Survival and long-term neurodevelopmental outcome of the extremely preterm infant

A systematic review

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ABSTRACT

لقد كان معدل نجاة المواليد للعام 1990م في مراكز الدرجة الثالثة للنساء والولادة بأمريكا الشمالية كالتالي: 28% في الأسبوع 23، و52% في الأسبوع 24، و70% في الأسبوع 25، و83% في الأسبوع 26 من الحمل، وقد كان هناك اختلافاً كبيراً بين هذه المراكز. بالمقابل فقد كان معدل نجاة المواليد للعام 2010م في مراكز الدرجة الثالثة بالولايات المتحدة والمشاركة في شبكة فيرمونت أوكسفورد كالتالي: 34% في الأسبوع 23، و61% في 24 أسبوع، و79% في 25 أسبوع، و87% في 26 أسبوع. لقد قمنا في هذا المقال بمراجعة التطور العصبي للأطفال الخدج الذين لم يكملوا طور الحمل والتي وردت نتائجهم في الأدب الطبي. لقد كانت هذه النتائج مختلفة ومتغيره فيما بينها، وقد تمثلت أكبر العوائق في اختلاف المعايير الموضوعة لدراسة الإعاقة، حيث كانت نتائج الأطفال الذين يعانون من إعاقات كبيرة متغيرة من الناحية الوظيفية. وهكذا فقد وصل معدل انتشار الإعاقة في الأدب إلى 36%، إلا أنه تراوح ما بين 10%–61.

Survival rates among live births in North American tertiary perinatal centers since 1990 were 28% at 23 weeks, 52% at 24, 70% at 25 and 83% at 26 weeks. However, there is wide variation among centers. Survival rates in 2010 among tertiary centers in the United States participating in the Vermont-Oxford Network were 34% at 23 weeks, 61% at 24, 79% at 25, and 87% at 26. All reports of neurodevelopmental outcome of extremely preterm infants in the English literature were reviewed. This literature is very heterogeneous and prevalence highly variable. Major limitations are astonishing variation in criteria for major disability and that, even with the same disability criteria, children with major disabilities are functionally very heterogeneous. Mean prevalence of disability in the literature is 36%, but ranges from 10-61%. This literature could be improved if survivors were followed until early school age, there were more uniform reporting by week of gestation, and outcomes of term control groups were included.

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The most current mortality and morbidity information is required to counsel parents, to guide appropriate perinatal care decisions, and to anticipate healthcare resource needs of survivors of extreme prematurity. There have been significant advances in perinatology and neonatology since the mid 1980s. Survival of extremely preterm infants improved significantly with the availability of exogenous surfactant in the late 1980s and with more prevalent use of antenatal steroids[1-7] and has continued to improve in the 1990s and into the first decade of this century.[8-15] The literature about whether long-term neurodevelopmental outcome has changed during these periods is conflicting[4,5,9,11,14,16,17] and there is little data regarding outcomes of extreme prematurity over the last decade, but there is concern that the prevalence of disability among survivors may increase as more immature and more critically ill infants are salvaged.[17] The purpose of this paper is to update a previously published systematic and quantitative review of survival and long-term neurodevelopmental outcome of extremely preterm infants. As in the previous[18] review,

extreme prematurity is defined as a gestational age less than or equal to 26 completed weeks.

Survival. Medline was searched for reports published in English language peer-reviewed journals that reported mortality among live births between 1990 to January 2011 within tertiary care centers in North America of infants 23-26 weeks completed gestational age. Data are restricted to extremely preterm births within perinatal care centers since 1990 to reflect survival when optimal perinatal and neonatal care is available in the era in which exogenous surfactant was commercially available and antenatal steroid therapy was more prevalent. They were restricted to centers within North America because obstetric and neonatal care is reputed to be more aggressive than in other countries in this gestational age range. These restrictions would be anticipated to result in higher neonatal survival. Seventeen reports met these criteria (**Table 1**). All reports defined gestational age as completed weeks.

Limitations of the data. Published reports provide information about the probability of survival in practice. This may not be the maximum possible survival, particularly for gestational ages less than 23 to 24 weeks, because at these gestational ages information is either insufficient to determine whether strategies of obstetric and neonatal intensive care that maximize neonatal survival were employed or it is specified that such strategies were not employed at the lowest gestational ages or birth weights. Bottoms et al[19] have shown that the willingness of the obstetrician to perform a cesarean section for fetal indications was associated with increased survival even when controlling for birth weight. Moreover, the prevalence of antenatal steroid exposure is more than 50% in only 3 of the 11 reports that specify the prevalence of this exposure.[20-22] The prevalence of antenatal steroid therapy has increased significantly above this level since the NIH Consensus Statement in 1994.[23] Moreover, Richardson et al[6] estimated that two thirds of the 50% decrement in mortality in infants <1500 g birth weight between 1989-1990 and 1994-1995 in 2 hospitals in Boston could be attributed to greater aggressiveness

Table 1 - Summary of reports of survival of extremely preterm infants born alive in tertiary care centers in North America in the last 2 decades.

Cohort	Birth dates	Country	GA method	GA	ANS %	C/S	Resuscitation	Surfactant %	Age	Live births
Hack et al[72,*]	1990-1992	USA	LMP/US or PE	22-26	10	ns	ns	40	20 Mo	114
Kramer et al[36,†,‡,§]	7/89-12/93	USA	LMP/OB/US	23-26	15	Sel <24 wk 51% ≥24 wk	100%	Proph	6 Mo	90
Fanaroff et al[25,‡,§]	1991-1992	USA	LMP/OB/US	24-26	21	ns	ns	46	Discharge	4279
Battin et al[26]	1991-1993	USA	LMP/US	23-26	38	35% >23 wk	ns	45	Discharge	173
Jacobs et al[32]	4/90-12/94	Canada	OB/US	23-26	Yes	ns	100% >24 wk	All vent	18-24 Mo	281
Batton et al[34,†]	1990-1995	USA	LMP/US or PE	23-25	31	ns	all	Rescue	Discharge	142
Bahado-singh et al[35,§§]	1990-1995	USA	LMP/US	22-26	Yes	Sel <24 wk	Sel <24 wk	Yes	Discharge	122
Paranka et al[73]	1990-1996	USA	LMP/US	24-26	31	Sel <24 wk	100% >3 wk	Rescue	Discharge	77
Bottoms et al[19,§,¶]	11/92-10/93	USA	OB/US	21-26	ns	Sel	ns	ns	Discharge	421
Effer et al[20]	1991-1996	Canada	LMP/US	24-25	45-66	Yes	ns	ns	Discharge	860
Stevenson et al[27,‡]	1993-1994	USA	LMP/OB/US	24-26	35	49%	ns	48	Discharge	4593
Leblanc et al[37,**]	8/92-8/96	USA	LMP/OB/US or PE	23-26	Yes	Sel 26 wk & <600g	100%	All intub	Discharge	230
Doron et al[38,†,††]	11/94-10/95	USA	OB/PE	23-26	ns	ns	76%	All vent	Discharge	41
El-Metwally et al[28,‡,††]	1993-1997	USA	LMP/US	23-25	44	ns	All but 2 at 23 wk	56	Discharge	694
Lemons et al[21,‡‡]	1995-1996	USA	LMP/OB/US	23-26	71	ns	ns	52	Discharge	1332
McElrath et al[22]	1995-1999	USA	LMP/US	23	74	ns	ns	ns	Discharge	33
Aslam et al[33]	1997-2004	USA	LMP/US or PE	21-26	ns	ns	ns	ns	Discharge	142

GA - gestational ages in weeks for which survival is reported, ANS - antenatal steroid therapy, C/S - cesarean section delivery for fetal indications, resuscitation - resuscitation attempted in the delivery room, age, age to which survival was ascertained, USA - United States of America, LMP - menstrual history, US - prenatal ultrasonography, OB - best obstetric estimate, PE - postnatal physical examination, ns - not specified, mo - months, sel - selective intervention, wk - weeks, proph - surfactant administered prophylactically, all vent - surfactant administered to all ventilated infants, g - grams, all intub - surfactant administered to all infants intubated in the delivery room. Percents in columns - live births who received the treatment. *Infants with birth weights <500 or >749 grams excluded. †Neonatology attending or fellow attended all deliveries. ‡Infants with birth weights <501 grams excluded. §Infants with major congenital anomalies excluded. §§Infants with birth weight <401 or >999 grams excluded. ¶ Infants with birth weights >1000 grams excluded. **Infants with birth weight <10th percentile or >90th percentile excluded. †† Specified that intensive care was withheld from some infants. ‡‡Infants with birth weights <401 or >1500 grams excluded.

of respiratory and cardiovascular care. Tyson et al[24] estimated that if all infants 501-800 g birth weight had received mechanical ventilation a modest improvement in survival (as high as 65% versus 57%) would have resulted in a sample of 325 infants cared for in the 12 centers in the National Institute of Child Health and Development Neonatal Research Network between 1994 and 1995. This is not to imply that strategies to maximize survival should be employed at all gestational ages and birth weights; it does mean that survival in the smallest and most immature infants could potentially be better than those reported. Moreover, survival data are rarely reported as functions of factors that have been reported to effect mortality, such as antenatal steroid exposure, gender, race, appropriateness for gestational age, maternal magnesium sulfate exposure, and condition at birth.[6,19,22,24-27,28-31] In the absence of fetal compromise survival was 40.6% at 23 weeks' gestation in one report.[32]

Survival in North America in the last 2 decades. Survival rates at 23, 24, 25, and 26 weeks are shown in **Figure 1**. Note that the variability in survival decreases with each week increase in gestational age. This is at least in part related to the increasing uniformity with which obstetrical intervention for fetal indications and neonatal intensive care is offered as gestational age increases. At 23 weeks, the reported survival ranged from 4.8%[5] to 48.1%.[33] In 4 reports,[28,33-35] the survival was greater than 40%. In one study,[34] resuscitation of nearly all live born infants attempted by an attending neonatologist and intensive care was initiated in all infants in whom resuscitation was successful; in the other reports resuscitation was provided more selectively[28,35] or this information was not provided.[33] Survival was 18.8% and 25.9% in 2 other reports in which resuscitation of all live births was attempted at this gestation.[36,37] Notably, only 13% received the benefit of antenatal steroid exposure at 23 weeks in the former report. Among 609 live births reported in the literature, mean survival was 28.1%. At 24 weeks, the reported survival ranged from 16.7% (in a study in which resuscitation was withdrawn in a third live births and

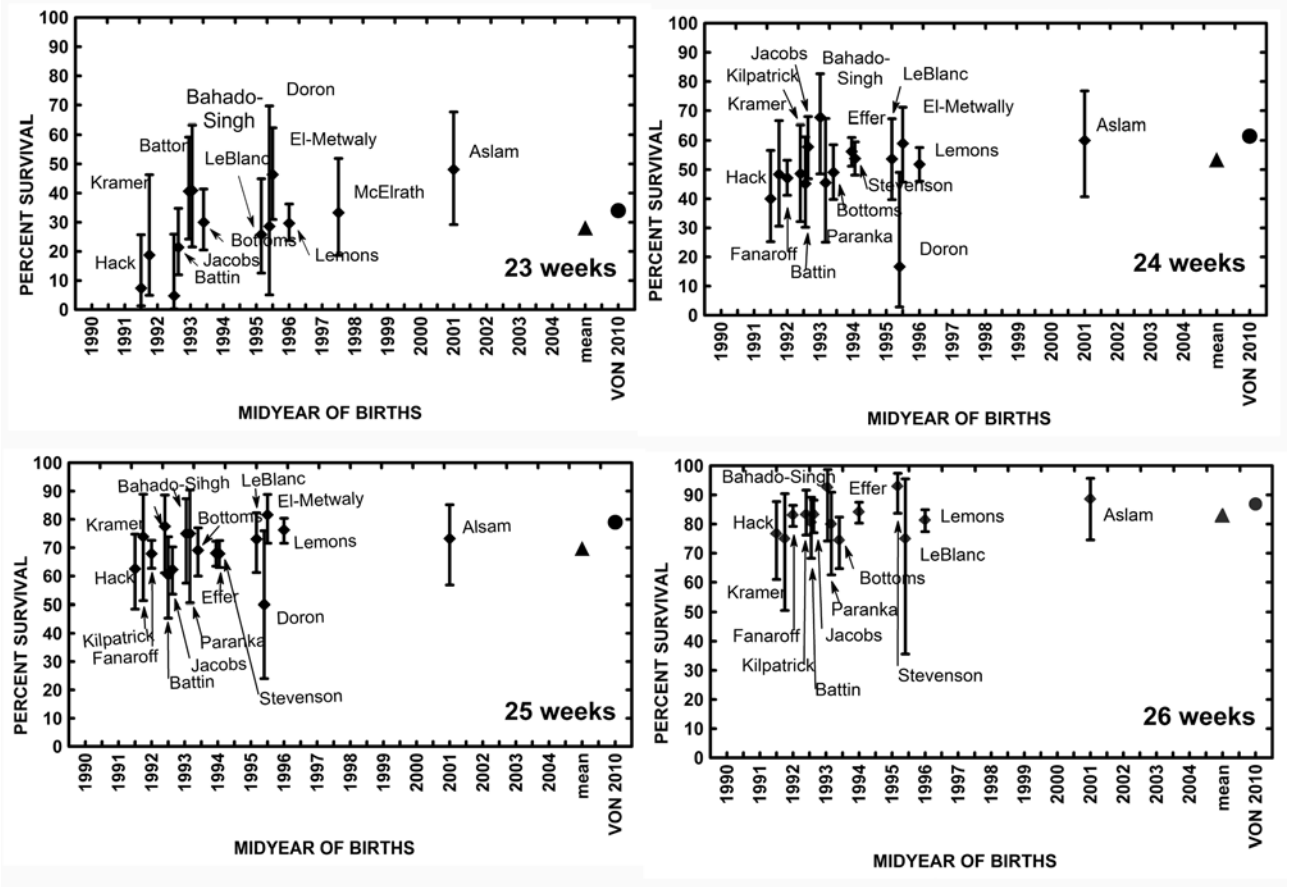

Figure 1 - Survival rates at 23, 24, 25, and 26 weeks of completed gestation reported from tertiary care centers in North American in the last 2 decades. Footnotes: Each open diamond represents the mean prevalence in an individual cohort. Bars represent the 95% confidence limits. Labels are the name of first author of report as listed in Table 1. The filled triangle represents the mean prevalence for all the individual cohorts combined. The filled circle represents mean survival in all tertiary care centers in the United States of America in the Vermont-Oxford Network (VON) in 2010.

intensive care another 50%[38]) to 68.0%[35]. Among 1865 live births reported in the literature, the mean survival was 53%. At 25 weeks, reported survival ranged from 60.4[26] to 88.8%.[28] Among 2244 live births reported in the literature, the mean survival was 69.8%. At 26 weeks reported survival ranged from 74.5%[19] to 93%.[37] Among 1897 live births reported in the literature, mean survival was 82.8%.

Neurodevelopmental outcome. Medline was searched for reports published in English language, peer-reviewed journals from 1970 to January 2011 that reported survival and the prevalence of one or more major neurodevelopmental disabilities (defined as mental retardation, cerebral palsy, blindness, deafness) of >70% of survivors at 23, 24, 25, and/or 26 weeks of gestational were directly examined and formally tested at age 18 months or older. Data are restricted to reports that included survival rate so that the relationship between the survival rate and prevalence of major disability could be examined; to those with a follow-up rate of >70% due to loss to follow-up can bias the results;[39,40] to those in which all survivors were directly examined and formally tested at 18 months of age due to survey of survivors' parents and physicians are unreliable,[41,42] and at least 18 months because at 18-24 months of corrected age cognitive and motor abilities diverge, language and reasoning skill are developing, and better prediction of outcome begins at early school age.[19,43] No birth dates or countries were excluded. Thirty-one publications reporting 38 cohorts met these criteria (**Table 2**). All these reports define gestational age as completed weeks.

Limitations of the data. This is a very heterogeneous literature. Mortality, range of gestational ages, age at follow-up, and definitions of major disabilities vary widely. The lower gestational age limits of these cohorts are 22, 23, or 24 weeks. No lower limit is specified in several reports. The upper limits are 25 or 26 weeks. In several reports there are also birth weight restrictions. Age at follow-up varies from 16 months to 10 years. There are only 2 reported cohorts for which outcome is available for all subjects beyond age 5 years. The criteria for cognitive impairment vary from >1 standard deviation (or <80) below the mean to >3 standard deviations (or 50) below the mean. In 2 reports, the instrument used to evaluate cognition are not specified.[4,44] Preschool cognitive tests are not pure measures of cognition, they are affected by motor ability as well as hearing. The definition of cerebral palsy varies from "abnormal tone" to "no head control or unable to sit, dress, or feed self". Blindness is usually not otherwise defined. Unilateral blindness is included as a major disability in 2 reports. The criterion for deafness is rarely more specific than the requirement of a hearing aid. The criteria for deafness range from unilateral deafness[47] to "no useful hearing".[48] Some, but not all, studies include microcephaly, hydrocephalus, seizures, hypertonia, hypotonia and/or autism as major disabilities as well. It is not possible to determine whether these differences in the criteria for major disability, differences in populations or cultures or postnatal environment, differences in perinatal practices and complications, or chance is responsible for the great variability in the reported prevalences of major disabilities among extremely premature infant cohorts.

These major disabilities do not provide much information about current or ultimate functional abilities of the children with one or more of these major disabilities. Moreover, with little information beyond preschool age, there is also little information about more subtle impairments, such as learning disabilities, language disorders, visual-perceptual problems, attention deficits, hyperactivity, school problems, behavior problems, or minor motor dysfunction. Forty to 50% of extremely low birth weight and/or extremely preterm survivors without major disabilities are reported to have these problems at school age.[49-56]

The applicability and generalizability of these data may be questioned as well. These outcomes are the result of newborn intensive care delivered 7-34 years ago. Many infants were cared for before antenatal steroid therapy was prevalent and before the availability of surfactant therapy, although neither antenatal steroids[57,58] nor surfactant therapy[59-62] have been shown to improve neurodevelopmental outcome. Cognitive function is also greatly affected by the post-discharge environment,[63,64] but information about the latter is rarely included in these reports and outcomes are not stratified by this variable. Finally, early cognitive testing underestimates eventual cognitive ability at later ages.[43,63,64]

Optimally, long-term neurodevelopmental outcome data from each tertiary newborn intensive care unit should be reviewed and used in parental counseling. However, the number of survivors at these very low gestational ages and the proportion of survivors for which follow-up data is available is usually relatively low. The effort and expense of tracking and testing survivors is considerable. Therefore, the completeness of follow-up, precision, and reliability of center specific data may not be adequate to be useful.

Cognitive impairment (**Table 3**). Reported prevalences of cognitive impairment vary widely from 4.0%[44] (in which there were no survivors <25 weeks' gestation and which employed the criteria of developmental quotient <70 at 3-10 years of age) to 51.0[16] (which employed the criteria of Mental Developmental Index of < 70 on the Baley Infants Scales of Development-II at a corrected age of 18-22 months).

The mean prevalence in 5155 reported survivors is 32.1%.

Cerebral palsy **(Table 3).** Reported prevalences of cerebral palsy vary widely from approximately 3.9%[48] (in which the criteria for cerebral palsy was the most stringent criteria: no head control, nearly unable to sit, no independent walking, unable to dress or feed self) to 34%[68] (in which the criteria for cerebral palsy was the least stringent: abnormal muscle tone and reflexes) . The mean prevalence in 5025 reported survivors is 13.1%.

Blindness **(Table 3).** Reported prevalences of blindness vary widely from 0%[69] to 17.5%;[5] in each of these reported "blindness". The prevalence of unilateral

Table 2 - Summary of reports of neuro-developmental outcome of extremely preterm infants.

Cohort	Birth dates	Country	GA	Survival (%)	Age at f/u	Follow-up (%)	N
Doyle[69]	1977-3/82	Australia	24-26	20	60 months	100	39
Yu et al[74,*]	1977-1984	Australia	23-26	35	12-24 months	98	60
Nwaesei et al[75]	1980-1982	Canada	23-26	28	24-48 months	100	12
vanZeben et al[71,†]	1983	Netherlands	23-26	22	24 months	100	33
Weissman et al[70,‡]	1982-1986	Israel	24-26	17	30-60 months	100	15
Whyte et al[76]	1982-6/87	Canada	23-26	61	24 months	93	322
Cooke[77]	1980-1989	UK	24-26	36	36 months	100	127
Tin et al[4]	1983-1986	UK	23-26	14	24 months	100	24
Johnson et al[78]	1984-1986	UK	≤26	26	48 months	93	42
Synnes et al[79]	1983-1989	Canada	23-25	43	18 months	93	129
Eg-Anderson[44,*]	1984-1987	Denmark	24-26	48	16-48 months	100	25
Elmsley et al[5,§]	1984-1989	UK	23-25	27	3-10 years	92	24
Doyle[45]	1985-1987	Australia	24-26	30	> 60 months	99	94
D'Angio et al[80,‡]	1985-1987	USA	24-26	37	4-10 years	100	92
Tin et al[4]	1987-1990	UK	23-26	24	24 months	100	49
Hoekstra et al[59]	1986-1992	USA	23-26	68	Average 23 months	80	242
Lefebvre et al[46]	1987-1992	Canada	23-26	49	16-25 months	87	73
VICSG[81]	1991-1992	Australia	23-26	49	24 months	98	145
Elmsley et al[5,§]	1990-1994	UK	23-25	41	19-73 months	100	40
Piecuch et al[82]	1990-1994	USA	24-26	67	10-66 months	94	86
Battin et al[26]	1991-1993	Canada	23-26	42	18 months	94	44
Rattihalli et al[14]	1991-1993	UK	≤25	24	21-27 months	93	55
Jacobs et al[32]	4/90-12/94	Canada	23-26	65	18-24 months	88	270
Tin et al[4]	1991-1994	UK	23-26	22	24 months	100	50
Hack et al[47,§]	1992-1995	USA	23-26	ns	20 months	92	126
Vohr et al[9,‡‡]	1993-1994	USA	22-26	54	18-22 months	72	665
Wood et al[83,¶]	3/95-12/95	UK/Ireland	22-25	27	28-40 months	99	306
Neubauer et al[49,¶]	1993-1998	Germany	< 24-26	83	Average 8.4 years	82	78
Vohr et al[9,‡‡]	1995-1996	USA	22-26	55	18-22 months	82	716
Rjiken et al[68]	1996-1997	Netherlands	23-26	65	24 months	93	28
Mikkola et al[84,§]	1997	Finland	22-26	57	60 months	99	198
Roberts et al[50]	1997	Australia	22-26	71	8 years	96	105
Vohr et al[9,‡‡]	1997-1998	USA	22-26	61	18-22 months	83	910
Steinmacher et al[85]	7/96-6/99	Germany	22-26	76	60 months	96	67
DeGroote et al[48,¶]	1999-2000	Flanders	23-25	54	30-42 months	84	77
Hintz et al[16,**]	1999-2001	USA	22-24	35	18-22 months	91	411
Rattihalli et al[14]	2001-2003	UK	22-25	36	24 months	97	100
Hintz et al[16,**]	2002-2004	USA	22-24	32	18-22 months	92	405

GA - gestational age range in weeks included in study; f/u - follow-up; follow-up, percent of survivors seen at follow-up;
N - number of survivors seen at follow-up. [*]no survivors <25 weeks, [†]follow-up was at 12 months for infants born in 1984, [‡]number or survivors with one or more disabilities not reported, [§]Infants with birth weight >999 gram excluded, [††]Infants with birth weight <401 or >1000 gram excluded, [¶]no survivors < 23 weeks, [**]Infants with birth weight <601 or >1000 gram excluded.

Table 3 - Definitions and prevalences of major disabilities in neurodevelopmental outcome of extremely premature infants.

Cohort	Cognitive impairment		Cerebral palsy		Blindness		Deafness	
	Definition	%	Definition	%	Definition	%	Definition	%
Doyle[69]	WPPSI-R≥2 SD below mean	8	Ambulatory w/severe limitation	5	Blind	0	Requiring HA	3
Yu et al[74,*]	BSID >2 SD below mean	ns	Any type or severity	ns	Blind	ns	Deaf	ns
Nwaesei et al[75]	BSID, MGCI <69	17	Spastic di-, hemi-, or quadriplegic	8	Blind	8	Deaf	8
Vanzeben et al[71,†]	Gesell < 80	ns	Severe	ns	Severe loss	ns	Severe loss	ns
Weissman et al[70,‡]	Not evaluated	--	CP not otherwise specified	20	Blind	13	Deaf	13
Whyte et al[76]	BSID <70	13	Nonambulatory even with aid	8	Severe myopia	7	Deaf	3
Cooke[77]	BSID <70	15	Spastic di-, hemi-, or quadriplegic	15	Blind	9	>70 db loss	2
Tin et al[4]	Griffith <50	ns	No head control, unable to sit or feed self, or non-ambulatory with aid	ns	Blind	ns	Impaired with HA	ns
Johnson[78]	Griffith <70	ns	CP with severe limitation of function	ns	Total vision loss	ns	Deaf	ns
Synnes et al[79]	BSID >SD below mean	16	Abnormal tone or reflexes	26	<20/200 corr	15	Requiring HA	3
Eg-anderson[44,*]	<50 (instrument ns)	4	Spastic di-, hemi-, or quadriplegic	8	Blind	8	Not specified	ns
Elmsley et al[5,§]	DQ <70 (instrument ns)	12	Spastic di-, hemi-, or quadriplegic	21	Blind	4	>70 db loss	8
Doyle[45]	WPPSI-R≥2 SD below mean	7	Ambulatory w/severe limitation	5	< 20/200 corr	5	Requiring HA	2
D'angio et al[80,‡]	Not specified	ns	CP not otherwise specified	10	Not specified	ns	Not specified	ns
Tin et al[4]	Griffith <50	ns	No head control, unable to sit or feed self, or non-ambulatory with aid	ns	Blind	ns	Impaired with HA	ns
Hoekstra et al[59]	BSID, ELMS, SB >2SD below mean	ns	Spasticity	ns	Blind	ns	Deaf	ns
Lefebvre et al[46]	Griffith <80	23	Severe	12	Blind	1	Deaf	1
VICSG[81]	WPPSI-R >2 SD below mean	ns	Ambulatory with severe limitation	ns	<20/200 corr	ns	Requiring HA	ns
Elmsley et al[5,§]	DQ <70 (instrument not specified)	15	Spastic di-, hemi-, or quadriplegic	18	Blind	18	>70 db loss	2
Piecuch et al[82]	BSID,SB,MSCA>2SD below mean	23	Spastic di-, hemi-, or quadriplegic	14	Blind	1	Deaf	2
Battin et al[26]	BSID >2 SD below mean	18	Abnormal tone or reflexes	20	<20/200 corr	9	Requiring HA	9
Rattihalli et al[14]	Griffith <70	31	Any neuromotor impairment	16	≤20/80 corr	2	> 60 db loss	9
Jacobs et al[32]	BSID <70	ns	Not sitting by age 2 years	ns	Blind	ns	Requiring HA	ns
Tin et al[4]	Griffith <50	ns	No head control, unable to sit or feed self, or non-ambulatory with aid	ns	Blind	ns	Impaired with HA	ns
Hack et al[47,§]	BSID <70	48	Abnormal tone	24	Unilateral blind	ns	Unilateral deaf	10
Vohr et al[9,‡‡]	BSID-II <70	42	Ambulatory with aid	12	No useful vision	2	Requiring HA	4
Wood et al[83,§]	BSID-II <50	17	No head control or unable to sit, dress, or feed self	9	Blind	2	Impaired with HA	2
Neubauer et al[49]	HAWIK <70	ns	CP not otherwise specified	ns	Blind	ns	Deaf	ns
Vohr et al[9,‡‡]	BSID-II <70	38	Ambulatory with aid	11	No useful vision	2	Requiring HA	2
Rjiken et al[68]	BSID <70	ns	Abnormal tone or reflexes	34	Blind	4	Deaf	7
Mikkola et al[84,§]	WPPSI-R <50	10	More than clumsiness and/or non-fluent gait	ns	Uni amaurosis, amblyopia or myopia with severe astigmat	9	Requiring HA	4
Roberts et al[50]	WICS-IV >2SD below mean	16	Ambulatory with consider difficulty	10	<20/200 corr	2	Requiring HA	3
Vohr et al[9,‡‡]	BSID-II <70	37	Ambulatory with aid	10	No useful vision	1	Requiring HA	2
Stenmacher et al[85]	KABC ≤70	27	Moderately impaired mobility	ns	Blind	ns	Requiring HA	ns
DeGroote et al[48]	BSID-II <55	22	No head control, unable to sit or feed self, or non-ambulatory with hearing aid	4	No useful vision	3	No useful vision	0
Hintz et al[16,**]	BSID-II >2SD below mean	45	Ambulatory with aid	15	No function vision	2	Requiring HA	2
Rattihalli et al[14]	Griffith >2SD below mean	21	Any neuromotor impairment	28	<20/80 corr	3	>60 db loss	7
Hintz et al[16,**]	BSID-II >2SD below mean	51	Ambulatory with aid	21	No functional vision	2	Requiring HA	4

Percentage of survivors seen at follow-up with the respective disability, WPPSI-R - Weschler Preschool and Primary Scales of Intelligence-Revised, SD - standard deviation, BSID - Baley Scales of Infant Development Mental Developmental Index, MGCI, McCarthy General Cognitive Index, CP - cerebral palsy, ns - not specified, db - decibel, <20/200 corr - <20/200 corrected in the best eye, DQ - developmental quotient, ≤20/80 corr - ≤20/80 corrected in the best eye, ELMS - Early language Milestone Scale, SB - Stanford-Binet Intelligence, MSCA - McCarthy Scales of Children's Abilities, HAWIK - Hamburg-Wechsler Intelligence Test for Children, uni - unilateral, astigmat - astigmatism, WICS-IV - Wechsler Intelligence Scale for Children, fourth edition KABC - Kaufman Assessment Battery for Children, funct - functional, HA - hearing aid,*no survivors <25 weeks, †follow-up was at 12 months for infants born in 1984, ‡number or survivors with one or more disabilities not reported, §Infants with birth weight >999 gram excluded, ††Infants with birth weight <401 or >1000 gram excluded, ¶no survivors <23 weeks, **Infants with birth weight <601 or >1000 gram excluded.

blindness was 1.4% in the only study that reported the prevalence of blindness using this criteria.[46] The mean prevalence in 5005 reported survivors is 3.2%.

Deafness (**Table 3**). Reported prevalences of hearing impairment vary widely from 0% in a report which the criteria was "no useful hearing"[48] to 13.3% in a report that specified "neurosensory deafness".[70] The prevalence of unilateral deafness was 10.3%[47] in the one report which used this criterion for deafness. The mean prevalence in 5106 reported survivors is 3.0%.

Disability (**Figure 2**). Reported prevalences of at least one major disability vary widely from 9.1%[71] to 58.8%.[16] The mean prevalence in 6032 reported survivors is 37%. All 5 cohorts with prevalences of major disability ≥45% were from the USA and all excluded infants >999 or 1000g. Interpretation of whether the prevalence of major disability has changed with increasing survival or over time is complicated by the heterogeneity of the studies. However, in 4 reports[4,5,9,14] that presented neurodevelopmental outcome for extremely premature survivors using the same inclusion criteria and same criteria for disability from the same population during successive eras, there was no significant change in the prevalence of major disability over time, although the survival rate did increase. In a fifth report[16] that presented neurodevelopmental outcome for extremely premature survivors over 2 eras, there was a significant increase in the prevalence of major disability (50.1 versus 58.8%, p=0.02) over 2 eras spanning 6 years from 1999 to 2004 without a change in survival.

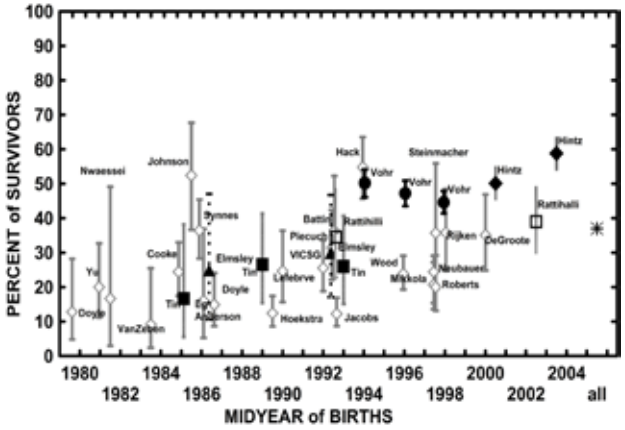

Figure 2 - Prevalences of major disability in cohorts of infants 23-26 weeks of completed gestation. Each symbol represents the mean prevalence in an individual cohort. Bars represent the 95% confidence limits. Labels are the name of first author of report as listed in Table 2. Filled squares represent mean prevalences in three cohorts from Northern Regional Network in the United Kingdom during different eras.[4] Filled triangles represent prevalences in 2 cohorts from North Western Health Authority of the United Kingdom during different eras.[5] Open squares represent prevalences in 2 cohorts from the Trent Health Region of the UK during different eras.[14] Filled circles represent prevalences in three cohorts 22-26 weeks' gestation from the National Institute of Child Health and Development Neonatal Research Network during 3 different eras.[9] Filled diamonds represent prevalences in 2 cohorts 22-25 weeks' gestation from the National Institute of Child Health and Development Neonatal Research Network during 2 different eras.[16] The cross represents the mean prevalence of the individual cohorts combined.

Summary. Survival of extremely preterm infants has steadily increased over the last 2 decades. Half of live births at 24 weeks' gestation will survive today. The majority of infants ≥25 weeks gestation survive. Survival of infants 23 weeks' gestation is lower, but by no means negligible. Reports of survival of infants <22 weeks or <500 g birth weight are not unique. Moreover, the maximum survival of infants ≤25 weeks possible with provision of current state-of-the-art care to all is not known.

Although reported prevalences of major neurodevelopmental disabilities vary substantially and this literature is very heterogeneous, the majority of extremely premature infants who survive will be free of major disability. Overall, approximately one third of survivors have at least one major disability. Impaired mental development is the by far the most prevalent form of disability, followed by cerebral palsy. The functional abilities of even disabled survivors, however, vary considerably. Based on studies of extremely low birth weight infants, it can be anticipated that approximately another 40-50% of all extremely premature survivors will have less severe neurodevelopmental problems in the school and teenage years. The rapidly evolving nature of newborn intensive care and the inability to reliably diagnose even major disability until 18-36 months of age preclude knowing the outcomes of current practices with confidence. Nevertheless, there is little evidence to suggest that long-term neurodevelopmental outcome has changed over time or with increasing survival.

This literature could be significantly improved if more centers reported long-term outcomes, survivors were followed to at least early school age, there was more uniform reporting (as has been repeatedly proposed[65-67]) by each week of gestation, and outcomes of term control groups were included in the reports.

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