Magnitude and determinants of newborn mortality in neonatal intensive care unit hospitals in Ethiopia: a systematic review and meta-analysis

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Abstract
Background: In Ethiopia, the neonatal mortality rate has not shown significant changes over time and is among the highest in the world. Exploring the magnitude and the causes of neonatal mortality in the hospital where neonatal intensive care unit is functioning could be supremely important to step towards improving the quality of neonatal care services. Therefore, this review aimed to explore the pooled magnitude and determinates of neonatal mortality in the neonatal intensive care unit hospitals in Ethiopia. Methods: The research team retrieved global peer-reviewed journal articles available as electronic databases including PubMed, Popline, and Scopus databases. Google Scholar, institutional repositories, and Google were used to retrieve grey literature. Random-effects meta-analysis model was used to pool the estimates of the magnitude of mortality among studies. The results were presented as the pooled estimates (odds ratio and proportion) with 95% confidence intervals, at less than 0.05 significant levels. Results: In this review, 10 studies were included with a total of 8,729 neonates. Of these, 1,779 (20.4%) neonates died in the neonatal intensive care unit. The pooled neonatal mortality rate was 19.0% (95% CI: 14.0-25.0). The neonatal mortality is three times higher among early age (OR: 2.80; 95% CI: 1.45-5.40) and preterm newborns (OR: 3.27; 95% CI: 2.12-5.07) than their counterparts. Early age of the newborn, prematurity, low birth weight, perinatal asphyxia, mode of delivery, hypothermia, late initiation of breastfeeding, and having antenatal care visits were the main determinants for neonatal mortality. Likewise, perinatal asphyxia, hyaline membrane disease, respiratory distress syndrome, and prematurity were identified as the most determinant and statistically associated with the death of premature neonates admitted to intensive care units. Conclusion: Neonatal mortality in the intensive care unit is high. It is unacceptably high amongst early and preterm neonates. Special care for preterm and early age newborns, timely initiation of breastfeeding, exclusive breastfeeding, and appropriate mode of delivery, essential obstetric and newborn care, and promoting antenatal visits are recommended to reduce neonatal mortality. Protocol registration: The protocol was registered at the International prospective register of systematic reviews (PROSPERO) with registration number CRD42019123195.

Background
The global neonatal mortality rate (NMR) declined from 36 deaths per 1,000 live births in 1990 to 19 per 1,000 live births in 2015 [1]. In 2015, an estimated 1.3 million intrapartum stillbirths [2] and 2.7 million neonatal deaths occurred globally [2, 1]. The neonatal mortality in sub-Saharan Africa is 29 per 1,000 live births accounting for 36% of under-five mortalities with a slow decline over the past 25 years (i.e., 1990–2015) [1]. In Ethiopia, neonatal mortality has declined from 61 to 28 deaths per 1,000 live births during the same period [3, 4]. Despite progress, the NMR is unacceptably high that has not shown a significant decline since 2000 [5–7], and far from the Sustainable Development Goals (SDGs) global targets to reduce NMR to 12 per 1,000 live births by 2030 [8, 9]. Moreover, the 2016 national Demographic and Health Survey (DHS) showed that NMR varies significantly among regions. The NMR in Amhara region has no significant change over time and higher than other regions in the country which stands at 47 per 1,000 live births and accounts for 55% of under-five mortality in the region in 2015 [7].

Three-quarters of neonatal deaths occur in the first week, and more than one-quarter of deaths occur in the first 24 hours. These large fractions of deaths are preventable [10]. Globally, nearly 80% of neonatal deaths are caused by perinatal asphyxia (PNA), infections, and complications of premature birth. Evidence shows that available interventions can reduce the three most common causes of neonatal mortality—preterm, intrapartum, and infection-related deaths—by 58%, 79%, and 84%, respectively [11]. However, in low-and-middle-income countries, access to these evidence-based high impact interventions is often low [12, 3, 13].

Until the 2010–2015 National Fourth Health Sector Development Plan (HSDP IV), newborns received very little programmatic attention from the health system in the country. Since then, newborn health is now one of the country’s priorities. Since 2015, to address service quality, Ethiopia has produced a national quality strategy and health sector transformation in quality (HSTQ) to guide the national efforts to ensure service quality [14]. Ethiopia is also committed to improving neonatal care services at all levels of the health system through the Health Sector Transformation Plan (HSTP). The country developed different strategies and programs to address newborn survival at health facility and community level including integrated management of neonatal and childhood illness (IMNCI),
community-based neonatal care (CBNC), newborn corner initiative, neonatal intensive care unit (NICU), pediatric referral care, and quality improvement program to address neonatal complications (prematurity, asphyxia, neonatal sepsis, neonatal tetanus, neonatal pneumonia, and other neonatal causes), the leading causes of under-five mortality in the country [15]. Realizing more than two-thirds of childbirths still take place at home, provision of essential neonatal care at the community level (i.e., CBNC) through the Health Extension Program (HEP) has been implemented in the country since 2012 [16]. Moreover, the Ministry of Health (MOH) has established newborn corners in primary health facilities to improve neonatal care and the MOH seeks to enable all public hospitals to provide delivery services to establish neonatal intensive care services [17].

Besides the national efforts of expanding NICU to improve the survival of newborns in recent years, neonatal mortality still persistently high with no significant change over the last decade. Evaluating the causes of neonatal morbidity and mortality is an essential step toward improving the quality of existing practices. Therefore, this study systematically evaluated the factors of neonatal mortality and pooled the magnitude of mortality in the NICU hospitals in Ethiopia.

Review questions

1. What are the magnitudes of newborn mortality in NICU hospitals in Ethiopia?
2. What are the determinant factors of newborn mortality in NICU hospitals in Ethiopia?

Methods

Inclusion and exclusion criteria

Observational studies, including cross-sectional, case-control/case-referent, cohort, case-cohort designs, reported at least one component of factors that affect neonatal mortality or magnitude of mortality and published in English language since 2012, where the country plans to expand NICU in the hospitals, were included.

Commentaries, letters, duplicate studies, editorials, and studies written by different languages other than English were excluded from the review. Additionally, studies conducted at community settings, studies done outside of Ethiopia, and studies conducted among neonates out of age range between 0 and 28 days admitted for treatment at NICU were excluded from the study.

Search strategy
The research team systematically examined global peer-reviewed journal articles available as electronic databases including PubMed, Popline, and Scopus databases. In addition, a snowball approach was employed by searching literature in the reference lists of the initial search. Search terms (including synonyms and MeSH terms) were identified as Condition (Co), Context (Co), Population (Po), and Exposure (E) themes and used in a variety of combinations for neonatal mortality, infant mortality, hospital, and determinant, associated, or risk factors, and Ethiopia. A search strategy for Medline database is presented in below 1 below.

### Table 1

| #1 Condition | #2 Context | #3 Population | #4 Exposure | #5 Overall |
|--------------|------------|---------------|-------------|-----------|
| ((((("infant mortality" [MeSH Terms] OR 
  "infant"[All Fields] AND "mortality"[All Fields]) OR "neonatal mortality"[All Fields] OR ("neonatal"[All Fields] AND "mortality"[All Fields]) OR neonatal mortality) OR neonatal death) OR "Perinatal Death" [Mesh]) OR newborn death) OR perinatal mortality | (((hospital*) OR "Health System") OR Ethiopia) | (((Neonates at neonatal intensive care unit) OR Neonates admitted at hospital) OR Neonates admitted at intensive care unit OR neonates | (((determinants) OR "Social Determinants of Health"[Mesh]) OR risk factors) OR associated factors) OR predictors | (#1 AND #2 AND #3 AND #4 Filters: published in the last 5 years; Humans |

And the search strategy used for the Scopus database is:

"((TITLE-ABS-KEY ("Neonatal mortality") OR TITLE-ABS-KEY ("neonatal death") OR TITLE-ABS-KEY ("early neonatal death") OR TITLE-ABS-KEY ("early neonatal mortality") OR TITLE-ABS-KEY ("late neonatal death") OR TITLE-ABS-KEY ("late neonatal mortality") OR TITLE-ABS-KEY ("perinatal death")[nicu]) AND ((TITLE-ABS-KEY ("Ethiopia") OR TITLE-ABS-KEY (hospital) OR TITLE-ABS-KEY ("health facility"))) AND ( TITLE-ABS-KEY ( neonates ) ) AND ((TITLE-ABS-KEY (determinants) OR TITLE-ABS-KEY ( "risk factors") OR TITLE-ABS-KEY ( "associated factors") OR TITLE-ABS-KEY (predictors)) AND ( LIMIT-TO ( DOCTYPE, "ar" )) AND (LIMIT-TO (LANGUAGE, "English"))"

The search activity was performed from 01–15 February 2019 and resulted in 290 from Scopus, 96 from Medline, and 9 from Google Scholar and Popline.

Study selection procedure
Endnote reference manager was used to upload search results and create library of all search results. The search returned 283 records after removing duplicates. The titles and abstracts of articles were reviewed to determine which full-text articles need to be retrieved based on the inclusion and exclusion criteria. The review authors independently screened the titles and abstracts yielded by the search against the inclusion criteria. We obtained full reports for all titles that appear to meet the inclusion criteria.

Accordingly, 28 full articles were screened reading titles and abstracts. The final synthesis included 10 papers. The results of the search and the process of screening and selecting studies for inclusion are illustrated using a Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) flow diagram below (Fig. 1).

Critical appraisal
Authors independently reviewed the methodological quality of each included study using the Joanna Briggs Institute (JBI) critical appraisal checklists for different study designs as appropriate [18-20]—to assess the methodological quality of studies and to determine the extent to which included studies have addressed the possibility of bias in its design, conduct, and analysis. Discrepancies between scores were resolved through discussions. To obtain an overall quality score, publications scored “1” point for each item fully met and “0” for none or very little information reported. Studies that scored 75% or more were categorized as high quality, scores in the range of 50–74% were ranked as medium, and scores less than 50% were rated as poor.

The standard review protocol, PRISMA checklist, was followed to establish minimum information that should be included when reviewing and reporting [21]. Moreover, the protocol was registered at the International prospective register of systematic reviews (PROSPERO) with registration number CRD42019123195.

Data abstraction and synthesis
Reviewers completed the data extraction form for all studies using an excel spreadsheet. Descriptive information about the eligible studies was summarized using text and tables. A narrative synthesis was used to analyze and interpret the findings.
Random-effects meta-analysis model was used to pool the estimates of the magnitude of mortality and determinant factors accounting for the variability among studies using Stata v15 [22]. The results were presented as the pooled estimates (odds ratio (OR) and proportion) with 95% confidence intervals (CI), at less than 0.05 significant levels, and the estimates of Tau² and I² statistic for heterogeneity. We also investigated the presence of publication and other bias in the extracted data using a funnel plot and Stata’s “metabias” command [23, 22].

**Assessment of heterogeneity**

The P-value of the Chi-squared test of heterogeneity and the I² and Tau² statistics were examined for heterogeneity between the studies to judge whether there were any apparent differences in the direction or size of the estimate between studies. We did a subgroup analysis to examine the pooled magnitude of mortality varied by administrative region, age of the neonate at admission, gestational age at birth, and research design. Moreover, sensitivity analysis was conducted to examine the effect of studies that are exclusively reported magnitude of mortality on early neonates and preterm as well as studies with a large sample.

**Results**

**Description of studies**

The characteristics of included studies are given in Table 2 below. Ten articles were included: four in Amhara, two in Addis Ababa, two in Oromia, one in Southern Nations, Nationalities, and Peoples’ (SNNP), and one in Somali region. All studies were published from 2012 to 2019. Six of the studies identified employed hospital-based cohort designs [24–29]; the remaining four applied cross-sectional designs [30, 31] (Table 1).

The capacity of NICU in terms of bed-size and staffing varied from hospital to hospital. It ranged from 16-beds NICU [32] to 50-beds NICU [26] and some hospitals had comprehensive neonatal care that included intensive care, KMC, and isolation rooms [30, 24, 27, 28, 26]. It was staffed with medical interns, pediatric residents, physicians, and nurses.

| Study ID | Design | Objective | Region | Hospital | NICU capacity | Age of neonate | # of newborn deaths | Sample size | NMR (%) |
|---------|--------|-----------|--------|----------|---------------|----------------|---------------------|-------------|---------|

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Table 2: Characteristics of included studies
| Demise 2017 | Cross-sectional | Identify the patterns of neonatal admission and factors associated with mortality | Amhara | Gondar University Hospital | A 32-beds NICU with 4 separate rooms (1 room for each of preterm babies, term babies, isolation room for communicable diseases, and for those who need KMC). It was staffed with 7 medical interns, 2 pediatric residents, 1 pediatrician, and 17 nurses | < 28 days | 110 | 769 | 14.3 |
| Farah 2018 | Retrospective cohort | Examine the trends of admission, specific causes and rate of neonatal mortality as well as predictors of neonatal mortality | Somali | Karamara General Hospital | A fully-functional 12-beds NICU that has 3 rooms (1 room for intensive care, 1 for kangaroo mother care, and another for septic neonates) | < 28 days | 45 | 792 | 5.7 |
| Orsido 2019 | Retrospective cohort | Describe the reasons for admission and the magnitude of mortality | SNNP | Wolaita Sodo University Hospital | A 20-beds NICU | < 28 days | 159 | 964 | 16.5 |
| Tekleab 2017 | Cross-sectional | Describe the reasons for admission and the magnitude of neonatal mortality | Addis Ababa | St Paul’s Hospital Millennium Medical College | A fully-functional NICU providing services for 24-hours a day and nurses, intern doctors, pediatric resident doctors, and pediatricians were working in the unit. | < 28 days | 50 | 216 | 23.2 |
| Tewabe | Cross-Assess | The | Amhara | Felege | | < 28 days | 52 | 391 | 13.3 |
| Year | Design | Sectional | Neonatal Mortality Rate | Hospital | NICU Bed & Staffing | NICU ICU Bed & Staffing | NICU NICU Bed & Staffing | NICU NICU Bed & Staffing | NICU NICU Bed & Staffing |
|------|--------|-----------|-------------------------|----------|--------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| 2018 | Sectional | Neonatal mortality rate | Hiwot General Hospital | Neonatal unit had 60 beds and staffed with 5 pediatricians and 20 nurses. About 6,300 neonates were seen annually. | | | | | |
| 2014 | Cross-sectional | Examine the risk factors, antimicrobial use pattern and clinical outcomes of neonatal sepsis | Oromia Bishoftu General Hospital | NICU had 16 beds and staffed with 2 physicians, 3 nurses, and 2 cleaners. More than 1,000 of neonates admitted at NICUs annually | | < 28 days | 40 | 306 | 13.1 |
| 2012 | Prospective cohort | Assess the independent predictors of early neonatal mortality | Addis Ababa Tikur Anbessa Specialized Hospital | It had 50 beds and it is the largest ICU in the country with a very high patient admission | | < 7 days | 881 | 3789 | 23.3 |
| 2017 | Retrospective cohort | Model survival probability of preterm infants and identify risk factors | Oromia Jimma University Specialized Hospital | No data | | < 28 days & preterm | 171 | 490 | 34.9 |
| 2015 | Retrospective cohort | Compare survival of preterm infants using the Cox proportional hazard model and the semi-parametric gamma frailty model and examine the risk factors of death | Amhara Gondar University Hospital | Same as "Demise 2017" death | | < 28 days & preterm | 122 | 485 | 25.2 |
| 2019 | Retrospective | Assess time to | Amhara Gondar University | Same as "Demise 2017" | | < 28 days & preterm | 149 | 516 | 28.9 |
Methodological quality of included studies

According to the JBI quality appraisal tool, six of the cohort studies scored high quality (81%).

Likewise, the seven cross-sectional studies scored medium quality (72%) in which most studies lacked strategies to deal with confounding.

The results of our review are presented under three sections: 1) magnitude of neonatal mortality, 2) determinants of neonatal mortality, and 3) determinants of preterm mortality.

Magnitude of neonatal mortality

In this review, 10 studies involving 8,718 neonates with 1,779 (20.4%) neonatal deaths were included.

As presented in Fig. 1 below, the random effects pooled analysis showed that neonatal mortality rate is 19.0% (95% CI:15.0–23.0).

Sensitivity analysis

To determine the proportion of the pooled magnitude of mortality driven by some studies, we conducted three different analysis by excluding studies early neonates which is also large sample [26], on preterm [28, 29, 27], and both preterm and early neonates [28, 29, 27, 26]. Following the removal of a study on the early neonate, the overall pooled estimate was not changed. On the other hand, excluding studies on preterm neonates, the pooled estimate was decreased to 15% (95% CI: 0.10–0.21) without lowering heterogeneity between studies, and excluding both studies on preterm and early neonate, the NMR decreased to 14% (95% CI: 0.09–0.19) with reduced heterogeneity. As a
result, we conducted a sub-group analysis for preterm and early neonates to compare the magnitude of mortality with their counterparts.

**Sub-group analysis**

Three different subgroup analyses were conducted to investigate whether the observed magnitude of mortality is consistent across regions, preterm and term neonates, early and late neonates. We divided regions geographically into three groups as Amhara, Addis Ababa, Oromia, and other regions including SNNP and Somali regions. Gestational age is classified as preterm, born before 37 weeks of gestation, and term/post-term, born after completed 37 weeks of gestation. On the other hand, newborn age is divided as early neonates, neonates with less than 7 days of age at admission and late neonates, neonates with 7 days and above age. Accordingly, three different sub-group analyses were conducted.

**Mortality by region**

The subgroup analysis showed that NMR is significantly higher in Oromia than other regions; likewise, NMR is significantly lower in other regions category (SNNP and Somali) (Fig. 3).

**Preterm mortality**

Six studies [30, 24, 31, 26, 33, 25] reported neonatal mortality disaggregated by gestational age and the other three studies [28, 29, 27] were conducted among preterm neonates. Accordingly, mortality rates were compared among preterm and term/post-term neonates. The pooled mortality by gestational age at birth indicated that preterm neonates had three times (OR: 3.27; 95% CI: 2.12–5.07) higher odds of death as compared to term and post-term neonates (Fig. 4).

**Early neonatal mortality**

One study [26] conducted among early neonates. The other three studies [31, 24, 25] reported neonatal mortality disaggregated by age of neonate. We compared the neonatal mortality rate by age of newborn at admission. As such, the neonatal mortality is about three times (OR: 2.80; 95% CI: 1.45–5.40) higher among early age newborns than late age neonates (Fig. 5).

**Determinants of neonatal mortality**

In this review, many factors that could have influenced neonatal mortality were identified. As presented in Table 3, newborn age, gestational age, birth weight, PNA, mode of delivery, hypothermia, breastfeeding, and antenatal care (ANC) visit are the main determinants pooled from
the studies. The detail is as follows.

**Age of neonate**

Early age of the newborn was significantly associated with neonatal mortality in three studies [24, 25, 31].

**Gestational age**

Six studies, two studies among preterm neonates [27, 29] and four among all neonates [31, 24, 26, 33], reported gestational age as an independent predictor of neonatal mortality.

**Perinatal Asphyxia**: As presented in Fig. 4 below, four studies identified PNA is 2.51 times higher than neonates with no PNA (OR: 2.51; 95% CI: 1.85–3.40). Moreover, Demise et al [30] report respiratory distress had 12.97 times higher odds of death (95% CI: 5.37, 31.30); Worku et al [26] present a first minute APGAR of 3 or less was independently associated with NMR. Neonates who were resuscitated had two times higher risk of death than neonates who were not resuscitated (AHR: 2.28; 95% CI: 1.54–3.38).

**Hypothermia**: Orsido et al [25] reported neonates who had a temperature of < 35.5 °C at admission had 1.6 times higher risk of death than neonates temperature at admission 35.5–37.5 °C (AHR: 1.58; 95% CI: 1.06–2.34). Another study [30] also reported that severe hypothermia had more than 10 times higher odds of death that neonates with normal body temperature (AOR: 10.45; 95% CI: 1.04, 104.66).

**Mode of delivery**: Demise et al [30] reports instrumental delivery increased risk of neonatal mortality as compared with vaginal delivery (AOR: 2.99; 95% CI: 1.08–8.31); while same study presents cesarean delivery had 87% higher odds of death than normal deliveries but not statistically significant (AOR: 0.87; 95% CI: 0.46–1.64). On the other hand, Orsido et al [25] reported cesarean delivery had a 66% lower risk of death as compared with vaginal delivery (AHR:0.34; 95% CI:0.19–0.61).

**Breastfeeding**: A study by Orsido et al [25] reports that neonates who were not breastfed within one hour of birth had 2.6 times higher risk of death than their counterparts (AHR:2.62; 95% CI:1.60–4.30). Tewabe et al [31] also identified late initiation of breastfeeding and non-exclusive breastfeeding is an independent predictor of neonatal mortality.

**Antenatal care**

No ANC consultation was identified independent predictor of neonatal mortality in two studies [25, 31].
Moreover, Orsido et al [25] neonates admitted with the problem hyaline membrane disease (HMD) and birth order and Worku et al [26] reports number of siblings, marital status (not in union), presence of any congenital anomaly, presence of perinatal asphyxia, presence of sepsis, requirement of oxygen therapy and a lower birth weight were identified as independent predictor of neonatal mortality. A normal length at birth and the presence of jaundice were protective of early neonatal mortality [26]. The average length of stay below two days (AOR: 0.418; 95% CI:0.186, 0.936) were independently associated with neonatal mortality and showed a protective effect on neonatal death in the NICU [24].

| Domain                        | Determinants | (%)  | Measure | AOR/ AHR | 95% CI   | P-value | Study ID |
|-------------------------------|--------------|------|---------|----------|----------|---------|----------|
| Mode of delivery              | Instrumental delivery | 8    | OR      | 2.99     | 1.07 8.31 | < 0.05  | Demise 2017 |
|                               | CS delivery  | 13   | HR      | 0.34     | 0.19 0.61 | < 0.001 | Orsido 2019 |
| Hypothermia                   | Severe hypothermia | 5    | OR      | 10.45    | 1.04 104.7 | < 0.05 | Demise 2017 |
|                               | Temperature of neonate at admission (< 35.5) | 110  | HR      | 1.58     | 1.06 2.34 | < 0.05 | Orsido 2019 |
| Sepsis                        | Early onset of neonatal sepsis | 88   | OR      | 2.66     | 1.16 6.11 | < 0.05 | Demise 2017 |
|                               | Late onset of neonatal sepsis | 11   | OR      | 13.51    | 2.64 69   | < 0.05 | Demise 2017 |
| Asphyxia                      | PNA (Yes)    | 33   | OR      | 5.97     | 3.06 11.64 | < 0.05 | Demise 2017 |
|                               | PNA (Yes)    | 58   | HR      | 1.81     | 1.24 2.63 | < 0.05 | Orsido 2019 |
|                               | PNA (Yes)    | 14   | OR      | 5.817    | 1.61 21   | < 0.05 | Tekleab 2017 |
|                               | PNA (Yes)    | 174  | OR      | 1.82     | 1.32 2.51 | < 0.001| Worku 2012 |
| Respiratory Distress Syndrome (RDS) | RDS (Yes) | 43   | OR      | 12.97    | 5.37 31.3 | < 0.05 | Demise 2017 |
| Resuscitation                 | Neonate resuscitated (Yes) | 122  | HR      | 2.28     | 1.06 2.34 | < 0.05 | Orsido 2019 |
| APGAR score                   | APGAR score at 1st min (<= 3) | 185  | OR      | 2.12     | 1.39 2.23 | < 0.001| Worku 2012 |
| Length of stay (LOS)          | Average LOS (> = 8+) | 9    | OR      | 0.418    | 0.19 0.936 | 0.01  | Farah 2018 |
|                               | Average LOS (< = 22) | 22   | OR      | 9.5      | 0.19 0.936 | 0.034 | Farah 2018 |
| Multiple pregnancy | Birth level (Multiple) | 69 | 48.3 | HR | 1.8 | 1.1 | 2.94 | < 0.05 | Orsido 2019 |
|--------------------|------------------------|----|------|----|-----|-----|------|--------|------------|
|                    | Gestation (single)     | 723| 22.0 | OR | 0.7 | 0.54| 0.9  | < 0.05 | Worku 2012 |
| ANC visit          | ANC (None)             | 80 | 48.2 | HR | 6.02| 3.52| 10.27| < 0.001| Orsido 2019 |
|                    | ANC (None)             | 106| 34.1 | OR | 1.7 | 1.28| 2.26 | < 0.001| Worku 2012 |
| HMD                | HMD (Yes)              | 31 | 66.0 | HR | 2.04| 1.16| 3.59 | < 0.05 | Orsido 2019 |
| Breastfeeding      | Breastfeeding initiated (after 1 h) | 137| 30.8 | HR | 2.62| 1.6 | 4.3  | < 0.001| Orsido 2019 |
|                    | Late breastfeeding initiation time | 33 | 22.0 | OR | 2.89| 0.1 | 8.38 | < 0.05 | Tewabe 2018 |
|                    | Exclusive breastfeeding (No) | 18 | 7.1  | OR | 6.77| 3.04| 15.07| < 0.001| Tewabe 2018 |
| Prematurity        | Prematurity (Yes)      | 14 | 8.9  | OR | 0.492| 0.25| 0.957| 0.037 | Farah 2018 |
|                    | Gestational age (GA) (less than the mean (36.6 wks.) | | OR | 0.683| 0.59| 0.795| < 0.05 | Tekleab 2017 |
|                    | GA (< 37 wks.)         | 21 | 33.3 | OR | 2.14| 1    | 4.52 | < 0.05 | Tewabe 2018 |
|                    | GA (< 32 wks.)         | 347| 52.5 | OR | 10.46| 5.39| 20.31| < 0.001| Worku 2012 |
|                    | GA (32–37 wks.)        | 227| 21.2 | OR | 3.6 | 1.39| 6.69 | < 0.01 | Worku 2012 |
|                    | GA (37–42 wks.)        | 248| 15.2 | OR | 2.05| 1.16| 3.364| < 0.05 | Worku 2012 |
| Age of admission   | Age of newborn at admission (early) | 43 | 15.6 | OR | 0.39| 0.16| 0.97 | < 0.05 | Tewabe 2018 |
|                    | Age of newborn at admission (≤ = 1 day) | 693| 24.6 | OR | 2.53| 1.66| 3.85 | < 0.001| Worku 2012 |
|                    | Age of newborn at admission (1–3 days) | 158| 18.6 | OR | 2.2 | 1.38| 3.48 | < 0.001| Worku 2012 |
| Length             | Length (45–51 cm)      | 261| 16.2 | OR | 0.58| 0.4 | 0.85 | < 0.05 | Worku 2012 |
| Congenital anomaly | Congenital anomaly (any) | 108| 34.4 | OR | 2.02| 1.33| 2.51 | < 0.05 | Worku 2012 |
| Oxygen treatment   | Oxygen treatment (Yes) | 755| 31.6 | OR | 2.65| 1.89| 3.72 | < 0.001| Worku 2012 |
| Jaundice           | Jaundice at admission (No) | 745| 27.4 | OR | 2.65| 1.89| 3.72 | < 0.001| Worku 2012 |
| Birth weight       | Birth weight (< = 1500 gm) | 268| 59.3 | OR | 9.64| 3.32| 27.97| < 0.001| Worku 2012 |
Determinants of preterm mortality

Three studies reported determinants of preterm mortality among neonates admitted at NICU [29, 27, 28]. The leading causes of death were PNA [29, 27, 28], HMD [27, 29], and RDS [28, 29]. PNA [29, 27, 28], HMD [27, 29], and RDS [28, 29], and prematurity [29, 27] were identified as the most determinant and statistically associated with the death of premature infants admitted to NICU.

In addition, Yismawet al [27] identified the place of delivery, type of pregnancy, neonate cried immediately at birth, jaundice, receiving kangaroo mother care (KMC) and hypoglycemia remained statistically significant predictors of to death of preterm neonates. And, Yehuala et al [28] identifies ANC visit, multi-gravidity, HIV status of the mother, RDS, PNA, anemia and early breastfeeding initiation as the most determinant and statistically associated with the death of premature infants admitted to NICU. Wosenu et al [29], on the other hand, reported having, sepsis, jaundice, and initial temperature significantly contribute to a shorter survival time of premature infants (Table 4).

Table 4
Determinant factors for preterm mortality among neonates admitted at NICU

| Domain          | Determinants      | (%)  | Measure | AOR/ AHR | 95% CI  | P-value | Study ID |
|-----------------|-------------------|------|---------|----------|---------|---------|----------|
| ANC             | ANC (Yes)         | 88   | HR      | 0.5247   | 0.338   | 0.814   | < 0.05   | Yehuala 2015 |
|                 |                   |      |         |          |         |         |          |          |
| Gravity         | Gravidity (6–10)  | 17   | HR      | 2.072    | 1.001   | 4.289   | < 0.05   | Yehuala 2015 |
|                 |                   |      |         |          |         |         |          |          |
| RDS             | RDS (Yes)         | 54   | HR      | 7.774    | 4.712   | 12.826  | < 0.001  | Yehuala 2015 |
|                 |                   |      |         |          |         |         |          |          |
|                 | RDS (Yes)         | 114  | OR      | 3.287    | 2.033   | 5.315   | < 0.001  | Wesenu 2017 |
|                 |                   |      |         |          |         |         |          |          |
| HMD             | HMD (Yes)         | 107  | OR      | 2.636    | 1.597   | 4.352   | < 0.001  | Wesenu 2017 |
|                 |                   |      |         |          |         |         |          |          |
|                 | HMD (Yes)         | 39   | HR      | 3.02     | 1.86    | 4.88    | < 0.001  | Yismaw 2019 |
|                 |                   |      |         |          |         |         |          |          |
| PNA             | PNA (Yes)         | 46   | HR      | 1.55     | 1.09    | 2.2     | < 0.05   | Yismaw 2019 |
|                 |                   |      |         |          |         |         |          |          |
|                 | PNA (Yes)         | 27   | OR      | 2.479    | 1.239   | 4.959   | < 0.05   | Wesenu 2017 |
|                 |                   |      |         |          |         |         |          |          |
|                 | PNA (Yes)         | 63   | HR      | 2.123    | 1.42    | 3.18    | < 0.001  | Yehuala   |

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**Publication bias**

The funnel plot (Fig. 7) appeared symmetrical, which suggests no evidence of small-study effects. The Egger’s test also indicated the low possibility of publication bias (Coef. = -5.472; p = 0.476).

**Discussions**

In this review, the pooled neonatal mortality rate was 19.0% which is higher among early age and preterm newborns than their counterparts. Early age of the newborn, prematurity, low birth weight, perinatal asphyxia, mode of delivery, hypothermia, late initiation of breastfeeding, and having antenatal care visits were the main determinants for neonatal mortality among neonates admitted to
intensive care units.

Previous literature indicated that the overall mortality rate in NICU of developing countries ranged from 0.2–64.4% [34]. In our systematic review and meta-analysis, using the random effect model, the pooled neonatal mortality rate was estimated to be 19% (95% CI: 15.0–23.0%) which is higher than the pooled estimate of neonatal mortality at NICU of Iran (11.40%) [35]. However, previously in Brazil, a wide variation in the mortality rates was found among intensive care units (9.5–48.1%), with an overall mortality rate for newborns admitted at nine NICU sites being 18.6% [36] which is comparable to our result. It is also indicated that neonatal mortality rate varies significantly between the central and western parts of Iran [35]. This is comparable to our subgroup analysis that showed a significantly higher NMR in Oromia region than other regions. This variation might be related to the difference in availability of equipment type, and severity of disease in admitted neonates, as well as the performance of physicians, midwifes and neonatal nurses in different regions of Ethiopia.

Moreover, the regional variation would be associated with suboptimal NICU neonatal services across the country [24, 30].

Our stratified analysis also showed that preterm neonates had three times higher odds of death as compared to preterm and term and post-term neonates. A recently conducted individual study conducted in Ethiopia indicated that the odds of neonatal mortalities among preterm neonates were 2.2 times higher than that of term neonates [37]. A systematic review and meta-analysis result showed that neonatal mortality was the lowest in the full-term newborn infants but higher among neonates with a gestational age of 28–32 weeks [38]. The most common causes of mortality in NICUs of Iran were prematurity (44.14%) [35]. This could be also supported by the previous study as preterm birth (40.8%) and intrapartum complications (27.0%) accounted for most early neonatal deaths [39]. This is due to the fact that preterm newborn had immaturity of immune systems and other body defense mechanisms which help to control newborn infection and disease susceptibility. Other possible explanations for the high death rate of preterm neonates might be due to delay in receiving adequate health care due to poor facilities and lack of medical supplies in Ethiopia.

In this review, gestational age or prematurity was related to as a factor to neonatal mortality. The
finding is also consistent with the systematic review in developing and developed countries [34]. It might be due to their intrinsic susceptibility to infection due to lack of immunologic competence, the lack of appropriate treatment modalities, such as mechanical ventilation, surfactant administration, parenteral nutrition and delay in the initiation of health care services [27, 33].

Perinatal asphyxia is identified as a risk factor for neonatal mortality. The reason might be the quality and access of emergency obstetric newborns and comprehensive emergency obstetric services are inadequate in a clinical setting [25, 27]. Training of health care workers to detect risk factors, fetal asphyxia during labor and delivery including provision of neonatal resuscitation must be given [33]. We observed that mode of delivery showed a variation in the rate of neonatal mortality. Instrumental mode of delivery is also identified as a risk factor for neonatal mortality [30]. It gives a clue as there is fetus suffocation, early rupture of membrane and environmental contamination with nosocomial infections during delivery [26]. On the other hand, it is also reported that cesarean mode of delivery had a protective effect on the risk of neonatal mortality [25]. This finding is consistent with the study done in Brazil [36]. It might be related to the use of timely decisions rather than waiting for vaginal delivery. Delivering by cesarean section reduces the risk of death and complications that can come due to prolonged labor [25]. On the contrary, it is reported that the cesarean section had increased neonatal mortality which could have resulted from the delay in decision making during prolonged labor, poor quality of operation procedure and its prohibition effect on early breastfeeding initiation [30, 25, 32].

Delayed breastfeeding after 1 hour of birth results in a higher risk of neonatal mortality compared to their counterpart [25, 31]. This indicates the sub-optimal practice of early initiation of breastfeeding despite its great importance in the reduction of neonate death. It is also important to consider the neonates who are sick that might not be able to suck breast milk as compared to a healthier one [25]. Neonates born from mothers who had no ANC visit are more likely to die compared to neonates born from mothers who have ANC follow up [30, 26, 25, 31]. ANC visit saves the lives of babies by early detection and management of the problems related to the pregnancy by promoting and establishing good health [25, 31].
The current systematic review and meta-analysis are the first of its kind to be conducted at the NICU hospitals of Ethiopia to assess the burden and determinant factors associated with neonatal mortality in Ethiopia. The information obtained may improve knowledge on the cause of neonatal mortality at NICU so as to reduce neonatal mortality rates in Ethiopia. But the inclusion of only English language articles in the review is a limitation. Moreover, all the studies are based on facility-based records that are subject to information bias.

**Conclusions**

Neonatal mortality at NICU hospitals in Ethiopia is unacceptably high. Subgroup analysis shows that the mortality rate is also higher among early and preterm neonates. Gestational age, mode of delivery, ANC follow up, breastfeeding, hypothermia, age of the neonate, hypoglycemia, place of delivery, and low birth weight were among the factors identified for neonatal mortality rate at NICU hospital in Ethiopia. Almost all identified factors associated with neonatal mortality at NICU hospital are preventable. Therefore, special care for preterm and early age newborns, timely initiation of breastfeeding, exclusive breastfeeding, appropriate mode of delivery, essential obstetric and newborn care, and promoting antenatal visits are recommended to reduce neonatal mortality. Moreover, the finding calls policymakers and program managers to focus on strengthen NICU services by revising the strategies set in place for optimal quality services and on the prevention of risk factors with neonatal mortality at NICU hospital during, pregnancy, delivery and postnatal period.

**Abbreviations**
Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

GT, TM, AS, DG, TA, TAA, AN, and TZ conceptualized the paper. GT, TM, AS, DG, and TA, performed article search, data extraction, and data analysis. GT, TM, AS, DG, TA, TAA, and MH did critical review. GT, TM, and AS produced the first draft of the manuscript. All authors contributed to the interpretation, commented on multiple versions, and approved the final manuscript.

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Figures
Figure 1

Study flow diagram
Figure 2: Magnitude of Neonatal Mortality in Neonatal Intensive Care Unit

| Study   | Hospital                | ES (95% CI)     | Weight |
|---------|-------------------------|-----------------|--------|
| Demise 2017 | Gondar UH                | 0.14 (0.12, 0.17) | 10.15  |
| Farah 2018  | Karamara                | 0.06 (0.04, 0.08) | 10.16  |
| Orsido 2019 | Wolaita Sodo UH         | 0.16 (0.14, 0.19) | 10.21  |
| Tekleab 2017 | St Paul’s Hospital     | 0.23 (0.18, 0.29) | 9.48   |
| Tewabe 2018 | Felege Hiwot            | 0.13 (0.10, 0.17) | 9.89   |
| Woldu 2014  | Bishoftu                | 0.13 (0.10, 0.17) | 9.74   |
| Worku 2012  | Tikur Anbessa           | 0.23 (0.22, 0.25) | 10.38  |
| Wesenu 2017 | Jimma USH               | 0.35 (0.31, 0.39) | 9.99   |
| Yehuala 2015 | Gondar UH              | 0.25 (0.21, 0.29) | 9.99   |
| Yismaw 2019 | Gondar UH               | 0.28 (0.25, 0.33) | 10.01  |
| Overall   | (I^2 = 97.14%, p = 0.00) | 0.19 (0.14, 0.25) | 100.00 |

**Figure 2**

Forest plot of the magnitude of neonatal mortality at NICU hospitals
Figure 3: Magnitude of Neonatal Mortality in NICU by Region

Subgroup analysis of NMR by region
Figure 4: The pooled odds ratio of the association between GA and NMR

| Study            | OR (95% CI)    | Weight |
|------------------|----------------|--------|
| Demise 2017      | 2.08 (1.35, 3.20) | 17.69  |
| Farah 2018       | 1.09 (0.58, 2.06)  | 14.77  |
| Orsido 2019      | 5.92 (4.12, 8.53)  | 18.59  |
| Tekleab 2017     | 6.80 (3.33, 13.89) | 13.59  |
| Tewabe 2018      | 4.79 (2.52, 9.10)  | 14.63  |
| Worku 2012       | 2.93 (2.49, 3.45)  | 20.73  |
| Overall (I-squared = 84.7%, p = 0.000) | 3.27 (2.12, 5.07) | 100.00 |

NOTE: Weights are from random effects analysis

Figure 4

Forest plot of the magnitude of neonatal mortality admitted at NICU by gestational age
Figure 5: The pooled odds ratio of the association between age of newborn and NMR

| Study       | OR (95% CI)          | Weight |
|------------|----------------------|--------|
| Farah 2018 | 1.22 (0.28, 5.20)    | 15.59  |
| Orsido 2019| 4.20 (2.77, 6.63)    | 49.81  |
| Tewabe 2018| 2.20 (1.04, 4.68)    | 34.69  |
| Overall    | 2.80 (1.45, 5.40)    | 160.00 |

NOTE: Weights are from random effects analysis

Figure 5

Forest plot of the magnitude of neonatal mortality admitted at NICU by neonatal age
Figure 6: The pooled odds ratio of the association between PNA and NMR

| Study           | OR (95% CI)  | Weight |
|-----------------|--------------|--------|
| Demise 2017     | 4.05 (2.50, 6.57) | 21.40  |
| Orsido 2019     | 1.80 (1.25, 2.58) | 26.12  |
| Tekleab 2017    | 2.69 (1.25, 5.79) | 11.75  |
| Worku 2012      | 2.40 (1.97, 2.94) | 38.76  |
| Overall (I-squared = 57.6%, p = 0.070) | 2.51 (1.86, 3.40) | 100.00 |

NOTE: Weights are from random effects analysis

Figure 6
Forest plot of the effect of PNA on NMR at NICU
Funnel plot for neonatal mortality outcome

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