

# Clinical outcome and associated factors of respiratory distress syndrome among preterm neonates admitted to the neonatal intensive care unit of Adama Hospital and Medical College

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## Abstract

**Objective:** Aim of the study was to assess the clinical outcome and associated factors of respiratory distress syndrome among preterm neonates admitted to the neonatal intensive care unit of Adama Hospital and Medical College.

**Methods:** Hospital-based cross-sectional study was conducted using 242 randomly selected medical records of preterm neonates admitted to Adama comprehensive specialized hospital. Clinical outcome was categorized as poor if the neonate died or left against advice and good if discharged after improvement. Data were coded, entered into Epidata v.7.4.2 and exported to SPSS v.27 for analysis. After initial bi-variable logistic regression analysis, predictor variables with *p*-value of <0.2 were included in multivariable analysis. Significant association of factors with clinical outcome was claimed at *p*-value <0.05 and calculated 95% adjusted odds ratio.

**Results:** Majority of admissions were male (63.2%), mean birth weight of 1440.3g (+321.2SD) and sepsis (82%), hypothermia (73%), and apnea (21.5%) were leading comorbidities. One hundred fifty-two (62.8%) of preterm neonates had poor outcomes. Neonates born singleton were 47% less likely to develop poor clinical outcomes (adjusted odds ratio 0.53 (0.48–0.94)). The odds of poor clinical outcomes were higher during the first 3 days of admission (adjusted odds ratio 3.83 (3.28–14.77)). Extremely preterm neonates (adjusted odds ratio 4.16 (4.01–12.97)), extremely low birth weight preterm neonates had higher odds of poor clinical outcome.

**Conclusion:** The study found higher poor clinical outcome among preterm neonates admitted with respiratory distress syndrome. Poor outcome was higher in lower gestational age, lower birth weight, twins and majority of it happened during 3 days of their life. Effective preventive care and initiation of low-cost, life-saving interventions including heated humidified high-flow nasal cannula and surfactant administration could significantly improve the clinical outcome of the neonates.

## Keywords

Preterm neonates, respiratory distress syndrome, neonatal mortality, clinical outcome

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## Introduction

World Health Organization defined preterm birth as all births before 37 weeks of gestation or <259 days from the last normal menstrual period of the women.<sup>1</sup> Preterm births are further classified as extreme preterm (<28 weeks), very preterm (28–31<sup>6/7</sup> weeks), moderate (32–33<sup>6/7</sup> weeks), and late preterm (34–36<sup>6/7</sup> weeks).<sup>2,3</sup>

Every year, an estimated 15 million infants are born preterm, and it is increasing globally.<sup>4</sup> The rate of survival and morbidities of preterm babies indicate the quality of care at

the health facilities. Despite progress in the advancement of care and survival rate of preterm neonates, there is still a long way to go for lower- and middle-income countries (LMICs),<sup>5,6</sup>

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For instance, 90% of preterm neonates born before 28 weeks of gestational age die in LMICs, compared to <10% in developed nations.<sup>7</sup> In Ethiopia, prematurity is the leading (34%) cause of neonatal deaths and the fourth (11%) cause of under-five mortality.<sup>8,9</sup>

Respiratory distress syndrome (RDS) is a neonatal respiratory disorder that appears shortly after birth.<sup>10</sup> It is one of the most common causes of admission to the neonatal intensive care unit (NICU) and respiratory failure in neonates. Neonatal mortality attributable to RDS is evident in all complications of prematurity.<sup>11</sup> RDS accounted for a preterm newborn death rate of 12.8% in Poland, 46.9% in Nigeria, and 45% in Ethiopia.<sup>12–14</sup> Another study reported that the preterm newborn death rate in hospitals in low-resource countries ranged from 40% to 60% and the majority have only oxygen therapy.<sup>15</sup> However, a case fatality rate of 100% in a community-based setting was also reported.<sup>16</sup> In Ethiopia, RDS is the leading cause of morbidity and mortality in preterm neonates.<sup>17,18</sup>

Access to early screening and adequate care could save a three-quarter of preterm neonates with RDS.<sup>19</sup> Caring for the critically ill neonate in developing countries is a challenge, where health needs often surpass available resources including infrastructures. Despite WHO recommendation of surfactant replacement therapy for preterm neonates with RDS, high flow nasal oxygen administration and corticosteroid therapy for the at-risk mother, the trend in its morbidity and mortality is increasing.<sup>3,20,21</sup> Respiratory distress syndrome in premature neonates typically manifests as a double burden due to comorbidity with major neonatal killers. For instance, various studies reported leading comorbidity as neonatal sepsis (26.1%–71%), hypothermia (63%), and apnea of prematurity (28.6%).<sup>22–25</sup> Beyond the impact of RDS on the neonate, the family and health system itself suffer repercussions.<sup>26</sup>

Despite significant reduction in under-five mortality in Sub-Saharan Africa, neonatal mortality is still stagnant.<sup>27–30</sup> In Ethiopia, few studies reported varying levels of mortality and identified compound fetal presentation during delivery, longer duration of hospitalization, male sex as the factors associated with RDS mortality in preterm neonates.<sup>31,32</sup> There is a dearth of evidence on its clinical outcomes and examining broader associated factors; specifically among preterm newborns. As RDS often manifests alongside co-morbidities, a more thorough identification of the predictors of good or poor clinical outcome is essential to filling a crucial void in medical care. The findings highlight the contributions of RDS-related preterm newborn mortality to the slow decline in neonatal mortality in Ethiopia. Therefore, this study aimed to assess the admission outcome of RDS and its associated factors among preterm neonates admitted to the NICU of Adama comprehensive specialized hospital.

## Methods and materials

### Study area and period

The study was conducted in the preterm neonates' unit of Adama comprehensive and specialized hospital medical college's NICU. It is found in Adama town, 99 km South-East of the capital, Addis Ababa, Ethiopia. The town is found in East Shewa zone of Oromia region situated between the western foot of an escarpment and the Eastern Great Rift Valley. National census of 2007 reported total residents of the town as 388,925 of which 196,407 are males.<sup>33</sup> There are 8 public health facilities in the town (one hospital, the rest health centers), 9 private hospitals, 6 non-governmental health centers, and 104 private clinics. The hospital serves an estimated five million catchment and surrounding population, and also serves as a teaching center for specialty programs (Pediatrics, Internal Medicine, general surgery, and Gynecology and obstetrics), and other general medical fields. It has a 212-bed capacity of which 77 beds are allocated for NICU. The hospital has admitted 659 preterm neonates with RDS during the past 3 years (1 January 2019–31 December 2021), with an average of 18 cases per month. The study period was from 7 February to 7 March 2022.

### Study design

A retrospective, hospital-based cross-sectional study design was used.

### Population and eligibility criteria

The source population was all preterm babies who were admitted to the NICU of Adama Hospital and Medical College with RDS. The total preterm admitted for RDS during the 3 years retrieved from the register was 659 admissions. The study population was randomly selected preterm neonates admitted to a preterm unit with RDS for 3 years (1 January 2019–31 December 2021). All preterm babies admitted with RDS regardless of the place of delivery were included while those whose medical record was not found and were incomplete were excluded. Preterm neonates having any form of congenital anomaly and birth weight >2500 g were excluded.

### Sample size and sampling procedure

The sample size was calculated by single population proportion formula using assumptions of 95% confidence level, 5% margin of error and estimated good clinical outcome from RDS was 50.5%.<sup>34</sup> However, after adjustment using the correction formula the final sample size was 242. Systematic random sampling with a sampling interval of three was used to select preterm neonates' records using their medical record numbers.

### Data collection method and tool

A pre-designed structured checklist was used to collect data on the variables of the study. The checklist was adapted from two studies,<sup>9,26</sup> and includes socio-demography, neonatal, intrapartum and maternal obstetric factors. Four medical interns collected data and one public health expert supervised the task. One of them retrieved the medical record number of preterm neonates treated for RDS from the NICU registration book and three filled the tool queries using the record checklist.

### Data quality management

The three data collectors and a supervisor were trained for a day on the objective of the study, sampling procedures and ethical issues. The principal investigator monitored data completeness daily. Before actual data collection, the checklist was pretested on 5% (13 records of preterm babies with RDS) in a similar unit, but in a different period. After checking for clarity, sensitivity, and consistency, necessary amendments were adopted. Two data clerks entered data separately and were cross-checked for its consistency.

### Statistical analysis

Data were coded and entered into Epi-info v7.2.4.0, exported and analyzed using IBM SPSS statistics *Version.27*. The study used assumptions of 95% confidence interval, 5% margin of error and significance level of  $p$ -value of  $<0.05$  in computing crude odds ratio (COR) and adjusted odds ratio. The initial association of variables with the outcome variable was analyzed using bivariate logistic regression and those with a  $p$ -value of  $<0.2$  was included for multiple variable logistic regression. Multi-collinearity was checked by using variance inflation factors and tolerance test. Finally, multiple binary logistic regression was used to determine the independent association of each predictor variable to the outcome variable at a significance level of  $p$ -value  $<0.05$ . Model fitness was assessed using Hosmer-Lemeshow tests and Omnibus tests of coefficients.<sup>35,36</sup> Descriptive statistics including frequencies, mean, standard deviation, and percentage were used to summarize the findings and presented using tables and charts.

### Study variables and operational definitions

Discharge outcome of the preterm neonate was outcome variable dichotomized as good if discharged alive after improvement and poor if dead or left against medical advice. Independent variables were sex, age on admission, gestational age, birth weight, appearance, pulse, grimace, activity and respiration (APGAR) score (at the first and fifth minute), length of hospital stay (from admission up to occurrence of either of clinical outcomes), place of delivery, mode of

delivery and also maternal factors including the number of gestations, parity, history of obstetric complication, preventive corticosteroid therapy, and full antenatal care. Range of fifth minute APGAR score used high for poor outcome (4–6), normal (7–10), and unknown for those outborn babies or lacking record.<sup>37</sup>

- ❖ **RDS:** formerly known as “hyaline membrane disease,” is chiefly in premature neonates characterized by the deficiency of surfactant coating the inner surface of the lungs resulting in labored breathing and lung collapse. In this study, any clinically or radiographically diagnosed preterm neonates treated with RDS were included. Clinical diagnosis referred to signs of respiratory distress (grunting, nasal flaring, chest indrawing, inter/sub-costal retractions, and cyanosis), decreased oxygen saturation, and decreased breath sound on auscultation. Chest X-rays conducted were seldom suggestive of low lung volume, diffuse, bilateral and symmetrical granular opacities and air-bronchograms.
- ❖ **Obstetric complications:** is the presence of at least one maternal obstetric illness including placental abruption, Chorio-amnitis, PROM, antepartum hemorrhage, pre-eclampsia and others listed in national guideline.

### Ethical clearance

The ethical review committee of the Adama Hospital and Medical College granted ethical approval and waived informed consent. In addition, a formal letter of cooperation from the college aided in accessing the patient medical record.

### Result

#### *Socio-demographic and clinical characteristics of preterm neonates*

The majority (63.2%) of preterm neonates admitted with RDS were male with a male to female ratio of 1.6:1 and more than half of them 140 (57.9%) were born to mothers residing in the rural area. Two hundred thirty-four (96.7%) preterm neonates were admitted with RDS during the first 3 days of their life and had a mean birth weight of 1440.3g ( $\pm 321.2$  SD). The most common gestational age at birth was very preterm category ( $n = 114$ ; Table 1).

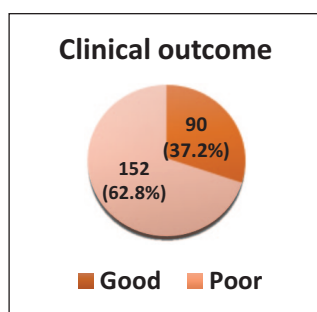
#### *Clinical outcome of preterms admitted with RDS*

Of the overall preterm admissions with RDS, the majority (62.8%) had poor clinical outcomes and 90 (37.2%) were discharged with a good outcome or after clinical improvement (Figure 1).

**Table 1.** Socio-demographic, clinical characteristics and outcomes of preterm neonates admitted with RDS at Adama Hospital and Medical College, Ethiopia ( $n = 242$ ).

Variables	Categories	Frequency
		No (%)
Sex of neonate	Male	153 (63.2)
	Female	98 (36.8)
Age at admission	Birth-24 h	234 (96.7)
	24.1–72 h	4 (1.7)
	>72 years	4 (1.7)
Gestational age at birth(weeks) Mean 31.12 weeks (+ 2.3 SD)	Late preterm (34 to <37)	38 (15.7)
	Moderate preterm (32 to <34 weeks)	84 (34.7)
	Very preterm (28 to <32 weeks)	114 (47.1)
	Extremely preterm (<28 weeks)	6 (2.5)
Birth weight Mean = 1440.3 g(+321.2 SD)	LBW (1500 to <2500 g)	113 (46.7)
	VLBW (1000 to <1500 g)	120 (49.6)
	ELBW(<1000 g)	9 (3.7)
APGAR score At fifth minute	4–6	59 (24.4)
	7–10	168 (69.4)
	Unknown	15 (6.2)
Length of stay (7.13 days + 8.9 SD)	0–3	100 (41.3)
	4–7	72 (29.8)
	>7	70 (28.9)

\*APGAR: appearance, pulse, grimace, activity and respiration; LBW: LBW; VLBW: very low-birth weight; ELBW: extremely low-birth weight.

**Figure 1.** A pie chart showing clinical outcomes of preterm neonates admitted with RDS.

### Comorbidity pattern among preterm neonates admitted with RDS

Sepsis was the most common comorbidity presenting concomitantly in 82.6% of preterm babies with RDS, followed by hypothermia 179 (73.9%) and apnea 52 (21.5%) respectively (Figure 2).

### Maternal obstetric and Intra-partum factors

In this study, the mean age of mothers was  $33.22 \pm 4.93$ (SD) years and the majority (45%) of them were in the age group of 18–24 years. More than three-fold of them (78.1%) gave birth to singleton, 137 (56.6%) were para-I and only a few

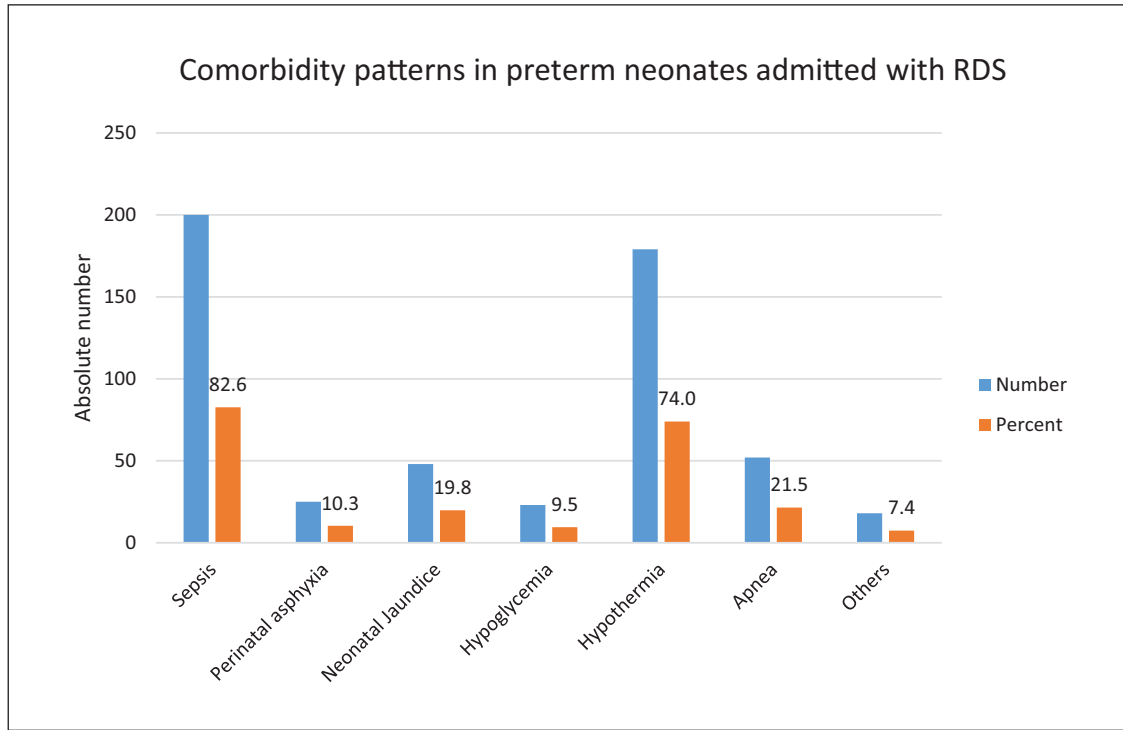
(2.9%) lacked any antenatal care visit. The majority of mothers 154 (63.6%) had no previous history of obstetric complications and 198 (81.8%) received prenatal corticosteroid therapy. Two hundred thirty-two (95.9%) women delivered their newborn at a health institution, of which 195 (80.6%) were through spontaneous vertex delivery (Table 2).

### Predictors of clinical outcome of preterm newborns admitted with RDS

After bi-variable logistic regression 10 variables from neonatal clinical and socio-demographic characteristics, maternal obstetric history, and intrapartum factors having a  $p$ -value  $\leq 0.2$  were fitted into the final model. Then, the number of gestations, APGAR score at the fifth minute after birth, hospital stay, gestational age, and birth weight were significantly associated with clinical outcome, whereas the age of the mother, parity, maternal history of antenatal and corticosteroid therapy, and mode of delivery were not significantly associated with clinical outcome (Table 3).

### Discussion

This study aimed to assess the admission outcome of RDS and its associated factors among preterm neonates admitted at the NICU of Adama comprehensive specialized hospital from 1 January 2019, to 31 December 2021. Preterm neonates born



**Figure 2.** Bar graph showing common comorbidity patterns of preterm neonates admitted with RDS. Sum is more than 100% because of more than one comorbidity per case.

**Table 2.** Obstetric and intrapartum characteristics of mothers of preterm neonates admitted with RDS at dama Hospital and Medical College, Ethiopia (n = 242).

Variables	Categories	Frequency No (%)
Age of mother Mean age 24.79(SD ± 4.93)	<18	18 (7.4)
	18–24	109 (45.0)
	25–34	104 (43.0)
	>35	11 (4.5)
Number of gestations	Single	189 (78.1)
	Multiple	53 (21.9)
Parity	Para-I	137 (56.6)
	Para-II–IV	93 (38.4)
	Para-V and more	12 (5.0)
Maternal hx of obstetric complications	Yes	154 (63.6)
	No	88 (36.4)
Corticosteroid therapy	Yes	198 (81.8)
	No	44 (18.2)
ANC follow-up	Yes	235 (97.1)
	No	7 (2.9)
Place of delivery	Health institution	232 (95.9)
	Home	10 (4.1)
Mode of delivery	SVD	195 (80.6)
	Assisted (breech, instrumental)	4 (1.7)
	C/S	43 (17.8)

Abbreviations: ANC: antenatal care; Hx: history; SVD: spontaneous vertex delivery; C/S: cesarean section.

twin, lower APGAR score at fifth minute after birth, lower extremes of birth and gestational ages and length of hospital stay were significantly associated with poor clinical outcomes. This study showed that 62.8% of preterm neonates admitted with RDS had poor clinical outcome.

This finding is higher compared to other countries including Nepal (6.3%), Sudan (41%), Tanzania (20.8%), and Ghana (39.27%).<sup>38–41</sup> However, this finding is in line with reports from other studies.<sup>7,42,43</sup> The similarities and differences could be partly due to varying healthcare systems, quality of perinatal care, and advancement of technologies in the prevention and management of RDS in preterm neonates. In addition, delayed presentation of the outborn preterm neonates to health facility, inadequate dose coverage of corticosteroid therapy for pregnant mothers at risk of preterm birth, and non-invasive respiratory support (unavailable heated humidified high-flow nasal cannula (HHHFNC) and irregular use of nasal continuous positive airway pressure (nCPAP)) had contributions.

The study revealed that RDS was higher (63.2%) in male preterm neonates. This is consistent with studies from Egypt and Poland.<sup>44,45</sup> This might be because, during gestation, the female fetal lung produces surfactant earlier than the male as a result of androgen delaying lung fibroblasts secretion of fibroblast-pneumocyte factor and estrogen mediation of fetal lung development by increasing alveolar type II cells.

Poor outcomes were more likely in preterm neonates born with <7 APGAR score at fifth minute after birth compared to those with higher score. This is consistent with studies



**Table 3.** Bi-variable and multivariable logistic regression of predictors of clinical outcome among preterm babies admitted with RDS at Adama Hospital and Medical College, Ethiopia ( $n=242$ ).

Variables	Response category	Clinical outcome		COR 95%CI	AOR 95%CI	p-Value
		Poor	Good			
Number of gestation	Single	74	115	0.79 (0.16–0.88)	0.53 (0.48–0.94)	0.002
	Multiple	16	37			
APGAR score at five minutes after birth	Unknown	12	3	2.21 (1.54–12.36)	1.87 (1.24–6.91)	0.04
	4–6	43	16	3.42 (3.22–10.48)	4.62 (4.19–9.26)	0.03
	7–10	97	71			
Length of hospital stay (days)	<3	96	4	2.71 (2.11–8.25)	3.83 (3.28–14.77)	0.016
	3–7	47	25	3.49 (2.93–13.49)	1.65 (1.09–9.48)	0.039
	>7	9	61			
Gestational age (weeks)	<28	5	1	3.75 (3.10–8.81)	4.16 (4.01–12.97)	0.001
	28–31.9	84	30	3.51 (3.06–14.26)	2.29 (2.13–9.74)	0.019
	32–33.9	45	39	4.21 (2.97–16.21)	1.61 (0.33–6.81)	0.054
	34–37	17	21			
Birth weight	<1000	9	0	4.29 (2.97–11.49)	5.771 (4.67–12.95)	0.022
	1000 to <1500	95	25	1.66 (1.19–12.31)	2.81 (1.94–7.86)	0.006
	1500 to <2500	48	65			

Abbreviations: APGAR: appearance, pulse, grimace, activity, and respiration; COR: crude odds ratio; AOR: adjusted odds ratio.

conducted in Brazil and USA.<sup>46,47</sup> This is attributable to asphyxia causing reduced cardiopulmonary fraction and its association to sympatho-adrenal activity at birth.<sup>48,49</sup>

Preterm babies born singleton were less likely to develop poor outcome compared to twins. This is similar with findings of other studies.<sup>50,51</sup> This could be due to higher risk of second twin to asphyxia, growth discrepancy, and genetic dispositions at the earlier gestations.<sup>52,53</sup>

The mean length of hospital duration until the occurrence of clinical outcome was 7.13 days  $\pm$  8.9 SD. The greater majority (94%) of poor outcomes from RDS occurred during the first 7 days of admission and 63% in the first 72 h of hospital admission. This is consistent with another study that reported 85% of poor outcome during a week of admission, of which 43% was within the first 3 days of hospital admission with RDS.<sup>54</sup> This implies that initiating care within the first week of neonatal age and strengthening community-based referral strategies for outborn babies will aid in saving the lives of the newborn.<sup>55</sup>

Preterm mortality was four-fold higher among extremely preterm neonates and twice in very preterm neonates compared to moderate preterm neonates. Likewise, similar findings were observed in Orotta Pediatric Hospital of Eritrea and New Haven Hospital United States.<sup>53,56,57</sup> Convergence of the findings could be because the lower their gestational age the weaker their body sustains the sequela of RDS.

In this study, the odds of poor clinical outcome was six-fold in extremely LBW and thrice in very LBW infants compared to moderate LBW. This is higher compared to findings from Ghana and Gitwe district hospital, Rwanda; which reported a 14.3% survival rate in ELBW and 20% in the

VLBW category.<sup>41,51,58</sup> The divergence might be due to geographical differences and varying levels of care quality.

### Strength and limitation

This study used previous 3 years' data which helps endure seasonal variability of cases attributed to delivery season. The findings can be generalizable to similar settings in the country with the same levels of facilities. The study included three records of newborns who left against medical advice as poor outcome; although their status was untraceable. Unlike other studies, the study did not reveal a significant association between mode of delivery, previous history of corticosteroid therapy, and maternal age. Further longitudinal studies starting from the perinatal period might illustrate further real-time inquiries.

### Conclusion

This higher poor clinical outcome of RDS among preterm neonates indicates the major proportion of overall neonatal mortality which is the hallmark of quality of care provided in saving the life of newborns. The identified comorbidities are among the top killers of the neonate, urging for prompt follow-up, care, and intervention. Major factors associated with the clinical outcome are calling to attention the concerted efforts of stakeholders in availing advanced, life-saving services ranging from initiation of surfactant administration to provision of HHHFNC and liaising network of referral among facilities for screening of at-risk mothers for reduction of RDS incidence and complications.

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## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval was obtained from the ethical review committee of Adama Hospital and Medical College (Approval No. AHMC/ER13/13). Informed consent was waived by the committee.


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## Informed consent

Informed consent was waived by the ethics committee for the present study. However, confidentiality of their records has been maintained.

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## Supplemental material

Supplemental material for this article is available online.

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