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# Risk Factors of Nosocomial Infection for Infants in Neonatal Intensive Care Units: A Systematic Review and Meta-Analysis

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Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** The aim of this study was to identify the nosocomial infection (NI) risk factors in neonatal Intensive Care Units (NICU).





**Material/Methods:** Databases (PubMed, Embase, Cochrane, VANFUN, CNKI, and VTTMS) were searched using index words to find relevant studies published before November 2018. Meta-analyses of relative risk (RR) were performed for the identification of risk factors.

**Results:** Data from 22 cohort studies (2270 infants with and 21 605 infants without NI) were included in the meta-analysis. Infant weight of <2500 g (RR: 3.44, 95% CI: 2.31–5.11), gestational age of <37 weeks (RR: 3.85, 95% CI: 1.87–7.92), mechanical ventilation use (RR: 3.16, 95% CI: 2.21–4.50), venipuncture (RR: 3.01, 95% CI: 1.20–7.57), the incidence of asphyxia (RR: 1.68, 95% CI: 1.04–2.71), and feeding intolerance (RR: 2.12, 95% CI: 1.60–2.81) were identified as the risk factors for the incidence of NI. There was no significant publication bias.

**Conclusions:** This study shows that <2500 g infant body weight, gestational age of <37 weeks, mechanical ventilation utility, venipuncture, asphyxia incidence, and feeding intolerance are the risk factors for NI nosocomial infection in infants in NICU. Appropriate preventive measures and targeted interventions are needed.

**MeSH Keywords:** **Behavioral Risk Factor Surveillance System • Cross Infection • Meta-Analysis**

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## Background

Nosocomial infection (NI) is a significant cause of morbidity and mortality in neonatal Intensive Care Units (NICU) globally [1]. It is defined as an infection acquired during the period of hospitalization that was absent before or at the time of admission and that must occur up to 48 hours after hospital admission. NI has strong influence on many aspects of the healthcare system as it increases the duration of hospitalization and use of medical resources, in addition to an increased cost of care, particularly in developing countries where this is a major public health issue. The incidence of NI in NICU is approximately 30% and is responsible for up to 40% of reported neonatal deaths in developing countries [2,3].

Newborns, particularly those hospitalized in an NICU, are one of the most vulnerable groups among different age groups to acquire NI. Neonates in the NICU face significant exposure to medical devices, antimicrobial drugs, and various other causative organisms. A slower maturation of the infant's immune system increases the likelihood of NI incidence. NI is a blanket term for a range of infections including pneumonia, urinary tract infections, bloodstream infections, meningitis, secondary skin infections, and infections of the throat, eye, ear, or nose. These may be caused by bacteria, viruses, fungi, or several of these combined [4,5].

NI continue to be a substantial source of avoidable morbidity and mortality in developing countries where rates of infection are excessive because of inadequate infection control practices, overcrowding in hospitals, inappropriate use of limited resources, and lack of supervision [6,7]. The major pathogens causing infections in neonates are different not only from country to country and in different units, but also change over time within the same unit [8].

Antibiotic resistance is a significant risk factor for adverse outcomes in infants with NI [9], which can increase mortality risk by 27% for every additional resistance to an antibiotic class [10]. Drug-resistant infections such as *Serratia marcescens* infect blood, urinary tract, and surgical wounds and may cause keratitis, conjunctivitis, pneumonia, sepsis, and meningitis [11]. Gram-negative infections are more resistant than gram-positive organisms [12].

The present investigation aimed at identifying the risk factors of NI in NICUs by using the incidence rates of NI reported by the relevant studies to perform a meta-analysis of relative risks of important risk factors.

## Material and Methods

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol.

### Search strategy

The electronic databases PubMed, Cochrane, Embase, VANFUN, CNKI, and VTTMS were searched for studies reporting the incidence of NI in the NICU published before November 2018. Search terms used were newborn, neonatal, infant, NICU, Neonatal Intensive Care Unit, nosocomial infection, hospital infection, hospital-acquired infection, pathogenic bacteria, and pathogen. These terms were used with "AND" or "OR" in logical combinations. References lists of related studies were also screened. Two reviewers performed literatures search independently and while unifying the results, the help of a third reviewer was sought if any disagreement arose.

### Inclusion and exclusion criteria

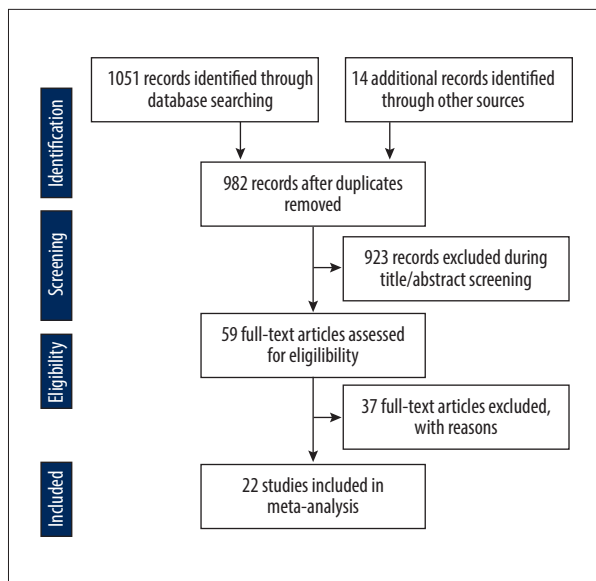
Studies were included if they reported the incidence of NI in infant cohorts studied at an NICU and published in English or Chinese language. Studies were excluded if they lacked a control group, or if they were case reports, theoretical research, systematic reviews and/or meta-analysis, conference reports, expert comments, or economic analysis.

### Data extraction and quality assessment

Data were extracted from eligible studies and organized into 2 categories: (I) basic information and (II) key outcomes. Basic information included author name, sample size, publication year, and identified risk factors. Key outcomes included clinical outcome data pertaining to infant body weight, gestational age, mechanical ventilation use, venipuncture, incidence of asphyxia, and feeding intolerance. Data were extracted by 2 independent reviewers and the help of a third author was sought when any disagreement arose while unifying the results.

### Statistical analysis

Categorical data reported by the individual studies were used to calculate relative risk (RR). For the identification of risk factors, meta-analyses of RR in the incidence of NI were performed between: (i) under vs. over 2500 g body weight, (ii) less vs. more than 37 weeks gestation, (iii) use vs. no use of mechanical ventilation, (iv) venipuncture vs. no venipuncture, (v) incidence of asphyxia vs. no incidence), and (vi) prevalence of feeding intolerance vs. no prevalence.



**Figure 1.** Flow diagram of the literature search and selection process.

Statistical indices,  $I^2$ , and chi-squared ( $\chi^2$ ) test were used to evaluate data heterogeneity and to select the meta-analysis model. When results had a  $\chi^2 P \leq 0.05$  and/or  $I^2 > 50\%$ , data were considered heterogeneous and the random-effects model was used; otherwise, the fixed-effects model was used. Publication bias assessment was performed with Egger's test or Begg's test after visualizing the funnel plot of an outcome measure. Stata software (version 10; Stata Corp., TX, USA) was used for meta-analyses.

## Results

### Characteristics of included studies

The literature search identified 982 abstracts, of which 923 were excluded after inspection of the title and/or abstract, which left a total of 59 articles for further consideration, which were then downloaded from databases. A review of these research articles led to the exclusion of 37 articles for failing to meet the inclusion criteria; among these, 9 were descriptive studies, 10 had no clinically relevant outcomes, and 4 were duplicate studies. In total, the meta-analysis included 22 cohort studies with an overall population of 2270 infants with and 21 605 infants without NI [13–34]. Figure 1 presents the study selection method, and key characteristics of the studies are displayed in Table 1. The funnel plot of log RR of infant body weight showed the absence of significant publication bias, which was confirmed by the outcomes of Begg's test ( $Z=1.49$ ,  $p=0.137$ ) and Egger's test ( $p=0.104$ ).

### Infant body weight as a risk factor

Sixteen studies reported body weight of 1666 infants with and 18 532 infants without NI. Random-effects meta-analysis showed that the incidence of NI was significantly higher in infants with a body weight of  $<2500$  grams (g) in comparison with those with  $\geq 2500$  g weight (RR: 3.44, 95% CI: 2.31–5.11; Figure 2).

### Gestational age as a risk factor

Ten studies reported the gestational age of 791 infants with and 9774 infants without NI. Random-effects meta-analysis showed that a gestational age of  $<37$  weeks posed a significantly higher NI risk (RR: 3.85, 95% CI: 1.87–7.92; Figure 3).

### Mechanical ventilation as a risk factor

Ten studies (981 infants with and 5953 infants without NI) reported the use of mechanical ventilation for infants. Random-effects meta-analysis showed that infants who underwent mechanical ventilation had higher NI incidence compared with the infants who did not undergo mechanical ventilation (RR: 3.16, 95% CI: 2.21–4.50; Figure 4).

### Venipuncture as a risk factor

Nine studies (724 infants with and 4890 infants without NI) reported that infants underwent venipuncture. Random-effects meta-analysis showed that infants who underwent venipuncture had a higher incidence of NI than infants who did not undergo venipuncture (RR: 3.01, 95% CI: 1.20–7.57).

### Asphyxia incidence as a risk factor

Six studies (654 infants with and 3913 infants without NI) reported the incidence of asphyxia. Random-effects meta-analysis indicated that the incidence of NI was greater in infants with asphyxia than normal infants (RR: 1.68, 95% CI: 1.04–2.71).

### Feeding Intolerance as a risk factor

Five studies (506 infants with and 2654 infants without NI) reported the prevalence of feeding intolerance. Random-effects meta-analysis showed that the incidence of NI was greater in infants with feeding intolerance in comparison with those without feeding intolerance (RR: 2.12, 95% CI: 1.60–2.81).

## Discussion

In this meta-analysis of 22 studies that reported outcomes of 2270 infants with and 21605 infants without NI, we found that

**Table 1.** Description of included studies and their identified risk factors.

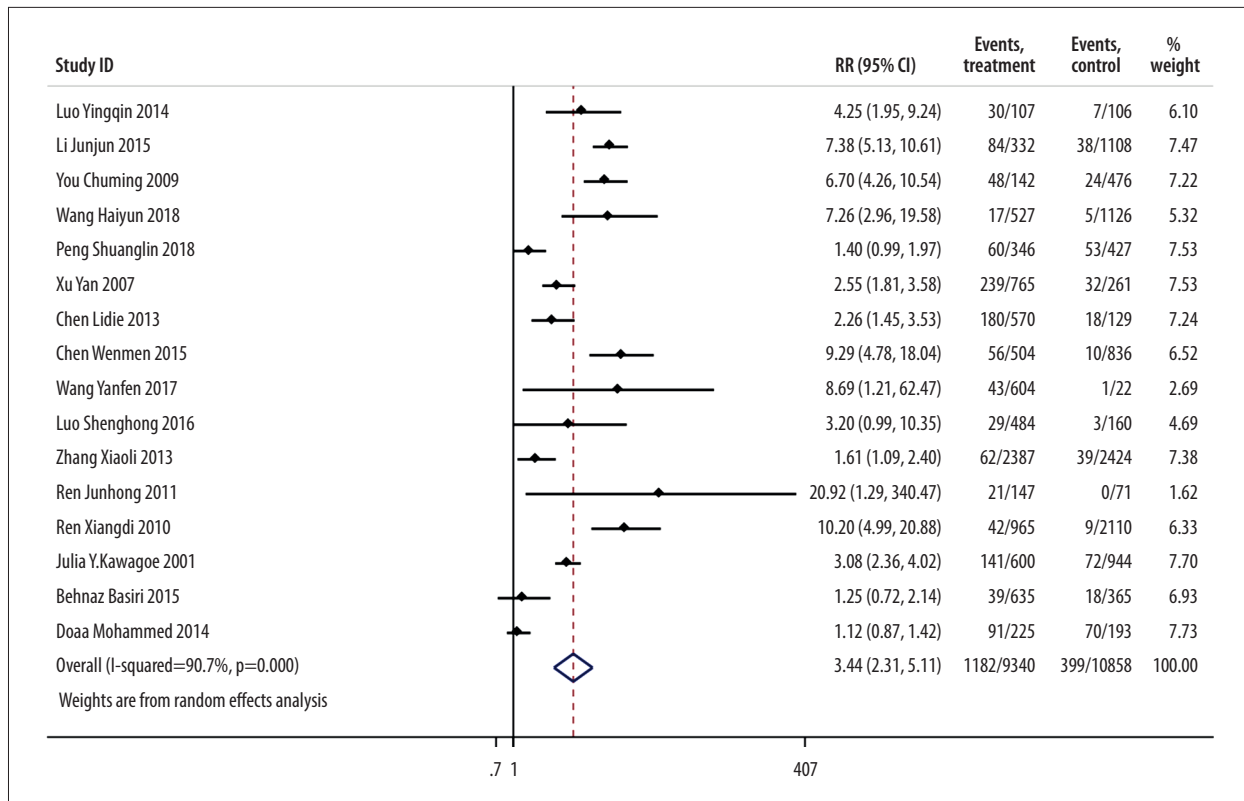
Study (ref. no.)	n		Identified risk factors
	T	C	
Kawagoe 2001 [13]	1544	213	Weight
Xu Yan 2007 [14]	1026	266	Weight
You 2009 [15]	618	72	Weight, gestational age, asphyxia
Ren X 2010 [16]	3075	51	Weight, gestational age
Ren J 2011 [17]	218	21	Weight, gestational age, mechanical ventilation, venipuncture, asphyxia
Zhang S 2011 [18]	660	197	Mechanical ventilation, asphyxia, feeding intolerance
Chen K 2013 [19]	240	20	Mechanical ventilation, venipuncture
Chen L 2013 [20]	699	198	Weight
Zhang X 2013 [21]	903	110	Mechanical ventilation, venipuncture
Zhang XL 2013 [22]	4811	101	Weight
Chi 2014 [23]	658	30	Venipuncture, asphyxia, feeding intolerance
Doaa 2014 [24]	418	161	Weight, gestational age, mechanical ventilation, venipuncture
Luo 2014 [25]	213	37	Weight
Behnaz 2015 [26]	1000	57	Weight, gestational age, mechanical ventilation, venipuncture
Chu 2015 [27]	1340	60	Weight
Li J 2015 [28]	1440	122	Weight, gestational age
Luo 2016 [29]	644	32	Weight, gestational age, mechanical ventilation, venipuncture, feeding intolerance
Yu 2017 [30]	760	198	Mechanical ventilation, venipuncture, asphyxia, feeding intolerance
Wang Y 2107 [31]	726	44	Weight, gestational age
Zhao 2017 [32]	438	49	Mechanical ventilation, feeding intolerance
Peng 2018 [33]	773	95	Weight, gestational age, venipuncture
Wang H 2018 [34]	1653	136	Weight, gestational age, mechanical ventilation, asphyxia

infant body weight of under 2500 grams, a gestational age of less than 37 weeks, use of mechanical ventilation, venipuncture, incidence of asphyxia, and feeding intolerance during infancy are the risk factors for NI.

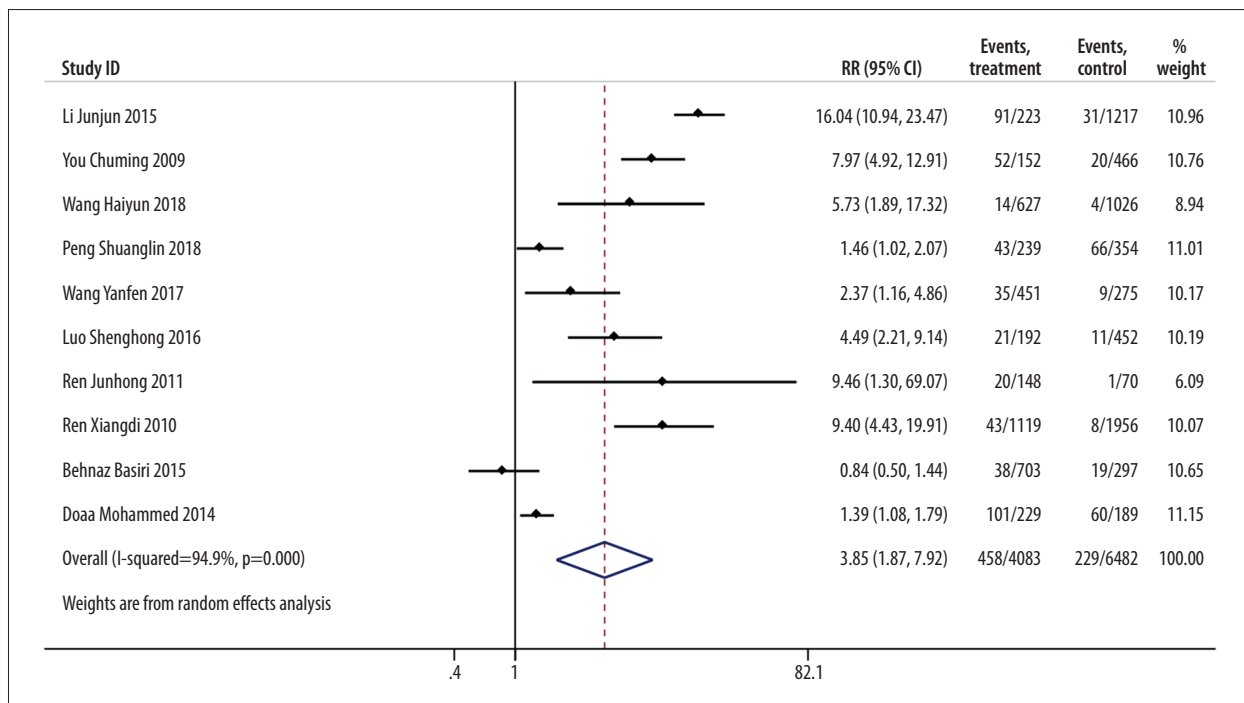
A similar meta-analysis by Zhang et al. [35] that included 8 studies found body mass of  $\leq 2500$  g (OR: 2.71, 95% CI: 1.59–4.59), mechanical ventilation (OR: 2.66, 95% CI: 1.39–5.11), use of central venous indwelling (OR: 6.91, 95% CI: 3.87–12.35), total parenteral nutrition (OR: 2.45, 95% CI: 1.06–5.68), nasogastric tube indwelling (OR: 3.22, 95% CI: 1.08–9.61), and the use of prophylactic antibacterial drugs (OR: 2.57, 95% CI: 0.84–7.80) are significant risk factors for the incidence of NI.

Li et al. [36] identified 13 risk factors related to colonization or infection with extended-spectrum  $\beta$ -lactamase generating bacteria in the NICU. These included parenteral nutrition (OR: 7.51), mechanical ventilation (OR: 4.8), birthweight (standardized mean difference; SMD: 1.17), caesarean delivery (OR: 1.76), gestational age (SMD: 1.36), length of NICU stay (SMD: 0.72), endotracheal intubation (OR: 2.82), continuous positive airway pressure (OR: 5.0), central venous catheter use (OR: 2.85), malformations (OR: 2.89), previous antibiotic use (OR: 6.72); cephalosporin use (OR: 6.0), and ampicillin/gentamicin use (OR: 2.31).

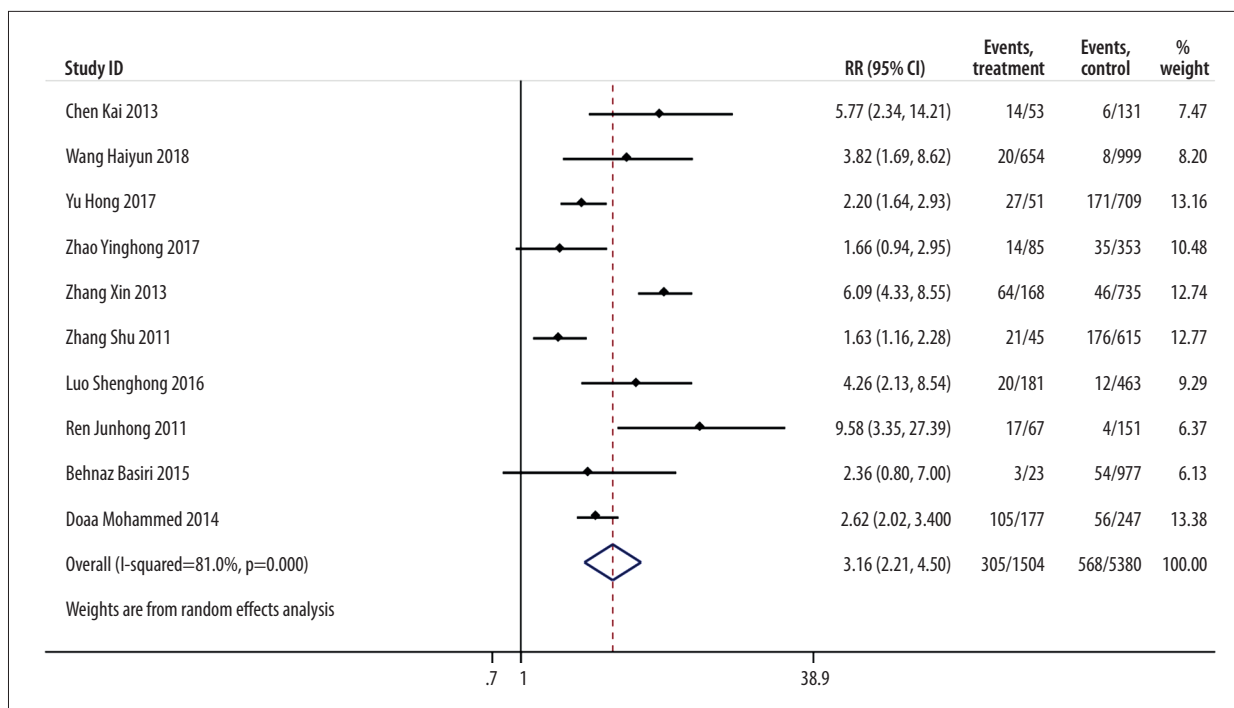
In our study, the results showed weight  $< 2500$  g, gestational age of  $< 37$  weeks, mechanical ventilation, venipuncture, asphyxia, and feeding intolerance were the risk factors for NI



**Figure 2.** Forest plot showing the relationship between weight and the incidence of NI (RR between infants with under and over 2500 grams body weight in the incidence of NI).



**Figure 3.** Forest plot showing the relationship between gestational age and the incidence of NI (RR between infants with under and over 37 weeks of gestation in the incidence of NI).



**Figure 4.** Forest plot showing the relationship between mechanical ventilation and the incidence of NI (RR between infants with and without mechanical ventilation use in the incidence of NI).

in infants who were kept in the NICU. This suggests that the NICU environment during early life may be of significance in NI incidence. As compared to vaginal delivery, neonates delivered by caesarean section have a higher prevalence of abnormal respiratory function and have weaker immune function.

Body mass is the most important independent risk factor for critically ill premature infants. Newborns with low weight have poor physical development, underdeveloped body organ function, and poor immune system function, and therefore have weaker ability to remove invading bacteria [37]. Mechanical ventilation is also a key independent risk factor for infant NI. Preventing the occurrence of respiratory distress syndrome, routine use of non-invasive ventilators as much as possible, evaluating the need for mechanical ventilation, and reducing the mechanical ventilation time wherever possible are key recommendations to reduce the incidence of NI [38]. Overall, these outcomes suggest that invasive procedures should be avoided, and alternative approaches should be taken to reduce the incidence of infection in NICUs.

The prevalence of NI is high. Sohn et al. (2001) reported an 11.4% prevalence of NI after surveying 827 patients in 29 Pediatric Prevention Network NICUs in the USA [39]. NI not only poses risk of morbidity and mortality, but may also alter neurobehavioral development. Early development has long-lasting consequences in later life, which may be affected by NI-altered physiology and increased NICU stay, during which neonates

may be exposed to invasive procedures and antibiotics [40]. Nurses can play a vital role in reducing the incidence of NI by implementing a systematic protocol for improvement. In one example, a nurse-driven quality improvement program at an NICU for the reduction of central line-associated bloodstream infection incidence has successfully led to reduced NICU stay and healthcare costs [41].

NI rates are found to be well-managed with good teamwork. A survey found that the odds of an infant having NI decreased by 18% with each 10% increase in NICU staff responding that there was good teamwork in the NICU [42]. Overall burnout prevalence in NICU staff has not been found to be associated with the prevalence of NI, but perceptions of hardships in work were reported to be associated with increased rates of NI in very low birthweight infants [43].

There are several strengths of this meta-analysis. Included cohort studies offered several advantages including: (i) NI risk factors could be quantitatively estimated using large pooled sample sizes; (ii) stringent inclusion and exclusion criteria were used for the selection of infants; (iii) to ensure accuracy, standard statistical methods were used for data analysis, and (iv) the number of included studies was sufficient for meta-analytical power. Many of these studies had long follow-up times, making the conclusions clinically relevant.



There are, however, some limitations of this study which should also be noted: (I) only cohort studies were included, (II) only English and Chinese articles were included, (III) the infants' conditions were not consistent across the included studies, (IV) numerous treatment regimens were used during NICU stay, (V) the severity of risk factors was variable, and (VI) pooled data were used for the meta-analysis, as individual patient data were unavailable.

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## Conclusions

Based on the evidence obtained in this meta-analysis, infant body weight of <2500 g, gestational age of <37 weeks, use of mechanical ventilation, venipuncture, incidence of asphyxia, and feeding intolerance during infancy are the significant risk factors for the incidence of NI in infants placed in the NICU. Considering the epidemiological nature of this data, it is recommended that NI risk assessment should be performed in even larger and wider datasets to refine the evidence achieved herein.

## Conflict of interest

None.

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