differences in the location of NEC in the two populations. This could be due to the fact that only one study reported the exact area of the bowel involved in the NEC process.[45] In this study, the small intestine was the predominant location of NEC.[45] This finding is similar to that reported by Hebra et al,[84] who reported that 40% of infants with hypoplastic left heart syndrome had NEC detected in the small intestine.

In our study, the mortality rate of infants with cardiogenic NEC was higher than those with classical NEC (►Fig. 6). This difference can be explained by the fact that CHD infants bear also the mortality risk associated with their cardiac anomaly. Some studies on CHD infants have reported higher mortality rates than others.[25,42] This variability may be explained by the heterogeneity in the severity of cardiac defect reported in each study. Nonetheless, the mortality rate remains very high for both populations of infants who develop NEC.

Limitations of the Study

We acknowledge that there are some limitations in our present study, which are mainly due to the fact that a meta-analysis relies on the quality of the studies and data available in the literature. In our meta-analysis, five studies were retrospective and only three were cohort studies of prospectively collected data (►Table 2). None of the studies reached the gold standard cut-off on MINORS of 19.8 out of 24 (►Table 3). None of the studies reported a blinded evaluation of objective end points, most of follow-up period were not appropriate to the aim of the study, and only a paper provided sample size calculations.[55] Moreover, only two studies reported detailed demographics in both groups

Table 3 Risk of bias assessment for individual studies using methodological index for nonrandomized studies[18]

Item	Dees et al[26]	Pickard et al[33]	Cozzi et al[45]	Bain et al[51]	Motta et al[55]	Fisher et al[53]	Steurer et al[63]	Velazco et al[64]
1. A clearly stated aim	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2
3. Prospective collection of data	1	1	1	2	1	2	1	2
4. End points appropriate to the aim of the study	1	2	2	1	2	1	1	2
5. Unbiased assessment of the study end point	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	0	0	0	0	1	0	1
7. Loss to follow-up less than 5%	1	0	0	0	0	0	0	0
8. Prospective calculation of the study size	0	0	0	0	1.5	0	0	0
9. An adequate control group	1.5	2	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	1	2	2	2	2	2	2	2
12. Adequate statistical analyses	1.5	2	1.5	1	2	2	2	2
Total score	15	15	14.5	14	16.5	16	14	17

Note: 0 ¼ not reported; 1 ¼ reported but inadequate; 2 ¼ reported and adequate.

of patients.[33,45] Nonetheless, when independently assessed by two authors using AMSTAR, the present systematic reviews and meta-analysis received a relevant score (►Supplementary Material B, available in the online version). Moreover, the PRISMA checklist of our study was completed (►Supplementary Material C, available in the online version).

Conclusion

With this systematic review and meta-analysis, we have provided for the first time an evidence-based proof that cardiogenic NEC is a clinically distinct entity from classical NEC. The two populations of infants with NEC have different demographics that most likely explain different pathogenic mechanisms. Moreover, the outcome of NEC in these two populations of infants is also different. The need for intestinal surgery in infants with cardiogenic NEC is lower than that of infants with classical NEC, whereas the mortality of babies with cardiogenic NEC is higher compared with that of babies with classical NEC.

The present analysis, that relies mainly on nonrandomized observational studies, has highlighted that there is a paucity of information on infants with cardiogenic NEC in the literature. Further studies are needed to better define the characteristics of these infants, to establish specific preventative and management interventions that would reduce the incidence and the mortality of NEC in this fragile population of babies.

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