

Effect of Birth Weight, Gestational Age, Sex and Intrauterine Growth on Mortality and Morbidity Profile of very Low Birth Weight Babies (VLBW)

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Abstract

Introduction: Very Low birth weight is associated with serious neonatal morbidity. Biologic factors are major determinants in their outcome. We analysed the effect of birth-weight, gestation, sex and intrauterine growth in the mortality and morbidity profile of VLBW babies during the neonatal period. **Methodology:** This is a cross sectional retrospective observational study from April-2012 to August-2014. Baseline demographics, disease features of 97 VLBW babies were analyzed. **Results:** Survival at discharge was 91.75%. There was significant difference in need of ventilation, surfactant, Apnea, ROP, IVH \geq Grade-II, Culture-negative Sepsis among all gestational subgroups. Survival increased as gestation advanced. Maximum decrease in mortality has occurred beyond 28 weeks. Maximum odds difference in need of ventilation, BPD was noted around 28 weeks. Major difference in HS-PDA, IVH, NEC were noted around 30 weeks. Significant difference in need of surfactant, apnea and anemia was observed around 32 weeks. Major decrease in HMD, Hyperbilirubinemia and sepsis were identified around 34 weeks. Analysing intrauterine growth, Significant difference in Need of ventilation, surfactant use, IVH, NEC, Anemia and death was noted between AGA and SGA. Analysing birth weight wise, Survival improved as birth-weight increased. There was significant difference in HS-PDA and IVH in all birth-weight subgroups. Maximum decrease in death was noted in babies >1000 g. Maximum odds difference in BPD, Apnea, Hyperbilirubinemia, IVH, Anemia, ROP and culture negative sepsis occurred around 800g. Major difference in HMD, NEC, Culture positive sepsis was observed around 1000g. Significant odds difference in HS-PDA occurred around 1200g. Maximum decrease in need of surfactant and ventilation was noted around 1400g. **Conclusion:** There was no difference between male and female in survival or morbidities. Survival improved with advancing Gestation, Intrauterine growth and Birth-weight. Analysing intrauterine growth, Significant difference in Need of ventilation, surfactant, IVH, NEC, Anemia and death was noted between AGA and SGA. Significant variations in morbidity profile were noted among birth weight and gestational age subgroups.

Keywords: Survival, Very low birth weight, gestational age, Intrauterine growth retardation

Introduction

The very low birth weight babies are at risk from a wide range of hazards resulting from immaturity of structure and function of various organs [1]. With advanced perinatal & neonatal care, survival of VLBW infants has increased globally. Well equipped, experienced NICUs also have contributed to the increasing survival of VLBW neonates [2,3,4,5]. Studies have reported normal outcomes in 73% of these babies figures vary widely from country to country with reports of up to 90% survival from developed countries to 40% in the developing world [6]. According to 2010 National Vital Statistics Report, in 2006 the mortality rate among infants with VLBW was

240.4 per 1000 live births [7]. There is paucity of data regarding outcome of VLBW babies based on gestational age, birth weight applicable to our population. Outcomes in VLBW infants are best understood as an interaction between biological vulnerability & environmental factors. Does biological factors (birth weight, gestational age, sex, intrauterine growth) has a significant impact on survival and morbidity profile during neonatal period is our research question.

Primary Outcome: To determine the effect of gestational age, birth weight, sex and intrauterine growth in the mortality and morbidity profile of very low birth weight babies during the neonatal period.

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Secondary Outcome: To analyse the morbidities like Respiratory Distress Syndrome (RDS/HMD), surfactant usage, Bronchopulmonary Dysplasia (BPD), Apnea, Hemodynamically significant Patent Ductus Arteriosus (HS-PDA) requiring treatment, Necrotising Enterocolitis (NEC), Intraventricular Hemorrhage (IVH) \geq Grade II, Anemia requiring PRBC transfusion, Sepsis (both culture positive and culture negative Sepsis) and Retinopathy of Prematurity (ROP).

Study Period: 2 years and 5 months (April 2012 to August 2014).

Study Design: Cross sectional Retrospective observational study.

Inclusion Criteria: All babies with birth weight less than 1.5 kg, admitted at Sunrise Superspecialty Children's Hospital were included in the study.

Methodology: This cross-sectional retrospective study was performed from April 2012 to August 2014 on all hospitalized VLBW babies. Relevant pre and perinatal data upto the time of discharge or death, including complications during the course of hospitalization, were collected from the case notes, documented on a predesigned proforma with preformed diagnostic criteria and analysed. The gestational ages were determined by obstetric assessment and modified Ballards score, when antenatal reports were not available [8]. Hyaline membrane disease was diagnosed according to clinical and radiological findings. Retinopathy of prematurity was diagnosed by an ophthalmologist and classified in grades 1 to 5 according to international classification [9]. BPD was diagnosed according to the criteria of Bancalari et al [10] including clinical and radiographic features together with the requirement of oxygen therapy at 28 days of age. Bronchopulmonary dysplasia (BPD) was defined by oxygen requirements at 28 days of life and chronic radiographic changes [11]. The diagnosis of sepsis was confirmed by isolation of the organism in the blood. Patent ductus arteriosus was diagnosed clinically and

confirmed by echocardiography. The diagnosis of Intraventricular Hemorrhage was made by ultrasonogram and was classified according to Papile and Bursten [12]. NEC was determined by the clinical and radiological criteria of Bell et al [13] and only definite NEC (Bell stages II-III) was included. Growth was plotted in Fenton growth charts. **Interventions:** Preterm care as per standard unit protocol. **Data Analysis:** Detailed information including gestational age at diagnosis, birth weight were collected from hospital records of all VLBW admissions. Outcomes were classified as neonatal survival or death. Categorical variables were analyzed using Chi-square analysis with Yates correction. Student 't' test was used to compare the means. A p-value of <0.05 was considered significant.

Results

There were total 1191 newborn admissions during the study period. Among these 1191 babies, 97 babies (8.14%) were very low birth weight babies and were included in the study. Survival rate at discharge among VLBW babies was 91.75%. Among VLBW babies 55.67% (n=54) were male & 44.32% (n=43) were female. However there was no statistical significance (2-Tailed probability=0.2633). Analysing gestational age distribution, 24.74% (n=24) were 31-32 weeks, 20.61% (n=20) were 29-30 weeks and 18.55% (n=18) were 33-34 weeks of gestation. For statistical analysis, birth weight was divided in to 5 subgroups. 7 babies were <800 g, 10 babies between 800 to 1000g, 31 babies between 1000 to 1200g, 24 babies between 1200 to 1400 g and 25 babies were between 1400 to 1500g. When birth weights were plotted against the gestational age on Fenton growth charts, 56.7% (n=55) were AGA, 43.29% (n=42) were SGA. However 2 tailed probability=0.1857 was not significant. For statistical analysis, gestational age was divided in to 5 subgroups. 10 babies were <28 weeks, 21 babies between 28 to 30 weeks, 34 babies between 30 to 32 weeks, 25 babies between 32 to 34 weeks and 7 babies were >34 weeks.

Effect of Gestational Age on Mortality & Morbidity Profile of VLBW Babies

Analysing the gestational subgroups, we estimated the morbidity and mortality between the subgroups.

Figure: 1

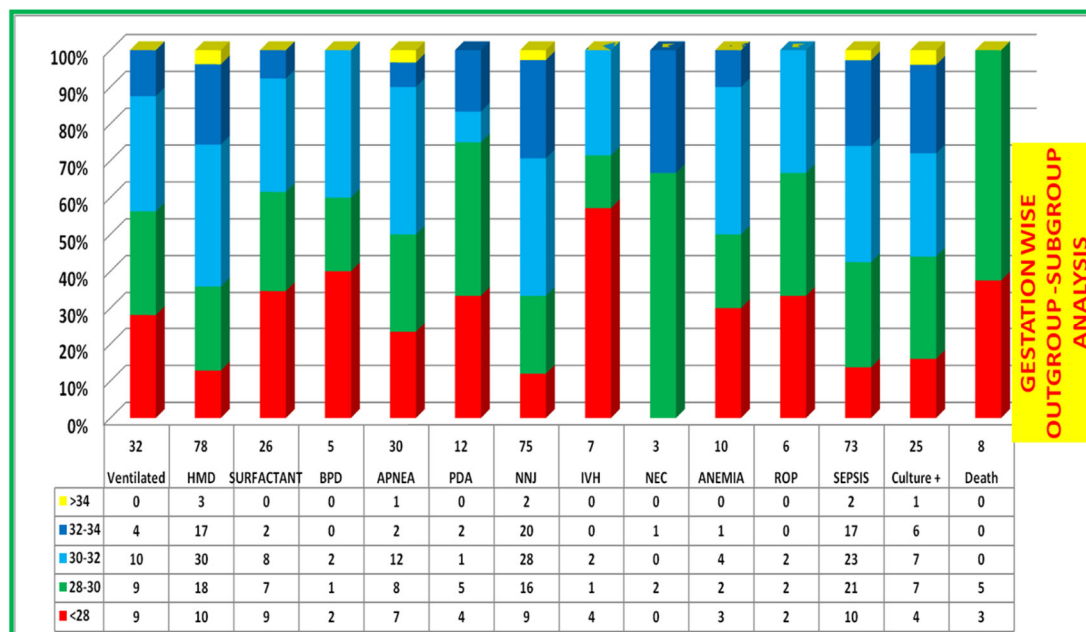


Figure 1 shows the outcome of VLBW babies based upon the gestational subgroups.

Table1: Distribution of Morbidity Profile-Gestation Wise-Subgroup Analysis

	<28	>28	p	<30	>30	p	<32	>32	p	<34	>34	p
Ventilated %	90	26.43	< 0.00001	58.06	21.21	< 0.00001	41.17	12.5	0.0001	35.55	0	< 0.00001
Hmd %	100	78.16	0.1217	90.32	75.75	0.2652	89.23	62.5	0.0310	83.33	42.85	0.0002
Surfactant %	90	19.54	< 0.00001	51.61	15.15	< 0.00001	36.92	6.25	< 0.00001	28.88	0	< 0.00001
Bpd %	20	3.44	0.0005	9.67	3.03	0.0648	7.69	0	< 0.00001	5.55	0	< 0.00001
Apnea%	70	26.43	< 0.00001	48.38	22.72	0.0022	41.53	9.37	< 0.00001	32.22	14.28	0.0085
Pda%	40	9.19	< 0.00001	29.03	4.54	< 0.0001	15.38	6.25	0.0515	12.22	14.28	< 0.0001
Nnj %	90	75.86	0.2794	80.64	75.75	0.7008	81.53	68.75	0.3045	81.11	28.57	< 0.0001
Ivh %	40	3.44	< 0.00001	16.12	3.03	0.0026	10.76	0	< 0.00001	7.77	0	< 0.00001
Nec %	0	3.44	< 0.00001	6.45	1.51	0.083	3.07	3.12	0.9842	3.33	0	< 0.00001
Anemia %	30	8.04	0.0003	16.12	7.57	0.0820	13.84	3.12	0.0093	11.11	0	< 0.00001
Rop %	20	4.59	0.0017	12.9	3.03	0.0136	9.23	0	< 0.00001	6.66	0	< 0.00001
Sepsis%	100	72.41	0.0438	100	63.63	0.0055	83	59.37	0.0494	78.88	28.57	< 0.00001
Culture +%	40	24.13	0.0493	35.48	21.21	0.0603	27.69	21.87	0.4159	26.66	14.28	0.055
Death%	30	5.74	< 0.00001	25.8	0	< 0.00001	7.69	0	< 0.00001	8.88	0	< 0.00001

Table 1 shows the distribution of morbidity profile based upon the gestational subgroups.

A one-sample t-test between proportions was performed to determine whether there was a significant difference among morbidities and death based on gestational age subgroups. The t-statistic was analysed and p value<0.05 was considered significant. Gestation wise < 28 & >28weeks; <30 & >30 weeks; <32 & >32 weeks; <34 & >34 weeks were analysed. It is well known that immature infants (particularly those born <32weeks) are at higher risk for mortality and morbidity and failure to consider gestational age leads to major problem in interpretation that hinder decision-making at both clinical and public health levels [17]. There was significant difference in need of ventilation and surfactant use, Apnea, ROP, (IVH) >= Grade II, Culture negative Sepsis in all subgroups. However culture positive was more significant between <28 & >28weeks. Significant difference in Jaundice was noted between <34 & > 34weeks. Significant difference in HMD was noted between < 32& >32weeks and <34 & >34weeks. BPD and anemia requiring PRBC transfusion, was significant in all subgroups except <30 & >30 weeks. Hemodynamically significant Patent Ductus Arteriosus (HS-PDA) requiring treatment, was significant in all subgroups except <32 & >32weeks. NEC was significant between < 28 & >28weeks and <34 & > 34weeks. Statistical significant difference in death was noted in all subgroups. Survival increased significantly as gestation advanced.

Table 2: Comparison of Proportions / Odds among Gestational Subgroups

Morbidity	</>28	</>30	</>32	</>34
Ventilated	3.4	2.73	3.29	>
HMD	1.27	1.19	1.42	1.94
Surfactant	4.6	3.4	5.9	>
BPD	5.81	3.19	>	>
Apnea	2.64	2.12	4.43	2.25
PDA	4.35	6.39	2.46	>
NNJ	1.18	1.06	1.18	2.83
IVH	11.6	5.32	>	>
NEC	0	4.27	0.98	>
Anemia	3.73	2.12	4.43	>
ROP	4.35	4.25	>	>
sepsis	1.38	1.57	1.39	2.76
Culture+	1.65	1.67	1.26	1.86
DEATH	5.22	>	>	>

Table 2 depicts the comparison of proportions based upon gestational subgroups.

Analysing the proportions of morbidities and mortality among each gestational subgroup, we compared the ratio of morbidities and mortality in each subgroup to

1. estimate maximum risk difference of morbidity and mortality
2. to analyse the gestational age when 0 mortality and 0 individual morbidity was attained.

No death was noted beyond 30 weeks. No BPD, IVH \geq Grade II & ROP were noted beyond 32 weeks. No need of assisted ventilation, surfactant need, Hemodynamically significant Patent Ductus Arteriosus, NEC & Anemia requiring transfusion were noted beyond 34 weeks. Maximum difference in death, need of assisted ventilation & BPD were noted around 28 weeks. Maximum difference in Hemodynamically significant Patent Ductus Arteriosus, IVH \geq Grade II & NEC were noted around 30 weeks. Maximum difference in surfactant usage, apnea and anemia were noted around 32 weeks. Maximum difference in the occurrence of HMD, Hyperbilirubinemia and sepsis were noted around 34 weeks.

Effect of sex in mortality & morbidity profile of VLBW babies

Figure: 2- Sex wise distribution of morbidity profile-subgroup analysis

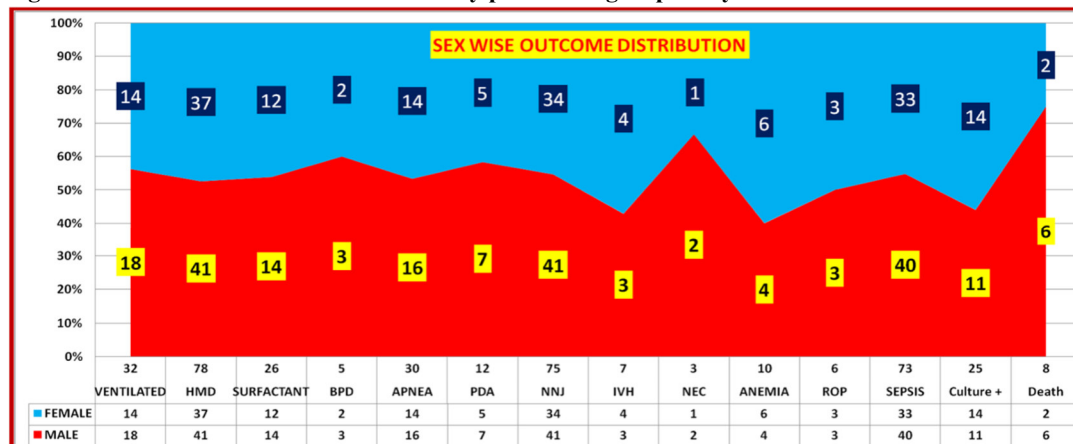


Table 3: Sex Wise Distribution Of Morbidity Profile-Subgroup Analysis

	MALE	FEMALE	p
VENTILATED %	33.33	32.55	0.9248
HMD %	75.92	86.04	0.4340
SURFACTANT %	25.92	27.9	0.7909
BPD %	5.55	4.65	0.7819
APNEA %	29.62	32.55	0.7150
PDA %	12.96	11.62	0.7906
NNJ %	75.92	79.06	0.8043
IVH %	5.55	9.30	0.3380
NEC %	3.7	2.32	0.5803
ANEMIA %	7.4	13.95	0.1617
ROP %	5.55	6.97	0.6933
SEPSIS %	74.07	76.74	0.8309
CULTURE POSITIVE %	20.37	32.55	0.0977
DEATH %	11.11	4.65	0.1076

Table 3 shows the sex wise comparison of morbidity profile of VLBW babies. There was no Statistical significant difference in death and morbidities between male and female subgroups.

Effect of Intrauterine Growth in Mortality & Morbidity Profile of VLBW Babies

Figure 3: Intrauterine Growth Wise Distribution of Morbidity Profile-Subgroup Analysis

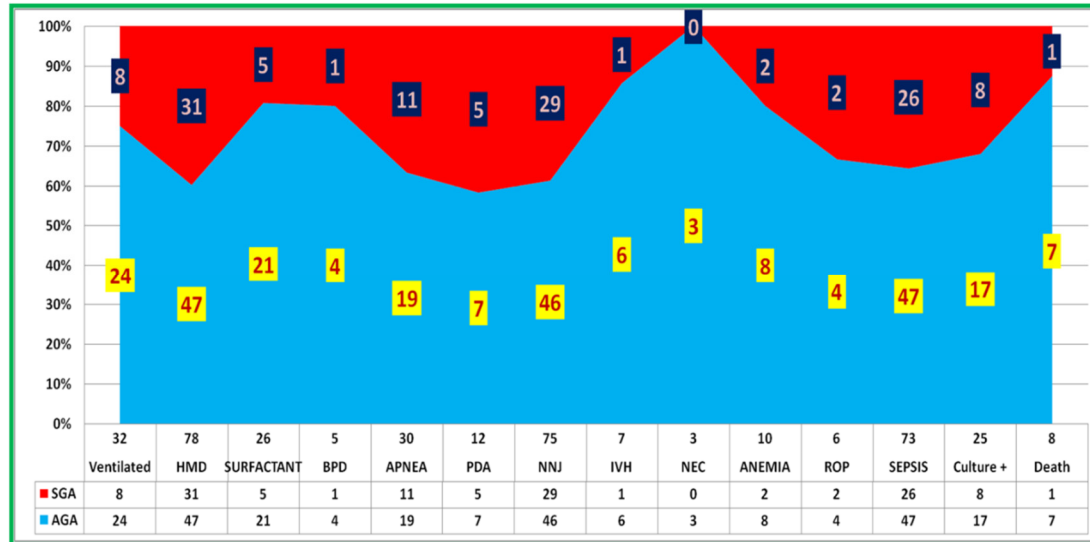


Figure 3 shows the outcome of VLBW babies based upon intrauterine growth.

Table 4 : Growth Wise Distribution of Morbidity Profile- Subgroup Analysis

	AGA	SGA	p
VENTILATED %	43.63	19.04	0.0018
HMD %	85.45	73.8	0.3635
SURFACTANT %	38.18	11.9	0.0002
BPD %	7.27	2.38	0.1197
APNEA %	34.54	26.19	0.2912
PDA %	12.72	11.9	0.8710
NNJ %	83.63	69.04	0.2444
IVH %	10.9	2.38	0.0199
NEC %	5.45	0	<0.0001
ANEMIA %	14.54	4.76	0.0268
ROP %	7.27	4.76	0.4766
SEPSIS %	85.45	61.9	0.0544
CULTURE + %	30.90	19.04	0.0969
DEATH %	12.72	2.38	0.0078

Table 4 shows the intrauterine growth wise comparison of morbidity profile of VLBW babies.

There was significant difference in Need of ventilation, surfactant use, IVH, NEC, Anemia and death was noted between AGA and SGA.

Effect of Birth Weight in Mortality & Morbidity Profile of VLBW Babies

Analysing the Birth Weight subgroups, we estimated the morbidity and mortality between the subgroups. We analysed the variation of mortality and morbidity among,

Figure 4 : Birth Weight Wise Distribution Of Morbidity Profile-Subgroup Analysis

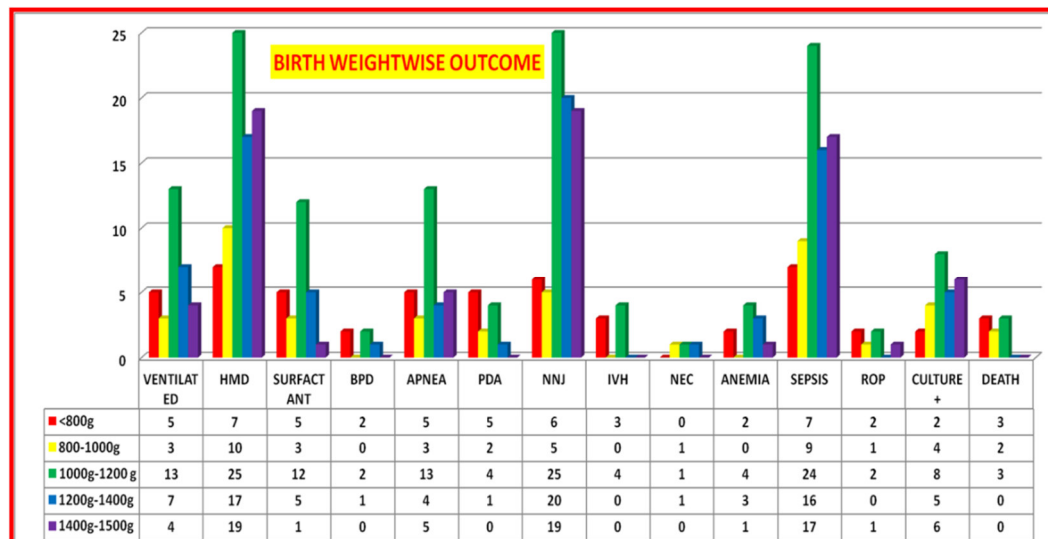


Table 5: Weight Wise Distribution of Morbidity Profile- Subgroup Analysis

	<0.8	>0.8		<1	>1		<1.2	>1.2		<1.4	>1.4	
VENTILATED %	71.42	30	<0.0001	47.05	30	0.0541	43.75	22.4	0.0087	38.88	16	0.0019
HMD %	100	78.88	0.1361	100	76.25	0.0890	87.5	73.46	0.2755	81.94	76	0.6423
SURFACTANT %	71.42	23.33	<0.0001	47.05	22.5	0.0031	41.66	12.24	<0.0001	34.72	4	<0.0001
BPD %	28.57	3.33	<0.0001	11.76	3.75	0.0435	8.33	2.04	0.2322	6.94	0	<0.0001
APNEA%	71.42	27.77	<0.0001	47.05	27.5	0.0242	43.75	18.36	0.0563	34.72	20	0.0483
PDA%	71.42	7.77	<0.0001	41.17	6.25	<0.0001	22.91	2.04	<0.0001	16.66	0	<0.0001
NNJ %	85.71	76.66	0.4848	64.70	71.11	0.5887	75	79.59	0.7168	77.77	76	0.8885
IVH %	42.85	4.44	<0.0001	17.64	5	0.0079	14.58	0	<0.0001	9.72	0	<0.0001
NEC %	0	3.33	<0.0001	5.88	2.5	0.2498	4.16	2.04	0.4021	4.16	0	<0.0001
ANEMIA%	28.57	8.88	0.0012	11.76	10	0.7108	12.5	8.16	0.3472	12.5	4	0.0377
ROP %	28.57	4.44	<0.0001	17.64	3.75	0.0025	10.41	2.04	0.0181	6.94	4	0.3816
SEPSIS%	100	73.33	0.0524	94.11	71.25	0.0784	83.33	67.34	0.1988	77.77	68	0.4259
CULTURE + %	28.57	25.55	0.6866	35.29	23.75	0.1379	29.16	22.44	0.3571	26.38	24	0.7418
DEATH%	42.85	5.55	<0.0001	29.41	3.75	<0.0001	16.66	0	<0.0001	11.11	0	<0.0001

Table 5 shows the distribution of morbidity profile based upon the Birth weight subgroups.

A one-sample t-test between proportions was performed to determine whether there was a significant difference among morbidities and death based on birth weight subgroups. The t-statistic was analysed and p value <0.05 was considered significant. Birth weight wise < 800g & >800g; <1000g & 1000g; <1200g & 1200g; <1400g & 1400g were analysed.

There was significant difference in Hemodynamically significant Patent Ductus Arteriosus (HS- PDA) requiring treatment and (IVH) >= Grade II in all subgroups. Statistical difference in need of ventilation was significant in all subgroups except between <1kg & >1kg. Significant difference in Surfactant use, BPD was noted in all subgroups except between <1.2 & >1.2Kg. There was no significant difference in HMD, Culture positive and culture negative sepsis among subgroups. Significant difference in Apnea was noted between <800 & >800g. Significant difference in ROP was noted between < 800 & >800g and between <1000 & >1000g. No statistical difference was noted in Hyperbilirubinemia among all subgroups. Significant difference in NEC, Anemia requiring PRBC transfusion was observed between <800 & >800g and <1400g & >1400g.

Table 6: Comparison Of Proportions / Odds Among Birth Weight Subgroups

Morbidity	</> 800	</> 1000	</> 1200	</> 1400
Ventilated	2.38	1.56	1.95	2.43
HMD	1.26	1.31	1.19	1.07
Surfactant	3.06	2.09	3.4	8.68
BPD	8.57	3.13	4.08	>
Apnea	2.57	1.71	2.38	1.73
PDA	9.19	6.58	11.23	>
NNJ	1.11	0.9	0.94	1.02
IVH	9.65	3.52	>	>
NEC	0	2.35	2.03	>
Anemia	3.21	1.17	1.53	3.12
ROP	6.43	4.7	5.1	1.73
sepsis	1.36	1.32	1.23	1.14
Culture+	1.11	1.48	1.29	1.09
DEATH	7.77	7.84	>	>

Table 6 depicts the comparison of proportions based upon Birth Weight subgroups.

No IVH \geq Grade II & death were noted in babies with birthweight more than 1200g. No Hemodynamically significant Patent Ductus Arteriosus, BPD & NEC were noted in babies with birthweight more than 1400g. Maximum difference in BPD, Apnea, Hyperbilirubinemia, IVH \geq Grade II, Anemia, ROP and culture negative sepsis were noted around 800g birthweight. Maximum difference in death, HMD, NEC, Culture positive sepsis were noted around 1000g. Maximum difference in Hemodynamically significant Patent Ductus Arteriosus was noted around 1200g. Maximum difference in need of surfactant and need of ventilation was noted around 1400g birth weight.

34weeks.

Discussion

Survival rate at discharge among VLBW babies in our study was 91.75%. There has been global improvement in VLBW survival. The American Academy of Pediatrics policy statement on neonatal care states that only Level III hospitals should take care for infants less than 32 weeks gestation [14]. Since 1990, Healthy People Objective for 2000, 2010 and 2020 have included the goal to increase the proportion of VLBW infants born at LEVEL III hospitals to 90 percent [15]. In 2008 the National Quality Forum endorsed a series of 17 quality measures for perinatal care. One of these quality measures states that infants <1500g should be delivered at a hospital with a Neonatal Intensive care unit [16]. Though majority of our VLBW babies were out born, we noted good survival due to prompt early referral and golden hour management including temperature. There was significant difference in need of ventilation, surfactant, Apnea, ROP, IVH \geq Grade-II, Culture-negative Sepsis among all gestational subgroups in our study. Survival increased as gestation advanced. Maximum decrease in mortality occurred beyond 28 weeks. Maximum odds difference in need of ventilation, BPD was noted around 28weeks. Major difference in HS-PDA, IVH, NEC occurred around 30 weeks. Significant difference in need of surfactant, apnea, anemia was observed around 32weeks. Major decrease in HMD, Hyperbilirubinemia, and sepsis occurred around

J C Velaphi et al in his study found that female gender had lesser morbidity than male. Similar findings were also noted by Cartlidge et al and Stevenson DK et al [18,19,20]. However we did not observe the male disadvantage in our study. Birth weight in particular is strongly associated with fetal, neonatal and postneonatal mortality and with infant and child morbidity [21,22]. Impairments in fetal growth can have adverse consequences in terms of mortality, morbidity, growth and performance [21,22,23]. We noted Statistical significant difference in Need of ventilation, surfactant use, IVH (\geq Grade II), NEC, Anemia requiring PRBC transfusion and death between AGA and SGA. Sorina Grisaru et al in his study found that SGA infants were at increased risk for grades 3-4 ROP (OR 2.07), BPD (OR 2.52), NEC (OR 1.32) and Mortality (OR 2.37) [24]. Dhaliwal CA et al in his study found that SGA infants

were reported to be more likely to develop any stage of ROP compared to AGA peers [25]. Zaw W et al, Hallstrom M et al, Westby Word SH et al in their studies observed that SGA neonates were at increase risk for NEC [26,27,28]. We noted in our study that there was significant difference in Need of ventilation, surfactant use, IVH, NEC, Anemia and death was noted between AGA and SGA. While Analysing birthweight wise,

Survival improved as birth-weight increased in our study. There was significant difference in HS-PDA and IVH in all birth-weight subgroups. Maximum decrease in death was noted in babies >1000g. Maximum odds difference in BPD, Apnea, Hyperbilirubinemia, IVH, Anemia, ROP and culture negative sepsis occurred around 800g. Major difference in HMD, NEC, and Culture positive sepsis was observed around 1000g. Significant odds difference in HS-PDA occurred around 1200g. Maximum decrease in need of surfactant and ventilation was noted around 1400g. S C Velaphi et al in his study noted that the increase in survival rates by 100g increments was marked between 600 and 1000g compared with between 1000 and 1499g, reflecting severe organ immaturity at the limits of viability. He noted that the odds of survival to hospital discharge were much lower among infants weighing less than 1000g and increases with increasing Birth weight, almost doubling with each increase of 100g when compared with infants in the 1000-1099g weight group. There were no differences in odds of survival for infants in the 1100-1199g and 1000-1099g weight groups[18]. We noted Statistical significant difference in death was noted in all subgroups. Survival increased significantly as birth weight increased.

Conclusion

With advances in neonatal care particularly with VLBW and premature babies there is improvement in survival with decreasing morbidities. There was no difference between male and female in survival or morbidities. We noted improved survival with advancing Gestation, Intrauterine growth and Birth weight. Analysing intrauterine growth, significant difference in Need of ventilation, surfactant, IVH, NEC, Anemia and death was noted between AGA and SGA. Significant variations in morbidity profile were noted among different birth weight and gestational age subgroups. The present study is limited because the study population is small and the study period is short. However, a good initial database is presented and can be useful for future research in this region. If substantiated by future prospective studies, these data may help clinicians to counsel families regarding the adverse morbidity and mortality based on gestation, sex, intrauterine growth and birth weight.

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Permission from IRB: Yes

Abbreviations

VLBW : Very Low Birth Weight, **ROP :** Retinopathy Of Prematurity, **IVH :** Intraventricular Hemorrhage, **HS-PDA :** Hemodynamically Significant Patent Ductus

Arteriosus, NEC : Necrotising Enterocolitis, **BPD:** Bronchopulmonary Dysplasia, **RDS :** Respiratory Distress Syndrome, **HMD :** Hyaline Membrane Disease, **PRBC :** Packed Red Blood Cell, **NNJ :** Neonatal Jaundice, **AGA :** Appropriate For Gestational Age, **SGA :** Small For Gestational Age, **NICU:** Neonatal Intensive Care Unit

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