Survival and Impairment of Extremely Premature Infants: A Meta-analysis

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abstract

CONTEXT: Survival of infants born at the limit of viability varies between high-income countries.

OBJECTIVE: To summarize the prognosis of survival and risk of impairment for infants born at 22 + 0/7 weeks' to 27 + 6/7 weeks' gestational age (GA) in high-income countries.

DATA SOURCES: We searched 9 databases for cohort studies published between 2000 and 2017 in which researchers reported on survival or neurodevelopmental outcomes.

STUDY SELECTION: GA was based on ultrasound results, the last menstrual period, or a combination of both, and neurodevelopmental outcomes were measured by using the Bayley Scales of Infant Development II or III at 18 to 36 months of age.

DATA EXTRACTION: Two reviewers independently extracted data and assessed the risk of bias and quality of evidence.

RESULTS: Sixty-five studies were included. Mean survival rates increased from near 0% of all births, 7.3% of live births, and 24.1% of infants admitted to intensive care at 22 weeks' GA to 82.1%, 90.1%, and 90.2% at 27 weeks' GA, respectively. For the survivors, the rates of severe impairment decreased from 36.3% to 19.1% for 22 to 24 weeks' GA and from 14.0% to 4.2% for 25 to 27 weeks' GA. The mean chance of survival without impairment for infants born alive increased from 1.2% to 9.3% for 22 to 24 weeks' GA and from 40.6% to 64.2% for 25 to 27 weeks' GA.

LIMITATIONS: The confidence in these estimates ranged from high to very low.

CONCLUSIONS: Survival without impairment was substantially lower for children born at <25 weeks' GA than for those born later.

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Dr Myrhaug selected the studies, critically appraised the included studies, assessed the quality of evidence, extracted data, drafted the initial manuscript, critically reviewed the manuscript, and contributed to the decisions of the objective, eligibility criteria, and meta-analyses; Dr Brurberg participated in the selection of studies, extracted data, conducted the analyses, critically reviewed the manuscript, and contributed to the decisions of the objective, eligibility criteria, and meta-analyses; Ms Hov selected the studies, critically appraised the included studies, assessed the quality of evidence, extracted data, critically reviewed the manuscript, and contributed to the decisions of the objective, eligibility criteria, and meta-analyses; Dr Markestad participated in the selection of studies, drafted the initial manuscript, critically reviewed the manuscript, and contributed to the decisions of the objective, eligibility criteria, and meta-analyses; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Proactive life support for infants born at 22 to 24 weeks' gestational age (GA) is a relatively new phenomenon, and we have limited knowledge on the chance of survival and survival without significant impairments. Indeed, reported survival rates vary considerably between otherwise similar high-income countries, probably in large part because of different attitudes toward providing life support on the part of health care professionals, parents, and societies.[1–3] For example, life-saving treatment is commonly offered from 22 weeks' GA in Sweden[4] and some institutions in Japan,[5] Germany,[6] and the United States[7] but is generally not even offered at 23 weeks' GA in the Netherlands and France.[2,8]

The decision to provide or withhold life-saving treatment at the limit of viability is ethically challenging both in terms of what may be regarded as in the best interest of the child and the family, the norms of the society, and who should be part of the decision process.[9] As far as possible, ethical deliberations and sound decision-making processes should be based on medical facts, preferably presented in updated rigorous systematic reviews. In 2013, Salihu et al[10] summarized the prognosis of survival for infants born at <24 weeks' GA or with birth weight (BW) <500 g in the United States, and Moore et al[11] reviewed cohort studies on the likelihood of neurodevelopmental impairment. As far as we know, there are no updated systematic reviews that have summarized the prognosis of both survival and functional outcomes for infants born at the limit of viability. Therefore, in the present systematic review, we aimed to summarize cohort studies in which researchers have examined the prognosis of survival and risk of impairments as assessed by using the Bayley Scales of Infant Development (BSID)[12,13] for each week of GA from 22 through 27 weeks.

METHODS

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD 42016047230), and the systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[14]

Search Strategy

We searched the Cochrane Central Register of Controlled Trials, PubMed, Medline, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, Institute for Scientific Information Web of Science, SveMed+, and Maternity and Infant Care in June 2015 and March 2017. The search strategy consisted of text words and subject headings adapted to each database (see Supplemental Information for details).

Selection Criteria

We included cohort studies that reported survival or risk of impairment as assessed by using the BSID II or III at 18 to 36 months of age in children born at 22 + 0/7 through 27 + 6/7 weeks' GA. We chose this age range to capture most published cohorts on follow-up and the use of the BSID because this method was used nearly exclusively at this age. Because it is common practice to provide life-saving treatment to most infants born at 25 to 27 weeks' GA in high-income countries, we considered that data from these GAs were important as a reference when assessing reported outcomes for the more immature infants. The GA had to be determined by using ultrasound, the last menstrual period, or a combination of both. To reduce the degree of variability, we only included studies from high-income countries[15] published in peer-reviewed journals between 2000 and March 2017. Studies had to be available in English, German, French, or a Scandinavian language.

Selection of Studies and Data Extraction

Titles and abstracts of all references retrieved from the systematic search were screened for eligibility. Articles were retrieved in full text if the abstract was deemed relevant by at least 1 author. Relevant articles were reviewed and included if they met the inclusion criteria. The following data were extracted from each of the included studies: population characteristics, method of determining GA, country of birth, year of birth, and outcome measures. Two reviewers independently performed each step of the selection and extraction process. Any disagreements were resolved by discussion or by involving a third author.

Risk of Bias

We used a modified checklist for prognosis studies to assess the risk of bias.[16] Studies we viewed as having a low risk of bias met the following criteria: (1) the included children had to be representative of the defined population, (2) GA and outcomes had to be assessed consistently and with reliable outcome measures, and (3) participants had to be managed sufficiently long enough to allow for the detection of positive and negative outcomes.

Data Analysis

Population characteristics, methods of determining GA, outcome measures, age at follow-up, and risk of bias were taken into consideration when determining which studies were reasonable to pool in meta-analyses.

The meta-analyses were limited to births after 1998 for survival and births after 1994 for neurodevelopmental outcomes. These limits were chosen to reasonably reflect current life-saving and

follow-up practices. Because the thresholds for initiation, continuation, or discontinuation of life support vary, we calculated survival in 3 dimensions: as a proportion of all births, live births, and children admitted to a NICU. To be included in the meta-analysis, studies that reported survival had to be of low risk of bias. Studies on neurodevelopmental outcomes had to be based on the BSID II[13] or III[12] with impairment categorized as none, mild, moderate, or severe. Moderate and severe impairments were sometimes reported together and therefore are presented as such in the current study. Because the rates of these categories may differ for the BSID II and III,[17,18] we also compared outcomes for studies based on either of them.

For each study, we calculated event rates for specific outcomes (eg, survival rate and risk of severe impairment). We performed double-data entries. Because many studies had few participants and researchers reported event rates close to 0% or 100%, we performed meta-analyses on proportions based on logit-transformed data. Meta-analyses and forest plots were prepared in R (R Core Team) by using the "metafor"[19] and "forestplot"[20] packages. Because we expected some degree of heterogeneity, the meta-analyses were based on a random effect model in which we used the DerSimonian-Laird estimator. To be able to construct a confidence interval (CI) for studies without events also, we added a small value (0.01) to the nominator and the denominator. The weight given to each study in the meta-analyses was proportional to the number of participants in the study. For each gestational week and available study, we plotted the survival rate versus the risk of impairment. We performed post hoc meta-regression analyses to examine if the year of birth had a moderating effect on the observed survival, survival without impairment, or risk of impairment.

The Quality of Evidence

We used an adapted Grading of Recommendations Assessment, Development, and Evaluation methodology to assess our confidence in the overall prognostic estimates, as described by Iorio et al.[21] Briefly, we assessed our confidence in the estimates of survival and risk of no or severe impairment among surviving infants born at 22 to 24 weeks' GA and categorized our confidence in the prognostic estimates as either high, moderate, low, or very low (Supplemental Table 3).

RESULTS

The searches yielded 6718 unique references (Fig 1). We excluded 6150 references after screening the titles and abstracts and reviewed 568 in full text. Of these, we included 65 articles from Australia (n = 5), Austria (n = 2), Belgium (n = 2), Canada (n = 3), France (n = 5), Germany (n = 6), Italy (n = 1), Japan (n = 3), South Korea (n = 1), Portugal (n = 2), mixed countries (n = 1[22]), Norway (n = 2), Singapore (n = 2), Spain (n = 3), Sweden (n = 2), Switzerland (n = 4), Taiwan (n = 1), the Netherlands (n = 2), the United Kingdom (n = 4), and the United States (n = 14). An overview of the included studies is presented in Supplemental Table 4.

Risk of Bias

Thirty-two of the 63 articles in which researchers assessed the prognosis of survival had a low risk of bias (Table1), whereas 8 of 15 articles in which researchers assessed the risk of impairment at 18 to 36 months of age had a high risk of bias. High risk of bias was mainly due to uncertainty regarding the representativeness of the population and the blinding of outcome assessors.

Prognosis of Survival

Twenty-seven* of 63 articles were included in the meta-analyses of survival (Supplemental Table 5). Five articles[28,30,64,73,80] were excluded because of poor reporting of prognosis estimates, year of birth being 1997–1998, and survival data being from the same cohort.[64,81] The remaining 31 articles† were excluded because of the unclear or high risk of bias (Table 1). Survival was assessed at discharge or at 1 to 6 years of age. These data were pooled irrespective of the duration of follow-up.

The overall survival rate increased, whereas the difference in survival calculated as the proportion of all births, live births, and infants transferred to a NICU decreased for each GA (Fig 2). The survival rates of infants born at 22 weeks' GA were estimated to near 0% (95% CI 0%–37.1%; 5 studies[22,36,54,66,72]; 948 participants) when calculated as a proportion of all births, 7.3% (95% CI 3.9%–13.1%; 19 studies‡; 4657 participants) as a proportion of live births, and 24.1% (95% CI 17.6%–32.0%; 13 studies§; 707 participants) as a proportion of infants transferred to a NICU. The respective figures were 9.0% (95% CI 5.3%–14.7%), 25.7% (95% CI 20.3%–31.9%), and 38.2% (95% CI 31.0%–45.9%) for 23 weeks' GA and 29.9% (95% CI 23.0%–37.9%), 53.9% (95% CI 48.0%–59.6%), and 59.7% (95% CI 54.0%–65.1%) for 24 weeks' GA. For infants born alive, the survival rate increased from 74.0% for children born at 25 weeks' GA to 90.1% for children born at 27 weeks' GA. More information is provided in Supplemental Tables 4 and 5 and Supplemental Figs 5–22. In

* Refs 6,23,24,26,29,31,35,37,38,41,42,44,47–49,53,55–61,63,65,67,70,71,75,78,79.

† Refs 6,23,24,26,29,31,35,37,38,41,42,44,47–49,53,55–61,63,65,67,70,71,75,78,79.

‡ Refs 3,8,22,25,27,33,36,40,45,50–52,54,66,68,69,72,74,76,77,81.

§ Refs 3,5,22,25,36,45,50,51,54,66,72,76,77.

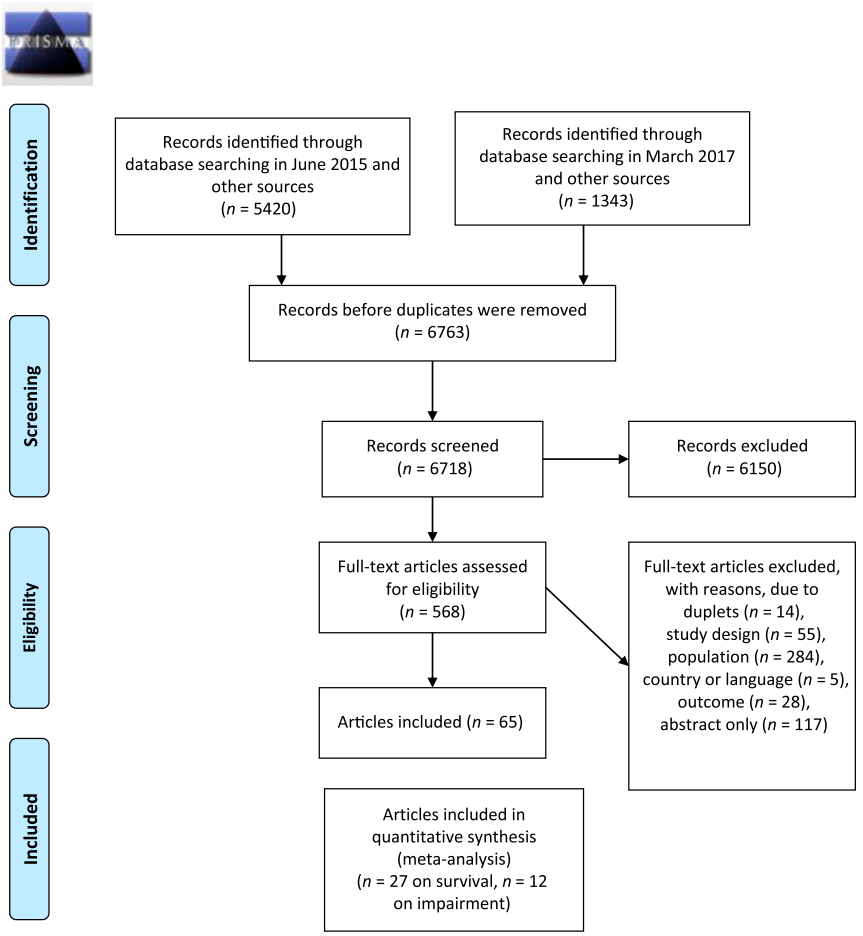

FIGURE 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. For more information, visit www.prisma-statement.org.

a cumulative meta-analysis of the low risk of bias studies of children born during the years 2000–2015, there was no evidence of change in survival rates with year of birth. Some survival estimates seem higher during the first than later years, an observation that can be explained by the impact of single studies with high survival rates at the beginning of the period[52,69,77] (Supplemental Fig 23).

The quality of evidence for infants born at 22 weeks' GA was graded as low for survival rates of live-born infants and infants transferred to a NICU, primarily because of heterogeneity in survival rates between the studies and wide CIs. For infants born at 23 and 24 weeks' GA, the evidence of survival was graded as being of moderate-to-high quality (Supplemental Table 6).

Prognosis of Survival With or Without Impairment

Of the 15 studies that met the criteria for inclusion, 3 were not included in the meta-analyses because of insufficient reporting of estimates.[7,46,76] Of the 12 included studies,‖ the risk of bias was high for eight[3,26,38,48,49,56,58,75] and unclear for four[39,62,77,81] (Table 1). The overall risk of no, moderate-to-severe, and severe impairment for each GA is presented in Fig 3. Twenty-three percent (95% CI 3.8%–70.7%) of the surviving children born at 22 weeks' GA survived without impairment compared with 35.0% (95% CI 24.6%–47.1%) of infants born at 23 weeks' GA and 39.3% (95% CI 27.4%–52.5%) of those born at 24 weeks' GA (Fig 4, Supplemental Table 7). For 25 to 27 weeks' GA, the probability of survival without impairment increased from 54.6% (95% CI 39.8%–68.6%) to 70.8% (95% CI 56.6%–81.9%; Fig 4, Supplemental Table 7).

The calculated risk of severe impairment was 36.3% (95% CI 23.5%–51.3%) for survivors born at 22 weeks' GA, 22.1% (95% CI 11.5%–38.1%) for those born at 23 weeks' GA, and 19.1% (95% CI 11.2%–30.8%) for those born at 24 weeks' GA (Fig 4). For survivors born at 25 to 27 weeks' GA, the risk of severe impairment decreased from 14.0% (95% CI 10.2%–19.0%) to 4.2% (95% CI 0.3%–43.2%; Fig 4, Supplemental Table 7). The risks of no, moderate-to-severe, and severe impairment did not differ significantly between studies based on the BSID II or III (Supplemental Table 7).

The chance of survival without any impairment for infants born alive increased from 1.2% (95% CI 0.4%–3.7%) for 22 weeks' GA to 64.2% (95% CI 49.8%–76.9%) for 27 weeks' GA, but the major increase occurred from 24 weeks' GA (9.3; 95% CI 31.6%–50.3%) to 25 weeks' GA (40.6; 95% CI 31.6%–50.3%; Table 2). There were no significant differences in the rates of impairment with different follow-up rates (data not shown).

We graded the quality of evidence on the prognosis of neurodevelopmental outcomes as very low and low for children born at 22 to 24 weeks' GA because of the risk of bias due to small numbers, large variations in the

‖ Refs 3,26,38,39,48,49,56,58,62,75,77,81.

TABLE 1 Risk of Bias

Author, y	Outcome	Overall Risk of Bias
Abdel-Latif et al[23] 2013	Survival per d	Unclear
Agarwal et al[24] 2013	Survival at discharge	Unclear
Ancel et al[8] 2015	Survival at discharge	Low
Anderson et al[25] 2016	Survival at 1 y	Low
Backes et al[26] 2015	Survival at discharge	Unclear
	Neurologic development	High
Berger et al[27] 2012	Survival at discharge	Low
Binet et al[28] 2012	Survival at discharge	Low
Bode[29] 2009	Survival at discharge	Unclear
Bodeau-Livinec et al[30] 2008	Survival at discharge	Low
Boland et al[31] 2017	Survival at 1 y	Unclear
Bolisetty et al[32] 2015	Survival at discharge	Low
Boussicault et al[33] 2012	Survival at discharge and at 2 y follow-up	Low
Chen et al[34] 2016	Survival at discharge	Low
Crane et al[35] 2015	Survival at discharge	Unclear
Costeloe et al[36] 2012	Survival at discharge	Low
D'Amore et al[37] 2011	Survival at discharge	Unclear
De Groote et al[38] 2007	Survival at discharge	High
	Neurologic development at 3 y of age	High
de Waal et al[39] 2012	Survival at discharge	Low
	Neurologic development	Unclear
Doyle et al[40] 2010	Survival at 2 y	Low
Durães et al[41] 2016	Survival at discharge	Unclear
Goya et al[42] 2015	Survival at 2 y	Unclear
Herber-Jonat et al[43] 2006	Survival at discharge	Low
Hintz et al[7] 2011	Neurologic development at 18–22 mo	Unclear
Hornik et al[44] 2016	Survival at discharge	Unclear
Ishii et al[5] 2013	Survival at 3 y	Low
Itabashi et al[45] 2009	Survival at discharge	Low
Johnson and Marlow[46] 2016	Neurologic development at 2, 5, 6, and 11 y	Unclear
Klebermass-Schrehof et al[47] 2013	Survival at discharge	High
Kutz et al[48] 2009	Survival at discharge	Unclear
	Neurologic development	High
Kyser et al[49] 2012	Survival	Unclear
	Neurologic development	High
Landmann et al[50] 2008	Survival at discharge	Low
Lemyre et al[51] 2016	Survival at discharge	Low
Malloy[52] 2015	Survival at 1 y	Low
Manuck et al[53] 2016	Survival at discharge	Unclear
Markestad et al[54] 2005	Survival at discharge	Low
Mehler et al[6] 2016	Survival at discharge	Unclear
Michikata et al[55] 2010	Survival at discharge and at 2 y of age	Unclear
Morgillo et al[56] 2014	Survival at discharge	Unclear
	Neurologic development at 18–24 mo	High
Nguyen et al[57] 2012	Survival at discharge	Unclear
Poon et al[58] 2013	Survival at discharge	Unclear
	Neurologic development at 2.5, 5 and 8 y	High
Rysavy et al[3] 2015	Survival at 1.5–2 y	Low
	Neurologic development at 1.5–2 y	High
Rieger-Fackeldey et al[59] 2005	Survival at discharge	Unclear
Rocha and Guimarães[60] 2011	Survival at discharge	Unclear
Rodrigo et al[61] 2015	Survival at discharge	Unclear
Schlapbach et al[62] 2012	Survival at 2 y	Low
	Neurologic development at 2 y	Unclear
Seaton et al[63] 2013	Survival at discharge	Unclear
Serenius et al[4] 2013	Survival at 1 and 2.5 y	Low
	Neurologic development at 2.5 y	Unclear
Serenius et al[64] 2016	Survival at 6.5 y	Low
Shim et al[65] 2015	Survival at discharge	Unclear
Smith et al[22] 2017	Survival at discharge	Low

prognosis, and wide CIs (Table 1, Supplemental Table 8).

Correlations Between Survival Rate and Risk of Impairments

There were no apparent correlations between survival rates (or live births; data not shown) and risks of neurodevelopmental impairments. However, statistical analyses were impeded by limitations in the available data, particularly due to many small and heterogeneous samples of infants born at 22 to 24 weeks' GA (Supplemental Fig 24).

Year of Birth As a Moderator

In the meta-analysis of studies published between 2000 and 2015, year of birth did not appear to have a moderating effect on rates of survival, survival without impairments of live-born children, or rates of severe or no impairments among survivors for any of the GAs. However, the estimates are uncertain because of limited data and low statistical power (data not shown).

DISCUSSION

In this systematic review on infants born in high-income countries at 22 to 27 weeks' GA, the survival rate of all infants, including stillbirths, increased from near 0% when born at 22 weeks' GA to ~80% at 27 weeks' GA. For infants transferred to a NICU, the respective survival rates increased from ~24% to 90%. Differences in survival rates between cohorts increased with decreasing GA and were particularly large for infants born at <25 weeks' GA, probably reflecting variations in attitudes toward providing life support at lower GAs. We categorized the evidence of prognosis for survival as being of low to high quality when born at 22 to 24 weeks' GA, implying that the true prognosis (probability of future events) was close to or substantially different from the estimates.

TABLE 1 Continued

Author, y	Outcome	Overall Risk of Bias
Stensvold et al[66] 2017	Survival at 1 y	Low
Steurer et al[67] 2017	Survival at 1 y	Unclear
Stichtenoth et al[68] 2012	Survival at discharge	Low
Stoll et al[69] 2015	Survival at discharge	Low
Su et al[70] 2015	Survival at discharge	Unclear
Uccella et al[71] 2015	Survival at discharge	Unclear
Vanhaesebrouck et al[72] 2004	Survival at discharge	Low
Veit-Sauca et al[73] 2008	Survival	Low
Weber et al[74] 2005	Survival at 1 y	Low
Wong et al[75] 2014	Survival at discharge	Unclear
	Neurologic development at 2–3 y of age	High
Younge et al[76] 2017	Survival at 18–22 mo	Low
	Neurologic development at 18–22 mo	Unclear
Zayek et al[77] 2011	Survival at 1.5 and 2 y	Low
	Neurologic development at 3.5 and 5.5 y	Unclear
Zeballos-Sarrato et al[78] 2016	Survival at discharge	High
Zegers et al[79] 2016	Survival	Unclear
Zeitlin et al[80] 2010	Survival at discharge	Low

If it is true that there is no clear improvement in survival between 2000 and 2015, this may reflect both unchanged attitudes toward providing life support to the most immature infants and current therapeutic limitations. Among the included cohorts, the highest reported survival rates of infants born alive were 40% at 22 weeks' GA, 63% at 23 weeks' GA, and 81% at 24 weeks' GA.[77] These survival rates were reported for children treated at a single NICU in the United States and may reflect what is possible to obtain under ideal conditions and adherence to proactive perinatal care, such as the early use of prenatal steroids, a liberal use of cesarean delivery, and active life support provision to infants born alive. Salihu et al[10] pooled the overall prognosis of early survival of US infants born alive at <24 weeks' GA or with a BW <500 g from 2003 to 2013 and estimated a survival rate of 46% (95% CI 41%–52%). The current review and the review of Salihu et al[10] are not directly comparable because of differences in selection criteria.

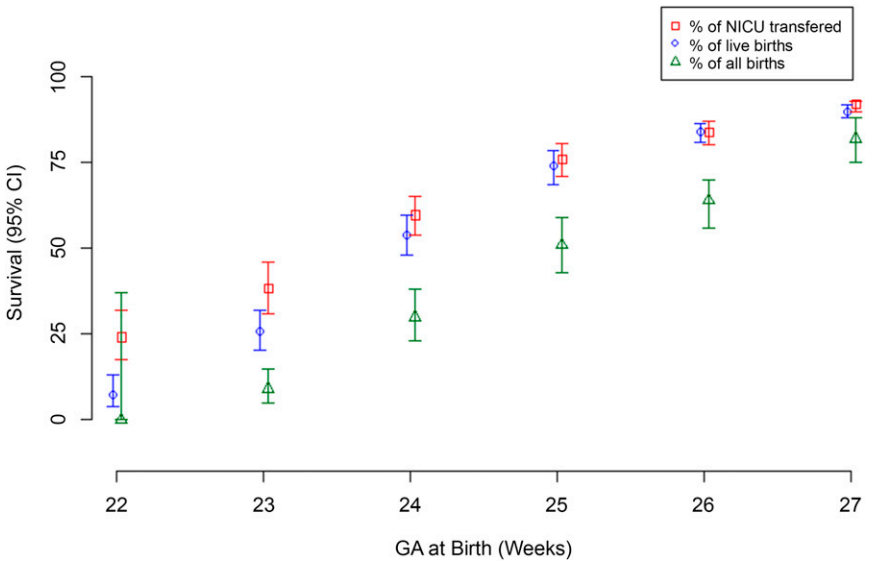

FIGURE 2
The overall prognosis of survival (risk and 95% CI) for children born at 22 to 27 weeks' GA calculated as proportions of all births, live-born infants, and infants transferred to a NICU nursery.

For surviving children, the chance of survival without obvious impairment increased from 23.5% at 22 weeks' GA to 70.8% at 27 weeks' GA, whereas the risk of severe impairment decreased from 36.3% at 22 weeks' GA to 19.1% at 24 weeks' GA and 4.2% at 27 weeks' GA. Our confidence in these estimates is limited, indicating that the true prognosis (probability of future events) may be substantially different from the estimate. Compared with using the BSID II, researchers using the BSID III may underestimate the risk of impairments.[17,18] Because the risk estimates were similar for studies based on the BSID II and III, and the BSID III was used in the most recent studies, the results suggest that the risk of impairment was not reduced for the children born in the most recent years. For infants born alive, there was a marked difference in survival without impairment from <25 weeks' GA (1%–9%) to 25 weeks' GA (41%). This threshold difference may partly reflect a difference in vulnerability but probably largely reflects differences in attitudes toward providing life support at <25 weeks' GA. In the meta-analysis of Moore et al,[11] the risk of severe impairment among children born at 22 and 23 weeks' GA was somewhat lower (31% and 17%, respectively) than in our pooled estimates. The difference in risk estimates may at least partly be due to different tools for assessing outcomes.

Studies have suggested that increased survival does not necessarily lead to an increased rate of survivors with severe neurodevelopmental impairments,[4,76,82] but our available data did not allow for firm conclusions. Nevertheless,

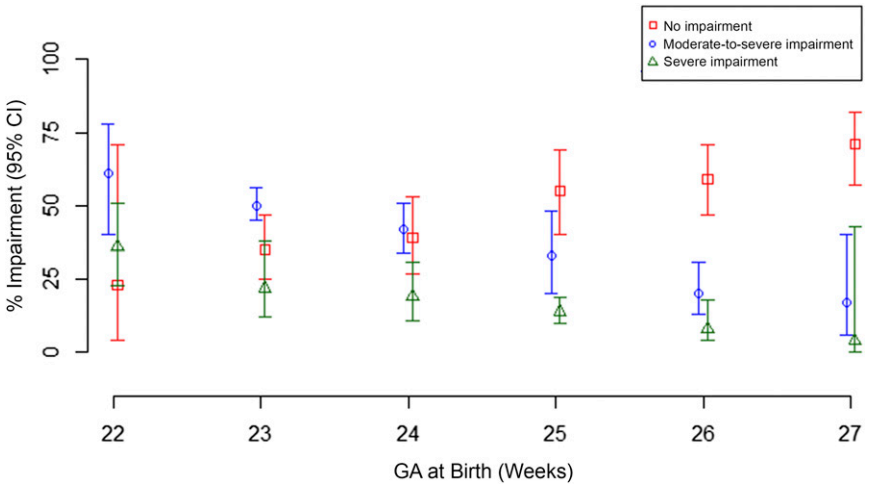

FIGURE 3
The overall risk of no, moderate-to-severe, and severe neurodevelopmental impairment according to GA of survivors at 18 to 36 months of age.

neurodevelopmental outcomes, as assessed with the BSID at 18 to 36 months of age in the present review, may significantly underestimate the risk of significant neurodevelopmental disabilities (NDDs) in later childhood. For example, in the Extremely Preterm Infants in Sweden Study, the rate of moderate and severe NDD increased from 26.6% at 2.5 years corrected age (assessed with the BSID III) to 33.5% at 6.5 years corrected age (assessed with the Wechsler Intelligence Scale for Children, Fourth Edition) for children born at <27 weeks' GA.[64] Furthermore, a substantial proportion of children born extremely premature with BSID scores within the normal range or with mild delays may have significant cognitive or mental difficulties in later childhood.[83] For instance, symptoms of mental health difficulties were 5 times more common at 11 years of age among children born extremely premature who had no significant impairments at 5 to 6 years of age than for a reference group in a Norwegian study.[84] In a study from the United Kingdom, 70% of all children born at <26 weeks' GA had special educational needs at the age of 11 years compared with 11% of their classmates.[85] The early prediction of later NDD difficulties tends to be most effective for severe disabilities, such as cerebral palsy, whereas more subtle developmental problems can be difficult to predict early in life.[86] Environmental, social, and biological interactions may have more influence on long-term outcomes in children with subtle developmental problems than for children with more severe impairments.[86] Therefore, longitudinal assessments may be more predictive than a single assessment because they include information on developmental progression, including peaks, plateaus, and regressions.[87]

On the basis of the unchanged prognosis estimates from the cumulative analyses, the chance of increasing survival rates among infants born at the limit of viability may be small unless major therapeutic advances are introduced, and attitudes toward providing life support are changing. Therapeutic means are constantly being refined, but the lack of improvement in outcomes during the period of this review suggests that improvements have not been sufficient to substantially alter overall prognosis and thereby attitudes toward providing life support at the limit of viability. Indeed, a recent comparison of national Norwegian cohorts of extremely premature infants born in 1999–2000 and 2013–2014 did not reveal differences in survival or early morbidity.[66] We are not aware of upcoming new technologies that may substantially alter prognosis and thereby attitudes to providing life support. The relatively high and persistent rates of significant neurodevelopmental impairment and uncertainties related to long-term functional prognosis may continue to deter professionals as well as parents from pushing the limits of life-sustaining interventions.

Our analyses and certainty in the evidence were influenced by large interstudy heterogeneity, which is probably related to varying factors, including the methods used to predict the date of expected term birth and the poor description of variation in treatment strategies in many of the included studies. We tried to reduce the study variability by only including studies from high-income countries. However, there are different attitudes toward providing life-saving treatment to the most immature infants across the different settings. Moreover, differences in socioeconomic conditions, general health, and lifestyles may affect survival and morbidity. These factors were also poorly described in the studies.

CONCLUSIONS

The prognosis for survival and survival without impairment, as assessed with the BSID, were markedly poorer for infants born at <25 weeks' GA than those born at ≥25 weeks' GA. This threshold difference was probably related to variations in attitudes toward providing life support to the most immature infants because the variation between cohorts was particularly large at <25 weeks' GA.

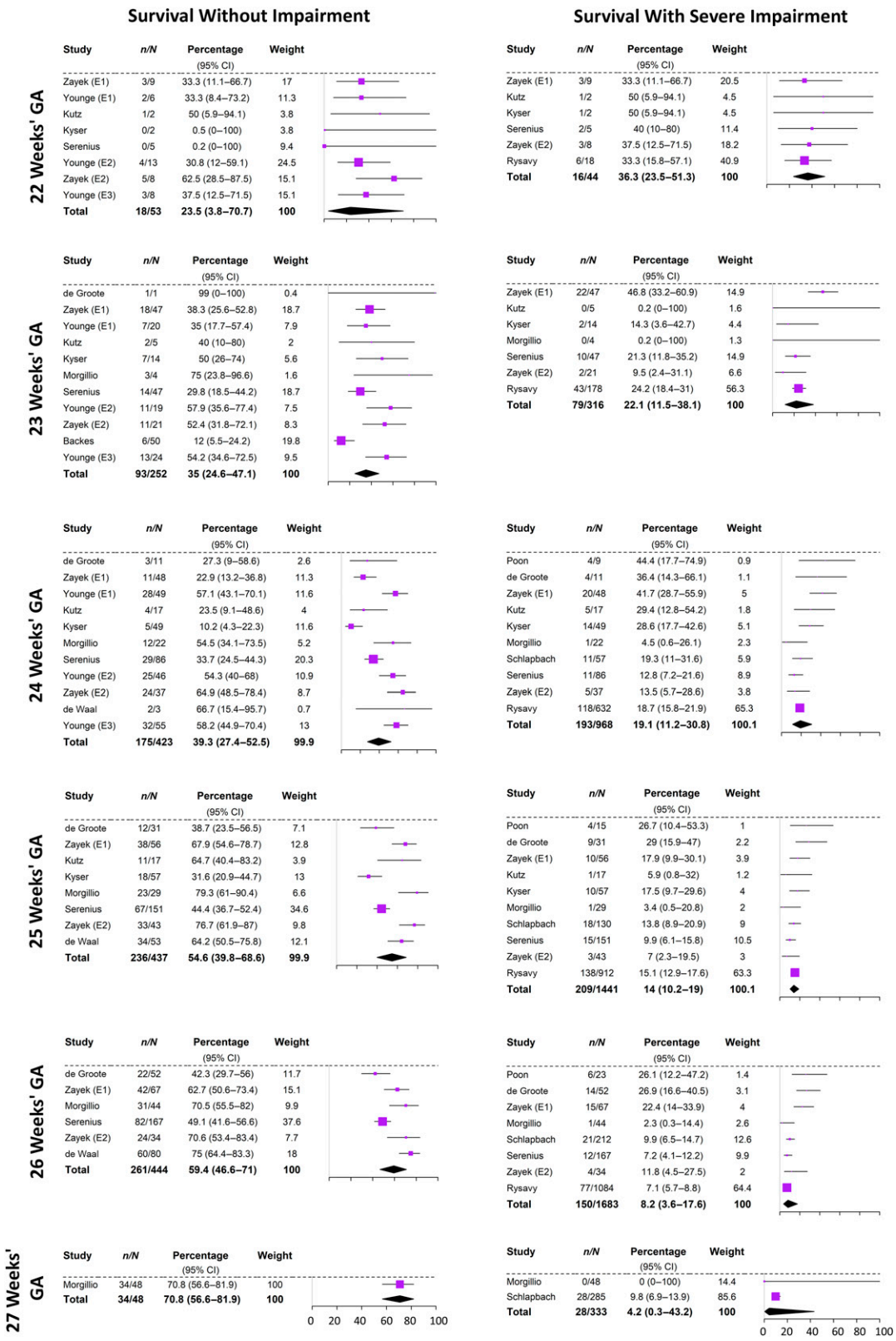

FIGURE 4

Meta-analyses on the prognosis of no impairment and severe impairment for infants born at 22 to 27 weeks' GA.

TABLE 2 Chance of Survival Without Any Impairment for Live-Born Infants

GA, wk	Survival Without Any Impairment, % (95% CI)
22	1.2 (0.4–3.7)
23	4.5 (2.1–9.6)
24	9.3 (3.5–22.7)
25	40.6 (31.6–50.3)
26	52.6 (35.7–68.9)
27	64.2 (49.8–76.9)[a]

[a] Estimate available from 1 study.

Because of the small number and size of the studies, the risk-of-impairment estimates for the lowest GAs were uncertain.

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ABBREVIATIONS

BSID: Bayley Scales of Infant Development
BW: birth weight
CI: confidence interval
GA: gestational age
NDD: neurodevelopmental disability

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