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Original Article

Survival Predictors and Morbidity Risk Factors in Extremely Preterm Infants: A Clinical Cohort Study

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ABSTRACT

Aim: Extremely preterm infants (born before 28 weeks of gestation) face substantial risks of mortality and severe morbidity. This study aimed to identify early clinical predictors of survival and major complications in this vulnerable population in order to guide individualized neonatal care strategies.

Materials and Methods: A retrospective cohort analysis was conducted on 102 infants born between 22+0 and 27+6 weeks of gestation and admitted to a tertiary neonatal intensive care unit from 2017 to 2020. Demographic, perinatal, and clinical variables were extracted from their medical records. Survival and morbidity outcomes were compared across gestational subgroups. Statistical analyses included chi-square, t-tests, and receiver operating characteristic (ROC) curve analysis.

Results: The overall survival rate was significantly influenced by gestational age, birth weight, and the type of respiratory support received. Infants born at 22-25 weeks exhibited lower survival rates and higher incidences of respiratory distress syndrome, invasive ventilation, and patent ductus arteriosus (PDA). Mortality was independently associated with lower birth weight ($p<0.0001$), invasive ventilation ($p=0.0014$), and the presence of hemodynamically significant PDA ($p=0.0243$). In contrast, longer durations of non-invasive ventilation correlated with improved survival ($p<0.0001$). ROC analysis demonstrated high predictive performance for birth weight [area under the curve (AUC)=0.82] and non-invasive ventilation duration (AUC=0.96).

Conclusion: Early postnatal respiratory parameters, birth weight, and cardiovascular status are critical determinants of survival in extremely preterm infants. Optimizing non-invasive ventilation strategies and timely PDA management may enhance outcomes. Notably, the rate of antenatal corticosteroid administration was markedly low in our cohort, which may have contributed to adverse respiratory and survival outcomes, underscoring the need for improved perinatal care strategies in extremely preterm births.

Keywords: Extremely preterm infants, neonatal survival, respiratory support, patent ductus arteriosus, morbidity

Introduction

Preterm birth, defined as delivery before 37 completed weeks of gestation, remains a major global public health concern, accounting for an estimated 13.4 million births annually and contributing to over one million deaths among children under the age of five each year (1,2). Among these, extremely preterm infants, those born before 28 weeks of gestation, represent the most vulnerable subgroup facing a substantially higher risk of mortality and severe long-term morbidities (3,4). The immaturity of vital organs such as the lungs, brain, and gastrointestinal system

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underlies many of the complications encountered by these infants. These include respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and sepsis, all of which significantly contribute to neonatal morbidity and mortality (5-8). Survivors often face lifelong challenges including neurodevelopmental impairment, growth restriction, and chronic respiratory disease (9-12).

Despite global advances in neonatal care, survival outcomes for extremely preterm infants remain variable and are influenced not only by gestational age and birth weight, but also by postnatal factors such as the need for respiratory support, the presence of hemodynamically significant patent ductus arteriosus (PDA), and exposure to antenatal corticosteroids (ACS) (13-16). In this context, ACS therapy has been shown to enhance fetal lung maturation and improve neonatal outcomes when administered to mothers at risk of preterm delivery (17-19). Several maternal and perinatal conditions, including preeclampsia, maternal diabetes, oligohydramnios, and placental abruption, have also been implicated as risk factors for extreme prematurity and its associated complications (20-22).

Preterm birth continues to pose a significant clinical challenge worldwide, and extremely preterm infants remain at high risk of adverse outcomes, particularly in centers with varying levels of neonatal care capacity. Differences in perinatal management strategies and neonatal care practices contribute to heterogeneity in survival and morbidity rates across institutions.

This study aimed to evaluate the survival dynamics and early clinical predictors of mortality and morbidity among extremely preterm infants born before 28 weeks of gestation in a tertiary neonatal intensive care unit (NICU). By identifying critical early risk factors, we aimed to contribute to risk stratification models and support evidence-based, individualized care approaches which can enhance survival and reduce long-term complications in this vulnerable patient group.

Materials and Methods

Study Design

This retrospective cohort study was conducted with data from the tertiary NICU of MP İzmir Hospital. Medical records from January 2017 to December 2020 were retrospectively reviewed.

Study Population

A total of 102 extremely preterm infants born between 22+0/7 and 27+6/7 weeks of gestation and admitted to the NICU were included in this study.

Inclusion Criteria

- Infants born at gestational ages between 22+0/7 and 27+6/7 weeks
- The availability of complete medical records

Exclusion Criteria

- Infants born at or after 28+0 weeks of gestation
- Major congenital anomalies incompatible with life
- Missing or incomplete clinical data

Data Collection

The patient data were retrieved from the electronic medical records and included:

- Demographic characteristics: Gestational age, sex, birth weight, mode of delivery, Apgar scores
- Perinatal variables: ACS administration, maternal age, parity, preeclampsia, diabetes, preterm premature rupture of membranes (PPROM), oligohydramnios, and multiple gestation
- Neonatal outcomes: The need for resuscitation and intubation at birth, the presence of RDS, surfactant therapy, PDA, NEC, IVH, BPD, ROP requiring treatment, feeding intolerance, and mortality
- Respiratory support variables: The duration and mode of mechanical ventilation (invasive vs. non-invasive)
- Cardiovascular interventions: Medical or surgical PDA closure

Ethical Approval

This study protocol was reviewed and approved by the Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 2024/368, date: 25.12.2024). As this was a retrospective study using anonymized data, informed consent was waived. Its procedure complied with the Declaration of Helsinki guidelines.

Statistical Analysis

Descriptive statistics were calculated for all variables. Continuous variables are presented as mean ± standard deviation and compared using independent samples t-tests. Categorical variables are summarized as frequencies and percentages, and comparisons between groups were made

using Pearson's chi-square or Fisher's exact test where appropriate. Statistical significance was set at a two-tailed p-value of <0.05. All analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 102 extremely preterm infants were included in this study. Among them, 59.8% were male and 40.2% were female, with a mean gestational age of 25.62±1.42 weeks. Cesarean section was the predominant mode of delivery (78.4%). Half of the mothers were aged between 26 and 35 years, and maternal risk factors such as PPROM (40.2%), multiple gestation (29.4%), and primiparity (47.1%) were frequently observed. Detailed demographic and maternal characteristics are presented in Table Ia.

Regarding neonatal outcomes, 40.2% of the infants required resuscitation at birth, and 32.4% underwent intubation in the delivery room. ACS therapy was administered to 37.3% of the cases. RDS was diagnosed in 91.2% of the infants, all of whom required surfactant therapy. Pneumothorax occurred in 3.9% of the cases, while culture-proven early- or late-onset sepsis were observed in 2.9% and 13.7% of the infants, respectively. Congenital anomalies were identified in 5.9% of the infants. The neonatal clinical findings are summarized in Table Ib.

A subgroup analysis comparing those infants born at 22+0–25+6 weeks and 26+0–27+6 weeks revealed significant differences in their clinical outcomes. The lower gestational age group had significantly higher rates of intubation at birth (p=0.042), invasive mechanical ventilation (p<0.001),

Table Ia. Demographic and maternal characteristics of extremely preterm infants (n=102)

	Category	**n**	**%**
Sex	Male	61	59.8
	Female	41	40.2
Gestational age	26+0 - 27+6 weeks	55	53.9
	22+0 - 25+6 weeks	47	46.1
Mode of delivery	Cesarean section	80	78.4
	Vaginal delivery	22	21.6
Maternal age	17-25 years	28	27.5
	26-35 years	51	50.0
	36-45 years	23	22.5
Maternal diabetes	Yes	4	3.9
	No	98	96.1
Maternal preeclampsia	Yes	5	4.9
	No	97	95.1
Preterm premature rupture of membranes	Yes	41	40.2
	No	61	59.8
Placental abruption	Yes	6	5.9
	No	96	94.1
Oligohydramnios	Yes	9	8.8
	No	93	91.2
Polyhydramnios	No	102	100.0
Maternal smoking	Yes	8	7.8
	No	94	92.2
Multiple pregnancy	Twins	30	29.4
	Singleton	72	70.6
Primiparity	Yes	48	47.1
	No	54	52.9

Values are presented as number and % unless otherwise stated

Table Ib. Neonatal clinical characteristics of extremely preterm infants (n=102)			
	Category	**n**	**%**
Apgar score (1st minute)	1-3	27	26.5
	4-6	53	52.0
	7-8	22	21.5
Apgar score (5th minute)	4-6	40	39.2
	7-9	62	60.8
Resuscitation at birth	Yes	41	40.2
	No	61	59.8
Intubation in delivery room	Yes	33	32.4
	No	69	67.6
Antenatal corticosteroids	Yes	38	37.3
	No	64	62.7
Respiratory distress syndrome	Yes	93	91.2
	No	9	8.8
Surfactant therapy	Yes	93	91.2
	No	9	8.8
Pneumothorax	Yes	4	3.9
	No	98	96.1
Early-onset sepsis (culture proven)	Yes	3	2.9
	No	99	97.1
Late-onset sepsis (culture proven)	Yes	14	13.7
	No	88	86.3
Congenital anomalies	Present	6	5.9
	Absent	96	94.1

and surfactant use (p=0.004). Additionally, all infants in this group were diagnosed with RDS (p=0.004). In contrast, non-invasive ventilation was more commonly used in the higher gestational age group (p<0.001). Mean birth weight was also significantly lower in the younger group (701.7±135.5 g vs. 955.8±211.1 g; p<0.001). These findings are summarized in Table II. A full comparison of all recorded variables is presented in Supplementary Table SI.

PDA was significantly more common in the lower gestational age group and was strongly associated with an increased risk of invasive ventilation (p=0.045) and hemodynamically significant ductal shunting (p<0.001). While associations with ROP and IVH were not statistically significant, higher frequencies were noted in those infants with PDA. Those infants with PDA also had significantly lower birth weights (701.7±135.5 g vs. 955.8±211.1 g; p<0.001). These findings are summarized in Table III.

Mortality was significantly associated with lower birth weight (p<0.0001), an increased need for invasive mechanical ventilation (p=0.0014), and the presence of hemodynamically significant PDA (p=0.0243). Survivors showed longer durations of non-invasive ventilation (p<0.0001) and a higher prevalence of bronchopulmonary dysplasia (BPD) (p<0.0001), likely reflecting a survival bias. No significant associations were found for small for gestational age (SGA) or ROP. SGA and treatment-requiring ROP were more frequently observed among non-survivors; however, these differences did not reach statistical significance (p=0.061 and p=0.165, respectively). These findings are summarized in Table IV.

Receiver operating characteristic (ROC) curve analyses were performed in order to assess the predictive value of clinical variables for neonatal mortality. The area under the curve for birth weight was 0.82, and for non-invasive ventilation duration, it was 0.96, indicating high

Table II. Comparison of significant clinical variables by gestational age group

	22+0 - 25+6 weeks (n=47)	26+0 - 27+6 weeks (n=55)	p-value
Intubation in delivery room	42.6%	23.6%	0.042
Invasive mechanical ventilation	59.7%	40.3%	<0.001
Non-invasive ventilation	36.7%	63.3%	<0.001
Respiratory distress syndrome	100.0%	83.6%	0.004
Surfactant therapy	100.0%	83.6%	0.004
Birth weight (mean ± SD)	701.7 ± 135.5 g	955.8 ± 211.1 g	<0.001

Data are presented as % or mean ± SD as appropriate. p-values were calculated using chi-square test or independent samples t-test
SD: Standard deviation

Table III. Clinical associations of PDA and gestational age

	PDA absent	PDA present	p-value
Treatment-requiring ROP	26.1%	73.9%	0.345
Intraventricular hemorrhage	26.7%	73.3%	0.499
Invasive ventilation required	8.0%	27.3%	0.045
Hemodynamically significant PDA	0.0%	100.0%	<0.001
Postnatal steroid use	30.0%	62.9%	0.461
Gestational age ≤ 25+6 weeks	29.8%	70.2%	0.373
Birth weight (mean ± SD)	955.8± 211.1 g	701.7±135.5 g	<0.001

Data are presented as % or mean ± SD. p-values were calculated using chi-square test or independent samples t-test as appropriate
ROP: Retinopathy of prematurity, SD: Standard deviation, PDA: Patent ductus arteriosus

Table IV. Clinical risk factors associated with mortality in extremely preterm infants

	Survivors (mean ± SD or %)	Deaths (mean ± SD or %)	p-value
Birth weight (g)	903.63±200.65	658.37±165.71	<0.0001
Duration of non-invasive ventilation (days)	36.40±16.55	2.56±8.24	<0.0001
Invasive ventilation required	67	100	0.0014
PDA	59	85	0.0243
BPD	77	15	<0.0001
SGA	7	22	0.0611
ROP requiring treatment	27	11	0.1645

Data are presented as % or mean ± SD. p-values were calculated using chi-square test or independent samples t-test as appropriate
SD: Standard deviation, PDA: Patent ductus arteriosus, BPD: Bronchopulmonary dysplasia, ROP: Retinopathy of prematurity, SGA: Small for gestational age

discriminatory ability (Figure 1). Additionally, the presence of invasive mechanical ventilation was significantly associated with mortality. All infants who died had received invasive ventilation, whereas a substantial proportion of survivors did not. This yielded an infinite (odds ratio=∞; 95% confidence interval: ∞-∞; p<0.0001), indicating a strong statistical and clinical association.

Discussion

This study investigated the early clinical characteristics and survival dynamics of extremely preterm infants in a tertiary NICU. The findings indicate that lower birth weight, the need for invasive mechanical ventilation, and the presence of hemodynamically significant PDA were associated with increased mortality, while prolonged use of non-invasive ventilation was linked to improved survival outcomes.

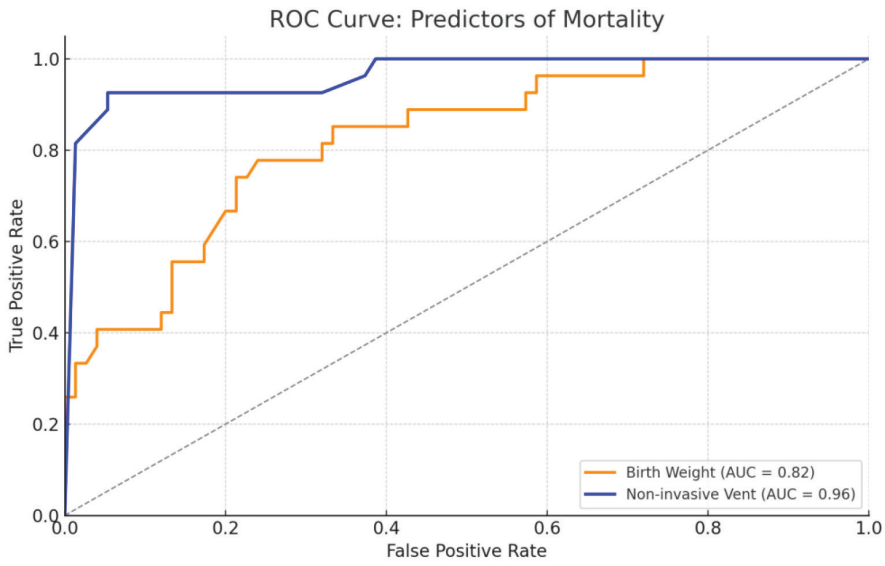

Figure 1. ROC curve analysis for predictors of mortality

ROC curve analysis of birth weight and non-invasive ventilation duration for predicting in-hospital mortality among extremely preterm infants. The area under the curve (AUC) was 0.82 for birth weight and 0.96 for non-invasive ventilation duration, indicating high discriminatory ability for both variables.
ROC: Receiver operating characteristic

Consistent with previous large-scale cohort studies, our results confirm that birth weight and gestational age remain key predictors of neonatal survival among extremely preterm infants (23,24). Infants born at 22-25 weeks of gestation had significantly lower survival rates, higher incidences of RDS, and greater reliance on invasive respiratory support compared to those born at 26-27 weeks. These findings highlight the importance of even slight increases in gestational maturity in improving neonatal outcomes, particularly for those on the threshold of viability (25).

The association between invasive mechanical ventilation and mortality observed in our cohort echoes findings from earlier reports, which suggest that prolonged or early invasive ventilation may contribute to lung injury and systemic inflammation (26,27). Conversely, the positive correlation between prolonged non-invasive ventilation and survival supports the growing preference for gentle ventilation strategies aimed at reducing iatrogenic harm in fragile preterm lungs.

In our study, both birth weight and the duration of non-invasive ventilation were found to be strong indicators of survival among extremely preterm infants. The high predictive performance observed in ROC analyses suggests that these variables can be effectively used in early clinical risk assessment. Additionally, all infants who did not survive required invasive mechanical ventilation, indicating a strong association between the need for advanced respiratory support and mortality. While this relationship is noteworthy, it likely reflects the severity of the infant's underlying condition. Infants with more severely critical illnesses are inherently more likely to require invasive ventilation, making it both a marker of disease severity and a potential contributor to adverse outcomes.

PDA was another critical factor influencing neonatal outcomes. Hemodynamically significant PDA was exclusively observed in the lower gestational age group and was significantly associated with increased mortality. These findings are in line with previous studies indicating that persistent PDA can lead to pulmonary overcirculation, systemic hypoperfusion, and an increased risk of IVH and BPD (28,29). Targeted echocardiographic screening and individualized medical or surgical closure strategies may be necessary in order to improve outcomes in this subgroup.

Our analysis also identified a potential association between invasive ventilation and the development of treatment-requiring ROP. Those infants requiring invasive respiratory support exhibited higher rates of severe ROP, which is in accordance with the prior literature linking excessive oxygen exposure and mechanical ventilation with retinal vascular proliferation (30). This finding emphasizes the need for precise oxygen targeting and careful respiratory management in this population.

Although feeding intolerance and NEC were more frequent among the most immature infants, no statistically significant associations were observed. Nonetheless, these complications remain clinically important in extremely preterm infants, where intestinal immaturity and altered microbial colonization may predispose to gastrointestinal injury (31,32). Strategies promoting enteral nutrition with breast-milk and cautious advancements of feeding volumes should remain central to NEC prevention protocols.

While the associations between SGA and ROP with mortality did not reach statistical significance in our cohort, both conditions were observed more frequently among non-survivors. The higher rate of SGA in the mortality group (22% vs. 7%) aligns with previous studies demonstrating increased morbidity and mortality among very preterm SGA infants (33). Similarly, those infants who died also had a higher proportion of treatment-requiring ROP (11% vs. 27%), consistent with known associations of ROP development with extreme prematurity, low birth weight, and oxygen-related retinal injury (34). While these trends did not achieve significance, likely due to limited sample size, they warrant further investigation in larger prospective cohorts.

An unexpected finding was that BPD was significantly more common among survivors. This may reflect a form of "survivor bias", wherein infants must live long enough in order to manifest chronic lung disease. While BPD is typically associated with long-term morbidity, its presence in survivors should not be interpreted as protective but rather as a marker of prolonged NICU stay and ventilation (35).

Maternal factors such as preeclampsia, PPROM, and multiple gestation were frequently observed in this cohort, consistent with known etiologies of spontaneous and indicated preterm birth (36). Despite the recognized benefits of ACS in promoting fetal lung maturation and improving survival outcomes (37), only 37.3% of mothers in this cohort received ACS. This unexpectedly low rate of ACS administration may be attributed to factors such as delayed maternal admission, lack of timely prenatal care, or emergent deliveries which precluded the opportunity for full steroid course administration. Future quality improvement efforts should focus on ensuring that eligible mothers receive timely and complete antenatal steroid therapy in order to optimize neonatal outcomes.

Study Limitations

This study contributes meaningful insights into the clinical trajectories of extremely preterm infants, particularly in relation to early survival and morbidity; nonetheless, certain limitations warrant consideration. Although our analysis is based on systematically documented clinical data, its retrospective nature may introduce biases related to data accuracy and completeness. The single-center design, shaped by institution-specific practices and resource availability, may also limit the broader applicability of our findings. Additionally, the absence of long-term neurodevelopmental follow-up data restricts conclusions regarding the translation of early survival into later functional, cognitive, or behavioral outcomes. In order to strengthen external validity and inform long-term care strategies, future studies incorporating prospective, multicenter designs with extended follow-ups are needed.

Conclusion

This study highlights the critical importance of early respiratory support modalities, birth weight, and cardiovascular status in determining survival outcomes among extremely preterm infants born before 28 weeks of gestation. Those infants with lower birth weight, increased need for invasive mechanical ventilation and hemodynamically, significant PDA, exhibited markedly higher mortality rates. In contrast, prolonged use of non-invasive ventilation was associated with improved survival, supporting the implementation of lung-protective, individualized respiratory strategies in the early postnatal period. ACS therapy, a well-established intervention known to reduce respiratory morbidity and mortality, was notably underutilized in our cohort (administered in only 37.3% of cases). This finding underscores a significant gap in perinatal care which may have adversely impacted neonatal outcomes and represents an actionable target for quality improvement in delivery room management. To the best of our knowledge, this is one of the few clinical cohort studies from a tertiary NICU in a middle-income setting which rigorously evaluates the combined predictive value of non-invasive ventilation duration, PDA status, and birth weight on survival rates in extremely preterm infants. These findings may contribute to enhanced risk stratification models and inform the development of targeted care protocols aimed at improving early survival. Future multicenter studies incorporating long-term neurodevelopmental outcomes are warranted in order to validate these results and ensure that early survival gains translate into meaningful long-term health benefits in this highly vulnerable population.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 2024/368, date: 25.12.2024).

Informed Consent: As this was a retrospective study using anonymized data, informed consent was waived.

Footnotes

Authorship Contributions

Concept: M.T.A., S.G., A.A.S., B.C., S.Ş., Design: M.T.A., S.G., A.A.S., B.C., S.Ş., Data Collection or Processing: S.G., A.A.S., B.C., Analysis or Interpretation: M.T.A., Literature Search: M.T.A., S.G., S.Ş., Writing: M.T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Table SI. Full comparison of perinatal and clinical characteristics in extremely preterm ınfants stratified by gestational age group

	Categories	Premature babies between 26+0 and 27+6 weeks		Premature babies between 22+0 and 25+6 weeks		P-value
		N	%	N	%	
Gender	Female	26	47.30	15	31.90	0.115
	Male	29	52.70	32	68.10	
Birth type	Cesarean Section	47	85.50	33	70.20	0.062
	Vaginal delivery	8	14.50	14	29.80	
Apgar score (1st minute)	1	2	3.60	2	4.30	0.502
	2	2	3.60	4	8.50	
	3	9	16.40	8	17.00	
	4	6	10.90	3	6.40	
	5	7	12.70	7	14.90	
	6	16	29.10	14	29.80	
	7	8	14.50	9	19.10	
	8	5	9.10	0	0.00	
Apgar score (5th minute)	4	0	0.00	1	2.10	0.288
	5	3	5.50	3	6.40	
	6	15	27.30	18	38.30	
	7	24	43.60	20	42.60	
	8	9	16.40	5	10.60	
	9	4	7.30	0	0.00	
Resuscitation needed at birth	No	35	63.60	26	55.30	0.393
	Yes	20	36.40	21	44.70	
Intubation needed in delivery room	No	42	76.40	27	57.40	0.042
	Yes	13	23.60	20	42.60	
Antenatal steroid administration	No	30	54.50	34	72.30	0.064
	Yes	25	45.50	13	27.70	
Need for admission to the neonatal intensive care unit	Yes	55	100.00	47	100.00	
Respiratory distress syndrome (RDS)	No	9	16.40	0	0.00	0.004
	Yes	46	83.60	47	100.00	
Surfactant requirement	No	9	16.40	0	0.00	0.004
	Yes	46	83.60	47	100.00	
Pneumothorax	No	52	94.50	46	97.90	0.388
	Yes	3	5.50	1	2.10	
Early-onset neonatal sepsis (culture-proven)	No	54	98.20	45	95.70	0.468
	Yes	1	1.80	2	4.30	
Late-onset neonatal sepsis (culture-proven)	No	50	90.90	38	80.90	0.141
	Yes	5	9.10	9	19.10	

Supplementary Table SI. Continued

	Categories	Premature babies between 26+0 and 27+6 weeks		Premature babies between 22+0 and 25+6 weeks		P-value
		N	%	N	%	
Congenital anomaly	Cleft palate	1	1.80	0	0.00	0.374
	Congenital cataract	0	0.00	1	2.10	
	Hydrops fetalis	1	1.80	0	0.00	
	No	53	96.40	43	91.50	
	Omphalocele	0	0.00	1	2.10	
	Polydactyly	0	0.00	1	2.10	
	Tracheoesophageal fistula	0	0.00	1	2.10	
Feeding intolerance during hospitalization	No	24	0.649	13	0.351	0.094
	Yes	31	0.477	34	0.523	
Patent ductus arteriosus (PDA)	No	21	0.6	14	0.4	0.373
	Yes	34	0.507	33	0.493	
Small for gestational age (SGA)	No	47	0.516	44	0.484	0.185
	Yes	8	0.727	3	0.273	
Large for gestational age (LGA)	No	54	0.535	47	0.465	0.353
	Yes	1	1	0	0	
Necrotizing enterocolitis (NEC)	No	44	0.53	39	0.47	
	Yes	11	0.579	8	0.421	
Bronchopulmonary dysplasia (BPD)	No	20	0.5	20	0.5	0.700
	Yes	35	0.565	27	0.435	
Invasive Mechanical Ventilation Required	No	24	0.96	1	0.04	0.000
	Yes	31	0.403	46	0.597	
Non-Invasive Mechanical Ventilation Required	No	5	0.217	18	0.783	0.000
	Yes	50	0.633	29	0.367	

Data are presented as % or mean ± SD. P-values were calculated using chi-square test or independent samples t-test where appropriate