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The Prognosis of Preterm Infants Born at the Threshold of Viability: Fog Over the Gray Zone – Population-Based Studies of Extremely Preterm Infants

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The limit of viability for premature newborns has changed in recent decades, but whether to initiate or withhold active care for periviable infants remains a subject of debate because the chances of survival and the extent of severe neurological impairment can be unclear. In our review, we analyzed large population-based studies of periviable infants from the past 2 decades. We compared survival rates and the incidence of early complications among survivors, including bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and necrotizing enterocolitis. Moreover, we assessed the perinatal factors that may affect the survival of preterm infants. We analyzed 15 studies reporting data on preterm infants born between 22 and 28 gestational weeks. None of these studies reported survival of an infant born before 22 gestational weeks. Survival rates of infants born at 24 weeks' gestation were above 50% in most studies. The incidence of each complication was also higher among infants born at ≤ 24 weeks. Of the analyzed perinatal factors, antenatal corticosteroid therapy, birth weight, female sex, cesarean delivery, singleton pregnancy, and birth in a tertiary-level Neonatal Intensive Care Unit were found to be associated with improved survival in some studies. The different methodologies of the studies limited comparison of the results. Further investigations are needed to gain up-to-date information on the limit of viability, and standardized methods in future studies would enable more accurate comparisons of findings.

MeSH Keywords: **Fetal Viability • Infant, Extremely Low Birth Weight • Infant, Extremely Premature • Premature Birth**

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Background

The legal definition of viability centers on the ability of the fetus to survive outside the uterus after birth when supported by the most advanced medical care. This definition does not consider the chances of survival or the individual's quality of life; hence, it is essential to know the limit at which a preterm infant has a significant chance to survive without severe neurological impairment [1]. This second consideration, in contrast to the legal definition of viability, raises numerous questions. What does *significant chance* mean? Is there an exact percentage for it? What constitutes *severe neurological impairment*? Currently, these questions have no widely accepted answers.

A gray zone of viability lies between these 2 approaches. The care of neonates born within this gray zone represents a major moral and ethical dilemma for perinatal health care providers. The care of these infants is regulated differently depending on the culture and society. In some countries, the line between initiating or withholding intensive care is clear, while in other countries, parents are involved in the decisions [2,3].

Multiple population-based studies have been conducted to define the viability of extremely preterm infants, and the definition

has changed over time. Since 1980, the limit of viability has shifted from 28 to 22–24 weeks of gestational age. Updated information on the possible outcomes for these infants is crucial to make the best therapeutic decisions for their care.

Our aim was to review studies of periviable infants published over the last 20 years that reported survival rates and the incidence of complications (Table 1). Most of these population-based studies had large samples, and we assessed the perinatal factors that can affect the survival of extremely preterm infants.

Survival Rate According to Gestational Age

The different designs of the studies limited the comparison of survival rates. Six studies reported the survival rate in the proportion of all preterm infants [4–9], while 6 other studies focused on the survival rate of infants receiving care in the Neonatal Intensive Care Unit (NICU) [10–15]. Three studies reported survival rates in both groups [16–18]. In the EPIBEL study [4], infants who were transported from lower-level care to a tertiary-level NICU after birth were excluded; in a Californian study [6] and the EPI-SEN study [15], neonates with major congenital malformations were excluded.

Table 1. Selected large population-based studies on extremely preterm infants.

Study	Country/State	Years of the study	Gestational age	The number of all infants	The number of actively treated infants
EPIBEL [4]	Belgium	1999–2000	22–26	525	303
NEPS1 [16]	Norway	1999–2000	22–27	638	464
NEPS2 [17]	Norway	2013–2014	22–26	275	251
Kugelman [7]	Israel	1995–2008	23–26	4408	–
Agarwal [8]	Singapore	2000–2009	23–28	–	887
EPICURE [18]	UK	2006	22–26	3133	1686
EXPRESS [10]	Sweden	2004–2007	22–26	–	707
Ishii [11]	Japan	2003–2005	22–25	–	1057
Doyle [12]	Victoria State (Australia)	2005	22–27	–	270
Su [13]	Taiwan	2007–2012	23–28	–	1718
EPIPAGE-2 [5]	France	2011	22–26	–	1054
Stoll [14]*	USA	2008–2012	22–28	–	8877
Anderson [6]	California	2007–2011	22–28	6009	5340
EPI-SEN [15]*	Spain	2007–2011	22–26	2937	2734
Fischer [9]	Swiss	2000–2004	22–25	516	–

* These studies were divided to several periods. Data were reviewed only from the last period (shown in the table) of these studies.

Table 2. Survival rates of extremely preterm infants by gestational age.

Study	All infants/Infants who received intensive care	Survival rates (%) by gestational age (week)						
		22.	23.	24.	25.	26.	27.	28.
EPIBEL [4]	All	0	5.5	29.2	55.5	71.4	–	–
NEPS1 [16]	All	0	16	44	66	72	82	–
NEPS1 [16]	Intensive care	0	39	60	80	84	93	–
NEPS2 [17]	All	18	29	56	84	90	–	–
NEPS2 [17]	Intensive care	60	35	58	86	92	–	–
EPICURE [18]	All	2	19	40	66	77	–	–
EPICURE [18]	Intensive care	15.8	30.4	46.4	69.4	78.4	–	–
Kugelman [7]	All	–	6.2	26.5	47.4	70.1	–	–
Agarwal [8]	All	–	19	57	79	86	91	93
EXPRESS [10]	Intensive care	9.8	53	67	82	85	–	–
Ishii [11]	Intensive care	36	62.9	77.1	85.2	–	–	–
Doyle [12]	Intensive care	5	22	51	67	82	89	–
Su [13]	Intensive care	–	22	50	70	84	88	92
EPIPAGE2 [5]	All	0	1	31.2	59.1	75.3	–	–
Stoll [14]	Intensive care	7	32	62	77	85	90	94
Anderson [6]	All	6.4	26.9	59.8	78	85.9	90.8	94
EPI-SEN [15]	Intensive care	14.3	19.9	35.9	59.7	73.3	–	–
Fischer [9]	All	0	5	30	50	–	–	–

* These studies were divided to several periods. Data were reviewed only from the last period (shown in the table) of these studies.

Data on preterm infants born at 22 weeks were not obtained in 3 studies [7,8,13], 4 publications reported no survivors among infants at 22 weeks' gestation [4,5,9,16], and 4 studies found a survival rate lower than 10% [6,10,12,14]. Analyzing data on infants born at 23 weeks' gestation, 9 studies reported survival rates lower than 30% [4–9,12,13,15]. Studies analyzing the survival rate of preterm infants among infants treated in the NICU found $\geq 10\%$ survival rate at 22 weeks [11,15,17,18] and $\geq 30\%$ survival rate at 23 weeks [10,11,14,16–18].

Among infants born at 24 weeks' gestation, 9 studies found at least 50% survival [6,8,10–14,16,17], while in 6 reports, survival did not reach 50% [4,5,7,9,15,18]. All studies except for one [7] demonstrated a survival rate above 50% among neonates at 25 weeks' gestational age, and 7 studies found a rate above 75% [6,8,10,11,14,16,17]. Data on infants at 26 weeks' gestation showed more than 70% survival in all studies, and 8 studies revealed a proportion above 80% [6,8,10,12–14,16,17]. All 6 reports analyzing 27-week infants found $\geq 88\%$ survival rate [6,8,12–14,16]. All 4 studies assessing infants at 28 weeks showed more than 90% survival [6,8,13,14]. In most studies, more than 90% of infants who were born >24 weeks received active medical treatment (Table 2).

The Role of Perinatal Factors

Many of the large population-based studies assessing neonates born at the threshold of viability analyzed the perinatal risk factors affecting survival [4,6–8,10,16–18]. These factors included antenatal corticosteroid therapy, birth weight, multiple pregnancy, cesarean delivery, and admission to a tertiary-level NICU after birth.

A link between antenatal steroid therapy and survival of preterm infants was demonstrated by 6 studies. Three studies analyzed the data of infants who received complete antenatal steroid treatment [8,17,18], while the other 3 studies reported on infants who were given only a partial course [7,10,16]. Four studies showed lower mortality in infants who received antenatal corticosteroid therapy [7,10,17,18]. Two studies did not find link between survival and antenatal corticosteroid therapy [8,16].

In addition to the analyzed 15 studies, 2 other studies with a large number of infants focused on the association of antenatal steroid corticosteroid use with mortality and complications among infants born at 22–25 weeks' gestation. Both studies reported lower mortality and higher survival without severe neurological impairment among infants born at 23–25

weeks' gestation whose mothers were exposed to only to a partial antenatal course. Ehret et al. [19] found lower mortality and higher survival without severe neurological impairment, while Carlo et al. [20] did not find a decrease in either mortality or late neurological impairment among infants at 22 weeks.

Three publications found an association between birth weight and survival [6–8], but 3 other studies did not find a link between these 2 factors [4,16,17]. Three publications noted a higher survival rate among female preterm infants [6,8,18], and 1 study showed higher survival among female infants at 25 to 26 weeks [7]. Four studies did not find a difference between the survival of female and male infants [4,10,16,17]. None of the studies found a significant link between multiple pregnancy and mortality. Tyson et al. [21] found that higher birth weight, female sex, and antenatal steroid therapy were all associated with improved survival, while multiple pregnancies were linked to lower survival.

The benefit of cesarean delivery is controversial [22,23]. Three studies found higher survival rate of infants born by cesarean delivery [4,8,16], and 1 study found a lower rate [18]. One study demonstrated lower mortality in infants at 22–24 weeks born by cesarean delivery and in infants at 25–28 weeks born by vaginal delivery [6]. Three studies did not find a difference in mortality among preterm infants based on method of delivery [10,17,18].

Two studies demonstrated higher survival rates of infants born in a regional- or tertiary-level NICU [6,10] and 1 study did not [4].

Morbidity According to Gestational Age (Figures 1, 2)

Maturity at birth plays an essential role not only in survival, but also in neonatal complications. In some studies, morbidity was not reported based on gestational age, which limited the comparison of results between studies. In all publications except one, the incidence of complications was reported only for surviving infants. The exception was a Japanese study [11] that reported complications for all infants; therefore, we could not compare it to the other studies.

Nine studies reported the incidence of bronchopulmonary dysplasia (BPD) according to gestational age. Eight studies defined BPD as the use of supplemental oxygen at the postmenstrual age of 36 weeks [5,6,8,10,15–18]. In an Israeli study [7], BPD was defined as the need for oxygen supplementation at 40 weeks' postmenstrual age. Seven publications reported a rate of BPD > 50% in infants born at <24 weeks [5,6,8,15–18], and 4 other studies found an incidence of >80% [5,8,15,18]. Assessing

neonates at >24 weeks' gestation, 2 studies found a BPD rate that was substantially higher than 50% [15, 18], while BPD rates in 3 studies were below 30% [5,7,10] (Supplementary Table 1).

Eight publications reported the incidence of intraventricular hemorrhage (IVH) according to gestational age. Six publications demonstrated only grade 3–4 IVH [5,6,8,10,16,17]. The Israeli study analyzed the rate of grade 4 IVH [7], while the EPICURE study showed the rate of serious abnormalities on cerebral ultrasonography [18]. One study showed a 20% rate of severe IVH at 22 weeks' gestation [10], and 2 studies reported a rate higher than 30% [6,18]. The proportion of infants born at 23 and 24 weeks' gestation who had IVH was >15% in 4 studies [5,6,8,10] and ≤15% in 4 other studies [7,16–18]. Among infants at >24 weeks' gestation, the incidence of severe IVH was not more than 15% in all 8 studies (Supplementary Table 2).

The incidence of periventricular leukomalacia (PVL) by gestational age was published in 6 studies [5–8,10,17]. Cystic PVL can be diagnosed by ultrasonography, while the noncystic form can only be seen on magnetic resonance imaging [24,25]. Four studies analyzed cystic PVL [5,8,10,17], and 2 studies did not specify the diagnostic method of PVL [6,7]. Except for the Israeli study [7], none of the studies reported higher than 10% incidence [5,6,8,10,17] (Supplementary Table 3).

The incidence of retinopathy of prematurity (ROP) by gestational age was reported in 6 publications [5,6,8,10,17,18]. Two studies reported the incidence of ROP treated with laser photocoagulation [6,18], and 4 studies reported stage ≥3 ROP [5,8,10,17]. The rate of ROP treated with laser photocoagulation reached or exceeded 30% in infants at <24 weeks' gestation, and it was between 20% and 30% at 24 weeks of gestational age. It was <20% at 25 weeks and <10% at 26 weeks, and at 27 weeks of gestational age, it was under 5%. The rates of stage ≥3 ROP were above 60–83% among infants at <24 weeks in the EXPRESS study and a study in Singapore [8,10]. The rate of severe ROP was under 50% in infants at >24 weeks of gestation, and was lower than 20% in infants at >25 weeks of gestation [5,8,10,17] (Supplementary Table 4).

The incidence of necrotizing enterocolitis (NEC) by gestational age was reported in 6 studies. The EPICURE study showed the rate of surgically treated NEC [18], and the other 5 studies reported stage ≥2 NEC (according to Bell criteria) [5,6,8,10,17]. Differentiating NEC from spontaneous intestinal perforation could be problematic [26,27]. Only 1 study analyzed the incidence of NEC without spontaneous intestinal perforation [8]. Most of the studies showed the rate of stage ≥2 NEC as below 10% and mainly about 5% [5,8,10,17] (Supplementary Table 5).

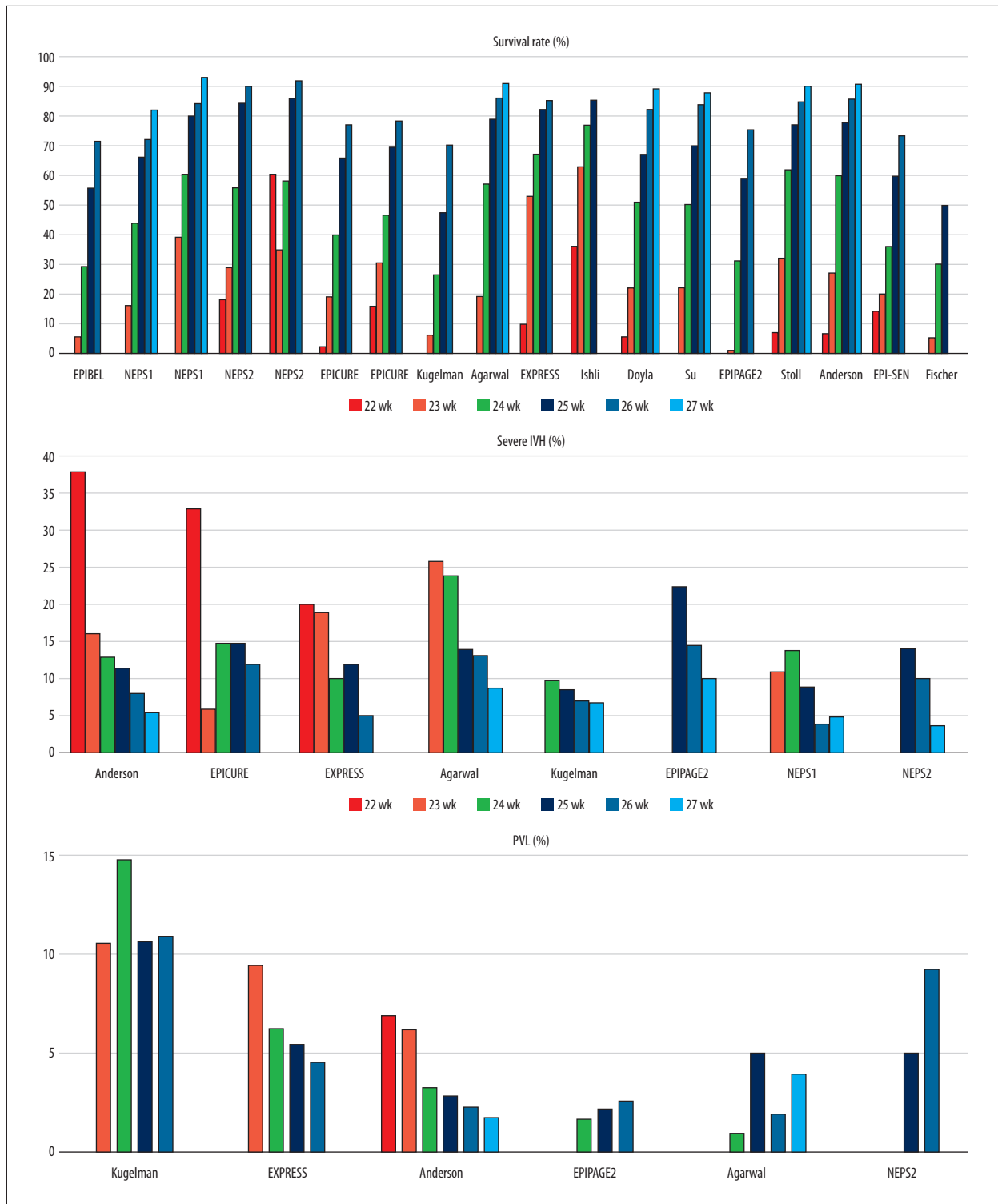


Figure 1. Survival, severe intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) rates by gestational age in the reviewed studies.

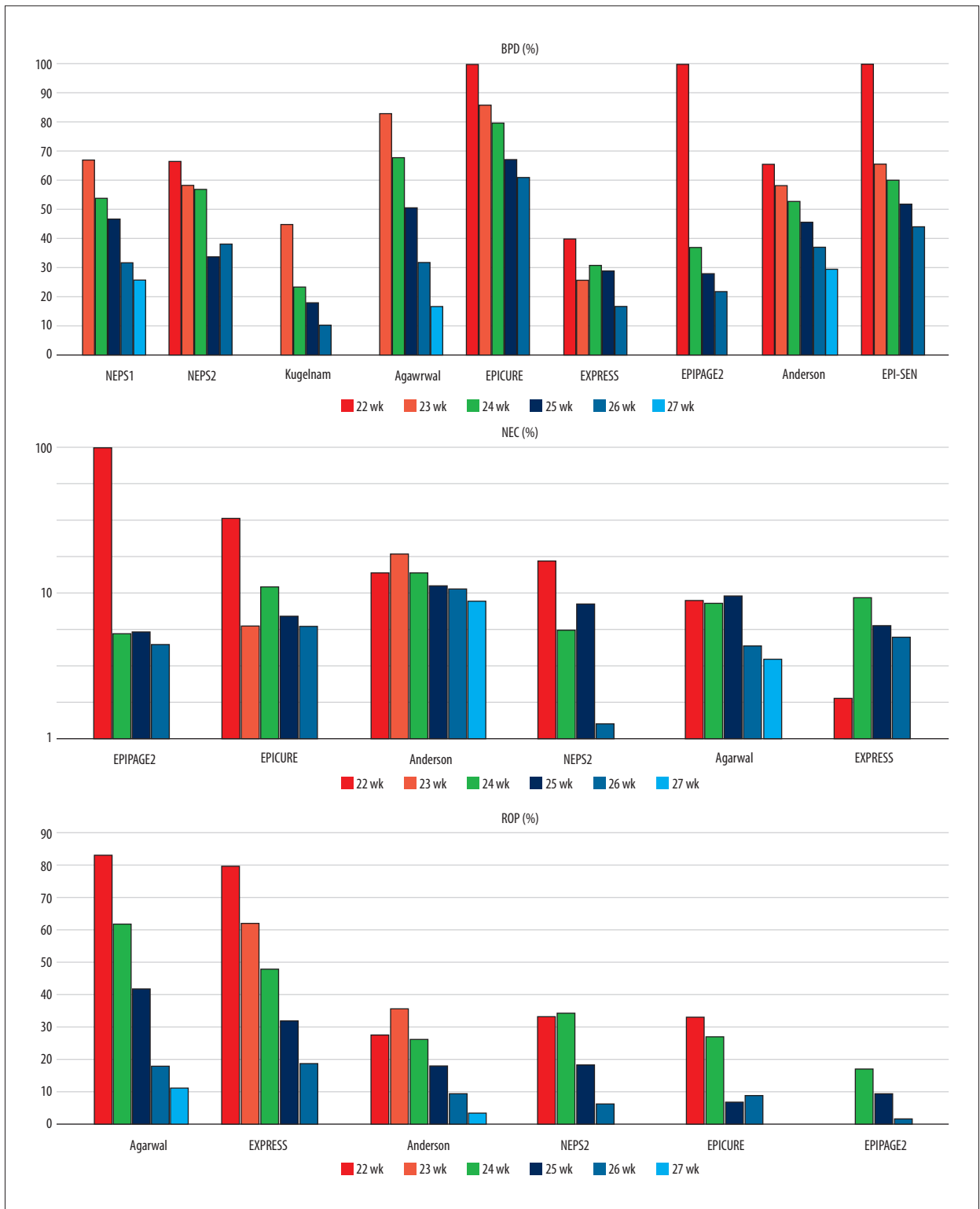


Figure 2. Bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) rates by gestational age in the reviewed studies.

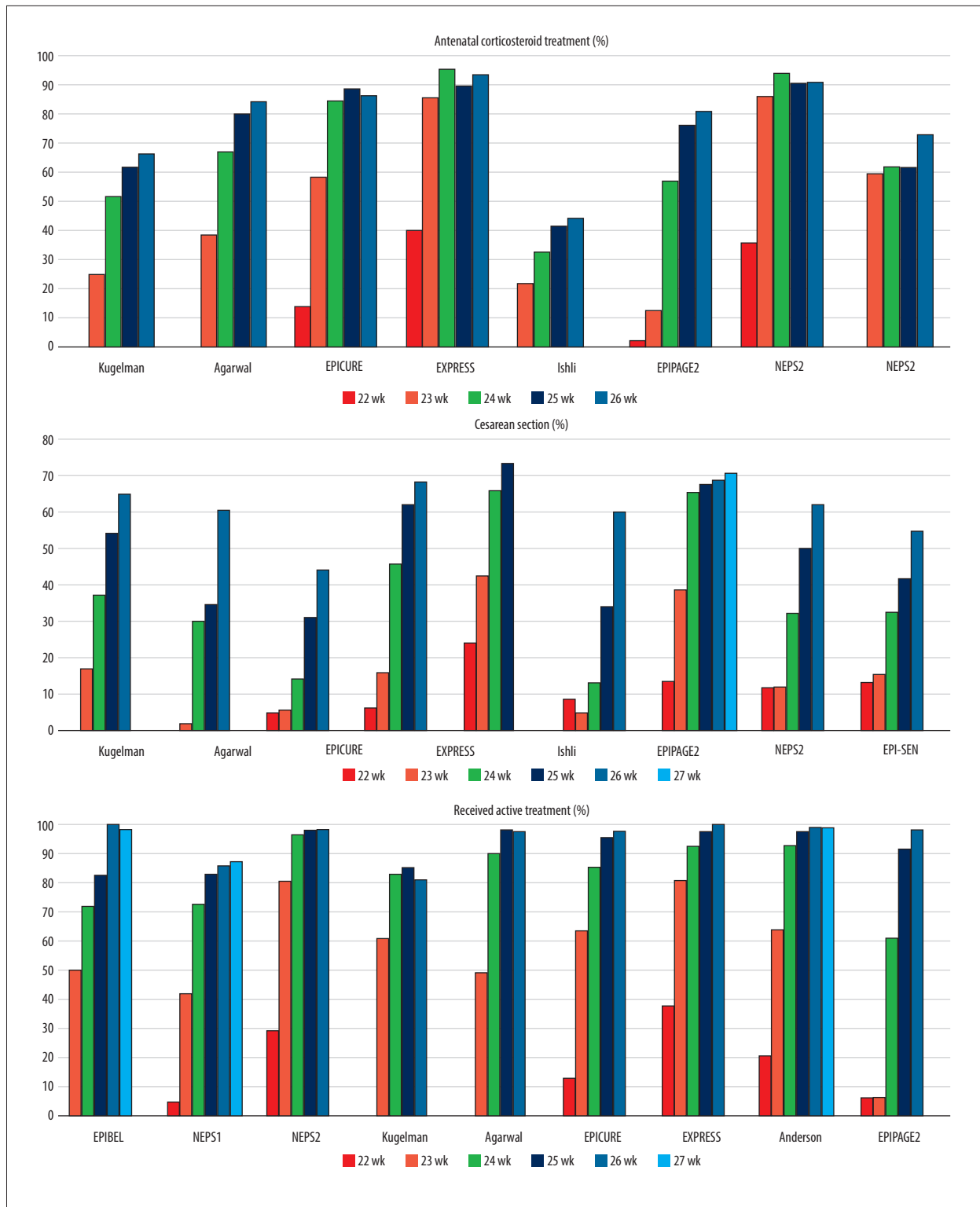


Figure 3. The rate of antenatal corticosteroid treatment, cesarean delivery, and the rate of preterm infants who received active treatment in the reviewed studies; data are shown by gestational age.

Discussion

Review limitations

Each study used a different calculation method for survival rates, which hindered comparison between studies [28]. Comparability could have been more accurate if the survival rates were based on the proportion of all preterm infants as well as the proportion of actively treated infants. It would also be important to know whether infants who received active care were only those admitted to NICU or whether this group also included infants who received active treatment in the delivery room but died before NICU admission. In addition, it would be helpful to know the survival rates for infants born in a tertiary center and those who underwent transportation to a tertiary-level NICU. Regarding the comparability of antenatal steroid therapy, it is important to define treatment precisely and differentiate between receiving a complete course of steroid treatment and receiving a partial course.

The incidence of each complication was shown based on the number of surviving infants in most studies; however, the complications themselves were described differently in each study. Most studies reported the complications as follows: BPD as the condition in which infants need oxygen supplementation at 36 weeks' postmenstrual age, severe stages ($\geq 2-3$) of IVH, cystic form of PVL (diagnosed by cranial ultrasound), stage ≥ 3 ROP, and stage ≥ 2 NEC.

Future large population-based studies should use a unified methodology in every investigation, which would allow accurate comparisons between investigations [28]. The threshold of viability has changed over the past few decades, and future studies are necessary to observe further changes. Knowing the latest findings is crucial to make the best decisions on the care of preterm infants.

Possible paradox

Out of 15 large population-based studies, none of them reported any survivors among infants born before 22 weeks' gestation. Most of the studies reported at least 50% survival rate among infants born at 24 weeks. The chance of developing complications was less in infants born after 24 weeks than among those born before 24 weeks. The survival rate without complications was also higher in babies born after 24 weeks.

Infants born before 24 weeks' gestation tended to receive less active care than infants born after 24 weeks' gestation, which limited the ability to compare outcomes (Figure 3). Antenatal

corticosteroid therapy was given to 1.8% to 40% of infants born at 22 weeks, as opposed to 66% to 93% of infants born at 26 weeks [5,7,8,10,11,16–18] (Supplementary Table 6). Infants at 22 weeks were delivered by cesarean delivery in 2% to 24% of cases, while the rate ranged from 44% to 68% for infants at 26 weeks [5–8,10,11,17,18] (Supplementary Table 7). Initiation of intensive care for infants born before 24 weeks varied broadly, with 6% to 81% of the infants receiving intensive care. At 24 weeks' gestation, preterm babies received active medical care in 60.8% to 96.8% of cases and the rate was beyond 90% when the gestational age reached 25 weeks [4–7,10,16–18] (Supplementary Table 8). The lower survival and the development of complications in infants born before 24 weeks could be attributable to the lower rate of antenatal corticosteroid use, the lower rate of cesarean delivery, and less admission to NICU.

In a recent study, Backes et al. [29] analyzed data from infants born at the 22 weeks of gestation in 2 different centers. One center provided proactive care, with all mothers received antenatal corticosteroid treatment, if it was possible, and all infants receiving active care in the delivery room. The other center provided selective care of preterm infants; the parents were involved in all therapeutic decisions including antenatal corticosteroid use, delivery room management, and initiation of intensive care. The proactive center achieved a higher survival rate of more than 50% among infants born at 22 weeks of gestation. Due to the modest sample size, the authors did not draw conclusions about morbidity rates.

Conclusions

In most studies the proportion of infants who received active care was substantially lower among those were born before 24 weeks' gestation compared with those born after 24 weeks. Despite many large population-based studies having been conducted, accurate comparative data are still lacking regarding the prognosis of premature babies born before and after 24 weeks [30]. This situation creates a possible paradox in care for extremely preterm infants born at the threshold of viability. If we presume a poor outcome of these infants, why would we treat them? However, if we do not initiate intensive care for these infants, how can we know that they would have poor outcomes?

Conflicts of interest

None.

Supplementary Data

Supplementary Table 1. BPD rates of survived extremely preterm infants by gestational age.

Study	BPD O ₂ dependency	BPD rates (%) by gestational age (week)					
		22.	23.	24.	25.	26.	27.
NEPS1 [16]	36. week	–	67	54	47	32	26
NEPS2 [17][36. week	66.7	58.3	57.1	33.9	38.2	–
Kugelman [7]	40. week	–	45	23.6	18.22	10.5	–
Agarwal [8]	36. week	–	83	68	50.5	32	17
EPICURE [18]	36. week	100	86	80	67	61	–
EXPRESS [10]	36. week	40	26	31	29	17	–
EPIPAGE2 [5]	36. week	–	100	37.3	28	21.9	–
Anderson [6]	36. week	65.5	58	53.1	45.7	37.3	29.6
EPI-SEN [15]	36. week	100	65.6	60.2	52.0	44.4	–

Supplementary Table 2. Severe IVH rates of survived extremely preterm infants by gestational age.

Study	Cranial ultrasonography	Severe IVH rates (%) by gestational age (week)					
		22.	23.	24.	25.	26.	27.
Kugelman [7]	Grade 4 IVH	–	10	8.7	7.2	7.0	–
EPICURE [18]	Serious abnormality	33	6	15	15	12	–
NEPS1 [16]	Grade 3-4 IVH	–	11	14	9	4	5
NEPS2 [17]	Grade 3-4 IVH	0	0	14.3	10.2	3.9	–
Agarwal [8]	Grade 3-4 IVH	–	26	24	14	13.2	9
EXPRESS [10]	Grade 3-4 IVH	20	19	10	12	5.2	–
EPIPAGE2 [5]	Grade 3-4 IVH	–	0	22.4	14.4	10.3	–
Anderson [6]	Grade 3-4 IVH	37.9	16.1	13.1	11.6	8.1	5.4

Supplementary Table 3. PVL rates of survived extremely preterm infants by gestational age.

Study	Definition of PVL	PVL rates (%) by gestational age (week)					
		22.	23.	24.	25.	26.	27.
Agarwal [8]	UH cystic	–	0	1	5	2	4
Kugelman [7]	Not defined	–	10.5	14.7	10.6	10.9	–
EXPRESS [10]	Cystic	0	9.4	6.2	5.4	4.5	–
EPIPAGE2 [5]	Cystic	–	0	1.7	2.2	2.6	–
Anderson [6]	Not defined	6.9	6.2	3.3	2.9	2.3	1.8
NEPS2 [17]	UH cystic	0	0	0	5.1	9.2	–

Supplementary Table 4. ROP rates of survived extremely preterm infants by gestational age.

Study	Severe ROP	ROP rates (%) by gestational age (week)					
		22.	23.	24.	25.	26.	27.
EPIPAGE2 [5]	>2 stage	–	0	17.2	9.4	1.9	–
Agarwal [8]	>2 stage	–	83.4	62	42	18	11
EXPRESS [10]	>2 stage	80	62	48	32	19	–
NEPS2 [17]	>2 stage	0	33.3	34.3	18.6	6.6	–
EPICURE [18]	Surgically treated	0	33	27	7	9	–
Anderson [6]	Surgically treated	27.6	35.8	26.4	18	9.6	3.5

Supplementary Table 5. NEC rates of survived extremely preterm infants by gestational age.

Study	Survived/ All infants	Surgically treated/ Stage ≥2 by Bell's criteria	NEC rates (%) by gestational age (week)						
			22.	23.	24.	25.	26.	27.	28.
EPICURE [18]	Survived	Surgically treated	33	6	11	7	6	–	–
EXPRESS [10]	Survived	Stage ≥2	0	1.9	9.4	6.0	5.1	–	–
Agarwal [8]	Survived	Stage ≥2 SIP excluded	0	9	8.6	9.6	4.4	3.6	5.8
EPIPAGE2 [5]	Survived	Stage ≥2	–	100	5.3	5.5	4.5	–	–
Anderson [6]	Survived	Stage ≥2	13.8	18.5	13.8	11.3	10.9	8.9	6.7
NEPS2 [17]	Survived	Stage ≥2	0	16.7	5.7	8.5	1.3	–	–

Supplementary Table 6. Rates of antenatal corticosteroid use among extremely preterm infants by gestational age.

Study	Partial/Complete antenatal steroid therapy	Rates of antenatal corticosteroid use (%) by gestational age (week)				
		22.	23.	24.	25.	26.
Kugelman [7]	Partial	–	25	51	61	66
Agarwal [8]	Complete	–	38	67	72	80
EPICURE [18]	Complete	14	58	84	88	86
EXPRESS [10]	Partial	40	85	95	89	93
Ishii [11]	Partial	21.3	32.2	41.3	43.7	–
EPIPAGE2 [5]	Partial	1.8	12.3	56.7	75.5	80.6
NEPS1 [16]	Partial	35.3	85.7	93.5	90	90.5
NEPS2 [17]	Complete	0	59.5	61.3	61.4	72.6

Supplementary Table 7. Rates of extremely preterm infants delivered by Cesarean section by gestational age.

Study	Rates of extremely preterm infants delivered by Cesarean section (%) by gestational age (week)						
	22.	23.	24.	25.	26.	27.	28.
Kugelman [7]	–	17	37	54	65	–	–
Agarwal [8]	–	2	30	35	60	–	–
EPICURE [18]	5	6	14	31	44	–	–
EXPRESS [10]	6	16	46	62	68	–	–
Ishii [11]	24	42.4	65.7	73.3	–	–	–
EPIPAGE2 [5]	8.8	4.6	13.5	34	59.9	–	–
Anderson [6]	13.6	38.4	65	67.2	68.4	70.2	72.9
NEPS2 [17]	11.8	11.9	32.3	50	61.9	–	–
EPI-SEN [15]	13.0	15.6	32.3	41.5	54.8	–	–

Supplementary Table 8. Rates of extremely preterm infants who received neonatal intensive care.

Study	Actively treated/ Admitted to NICU	Rates of extremely preterm infants who received neonatal intensive care (%) by gestational age (week)						
		22.	23.	24.	25.	26.	27.	28.
EPIBEL [4]	NICU	50	72.2	83	100	98.7	–	–
NEPS1 [16]	NICU	5	42	73	83	86	88	–
NEPS2 [17]	NICU	29.4	81	96.8	98.6	98.8	–	–
Kugelman [7]	Active care	–	61	83	85	81	–	–
Agarwal [8]	Active care	–	49	90	98.5	98	–	–
EPICURE [18]	NICU	13	64	86	96	98	–	–
EXPRESS [10]	NICU	38	81	93	98	100	–	–
Anderson [6]	Active care	20.7	64	92.8	97.4	99.5	99.3	99.5
EPIPAGE2 [5]	NICU	6.1	60.8	91.9	98.9	–	–	–

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