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SYSTEMATIC REVIEW

NEONATAL MORTALITY IN NEONATAL INTENSIVE CARE UNIT HOSPITALS IN ETHIOPIA REMAINS HIGH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction : *In Ethiopia, the neonatal mortality rate has not shown significant changes over time and is among the world's highest. This review aimed to explore the pooled magnitude and determinates of neonatal mortality in 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. 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, ten 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.*

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.*

Keywords: *neonatal mortality, neonatal intensive care unit, Ethiopia, determinants, risk factors,*

INTRODUCTION

The neonatal mortality rate (NMR) 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. (2, 3) Despite progress, the NMR is high and far from the sustainable development global targets to reduce NMR to 12 per 1,000 live births by 2030. (4, 5)

Until the 2010-2015 National Fourth Health Sector Development Plan, newborns received very little programmatic attention from Ethiopia's health system. Since then, newborn health is now one of the country's priorities. The country developed different strategies and programs to address newborn survival at health facility and community level, including integrated management of the neonatal and childhood illness, community-based neonatal care, newborn corner initiative, and neonatal intensive care unit (NICU). (6) Besides the national efforts of expanding NICU to improve newborn's survival in recent years, neonatal mortality is still persistently high with no significant change over the last decade. (7-9).

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.

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

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that affect neonatal mortality or magnitude of mortality and published in the 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.

Search strategy

The research team systematically examined global peer-reviewed journal articles available as electronic databases, including PubMed, Popline, and Scopus databases. Search terms were identified as Condition, Context, Population, and Exposure 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 presented as supplemental material.

Study selection procedure

The search returned 283 records after removing duplicates. The review authors independently screened the titles and abstracts yielded by the search against the inclusion criteria. Accordingly, 28 full articles were screened reading titles and abstracts. The final synthesis included ten papers (Figure 1).

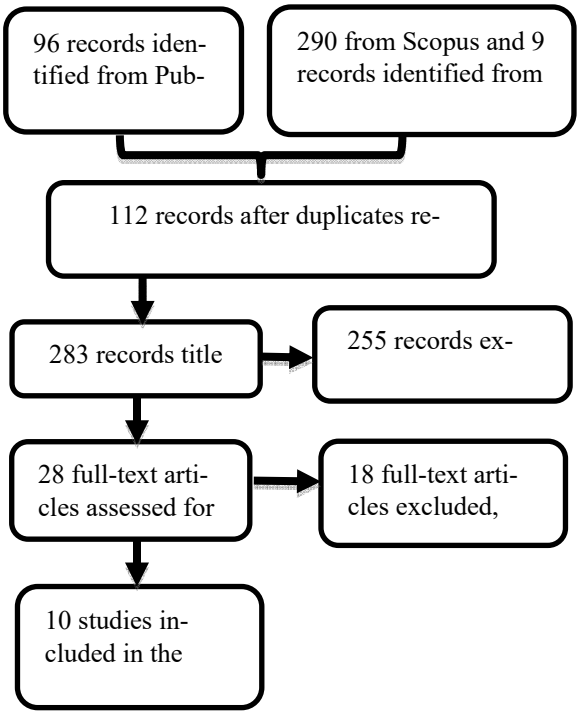


Figure 1: Study flow diagram

Critical appraisal

Authors independently reviewed each included study's methodological quality using the Joanna Briggs Institute (JBI) critical appraisal checklists for different study designs as appropriate. (10-12) 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 a medium, and scores less than 50% were rated as poor. 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 standard review protocol, Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) checklist, was followed to establish minimum information that should be included when reviewing and reporting. (13) Moreover, the protocol was registered at the International prospective register of systematic reviews (PROSPERO) with registration number CRD42019123195.

Data synthesis

A narrative synthesis was used to analyze and interpret the findings. A 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. (14) 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 Tau^2 and I^2 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. (14, 15).

Assessment of heterogeneity

The *P*-value of the Chi-squared test of heterogeneity and the I^2 and Tau^2 statistics were examined for heterogeneity between the studies. We did a subgroup analysis to examine the pooled magnitude of mortality varied by administrative region, age of the neonate at admission, and gestational age at birth.

Moreover, sensitivity analysis was conducted to examine the effect of studies that are exclusively reported of the magnitude of mortality on early neonates, preterm and studies with a large sample.

RESULTS

Description of studies

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 the Somali region. All studies were published from 2012 to 2019. Six of the studies identified employed hospital-based cohort designs; (16-21) the remaining four applied cross-sectional designs (22, 23) (Table 1).

Table 1: Characteristics of included studies

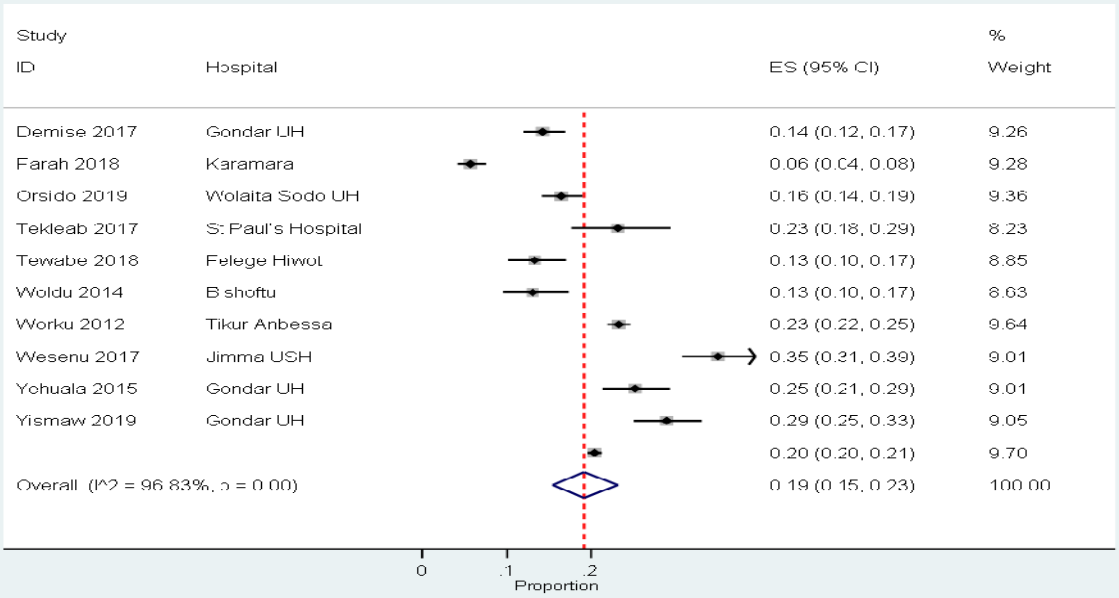
Study ID	Design	Objective	Region	Hospital	NICU capacity	Age of neonate	# of newborn deaths	Sample size	NMR (%)
Demise 2017	Cross-sectional	Identify the patterns of neonatal admission and factors associated with mortality	Amhara	Gondar University Hospital	A 32-beds NICU with 4 separate rooms (1 room for 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 2018	Cross-sectional	Assess neonatal mortality rate	Amhara	Felege Hiwot General Hospital	The neonatal unit had 60 beds and staffed with 5 pediatricians and 20 nurses. About 6,300 neonates were seen annually	<28 days	52	391	13.3
Woldu 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
Worku 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
Wesenu 2017	Retrospective cohort	Model survival probability of premature infants and identify risk factors	Oromia	Jimma University Specialized Hospital	No data	<28 days & preterm	171	490	34.9
Yehuala 2015	Retrospective cohort	Compared survival of premature 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"	<28 days & preterm	122	485	25.2
Yismaw 2019	Retrospective cohort	Assess time to death and predictors among preterm neonates	Amhara	Gondar University Hospital	Same as "Demise 2017" The neonatology department had 1:5 nurse-patient and 1:10 physician-patient ratio for 24 h and seven days with 40 neonatal beds providing an outpatient and inpatient medical service for neonates	<28 days & preterm	149	516	28.9

The capacity of NICU in terms of bed-size and staffing varied from hospital to hospital. It ranged from16-beds NICU (24) to 50-beds NICU (18), and some hospitals had comprehensive neonatal care that included intensive care, kangaroo mother care (KMC), and isolation rooms. (16, 18-20, 22) It was staffed with medical interns, pediatric residents, physicians, and nurses.

Magnitude of neonatal mortality

In this review, ten studies involving 8,718 neonates with 1,779 (20.4%) neonatal deaths were included. As presented in Figure 2 below, the random effects pooled analysis showed that the neonatal mortality rate is 19.0% (95% CI:15.0-23.0).

Figure 2: Magnitude of Neonatal Mortality in Neonatal Intensive Care Unit



Sensitivity analysis

We conducted three different analyses by excluding studies on early neonates which is also a large sample, (18) on preterm, (19-21), and both preterm and early neonates. (18-21) 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.

Mortality by region

The subgroup analysis showed that NMR is significantly higher in Oromia than in other regions; likewise, NMR is significantly lower in other regions category (SNNP and Somali) (Table 2).

Preterm mortality

Six studies (16-18, 22, 23, 25) reported neonatal mortality disaggregated by gestational age, and the other three studies (19-21) 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 (Table 2).

Early neonatal mortality

One study (18) was conducted among early neonates. The other three studies (16, 17, 23) reported neonatal mortality disaggregated by neonatal age. We compared the neonatal mortality rate by age of the newborn at admission. As such, neonatal mortality is about three times (OR: 2.80; 95% CI: 1.45-5.40) higher among early age newborns than late age neonates (Table 2).

Table 2: Subgroup analysis for neonatal mortality by region, neonatal age, and gestational age

Predictor variables	# of studies	Random-effects model		Fixed-effects model		Test for heterogeneity		p-value for subgroup heterogeneity
		%	95% CI	%	95% CI	I2 (%)	p-value	
Overall	10	0.19	0.15-0.23	0.20	0.19-0.21	96.8	<0.01	NA
Region								
Amhara	4	0.20	0.13-0.28	0.20	0.18-0.21	97.1	<0.01	<0.01
Addis Ababa	2	0.23	0.22-0.25	0.23	0.22-0.25	.	.	
Oromia	2	0.26	0.23-0.29	0.26	0.23-0.29	.	.	
Other regions	2	0.11	0.10-0.13	0.11	0.10-0.13	.	.	
Gestational age								
Preterm	9	0.28	0.18-0.39	0.25	0.24-0.26	98.3	<0.01	<0.01
Term & post-term	6	0.09	0.06-0.13	0.11	0.10-0.12	91.6	<0.01	
Age of neonate								
Early	3	0.16	0.08-0.27	0.20	0.19-0.21	98.3	<0.01	<0.01
Late	4	0.06	0.05-0.09	0.06	0.05-0.09	.	.	

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, perinatal asphyxia (PNA), mode of delivery, hypothermia, breastfeeding, and antenatal care (ANC) visit are the main determinants pooled from the studies.

Age of neonate: Early age of the newborn was significantly associated with neonatal mortality in three studies. (16, 17, 23)

Gestational age: Six studies, two studies among preterm neonates (19, 21), and four among all neonates (16, 18, 23, 25) reported gestational age as an independent predictor of neonatal mortality.

Perinatal Asphyxia: Four studies identified PNA as 2.51 times higher than neonates with no PNA (OR: 2.51; 95% CI: 1.85-3.40). Moreover, Demise et al. (22) report respiratory distress had 12.97 times higher odds of death (95% CI:5.37,31.30); Worku et al. (18) 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).

Mode of delivery: Demise et al (22) reports instrumental delivery increased risk of neonatal mortality as compared with vaginal delivery (AOR: 2.99; 95% CI: 1.08–8.31); while the 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. (17) 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. (17) reports that neonates who were not breastfed within one hour of birth had a 2.6 times higher risk of death than their counterparts (AHR:2.62; 95% CI:1.60–4.30). Tewabe et al. (23) also identified late breastfeeding initiation and non-exclusive breastfeeding as independent neonatal mortality predictors.

Determinants of preterm mortality

Three studies reported determinants of preterm mortality among neonates admitted at NICU. (19-21) The leading causes of death were PNA, (19-21) hyaline membrane disease (HMD), (19, 21), and respiratory distress syndrome (RDS). (20, 21) Perinatal asphyxia (19-21) HMD, (19, 21) and RDS (20, 21), and prematurity (19, 21) were identified as the most determinant and statistically associated with the death of premature infants admitted to NICU (Table 4).

Table 3: Determinant factors for neonatal mortality among neonates admitted at NICU

Domain	Determinants	n	(%)	Measure	AOR/ AHR	95% CI		P-value	Study ID
Mode of delivery	Instrumental delivery	8	21.6	OR	2.99	1.07	8.31	<0.05	Demise 2017
	CS delivery	13	6.5	HR	0.34	0.19	0.61	<0.001	Orsido 2019
Hypothermia	Severe hypothermia	5	71.2	OR	10.45	1.04	104.7	<0.05	Demise 2017
	Temperature of neonate at admission (<35.5)	110	34.1	HR	1.58	1.06	2.34	<0.05	Orsido 2019
Sepsis	Early onset of neonatal sepsis	88	19.2	OR	2.66	1.16	6.11	<0.05	Demise 2017
	Late onset of neonatal sepsis	11	17.2	OR	13.51	2.64	69	<0.05	Demise 2017
Asphyxia	PNA (Yes)	33	34.4	OR	5.97	3.06	11.64	<0.05	Demise 2017
	PNA (Yes)	58	22.9	HR	1.81	1.24	2.63	<0.05	Orsido 2019
	PNA (Yes)	14	40.0	OR	5.817	1.61	21	<0.05	Tekleab 2017
	PNA (Yes)	174	30.6	OR	1.82	1.32	2.51	<0.001	Worku 2012
Respiratory Distress Syndrome (RDS)	RDS (Yes)	43	51.2	OR	12.97	5.37	31.3	<0.05	Demise 2017
Resuscitation	Neonate resuscitated (Yes)	122	27.2	HR	2.28	1.06	2.34	<0.05	Orsido 2019
APGAR score	APGAR score at 1st min (<=3)	185	39.7	OR	2.12	1.39	2.23	<0.001	Worku 2012
Length of stay (LOS)	Average LOS (>=8+)	9	4.5	OR				0.01	Farah 2018
	Average LOS (<=2)	22	9.5	OR	0.418	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 (<=1500 gm)	268	59.3	OR	9.64	3.32	27.97	<0.001	Worku 2012
Birth weight	Birth weight (1501-2449 gm)	281	21.6	OR	3.54	1.28	9.78	<0.05	Worku 2012
	Birth weight (2500-3999 gm)	241	15.5	OR	3.16	1.21	8.24	<0.05	Worku 2012
# of siblings	# of siblings (3+)	155	29.8	OR	2.04	1.15	3.64	<0.05	Worku 2012
Birth order	Birth order (2nd)	229	26.4	OR	1.79	1.28	2.51	<0.05	Worku 2012
Marital status	Marital status (not in marriage)	119	29.2	OR	1.55	1.2	2	<0.05	Worku 2012

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

Domain	Determinants	n	(%)	Measure	AOR/ AHR	95% CI		P-value	Study ID
ANC	ANC (Yes)	88	18.1	HR	0.5247	0.338	0.814	<0.05	Yehuala 2015
Gravidity	Gravidity (6-10)	17	3.5	HR	2.072	1.001	4.289	<0.05	Yehuala 2015
RDS	RDS (Yes)	54	31.8	HR	7.774	4.712	12.826	<0.001	Yehuala 2015
	RDS (Yes)	114	32.9	OR	3.287	2.033	5.315	<0.001	Wesenu 2017
HMD	HMD (Yes)	107	57.2	OR	2.636	1.597	4.352	<0.001	Wesenu 2017
	HMD (Yes)	39	26.0	HR	3.02	1.86	4.88	<0.001	Yismaw 2019
PNA	PNA (Yes)	46	31.0	HR	1.55	1.09	2.2	<0.05	Yismaw 2019
	PNA (Yes)	27	64.3	OR	2.479	1.239	4.959	<0.05	Wesenu 2017
	PNA (Yes)	63		HR	2.123	1.42	3.18	<0.001	Yehuala 2015
	Neonate cry immediately at birth (Yes)	385		HR	0.57	0.39	0.83	<0.05	Yismaw 2019
Jaundice	Jaundice (Yes)	10	7.0	HR	1.62	1.12	2.35	<0.05	Yismaw 2019
	Jaundice (Yes)	90	76.3	OR	2.737	1.718	4.361	<0.001	Wesenu 2017
Sepsis	Sepsis (Yes)	52	47.3	OR	2.072	1.242	3.459	<0.05	Wesenu 2017
GA	GA (30-32)	33	37.1	OR	0.336	0.138	0.822	<0.05	Wesenu 2017
	GA (32-34)	32	27.6	OR	0.241	0.099	0.589	<0.05	Wesenu 2017
	Small weight for GA at birth	109		HR	1.65	1.12	2.43	<0.05	Yismaw 2019
	GA			HR	0.82	0.74	0.91	<0.001	Yismaw 2019
Home delivery	Home delivery	23		HR	2.29	1.05	4.98	<0.05	Yismaw 2019
KMC	KMC (Yes)	68		HR	0.23	0.1	0.51	<0.001	Yismaw 2019
Hypoglycemia	Hypoglycemia (Yes)	112		HR	1.75	1.21	2.54	<0.001	Yismaw 2019
HIV status	HIV status (Positive)			HR	1.803	1.037	3.135	<0.05	Yehuala 2015
Anemia	Anemia (Yes)			HR	4.67	1.769	12.33	<0.05	Yehuala 2015
Breastfeeding	BF initiated (<1 h)			HR	0.102	0.045	0.233	<0.001	Yehuala 2015
	BF initiated (1-2 h)			HR	0.129	0.068	0.246	<0.001	Yehuala 2015
	BF initiated (>2 h)			HR	0.375	0.225	0.625	<0.001	Yehuala 2015
Temperature	Temperature			OR	0.811	0.683	0.964	<0.05	Wesenu 2017
Maternal illness	Maternal illness/disease (Yes)			HR	1.57	1.1	2.26	<0.05	Yismaw 2019
Type of pregnancy	Type of pregnancy (Single)	331		HR	2.35	1.58	3.5	<0.001	Yismaw 2019

Publication bias

The funnel plot 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; $p = 0.476$).

DISCUSSION

In this review, the pooled neonatal mortality rate was 19.0%. 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% to 64.4%. (26) A wide variation in the mortality rates among NICUs was also reported in Brazil (9.5-48.1%), with an overall mortality rate for newborns admitted at nine NICU sites being 18.6% (27) which is comparable to our result. These higher rates of mortality could be associated with suboptimal NICU neonatal services across the country. (16, 22)

Our stratified analysis also showed that preterm neonates had three times higher odds of death than preterm and term and post-term neonates. Previous studies also documented a similar higher risk of death amongst preterm neonates in NICUs. (28-31) This is because preterm newborns had immaturity of immune systems and other body defense mechanisms that help control newborn infection and disease susceptibility. Other possible explanations for preterm neonates' high death rate might bs a 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 as a factor in neonatal mortality. The finding is also consistent with the systematic review in developing and developed countries. (26) 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. (19, 25)
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. (17, 19) Training of health care workers to detect risk factors, fetal asphyxia during labor and delivery including neonatal resuscitation provision ,must be given. (25)

We observed that the mode of delivery showed a variation in the rate of neonatal mortality. Instrumental mode of delivery is identified as a risk factor for neonatal mortality. (22) On the other hand, the mode of delivery had a protective effect on the risk of neonatal mortality. (17, 27)

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. (17) 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. (17, 22, 24)

Delayed breastfeeding after 1 hour of birth results in a higher risk of neonatal mortality than their counterpart. (17, 23) 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 who might not be able to suck breast milk instead of a healthier one. (17)

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. (17, 18, 22, 23) 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. (17, 23)

As to authors' knowledge, the current systematic review and meta-analysis are the first of their kind to be conducted at the NICU hospitals of Ethiopia. The information obtained may improve knowledge on the cause of neonatal mortality at NICU to reduce neonatal mortality rates in Ethiopia. Nevertheless, 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 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 hospitals are preventable.

Therefore, special care for preterm and early age newborns, timely initiation of breastfeeding, exclusive breastfeeding, the 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 strengthening NICU services by revising the strategies set in place for optimal quality services and the prevention of risk factors with neonatal mortality at NICU hospital during, pregnancy, delivery, and postnatal period.

Abbreviations

NMR	neonatal mortality rate
AHR	adjusted hazard ratio
ANC	antenatal care
AOR	adjusted odds ratio
AP-GAR	Appearance, Pulse, Grimace, Activity, and Respiration
CI	confidence interval
GA	gestational age
HMD	hyaline membrane disease
JBI	Joanna Briggs Institute
KMC	kangaroo mother care
LOS	length of stay
NICU	neonatal intensive care unit
OR	odds ratio
PNA	perinatal asphyxia
PRISMA	Preferred Reporting Items for Systematic and Meta-Analysis
PROSPERO	International prospective register of systematic reviews
RDS	respiratory distress syndrome
SNNP	Southern Nations, Nationalities, and Peoples'

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 of interest

All contributing authors declare no conflicts of interest.

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REFERENCES

1. UN IGME. Levels & Trends in Child Mortality: Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation. Report 2019. Geneva, Switherland: World Health Organization; 2019.
2. WHO, UNICEF, UNFPA, World Bank Group, United Nations Population Division. Trends in Maternal Mortality: 1990 to 2015 Population and Development Review. Geneva: World Health Organization2015.
3. UNICEF, World Health Organization, The World Bank, United Nations DESA/Population Division. Lev els & Trends in Child Mortality. Report 2015. Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation. New York: UNICEF2015.
4. WHO. Strategies toward ending preventable maternal mortality (EPMM). Geneva, Switzerland: World Health Organization2015.
5. Chou D, Daelmans B, Jolivet RR, Kinney M, Say L. Ending preventable maternal and newborn mortality and stillbirths. BMJ. 2015;351:h4255.
6. FMoH. National Strategy for Newborn and Child Survival in Ethiopia: 2016-2020. Addis Ababa, Ethio pia: Federal Ministry of Health; 2015.
7. Central Statistical Agency [Ethiopia], International I. Ethiopia Demographic and Health Survey 2011. Addis Ababa, Ethiopia and Calverton, Maryland, USA: Central Statistical Agency and ICF International; 2012.

8. Central Statistical Agency [Ethiopia], Macro O. Ethiopia Demographic and Health Survey 2005. Addis Ababa, Ethiopia and Calverton, Maryland, USA: Central Statistical Agency and ORC Macro.; 2006.
9. Central Statistical Agency (CSA) [Ethiopia], ICF. Ethiopia Demographic and Health Survey 2016. Addis Ababa, Ethiopia, and Rockville, Maryland, USA: CSA and ICF; 2016.
10. Lockwood C, Munn Z, Porritt K. Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation. International journal of evidence-based healthcare. 2015;13(3):179-87.
11. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness: The Joanna Briggs Institute; 2017.
12. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk: The Joanna Briggs Institute; 2017.
13. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Annals of internal medicine. 2018;169(7):467-73.
14. StataCorp. Stata: Release 15. Statistical Software. College Station, Texas: Stata Press; 2017.
15. Sterne JA, Palmer TM. Meta-analysis in Stata: an updated collection from the Stata Journal. 2 ed: Stata Corp LP; 2016.
16. Farah AE, Abbas AH, Ahmed AT. Trends of admission and predictors of neonatal mortality: A hospital based retrospective cohort study in Somali region of Ethiopia. PloS one. 2018;13(9).
17. Orsido TT, Asseffa NA, Berheto TM. Predictors of Neonatal mortality in Neonatal intensive care unit at referral Hospital in Southern Ethiopia: a retrospective cohort study. BMC pregnancy and childbirth. 2019;19(1):83.
18. Worku B, Kassie A, Mekasha A, Tilahun B, Worku A. Predictors of early neonatal mortality at a neonatal intensive care unit of a specialized referral teaching hospital in Ethiopia. Ethiop J Health Dev. 2012;26 (3):200-7.
19. Yismaw AE, Gelagay AA, Sisay MM. Survival and predictors among preterm neonates admitted at Uni versity of Gondar comprehensive specialized hospital neonatal intensive care unit, Northwest Ethiopia. Ital J Pediatr. 2019;45(1):4.
20. Ayalew S YS. Survival Analysis of Premature Infants Admitted to Neonatal Int ensive Care Unit (NICU) in Northwest Ethiopia using Semi-Parametric Fr ailty Model. Journal of Biometrics & Biostatistics. 2015;06(01).
21. Wesenu M, Kulkarni S, Tilahun T. Modeling Determinants of Time-To-Death in Premature Infants Ad mitted to Neonatal Intensive Care Unit in Jimma University Specialized Hospital. Annals of Data Science. 2017;4(3):361-81.
22. Demisse AG, Alemu F, Gizaw MA, Tigabu Z. Patterns of admission and factors associated with neonatal mortality among neonates admitted to the neonatal intensive care unit of University of Gondar Hospital, Northwest Ethiopia. Pediatric Health Med Ther. 2017;8:57-64.
23. Tewabe T, Mehariw Y, Negatie E, Yibeltal B. Neonatal mortality in the case of Felege Hiwot referral hospital, Bahir Dar, Amhara Regional State, North West Ethiopia 2016: a one year retrospective chart review. Ital J Pediatr. 2018;44(1):57.
24. Woldu M, Guta M, Lenjisa J, Tegegne G, Tesafye G, Dinsa H. Assessment of the incidence of neonatal sepsis, its risk factors, antimicrobial use and clinical outcomes in Bishoftu General Hospital. Neonatal Intensive Care Unit, Debrezeit-Ethiopia Pediat Therapeut. 2014;4(214):2161-0665.1000214.
25. Tekleab AM, Amaru GM, Tefera YA. Reasons for admission and neonatal outcome in the neonatal care unit of a tertiary care hospital in Addis Ababa: a prospective study. Research and Reports in Neonatology. 2016.
26. Chow S, Chow R, Popovic M, Lam M, Popovic M, Merrick J, et al. A selected review of the mortality rates of neonatal intensive care units. Frontiers in public health. 2015;3:225.
27. Weirich CF, Andrade ALS, Turchi MD, Silva SA, Morais-Neto OL, Minamisava R, et al. Neonatal mor tality in intensive care units of Central Brazil. Revista de saude publica. 2005;39(5):775-81.
28. Karimi P, Mahmudi L, Azami M, Badfar G. Mortality in Neonatal Intensive Care Units in Iran: A Sys tematic Review and Meta-Analysis. Iranian Journal of Neonatology IJN. 2019;10(3):70-80.
29. Seid SS, Ibro SA, Ahmed AA, Akuma AO, Reta EY, Haso TK, et al. Causes and factors associated with neonatal mortality in Neonatal Intensive Care Unit (NICU) of Jimma University Medical Center, Jimma, South West Ethiopia. Pediatric health, medicine and therapeutics. 2019;10:39.
30. Zhang B, Dai Y, Chen H, Yang C. Neonatal Mortality in Hospitalized Chinese Population: A Meta-Analysis. BioMed research international. 2019;2019.
31. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. Bulletin of the World Health Organization. 2014;93:19-28.