

Cumulative evidence for association of sepsis and retinopathy of prematurity

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Abstract

Background: Retinopathy of prematurity (ROP) is a retinal vasoproliferative disease affected by multiple factors such as infection and preterm birth. The role of sepsis in the development of ROP remains controversial. This systematic review and meta-analysis aimed to identify the impact of sepsis on ROP.

Methods: The PubMed, Embase, and Cochrane Library databases were searched using terms related to sepsis and ROP. Cohort or case-control studies that reported the association of sepsis and ROP were eligible. The odds ratios (ORs) together with the 95% confidence interval (CI) were extracted from the studies or computed by authors if not provided.

Results: Thirty-four studies were ultimately included in this meta-analysis. The pooled results showed that sepsis increased the risk for the development of any stage ROP (OR=2.16; 95% CI: 1.65–2.82). Both early onset (OR=2.50; 95% CI: 1.97–3.18) and late-onset (OR=1.37; 95% CI: 1.22–1.55) sepsis were associated with severe ROP. Furthermore, both bacterial sepsis (OR=1.74; 95% CI: 1.21–2.50) and fungal sepsis (OR=2.96; 95% CI: 2.05–4.28) were also found to be associated with severe ROP.

Conclusion: Sepsis increased the risk of any stage ROP, especially for the severe ROP. Further high-quality clinical studies are needed to eliminate heterogeneity and publication bias to validate these findings.

Abbreviations: CIs = confidence intervals, NOS = Newcastle–Ottawa scale, ORs = odds ratios, ROP = retinopathy of prematurity.

Keywords: meta-analysis, neonate, retinopathy of prematurity, sepsis, systematic review

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This is a systematic review and meta-analysis, thus the ethical approval was not necessary.

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1. Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease that affects the developing retinal vascular system in premature infants.^[1] Blindness and visual disability are the main long-term visual outcomes of ROP.^[2] It has been reported that ROP blinds approximately 20,000 infants annually.^[3] With increased survival of premature infants due to advanced neonatal care, the number of children affected by ROP is rising in low- and middle-income countries.^[3] Increasing evidence indicates that infants with ROP are at increased risk of dysfunctions associated with nonvisual neural defects.^[4,5] Therefore, retinopathy and brain injury in premature infants may share an etiology with similar risk factors.

Infection is an important risk factor for neonatal brain damage in premature infants.^[6] Sepsis is a key cause of neonatal inflammation, which contributes to neonatal morbidity.^[6,7] Recently, neonatal inflammation has been reported to be associated with ROP.^[8,9] Although a meta-analysis has reported that systemic fungal infection is associated with the development of any stage ROP, including severe ROP, in very low birth weight infants,^[10] there have been conflicting findings regarding the role of fungal sepsis as an independent risk factor for severe ROP.^[11,12] In addition, bacterial sepsis has been identified as an independent risk factor in a study of extremely low gestational age newborns.^[13]

Thus, the objective of this systematic review and meta-analysis was to investigate the impact of sepsis on the development of any stage of ROP, as well as of severe ROP, in particular.

2. Materials and methods

This study was conducted according to PRISMA and MOOSE Guidelines for meta-analysis.

2.1. Study identification and selection

The PubMed, Embase, and Cochrane Library databases were searched. The search keywords and Medical Subject Headings (MeSH) terms were the following: “Sepsis” OR “Bacteremia” OR “Fungemia” OR “Bacterial sepsis” OR “Fungal sepsis” AND “Retinopathy of Prematurity” OR “ROP” OR “Retrolental Fibroplasia.” The last search was updated on October 24, 2018. The search was limited to human studies and was restricted to English language reports. Potential studies were identified by initially screening the titles and abstracts of all studies. If the title and abstract suggested that the study discussed risk factors for ROP, the full text of the report was read independently by 2 of the authors (YL and HC) to determine its eligibility according to the following inclusion criteria: studies investigated the association between sepsis and ROP; with the diagnosis of ROP based on the results of ophthalmoscopy; classification of the ROP stage from 1 to 5 according to the International Classification of ROP,^[14] with ROP defined as any stage ROP and severe ROP (stages 3 to 5, plus disease, surgical, and threshold ROP); sepsis was diagnosed as culture-proven sepsis (fungal sepsis was diagnosed by the positive fungal culture but not the indirect mycological tests) and clinical sepsis without culture evidence; case–control or cohort studies; and studies that reported risk ratios or odds ratios (ORs) and corresponding 95% confidence intervals (CIs) or with other data available for calculating the CIs. The following exclusion criteria were also applied: studies with overlapping populations; those that did not include a control group; and those for which the original data were not available. Therefore, to accurately evaluate the association between sepsis and ROP, we only included the studies of culture-positive sepsis in the meta-analysis. Any disagreements were reconciled by a third author (YT), who independently reviewed the studies, and then discussed disagreements with the initial 2 reviewers until a consensus was reached.

2.2. Data extraction

Two authors (YL and HC) independently collected data from each study and then compared results. Any disagreement was resolved by discussions with a 3rd author (TZ). The extracted data included the 1st author, publication year, country, study design, included population, diagnosis of ROP, sample size, birth weight, gestational age, impact of sepsis on ROP as primary outcome, risk of bias, and adjustment of confounding factors. The ORs together with the 95% CI were extracted from the studies or computed by authors if not provided.

2.3. Quality evaluation

To assess the methodological quality of each included study, 2 authors (YT and TZ) independently screened the study design, the representativeness of the study population, the quality of the statistical analysis, and the validity of outcomes by using the Newcastle–Ottawa scale (NOS).^[15] The NOS was widely applied to evaluate cohort or case–control studies, based on group selection (4 items); comparability between groups (1 item); and outcome and exposure assessment (3 items). The maximum score

was 9 stars. Studies with at least 5 stars were considered to be high-quality studies.^[16] Disagreements between the 2 reviewing authors were examined by a 3rd author (JH) and resolved by discussion.

2.4. Statistical analysis

The ORs of each included study were pooled to assess the association between sepsis and any stage ROP or severe ROP in particular. The pooled OR was calculated by using a random-effects model if statistical heterogeneity was found among studies.^[17,18] Otherwise, a fixed-effects model was used. Q statistics and I^2 tests were applied to estimate heterogeneity among studies. Data were considered statistically heterogeneous if $P < .1$ and $I^2 > 50\%$. Forest plots were used to show the ORs and 95% CIs of each individual study, as well as the pooled ORs and 95% CIs. To find the source of the heterogeneity, we performed subgroup analysis combined with meta-regression analysis according to the variance in the studies. Publication bias was evaluated by funnel plots and Begg test,^[19] where a value of $P < .05$ was considered to be statistically significant. The nonparametric “trim and fill” procedure was also performed to assess the possible effect of publication bias.^[20,21] All statistical tests were performed using Review Manager 5.3 or STATA 12.0 software.

3. Results

3.1. Study selection process and characteristics

The literature search identified 639 studies based on our search strategy. After careful screening, we excluded the studies with culture-negative sepsis (31 studies) because the diagnosis criteria of clinical sepsis in different studies were inconsistent and the confounders were commonly existed in those studies. Finally, 34 studies were ultimately selected for the meta-analysis. A flow diagram detailing the selection process is shown in Figure 1. Characteristics of the included studies are summarized in Table 1. These included studies were published between 1985 and 2018. The sample sizes (case/control) varied from a maximum of 2547/22,001 to a minimum of 25/49. All the studies involved preterm neonates (gestational age before 37 weeks, and birth weight <2500g). For the assessment of ROP, the included studies measured or used data from medical records, based on ophthalmoscopy. According to the onset time and etiology of sepsis, 6 studies reported late-onset sepsis, 4 reported early onset sepsis, 10 reported bacterial sepsis, and 7 reported fungal sepsis. Outcomes were categorized into 2 broad categories: “any stage ROP” and “severe ROP.”

3.2. Quality of included studies

A total of 28 cohort studies and 6 case–control studies were selected in this meta-analysis. The methodologic quality scores ranged from 4 to 8 stars. Most studies were deemed to be high quality, except for 1 study.^[38] Three studies^[25,33,41] included all preterm neonates without restriction of birth weight or gestation age, but the selection of cases in the other studies may have lacked representativeness. Most studies adjusted for potential confounding factors, but 8 did not.^[25,27,38,42,45,46,50,51] Most ORs were evaluated by multiple logistic regression analysis, adjusted for gestational age (24 studies), birth weight (16 studies), oxygen use (14 studies), mechanical ventilation (11 studies), and

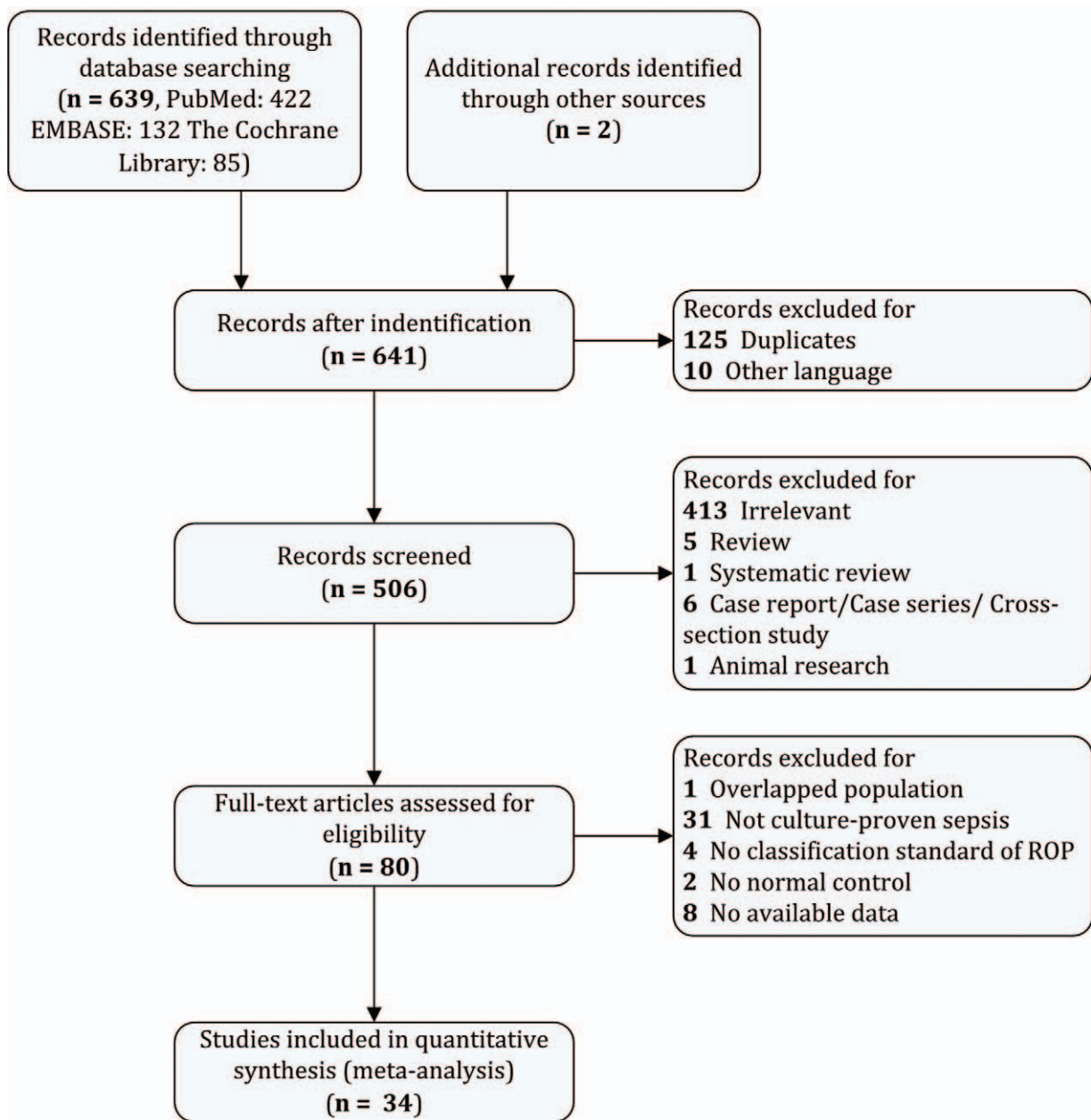


Figure 1. Flow chart of study selection process.

sex (8 studies) (Supplemental Digital Content, Table S1, <http://links.lww.com/MD/D299>). Thirteen cohort studies and 1 case-control study provided a no-response rate at the end of follow-up (Supplemental Digital Content, Tables S2 and S3, <http://links.lww.com/MD/D299>). All included publications were assessed using the NOS (Supplemental Digital Content, Tables S2 and S3, <http://links.lww.com/MD/D299>).

3.3. Sepsis and any stage ROP

Twenty-two ORs of any stage ROP were pooled in the meta-analysis. The pooled OR from the random-effects model was 2.16 (95% CI: 1.65–2.82) (Fig. 2). Substantial heterogeneity was observed ($P < .001$; $I^2 = 84\%$). According to the onset time and etiology of sepsis, we estimated the respective impacts of early

onset sepsis, late-onset sepsis, bacterial sepsis, and fungal sepsis on any stage ROP. The pooled ORs are shown in Table 2. Fungal sepsis had a significant impact on any stage ROP (OR=4.00; 95% CI: 1.71–9.33; $P = .001$).

3.4. Sepsis and severe ROP

Twenty ORs of severe ROP were pooled in the meta-analysis. The pooled OR from the random-effects model was 1.87 (95% CI: 1.53–2.29) (Fig. 3). Substantial heterogeneity was observed ($P < .001$; $I^2 = 78\%$). Based on the onset time and etiology of sepsis, we estimated the respective impacts of early onset sepsis, late-onset sepsis, bacteria sepsis, and fungal sepsis on the development of severe ROP. The pooled ORs are shown in Table 2. We found that early onset sepsis (OR=2.50; 95% CI:

Table 1

Characteristics of included studies.

First author	Year	Country	Study design	ROP diagnosis	Size (case/control)	BW, g/GA, wk	Impact of sepsis on ROP	
							Any stage ROP	Severe ROP
Bas ^[22]	2018	Turkey	Retrospective cohort	Medical record	414/1695	BW ≤1500 g	-	Late onset: OR = 1.423 (1.016–1.994); early onset: OR = 2.694 (2.149–3.378)
Cantley ^[23]	2018	USA	Retrospective cohort	Medical record	383/1859	VLBW	Late onset and bacteria: OR = 0.86 (0.54–1.37)	-
Lundgren ^[24]	2018	Australia	Retrospective cohort	Medical record	202/25	GA <28 wk	OR = 3.01 (1.54–7.85)	Early onset: OR = 0.85 (0.233–3.099); late onset: OR = 7.321 (0.901–59.474); fungal: OR = 2.346 (0.622–8.842)
Ali ^[25]	2017	Egypt	Retrospective cohort	Medical record	11/97	BW <2500 g or GA <37 wk	-	-
Reyes ^[26]	2017	Oman	Retrospective cohort	Medical record	69/102	GA 24–32 wk	Late onset: OR = 7.472 (1.212–46.047)	-
Yum ^[27]	2016	Korea	Case-control	Medical record	42/105	GA 30–33 wk	OR = 3.54 (1.49–8.41)	Bacteria: OR = 1.23 (1.06–1.42)
Lee ^[28]	2016	USA	Case-control	Medical record	2547/22,001	ELBW and GA ≤32 wk	OR = 0.84 (0.73–0.96)	OR = 0.92 (0.75–1.14)
Huang ^[29]	2015	China	Retrospective cohort	Registry data	2785/2933	VLBW	-	Bacteria: OR = 1.4 (0.9–2.2)
Ohlin ^[30]	2015	Sweden	Prospective cohort	Medical record	173/324	GA ≤27 wk	-	-
Ortega-Molina ^[31]	2015	Spain	Retrospective cohort	Medical record	93/165	GA ≤32 wk	OR = 2.9 (1.62–5.27)	-
Thomas ^[32]	2015	Canada	Retrospective cohort	Registry data	1163/8024	BW <1500 g	-	Late onset: OR = 1.35 (1.16–1.67)
Araz-Ersan ^[33]	2013	Turkey	Case-control	Medical record	1200/1744	GA <37 wk	OR = 2.165 (1.254–3.738)	OR = 6.864 (3.142–14.993)
Borroni ^[34]	2013	Italy	Prospective cohort	Registry data	265/156	BW <750 g and/or GA ≤27 wk	OR = 1.43 (0.89–2.29)	OR = 1.58 (0.8–3.12)
Küçükcencioglu ^[35]	2013	Turkey	Prospective cohort	Medical record	340/400	BW <1501 g and/or GA ≤34 wk	OR = 1.719 (0.995–2.968)	OR = 1.090 (0.474–2.509)
Abdel ^[36]	2012	Egypt	Ambispective cohort	Medical record	23/139	BW ≤1500 g and GA ≤32 wk	OR = 1.251 (1.082–1.458)	-
Giapros ^[37]	2011	Greece	Retrospective cohort	Medical record	24/165	GA 24–32 wk or BW <1500	OR = 2.4 (0.5–12)	-
Kumar ^[38]	2011	India	Retrospective cohort	Medical record	33/671	BW ≤1500 g or GA ≤32 wk	-	OR = 4.7 (2.3–9.8)
Toisma ^[39]	2011	USA	Retrospective cohort	Medical record	283/776	GA <28 wk	-	Late onset and bacteria: OR = 1.42 (1.10–1.83)
Weintraub ^[13]	2011	Israel	Case-control	Medical record	55/110	BW <1500 g and GA <32 wk	OR = 12.376 (2.532–60.503)	Bacteria: OR = 4.10 (2.48–6.77); fungal: OR = 6.63 (2.0–21.93)
Chen ^[40]	2010	USA	Case-control	Registry data	293/329	BW <1501 g or GA <30 wk	OR = 2.1 (1.4–3.2); late onset OR = 2.2 (1.5–3.2); early onset OR = 9.9 (1.2–83.4); bacteria OR = 3.14 (0.77–12.80); fungal OR = 3.3 (1.3–8.9)	-
Ebrahim ^[41]	2010	Iran	Retrospective cohort	Medical record	33/140	GA <37 wk	OR = 0.6 (0.035–10.386)	-
Fortes Filho ^[42]	2010	Brazil	Prospective cohort	Medical record	111/356	BW ≤1500 g or GA ≤32 wk	OR = 1.86 (1.14–3.01)	Early onset: OR = 2.04 (1.32–3.16)
Klinger ^[43]	2010	Israel	Prospective cohort	Registry data	789/15,050	VLBW	-	-
Mutlu ^[44]	2008	Turkey	Retrospective cohort	Medical record	118/200	GA ≤34 wk	OR = 2.37 (1.17–4.81)	Bacteria: OR = 2.10 (1.06–4.14)
Manzoni ^[45]	2006	Italy	Retrospective cohort	Medical record	96/205	VLBW	Bacteria: OR = 2.59 (1.58–4.25)	-
Yanovitch ^[46]	2006	USA	Retrospective cohort	Medical record	12/248	BW 1250–1800g	OR = 9.33 (2.79–31.20)	Bacteria: OR = 0.31 (0.07–1.40); fungal: OR = 7.39 (1.70–32.14)
Noyola ^[12]	2002	USA	Retrospective cohort	Registry data	34/114	BW ≤1500 g or GA ≤28 wk	-	Fungal: OR = 2.886 (1.18–7.06)
Tadesse ^[47]	2002	USA	Retrospective cohort	Medical record	35/58	ELBW	-	Bacteria: OR = 3.98 (1.56–10.19); fungal: OR = 1.5626 (0.3216–7.5921)
Haroon Parupia ^[48]	2001	USA	Retrospective cohort	Medical record	69/62	BW <1000 g	-	OR = 3.5 (1.02–12.2)
Al-Essa ^[49]	2000	Kuwait	Prospective cohort	Medical record	34/200	BW <1501 g	OR = 4.43 (2.47–7.93)	Fungal: OR = 1.60 (0.89–2.89)
Karłowicz ^[11]	2000	USA	Prospective cohort	Medical record	58/391	BW ≤1000 g	-	Fungal: OR = 4.87 (1.92–12.35)
Mittal ^[50]	1998	USA	Prospective cohort	Medical record	96/37	ELBW (BW ≤1000 g)	Bacteria: OR = 1.65 (0.77–3.54)	-
Bassiouny ^[51]	1996	Egypt	Prospective cohort	Medical record	56/56	BW <1500 g and/or GA <32 wk	OR = 2.88 (0.85–9.77)	-
Cats ^[52]	1985	The Netherlands	Case-control	Medical record	25/49	GA <32 wk	OR = 3.08 (1.21–7.84)	-

BW (g) = birth weight (grams), CI = confidence interval, ELBW = extremely low birth weight, GA (wk) = gestational age (weeks), OR = odds ratio, VLBW = very low birth weight.

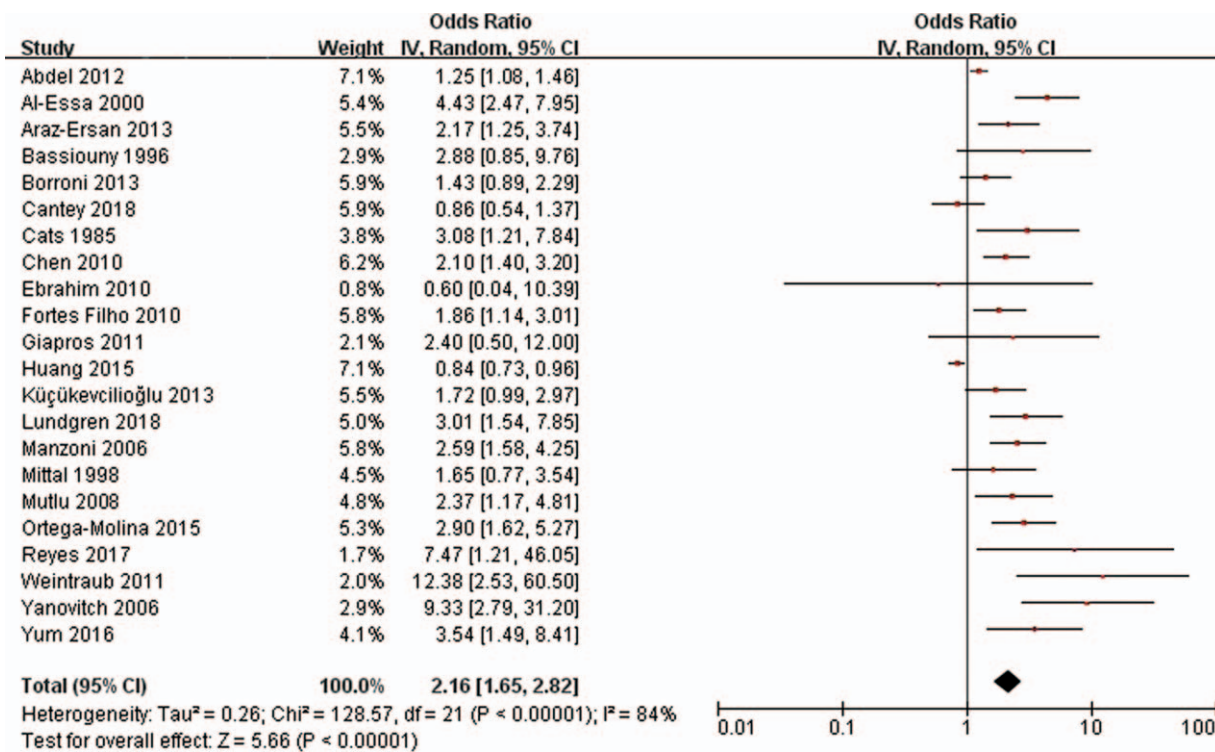


Figure 2. Forest plot showing the association between sepsis and any stage of retinopathy of prematurity. The pooled odds ratios (ORs) of association between sepsis and any stage of retinopathy of prematurity were calculated. Diamond marker indicates pooled effect sizes. Some ORs could slightly differ (centesimal) from published values owing to the rounding of primary values. CI = confidence interval.

Table 2

The pooled ORs of association between retinopathy of prematurity and sepsis according to the onset time and etiology.

Group	Authors	Pooled OR (95% CI)	P-value	P _{het}				
Any stage ROP	Late-onset sepsis Cantey (2018) Reyes (2017) Chen (2010)	1.81 (0.74–4.43)	.19	.002				
					Early onset sepsis Ali (2017) Chen (2010)	2.51 (0.23–27.34)	.45	.05
Fungal sepsis Chen (2010) Mittal (1998)	4.00 (1.71–9.33)	.001	.33					
Severe ROP	Late-onset sepsis Bas (2018) Thomas (2015) Tolsma (2011)	1.37 (1.22–1.55)	<.001	.92				
					Early-onset sepsis Bas (2018) Klinger (2010)	2.50 (1.97–3.18)	<.001	.27
Fungal sepsis Haroon Parupia (2001) Weintraub (2011) Tadesse (2002) Noyola (2002) Haroon Parupia (2001) Karlłowicz (2000) Mittal (1998)	2.96 (2.05–4.28)	<.001	.12					

CI=confidence interval, OR=odds ratios, P_{het}=P-value of heterogeneity, ROP=retinopathy of prematurity.

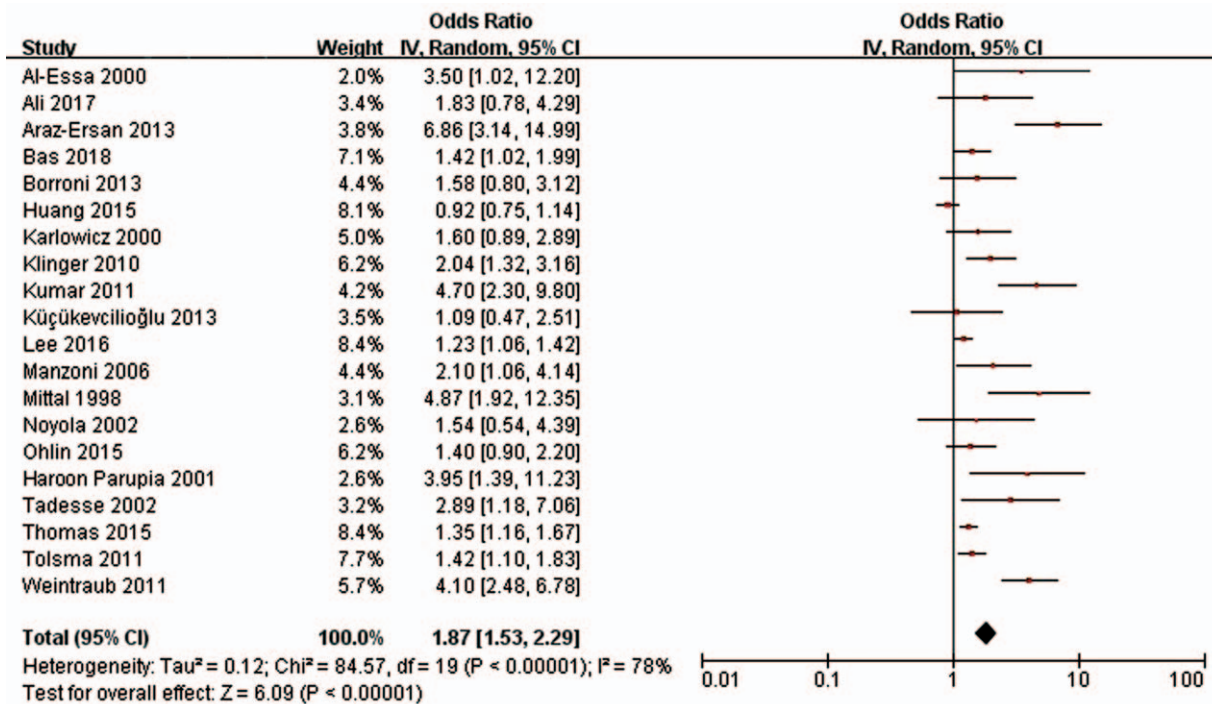


Figure 3. Forest plot showing the association between sepsis and severe retinopathy of prematurity. The pooled odds ratios (ORs) of association between sepsis and severe retinopathy of prematurity were calculated. Diamond marker indicates pooled effect sizes. Some ORs could slightly differ (centesimal) from published values owing to the rounding of primary values. CI = confidence interval.

1.97–3.18; $P < .001$), late-onset sepsis (OR=1.37; 95% CI: 1.22–1.55; $P < .001$), bacterial sepsis (OR=1.74; 95% CI: 1.21–2.50; $P = .003$), and fungal sepsis (OR=2.96; 95% CI: 2.05–4.28; $P < .001$) each had a significant impact on the development of severe ROP.

3.5. Subgroup analysis

With adjustment for confounding factors, study design, classification of birth weight or gestation age, and sample size, a stratified meta-analysis, using subgroups, was performed to explore study heterogeneity. Control for confounding factors (adjusted $R^2 = 26.32\%$, $P = .059$ for any stage ROP; adjusted $R^2 = 32.32\%$, $P = .068$ for severe ROP) and sample size (adjusted $R^2 = 19.23\%$, $P = .031$ for any stage ROP; adjusted $R^2 = 30.45\%$, $P = .053$ for severe ROP) were significant factors in study heterogeneity (Supplemental Digital Content, Table S4, <http://links.lww.com/MD/D299>).

3.6. Publication bias

Asymmetries were shown in funnel plots (Fig. 4) and publication biases were found by Begg test in both any stage ROP ($P < .001$) and severe ROP ($P = .001$). Therefore, we performed a sensitivity analysis and used the “trim and fill” method to produce symmetrical funnel plots by imputing hypothetical negative unpublished studies (Fig. 4). When we incorporated these hypothetical studies, the pooled analysis continued to show a statistically significant association between sepsis and severe ROP (OR=1.296; 95% CI: 1.047–1.605; $P = .017$). However, the pooled analysis showed no statistically significant association

between sepsis and any stage ROP (OR=1.276; 95% CI: 0.980–1.691; $P = .07$).

4. Discussion

To our knowledge, no previous meta-analysis had assessed the association between sepsis and the development of ROP based on currently available studies. The meta-analysis showed that sepsis was significantly associated with the development of any stage ROP as well as of severe ROP in particular. Based on the onset time and etiology of sepsis, fungal sepsis increased the risk for the development of any stage ROP. Moreover, early onset sepsis, late-onset sepsis, bacterial sepsis, and fungal sepsis each associated with the development of severe ROP.

The internal association underlying the sepsis and development of ROP may summarized by the relationship between inflammation and angiogenesis.^[53] Some proinflammatory proteins and angiopoietins have been reported to play multiple roles in vascular processes,^[53–55] which may promote the abnormal angiogenesis of retina. In this meta-analysis, a stronger association with severe ROP was revealed for early onset sepsis than for late-onset sepsis. Neonatal early onset sepsis is secondary to intrauterine infection in most cases, which may increase the risk for the development ROP.^[56,57] Moreover, infants with intrauterine infection after birth always have a worse respiratory condition, which is typically treated with a higher concentration of oxygen and more advanced mechanical ventilation (such as invasive mechanical ventilation), which also increases the likelihood of ROP occurrence.^[58,59] On the contrary, we found that the association of fungal sepsis with ROP was stronger than that of bacterial sepsis. In terms of the etiology of fungal sepsis, of

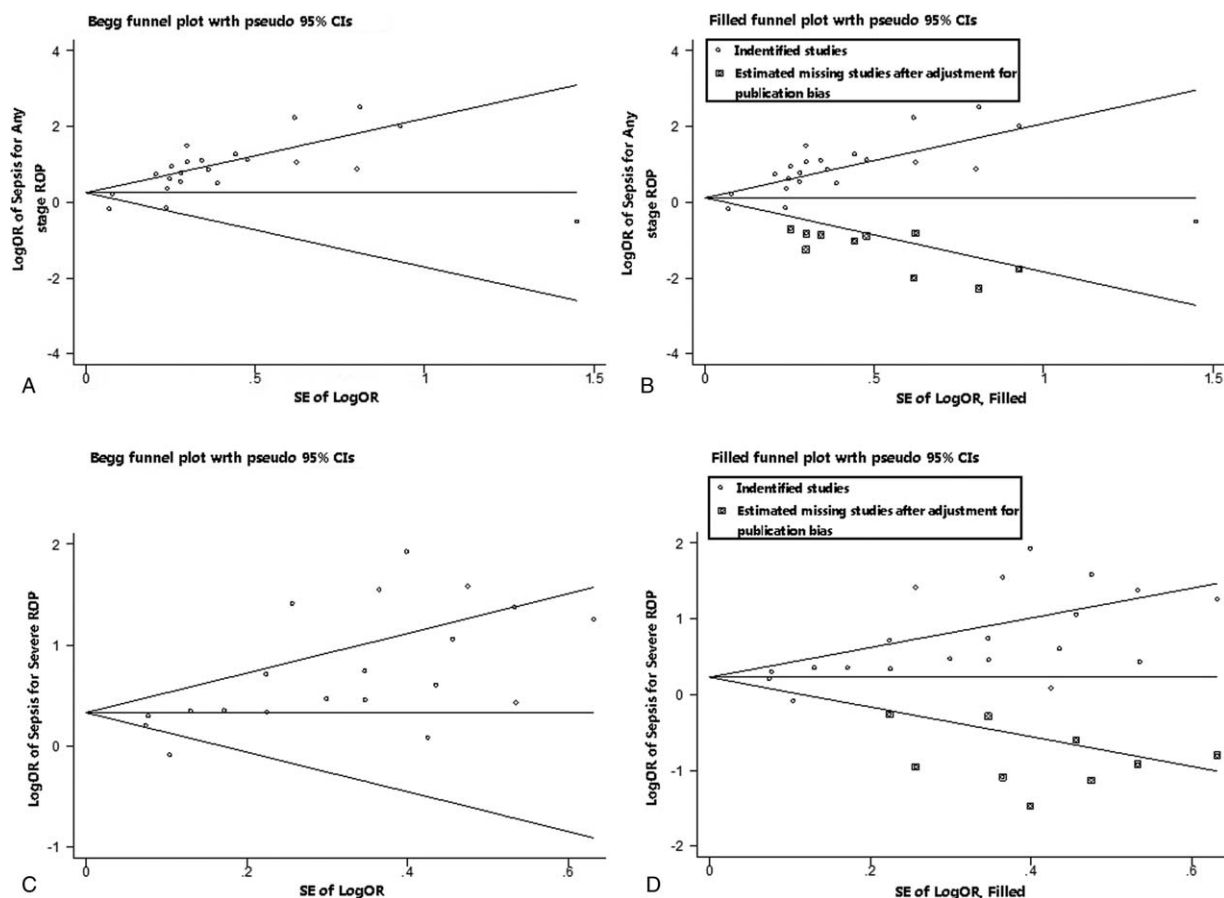


Figure 4. Funnel plots without and with trim and fill. The pseudo 95% confidence interval (CI) is computed as part of the analysis that produces the funnel plot, and corresponds to the expected 95% CI for a given standard error (SE). OR = odds ratio.

the 7 studies included, 5 studies involved *Candida* sepsis.^[11,12,45,47,50] As far as the type of bacteria resulted in the sepsis, 4 studies identified the specific bacteria. Three of them^[13,23,30] investigated the relationship of coagulase-negative *Staphylococcus* (CoNS) sepsis and ROP. However, there was no study to identify the different impact factors on ROP between bacterial and fungal sepsis. Therefore, further studies should be carried out to explain this difference.

Subgroup analysis indicated that control for confounding factors is one of the significant factors in study heterogeneity. The various possible confounders and the control for different confounders in studies may affect the final pooled results. Gestational age and birth weight were the main adjusted confounders in the included studies, which are 2 well-recognized risk factors for ROP.^[59] Moreover, recent studies have identified the impact of the use of oxygen and mechanical ventilation on the development of ROP.^[58,60] Thus, it is important to adjust for the influence of oxygen and mechanical ventilation on the relationship of sepsis and ROP. However, of the 34 studies included, only 7 studies^[22,26,33,35,36,40,44] had concurrently adjusted for this 2 factors. In addition, although there are 14 studies which adjusted the confounder of oxygen use, the bias may still exist because it is difficult to adjust appropriately for oxygenation to normalizing the oxygenation among studies.

This study has several limitations. First, significant heterogeneity was found in the meta-analysis, caused by adjustment for

confounding factors and sample size, according to a subgroup analysis and meta-regression analysis. The various possible confounders mentioned above might be the main source of the heterogeneity and skewing of results. Second, significant publication bias was also found in this meta-analysis. After the “trim and fill” procedure, the association between sepsis and severe ROP was significant and stable, while that of sepsis and any stage ROP was not. This instability of association of sepsis and any stage ROP may come from the strict inclusion of studies and some unpublished negative results. Our review only included English publications, some results in non-English studies may be missed.

5. Conclusion

Our systematic review and meta-analysis showed that neonatal sepsis increased the risk of any stage ROP as well as that of severe ROP, in particular. To eliminate the heterogeneity and publication bias of our results, more high-quality clinical studies are needed to provide convincing evidence for the impact of sepsis on ROP occurrence.

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