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Meta-Analysis

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Outcomes of Neonates with a 10-min Apgar Score of Zero: A Systematic Review and Meta-Analysis

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Keywords
Neonate · Apgar · Perinatal asphyxia · Hypoxic-ischemic encephalopathy · Therapeutic hypothermia

Abstract
Introduction: The Apgar score is a standardized method of assessing the primary adaptation and clinical status of a neonate after birth. Our objective was to systematically review and meta-analyze the survival and the survival without moderate-to-severe neurodevelopmental impairment (NDI) of neonates with a 10-min Apgar score of zero. ***Methods:*** Six electronic databases were searched for reports published until November 2021 of neonates with a 10-min Apgar score of zero. Risk of bias was assessed using the Newcastle-Ottawa scale for cohort studies and the Joanna Briggs Institute Critical Appraisal Checklist for case series/reports. Meta-analyses of the proportion of outcomes were conducted using a random-effects model for studies published after year 2000 and reporting >5 neonates. Meta-regression using the median year of the study period and subgroup analyses by treatment with therapeutic hypothermia and by gestational age were conducted. ***Results:*** Twenty-eight studies of 820 neonates with moderate risk of bias were included. Survival was 40% (95% confidence interval 30–50%, 16 studies, 646 neonates, $I^2 = 83\%$), and it increased by 2.3% per year (95% CI 1.3–3.2%, $p < 0.001$). Survival without moderate-to-severe NDI was 19% (95% confidence interval 11–27%, 13 studies, 211 neonates, $I^2 = 62\%$). Survival was higher for neonates who received therapeutic hypothermia and for those with a gestational age ≥32 weeks compared to <32 weeks. ***Conclusion:*** Approximately 2 in 5 neonates with a 10-min Apgar score of zero survived, and 1 in 5 survive without moderate-to-severe NDI survived. Survival has improved over the years, especially since the era of therapeutic hypothermia.

Introduction

The Apgar score, a standardized assessment of the primary adaptation of neonates, is reported at 1 and 5 min after birth [1]. If it is less than 7 at 5 min, the Neonatal

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Resuscitation Program (NRP) guidelines state that the assessment should be repeated every 5 min [2]. According to the 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, a 10-min Apgar score of zero is a predictor of mortality and morbidity in late preterm and term infants and suggest that if the heart rate remains undetectable at 10 min of age, it may be reasonable to stop active resuscitation; nevertheless, this decision should be individualized. Considerations should be given to factors such as the optimization of resuscitation, specific circumstances before delivery, and the family's wishes [3–8]. These recommendations were based on non-recent studies with small sample sizes [3–8] that did not account for improvements in neonatal care, such as the resuscitation of extremely preterm neonates or the use of hypothermia treatment for near-term and term neonates [9–11].

Some studies have raised controversies concerning the discontinuation of neonates' resuscitation at 10 min since an increasing number of neonates with a 10-min Apgar score of zero (especially term neonates) were surviving without major impairments [12–15]. Some of these controversies include lack of data about the duration of asystole before delivery, the unknown etiology of the cardiac arrest, the unreliability of assessing cardiac activity during resuscitation, the quality of resuscitation, the impact of gestational age, and the potential benefit of therapeutic hypothermia (TH) [15–17]. This debate is reflected in the 8th edition Textbook of Neonatal Resuscitation published in 2020 by the American Academy of Pediatrics and American Heart Association. It recommends individualizing management but suggests that a reasonable timeframe for considering cessation of resuscitation efforts may be extended to 20 min after birth [18]. Evidence synthesis was the backbone of this recommendation change that was supported by Foglia et al.'s [19] review of the literature that indicated a high risk of bias and inconsistency in results. Their conclusion was that survival is possible without neurodevelopmental disability, even when the 10-min Apgar score is zero. However, their study did not fully explore the inconsistencies in the studies to identify reasons for the differences in the results between the studies and meta-analyses. The objective of our study was to perform a systematic review and meta-analysis of the published literature that reported the outcomes of neonates with a 10-min Apgar score of zero and to investigate the reasons for heterogeneity by conducting subgroup analyses and a meta-regression.

Methods

This study uses the PRISMA reporting guidelines [20] (online suppl. Material 1; see www.karger.com/doi/10.1159/000525926 for all online suppl. material) and was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines [21].

Data Sources and Searches

Expert librarians developed and executed search strategies for the following bibliographic databases up to November 2021: the Cochrane Central Register of Controlled Trials (2020 Issue 6), the Cochrane Database of Systematic Reviews (2020 issue 6), Medline, PubMed, Embase, and CINAHL. We used the usual combination of MeSH terms and text words. The search strategy is described in online supplementary Material 2. We reviewed the reference lists of the identified articles, and we did not restrict the language of publication. We contacted the authors of the studies when information was missing or incomplete.

Inclusion Criteria

We included cohort studies, case-control studies, case series, and case reports; and we excluded reviews, editorials, and letters to the editors. We included studies of term and preterm neonates who presented with a 10-min Apgar of zero despite active resuscitation at birth using accepted local guidelines. Our primary outcome of interest was survival. Secondary outcomes were survival without moderate-to-severe neurodevelopmental impairment (NDI) (defined as reported in included studies which mostly included moderate to severe cerebral palsy, moderate to severe cognitive delay, and moderate to severe hearing or vision impairment) and brain injury (either parenchymal injury or grade 3 or 4 intraventricular hemorrhage) diagnosed with brain imaging (ultrasonography or MRI). The studies that we included must have reported on at least one of these outcomes of interest.

Selection of Studies

Five authors (B.K., K.C.K., M.D., Y.J.Z., and W.A.) independently assessed the titles and abstracts of the articles identified by the literature searches to determine their eligibility for inclusion in the present study. At least four authors reviewed each study. Any disagreements regarding the eligibility of the studies were resolved by discussion, and if necessary, by two other authors (P.W. and P.S.S.).

Data Extraction

Data from the included studies were independently extracted by five authors (B.K., K.C.K., M.D., Y.J.Z., and W.A.) using a specific collection form. Data were compared, and discrepancies were resolved by consensus or consultation with two other authors (P.W. and P.S.S.). The data extracted included study design, study setting, study location, time and duration of study, number of participants, sex, gestational age, 10-min Apgar scores, TH, and outcomes.

Risk of Bias Assessment

We evaluated all studies included in the present study for risk of bias using either the Newcastle-Ottawa scale for cohort studies or the Joanna Briggs Institute (JBI) checklist for case series [22, 23]. The Newcastle-Ottawa scale consists of eight stems for assessing

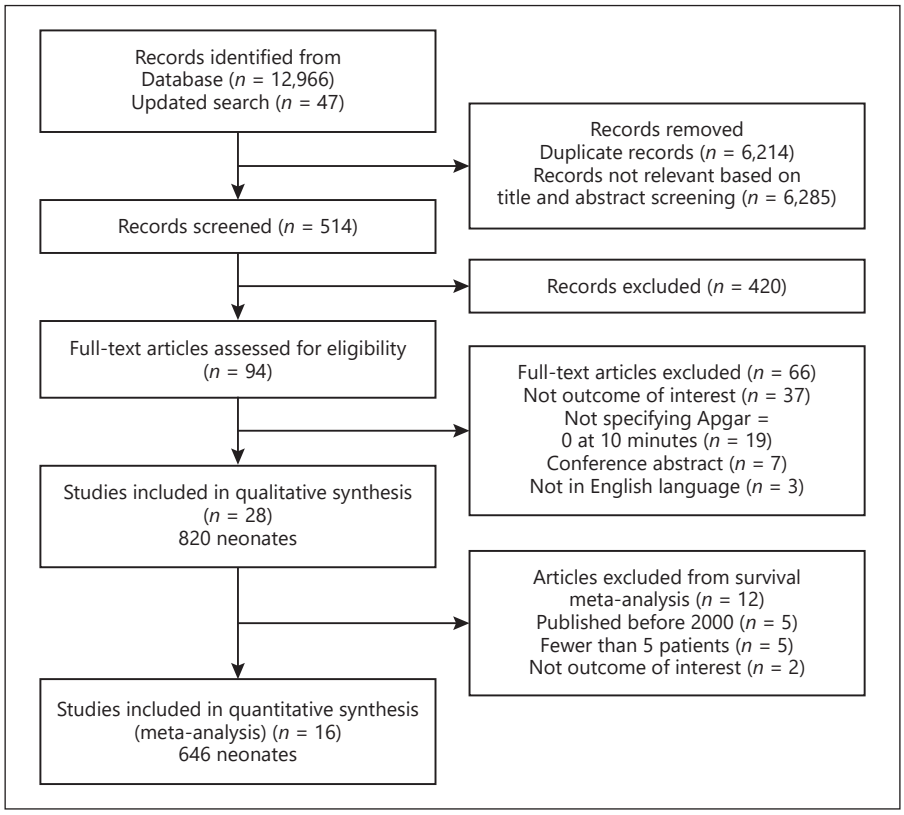


Fig. 1. Flow diagram of study inclusion.

the selection of the study population, comparability, and evaluation of outcome. The scores vary between 0 and 9 [22]. Two of the three authors (B.K., K.C.K., M.D.) independently assessed the risk of bias of the included studies and classified studies as low-risk (7–9), moderate risk (4–6), or high-risk (0–4) of bias. PSS was consulted when the two first reviewers did not agree.

Statistical Analysis

We reported data for outcomes as rates/proportions. Using a generic inverse variance technique, we decided to a priori meta-analyze data that were reported as incidence rates when these rates were reported in two or more studies. Concerning our meta-analysis, we included only the studies with >5 neonates published after 2000 to remain contemporary with the advances in the management and support of such neonates. We calculated pooled proportions and a 95% confidence interval (CI), when appropriate, using the DerSimonian Laird random-effects approach. We used the Freeman Tukey's double Arscine method to summarize proportions in our meta-analyses. If data were available, we carried out pre-planned subgroup analyses for (a) receipt of TH or not and (b) gestational age subgroups (≥36 weeks, 32–35 weeks, and <32 weeks GA). Based on a priori knowledge of changes in outcomes over the years, we also planned a meta-regression using the median year of the study period as a covariate. We calculated the between studies heterogeneity using I^2 values [24]. A p value of <0.05 was considered for statistical significance. We used Open Meta Analyst version 5.12.14 (available at www.cebm.brown.edu/openmeta) for the analyses.

Results

Detailed search results are reported in Figure 1. We included twenty-eight studies reporting a total of 820 neonates with a 10-min Apgar score of zero in our systematic review. We excluded 12 studies with a total of 174 neonates from the meta-analysis; 5 studies were published prior to 2000, and 5 studies published after 2000 had fewer than 5 cases; we did not include Laptook et al.'s [6] study since Natarajan et al.'s [14] study reported the neurodevelopmental outcome from the same cohort, and we did not include Persson et al.'s [25] study in the meta-analysis as they reported cerebral palsy in survivors without severity. Included studies were from nine countries (Australia, Canada, Israel, Japan, New Zealand, The Netherlands, Sweden, the UK, and the USA). Nine were cohort studies with a comparison group, 16 were case series, and 3 were case reports.

The characteristics of the included studies are reported in Table 1. According to the Newcastle-Ottawa Scale, the cohort studies were at moderate risk of bias. According to the JBI scale, 3 out of 21 case series/reports received the answer "yes" for 8 out of 10 questions; however, this in-

Table 1. Characteristics of included studies and risk of bias

Author, publication year, study design	Country, single/ multicenter/ timeframe/median study year*	Infant characteristics of neonates with 10-min Apgar score = 0 number of infants (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g (BW) sex % (male/total) follow-up timeframe TH (number/total) infants lost to follow-up	Comparative group characteristics number of infants (Apgar score at 10 min) (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g BW sex % (male/total) (sex) follow-up timeframe TH (number/total)	Risk of bias
Cnattingius et al., 2020, retrospective cohort [26]	Sweden, multicenter, 1992–2016, 2004	N: 137 GA: NA (22^0–36^6) BW: NA Sex: NA FU: 27 days of life TH: Not available	N: 302 (Apgar 1 at 10 min) GA: NA (22^0–36^6) BW: NA Sex: NA FU: 27 days of life TH: Not available	NOS 7 stars
Shibasaki et al., 2020, case series [27]	Japan, multicenter, 2010–2016, 2013	N: 28 GA: 38.6±1.8 (35–42) BW: 2,994±627 (2,091–5,274) Sex: NA FU: 18–22 months TH: Yes 28/28	No comparative group	JBI 6 YES
Zhang et al., 2019, retrospective cohort [28]	USA, multicenter, 2010–2017, 2013	N: 5 GA: 28.4±4.5 (23–34) BW: 1,399±793 (605–2,514) Sex: 40% FU: 15–24 months TH: No	N: 7 (Apgar 1 at 10 min) GA: 32.3±6.3 (24–42) BW: 2,064±1,302 (660–3,880) Sex: 42% FU: 15–24 months TH: 2/7	NOS 4 stars
Zhong et al., 2019, retrospective cohort [15]	Canada, multicenter, 2010–2016, 2014	N: 177 GA: no range, grouped into <32, 32–35+6, and ≥36 BW: NA Sex: 52% FU: NICU discharge TH: 101/177	N: 176 (Apgar 1–2 at 10 min) GA: NA BW: NA Sex: 52% FU: NICU discharge TH: 81/176	NOS 6 stars
Ayrapetyan et al., 2019, retrospective cohort [29]	USA, single center, 2006–2018, 2011	N: 17 GA: 38±2 (≥35) BW: 3,200±700 Sex: 47% FU: 4 months–5 years TH: 17/17	N: 109 (Apgar median: 3, range: 2–4 at 10 min) GA: 39±1.8 BW: 3,240±650 Sex: 44% FU: 4 months–5 years TH: 109/109	NOS 4 stars

Table 1 (continued)

Author, publication year, study design	Country, single/ multicenter/ timeframe/median study year*	Infant characteristics of neonates with 10-min Apgar score = 0	Comparative group characteristics	Risk of bias
		number of infants (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g (BW) sex % (male/total) follow-up timeframe TH (number/total) infants lost to follow-up	number of infants (Apgar score at 10 min) (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g BW sex % (male/total) (sex) follow-up timeframe TH (number/total)	
Billimoria et al., 2019, retrospective cohort [13]	USA, multicenter, 2005–2014, 2010	N: 109 GA: NA (28-40) BW: NA (1,590–3,506) Sex: 37% FU: 1 year of age TH: Not available	N: 90 (Apgar ≥1 at 10 min) GA: NA (29–39) BW: NA (1,361–3,576) Sex: 39% FU: 1 year of age TH: Not available	NOS 5 stars
Persson et al., 2018, retrospective cohort [25]	Sweden, multicenter, 1999–2012	N: 89 GA: NA (≥37) BW: NA Sex: NA FU: 16 years of age TH: No	10-min Apgar score of range 0–2: N = 34/267with CP N = 2/276 with epilepsy GA: NA (≥37) BW: NA Sex: NA FU: 16 years of age TH: Not available	NOS 5 stars
Sproat et al., 2017, case series [30]	UK, single center, 2009–2013, 2011	N: 17 GA: NA (23-41) BW: 2,650 (SD: NA) Sex: 45% FU: 2 years of age TH: 10/22	No comparative group	JBI 6 YES
Nanavati et al., 2015, case report [31]	USA, single center, 2009–2013	N: 1 GA = 38 BW= 3,000 Sex: The patient was female FU: 48 months TH:1/1	No comparative group	JBI 6 YES
Tokuhisa et al., 2015, case report [32]	Japan, single center, 2000–2008	N: 1 GA = 37+6 BW = 2,304 Sex: NA FU: 18 months TH: 1/1	No comparative group	JBI 7 YES

Table 1 (continued)

Author, publication year, study design	Country, single/ multicenter/ timeframe/median study year*	Infant characteristics of neonates with 10-min Apgar score = 0 number of infants (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g (BW) sex % (male/total) follow-up timeframe TH (number/total) infants lost to follow-up	Comparative group characteristics number of infants (Apgar score at 10 min) (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g BW sex % (male/total) (sex) follow-up timeframe TH (number/total)	Risk of bias
Shah et al., 2015, case series [12]	Australia, multicenter, 2007–2013, 2010	N: 13 GA: 38.4±2.1 (≥35) BW: 3,237±446.6 Sex: NA FU:1–2 years TH: 11/13	No comparative group	JBI 8 YES
Kasdorf et al., 2015, case series [5]	USA, single center, 2007–2012, 2010	N: 9 GA: 39±0.9 (≥35) BW: 3,582±650 Sex: 33% FU: 18–24 months TH: 9/9	No comparative group	JBI 6 YES
Natarajan et al., 2013, retrospective cohort [14]	USA, multicenter, 2000–2003, 2002	N: 24 GA: NA (≥36) BW: NA (≥1,800) Sex: NA FU: 6–7 years TH: 13/24	N: 11 (Apgar 1 at 10 min) GA: NA (≥36) BW: NA (≥1,800) Sex: NA FU 6–7 years TH: 3/10	NOS 7 stars
Nelson et al., 2011, cohort [33]	USA, 2002–2007, 2004	N: 7 GA: 35.1 (5.7) (>24) BW: 2,394.3 (1,343.1) Sex: 55% FU: NICU discharge TH: 0/7	Neonates with 1-min Apgar score of 0 N: 7 GA: 36.3 (4.9) BW: 2,735.8 (1,079.7) FU: NICU discharge TH: 0	NOS 6 stars
Christensen, 2012, case report [34]	Utah, single center, USA	N:1 GA = 39.1 BW = 2,951 Sex = The patient was female FU: unknown TH:1/1	No comparative group	JBI 6 YES

Table 1 (continued)

Author, publication year, study design	Country, single/ multicenter/ timeframe/median study year*	Infant characteristics of neonates with 10-min Apgar score = 0 number of infants (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g (BW) sex % (male/total) follow-up timeframe TH (number/total) infants lost to follow-up	Comparative group characteristics number of infants (Apgar score at 10 min) (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g BW sex % (male/total) (sex) follow-up timeframe TH (number/total)	Risk of bias
Landau, 2011, case report [35]	Israel, single center, 2008–2009	N: 1 GA = 41 BW = 4,200 Sex = M FU: 7.5 months TH: 1/1	No comparative group	JBI 6 YES
Jacobs et al., 2011, cases from randomized cohort [36]	2001–2007, Australia, UK, New Zealand, Canada, USA, 2010	N:11 GA: ≥35 FU: 24 months BW: NA Sex: NA FU: 2 years TH: 5/11	No comparative group	JBI 8 YES
Sarkar et al., 2010, case series [8]	USA, single center, 2003–2009, 2006	N: 12 GA: NA (≥36) BW: NA Sex: NA FU: 18–24 months TH: 12/12	No comparative group	JBI 8 YES
Azzopardi et al., 2008, cases from randomized cohort [37]	2002–2006, multicenter, UK, 2004	N: 33 GA: ≥36 BW: NA Sex: NA FU: approximately 18 months TH: 16/33	No comparative group	JBI 7 YES
Harrington et al., 2007, case series [4]	1991–2004, UK, single center, 1998	N: 9 GA: 37±3.7 (≥24) BW: 2,685±828 Sex: NA FU: 2 years TH: No	No comparative group	JBI 6 YES

Table 1 (continued)

Author, publication year, study design	Country, single/ multicenter/ timeframe/median study year*	Infant characteristics of neonates with 10-min Apgar score = 0 number of infants (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g (BW) sex % (male/total) follow-up timeframe TH (number/total) infants lost to follow-up	Comparative group characteristics number of infants (Apgar score at 10 min) (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g BW sex % (male/total) (sex) follow-up timeframe TH (number/total)	Risk of bias
Patel et al., 2004, case series [7]	1992–2003, Australia, multicenter, 1998	N: 29 GA: NA (≥36) BW: NA Sex: NA FU: post-discharge, unspecified TH: No	No comparative group	JBI 3 YES
Haddad et al., 2000, retrospective cohort [38]	USA, single center, 1986–1999, 1992	N: 16 GA: NA (>22) BW: NA (>500) Sex: NA FU: 3 months–5 years TH: No	N: 16 (Apgar 1–3 at 10 min) GA: NA (>22) BW: NA (>500) Sex: NA TH: No	NOS 4 stars
Azzopardi et al., 2000, case series [39]	UK, 2 sites	N: 3 GA: ≥36 BW: NA Sex: NA FU: 3–18 months TH: 3/3	No comparative group	JBI 7 YES
Casalaz et al., 1998, case series [3]	1986–1994, UK	N: 4 GA: 39±2.5 (≥36) BW: 3,672.5±939 Sex: 50% FU: 20 months–8 years TH: 0/4	No comparative group	JBI 7 YES
Thornberg et al., 1995, case series [40]	1985–1991, Sweden	N: 5 GA: ≥37 BW: NA Sex: NA FU: 18 months TH: 0/5	No comparative group	JBI 5 YES

Table 1 (continued)

Author, publication year, study design	Country, single/ multicenter/ timeframe/median study year*	Infant characteristics of neonates with 10-min Apgar score = 0	Comparative group characteristics	Risk of bias
		number of infants (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g (BW) sex % (male/total) follow-up timeframe TH (number/total) infants lost to follow-up	number of infants (Apgar score at 10 min) (N) GA mean±SD (≥week) (GA) BW mean±SD (≥) in g BW sex % (male/total) (sex) follow-up timeframe TH (number/total)	
Socol et al., 1994, case report [41]	1984–1991, USA	N: 1 GA: ≥34 BW: NA Sex: NA FU: 1 year–7 years and 10 months TH: 0/1	No comparative group	JBI 5 YES
Jain et al., 1991, case series [42]	1982–1986, USA	N: 58 GA: NA BW: NA Sex: NA FU: 4–60 months corrected GA TH: 0/58	No comparative group	JBI 7 YES
Koppe et al., 1984, case series [43]	1965–1975, The Netherlands	N: 3 GA: ≥37 BW: 2,727.5±1,579 (≥2,500,g) Sex: 33.3% FU: none survived to follow-up TH: 0/3	No comparative group	JBI 5 YES

BW, birth weight; GA, gestational age; FU, follow-up; N/A, not available; NICU, neonatal intensive care unit; TH, therapeutic hypothermia. * Median study year reported for studies used in meta-regression.

Table 2. Raw outcomes data from individual studies

Study, year	Gestational age	Infants with 10-min Apgar = 0	Overall survival	Overall survival without moderate-to-severe NDI	TH				No TH			
					treated with TH	survival	survival without moderate-to-severe NDI	lost to follow-up	not treated with TH	survival	survival without moderate-to-severe NDI	lost to follow-up
Cnattingius et al., 2020 [26]	$22^{0/7}$–$36^{6/7}$	137	35	NA	0				137	35		
Shibasaki, 2020 [27]		28	19	3	28	19	3	0	0			
	$<32^{0/7}$	0	0	0	0	0	0		0			
	$32^{0/7}$–$35^{6/7}$	2	1	0	2	1	0		0			
	$\geq 36^{0/7}$	26	18	3	26	18	3		0			
Zhong et al., 2019 [15]		177	99	NA	101	65	27	5	76	33	9	15
	$<32^{0/7}$	31	11	5	0	0	0	0	31	11	5	1
	$32^{0/7}$–$35^{6/7}$	26	14	3	0	0	0	0	26	14	3	7
	$\geq 36^{0/7}$	120	73	28	101	65	27	5	19	8	1	7
Zhang et al., 2019 [28]		5	2	2	0				5	2	2	0
	$<32^{0/7}$	4	2	2	0				4	2	2	0
	$32^{0/7}$–$35^{6/7}$	1	0	0	0				1	0	0	0
	$\geq 36^{0/7}$	0	0	0	0				0			
Ayrapetyan, 2019 [29]	$\geq 36^{0/7}$	17	8	6	17	8	6	1	0			
Billimoria, 2019 [13]		109	50	NA	0				109	50		
	$<30^{0/7}$	29	1		0				29	1		
	$30^{0/7}$–$35^{6/7}$	16	6		0				16	6		
	$\geq 36^{0/7}$	64	43		0				64	43		
Persson et al., 2018* [25]	$\geq 37^{0/7}$	89		NA*	0							
Sproat et al., 2017** [30]		17	8	5	10	6	4	1	7	2	1	0
	$<32^{0/7}$	5	0	0	0				5	0	0	0
	$32^{0/7}$–$35^{6/7}$	2	2	1	0				2	2	1	0
	$\geq 36^{0/7}$	10	6	4	10	6	4	1	0	0	0	0
Nanavati et al., 2015 [31]	$\geq 36^{0/7}$	1	1	0	1	1	0	0				
Tokuhisa et al., 2015 [32]	$\geq 36^{0/7}$	1	0	0	1	0	0	0	0			
Shah et al., 2015 [12]		13	5	3	11	5	3	0	2	0	0	0
	$<32^{0/7}$	0	0	0	0				0			
	$32^{0/7}$–$35^{6/7}$	2	1	1	2	1	1	0	0			
	$\geq 36^{0/7}$	11	4	2	9	4	2	0	2	0	0	0
Kasdorf et al., 2015 [5]	$\geq 36^{0/7}$	9	8	5	9	8	5	0				
Natarajan, 2013 [14]	$\geq 36^{0/7}$	24	11	5	13	7	3	0	11	4	2	0
Nelson et al., 2011 [33]	>24	7		2	0				7		2	0

Table 2 (continued)

Study, year	Gestational age	Infants with 10-min Apgar = 0	Overall survival	Overall survival without moderate-to-severe NDI	TH				No TH			
					treated with TH	survival	survival without moderate-to-severe NDI	lost to follow-up	not treated with TH	survival	survival without moderate-to-severe NDI	lost to follow-up
Christensen et al., 2012 [34]	≥$36^{0/7}$	1	1		1	1			0			
Landau et al., 2011 [35]	≥$36^{0/7}$	1	1	1	1	1	1	0	0			
Jacobs et al., 2011 [36]	≥$35^{0/7}$	11		2	5		1	0	6		1	0
Sarkar et al., 2010 [8]	≥$36^{0/7}$	12	3	0	12	3	0	0	0			
Azzopardi et al., 2008 [37]	≥$36^{0/7}$	33		9	16		5	0	17		4	0
Harrington et al., 2007 [4]		9	2	1	0				9	2	1	0
	<$32^{0/7}$	1	1	1	0				1	1	1	0
	$32^{0/7}$–$35^{6/7}$	1	0	0	0				1	0	0	0
	≥$36^{0/7}$	7	1	0	0				7	1	0	0
Patel et al., 2004 [7]	≥$36^{0/7}$	29	9	1	0				29	9	1	0
Haddad et al., 2000 [38]	≥$30^{0/7}$	16	2	NA	0				16	2		0
Azzopardi et al., 2000 [39]	≥$36^{0/7}$	3	1	0	3	1	0	0	0			
Casalaz et al., 1998 [3]	≥$36^{0/7}$	4	1	0	0				4	1	0	0
Thornberg et al., 1995 [40]	≥$37^{0/7}$	5	0	0	0				5	0	0	0
Socol et al., 1994 [41]	≥$34^{0/7}$	1	1	1	0				1	1	1	0
Jain et al., 1991 [42]	–	58	1	0	0				58	1	0	0
Koppe et al., 1984 [43]	≥$37^{0/7}$	3	0	0	0				3	0	0	0

* Persson et al. [25] reported data on neurodevelopmental outcome among survivors, and they reported 83/86 survived without cerebral palsy. These data were not included in the meta-analyses since they did not meet our definition of moderate-to-severe NDI. ** Sproat et al. [30] data provided from supplemental information from authors.

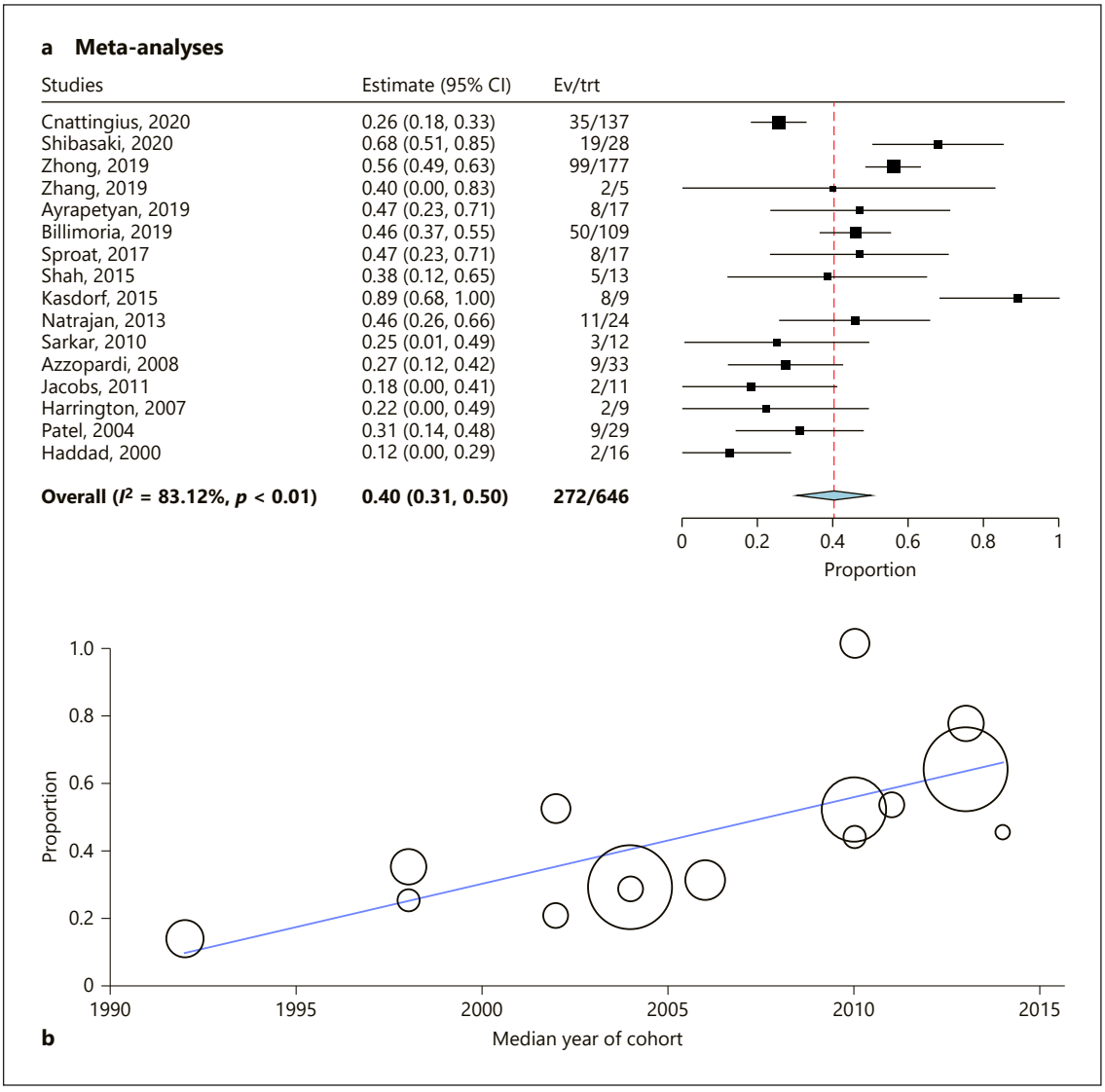
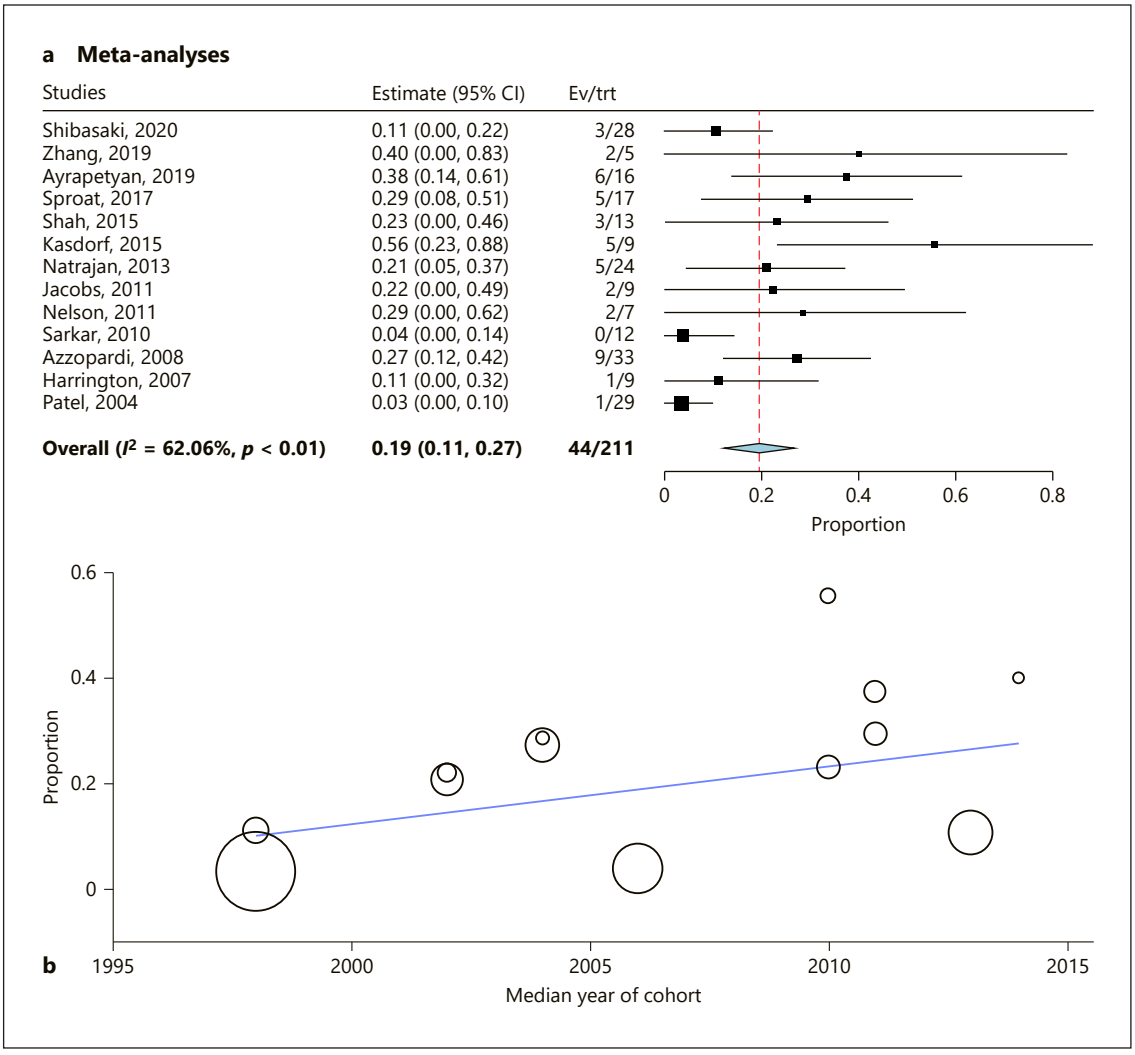


Fig. 2. Meta-analyses and meta-regression of the primary outcome of survival. **a** Forest plot for meta-analyses. **b** Meta-regression plot with median year of cohort as an independent variable.

formation should be received with caution since these questions do not fully explore the possibility of selection bias in case reports/case series (online suppl. Material 3). The raw numbers for the outcomes of each study are summarized in Table 2.

Meta-Analyses

- **Survival**: Our meta-analyses of 16 studies including 646 neonates (published in year 2000 and later) revealed that the pooled survival was 40% (95% CI 30–50%, I^2 = 83%, shown in Figure 2a). Our meta-regression revealed that survival improved 2.3% per year (95% CI 1.3–3.2%, p < 0.001; shown in Fig. 2b). Data on survival from the comparator groups (different groups included in different studies, with Apgar score ranging from 1 to 4 at 10 min) are reported in online suppl. Material 4. No meta-analysis was conducted due to different comparator groups. Nelson et al.'s [33] study reported on survival without NDI and therefore was excluded from survival analysis. Post hoc sensitivity analyses of including studies at low risk of selection bias revealed similar results (7 studies, 505 participants, pooled survival rate 38% [95% CI 26–50%], i^2 = 85%).



Color version available online

Fig. 3. Meta-analyses and meta-regression of the secondary outcome of survival without significant NDI. **a** Forest plot for meta-analyses. **b** Meta-regression plot with median year of cohort as an independent variable.

- **Brain injury on imaging**: Our meta-analysis of 5 studies of 94 neonates revealed that the pooled proportion of brain injury diagnosed via imaging was 53% (95% CI 40–65%; I^2 = 0%) (online suppl. Material 5).
- **Survival without moderate-to-severe NDI**: Our meta-analyses of 13 studies reporting on 211 neonates revealed that the pooled survival without moderate-to-severe NDI was 19% (95% CI 11–27%, I^2 = 62%, shown in Fig. 3a). Our meta-regression revealed that there was improvement in survival without moderate-to-severe NDI of 1.1% per year (95% CI 0–2%, p = 0.10; shown in Fig. 3b), but this rate was not statistically significant.

Subgroup Analyses

For the primary outcome of survival, we conducted two subgroup analyses.

1. **TH**: Nine studies reported the survival outcome of 204 neonates treated with TH, and the pooled analyses revealed a survival rate of 57% (95% CI 46–69%, I^2 = 41%; online suppl. Material 6a). Ten studies reported the survival outcome of 292 neonates who were not treated with TH, and the pooled analyses revealed a survival rate of 29% (95% CI 21–37%, I^2 = 36%; online suppl. Material 6b).
2. **Gestational age**: Four studies reported the survival outcome of 51 neonates of <32 weeks' gestation, and

the pooled analyses revealed a survival rate of 33% (95% CI 10–56%, I^2 = 56%; online suppl. Material 7a). Six studies reported the survival outcome of 34 neonates of 32–36 weeks' gestation, and the pooled analyses revealed a survival rate of 54% (95% CI 38–69%, I^2 = 0%; online suppl. Material 7b). Twelve studies reported the survival outcome of 332 neonates of >36 weeks' gestation, and the pooled analyses revealed a survival rate of 50% (95% CI 39–62%, I^2 = 61%; online suppl. Material 7c).

Discussion

In this comprehensive systematic review and meta-analyses of 28 studies with a moderate risk of bias mainly due to selection bias, approximately 2 in 5 neonates with a 10-min Apgar score of zero survived, and 1 in 5 survived without moderate-to-severe NDI. Moreover, over the past 20 years, survival has improved significantly, with a significant improvement of 2.3% each year compared to the previous year. Also, there is an indication that the provision of TH in recent years has been associated with higher survival and that the likelihood of survival improved with increasing gestational age. However, the number of neonates and the number of studies contributing to both subgroup analyses were lower.

Until 2021, the NRP suggested that if an infant had a 10-min Apgar score of zero, resuscitative measures should be stopped [18, 44, 45]. This recommendation assumed that if an infant remained asystolic or severely hypoxemic for 10 min or more, the insult would lead to severe brain damage resulting in infant death or survival with moderate-to-severe NDI. Foglia et al. [19] evaluated the association between the duration of resuscitation and rates of mortality and NDI. Based on this review by the International Liaison Committee on Resuscitation Neonatal Life Support Task Force, the 8th version of NRP removed the recommendation to discontinue cardiopulmonary resuscitation after 10 min, even if the Apgar score remained zero [18]. Their review included 16 studies of 579 neonates, and they reported a 41% (237/539) survival rate at the latest follow-up, and a survival rate without moderate-to-severe NDI of 11% (30/277). However, their reported outcomes consisted of only the addition of all cases and outcomes without any consideration for study size and its effect on estimates. Despite the homogeneity of the exposure ascertainment and the survival outcome in their included studies, questions remain about their selection of cases and cohort conception. Our review included 28 studies of 820 neonates, we meta-analyzed proportions and conducted a meta-regression. The meta-regression on the median year of the study period as a covariate was important since neonatology as a field has evolved over years, and a significant improvement has occurred in survival rates, as acknowledged in studies that have reported on recent years' data compared to data from the past, and on the availability of TH as a modality of treatment in recent years. The results of Foglia et al.'s [19] study and those of the present study should question the use of a rigid timeframe for discontinuing resuscitation, as well as provide insights into the possibility of survival without moderate-to-severe NDI for neonates.

The use of the Apgar score itself has many caveats. First, it has several subjective components, such as an infant's color or activity [46]. Second, since the Apgar score was developed for term infants without comorbidities, its applicability to various gestational ages and to infants with congenital malformations can be subjective [47]. However, in a large international cohort of neonates of 24–29 weeks' gestation, a 5-min Apgar score was associated with mortality in a graded manner [48]. Third, maternal factors such as medications and sedation also can have impact on a neonate's Apgar score [1]. Fourth, a concern exists with inter-rater variability in assigning an Apgar score. Nevertheless, inter-rater variability is less likely to play a role when the assigned score is zero at 10 min since this score reflects an absence of activity in all parameters including heart rate.

The concern that asystole in the first 10 min of life leads to tissue hypoxia is well described [49]. The acute phase of decreased cerebral perfusion and glucose delivery leads to anaerobic metabolism, cell necrosis, and apoptosis. The introduction of TH as a standard of care treatment for neonates with moderate to severe hypoxic-ischemic encephalopathy may have contributed to improvement in survival in recent years. With resuscitation and subsequent reperfusion, a latent phase precedes a secondary phase of injury. This latent phase is the window for TH. The prevention of secondary injury in some neonates by using TH may have translated into improved neurodevelopmental outcomes. A better identification of the candidates for TH, an earlier initiation of TH, and an improved standardized care during TH focusing on the restoration of homeostasis and neuroprevention [50–52] may help to explain the continued improvement of outcome over the years. Other reasons may include quality improvement initiatives, with the goal to improve the outcomes of neonates with hypoxic-ischemic encephalopathy [52–54]. Clinicians also may have become reluc-

tant to discontinue resuscitation efforts considering their knowledge of reports of survivors and survivors without moderate-to-severe NDI. The ability of neonates to survive without moderate-to-severe NDI also speaks to the plasticity of the developing brain [55].

Our meta-analysis demonstrates that survival is dependent on gestational age. Neonates born at <32 weeks' GA had significantly lower survival rates. This outcome could be explained because they are less reactive to resuscitative measures (i.e., inner fragility) but could also be the result of a provider's perception of the reduced resilience of such neonates. We could not differentiate between these possibilities with our dataset [15, 56, 57]. These results prompt the need for further research into establishing how resuscitation could be further improved for preterm neonates.

Clinically, these results encourage an ongoing questioning of the measures that neonatologists use and their reliability for prognostication. An Apgar score should not be a used in isolation to decide on the provision of clinical care [47]. Moving away from the time stamps dictated by Apgar scores also allows more time and room for the individualization of care around a family's priorities and values. This approach also can enable families to participate in decision-making and be present next to their child since if resuscitative measures are stopped so shortly after birth, parents often only barely meet their child, let alone participate meaningfully in any decision-making conversations.

The strengths of this present review include a comprehensive literature search, an inclusion of all types of studies, a clarification of information from authors, a summarization of the literature allowing for the effect size and sample size of each study considered in the analyses, and hypothesis generating subgroup analyses based on gestational age and TH. However, there are limitations. First, our included studies were clinically and methodologically heterogeneous. Variations exist in delivery room protocols, resulting from the multiple iterations of the NRP guidelines over the years. Second, the issues of adherence to protocols and uncertainty exist around what happened during the resuscitation. Third, variations exist concerning age at follow-up and how neurodevelopment was assessed and quantified in severity. Although the tests used were mostly standard, such as Bayley scores or Griffith assessments, not all our included studies reported all outcomes. We accepted definition used in each individual study with regards to moderate-severe NDI. Fourth, although we did not restrict the country of the study, our included studies were mainly from high-income countries. Therefore, the generalizability of these findings may be limited. Fifth, a major issue lies with selection bias. When single case reports or small case series are reported in this context, unless they are systematically collected from existing datasets, they are prone to "reporting bias." Thus, we only included larger case series in our meta-analyses rather than including case reports. However, our included studies still had a moderate to high risk of bias mainly due to selection bias. Sixth, survivor bias/reporting bias may play a role in the outcome ascertainment as some neonates may not have survived resuscitation and may not have been reported in analyses including neonatal admission. It is also likely that such bias will have higher influence at lower gestational age.

Conclusion

In conclusion, our comprehensive meta-analysis demonstrates that children with a 10-min Apgar score of zero, contrary to previous beliefs, has approximately a ~40% rate of survival and a 19% rate of survival without moderate-to-severe NDI. Moreover, the survival of children with 10-min Apgar scores of zero has been improving over the last 20 years. The provision of TH may have helped improve both the survival of neonates and the survival of neonates without moderate-to-severe NDI. However, most of our data came from small sample sized studies, and so a concerted effort to standardize the reporting on all such neonates from larger registries with detailed information on resuscitative measures will help to clarify the best resuscitation approaches for these neonates.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pia Wintermark and Prakesh S. Shah conceived and supervised the study. Bita Khorram, Keira C. Kilmartin, Maya Dahan, You Jia Zhong, and Wael Abdelmageed contributed substantially to the selection of studies, data extraction, and interpretation. Bita Khorram and Keira C. Kilmartin assessed the risk of bias for the included articles. Prakesh S. Shah conducted all the statistical analyses. Pia Wintermark, Prakesh S. Shah, Bita Khorram, Keira C. Kilmartin, Maya Dahan, You Jia Zhong, and Wael Abdelmageed approved the final manuscript and agreed to be accountable for the integrity of the work.

Data Availability Statement

All analyzed data are included in this review. Further inquiries can be directed to the corresponding author.

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