

# Short-term outcomes of extremely low birth weight infants in a tertiary neonatal intensive care unit in Türkiye

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## ABSTRACT

**Background.** Advances in neonatal care have led to increased survival of extremely preterm infants. Extremely low-birth-weight (ELBW) infants, defined as infants weighing less than 1000 g at birth, constitute a significant portion of neonatal intensive care unit (NICU) patients. The aim of this study is to determine the mortality and short-term morbidities of ELBW infants and assess the risk factors related to mortality.

**Methods.** The medical records of ELBW neonates hospitalized in the NICU of a tertiary-level hospital between January 2017 and December 2021 were evaluated retrospectively.

**Results.** 616 ELBW (289 females and 327 males) infants were admitted to the NICU during the study period. Mean birth weight (BW) and gestational age (GA) for the total cohort were  $725 \pm 134$  g (range 420-980 g) and  $26.3 \pm 2.1$  weeks (range 22-31), respectively. The rate of survival to discharge was 54.5% (336/616) [33% for the infants with  $\leq 750$  g BW, 76% for the infants with 750-1000 g BW], and 45.2% of survived infants had no major neonatal morbidity at discharge. Independent risk factors for mortality of ELBW infants were asphyxia at birth, birth weight, respiratory distress syndrome, pulmonary hemorrhage, severe intraventricular hemorrhage, and meningitis.

**Conclusions.** The incidence of mortality and morbidity was very high in ELBW infants, particularly for neonates born weighing less than 750 g in our study. We suggest that preventive and more effective treatment strategies are needed for improved outcomes in ELBW infants.

**Key words:** extremely low birth weight infant, survival, morbidity.

The improved survival of preterm infants due to recent advances in perinatal and neonatal care has produced a new population of infants at very high risk of developing neonatal mortality and morbidities. In current practice, extremely low-birth-weight (ELBW) infants, defined as infants weighing less than 1000g at birth, constitute a significant portion of patients in neonatal intensive care units (NICUs).<sup>1-3</sup> Gestational age is a significant predictor for the survival of ELBW infants. Extremely low-birth-weight infants constitute the highest risk

group for mortality and morbidity. Being small for gestational age (SGA) with more advanced gestation represents different pathophysiologic processes. So, this distinction by gestational age is important.<sup>4,5</sup> Despite our knowledge and recognizing the vulnerability of these infants, care of ELBW newborns is challenging, they remain at high risk for mortality and major morbidities. As the survival of ELBW infants is increasing worldwide, mortality and neonatal morbidities of these infants need to be reported. Monitoring the outcomes in the NICU could guide the development of programs to improve preterm care. In this study, we aimed to evaluate the mortality and short-term morbidities of ELBW infants and assess the risk factors related to mortality.

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Received 29th November 2022, revised 24th January 2023, accepted 1st February 2023.

## Material and Methods

### Study Design and Subjects

This retrospective study was performed at Etlik Zubeyde Hanım Women's Health Training and Research Hospital. The medical records of ELBW infants hospitalized in the NICU between January 2017 and December 2021 were reviewed. The institutional ethics committee approved this study (17.06.22-08/24). Etlik Zubeyde Hanım Women's Health Training and Research Hospital is a reference center for high-risk pregnancies and preterm births and has one of the largest NICUs in Türkiye with 79 level III beds. An average of 350 preterm infants with birth weight (BW) <1500 g and GA <32 weeks are hospitalized annually.

### Clinical Data and Definitions

Perinatal and neonatal characteristics of the infants and outcomes at discharge were collected from the medical records. The data recorded for each neonate included GA, BW, gender, mode of delivery, 5-minute Apgar score, singleton or multiple gestations, being SGA and antenatal steroid administration (two doses of 12 mg betamethasone given intramuscularly 24 hours apart before delivery). Clinical data of mothers including maternal age, preterm prelabor rupture of membranes (PPROM), chorioamnionitis (clinical or histopathological), gestational diabetes, preeclampsia, eclampsia, and maternal systemic diseases were recorded.

During the neonatal follow-up, respiratory distress syndrome (RDS), surfactant treatment, duration of respiratory support (noninvasive/invasive mechanical ventilation, and supplemental oxygen), duration of parenteral nutrition, and presence of complications related to prematurity; hemodynamically significant patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH) (according to Papile criteria)<sup>6</sup>, late-onset sepsis, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) ( $\geq$  stage 2 NEC according to modified Bell staging criteria)<sup>7</sup>, bronchopulmonary dysplasia (BPD)

(oxygen requirement at 36th postmenstrual age)<sup>8</sup> and osteopenia of prematurity (OP) were recorded. Retinopathy of prematurity was defined according to Early Treatment for Retinopathy of Prematurity Cooperative Group criteria.<sup>9</sup> Osteopenia of prematurity was defined as hypophosphatemia (phosphorus levels <4 mg/dl), ALP levels >450 U/L, or signs of decreased mineralization in the x-ray of the forearm at four weeks of age.

Gestational age was calculated according to the date of the maternal last menstrual period, early pregnancy ultrasound examination findings, or the New Ballard score. SGA was defined as BW below the 10th percentile for their GA according to Fenton's growth curve.<sup>10</sup>

### Outcome Measures

The primary outcome measure was the survival rate until discharge. Secondary outcome measures were major short-term morbidities of preterm birth. The major morbidities were defined as late-onset sepsis, severe IVH (>grade II IVH according to Papile criteria), NEC ( $\geq$  stage 2, according to the modified Bell's criteria), severe ROP requiring treatment, and BPD.

### Statistical analysis

Statistical analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL). Categorical data are presented as numbers (n) and percentages (%). The Chi-square test was used to compare categorical variables. Variables were tested for normality using the Shapiro-Wilk test. The results for variables with normal distribution were reported as mean  $\pm$  SD, while the non-normally distributed parameters were reported as median (interquartile range [IQR]). Mann-Whitney U test or independent samples t-test were used to compare the numerical variables, where appropriate. Statistical significance was accepted if the p-value  $\leq$  0.05.

Probable risk factors for mortality of ELBW infants were evaluated. The multivariate analysis of logistic regression was performed with mortality as a dependent variable and

clinical outcomes as independent variables. The risk factor with a p-value <0.1 in the univariate analysis was included in the multivariate analysis. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. Odds ratios and 95% confidence intervals for each risk factor were determined.

## Results

During the study period 1549 preterm infants with GA <32 weeks, 616 of whom were ELBW, were admitted to the NICU. Medical records of 616 ELBW (289 females and 327 males) infants were reviewed. Mean BW and GA for the total cohort were  $725 \pm 134$  g (range 420-980g) and  $26.3 \pm 2.1$  weeks (range 22-31 weeks), respectively. The ratio of extremely preterm infants ( $\leq 28$  weeks GA) was 85%. Of the total cohort 26 (3.4%) preterm infants were <500 g BW and  $\leq 23$  weeks GA. A total of 129 (21%) infants were SGA. The rate of resuscitation at the delivery room was 70.4%, and the median Apgar scores at 5 minutes were 6.

The most common perinatal complication was preeclampsia (29%), the others were; PPRM in 160 (26%), chorioamnionitis in 70 (11.4%), and gestational diabetes in 30 (5%) cases, respectively. The rate of cesarean section was 71%. When maternal characteristics were considered the mean maternal age was  $29 \pm 5$  years. Complete antenatal corticosteroid administration was performed in 42% of the mothers. Neonatal and maternal characteristics of the total cohort are detailed in Table I.

The rate of survival to discharge for the total cohort was 54.5% (336/616). None of the infants with <500 g BW and <23 weeks GA survived to discharge. The survival rate of infants with  $\leq 750$  g BW was 33%, whereas it increased to 76% with 751-1000 g BW. The same trend was observed in extremely preterm infants, where the survival rate was 21.2% (24/113) at 22-24 weeks. The survival rate of ELBW infants improved to 44% (84/192) after 24 weeks, and 78% (73/94) 28-32 weeks. The rate of survival to discharge without

**Table I.** Demographic characteristics of infants.

Infant characteristics	n= 616
Birth weight (g), mean $\pm$ SD	724.91 $\pm$ 133.65
$\leq 500$ , n (%)	21 (3.4%)
501- 750, n (%)	270 (43.8%)
751-1000, n (%)	325 (52.7%)
Gestational age (weeks)*	26.31 $\pm$ 2.11
$\leq 28$ weeks, n (%)	
22-24	113 (18.3%)
25-26	192 (31.1%)
27-28	217 (35.2%)
>28 weeks, n (%)	94 (15.2%)
F/M	289/327
SGA, n (%)	129 (21%)
Multiple pregnancy, n (%)	
Twin	64 (10.3%)
Triplet	2 (1.9%)
Resuscitation, n (%)	441 (71.5%)
Apgar score, median (IQR)	6 (5-7)
Maternal characteristics	
Age yr, mean $\pm$ SD	29.4 $\pm$ 5.4
Cesarean section, n (%)	437 (71%)
IVF, n (%)	72 (11.8%)
Antenatal corticosteroid, n (%)	
Complete	259 (42%)
Incomplete	217 (35.2%)
None	140 (22.8%)
Preeclampsia, n (%)	178 (29%)
PPROM, n (%)	160 (26%)
Chorioamnionitis, n (%)	70 (11.4%)
Gestational diabetes, n (%)	30 (4.9%)

F/M: Female/Male, SGA: Small for gestation al age, IVF: In vitro fertilization, IQR: interquartile range, PPRM: Premature prelabor rupture of membranes.

any major morbidity was 45%. Survival rates of infants by BW and GA are given in Table II.

Clinical outcomes of ELBW infants during hospitalization are given in Table III. Respiratory distress syndrome requiring surfactant therapy was present in 77% of the infants, and pulmonary hemorrhage occurred in 7.7% of them. Hemodynamically significant PDA requiring treatment was detected in 262 (51%) infants. Twelve of them (7 infants with BW 500-750 g, 5 infants with BW 751-1000 g)

**Table II.** Survival rates by birth weight and gestational age.

		Survival	Survival without morbidity*
Birth weight (g)	Overall	336/616 (54.5%)	151/336 (45.2%)
	≤ 500	0/21 (0)	-
	501- 750	89/270 (32.9%)	24/89 (26.9%)
	751-1000	247/325 (76%)	127/247 (51.4%)
Gestational age (weeks)	22-24	24/113 (21.2%)	4/24 (16.6%)
	25-26	84/192 (43.7%)	24/84 (28.2%)
	27-28	155/217 (71.4%)	70/155(45.1%)
	>28	73/94 (77.6%)	53/73 (72.6%)

\*Rates of survival to discharge without major morbidity (severe intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis ≥ stage II, retinopathy of prematurity requiring treatment, culture proven sepsis) among infants who survived to discharge

**Table III.** Morbidities and mortality during hospitalization (Presented as number and percentages unless indicated otherwise).

	BW <500 g (n=21)	BW 501- 750 g (n=270)	BW 751-1000 g (n=325)	Overall (n=616)
RDS	21 (100%)	242 (89.8%)	265 (81.7%)	528 (85.7%)
Surfactant treatment	21 (100%)	224 (83%)	230 (70.7%)	475 (77.1%)
Pulmonary hemorrhage	3 (9.5%)	22 (8.1%)	9 (2.7%)	34 (5.5%)
Intraventricular hemorrhage*				
Grade 2	-	38 (18.1%)	28 (9.4%)	66 (31.5%)
Grade ≥ 3	4	26 (12.4%)	17 (5.7%)	43 (14.5%)
PDA requiring treatment**	5 (62.5%)	104 (50.2%)	156 (51.3%)	265 (50.7%)
Late-onset sepsis**	2 (50%)	63 (23.3%)	83(25.5%)	148 (24%)
Culture proven	-	52 (19.2%)	73 (22.4%)	125 (20.2%)
Meningitis	-	18 (9.6%)	21 (7%)	39 (7.9%)
NEC (≥ stage II)	-	14 (7.4%)	9 (3%)	23 (4.6%)
ROP †				
Any stage	-	54 (56.2%)	106 (41.5%)	160 (45.5%)
Severe ROP	-	19 (19.7%)	28 (10.9%)	47 (13.3%)
BPD ††	-	51 (53.1%)	112 (43.9%)	163 (46.4%)
Osteopenia of prematurity †††	-	47 (48.9%)	119 (46.6%)	166 (47.2%)
Duration of hospitalization, days, mean ± SD ††††		111 ± 33.95	82.95 ± 29.12	97.20±48.42
Postnatal time until death, days, PDA: patent ductus arteriosus				
<1	10/21	44/181	11/78	65/280
1-3	5/21	39/181	14/78	58/280
4-7	4/21	45/181	22/78	71/280
8-28	2/21	46/181	23/78	71/280
>28	0/21	7/181	8/78	15/280

BPD: bronchopulmonary dysplasia, BW: birth weight, NEC: necrotizing enterocolitis, RDS: respiratory distress syndrome, ROP: retinopathy of prematurity.

\* Data available for 511 patients.

\*\* Data available for 522 patients.

† Represents data among survivors at 28 days of life .

†† Represents data among survivors at PMA of 36 weeks.

were referred for surgical closure. In general, the incidence of severe IVH was 7.6%, whereas it increased to 10.3% in infants with  $\leq 750$  g BW. A total of 166 neonates [67 (36%) with 500-750 g BW, 98 (33%) with 751-1000 g BW] developed culture-proven sepsis, and 39 (8%) of them had meningitis. Advanced NEC (stage 2 to 3) occurred in 23 infants [14 (7.4%) with 500-750 g BW, 9 (3%) with 751-1000 g BW]. Osteopenia of prematurity, ROP, and BPD were evaluated in infants who survived more than 28 days. Osteopenia of prematurity developed in 166 (42%) infants, 47 (49%) of them had 500-750 g BW. Any stage ROP was detected in 160 (46%) infants, in which 47(13%) of them had severe ROP requiring treatment. BPD developed in 163 (46%) infants. Postnatal corticosteroids were given to 56 infants for BPD. Two neonates with 500-750 g BW required tracheostomy for severe BPD. The mean duration of hospitalization of survived infants was  $97.2 \pm 48.4$  days. When all deaths were considered 65 (23%) deaths occurred within the first day of life and 194 (69%) occurred in the first week. Nearly half of the neonates with  $<500$  g BW (48%) died within the first day of life.

Treatment methods during hospitalization are given in Table IV. The rate of resuscitation at the delivery room was 70.4%, and 235 (38%) infants required intubation. Noninvasive ventilation

was the most common initial modality of respiratory support (n=381, 62%) in this cohort. The mean duration of invasive and noninvasive mechanical ventilation among survivors was  $7.4 \pm 12.1$  days and  $23 \pm 13$  days, respectively.

Gestational age, hemodynamically significant PDA, presence of culture-proven sepsis, meningitis, NEC ( $\geq$  stage 2, according to the modified Bell's criteria), RDS, pulmonary hemorrhage, asphyxia at birth, multiple pregnancies, gender, and severe IVH were put in the regression model. We found that asphyxia at birth, RDS, pulmonary hemorrhage, severe IVH, NEC ( $\geq$  stage 2, according to the modified Bell's criteria), and meningitis were independent risk factors for mortality among ELBW infants. Being born with  $\leq 750$  g BW was associated with a 5.7-fold increased risk for mortality (Table V).

## Discussion

This report provided detailed documentation of short-term outcomes of ELBW infants in a tertiary NICU for 5 years. Although ELBW infants with extreme prematurity account for 5% of preterm births, they are at increased risk of mortality and morbidity. Management of ELBW infants, typically born at 27 weeks gestation or younger has great challenges for neonatologists.

**Table IV.** Treatment methods during hospitalization.

	BW 501- 750 g n=89	BW 751-1000 g n=247	Overall n=336
Duration of invasive MV* (days)	15.16 $\pm$ 18.56	5.21 $\pm$ 8.36	7.41 $\pm$ 12.11
Duration of non-invasive MV* (days)	29.06 $\pm$ 15.69	21.34 $\pm$ 11.60	23.05 $\pm$ 12.99
Duration of oxygen therapy* (days)	28.63 $\pm$ 17.42	22.81 $\pm$ 15.77	24.10 $\pm$ 16.29
Duration of TPN* (days)	16.25 $\pm$ 5.74	13.90 $\pm$ 3.96	14.42 $\pm$ 4.51
Postnatal corticosteroids for BPD*, n (%)	22 (24.7%)	34 (13.7%)	56 (16.6%)
Tracheostomy for severe BPD*, n (%)	2 (2.2%)	0	2 (0.5%)
Surgical closure of PDA*, n (%)	7 (7.8%)	5 (2%)	12 (3.5%)
Laser therapy for ROP*, n (%)	13 (14.6%)	18 (7.2%)	31 (9.2%)

BPD: bronchopulmonary dysplasia, BW: birth weight, MV: mechanical ventilation, PDA: patent ductus arteriosus, ROP: retinopathy of prematurity, TPN: total parenteral nutrition.

\*Represents data among survivors

**Table V.** Binary logistic regression analysis to identify independent risk factors for mortality.

	Odds ratio	95% CI	p value
Asphyxia at birth	2.03	1.264-3.276	0.003
Pulmonary hemorrhage	6.53	2.113-20.209	0.001
RDS	2.99	1.607- 5.576	0.001
NEC	2.68	0.904-7.947	0.075
Severe IVH	2.40	1.154-5.002	0.019
Meningitis	0.40	0.177-0.937	0.035
Birth weight*	5.70	3.898-8.349	0.000

CI: confidence interval, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis ( $\geq$  stage II), RDS: respiratory distress syndrome.

\*Odds ratio for birth weight <750 g

Developed centers reported increased survival rates for neonates born at 23-24 GA as survival to discharge was 33% at 23 weeks of GA and 65% at 24 weeks of GA<sup>11</sup> whereas significant variable rates of survival are observed in resource limited centers.<sup>12,13</sup> Trotman from a University Hospital of the West Indies reported the survival rate as 7% for the neonates with <27 weeks of GA.<sup>13</sup>

Our results indicated that the incidence of mortality and morbidity is still very high in these vulnerable infants. In the present study, the overall rate of survival to discharge was 54.5 % in ELBW infants with improved survival in higher birth weights. The rate of survival for infants with  $\leq$ 750 g BW was 33%, whereas it increased to 76% for infants born weighing 751-1000 g. The short-term outcomes of very low birth weight (VLBW) infants have been reported by different NICUs in Türkiye<sup>14,15</sup>, however, there is no recent documented data regarding the outcomes of ELBW infants. Turkish Neonatal Society publishes the mortality rates of preterm infants annually based on the data of the involved NICUs. In the last report, the mortality rate was 50.7% for preterm infants with 500-749 g BW in 2020.<sup>16</sup> The survival rate of ELBW infants in our cohort is less than that of developed centers where the survival rate was 33% for infants born at 23 weeks in the US.<sup>11</sup> Also, recent data from the UK reported improved survival for preterm infants, particularly at the lowest gestations. The rates of survival to discharge of infants born at 22

GA, 23 GA, 24 GA, and 25 GA were 17.9%, 35.9%, 58.6%, and 74%, respectively.<sup>17</sup> There is an important retrospective cohort study from our hospital analyzing the survival rates of periviable infants. In that cohort, the rate of survival to discharge was found to be 7.5% at 23 weeks, 29 % at 24 weeks, and 43.5% at 25 weeks.<sup>18</sup> Similarly in this report, survival rates for the infants born at 22-24 weeks of gestation remained at 21% most likely as an indication of the biological limit of viability.

According to the legal regulations in our country <20 weeks GA is considered abortion however performing resuscitation is proposed to each baby with any sign of vitality regardless of gestational age.<sup>19</sup> Twenty-one neonates with <500 g BW and <23 weeks GA were admitted to the NICU during this study period however, none of them survived to discharge. Nearly half of the infants at the limits of viability died within the first day of life and almost all of those remaining had died by the end of the first week. Likewise, according to the results of EPIPAGE 2 the chance of survival of neonates below 24 weeks did not change between the two study periods, none of the infants born alive at 22- 23 weeks survived to discharge.<sup>20</sup>

Perinatal characteristics such as older GA, higher BW, female gender, singleton birth, and antenatal steroid administration are known predictors for the survival of ELBW infants. Although in this study, ELBW infants who died in the NICU were found to be more premature,

singleton and male, have lower GA, and lower rates of antenatal corticosteroid administration. Only low BW, multiple births, and asphyxia at birth were found to be independent risk factors for mortality. According to our results being born with  $\leq 750$  g BW was associated with 5.7 times increased risk for mortality. When it was evaluated in terms of morbidities related to mortality in the NICU; RDS, pulmonary hemorrhage, severe IVH, advanced NEC, and meningitis were independent risk factors for mortality of ELBW infants. In a large cohort from China being SGA, being male, multiple births, low Apgar score, and being born to a mother with gestational diabetes were associated with a decreased chance of survival.<sup>21</sup>

As the survival of ELBW neonates increased, concerns have been raised regarding whether the same improvement was observed in morbidities. In this study severe IVH, BPD, advanced NEC, severe ROP requiring treatment and culture-proven sepsis were considered as major morbidities. We showed that 45.2% of the survived neonates had no major morbidity; the rate of survival without major morbidity was 27% in babies  $\leq 750$  g BW where it raised to 51% for the babies 751-1000 g BW. The same trend was observed when it was evaluated according to GA. The rate of survival without major morbidity was 28% for infants at 25-26 weeks GA, 45% at 27-28 weeks GA, and 73% between 28-32 weeks GA in this study. These rates are slightly lower than those in developed countries. According to the NICHD network data, 20% of babies at 25 weeks GA, 34% of babies at 26 weeks GA, and 44% of babies at 27 weeks GA had no morbidity at discharge.<sup>22</sup>

Intraventricular hemorrhage is the most common acute central nervous system complication of a preterm birth. The risk of IVH increases with decreasing GA and BW. In this study, the incidence of severe IVH was 12.4% in neonates  $\leq 750$  g BW, and 5.7% in neonates between 750-1000 g BW. The data of NICHD Neonatal Research reported an increased prevalence of severe IVH with rates of 38% and 36% for infants with 22 and 23 GA and 11% and 7% for infants

with 27 and 28 GA, respectively.<sup>22</sup> Prematurity is the most closely related clinical condition to IVH. Other risk factors associated with the risk of IVH include lack of antenatal glucocorticoid therapy, neonatal transport, prolonged neonatal resuscitation, and respiratory distress requiring mechanical ventilation.<sup>23</sup> In this cohort, 61.2% of neonates with severe IVH had no antenatal glucocorticoid administration.

Sepsis is an important cause of morbidity and mortality among preterm neonates with increasing rates at low GA and BW. The estimated rate of culture-proven sepsis was reported as 43% among infants with  $\leq 750$  g BW and 28% among neonates with 750-1000 g BW.<sup>11</sup> In this study, late-onset sepsis was diagnosed in 24% of ELBW neonates, and the rate of culture-proven sepsis was 20.2%, which is comparable with developed centers.

Necrotizing enterocolitis (NEC) occurs in 2 to 10 percent of VLBW infants.<sup>24</sup> In accordance with the literature we found the overall incidence of advanced NEC as 4.6% in ELBW infants and 7.4% for the neonates with  $<750$  g BW. Appropriate enteral feeding protocol and the high rate of breastfeeding in our unit are important factors to reduce NEC in preterm infants.

Retinopathy of prematurity affects a considerable number of preterm infants worldwide. The increased incidence and severity of ROP with decreasing GA have been demonstrated in previous studies.<sup>25,26</sup> In a multicenter study from the US, the incidence of ROP in preterm infants with  $<1251$  g BW was 68%.<sup>25</sup> The overall incidence of severe ROP among infants born  $<32$  weeks GA was reported as 10 % in a population-based cohort study from New Zealand and Australia, severe ROP increased from 3 to 34 % as GA decreased from 27 to 24 weeks, respectively.<sup>26</sup> A recent study from Türkiye (TR-ROP study) reported the incidence of any stage of ROP as 27% and severe ROP as 6.7%.<sup>27</sup> In our study any stage ROP was detected in 45.5% of ELBW infants, 13.3% of them were severe ROP requiring treatment. The

most important risk factor for developing ROP is prematurity however nearly all the morbidities in the NICU are thought to contribute. Better neonatal care and all preventive strategies to prevent neonatal morbidities may reduce the prevalence of ROP in preterm infants.

The rate of BPD varies among institutions, approximately a rate of 40% is reported for extremely preterm infants besides infants with <1250 g BW account for 97% of the cases of BPD.<sup>28,29</sup> In this study, the rate of BPD was 46.4% for the total cohort and 53% for infants with  $\leq 750$  g BW.

Pulmonary hemorrhage occurs most commonly in extremely preterm infants and it is associated with increased mortality. In a large cohort from the US, the incidence of pulmonary hemorrhage was reported as 9% among infants born at 24 weeks gestation with a higher mortality rate (41%) at seven days of age.<sup>30</sup> In our cohort, pulmonary hemorrhage occurred in 34 (5.5%) neonates with a peak incidence of 8% for infants with 500-750 g BW. In this study, we showed that pulmonary hemorrhage was an independent risk factor for the mortality of ELBW infants.

Major complications in NICUs have been associated with neurodevelopmental impairments in neonates. So, monitorization of outcomes of preterm infants is an essential component of patient management in the NICU. Defining patient characteristics and outcomes help achieve proper clinical management and policy making. Currently, the care of ELBW infants occupies an important part of duties in the NICU. Given the paucity of data regarding the outcomes of ELBW infants in Türkiye, we conducted a cohort study focusing on morbidities in ELBW infants. We are aware that our study has some limitations. First, this study is from a single center and the results may not reflect the other centers in our country. The retrospective nature and lack of long-term outcomes are the other limitations.

Nevertheless, the results of this study suggest that ELBW infants, particularly those with  $BW \leq 750$  g are at high risk of mortality. Major morbidities related to prematurity such as asphyxia at birth, RDS, pulmonary hemorrhage, and severe IVH are strongly related to mortality.

In conclusion, the short and long-term prognosis for preterm infants born weighing less than 750 g remain less favorable. Management of these infants requires high medical and nursing standards. General and institutional guidelines and more effective perinatal treatment strategies are needed to improve the outcomes of these neonates. Multicenter trials are necessary to define national data regarding the mortality and morbidity of ELBW infants.

### **Ethical approval**

The institutional ethics committee at Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital approved this study (17.06.22-08/24).

### **Author contribution**

The authors confirm contribution to the paper as follows: study conception and design: SK, AYB; data collection: SK, Fİ, MT, DUI; analysis and interpretation of results: SK, DUI; draft manuscript preparation: SK, AYB, ND. All authors reviewed the results and approved the final version of the manuscript.

### **Source of funding**

The authors declare the study received no funding.

### **Conflict of interest**

The authors declare that there is no conflict of interest.



## REFERENCES

1. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet* 2008; 371: 164-175. [https://doi.org/10.1016/S0140-6736\(08\)60108-7](https://doi.org/10.1016/S0140-6736(08)60108-7)
2. Bode MM, D'Eugenio DB, Forsyth N, Coleman J, Gross CR, Gross SJ. Outcome of extreme prematurity: a prospective comparison of 2 regional cohorts born 20 years apart. *Pediatrics* 2009; 124: 866-874. <https://doi.org/10.1542/peds.2008-1669>
3. Fanaroff A, Poole K, Duara S, et al. Micronates: 401-500 grams: the NICHD neonatal research network experience 1996-2001. *Pediatr Res* 2003; 53: 398A.
4. Doyle LW. Evaluation of neonatal intensive care for extremely-low-birth-weight infants. *Semin Fetal Neonatal Med* 2006; 11: 139-145. <https://doi.org/10.1016/j.siny.2005.11.009>
5. Bardin C, Zelkowitz P, Papageorgiou A. Outcome of small-for-gestational age and appropriate-for-gestational age infants born before 27 weeks of gestation. *Pediatrics* 1997; 100: E4. <https://doi.org/10.1542/peds.100.2.e4>
6. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978; 92: 529-534. [https://doi.org/10.1016/s0022-3476\(78\)80282-0](https://doi.org/10.1016/s0022-3476(78)80282-0)
7. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 1986; 33: 179-201. [https://doi.org/10.1016/s0031-3955\(16\)34975-6](https://doi.org/10.1016/s0031-3955(16)34975-6)
8. Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr* 2011; 23: 167-172. <https://doi.org/10.1097/MOP.0b013e3283423e6b>
9. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003; 121: 1684-1694. <https://doi.org/10.1001/archophth.121.12.1684>
10. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013; 13: 59. <https://doi.org/10.1186/1471-2431-13-59>
11. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* 2015; 314: 1039-1051. <https://doi.org/10.1001/jama.2015.10244>
12. Kalimba EM, Ballot D. Survival of extremely low-birth-weight infants. *S Afr J CH* 2013; 7: 13-16. <https://doi.org/10.7196/sajch.488>
13. Trotman H, Lord C. Outcome of extremely low birthweight infants at the University Hospital of the West Indies, Jamaica. *West Indian Med J* 2007; 56: 409-413.
14. Atasay B, Günlemez A, Unal S, Arsan S. Outcomes of very low birth weight infants in a newborn tertiary center in Turkey, 1997-2000. *Turk J Pediatr* 2003; 45: 283-289.
15. Güran O, Bülbül A, Uslu S, Dursun M, Zubarioğlu U, Nuhoğlu A. The change of morbidity and mortality rates in very low birth weight infants over time. *Turk Arch Ped* 2013; 48: 102-109. <https://doi.org/10.4274/tpa.1062>
16. Turkish Neonatal Society. Türkiye'deki yenidoğan merkezlerinde mortalite. *Türk Neonatoloji Derneği Bülteni* 2021; 33: 46-48.
17. Santhakumaran S, Statnikov Y, Gray D, et al. Survival of very preterm infants admitted to neonatal care in England 2008-2014: time trends and regional variation. *Arch Dis Child Fetal Neonatal Ed* 2018; 103: F208-F215. <https://doi.org/10.1136/archdischild-2017-312748>
18. Kulali F, Bas AY, Erol S, et al. Survival of periviable infants: 5-year experience at a single center. *J Matern Fetal Neonatal Med* 2020; 33: 3725-3731. <https://doi.org/10.1080/14767058.2019.1583734>
19. Oygür N, Önal EE, Zenciroğlu A. National guidelines for delivery room management. *Turk Pediatr Ars* 2018; 53: S3-S17. <https://doi.org/10.5152/TurkPediatrArs.2018.01803>
20. Ancel PY, Goffinet F; EPIPAGE-2 Writing Group, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr* 2015; 169: 230-238. <https://doi.org/10.1001/jamapediatrics.2014.3351>
21. Zhu Z, Yuan L, Wang J, et al. Mortality and morbidity of infants born extremely preterm at tertiary medical centers in China from 2010 to 2019. *JAMA Netw Open* 2021; 4: e219382. <https://doi.org/10.1001/jamanetworkopen.2021.9382>
22. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010; 126: 443-456. <https://doi.org/10.1542/peds.2009-2959>

23. Kenet G, Kuperman AA, Strauss T, Brenner B. Neonatal IVH-mechanisms and management. *Thromb Res* 2011; 127 Suppl 3: S120-2. [https://doi.org/10.1016/S0049-3848\(11\)70032-9](https://doi.org/10.1016/S0049-3848(11)70032-9)
24. Battersby C, Santhalingam T, Costeloe K, Modi N. Incidence of neonatal necrotising enterocolitis in high-income countries: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2018; 103: F182-F189. <https://doi.org/10.1136/archdischild-2017-313880>
25. Good WV, Hardy RJ, Dobson V, et al. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. *Pediatrics* 2005; 116: 15-23. <https://doi.org/10.1542/peds.2004-1413>
26. Darlow BA, Hutchinson JL, Henderson-Smart DJ, et al. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics* 2005; 115: 990-996. <https://doi.org/10.1542/peds.2004-1309>
27. Bas AY, Demirel N, Koc E, et al. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. *Br J Ophthalmol* 2018; 102: 1711-1716. <https://doi.org/10.1136/bjophthalmol-2017-311789>
28. Poindexter BB, Feng R, Schmidt B, et al. Comparisons and limitations of current definitions of bronchopulmonary dysplasia for the prematurity and respiratory outcomes program. *Ann Am Thorac Soc* 2015; 12: 1822-1830. <https://doi.org/10.1513/AnnalsATS.201504-218OC>
29. Walsh MC, Szefer S, Davis J, et al. Summary proceedings from the bronchopulmonary dysplasia group. *Pediatrics* 2006; 117: S52-S56. <https://doi.org/10.1542/peds.2005-0620I>
30. Ahmad KA, Bennett MM, Ahmad SF, Clark RH, Tolia VN. Morbidity and mortality with early pulmonary haemorrhage in preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 2019; 104: F63-F68. <https://doi.org/10.1136/archdischild-2017-314172>