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Original Article

Short-term outcomes of very preterm infants in a tertiary level neonatal intensive care unit in southeast region of Turkey

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Abstract

Aim: To examine the mortality and short-term outcomes of very preterm infants (≤32 weeks' gestation) at Sanliurfa Training and Research Hospital.

Materials and Methods: Very preterm infants hospitalized between September 2017 and February 2019 were retrospectively included in the study. Selected short-term outcomes were bronchopulmonary dysplasia, severe intraventricular hemorrhage, sepsis, periventricular leukomalacia, severe retinopathy of prematurity and necrotizing enterocolitis.

Results: Within 18 months period 486 live born very preterm infants were included in the study. The mean birth weight was 1306 ± 459 g and gestational age was 29.1 ± 2.8 weeks. The antenatal steroid administration rate was 30.9%. The mortality rate was 30.5%. In the whole group survival rate without a major neonatal morbidity was 44.2%. The incidence of respiratory distress syndrome was 73.9%, patent ductus arteriosus was 20.4%, intraventricular hemorrhage grade III-IV was 7.6%, bronchopulmonary dysplasia was %16.9, periventricular leukomalacia was 7.6%, late onset sepsis was 42.6%, and culture proven sepsis was 14%, severe retinopathy of prematurity was 5.6%, and necrotizing enterocolitis was 2.1%.

Conclusion: The mortality rate is higher than that of Turkey, while short-term morbidity rates are similar to the average in Turkey. The priority for Sanliurfa is to reduce the mortality rate in very preterm infants.

Keywords: Morbidity; outcome; survival rate; very-low birth weight; very preterm infant

INTRODUCTION

The survival rate of very preterm infants (≤32 weeks' gestation) increased as a consequence of improved perinatal and neonatal care together with the use of antenatal steroid, postnatal surfactant and the implementation of technological advancements in neonatal intensive care units (NICU) (1-3). However, the survival rate and outcomes of very preterm infants vary from country to country and even in different regions of the same country. Recently, a significant improvement has been made in perinatal and neonatal care and survival rates in Turkey (4). But still, mortality and morbidity rates of very preterm and very-low birth weight (VLBW) infants are reported to be higher than in developed countries (5). Higher rates can be observed in the country, especially in regions with higher birth rates and insufficient perinatal and neonatal care. Evaluation of the data of each center is important for determining the measures to be taken. Sanliurfa, located in the southeast region of Turkey, has the highest total fertility rate in Turkey with 4.13 children in 2018 (6). The neonatal mortality is significantly higher in Sanliurfa and prematurity was reported as the leading cause of death (7).

The objective of this study was to examine the mortality rate and short-term outcomes of very preterm infants in a tertiary level NICU which was the main admission center in Sanliurfa.

MATERIALS and METHODS

This was a retrospective study conducted at Sanliurfa Training and Research Hospital. The hospital provides care for about 30000 inborn deliveries which is about 50% of all deliveries in the city each year. The NICU of the hospital is the most important third level reference center for high risk pregnancies and high-risk newborns with 107 bed capacity (54 level III and 53 level II) in the city. The NICU accepts over 2000 admissions per year.

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Preterm infants with ≤32 weeks' gestation born in Sanliurfa Training and Research Hospital and admitted to the hospital NICU between September 1, 2017 and February 28, 2019 were included in the study. Data were collected from hospital records and patient files. The infants with <22 weeks' gestation and out-born infants were excluded.

The data on antenatal steroid therapy, multiple births, preeclampsia, gestational hypertension, gestational diabetes, chorioamnionitis, early rupture of membranes, oligohydramnios, maternal age, mode of delivery, gestational age, birth weight, gender, being small for gestational age (SGA) (birth weight <10th percentile for gestational age), tracheal intubation in delivery room, illness severity score (Clinical Risk Index for Babies-CRIB) (8), major malformations, respiratory distress syndrome (RDS), surfactant administration, pulmonary hemorrhage, hemodynamically significant patent ductus arteriosus (PDA) were recorded from hospital files. Gestational age was determined from the date of last menstrual period or by fetal ultrasound assessment. Antenatal steroid therapy was considered to be given if a full course of betamethasone was administered to the mother prior to delivery.

Major neonatal morbidity was defined as presence of at least one of the mentioned conditions before discharge: bronchopulmonary dysplasia (BPD) moderate or severe defined as supplemental oxygen dependency at 36 weeks postmenstrual age or at discharge (9), late onset sepsis, severe intraventricular hemorrhage (IVH) (grade III or IV according to Papile staging) (10), Bell's stage II or III necrotizing enterocolitis (NEC) according to modified Bell criteria (11), periventricular leukomalacia (PVL) defined as periventricular hyper-echogenicity lasting more than 15 days or cystic degeneration in periventricular area (12), or severe retinopathy of prematurity (ROP) requiring treatment graded using the international classification of ROP (13). Late-onset sepsis was defined as presence of clinical and laboratory signs of sepsis developed after 72 hours of life and culture proven sepsis was defined if this condition was associated with positive blood cultures.

Mortality was defined as death before discharge. Survival at discharge and survival free of a major neonatal morbidity were examined. The results were analyzed based on total number of admissions. Major morbidities were also presented based o surviving infants.

Harran University institutional ethics committee approved the study.

Statistical analysis

The data for categorical variables were presented as frequencies and percentages, and for continuous variables as means ± standard deviations (SD) and medians (minimum-maximum). The Student's t-test was used for continuous variables that were normally distributed and Mann-Whitney U test was used for non- normally distributed continuous variables. $\chi 2$ test along with Fischer exact test was used for comparison of categorical data. All statistical analyses were performed using the SPSS for windows software version 17.0 (SPSS Inc., Chicago, IL, USA). A p value below 0.05 was considered significant.

RESULTS

Over the 18 months period a total of 486 live born very preterm infants were admitted to NICU. The mean birth weight was 1306 ± 459 g and gestational age was 29.1 ± 2.8 weeks. Of the 486 infants 49.4% were males, 66.7% were delivered by cesarean section. Twenty four percent of mothers were primiparous, 31.5% were Syrian refugee, 22% had multiple births, 25.5% had early rupture of membranes, 26.1% had preeclampsia, 13.2% had pregnancy induced hypertension, 11.5% had

Table 1. Demographic characteristics and outcomes by gestational age groups

	22-24 wk n = 42	25-26 wk n = 75	27-28 wk n = 78	29-30 wk n= 69	31-32 wk n = 222	Total n = 486
Birth weight, g[a]	560 ± 94	813 ± 164	1058 ± 193	1365 ± 281	1682 ± 248	1306 ± 459
Male gender, n (%)	27 (64.3)	39 (52)	40 (51.3)	34(49.3)	100 (45)	240 (49.4)
Cesarean delivery, n (%)	28 (66.7)	49 (65.3)	49 (62.8)	44 (63.8)	154 (69.4)	324 (66.7)
Primiparous, n (%)	15 (35.7)	25 (33.3)	10 (12.8)	16 (23.2)	52 (23.4)	118 (24.2)
Antenatal steroid therapy, n (%)	8 (19)	22 (29.3)	24 (30.8)	22 (31.9)	74 (33.3)	150 (30.9)
Syrian refugee, n (%)	15 (35.7)	19 (25.3)	29 (37.2)	21 (30.4)	69 (31.1)	153 (31.5)
Rupture of membranes ≥18 hours, n (%)	7 (16.7)	25 (33.3)	25 (32.1)	16 (23.2)	51 (23)	124 (25.5)
Multiple birth, n (%)	8 (19)	19 (25.3)	10 (12.8)	14 (20.3)	56 (25.2)	107 (22)
Preeclampsia, n (%)	19 (45.2)	25 (33.3)	28 (35.9)	20 (29)	35 (15.8)	127 (26.1)
Pregnancy induced hypertension, n (%)	5 (11.9)	14 (18.7)	9 (11.5)	13 (18.8)	23 (10.4)	64 (13.2)
Chorioamnionitis, n (%)	0 (0)	18 (24)	19 (24.4)	10 (14.5)	9 (4.1)	56 (11.5)
Oligohydramnios, n (%)	4 (9.5)	6 (8)	2 (2.6)	4 (5.8)	11 (5)	27 (5.6)
Gestational diabetes, n (%)	0 (0)	0 (0)	2 (2.6)	2 (2.9)	7 (3.2)	11(2.3)

CRIB score[b]	17 (11-20)	12 (3-19)	6 (2-18)	4 (0-19)	2 (0-15)	4 (0-20)
Tracheal intubation in delivery room, n (%)	42 (100)	66 (88)	48 (61.5)	35 (50.7)	74 (33.3)	265 (54.5)
SGA, n (%)	7 (16.7)	7 (9.3)	4 (5.1)	8 (11.6)	22 (9.9)	48 (9.9)
RDS, n (%)	40 (95.2)	70 (93.3)	73 (93.6)	50 (72.5)	126 (56.8)	359 (73.9)
Received surfactant, n (%)	40 (95.2)	68 (90.7)	65 (83.3)	44 (63.8)	88 (39.6)	305 (62.8)
PDA requiring treatment, n (%)	10 (23.8)	30 (40)	31 (39.7)	11 (15.9)	17 (7.7)	99 (20.4)
Pulmonary hemorrhage, n (%)	12 (28.6)	28 (37.3)	13 (16.7)	10 (14.5)	7 (3.2)	70 (14.4)
IVH grade III-IV, n (%)	13 (31)	11 (14.7)	7 (9)	3 (4.3)	3 (1.4)	37 (7.6)
BPD, n (%)	2 (4.8)	25 (33.3)	27 (34.6)	15 (21.7)	13 (5.9)	82 (16.9)
Late onset sepsis, n (%)	7 (16.7)	42 (56)	59 (75.6)	44 (63.8)	55 (24.8)	207 (42.6)
Culture proven sepsis, n (%)	4 (9.5)	21 (28)	17 (21.8)	9 (13)	17 (7.7)	68 (14)
NEC stage II-III, n (%)	0 (0)	0 (0)	2 (2.6)	0 (0)	8 (3.6)	10 (2.1)
PVL, n (%)	2 (4.8)	12 (16)	2 (2.6)	8 (11.6)	13 (5.9)	37 (7.6)
Any degree ROP, n (%)	2 (4.8)	16 (21.3)	17 (21.8)	6 (8.7)	5 (2.3)	46 (9.5)
Severe ROP, n (%)	2 (4.8)	10 (13.3)	7 (9)	6 (8.7)	2 (0.9)	27 (5.6)
Mortality, n (%)	40 (95.2)	49 (65.3)	19 (24.4)	14 (20.3)	26 (11.7)	148 (30.5)

[a] mean ± SD, [b] median (min-max)
BPD: Bronchopulmonary dysplasia, CRIB: Clinical Risk Index for Babies, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, PVL: Periventricular leukomalacia, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity, SGA: Small for gestational age

chorioamnionitis, 5.6% had oligohydramnios, 2.3% had gestational diabetes. The antenatal steroid administration rate was 30.9%. The rate of infants who needed tracheal intubation in delivery room was 54.5%. RDS was present in 73.9% of infants and surfactant was administered to 62.8% of infants. The incidence of PDA requiring treatment was 20.4%, pulmonary hemorrhage was 14.4%, IVH grade III-IV was 7.6%, BPD was %16.9, PVL was 7.6%, any degree ROP was 9.5%, severe ROP was 5.6%, NEC was 2.1%, late onset sepsis was 42.6% and culture proven sepsis was 14%. The distribution of demographic characteristics and outcomes by gestational age and birth weight groups are expressed in Table 1 and Table 2.

The overall survival rate for very preterm infants at discharge was 69.5%. Within the surviving infants, 63.6% survived without a major neonatal morbidity. In the whole group survival rate without a major neonatal morbidity was 44.2% (215/486). RDS was diagnosed in 64.2% (217/338) of survived infants and 49.4% received surfactant. Fifty-six infants (16.6%) had hemodynamically significant PDA. When major morbidities were evaluated, BPD was observed in 22.8% of survived infants, severe ROP in 8%, culture proven sepsis in 14.5%, NEC in 2.1%, severe IVH in 1.8% and PVL in 9.2%. Table 3 and 4 show the clinical characteristics and outcomes of survived infants at discharge by gestational age and birth weights.

Table 2. Demographic characteristics and outcomes by birth weight groups

	≤500 g n = 21	501-750 g n = 45	751-1000 g n = 89	1001-1250 g n= 64	1251-1500 g n = 88	1500 g n = 179
Gestational age, wk[a]	24 ± 1.1	24.9 ± 1.4	26.7 ± 1.3	28.5 ± 1.8	30.4 ± 1.2	31.5 ± 0.8
Birth weight, ga	474 ± 35	634 ± 62	877 ± 83	1129 ± 66	1425 ± 77	1790 ± 154
Male gender, n (%)	15 (71.4)	24 (53.3)	43 (48.3)	29 (45.3)	40 (45.5)	89 (49.7)
Cesarean delivery, n (%)	17 (81)	24 (53.3)	66 (74.2)	36 (56.3)	64 (72.7)	117 (65.4)
Primiparous, n (%)	7 (33.3)	24 (53.3)	19 (21.3)	9 (14.1)	17 (19.3)	42 (23.5)
Antenatal steroid therapy, n (%)	4 (19)	13 (28.9)	25 (28.1)	19 (29.7)	33 (37.5)	56 (31.3)
Syrian refugee, n (%)	6 (28.6)	14 (31.1)	25 (28.1)	28 (43.8)	32 (36.4)	48 (26.8)
Rupture of membranes ≥18 hours, n (%)	4 (19)	8 (17.8)	33 (37.1)	10 (15.6)	26 (29.5)	43 (24)
Multiple birth, n (%)	4 (19)	6 (13.3)	19 (21.3)	13 (20.3)	24 (27.3)	41 (22.9)
Preeclampsia, n (%)	7 (33.3)	24 (53.3)	27 (30.3)	27 (42.2)	19 (21.6)	23 (12.8)
Pregnancy induced hypertension, n (%)	3 (14.3)	14 (31.1)	15 (16.9)	11 (17.2)	10 (11.4)	11 (6.1)
Chorioamnionitis, n (%)	0 (0)	2 (4.4)	23 (25.8)	15 (23.4)	5 (5.7)	11 (6.1)

Oligohydramnios, n (%)	2 (9.5)	4 (8.9)	4 (4.5)	7 (10.9)	6 (6.8)	4 (2.2)
Gestational diabetes, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	10 (5.6)
CRIB score[b]	17 (12-20)	16 (7-20)	11 (3-19)	4 (0-17)	2 (0-15)	2 (0-15)
Tracheal intubation in delivery room, n (%)	21 (100)	45 (100)	64 (71.9)	39 (60.9)	33 (37.5)	63 (35.2)
SGA, n (%)	11 (52.4)	5 (11.1)	10 (11.2)	14 (21.9)	8 (9.1)	0 (0)
RDS, n (%)	19 (90.5)	43 (95.6)	86 (96.6)	56 (87.5)	60 (68.2)	95 (53.1)
Received surfactant, n (%)	19 (90.5)	42 (93.3)	82 (92.1)	50 (78.1)	48 (54.5)	64 (35.8)
PDA requiring treatment, n (%)	1 (4.8)	18 (40)	35 (39.3)	25 (39.1)	8 (9.1)	12 (6.7)
Pulmonary hemorrhage, n (%)	8 (38.1)	12 (26.7)	24 (27)	13 (20.3)	6 (6.8)	7 (3.9)
IVH grade III-IV, n (%)	6 (28.6)	11 (24.4)	10 (11.2)	4 (6.3)	3 (3.4)	3 (1.7)
BPD, n (%)	0 (0)	5 (11.1)	45 (50.6)	13 (20.3)	11 (12.5)	8 (4.5)
Late onset sepsis, n (%)	2 (9.5)	19 (42.2)	67 (75.3)	37 (57.8)	47 (53.4)	35 (19.6)
Culture proven sepsis, n (%)	2 (9.5)	11 (24.4)	22 (24.7)	8 (12.5)	15 (17)	10 (5.6)
NEC stage II-III, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	6 (6.8)	4 (2.2)
PVL, n (%)	0 (0)	3 (6.7)	13 (14.6)	9 (14.1)	7 (8)	5 (2.8)
Any degree ROP, n (%)	0 (0)	6 (13.3)	27 (30.3)	10 (15.6)	1 (1.1)	2 (1.1)
Severe ROP, n (%)	0 (0)	4 (8.9)	18 (20.2)	2 (3.1)	1 (1.1)	2 (1.1)
Mortality, n (%)	21 (100)	39 (86.7)	29 (32.6)	24 (37.5)	16 (18.2)	19 (10.6)

[a] mean ± SD, [b] median (min-max)
BPD: Bronchopulmonary dysplasia, CRIB: Clinical Risk Index for Babies, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, PVL: Periventricular leukomalacia, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity, SGA: Small for gestational age

The characteristics of mortality and survival groups are given in Table 5. The mortality rate was 30.5% (148/486). The mean gestational age and median birth weight were significantly lower in the mortality group compared to survival group (26.8 ± 2.8 vs 30.1 ± 2.1 weeks, p < 0.001; 845 (370-2250) vs 1500 (550-2250) g, p < 0.001, respectively). The mortality rate in infants with birth weight ≤750 g was 90.9%, ≤1000 g was 57.4% and ≤28 weeks' gestation was 55.4%. Of the 148 deaths 108 (73%) were ≤28 weeks' gestation, 89 (60.1%) were ≤1000 g birth weight and 60 (40.5%) were ≤750 g birth weight. A significantly higher percentage of infants were male in the mortality group (p = 0.03). Antenatal steroid administration rate was significantly lower in the mortality group compared to survival group (20.3% vs 35.5%, p = 0.001). The rates of RDS, pulmonary hemorrhage, PDA and IVH grade III-IV were significantly higher in the mortality group (p < 0.001 for all). The incidence of chorioamnionitis was higher in mothers of mortality group (p = 0.006). Major congenital anomalies were significantly more commonly observed in the mortality group (p = 0.002).

Table 3. Clinical characteristics and outcomes of surviving infants by gestational age groups

	22-24 wk n = 2	25-26 wk n = 26	27-28 wk n = 78	29-30 wk n= 69	31-32 wk n = 222	Total n = 338
Birth weight, g[a]	550 ± 0	810 ± 88	1044 ± 171	1391 ± 259	1688 ± 241	1453 ± 386
Male gender, n (%)	0 (0)	13 (50)	24 (40.7)	29 (52.7)	90 (45.9)	156 (46.2)
Cesarean delivery, n (%)	0 (0)	16 (61.5)	42 (71.2)	35 (63.6)	140 (71.4)	233 (68.9)
Antenatal steroid therapy, n (%)	1 (50)	9 (34.6)	22 (37.3)	18 (32.7)	70 (35.7)	120 (35.5)
SGA, n (%)	0 (0)	0 (0)	4 (6.8)	5 (9.1)	18 (9.2)	27 (8)
RDS, n (%)	2 (100)	24 (92.3)	54 (91.5)	35 (63.6)	102 (52)	217 (64.2)
Received surfactant, n (%)	2 (100)	24 (92.3)	46 (78)	31 (56.4)	64 (32.7)	167 (49.4)
PDA requiring treatment, n (%)	2 (100)	8 (30.8)	22 (37.3)	8 (14.5)	16 (8.2)	56 (16.6)
IVH grade III-IV, n (%)	0 (0)	4 (15.4)	2 (3.4)	0 (0)	0 (0)	6 (1.8)
BPD, n (%)	2 (100)	22 (84.6)	27 (45.8)	15 (27.3)	11 (5.6)	77 (22.8)

Late onset sepsis, n (%)	2 (100)	26 (100)	52 (88.1)	41 (74.5)	50 (25.5)	171 (50.6)
Culture proven sepsis, n (%)	2 (100)	10 (38.5)	17 (28.8)	7 (12.7)	13 (6.6)	49 (14.5)
NEC stage II-III, n (%)	0 (0)	0 (0)	2 (3.4)	0 (0)	5 (2.6)	7 (2.1)
PVL, n (%)	2 (100)	8 (30.8)	2 (3.4)	8 (14.5)	11 (5.6)	31 (9.2)
Any degree ROP, n (%)	2 (100)	12 (46.2)	17 (28.8)	6 (10.9)	5 (2.6)	42 (12.4)
Severe ROP, n (%)	2 (100)	10 (38.5)	7 (11.9)	6 (10.9)	2 (1)	27 (8)
Major morbidity, n (%)	2 (100)	24 (92.3)	37 (62.7)	23 (41.8)	37 (18.9)	123 (36.4)

[a] mean ± SD
BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, PVL: Periventricular leukomalacia, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity, SGA: Small for gestational age

Table 4. Clinical characteristics and outcomes of surviving infants by birth weight groups

	501-750 g n = 6	751-1000 g n = 60	1001-1250 g n= 40	1251-1500 g n = 72	1500 g n = 160
Gestational age, wk[a]	25.3 ± 1	26.9 ± 1.3	29.1 ± 1.5	30.5 ± 1.2	31.5 ± 0.7
Male gender, n (%)	2 (33.3)	24 (40)	19 (47.5)	33 (45.8)	78 (48.8)
Cesarean delivery, n (%)	2 (33.3)	45 (75)	24 (60)	54 (75)	108 (67.5)
Antenatal steroid therapy, n (%)	4 (66.7)	21 (35)	13 (32.5)	29 (40.3)	53 (33.1)
SGA, n (%)	0 (0)	9 (15)	11 (27.5)	7 (9.7)	0 (0)
RDS, n (%)	4 (66.7)	59 (98.3)	33 (82.5)	45 (62.5)	76 (47.5)
Received surfactant, n (%)	4 (66.7)	57 (95)	27 (67.5)	34 (47.2)	45 (28.1)
PDA requiring treatment, n (%)	2 (33.3)	19 (31.7)	18 (45)	5 (6.9)	12 (7.5)
IVH grade III-IV, n (%)	0 (0)	6 (10)	0 (0)	0 (0)	0 (0)
BPD, n (%)	4 (66.7)	43 (71.7)	13 (32.5)	9 (12.5)	8 (5)
Late onset sepsis, n (%)	6 (100)	59 (98.3)	33 (82.5)	38 (52.8)	35 (21.9)
Culture proven sepsis, n (%)	4 (66.7)	20 (33.3)	6 (15)	9 (12.5)	10 (6.3)
NEC stage II-III, n (%)	0 (0)	0 (0)	0 (0)	3 (4.2)	4 (2.5)
PVL, n (%)	2 (33.3)	10 (16.7)	9 (22.5)	5 (6.9)	5 (3.1)
Any degree ROP, n (%)	4 (66.7)	25 (41.7)	10 (25)	1 (1.4)	2 (1.3)
Severe ROP, n (%)	4 (66.7)	18 (30)	2 (5)	1 (1.4)	2 (1.3)
Major morbidity, n (%)	6 (100)	46 (76.7)	28 (70)	19 (26.4)	26 (16.3)

[a] mean ± SD
BPD: Bronchopulmonary dysplasia, CRIB: Clinical Risk Index for Babies, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, PVL: Periventricular leukomalacia, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity, SGA: Small for gestational age

Table 5. Demographic and Clinical Characteristics of Very Preterm Infants by Mortality and Survival

	Mortality n = 148	Survival n = 338	p
Gestational age, wk[a]	26.8 ± 2.8	30.1 ± 2.1	<0.001*
Birht weight, g[b]	845 (370-2250)	1500 (550-2250)	<0.001*
Male gender, n (%)	84 (56.8)	156 (46.2)	0.03*
Cesarean delivery, n (%)	91 (61.5)	233 (68.9)	0.11
Maternal age, y[a]	27 ± 7	28 ± 6	0.5
Primiparous, n (%)	43 (29.1)	75 (22.2)	0.12
Antenatal steroid therapy, n (%)	30 (20.3)	120 (35.5)	0.001*
Rupture of membranes ≥18 hours, n (%)	33 (22.3)	91 (26.9)	0.28
Multiple birth, n (%)	30 (20.3)	77 (22.8)	0.54

Preeclampsia, n (%)	42 (28.4)	85 (25.1)	0.45
Gestational hypertension, n (%)	16 (10.8)	48 (14.2)	0.3
Chorioamnionitis, n (%)	26 (17.6)	30 (8.9)	0.006*
Oligohydramnios, n (%)	10 (6.8)	17 (5)	0.44
Syrian refugee, n (%)	51 (34.5)	102 (30.2)	0.2
CRIB score[b]	12 (2-20)	3 (0-19)	<0.001*
SGA, n (%)	21 (14.2)	27 (8)	0.035*
RDS, n (%)	142 (95.9)	217 (64.2)	<0.001*
Received surfactant, n (%)	138 (93.2)	167 (49.4)	<0.001*
Pulmonary hemorrhage, n (%)	62 (41.9)	8 (2.4)	<0.001*
PDA requiring treatment, n (%)	43 (29.1)	56 (16.6)	<0.001*
IVH grade III-IV, n (%)	31 (20.9)	6 (1.8)	<0.001*
Major congenital anomaly, n (%)	11 (7.4)	6 (1.8)	0.002*
Late onset sepsis (culture proven), n (%)	19 (12.8)	49 (14.5)	0.7

[a] mean ± SD, [b] median (min-max), * p <0.05
CRIB: Clinical Risk Index for Babies, IVH: Intraventricular hemorrhage, PDA: Patent ductus arteriosus, RDS: Respiratory distress syndrome, SGA: Small for gestational age

Of the 148 deaths, 120 were early neonatal deaths occurring within the first 7 days of life. Of these 120 early neonatal deaths, 36 occurred on postnatal first day of life, 30 occurred on postnatal second day of life and 54 occurred beyond the second postnatal day. The primary underlying cause of death was pulmonary hemorrhage in 40 (27%) infants, severe RDS and pulmonary hypertension in 26 (17.6%) infants, neonatal sepsis in 25 (16.9%) infants, IVH in 14 (9.5%) infants, immaturity in 14 (9.5%) infants, asphyxia in 11 (7.4%) infants, congenital anomaly in 11 (7.4%) infants and other causes in 7 (4.7%) infants.

DISCUSSION

The overall mortality rate was 30.5% in very preterm infants, and at least one major morbidity was observed in more than one-third of the surviving infants. The survival rate without a major neonatal morbidity was 44.2% in the whole group.

The mortality rate is reported to be as low as 7.4-13% in very preterm and VLBW infants in developed countries (14, 15). In our study, the mortality rate was obviously higher than in developed countries and the Turkey average which was reported as 22% by Turkish Neonatal Society (5). According to the Turkish Neonatal Society's 2018 mortality report, mortality rates from two university hospitals and three state hospitals with annual hospitalization number over 1000 from Southeast Anatolian region were 66.2-83.6% in <750 g, 43.3-60% in <1000 g and 32.7-52.7% in ≤28 weeks' gestation infants (16). The Sanliurfa Training and Research Hospital's NICU accepts over 2000 admissions per year. In the present study, the mortality rate decreased with the increasing gestational age and birth weight. Although we observed a comparable mortality rate with state and university hospitals having similar intensity to our hospital in infants with ≤28 weeks' gestation and ≤1000 g birth weight, the mortality rate in infants with birth weight ≤750 g was significantly higher in our study. Full course antenatal steroid administration rate was observed to be quite low as 30.9%. As it is well known, treatment with antenatal steroids reduces the mortality and the most severe neonatal morbidities including RDS, IVH, NEC and sepsis in the first two days of life among preterm infants (17). Antenatal steroid therapy is one of the most important and strongly recommended antenatal practices for improving preterm infants' outcomes (18). Antenatal steroid administration rate is strikingly high in developed countries which are above 90% (14,19,20). Recently, Wu et al. (21) reported antenatal steroid therapy rate as %47.6 among a large population from China which is a developing country. Their survival rate was 52.5% in infants under 28 weeks of gestation which was lower than developed countries but higher than the present study. In Turkey, antenatal steroid use was reported to be between 34-67% from different NICUs (22-24). The Turkish Neonatal Society reported the antenatal steroid administration rate as 39.8% across Turkey in a multicenter trial (5). The rate of antenatal steroid therapy was significantly higher in surviving infants in our study which was 35.5% compared to non-survivors but, this rate was still lower than the rate reported by Turkish Neonatal Society. In our region advanced labor and lack of attendance to regular prenatal follow-up by pregnant women were the major causes for underuse of antenatal steroids. We think that lower rate of antenatal steroid therapy is the main contributing factor to the increased mortality rate compared to the data of developed countries and our country.

Nearly half of the deaths occurred within the first 48 hours of life and in most of the deaths the major causes of death were prematurity associated pulmonary hemorrhage, hypoxic respiratory failure and IVH. Intrapartum asphyxia, PDA, resuscitation requirement in the delivery room, lower gestational age, and birth weight, and lack of

antenatal steroid therapy were identified as risk factors for pulmonary hemorrhage (25,26). Antenatal steroid therapy has been identified as an important protective factor against the occurrence of pulmonary hemorrhage (27). This protective effect was thought to be due to glucocorticoid-induced surfactant synthesis and reduced capillary permeability. In different studies, the incidence of pulmonary hemorrhage was reported to be 6-12% in VLBW infants (26,28,29). The risk of pulmonary hemorrhage increases with decreasing birth weight and gestational age (30). In a report from Turkey pulmonary hemorrhage was observed at a rate of 10.8% in very preterm infants (31). We observed higher incidence of pulmonary hemorrhage as 14.4% in very preterm infants. In majority of our cases, pulmonary hemorrhage occurred at the end of the second postnatal day similar to the findings of Ferreira et al. (26) and Tomaszewska et al. (32). Pulmonary hemorrhage is associated with an increased risk of death (26,30) and most infants die within 72 hours of life (29). Pulmonary hemorrhage can cause fluctuations in the cerebral blood flow, coagulation disturbances, hypoxemia, and IVH. Severe IVH as in our study, usually develops in most of the infants immediately after the onset of pulmonary hemorrhage and further contributes to increased risk of mortality. Lower rates of antenatal steroid therapy both by increasing IVH risk and by indirectly increasing pulmonary hemorrhage contributes to increased mortality rate. In our study, antenatal steroid administration rates were observed to be quite low especially in non-surviving infants and most infants died due to pulmonary hemorrhage and IVH besides severe RDS in the early neonatal period.

Despite the decline in neonatal mortality rates, the improvement in short and long-term outcomes of especially extremely preterm infants is not at the desired level. Horbar et al. (2) reported that in 2009, nearly half of the VLBW infants and 89% of infants with birth weight 501 to 750 g died or survived after experiencing at least one major morbidity. Chee et al. (33) reported a survival rate of 87% in VLBW infants, while they reported a 40% survival rate free of major morbidity. The survival rate without a major morbidity was 37.4% in VLBW infants in the multicenter study of Turkish Neonatal Society (5). In the present study, survival rate without a major neonatal morbidity was 44.2% which was higher than Turkey average. However, in our study, the mortality rate in smaller infants in whom preterm morbidities develop more frequently is high, so our morbidity-free survival rate appears to be higher.

The incidence of RDS, surfactant treatment, PDA and IVH in surviving infants was lower than the incidence reported by Turkish Neonatal Society, whereas when whole group was examined, we observed these early morbidities at a similar or higher rate. We think that lower antenatal steroid administration rate and inadequate antenatal and delivery room care increase morbidities like RDS, IVH, PDA and consequently increase mortality in the early neonatal period.

Bronchopulmonary dysplasia and ROP are serious morbidities associated with poor neurodevelopmental outcome (34,35). The incidence of BPD and ROP is reported to be between 14-28% and 1.3-14% in developed countries (2, 14, 36). Koc et al. (5) reported the incidence of BPD as 19.1% and severe ROP as 8.2% in infants with ≤32 weeks' gestation. We observed BPD in 22.8% and severe ROP in 8% of surviving infants which were comparable with the literature.

Late onset sepsis is an important complication which increases the duration of hospitalization, duration of ventilation, and other morbidities like BPD and mortality risk (37). The incidence of culture proven sepsis varies between 15-29% (2,20). In our whole study group, the rate of late onset sepsis was 42.6% and the rate of culture proven sepsis was 14%. Sepsis was primarily responsible for 16.9% of deaths. Culture proven sepsis rate was within the similar limits reported in the literature and lower than the rate reported by Turkish Neonatal Society.

The incidence of NEC in very preterm infants was reported as 8.4% in Turkey (5). In another study from Turkey who reported total mortality rate as 41.6%, the incidence of NEC was found to be 13% (31). In developed countries NEC incidence varies between 1.7% and 7% (20,33,36). The incidence of NEC was 2.1% both in the surviving infants and whole study group which was lower than the rate reported by Turkish Neonatal Society. NEC often develops in infants with lower gestational age and birth weight. And it has a later onset in the most immature infants (38). In this study, the mortality rate was considerably high in the group of infants with increased risk of developing NEC and most of the deaths were in early neonatal period before the onset pathophysiology of NEC. We observed NEC at higher gestational ages.

Periventricular leukomalacia is an ischemic brain injury resulting in cerebral palsy in preterm infants (39). The reported rate of PVL changes between 2.2-5.7% in developed countries (20,36). The rate of PVL was 9.2% in surviving infants in the present study which was higher than the rate of developed countries. With the adequate antenatal care, appropriate antibiotic approaches for early rupture of membranes, antenatal maternal infections and chorioamnionitis, improving delivery room care by increasing number of neonatal resuscitation program certified health staff, prevention of acidosis and asphyxia, the incidence of PVL and future neurodevelopmental impairment can be reduced.

CONCLUSION

This study provides an insight on the early outcomes of very preterm infants in Sanliurfa which is one of the provinces with highest intensity of NICU and birth rate in our country. The mortality rate of our unit which is the major perinatal and neonatal center in Sanliurfa is higher than the Turkey average. For Sanliurfa, measures to reduce mortality in very preterm infants are a priority. With

appropriate antenatal follow-up, significantly increasing use of antenatal steroids, treatment of antenatal maternal infections, improving delivery room and neonatal care, the mortality in very preterm infants can be reduced. Since major neonatal morbidities are predictive of long-term neurodevelopmental impairment, it may be possible to improve the long-term neurodevelopmental outcome by improving early neonatal outcomes.

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