Original Article

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Incidence, Outcome and Predictors of Mortality in Respiratory distress syndrome (RDS): A Prospective Cohort Study at Tertiary Care Hospital in Nepal

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Abstract

Introduction: With advances in therapies during antenatal and perinatal period, there has been apparent decrease in incidence and mortality due to respiratory distress syndrome (RDS). However, there is paucity of data on exact incidence and outcome of RDS in resource limited setting. This study was conducted with the primary aim to describe the outcome of RDS and analyze the predictors for mortality.

Methods: A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) and Neonatal Unit of Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal from October 2019 to April 2021.

Results: A total of 94 preterm newborns developed RDS giving prevalence of 20.5 per 1000 live birth cohort at TUTH. Incidence of RDS among preterm babies was 14.6%. The median duration of continuous positive airway pressure (CPAP) was 48 hours (Range 8 - 192 hours). Inhospital mortality rate was 15 (15.96%). Lower gestational age and premature rupture of membrane (PROM) were significantly associated with higher mortality whereas Normal Vaginal delivery (NVD) was associated with lower mortality. Logistic regression analysis for risk of dying for the cohort predicted that lower birth weight (AOR = 0.99; 95% CI = 0.99 - 0.99; P = 0:01), sepsis (AOR = 145.14; 95% CI = 5.04 - 4175.15; P = 0:004) are independently associated with increased risk of dying whereas increase duration of NICU stay decreased the risk (AOR = 0.71; 95% CI = 0.54 - 0.91; P = 0:01).

Conclusions: The mortality rate decreases with increasing gestational age and birth weight. A number of neonatal factors, either in isolation or in combination, were significantly associated with in-hospital mortality

Introduction

It is estimated that 15 million babies are born preterm, with 60% occurring in South Asia and sub-Saharan Africa and this number is rising.[1,2] Respiratory distress syndrome (RDS) occurs in 60 - 80% of infants < 28 weeks, 50% of born between 28 – 32 weeks, 15 - 30% of infant 32 - 36 weeks and rarely in those > 37 weeks gestational age.[3,4] The incidence of RDS is reported to be 6.8 - 14.1% of preterm live births and contributed 13.5% of total neonatal deaths in India.[5,6] However, incidence of RDS and its mortality rate has substantially reduced by improved antenatal and intrapartum care of preterm pregnancies. Similarly, optimal respiratory support in the form of continuous positive airway pressure (CPAP) or mechanical ventilation and surfactant replacement therapy

(SRT) has been identified as important interventions that could save many premature babies suffering from RDS.[7,8] But the important fact is that these recommendations are based on published trials done in high-income countries where care for premature babies in neonatal intensive care unit (NICU) is undertaken by trained doctors and nursing staff, facilities for round the clock monitoring, laboratory and radiological services and optimal CPAP devices are available. Without optimal equipment and skilled manpower, it is likely that these therapies may not be as effective and possibly less safe.

It has been more than a decade that CPAP and SRT are in use for the management of RDS at level III NICU in Nepal. However, these technologies for RDS treatment are used inconsistently in different health care settings and there has been wide variation in the optimal care that the newborn receive in NICU.

Thus, it is crucial for us to analyze the impact of providing special care and respiratory support to preterm infants on RDS related survival and to identify important factors contributing to mortality. Therefore, this study was designed with the aim to determine the incidence, describe the outcome and evaluate the predictors of mortality among preterm infant delivered at tertiary care center of Nepal.

Methods

This is a prospective cohort study was conducted over one and half year period between October 2019 to April 2021, at Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal after approval from institutional research committee. All neonates born before 37 weeks of gestation delivered at TUTH and clinically diagnosed as RDS based on the need of respiratory support within six hours for at least for 24 hours were enrolled in the study. Respiratory support was given if at least two out of five clinical signs (Respiratory Rate > 60 / min, expiratory grunting, suprasternal / intercostal / subcostal retraction, cyanosis at room air, flaring of the alae nasi) were present. The neonates were excluded if they were < 22 weeks of age or < 500 gm, and had any one of the following; perinatal asphyxia requiring endotracheal intubation at birth, major or life threatening congenital abnormality, suspected heart disease in antenatal echocardiography, delivered through meconium stained liquor, confirmed diagnosis of congenital pneumonia or early onset (within 72 hours) sepsis. All eligible premature babies fulfilling inclusion criteria and admitted in NICU were enrolled in the study after obtaining written consent from their parents. All these babies were monitored for the signs of respiratory distress using Silverman's Anderson scale and were followed up every day until discharge. A detailed history, clinical examination and hospital course were recorded in pre designed study Performa. Respiratory support for RDS was provided as per the NICU protocol of the department which are as follows

- For newborn < 30 weeks' gestation and less than 1500 gm who do not need intubation for stabilization, was started on prophylactic CPAP immediately after birth even in absence of signs of respiratory distress.

- For newborn > 30 week gestation and more than 1500 gm, they were observed for signs of respiratory distress using Silverman's scoring. If they developed any signs of respiratory distress, they were put on oxygen by head box. If RDS score was ≥ 3 CPAP was started.

All new born started on CPAP were re-assessed every 15 minutes. CPAP was increased up to 7 cm H2O unless RDS score is ≤ 3. Even after nCPAP of at least 7 cm for at least 15 minutes, if the infant requires FiO_2 > 0.30 to maintain oxygen saturation between 88 - 92% or RDS score persistently remain > 3, early rescue surfactant was given. The SRT preferably be given within two hours after birth. Primary outcomes were death or discharge from hospital and the secondary outcome were BPD defined as oxygen dependency at twenty eight days of life. Other outcome includes neonatal sepsis, pneumothorax and retinopathy of prematurity. Data collected were entered into SPSS version 26 for analysis. Descriptive statistics were used for continuous variables whereas frequency listings and percentages were used to describe categorical variables. The log-rank test was used to test for associations among various GA and birth weight categories presented in the Kaplan-Meier survival curves. The Fischer's exact and Pearson's Chi square tests were used to test for associations among socio-demographic and treatment variables with the outcome death. A p-value < 0.05 was considered statistically significant at 95% confidence interval. Multiple logistic regression (odds ratio) was used to determine independent variables for the outcome death.

Results

During the study period, there was 4578 live delivery and among them 644 (10%) were preterm. 94 developed RDS giving prevalence of 20.5 per 1000 live birth cohort. Incidence of RDS among preterm babies was 14.6%. A total of 739 inborn newborns were admitted to NICU and neonatal unit and RDS accounted for 12.7% of all neonatal admissions for the study period. As demonstrated in table 1, among 94 premature neonates with RDS, 49 (52.1 %) were males. The mean gestation was 31.96 ± 2.04 weeks and mean birth weight was 1581.61 ± 430.69 grams. Majority of them were between 28 to < 34 weeks of gestation. Incidence of RDS was highest among preterm babies between 28 to < 32 weeks (80.49%).

Table 1. Neonatal demographic characteristics and maternal risk factors for premature delivery

Characteristics	Study population (N = 119)
Gender Male, n (%) Female, n (%)	 49 (52.1) 45 (47.9)
Mode of delivery NVD, n (%) LSCS, n (%)	 25 (26.6) 69 (73.4)
Birth weight at admission (grams) <1000, n (%) 1000 - 1499 grams, n (%) 1500 - 2500 grams, n (%)	 6 (6.4) 39 (41.5) 49 (52.1)
Mean Gestational age (± SD)	31.96 (2.04)
Gestational age (weeks) < 28, n (%) 28 to < 32, n (%) 32 to < 34, n (%) 34 to < 37, n (%)	 3 (3.2) 33 (35.2) 33 (35.2) 25 (26.6)
Gestational age (weeks) 28 > to < 32 28 to < 34 32 to < 37 34	Mean Birth weight in grams (± SD) 1181.67 (189.24) 1332 (338.73) 1670.91 (376.13) 1841.21 (432.86)
Weight for gestational age according to WHO fetal growth chart Appropriate for gestational age (AGA), n (%) Small for gestational age (SGA), n (% Large for gestational age (LGA), n (%)	 37 (39.4) 53 (56.4) 4 (4.3)
(%) Resuscitation required, n	17 (18.1)
Mean Maternal age (± SD)	28.98 (4.64)
Parity Primgravida, n (%) Multigravida, n (%)	 48 (51.1) 46 (48.9)
Antenatal Steroids Complete, n (%) Incomplete, n (%) None, n (%)	 54 (57.4) 26 (27.7) 14 (14.9)
PROM for more than 18 hours, n (%)	24 (25.5)
Pregnancy Induced Hypertension (PIH), n (%)	29 (30.9)
Gestational Diabetes Mellitus (GDM), n (%)	6 (6.4)

Table 2 shows incidence of RDS and comparison of respiratory support given to neonates according to the gestational age. Incidence of RDS was highest in gestational age between 28 to < 32 weeks (80.49%). Majority of the enrolled preterm babies (86.18%) were managed on CPAP. INSURE was done in 50 (52.6%) babies and one them required repeat dose. There were 15 (15.96%) deaths during the study period with six (40%) occurring within the first week of life.

Table 2. Incidence of RDS and Comparison of treatment in different gestational age

Gestational age (weeks)	< 28 (n = 3)	28 to < 32 (n = 33)	32 to < 34 (n = 33)	34 to < 37 (n = 25)	Total (n = 94)
Incidence of RDS among Preterm babies, (%)	21.43	80.49	40.74	4.93	14.6
Primary respiratory support O^2, only, n (%) CPAP, n (%) Mechanical Ventilation (MV), n (%)	 0 2 (66.7) 1(33.3)	 1 (3.03) 30 (90.91) 2 (6.61)	 4 (12.13) 28 (84.85) 1 (3.03)	 3 (12) 21 (84) 1 (4)	 8 (8.4) 81 (86.18) 5 (5.2)
SRT, n (%)	3 (100)	23 (69.7)	11 (30)	13 (52)	(52.6) 50
MV required, n (%) Primary respiratory support, n (%) CPAP failure, n (%) After 96 hours of life, n (%)	2 (66.7) 1 1 0	14 (42.43) 2 6 6	2 (6.07) 1 1 0	8 (32) 1 5 2	26 (28.43) 5 13 8
Death, n (%) Early Late	2 (66.7) 2	10 (30.31) 4 6	1 (3.04) 1	2 (8) 2	15 (15.96) 6 9

The median duration of CPAP was 48 hours (range 8 - 192 hours). The median duration of hospital stay was 14 days (range 4 - 54 days). The most common complication was sepsis followed by apnea. (Table 3).

Table 3. Duration of respiratory support and Morbidity profile of survived newborns

Duration of respiratory support: Median duration of CPAP (Range) Median duration of MV (Range) Median duration of respiratory support (Range) Median duration of hospital stay	 48 (8 - 192) Hours 96 (32 - 264) Hours 96 (22 - 632) Hours 14 (4 - 54)days
Complications: Retinopathy of prematurity (%) Bronchopulmonary Dysplasia (%) Pneumothorax (%) Sepsis (%) Apnea (%)	 3 (3.2) 1 (1.1) 3 (3.2) 27 (28.7) 10 (12.7)

Survival by gestational age is illustrated in figure 1 by Kaplan Meier graph. For those with GA of 32 weeks and above, survival was 97%, 95% and 95% on day 10, 20 and 30 respectively. However, for those with GA below 32 weeks, survival was 80%, 66% and 61% on day 10, 20 and 30 respectively. From the log rank test, survival distribution of different GA categories comparing those born with a GA of < 32 weeks and ≥ 32 weeks was statistically significant (P = 0.015) indicating that having a GA above 32 weeks is significantly associated with better survival.

Figure 1. Chance of survival by gestational age

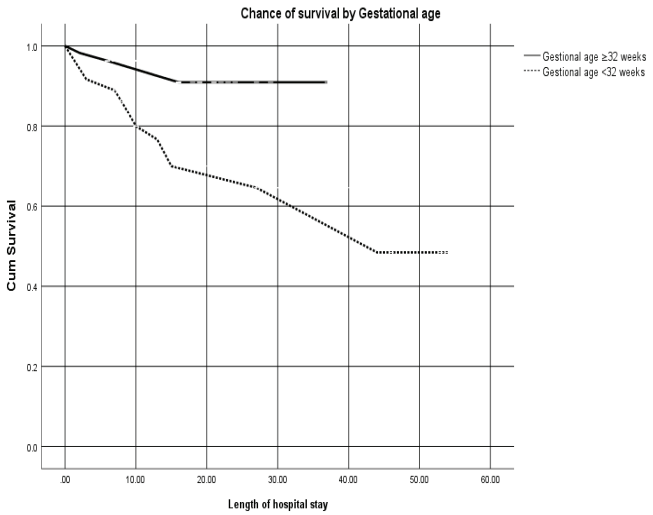

Table 4 describes the maternal characteristics and risk factors for survivors versus non-survivors. Lower gestational age (P = < 0.001) and PROM (OR 3.19; 95%CI 1.02 ± 10.05; P = 0.04) were significantly associated with higher mortality whereas NVD (OR 0.240, 95% CI 0.08 ± 0.76; P = 0.01) is associated with lower mortality.

Table 4. Comparison of maternal characteristics between survivors and non-survivors

	Survivor N (%)	Non survivor N (%)	Relative Risk	P Value
Total	79 (84.05)	15 (15.96)		
Maternal age	29.02 ± 4.81	28.81 ± 3.77		0.88
Parity	1.7722 ± .98644	1.8667 ± .91548		0.74
Delivery Mode NVD	17 (21.5)	8 (53.34)	0.240 (0.08 ± 0.76)	0.01
Mean Gestational age ± SD (weeks) < 28 (n= 3) 28 to < 32 (n = 33) 32 to < 34 (n = 33) 34 to < 37 (n = 25)	32.33 ± 1.81 1 (33.3) 23 (69.7) 32 (97) 13(92)	30.0 ± 2.14 2 (66.7) 10 (30.3) 1(3) 2(8)		<0.001
Maternal PIH	24 (30.4)	(33.33) 5	1.15 (.354 ± 3.72)	0.82
Maternal Heart disease	4 (5.06)	1 (6.67)	1.34 (0.14 ± 12.90)	0.80
Maternal GDM	5 (6.33)	1 (6.67)	(9.76 ± 0.12) 1.06	0.97
PROM	17 (21.52)	7 (46.67)	(10.05 ± 1.02) 3.19	0.04
Twin Pregnancy	8 (10.12)	1 (6.67)	(5.48 ± 0.08) 0.64	0.67
APH	11 (13.93)	1 (6.67)	(3.71 ± 0.05) 0.45	0.45

Table 5 depicts the finding of logistic regression analysis for risk of dying for the cohort. Lower birth weight (AOR = 0.99; 95% CI = 0.99-0.99; P=0:01), sepsis (AOR = 145.14; 95%CI = 5.04 - 4175.15; P = 0:004) were independently associated with increased risk of dying whereas increase duration of NICU stay decreased the risk (AOR = 0.71; 95%CI = 0.54 - 0.91; P = 0:01).

Table 5. Logistic regression model for mortality in RDS

	Adjusted OR	95% CI	P value
Birth weight	0.99	0.99 - 0.99	0.01
Male Sex	0.41	0.04 - 4.06	0.45
Need of resuscitation at birth	0.23	.01 - 5.75	0.36
Pneumothorax	36	.01 - 36	0.38
Sepsis	145.14	5.04 – 417.51	0.004
SRT	0.34	.026 - 4.320	0.41
MV needed	0.01	0.01- 0.01	0.99
Length of NICU stay	0.71	0.54 - 0.91	0.01
Duration of respiratory support	1.00	0.99 - 1.01	0.47
Apnea	0.97	.02 - 76.76	0.99

Discussion

The incidence of RDS among preterm in our study was 14.6% which was similar to the incidence reported from India.[5,6] Lower the gestational age higher would be RDS incidence. However, we observed higher incidence of RDS among infant born between 28 - 32 weeks as compared to those < 28 week ((80.49 Vs 21.43%). This contrast finding of the study may be due to the fact that only newborn admitted in NICU or neonatal unit were enrolled in the study and considering poor outcome of extremely premature babies in our setup, most of the family opted not to treat their babies. In the present study, the neonatal mortality rate due to RDS was 15.94%. Various studies done in NICU of medical colleges of India over last 10 years have reported the mortality rate as 44.7% to 15%.[9-11] In the retrospective study done over three months period at NICU of tertiary center in Western Nepal among preterm newborn, the RDS prevalence was found to be 14% with mortality rate of 46.15%.[12] In a similar study done in Kenya in 2015, the mortality rate due to RDS was found to be 72.3%.

In our study CPAP was provided in 86.18% and 5.2% of the preterm babies were mechanically ventilated as a primary respiratory support. In the study done by Sambhaji S W et al,[11] 87% of newborn received CPAP and 13% received ventilation as compared to study done by Phirke DS et al[13]where 78% received CPAP and 22% were ventilated. In our NICU, we follow protocol of providing prophylactic CPAP for newborn born less than 30 weeks and early CPAP for those born above 30 weeks. This might be the plausible explanation for less frequent mechanical ventilation.

Incidence of BPD and ROP observed in this study is low compared to the findings from western world.[14] This could be due to low survival rate among babies less than 28 weeks in our center. Nevertheless, resuscitation in room air and meticulous FiO2 monitoring while providing respiratory support could decrease the oxidative stress and related pulmonary and eye injury. Gestational age is a key factor in the survival of preterm babies world-wide. This is demonstrated in the present study as well where we found significant association between lower GA and birth with higher mortality in bivariate analysis. Two thirds of the babies less than 28 weeks died hence our biggest challenge is to save lives of babies less than 28 weeks.

In the present study, sepsis was observed in 28.7% of neonates and was strongly associated with neonatal mortality. Studies in India have shown the incidence of sepsis ranging 31.8% to 43.5%.[11,15] Sepsis was the most common co- morbidity among newborn with RDS receiving SRT. Mortality due to sepsis among

babies with RDS ranges from 25 to 49% in the other studies done in India.[9,16] Sepsis rate in our study is higher than that observed in Korean study[17]and studies from Greece[18] indicating importance of infection prevention practices for improving preterm survival.

This is one of the few prospective studies on the outcome of RDS at tertiary care center of Nepal. However, there are few limitations of the study. Chest x-ray was not evaluated in present study as most of the time chest X-ray was taken after surfactant administration and radiologist report was not available for many of them. Since, our NICU protocol for starting respiratory support is based on the clinical monitoring, we did not analyze admission ABG which was not available in many newborns. Similarly, due to limited oxygen blender we could not also keep record of highest FiO_2 requirement in all newborns. Hence, findings of chest X-ray, FiO_2 requirement and ABG parameters could not be done analyzed as predictors of mortality.

Conclusions

Our study provides gestational age specific incidence of RDS at tertiary care center of Nepal. Lower gestational age, birth weight and PROM were significantly associated with higher mortality whereas NVD is associated with lower mortality. Considerable attention should be directed toward prevention of infection for better survival of preterm babies with RDS.

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