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Determinants of neonatal sepsis among neonates admitted to neonatal intensive care units in ethiopian hospitals: A systematic review and meta-analysis

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ABSTRACT

Objective: Several studies have identified risk factors for neonatal sepsis, but they are limited to specific geographical areas with results that may not be generalizable to other populations. Hence, the objective of this study was to determine the contributing factors, representative at a national level, that influence the occurrence of neonatal sepsis in neonates receiving hospital care in Ethiopia.

Methods and materials: A thorough search was conducted across PubMed/Medline, Hinari, Cochrane Library, and Google Scholar to identify relevant studies. The pooled odds ratio was estimated using the random effect model. The heterogeneity among the included studies was evaluated using the I2 and Cochrane Q-statistics tests. Egger's tests used to assess publication bias.

Results: A total of 19 studies comprising 6190 study participants were included. Neonatal sepsis was positively associated with several factors, namely: prolonged premature rupture of membrane (OR: 3.85, 95% CI: 2.31–6.42), low first minute APGAR score (OR: 3.74, 95% CI: 1.29–10.81), low fifth minute APGAR score (OR: 4.17, 95% CI: 1.76–9.91), delayed initiation of breastfeeding (OR: 3.41, 95% CI: 2.18–5.36), and infection of the maternal urinary tract (OR: 3.17, 95% CI: 1.87–5.35).

Conclusion: Duration of rupture of membrane, APGAR score, time of initiation of breastfeeding, and urinary tract infection have a role in the development of neonatal sepsis.

1. Introduction

Neonatal sepsis (NS) is septicemia in infants less than three months old. It is classified as early and late. Early-onset sepsis occurs in the first seven days of life, and late-onset sepsis occurs after seven days to 90 days of age [1]. Sepsis is a deadly infection that occurs

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when the body reacts to an infection by damaging its organs and tissues [2]. Sepsis can affect anyone, but newborns and infants are more susceptible [3]. Besides, newborns, especially preterm infants, have a weakened immune system and are at risk. Although certain antibodies from the pregnant mother enter the baby through the placenta, the antibodies in the fetus' blood may not be sufficient to fight infection [4]. Left untreated, they can lead to organ failure and death [3].

The World Health Organization (WHO) reported that about 6.5–38/1000 live births in the hospital developed neonatal sepsis globally in 2017 and are responsible for 4%–56% of neonatal deaths [5]. Southeast Asia and Sub-Saharan Africa account for three-fourths of all newborn mortality [5]. In the same year, WHO reported that NS kills about one million newborns each year [2]. In 2017, the global burden of diseases (GBD) study group estimated 1.3 million neonatal sepsis cases and 20300 neonatal deaths secondary to NS [6]. UNICEF reports a rise in the number of neonatal deaths during the first month of life, reaching 2.4 million deaths in 2020. On average, this translates to approximately 6500 deaths per day [7]. The report of the global systematic review is the largest of all, which reported 3 million NS cases in 2018 [8].

Previously, studies have used socio-demographic and obstetric variables to assess their association with NS. For example, various studies have assessed the association between prolonged rupture of membrane and NS [9–11], mode of delivery, and NS [10,12–15]. The meta-analysis study conducted in Ethiopia showed a positive association between preterm birth, decreasing gestational age, urinary tract infection, and high intrapartum fever [16,17]. However, these meta-analysis studies focused on a few variables and failed to include important variables. Other primary studies are also conducted to assess the determinants of NS, but they are restricted to a specific area. They present fragmented results confined to the specified area and do not represent the national level. Hence, the absence of the study at the national level was identified as a gap. Thus, this study aimed to pinpoint determinants of neonatal sepsis in Ethiopia among newborn babies who develop sepsis.

2. Methods and materials

2.1. Eligibility criteria

2.1.1. Inclusion criteria

The studies included in this study were limited to Ethiopia. Concerning the design of the study, observational and randomized studies reporting the determinants of neonatal sepsis were encompassed. Any language on our study topic can be included, even though only articles published in English were found and have been retrieved for review. Both published and unpublished articles (in order not to miss gray literature) were considered for this systematic review. The study population included all newborns admitted to a neonatal intensive care unit. Mode of delivery, prolonged rupture of membranes, low APGAR score, and delayed breastfeeding were exposure variables in this study, and neonatal sepsis was the outcome of interest. All studies in Ethiopia on the outcome of interest published before May 5, 2023, were included.

2.1.2. Exclusion criteria

The study for which we were unable to get the relevant information after contacting the authors via email [18] and studies focused on only early or late neonatal sepsis were excluded from the analysis. Systematic reviews, letters to the editor, case series, case studies, and qualitative studies were excluded because they did not have the exposures of interest.

Table 1
Characteristics of the studies included in the systematic review and meta-analysis for the association between neonatal sepsis and independent variables of interest.

s.no	Name	Publication year	Region	setting	Design	Sample size	Response rate
1	Abebe [33]	2019	Oromia	Hospital	cross-sectional	303	100
2	Akalu et al. [9]	2020	Amhara	Hospital	case-control	231	100
3	Alemu et al. [25]	2019	Amhara	Hospital	case-control	246	100
4	Astawus et al. [15]	2021	Harar	Hospital	cross-sectional	386	100
5	Atkuregn [26]	2020	SNNPR[a]	Hospital	case-control	385	100
6	Belayneh et al. [27]	2022	SNNPR	Hospital	case-control	248	100
7	Bulto et al. [28]	2021	Oromia	Hospital	case-control	544	94.4
8	Etafa et al. [29]	2020	Oromia	Hospital	case control	300	93.8
9	G/eyesus et al. [14]	2017	Amhara	Hospital	cross-sectional	251	100
10	Gebremedhin et al. [11]	2016	Tigray	Hospital	case-control	234	100
11	Mersha et al. [30]	2019	SNNPR	Hospital	case-control	275	100
12	Minyahil et al. [12]	2014	Oromia	Hospital	cross-sectional	306	100
13	Molla et al. [10]	2021	Amhara	Hospital	cross-sectional	412	100
14	Mustefa et al. [34]	2020	SNNPR	Hospital	cross-sectional	351	100
15	Yismaw et al. [35]	2019	Amhara	Hospital	cross-sectional	423	100
16	Birrie et al. [36]	2022	Amhara	Hospital	cross-sectional	344	100
17	Roble et al. [37]	2022	Somali	Hospital	cross-sectional	356	98.6
18	Bejitual et al. [32]	2022	Sidama	Hospital	case-control	331	100
19	Shifera et al. [31]	2023	Sidama	Hospital	case-control	264	100

[a] = Southern nations, nationalities, and peoples of the region.

2.1.3. Information sources and search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis were used to conduct this review and meta-analysis. (PRISMA) [19]. PubMed, Hinari, and Google Scholar databases were searched for related studies. Google and institutional repository of Addis Ababa University were searched to include gray literature. Manual search of the reference lists of the included studies were also conducted. The identified articles were promptly transferred to EndNote ™ X9 citation manager for inclusion in the analysis.

Search keywords like "((((neonatal [Title]) OR (neonatal [MeSH Terms])) AND (sepsis [MeSH Terms])) OR (sepsis [Title])) AND (Ethiopia [Title])" were used. To combine search terms, the Boolean operators 'OR' and 'AND' were utilized. Supporting information (**S1 Table 1**) contains examples of search strategies that were fit for all databases.

These procedures were used to conduct this systematic review. First, the electronic database search results were entered into the EndNote ™ X9 citation manager software. The duplicates were removed in the second step. Then, the title, abstract, and full text of all articles were examined in terms of eligibility criteria. Fourth, a full review of the paper has been conducted, and studies have been eliminated to the aforementioned criteria. The Joana Briggs Institute (JBI) critical appraisal tool was employed to assess the quality of the articles included in the study [20].

2.1.4. The selection process

Four researchers (KS, CK, NE, and GG) independently assessed the first 125 records' titles and abstracts and addressed inconsistencies by consensus. The researchers then screened the titles and abstracts of all papers obtained in pairs. In the event of a disagreement, a discussion was held to determine which articles should be screened in full text. If necessary, the remaining researchers were consulted to reach a final conclusion. The full-text publications were assessed for inclusion by two researchers (KS and BS). In cases where there was disagreement, the fourth researcher (GG) was consulted to establish a consensus on whether to include or exclude the publication.

2.1.5. Data collection process

Data collection processes were done by KS and BS based on eligibility criteria using Microsoft Excel™. The data collection form comprised the author's name, publication year, study area, setting, response rate, sample size, and type of study design. The odds ratios with 95% confidence intervals for the variables included were retrieved. The retrieved data were imported into STATA 14 for analysis. The data was collected and verified by KS and TM.

2.1.6. Outcome measurement

The outcome of this study was neonatal sepsis. Neonatal sepsis is septicemia in infants less than three months old. No study reported determinants or associated factors of neonatal sepsis were excluded. We collected data on author, publication year, response rate, sample size, and study design.

2.1.6.1. Risk of bias. The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional [21] and case-control studies [22]. The checklist for analytical cross-sectional studies comprised eight parameters, including the clear definition of inclusion criteria for the sample, detailed description of study subjects and settings, valid and reliable measurement of exposure, utilization of objective and standard criteria for measuring the condition, identification of confounding factors, declaration of strategies to handle confounding factors, valid and reliable measurement of outcomes, and the utilization of appropriate statistical analysis **(S2 Table)**. On the other hand, the checklist for case-control studies encompassed ten parameters. These included assessing the comparability of groups, appropriate matching of cases and controls, consistent criteria for identifying cases and controls, standard, valid, and reliable measurement of exposure, uniform measurement of exposure for cases and controls, identification of confounding factors, declaration of strategies to manage confounding factors, standard, valid, and reliable assessment of outcomes for cases and controls, ensuring a meaningful exposure period of interest, and employing appropriate statistical analysis. NE and CK individually performed the evaluation of bias, with any disagreements resolved by the involvement of another author (TM). **Table S2** contains the assessment results for both case-control and cross-sectional studies.

2.1.7. Data synthesis

The odds ratios obtained from the primary studies were combined, and the standard error of the odds ratios was calculated. The collected odds ratios, along with their corresponding 95% confidence intervals (CI), were presented using a forest plot. Both random-effect and fixed-effect models were employed to determine the association between the independent and dependent variables. To assess the heterogeneity of the pooled odds ratio, the Cochrane Q-statistic and I2 statistics were calculated. The I2 test statistics yielded results of 25%, 50%, and 75%, which indicated low, moderate, and high heterogeneity, respectively [23]. For all statistical analyses, the STATA version 14 software (StataCorp LP.2015, College Station, TX: USA) was utilized.

2.1.8. Publication bias

Publication bias was assessed using Egger's test and funnel plots. The publication bias was declared using a P-value less than 0.05.

2.1.9. Sensitivity analysis

Leave-one-out sensitivity analysis was performed to assess the influence of a single study on the overall pooled estimate.

2.1.10. Operational definition

Vaginal delivery: the birth of a baby through the vagina, including spontaneous vaginal and instrumental delivery.
Cesarean section: the birth of a baby through an incision in the wall of the abdomen and uterus.
Prolonged rupture of membrane: rupture of membrane for more than 18 h before the onset of labor [24].
A low APGAR score is an APGAR score of <7/10 [14].
Delayed breastfeeding: Is the initiation of breastfeeding 1 h after the birth of the baby.

3. Results

3.1. Selection of sources of evidence

During the initial search, a total of 162 articles were identified. Out of these, 91 articles were eliminated because they were duplicates. Additionally, after reviewing the titles and abstracts of the remaining 71 articles, 30 more were excluded as they did not meet the inclusion criteria. The remaining 41 articles were thoroughly read, and 19 of them, which met the criteria, were selected for the final analysis (**Fig. 1**).

3.2. Characteristics of the included studies

This systematic review and meta-analysis include a total of nineteen studies, out of which ten follow a case-control design [9,11,25–32], while the remaining studies are cross-sectional [10,12,14,15,33–37]. Six studies were conducted in the Amhara region [9,10,14,25,35,36], four in Oromia [12,28,29,33], four in the southern nation nationalities and peoples of the region (SNNPR) [26,27,30,34], two in Sidama [31,32], and one each in Somali [37], one from Harari [15], and one Tigray [11]. The total sample size across the original studies included in this meta-analysis is 6190. The smallest sample size was reported in the study conducted in the Amhara region, with 231 participants [9], whereas the largest study was conducted in Oromia with 544 participants [28]. All studies had a

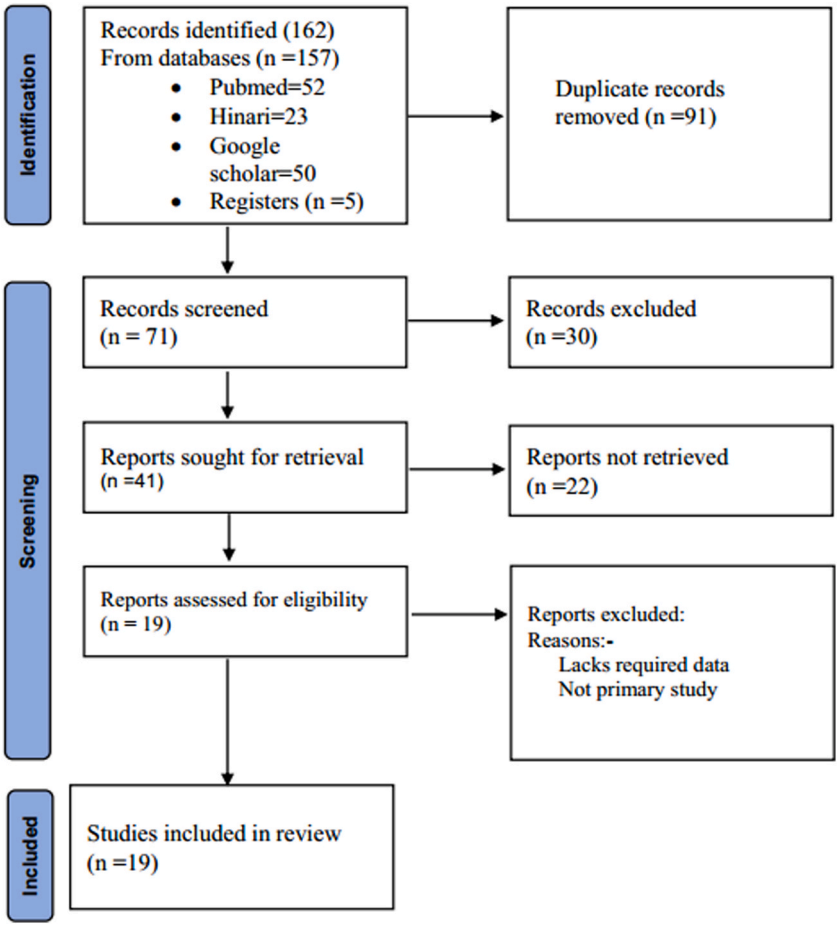

Fig. 1. PRISMA flow diagram for selection of studies for systematic review and meta-analysis of the determinants of neonatal sepsis.

good response rate, exceeding 93% (**Table 1**).

3.3. Association with mode of delivery

Five studies were used to determine the association between mode of delivery and neonatal sepsis [10,12,14,15,32]. The pooled odds ratio (OR: 1.51, 95 CI: 0.79–2.87) showed cesarean section delivery is not associated with neonatal sepsis. The study showed high heterogeneity ($I^2 = 84.8\%$, $p < 0.001$). A random effects model was employed in **Fig. 2**. Egger's test was used to check for publication bias, revealing that the study has no significant publication bias ($p = 0.93$). A leave-one-out sensitivity analysis revealed that two studies affected the overall pooled estimate **S1 Fig**.

3.4. Association with low first-minute APGAR score

The studies examining the association between low first-minute APGAR scores were based on four studies' pooled results [9,26,34,35]. The pooled odds ratio (OR:3.74, 95:CI, 1.29–10.81) showed that neonates with low first-minute APGAR scores were 3.33 times more likely to acquire neonatal sepsis. The study revealed significant heterogeneity (I2 = 90.9, P0.001) **Fig. 2.**

A leave-one-out sensitivity analysis was performed and revealed that there is no effect of a single study on the overall pooled estimate. The pooled odds ratio ranges from 2.46 (1.70–3.55) to 5.95 (4.04–8.75) **S1 Fig**.

3.5. Association with delayed breastfeeding

The association was investigated based on the findings of two studies [27,30]. The pooled odds ratio (OR: 3.41,95 CI: 2.18–5.35) revealed that delayed breastfeeding is associated with the onset of neonatal sepsis. There is no heterogeneity ($I^2 = 0.0\%$, $P = 0.442$). A random effect model was employed, as shown in **Fig. 2.**

3.6. Association with prolonged rupture of membrane

The association between neonatal sepsis and prolonged PROM was examined based on the results of ten studies [9–11,27,28,31,33,34,36,37]. This meta-analysis indicated that a neonate from pregnant mothers with prolonged PROM were 3.85 (OR: 3.85, 95: CI: 2.31–6.42) times more likely to develop neonatal sepsis than their counterparts. The study revealed significant heterogeneity (I2 =

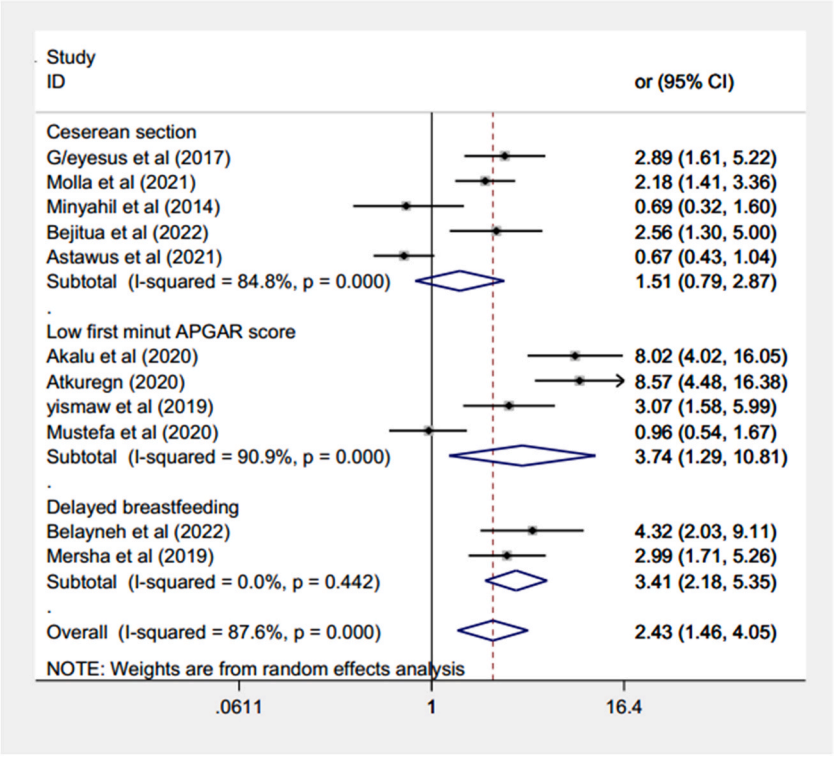

Fig. 2. Forest plot of the pooled odds ratios of association between c/s, low first minute APGAR score, delayed initiation of breastfeeding and neonatal sepsis.

78.7%, P0.001). As a result, a random effect meta-analysis approach was employed. The Egger test found publication bias (p value = 0.002), as seen in Fig. 3. The funnel plot produced an unbalanced outcome (S2 Fig).

A sensitivity analysis was performed and revealed that the type of study design does not affect the pooled estimate. The pooled odds ratio varied from 2.38 (1.74–3.26) to 3.92 (2.79–5.52) S1 Fig.

3.7. Association with low fifth-minute APGAR score

The association between a low fifth APGAR score and neonatal sepsis was evaluated in seven studies [11,14,25,29,31,33,37]. The combined analysis of these studies yielded a pooled odds ratio (OR) of 4.17, with a 95% confidence interval (CI) ranging from 1.76 to 9.91. This indicates that newborns with low fifth APGAR scores have a 4.00 times higher likelihood of developing neonatal sepsis. Notably, the study exhibited significant heterogeneity ($I2 = 88.4$, $P < 0.001$). Therefore, the random effect model was utilized in (Fig. 3) to account for this heterogeneity.

The sensitivity analysis for this study revealed the absence of the effect of study design on the pooled estimate of the odds ratio. The pooled odds ratio ranges from 2.01 (1.41–2.88) to 5.22 (3.63–7.51) S1 Fig.

3.8. Association with urinary tract infection

This result was pooled from two studies [31,38]. The pooled odds ratio indicated that a neonate born to a mother with a urinary tract infection is 3.80 (OR = 3.80, 95% CI: 2.58–5.58) more likely to develop neonatal sepsis than mothers without urinary tract infection (Fig. 3).

4. Discussion

This study have assessed the relationship between prolonged membrane rupture, low APGAR score, infection of urinary tract, and breastfeeding initiation time and neonatal sepsis. This meta-analysis showed that all the above variables had positive association with neonatal sepsis.

Prolonged membrane rupture was found to have positive association with neonatal sepsis. This is in line with the Global meta-

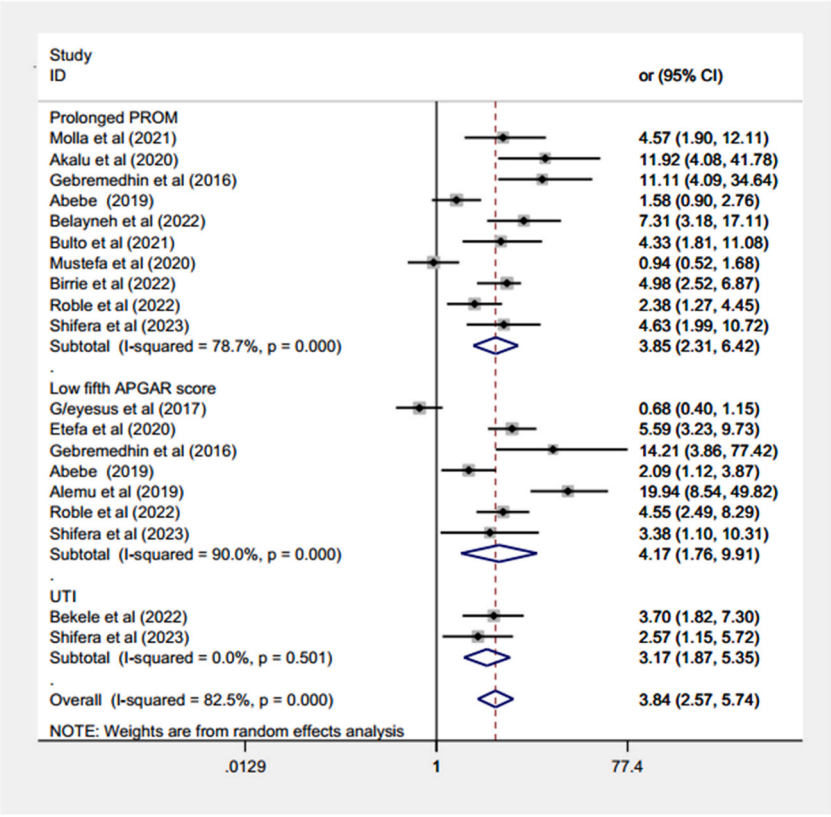

Fig. 3. Forest plot of the pooled odds ratios of association between c/s, low first minute APGAR score, delayed initiation of breastfeeding and neonatal sepsis.

analysis [39] and the primary study conducted in Tanzania [40] and Mexico [41]. After the membrane is torn, it loses its protective function, allowing pathogens in the lower birth canal to ascend and colonize the amniotic fluid. Therefore, the baby is infected with pathogenic bacteria and shows signs of sepsis after birth.

This meta-analysis indicated low first and fifth-minute APGAR scores are linked with neonatal sepsis. The studies done in Ghana [42] and Indonesia [43] also reported a positive association between low first-minute APGAR scores. Similarly, there is association between a low fifth-minute APGAR score and the occurrence of neonatal sepsis. This agrees with the study conducted in Bangladesh [44]. The study indicated that the perinatal factor associated with low APGAR score is also associated with neonatal sepsis. Hence, NS in a neonate with a low APGAR score might be because of perinatal complications necessitating resuscitation [42]. Babies with low APGAR scores usually have asphyxia. Asphyxia causes damage to the immune system, and the resuscitation procedure will further expose the newborns to pathogenic microbes [44]. It is a fact that a neonate with a low APGAR score needs artificial resuscitation. The meta-analysis study conducted in India indicated that the need for artificial resuscitation is associated with neonatal sepsis [45].

Delayed initiation of breastfeeding was also associated with neonatal sepsis. This finding aligns with a meta-analysis study conducted in 2016 [46]. Initiating breastfeeding soon after birth, preferably within the first hour, provides protection against infections and reduces newborn mortality. It also promotes the emotional bond between the mother and the baby and has a positive impact on exclusive breastfeeding. The early milk known as colostrum, which has a yellow or golden appearance, is a valuable source of nourishment and immune protection for newborns [47]. Thus, delayed breastfeeding affects the aforementioned benefits that the baby would get.

There is a clear association between infection of maternal urinary tract and neonatal sepsis. This association is likely attributed to the vertical transmission of maternal sepsis to the fetus and newborn [48,49]. The bacteria that cause UTI may enter the uterus during pelvic examination. These bacteria, including E. coli, Staphylococcus, Proteus, or Klebsiella [50], are found in the vagina and may increase the risk of vertical transmission.

4.1. Limitations of the study

The evidence in this study is based on studies done in hospitals having neonatal intensive care units. A hospital without a NICU admits neonates with sepsis to the pediatric ward. The failure of primary studies to consider this can be considered a limitation. Besides, the available evidence did not cover the country's whole region, limiting the findings' generalizability. Despite the use of a random effect model in the analysis, the presence of substantial heterogeneity was also considered a constraint. Even though we searched different databases, Scopus and Web of Science, we might have missed some articles that are not freely available, which is also considered a shortcoming.

5. Conclusion

Various obstetric complications related to childbirth have a role in the occurrence of neonatal sepsis. In this study, prolonged rupture of membrane, low first-minute, and fifth-minute APGAR score, and delayed breastfeeding initiation were found to be associated with neonatal sepsis in Ethiopia. Hence, sticking to the standard guideline during the perinatal period may prevent or minimize the occurrence of neonatal sepsis. Further studies examining the association between low APGAR score and the occurrence of neonatal sepsis is important.

Registration and protocol

This systematic review was submitted for inclusion in the International Prospective Register of Systematic Reviews (PROSPERO), but it has yet to be accepted, and the protocol has not been published.

Author contribution statement

Kenbon S: Conceived and designed the experiments; Performed the experiments; Analyzed; and interpreted the data; and wrote the paper.

Biniyam S, Chala K, Girma G,: Analyzed and interpreted the data; materials; analysis tools or data; and Wrote the paper.

Degefa G, Neway E, Telila M, Vijay Kumar C: Designed the experiments; performed the experiments; Analyzed; and interpreted the data.

Data availability statement

Data included in article/supplementary material/referenced in article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20336.

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