

TITLE PAGE

Care practices and outcomes of extremely preterm neonates born at 22-24 weeks - A single centre experience

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ABSTRACT

Background and Aim : There are wide variations in the care practices and consequently survival rates of neonates born at peri-viable gestational ages of 22⁺⁰ - 24⁺⁶ weeks between centres. This study compares the care practices and short term outcomes from a single centre with others.

Design : Retrospective study of neonates born at 22⁺⁰ - 24⁺⁶ weeks from a Level 3 neonatal intensive care unit over a period of 4 years (2016-2019) from United Kingdom.

Results: 94 neonates [22 wks (n=4), 23 wks (n=46), 24 wks (n=44)] given active care were included. At discharge, survival rate was 51.1% (22 - 23 wks- 44%, 24 wks-59.1%) and survival with no severe neurological morbidity [grade III/IV intraventricular hemorrhage, cystic periventricular leukomalacia] was 38.3% (22 - 23 wks- 32%, 24 wks- 45.4%). Of those neonates surviving until discharge, 75% had no severe neurological morbidity (22-23 wks - 72.7%, 24 wks - 76.9%). Neonates on invasive mechanical ventilation and not ready to be extubated in the first 72 hours of life, not received postnatal dexamethasone and those who required rescue high frequency ventilation had significantly higher risk of death or severe neurological morbidity [adjusted OR (95% CI) -7.17 (2.24-25.79); 0.19 (0.05-0.62); 0.21 (0.05-0.70) respectively].

Conclusion:

Most neonates who survived until discharge had no severe neurological morbidity. Severe respiratory disease in the initial days as indicated by not ready to be extubated from invasive mechanical ventilation within the first 72 hours of life and requirement of rescue HFOV was associated with a higher risk of death or severe neurological morbidity. Postnatal dexamethasone use was associated with a survival advantage.

INTRODUCTION

The survival of extremely preterm neonates born at gestational ages 22 - 24 weeks has improved considerably over the last three decades with significant variability in survival of these premies between nations as well as centres within the same country. [1-6] Recent data from United Kingdom indicates that the survival of the neonates born at 22 weeks and who are offered active support have

improved considerably over the past decade [7]. Watkins et al. (Iowa centre, USA) had reported encouraging results especially in relation to their long term survival [8]. Though many networks have published their short- and long term survival of these premies, very few have described the care practices and the course of stay of these neonates in detail [1]. Bettering survival in this sub-group of neonates mandates improved evidence based practices for which there is paucity in literature. Knowing the differing neonatal care practices between centres with varying survival rates would in turn lead to furthering the efforts to bridge the existing survival gap between them. We present our local data together with our clinical practices and compare our results to published data.

MATERIALS/ SUBJECTS AND METHODS

Study place / subjects / time period

This is a retrospective observational study which included neonates of gestational ages 22⁺⁰ to 24⁺⁶ weeks born at the John Radcliffe Hospital (JRH), Oxford, United Kingdom over a 4 year period from 1st January 2016 - 31st December 2019. The JRH is a regional tertiary referral centre, admitting approximately 200 very low-birth weight (VLBW) neonates per year. Out-born neonates and those who died in the delivery room were excluded from the analysis. The gestational age was determined by the best obstetric estimate based on the first trimester scan and the last menstrual period.

The management protocol is provided in the supplement file.

Outcomes

The primary outcome of the study was survival to discharge with no severe neurological morbidity [Grade III / IV intraventricular hemorrhage (IVH) [9], cystic periventricular leukomalacia (PVL)]. The secondary outcomes were survival to discharge, respiratory outcomes [incidence of non-invasive respiratory support (NRS) failure (within 72 hours and until discharge), duration of NRS, requirement and duration of mechanical ventilation (MV) (conventional and high frequency), incidence of BPD [10], air leak, echocardiography diagnosed persistent pulmonary hypertension (PPHN), pulmonary hemorrhage, home oxygen therapy], patent ductus arteriosus (PDA) requiring medical or surgical

treatment, sepsis related outcomes {incidence of early onset and late onset sepsis/ septic shock requiring inotropes/ meningitis [11,12], incidence of ventilator associated pneumonia (VAP) [13], duration of antibiotics expressed as antibiotics use rate (AUR) [14]}, nutritional outcomes {incidence of necrotising enterocolitis (NEC) stage II or more [15,16], incidence of surgical NEC, incidence of osteopenia of prematurity (defined as serum phosphate < 4.1 mg/dl with alkaline phosphates >800 IU/L and/or radiographic changes , incidence of extra uterine growth retardation at 36 weeks post menstrual age (PMA) (EUGR) [17]}, transfusion practices, neurological outcomes, incidence of retinopathy of prematurity (ROP) [18], incidence of ROP requiring treatment and duration of stay in the hospital.

Statistical analyses

Infants who survived to discharge and those who died were compared as two separate groups. Continuous variables were expressed as mean with standard deviation (SD) as well as median with interquartile range (IQR). p-value was calculated using t-test / ANOVA for normally distributed parameters and Mann Whitney U-test / Kruskal Wallis for non-normally distributed parameters. Categorical data was compared using chi-square test and Fischer's exact test. p-value of <0.05 was considered significant. Multivariate logistic regression was used for calculating the adjusted odd's ratio with 95% confidence interval [aOR (95% CI)] for explanatory analysis as well as for prediction models [19]. For aOR calculation, the baseline characteristics such as gestational age, small for gestational age (SGA) status, sex, receipt of antenatal steroids and maternal chorioamnionitis were adjusted. The final model for prediction was selected based on comparisons using the partial likelihood ratios test [20]. Linearity assumption was tested wherever appropriate using scatter plots [21]. Time to event data was analysed using Kaplan Meier plots as well by Cox proportional hazards regression analysis and expressed as adjusted hazard's ratio (95% confidence interval) [aHR (95% CI)][21]. Proportional hazards assumption was tested using Schoenfeld residuals [22]. With a sample size of 94, overfitting was avoided by selecting a maximum of 9 variables for regression analysis

[23]. All the statistical analyses was done using R software (R version - 3.6.2, packages - *survival*, *survminer*, *ggplot2* and *epiR*)

Ethics

This work was reviewed and authorized by the Joint Research Office study classification group of the institution as per the Department of Health's UK Policy Framework for Health and Social Care.

RESULTS

A total of 94 neonates born at 22 0/7 - 24 6/7 gestational age and admitted in the NICU for active care were included in the study [22 wks (n=4), 23 wks (n=46), 24 wks (n=44)] . The baseline characteristics of the enrolled neonates is summarised in **Table 1**.

Survival with no severe neurological morbidity

The survival till discharge rate was 51.1% (22-23 wks - 44%, 24 weeks - 59.1%). 75% of the survivors were free from any apparent severe neurological morbidity (22-23 wks - 72.7%, 24 wks - 76.9%). 38.3% of the neonates survived with no severe neurological morbidity (22-23 wks - 32%, 24 wks - 45.4%). These are illustrated in **Figure 1**. Multiple births, requirement of inhaled nitric oxide, not receiving postnatal dexamethasone, air leak, grade III and grade IV IVH were significantly associated with mortality. The aHRs are depicted in **Figure 2**. Those neonates with requirement of MV and not qualifying for extubation within the first 72 hours, not received postnatal dexamethasone and required rescue high frequency oscillation ventilation (HFOV) had significantly high risk of death or severe neurological morbidity [aOR - 7.17 (2.24-25.79), p=0.00; 0.19 (0.05-0.62), p=0.00; 0.21 (0.05-0.70), p=0.01 respectively].

Delivery room practices

Eight six percentage of the neonates were intubated in the delivery room, 75.5% of the neonates received rescue surfactant, 1 neonate received chest compression and 7.4% had severe perinatal asphyxia. Only 21.1% of the neonates were eligible to be supported on a NRS modality.

Respiratory care

Surfactant use

Of the 88 (94.6%) neonates who received surfactant, 45 (48.4%, n=94) neonates received it in the NICU. Only 10.1% received surfactant through INSURE (Intubate-Surfactant-Extubation) or LISA (Less Invasive Surfactant Administration). The median (IQR) age of surfactant administration was 15 minutes (11-20) and the median number of doses was 1 (1-2) with no differences between the neonates who survived and who did not ($p=0.06$).

Non-invasive respiratory support

A total of 35 neonates (37.2%,) were initiated on a NRS modality within the first 72 hours, of which 21 (22.5%) of them received a NRS modality (HHHFNC=20.4%, BiPAP=2.1%) as primary respiratory support within the first 24 hours. The incidence of NRS failure within the first 72 hours was 74.3% and it occurred at a mean (SD) of 19.7 (\pm 16.1) hours. There was a statistically significant difference in the NRS failure rate between survivors and non-survivors (70.4% vs 87.5%, $p<0.01$). Cox regression analysis after adjusting for the baseline characteristics revealed gestational age to be the only significant factor predicting NRS failure [aHR (95% CI) for 23 wks vs 22 wks - 0.08 (0.00-0.91); 24 wks vs 22 wks - 0.03 (0.00-0.43)]. The duration of NRS in the first 72 hours and during the hospital stay is given in **Table 2**.

Mechanical ventilation

There was a statistically significant difference in the duration of any MV (conventional and HFOV) between the different gestational ages ($p=0.03$) (**Table 2**). The requirement of rescue HFOV was 69.1% with significant differences between those survivors and non-survivors (56.3% vs 82.6%, $p<0.01$). Respiratory morbidities and drug use for prevention / treatment of BPD are shown in **Table 2**.

Cardiovascular morbidity

Seventy percentage of the studied neonates required either medical or surgical therapy for PDA. Intravenous/ oral paracetamol was the first line drug used in the majority of the neonates (62.1%). 16.7% of the surviving neonates required ligation of the PDA after failed medical therapy. The mean (SD) age of ligation was 46.7 (\pm 24.5) days. The details of iNO is given in **Table 3**.

Sepsis

About 42.5% of the neonates had blood culture proven sepsis. Of these only 4.2% were early onset (<72 hours). *E.coli* was the predominant organism in early onset sepsis (EONS) and Coagulase negative staphylococcus (CONS) was the predominant organism amongst the neonates with late onset neonatal sepsis (LONS). Among the survivors, the incidence of LONS was 50%. The mean antibiotic use rate (AUR) was 28.3% (22.8% for survivors; 71.7% for those who died). The other aspects related to sepsis are given in **Table 3**.

Nutrition and NEC

The incidence of NEC II or above was 32.9% and that of surgical NEC / perforation was 23.4%. The median (IQR) postnatal and post menstrual age of diagnosis of NEC II or above was 9 days (6.3 - 15.7 days) and 25.3 weeks (24.5 - 26.1 weeks). The risk of EUGR was statistically high in neonates who were of female sex [aOR=5.0 (1.33 - 25.00)], received dexamethasone [aOR -5.55 (1.58-21.98)], and diuretics [aOR - 15.02 (4.10 -70.67)]. Some of the aspects related to nutrition, blood products transfusion practices and incidence of acute kidney injury are given in **Table 3**.

Neurological and visual outcomes

IVH of any extent was diagnosed in 70.2% of the neonates, 18.1% (survivors - 10.4%) with grade III and 22.3% (survivors - 6.2%) with grade IV IVH. The incidence of cystic PVL was 10.4% among the neonates who survived until discharge. While ROP was diagnosed in 75% of those who survived, 35.4% of the total survivors required therapy for the same.

The total duration of stay and the etiology of mortality are provided in **Table 3**.

DISCUSSION

In this single-centre retrospective study, the survival with no severe neurological morbidity was 38.3% (22-23 wks - 32%, 24 wks- 45.4%). Of those who survived until discharge, 75% did not have any severe neurological morbidity (22 - 23 wks - 72.7%, 24 wks - 76.9%). Neonates born at 22 weeks

were given active resuscitation in this centre since 2019 and hence only four neonates of this gestation were included.

The survival rates of neonates of this study are similar to that reported in the recent systematic review and meta-analysis (2019), the UK-MBRACE data (2016); lesser than the ones from Sweden (EXPRESS-2, 2019), Japan (NRNJ, 2017), Germany (single centre, Cologne, 2016), USA (single centre, Iowa, 2020) and higher than those from UK (EPICure-2, 2012), France (EPIPAGE, 2015) [2, 5-8, 24-26]. The comparison of the primary outcome (survival with no severe neurological morbidity) is difficult as the definitions used in many of the studies to define 'severe morbidity' differ with many studies including severe BPD, ROP requiring treatment and NEC/ perforation requiring laparotomy as severe morbidities [1,26]. Most of these outcomes are reported in this study and since neurological morbidities are highly associated with poor long term outcomes, they were included in the primary analysis. Also, the denominator used in this study was all the neonates who were shifted to NICU for active care. 'Denominator bias' is a known aspect of studies reporting preterm survival and unless specified can result in spurious survival rates [27].

There are many reasons for differing survival rates between centres caring for neonates born at threshold of viability. A recent study had shown that centres that have a comprehensive approach in giving active care for these vulnerable premies have better survival than those that follow a selective approach [28]. Differing care practices also contribute to the variability in survival rates. Watkins et al. in their Iowa centre study had reported some care practices which are different from our centre such as caesarian section for fetal compromise, inborn deliveries, provision of a separate NICU with experienced staff and use of high frequency ventilation as a primary mode of respiratory support [8]. Isayama et al had reported certain other unique practices that are followed in Japan which are contrasting to ours such as monitoring internal cerebral vein velocity pattern in acute phase to prevent IVH, circulatory management guided by certain functional echocardiography parameters such as end-systolic wall stress, preference for invasive MV in the initial postnatal period to prevent intraventricular hemorrhage, use of gloves / masks/ gowns even for routine care practices for

prevention of nosocomial infection as well as serial monitoring of CRP values to detect and treat bacterial infection and ubiquitous sedation for all ventilated neonates [29]. Some of these practices such as use of primary high frequency ventilation, routine sedation of ventilated neonates, use of serial CRP values in preventing or treating sepsis and universal gowning have been proven to be of doubtful benefit in relatively higher gestational age neonates [30-33]. Clearly, the general dearth of clinical studies on neonates of these low gestational age groups mandate further studies to explore many of these aspects.

In our cohort, severe respiratory disease in the initial postnatal life as indicated by not ready to be extubated in the first 72 hours and requirement of HFOV was associated with an increased risk of mortality or severe neurological outcome. Laughon et al. had reported similar findings in neonates of 23 - 30 weeks gestation, with higher FiO₂ requirement and requirement of conventional as well as HFOV being independently associated with the combined outcome of mortality or BPD [34]. Use of postnatal dexamethasone had a survival advantage which was in agreement with the meta-analysis by Doyle et al. which reported that the use of dexamethasone in neonates whose risk of BPD was more than 60% resulted in a decreased incidence of death or cerebral palsy [35]. The NRS failure rate within 72 hours was 74.3% which was much higher than reported by the single centre study from Cologne, Germany (50%) which uses NRS as a preferential initial mode where ever appropriate similar to our centre [25]. This might be explained by the use of HFNC as a primary mode of respiratory support in our centre compared to CPAP that was used in the Cologne study [36]. The incidence of blood culture proven late onset neonatal sepsis in our cohort was 38.3% overall and 50% among the survivors which was comparable to the NICHD-NRN data (40.7%) [1]. The mean AUR was 28.3% for the neonates included in the study. Not that many studies have reported the antibiotic exposure in this vulnerable group of premies. Schulman et al. in his study of AUR in all neonates admitted in NICUs from California had reported a mean AUR of 21.8% [37]. The incidence of surgical NEC was 23.4% which was higher than reported by the Japan NRNJ (10.1%) [24]. Most of the nutritional practices in the present study NICU such as use of human milk, early use of minimal

enteral feeds and probiotics are similar to that reported by Isayama et al. from Japan. However, NEC is a multifactorial disease with genetic disposition as well [38].

This study has several limitations. It was retrospective in nature. It had not reported on the still birth rates as well as the delivery room deaths and the long term neurodevelopmental outcomes of the studied neonates. The main strength of this study is that it had reported in detail the various care practices related to the neonates born at 22-24 weeks and contrasted them with centres reporting better outcomes. Also, it had tried to explore the various postnatal risk factors for mortality and severe short term neurological outcomes which has not been addressed before.

CONCLUSION

Most neonates who survived until discharge had no severe neurological morbidity. The survival rates amongst the neonates born at peri viable gestations of 22-24 weeks are better than those reported by the EPICure 2 and EPIPAGE-2 studies but much lesser than those reported from Japan, Sweden and some centres from USA, Germany. There are wide variations in care practices between various centres which might explain the differences in survival. Severe respiratory disease in the initial days as indicated by not ready to be extubated within the first 72 hours of life and requirement of rescue HFOV was associated with a higher risk of death or severe neurological morbidity. Postnatal dexamethasone use was associated with a survival advantage.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- Wide survival gap exists for neonates born at peri viable gestational ages of 22-24 weeks between developed countries.
- Perinatal factors such as maternal chorioamnionitis, multiple gestation, not receiving antenatal corticosteroids, extramural birth, male sex and small for gestational age can adversely affect the survival.

WHAT THIS STUDY ADDS?

- Comprehensive data describing the care practices of 22-24 weeks gestation neonates from a level 3 NICU in United Kingdom
- Contrasts the care practices along with short term outcomes with other centres /countries.
- Elucidates some of the postnatal risk factors for mortality or severe short term neurological morbidities

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Table 1 : Demographic details of the enrolled subjects

Baseline Demographics	N=94	Survived (n=48)	Non-survivors (n=46)	p-value*
Mean gestational age (+/-SD) (weeks)	23.7 +/- 0.6	23.8+/-0.6	23.7+/-0.6	0.29
Mean birth weight (+/-SD) (grams)	633.3 +/-99.8	646.4+/-94.7	619.4+/-104.1	0.19
SGA*	9 (9.6%)	1 (2.1%)	8 (17.4%)	0.03
Multiple gestation	23 (24.5%)	8 (16.6%)	15(32.6%)	0.12
Sex				
Male	53 (56.4%)	26 (54.2%)	27 (58.7%)	0.80 \
Female	41 (43.6%)	22 (45.8%)	19 (41.3%)	
Mode of Delivery				
C-section	86 (91.4%)	41 (85.4%)	45(97.8%)	0.07
Vaginal	8 (8.6%)	7 (14.6%)	1(2.2%)	
Antenatal steroids				
None	6 (6.4%)	4 (8.3%)	2 (4.3%)	0.43
Partial [#]	30 (31.9%)	12 (25%)	18 (39.1%)	0.14
Full ⁺	58 (61.7%)	32 (66.7%)	26 (56.5%)	0.45
Dexamethasone	26/88 (29.5%)	16/44 (36.4%)	8/44 (18.4%)	0.31
Betamethasone	62/88 (70.5%)	28/44 (63.6%)	36/44 (81.8%)	0.06
Received Magnesium Sulphate	80 (85%)	38 (79.1%)	42 (91.3%)	0.24
Place of birth				
Intramural	76 (80.8%)	39 (81.2%)	37 (80.4%)	0.75
Extramural	18 (19.2%)	9 (18.8%)	9 (19.6%)	
Chorioamnionitis	35 (37.3%)	18 (37.5%)	17 (36.9%)	0.96
pPROM>18 hours*	25 (48.1%)	16 (33.3%)	9 (19.6%)	0.17

* SGA - Small for gestational age defined as birth weight for gestational age less than 10th centile,
pPROM - preterm premature rupture of membranes

At least 1 dose of either betamethasone or dexamethasone received >= 8 hours prior to delivery

+ At least 2 doses of betamethasone or 4 doses of dexamethasone received >= 24 hours but within 1 week before delivery

Table 2 - Duration of respiratory support and respiratory morbidities in survivors and non-survivors

Respiratory support/ Morbidity	All neonates (n=94)	Survived (n=48)	Non-survivors (n=46)	p-value*
Primary respiratory support in NICU (hours) (mean+/-SD)				
HFNC in first 72 hours	32.2+/-25.4	34.3+/-25.3	20.8+/-25.2	0.31
BiPAP in first 72 hours	30.2+/-31.9	21.8+/-0.0	72.0+/-0.0	-
CMV in first 72 hours ⁺	52.8+/-23.0	49.4+/-23.2	56.5+/-22.6	0.43
HFOV in first 72 hours [#]	39.5+/-22.2	11.1+/-14.2	35.3+/-25.7	0.17
Respiratory support duration during hospital stay (days) (mean+/-SD)				
CMV	17.8+/-13	23+/-12.1	11.5+/-11.1	-
HFOV	8.2+/-8.2	11.1+/-8.9	6.1+/-7.1	
CMV+HFOV	22.3+/-17.1	29.4+/-15.1	15.0+/-16.0	
NRS	48.7+/-28.8	58.7+/-22.0	6.7+/-8.3	
NRS+Low flow O2	67.3+/-38.1	81.0+/-25.6	5.5+/-7.6	
Any respiratory support	62.5+/-38.1	109.8+/-33.4	16.2+/-7.7	
MV for different gestational age subgroups (days)(mean+/-SD)[^]				
CMV 22 wks	28.7+/-13.6	25+/-16.9	36+/-0	0.32
CMV 23 wks	17.7+/-13.6	14.1+/-10.6	20.6+/-12.6	
CMV 24 wks	16.9+/-13.8	18.3+/-15.1	15.5+/-12.4	
HFO 22 wks	15.7+/-5.9	19.0+/-1.4	9+/-0	
HFO 23 wks	8.9+/-8.0	8.0+/-7.5	9.5+/-8.5	0.13
HFO 24 wks	6.4+/-8.3	6.5+/-7.6	6.4+/-8.8	
CMV +HFOV 22 wks	44.3+/-13.0	44.0+/-18.4	45+/-0	
CMV +HFOV 23 wks	23.9+/-16.7	19.2+/-14.9	27.6+/-17.3	0.03
CMV +HFOV 24 wks	19.1+/-16.7	21.2+/-17.7	17.3+/-16.0	
Drugs for BPD				
Dexamethasone for BPD	34/94(36.1%)	28/48 (58.3%)	6/46 (13.0%)	-
Age of initiation of dexamethasone	25.9+/-12	25.8+/-11.0	26.5+/-15.8	
>1 course	5/94(5.3%)	5/48 (10.4%)	0/46 (0%)	
Inhaled Budesonide	31/94(33%)	28/46 (58.3%)	3/46 (6.5%)	
Day of initiation	31.2+/-22.6	31.2+/-23.4	31.7+/-15.6	
Duration of budesonide	26.1+/-20.6	26.2+/-21.7	25.7+/-4.1	
Diuretics use	39/94(41.5%)	31/48 (64.6%)	8/46 (17.4%)	

BPD	-	48/48 (100%)	-	-
Mild		15/48 (31.2%)		
Moderate		31/48 (64.6%)		
Severe		2/48 (4.2%)		
Home oxygen	10/94(10.6%)	10/48(20.8%)	-	-
Air leak	18/94(19.1%)	6/48(12.5%)	12/46(26.1%)	0.17
PPHN	16/94(17.0%)	5/48(10.4%)	11/46(23.9%)	0.15
Pulmonary hemorrhage	17/94(18.1%)	5/48(10.4%)	12/46(26.1%)	0.09
<p>*p-values in bold are significant. + Conventional mechanical ventilation # High frequency oscillation ventilation ^ ANOVA used for multiple mean comparisons</p>				

Table 3 - Details of non-respiratory care practices and morbidities in survivors and non-survivors

Outcome	All neonates (n=94)	Survived (n=48)	Non-survivors (n=46)	p-value*
Cardiovascular outcome - Nitric Oxide use				
PDA requiring therapy	66/94(70.2%)	45/48(93.75%)	21/46(45.6%)	<0.001
iNO	30/94 (31.9%)	10/48 (20.8%)	20/46 (43.5%)	0.02
Starting age (days)(median)(IQR)	8.5 (0.6-17.8)	22.5(13.5-36.5)	2.5 (0.3-10.3)	0.03
Response	13/30 (43.3%)	7/10 (70%)	6/20 (30%)	0.04
Duration (days)(median)(IQR)	4.5 (2.0-9.8)	6 (4.3-8.5)	3 (1-10.5)	0.72
Sepsis				
<i>EONS</i>				
Meningitis	1/71 (1.4%)	1/41 (2.4%)	0/30 (0%)	- [^]
Shock	33/71 (46.4%)	18/41 (43.9%)	15/30 (50%)	0.61
<i>LONS</i>				
Meningitis	2/67 (3.2%)	2/45 (4.4%)	0/22 (0%)	-
Shock	14/67 (20.9%)	6/45 (13.3%)	8/22 (36.3%)	0.03
VAP	25/94 (26.6%)	18/48 (37.5%)	7/46 (15.2%)	-
Nutrition				
Day of starting feeds(mean+/-SD)	2.4 (+/-2.2)	2.1 (+/-1.9)	2.8 (+/-2.0)	-
Day of full feeds (mean+/-SD)	21.3 (+/-22.1)	22.8 (+/-24.4)	15.6 (+/-7.1)	-
Day of regaining birth weight (mean+/-SD)	7.7 (+/-4.1)	8.6 (+/-4.3)	6.0 (+/-3.0)	0.00
TPN duration(days)(mean+/-SD)	22.4 (+/-28.2)	32.1 (+/-36.0)	13.2 (+/-12.9)	-
Central line duration(days)(mean+/-SD)	21.8 (+/-21.6)	29.9 (+/-25.0)	13.6 (+/-13.2)	-
EUGR		28/48 (58.3%)		
OOP		19/48 (39.6%)		
Transfusion practices and AKI				
PRBC transfusion	93/94	48/48	45/46	-
Number of PRBC (median)(IQR)	5(3-7)	7(5-9)	3 (2-6)	-
Day of 1st PRBC(median)(IQR)	2(1-4)	2(1-4)	1(1-4)	-
Platelets transfusion	33//94(35.1%)	12/48(25%)	21/46(45.6%)	-
FFP transfusion	28/94(29.8%)	11/48(22.9)	17/46(36.9%)	0.45
AKI	27/94(28.7%)	12/48(25%)	15/46(32.6%)	-
Duration of stay				

Duration of stay (days) (mean+/-SD)		122.3 (+/-30.1)	16.2 (+/-17.8)	-
PMA at discharge/ death (weeks)(mean+/-SD)		41.3 (+/-4.0)	26.0 (+/-2.5)	-
Causes of mortality				
Sepsis	7/46 (15.2%)	-	-	-
NEC	14/46 (30.4%)			
IVH	17/46(36.9%)			
Others	8/47(17.4%)			
<p>*p-values in bold are significant.</p> <p>^p-values are given for outcomes where clinically significant comparisons are possible</p>				