Meta-Analysis of Observational Studies in Epidemiology

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Protective effects of different doses of human milk on neonatal necrotizing enterocolitis

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Abstract

We aim to summarize the evidence focusing on the effects of various doses of human milk on the risk of neonatal necrotizing enterocolitis (NEC). The eligible articles in the study were those investigating the association between human milk and NEC published before June 26, 2019, in the PubMed, EMBASE, the Cochrane Library, VIP database, CNKI database, and Wangfang database. The included criteria were as follows: premature infants of <37 weeks; randomly controlled trials (RCTs); those fed by mother's own milk or donor human milk; studies focused on the comparison of human milk and formula milk, involving various breast milk doses; and NEC-related studies. Compared with the exclusive formula, the incidence of NEC in the infants fed by exclusive human milk was significantly lower. The incidence of NEC in the infants fed by exclusive human milk was significantly lower than that of partial human milk [risk ratio (RR) = 0.54, 95% confidence interval (95% CI): 0.36–0.79, $P < .05$]. The incidence of NEC in the infants fed mainly by human milk was significantly lower than that of mainly fed by formula. Incidence of NEC in the infants fed by exclusive human milk was significantly lower than that of any formula (RR = 0.49, 95% CI: 0.34–0.71, $P < .05$). In summary, this meta-analysis was based on the RCTs involving the prevention of NEC using human milk. Exclusive human milk and partial human milk reduced the incidence of NEC in premature infants, especially in the those fed by high proportion of human milk. In addition, more RCTs are needed to further validate such conclusion.

Abbreviations: 95% CI = 95% confidence interval, DHM = donor human milk, ELBW = extremely low birth weight infants, FM = formula milk, HM = human milk, MD = mean difference, MOM = mother' own milk, NEC = neonatal necrotizing enterocolitis, OR = odds ratio, PH = potential of hydrogen, PRISMA = Preferred Reporting Items for Systematic Reviews, RCT = randomized controlled trial, RR = risk ratio, VLB = very low birth weight infants, WMD = weighted mean difference.

Keywords: formula milk, human milk, neonatal necrotizing enterocolitis, systematic review

1. Introduction

The survival of premature infants, especially the very low birth weight infant, increases with the advances of reproductive techniques and perinatology, as well as the extensive establishing of the neonatal intensive care unit. On this basis, the neonatal necrotizing enterocolitis (NEC) associated with neonatal feeding and infection is on an increasing trend, which is one of the major causes for neonatal death and disability.[1] The incidence of NEC among the premature infants is high, resulting in an extremely high mortality. To our best knowledge, NEC has been related to various factors, including premature labor, low-body weight, infection, posthypoxic and postischemic reperfusion injury in intestinal tract, as well as improper feeding.[2,3]

NEC was closely related to the gestational age. In the previous studies, the majority of the NEC cases (85%) were premature infants with a gestational age of less than 35 weeks, while the incidence of NEC in the infants with a body weight of less than 1.5 kg increased from 0.7% to 6.6%.[4–6] Nowadays, the incidence of NEC among the very low birth weight infants was in a range of 5% to 12% in the developed countries. For example, about 5.1% of the infants with a gestational age of less than 33 weeks in Canada were affected by NEC.[4,7,8]

Most of the patients (>90%) presented NEC after enteral feeding. Therefore, enteral feeding is a pacing factor for the pathogenesis of NEC.[2,9] Infection or improper feeding may induce local immunity in intestinal tracts, which then resulted in massive release of inflammatory factors and injury of intestinal mucosa. Meanwhile, under the stress states, the blood would flow into most of the crucial organs such as heart, brain, and kidneys, leading to reduction of blood supply in the intestinal tract, together with local ischemia in intestinal mucosa and immunologic barrier damages. In addition, the peristalsis of the intestinal tract showed reduction and the bacterial proliferation in the

Editor: Vasile Valeriu Lupu.

This study was supported by the Young Talent Program of Fujian Health Bureau (No. 2019-1-16) and the Social Developmental Induction Program of Fujian Province (No. 2018Y0006).

This study was approved by the Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University.

The authors declare that they have no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Zhang B, Xiu W, Dai Y, Yang C. Protective effects of different doses of human milk on neonatal necrotizing enterocolitis. Medicine 2020;99:37(e22166).

Received: 23 October 2019 / Received in final form: 27 March 2020 / Accepted: 13 August 2020

http://dx.doi.org/10.1097/MD.0000000000022166

intestinal tract was more obvious. All these may trigger the pathogenesis of NEC.[10,11]

For the patients with severe NEC, wide excision is usually required due to massive intestinal tract necrosis. The survived infants are apt to develop complications such as intestinal dysfunction, growth delay, and nervous system disorders. Therefore, the mortality of NEC is very high and the long-term prognosis is usually poor, which severely affects the life quality of these survivors. In the past 2 decades, the NEC is still not well controlled despite the advances in the management of such condition, including application of antibiotics, probiotics, and novel feeding strategies.[12–14] Therefore, it is urgent to develop new methods for the prevention of NEC.

Human milk contains many nutritive materials and bioactive substances, which can contribute to the neonatal growth and enhance the innate immunity and antibiosis. Thus, it contributes to the prevention of NEC.[15,16] Nevertheless, a part of the neonates are partially fed by human milk, and even some others fed by formula milk. In this meta-analysis, we aim to investigate the protective effects of various doses of human milk on the NEC, as well as the relationship between human milk and NEC.

2. Materials and methods

2.1. Literature search

A comprehensive literature search was performed to the Chinese and English articles on human milk and NEC. The publication time was before June 26, 2019. The articles were obtained from PubMed, EMBASE, Cochrane Library, CNKI database, VIP database, and Wanfang database. The key words used in the literature search were as follows: "breast feeding" or "breast-feeding" or "breast milk" or "breastmilk" or "humanmilk" or "human milk" or "donor milk" or "donormilk" or "maternal milk" or "maternalmilk" or "mother milk" or "mothermilk" or "breast feed" or "breastfeed" or "Breast-fed" or "formula milk" AND "Necrotizing enterocolitis" or "NEC" or "premature infant" or "very low birth weight infants" or "VLBW" or "extremely low birth weight infants" or "ELBW." In addition, manual search was given to the articles obtained from these databases focusing on the relationship between human milk and NEC.

2.2. Eligible studies

The inclusion criteria were as follows: premature infants with a gestational age of less than 37 weeks old; randomly controlled trials (RCTs); those fed by mother's own milk or donor human milk; studies focused on the comparison of human milk and formula milk, involving various human milk doses; NEC-related studies. The exclusion criteria were as follows: studies performed in special population other than premature infants, such as those with a certain disease; studies with no adequate information or errors; duplicated publication; cohort studies, case–control studies, review articles, case report, correspondence or animal studies.

2.3. Data extraction

Two experienced researchers read the whole texture of each article and did the data extraction independently. In cases of any disputes, a comprehensive discussion was given until consensus. Epidata 3.02 software was used for the data entry. The extracted information included title, authors, year of publication, region and duration of the research, study protocols, sample size, gestational age, weight at birth, feeding type, NEC diagnostic standards, case number, as well as NEC staging.

2.4. Evaluation of article quality

Cochrane Risk of Bias Tool 19 was utilized to assess the risk of bias in the eligible trials. The trials were considered as high risk of bias, low risk of bias, or unclear risk of bias according to the sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, reporting bias, and other possible sources of bias.

2.5. Statistical analysis

Cochrane Collaboration's Review Manager V 5.3 was used for the data analysis. The relative risk (RR) for dichotomous outcomes and weighted mean difference (WMD)/mean difference (MD) for continuous outcomes was evaluated, by using a 95% confidence interval (95% CI). Heterogeneity was determined using the P value and I^2 statistic. In the presence of no significant heterogeneity in the analysis ($P > .10$ or $I^2 < 50\%$), a fixed-effect model was adopted. In cases of significant heterogeneity ($P < .10$ or $I^2 \geq 50\%$), a random-effect model was adopted. Subgroup analysis was conducted according to the dose of human milk. Sensitivity analysis was utilized to evaluate the influence of every single study on the pooled effects. The results were reported using the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. $P < .05$ was considered to be statistically significant.

3. Results

3.1. Features of the eligible studies

In total, 3642 citations were identified after electronic search and other sources. Upon screening the titles, abstracts, and full-text, 3631 studies were excluded after excluding duplication, letters, reviews, none-RCTs, or reporting no NEC outcomes. Finally, there were 12 RCTs that met the inclusion criteria involving a total of 2677 infants. Flow diagram of studies identified in this meta-analysis is shown in Fig. 1. The mean gestational age and birth weight were in a range of 24.8 to 33.8 weeks and 690 to 1912 g, respectively. The feeding strategy and NEC were variable in different studies. Among the included patients, 131 infants showed NEC. For the data entry, the feeding types of the infants were divided into 6 categories: exclusive human milk (100% human milk feeding), partial human milk (0<human milk feeding<100%), mainly human milk (50%<human milk feeding<100%), exclusive formula (100% formula feeding), mainly formula (50%<formula feeding<100%), and any formula (0<formula feeding≤100%). Patients with any stage of NEC were defined as NEC (Table 1).

3.2. Sensitivity analysis and publication bias

Sensitivity analysis was performed through gradual exclusion. No obvious changes were noticed after incorporation of OR values. Sensitivity analysis indicated that all the studies showed satisfactory homogeneity. The results of the meta-analysis were reliable. The risk of bias is shown in Fig. 2. The funnel plot was symmetric (Fig. 3), which indicated a small publication bias. This

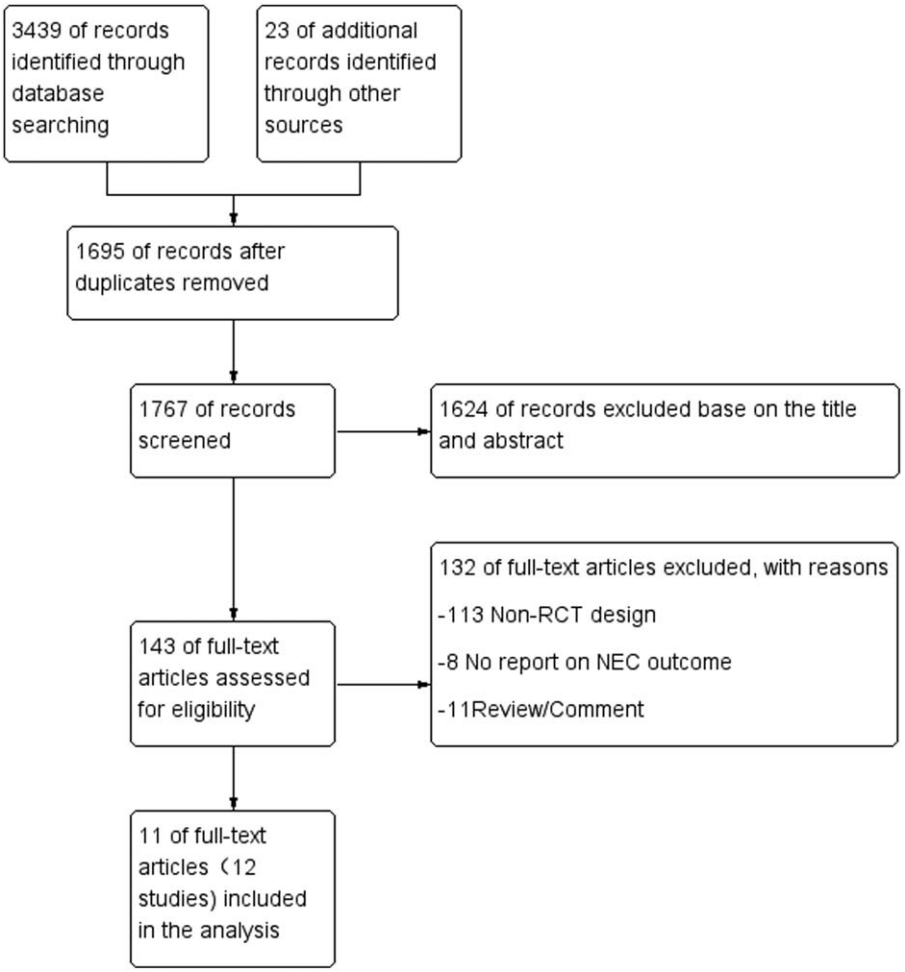

Figure 1. The flow diagram of selected studies.

implied that the included studies showed satisfactory representativeness.

3.3. Feeding and NEC

For the further analysis, meta-analysis was performed after dividing the feeding strategies into 4 groups (e.g., exclusive human milk vs exclusive formula; exclusive human milk vs partial human milk; mainly human milk vs mainly formula; and exclusive human milk vs any formula). Heterogeneity analysis demonstrated that there were no heterogeneities in the subgroup analysis. On this basis, fixed effect model was utilized for the incorporation of effects. In total, 6 studies[17–22] compared the incidence of NEC between infants received exclusive human milk or exclusive formula. Meta-analysis showed that compared with the exclusive formula, the incidence of NEC in the infants fed by exclusive human milk was significantly lower (RR = 0.24, 95% CI: 0.08–0.77, $P < .05$). Five studies[19,23–26] compared the incidence of NEC among the infants fed by exclusive human milk or partial human milk. Meta-analysis showed that the incidence of NEC in the infants fed by exclusive human milk was significantly lower than that of partial human milk (RR = 0.54, 95% CI: 0.36–0.79, $P < .05$). Nine studies[17–22,26,27] focused on the comparison of NEC incidences between the infants fed by mainly human milk or mainly formula. The data indicated that the incidence of NEC in the infants fed by mainly human milk was significantly lower than that of mainly formula (RR = 0.50, 95% CI: 0.30–0.83, $P < .05$). Eleven studies[17–26] focused on the comparison of NEC incidence between the infants fed by exclusive human milk and any formula, which indicated that the incidence of NEC in the infants fed by exclusive human milk was significantly lower than that of any formula (RR = 0.49, 95% CI: 0.34–0.71, $P < .05$, Fig. 4).

4. Discussion

In this study, we first investigated the effects of various doses of human milk on the prevention of NEC through a meta-analysis based on RCTs. Our data indicated that the incidence of NEC showed significant decline in the premature infants fed mainly by human milk ($P < .05$). In addition, the incidence of NEC showed a tendency of decline with the increase of human milk proportion. In contrast, with the increase of formula milk proportion, the incidence of NEC showed a tendency of increase. Such correlation between the NEC incidence and proportion of human milk has never been reported before. In the previous studies,[28–30] there was a negative correlation between the proportion of human milk uptake and complications, hospital

Table 1

The characteristics of the 12 studies included in the meta-analysis.

Ref.	Country	Study design	Sample size	Feeding categorical, NEC/n	Gestational age, wk	Birth Weight, g	NEC diagnosis
Wu[17],2016	China	RCT Single-Centered	122	Gp1: MOM+DHM:0/62 Gp2: FM:0/60	Gp1: 29.64±1.8. Gp2: 30.03±1.7	Gp1: 1274±197.67. Gp2: 1282±171.03.	NEC (≧Bell's stage 2)
Cristofalo[18],2013	USA Austria	RCT Multi-Centered In 7NICU	53	Gp1: DHM:1/24 Gp2: FM:5/29	Gp1: 27.5±2.4 Gp2: 27.7±1.5	Gp1: 983±207 Gp2: 996±152	NEC (≧Bell's stage 2)
Lucas-A [19],1990	UK	RCT Multi-Centered In 3NICU	162	Gp1: DHM:1/86 Gp2: FM:4/76	All case 31±3	All case 1370±320	NEC:classic radiological features or established surgically or at necropsy
Lucas-B [19],1990	UK	RCT Multi-Centered In 3NICU	502	Gp1: MOM+DHM:3/253 Gp2: MOM(48%)+FM:9/249	All case 31±3	All case 1370±320	NEC:classic radiological features or established surgically or at necropsy
Gross[20], 1983	USA	RCT Single-Centered	67	Gp1: DHM,term:1/21 Gp2: DHM,preterm:0/20 Gp3: FM: 3/26	Gp1: 31±0.4 Gp2: 30.6±50.4 Gp3: 31±0.3	Gp1: 1321±59 Gp2: 1322±54 Gp3: 1324±49	Not Mention
Tyson[21], 1983	USA	RCT Single-Centered	81	Gp1: DHM:0/37 Gp2: FM:1/44	Gp1: 29.4±3.1 Gp2: 29.4±2.4	Gp1: 1238±190 Gp2: 1226±197	Not Mention
Svenningsen[22],1982	Sweden	RCT Single-Centered	48	Gp1: HM(1.6g protein per 100 kcal): 0/18 Gp2: FM(2.3g protein per 100 kcal): 0/14 Gp3: FM(3.0g protein per 100 kcal): 0/16	Gp1: 30.6±3.2 Gp2: 31.7±2.2 Gp3: 1339±317	Gp1: 1356±388 Gp2: 1519±393 Gp3: 1339±317	Not Mention
Corpeleijn[23],2016	Netherland	RCT Multi-Centered in 6NICU	373	Gp1:MOM+DHM:17/183 Gp2:MOM(84.5%)+FM:17/190	Gp1:28.3±2.3 Gp2:28.6±2.2	Gp1:1065(830,1265) Gp2:1077(854,1275)	NEC (≧Bell's stage 2)
O'Connor[24], 2016	Canada	RCT Multi-Centered In 4NICU	363	Gp1: MOM+DHM:3/181 Gp2:MOM(63.3%)+FM:12/182	Gp1:27.5±2.4 Gp2:27.8±2.7	Gp1:995±273 Gp2:996±272	NEC (≧Bell's stage 2)
Sullivan[25],2010	USA Austria	RCT Multi-Centered In 12NICU	207	Gp1: MOM+DHM((fortified at 100 mL/kg): 3/67 Gp2:MOM+DHM ((fortified at 40 mL/kg): 5 /71 Gp3: MOM(82%)+FM: 11/69	Gp1: 27.2±2.2 Gp2: 27.1±2.3 Gp3: 27.3±2.0	Gp1: 945±202 Gp2: 909±193 Gp3: 922±197	NEC(clinical+radiographic evidence)
Schanler[26], 2005	USA	RCT Single-Centered	236	Gp1: MOM+DHM:5/78 Gp2: MOM:4/70 Gp3: MOM(38.9%)+FM:10/88	Gp1: 27±2 Gp2: 27±2 Gp3: 27±2	Gp1: 947±233 Gp2: 999±259 Gp3: 957±267	NEC (≧Bell's stage 2)
O'Connor[27], 2003	USA UK Chile	RCT Multi-Centered In 14NICU	463	Gp1: HM(>80%)+FM: 0/43 Gp2: HM(>50%)+FM: 5/98 Gp3: HM(<50%)+FM: 1/203 Gp4: HM(<20%)+ FM: 7/119	Gp1: 29.7±2.0 Gp2: 29.6±1.9 Gp3: 29.5±2.1 Gp4: 29.9±2.0	Gp1: 1275±312 Gp2: 1287±279 Gp3: 1288±287 Gp4: 1332±279	Not Mention

DHM=donor human milk, FM=formula milk, HM includes MOM and DHM, HM=human milk, MOM=mother' own milk, NEC=neonatal necrotizing enterocolitis, RCT=randomized controlled trial.

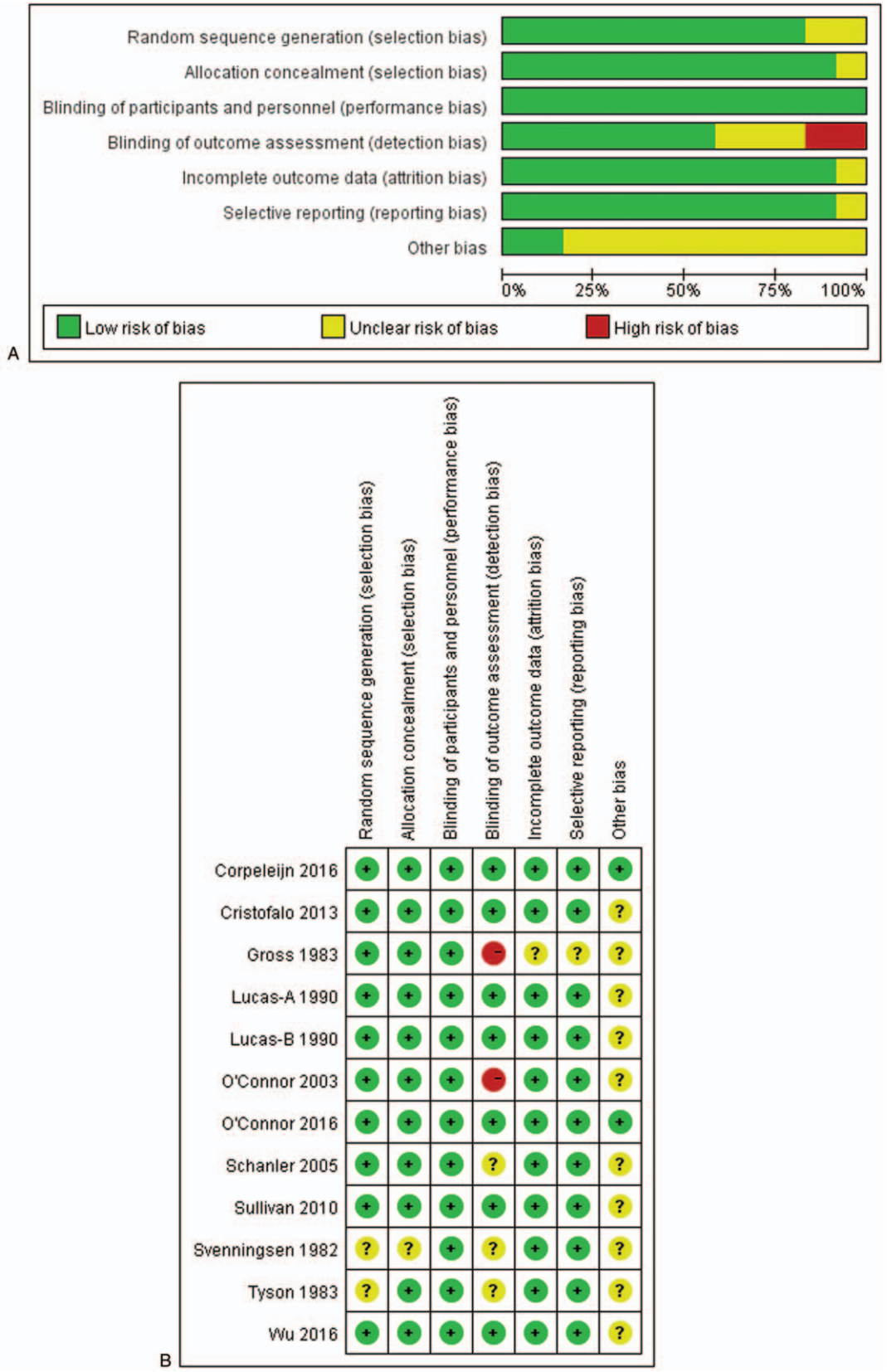

Figure 2. Quality evaluation data of RCTs.

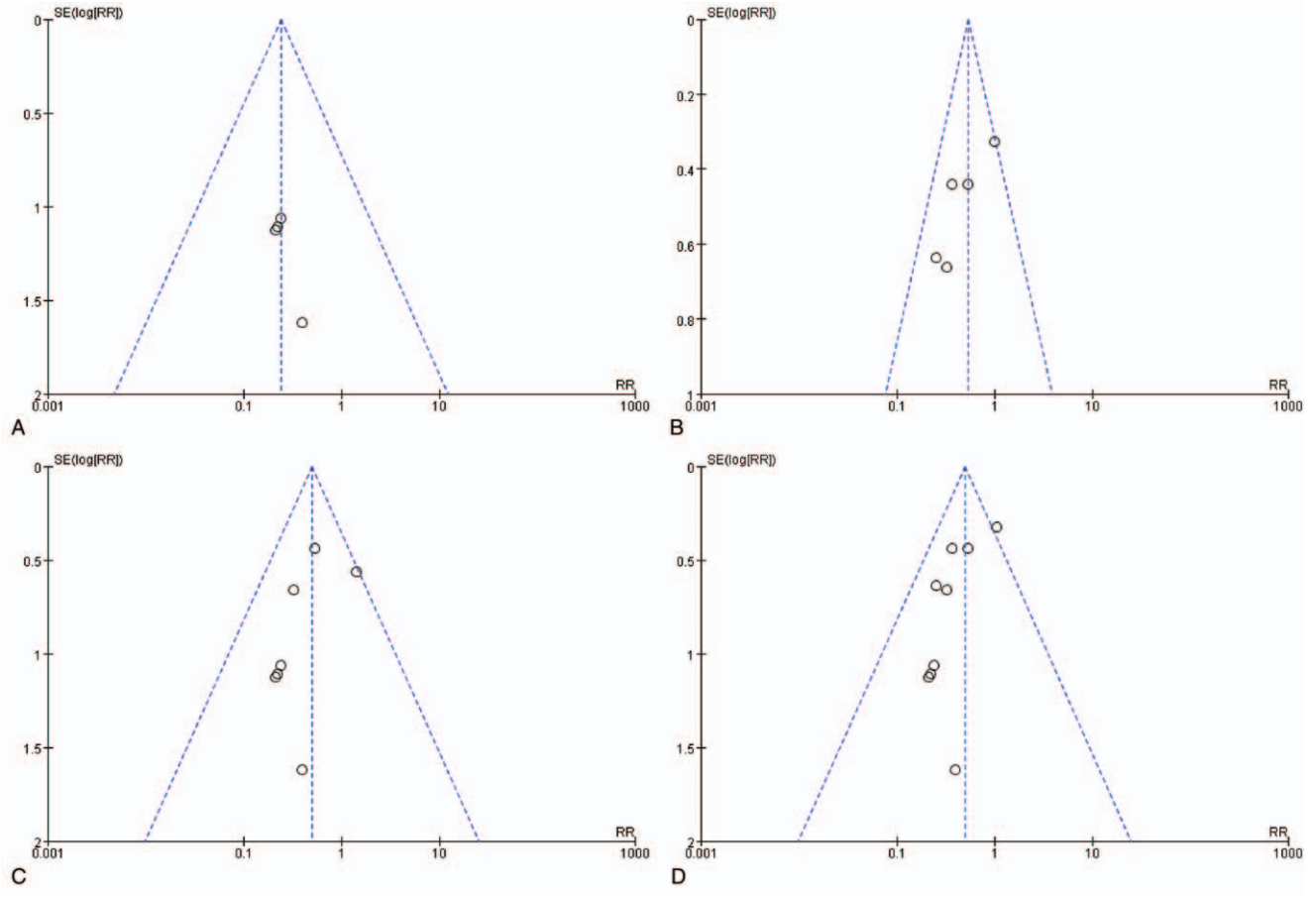

Figure 3. Funnel plot of human milk and formula. (A) Funnel plot of exclusive human milk versus exclusive formula. (B) Funnel plot of exclusive human milk versus partial human milk. (C) Funnel plot of mainly human milk versus mainly formula. (D) Funnel plot of exclusive human milk versus any formula.

stay, and the financial expenditure in the premature infants. Moreover, human milk contributed to the feeding of the premature infants, as well as the development of the physical and nervous behaviors. In some studies, in the premature infants with NEC, the conditions in the infants fed by formula milk were more severe than those fed by human milk, leading to a higher requirements for the surgical intervention.[31–33] This implied that feeding strategy was associated with the severity of NEC. However, in this meta-analysis, we did not divide the NEC into different groups based on the severity. Therefore, no subgroup analysis was performed to the NEC severity in our study. Interestingly, in a previous study, Cristofalo et al[18] demonstrated that premature infants fed by human milk showed a lower incidence of severe NEC and requirement of surgical intervention compared with the counterparts fed by formula milk. Besides, the long- and short-term outcomes after treatment were much better, which implied that premature infants fed by human milk showed mild severity and good outcome compared with the others. To date, no RCTs have been conducted to investigate the effects of human milk or formula milk on the mortality of NEC.

Human milk could prevent the onset of NEC, as the nutrients in the human milk could be easily absorbed by the premature gastrointestinal tracts. Besides, there are many biologically active components in the human milk that can regulate the host immune system to inhibit the activation of local immunity and decrease the injury of intestinal mucosa. In addition, epidermal growth factors in the human milk can directly repair the injury in the intestinal mucosa. Furthermore, the human milk could lower the potential of hydrogen value in the intestinal tract, leading to formation of acidic environments in the intestinal tract that inhibited the growth of inimical bacteria. This would finally enhance the natural barrier of the intestinal mucosa.[15,34–36]

As far as we know, this is the first study to investigate the protective effects of various doses of human milk on NEC. We only collect RCTs that were rigorously designed with adequate cases and strong representativeness. This study showed strong evidence. Finally, all the comparison analyses showed a strong consensus. This implied that both exclusive human milk and partial human milk could reduce the incidence of NEC. Sensitivity analysis revealed that our findings were not affected by the fluctuation of certain studies.

Indeed, there are some limitations in this study. For example, we only focused on the English and Chinese articles, and not included the articles published in other languages. In addition, most of the included studies did not divide the NEC severity. Therefore, we cannot perform the subgroup analysis based on the NEC severity, which may lead to possibility of heterogeneity. Finally, human milk included mother' own milk and donor human milk, and may present differences in the prevention of NEC for different types of human milk. Nevertheless, as most of

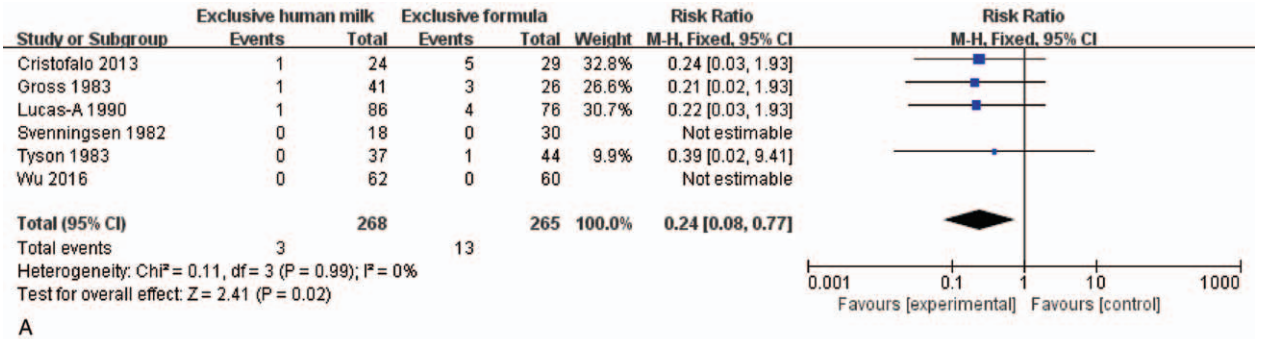

Figure 4. Forest plots of human milk versus formula. (A) Forest plots of exclusive human milk versus exclusive formula; The fix effects model was selected in the presence of I^2 value <50% and $P > .1$; RR = 0.24 indicates that the RR of NEC in preterm infants with exclusive human milk was 0.24-fold, compared with exclusive formula. (B) Forest plots of exclusive human milk versus partial human milk; The fixed effects model was selected in the presence of I^2 value <50% and $P > .1$; RR = 0.54 indicates that the RR of NEC in preterm infant with the exclusive human milk was 0.54-fold, compared with partial human milk. (C) Forest plots of mainly human milk versus mainly formula; The fixed effects model was selected in the presence of I^2 value <50% and $P > .1$; RR = 0.50 indicated that the RR of NEC in preterm infant with mainly human milk is 0.50-fold, compared with mainly formula. (D) Forest plots of exclusive human milk versus any formula; The fix effects model was selected because the I^2 value <50% and $P > .1$; RR = 0.49 indicates that the RR of NEC in preterm infant with the exclusive human milk was 0.49-fold, compared with any formula.

the studies did not categorize the human milk, we did not perform the subgroup analysis to investigate the efficiency of various types of human milk on NEC prevention. This may lead to heterogeneity.

5. Conclusion

This meta-analysis was based on the RCTs involving the prevention of NEC using human milk. It indicated that human milk was effective for preventing NEC, and there was a negative correlation between uptake of human milk and incidence of NEC. Meta-analysis demonstrated that the premature infants fed by human milk showed a lower incidence of NEC than those fed by formula milk, especially those fed mainly or completely by human milk. In future, more RCTs are required to provide conclusions in strength and capacity.

Author contributions

Authorship: ZBQ wrote the manuscript; YCY revised the manuscript; XWL did the data analysis; DY did the data collection.

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