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Clinical paper

Neonates with a 10-min Apgar score of zero: Outcomes by gestational age

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Abstract

Background: The current resuscitation guidelines for neonates recommend considering stopping resuscitation efforts if the heart rate remains undetectable after 10 min of adequate resuscitation. However, this recommendation does not take into account the gestational age (GA) of the neonates. We determined the outcomes of neonates with a 10-min Apgar score of zero ($Apgar^{10} = 0$) with respect to their GA.

Methods: In a retrospective matched cohort study, we studied neonates admitted to the Canadian Neonatal Network NICUs between 2010 and 2016 with an $Apgar^{10} = 0$. The neonates were divided into 3 subgroups according to their GA: (1) ≥36 weeks', (2) $32^{0/7}$–$35^{6/7}$ weeks', and (3) <32 weeks'. Each neonate with $Apgar^{10} = 0$ was matched 1:1 with neonates of same GA and sex but $Apgar^{10} = 1$–2 and $Apgar^{10} = 3$–5. Survival and brain injury were compared between matched groups.

Results: 177 neonates had $Apgar^{10} = 0$. Survival to discharge was significantly different between GA groups [≥36 weeks' 61% vs. $32^{0/7}$–$35^{6/7}$ weeks' 58% vs. <32 weeks' 35%, $p = 0.04$]. Survival to discharge was similar to their matched cohort with $Apgar^{10} = 1$–2 for neonates born at ≥36 weeks' (61% vs. 66%) and between $32^{0/7}$ to $35^{6/7}$ weeks' (58% vs. 54%), but significantly different for neonates <32 weeks (35% vs. 61%, $p = 0.04$).

Conclusion: Neonates with $Apgar^{10} = 0$ had different outcomes depending on their GA. Less than half of neonates born at <32 weeks GA survived; however, a majority of neonates born at $32^{0/7}$–$35^{6/7}$ weeks' and ≥36 weeks' GA survived at similar rates than their matched neonates with $Apgar^{10} = 1$–2.

Keywords: Apgar score, Brain injury, Gestational age, Neonatal resuscitation, Therapeutic hypothermia

Introduction

Approximately 5% of neonates require some form of resuscitation at birth.[1] The neonate's primary adaptation at birth and response to resuscitative efforts are typically quantified with the Apgar score.[2] It is usually assessed at 1 and 5 min after birth; although subsequent scoring at 5-min intervals is suggested if the 5-min Apgar score is lower than 7.[3]

The International Liaison Committee on Resuscitation worksheet recommendations and the Neonatal Resuscitation Program guidelines currently recommend that it may be reasonable to consider stopping resuscitation efforts if the heart rate remains undetectable after 10 min

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of complete and adequate resuscitation efforts.[1] These guidelines are based on evidence that the 10-min Apgar score is a predictor of mortality and morbidity in late-preterm and term infants.[4–9] However, most of this evidence is based on non-recent studies with small sample sizes that did not take into account some of the improvements in the neonatal care provision, such as the resuscitation of extremely preterm neonates or the use of hypothermia treatment for near-term and term neonates.

Thus, the objective of this study was (1) to determine the outcomes of neonates with a 10-min Apgar score of zero ($Apgar^{10} = 0$) born between 2010 and 2016 and admitted to the tertiary-level NICUs of the Canadian Neonatal Network (CNN); and (2) to examine whether their outcomes vary between different gestational ages (GA) or Apgar score groups at birth.

Methods

Study design

We used a retrospective matched-cohort study design using data from the CNN database. The CNN maintains a national perinatal-neonatal database that collects data for all infants admitted to 31 tertiary-level NICUs in Canada. Data were abstracted from infant medical records at each site according to standardized definitions and electronically transmitted to the CNN coordinating center as previously described.[10,11] As shown previously, the CNN database is remarkably consistent and reliable.[12] Data collection at each site was approved by the respective institutional research ethics board or appropriate quality improvement committee. The retrospective evaluation of de-identified data for this study was approved by the local institutional research ethics board and CNN Executive Committee.

Study population

Neonates with an assigned $Apgar^{10} = 0$ and admitted to one of the CNN tertiary-level NICUs between January 1st, 2010 and December 31st, 2016 were included in this study. The neonates were divided into 3 subgroups according to their GA: (1) ≥36 weeks', (2) between $32^{0/7}$ and $35^{6/7}$ weeks', and (3) <32 weeks' GA.

Exposure

We obtained information on Apgar score from the CNN database. Each neonate with $Apgar^{10} = 0$ was randomly matched with 2 neonates of same GA (in weeks) and sex, but different 10-min Apgar score; for example, a male neonate born at 29 weeks' GA with $Apgar^{10} = 0$ was matched with two other males born at 29 weeks' GA, one with an $Apgar^{10} = 1–2$ and another with an $Apgar^{10} = 3–5$. Of note, in the CNN database, when the 10-min Apgar score was missing, it was assumed to be ≥5 in neonates who had a 5-min Apgar score that was ≥5. The 10-min Apgar score was marked as missing if both the 5-min and 10-min Apgar scores were missing. Apgar scores were assigned by the individuals involved in the resuscitation at each site. The method of heart rate detection used at each individual hospital during the initial resuscitation was not recorded. Similarly, time needed to achieve return of spontaneous circulation was not recorded in the database.

Variables

Study variables were defined according to the CNN Abstractors' Manual.[10] Birth variables included birth weight, GA, sex, and mode of delivery. GA was calculated based on the best available information: date of conception via in-vitro fertilization pregnancy, early ultrasound, date of last menstrual period, and/or neonatal assessment at birth in that hierarchical order. Information regarding the use of antenatal steroids and postnatal anti-convulsants was collected. As many neonates born at ≥36 weeks' GA with $Apgar^{10} = 0$ were likely to have components of birth asphyxia, the initial severity of encephalopathy and treatment with hypothermia were collected for these neonates. Criteria for hypothermia treatment were similar to those described in the trials (https://www.cps.ca/en/documents/position/hypothermia-for-newborns).

Outcomes

The primary outcome was defined as survival to discharge, and the secondary outcome was evidence of brain injury. Brain injury in neonates born at ≥36 weeks' GA was defined as injury to the basal ganglia, white matter, and/or grey matter on their brain magnetic resonance imaging. Brain injury in neonates born between $32^{0/7}$ and $35^{6/7}$ weeks' GA was considered if intraventricular hemorrhage (grade 2 or higher) and/or periventricular white matter injury were identified on their head ultrasound, or if injury to basal ganglia, white matter, and/or grey matter were identified on their brain magnetic resonance imaging. Brain injury in neonates born at <32 weeks' GA was defined as intraventricular hemorrhage and/or periventricular white matter injury on their head ultrasound or magnetic resonance imaging (if performed). Of note, repeated head ultrasounds are the standard of care in premature neonates in Canada to diagnose brain injury; obtaining a brain MRI at term-corrected age in these neonates is not current practice in all tertiary-level NICUs.

Data analysis

Descriptive statistical methods were used to summarize the study cohort. For primary analyses, general characteristics and survival to discharge among neonates with $Apgar^{10} = 0$ were compared between the different GA subgroups. For secondary analyses, outcomes including survival to discharge and brain injury were compared between the neonates with $Apgar^{10} = 0$ and their matched cohort with $Apgar^{10} = 1–2$ and $Apgar^{10} = 3–5$. Comparisons were done using the chi-square test or Fisher's exact test for categorical variables and student t-test or Mann–Whitney test for continuous variables. A p value of <0.05 was considered to be significant. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina, USA) software.

Results

Study cohort

Between 2010 and 2016, 102 674 neonates were admitted to the CNN tertiary-level NICUs (Fig. 1). 9618 infants were excluded for major congenital anomalies or missing 10-min Apgar scores. Among the remaining neonates, 177 had $Apgar^{10} = 0$, which represented an incidence rate of 0.19% (177/93 056; 95% CI 0.16–0.22). Most of the neonates with $Apgar^{10} = 0$ were born at ≥36 weeks' GA (68%, 120/177); however, 15% (26/177) were born between $32^{0/7}$ and $35^{6/7}$ weeks' GA and 17% (31/177) were born at <32 weeks' GA. The percentage of males was similar across all three GA categories. Neonates born between $32^{0/7}$ and $35^{6/7}$ weeks' GA and neonates born at ≥36 weeks' GA with $Apgar^{10} = 0$ were more often delivered by

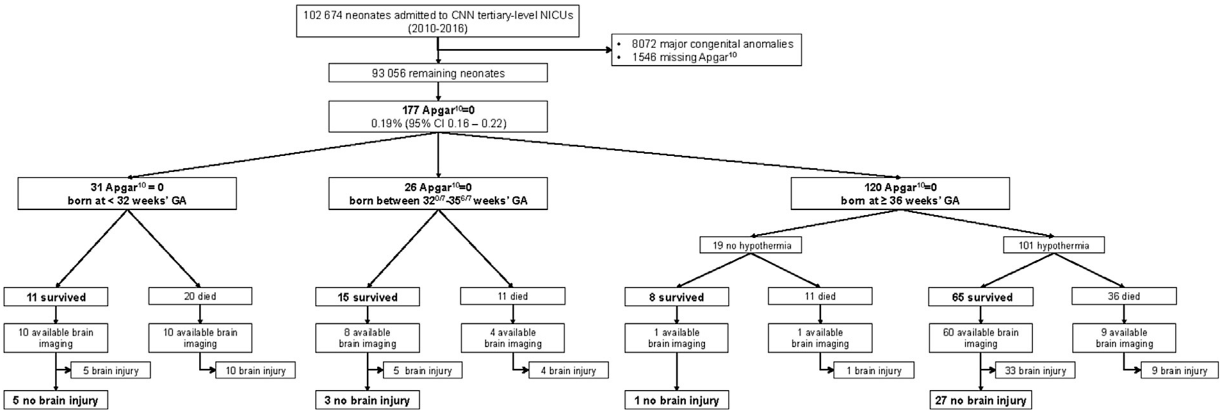

Fig. 1 – Flow chart of the neonates included in the study.
Abbreviations: Apgar^{10}0, Apgar score at 10 min equal to 0; GA, gestational age.

Table 1 – Characteristics and outcomes of neonates with Apgar^{10} = 0.

Characteristics and outcomes 2010–2016	<32 weeks' GA (N = 31)	$32^{0/7}$-$35^{6/7}$ weeks' GA (N = 26)	≥$36^{0/7}$ weeks' GA (N = 120)	*p* value
General characteristics				
GA (weeks), mean ± SD	26.0 ± 2.3	33.7 ± 1.2	39.0 ± 1.6	*<0.001*
Male, n (%)	18 (58)	12 (46)	62 (52)	*0.66*
Birth weight (grams), mean ± SD	934 ± 410	2270 ± 644	3413 ± 709	*<0.001*
Vaginal birth, n (%)	20 (65)	10 (38)	41 (34)	*0.009*
Inborn, n (%)	22 (71)	17 (65)	46 (38)	*0.001*
Outcomes				
Alive to discharge, n/N (%)	**11/31 (35)**	**15/26 (58)**	**73/120 (61)**	***0.04***
Brain imaging available, n/N (%)	10/11 (90)	8/15 (53)	61/73 (84)	*0.02*
No brain injury, n/N (%)	**5/10 (50)**	**3/8 (38)**	**28/61 (46)**	***0.86***

Abbreviations: Apgar^{10} = 0, Apgar score at 10 min equal to 0; GA, gestational age; N, total number in group; n, total number in category; SD, standard-deviation. The bold was to highlight better the lines with important results.

cesarean section, compared to neonates born at <32 weeks' GA, who were more often born by vaginal delivery ($p = 0.009$). Neonates born at ≥36 weeks' GA with Apgar^{10} = 0 were more often outborn and transferred to the tertiary-level NICUs after birth, compared to neonates born at <36 weeks' GA, who were more often inborn ($p = 0.001$) (Table 1).

Survival to discharge varied significantly across the GA groups (≥36 weeks' 61% (73/120) vs. $32^{0/7}$–$35^{6/7}$ weeks' 58% (15/26) vs. <32 weeks' 35% (11/31), $p = 0.04$) (Table 1). Neonates born at <32 weeks' GA had the lowest rates of survival to discharge, but more than half of the neonates born between $32^{0/7}$ and $35^{6/7}$ weeks' GA and neonates born at ≥36 weeks' GA with Apgar^{10} = 0 survived. Availability of brain imaging also varied significantly different across the GA groups ($p = 0.02$), with neonates born between $32^{0/7}$ to $35^{6/7}$ weeks' GA having the least availability of brain imaging. Among the neonates with available brain imaging, survival to discharge without brain injury was not different between the GA subgroups: i.e., 46% in those ≥36 weeks vs. 38% in those between $32^{0/7}$ to $35^{6/7}$ weeks vs. 50% in <32 weeks groups.

Neonates born at ≥36 weeks' GA

Sixty-one percent of these neonates with Apgar^{10} = 0 survived (Table 2). Sixty-four percent (65/101) neonates with Apgar^{10} = 0 survived when they were treated with hypothermia, while only 42% (8/19) survived when they did not receive hypothermia. When compared to their GA and sex-matched cohorts, more neonates with Apgar^{10} = 0 were treated with hypothermia, had severe encephalopathy, and received anti-convulsants than neonates with Apgar^{10} = 1–2 or Apgar^{10} = 3–5 ($p < 0.001$) (Table 2). Despite differences in hypothermia treatment rates and severity of encephalopathy, the survival rate of neonates in the Apgar^{10} = 0 group was similar to matched neonates with an Apgar^{10} = 1–2, but lower than matched neonates with an Apgar^{10} = 3–5 ($p < 0.001$) (Table 2). In those who survived to discharge, brain imaging was more often performed in the Apgar^{10} = 0 group ($p < 0.001$) (Table 2). Of neonates with Apgar^{10} = 0 who survived and had brain imaging, 46% did not demonstrate evidence of brain injury, which was not significantly lower than the Apgar^{10} = 1–2 and Apgar^{10} = 3–5 groups (Table 2).

Reasons for not performing MRI were not available through the database. Reasons for not cooling neonates born at ≥36 weeks' GA with Apgar^{10} = 0 included no encephalopathy (n = 6), mild encephalopathy (n = 5), severe encephalopathy and extreme condition (n = 8), and/or delayed transfer (n = 1), possibly explaining why MRIs were most often not obtained in these neonates who were not cooled. Among neonates born at ≥36 weeks' GA with Apgar^{10} = 0 who died, the majority (79%, 37/47) did not have a brain imaging. For those who died without available brain

Table 2 – Characteristics and outcomes of neonates born at ≥36 weeks' GA with Apgar scores ≤5 at 10 min.

Characteristics and outcomes 2010–2016	Apgar[10] = 0 (N = 120)	Apgar[10] = 1–2 (N = 119)[a]	Apgar[10] = 3–5 (N = 120)	*p* value
General characteristics				
GA (weeks), mean ± SD	39.0 ± 1.6	39.0 ± 1.6	39.0 ± 1.6	[b]
Male, n (%)	62 (52)	62 (52)	62 (52)	[b]
Birth weight (grams), mean ± SD	3413 ± 709	3337 ± 636	3352 ± 631	*0.64*
Vaginal birth, n (%)	41 (34)	56 (47)	69 (58)	*<0.001*
Inborn, n (%)	46 (38)	39 (33)	41 (34)	*0.64*
Postnatal characteristics				
Hypothermia treatment, n/N (%)	101/120 (84)	81/119 (68)	53/120 (44)	*<0.001*
Initial severity of encephalopathy				*<0.001*
Mild, n/N (%)	3/101 (3)	5/81 (6)	5/53 (9)	
Moderate, n/N (%)	23/101 (23)	37/81 (46)	33/53 (63)	
Severe, n/N (%)	67/101 (66)	35/81 (43)	9/53 (17)	
Not available, n/N (%)	8/101 (8)	4/81 (5)	6/53 (11)	
Anti-convulsants, n/N (%)	73/120 (61)	54/119 (45)	30/120 (25)	*<0.001*
Outcomes				
Alive to discharge, n/N (%)	**73/120 (61)**	**78/119 (66)**	**110/120 (92)**	***<0.001***
Brain imaging available[c], n/N (%)	61/73 (84)	50/78 (64)	41/110 (37)	*<0.001*
Alive without brain injury[d], n/N (%)	**28/61 (46)**	**32/50 (64)**	**26/41 (63)**	***0.09***

Abbreviations: Apgar[10] = 0, Apgar score at 10 min equal to 0; Apgar[10] = 1–2, Apgar score at 10 min equal to 1–2; Apgar[10] = 3–5, Apgar score at 10 min 3–5; GA, gestational age; N, total number in group; n, total number in category; SD, standard-deviation.
The bold was to highlight better the lines with important results.
[a] Only 119 neonates were included in the Apgar[10] = 1–2 matching subgroup, because a matching neonate with Apgar[10] = 1–2 could not be identified for one neonate with Apgar[10] = 0.
[b] Not compared as these variables were used as matching criteria.
[c] Brain imaging for that gestational age's subgroup included results from brain magnetic resonance imaging.
[d] Brain injury was defined at that gestational age as injury to the basal ganglia, white matter, and/or grey matter.

imaging (n = 37), age at the time of death was 2.3 ± 1.2 days (range: 1–6), explaining why neuroimaging was not yet obtained in these neonates. Reported causes of deaths included (mostly severe) encephalopathy, multiorgan failure, cardiac dysfunction and refractory hypotension, persistent pulmonary hypertension, pulmonary haemorrhage, renal failure, coagulopathy and/or sepsis. For those who died with available brain imaging (n = 10), age at the time of death was 7.4 ± 5.9 days (range: 1–23). Reported causes of deaths included (mostly severe) encephalopathy, multiorgan failure, brain injury and/or sepsis.

Neonates born between $32^{0/7}$ and $35^{6/7}$ weeks' GA

Fifty-eight percent of these neonates with a 10-min Apgar score of zero survived (Table 3). The survival rate of neonates in the Apgar[10] = 0 group was similar to matched neonates with an Apgar[10] = 1–2, but lower than matched neonates with an Apgar[10] = 3–5 (p = 0.01) (Table 3). At this GA, many neonates with an Apgar[10] = 0 did not have brain imaging, including 64% (7/11) of those who died and 47% (7/15) of those who survive. Among the neonates who survived and had a brain imaging, 38% of neonates with Apgar[10] = 0 did not demonstrate evidence of brain injury, which was not significantly lower than the Apgar[10] = 1–2 and Apgar[10] = 3–5 groups (Tables 2 and 3).

For those who died without available brain imaging (n = 7), age at the time of death was 2.1 ± 1.9 days (range: 1–6). Reported causes of deaths included encephalopathy, multiorgan failure, pulmonary hypoplasia, persistent pulmonary hypertension, pulmonary haemorrhage and/or severe hydrops. For those who died with available brain imaging (n = 4), age at the time of death was 5.3 ± 1.5 days (range: 4–7). Reported causes of deaths included encephalopathy, multiorgan failure, and/or brain injury.

Neonates born at <32 weeks' GA

Only 35% (11/31) of these neonates with Apgar[10] = 0 survived, which tended to be lower than their matched neonates with an Apgar[10] = 1–2 or Apgar[10] = 3–5 (p = 0.06) (Table 4). Compared to their GA and sex-matched cohorts, the neonates with Apgar[10] = 0 received antenatal steroids less often than neonates with Apgar[10] = 1–2 or Apgar 3–5

Table 3 – Characteristics and outcomes of neonates born between $32^{0/7}$ and $35^{6/7}$ weeks' GA with Apgar scores ≤5 at 10 min.

Characteristics and outcomes 2010–2016	Apgar[10] = 0 (N = 26)	Apgar[10] = 1–2 (N = 26)	Apgar[10] = 3–5 (N = 26)	*p* value
General characteristics				
GA (week), mean ± SD	33.7 ± 1.2	33.7 ± 1.2	33.7 ± 1.2	[a]
Male, n (%)	12 (46)	12 (46)	12 (46)	[a]
Birth weight (gram), mean ± SD	2270 ± 644	2238 ± 646	2389 ± 846	*0.73*
Vaginal birth, n (%)	10 (38)	8 (31)	3 (12)	*0.08*
Inborn, n (%)	17 (65)	17 (65)	21 (81)	*0.37*
Prenatal treatments				
Antenatal steroids, n (%)	7 (28)	8 (31)	10 (40)	*0.64*
Postnatal treatments				
Anti-convulsants, n (%)	11 (42)	5 (19)	4 (15)	*0.07*
Outcomes				
Alive to discharge, n/N (%)	**15/26 (58)**	**14/26 (54)**	**24/26 (92)**	***0.01***
Brain imaging available[b], n/N (%)	8/15 (53)	10/14 (71)	12/24 (50)	*0.46*
Alive without brain injury[c] n/N (%)	**3/8 (38)**	**7/10 (70)**	**9/12 (75)**	*0.25*

Abbreviations: Apgar[10] = 0, Apgar score at 10 min equal to 0; Apgar[10] = 1–2, Apgar score at 10 min equal to 1–2; Apgar[10] = 3–5, Apgar score at 10 min 3–5; GA, gestational age; N, total number in group; n, total number in category; SD, standard-deviation.
The bold was to highlight better the lines with important results.
[a] Not compared because used as matching criteria.
[b] Brain imaging for that gestational age's subgroup included head ultrasound and/or brain magnetic resonance imaging.
[c] Brain injury was considered at that gestational age if intraventricular hemorrhage and/or periventricular white matter injury were identified on their head ultrasound, or if injury to basal ganglia, white matter, and/or grey matter were identified on their brain magnetic resonance imaging.

Table 4 – Characteristics and outcomes of neonates born at <32 weeks of gestational age with Apgar scores ≤5 at 10 min.

Characteristics and outcomes	Apgar[10] = 0 (N = 31)	Apgar[10] = 1–2 (N = 31)	Apgar[10] = 3–5 (N = 31)	*p* value
General characteristics				
GA (week), mean ± SD	26.0 ± 2.3	26.0 ± 2.3	26.0 ± 2.3	[a]
Male, n (%)	18 (58)	18 (58)	18 (58)	[a]
Birth weight (gram), mean ± SD	934 ± 411	955 ± 404	879 ± 309	*0.71*
Vaginal birth, n (%)	20 (65)	14 (45)	17 (55)	*0.31*
Inborn, n (%)	22 (71)	25 (81)	24 (77)	*0.66*
Prenatal treatments				
Antenatal steroids, n (%)	11 (35)	16 (52)	17 (55)	*0.01*
Outcomes				
Alive to discharge, n/N (%)	**11/31 (35)**	**19/31 (61)**	**19/31 (61)**	***0.06***
Brain imaging available[b], n/N (%)	10/11 (90)	19/19 (100)	18/19 (95)	*0.45*
Alive without brain injury[c], n/N (%)	**5/10 (50)**	**9/19 (47)**	**12/18 (67)**	***0.46***

Abbreviations: Apgar[10] = 0, Apgar score at 10 min equal to 0; Apgar[10] = 1–2, Apgar score at 10 min equal to 1–2; Apgar[10] = 3–5, Apgar score at 10 min 3–5; GA, gestational age; N, total number in group; n, total number in category; SD, standard-deviation.
The bold was to highlight better the lines with important results.
[a] Not compared because used as matching criteria.
[b] Brain imaging for that gestational age's subgroup included head ultrasound and/or brain magnetic resonance imaging.
[c] Brain injury was defined as intraventricular hemorrhage and/or periventricular white matter injury.

($p = 0.01$) (Table 4). At this GA, brain imaging was not performed in many neonates with Apgar[10] = 0 who died (50%, 10/20). Among the neonates who survived and had a brain imaging, 50% of neonates with Apgar[10] = 0 did not demonstrate evidence of brain injury, which was a similar incidence of survival without brain injury as neonates in the Apgar[10] = 1–2 and Apgar[10] = 3–5 groups (Table 4).

For those who died without available brain imaging (n = 10), age at the time of death was 1.1 ± 0.3 days (range: 1–2). Reported causes of deaths included prematurity, encephalopathy, multiorgan failure, tension pneumothorax, pulmonary hypoplasia and/or coagulopathy. For those who died with available brain imaging (n = 10), age at the time of death was 34.7 ± 64.9 days (range: 1–185). Reported causes of deaths included prematurity, encephalopathy, brain injury, multiorgan failure, refractory hypotension, respiratory failure, pulmonary hypertension, pulmonary haemorrhage and/or sepsis.

Discussion

Making the decision to stop resuscitating a neonate after 10 min of complete and adequate resuscitation efforts after birth remains a clinical and ethical challenge for health care providers. This decision is complicated by the unpredictable potential outcomes of death or survival with long-term disabilities. Further complicating decision-making also often includes the inability to adequately inform and counsel parents during the acute event (e.g., maternal general anesthesia). Our study in a large cohort of neonates in multiple sites over several recent years adds the important observation that short-term outcomes of neonates admitted with an $Apgar^{10} = 0$ may not be universally poor and may vary based on their GA.

In our study, 61% (73/120) born at ≥36 weeks' GA with an $Apgar^{10} = 0$ and 58% (15/26) of neonates born between $32^{0/7}$ to $35^{6/7}$ weeks' GA were alive at discharge from the hospital; 46% (28/61) of neonates born at ≥36 weeks' GA were alive without evidence of brain injury. Similar survival rates were recently highlighted in term neonates by other authors.[13–17] Laptook et al.[14] reported that 52% (13/25) neonates born at ≥36 weeks' GA with $Apgar^{10} = 0$ survived, and 46% (6/13) of them had minor or no disability at 18 to 22 months of age. Natarajan et al.[15] described 24 neonates of ≥36 weeks' gestation with $Apgar^{10} = 0$ and reported a survival rate of 46% (11/24) in those neonates, with 21% (5/24) of them surviving with no or mild disability at 6–7 years. Kasdorf et al.[13] concluded that 89% (8/9) of those neonates of ≥36 weeks gestation with $Apgar^{10} = 0$ survived, with 63% (5/8) surviving with normal outcome. Shah et al.[16] reported that only 38% (5/13) of neonates born at ≥35 weeks' GA with $Apgar^{10} = 0$ survived to discharge, but 60% (3/5) of survivors had normal neurodevelopment at 2 years of age. Sproat et al.[17] reported that all the neonates born at >37 weeks' GA were treated with hypothermia and 67% (6/9) of them survived; in addition, 67% (2/3) of the neonates born between 32 and 37 weeks' GA survived. Finally, Shibasaki et al.[18] reported that 69% (18/26) of their neonates ≥36 weeks gestation with $Apgar^{10} = 0$ and treated with hypothermia survived, with 17% (3/18) has a favorable outcome. Our data, in addition of these more recent data, suggest that an $Apgar^{10} = 0$ does not provide an acceptable basis for judging futility and considering stopping resuscitation. These results are in contrast with older studies (respectively, in 4, 9 and 12 newborns),[4,5,8] showing the outcomes of neonates with a $Apgar^{10} = 0$ as being uniformly poor, with high mortality and/or high incidence of severe disabilities among survivors, explaining why the current guidelines for resuscitation suggest to stop any measures by 10 min after birth.[6]

The major therapeutic advance that could explain the improved survival rates for neonates born at ≥36 weeks' GA with an $Apgar^{10} = 0$ is the widespread use of therapeutic cooling to treat neonatal encephalopathy in near-term and term neonates. Therapeutic hypothermia has been demonstrated to reduce the rates of mortality and moderate/severe neurodevelopmental disability at 18 months of age[19] and at 6–7 years of age.[15] Therapeutic hypothermia became standard of care in Canada around 2010, probably explaining some of the differences in survival rate for this GA subgroup between our cohort (61%) and a previous 2003–2009 cohort from the same database, where survival in this GA subgroup was only 48%. Survival to discharge also varied significantly across the GA groups in that earlier cohort: ≥36 weeks' 48% (35/73) vs. $32^{0/7}$–$35^{6/7}$ weeks' 76% (13/17) vs. <32 weeks' 34% (16/47) ($p = 0.01$). These results may also reflect the fact that health care providers, who can offer hypothermia treatment to these neonates, may more frequently continue to resuscitate them beyond 10 min of life. Starting hypothermia in near-term or term neonates with $Apgar^{10} = 0$ may provide them time to recover, and it would not preclude the option to withdraw care later if the neonates' prognosis is deemed poor.[20]

In our study, outcomes of neonates with $Apgar^{10} = 0$ varied according to their GA. Outcomes remained poor in the neonates born at <32 weeks' GA; only 35% (11/31) of these neonates with $Apgar^{10} = 0$ survived to discharge. Similarly, Zhang et al.[21] reported that 50% (2/4) of their neonates born at <32 weeks' GA with $Apgar^{10} = 0$ survived to discharge, and 50% (1/2) of them presented without delays at 15 months. Sproat et al.[17] reported that none of the 7 neonates born at <32 weeks' GA in their study survived. These results correlated with the suggestion by Haddad et al.[22] (16 neonates) and Jain et al.[6] (58 neonates) that birth weight and GA influence survival of neonates with an $Apgar^{10} = 0$, with worst outcomes in the neonates born earlier and at lower birth weights.

Similar to what was described by Laptook et al.[14] (25 neonates), we found the outcomes of neonates born between $32^{0/7}$ and $35^{6/7}$ weeks' GA or born at ≥36 weeks' GA with $Apgar^{10} = 0$ were similar to the outcomes of their matched neonates with $Apgar^{10} = 1$–2. This is of importance, considering that all health care providers will pursue initial care in neonates who have an heart rate at 10 min ($Apgar^{10} \geq 1$–2), but some will stop at the 10-min mark if no heart rate is detected ($Apgar^{10} = 0$) on the basis of futility as per the current resuscitation guidelines. Our results again suggest that an $Apgar^{10} = 0$ may not provide an acceptable justification for considering stopping resuscitation at 10 min. However, neonates born at <32 weeks' GA with $Apgar^{10} = 0$ had significantly lower survival rates than their matched neonates with an $Apgar^{10} = 1$–2. The lower rates of survival in these very premature neonates, despite of their advantage of being more frequently born in a tertiary center than the neonates born at ≥36 weeks' GA with $Apgar^{10} = 0$, may be because they are less reactive to resuscitative measures (i.e., inner fragility), but could also result from medical bias (i.e., health care provider may be less aggressive with resuscitative measures in younger neonates than older neonates); we could not differentiate between these possibilities with our dataset.

The main strength of our study is that it is the largest and most recent cohort of 178 neonates, which allowed us to analyze the data according to GA. For comparison, the current guidelines for resuscitation[1,3] are based on several case series published from 1965 to 2010 that describe a limited number (4–58) of neonates with $Apgar^{10} = 0$ mostly born at ≥36 weeks of GA.[4–6,8] Our groups of neonates born <36 weeks' GA with $Apgar^{10} = 0$ remains still small (31 born at <32 weeks' GA and 26 born between $32^{0/7}$ and $35^{6/7}$ weeks' GA), but they are the largest of such gestational age described in the literature (4–16 neonates in previous studies[17,21,22]) and raised the discussion that more information should be collected for these neonates. The main limitation of our study is that we were only able to include neonates born in or referred to tertiary-level NICUs of the CNN. Some neonates with $Apgar^{10} = 0$ born at community hospitals may not have been included in the database if they were not referred to one of those NICUs. Labor room practices and willingness to continue ongoing resuscitation on such neonates and refer them to a tertiary-level NICU may vary between hospitals. It was not possible to identify the exact denominator of all neonates born with Apgar^{10} = 0 throughout Canada during the study period, as they are not automatically recorded in a database system. However, our sample covers >90% of all neonates admitted in Canadian NICUs andrepresents a near-national cohort. Another limitation was that the time to first heart beat was not available from the CNN database, making it impossible to determine the exact time beyond which prognosis was always poor for the neonates born between $32^{0/7}$ to $35^{6/7}$ weeks' GA and born at ≥36 weeks' GA; as no standardization of procedures exists yet beyond 10 min, variations may exist between hospitals and even between health care providers in a respective hospital in resuscitation practices beyond 10 min and in the time needed to achieve return of spontaneous circulation. The time from last fetal heart beat was also not available in the database and may have influenced outcome, since an absent heart rate at birth could mean the heart rate has just become absent or may have been already absent for an unknown period of time prior to delivery. In addition, the collected causes of death for neonates with Apgar^{10} = 0 did not describe how the initial Apgar score was used in evaluating prognosis and deciding how to care for these neonates. Sentinel events that might explain the 10-min Apgar score were also not recorded in the database. Finally, the long-term neurodevelopmental outcomes of the neonates with Apgar^{10} = 0 were not available in the CNN database, so brain injury on imaging was used as a surrogate. Neuroimaging in the perinatal period is reported to be feasible, even in the near-term/term neonates treated with cooling,[23,24] provides information about the extent of brain injury,[25,26] and is predictive of later outcomes.[27] Older studies used for the current guidelines for resuscitation did not usually report brain injury, but rather outcome at discharge from the NICU[28] or neurodevelopmental outcome at variables ages (2 months–12 years).[4,5,6,8,20] Using neuroimaging instead of the long-term neurodevelopmental outcomes may have overestimated the number of neonates with adverse outcomes, because not all neonates with brain injury develop major disability.[27] In addition, only the presence of brain injury, but not its severity, was taken into account in our study, probably again overestimating the number of neonates with adverse outcomes.

In conclusion, neonates with Apgar^{10} = 0 have different outcomes depending on their GA. A minority of neonates with Apgar^{10} = 0 survived among the neonates born at <32 weeks' GA. However, the majority of neonates born between $32^{0/7}$ to $35^{6/7}$ weeks' GA and born at ≥36 weeks' GA with Apgar^{10} = 0 survived and their survival rates were not different than their matches with Apgar^{10} = 1-2. In the future, the recommendations of the International Liaison Committee on Resuscitation (ILCOR) and the Neonatal Resuscitation Program Guidelines may need to be adjusted according to GA. Population-based prospective data collection including time to first heart beat, time from last fetal heart beat, time needed to achieve return of spontaneous circulation and sentinel events, as well as detailed imaging and neurodevelopmental outcome assessment are warranted to develop appropriate recommendations adjusted for GA. In the meantime, considering our data, even if only of retrospective nature, it may become questionable to consider stopping resuscitation at the 10-min time in all neonates, especially those ≥32 weeks' GA.

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