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REVIEW

Risk factors for ventilator-associated pneumonia in the neonatal intensive care unit: a meta-analysis of observational studies

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Abstract Ventilator-associated pneumonia (VAP) is a common and serious problem among mechanically ventilated patients in intensive care units (ICU), especially for the newborn. However, limited literatures have been reviewed to synthesize the finding of previous papers to investigate the risk factors for VAP although it has been a serious complication of mechanical ventilation (MV) with a high morbidity and mortality in the newborn. We performed this meta-analysis to extend previous knowledge for developing VAP prevention strategies by identifying the potential risk factors related to VAP in the neonatal intensive care unit (NICU). The relevant literatures published up to July 2013 were searched in the databases of PubMed, Cochrane Central Register of Controlled Trials, Embase, and Web of Science. Three reviewers screened those literatures and extracted data according to the inclusion and exclusion criteria independently. A total of eight studies including 370 cases and 1,071 controls were identified. Ten risk factors were found to be related to neonatal VAP which were listed as follows in order by odds ratios (ORs): length of stay in NICU (OR 23.45), reintubation (OR 9.18), enteral feeding (OR 5.59), mechanical ventilation (OR 4.04), transfusion (OR 3.32), low birth weight (OR 3.16), premature infants (OR 2.66), parenteral nutrition (OR 2.30), bronchopulmonary dysplasia (OR 2.21), and tracheal intubation (OR 1.12). *Conclusion*: We identified ten variables as independent risk factors for the development of VAP: length of stay in NICU, reintubation, enteral feeding, mechanical ventilation, transfusion, low birth weight, premature infants, parenteral nutrition, bronchopulmonary dysplasia, and tracheal intubation. Due to several limitations in the present study, further large and well-designed studies are needed to confirm the conclusion.

Keywords Neonatal · Ventilator-associated pneumonia · Risk factors · Meta-analysis

Abbreviations

VAP	Ventilator-associated pneumonia
ICU	Intensive care units
NICU	Neonatal intensive care unit
PICU	Pediatric intensive care unit
MV	Mechanical ventilation
OR	Odds ratio
CI	Confidence interval
NOS	Newcastle–Ottawa Scale
RCT	Randomized controlled trial
PARP	Population attributable risk proportion
LBW	Low birth weight
LOS	Length of stay
UVC	Umbilical vein catheterization
NRDS	Neonate respiratory distress syndrome
MAS	Meconium aspiration syndrome
HIE	Hypoxic ischemic encephalopathy
BPD	Bronchopulmonary dysplasia
BSI	Bloodstream infection
SD	Standard deviation

Introduction

VAP is defined as the nosocomial pneumonia developed more than 48 h in mechanically ventilated patients after the initiation of mechanical ventilation [19]. It is a common problem among mechanically ventilated patients in intensive care units (ICU). With the improvement of neonatal intensive care, MV

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has become an essential feature of modern neonatal intensive care unit (NICU). Unfortunately, it may be associated with a substantial risk of ventilator-associated pneumonia. Tracheal intubation is associated with a 3- to 21-fold risk of developing pneumonia. VAP occurs in 3 to 10 % of ventilated pediatric intensive care unit (PICU) patients [2, 12]. Surveillance studies of nosocomial infections in NICU patients indicate that pneumonia comprises 6.8 to 32.3 % of nosocomial infections in this setting [11, 15, 19]. So VAP will impose a serious burden to the patients as well as the whole health care system with its high mortality rates [6, 21, 31].

Till now, epidemiology, risk factors, and outcomes have been extensively described in adult and pediatric patients [8, 12], but scant data exist for neonates, particularly with respect to risk factors. What is more, previous studies reported that the findings on risk factors for VAP were inconsistent [14, 18, 19, 27, 32]. To resolve these conflicting results, a larger sample size is needed. A meta-analysis has characteristics such as larger sample sizes; therefore, we performed this meta-analysis in the hope of identifying the relationship between risk factors and neonatal VAP.

Methods

Data source collection and screening strategy

A meta-analysis was conducted to evaluate the literatures in English published up to July 2013. The databases of PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science were searched using the following key Medical Subject Heading terms: pneumonia, ventilator-associated (MeSH) OR pneumonia, ventilator associated OR ventilator-associated pneumonia OR ventilator associated pneumonia AND risk factors (MeSH) OR factor, risk OR factors, risk OR risk factor or dangerous factors OR hazards OR causes AND newborn OR neonatal OR infant OR NICU. References to all identified publications were entered into reference-managing software (EndNote, version X6).

Inclusion and exclusion criteria

Inclusion criteria

We first performed initial screening of titles and abstracts by two reviewers independently (Bin Tan, Fan Zhang). A second screening was based on full-text review by the same reviewers. Then we compared the final included studies whether they were in accordance with the method of cross-check. Disagreements were discussed, and the consensus was reached with a third party (Jing-Fu Qiu) being involved when necessary. A study was considered appropriate for the meta-analysis when it met the following criteria:

1. The study was about the risk factors for VAP.
2. The patients were from NICU (birth age <28 days).
3. It was a case–control or cohort study.
4. The definition of and diagnostic criteria for VAP were identical with those of the Centers for Disease Control and Prevention (CDC) for infants less than 1 year of age [14]: the time of mechanical ventilation >48 h, new or persistent infiltrations on chest X-ray, worsening gas exchange, and at least three of the following: (a) temperature instability with no other recognized cause, (b) new onset of purulent sputum, (c) increase in respiratory secretions or increased need for suctioning, (d) WBC <4,000/mm^3 or >15,000/mm^3, (e) respiratory signs (apnea, tachypnea, nasal flaring, retraction, wheezing, rales, or ronchi) and bradycardia or tachycardia.
5. Published in the English language.

Exclusion criteria

A study was excluded if:

1. It was duplicated.
2. The time of mechanical ventilation is <48 h or not mentioned in the original studies.
3. It did not provide sufficient information to allow the calculation of ORs and 95 % confidence interval (CI) for the risk of VAP.
4. It was a review or a report.

Data extraction

Three reviewers (Bin Tan, Fan Zhang, and Xian Zhang) independently extracted relevant data according to the previously made data extraction form. The extraction results were evaluated by other reviewers (Jing-Fu Qiu, Xiao Liu). Disagreements were resolved by discussion. The extracted data included (1) title of studies and countries, (2) the names of the first authors and years of publication, (3) study designs, (4) number of cases and control patients, (5) ORs calculated from both univariate and multivariate logistic regression analyses, and (6) incidence of neonatal VAP.

Quality assessment

The Newcastle–Ottawa Scale (NOS) [33] was used to assess the quality of each study. Aspects of methodology were assessed in those which were not a randomized controlled trial (RCT), which included the selection of cases (4 items, 4 points), comparability of cases and controls (1 item, 2 points), and ascertainment of exposure to risks (3 items, 3 points) (9 points in total). Research of low quality was scored 0~4

points and studies with scores of 5~9 points were identified as high-quality research [28]. The quality of each study was assessed independently by three reviewers (Yu-Shuang Gao, Ying-Li Li, and Ya-Ling Huang). The disagreements on rating were resolved through discussion by the research group until the consensus was reached.

Statistical analysis

A meta-analysis was performed using Review Manager 5.1 and Stata 11.0. Heterogeneity among the results of the included studies was evaluated by χ^2 and I^2 statistic tests. Once effects were found to be heterogeneous ($I^2>50$ % or $P<0.05$), the random effects model was used. Otherwise, the fixed effects model would be used. Sensitivity analyses were conducted by omitting individual studies sequentially and through the comparison of the P value of pooled ORs for the random effects model and fixed effects model. The results were identified credible when the corresponding P value of pooled ORs was not substantially different. In addition, publication bias was examined using Begg's test and Egger's test by the software Stata 11.0. We used ORs and the 95 % CI to compare the risk factors for neonatal VAP. Results were considered to be statistically significant when $P<0.05$. Moreover, the overall population exposure rate was substituted for the pool exposure rate (P_e) of controls to calculate the population attributable risk proportion (PARP). The formula is as follows: $\mathrm{PARP}=P_e(\mathrm{OR}-1)/P_e(\mathrm{OR}-1)+1$.

Results

A total of 206 potentially relevant publications up to July 2013 were systematically identified through electronic databases. After screening the titles and abstracts, 29 studies were left excluding duplicates, studies not pertinent to risk factors for neonatal VAP, reviews, and reports. Among them, 21 studies were excluded by full-text screening because they did not match the inclusion criteria described above. Finally, eight studies [1, 3, 7, 10, 27, 29, 30, 34] were included for the meta-analysis (Fig. 1).

The included studies were published from 2002 to 2013. They were conducted in different countries including China [10, 34], Spain [7], USA [3], Iran [1], Thailand [29], Egypt [27], and India [30]. Cohort study designs were used in four studies while the other four studies used case–control designs. The results of one cohort study [7] and one case–control study [27] did not adjust for any potential confounders, whereas the remaining studies included adjustment for several conventional risk factors, including reintubation, transfusion, parenteral nutrition, gender, prematurity, birth weight, and MV. After assessment of risk bias using the NOS, all studies were assessed as high-quality research. Table 1 shows the detailed characteristics of the included studies.

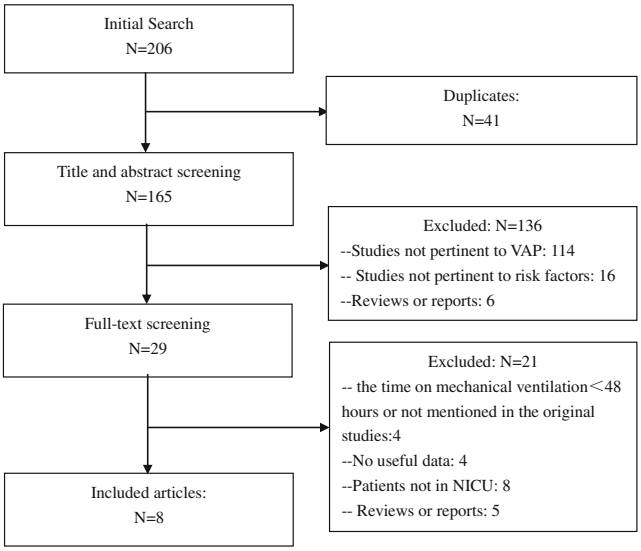

Fig. 1 Flow diagram of the selection process

Incidence of VAP

A total of 1,441 participants (370 cases and 1,071 controls) were retrieved in our study. We found that the incidence of neonatal VAP was higher than that in PICU patients, ranging from 8.1 to 57.1 % as shown in Table 1.

Risk factors for VAP

The risk factors for neonatal VAP and heterogeneity in the meta-analysis are shown in Table 2. The I^2 statistic was calculated to determine the size of heterogeneity [20]. We observed a significant relationship between neonatal VAP and the risk factors length of stay in NICU, reintubation, enteral feeding, mechanical ventilation, transfusion, LBW (birth weight <25,000 g), premature infants (gestational age <37 weeks), parenteral nutrition, bronchopulmonary dysplasia, and tracheal intubation in all patients in NICU. A forest plot describing the relationship between MV and neonatal VAP is provided in Fig. 2.

PARP of risk factors

We further tried to carry out the PARP of risk factors for neonatal VAP. Table 3 shows that the PARP of reintubation was up to 68.47 %. The other variables such as premature infants, enteral feeding, parenteral nutrition, reintubation, transfusion, and bronchopulmonary dysplasia were the high-risk factors to develop to VAP among newborns. The risk factors tracheal intubation, MV, and NICU LOS are not displayed in Table 3 because the original literatures did not

Table 1 Characteristics of studies included in the meta-analysis

Study	Country	Type of study	Period	Case/ controls	Incidence (%)	Quality assessment[a]	Adjusted variables
Yuan, 2007 [34]	China	Cohort study	January 1998~ December 2002	52/207	20.1	8 points	Reintubation, MV, treatment with central inhibitors, endotracheal suctioning, transfusion, parenteral nutrition
Cernada, 2013 [7]	Spain	Cohort study	April 2009~ March 2011	16/182	8.1	7 points	NA
Anucha, 2003 [3]	USA	Cohort study	November 2000~ July 2001	24/205	10.5	6 points	BSI before VAP, duration of endotracheal intubation
Afjeh, 2012 [1]	Iran	Cohort study	December 2008~ November 2009	14/67	17.3	6 points	Gender, prematurity, birth weight, MV, surfactant dose, ranitidine therapy, dexamethasone treatment, tracheal aspirate positive, sputum
Petdachai, 2004 [29]	Thailand	Case–control study	August 1994~ August 2001	85/85	50.0	7 points	Sex, birth asphyxia, hypoglycemia, hyperbilirubinemia, prematurity, umbilical catheterization, respiratory distress syndrome, orogastric tube, hematocrit, leukocyte count, percentage of neutrophils, pH, pCO_2, pO_2
Mohamed, 2002 [27]	Egypt	Case–control study	January 2010~ November 2010	32/24	57.1	6 points	NA
Deng, 2011 [10]	China	Case–control study	January 2002~ July 2008	117/232	33.5	7 points	Birth weight (<2,500 g), NRDS, parenteral alimentation, reintubation, MV
Shalini, 2009 [30]	India	Case–control study	September 2004~ August 2005	30/69	30.6	6 points	MV, very low birth weight, prematurity, reintubation

NA not available, *NRDS* neonate respiratory distress syndrome, *BSI* blood stream infection

[a] Low-quality research, 0–4 points; high-quality research, 5–9 points

provide sufficient information on the calculation of the P_e value.

Sensitivity analysis

Sensitivity analyses were conducted by omitting individual studies one by one sequentially and through the comparison between the results of pooled ORs for the random effects model and fixed effects model. We found that the corresponding pooled ORs were not significantly different in all the risk factors and in some conditions, the indicators for heterogeneity were reduced.

Publication bias

The publication bias among those included studies was assessed by Begg's test and Egger's test because those tests were often used to provide the evidence of publication bias. There was no obvious asymmetry of the risk factors shown in Table 2. An example Begg's funnel plot for bronchopulmonary dysplasia is shown in Fig. 3, because bronchopulmonary dysplasia is a chronic lung disease most commonly occurring in infants treated with mechanical ventilation and becoming an extremely important complication in NICU.

Discussion

We performed a meta-analysis aimed to identify risk factors related to neonatal VAP depending on published literatures. To our knowledge, there are extensive literatures on nosocomial infections that include VAP in general ICU and PICU. Although the development of VAP is associated with the same risk factors as those of other nosocomial infections, there are other factors specific to neonatal VAP, which need to be identified appropriately. But few studies are available on risk factors for VAP in the NICU previously, and there is no meta-analysis study on the topic until now. Accordingly, to fill the void in these published literatures, we performed this meta-analysis to identify the relationship between risk factors and neonatal VAP. Because meta-analyses have larger sample

Table 2 Heterogeneity and publication bias of risk factors of included studies

Risk factors	Combination studies	Case/ controls	OR [95 % CI]	*P*	Heterogeneity of study design			Analysis model	Begg's test (*P*)	Egger's test (*P*)
					χ^2	*P*	I^2 (%)			
LBW	6	220/342	3.16 [1.56,6.38]	0.000*	23.08	0.000	78	Random	0.707	0.397
MV	4	231/531	4.04 [1.14,6.95][a]	0.006*	173.78	0.000	95	Random	0.734	0.436
NICU LOS	3	161/367	23.45 [17.65,29.26][a]	0.000*	3.39	0.180	41	Fixed	1.000	0.966
Premature infants	6	221/387	2.66 [1.39,5.09]	0.003*	20.42	0.001	76	Random	0.452	0.268
Caesarean	2	24/129	0.98 [0.46,2.09]	0.960	0.25	0.620	0	Fixed	1.000	NA
Feeding										
Enteral feeding	2	30/62	5.59 [2.40,13.03]	0.000*	1.42	0.230	30	Fixed	1.000	NA
Parenteral nutrition	5	131/248	2.30 [1.64,3.24]	0.000*	6.62	0.090	55	Fixed	0.806	0.208
Invasive procedures										
Reintubation	4	122/189	9.18 [2.89,29.14]	0.000*	16.82	0.000	82	Random	0.308	0.063
Transfusion	2	113/157	3.32 [2.25,4.88]	0.000*	0.35	0.550	0	Fixed	1.000	NA
Thoracentesis	3	70/212	1.13 [0.72,1.80]	0.590	2.28	0.320	12	Fixed	0.296	0.331
Tracheal intubation	3	–	1.12 [0.97,1.27]	0.000*	4.30	0.117	54	Fixed	0.639	0.382
UVC	2	41/49	3.26 [0.38,28.23]	0.280	4.17	0.040	76	Random	1.000	NA
Underlying disease										
Asphyxia	3	75/114	1.07 [0.75,1.54]	0.710	2.58	0.280	22	Fixed	0.296	0.555
NRDS	4	112/120	2.42 [0.34,17.04]	0.380	10.86	0.001	91	Random	1.000	0.720
MAS	3	56/95	1.40 [0.94,2.08]	0.100	2.06	0.360	3	Fixed	0.602	0.791
HIE	2	48/19	3.26 [0.42,25.08]	0.260	5.72	0.020	83	Random	1.000	NA
BPD	4	41/50	2.21 [1.36,3.60]	0.001*	3.56	0.310	16	Fixed	0.308	0.739
BSI	4	62/204	3.46 [1.09,10.97]	0.030	14.93	0.002	80	Random	0.089	0.152
Medication										
Dexamethasone	2	18/26	1,22 [0.21,6.94]	0.830	4.83	0.030	79	Random	1.000	NA
Central inhibitors	4	92/250	1.57 [0.66,3.74]	0.300	16.26	0.001	82	Random	0.734	0.860
Antacids	4	96/99	1.96 [0.68,5.64]	0.210	14.39	0.002	79	Random	1.000	0.187
Surfactant	4	38/113	0.99 [0.42,2.38]	0.980	6.11	0.050	67	Random	1.000	0.781

LBW low birth weight, *MV* mechanical ventilation, *LOS* length of stay, *UVC* umbilical vein catheterization, *NRDS* neonate respiratory distress syndrome, *MAS* meconium aspiration syndrome, *HIE* hypoxic ischemic encephalopathy, *BPD* bronchopulmonary dysplasia, *BSI* bloodstream infection, *NA* not available

*$P<0.05$

[a] Mean difference

sizes, they reduce the difference caused by random errors and increase the test efficiency. Furthermore, they provide the best evidence for clinical practice.

According to the inclusion and exclusion criteria, 1,441 participants were retrieved in our study. We excluded six articles which were published in Turkish, Spanish, Russian, German, and Polish languages, but the studies were not pertinent to risk factors for VAP in NICU via screen titles and abstracts [4, 9, 13, 17, 23, 25]. Therefore, these literatures did not affect the results of the meta-analysis. Furthermore, all of the included studies were rated high quality during the quality assessment process. We concluded that the results based on the current evidences were relatively convincing.

Several studies reported the occurrence rate of VAP among PICU from 3 to 10 % [2, 12]. It is unclear whether VAP contributes to a higher incidence in NICU patients. Our study assessed that the incidence of VAP in NICU patients was from 8.1 to 57.1 % [1, 3, 7, 10, 27, 29, 30, 34]. Therefore, it can be seen that the incidence of VAP in newborns was higher than that in patients from PICU.

Furthermore, our meta-analysis revealed that the length of stay in NICU and MV may be independent risk factors associated with the development of VAP. The result may be explained by the fact that prolonged duration of ventilation and stay in NICU increases the risk of infection due to exposure to humidifiers and ventilator circuits that are proven to be an important source and medium for microorganisms [16].

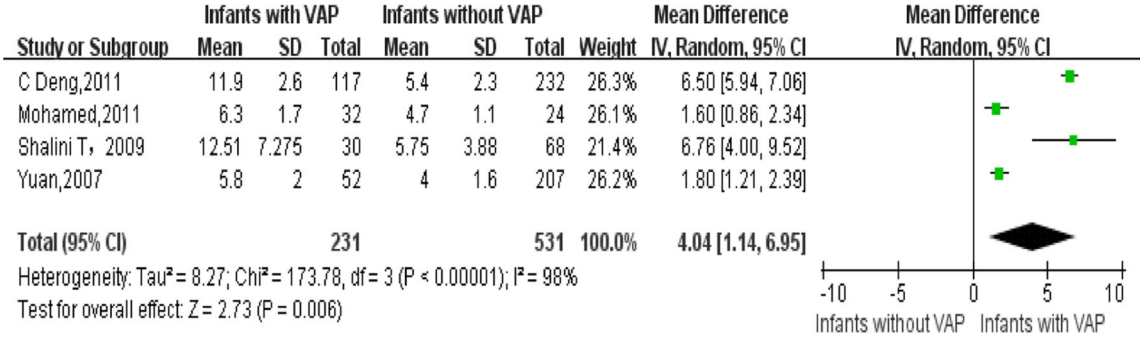

Fig. 2 Forest plot for mechanical ventilation (MV). The individual *block squares* denote the mean difference for each study of the risk factor MV, with an area proportional to the amount of statistical information in each study. The *horizontal line* denotes a 95 % CI. The pooled estimate and its 95 % CI are represented by a *diamond*. *Diamonds* plotted in the *right half* indicate increased VAP risk. The risk is considered significant only if the *horizontal line* or *diamond* does not overlap the *solid vertical line*

Afjeh et al. reported that low birth weight had not been an independent risk factor for VAP [1]. But some other studies showed that low birth weight was predicted to be a high risk of developing VAP. Our data demonstrated that low birth weight has a pool OR=3.16, 95 % CI=1.56–6.38, and PARP of 46.09 %. Thus, a conclusion can be drawn that low birth weight is an independent risk factor for neonatal VAP.

As the immune system of premature infants is not very strong, the normal respiratory barrier function is easily damaged. Premature infants have been shown to be more likely to develop VAP than full-term infants (OR=2.66, 95 % CI= 1.39–5.09, PARP 42.64 %). In addition, the treatment group received enteral feeds more frequently than controls (OR= 5.59, 95 %CI=2.40–13.03, PARP 74.15 %), which may increase the risk of stomach colonization with gram-negative microorganisms and consequently lead to an increased incidence of nosocomial pneumonia [26]. Transfusion (OR=3.32, 95 % CI=2.25–4.88) and parenteral nutrition (OR=2.30, 95 % CI=1.64–3.24) were identified as risk factors in the meta-analysis. This may be due to the immunosuppressive effects of transfusion and parenteral nutrition which were obvious in the patients. Additionally, the dependent risk factors reintubation, tracheal intubation, and bronchopulmonary dysplasia were found in this study. The sensitivity analyses also confirmed that the results for risk factors and neonatal VAP susceptibility were stable and statistically robust. Among those risk factors, reintubation can be prevented and controlled appropriately by a clinician (PARP was 68.47 %). Overall, according to the risk factors identified above, effective strategies should be undertaken to reduce the incidence and mortality of VAP substantially.

The results may be affected by additional confounding factors, such as enteral feeding or parenteral nutrition and length of stay in NICU. The results of the meta-analysis were based on the original literatures, but these studies did not prove the baseline data whether parenteral nutrition is a risk factor in the absence of enteral feeds. Although our study could theoretically get a clearer conclusion based on adjusted ORs, some of the included studies did not report adjusted ORs. In fact, only two of the eight studies had reported the adjusted ORs of enteral feeding or parenteral nutrition, and no study reported the adjusted ORs of length of stay in NICU. Therefore, these results should be interpreted with caution,

Table 3 The PARP of risk factors for neonatal VAP

Risk factors	OR [95 % CI]	P_e (%)	PARP (%)
Reintubation	9.18 [2.89,29.14]	26.55	68.47
Enteral feeding	5.59 [2.40,13.03]	30.10	58.01
LBW	3.16 [1.56,6.38]	39.58	46.09
BPD	2.21 [1.36,3.60]	6.95	45.68
Transfusion	3.32 [2.25,4.88]	35.76	45.34
Premature infants	2.66 [1.39,5.09]	44.79	42.64
Parenteral nutrition	2.30 [1.64,3.24]	35.79	31.75

LBW low birth weight, *BPD* bronchopulmonary

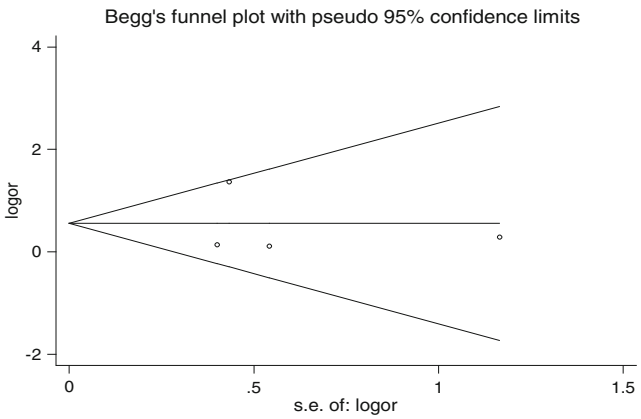

Fig. 3 Begg's funnel plot for bronchopulmonary dysplasia. The *horizontal line* in the funnel plot indicates the fixed effects summary estimate, while the *sloping lines* indicate the expected 95 % confidence intervals for a given standard error, assuming no heterogeneity between studies. No publication bias was observed among studies using Begg's (P=0.734) test, which suggested that there was no evidence of publication bias

and future prospective cohort studies with a more adequate reference group are needed to investigate the association further.

We should also pay attention to the several limitations of our study, which may increase the heterogeneity of some results. First, there is no gold standard for defining neonatal VAP currently, which was not differentiated from other infections in this patient population, so it is hard to diagnosis a VAP in NICU. In the absence of a gold criterion for diagnosing neonatal VAP, we just used a definition of VAP in NICU that was established through the CDC criteria for all infants <1 year of age, which lacks specificity. Therefore, some studies were excluded because of an unclear diagnosis criterion, which led to the extremely small dataset collection in the inclusion and limited the statistical power to detect some of the possible independent risk factors for VAP in NICU patients. Second, with the lack of a clear-cut definition of VAP in the included study, VAP was divided into early-onset VAP (<5 days of MV) and late-onset VAP (>5 days of MV) [22, 24]. But on the time of MV, expressed as mean±SD in the original literatures, a subgroup analysis could not be undertaken in our study, which was an important reason for the high heterogeneity of the results in Table 2 and the forest plots. Third, clinical heterogeneity between studies might exist since we had strict enrollment criteria of references (only included case–control or cohort study), the inclusive studies were undertaken in different countries, and some diagnostic levels such as chest X-ray and the basic condition of the eligible patients may vary greatly. This may result in a high heterogeneity between included studies. Finally, publication bias in the meta-analysis by Begg's test and Egger's test was not significant. However, the tests have low power for meta-analyses with few component studies [5]. There is also relatively little bias in the summary effect size estimate, so the results of these tests must be interpreted with caution in small-sample meta-analyses.

In conclusion, VAP is an important cause of morbidity and occurs at a significant rate in neonates on MV. Despite that our study has identified a number of factors associated with the development of ventilator-associated pneumonia in NICU patients, large randomized controlled trials and other intervention evaluation studies are needed to accurately define neonatal VAP and to develop effective preventive and therapeutic protocols in the future.

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Conflict of interest The authors declared that they have no conflict of interest. The authors have no financial relationship with the organization that sponsored the research.

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