Acta Clin Croat 2019; 58:446-454
doi: 10.20471/acc.2019.58.03.07

Original Scientific Paper

SURVIVAL UNTIL DISCHARGE OF VERY-LOW-BIRTH-WEIGHT INFANTS IN TWO CROATIAN PERINATAL CARE REGIONS: A RETROSPECTIVE COHORT STUDY OF TIME AND CAUSE OF DEATH

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SUMMARY – We investigated mortality, causes, timing and risk factors for death until hospital discharge in very-low-birth-weight (VLBW) infants born in two Croatian perinatal care regions. This retrospective study included 252 live born VLBW infants. The mortality rate until hospital discharge was 30.5% (77/252). VLBW infants who died had by 4 weeks lower gestational age (GA) than surviving infants (median GA, 25 *vs*. 29 weeks), lower birth weight (BW) (mean BW, 756.4 *vs*. 1126.4 g), lower 5-minute Apgar score (median 5 *vs*. 8) and were more often resuscitated at birth (41.6 *vs*. 19.4%; p<0.001 all). Infants who survived were more often small-for-gestational age (SGA) (28.0 *vs*. 15.6%; p=0.04) and more often received continuous-positive-airway-pressure (CPAP) in delivery room (13.1 *vs*. 2.6%; p=0.01). Multivariate logistic regression revealed that parameters influencing death until hospital discharge were 5-minute Apgar score (OR 0.780, 95% CI 0.648-0.939) and higher Clinical Risk Index for Babies (CRIB) score (OR 1.677, 95% CI 1.456-1.931). ROC analysis showed that CRIB score (AUC 0.927, sensitivity 92.2, specificity 81.1; p<0.001) was the strongest predictor of death until hospital discharge. In infants who died within 12 hours, death was most commonly attributed to immaturity and in those surviving >12 hours to necrotizing enterocolitis.

Key words: *Infant, very low birth weight; Cause of death; Hospital mortality; Croatia*

Introduction

Understanding the causes and timing of death in very-low-birth-weight (VLBW) neonates is important for planning of perinatal care and parental counseling. Neonatal mortality accounts for a major proportion of deaths in children under 5 years[1]. The leading cause of death among infants is prematurity and morbidities related to premature birth[2]. Advances in the field of neonatology, i.e. introduction of surfactant therapy[3] and antenatal corticosteroid administration[4] have led to a significant reduction of mortality, especially in developed countries[5-7]. Outcomes improve significantly with advancing gestational age, so Bajwa

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Received April 19, 2018, accepted July 24, 2018

et al. found that between 23 and 26 weeks of gestational age (GA), the overall decrease in mortality was 23% for each additional week of GA, yielding a 3% daily decrease in mortality[8].

There is an ongoing debate on decision making regarding infants born at the threshold of viability[9]. Gestational weeks 22 to 23 seem to be the limit of viability (GA at which a prematurely born fetus/infant has a 50% chance of long-term survival outside the mother's womb)[10]. Various countries have developed different approaches to treatment strategies in the periviable period[11]. In Croatia, there are no recommendations regarding initiation of intensive care in the periviable infants. Therefore, having reliable data on the causes and timing of death in VLBW infants is of paramount importance for appropriate parental counseling and further planning of perinatal care.

Patients and Methods

All live born infants in two Croatian perinatal care regions were considered eligible for inclusion in the study if they met the following four criteria: born between January 1, 2014 and December 31, 2016, GA at birth ≥22 0/7 weeks, birth weight <1500 g, and born in delivery wards in the regions (2 level III neonatal units, 2 level II neonatal units and 5 level I neonatal wards). The eligibility criteria were met by 256 infants. Of these, four infants were foreign residents and were transferred to their country of origin, thus data on their outcomes were unknown. Consequently, the cohort included in our analysis consisted of 252 infants. Enrolled infants were followed up actively from birth to hospital discharge.

Survival until discharge was defined as discharge home or to a palliative care facility. GA was determined based on obstetric examination with ultrasonography during the first trimester, taking into account the last menstrual period, and postnatal examination of the neonate. Small for gestational age (SGA) was defined as birth weight of more than 2 SD below the mean based on neonatal anthropometric charts[12]. Antenatal steroid use was defined as administration of dexamethasone to accelerate fetal maturity with at least 1 dose (incomplete) or at least 4 doses (complete). Chorioamnionitis was defined based on histologic findings; where histology was not performed (only infants born in level I and II neonatal care units), the diagnosis was based on the previously described criteria[13]. Maternal hypertension and late-onset sepsis were defined based on previous studies[14]. Delivery room resuscitation was defined as any endotracheal intubation and/or chest compression and/or fluid boluses and/or any epinephrine administration in the delivery room. The Critical Risk Index for Babies (CRIB) score was calculated according to the author's instructions[15].

The primary cause of death was defined as a single underlying disease that initiated the chain of events leading to the final cause of death. The cause of death had to be specific to the underlying disease and preceding all other causes. For example, if the infant had necrotizing enterocolitis (NEC) and died due to late-onset sepsis, death was attributed to NEC. As an exception, kidney failure was defined as a specific cause of death because we observed that a significant number of infants survived the initial cause of acute kidney injury (i.e. late-onset sepsis) but later died from kidney failure. The causes of death were as follows: immaturity, respiratory distress syndrome (RDS), kidney failure, infection, congenital malformations, central nervous system (CNS) injury, bronchopulmonary dysplasia (BPD), and NEC. The causes of death were defined as in previous studies[16]. Death due to kidney failure was defined as death following an episode of kidney failure according to the nRIFLE (loss or end-stage) criteria[17]. The causes of death that could not be classified as one of the aforementioned causes were classified as 'other'.

Data were processed by use of descriptive statistics methods. The Mann-Whitney *U* test was used to compare median between the two groups, while Fisher exact test was used to analyze differences between proportions. Logistic regression was used to analyze the independent factors associated with negative outcome. The receiver operating curve (ROC) was used to determine the optimal threshold, area under the curve (AUC), specificity and sensitivity of the tested parameters. Median survival was calculated using Kaplan-Meier analysis. The level of statistical significance was set at 0.05. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org. 2018).

Table 1. Demographic and clinical data of the study cohort of very-low-birth-weight neonates (N=252)

	Survival			p-value
	Yes (n=175)	No (n=77)	Total (n=252)	
Birth weight (g), mean (SD)	1126.49 (241.8)	756.4 (243.1)	1013.9 (294.8)	**<0.001***
Gestation (weeks), median (IQR)	29 (27 – 31)	25 (23 – 26)	28 (25 – 30)	**<0.001***
5-min Apgar sore, median (IQR)	8 (6 – 10)	5 (3 – 7)	7 (5 – 9)	**<0.001***
CRIB score, median (IQR)	1 (1 – 2)	9 (6.5 – 13.5)	2 (1 – 7)	**<0.001***
Male sex, n (%)	81 (46.3)	46 (59.7)	127 (50.4)	0.05†
Prenatal corticosteroids, n (%)	95 (54.3)	41 (53.3)	136 (54)	0.98†
Complete course	21 (12)	9 (11.7)	30 (11.9)	
Incomplete course	74 (42.3)	32 (41.6)	106 (42.1)	
Singleton/multiple, n/n (% of multiple birth), n (%)	130/45 (25.7)	61/16 (20.8)	191/61 (24.2)	0.43†
Chorioamnionitis, n (%)	78 (44.6)	42 (54.6)	120 (47.6)	0.13†
SGA, n (%)	49 (28)	12 (15.6)	61 (24.2)	**0.04†**
Delivery room resuscitation, n (%)	34 (19.4)	32 (41.6)	66 (26.2)	**<0.001†**
Delivery room CPAP, n (%)	23 (13.1)	2 (2.6)	25 (9.9)	**0.01†**
Outborn, n (%)	16 (9.1)	12 (15.6)	28 (11.1)	0.19†

*Mann Whitney U test; †Fisher exact test; IQR = interquartile range; CRIB = Critical Risk Index for Babies; SGA = small for gestational age; CPAP = continuous positive airway pressure; figures in bold = statistically significant

Table 2. Univariate logistic regression analysis of risk factors for death until hospital discharge

Parameter	β	Standard error	Wald	p	OR (Exp β)	95% CI
Birth weight	-0.006	0.001	55.5	**<0.001**	0.994	0.993-0.996
Gestational age	-0.668	0.088	57.7	**<0.001**	0.513	0.431-0.609
Singleton/multiple	-0.277	0.329	0.71	0.40	0.758	0.397-1.446
Female/male	0.544	0.277	3.84	0.05	1.722	0.999-2.97
5-min Apgar score	-0.513	0.073	49.59	**<0.001**	0.598	0.518-0.690
Prenatal corticosteroids, any	-0.042	0.274	0.02	0.87	0.959	0.560-1.642
Chorioamnionitis	0.400	0.274	2.12	0.15	1.49	0.871-2.557
Outborn	0.606	0.409	2.19	0.14	1.83	0.822-4.092
SGA	-0.745	0.356	4.368	**0.04**	0.475	0.236-0.954
CRIB score	0.521	0.063	67.68	**<0.001**	1.68	1.487-1.906
Delivery room resuscitation	1.081	0.299	12.99	**<0.001**	2.95	1.638-5.309
Delivery room CPAP	-1.736	0.751	5.35	**0.02**	0.18	0.041-0.767

SGA = small for gestational age; CRIB = Critical Risk Index for Babies; CPAP = continuous positive airway pressure; OR = odds ratio; CI = confidence interval; figures in bold = statistically significant

Table 3. Multivariate logistic regression analysis of risk factors significantly influencing death until hospital discharge

Parameter	β	Standard error	Wald	p	OR (Exp β)	95% CI
5-minute Apgar score	-0.248	0.094	6.925	**0.009**	0.780	0.648-0.939
CRIB score	0.517	0.072	51.39	**<0.001**	1.677	**1.456-1.931**
Constant	-0.599	0.723	4.88	**0.03**		

CRIB = Critical Risk Index for Babies; OR = odds ratio; CI = confidence interval; figures in bold = statistically significant

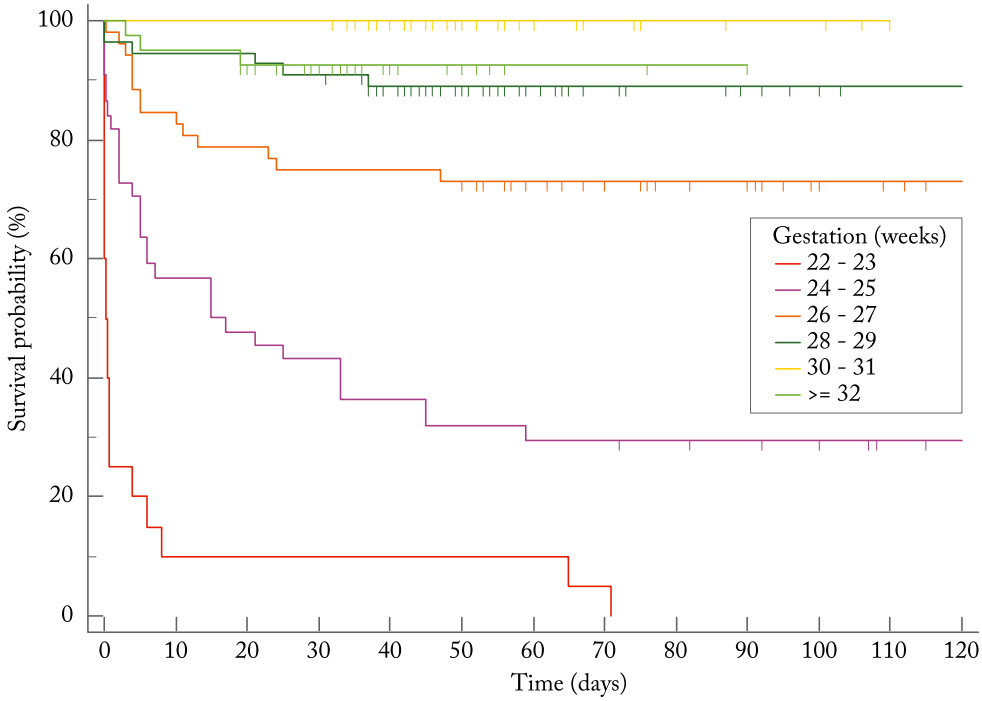

Fig. 1. Kaplan-Meier curve of survival in relation to gestational age in the cohort of very-low-birth-weight neonates (N=252).

Results

Parameters influencing death until hospital discharge

A total of 252 VLBW infants were included. An active approach was instituted in all but three infants (two due to immaturity and one due to congenital anomaly, i.e. anencephaly). Mortality until hospital discharge was 30.5% (77/252). Demographic and clinical data on the study cohort are shown in Table 1. VLBW infants who died had 4 weeks lower GA than surviving infants (median GA at birth 25 *vs.* 29 weeks), lower birth weight (mean 756.4 *vs.* 1126.4 g), lower Apgar score in the fifth minute of life (median 5 *vs.* 8) and were more frequently resuscitated at birth (41.6% *vs.* 19.4%; p<0.001). The infants who survived were more often SGA (28.0% *vs.* 15.6%; p=0.04) and more often received continuous-positive-airway-pressure (CPAP) in the delivery room (13.1% *vs.* 2.6%; p=0.01). Male sex, prenatal corticosteroid use, singleton or multiple pregnancy, chorioamnionitis and not being born at a neonatal unit level III did not vary between the groups. Results of the univariate logistic regression analysis (Table 2) revealed the impact of multiple factors on the probability of death until hospital discharge. Lower birth weight, lower GA, low 5-minute Apgar score, higher CRIB score and the need for delivery room resuscitation were the risk factors for death until hospital discharge. The only two factors that reduced the risk of death until hospital discharge were if the infant was SGA (OR 0.475, 95% CI 0.236-0.954) and received CPAP in the delivery room (OR 0.18, 95% CI 0.041-0.767). For the multivariate logistic regression analysis, a simplified model using backward stepwise regression was developed (Table 3). The parameters influencing death until hospital discharge were 5-minute Apgar score (OR 0.780, 95% CI 0.648-0.939) and CRIB score (OR 1.677, 95% CI 1.456-1.931). The strongest predictor was CRIB score, which gave a unique statistical contribution to the model. The ROC curve method was utilized to assess the value of the parameters for which multivariate analysis showed significant contribution to the model. In our data, the strongest association was found for CRIB score (AUC 0.927, sensitivity 92.2, specificity 81.1; p<0.001).

Death until hospital discharge and gestational age

Survival until hospital discharge depending on infant GA was as follows: GA 22-23 weeks 0% (0/20);

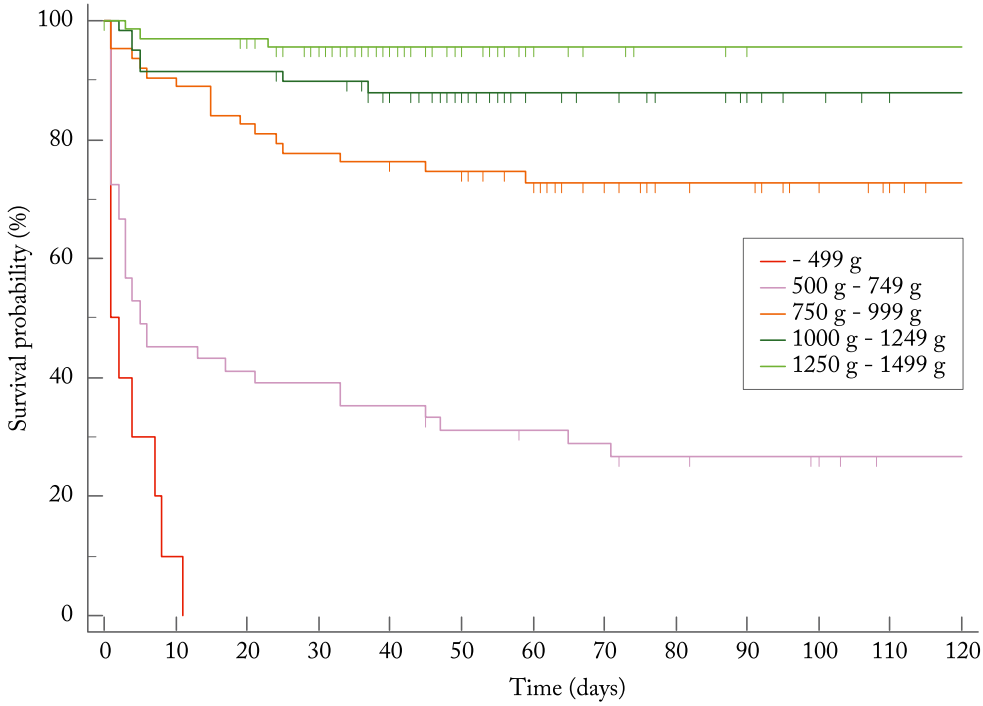

Fig. 2. Kaplan-Meier curve of survival in relation to birth weight in the cohort of very-low-birth-weight neonates (N=252).

GA 24-25 weeks 27.3% (12/44); GA 26-27 weeks 71.2% (37/52); GA 28-29 weeks 87.3% (49/56); GA 30-31 weeks 100% (0/40); and GA >32 weeks 92.5% (37/40) (Fig. 1). The limit of viability in our cohort of VLBW infants was 26 weeks of gestation (GA 25 weeks survival rate 30.4% *vs*. GA 26 weeks survival rate 65.0%).

Death until hospital discharge and birth weight

Survival until hospital discharge depending on birth weight of infants was as follows: <499 g: 0% (0/20), 500-749 g: 28.8% (14/52), 750-999 g: 69.8% (52/59), 1000-1250 g: 88.1% (64/68) and 1250-1499 g: 94.1% (64/68) (Fig. 2).

Cause of death in relation to postnatal age

Death in infants who died within 12 hours after birth was most commonly attributed to immaturity (Table 4). In infants surviving longer than 12 hours, death was most commonly attributed to NEC; this condition was considered to underlie 17.3% of deaths in the first 14 days and 19.8% of deaths in the first 28 days of life. Also, at 15 to 60 postnatal days, NEC was the most common cause of death. After 60 days, infection became the predominant cause of death (Fig. 3).

Cause of death in relation to gestational age

In infants born at 22 or 23 weeks of gestation, immaturity was the most common cause of death (Table 5). Deaths among infants born at 24 to 27 weeks of gestation were similarly attributed to NEC (14.2%), infection (12.9%), immaturity (12.9%) and kidney failure (11.6%).

Discussion

Mortality until hospital discharge

This was the first study to investigate timing and cause of death until hospital discharge in VLBW infants in Croatia. The overall mortality until hospital discharge was 30.5%, similar to the mortality reported in European transition countries. A study analyzing data on 1,460 singleton live births with VLBW (≤1500 g) during the 2000-2010 period in Latvia showed a mortality rate of 25.5% in the neonatal period[18]. Mortality in our cohort was significantly higher than those

Table 4. Timing and causes of death until hospital discharge in very-low-birth-weight neonates

	Number (%)							
Time of death	≤12 hours	13 hours--3 days	4-7 days	8-14 days	15-28 days	29-60 days	61-90 days	>90 days
Total, n (%)	22 (29)	11 (14)	16 (21)	4 (5)	11 (14)	8 (10)	2 (3)	3 (4)
Cause of death:								
Bronchopulmonary dysplasia	0	0	0	0	0	0	0	1 (1.3)
CNS injury	0	0	3 (18.8)	0	0	0	0	0
Congenital anomalies	2 (9.1)	0	0	0	1 (9.1)	0	0	0
Immaturity	16 (72.7)	6 (54.5)	2 (12.5)	0	0	0	0	0
Infection	2 (9.1)	0	3 (18.8)	0	1 (9.1)	3 (37.5)	1 (50)	2 (66.7)
Kidney failure	0	0	2 (12.5)	2 (50)	5 (45.5)	0	1 (50)	0
NEC	0	0	3 (18.8)	1 (25)	4 (36.4)	5 (62.5)	0	0
Other	0	1 (9.1)	1 (6.3)	0	0	0	0	0
Respiratory distress syndrome	2 (9.1)	4 (36.4)	2 (12.5)	1 (25)	0	0	0	0
Total, n (%)	22 (100)	11 (100)	16 (100)	4 (100)	11 (100)	8 (100)	2 (100)	3 (100)

CNS = central nervous system; NEC = necrotizing enterocolitis

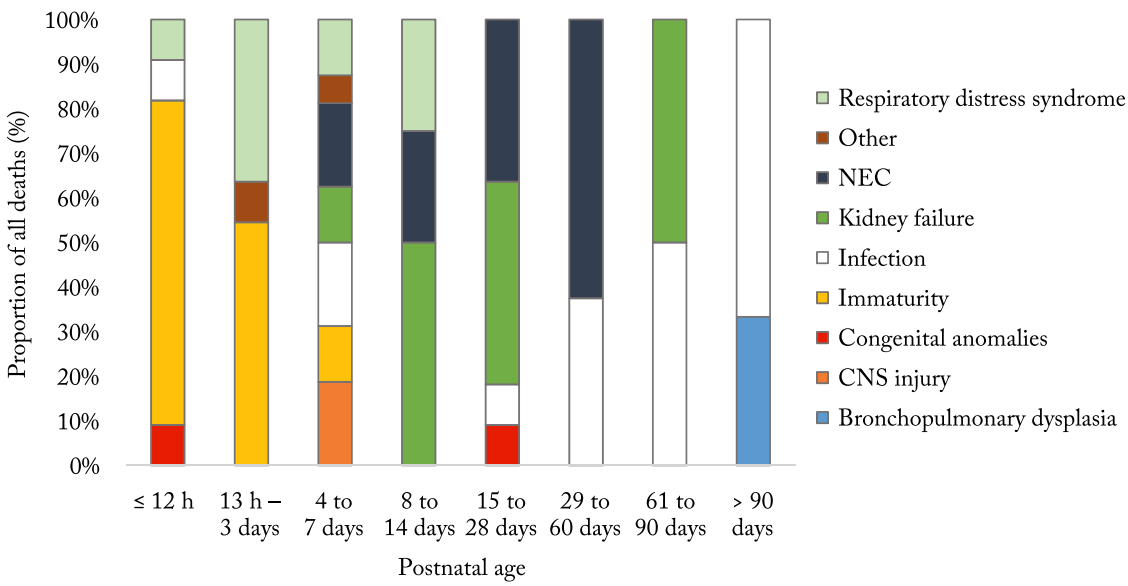

Fig. 3. Proportionate mortality for major causes of death in very-low-birth-weight neonates according to postnatal age.

CNS = central nervous system; NEC = necrotizing enterocolitis

reported in well-developed countries. In a German cohort of VLBW infants in 2008-2012, the overall mortality was 10.9%[19]. In the US, the overall mortality of VLBW infants (N=102493) during the 1997-2004 period was 22.53%[20], and in Korea the mortality of VLBW infants from January 2013 to June 2014 was 15.2%[21]. The mortality rate in our cohort corresponded to the mortality rate of 32.4% reported in South Korea in 1996[22].

In our cohort, there were no survivors born at 22 and 23 weeks of gestation, and mortality until hospital discharge in infants born ≤24 weeks of gestation was

Table 5. Cause of death according to gestational age

	Number (%) of infants according to gestational age						
Gestational age (weeks)	22-23	24-25	26-27	28-29	30-31	≥32	Total
n (% of total deaths)	20 (26)	32 (41,6)	15 (19,5)	7 (9,1)	0	3 (3,9)	77 (100)
Cause of death:							
Bronchopulmonary dysplasia	0	0	1 (6.7)	0	0	0	1 (1.3)
CNS injury	1 (5)	0	2 (13.3)	0	0	0	3 (3.9)
Congenital anomalies	0	1 (3.1)	1 (6.7)	1 (14.3)	0	0	3 (3.9)
Immaturity	14 (70)	7 (21.9)	1 (6.7)	1 (14.3)	0	1 (33.3)	24 (31.2)
Infection	2 (10)	4 (12.5)	4 (12.5)	2 (28.6)	0	0	12 (15.6)
Kidney failure	1 (5)	5 (15.6)	2 (13.3)	1 (14.3)	0	1 (33.3)	10 (13)
NEC	2 (10)	8 (25)	1 (6.7)	2 (28.6)	0	0	13 (16.9)
Other	0	0	2 (13.3)	0	0	0	2 (2.6)
Respiratory distress syndrome	0	7 (21.9)	1 (6.7)	0	0	1 (33.3)	9 (11.7)
Total	20 (100)	32 (100)	15 (100)	7 (100)	0	3 (100)	77 (100)

CNS = central nervous system; NEC = necrotizing enterocolitis

87.8%. In European countries, mortality rates until 30 days of life in infants born ≤24 weeks of gestation vary from 83.3% in The Netherlands to 43.8% in Sweden[24].

Our data showed that significant improvements could be done in perinatal and neonatal care, especially in extremely-low-gestational-age newborns. Factors contributing to significant reduction of mortality in VLBW neonates in Korea were attributed to Korean socio-economic environment, public demand, numerous study visits and lectures in Korea by distinguished foreign neonatologists, return of native Korean neonatologists trained at famous foreign institutions, and establishment of Korean medical societies (e.g., Korean Society of Perinatology and Korean Society of Neonatology)[24]. Also, several therapeutic advances, i.e. high-frequency ventilation, inhaled nitric oxide, new modes of mechanical ventilation, nasal CPAP, delivery room management strategies and others have lowered mortality rates[25].

Several observations can be made when comparing our cohort to a historical cohort of VLBW neonates (500-1499 g) born in 1998-1999, investigated by Filipović-Grčić[26]. In the historical cohort, comfort care was administered to 9.37% (63/672) of infants. This is in contrast to only 1.1% (3/252) of infants having received comfort care in our cohort. This may reflect changing attitudes of the Croatian neonatologists, especially concerning Croatian implementation of the WHO standards for reporting infants born at ≥22 weeks of gestation in their vital statistics since 2001[27].

Overall mortality until hospital discharge in the historical group was 47.5% (319/663) and was significantly higher as compared with our cohort (30.5%; 77/252). In our cohort of VLBW infants, the limit of viability (GA at which a prematurely born infant has a 50% chance of long-term survival outside the womb)[10] was 26 weeks of gestation as compared to 29-31 weeks (mortality 36.1%) in the historical cohort.

The potential factors that contribute to the reduction of overall mortality are better *in utero* transport to level III neonatal units. In the historical cohort, 38.6% (260/672) were born and primarily cared for in level I and II neonatal units, compared to only 11.2% (28/252) infants born and initially treated at level I and II neonatal units in our cohort. This conclusion is supported by Boland *et al.*[28], who found that mortality rates remained higher for outborn live births at 22-27 weeks of gestation compared with inborn peers. Conclusions on other factors contributing to better outcomes could not be drawn due to the lack of respective data.

Cause of death in relation to postnatal age

Death attributed to immaturity was prevalent in the first three days of life. This is consistent with findings reported from several studies[29]. Also, the finding

of NEC as the prevalent cause of mortality after 7 days of life is consistent with previously published multicenter studies[16]. To further reduce NEC rates in our population, appropriate strategies should be implemented (reducing ventilation days, prevention of late-onset sepsis, avoiding H2 blockers, initiation of early enteral feeds, initiation of breastfeeding, implementation of standardized feeding guidelines, etc.)[28].

Kidney failure was the fourth most common cause of death in our cohort following infections, and was responsible for 12.9% (10/77) of all deaths. This indicates that special care needs to be taken to maintain hemodynamic support in infants at risk of kidney failure.

There were several limitations to our study. Determining a single cause of death in VLBW neonates is challenging because multiple factors play role in outcomes. Also, subjectivity in identifying the cause of death must be taken into consideration. There may have been misclassifications, especially in attributing the causes of death to kidney failure *versus* immaturity or infection. Finally, our cohort may not have been representative for other perinatal care regions in Croatia and this may limit translation of our findings to the entire Croatian population of VLBW neonates.

In conclusion, mortality of VLBW infants was found to be higher as compared to countries with advanced perinatal care and was similar to other transitional countries; however, significant improvements in survival until discharge had been achieved when comparing our cohort to the cohort of VLBW infants investigated by Filipović-Grčić[26] in the 1998-1999 period. Most VLBW infants died in the first 12 hours of life. Immaturity was the leading cause of death in the first 7 days of life, and after the first week, NEC was the predominant cause of death.

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Sažetak

PREŽIVLJENJE DO OTPUSTA IZ BOLNICE NOVOROĐENČADI VRLO NISKE POROĐAJNE TEŽINE U DVIJE HRVATSKE PERINATALNE REGIJE: RETROSPEKTIVNA STUDIJA VREMENA I UZROKA SMRTI

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Istraživali smo smrtnost, uzroke, vrijeme i rizične čimbenike za smrt do otpusta iz bolnice u novorođenčadi vrlo niske porođajne težine (VNPT) rođene u dvije hrvatske perinatalne regije. Ova retrospektivna studija je uključila 252 živorođena novorođenčeta VNPT. Smrtnost do otpusta iz bolnice bila je 30.5% (77/252). Novorođenčad VNPT koja su umrla bila su 4 tjedna manje gestacijske dobi od novorođenčadi koja je preživjela (medijan gestacijske dobi 25 prema 29 tjedana; p<0,001), imala su manju porođajnu težinu (srednja vrijednost 756,4 prema 1126,4 g; p<0,001), niže vrijednosti Apgar zbroja u 5. minuti života (medijan 5 prema 8; p<0,001) i češće su bila reanimirana pri porođaju (41,6% prema 19,4%; p<0,001). Preživjela novorođenčad su češće bila mala za gestacijsku dob (28,0% prema 15,6%; p=0,04) i kod njih je češće primijenjen kontinuirani pozitivni tlak u rađaonici (13,1% prema 2,6%; p=0,01). Multivarijatna logistička regresija je pokazala da su parametri koji najsnažnije utječu na smrt do otpusta iz bolnice Apgar zbroj u 5. minuti (OR 0,780, 95% CI 0,648-0,939) i CRIB zbroj (*Critical Risk Index for Babies*) (OR 1,677, 95% CI 1,456-1,931). ROC analiza je pokazala kako je CRIB zbroj (AUC 0,927, osjetljivost 92,2, specifičnost 81,1; p<0,001) najznačajniji prediktor smrti do otpusta iz bolnice. Nezrelost je glavni uzrok smrti u novorođenčadi koja su umrla prije 12. sata hospitalizacije. U novorođenčadi koja je preživjela >12 sati glavni uzrok smrti je nekrotizirajući enterokolitis.

Ključne riječi: *Dojenče, vrlo niske porođajne težine; Uzrok smrti; Bolnička smrtnost; Hrvatska*