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Review Article

Effects of *Ureaplasma urealyticum* infection on neonates: a meta-analysis

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Abstract: Objective: *Ureaplasma urealyticum* (UU) is an opportunistic pathogen transmitted from mother to fetus, potentially causing neonatal diseases. Despite extensive research, its association with these diseases remains uncertain. This study analyzes the effects of UU infection on newborns. Methods: We performed an exhaustive literature review by searching various databases, including PubMed, EMBASE, and Cochrane, for research articles published before March 2024 on the impact of UU infection on neonates and its association with related diseases. Keywords included "*Ureaplasma urealyticum*", "Pregnancy Outcomes", "Sepsis", "Cerebral Intraventricular Hemorrhage", "Bronchopulmonary Dysplasia", and "Necrotizing Enterocolitis". Two authors independently screened the literature, extracted data, and evaluated study quality. Meta-analysis was conducted using Stata software, where either a fixed-effects model or a random-effects model was employed to calculate the odds ratio (OR) and 95% confidence interval (CI). The methodological quality of each study was assessed, and the quality of evidence for outcome measures was graded using the GRADE (Grades of Recommendations Assessment, Development and Evaluation, GRADE) system. Results: Thirteen studies, published between 2011 and 2024, were included, covering regions of China (two studies), South Korea (three studies), Japan (two studies), Austria (three studies), Germany (one study), Belgium (one study), and Italy (one study). Findings indicate that UU infection significantly increased the risk of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and sepsis in neonates. However, the correlation between UU infection and necrotizing enterocolitis (NEC) was found not to be significant. Additionally, a descriptive analysis of two studies on UU infection's impact on neonatal pneumonia showed no significant correlation. Conclusion: UU infection significantly increases the risk of BPD, IVH, and sepsis in newborns.

Keywords: Ureaplasma urealyticum, bronchopulmonary dysplasia, periventricular leukomalacia, necrotizing enterocolitis, intraventricular hemorrhage, neonatal sepsis

Introduction

Ureaplasma urealyticum (UU) is a common parasitic microorganism in the human genitourinary system [1]. In individuals with normal immune function, UU generally does not cause genitourinary infections. However, when immunity is compromised, UU may proliferate excessively, leading to cell damage and an inflammatory response. UU infections can result in urethritis and cervicitis. Failure to control inflammation in a timely manner may lead to local or systemic immune responses. In nonpregnant women, this may result in conditions such as salpingitis, endometritis, and pelvic inflammatory disease, damaging the immune barrier of the reproductive tract and possibly leading to infertility or ectopic pregnancy [2, 3]. In pregnant women, UU infection may disrupt immune system regulatory mechanisms that protect the embryo [4], posing risks such as premature rupture of membranes, miscarriage, preterm birth, low birth weight, and other adverse maternal and infant outcomes [3]. Notably, one meta-analysis showed that during pregnancy, UU infection increased the risk of preterm birth, chorioamnionitis, and premature rupture of membranes [5].

Additionally, maternal UU infection can affect the fetus through vertical transmission, leading to neonatal conditions such as congenital pneumonia, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH). In newborns with maternal cervical-vaginal UU infection, the

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Table 1. Literature retrieval strategies

Step	Index word
1	"*Ureaplasma urealyticum*" [Mesh]
2	"*Ureaplasma*" (Title/Abstract) OR "*Ureaplasma* species" (Title/Abstract)
3	"Cerebral Intraventricular Hemorrhage" [Mesh]
4	"Cerebral Intraventricular Hemorrhages" (Title/Abstract) OR "Hemorrhage, Cerebral Intraventricular" (Title/Abstract) OR "Intraventricular Hemorrhage, Cerebral" (Title/Abstract) OR "Cerebral Intraventricular Haemorrhage" (Title/Abstract) OR "Cerebral Intraventricular Haemorrhages" (Title/Abstract) OR "Haemorrhage, Cerebral Intraventricular" (Title/Abstract) OR "Intraventricular Haemorrhage, Cerebral" (Title/Abstract) OR "Intraventricular Haemorrhages, Cerebral" (Title/Abstract)
5	Search = (#1 OR #2) AND (#3 OR #4)

incidence of BPD is approximately 12.3%, whereas in newborns without maternal cervical-vaginal UU colonization, the incidence is approximately 3.8% [6]. A study by Chun *et al.* [7] found a vertical transmission rate of 34.9% for UU colonization from mother to newborn, with a strikingly high BPD rate of 55.3% in these cases. Although much research has examined the disease burden of UU infection, debate continues over its association with neonatal diseases [8, 9].

Therefore, using meta-analysis methods to synthesize data from multiple studies, we aimed to evaluate the effects of UU infection on newborns. This approach holds promise for reducing study variability and offering deeper insight into the effects of UU infection.

Materials and methods

This study was conducted in accordance with the PRISMA 2009 Checklist and has been registered in PROSPERO (CRD42024572928).

Literature resources

We performed an exhaustive literature review by searching various databases including PubMed, EMBASE, and Cochrane for research articles published before March 2024 on the effect of UU infection on neonates and its association with related diseases. This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10]. Since this study was based solely on published data, no ethical approval was obtained.

Literature retrieval strategy

We adopted a search strategy of subject terms plus free terms and conducted a systematic search of PubMed, EMBASE, Cochrane, and Web of Knowledge. The keywords searched included "*Ureaplasma urealyticum*", "Pregnancy Outcomes", "Neonatal Sepsis", "Cerebral Intraventricular Hemorrhage", "Bronchopulmonary Dysplasia", and "Necrotizing Enterocolitis". For each of the different databases, we adjusted the search strategy to optimize the search results.

Taking "*Ureaplasma urealyticum*" and "Cerebral Intraventricular Hemorrhage" as examples, the search strategy is shown in **Table 1**.

Inclusion and exclusion criteria

In this study, the included literature met all of the following criteria: (1) published articles in various databases examining the effect of UU infection on newborns; (2) observational study designs, including case-control, cohort (retrospective or prospective), and cross-sectional studies; (3) clear indication of UU infection status as positive or negative; (4) utilization of explicit UU infection detection methods; and (5) inclusion of at least one of the following conditions: sepsis, IVH, BPD, NEC, and neonatal pneumonia.

Literature was excluded if it met any of the following criteria: (1) review articles, case reports, meta-analyses, and animal experiments; (2) insufficient data for analysis; (3) Poor-quality literature with a Newcastle-Ottawa Scale (NOS) score of ≤5 points; and (4) duplicate publications.

Selection process

Two researchers collaboratively established the literature search strategy. Adhering to predefined inclusion and exclusion criteria, they

Table 2. Extracted data

Characteristic	Data
Characteristics of research	(1) Study design (cohort study, case-control study, randomized controlled trial, etc.) (2) Year (3) Study location (country or region)
Sample characteristics	(1) Sample size (2) Basic population information
Infection characteristic	(1) Specimen, detection method (2) Colonization of UU (e.g. negative, positive)
Outcome	Neonatal diseases such as "Neonatal Sepsis" "Cerebral Intraventricular Hemorrhage" "Bronchopulmonary Dysplasia" "Necrotizing Enterocolitis", etc.

Note: UU: Ureaplasma urealyticum.

independently screened the literature to ensure methodological rigor. In cases of disagreement, a consensus was reached through discussion, and cross-verification was performed to ensure selection consistency. Ultimately, selected literature and data were integrated for analysis.

The specific process for including literature was as follows: (1) Initial screening: Titles and abstracts were screened to determine the relevance of search results to the study's focus. (2) Full-Text Analysis: Literature deemed potentially eligible post-initial screening underwent a detailed full-text analysis to further assess its alignment with inclusion criteria. (3) Final Selection: After a thorough examination of full-text articles and considering the study's well-defined inclusion criteria, researchers finalized the selection of studies for analysis.

Data collection process

Two authors independently extracted the data according to a unified data extraction table (**Table 2**). Disagreements were resolved by consensus with the assistance of a third examiner.

Study risk of bias assessment

In this study, two researchers independently evaluated the quality of each included literature using the NOS [11]. The evaluation process was as follows: (1) Independent scoring: Each researcher independently scored the studies according to the specific NOS scoring criteria and calculated the total score for each study. (2) Results exchange: After scoring, the researchers exchanged their results. (3) Discussion of discrepancies: If discrepancies in scoring arose, each researcher provided specific reasons for their scoring decisions, and engaged in thorough discussions to reach a consensus. (4) Third-party arbitration: If a consensus could not be reached, a third researcher or mentor was consulted to assist in making a final consensus on evaluation results. (5) Quality level classification: Literature quality was categorized into three levels based on NOS scores: a score of 8-9 denoted high quality, 6-7 indicated moderate quality, and ≤5 signified low-quality. Low-quality studies were excluded from the final analyses.

Evidence quality grade evaluation

The quality of evidence for outcome indicators was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. This system evaluates evidence based on five criteria: limitations, inconsistency, indirectness, imprecision, and publication bias, classifying evidence quality into four levels: high, moderate, low, and very low.

Effect measures

The odds ratio (OR) was used as the effect measure, with a 95% confidence interval (CI) accompanying each effect size.

Statistical analysis

Statistical analyses were conducted using StataMP 17 software (StataCorp LLC, TX, USA). The I^2 statistic and Q test were employed to evaluate statistical heterogeneity in the aggregated data. A *P*-value > 0.1 or I^2 < 50% suggested homogeneity, thus supporting the use of a fixed-effects model for meta-analysis. In

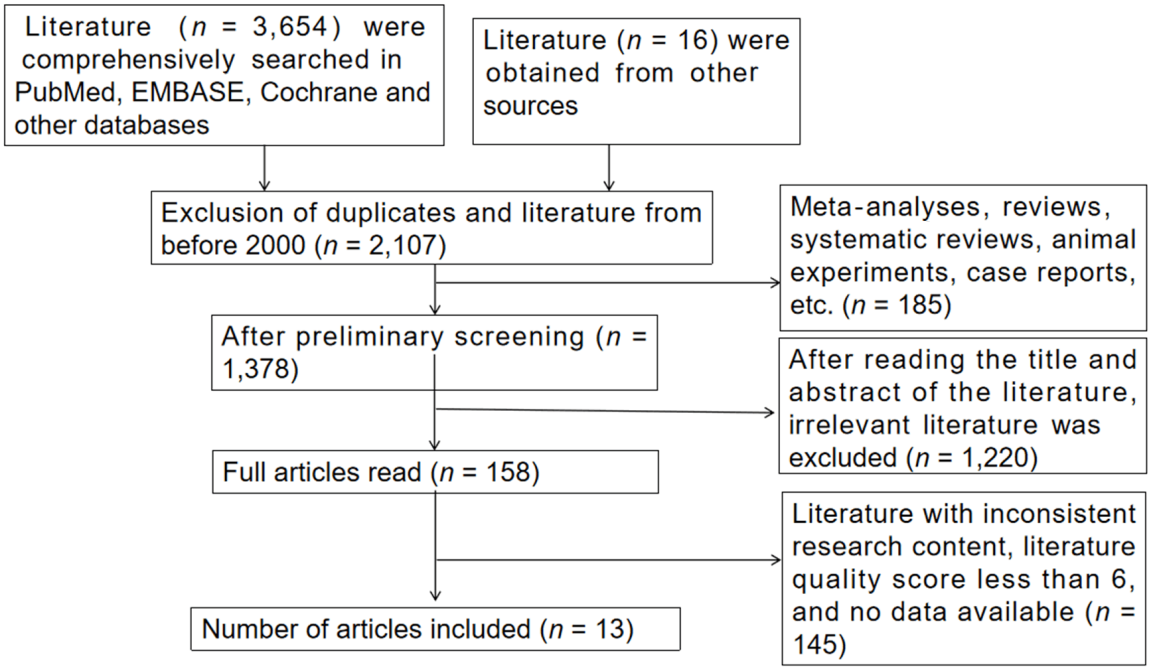

Figure 1. Literature retrieval and selection process.

contrast, a *P*-value < 0.1 and I^2 > 50% indicated significant heterogeneity, necessitating a random-effects model to account for variability and provide more generalizable results. The results of the pooled effect sizes from the statistical analysis were visually represented using a forest plot. Statistical significance was set at P < 0.05.

Subgroup analysis and sensitivity analysis

In the presence of heterogeneity, subgroup analyses were conducted to explore contributing factors (such as study region, study type, sample size, and detection methods). Sensitivity analysis was also performed by removing individual studies to assess the stability of the pooled effect size. If the pooled effect size remained unchanged, the results were considered stable; otherwise, the results were considered unstable. In addition, a funnel plot was used to assess publication bias, with asymmetry suggesting possible bias.

Trial sequential analysis (TSA)

TSA was applied to estimate the required sample size for the meta-analysis. This method helps reduce the likelihood of false-positive results caused by random errors when the number of included cases is limited.

Results

Search results and screening process

We identified 3,654 relevant articles, along with an additional 16 articles obtained from other sources. Subsequently, we excluded 1,036 duplicate articles and 527 articles published before 2000. During the initial screening, we excluded 185 articles, including meta-analyses, reviews, animal experiments, and case reports. After reviewing the titles and abstracts of the articles, 1,220 irrelevant articles were excluded. Upon full-text review, we excluded 145 articles due to misalignment with the research topic, a literature quality score below 6, or lack of retrievable data. Finally, 13 articles met the inclusion criteria [6, 7, 9, 12-21]. **Figure 1** gives an overview of the selection process.

Basic features of the included literature

The selected studies, spanning from 2011 to 2024, were geographically distributed as follows: two from China, three from South Korea, two from Japan, three from Austria, one from Germany, one from Belgium, and one from Italy. Quality assessment rated three studies as high quality, with the remaining 10 categorized as

Table 3. Basic features of the included literature

Author	Year	Region	Type	UU test method	Sample size (UU+/UU-)	Outcome	NOS
Van Mechelen K *et al.* [7]	2021	Belgium	a	AGAR medium	60/250	①	6
Chun J *et al.* [8]	2019	Korea	a	PCR	152/93	①⑤	7
Ma J *et al.* [10]	2024	China	b	PCR	561/496	①③④	8
Rittenschober-Böhm J *et al.* [13]	2021	Austria	c	PCR	106/116	①②③⑤	7
Miyoshi Y *et al.* [14]	2022	Japan	c	Urea-arginine broth method	54/40	⑤	7
Sun T *et al.* [15]	2021	China	b	PCR	86/205	①③⑤	8
Resch B *et al.* [16]	2016	Austria	b	AGAR medium	62/62	①②③⑤	8
Kim SH *et al.* [17]	2019	Korea	b	Real-time PCR	110/55	①②⑤	6
Inatomi T *et al.* [18]	2012	Japan	e	PCR	35/56	①⑤	7
Eun HS *et al.* [19]	2013	Korea	d	Real-time PCR	31/313	①②③	7
Glaser K *et al.* [20]	2019	Germany	d	Real-time PCR	40/63	①②③⑤	6
Gallini F *et al.* [21]	2022	Italy	a	PCR	32/222	①②③⑤	7
Kasper DC *et al.* [22]	2011	Austria	b	PCR	85/172	①②③⑤	7

Notes: a denotes retrospective cohort studies; b denotes retrospective case-control studies; c denotes prospective observational studies; d denotes prospective case-control studies; and e denotes prospective cohort studies. ① Bronchopulmonary dysplasia, ② Intraventricular hemorrhage, ③ Necrotizing enterocolitis, ④ neonatal pneumonia, ⑤ sepsis. PCR: Polymerase Chain Reaction, UU: Ureaplasma urealyticum.

medium quality. Detailed information is shown in **Table 3**.

Meta-analysis results

Effects of UU infection on neonates (preterm infants)

Bronchopulmonary Dysplasia (BPD): Twelve studies [6, 7, 9, 12, 14-21] evaluated the association between UU infection and BPD. Statistical heterogeneity was observed among the studies (I^2 = 72.0%, P < 0.001), which prompted the use of a random-effects model. The results showed that UU infection was significantly correlated with BPD, with a pooled effect size of OR = 2.57 (95% CI: 1.64, 4.03) (Z = 4.128, P < 0.001).

Meta-regression analysis was conducted using publication year, region, and detection method as covariates. *P*-values for these covariates were 0.855, 0.730, and 0.656, respectively, indicating that publication year and region did not contribute significantly to the heterogeneity observed.

Subgroup analyses based on the detection method divided studies into three subgroups: PCR, real-time PCR, and others, with I^2 values of 77.8%, 58.0%, and 0%, respectively. This revealed significant heterogeneity within the PCR and real-time PCR subgroups, but not in the other subgroups. Sensitivity analysis showed that excluding studies by Ma *et al.* [9] and Glaser *et al.* [19] reduced the overall heterogeneity (I^2 = 39.4%, P = 0.095), and yielded a pooled effect size of OR = 2.30 (95% CI: 1.65, 3.20) (**Figure 2**).

TSA results showed that the cumulative Z value crossed both the conventional and the TSA boundaries, reaching the required information threshold, thus confirming a significant correlation between UU infection and BPD (**Figure 3**).

Intraventricular Hemorrhage (IVH): Eight studies [12, 14-16, 18-21] evaluated the association between UU infection and IVH. No statistical heterogeneity was observed among studies (I^2 = 13.7%, P = 0.323), supporting the use of a fixed-effects model. The results showed that UU infection significantly correlated with IVH, with a pooled effect size of OR = 1.62 (95% CI: 1.23, 2.13) (Z = 3.448, P = 0.001) (**Figure 4**).

Sensitivity analysis was performed by sequentially excluding each study from the meta-analysis, and the *P*-values consistently changed in the same direction. This sensitivity analysis strengthened the credibility of the original results (**Figure 5**).

TSA results confirmed that the cumulative Z value crossed both the conventional boundary and the TSA boundary, reaching the required information threshold and validating a signifi-

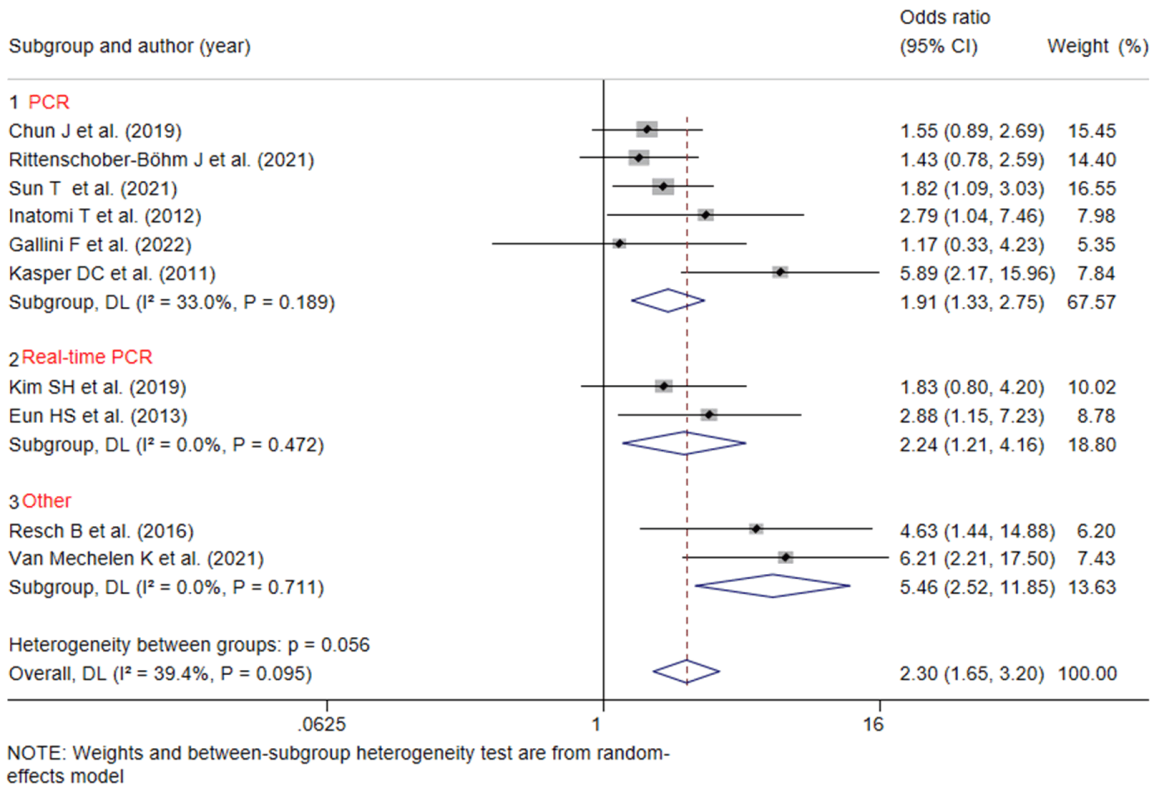

Figure 2. Forest plot of UU infection and BPD. Notes: PCR: Polymerase Chain Reaction, UU: Ureaplasma urealyticum, BPD: Bronchopulmonary dysplasia.

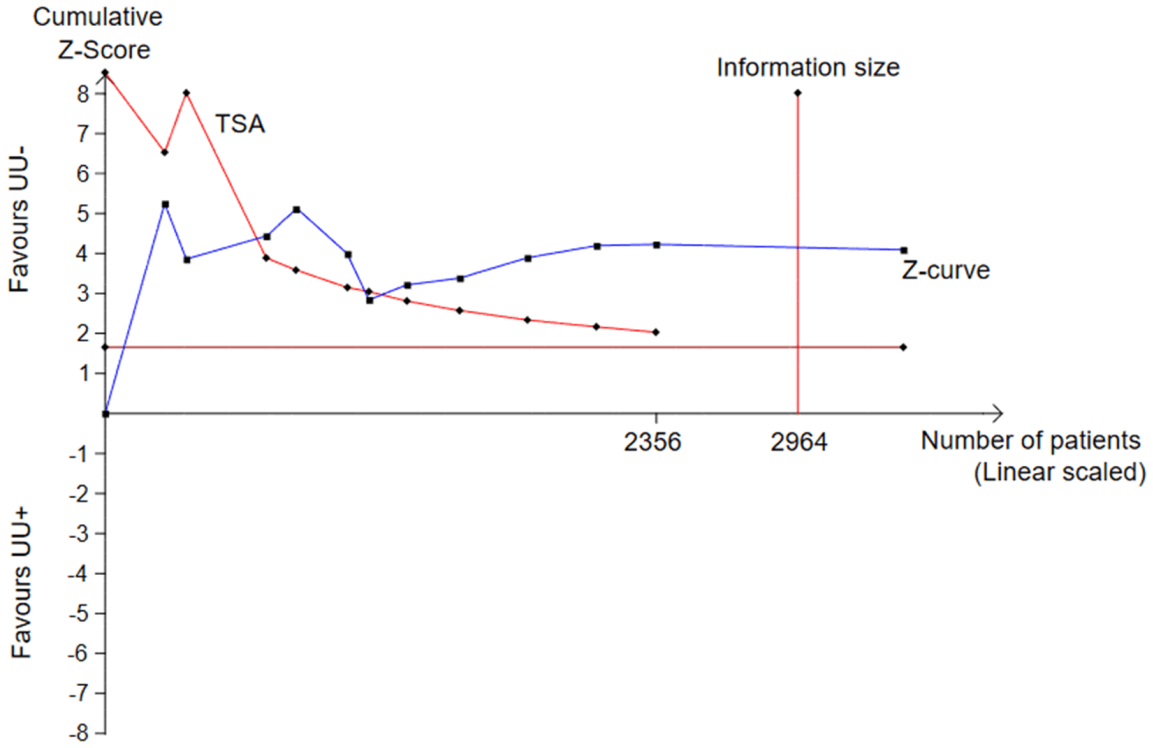

Figure 3. TSA results (UU infection and BPD).

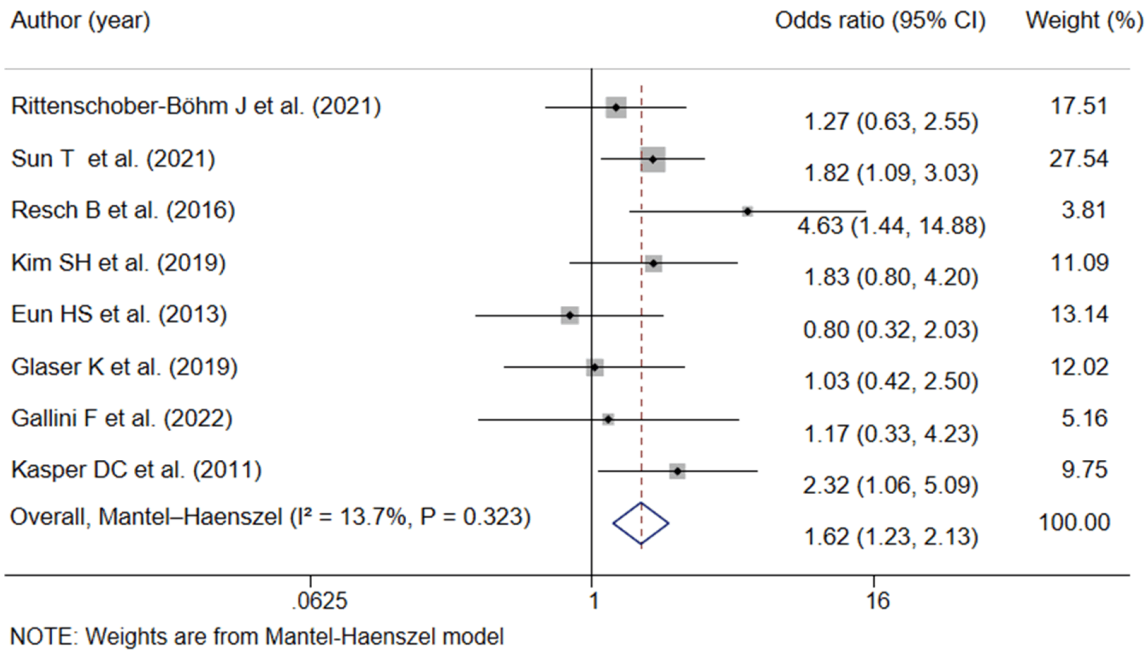

Figure 4. Forest plot of UU infection and IVH. Notes: UU: Ureaplasma urealyticum, IVH: Intraventricular hemorrhage.

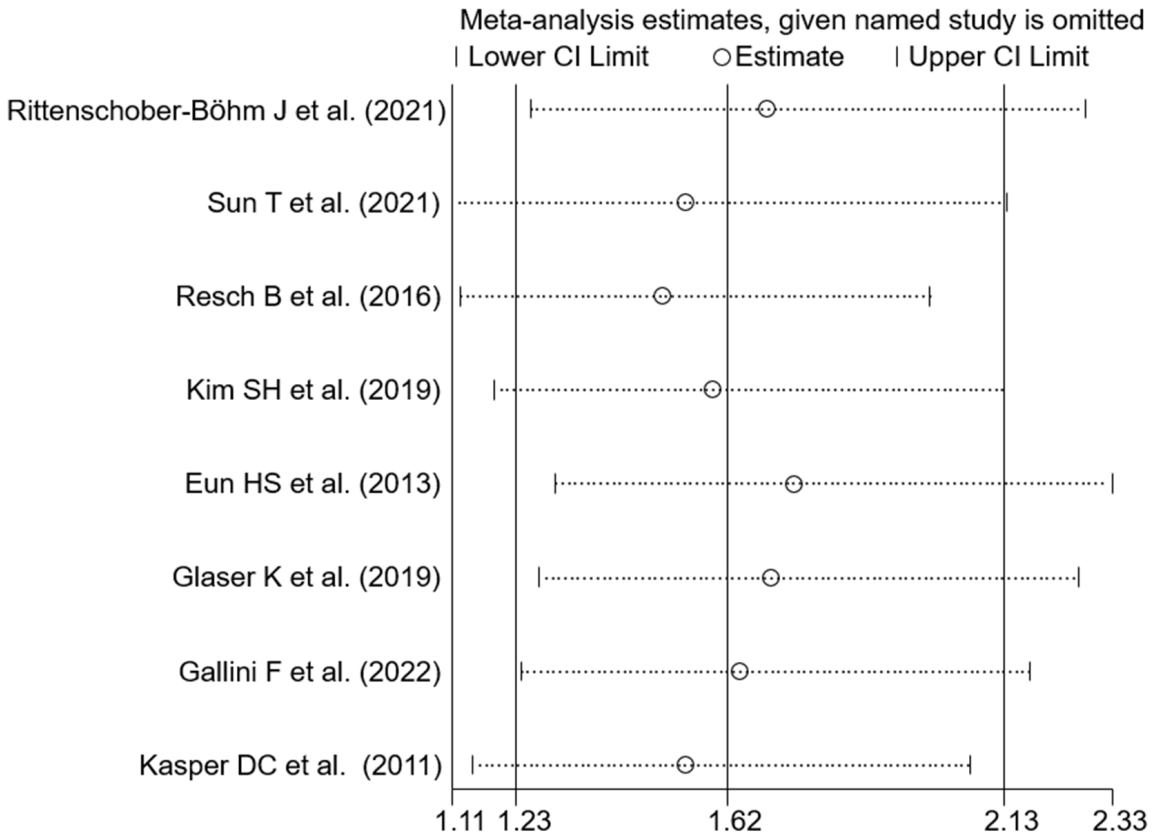

Figure 5. Sensitivity analysis (UU infection and IVH). Notes: UU: Ureaplasma urealyticum, IVH: Intraventricular hemorrhage.

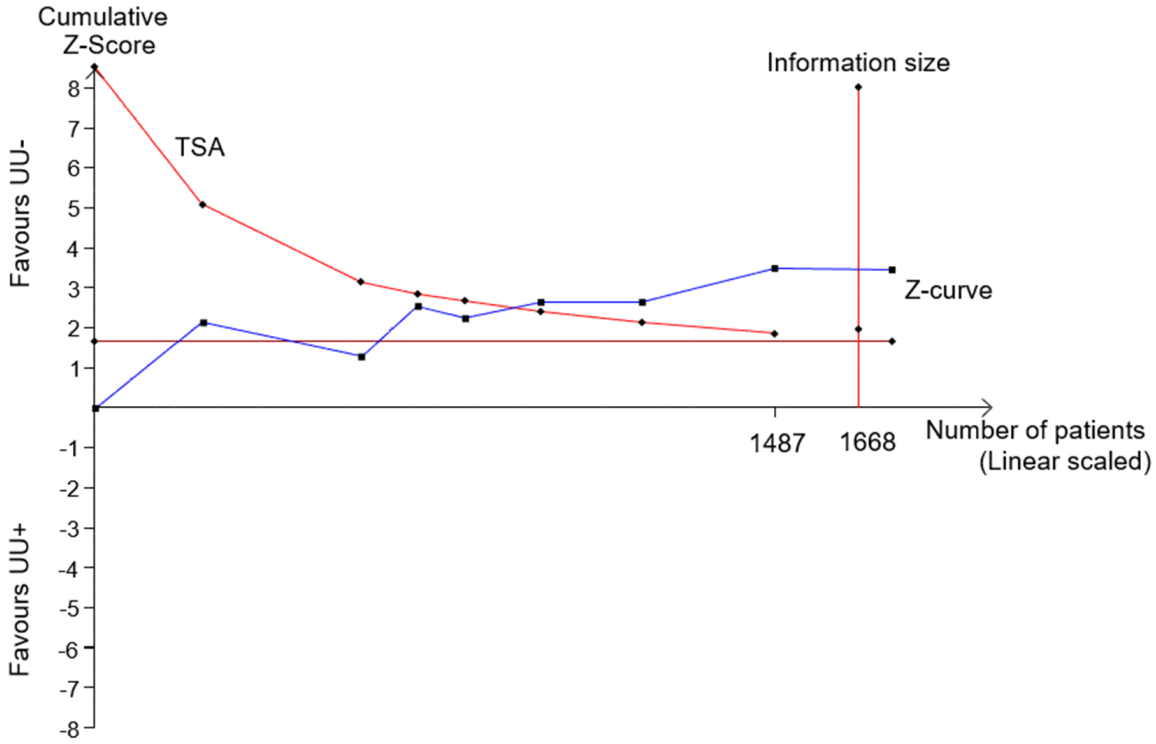

Figure 6. TSA results (UU infection and IVH).

cant correlation between UU infection and IVH (**Figure 6**).

Necrotizing Enterocolitis (NEC): Eight studies [9, 12, 14, 15, 18-21] assessed the association between UU infection and NEC. The heterogeneity among the studies was low (I^2 = 4.9% and P = 0.393), allowing for a fixed-effects model. The results revealed a pooled effect size of OR = 1.33 (95% CI: 0.91, 1.95) (Z = 1.487, P = 0.137). This *P*-value suggested that the correlation between UU infection and NEC was not significant (**Figure 7**).

Sensitivity analysis, performed by sequentially excluding each study from the meta-analysis, showed consistent *P*-value trends. This finding strengthened the credibility of the original results (**Figure 8**).

TSA results showed that the cumulative Z value did not cross the conventional boundary and the TSA boundary, nor did it reach the required information threshold, suggesting that UU infection was not significantly correlated with NEC (**Figure 9**).

Sepsis: Nine studies [7, 12, 13, 15-17, 19-21] assessed the association between UU infection and sepsis. The studies displayed no statistical heterogeneity (I^2 = 0%, P = 0.706), justifying the use of a fixed-effects model. The results showed that UU infection significantly correlated with sepsis, with a pooled effect size of OR = 1.54 (95% CI: 1.11, 2.13) (Z = 2.580, P = 0.010) (**Figure 10**).

Sensitivity analysis, conducted by removing each study one at a time, demonstrated consistent directional changes in *P*-values, reinforcing the reliability of the original results (**Figure 11**).

TSA results showed that the cumulative Z value crossed both the conventional and the TSA boundaries, reaching the required information threshold and confirming a significant correlation between UU infection and sepsis (**Figure 12**).

Neonatal pneumonia: Two studies, Ma *et al.* [9] and Inatomi *et al.* [17] reported on the association between UU infection and neonatal pneumonia. The findings indicated no substantial difference in pneumonia rates between neonates with UU infection and those without (18.18% vs. 17.74% and 8.57% vs. 7.14%, respectively; P > 0.05).

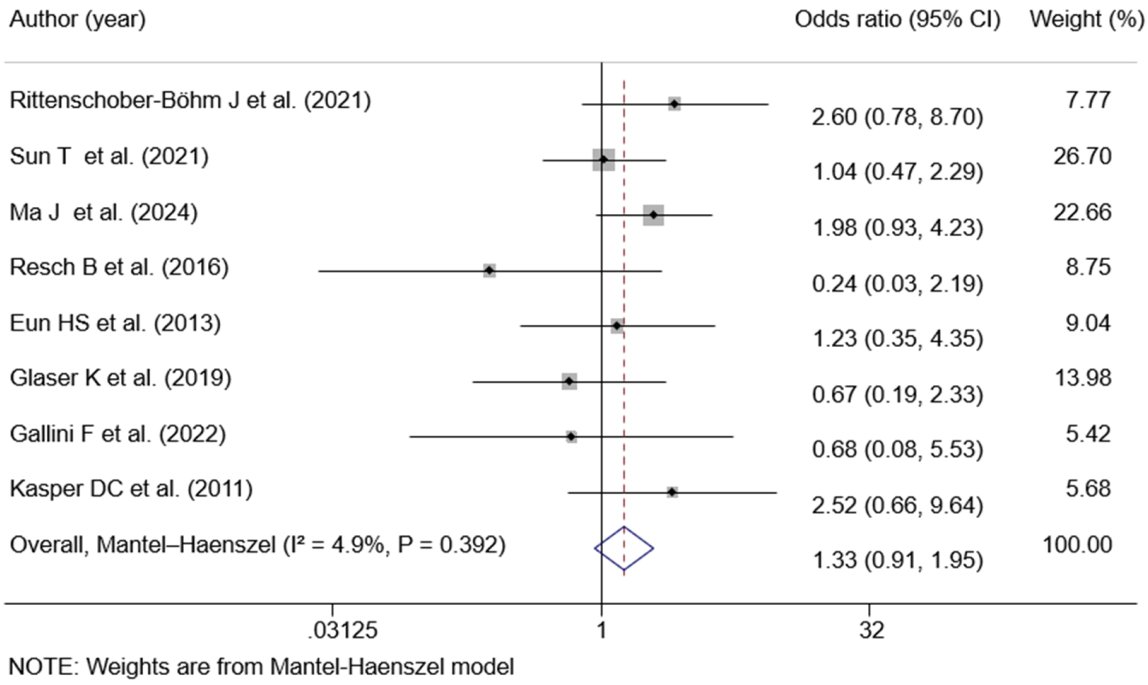

Figure 7. Forest plot of UU infection and NEC. Notes: UU: Ureaplasma urealyticum, NEC: Necrotizing enterocolitis.

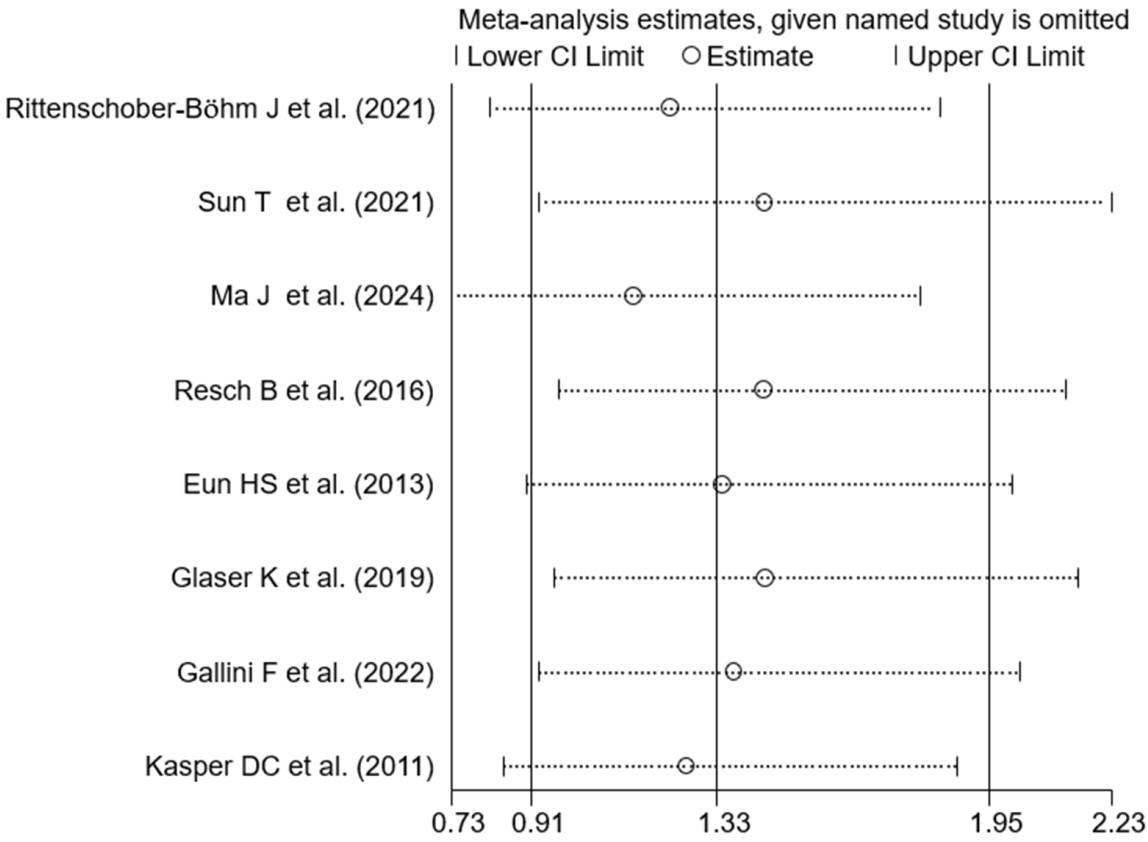

Figure 8. Sensitivity analysis (UU infection and NEC). Notes: UU: Ureaplasma urealyticum, NEC: Necrotizing enterocolitis.

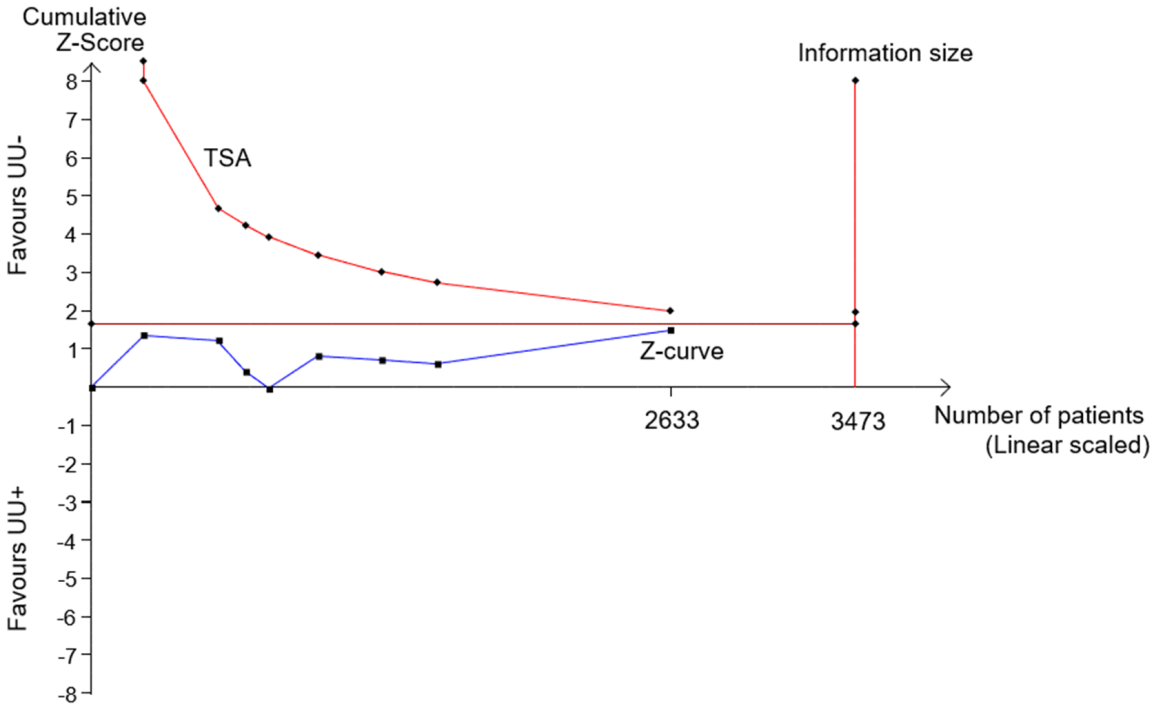

Figure 9. TSA results (UU infection and NEC).

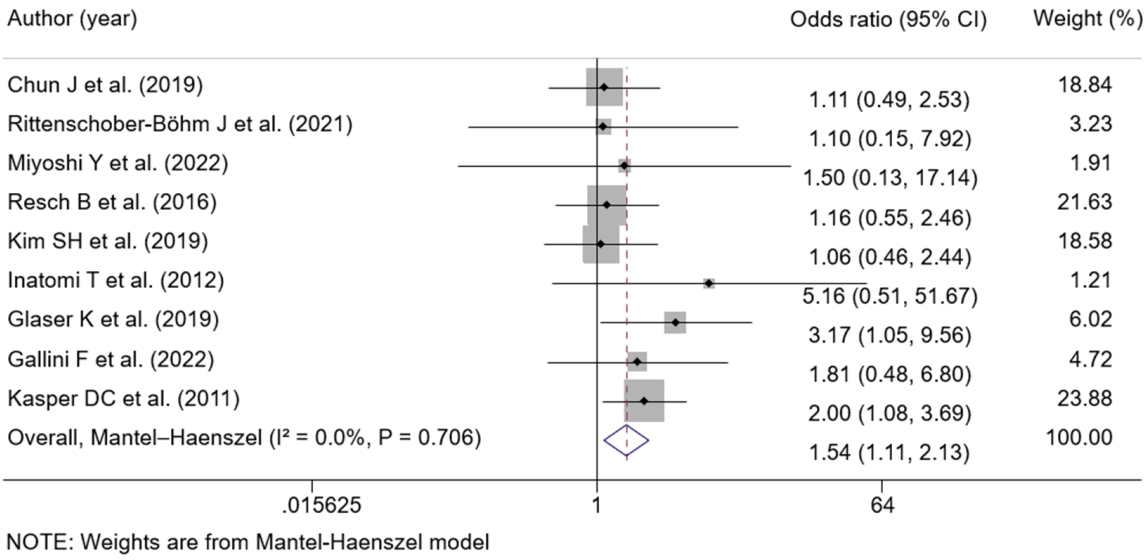

Figure 10. Forest plot of UU infection and sepsis. Note: UU: Ureaplasma urealyticum.

Publication bias

In this study, 10 articles were included for the outcome indicator of BPD, so a funnel plot was generated (**Figure 13**). The funnel plot is basically symmetrical, with the Begg test yielding a $P = 0.107$ and the Egger test yielding a $P = 0.050$, indicating no significant publication bias.

Grading of recommendations assessment, development and evaluation (GRADE) score

GRADE assessment for the five outcome measures in the included literature showed that the association with BPD was of low quality, mainly due to significant statistical heterogeneity, while that of NEC was of moderate quality, and IHV and septicemia were of high quality. In con-

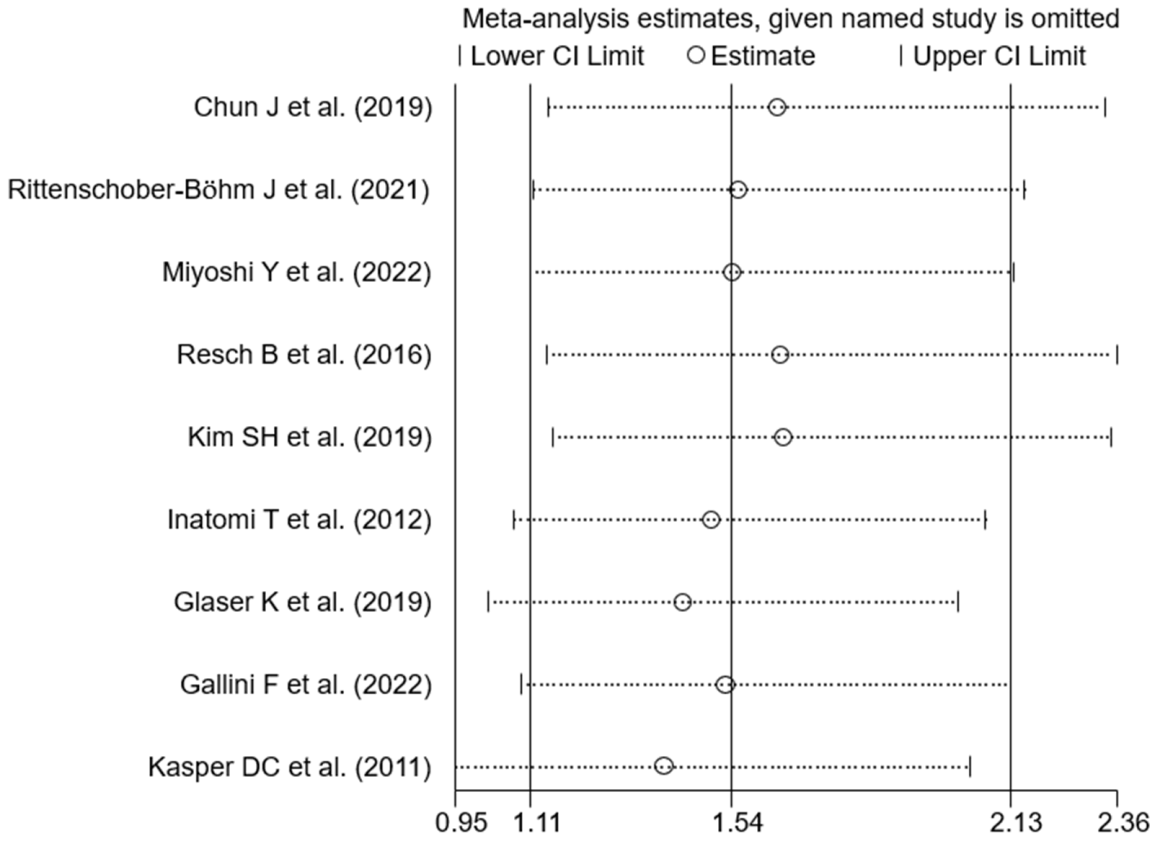

Figure 11. Sensitivity analysis (UU infection and sepsis). Note: UU: Ureaplasma urealyticum.

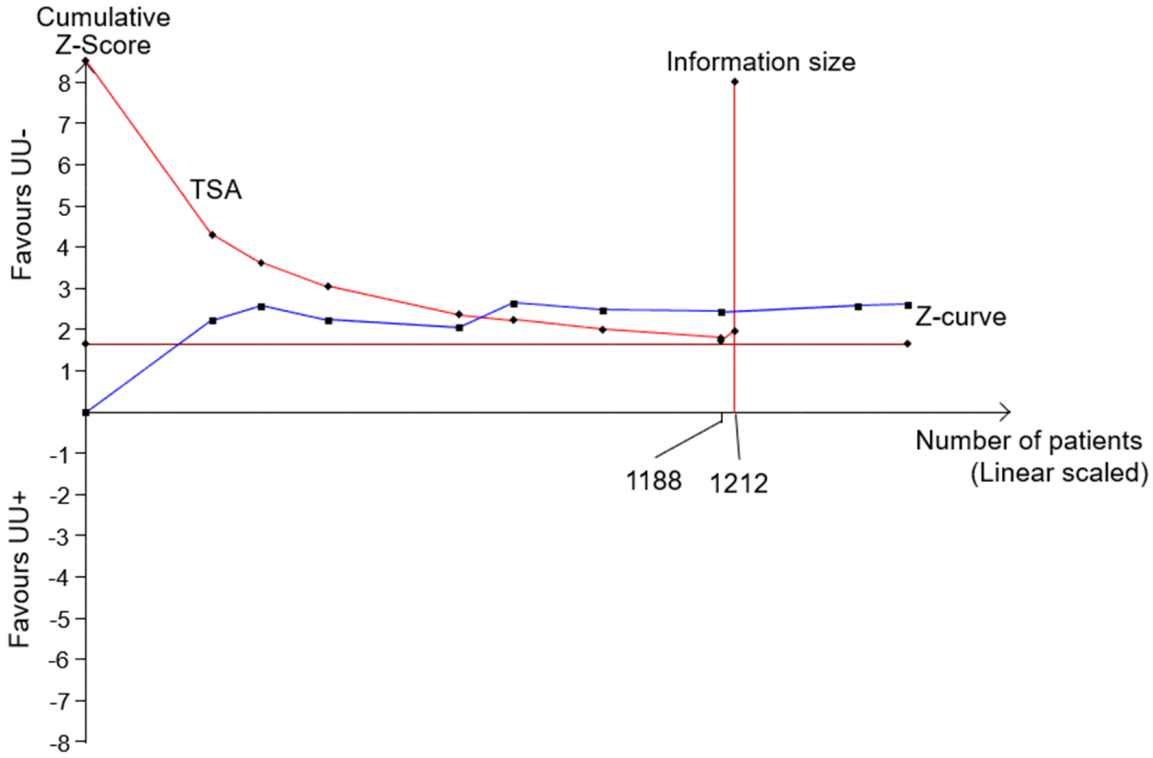

Figure 12. TSA results (UU infection and sepsis).

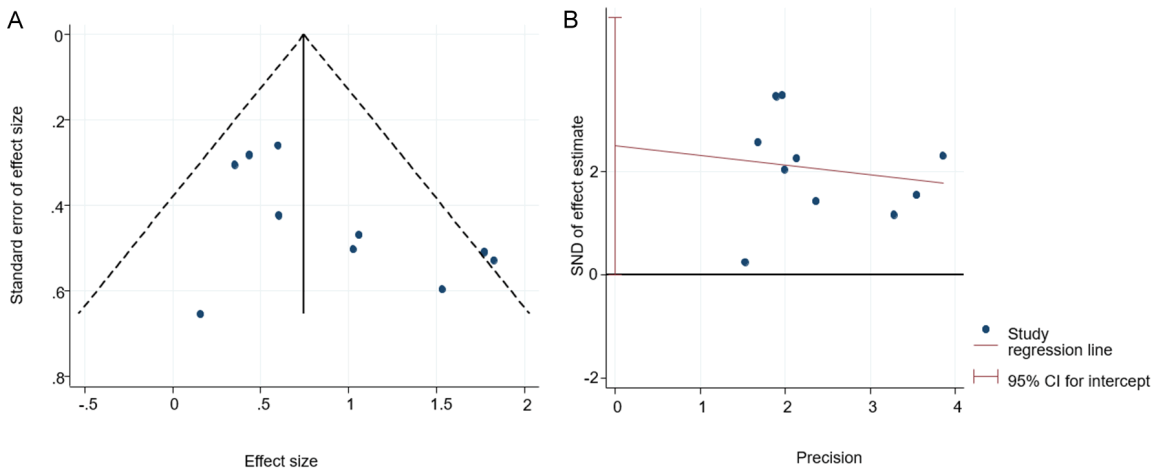

Figure 13. Publication bias analysis. (A) Funnel plot of UU infection and BPD, (B) Egger examines the funnel plot. Notes: UU: Ureaplasma urealyticum, BPD: Bronchopulmonary dysplasia.

trast, the quality of evidence for neonatal pneumonia was very low, limited by its small sample size and the imprecision of the results (**Table 4**).

Discussion

Previous reports indicated that the positivity rate for *Ureaplasma urealyticum* (UU) in the reproductive tracts of adult women ranges from 40% to 80%, with the highest occurrence among women aged 25-34 years, reaching up to 82% [22]. Liu *et al.* [23] studied gynecological and obstetric outpatients in Southwest China and found a UU positivity rate of 27.07%, particularly among women of childbearing age (25-34 years). In contrast, a study by Cai *et al.* [24] surveyed 13,303 gynecological outpatients and reported a UU positivity rate of 62.04%, identifying younger women (< 25 years) as a significantly affected group. These findings underscore the prevalence of UU in reproductive health, highlighting its possible effect on pregnancy outcome. UU can invade the reproductive tract, leading to conditions such as chorioamnionitis, which poses risks for fetal infections. Notably, literature indicates a vertical transmission rate of UU to newborns between 45% and 66%, with even higher rates observed in preterm infants. Many unexplained cases of preterm birth are attributed to UU infection [25]. Furthermore, UU has been detected in various tissues, including fetal umbilical cord blood, newborn blood, brain, cerebrospinal fluid, lungs, airway secretions, and gastric fluid. Its presence in these sites is strongly associated with adverse neonatal conditions, suggesting a critical role in neonatal morbidity [5, 26]. In summary, the high prevalence of UU among women of reproductive age and its ability to cause significant neonatal complications warrant further investigation into screening and management strategies during pregnancy to mitigate the risks associated with this infection.

A study suggested that UU colonization in extremely preterm infants is associated with an increased severity of BPD [27]. Our meta-analysis reveals a significant correlation between UU infection and the development of BPD in preterm infants, with an odds ratio of 2.30 (95% CI: 1.65-3.20), consistent with the results of Xu *et al.* [5]. While the specific mechanisms by which UU infection contributes to BPD remain unclear, it is hypothesized that UU induces severe intrauterine inflammatory responses, leading to immune-mediated lung injury. This includes the release of pulmonary cytokines and chemokines that can exacerbate lung damage [19]. Furthermore, UU infection may worsen mechanical ventilation-induced lung injuries by amplifying dysregulated inflammatory responses [19]. Animal studies have corroborated these findings, demonstrating that prenatal exposure to UU leads to lung inflammation, altered lung development, and pulmonary fibrosis-key characteristics of BPD [28].

Our analysis also included two studies examining the impact of UU infection on neonatal pneumonia and showed no significant differ-

Table 4. GRADE score

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sepsis	placebo	Relative (95% CI)	Absolute (95% CI)	
BPD											
12	non-randomized studies	not serious	very serious[a]	not serious	not serious	very strong association	382/1335 (28.6%)	450/2076 (21.7%)	OR 2.53 (2.04 to 3.14)	195 more per 1,000 (from 144 more to 248 more)	⊕⊕◯◯ Lowa
NEC											
8	non-randomized studies	not serious	not serious	not serious	not serious	dose response gradient	55/999 (5.5%)	89/1634 (5.4%)	OR 1.33 (0.91 to 1.95)	17 more per 1,000 (from 5 fewer to 47 more)	⊕⊕⊕◯ Moderate
IHV											
8	non-randomized studies	not serious	not serious	not serious	not serious	very strong association	147/548 (26.8%)	236/1193 (19.8%)	OR 1.62 (1.23 to 2.13)	88 more per 1,000 (from 35 more to 147 more)	⊕⊕⊕⊕ High
Sepsis											
9	non-randomized studies	not serious	not serious	not serious	not serious	very strong association	106/672 (15.8%)	91/864 (10.5%)	OR 1.54 (1.11 to 2.13)	48 more per 1,000 (from 10 more to 95 more)	⊕⊕⊕⊕ High
Neonatal pneumonia											
2	non-randomized studies	serious[b]	not serious	not serious	very serious[c]	publication bias strongly suspected	Two studies both reported UU infection and neonatal pneumonia. The findings indicated no substantial difference in pneumonia rates between neonates with UU infection and those without (18.18% vs. 17.74% and 8.57% vs. 7.14%, respectively; P > 0.05).				⊕◯◯◯ Very low[b,c]

Notes: CI: confidence interval, OR: odds ratio, RR: risk ratio, BPD: Bronchopulmonary dysplasia, NEC: Necrotizing enterocolitis, IVH: Intraventricular hemorrhage. a. After the combination, the I^2 values were large and the heterogeneity was high. b. No mention of blinding. c. Small sample size, so results are not accurate enough.

ences in pneumonia rates between neonates with and without UU infection (18.18% vs. 17.74%, and 8.57% vs. 7.14%, P > 0.05). The limited sample sizes of these studies might have constrained statistical power, potentially masking minor effects. Given these findings, further research is necessary to clarify the causal relationship between UU infection and BPD, as well as to explore effective prevention and treatment strategies. Understanding the mechanisms at play will be critical in developing targeted interventions for at-risk populations.

In addition to being isolated from respiratory secretions, UU can also be detected in gastric aspirates and rectal cultures. Abe et al. [29] used Polymerase Chain Reaction (PCR) to identify UU in gastric fluid samples from 47 newborns, finding a colonization rate of 19%. Notably, another study involving preterm infants with a gestational age of less than 33 weeks revealed that those with UU colonization had a 2.1-fold higher incidence of NEC compared to non-colonized infants. Among those with a gestational age of 28 weeks or less, the colonization rate was 3.3 times higher. Moreover, infants with UU colonization exhibited significant prenatal fetal inflammatory responses, evidenced by elevated levels of interleukin-1 beta and interleukin-6 in umbilical cord blood, both of which are linked to increased NEC risk after birth [30]. However, our analysis did not find a significant association between UU infection and NEC in newborns (OR = 1.33, 95% CI: 0.91-1.95). This finding aligns with existing literature [31], suggesting that the relationship may be influenced by multiple confounding factors, such as gestational age, birth weight, gut microbiome composition, timing of enteral feeding, and genetic susceptibility among preterm infants. The varied physiologic and immunological states across different gestational ages could affect both susceptibility to UU infection and the subsequent development of NEC. Additionally, the diagnostic criteria for NEC may differ based on gestational age, potentially leading to inconsistencies in reported outcomes.

Our study identified a significant correlation between UU infection and IVH in preterm infants (OR = 1.62, 95% CI: 1.23-2.13). It is hypothesized that UU infection can lead to conditions such as chorioamnionitis and fetal inflammatory response syndrome, both closely associated with an increased risk of IVH [32]. In premature infants, UU may trigger central nervous system inflammation through complex interactions that involve host susceptibility, serotype pathogenicity, and the inherent vulnerability of the central nervous system at different gestational ages [33]. Furthermore, UU appears to influence the expression of cell adhesion molecules and growth factors in endothelial cells lining the brain's microvessels, which may compromise the integrity of the blood-brain barrier and increasing susceptibility to neuroinflammation and injury [34].

Additionally, our research demonstrated a strong association between UU infection and neonatal sepsis (OR = 1.54, 95% CI: 1.11-2.13), consistent with previous findings [35]. The mechanism by which UU may elevate sepsis risk includes the potential for premature rupture of membranes, increasing exposure to other pathogens [36]. Moreover, the inflammatory response initiated by UU infection is known to elevate white blood cell counts and the levels of inflammatory cytokines, such as IL-17 and IL-8, in the bloodstream of newborns, further heightening the risk of sepsis [19].

Nonetheless, there are several limitations to this study: (1) Limited sample size, which may reduce the ability to detect small effect sizes or rare events; (2) Inherent information and selection biases associated with the retrospective design; (3) Lack of standardized diagnostic criteria across studies, which may affect the consistency of results; and (4) Absence of long-term health assessments for UU infections in newborns.

Future research should include long-term follow-up to evaluate the long-term impact of UU infection on newborn growth and neural development. Additionally, research should delve into host-pathogen interactions, genetic susceptibility factors, immune regulatory effects, and the efficacy of prevention and treatment strategies.

Conclusion

Overall, UU infections have adverse effects on newborns, increasing the risk of BPD, IVH, and sepsis. More research is needed to elucidate

the exact mechanisms underlying UU infection's effect on neonatal outcomes and to develop effective prevention and treatment strategies.

Disclosure of conflict of interest

None.

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