


BMJ Open Incidence and predictors of respiratory distress syndrome among low birth weight neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals, 2023: A retrospective follow-up study

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ABSTRACT

Introduction Respiratory distress syndrome is a catastrophic respiratory problem among low birth weight neonates. It increases the suffering of neonates and the economic expenditure of the countries. Notably, it is a major public health issue in low-income and middle-income countries such as Ethiopia. Despite this, studies regarding respiratory distress syndrome among low birth weight neonates were limited in Ethiopia.

Objective To assess the incidence and predictors of respiratory distress syndrome among low birth weight neonates in the first 7 days in Northwest Ethiopia Comprehensive Specialized Hospitals.

Method Multicentred institution-based retrospective follow-up study was conducted from 19 September 2021 to 1 January 2023, among 423 low birthweight neonates. A simple random sampling technique was used. The data were collected using a data extraction checklist from the medical registry of neonates. The collected data were entered into EPI-DATA V.4.6.0.6. and analysed using STATA V.14. The Kaplan-Meier failure curve and log-rank test were employed. Bivariable and multivariable Weibull regression was carried out to identify predictors of respiratory distress syndrome. Statistical significance was declared at a $p \leq 0.05$.

Result The incidence rate of respiratory distress syndrome was found to be 10.78 (95% CI 9.35 to 12.42) per 100 neonate days. Fifth minute Appearance, Pulse, Grimace, Activity, Respiration (APGAR score) <7 (AHR 1.86; 95% CI 1.18 to 2.92), multiple pregnancy (AHR 1.43; 95% CI 1.04 to 1.96), caesarean section delivery (AHR 0.62; 95% CI 0.41 to 0.93), prematurity (AHR 1.56; 95% CI 1.06 to 2.30) and birth weight <1000 g (AHR 3.14; 95% CI 1.81 to 5.40) and 1000–1499 g (AHR 2.06; 95% CI 1.42 to 2.83) were significant predictors.

Conclusion The incidence of respiratory distress syndrome was higher than other studies conducted on other groups of neonates. Multiple pregnancy, fifth minute APGAR score, caesarean section, prematurity, extremely

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study was conducted in multicentres (five hospitals), and it covers a diverse population, which increases generalisability and shows the relationship between exposure and outcome variables.
- ⇒ Due to its retrospective nature, important variables, such as maternal nutritional status, family income and educational level, were missed.
- ⇒ In addition, the hospital's service context and supplies were not assessed.

low birth weight and very low birth weight were predictors of respiratory distress syndrome. However, it needs further prospective study. Therefore, the concerned stakeholders should give due attention and appropriate intervention for these predictors.

BACKGROUND

Respiratory distress syndrome (RDS) is one of the major catastrophic and challenging respiratory problems among Low Birth Weight (LBW) neonates.^{1 2} RDS has a devastating course with different morbidity, and it escalates to mortality.^{3 4} Among LBW neonates, this problem causes significant admission in Neonatal Intensive Care Unit (NICU) ranging from 24.9% to 62.96%,^{2 3 5–7} and 31.3% of death in the perinatal period.⁸ According to the American Academy of Pediatrics, 15% of term, and 29% of preterm neonates admitted to NICU develop RDS.⁹ The burden of this respiratory problem is high in low-income and middle-income countries, notably, in South-east Asia and sub-Saharan African countries, including Ethiopia.¹⁰ In East Africa, RDS is

a common morbidity and it increases the probability of mortality three times in LBW neonates.⁴

The magnitude of RDS among LBW neonates varies across countries depending on the availability of medical services and the number of trained medical personnel. For instance, in Taiwan 60%–86%,^{11 12} Finland 76%,¹³ Thailand 70.7%,¹⁴ Karachi, Pakistan 11%–12.8%,^{15 16} Iran 76%,¹⁷ Afghanistan 58.8%¹⁸ and in Nigeria 10.9%¹⁹ of LBW neonates had RDS. In Ethiopia, RDS is the primary cause of admission with a mortality rate of 45.3% among LBW neonates.²⁰ These studies showed that different factors increase the risk of RDS among LBW neonates. Accordingly, maternal Diabetes Mellitus (DM),^{21–23} hypertension,²¹ mode of delivery,^{18 21 22 24} sex,^{12 18 21 22 24} prematurity,^{12 18 21 22} multiparity,²⁴ birth weight,^{12 18 22} antenatal steroid,^{12 25} hyperglycaemia,²⁶ sepsis,¹⁸ Antepartum Paemorrhage (APH),¹⁸ Premature Rupture of Membrane (PROM),^{18 27} first and fifth minute ((Appearance, Pulse, Grimace, Activity, Respiration) (APGAR)) score²⁸ were significant predictors of RDS.

To alleviate this problem and reduce newborn morbidity and mortality, World Health Organization (WHO) recommends the use of antenatal corticosteroid therapy for risky women, Kangaroo mother care, Continuous Positive Airway Pressure (CPAP), tocolytics for preterm labour and optimal oxygen therapy.²⁹ Furthermore, the Federal Ministry of Health has given due attention in the expansion of high-quality neonatal care to reduce neonatal morbidity like RDS.³⁰ Despite these efforts, RDS continues to be a major public health problem by increasing neonate suffering, and mortality, and escalating economic expenditures in low-income and middle-income countries, including Ethiopia.

Some studies were conducted regarding RDS inclusive of all neonates. However, studies regarding RDS, notably among LBW neonates, were limited in Ethiopia. Hence, this retrospective study aimed to assess the incidence and predictors of RDS among LBW in the first seven days of life in Northwest Ethiopia Comprehensive Specialised Hospitals. The findings of this study will provide new insight for different stakeholders, and it will help health professionals understand the significant predictors of RDS. Additionally, it will serve as baseline information for future studies, and it will give clues to mobilise resources towards the predictors of RDS.

METHODS

Stud design and period

An institution-based multicentred retrospective follow-up study was carried out from 19 September, 2021 to 1 January 2023 (the data were retrospectively extracted from 5 January 2023 to 19 February 2023).

Study setting

The study was conducted in the NICU of Northwest Ethiopia Comprehensive Specialized Hospitals. These hospitals are the University of Gondar Comprehensive Specialized Hospital (UoGCSH), Felege hiwot, Tibebe Ghion, Debre Tabor and Debre Markos Comprehensive Specialized Hospital. UoGCSH is found in Gondar town, this hospital

has an average annual admission of 697 LBW neonates in their first week of life. Felege hiwot and Tibebe Ghion CSH are found in Bahir Dar city, These, hospitals have an average annual admission of 675, and 683 LBW neonates in their first week of life respectively. Debre Tabor CSH is found in Debre Tabor town, with an average annual admission of 560 LBW neonates in their first 7 days of life. Debre Markos CSH is found in Debre Markos town, with an average annual admission of 594 LBW early neonates. These hospitals have NICUs with different health professionals (paediatricians, neonatologists, general practitioners, comprehensive nurses, paediatrics and neonatal nurses). This team in collaboration provides a diagnosis of the neonate's problem and holistic care including documentation. The major services in the NICU of these hospitals include general neonatal care services, blood and exchange transfusion, phototherapy, ventilation support such as Continuous Positive Air Pressure (CPAP, and other routine neonatal care.

Study population

All LBW neonates in the first 7 days of life admitted to the NICU of Northwest Ethiopia comprehensive specialized hospitals were the source population.

All LBW neonates in the first 7 days of life admitted to the NICU of Northwest Ethiopia Comprehensive Specialized Hospitals from 19 September 2021 to 1 January 2023, were taken as a study population.

Inclusion and exclusion criteria

LBW neonates in the first week of life who were admitted to NICU from 19 September 2021 to 1 January 2023, were included, whereas, neonates with an incomplete chart (outcome status and charts with one missed predictor of the following (gestational age, birth weight, neonatal age, sex, type of pregnancy, date of admission and discharge)), and neonates with major respiratory and cardiovascular malformation were excluded.

Sample size determination and sampling procedure

The minimum required sample size was determined using the single population proportion formula by considering the following statistical assumptions $z_{\alpha/2}$ =the corresponding Z score of 95% CI, and d =margin of error (5%), and proportion of RDS (P) (50%). The proportion of RDS was taken as 50% because there were no previous studies regarding the incidence of RDS among LBW neonates in the study setting. Therefore,

$$n = \frac{(\frac{Z_{\alpha}}{2})^2 p(1-p)}{d^2}$$

$$n = \frac{(1.96)^2 (0.5)(0.5)}{(0.05^2)}$$

So, $n = 384.16$.

Then, the incompleteness of medical records (chart attrition) was taken as 10%. Accordingly, the final estimated sample size was $422.576=423$. So, a total of 423 medical records of LBW neonates were reviewed. The total sample size was proportionally allocated to each hospital. Then the neonate's chart was selected by a

simple random sampling technique using computer-generated random number.

Variables of the study

Dependent variable: RDS in the first 7 days of life. It was dichotomised into RDS (event of interest=1) and censored (no RDS=0).

Independent variables: (1) Sociodemographic, medical and obstetric characteristics of mothers of LBW neonates such as maternal age, place of delivery, residence, type of pregnancy, gravidity, PROM, APH, mode of delivery, pre-eclampsia, Antenatal Care (ANC) follow-up, corticosteroid administration, DM, chronic hypertension, HIV/AIDS, anaemia and (2) neonate's clinical and other characteristics such as sex of the neonate, age of the neonate, perinatal asphyxia (PNA), sepsis, jaundice, hypothermia, hypoglycaemia, Necrotising Enter Colitis (NEC), first and fifth minute APGAR score, breast feeding, congenital anomalies, IntraUterine Growth Restriction (IUGR), birth weight and gestational age.

Operational definition

LBW: Weight at birth less than 2500 g regardless of gestational age.³¹

RDS: It is defined as the presence of the following two or more signs: abnormal respiratory rate, expiratory grunting, nasal flaring and chest wall recession with or without cyanosis.³²

Event: LBW neonates who develop RDS during the follow-up.

Censored: LBW neonates who did not develop RDS, discharged against medical advice, died, transferred/referred and lost the follow-up during the follow-up.

Extremely LBW: Neonates born with less than 1000 g of birth weight.³¹

Follow-up time: The time from admission to NICU to either death or censorship occurs.

Prematurity: Neonate born before 37 completed weeks of gestational age.³³

Very LBW: Neonates born with (1000–1499 g) of birth weight.³³

Data abstraction checklist and procedures

The data were collected using a data abstraction checklist which was adapted by reviewing different literature^{2 33–36} (online supplemental file 1). The neonates were followed from the time of admission until either the event of interest was developed or censored. The data were collected retrospectively by five BSc nurses and supervised by five experienced BSc nurses. The required number of neonates' medical charts was selected by a simple random sampling technique.

Data quality control

To ensure the quality of the data, the data abstraction checklist was evaluated by a research expert, and a pretest was done on 5% of the sample size. Based on the pretest findings necessary modifications were done. One-day training was given to data collectors and supervisors about the

purpose of the study, the data collection tool, data collection methods and ethical concerns during data collection. All the collected data were checked for completeness and consistency by the data collector and supervisors.

Data processing and analysis

Data were entered into Epi-Data V.4.6.0.6 and exported to STATA V.14 statistical software for cleaning, coding and analysis. Descriptive measures such as mean with SD, median with IQR, percentage and frequency were used to characterise the data.

The incidence rate of RDS was calculated for the entire follow-up by dividing the total number of new cases of LBW neonates with RDS by the total neonates-day of follow-up (time at risk). Kaplan-Meier failure curve was used to estimate the time to develop RDS. The log-rank test was employed to compare statistical differences between independent variables. The Proportional Hazard Assumption (PHA) was checked using both graphical and hypothesis tests (Schoenfeld residual test) for all predictors, and it revealed that the PHA was satisfied. The log-likelihood and Akaike Information Criteria (AIC) were applied to select the best-fitted model, and a model with minimum AIC was considered the best-fitted model. Based on this, the Weibull regression model with the (AIC=713.5962) value was the best-fitted model. In addition, the goodness-of-model fitness was also checked using the Cox-Snell residual test, and it was close to the 45° line. Variables having a $p < 0.25$ in the bivariable analysis were fitted into the multivariable Weibull regression model. Hazard Ratio (HR) with 95% CI were used to determine the strength of the association. Variables having a $p < 0.05$ in multivariable analysis were considered statistically significant.

Patient and public involvement

In this study, the study participants and/or public were not directly involved in the design, conduct, reporting and dissemination of this work.

RESULTS

Sociodemographic, medical and obstetric characteristics of mothers of LBW neonates

A total of 423 LBW neonates' charts were reviewed, and 405 (95.74%) met the enrolment criteria. In this study, two-thirds of the mothers 274 (67.65%) were in the age group of 21–34 years old with a mean of 27.4 (SD±6) years old, and 226 (55.80%) were from urban areas. Among the total enrolled mothers, 301 (74.32%) had given birth through spontaneous vaginal delivery, and three-fourths 304 (75.06%) of pregnancies were singleton. In this study, the majority of mothers 375 (92.59%) had ANC follow-ups in nearby health institutions, and one-fourth 302 (75.557%) of them had pre-eclampsia. Moreover, 82 (20.25%) mothers had taking corticosteroid treatment, and 16 (4.69%) had HIV/AIDS infection (table 1).

Clinical and other characteristics of LBW neonates

In this study, over half of the participants 218 (53.83%) were male, and 279 (68.89%) were admitted within 24 hours of

Table 1 Sociodemographic, medical and obstetric characteristics of mothers of low birthweight neonates admitted at NICU of Northwest Ethiopia CSH from (19 September 2021 to 1 January 2023) (N=405)

Variables		Frequency	Per cent
Maternal age	≤20 years	66	16.30
	21–34	274	67.65
	≥35	65	16.05
Residence	Urban	226	55.80
	Rural	179	44.20
Place of delivery	Health institution	389	55.80
	Out-of-health institution	16	44.20
ANC follow-up	Yes	375	92.59
	No	30	7.14
Types of pregnancy	Single	304	75.06
	Multiple	101	24.94
Mode of delivery	SVD	301	74.32
	Instrumental	16	3.95
	Caesarean section	88	21.73
Gravidity	Prim gravida	78	19.26
	Multi gravida	327	80.74
Pre-eclampsia	Yes	302	75.57
	No	103	24.43
Corticosteroid treatment	Yes	82	20.25
	No	323	79.75
PROM	Yes	55	13.58
	No	350	86.42
APH	Yes	41	10.12
	No	364	89.88
Chronic hypertension	Yes	12	2.96
	No	393	97.04
Maternal DM	Yes	3	0.74
	No	402	99.26
Maternal HIV infection	Reactive	19	4.69
	Non-reactive	386	95.31
Maternal anaemia	Anaemic	5	1.23
	Non-anaemic	400	98.77

ANC, antenatal care; APH, antepartum haemorrhage; CSH, Comprehensive Specialised Hospital; DM, diabetes mellitus; NICU, neonatal intensive care unit; PROM, premature rupture of membrane; SVD, spontaneous vaginal delivery.

birth. Regarding birth weight, three-fourths of neonates were between 1500 and 2499 g with a median weight of 1715 (IQR 800–2478). Above two-thirds 279 (68.89%) of neonates were premature, and the mean gestational age was 34.7 weeks with (SD±3.3). The common medical problems among LBW early neonates were sepsis 283 (69.88%) and

hypothermia 155 (38.27%). The other medical problems include jaundice, PNA, NEC, IUGR, hypoglycaemia and other congenital anomalies (table 2).

Proportional Hazard Assumption (PHA) test

The PHA was checked using the Schoenfeld residuals test. The test showed that the p value for each covariate and the whole covariates simultaneously were above 0.05 (p=0.6298).

Incidence of RDS and overall outcome of the follow-up

In this study, the neonates were followed for up to 7 completed days of age starting from the date of admission. The total number of neonate days' observations during the entire follow-up was 1771 neonate day observations. The total neonate's day observation (1771) was the sum of each neonate's time at risk during the follow-up (ie, the sum of the length of time in day each neonate was followed during the study). From the total enrolled LBW early neonates, during the follow-up 47.16% (95% CI 42.80% to 52.55%) developed the event of interest (RDS). The proportion of RDS was 38.37% for the UoGCSH, 50.00% for Feleghiwot Comprehensive Specialized Hospital, 43.24% for Tibebe Ghion Hospital, 58.14% for Debre Markos Hospital and 45.07% for Debre Tabor Comprehensive Specialized Hospital.

In this study, the overall incidence rate of RDS was found to be 10.78 per 100 neonates' day observation (95% CI 9.35 to 12.42). The incidence of RDS at the end of 24 hours, 2nd, 3rd, 4th, 5th, 6th and 7th days were 52.63, 26.72, 16.66, 10.63, 9.5, 7.99 and 5.91 per 100 neonate's day observation, respectively. Similarly, the incidence of RDS among extremely low birth weight (ELBW) (<1000 g), very low birth weight (VLBW) (1000–1499 g) and LBW (1500–2499) was 25.39, 18.98, and 8.26 per 100 neonate's day observation, respectively (table 3).

Overall failure function (survivorship function)

In this study, the median length of hospital stay was 6 days (95% CI 6 to 7), and the maximum follow-up time was 7 days. The overall Kaplan-Meier failure function showed that the probability of developing RDS was increasing as follow-up time increased. The cumulative probability of developing RDS at the end of the 1st day was 0.1630 (95% CI 0.1304 to 0.2027), at the end of the 3rd day was 0.3383 (95% CI 0.2945 to 0.3866) and at the end of the 7th day was 0.7704 (95% CI 0.7284 to 0.8100) (figure 1).

Comparison of failure function for some variables

In this study, neonates having ELBW (<1000 g) and VLBW (1000–1499 g) had a higher risk of developing RDS than LBW neonates (1500–2499 g). The mean hazard time for EVLBW and VLBW was 3.36 days and 4.11 days, respectively, as compared with those LBW neonates with a mean hazard time of 5.52 days. This study also revealed that premature neonates had a higher risk of developing RDS as compared with their counterparts. The mean hazard time to develop RDS was 4.84 days. Furthermore, neonates with fifth minute APGAR scores less than <7 had a higher probability of developing RDS as compared with

Table 2 Clinical and other characteristics of low birthweight early neonates admitted to Northwest Ethiopia CSH from 19 September 2021 to 1 January 2023) (N=405)

Variable		Frequency	Per cent
Sex	Male	218	53.83
	Female	187	46.17
Age of the neonate at admission in days	≤1	279	68.89
	2–3	76	18.77
	4–7	50	12.35
Gestational age in a week	< 37	279	68.89
	≥37	126	31.11
Birth weight	≤999	21	5.19
	1000–1499	84	20.74
	1500–2499	300	74.07
Breast feeding	Yes	384	94.81
	No	21	5.91
First minute APGAR score	<7	153	37.78
	≥7	252	62.22
Fifth minute APGAR score	<7	46	11.36
	≥7	359	88.64
Sepsis	Yes	283	69.88
	No	122	30.12
PNA	Yes	56	13.83
	No	349	86.17
NEC	Yes	17	4.20
	No	388	95.80
Jaundice	Yes	61	15.06
	No	344	84.94
Congenital anomaly	Yes	22	5.42
	No	383	94.57
Hypothermia	Yes	155	38.27
	No	250	61.73
IUGR	Yes	17	4.20
	No	388	95.80
Hypoglycaemia	Hypoglycaemic	14	3.46
	Non-hypoglycaemic	391	96.54

APGAR, Appearance, Pulse, Grimace, Activity, Respiration; CSH, Comprehensive Specialised Hospital; IUGR, intrauterine growth restriction; NEC, necrotising enterocolitis; PNA, perinatal asphyxia.

their counterparts. These differences were statistically significant with a ($p<0.0006$) in the log-rank test (online supplemental figure 1).

Model comparison and diagnostics

To select the most parsimonious models for the data set, a comparison of the semiparametric and parametric hazard models was done statistically using Akaike and Bayesian Information Criterion (AIC,BIC) and graphically using the Cox-Snell residual test. Based on this, the Weibull regression model with (AIC=713.5962) was the parsimonious model than the parametric exponential

(AIC=772.3843), Gompertz (AIC=721.98) and semiparametric Cox proportional hazard models (AIC=2064.185). So, all of the interpretations in this study were using the Weibull regression model.

The goodness of fit for the fitted model was also checked using the Cox-Snell residual test, and as shown in the figure, Weibull regression model was adequate (figure 2).

Predictors of RDS

In the bivariable Weibull regression, sex, mode of delivery, preeclampsia, PNA, NEC, IUGR, first and fifth-minute APGAR score, birth weight, gestational age and type of

Table 3 Incidence rate to birth weight and number of follow-up days among low birthweight neonates in Northwest Ethiopia CSH from 19 September 2021 to 1 January 2023) (N=405)

Variables	Category	RDS	Rate with (95% CI) per 100
Birth weight	ELBW	15	25.39 (15.55 to 41.45)
	VLBW	60	98 (14.74 to 24.45)
	LBW	118	8.26 (6.88 to 9.18)
No of follow-up days	1 day	30	52.63 (36.80 to 75.27)
	2 days	31	26.72 (18.79 to 38.00)
	3 days	23	16.66 (11.07 to 25.08)
	4 days	18	10.63 (6.60 to 17.09)
	5 days	19	9.5 (6.05 to 14.89)
	6 days	23	7.99 (53.07 to 12.01)
	7 days	48	5.91 (4.45 to 7.84)
Total incidence density			10.78 (9.35 to 12.42).

CSH, Comprehensive Specialised Hospital; ELBW, extremely low birth weight ; LBW, low birth weight; RDS, respiratory distress syndrome; VLBW, very low birth weight.

pregnancy were associated with RDS ($p < 0.25$). However, in the multivariable Weibull regression analysis only five variables were significant predictors of RDS ($p < 0.05$). Accordingly, the hazard of developing RDS was 1.43 times higher (Adjusted Hazard Ratio (AHR) 1.43; 95% CI 1.04 to 1.96) among neonates with multiple births as compared with singleton births. Similarly, neonates with APGAR

scores < 7 at the fifth minute were 1.86 times (AHR 1.86; 95% CI 1.18 to 2.92) more likely to develop RDS as compared with neonates with normal APGAR scores.

Moreover, neonates delivered via caesarean section were 62% times (AHR 0.62; 95% CI 0.41 to 0.93) more likely to develop RDS as compared with their counterparts. Additionally, neonates with birth weights less than 1000 g and 1000–1499 g were three times (AHR 3.14; 95% CI 1.81 to 5.40) and two times (AHR 2.06; 95% CI 1.42 to 2.83) at high risk of developing RDS as compared with their counterparts respectively. Finally, this study found that LBW early neonates who are preterm were 1.56 times (AHR 1.56; 95% CI 1.06 to 2.30) at a higher risk of developing RDS as compared with that of term neonates (table 4).

DISCUSSION

This study aimed to assess the incidence of RDS, and its predictor among LBW neonates admitted to Northwest Ethiopia Comprehensive Specialized Hospitals. Accordingly, this study found that at the end of the follow-up 47.16% (95% CI 42.80% to 52.55%) of neonates developed RDS. This finding was aligned with studies conducted in Thailand (44.15%),³⁷ and Ethiopia 49.83%,³⁸ The possible justification is due to similarities in study design, sample size and the presence of similar maternal health problems. On the other hand, this study was higher than two different studies conducted in Pakistan 11%–12.8%,^{15 16} India 38%,³⁹ Nepal 21.4%⁴⁰ and Nigeria 10.9%.¹⁹ The possible reason for this discrepancy is due to exclusion criteria. In those studies, neonates with any type of congenital disorders, and intrauterine

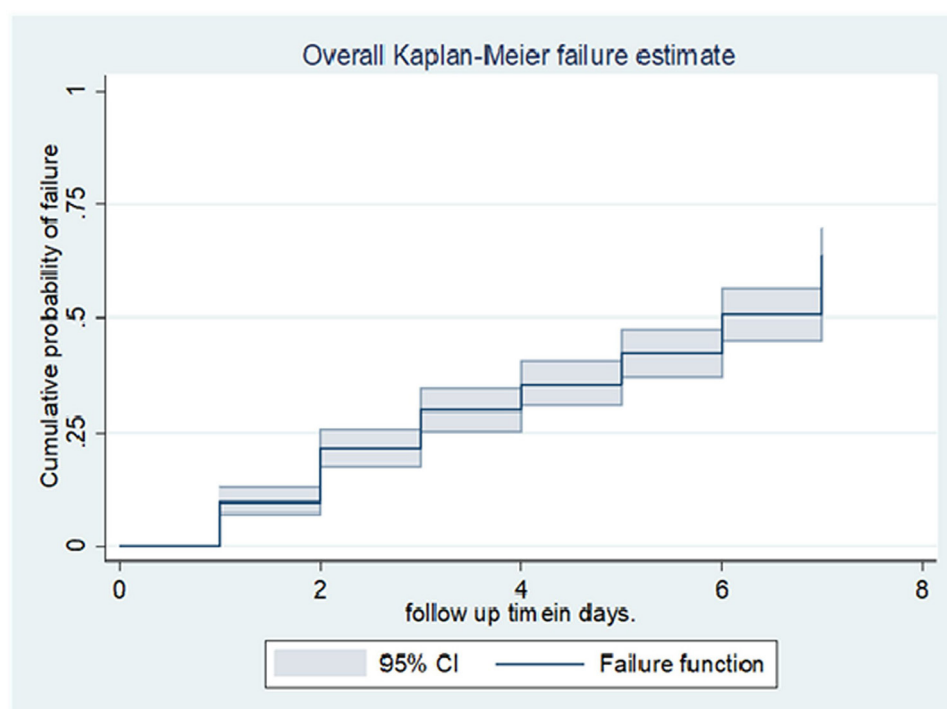


Figure 1 The overall Kaplan-Meier failure estimate curve with a 95% CI showing the time of developing Neonatal RDS in Northwest Ethiopia Comprehensive Specialized Hospital, 2023. RDS, respiratory distress syndrome.

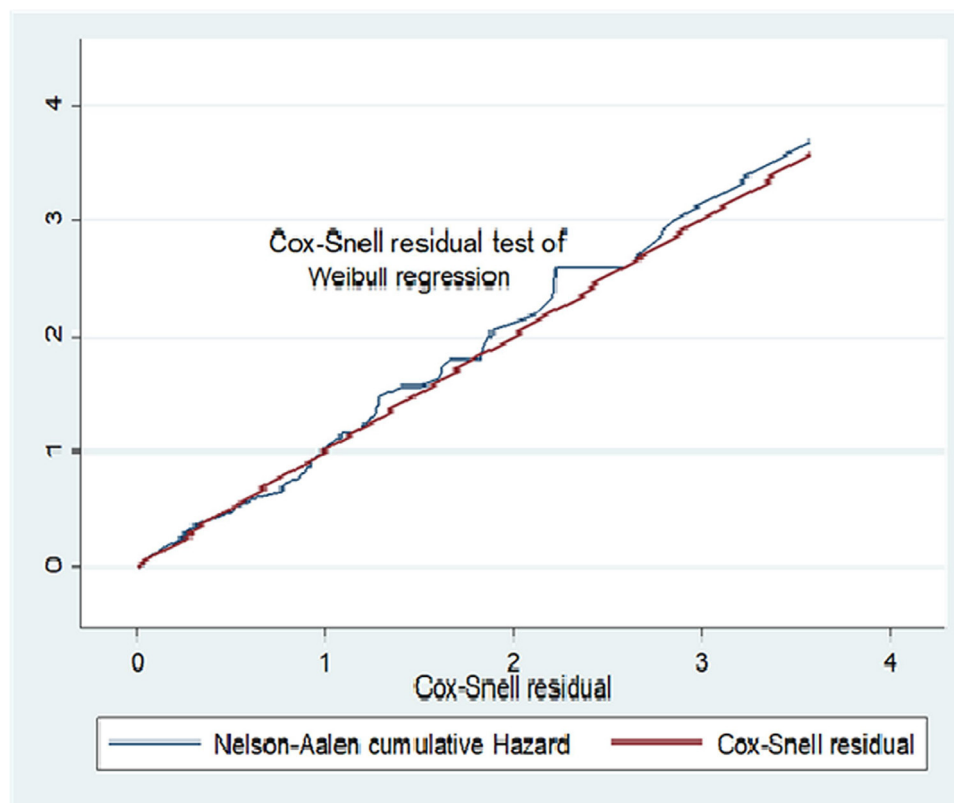


Figure 2 The Cox-Snell residual test of Weibull regression for Incidence of RDS. RDS, respiratory distress syndrome.

infection were excluded. But, the present study did not exclude those neonates. The second possible reason might be the diagnostic criteria, in those studies, they diagnose and include neonates who develop RDS within 4 hours of birth. Whereas, the present study considers neonates who develop RDS at any time of age during the follow-up. In addition to the above reasons, it might be due to the presence of skilled/trained medical teams in NICU across different departments to provide essential newborn care and postnatal care.⁴¹ Furthermore, it might be due to their advanced NICU setups, like the availability of bubble CPAP, surfactant therapy and advanced treatment technologies.⁴²

In contrast to the aforementioned studies, the present study was lower than studies conducted in Iran 76%,¹⁷ Taiwan 60%–86.5%,^{11 12} Thailand 70.7%,¹⁴ Finland 76%¹³ and Afghanistan 58.8%.¹⁸ This marked difference might be attributed to study subject recruitment criteria, because those studies include only very LBW and very preterm neonates, so due to anatomical and physiological organ immaturity the probability of RDS could be high.^{33 42} Whereas, the present study includes all categories of LBW and all categories of gestational age. The second possible explanation could be in those studies the magnitude of maternal morbidity such as DM, and pre-eclampsia/eclampsia was high.^{23 42} In addition, in those studies, congenital anomalies were high in percentage, whereas in the present study, it was low.¹⁸

In this study, the incidence of RDS was found to be 10.78 per 100 neonate's day (95% CI 9.35 to 12.42) with

1771 neonate day observations. The incidence of RDS at the end of 24 hours, 2nd, 3rd, 4th 5th, 6th and 7th days were 52.63, 26.72, 16.66, 10.62, 9.5, 7.98, 5.91 per 100 neonate's day observation respectively. Similarly, the incidence of RDS among ELBW (<1000 g), VLBW (1000–1499 g) and LBW (1500–2499) was 25.39 (95% CI 15.55 to 41.45), 18.98 (95% CI 14.74 to 24.45) and 8.26 (95% CI 6.88 to 9.18) per 100 neonate's day observation respectively. Accordingly, the incidence of RDS was high, and the highest incidence rate of RDS was observed within 24 hours of birth, this is due to the difficulty of adapting to the extra uterine environment secondary to anatomical and physiological organ immaturity,³² and lack of quality care immediately after birth.^{32 42} Moreover, it might be due to antenatal, and intrapartum birth complications too.¹

Being delivered through caesarean section is an independent predictor in this study and raises the risks of RDS in neonates with LBW. This finding is supported by Studies conducted in France,⁴³ China,^{44 45} Taiwan,¹² Korea,²⁴ Qatar⁴⁶ and Egypt.²¹ The possible justification is the residual amount of lung fluid in newborns who were delivered by caesarean section is greater, they produce less surfactant to the alveolar surface, and their lung fluid clearance is delayed.^{47 48} The other justification is following a caesarean section, amiloride-sensitive sodium channels in alveolar epithelial cells are less active, which results in impaired fluid evacuation.⁴⁹

In agreement with studies conducted in Taiwan,¹² Afghanistan,¹⁸ Saudi Arabia²¹ and China,²⁷ prematurity

Table 4 ; Bivariable and multivariable Weibull regression analysis for predictors of RDS among low birthweight neonates in their first 7 days of life in Northwest Ethiopia Comprehensive Specialised Hospitals from 19 September 2021 to 1 January 2023 (n=405)

Variable	Status		CHR (95%CI)	AHR (95%CI)
	Event	Censored		
Sex				
Male	95	123	0.78 (0.59 to 1.03)	0.82 (0.61 to 1.10)
Female	98	89	1	1
Mode of delivery				
Instrumental assisted	6	10	0.50 (0.22 to 1.13)	0.48 (0.205 to 1.32)
CS	35	53	0.60 (0.42 to 0.87)	0.62 (0.41 to 0.93)**
SVD	152	149	1	1
Type of pregnancy				
Multiple	60	41	1.50 (1.10 to 2.04)	1.43 (1.04 to 1.96)**
Single	133	171	1	1
Pre-eclampsia				
Yes	52	51	1.17 (0.85 to 1.61)	1.14 (0.80 to 1.62)
No	141	161	1	1
PNA				
Yes	28	28	1.24 (0.83 to 1.85)	1.26 (0.82 to 1.94)
No	165	184	1	1
NEC				
Yes	10	7	1.44 (0.76 to 2.72)	1.40 (0.73 to 2.69)
No	183	205	1	1
IUGR				
Yes	5	13	0.39 (0.14 to 1.03)	0.67 (0.24 to 1.86)
No	188	199	1	1
First-minute APGAR score				
<7	85	68	1.48 (1.11 to 1.97)	1.08 (0.77 to 1.51)
≥7	108	144	1	1
Fifth-minute APGAR score				
<7	32	14	1.94 (1.33 to 2.83)	1.86 (1.18 to 2.92)***
≥7	161	198	1	1
Gestational age in weeks				
<37	156	123	2.09 (1.43 to 3.05)	1.56 (1.06 to 2.30)**
≥37	37	89	1	1
Birth weight				
≤999	15	6	3.52 (2.11 to 5.86)	3.14 (1.81 to 5.40)***
1000–1499	60	24	2.43 (1.78 to 3.33)	2.06 (1.42 to 2.83)**
1500–2499	118	182	1	1

=Statistically significant variables with p-value <0.01, & *p<0.001.

1, reference; AHR, Adjusted Hazard Ratio; APGAR, Appearance, Pulse, Grimace, Activity, Respiration; CHR, Crude Hazard Ratio; CS, caesarean section; IUGR, intrauterine growth restriction; NEC, necrotising enterocolitis; PNA, perinatal asphyxia; SVD, spontaneous vaginal delivery.

is a predictor of RDS. This is explained by due to inadequate surfactant production or inactivation of surfactant in the context of immature lungs. Due to this, the synthesised surfactant is not adequate to maintain alveolar

stability, and this leads to atelectasis, and the neonate develops RDS.^{32 33 50} In addition, premature neonates are more vulnerable to different medical problems such as hypothermia, hypoglycaemia, sepsis, NEC and other

comorbidities while this increases the probability of developing RDS.^{38 42}

This study revealed that multiple pregnancy was an independent predictor of RDS. This finding is supported by a study conducted in China,⁵¹ the reason for this occurrence is due increased risk of preterm labour and preterm birth in multiple births, and the neonate delivered before their organ systems become completely matured.⁵² The other possible justification is multiple neonates have a higher risk of getting congenital anomalies and IUGR, which increases the risk of RDS.⁴²

The current study found that a low APGAR score <7 at the fifth minute is an independent predictor of RDS among LBW neonates. This finding is supported by different studies conducted in China,⁵³ Indonesia⁵⁴ and Saudi Arabia.² The possible reason for this is a low APGAR score, which is defined as asphyxia, and asphyxia at birth can cause direct harm to alveolar type II epithelial cells and impair the generation of surfactant, which will raise the incidence of RDS. Additionally, the following two factors are the other reasons for this: hypoxia decreases pulmonary surfactant activity and may even lead to its inactivation, whereas severe birth asphyxia diminishes pulmonary surfactant synthesis and secretion.²⁷

Being born extremely very low and very LBW increases the hazard of RDS among LBW neonates. This finding is supported by different studies conducted in China,⁴⁹ Indonesia,⁵⁴ Vietnam⁵⁵ and Saudi Arabia.² The possible justification for this is a lack of surfactant caused by lung immaturity is one example of the physiological and anatomical immaturities that can occur in newborns who have LBW.⁵⁶ The other reason is as birth weight decreases the risk of exposure/ vulnerability to various medical problems such as hypoglycaemia, sepsis and cold stress increases.^{33 42} Hence, these medical problems individually, or simultaneously, increase the risk of developing RDS.⁴² The present study has the following limitations: due to its retrospective nature, some important variables, such as maternal nutritional status, family income and educational level, were missed. In addition, the hospital's service context and supplies were not assessed.

Conclusion

The current study showed that the incidence of RDS was higher than other studies conducted on other groups of neonates. A high incidence rate was seen among extremely LBW and very LBW neonates. Fifth minute APGAR score, caesarian section, multiple births, prematurity, extremely LBW and very LBW were significant predictors of RDS. Hence, healthcare providers and other concerned stakeholders should give due attention, and appropriate intervention for LBW neonates with the aforementioned preventable and treatable factors. Furthermore, a prospective follow-up study needs to be conducted to assess the true association of predictors.

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Ethics approval Ethical approval was obtained from the Institutional Review Board (IRB) of the School of Nursing, College of Medicine and Health Science, University of Gondar with reference No. (Ref.no. SN/231/2014 E.C). The IRB of the School of Nursing, College of Medicine and Health Science has waived informed consent of the medical records of the neonates. The letter of permission was obtained from each Comprehensive Specialised Hospital clinical director and head of the unit. To maintain confidentiality personal identifiers (name, MRN) were not recorded. All of the procedures were carried out by considering the Declaration of Helsinki.

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Incidence and Predictors of respiratory distress syndrome among low birth weight neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals, 2023; A retrospective follow-up study.

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Abstract

Introduction: Respiratory distress syndrome is a catastrophic respiratory problem among low birth weight neonates. It increases the suffering of neonates and the economic expenditure of the countries. Notably, it is a major public health issue in low-income and middle-income countries like Ethiopia. Despite this, studies regarding respiratory distress syndrome among low birth weight neonates were limited in Ethiopia.

Objective: To assess the incidence and predictors of respiratory distress syndrome among low birth weight neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals.

Method: Multi-centered institution-based retrospective follow-up study was conducted from ~~January 5 to February 19, 2023~~ September 19, 2021, to January 1, 2023, among 423 low birth weight neonates. A Simple random sampling technique was used. The Data were collected using a data extraction checklist from the medical registry of neonates. The collected data were entered into EPI-DATA 4.6 0.6 and analyzed using STATA version 14. The Kaplan-Meier failure curve and Log-rank test were employed. Bi-variable and multivariable Weibull regression was carried out to identify predictors of respiratory distress syndrome. Statistical significance was declared at a P-value of ≤ 0.05 .

Result: The incidence rate of Respiratory distress syndrome was found to be 10.78 (95% CI: 9.35-12.42) per 100 neonate days. Fifth minute APGAR score < 7 (AHR=1.86;95% CI: 1.18-2.92), Multiple pregnancy (AHR=1.43;95% CI:1.04-1.96), Caesarean section delivery (AHR=0.62; 95%: 0.41- 0.93)), prematurity (AHR=1.56;95% CI: (1.06-2.30)), and birth weight < 1000 gram (AHR=3.14;95% CI:1.81-5.40) and 1000-1499 gram (AHR=2.06;95% CI:1.42-2.83); 95% CI:) were significant predictors.

Conclusion: The incidence of respiratory distress syndrome was higher than other studies conducted on other groups of neonates. Multiple ~~P~~pregnancy, fifth ~~—~~minute, APGAR score, cesarean section, Prematurity, extremely low birth weight, and very low birth weight were predictors of respiratory distress syndrome. However, it needs further prospective study. Therefore, the concerned stakeholders should give due attention, and appropriate intervention for these predictors.

Keywords: First seven days; Low-birth-weight; Predictors; Respiratory distress syndrome.

Strengths and limitations of this study

- This study was conducted in multi-centers (5 hospitals), and it covers a diverse population, which increases generalizability and shows the relationship between exposure and outcome variables.
- Due to its retrospective nature, important variables ~~this study has certain limitations,~~ such as maternal nutritional status, family income, and Educational level, ~~which~~ were missed.
- -In addition, the hospital's service context and supplies were not assessed.

Background

Respiratory distress syndrome (RDS) is one of the major catastrophic and challenging respiratory problems among Low Birth Weight (LBW) neonates (1, 2). RDS has a devastating course with different morbidity, and it escalates to mortality (3, 4). Among LBW neonates ~~This e-problem is the causes~~ significant ~~cause of~~ admission ~~to the in~~ Neonatal Intensive Care Unit (NICU) ~~among LBW neonates~~ ranging from 24.9-62.96% (2, 3, 5-7), and 31.3% of ~~death~~ ~~them died~~ in the perinatal period (8).

According to the American Academy of Pediatrics (AAP), 15% of term, and 29% of preterm neonates admitted to NICU develop RDS (9). The burden of this respiratory problem is high in low-income and middle-income countries, notably, in Southeast Asia and Sub-Saharan African countries, including Ethiopia (10). In East Africa, RDS is a common morbidity and it increases the probability of mortality three times in low birth weight neonates (4).

The magnitude of RDS among Low birth weight neonates varies across countries depending on the availability of medical services and the number of trained medical personnel. For instance, in Taiwan 60-86% (11, 12), ~~in~~ Finland 76% (13), ~~in~~ Thailand 70.7% (14), Karachi, Pakistan 11-12.8% (15, 16), Iran 76% (17), ~~in~~ Afghanistan 58.8% (18), and in Nigeria 10.9% (19) of Low birth weight neonates had RDS. In Ethiopia, RDS is the primary cause of admission with a mortality rate of 45.3% among low birth weight neonates (20). These studies ~~documented~~ showed that different ~~many casual~~ factors increase the ~~likelihood-risk~~ of ~~developing~~ respiratory

distress syndrome among LBW neonates. Accordingly, maternal diabetes mellitus ([DM](#)) ([21-23](#)), hypertension ([21](#)), mode of delivery ([18, 21, 22, 24, 25](#)), sex ([12, 18, 21, 22, 24](#)), prematurity ([12, 18, 21, 22](#)), multi-parity ([24](#)) birthweight ([12, 18, 22](#)), antenatal steroid ~~use~~ ([12, 26](#)), Hyperglycemia ([27](#)), Sepsis ([18](#)), Antepartum Hemorrhage ([APH](#)) ([18](#)), Premature Rupture of Membrane (PROM) ([18, 28](#)), first, and fifth minute ((Appearance, Pulse, Grimace, Activity, Respiration) ([APGAR](#))) score ([29](#)) were significant predictors of RDS.

To alleviate this problem and reduce newborn morbidity and mortality, World Health Organization (WHO) recommends the use of antenatal corticosteroid therapy for risky women, Kangaroo mother care, Continuous Positive Airway Pressure (CPAP), tocolytics for preterm labor, [and](#) optimal oxygen therapy ([30](#)). Furthermore, the Federal ministry of health has given due attention in the expansion of high ~~impact~~-quality neonatal care to reduce neonatal morbidity like RDS ([31](#)). Despite these efforts, RDS continues to be a major public health problem by increasing neonate suffering, and mortality, and escalating economic expenditures in low-income and middle-income countries, including Ethiopia.

~~Even though, there are Some~~ studies ~~were conducted~~ regarding RDS inclusive of all neonates, ~~However, s~~Studies regarding RDS, notably among low birth weight neonates were limited in ~~Ethiopia~~~~the study setting~~. Hence, this retrospective study aimed to assess the ~~i~~ncidence and predictors of respiratory distress syndrome among Low birth weight in the first seven days of life in Northwestern Ethiopia Comprehensive Specialized Hospitals. The findings of this study will provide new insight for different stakeholders, and it will help health professionals ~~to~~ understand the significant predictors of RDS ~~in NICU~~. Additionally, it will serve as baseline information for future studies, and it will give clues to mobilize resources toward the predictors ~~of~~ RDS.

Methods

Stud design, and period

An ~~—~~ institution-based multi-centered retrospective follow-up study was carried out from [September 19, 2021, to January 1, 2023 \(the data were retrospectively extracted from January 5 to February 19, 2023\).](#)

Study setting

The study was conducted in the Neonatal Intensive Care Unit (NICU) of Northwest Ethiopia Comprehensive Specialized Hospitals. These hospitals are the University of Gondar Comprehensive Specialized Hospital (UoGCSH), Felege hiwot, Tibebe Ghion, Debre Tabor, and Debre Markos Comprehensive Specialized Hospital. UoGCSH is found in Gondar town, this hospital has an average annual admission of 697 LBW in their first week of life. Felege hiwot and Tibebe Ghion CSH are found in Bahir Dar city, These hospitals have an average annual admission of 675, and 683 LBW neonates in their first week of life respectively. Debre Tabor CSH is found in Debre Tabor town, with an average annual admission of 560 LBW neonates in their first seven days of life. Debre Markos CSH is found in Debre Markos town, with an average annual admission of 594 LBW early neonates. These hospitals have NICUs with different health professionals (Pediatricians, neonatologists, General practitioners, Comprehensive Nurses, pediatrics, and Neonatal Nurses). This team in collaboration provides a diagnosis of the neonate's problem and holistic care including documentation. –The major services in the NICU ~~ward~~ of these Hospitals include general neonatal care services, blood and exchange transfusion, phototherapy, ~~and~~ ventilation support such as Continuous Positive Air Pressure (CPAP), and other routine neonatal care.

Study population

All LBW neonates in the first seven days of life admitted to the NICU of Northwest Ethiopia comprehensive specialized hospitals were the source population.

All low birth weight neonates in the first seven days of life admitted to the NICU of Northwest Ethiopia Comprehensive Specialized Hospitals from September 19, 2021, to January 1, 2023, were taken as a study population.

Inclusion and exclusion criteria

LBW neonates in the first week of life who were admitted to NICU from September 19, 2021, to January 1, 2023, were included, Whereas, Neonates with an incomplete chart (outcome status and charts with one missed predictor of the following (gestational age, birth weight, neonatal age, sex, type of pregnancy, date of admission, and discharge)), and Neonates with major Respiratory and Cardiovascular malformation were excluded.

Sample size determination and sampling procedure

The minimum required sample size was determined using the single population proportion formula by considering the following statistical assumptions $z_{\alpha/2}$ = The corresponding Z score of 95% CI, and d = margin of error (5%), and proportion of RDS(P) (50%). The proportion of RDS was taken as 50% because there were no previous studies regarding the incidence of RDS among LBW neonates in the study setting. ~~regarding the incidence of RDS among LBW neonates.~~

Therefore,
$$n = \frac{(Z_{\alpha/2})^2 p(1-p)}{d^2} \quad n = \frac{(1.96)^2 (0.5)(0.5)}{(0.05)^2} \quad \text{So, } n=384.16$$

Then, ~~the~~ incompleteness of medical records (Chart attrition) was taken as 10%. Accordingly, the final estimated sample size ~~were was~~ $422.576 \approx 423$. So, a total of 423 medical records of LBW neonates were reviewed. The total sample size was proportionally allocated to each hospital. Then the neonate's chart was selected by a simple random sampling technique using ~~a~~ computer-generated random number.

Variables of the study

Dependent variable: Respiratory Distress Syndrome (RDS) in the first seven days of life. It was dichotomized into RDS (event of interest=1) and censored (no RDS=0).

Independent variables: Includes 1) Socio-demographic, Medical, and obstetric characteristics of mothers of LBW neonates such as ~~variables such as~~ maternal age, place of delivery, residence, ~~type~~ type of pregnancy, gravidity, PROM, APH, mode of delivery, preeclampsia, Ante-Natal Care (ANC) follow-up, corticosteroid administration, DM, Chronic Hypertension~~HTN~~, HIV/AIDS, Anemia, and 2) neonate's clinical, and other characteristics such as sex of the neonate, age of the neonate, Perinatal Asphyxia (PNA), ~~RDS,~~ sepsis, jaundice, hypothermia, hypoglycemia, Necrotizing Enter colitis (NEC), 1st & 5th minute APGAR score, breastfeeding, congenital anomalies, Intra Uterine Growth Restriction (IUGR), birth weight, and gestational age.

Operational Definition

Low birth weight: Weight at birth less than 2,500 grams regardless of gestational age (32).

Respiratory distress syndrome: It is defined as the presence of the following two or more signs: abnormal respiratory rate, expiratory grunting, nasal flaring, and chest wall recession with or without cyanosis (33).

Event: LBW neonates who develop respiratory distress syndrome during the follow-up.

Censored: LBW neonates who did not develop respiratory distress syndrome, discharged against medical advice, ~~died~~, transferred/referred, and lost the follow-up during the follow-up.

Extremely low birth weight: Neonates born with less than 1000 grams of birth weight (32).

Follow-up time: The time from admission to NICU to either death or censorship occurs.

Prematurity: Neonate born before 37 completed weeks of gestational age (34).

Very low birth weight: Neonates born with (1000-1499 grams) of birth weight (34).

Data abstraction checklist and procedures

The data were collected ~~by~~ using ~~aa~~ data abstraction checklist ~~which was~~ adapted by reviewing different literature (2, 34-37) ~~(Error! Reference source not found. Supplementary file 1)~~. The neonates were followed from the time of admission until either the events of interest ~~were~~ developed or censored. The data were collected retrospectively by 5 BSc nurses and Supervised by 5 experienced BSc nurses. ~~Then, the~~ required number of neonates' medical charts was selected by a simple random sampling technique.

Data quality control

To ensure the quality of the data, the data abstraction checklist was evaluated by a research expert, and, a pretest was done on 5% of the sample size. ~~Based on the pretest findings and~~ necessary modifications were ~~done~~ ~~made based on the pretest findings~~. One-day training was given to data collectors and supervisors about the purpose of the study, the data collection tool, data collection methods, and ethical concerns during data collection. All the collected data were checked for completeness and consistency by the data collector and supervisors.

Data processing, and analysis

Data were entered into Epi-Data version 4.6.0.6, and exported to STATA version 14 statistical software for cleaning, coding, and analysis. Descriptive measures such as mean with standard deviation, median with interquartile range, percentage, and frequency~~yies~~ were used to characterize the data.

The incidence rate of RDS was calculated for the entire follow-up by dividing the total number of new cases of LBW neonates with RDS by the total ~~personneonates~~-days of follow-up (time at risk). Kaplan Meier failure curve was used to estimate the time to develop RDS. The log-rank test was employed to compare statistical differences between independent variables. The Proportional Hazard Assumption (PHA) was checked using both graphical and hypothesis tests (Schoenfeld residual test) for all predictors, and it revealed that the PHA was satisfied. The log-likelihood and Akaike Information Criteria (AIC) were applied to select the best-fitted model, and a model with minimum AIC was considered the best-fitted model. Based on this, the Weibull regression model with the (AIC=713.5962) value was the ~~best-best~~-fitted model. In addition, the goodness of model fitness was also checked using the Cox-Snell residual test, and it was close to the 45-degree line. Variables having a P-value <0.25 in the bi-variable analysis were fitted into the multivariable Weibull regression model. Hazard ratios with 95% CI, were used to determine the strength of the association. Variables having a p-value < 0.05 in multivariable analysis were considered statistically significant.

Patient and Public involvement

In this study, the study participants/Public were not directly involved in the design, conduct, reporting, and dissemination of this work.

Results

Socio-demographic, medical, and obstetric characteristics of mothers of LBW neonates

A total of 423 LBW neonates' charts were reviewed, and 405 (95.74%) met the enrollment criteria. In this study, two-thirds of the mothers 274(67.65%) were in the age group of 21-34 years old with a mean of 27.4(SD±6) years old, and 226 (55.80%) were from Urban areas.

Among the total enrolled mothers, 301~~2~~ (74.~~32~~~~57~~%) had given birth through spontaneous vaginal delivery, and ~~in three-fourths~~ 304 (75.06%) of pregnancies; ~~304 (75.06%)~~ were singleton.⁵ In this study, ~~the majority of mothers~~ 375 (92.59%) had ANC follow-ups in nearby health institutions, and one-fourth ~~of them~~ 203 ~~302~~ (26.68~~75.557~~%) ~~of them~~ had preeclampsia. Moreover, ~~185 (24.31%)~~ 82 (20.25%) ~~of~~ mothers had taking corticosteroid treatment, and 16(4.69%) had HIV/AIDS infection ([Table 1/](#)~~Table 1~~)

Table 1: Socio-demographic, medical, and obstetric characteristics of mothers of low birth weight neonates admitted at NICU of Northwest Ethiopia CSH from (September 19, 2021, to January 1, 2023) (N=405).

Variables		Frequency	Percent
Maternal age	≤20 years	66	16.30
	21-34	274	67.65
	≥35	65	16.05
Residence	Urban	226	55.80
	-Rural	179	44.20
Place of delivery	Health institution	389	55.80
	Out-of-health institution	16	44.20
ANC follow up	Yes	375	92.59
	No	30	7.14
Types of Pregnancy	Single	304	75.06
	Multiple	101	24.94
Mode of delivery	SVD	301 2	74. 32 57
	Instrumental	16	3.95
	Cesarean section(SC)	88 7	21. 73 48
Gravidity	Prim gravida	78 9	19.26
	Multi gravida	327	80.74
Preeclampsia	Yes	302	75.57
	No	103	24.43
Corticosteroid treatment	Yes	82	20.25
	No	323	79.75

PROM	Yes	55	13.58
	No	350	86.42
APH	Yes	41	10.12
	No	364	89.88
Chronic hypertension	Yes	12	2.96
	No	393	97.04
Maternal DM	Yes	3	0.74
	No	402	99.26
Maternal HIV infection	Reactive	196	4.69
	Non-reactive	386	95.31
Maternal anemia	Anemic-Yes	5	1.23
	Non-Anemic-No	400	98.77

ANC: Ante Natal care, PROM: Premature Rupture of Membrane, APH: Ante Partum Hemorrhage, SVD=Spontaneous Vaginal Delivery, CS=~~e~~Cesarean section. DM: Diabetes mellitus, HIV: Human immune deficiency virus, CSH=Comprehensive Specialized Hospital, NICU= Neonatal Intensive Care Unit.

Clinical and other characteristics of LBW neonates.

In this study, ~~above-over~~ half of the participants; 218 (53.83%) were male, and 279 (68.89%) were admitted within 24 hours of birth. Regarding birth weight, three-fourths of neonates were between 1500~~,-~~ and 2499 grams with a median weight of ~~+7150~~ 1715 (IQR: 800,2478)~~+550 IQ~~. Above two-thirds 279 (68.89%) of neonates were premature, and the ~~median-mean~~ gestational age was 34.7 weeks with ~~an~~-(IQRSD±3.3). The common medical problems among LBW early neonates were sepsis 283(69.88%), ~~and-~~ hypothermia 155(38.27%)~~,-~~ ~~and Low fifth minute APGAR score 366 (90.37%)~~ The ~~Other common~~ other common medical problems include jaundice, PNA, NEC, IUGR, hypoglycemia, and ~~other~~ congenital ~~anomaly-anomalies~~ (Table 2~~Table 2Table 2~~).

Table 2: Clinical and other characteristics of low birth weight early neonates admitted to Northwest Ethiopia CSH from September 19, 2021, to January 1, 2023) (N=405).

Variable		Frequency	Percent
Sex	Male	218	53.83

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	Female	187	46.17
Age of the neonate	≤1	66 279	46.30 68.89
at admission in days	2-3	27 476	67.65 18.77
	4-7	65 50	46.05 12.35
Gestational age	< 37	-279	68.89
in a week	≥37	126	31.11
Birth weight	≤999	21	5.19
	1000-1499	84	20.74
	1500-2499	300	74.07
Breast-feeding	Yes	384	94.81
	No	21	5.91
First-First -minute APGAR Score	<7	153	37.78
	≥7	252	62.22
Fifth-minute APGAR score	<7	46 39	11.36 9.63
	≤≥7	359 366	88.64 90.37
Sepsis	Yes	283	69.88
	No	122	30.12
PNA	Yes	56	13.83
	No	349	86.17
NEC	Yes	17	4.20
	No	388	95.80
Jaundice	Yes	61	15.06
	No	344	84.94
Congenital anomaly	Yes	22	5.42
	No	383	94.57
Hypothermia	Yes	155	38.27
	No	250	61.73
IUGR	Yes	17	4.20
	No	388	95.80

Hypoglycemia	<u>Hypoglycemic</u> Yes	14	3.46
	<u>Non-hypoglycemic</u> No	391	96.54

APGAR= Appearance, Pulse, Grimace, Activity, Respiration, PNA=Perinatal Asphyxia,
NEC=Necrotizing Entero colitis, IUGR=Intrauterine growth restriction.

Proportional hazard assumption test ~~by Schoenfeld test~~

The proportional hazard assumption was checked using the Schoenfeld residuals test. ~~individually and simultaneously (globally).~~ The test showed that the P-value for each covariate and the whole covariates simultaneously were above 0.05 (P-value= (0.6298)).

Incidence of Respiratory distress syndrome, and Overall ~~survival~~ outcome of the follow-up.

In this study, the neonates were followed for up to 7 completed days of age starting from the date of admission. The total number of neonate days' observations during the entire ~~follow-up~~ was 1771 neonate day observations. The total neonate's day observation (1771) was the sum of each neonate's time at risk during the follow-up (i.e. the sum of the length of time in day each neonate was followed during the study). ~~During the follow-up~~ From the total enrolled LBW early neonates, during the follow-up 47.16% (95% CI: 42.80-52.55) developed the event of interest (RDS). The proportion of RDS was 38.37% for the University of Gondar Comprehensive Specialized Hospital, 50.00 % for Feleghiwot Comprehensive Specialized Hospital, 43.24% for Tibebe Ghion Hospital, 58.14% for Debre Markos Hospital, and 45.07% for Debre Tabour Comprehensive Specialized Hospital.

In this study, the overall incidence rate of RDS was found to be 10.78 per 100 neonates' day observation (95% CI: 9.35-12.42). The incidence of RDS at the end of 24 hours, 2nd, 3rd, 4th, 5th, 6th, and 7th days were 52.63, 26.72, 16.66, 10.63, 9.5, 7.99, and 5.91 per 100 neonate's day observation respectively. Similarly, the incidence of RDS among ELBW (<1000gm), VLBW

(1000-1499gm), and LBW (1500-2499) was 25.39, 18.98, and 8.26 per 100 neonate's day observation respectively (Table 3).

Table 3: Incidence rate to birth weight, and number of follow-up days among Low-birth weight neonates in Northwest Ethiopia CSH from September 19, 2021, to January 1, 2023) (N=405).

Variables	Category	RDS	Rate with (95% CI) per 100
Birth weight	ELBW	15	25.39 (15.55-41.45)
	VLBW	60	18.98 (14.74-24.45)
	LBW	118	8.26 (6.88-9.18)
Number of follow-up days	1 day	30	52.63 (36.80-75.27)
	2 day	31	26.72 (18.79 -38.00)
	3 day	23	16.66 (11.07-25.08)
	4 day	18	10.63 (6.60-17.09)
	5 day	19	9.5 (6.05-14.89)
	6 day	23	7.99(5.07-12.01)
	7 day	48	5.91(4.45-7.84)
Total Incidence density			10.78 (9.35-12.42).
ELBW=Extremely Low Birth Weight , VLBW=Very Low Birth Weight, LBW=Low Birth Weight			

-Overall failure function (Survivorship Function)

In this study, the median length of hospital stay was 6 days (95% CI: 6-7), and the maximum follow-up time was 7 days. The overall Kaplan Meier failure function showed that the probability of developing RDS was increasing as follow-up time increased. —The cumulative probability of developing RDS at the end of the 1st day was 0.1630 (0.1304 —0.2027), at the end of the 3rd was 0.3383 (0.2945—0.3866) and at the end of the 7th day was 0.7704 (0.7284–0.8100) (Figure 1).

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Comparison of failure function for some variables.

In this study, neonates having ELBW (<1000gm) and VLBW (1000-1499gm) had a higher risk of developing RDS than low birth weight neonates (1500-2499gm). The mean hazard time for EVLBW, ~~and~~ VLBW was 3.36 days, and 4.11 days respectively, as compared to those LBW neonates with a mean hazard time ~~to~~ of 5.52 days. This study also revealed that premature neonates had a higher risk of developing RDS as compared with their counterparts. The mean hazard time to develop RDS was 4.84 days. Furthermore, Neonates with ~~low-fifth-minute~~ APGAR scores less than 7 (~~<7 APGAR score~~) had a higher probability of developing RDS as compared with their counterparts. These differences were statistically significant with a (P-value ≤ 0.0006) in the log-rank test ([Error! Reference source not found. Supplementary Figure 4](#))

Model comparison, and diagnostics

To select the most parsimonious models for the data set, a comparison of ~~both~~ the semi-parametric and parametric hazard models was done statistically using [Akaike and Bayesian](#) information criteria (AIC, BIC) and graphically using the Cox-Snell residual test. Based on this, the Weibull regression model with (AIC=713.5962) was the parsimonious model than the parametric exponential (AIC=772.3843), Gompertz (AIC=721.98), and semiparametric Cox proportional hazard models (AIC=2064.185). So, all of the interpretations in this study were using the Weibull regression model.

The goodness of fit for the fitted model was also checked using the Cox-Snell residual test, and as shown in the figure Weibull regression model was adequate ([Figure 2Figure 2](#)).

Predictors of Respiratory Distress Syndrome

In the bi-variable Weibull regression, sex, mode of delivery, preeclampsia, PNA, NEC, IUGR, first, and fifth-minute APGAR score, birth weight, gestational age, and type of pregnancy were associated with RDS (p-value < 0.25). However, in the multi-variable Weibull regression analysis only five variables were significant predictors of RDS (P-value < 0.05). Accordingly, the hazard of developing RDS was 1.43 times (AHR=1.43; 95% CI:1.04-1.96) higher among neonates with multiple births as compared to singleton births. Similarly, Neonates with ~~low~~

APGAR scores less than 7 at the fifth minute were 1.86 times (AHR=1.86;95% CI:1.18-2.92)) more likely to develop RDS as compared to neonates with highnormal-APGAR scores.

Moreover, neonates delivered via cesarean section were 62% times (AHR=0.62; (95CI:0.41-0.93)) more likely to develop RDS as compared to their counterparts. Additionally, Neonates with birth weights less than 1000gm. and 1000-1499 gm. were three times (AHR=3.14; (95% CI:1.81-5.40)) & twice (AHR=2.06;(95% CI:1.42-2.83)) at high risk of developing RDS as compared with their counterparts respectively. Finally, this study found that LBW early neonates who are preterm were 1.56 times (AHR:1.56;(95% CI:1.06-2.30)) at a higher risk of developing RDS as compared to that of term neonates. (~~Table 3~~Table 4)

Table 443; Bi-variable and multivariable Weibull regression analysis for predictors of RDS among low birth weight neonates in their first seven days ~~week~~ of life ~~admitted to NICU of in~~ Northwest~~ern~~ Ethiopia Comprehensive Specialized Hospitals from September 19, 2021, to January 1, 2023 (n=405).

Variable	Status		CHR(95%CI)	AHR(95%CI)
	Event	Censored		
Sex				
Male	95	123	0.78 (0.59-1.03)	0.82 (0.61-1.10)
Female	98	89	1	1
Mode of delivery				
Instrumental <u>assisted</u>	6	10	0.50 (0.22-1.13)	0.48 (0.205-1.32)
<u>delivery</u>	35	53	0.60 (.42-0.87)	0.62 (0.41- 0.93) **
CS ss	152	149		1
SVD				
Type of pregnancy				
Multiple	6058	413	1.50 (1.10-2.04)	1.43(1.04-1.96) **
Single	133	171		1
Preeclampsia				
Yes	52	51	1.17(0.85 1.61)	1.14 (0.80-1.62)
No	141	161	1	1

PNA				
Yes	28	28	1.24(0.83-1.85)	1.26 (0.82-1.94)
No	165	184	1	1
NEC				
Yes	10	7	1.44 (0.76-2.72)	1.40 (0.73-2.69)
No	183	205	1	1
IUGR				
Yes	5	13	0.39 (0.14-1.03)	0.67(0.24-1.86)
No	188	199	1	1
First-minute APGAR score				
<7	85	68	1.48 (1.11-1.97)	1.08 (0.77-1.51)
≥7	108	144	1	1
Fifth-minute APGAR score				
<7	32	14	1.94(1.33- 2.83)	1.86(1.18-2.92) ***
≥7	161	198	1	1
Gestational age in weeks				
<37	156 161	123 2	2.09 (1.43-3.05)	1.56(1.06-2.30) **
≥37	375 2	89 0	1	1
Birth weight				
≤999	157	6	3.52 (2.11-5.86)	3.14 (1.81-5.40) ***
1000-1499	605 9	24	2.43(1.78-3.33)	2.06 (1.42-2.83) **
1500-2499	118 7	182	1	1
NB: ***= Significant variable with p-value=0.00 & **=p-value≥0.001-0.05, 1= reference				

DISCUSSION

This study aimed to assess the incidence of respiratory distress syndrome, and its predictor among low birth weight neonates admitted to Northwest Ethiopia Comprehensive Specialized Hospitals. Accordingly, this study found that at the end of the follow up 47.16% (95% CI: 42.80-52.55) of neonates developed RDS. This finding was aligned with studies conducted in Thailand

(44.15%) (38), and Ethiopia 49.8 3% (39), The possible justification is due to similarities in study design, sample size, and the presence of similar maternal health problems. On the other hand, this study was higher than two different studies conducted in Pakistan 11%-12.8 (15, 16), India 38% (40), Nepal 21.4% (41), and Nigeria 10.9% (19), The possible reason for this discrepancy is due to exclusion criteria. In those studies, neonates with any type of congenital disorders, and intrauterine infection were excluded. But, the present study didn't exclude those neonates. The second possible reason might be the diagnostic criteria, in those studies they diagnose and include neonates who develop RDS within four hours of birth. Whereas, the present study considers neonates who develop RDS at any time of age during the follow-up. In addition to the above reasons, it might be due to the presence of skilled/trained medical teams in NICU across different departments to provide essential newborn care and postnatal care (42). Furthermore, it might be due to their advanced NICU setups, like the availability of bubble CPAP, surfactant therapy, and advanced treatment technologies (43).

In contrast to the aforementioned studies, the present study was lower than studies conducted in Iran 76% (17), Taiwan 60-86.5% (11, 12), Thailand 70.7% (14), Finland 76% (13), and Afghanistan 58.8% (18). This marked difference might be attributed to study subject recruitment criteria, because ~~thoseat-study studies~~ includes only very low birth weight and very preterm neonates, so due to anatomical and physiological organ immaturity the probability of RDS could be high (34, 43). Whereas, the present study includes all categories of LBW and all categories of gestational age. The second possible explanation could be in those studies the magnitude of maternal morbidity like DM, and pre/eclampsia was high (23, 43). In addition, in those studies, Congenital anomalies were high in percentage, whereas in the present study, it was ~~low~~ small (18).

In this study, the incidence of RDS was found to be 10.78 per 100 neonate's day (95% CI: (95% CI: 9.35-12.42) with 1771 neonate day observations. The incidence of RDS at the end of 24 hours, 2nd, 3rd, 4th 5th, 6th, and 7th days were 52.63, 26.72, 16.66, 10.62, 9.5, 7.98, 5.91 per 100 neonate's day observation respectively. Similarly, the incidence of RDS among ELBW (<1000gm), VLBW (1000-1499gm), and LBW (1500-2499) was 25. 39 (95%CI: 15.55-41.45), 18. 98 (95%CI: 14.74-24. 45), and 8.26 (95%CI: 6. 88-9.18) per 100 neonate's day observation respectively. Accordingly, the incidence of RDS was high, and the highest incidence rate of RDS

was observed within 24 hours of birth, this is due to the difficulty of adapting to the extra uterine environment secondary to Anatomical and physiological organ immaturity (33), and Lack of ~~appropriate~~ quality care immediately after birth (33, 43). Moreover, it might be due to antenatal, and intrapartum birth complications too (1).

Being delivered through Caesarean section is an independent predictor in this study and raises the risks of RDS in neonates with low birth weights. This finding is supported by Studies conducted in France (44), China (45, 46), Taiwan (47), Korea (25), Qatar (48), and Egypt (21). The possible justification is the residual amount of lung fluid in newborns who were delivered by cesarean section is greater, they produce less surfactant to the alveolar surface, and their lung fluid clearance is delayed (49, 50). The other justification is following a cesarean section, amiloride-sensitive sodium channels in alveolar epithelial cells are less active, which results in impaired fluid evacuation (51).

In agreement with studies conducted in Taiwan (12), Afghanistan (18), Saudi Arabia (21), and China (28), Prematurity is a predictor of RDS. This is explained by due to inadequate surfactant production or inactivation of surfactant in the context of immature lungs. Due to this, the synthesized Surfactant is not adequate to maintain alveolar stability, and this leads to atelectasis, and the neonate develops RDS (33, 34, 52). In addition, premature neonates are more vulnerable to different medical problems like hypothermia, hypoglycemia, sepsis, NEC, and other comorbidities while, this increase the probability of developing RDS (39, 43).

This study revealed that multiple pregnancy was an independent predictor of RDS. This finding is supported by a study conducted in China (53), the reason for this occurrence is due increased risk of preterm labor and preterm birth in multiple births, and the neonate delivered before their ~~bodies and~~ organ systems become completely matured (54). The other possible justification is multiple neonates have a higher risk of getting congenital anomalies, and Intrauterine Growth Restriction (IUGR), which increases the risk of RDS (43).

The current study found that a Low APGAR score <7 at the 5th minute is an independent predictor of RDS among low birth weight neonates. This finding is supported by different studies conducted in China (55), Indonesia (56), and Saudi Arabia (2). The possible reason for this is a low APGAR score, which- is defined as asphyxia, and asphyxia at birth can cause direct harm to alveolar type II epithelial cells and impair the generation of surfactant, which will raise the

incidence of RDS. Additionally, the following two factors are the other reasons for this: Hypoxia decreases pulmonary surfactant activity and may even lead to its inactivation, whereas severe birth asphyxia diminishes pulmonary surfactant synthesis and secretion (28).

Being born extremely very low and very low birth weight increases the hazard of respiratory distress syndrome among low birth weight neonates. This finding is supported by different studies conducted in China (51), Indonesia (56), Vietnam (57), and Saudi Arabia (2). The possible justification for this is a lack of surfactant caused by lung immaturity is one example of the physiological and anatomical immaturities that can occur in newborns who have low birth weight (58). The other reason is as birth weight decreases the risk of exposure/ vulnerability to various medical problems like hypoglycemia, Sepsis, and cold stress increases (34, 43). Hence, these medical problems individually, or simultaneously increase the risk of developing RDS(43).

The present study has the following limitations: Due to its retrospective nature, some important variables, such as maternal nutritional status, family income, and Educational level, were missed. In addition, the hospital's service context and supplies were not assessed.

Conclusion

The current study showed that the incidence of RDS was higher than other studies conducted on other groups of neonates. And high incidence rate was seen among extremely low birth weight and very low birth weight neonates. Fifth-minute APGAR score, caesarian section, Multiple births, prematurity, extremely low birth weight, and very low birth weight were significant predictors of respiratory distress syndrome. Hence, Health care providers and other concerned stakeholders should give due attention, and appropriate intervention for Low birth weight neonates with the aforementioned preventable, and treatable factors. Furthermore, a prospective follow-up study needs to be conducted to assess the true association of predictors.

Acronym and Abbreviations: - APGAR: Appearance, Pulse, Grimace, Activity, Respiration, CS: Caesarean Section, CSH: Comprehensive Specialized Hospital, ELBW: Extremely Low Birth Weight Neonates, LBW: Low Birth weight, NICU: Neonatal Intensive Care Unit, RDS: Respiratory Distress Syndrome, VLBW: Very Low Birth Weight

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Contributors: WTW: contributed to the conceptualization, Methodology, data acquisition, data interpretation, formal analysis, and writing of the original article. DEA.GTD, GDG, ATG, and YTK were involved in the Planning, supervision, Visualization, writing –reviewing& editing. BTL, GBM, ABZ, AEB, and CAW contributed to the conceptualization, methodology, data acquisition, critical revision, and data interpretation.

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Competing interest: ~~None declared~~ The authors declare no competing interest.

~~**Patient and public involvement:** The patient and/or public were not involved in the design, conduct, or reporting of this work.~~

Patient consent for publication: Not applicable

Ethical approval: Ethical approval was obtained from the Institutional Review Board (IRB) of the School of Nursing, College of Medicine and Health Science, University of Gondar with reference No. (Ref.no. SN/231/2014 E.C). The IRB of the School of Nursing, College of Medicine and Health Science has waived informed consent of the medical records of the neonates. The letter of permission was obtained from each Comprehensive Specialized Hospital clinical director and head of the unit. To maintain confidentiality personal identifiers (name, MRN) were not recorded. All of the procedures were carried out by considering the Helsinki Declaration.

Data availability statement: The data set used for this study is available upon reasonable request.

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Figure 1: The overall Kaplan Meier failure estimate curve with a 95% confidence interval showing the time of developing Neonatal RDS in Northwest Ethiopia Comprehensive Specialized Hospital,2023.

Figure 2: The Cox-Snell residual test of Weibull regression for Incidence of RDS.

Authors Response to the Editor, and Reviewers Concern

Title: “Incidence and Predictors of Respiratory Distress Syndrome among Low Birth Weight Neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals, 2023; A retrospective follow-up study”.

Manuscript ID: bmjopen-2023-079063

Date: October,19, 2023.

Subject: Revision of the manuscript

Thank you very much dear editor and reviewers for your insightful and comprehensive comments. We found that the comments are very helpful and constructive to further improve the manuscript. This is a point-by-point response of authors to reviewers' concern about a manuscript entitled “Incidence and Predictors of Respiratory Distress Syndrome among Low Birth Weight Neonates in the First Seven Days in Northwest Ethiopia Comprehensive Specialized Hospitals, 2023; A retrospective follow-up study” which has a Submission identification of “bmjopen-2023-079063” given by the journal. It is known that the manuscript has been reviewed by reviewers and sent back to the authors for revision and resubmission. As authors of this manuscript, the comments and concerns raised by the reviewers and editor were highly insightful suggestions and enabled us to improve the quality and plausibility of the manuscript. To do so, we have addressed all of the reviewer's concerns point by point. Therefore, we are very much pleased to resubmit the revised version of the manuscript for further revision process and facilitation of its publication on BMJ Open.

We look forward to hear from you at your earliest convenience.

With best regards.

On behalf of Co-authors.

Wubet Tazeb Wondie (Corresponding Author)

On behalf of Co-authors

Editor(s)' Comments and Authors Response

Concern 1: Please work to improve the quality of the writing throughout your manuscript. We recommend asking a colleague who is proficient in written English to assist you; alternatively, you could enlist the help of a professional copy editing service.

Authors Response: Thank you very much dear editor for your Golden suggestion. We have accepted and tried to correct the revised version of the manuscript.

Concern 2: Please revise the 'Strengths and limitations of this study' section of your manuscript (after the abstract) by using bullet points.

Authors Response: Thank you for your suggestion. We have accepted and corrected in the revised version of the manuscript.

Concern 3: Please ensure that you have fully discussed the methodological limitations of the study in the Discussion section of the main text.

Authors Response: Thank you for your Constructive comment. We have accepted and corrected the revised version of the manuscript.

Concern 4: Please include a statement whether or not the data charts were de-identified.

Authors response: Thank you dear editor for your valuable concern. We already included the de-identification process in the method and Ethical approval section. To make it clear, Records have a re-identification code, but any personal identifier information were **not recorded (i.e. personal identifier information was removed)**. And recorded information does not identify an individual.

Dear Editor, thank you for your Golden suggestions. If something is unclear/wrong, please let me know again!

Point-by-point Response Letter

Dear editorial office of BMJ open we have presented our point-by-point response in a way that the reviewers' concern is depicted first, and the authors' response has been given immediately next to it.

Reviewer 1(Dr. Razieh Sangsari): Concerns and authors response

Concern 1: The date of your study in the method of abstract is wrong.

Authors Response: Thank you dear reviewer for your golden suggestions. We have accepted and corrected in the revised version of the manuscript.

Concern 2: The sentences in the text are very similar to the references please correct similarity.

Authors Response: Thank you for your concern. We have accepted, and corrected in the revised manuscript.

Concern 3: You wrote in Iran 76% (17) of Low birth weight neonates had RDS, but the reference of that describes the cause of mortality rate in LBW infant in Iran.

Authors Response: Thank you dear reviewer for your concern. But Reference 17 is about both mortality and morbidity of Neonates with birth weight 1500 or below with Gestation age of 30 weeks or below. "*Navaei F, Aliabady B, Moghtaderi J, Moghtaderi M, Kelishadi R. Early outcome of preterm infants with birth weight of 1500 g or less and gestational age of 30 weeks or less in Isfahan city, Iran. World Journal of Pediatrics. 2010;6(3):228-32.*"

Concern 4: Respiratory Distress Syndrome (RDS) manifests in early hours of birth not the first seven days of life.

Authors Response: Thank you for your concern: As you have said RDS occurs in the early hours of birth, But, in our country due to a lack of appropriate postnatal follow-up care, these neonates develop RDS in the first seven days of life. In addition, in our study there were several comorbidities like PNA, sepsis...., these comorbidities cause respiratory epithelial cell injury, and inactivation of surfactant in the context of immature lung which increases the risk of developing RDS in the first seven days of life.

Concern 5: You must also write the complete word the first time you write the abbreviation

word. **Authors Response:** Thank you dear reviewer for your concern. We have accepted, and corrected in the revised manuscript.

Concern 6: Congenital anomalies should be exclusion criteria not independent variables.

Authors Response: Thank you for your golden Concern. As you have said We exclude neonates with major respiratory and cardiovascular anomalies, but we include other congenital anomalies.

Concern 7: In 65 cases age of the neonate at admission were in days 4-7 days but RDS manifests in early hours of birth not 4-7 days maybe that's why the disease is more in your study.

Authors response: Thank you for your Concern. As we have mentioned above, in this study, there were several comorbidities, so these comorbidities like perinatal asphyxia could cause inactivation of surfactant in the context of immature lung. In addition to this, some comorbidities (mainly sepsis) induce respiratory epithelial cell injury. Therefore, all of these factors increase the occurrence and exacerbation of RDS in our study.

Dear reviewer, thank you for your constructive concerns. If something is unclear/wrong, please let me know again!

Reviewer 2 -Dr. Shuping Han: Concerns and Authors response

Concern 1: In Page 9 line 53, the number of median weight is far above normal level of birth weight.

Authors Response: Thank you dear reviewer for your valuable concerns. It was an editorial problem and We have accepted and corrected in the revised version of the manuscript.

Concern 2: In Page 9 line 55, it is suggested to uniform the writing style of IQ.

Authors Response: Thank you for your concern. It was an editorial problem, and We have accepted and corrected in the revised version of the manuscript.

Concern 3: In Page 12 line 40, the author should provide the detail of the calculation of neonate day observation, how to get the number of 1771?

Authors response: Thank you for your golden suggestion. We have accepted, and corrected in the revised manuscript.

Concern 4: Why the author selected the first 7 days of life in this study? Whether this caused the missing of Clinical and other characteristics of LBW neonates, including the mortality of LBW neonates?

Authors response: Thank you dear reviewer for your concern. Due to organ immaturity, RDS occurs in the early hours of life. But in the presence of different comorbidities like PNA, Sepsisit occurs after a certain hours of life (Up to seven days of life), because these

comorbidities contribute to surfactant inactivation and respiratory epithelial cell injury after a certain hours/days of birth, probably up to seven days of life. So, we emphasis on the first seven days of life.

Regarding the missing of clinical and other characteristics of LBW neonates, including mortality, as we have mentioned above RDS occurs in the early age of life, most of the clinical characteristics and other contributing factors for RDS occurrence were available, and we assessed during the data collection, and consider them as a predictor.

Concern 5: It is suggested to supplement the relevant weakness of this study in Discussion.

Authors response: Thank you for your concern. We have accepted and included the relevant weakness of the study in the discussion section.

Dear reviewer, thank you for your valuable suggestions. If something is unclear/wrong, please let me know again!

Reviewer 3: Dr. Jackson Maina- Concerns and Authors response

Concern 1: Under the study setting the authors would need to provide some more background on who provides the care in these units e.g., is it neonatologists, or trainee doctors; this may have a bearing on the diagnosis and documentation in the clinical records. Also, information about the clinical records were these are paper-based or electronic medical records? has a bearing on the level of missing data.

Authors response: Thank you dear reviewer for your valuable concern. We have accepted and tried to include it in the revised manuscript. But to make it clear, the neonatal care in these hospitals were provided in team including Neonatologists, General practitioners, Comprehensive Nurse, , Pediatrics Nurses and Neonatal Nurses etc. Regarding the diagnosis, it is mainly done by Neonatologists and General practitioners, and the documentation were paper-based and made by the team.

Concern 2: I propose the authors write the abbreviations used in the report in full when first used e.g., the abbreviations on page 7 of the report need to be written in full.

Authors Response: Thank you dear reviewer for your suggestions. We have accepted and corrected in the revised version of our manuscript.

Concern 3: I suggest the data collection tool described on page 6 be added as supplementary material in this manuscript. Also describe more on how maternal data were collected, seeing presumably the charts we primarily neonatal data.

Authors response: Thank you for your dear reviewer for your concern. We have added it as supplementary material.

Regarding maternal data, in neonatal history the maternal profile and comorbid conditions were taken from the mother and were well documented in the neonate's chart (medical record). So important variables are available in the neonate's Chart and taken from it.

Concern 4: Under the results sections, I propose the authors edit tables 1 and 2. For example, binary outcomes "Yes" or "No" may be worth stating one instead of both. Also please explain all the abbreviations in the footnotes e.g., on page 10 the abbreviation PNA is not described.

Authors Response: Thank you dear reviewer for your concern. We have accepted and tried to correct it, but it is the nature of the variable's response.

Regarding the Abbreviation, we have accepted and corrected it in the revised manuscript.

Concern 5: In the diagnoses, I presume one baby may have had several disease conditions which may mimic the signs of RDS, perhaps worth presenting the diagnoses in a Venn diagram to help the readers understand the disease patterns better.

Authors response: Thank you for your valuable concern. As you have said, some neonates had several disease conditions. But When the neonates have two or more signs of respiratory distress syndrome it is diagnosed as RDS and if other comorbid conditions present, it is considered as additional comorbidity. So, the presence of other comorbid conditions is common, and Known, and it doesn't confuse readers.

Concern 6: For the diagnosis, I suggest the authors describe if these were admission diagnoses or any diagnoses during the babies' stay in the unit.

Authors response: Thank you dear reviewer for your suggestion. Regarding the diagnosis, we follow the neonates from the date of admission up to the seventh day of life. Starting from the admission date at any time they may develop RDS. So the diagnosis can be made at any time during the follow-up, not only admission date diagnosis.

Concern 6: On page 11, lines 44-53, this is very crucial information that can be better displayed as a table to allow the readers to better understand the outcome of interest in the study.

Authors Response: Thank you for your Golden suggestion. We have accepted and corrected it in the revised version of the manuscript.

Concern 7: For Table 3, I propose the authors look at the denominators again for some of the variables e.g., the numbers on mode or delivery differ slightly from what was described in the baseline data table.

Author Response: Thank you for your Golden suggestion. We have accepted and corrected in the revised manuscript.

Concern 8: In the results section, these are data from hospitals in different regions in Ethiopia, I wonder if there are any significant differences between these regions worth mentioning in this paper?

Author Response: Thank you dear reviewer your Suggestions. We have accepted and corrected in the revised manuscript.

Concern 9: The discussion section is clear and well written.

Authors Response: Thank you, dear reviewer.

Dear reviewer, thank you for your Golden suggestions. If something is unclear/wrong, please let me know again!

We thank the Editor and reviewers for their constructive suggestions.

Data abstraction checklist to assess Incidence and predictors of RDS

Data abstraction checklist to assess Incidence and Predictors of respiratory distress syndrome among low birth weight neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals, 2023; A retrospective follow-up study.

Instructions: Circle the possible responses or write them in the space provided corresponding to each question.

Hospital name -----

Name of data collector----- signature-----

Name of supervisor-----signature-----

Code of the questionnaires.....

Part I: Socio-demographic, medical, and obstetric characteristics of mothers of LBW neonates

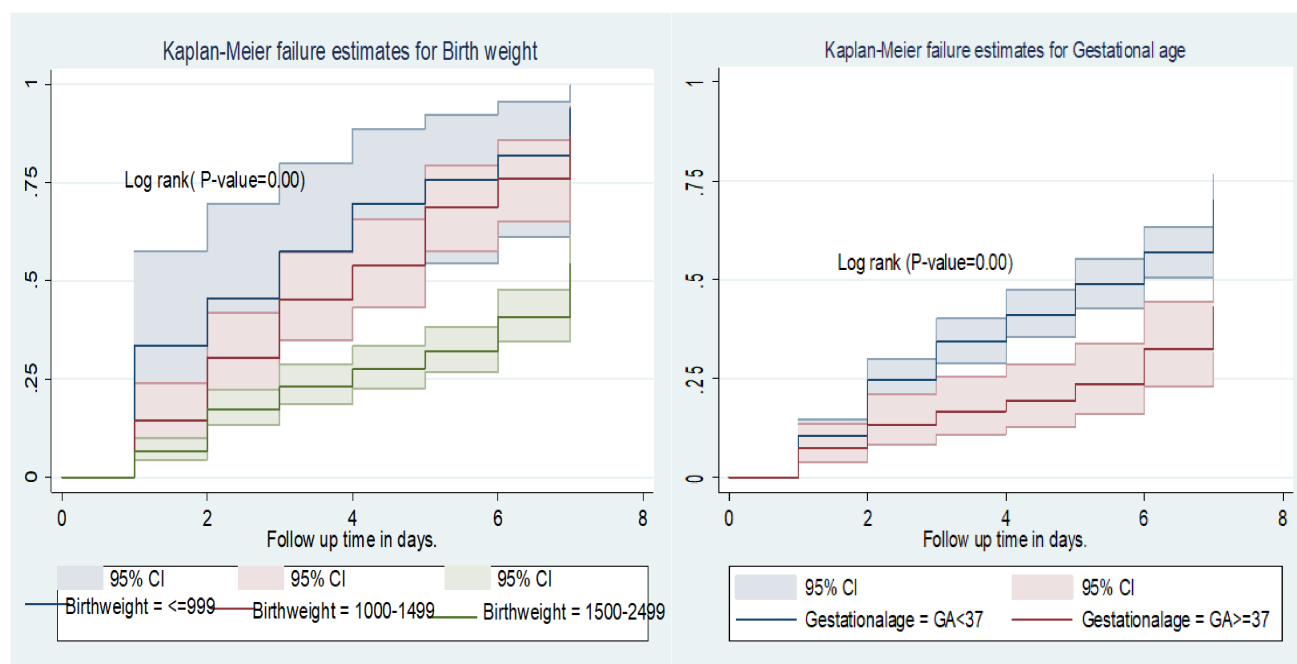
Code No	Variables	Response	Remark
101	Age of the mother	————— in yr.	
102	Residence	1.Urban 2. Rural	
103	Place of delivery	1. Health institution 2. Out of Health institution	
104	Does the mother have ANC follow up	1. Yes 2. No	
105	Mode of delivery	1.Spontaneous Vaginal Delivery (SVD) 2.Instrumental assisted 3.C/S	
106	Type of pregnancy	1. Single 2. Multiple	
107	Gravidity in number		
108	Parity in number?		
109	Does the mother take corticosteroid treatment in the last pregnancy?	1. Yes 2. No	

1010	Does the mother have Preeclampsia	1. Yes 2. No	
1011	Does the mother have a history of PROM in the last pregnancy?	1. Yes 2. No	
1012	Did the mother have bleeding during pregnancy (APH) in the last pregnancy?	1. Yes 2. No	
1013	Did the mother have CHTN	1. Yes 2. No	
1014	Maternal DM	1. Yes 2. No	
1015	Maternal HIV infection	1. Yes 2. No	
1016	Maternal Anemia	1. Anemic 2. Non-Anemic	

Part II: Clinical and other characteristics of LBW neonates..

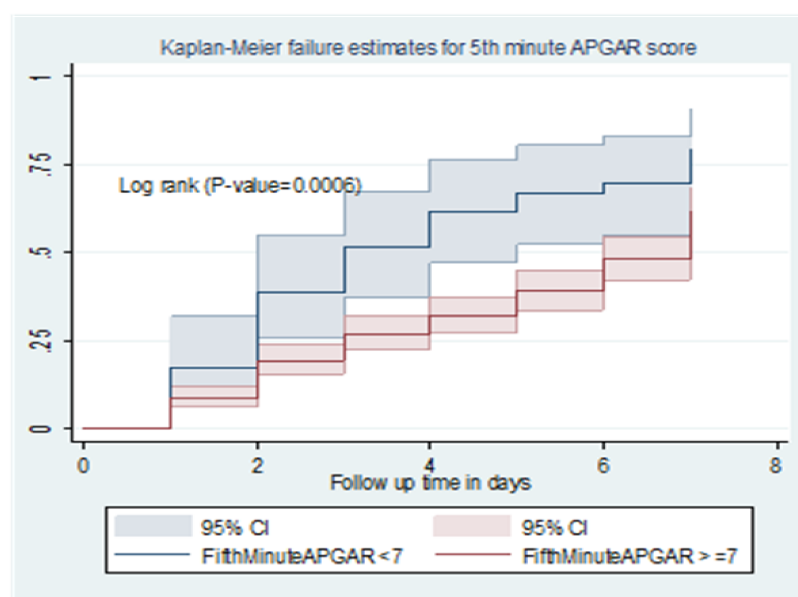
Code no	variables	Response	Remark
201	Age of the neonate on admission	————— in day.	
202	Sex of the neonate	1. Male 2. Female	
203	First-minute APGAR score		
204	5 th minute APGAR score		
205	Birth weight (in grams).	————.	
206	Gestational age of the neonate?	———— in week/day.	
207	Breastfeeding	1. Yes 2. No	
208	Common neonatal illnesses? (Multiple responses)	1. PNA. 2. Sepsis 3. RDS 4. Jaundice 5. NEC 6. Congenital anomalies	

		7. Hypo/hyperthermia 8. IUGR	
209	Random blood sugar at admission in mg/dl		
Part III: Outcome-related variables (Follow-up measures).			
301	Date of admission to NICU in DD/MM/Yr. in G.C	____/____/____ G.C	
302	Follow-up outcome of the neonate	1. RDS 2. Died 3. Discharge 4. Transferred in / referred 5. Left against medical advice 6. End of follow up	
303	Date of RDS diagnosis DD/MM/YY in G.C	____/____/____ G.C	
304	Date of censoring DD/MM/Yr. in G.C	____/____/____ G.C	
305	Total no of days the neonate has been followed (Length of hospital stay)?	_____in days	



A)

B)



C)

Supplementary figure 1: The Kaplan Meier failure estimates of low birth weight early neonates with respect to (A) Birth weight, (B); Gestational age, (C); Fifth minute APGAR score in Northwest Ethiopia CSH, from September 19, 2021, to January 1, 2023 (n=405).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No	Relevant text from the Manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1	Retrospective follow-up study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	A Retrospective follow-up study was conducted from September 19, 2021, to January 1, 2023 , among 423 low birth weight neonates in Northwest Ethiopia Comprehensive Specialized Hospitals. A Simple random sampling technique was used. The Data were collected using a data extraction checklist from the medical registry of neonates. The collected data were entered into EPI-DATA 4.6 and analyzed using STATA version 14. The Kaplan-Meier failure curve and Log-rank test were employed. Bi-variable and multivariable Weibull regression was carried out to identify predictors of respiratory distress syndrome. Statistical significance was declared at a P-value of ≤0.05 Result: The incidence rate of Respiratory distress syndrome was found to be 10.78 (95% CI: 9.35-12.42) per 100 neonate days. Fifth minute APGAR score <7 (AHR=1.86;95% CI: 1.18-2.92), Multiple pregnancy (AHR=1.43;95% CI:1.04-1.96), Caesarean section delivery (AHR=0.62; 95%: 0.41- 0.93)), prematurity (AHR=1.56;95% CI: (1.06-2.30)), and birth weight < 1000gram (AHR=3.14;95% CI:1.81-5.40) and 1000-1499 gram

				(AHR=2.06;95% CI:1.42-2.83); 95% CI:) were significant predictors.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4	
Objectives	3	State specific objectives, including any prespecified hypotheses	2	To assess the incidence of respiratory distress syndrome among low birth weight neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals,2023. To determine predictors of respiratory distress syndrome among low birth weight neonates in the first seven days in Northwest Ethiopia Comprehensive Specialized Hospitals,2023.
Methods				
Study design	4	Present key elements of study design early in the paper	4,	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5,6,7	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment	4,5, 6	

		and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> — For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> — For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6&7	Respiratory distress syndrome: It is defined as the presence of the following two or more signs: abnormal respiratory rate, expiratory grunting, nasal flaring, and chest wall recession with or without cyanosis Event: LBW neonates who develop respiratory distress syndrome during the follow-up.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at	6	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7&8	
		(b) Describe any methods used to examine subgroups and interactions		
		(c) Explain how missing data were addressed		
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		Censored: LBW neonates who did not develop respiratory distress syndrome, discharged against medical advice, transferred/referred and lost the follow up during the follow-up.
		(e) Describe any sensitivity analyses		

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive	14	(a) Give characteristics of study	9-14	

data	*	participants (eg demographic, clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	11&12	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	11	During the follow-up from the total enrolled LBW early neonates 47.16% (95% CI: 42.80-52.55) were developed the event of interest (RDS). In this study, the overall incidence rate of RDS was found to be 10.78 per 100 neonates' day observation (95% CI: 9.35-12.42).
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives	13-17	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any	1	

		potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17	
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18	Funding not applicable

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.