



Outcomes of infants with hypoxic-ischemic encephalopathy during COVID-19 pandemic lockdown in Canada: a cohort study

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Received: 21 April 2022 / Accepted: 1 June 2022 / Published online: 8 June 2022
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Abstract

Purpose To evaluate change in the severity of hypoxic-ischemic encephalopathy (HIE) and associated morbidities between pre- and during COVID-19 pandemic periods in Canada.

Methods We conducted a retrospective cohort study extracting the data from level-3 NICUs participating in Canadian Neonatal Network (CNN). The primary outcome was a composite of death in the first week after birth and/or stage 3 HIE (Sarnat and Sarnat). Secondary outcomes included rate and severity of HIE among admitted neonates, overall mortality, brain injury on magnetic resonance imaging (MRI), neonates requiring resuscitation, organ dysfunction, and therapeutic hypothermia (TH) usage. We included 1591 neonates with gestational age ≥ 36 weeks with HIE during the specified periods: pandemic cohort from April 1st to December 31st of 2020; pre-pandemic cohort between April 1st and December 31st of 2017, 2018, and 2019. We calculated the odds ratio (OR) and confidence intervals (CI).

Results We observed no significant difference in the primary outcome (15% vs. 16%; OR 1.08; 95%CI 0.78–1.48), mortality in the first week after birth (6% vs. 6%; OR 1.10, 95%CI 0.69–1.75), neonates requiring resuscitation, organ dysfunction, TH usage, or rate of brain injury. In the ad hoc analysis, per 1000 live births, there was an increase in the rate of infants with HIE and TH use.

Conclusions Severity of HIE, associated morbidities, and mortality were not significantly different during the pandemic lockdown compared to a pre-pandemic period in Canada. Anticipated risks and difficulties in accessing healthcare have not increased the mortality and morbidities in neonates with HIE in Canada.

Keywords Birth asphyxia · Resuscitation · Brain injury · Therapeutic hypothermia · Magnetic resonance imaging

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Introduction

Hypoxic-ischemic encephalopathy (HIE) is a devastating disease, leading to mortality and long-term morbidities in many neonates [1–3]. Incidence of HIE in developed countries varies between 0.9 and 3.8 per 1000 live births [4, 5]. HIE outcomes in neonates depend on the severity and duration of the initial insult [5, 6]. Some additional risk factors for HIE which warrant immediate attention are prolonged rupture of membranes, meconium-stained amniotic fluid, tight nuchal cord, umbilical cord prolapse, abruptio placenta, uterine rupture, and abnormal cardiotocography [5, 7, 8].

COVID-19 pandemic affected the healthcare services; many aspects are still unknown and unfolding. Visitations to the obstetric triage, high-risk clinics, and ultrasound clinics were delayed and decreased during the pandemic, with a resultant increase in the incidence of acute interventions and instrumental deliveries [9–12]. Substantial decrease in hospitalization of pregnant women was observed during the COVID-19 pandemic due to the fear of contracting the infection [13]. Although systematic reviews on pregnancy outcomes showed an increased incidence of pre-eclampsia and gestational diabetes mellitus, the incidence of stillbirths was similar, and preterm births were decreased during the COVID-19 pandemic [14, 15].

The publicly funded Canadian healthcare system and provinces have regionalized neonatal care, with some differences in the number of high-acuity neonatal beds [16]. The first case of COVID-19 in Canada was reported on January 25th, 2020, and the lockdown was implemented on March 18th, 2020. The lockdown stringency index in Canada was around 65–70 on a scale of 0–100 (100 being the strictest lockdown), and there was minimal variation between the provinces during 2020 [17–19]. This study aimed to compare the severity and outcomes of neonates with HIE admitted to tertiary NICUs in Canada before and during the pandemic.

Methods

Study design

We conducted a population-representative, retrospective cohort study of all neonates diagnosed with HIE admitted to tertiary Canadian Neonatal Network (CNN) centres before and during the pandemic. The pandemic cohort included neonates born during the COVID-19 lockdown between April 1st and December 31st of 2020. The pre-pandemic cohorts included neonates born from

April 1st to December 31st of 2017, 2018, and 2019 (the pre-pandemic cohort). We did not include infants born from January to March to reduce the potential bias due to seasonal variation in births and/or outcomes. Seasonality of births is a well-established phenomenon, where the climate, birth month preference, socioeconomic status, and contraceptive practices, among other factors, play a role. [20–22] We compared the pandemic cohort with the pre-pandemic cohort and analysed the differences in outcomes over the 4 years. We analysed the outcomes over 4 years to appreciate a general increase in the trends unrelated to the pandemic.

Patients and settings

We included term and near-term neonates (gestational age (GA) ≥ 36 weeks) with a diagnosis of HIE [23], admitted to one of the level 3 neonatal intensive care units (NICU) participating in the CNN during the specified periods. We excluded neonates with birth weight < 1.8 kg, surgical conditions, and major congenital anomalies.

Outcomes

The primary outcome of this study was a composite of death in the first week after birth and/or stage 3 HIE (based on Sarnat and Sarnat) [24]. The secondary outcomes were as follows: number of neonates with HIE of any grade, mortality in the first week after birth, overall mortality, difference in 5- and 10-min APGAR scores, number of neonates requiring chest compressions in the delivery room, seizures, organ dysfunction (cardiac, renal, and hepatic), incidence of brain injury on MRI, and rates of use of therapeutic hypothermia (TH).

We collected the demographic characteristics and outcomes from the CNN database. At each of the 31 sites participating in the CNN, neonatal data are collected from patient charts by trained abstractors according to standard definitions and entered electronically into a customized data entry program with built-in error checks. The database showed very high internal consistency and reliability [25]. Diagnosis of HIE was based on the presence of neonatal encephalopathy on admission, in association with a documented acute perinatal event, and evidence of intrapartum hypoxia (at least one of the following criteria: 10-min Apgar score ≤ 5 , ongoing mechanical ventilation or resuscitation at 10 min of birth, or cord pH ≤ 7.00 or postnatal blood gas pH ≤ 7.00 or base deficit ≤ -16 within 60 min of birth) [23]. Seizures were diagnosed clinically or by electroencephalography. Cardiac dysfunction was defined as receiving inotropes or echocardiography findings of cardiac dysfunction. Liver dysfunction was defined as elevated liver enzymes

(aspartate transaminase (AST) or alanine transaminase (ALT) > 100 IU) at any time in the first 7 days after birth. Renal failure was diagnosed as urine output < 0.5 ml/kg/h for 6 h or rising creatinine > 100 mmol/l within the first 72 h. Disseminated intravascular coagulation (DIC) was diagnosed based on laboratory or clinical evidence of coagulopathy. Persistent pulmonary hypertension (PPHN) was diagnosed on echocardiography. Evidence of brain injury was defined as signal abnormalities in MRI sequences in the watershed areas, deep gray matter, or a mixed pattern [23, 26–28].

Statistical methods

We compared neonates born in the pre-pandemic period to those admitted during the pandemic lockdown for primary analyses. Baseline characteristics were expressed as count and percentages for categorical variables and mean and standard deviation (SD) for continuous variables. Categorical variables were compared by Fisher's exact test or chi-square test and continuous variables by Student's *t*-test (two-sided) if normally distributed and Mann–Whitney *U*

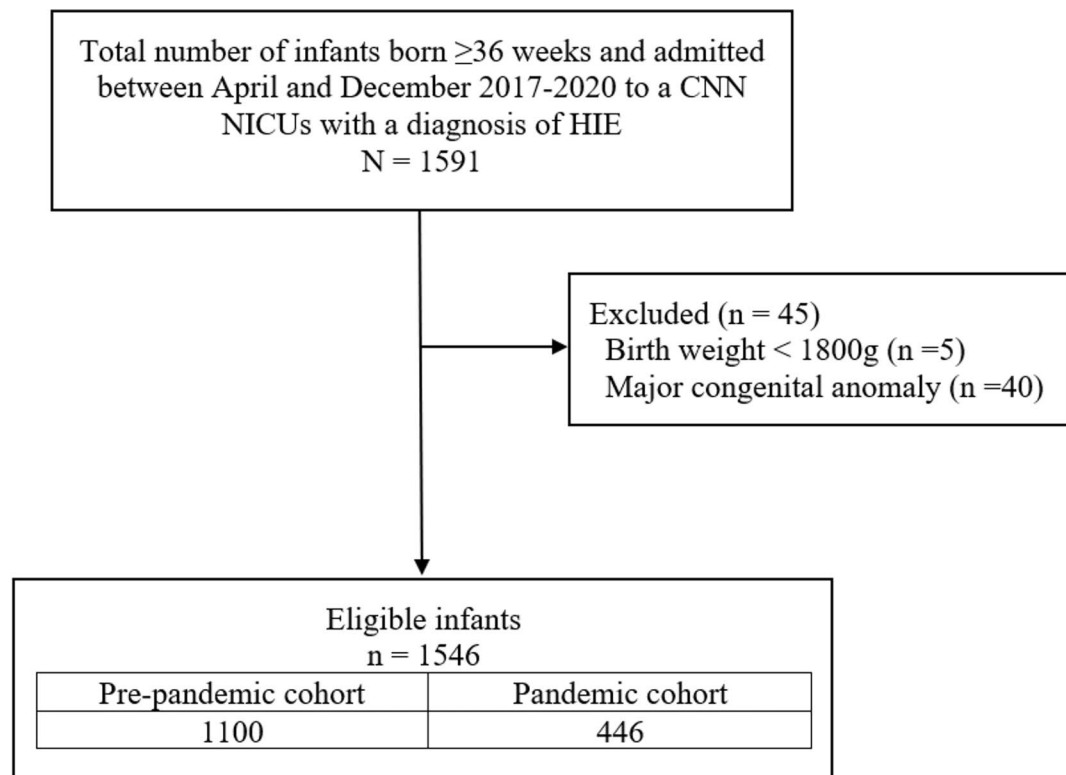
test if not normally distributed. We analysed the trends of outcomes of neonates with HIE over the 4 years (April 1st to December 31st of 2017–2020). The tests used were two-sided, and significance was defined as a *p*-value < 0.05. Data management and statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC).

Approvals

CNN Executive Committee approved the study, and the University of Calgary Conjoint Health Research Ethics Board provided ethics clearance (REB21-0497).

Results

The total number of neonates diagnosed with HIE during the study period was 1591, of which we excluded 45 neonates (birth weight < 1800 g = 5 neonates, and major congenital anomaly = 40 neonates) (Fig. 1). As reported in Table 1, baseline characteristics did not reveal any significant differences between pre-pandemic and pandemic periods. Results



(CNN: Canadian Neonatal Network, NICU: Neonatal Intensive Care Unit, HIE: Hypoxic Ischemic Encephalopathy)

Fig. 1 Flow diagram of the study population

Table 1 Demographic characteristics of infants admitted with HIE.^f

Variables	Pre-pandemic cohort (<i>n</i> = 1100)	COVID-19 pandemic cohort (<i>n</i> = 446)	<i>p</i>
Maternal characteristics			
Age ^a	30.7 (5.4)	30.6 (5.2)	0.75
Parity ^b	0 (0, 1)	0 (0, 1)	0.48
Pre-eclampsia	44 (4%)	16 (3.6%)	0.66
GDM ^c	128 (12%)	60 (14%)	0.15
Maternal chorioamnionitis	119 (11%)	55 (12%)	0.79
Neonatal characteristics			
Gestational age ^a	38.9 (1.5)	38.8 (1.6)	0.34
Birth weight ^d	3338 (576)	3337 (568)	0.97
SGA ^d	170 (16%)	64 (14%)	0.58
LGA ^e	122 (11%)	52 (12%)	0.75
Male sex	658 (60%)	263 (59%)	0.76
Multiple birth	23 (2%)	8 (2%)	0.71
5-min APGAR ^b	4 (3, 6)	4 (3, 6)	0.30
10-min APGAR ^b	6 (4, 7)	6 (4, 7)	0.52
Chest compression	251 (23%)	98 (22%)	0.72
Assisted ventilation	1050 (95%)	427 (96%)	0.81

^aMean (standard deviation)^bmedian (interquartile range)^cgestational diabetes mellitus^dsmall for gestational age^elarge for gestational age^fhypoxic ischemic encephalopathy. Data are expressed as *n* (%) unless otherwise specified

of the primary and secondary outcomes are reported in Table 2. The composite outcome of death in the first week after birth and/or stage 3 HIE was 16% in the pandemic and 15% in the pre-pandemic periods (OR 1.08; 95% CI 0.78–1.48). Mortality in the first week after birth was 6% in both cohorts (OR 1.10, 95% CI 0.69–1.75). Overall mortality was also similar between the pandemic and pre-pandemic cohorts (7% vs. 7%, OR 1.02, 95% CI 0.67–1.55).

There was no difference in the number of neonates requiring delivery room chest compression and assisted ventilation in both cohorts. About one-quarter of the neonates had mild HIE (26%), and nearly half had moderate HIE in the two time periods. The incidence of stage 3 HIE was also similar in both cohorts (13% in pre-pandemic and 14% in the pandemic period). Other secondary outcomes such as seizures, organ dysfunction, DIC, and PPHN in neonates with HIE were similar between the study periods. There was no difference in the incidence of brain injury on MRI scan among neonates with available MRI data (27% vs. 30%, OR 1.24, 95% CI 0.97–1.58).

We analysed the trends for outcomes over the 4 years to see a general increase in the rates of events unrelated

to the pandemic. There was an increasing trend over the 4-year study period for the total number of neonates with HIE. However, trends for primary and secondary outcomes were not statistically significant (Supplementary Table 1). Complete data on all births in the country during the study period was unavailable. Nevertheless, to explore the possible changes in the rates of HIE, we conducted an ad hoc analysis and calculated the rate of infants admitted with HIE to CNN sites among all live births in Canada during the corresponding periods [29]. When compared to the pre-pandemic cohort, there was a significant increase in the rates of neonates with HIE per 1000 live births in the pandemic cohort ($p < 0.001$; risk difference (RD) 0.04, 95% CI 0.02–0.05). The rate of use of TH per 1000 live births also was significantly higher in the pandemic cohort compared to the pre-pandemic period ($p = < 0.001$, RD 0.004; 95% CI 0.03–0.006).

Discussion

In this national population-representative cohort, we identified no significant difference in the composite of mortality and/or stage 3 HIE, mortality, or morbidities of neonates with HIE admitted to tertiary NICUs in Canada during the pandemic period when compared to a pre-pandemic period. There was also no difference in the trends of the outcomes studied.

During the COVID-19 pandemic lockdown, there was a difference in the profile of pregnant women presenting to the emergency room, health-seeking behaviours, difficulty in accessing healthcare, and a delay in providing care after admission to the hospital [9, 12, 13]. Concurrently, there were also increased rates of prolonged rupture of membranes, abruptio placenta, foetal distress, patients admitted in active labour, acute interventions in pregnant women, and operative deliveries during the pandemic lockdown [9–13, 30]. Some of these additional risk factors were found to be preventable and modifiable [31]. Pregnant women may also respond late to some of the warning signs of foetal distress such as absent/decreased foetal movements, signs of hypertension, bleeding, or worsening glucose control. A study from Nepal showed a decrease in the incidence of institutional deliveries and an increase in neonatal mortality [32]. All these could serve as risk factors for perinatal asphyxia and may increase the incidence of mortality and/or severe HIE. A population-based cohort study done in Sweden analyzing the risk factors for HIE concluded that careful assessment of acute obstetrical events and timely interventions could potentially decrease perinatal damage [5].

A recently published Canadian study, however, did not show a difference in the incidence of NICU admissions or neonatal deaths during the pandemic period [17, 33].

Table 2 Primary and secondary outcomes among infants admitted with HIE^a

Variables	Pre-pandemic cohort (<i>n</i> = 1100)	COVID-19 pandemic cohort (<i>n</i> = 446)	OR ^b (CI ^c)	<i>p</i>
Composite outcome	148 (14%)	65 (15%)	1.08 (0.78, 1.48)	0.64
Death in the first week after birth	61 (6%)	27 (6%)	1.10 (0.69, 1.75)	0.67
Overall mortality	80 (7%)	33 (7%)	1.02 (0.67, 1.55)	0.93
HIE staging	286 (26%)	114 (26%)		0.70
Mild	555 (50%)	226 (51%)		
Moderate	139 (13%)	64 (14%)		
Severe	120 (11%)	42 (9%)		
Unknown				
Hypothermia treatment	742 (68%)	342 (77%)	1.18 (0.89, 1.56)	0.25
Seizures	449 (41%)	192 (43%)	1.10 (0.88, 1.37)	0.42
Hepatic dysfunction	246 (22%)	107 (24%)	1.10 (0.85, 1.43)	0.48
Renal failure	204 (19%)	85 (19%)	1.04 (0.78, 1.37)	0.80
Cardiac dysfunction	106 (10%)	53 (12%)	1.27 (0.89, 1.80)	0.18
DIC ^d	105 (10%)	54 (12%)	1.31 (0.92, 1.85)	0.13
PPHN ^e	144 (13%)	65 (15%)	1.14 (0.83, 1.56)	0.43
Brain injury ^f	275/1029 (27%)	138/443 (30%)	1.24 (0.97, 1.58)	0.08

^aHypoxic ischemic encephalopathy^bodds ratio^cconfidence interval^ddisseminated intravascular coagulation^epersistent pulmonary hypertension^famong infants who had MRI. Data are expressed as *n* (%) unless otherwise specified

Kugelman et al. also reported that maternal and neonatal morbidity rates were not different during the pandemic, though there was an increase in the rates of emergency birth-related interventions [12]. Our hypothesis that neonates born during the pandemic period might have had higher mortality and/or severe injury based on the published poor perinatal outcomes was not supported by our results. Neonates born during the pandemic period did not have higher rates of HIE or associated morbidities.

In our ad hoc analysis, when compared to the total live births in Canada, there was an increase in the rate of infants with HIE per 1000 live births and the rate of infants receiving TH per 1000 live births in CNN sites which may be interpreted as an increase during the pandemic period. However, these results should be interpreted with caution for the following reasons: (1) Neonates with mild HIE may be born in the community and did not reach level 3 NICU; (2) There might be some immediate postnatal deaths that do not reach the tertiary NICU; and (3) There might be a difference in the referral practices over the 4-year study period unrelated to the pandemic lockdown.

There are several potential reasons for not finding a difference in the outcomes studied. Firstly, our sample size may be inadequate as we only included neonates born during 9 months (April to December 2020). Even though we had > 300 patients in each year, it may not be enough to detect minor differences. Secondly, contrary to our

speculation, access to the healthcare system may not have been as restricted. Data from the National Physician Database in Canada in 2021 showed that more patients chose virtual healthcare during the pandemic [34, 35]. Based on the data, though there was a significant shift to virtual care, patients with a higher level of morbidity were still provided appropriate healthcare through virtual platforms [34]. It is possible that in the context of the universal Canadian healthcare system and the fast adoption of virtual healthcare, pregnant women were attended to with similar rigour during the pandemic and thus did not compromise neonatal care.

Strengths and limitations

Our data extracted are population-representative and come from a robust data collection system. However, we acknowledge some limitations to our study. Data of neonates not admitted to the level 3 NICU and those who died (stillbirths or immediate postnatal deaths) at the referring centres were not captured in both periods. However, in Ontario, one of the large provinces of Canada, the stillbirth rate was not different during the pandemic period [17]. The database does not capture all the births; hence, some neonates with mild HIE cared for at level-2 units might have been missed. Referral practices also might have varied over the last 4 years; however, we did not see an increase in the incidence of mild HIE, as would be expected with increased

referrals. Finally, this study did not capture the phased lock-down relaxation period in 2021; however, it is unlikely we would have seen a change given there were no differences in outcome during strict lockdown.

Conclusion

The severity of HIE, mortality, and morbidity related to HIE during the COVID-19 pandemic period in Canada was not different from that of a pre-pandemic period. Creating awareness among pregnant women about timely access to the healthcare system may have helped prevent the unmeasured, unintended complications of the pandemic lockdown. Population-based studies that tend to capture complete data would help assess the actual difference. Further studies from larger cohorts and different healthcare system settings are needed to fully understand the impact of pandemic and lockdown.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s00381-022-05575-8>.

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Author contribution Khorshid Mohammad, Sujith Kumar Reddy Gurram Venkata, Marc Beltempo, and Prakesh S Shah contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Marc Beltempo. The first draft of the manuscript was written by Sujith Kumar Reddy Gurram Venkata and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Although no specific funding was received for this study, organizational support for the Canadian Neonatal Network, Canadian Preterm Birth Network, and the Canadian Neonatal Follow-Up Network was provided by the Maternal-infant Care Research Centre (MiCare) at Mount Sinai Hospital in Toronto, Ontario, Canada. MiCare is supported by a Canadian Institutes of Health Research (CIHR) Team Grant (CTP 87518) and the participating hospitals.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and patient consent The University of Calgary Conjoint Health Research Ethics Board approved the project and waved the need for parental consent (REB21-0497).

Disclaimer The funding bodies played no role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

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