Comparitive Study Of Short-Term Outcomes Of Preterm Babies ≤30 Weeks In A Tertiary Care Hospital Between India And The U.K

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Research article

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Abstract

Large numbers of preterm babies are born in middle income countries and neonatal care is improving in these countries. However, comparative clinical outcomes of preterm babies between a tertiary neonatal unit from middle income country and higher income country is limited.

Objective: To compare the clinical profile and short-term outcomes of preterm babies ≤ 30 weeks gestation admitted to a tertiary care hospital in India and the U.K.

Design: Retrospective cohort observational study using anonymised data from Electronic Patient Records.

Setting: Regional tertiary neonatal intensive care unit (NICU) of Manipal Hospitals, Bangalore, India and Homerton University Hospital, London, UK.

Participants: Preterm babies born at ≤ 30 weeks gestation admitted to NICUs over five year period (January 2011 to December 2015). Infants with major congenital abnormalities were excluded.

Intervention: This is an observational study and routine care was provided as per departmental standard protocols.

Main outcome measures: Comparison of neonatal unit mortality between two centres, infant morbidities till discharge from neonatal unit.

Results: A total of 740 babies from the U.K centre and 294 babies from Indian centre were enrolled into the study. The mean gestational age in the U.K cohort was 26.6 ± 2.16 weeks, whereas in Indian cohort was 28.4 ± 1.66 weeks (p,<0.001). A significantly lower number of mothers received antenatal steroid (37% v 73%), and higher number of babies were inborn (78.6%) in Indian centre compared to the UK centre (67.3%; p < 0.001). Incidence of BPD and IVH ≥ grade 2 was significantly lower, and ROP needing treatment was significantly higher in Indian centre. Higher number of babies were treated for ductus arteriosus and incidence of

culture positive sepsis was significantly high in Indian cohort babies. Survival of babies born at gestational age > 28 weeks was comparable between the U.K and Indian centres. Survival of babies born at ≤ 28 weeks gestation was lower in Indian centre.

Conclusions and relevance: The survival of babies above 28 weeks prematurity was comparable between a tertiary care centre in India and the U.K. However, survival of babies ≤ 28 weeks gestation was lower in Indian centre. Incidence of ROP and sepsis was higher in Indian centre.

Introduction

Every year 15 million babies are born premature and one in every 10 babies is a preterm around the world [1,2]. Preterm birth rates have been reported to range from 5% to 7% of live births in developed countries but are estimated to be higher in developing countries which is as high as 18%. Over 60% of preterm births occur in Africa and South Asia. Striking inequalities exist between developed and developing countries in terms of the survival chances of a preterm infant. In many developing countries, infants weighing less than 2000 g corresponding to about 32 weeks of gestation in the absence of intrauterine growth restriction have little chance of survival. More than half of the babies with gestation ≤26 weeks survive in developed countries compared to low income countries where 90% of babies die[3,4]. However there has been drastic improvement in the survival and outcome of these babies over the past decade even in the developing countries which is solely attributed to the improvement in the level of neonatal care**.** A survey done recently in India showed that the median survival rate in extremely low birth babies (birth weight less than 1000gram) is as high as 60% and that in very low birth weight babies (less than 1500grams) is about 88%[5]. This study helps us to understand and compare the preterm birth related factors, level of care, their morbidities, outcomes and overall survival between level 3 units in the United Kingdom and India.

Methods

A retrospective Electronic Patient Records (EPR) review of preterm infants born at gestational age ≤30 weeks who were admitted to a tertiary care hospital in India and the U.K over a period of 5 years (2011-2015) was conducted. Babies with major congenital (e.g.: heart defects like Transposition of great vessels (TGA) or genetic abnormalities (e.g.: trisomies) were excluded. The Indian center is the Manipal Hospitals, a multispecialty private teaching hospital in Bangalore, which is an accredited level 3b Neonatal Intensive Care Unit (NICU) by the National Neonatal Forum of India (NNFI) [6] with 30 cots capacity (14 ITU, 8 HDU & 8 SCBU). The nurse patient ratio is 1:1 for ventilated babies and 1:3 or 1:4 HDU/SCBU babies. The unit has support from various disciplines like cardiology, pediatric surgery, neurosurgery, ophthalmology, genetics, endocrinology and otorhinology (ENT). The hospital has a well-established fetal medicine and high risk obstetric unit. The unit provides care for inborn and outborn babies in equal numbers. Mothers of inborn babies receive appropriate antenatal care including fetal monitoring and antenatal steroid. The outborn babies are referred from different parts of Karnataka state and three other adjacent states (Andhra Pradesh, Telangana & Tamilnadu) with variable antenatal care and antenatal steroid uptake. The unit resuscitates babies from ≥24 weeks of gestation at birth as per ILCOR 2015 guidelines. The UK center is the Homerton University Hospital in London, which is a large tertiary NICU, and one of 4 NICUs in North East and North Central London Neonatal Operational Delivery Network, the unit provides regional medical intensive care services[7].The unit has 46 cots capacity (16 ITU, 8 HDU & 22 SCBU). The network agreed pathway is that all high-risk pregnancies and impending preterm deliveries of less than 28 weeks' gestation transferred in-utero to Homerton hospital. The hospital has a regional fertility, fetal medicine and high risk obstetric units. Babies requiring surgery will be transferred to Royal London Hospital (pediatric surgery), Guy's and St Thomas' Hospital (cardiac) and Great Ormond Street Hospital (cardiac & all other sub-specialties). The unit practice was to resuscitate

babies from ≥23 weeks of gestation at birth as per national guideline (since October 2019, the unit resuscitates babies born at 22 weeks' gestation after careful risk assessment) [8]. Almost all mothers receive full antenatal care and steroids uptake rate is more than 90%. The unit provide care to both inborn and outborn (ex-utero transfer) babies. There is a dedicated Neonatal Transfer Service (NTS) for London. Respiratory care provided in the both centers was as per European consensus [9] but in Indian center use of surfactant was physician's discretion due to cost factor. Use of CPAP, non-invasive and invasive ventilation, and indication for ventilation were similar in both centers as per consensus guidelines. Total Parenteral Nutrition and enteral feeding were given as per unit protocols prepared based on internationally accepted guidelines. Blood culture positive sepsis was defined as per CDC definition [10] in both centers.

Data was collected on antenatal factors including maternal risk factors, steroids, chorioamnionitis, etiology for preterm delivery (spontaneous and others), risk factors for sepsis (presence of ≥1 additional risk factors like maternal fever, chorioamnionitis, pre-labour rupture of membranes >18 hours, maternal Group-B streptococcus positive), mode of delivery, condition at birth, demographics of the baby, morbidities such as Intraventricular Hemorrhage, Patent Ductus Arteriosus (PDA), Necrotizing Enterocolitis (NEC), Retinopathy of Prematurity (ROP), Bronchopulmonary Dysplasia (BPD), blood culture proven infection, hypoglycemia, duration of neonatal unit admission, duration of ventilation, and final outcome (discharge to home or death). Babies with birthweight <10th centile was defined as intrauterine growth restricted (IUGR) [11] from both centers. Hypoglycemia was defined any episode of blood sugar level (glucometer) less than <45mg/dl (Indian center) or <2.6mmol/l (UK center) during NICU stay [12] , IVH was classified according JJ Volpe [13], NEC staging as per Modified Bell's staging [14] , ROP was classified according to International classification for retinopathy of prematurity [15] & BPD was defined as oxygen dependency for 28 days and classified at 36weeks post conceptional age based on severity [16]. Discharge criteria was similar in both hospitals: baby should be minimum 35 weeks post menstrual age (PMA), weighing 1.8 kg and on full feeds by bottle/paladay or breastfeeding. Stable BPD babies on low flow nasal cannula oxygen otherwise meeting discharge criteria were discharged home with home oxygen support from both centers.

Data from both centers were collected after approval from the Research Ethics Committee (London - Westminster Research Ethics Committee (Ref: 18/LO/0339) and Manipal REC at respective centers. Parents' consent was not obtained as this is a retrospective anonymized routinely collected clinical data study using Electronic Patient Records (EPR).

Patient and Public Involvement : Patient/Care takers were not involved in the study directly. This study was conducted using anonymised routinely collected clinical data from Electronic Patient Records (EPR).

Statistical analysis: Data was expressed as descriptive statistics using R software 3.2.3. Statistical analysis was done to compare outcomes of babies between two centres making adjustments for confounding factors. The categorical variables were analysed using Chi Square test and continuous

variables using parametric or non-parametric tests as appropriate. Statistical significance was set at p value <0.05.

Results

A total of 740 babies from the UK centre and 294 babies from Indian centre were enrolled into the study. The mean (SD) gestational age of babies in the UK cohort 26.6 (2.16) weeks was significantly lower compared to Indian cohort 28.4 (1.66) weeks ($p < 0.001$). The mean (SD) birth weight of babies in the UK cohort 923.0 (292.14) grams was significantly lower compared to Indian cohort 1121.0 (320.75) grams ($p < 0.001$). There was no significant difference in gestation specific birthweight between two cohorts. Sex distribution is similar in two centres with male predominance. A significantly higher percentage of mothers received antenatal steroid, and lower percentage of mothers had antenatal risk factors for preterm delivery and sepsis in the UK cohort (Table 1). A significantly higher number of babies were inborn (78.6%) in Indian centre compared to the UK centre (67.3%; $p < 0.001$). A significantly higher number of babies (73.5%) were delivered by c-section in Indian cohort (73.5%) compared to the UK cohort (45.5%; $p < 0.001$). Surfactant given in the delivery room and NICU in the UK cohort (86.9) compared to Indian cohort (49.3%; $p < 0.001$) is significantly higher. Other baseline characteristics are mentioned in Table 1. Similarly significantly higher number of babies in Indian centre developed hypoglycaemia, blood culture proven sepsis and pulmonary haemorrhage compared to the UK centre. The incidence of pneumothorax was comparable between two centres (Table 2). Higher number of babies were treated for PDA (32.3% v 10.7%; $p < 0.001$) and ROP (12.9% v 7.7%; p 0.002) in Indian centre. The incidence of BPD and IVH ≥ Grade 2 were significantly lower in babies managed at Indian centre. The incidence of NEC ≥ Stage 2 was comparable (Table 2). The mean (SD) duration of ventilation days in UK cohort was 10.9 (15.73) and Indian cohort 5.4 (4.90) (p 0.378); similarly the mean (SD) oxygen dependency days was 32.6 (34.07) and 9.9 (9.26), ($p < 0.001$) in the UK and Indian cohort respectively (Fig. 1a,1b). The mean (SD) total duration of NNU days in UK cohort was 43.1 (34.07) and in Indian cohort was 34.9 (24.38), (p 0.005) (Fig. 2).

Table 1
Baseline characteristics

Characteristics	U.K cohort		Indian cohort		P value
	Count	%	Count	%	
Sex					
Male	395	53.4	160	54.4	0.782
Female	345	46.6	134	45.6	
Place of birth					
Inborn	498	67.3	231	78.6	< 0.001
Outborn	242	32.7	63	21.4	
Birth order					
Primi	620	83.8	196	66.7	< 0.001
Multi	120	16.2	98	33.3	
Aetiology of Preterm					
Spontaneous	589	79.6	103	35.0	< 0.001
Known Aetiology	151	20.4	191	64.9	
Antenatal Steroids					
Yes	543	73.4	110	37.4	< 0.001
No	197	26.7	184	62.6	
Risk of factor for sepsis					
None	658	88.9	166	56.5	< 0.001
Known Risk Factors	82	11.0	128	43.6	
Mode of Delivery					
NVD	403	54.4	78	26.5	< 0.001
LSCS	337	45.5	216	73.5	
Apgar @ 10minutes					
≥ 4	735	99.3	281	95.6	< 0.001
< 4	5	0.7	13	4.4	

NVD – Normal vaginal delivery, IUGR -Intrauterine growth restriction

Characteristics	U.K cohort		Indian cohort		P value
	Count	%	Count	%	
Surfactant administered at delivery/neonatal unit					
Yes	643	86.9	145	49.3	< 0.001
No	97	13.1	149	50.7	
Antenatal Doppler Studies					
Abnormal	82	11.1	8	2.7	< 0.001
Normal	658	88.9	286	97.3	
IUGR babies					
Yes	96	13.0	16	5.4	< 0.001
No	644	87.0	278	94.6	
NVD – Normal vaginal delivery, IUGR -Intrauterine growth restriction					

Table 2

Comparison of preterm morbidities between two cohorts

Major morbidities	U.K Cohort n (%)	Indian Cohort n (%)	P value
Hypoglycaemia	139(18.8)	6 (2)	<0.001*
Pulmonary Haemorrhage	31(4.2)	29(9.9)	0.001*
Pneumothorax	38(5.1)	16(5.4)	0.877
Blood culture proven sepsis	13(1.7)	95(32.4)	<0.001*
Surgical conditions (any)	15(2)	12(4.1)	0.082
BPD at 36 weeks	229(30.9)	47(16)	<0.001*
PDA treated	79(10.7)	94(32.3)	<0.001*
IVH ≥grade 2	115(15.6)	24(8.2)	<0.001*
NEC ≥stage 2	85(11.5)	36(12.3)	0.884
ROP needing Laser/Avastin	56(7.7)	38(12.9)	0.002*

Table 3

Gestation specific survival at discharge between two cohorts

Gestational age	U.K cohort		India cohort		p value
	Number of babies admitted	Number of babies survived (%)	Number of babies admitted	Number of babies survived (%)	
22	1	1 (100)	1	0 (0)	-
23	43	27 (62.8)	1	0 (0)	-
24	116	92 (79.3)	3	1 (33)	0.232
25	109	86 (78.9)	12	6 (50)	0.026
26	89	77 (86.5)	31	14 (45.2)	< 0.001
27	103	94 (91.3)	29	23 (79.3)	0.144
28	102	96 (94.1)	57	47 (82.5)	0.038
29	82	81 (98.8)	52	50 (96.2)	0.687
30	95	91 (95.8)	108	103 (95.4)	0.844
Total	740	645 (87.2)	294	244 (83)	0.091

Survival

The overall survival rate in Indian (83%) and the UK (87.2%) cohorts was comparable (p 0.091). However, survival of babies born at ≤26 weeks gestation was significantly lower in Indian centre. Survival rate was lower for babies born at 27 weeks in Indian centre compared to the UK centre but this was not significant (p 0.144). Survival of babies born at 28 weeks gestation was significantly lower in India centre. Survival of babies born at 29 & 30 weeks gestation was similar between two centres (Table 3).

Discussion

The survival of preterm babies had increased over the past 2 decades especially for babies less than 28 weeks gestational age in developed countries [4] however the survival in developing countries at similar gestational age is still catching up. Recent studies have revealed that median survival of VLBW babies in India is as high as 88% [5].There is no comparative study of preterm survival between a level 3 centre in the U.K(country with advanced neonatal care) and comparable tertiary care centre in India. This study was intended to make such comparison. In our study the overall survival rate is 87.2% and 83% (p = 0.091) in U.K and Indian cohort respectively which perhaps is not the true reflection between two cohorts.

When the survival according to gestational age was analysed there is a wide discrepancy in survival rate of babies ≤ 28 weeks. Survival at 23 weeks, 24 weeks, 25 weeks, 26 weeks and 27 weeks is 62% vs nil, 73.9% vs 33%, 78.9%vs 50%, 86.5% vs 45.2%, 91.3% vs 79.3% in U.K and Indian Cohort respectively. The survival of babies at the U.K study centre is comparable or slightly better for babies born at 25 to 30 weeks and significantly better for ≤ 24 weeks gestational age when compared to gestation specific survival statistics for England [17] ($p < 0.001$) (Table 4). Similarly when the Indian study centre was compared to a similar centre data [18] (due to paucity of overall national published data for gestation specific mortality) from India, the outcomes were better in the Indian study centre with statistical significance ($p < 0.001$) at 28, 29 & 30 weeks' gestation. There is obvious significant difference in survival outcomes for babies less than 28 weeks of gestational age between the two study centres studied from India and the UK. Lower rate of antenatal steroid cover in Indian centre may be an important factor for increased mortality. In India resuscitation guidelines for babies less than 28 weeks is an ethical conundrum. There are no strict ethical guidelines, poor parental acceptability, financial constraints, lack of robust support post discharge from the state, leave against medical advice (LAMA) before discharge are known factors [19]. In summary many non-medical factors will influence the outcome in Indian scenario.

Table 4
Comparison of survival by gestational age at discharge in two study centres with respective country's data

Gestational age	Survival % UK study centre	Survival % England overall[μ]	p value	Survival % Indian study centre	Survival % Indian data[#]	p value
22	100 [$]	17.9	0.368	-	-	-
23	62.8	35.9	< 0.001*	-		-
≤ 24	-	-	-	20.0	9.1	0.541
24	79.3	58.6	< 0.001*	33.0	-	-
25	78.9	74,0	0.252	50.0	33.2	0.361
26	86.5	83.4	0.431	45.2	33.2	0.358
27	91.3	88.4	0.367	79.3	69.2	0.351
28	94.1	92.4	0.513	82.5	62.3	0.017*
29	98.8	95.7	0.169	96.2	80.0	0.017*
30	95.8	97.5	0.293	95.4	80.0	0.009*

*p value significant (p < 0.05)

[#] Single centre data from All India Institute of medical science[18]

[$] n = 1, at 22 weeks of gestation at Study centre

[μ] Gestation specific survival percentage – England (2008–2014)[17]

Babies managed in the UK centre were more immature compared to babies treated in Indian centre. A significantly higher number of babies were IUGR in the UK centre. The catchment area of Homerton hospital has a large ethnic minority population, significant deprivation and maternal co-morbidities such as diabetes and hypertension. Networking hospitals also transfer women with pregnancy induced hypertension and fetal growth restriction for specialist care to Homerton, which could explain higher number of IUGR babies in the UK centre. When the major preterm morbidities were analysed the rates of BPD was higher in the U.K cohort (30% vs 16%) due to increased survival of babies ≤26 weeks of gestation compared to Indian cohort. EPICure 2 study [4] showed nearly 60% of babies ≤26 weeks had BPD. Studies from India [20,21] reported an incidence of BPD of 28.7%, 10.7% & 11.2% in infants less than 28 weeks, 29-30 weeks and 31-32 weeks respectively The BPD rates from Indian centre in this study is lower than reported studies from India. Necrotising enterocolitis ≥stage 2 is 11.5% and 12.6% in U.K

and Indian cohort, results are comparable to the previous studies [23].Number of babies with severe Retinopathy of Prematurity (ROP) and number of ROP needing treatment with laser or Avastin was significantly higher in Indian centre (12.9% vs 7.7%) despite higher gestational age of cohort than the UK centre possibly explained by difference in practices or higher risk factors. EPICure study [4] from the UK has shown an increased incidence of ROP needing treatment (Laser/Avastin) from 13% to 22%, however data from India for babies with ROP needing treatment (laser/Avastin) is between 16.6-20.7%[23,24]. Intraventricular haemorrhage grade 2 and above was 15.6% and 8.2% ($p < 0.001$) in U.K and India respectively which is slightly less than the previous studies [4,25].

Significantly higher number of babies from Indian centre (32.3% vs 10.7%) received treatment (medical and surgical) for Patent Ductus Arteriosus (PDA). EPICure 2 study [4] revealed about 51% of babies ≤26 weeks received treatment (medical/ surgical) during their stay in neonatal intensive care unit. The percentage of babies treated for PDA in Indian cohort is high due to low threshold for PDA closure. Both the centres used different criteria for PDA treatment decision. At Homerton hospital (UK centre), only ECHO confirmed symptomatic PDA in a ventilated baby received PDA treatment. In Indian centre, ECHO confirmed symptomatic PDA and needing oxygen >30% criteria was used. From various previous studies we know that PDA treatment rates depend on the individual centres, treating neonatologist and many other factors [26]

The proportion of mothers who received at least one complete course of antenatal steroids was 73.4% in the U.K cohort as compared to only 37.4% in Indian cohort. According to NNAP U.K 2016 data around 86% of eligible mothers received antenatal steroids [27] and in India there is wide variation in steroid uptake rate ranging from 48% to 74% [24,28] from previous studies . The low rate in Indian cohort perhaps presumed to be due to more high risk mother where there was not enough time to give antenatal steroid. There is clear evidence that antenatal steroid helps in reducing mortality and complications of prematurity in developed and developing world [29]. A significantly lower number of babies received surfactant during resuscitation at birth or any time during first 72 hours (86.9% versus 49.3%) in Indian centre; this may be because of babies in Indian cohort were of higher gestation and did not require surfactant, and arguably cost is also a factor. A study form India [30] reported around 43% of babies less than 32 weeks received surfactant. The risk factor of sepsis prior to delivery like preterm pre-labour rupture of membranes (pPROM) >24hours, foul smelling liquor, chorioamnionitis, maternal fever was found to be 11% in U.K cohort as compared to significant 43.6% ($p<0.001$) in Indian cohort. This corroborates with a significant postnatal blood culture proven sepsis (1.7% v 32.4%) in Indian cohort, it is known from previous studies the increased incidence of sepsis in Indian context [31].

In U.K due to regionalisation of neonatal care the proportion of babies delivered at specialist care centres improved from 18% to 49% and the survival of premature babies has improved from 88% to 93% [32]. On the contrary, in India there is no regionalisation of neonatal care. There are only few centres of excellence in public sector where majority of babies are born. The lack of robust transport facility or collaboration [33] between public and private sectors, inability to bear the high expenses of preterm babies, lack of universal insurance coverage compels the health care providers and parents to go for withdrawal of life

supporting care or LAMA when faced with dilemma of treating babies less than 26weeks. The Government of India (GOI) through its National Health Mission (NHM) programme is providing many rural and urban districts now with special newborn care units (SNCUs) with provision for at least secondary level care along with providing trained manpower with the aim to reduce neonatal mortality rate (NMR) from the current 29 per 1000 live births to <10 per 1000 live births across the country by 2030 [34]. Since the start of NHM, 51% of pregnant women are receiving 4 or more antenatal visits and this has rose form 37% over past decade [35]. Improvement in coverage of antenatal check-up under NHM and uptake of antenatal steroids could perhaps leads to decrease in NMR as prematurity contributes to about 35% of neonatal mortality. Whether these strategies are enough or more robust strategies are needed like investing in advanced neonatal care (surfactant, CPAP, ventilators, parenteral nutrition) for extreme preterm babies is a question to reckon about.

Limitations

A large difference in sample size and significant difference in gestational age of babies managed between Indian and the UK centres. Details of antenatal care, day to day management of babies in NICU, details of early onset and late onset sepsis, death within 24 hours or labour ward deaths, and limitation of life supporting treatment (withdrawal, withholding or Do Not Resuscitate Order), leave against medical advice (LAMA), discharge weight and gestation were not studied. The other contributing factors such as family demographics, hospital settings including staff ratio to number of patients and level of staff training in neonatal medicine were not investigated.

Conclusion

The survival of babies born at more than 28 weeks of gestation treated in a tertiary neonatal unit from India and the UK is comparable. However, survival of babies born at ≤28 weeks of gestation is still a challenge in best of centres in India. Only 37% mothers received antenatal steroid from Indian centre. Significantly higher number of babies developed severe ROP and received treatment for PDA from Indian centre despite treating more mature babies compared to the UK centre. The overall survival and morbidities of preterm infants in middle income countries could be improved by increasing the antenatal steroid provision to all eligible pregnant women. Further studies including details of antenatal care are required to draw firm conclusion.

Declarations

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Contributors: NA, SD and KN developed the study design. SD: Conceived the idea, collected and sorted the data from two centres, drafted the initial manuscript. NA: Supervised the data collection from the UK and

also the final manuscript. KN: Supervised data collection from India and final manuscript. AK conducted statistical analysis of data. SD, NA, KN and AK approved the final manuscript.

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Conflicts of interest: Nil

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Figures

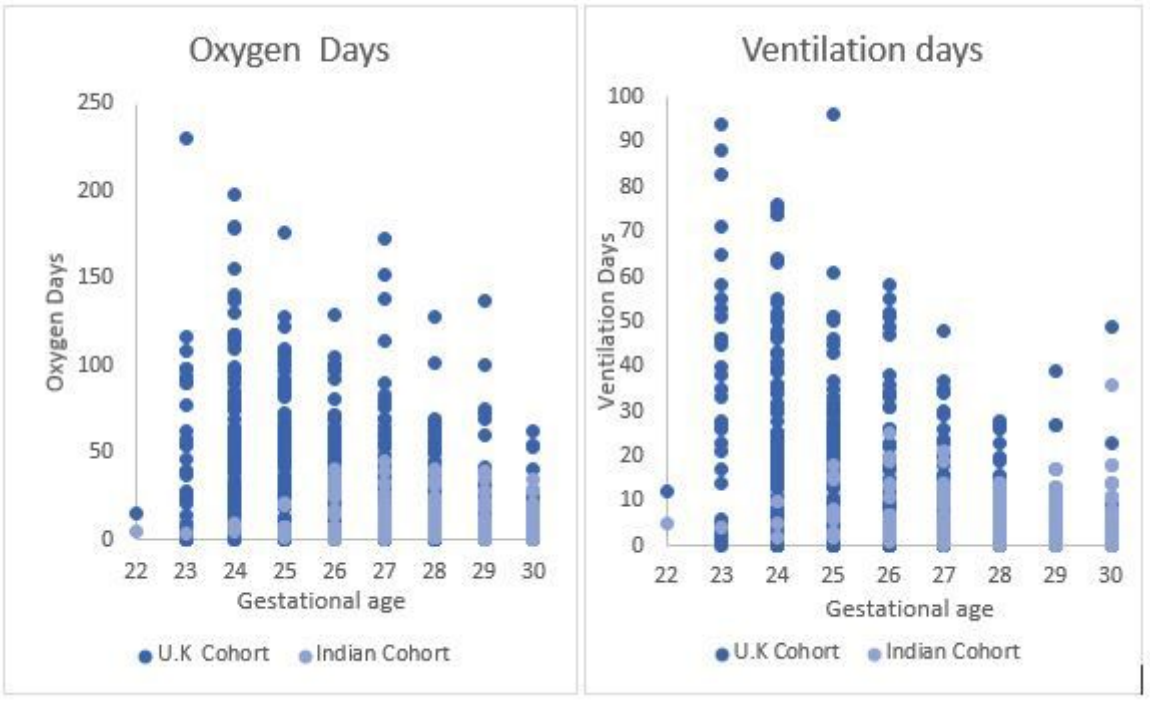
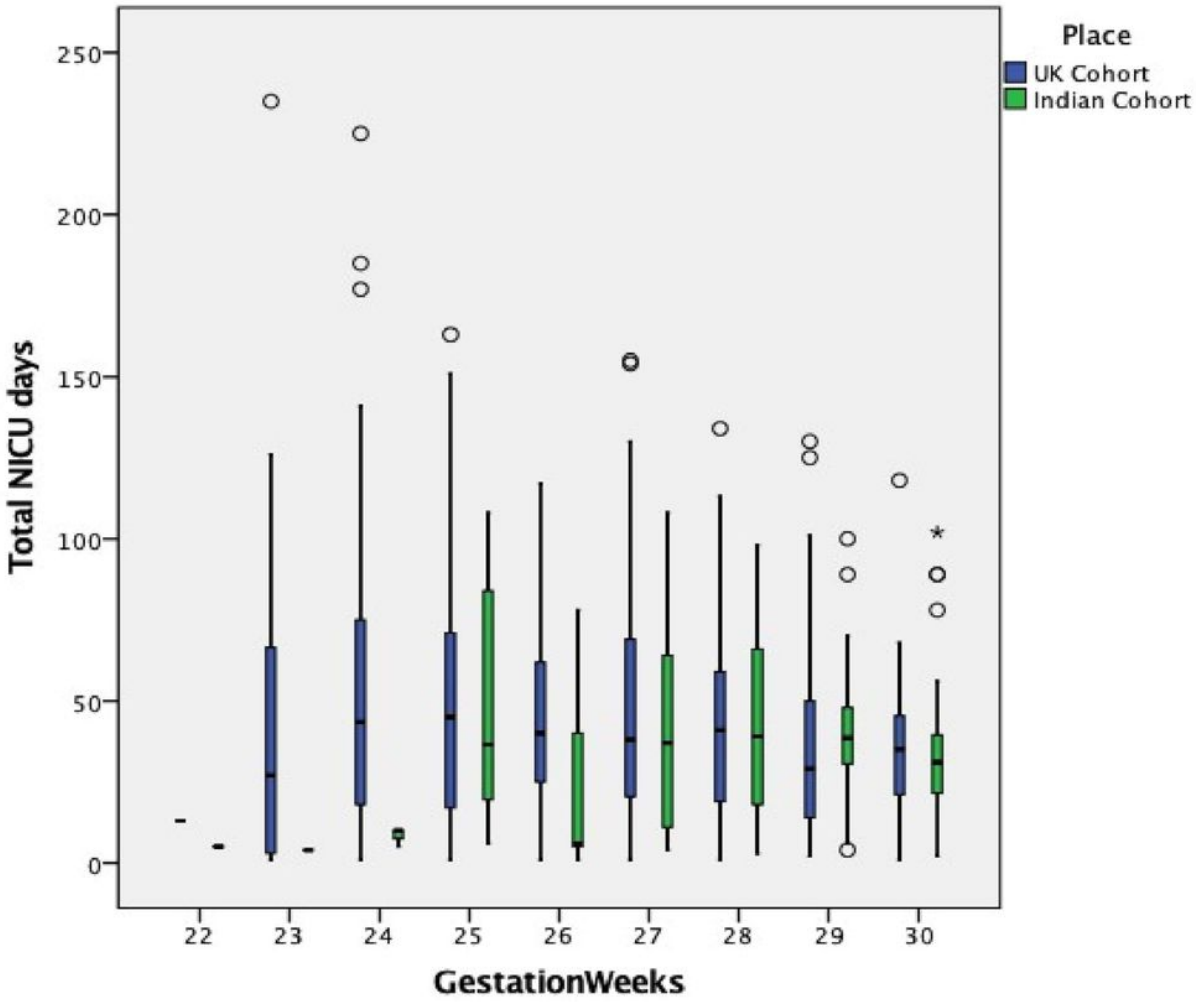


Figure 1

Depicts the number of oxygen days (OD) and ventilation days (VD) respectively. Mean OD was 32.6 and 9.9 (P<0.001) and VD was 10.9 and 5.4 days (p, 0.378) respectively in U.K and Indian cohort.



O – outlier, *- extreme outliers

Figure 2

Box and whisker plot comparing total Neonatal unit (NNU) stay days between two cohorts. Mean NNU days was 43.1 and 34.9 (p,0.05) in UK and Indian cohort.