Factors influencing pulmonary hemorrhage in very low-and extremely low-birth-weight infants: a meta-analysis

Qin-Chuan Shi
Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital

Fu-Ying Tao
Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital

Jing-Yang Li
Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital

Ying-Ying Tian
	tiangyingying0000@126.com

Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital

Bei-Bei Liu
Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital

Qian-Qian Wang
Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital

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Abstract

Background

Pulmonary hemorrhage is a common complication in preterm infants, especially in very low- and extremely low-birth-weight infants, and has high morbidity and mortality rates. Although some studies have analyzed the epidemiological incidence of pulmonary hemorrhage and related factors, there are discrepancies between the results of these studies due to differences in study populations and study designs. Therefore, we conducted a meta-analysis of the factors affecting pulmonary hemorrhage to provide a reference for early clinical recognition and prevention of pulmonary hemorrhage.

Methods

Systematic searches of the PubMed, Embase, Cochrane Library and other databases were performed to extract the results of logistic regression analyses of case-control or cohort studies related to the factors affecting pulmonary hemorrhage in very-low and extremely-low-birth-weight infants. The data were analyzed using RevMan 5.3 software.

Results

A total of 13 studies were included and 11 influencing factors were screened through quantitative integration. All factors were statistically significant except for hypothermia: birth weight (OR=0.75, 95% CI 0.59-0.97, P=0.03, I²=95%), coagulation disorders (OR=4, 95% CI 1.79-8.93, P<0.01, I²=66%), patent ductus arteriosus (OR=3.52, 95% CI 1.71-7.27, P<0.01, I²=80%), mechanical ventilation (OR=2.94, 95% CI 1.94-4.45, P<0.01, I²=0%), anemia (OR=5.15, 95% CI 2.92-9.07, P<0.01, I²=43%), 5-min Apgar score (OR=1.6, 95% CI 1.21-2.11, P<0.01, I²=46%), early-onset sepsis (OR=2.71, 95% CI 1.62-4.53, P<0.01, I²=0%), antenatal steroids (OR=0.39, 95% CI 0.21-0.73, P<0.01, I²=25%), preterm birth (OR=1.99, 95% CI 1.34-2.97, P<0.01, I²=47%), and blood product transfusion (OR=6.16, 95% CI 2.15-17.69, P<0.01, I²=0%).

Conclusion

This study revealed the factors affecting pulmonary hemorrhage in very-low and extremely-low-birth-weight infants, and the results of the meta-analysis will be supplemented by a standardized cohort study based on this study.

Trial registration

PROSPERO (CRD42023465025)

Introduction

Neonatal pulmonary hemorrhage (PH) is defined as massive hemorrhage of the lungs involving at least 2 lobes of the lungs and often occurs in very low-and extremely low-birth-weight infants[1,2]. Previous
studies have shown that the incidence of pulmonary hemorrhage in the normal neonatal population is 1-12 per 1000 live births, whereas the incidence of pulmonary hemorrhage in very low-and extremely low-birth-weight infants is 4%-12%[3-6]. Although the incidence of pulmonary hemorrhage has declined in recent years with the development of monitoring and rescue techniques, early diagnosis and treatment of pulmonary hemorrhage are difficult due to its complex etiology and pathogenesis, and the mortality rate of pulmonary hemorrhage is still high, especially in very low-and extremely low-birth-weight infants, whose mortality rate is as high as 50%-68%[7]. Therefore, clarification of the factors influencing the occurrence of pulmonary hemorrhage in very low-and extremely low-birth-weight infants is essential for the early identification of high-risk populations and the improvement of prognosis.

Although some studies have analyzed the factors affecting pulmonary hemorrhage in very low-and extremely low-birth-weight infants[8-10], there is not yet a broad consensus on the conclusions of these studies due to differences in the quality of the studies, the study populations and the types of studies. In addition, no study has conducted a meta-analysis of the factors influencing pulmonary hemorrhage in very low-and extremely low-birth-weight infants. Therefore, in this study, we conducted a systematic search and meta-analysis of the factors influencing the occurrence of pulmonary hemorrhage in very low-and extremely low-birth-weight infants to provide a reference for the construction of a risk prediction model for pulmonary hemorrhage while enhancing clinical awareness.

Materials and Methods

Registration

The meta-analysis was registered on the PROSPERO website under the registration number CRD42023465025. To ensure the standardization of the findings, this meta-analysis will be based on the PRISMA statement for result reporting.

Search strategy

According to the purpose of the study, the research team systematically searched the PubMed, Cochrane Library, Embase, Ovid, Scopus, and Web of Science databases. The search terms were constructed using a combination of subject terms and free words, and the search terms are shown in Table 1. The search time was set from the establishment of the databases on September 30, 2023.

Inclusion and exclusion criteria

Studies that met the following criteria were included: (1) had a clear diagnosis of neonatal pulmonary hemorrhage; (2) case-control studies or cohort studies. The exclusion criteria were as follows: (1) email, conference article, case report, review, systematic review and meta-analysis, commentary or editorial. (2) inability to access the full text. (3) There were no clear odds ratio (OR)/risk ratio (RR) values for relevant influencing factors. (4) Publication in languages other than English.
Quality assessment and data extraction

The Newcastle Ottawa Scale (NOS) was selected for quality assessment based on the type of studies included in the literature\(^\text{11}\). The scale evaluates the quality of the literature in terms of three dimensions: selection, comparability and exposure(outcome), ranging from 0 to 9 stars. Studies with ratings equal to or greater than 6 stars were considered to be of high quality. Data extraction followed the requirements of the JBI Assessment Manual, and the extracted information included basic information, type of study, sample size, factors, and OR/RR values\(^\text{12}\). The quality assessment and data extraction of the included studies were performed separately by two researchers. If the opinions of two researchers were in dispute, a third researcher coordinated until the opinions were harmonized.

Data analysis

When an influencing factor covered two or more studies, it was integrated into the meta-analysis. After logarithmic transformation, log(OR)/log(RR) and its standard error were entered into RevMan 5.3 software for analysis. The chi-square test with the \(\hat{I}^2\) statistic was used to verify the heterogeneity of the results. According to relevant studies, when \(\hat{I}^2>50\%\), \(P \leq 0.1\) indicated significant heterogeneity and needed to be combined with a random effects model. When \(\hat{I}^2 \leq 50\%\), \(P \leq 0.1\) indicated no obvious heterogeneity and a fixed effects model was used\(^\text{13-16}\).

Results

Characteristics of the included studies

A total of 251 studies were retrieved; after removing duplicates, initial screening and reading the full texts, a total of 13 studies were included\(^\text{17-29}\). The literature screening process is shown in Figure 1. In addition, the basic characteristics and NOS scores of the included studies are shown in Table 2.

Results of the meta-analysis

Initially, 21 factors were extracted from the included studies (Table 2). However, only 11 of these factors included two or more studies that were integrated into the meta-analysis, covering birth weight, mechanical ventilation, anaemia, coagulation disorders, 5 min Apgar score, patent ductus arteriosus (PDA), early-onset sepsis (EOS), hypothermia, antenatal steroids, prematurity, and blood product transfusion. According to our quantitative meta-analysis, all factors other than hypothermia were significantly different (OR=3.47, 95% CI 0.48-24.91, \(P=0.22\), \(\hat{I}^2=80\%\)).

Among the statistically significant factors, due to the high heterogeneity, birth weight (OR=0.75, 95% CI 0.59-0.97, \(P=0.03\), \(\hat{I}^2=95\%\)), coagulation disorders (OR=4, 95% CI 1.79-8.93, \(P<0.01\), \(\hat{I}^2=66\%\)), and patent ductus arteriosus (OR=3.52, 95% CI 1.71-7.27, \(P<0.01\), \(\hat{I}^2=80\%\)) were analyzed using a random effects model (Figure 2). Mechanical ventilation (OR=2.94, 95% CI 1.94-4.45, \(P<0.01\), \(\hat{I}^2=0\%\)), anaemia (OR=5.15, 95% CI 2.92-9.07, \(P<0.01\), \(\hat{I}^2=43\%\)), 5min Apgar score (OR=1.6, 95% CI 1.21-2.11, \(P<0.01\), \(\hat{I}^2=46\%\)), EOS
(OR=2.71, 95% CI 1.62-4.53, \(P<0.01\), \(I^2=0\%\)), antenatal steroids (OR=0.39, 95% CI 0.21-0.73, \(P<0.01\), \(I^2=25\%\)), preterm birth (OR=1.99, 95% CI 1.34-2.97, \(P<0.01\), \(I^2=47\%\)), and blood product transfusion (OR=6.16, 95% CI 2.15-17.69, \(P<0.01\), \(I^2=0\%\)) were associated with lower heterogeneity, and a fixed effects model was adopted for examination (Figure 3).

**Sensitivity analysis and publication bias**

In the sensitivity analysis, studies on each of the influencing factors were excluded one by one, and sensitivity was assessed by determining whether there was a substantial change in the \(P\) values and ORs of the remaining studies. Gezmu et al. [17], Zeng et al. [26], and Chai et al. [27] had an undue effect on \(P\) value and ORs of birth weight. No publication bias test was conducted in this meta-analysis because fewer than 10 studies involved each factor.

**Discussion**

Pulmonary hemorrhage, a fatal respiratory disease, particularly threatens the quality of life of very low- and extremely low-birth-weight infants in the neonatal intensive care unit (NICU). Previous studies have confirmed that many factors are associated with pulmonary hemorrhage in neonates. It is essential to clarify these factors to enable early identification and early intervention.

The results of the meta-analysis showed that among the statistically significant influencing factors, birth weight (OR=0.75, \(P=0.03\)) and antenatal steroid treatment (OR=0.39, \(P<0.01\)) had a preventive effect on pulmonary hemorrhage. It is well known that the incidence of pulmonary hemorrhage is significantly greater in very low- and extremely low-birth-weight infants than in normal newborns. Most likely, due to nutritional deficiencies and immunocompromise, low birth weight infants are vulnerable to viral and bacterial attacks, which can lead to pulmonary hemorrhage complications. In addition, low birth weight is closely related to preterm birth, and is associated with poorly developed body functions, which increases the risk of pulmonary hemorrhage[30, 31]. In addition, the results of the meta-analysis showed that the preventive effect of antenatal steroids on the occurrence of pulmonary hemorrhage is consistent with the findings of previous studies[32]. It has been demonstrated that steroid use promotes enhanced microvascular maturation and premature focal capillary fusion, thereby reducing the incidence of pulmonary hemorrhage[33].

Currently, relevant studies on the etiology of neonatal pulmonary hemorrhage are mainly focused on respiratory problems and hemodynamic changes[5]. With respect to respiratory problems, neonatal respiratory diseases such as neonatal respiratory distress syndrome (NRDS) and bronchopulmonary dysplasia (BPD) often require mechanical ventilation therapy to maintain breathing. The development of pulmonary hemorrhage is induced by excessive alveolar tension due to instrumental stimulation of tracheal intubation with poorly set parameters of mechanical ventilation therapy, resulting in stress injury to alveolar capillaries[34]. Therefore, PH is more common in the first days of life for ELBW and VLBW infants, during and after an NRDS or BPD usually appears later.
In terms of hemodynamics, the mechanisms of pulmonary hemorrhage induced by PDA, EOS, anemia, and blood product transfusion are similar. PDA triggers left-to-right shunting, leading to a high-flow and high-pressure state in the pulmonary vascular bed and causing pulmonary hemorrhage\(^{[35]}\). Similarly, when EOS occurs, it exacerbates the occurrence of pulmonary hemorrhage because endotoxin release can lead to increased vascular permeability, affecting hemodynamics while reopening or enlarging the patent ductus arteriosus\(^{[36]}\). A retrospective cohort study in Canada showed that anemia is a common complication in very low-and extremely low-birth-weight infants, and 55% of very low-birth-weight infants were treated with red blood cell transfusions during hospitalization\(^{[37]}\). The use of blood products for anemia or other reasons can cause a dramatic increase in blood volume, resulting in damage to the pulmonary capillary wall. In addition, sudden increases in fluid and protein flow can lead to left ventricular failure, both of which can lead to increased pulmonary capillary pressure and prompt pulmonary hemorrhage\(^{[4]}\).

Preterm birth is an indisputable risk factor for many diseases in neonates. In this study, preterm birth was closely related to low birth weight, mechanical ventilation, and blood product use. Therefore, the mechanism of pulmonary hemorrhage induced by preterm birth is complex and varied. Currently, few studies have specifically analyzed the correlation between coagulation disorders and neonatal pulmonary hemorrhage. Researchers have hypothesized that the mechanism of pulmonary hemorrhage triggered by coagulation disorders may be related to the fact that transfused plasma from adult donors adversely affects neonatal platelets, leading to disruption of the endothelial barrier of the pulmonary vasculature and triggering hemorrhage\(^{[38]}\). Finally, the mechanism of pulmonary hemorrhage triggered by a low 5 min Apgar score may consist of two points: pulmonary hemorrhage due to pulmonary edema triggered by high negative intrathoracic pressure as a result of neonatal asphyxia and hemorrhage due to excessive alveolar expansion caused by resuscitation or respiratory support, which ultimately damages the alveolar capillaries\(^{[39, 40]}\).

Although this study was conducted scientifically following the meta-analysis process, there are still some shortcomings. First, the heterogeneity of partial integration results in this study was high due to differences in the study population, study design, and data collection. Second, there were few studies on each influential factor, subgroup and publication bias analyses were not performed. In this study, the Chinese literature accounted for a large proportion of the total population, possibly because in recent years, due to changes in fertility policy and improvements in assisted reproductive technology, the number of elderly women giving birth has increased annually in China, and very low-and extremely low-birth-weight infants have become more common\(^{[41]}\). This may increase the risk of publication bias in the results of this meta-analysis. Third, the process of combining different influencing factors before meta-analysis was somewhat subjective.

**Conclusion**
After this meta-analysis, a total of 10 influencing factors for the occurrence of pulmonary hemorrhage in very low-and extremely low-birth-weight infants were identified to provide a reference for early clinical identification and intervention. In response to the problem of fewer studies on related influencing factors, our team will carry out standardized cohort studies in the future to continuously improve and update the results of this meta-analysis.

**Abbreviations**

PH  Pulmonary hemorrhage  
VLBW  Very low birth weight  
ELBW  Extremely low birth weight  
NOS  Newcastle Ottawa scale  
PDA  Patent ductus arteriosus  
EOS  Early-onset septicemia  
NICU  Neonatal intensive care unit  
BPD  Bronchopulmonary dysplasia  
NRDS  Neonatal respiratory distress syndrome

**Declarations**

**Acknowledgement**

We deeply thank all those who cooperated in this study.

**Contributor statement**

QCS: Study design, the collection, analysis, and interpretation of data and the writing of the report.  
FYT: The writing of the report.  
YJL, QQW: The collection, analysis, and interpretation of the data.  
YYT, BBL: The decision to submit the paper for publication.

**Funding Sources**

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Data availability statement

The data used for meta-analysis in this study are available upon contact with the corresponding author.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

The authors have no conflicts of interest to declare.

References


# Tables

## Table 1 Search strategy

<table>
<thead>
<tr>
<th>Factors</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very low birth weight infants</strong></td>
<td>(((&quot;Infant, Very Low Birth Weight&quot;[Mesh]) OR ((((((Very-Low-Birth-Weight Infant[Title/Abstract]) OR (Infant, Very-Low-Birth-Weight[Title/Abstract])) OR (Infants, Very-Low-Birth-Weight[Title/Abstract])) OR (Very Low Birth Weight Infant[Title/Abstract])) OR (Very-Low-Birth-Weight Infants[Title/Abstract])) OR (Very Low Birth Weight[Title/Abstract]))))</td>
</tr>
<tr>
<td><strong>Extremely low birth weight infant</strong></td>
<td>(&quot;Infant, Extremely Low Birth Weight&quot;[Mesh]) OR (Extremely Low Birth Weight Infant[Title/Abstract])))</td>
</tr>
<tr>
<td><strong>Pulmonary hemorrhage</strong></td>
<td>(((pulmonary heamorrhage[Title/Abstract]) OR (pulmonary haemorrhage[Title/Abstract])) OR (pulmonary hemorrhage[Title/Abstract])))</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>((relative[Title/Abstract] AND risk*[Title/Abstract]) OR (relative risk[Text Word]) OR risks[Text Word])</td>
</tr>
<tr>
<td><strong>Cohort</strong></td>
<td>cohort studies[MeSH:noexp] OR (cohort[Title/Abstract] AND stud*[Title/Abstract]))</td>
</tr>
</tbody>
</table>

## Table 2 Basic information and influencing factors
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of study</th>
<th>Cases</th>
<th>Controls</th>
<th>Factors</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chai et al</td>
<td>2015</td>
<td>Cohort</td>
<td>30</td>
<td>40</td>
<td>1,2,3,4</td>
<td>7</td>
</tr>
<tr>
<td>Chen et al</td>
<td>2017</td>
<td>Case-control</td>
<td>35</td>
<td>176</td>
<td>5,6,7</td>
<td>8</td>
</tr>
<tr>
<td>Cao et al</td>
<td>2022</td>
<td>Case-control</td>
<td>44</td>
<td>530</td>
<td>7,8,9,10</td>
<td>8</td>
</tr>
<tr>
<td>Li et al</td>
<td>2011</td>
<td>Cohort</td>
<td>15</td>
<td>166</td>
<td>6,12,13</td>
<td>7</td>
</tr>
<tr>
<td>Cao et al</td>
<td>2017</td>
<td>Case-control</td>
<td>71</td>
<td>364</td>
<td>1,5,6,14,15</td>
<td>7</td>
</tr>
<tr>
<td>Zeng et al</td>
<td>2016</td>
<td>Case-control</td>
<td>60</td>
<td>60</td>
<td>1,16</td>
<td>6</td>
</tr>
<tr>
<td>Wang et al</td>
<td>2019</td>
<td>Cohort</td>
<td>30</td>
<td>130</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Reibel et al</td>
<td>2021</td>
<td>Case-control</td>
<td>49</td>
<td>98</td>
<td>16</td>
<td>9</td>
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<tr>
<td>Wang et al</td>
<td>2022</td>
<td>Case-control</td>
<td>262</td>
<td>524</td>
<td>6,17</td>
<td>9</td>
</tr>
<tr>
<td>Gezmu et al</td>
<td>2023</td>
<td>Cohort</td>
<td>54</td>
<td>1296</td>
<td>1,2,3,7,11,17,18,19</td>
<td>8</td>
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<tr>
<td>Lee et al</td>
<td>2019</td>
<td>Cohort</td>
<td>339</td>
<td>4334</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Usemann et al</td>
<td>2017</td>
<td>Case-control</td>
<td>20</td>
<td>40</td>
<td>14,19,20</td>
<td>8</td>
</tr>
<tr>
<td>Li et al</td>
<td>2021</td>
<td>Case-control</td>
<td>51</td>
<td>548</td>
<td>4,6,21</td>
<td>7</td>
</tr>
</tbody>
</table>


**Figures**
Figure 1

Literature screening process. PubMed, Cochrane Library, Embase, Ovid, Scopus, Web of Science, and related Chinese database were systematic searched. After a preliminary search of 251 literatures, 13 relevant studies were finally included after independent screening by 2 researchers.
Figure 2

Results of random effects model analysis. Birth weight, Coagulation disorders, PDA and Hypothermia were combined using a random effects model due to the results of quantitative meta-analysis with $I^2 > 50\%$ and $P < 0.1$. 

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Odds Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
<td>log(Odds Ratio)</td>
<td>SE</td>
</tr>
<tr>
<td>Cao et al 2017</td>
<td>-0.002</td>
<td>0.001022</td>
</tr>
<tr>
<td>Chai et al 2015</td>
<td>-0.46204</td>
<td>0.071418</td>
</tr>
<tr>
<td>Gezmu et al 2023</td>
<td>-0.16252</td>
<td>0.05089</td>
</tr>
<tr>
<td>Zeng et al 2016</td>
<td>-1.38629</td>
<td>0.42848</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.75 [0.59, 0.97]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.05; \text{Chi}^2 = 61.85, \text{df} = 3 (P < 0.0001); \hat{P} = 95\%$

Test for overall effect $Z = 2.23 (P = 0.03)$

<table>
<thead>
<tr>
<th>Coagulation disorders</th>
<th>Odds Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
<td>log(Odds Ratio)</td>
<td>SE</td>
</tr>
<tr>
<td>Chai et al 2015</td>
<td>1.047319</td>
<td>0.235289</td>
</tr>
<tr>
<td>Li et al 2021</td>
<td>1.880991</td>
<td>0.428831</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>4.00 [1.79, 8.93]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.23; \text{Chi}^2 = 2.90, \text{df} = 1 (P = 0.09); \hat{P} = 66\%$

Test for overall effect $Z = 3.39 (P = 0.0007)$

<table>
<thead>
<tr>
<th>PDA</th>
<th>Odds Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
<td>log(Odds Ratio)</td>
<td>SE</td>
</tr>
<tr>
<td>Cao et al 2017</td>
<td>0.79118092</td>
<td>0.31193843</td>
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<tr>
<td>Chen et al 2017</td>
<td>1.31291899</td>
<td>0.4391559</td>
</tr>
<tr>
<td>Li et al 2011</td>
<td>1.75054734</td>
<td>0.67036293</td>
</tr>
<tr>
<td>Li et al 2021</td>
<td>2.4356136</td>
<td>0.44114961</td>
</tr>
<tr>
<td>Wang et al 2022</td>
<td>0.43825483</td>
<td>0.19426299</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>3.52 [1.71, 7.27]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.51; \text{Chi}^2 = 20.34, \text{df} = 4 (P = 0.0004); \hat{P} = 80\%$

Test for overall effect $Z = 3.40 (P = 0.0007)$

<table>
<thead>
<tr>
<th>Hypothermia</th>
<th>Odds Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
<td>log(Odds Ratio)</td>
<td>SE</td>
</tr>
<tr>
<td>Cao et al 2022</td>
<td>2.451781</td>
<td>0.8929</td>
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<tr>
<td>Lee et al 2019</td>
<td>0.405455</td>
<td>0.196085</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>3.47 [0.48, 24.91]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.68; \text{Chi}^2 = 5.01, \text{df} = 1 (P = 0.03); \hat{P} = 80\%$

Test for overall effect $Z = 1.24 (P = 0.22)$
### Results of fixed effects model analysis

Mechanical ventilation, Anaemia, 5 min apgar score, EOS, Antenatal steroids, premature, and blood product transfusion were combined using a fixed effects model due to the results of quantitative meta-analysis with $I^2<50\%$ and $P>0.1$.

#### Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx