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Evidence of selection bias in preterm survival studies: a systematic review

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Abstract

Objective—To determine by how much selection bias in preterm infant cohort studies results in an overestimate of survival.

Design—Systematic review of studies reporting survival in infants less than 28 weeks of gestation published 1978–1998. Studies were graded according to cohort definition: A, stillbirths and live births; B, live births; C, neonatal unit admissions. Proportions of infants surviving to discharge were calculated for each week of gestation.

Results—Sixty seven studies report data on 55 cohorts (16 grade A, 23 grade B, 16 grade C). Studies that are more selective report significantly higher survival between 23 and 26 weeks of gestation (grade C > grade B > grade A, $p < 0.01$), exaggerating survival by 100% and 56% at 23 and 24 weeks respectively.

Conclusion—To minimise the potential for overestimating survival around the limits of viability, future studies should endeavour to report the outcome of all pregnancies for each week of gestation (terminations, miscarriages, stillbirths, and all live births).

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Keywords: preterm; survival; selection bias

The collection of valid data relating to the survival of preterm infants is important for a number of reasons. It is necessary for clinicians to counsel pregnant women accurately with regard to potential survival. Neonatal and perinatal mortality is often used as an outcome measure in studies evaluating effectiveness of

interventions. There is an increasing tendency to compare survival data between institutions as an audit of performance of obstetric and neonatal services, despite problems identified with this approach.¹

A large number of publications present survival data for preterm infants related to each week of gestation. Inspection of the survival figures shows great heterogeneity in the estimates of survival, particularly in the 23–27 week gestational age groups.

There are a number of potential explanations for such wide variation in reported survival. The differences between studies may be simply a reflection of differences in the population under study (clinical heterogeneity). Factors that may vary across studies are the sociodemographic characteristics of the cohort, the time period of the study, or uptake of interventions known to improve survival, such as antenatal steroids and postnatal surfactant treatment.

It is also possible that systematic error within studies will vary and cause variation in reported survival. Specifically, there is potential for selection bias in preterm cohort studies that only report survival in infants admitted to neonatal units and, to a lesser extent, in studies that include live births but exclude stillbirth data. Cohort studies comprising exclusively neonatal unit admissions may ignore live births that could not be (or were not) resuscitated and will therefore overestimate survival. Studies that report all live births but do not report stillbirth data may overlook pregnancies that were not monitored during labour in the expectation that the pregnancy would result in stillbirth because of poor prognostic factors. Such selection bias results in the reporting of data relating to infants and fetuses with a better prognosis

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Table 1 Search strategy for Medline (Ovid)

001	exp infant, low birth weight/
002	exp infant, premature/
003	(low adj1 birth?weight).ti,ab,sh.
004	(pre?term adj5 infant\$).ti,ab,sh.
005	(pre?term adj5 bab\$).ti,ab,sh.
006	(premature adj5 infant\$).ti,ab,sh.
007	(premature adj5 bab\$).ti,ab,sh.
008	exp infant mortality/
009	death.ti,ab,sh.
010	surviv\$.ti,ab,sh.
011	exp cohort studies/
012	exp gestational age/
013	or/1-7
014	or/8-10
015	11 or 12
016	13 and 14 and 15

and is likely to lead to an overestimate of survival.

Selection bias may also be present in cohorts that are defined by hospital institution, rather than by geographical location. It is difficult to predict its effect on survival. Tertiary centres, which are often the origins of preterm cohorts in the literature, may claim a higher quality of care but also may have a concentration of higher risk pregnancies, depending on referral patterns.

The objective of this study was to determine whether selection bias influences the reported estimate of survival and, if it does, to gain some idea of the magnitude of effect. The specific hypothesis under test was that reported survival would be higher in studies with increased potential for selection bias. The secondary objective was to determine how comprehensively clinical factors influencing survival, such as antenatal steroid and surfactant use, were reported in the literature.

Methods

CRITERIA FOR CONSIDERING STUDIES

The objective of the literature search was to identify all cohort studies reporting survival in preterm infants and published within the period 1978–1998. The search was restricted to the developed countries within the following geographical boundaries: North America, Western Europe, Japan, Australia, and New Zealand. This was to maintain a degree of conformity in standards of perinatal care; these countries reported infant mortality of 4–7 per 1000 births in 1998.² Only data relating to infants of less than 28 completed weeks of gestation were considered and the studies had to report survival in one week gestational age bands. Studies exclusively reporting the outcome of multiple pregnancies were disregarded.

LITERATURE SEARCH

Electronic databases were searched using a combination of free text (textword) and subject headings (MeSH), if supported by the database. Table 1 gives the Medline search strategy. The following databases were searched: Medline 1978–1998, Biological Abstracts 1986–1998, EMBASE 1989–1998, SIGLE 1980–1998, and CINAHL 1982–1998.

The following paediatric journals were hand searched for abstracts and articles not detected by electronic searching: *Archives of Disease in*

Childhood, Early Human Development, Pediatric Research, Pediatrics, and Journal of Pediatrics (all 1990–1998). References that were cited by the cohort studies and any review articles were also examined.

APPRAISAL AND GRADING OF STUDIES

Each study was graded according to the definition of the preterm cohort, without consideration of the results. Grade A studies were those that presented information on the outcome of all pregnancies (live births and stillbirths). Grade B studies reported the outcome of live births but did not report numbers of stillbirths, and grade C studies only reported the outcome of those infants admitted to the neonatal unit.

Other methodological factors that may influence the estimate of survival were recorded. These included any exclusion criteria (such as congenital malformations), whether the cohort was geographically or hospital defined, the method by which gestational age was assessed, and the postnatal age at which mortality was defined.

Clinical factors, which might influence survival of preterm infants, were also recorded from the manuscripts of the selected studies. These included the period during which the cohort was born, any sociodemographic and ethnic details of the population reported, and the use of antenatal steroids and postnatal surfactant treatment.

ANALYSIS

For the purposes of this review, survival was defined as the proportion of live births surviving until discharge from hospital. For each study and for each week of gestation, the proportion of liveborn preterm infants surviving until discharge was calculated. Combined estimates of survival for each grade of cohort study were then calculated by combining proportions from studies in a weighted average.

The hypothesis that there would be a gradient in the estimates of survival, increasing from grade A through to grade C studies, was tested by χ^2 analysis to detect a gradient in qualitatively ordered proportions.³

Studies that defined survival at other times—for example, expected date of delivery, 28 days, 6 months postnatal age—were included because it was assumed that death rates would be greatest in the first week of life. Thus survival to any time outside the early neonatal period and within the first year of life was assumed to approximate. The effect of this assumption was tested by reanalysing the data from only those studies that reported survival to discharge.

Results

DESCRIPTION OF SELECTED COHORT STUDIES

From the literature search, 191 articles published in 1978–1998 reported survival of preterm infants. Thirty one (16%) were not appraised (non-English language), 56 (29%) reported data relating to birth weight and not gestational age, and 37 (19%) reported survival in broad categories, rather than one week gestational age bands. The remaining 67 published articles reported data on 55 preterm cohorts.

Table 2 Characteristics of preterm cohorts from grade A studies reporting outcome of all pregnancies (stillbirths and live births)

Reference	Cohort birth period	Exclusions (details in text)	Geographical cohort	Antenatal steroids	Postnatal surfactant	Age at survival	Proportion of live births surviving for each week of gestation (%)				
							23	24	25	26	27
EPICure ⁴	Mar 95–Dec 95	No	Yes	Yes (64%)	Yes (87%)	dis	11	27	47		
Cartledge ⁵	1993–1994	Yes	Yes	Yes*	Yes*	neo	5	26	59	69	74
Tin ⁶	1991–1994	Yes	Yes	Yes*	Yes*	1 y	2	17	35	53	70
Kilpatrick ⁷	1990–1994	Yes	No	Yes (83%)	Yes (95%)	dis		49	78	83	
Kramer ⁸	Jul 89–Dec 93	No	No	Yes (18%)	Yes (100%)	6 m	19	48	25	75	71
Lefebvre ⁹	1987–1992	Yes	No	Yes*	Yes*	dis	0	23	50	64	78
Allen ¹⁰	May 88–Sep 91	No	No	No	Yes*	6 m	17	56	79		
Gray ¹¹	Jun 88–May 90	Yes	No	Yes*	No	dis		57	68	83	89
Tin ⁶	1987–1990	Yes	Yes	Yes*	Yes*	1 y	18	17	33	45	64
Synnes ¹²	1983–1989	No	No	No	No	dis	16	43	55	63	77
EC Study ¹³	1986	Yes	Yes	No	No	dis	17	13	27	50	36
EC Study ¹³	1986	Yes	Yes	No	No	dis	0	0	40	18	50
Nicholl ¹⁴	1983–1989	Yes	No	No	No	dis	8	43	59	65	85
EC Study ¹³	1985	Yes	Yes	No	No	dis	0	5	19	48	48
Tin ⁶	1983–1986	Yes	Yes	No	No	1 y	3	10	21	42	59
EC Study ¹³	1983	Yes	Yes	No	No	dis	0	0	14	37	52
					Combined estimate (95% CI)		10 (8–12)	27 (24–30)	44 (41–47)	55 (52–58)	67 (64–70)

*Percentage not specified.

neo, neonatal period (28 days); 1 y, 1 year of age; dis, discharge from hospital; 6 m, 6 months of age.

Of these 55 cohorts, 16 (29%) comprised stillbirths and all live births (grade A), 23 (42%) cohorts comprised live births only (grade B), and 16 (29%) cohorts consisted of only those infants admitted to the neonatal unit (grade C). Tables 2–4 present further details of these cohorts, ordered in reverse chronological order of the mid-range of the cohort birth period—that is, most recent first.

Exclusion criteria were stated in studies relating to 24 (44%) cohorts. Congenital malformations were excluded from 13 cohorts (“lethal malformations” in three cohorts,^{20 39 50} “major malformation” in one cohort,⁴³ “antenatally diagnosed malformation” in one cohort,¹⁴ severity of malformation not specified in eight cohorts.^{7 16 18 27 30 35 49}) Registered terminations of pregnancy were excluded in eight (15%) cohorts,^{6 7 13} intrauterine deaths were excluded in two cohorts,^{7 9} and stillbirths at less than 24 weeks were excluded in one cohort.⁵

One study reporting data on four cohorts excluded all births of infants with a weight of less than 500 g,¹³ and another excluded those less than 400 g.¹⁶

Fourteen (25%) cohorts were geographical in nature. In 19 (35%) cohorts, the use of antenatal steroid treatment was reported, but the actual proportion of women receiving steroids was only stated in seven cohorts, and this ranged from 18 to 83%. Likewise, surfactant treatment was reported in 17 (31%) cohorts, but only seven cohorts reported the proportion of infants receiving surfactant. All studies used early ultrasound (before 24 weeks) to guide assessment of gestational age. The gestational age was taken either from the maternal dates, provided that these were within two weeks of the date calculated from ultrasound, or directly from the ultrasound estimation. Only four (7%) studies reported information on the socioeconomic and ethnic mix of the cohort.

Table 3 Characteristics of preterm cohorts from grade B studies reporting outcome of live births

Reference	Cohort birth period	Exclusions (details in text)	Geographical cohort	Antenatal steroids	Postnatal surfactant	Age at survival	Proportion of live births surviving for each week of gestation (%)				
							23	24	25	26	27
Batton ¹⁵	1994–1997	No	No	Yes (64%)	Yes (81%)	dis	57	74	85		
Bahado-Singh ¹⁶	1990–1995	Yes	No	Yes*	Yes*	dis	41	68	75		
Doyle ¹⁷	1991–1992	No	Yes	No	No	2 y	10	33	58	72	77
Gultom ¹⁸	1989–1994	Yes	No	No	No	dis	5	35	57	79	85
Hack ¹⁹	1990–1992	No	No	Yes (40%)	Yes (10%)	20 m	7	40	63	77	83
Katz ²⁰	Jul 89–Aug 91	Yes	No	No	No	dis		45	64	72	89
Holtrop ²¹	Jan 88–Dec 91	No	No	No	No	dis	19	59	59		
Magowan ²²	1985–1994	No	Yes	No	No	neo		21	48	60	70
Ferrara ²³	1986–1990	No	No	No	Yes (50%)	dis	44	44	70	78	
Philip ²⁴	1982–1991	No	No	No	No	dis				65	80
Gultom ¹⁸	1983–1988	Yes	No	No	No	dis	0	0	35	57	72
Johnson ²⁵	1984–1986	No	Yes	No	No	dis			22	48	62
Hack ²⁶	Jul 82–Jun 88	No	No	No	No	dis	8	16	53	63	72
Whyte ²⁷	Jan 82–Jun 87	Yes	No	Yes*	No	dis	25	47	65	74	
Van Zeben ²⁸	1983	No	Yes	No	No	dis		0	15	38	54
Gilstrap ²⁹	Jul 79–Mar 84	Yes	No	Yes*	No	dis	0	50	29	67	100
Nwaesei ³⁰	1980–1982	Yes	No	Yes*	No	dis	0	10	38	46	76
Kitchen ³¹	Oct 80–Mar 82	No	No	No	No	8 y		10	14	42	55
Yu ³²	1977–1984	No	No	No	No	1 y	7	33	25	56	72
Milligan ³³	1979–1982	No	No	No	No	dis	14	39	64	76	75
Kitchen ³⁴	Jan 77–Mar 82	No	No	Yes*	No	dis		7	20	45	55
Herschel ³⁵	1977–1980	Yes	No	Yes*	No	dis		29	11	45	61
Kitchen ³⁶	1977–1978	No	No	No	No	dis		9	17	50	73
					Combined estimate (95% CI)		18 (14–21)	33 (30–36)	50 (48–53)	63 (61–65)	72 (66–74)

*Percentage not specified.

2 y, 2 years of age; neo, neonatal period (28 days); dis, discharge from hospital; 20 m, 20 months of age.

Table 4 Characteristics of preterm cohorts from grade C studies reporting outcome of neonatal unit admissions

Reference	Cohort birth period	Exclusions (details in text)	Geographical cohort	Antenatal steroids	Postnatal surfactant	Age at survival	Proportion of live births surviving for each week of gestation (%)					
							23	24	25	26	27	
Martens ³⁷	1991–1996	No	No	No	No	neo		57	62	72		
Emsley ³⁸	1990–1994	No	No	Yes (23%)	Yes (54%)	dis			54			
Bohin ³⁹	1991–1993	Yes	Yes	No	No	dis	3	28	37	55	71	
Hussain ⁴⁰	Aug 89–Jul 93	No	No	No	Yes*	dis	27	57	64	87	87	
Wilson ⁴¹	Apr 90–Apr 92	No	No	Yes*	Yes*	dis	0	42	56	59	92	
Cooper ⁴²	Jul 86–Dec 93	No	No	Yes (20%)	Yes*	dis	27	51	67	66	66	
Holmsgaard ⁴³	Jan 87–Dec 90	Yes	No	Yes*	Yes*	2 y		54	67	71	86	
Nishida ⁴⁴	Oct 84–Dec 91	No	No	No	No	neo	43	94	85	84	90	
Wood ⁴⁵	Jan 86–Apr 88	No	No	No	No	dis		10	43	80	83	
Emsley ³⁸	1984–1989	No	No	No	No	dis			33			
Ruys ⁴⁶	1985–1987	No	No	No	No	dis		75	50	60	46	
Eg-Andersen ⁴⁷	1984–1987	No	No	No	No	dis		0	88	44	63	
Cooke ⁴⁸	1980–1989	No	No	No	No	dis		14	43	44	64	
Lamont ⁴⁹	Aug 79–Jun 82	Yes	No	No	No	dis				11	55	
Marlow ⁵⁰	1976–1980	Yes	No	No	No	dis	0	31	45	66	78	
Philip ⁵¹	1976–1979	No	No	No	No	dis			11	36	47	
					Combined estimate (95% CI)		20 (15–26)	42 (38–46)	52 (48–55)	62 (59–65)	71 (69–74)	

*Percentage not specified.

dis, discharge from hospital; neo, neonatal period (28 days); 2 y, 2 years of age.

Most cohorts defined survival at discharge from hospital (75%). Four cohorts reported survival during the neonatal period (28 days), and 10 cohorts reported survival at times ranging from six months to eight years (tables 2–4).

ANALYSIS OF SURVIVAL DATA

Figure 1 depicts the combined estimates of survival (proportion of liveborn infants surviving to discharge from the neonatal unit) for each week of gestation and for each grade of cohort study. For infants of 23–26 weeks of gestation, there was a significant trend towards increased survival in cohorts with a higher risk of selection bias (grade C > grade B > grade A; $p < 0.01$). The value of χ^2 was greatest for lower gestations, particularly at 23 and 24 weeks. Grade C studies exaggerated survival compared with grade A studies, by 100% at 23 weeks (20% v 10%), 56% at 24 weeks (42% v 27%), 18% at 25 weeks (52% v 44%), and 13% at 26 weeks (62% v 55%).

Excluding from the analysis cohorts where survival was defined at times other than hospital discharge did not affect the observed trend in survival. An identical trend in χ^2 values was observed (highest value $\chi^2 = 49.2$ at 24 weeks, ranging to lowest value $\chi^2 = 9.0$ at 27 weeks).

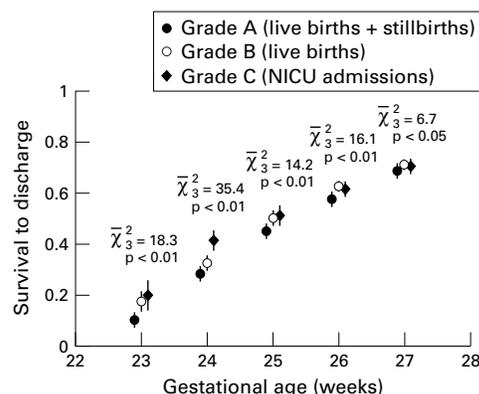


Figure 1 Survival of preterm infants associated with gestational age and methodological grade of cohort study. Bars indicate 95% confidence intervals. NICU, Neonatal intensive care unit.

Owing to the paucity of reported data, it was not possible to examine any further associations between trends in survival and other factors such as antenatal steroid usage, surfactant treatment, and the geographical nature of the cohort.

Discussion

The results of this systematic review indicate that the potential for selection bias in preterm infant cohort studies is associated with higher estimates of survival, most pronounced at the lower gestations.

A POSSIBLE MECHANISM FOR SELECTION BIAS

Studies that report the outcome of admissions to the neonatal unit are ignoring the outcome of neonates who could not be resuscitated. In this case, the outcome of the neonates admitted would be better than the total population of live births as they represent infants who survived until neonatal unit admission. Studies reporting the outcome of all liveborn infants also give a higher estimate of survival than those reporting outcomes of all pregnancies, despite survival being expressed as a proportion of live births—that is, using the same denominator. Selective obstetric monitoring and intervention during favourable pregnancies may account for the apparent improvement in survival. This effect appears to be more pronounced at lower gestational ages, which would concur with the notion that obstetricians are more likely to be selective about the care of pregnancies around the limit of viability.

There is potential for ambiguous classification of a delivery around the limit of viability. A delivery before 24 weeks of gestation may be treated as a miscarriage on a gynaecology ward. Conversely, it may be classed as a neonatal death on a labour ward if the labour was aggressively managed and signs of life were sought and found present after birth. It is also possible for late terminations of pregnancy to be missed if they occur outside of the maternity unit. Only two studies stated that the investigators actively sought to check admissions to gynaecological wards.^{6 9}

Table 5 Recommended data to be included when reporting preterm cohort studies

<i>Cohort characteristics</i>
<ul style="list-style-type: none"> ● Institution or geographical area ● Time period of birth cohort ● Maternal sociodemographic details ● Ethnic characteristics
<i>Clear recording of all previous publications (including abstracts) relating to cohort</i>
<i>Coexistent perinatal therapies</i>
<ul style="list-style-type: none"> ● Antenatal steroid uptake ● Postnatal surfactant usage
<i>Reporting of outcome</i>
<ul style="list-style-type: none"> ● Report outcome of all pregnancies (terminations, miscarriages, stillbirths, live births) ● Outcome reported in one week gestational age bands ● Report survival to a standardised age—for example, expected date of delivery ● Initially report outcomes including all congenital malformations included then report separate subgroup analysis excluding congenital malformations

ARE THERE OTHER PLAUSIBLE EXPLANATIONS?

There is still a large degree of variation in survival within each grade of study and therefore other factors may interact with, or exist instead of, selection bias. There is an observed increase in survival over the period of this systematic review, presumably reflecting improvements in perinatal care. This trend has also been seen within individual studies that compared cohorts from different periods using the same methods.^{6 18 38} Could the improved survival over time be confounding the association between selection bias and survival? There is no evidence that more grade A studies (live births and stillbirths) were conducted in the first half of the period than the other grades ($\chi^2 = 1.84$ (df2) $p > 0.2$). In an attempt to examine whether this observed trend over time confounds the trend associated with the grade of the study cohort, the cohorts were stratified into two equal groups (1977–1986 and 1987–1996). The stratification was performed by taking each mid-point of the period during which a cohort was born. The gradient associated with grade of study cohort was still observed to be present for the 1987–1996 period but not for the earlier period. It was not possible to test more precisely whether selection bias and year of birth act independently because studies did not report survival for individual years, and the periods during which cohorts were born overlapped considerably.

The effect of clinical heterogeneity, arising from different rates of antenatal steroid administration, surfactant treatment, and the different socioeconomic and ethnic status of the populations under study, on survival was not examined. In general, reporting of these factors was poor, and therefore they were not analysed.

WHAT ARE THE WEAKNESSES OF THIS SYSTEMATIC REVIEW?

Although the intention was to be systematic in the identification of studies and extraction of data, several problems were encountered. Studies in languages other than English were not appraised because of a lack of resources. Data relating survival to birth weight, rather than gestational age, were ignored and could not be combined with the gestational age specific data. This was because the intention was to provide information of use to obstetricians and prospective parents before delivery, when the birth weight would not be accurately known. It was noted that the studies excluded

for this reason were predominantly North American in origin, representing a non-random sample of published studies.

The literature search was confined to published studies. Publication bias may be more pronounced for recent cohorts. Many neonatal units now routinely record information on neonatal outcomes, but this information may be viewed by editors and reviewers as uninteresting and unworthy of publication, unless the outcomes are unusually good.

Many cohorts are the subjects of more than one publication, which can lead to duplication bias. Every attempt was made to ensure that this did not occur by considering the cohorts as the unit of analysis rather than the study. Partial duplication, where cohorts overlap but no study completely encompasses all patients, was a problem in three studies.^{32 34 36}

It was not possible to test whether other clinical factors, such as surfactant treatment, have an effect on survival independent of methodological factors. This would require a systematic review using individual patient data.

IMPLICATIONS FOR FUTURE RESEARCH

Those concerned with the provision and evaluation of perinatal care are required to continuously collect data on survival and outcome of preterm infants. The outcomes of all pregnancies should be reported for each week of gestation. There should be sufficient information to avoid duplication bias—that is, sufficient descriptive data to identify a cohort uniquely. If the study reports longer term outcomes from a cohort where the short term outcomes had previously been described, this fact should be made explicit. It is important that data are comprehensive and include factors such as use of antenatal steroids and postnatal surfactant. It would be desirable to develop conformity of definitions between studies—for example, exclusion of congenital malformations and age at which survival is assessed. Such considerations could form the basis of a minimum dataset for future publications (table 5).

IMPLICATIONS FOR CLINICIANS

In the modern era of evidence based medicine, it is logical and appropriate that the decisions surrounding the provision of expensive intensive care to extremely preterm neonates are based on the best available external evidence. This process may involve parents, obstetricians, neonatologists, developmental paediatricians, and health economists. All these parties need to be aware of the potential bias and the effect that this will have on reported survival figures. It is well known that selection bias is a source of non-random error in cohort studies, but this is the first systematic review to attempt to quantify its effect on studies of preterm survival. The effect appears to be substantial around the limit of viability, with the potential to overestimate survival by 100% and 56% at 23 and 24 weeks respectively. Although not tested in this review, there is every reason to suspect that this effect also exists when the subsequent neurodevelopmental outcome of these infants is considered.

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