Incidence Trends and Risk Factor Variation in Severe Intraventricular Hemorrhage across a Population Based Cohort

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Objective To quantify the current burden of severe intraventricular hemorrhage (IVH), describe time trends in severe IVH, identify IVH-associated risk factors, and determine the contribution of mediating factors.

Study design The retrospective cohort included infants $22^{0/7}$-$31^{6/7}$ weeks of gestation without severe congenital anomalies, born at hospitals in the California Perinatal Quality Care Collaborative between 2005 and 2015. The primary study outcome was severe (grade III or IV) IVH.

Results Of 44 028 infants, 3371 (7.7%) had severe IVH. The incidence of severe IVH decreased significantly across California from 9.7% in 2005 to 5.9% in 2015. After stratification by gestational age, antenatal steroid exposure was the only factor associated with a decreased odds of severe IVH for all gestational age subgroups. Other factors, including delivery room intubation, were associated with an increased odds of severe IVH, though significance varied by gestational age. Factors analyzed in the mediation analysis accounted for 45.6% (95% CI 38.7%-71.8%) of the reduction in severe IVH, with increased antenatal steroid administration and decreased delivery room intubation mediating a significant proportion of this decrease, 19.4% (95% CI 13.9%-27.5%) and 27.3% (95% CI 20.3%-39.2%), respectively. The unaccounted proportion varied by gestational age.

Conclusions The incidence of severe IVH decreased across California, associated with changes in antenatal steroid exposure and delivery room intubation. Maternal, patient, and delivery room factors accounted for less than one-half of the decrease in severe IVH. Study of other factors, specifically neonatal intensive care unit and hospital-level factors, may provide new insights into policies to reduce severe IVH. *(J Pediatr 2018;200:24-9).*

Severe intraventricular hemorrhage (IVH) is a significant source of morbidity for very low birth weight infants and is associated with adverse long-term outcomes.[1,2] The incidence of severe IVH reported by the National Institute of Child Health and Human Development Neonatal Research Network in 2012 was 13%.[3] Data from the Vermont Oxford Network reported a decrease in the median incidence of severe IVH from 9.4% (IQR 8.7%-10.2%) in 2005 to 7.9% (IQR 7.6%-8.2%) in 2014.[4] These data demonstrate the variable, but persistent burden of severe IVH for very low birth weight infants.

Many previous epidemiologic studies focused on the identification of IVH-associated risk factors to assess or calculate severe IVH risk, including gestational age, sex, antenatal steroid exposure, mode of delivery, and low Apgar scores.[5-7] However, aside from antenatal steroids, the relative impact and contribution of these factors in the development of IVH is not well described.[7] It is unknown whether changes in these factors help explain potential changes in the incidence of IVH over time and whether risk factors for IVH differ between infants of different gestational ages.

The goal of this study was to examine contemporary, population-based, generalizable data to characterize the changing landscape of severe IVH through describing the current burden of severe IVH, trends in severe IVH over time, and IVH-associated variables. We hypothesized that a detailed analysis of IVH-associated variables of infants at varying degrees of prematurity and a mediation analysis to quantify the contribution of relevant IVH-associated variables would provide new insights into risk factors for the development of severe IVH.

Methods

The California Perinatal Quality Care Collaborative (CPQCC) prospectively collects data from >90% of neonatal intensive care units (NICUs) in California, which at the time of this study reflected 127 NICUs. The CPQCC eligibility criteria include infants with a birth weight between 401 and 1500 g or a gestational age between $22^{0/7}$ and $29^{6/7}$ weeks. In addition, infants with a gestational age ≥30 weeks are included if the birth weight was <1500 g or if they met 1 of the following criteria:

CPQCC	California Perinatal Quality Care Collaborative
CPR	Cardiopulmonary resuscitation
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit

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noninvasive ventilation for >4 hours, intubation and ventilation for >4 hours, severe hyperbilirubinemia, early bacterial sepsis, surgery, acute transfer in or out of a NICU, and death.

The study cohort included infants born at $22^{0/7}$-$31^{6/7}$ gestational age weeks from January 2005 to December 2015. Gestational age was determined by the best available estimate in weeks and days. Where sources disagreed, obstetric measures based on last menstrual period or prenatal ultrasound took precedence over the neonatologist's estimate based on physical examination. Infants were assigned "year" based on their birth year. Prior to the application of exclusion criteria, there were 61 021 infants in the cohort. To minimize the incorrect estimation of gestational age, infants with a birth weight below the first percentile for gestational age or above the 99th percentile were excluded (n = 288). Additional exclusion criteria were infants with major congenital anomalies or anomalies of unknown severity (n = 4000), those who died in the delivery room (n = 2546), those without IVH imaging data (n = 3017), and those born in non-CPQCC associated NICUs (n = 7142). The final cohort included 44 028 infants.

Outcomes and Variables

Severe IVH was defined as any grade III or IV IVH documented in a CPQCC NICU by cranial imaging obtained prior to 28 days of life.[8] Information regarding the exact timing of imaging/diagnosis of IVH was not available. If bleeds of different severity were documented, the most severe grade was assigned to the patient and used for analysis. Infants with severe IVH were compared with those without severe IVH or with grade I or II IVH. Based on previous literature, variables of interest included birth weight, gestational age, birth weight small for gestational age, sex, multiple gestation, antenatal steroids, prenatal care, maternal hypertension, chorioamnionitis, maternal bleed, race/ethnicity, mode of delivery (cesarean or vaginal delivery), Apgar scores at 1 and 5 minutes, delivery room intubation, delivery room cardiopulmonary resuscitation (CPR), defined as the receipt of chest compressions and/or epinephrine), surfactant administration, death prior to hospital discharge, and birth year.[5,9-14] Data collection is performed by trained data abstractors based on definitions from the CPQCC, which uses standard definitions developed by the Vermont Oxford Network.[15,16]

Statistical Analyses

Analysis was completed using SAS v 9.4 (SAS, Cary, North Carolina) and Stata v 14.2 (StataCorp, College Station, Texas). The cohort was stratified into gestational age subgroups, 22-$23^{6/7}$, 24-$25^{6/7}$, 26-$27^{6/7}$, 28-$29^{6/7}$, and 30-$31^{6/7}$ gestational age weeks. Rates of severe IVH were calculated as crude and risk-adjusted rates that accounted for patient and hospital level factors. One-way ANOVA and Kruskal-Wallis tests were used to compare maternal and neonatal characteristics for infants with severe IVH to those without IVH or with grade I or II IVH. Multivariable logistic models were used to examine factors associated with severe IVH. Variables in the model included sex, birth weight, gestational age, multiple gestation, race/ethnicity, antenatal steroids, prenatal care, maternal hypertension, chorioamnionitis, mode of delivery, 1-minute Apgar score <3, 1-minute Apgar score <7, 5-minute Apgar score <3, 5-minute Apgar score <7, delivery room intubation, delivery room CPR, and surfactant administration with hospital applied as a random effect to adjust for clustering by site. Because of the collinearity of delivery room intubation and surfactant, only 1 variable, delivery room intubation, was kept in the final model. Infants, without cranial imaging, were unlikely to have IVH as they were bigger (mean birth weight 1242.9 g ± 528.1g) and older (mean gestational age 28.0 ± 3.2 weeks). There was no change in the frequency of missing IVH imaging data over the study period ($P = .91$). In addition, a sensitivity analysis was completed where infants without cranial imaging who survived to day of life 7 were included as infants without IVH.

A frequency analysis was performed to determine the incidence of severe IVH over time, stratified by gestational age. Linear regression models were used to determine if the change in the incidence of severe IVH was significant over time, as well as the rates of antenatal steroid exposure and delivery room intubation. A mediation analysis was performed to determine the proportion of the effect attributable to a variable or subset of variables in the change in the incidence of severe IVH over time. This was performed using serial multivariable generalized linear models and determining the change in the model coefficient for year ([base model coefficient-new model coefficient]/base model coefficient) with the addition of intermediary variables. This analysis produced an attributable percentage, which was the change in severe IVH incidence over time attributable to the new variables added to the model. The following sequential, additive models were run, with the specified variables added to the base model: (1) year and hospital, (2) sex, gestational age, and multiple gestation, (3) antenatal steroids, mode of delivery, and delivery room intubation were added individually, and then (4) all together. This analysis was also repeated with surfactant in place of delivery room intubation, and the results were unchanged. Given the interest in modifiable factors associated with severe IVH, the results associated with delivery room intubation are reported. The mediation analysis was performed for the whole cohort and then for each gestational age subgroup. To determine CIs for the attributable percentage in the mediation analysis, we performed a bootstrap analysis with 1000 iterations.

Results

During the study period, 44 028 infants met inclusion criteria. Of those, 24.2% (n = 10 640) had IVH, with 7269 (16.5%) developing grade I or II and 3371 (7.7%) developing grade III or IV. The rate of severe IVH was highest in the youngest subgroup, 22-$23^{6/7}$ gestational age weeks at 36.1% and decreased with increasing gestational age, 20.8% in 24-$25^{6/7}$, 9.5% in 26-$27^{6/7}$, 3.3% in 28-$29^{6/7}$, and 1.2% in 30-$31^{6/7}$. Cohort characteristics for those without IVH, with grade I or II IVH, and severe IVH were significantly different for the whole cohort (**Table I**; available at www.jpeds.com) and gestational age subgroups (**Table II**; available at www.jpeds.com). After multivariable analysis of the gestational age subgroups, significant,

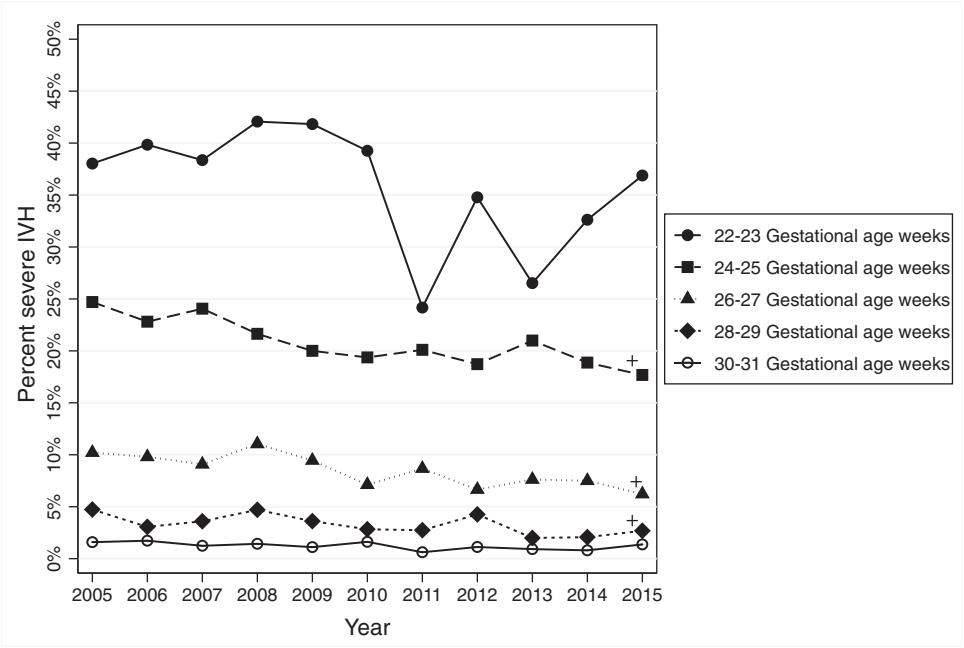

Figure 1. Severe IVH by gestational age over time. + Indicates significant change over time.

and potentially modifiable variables, shown in **Table III** (available at www.jpeds.com), included antenatal steroids, mode of delivery, and delivery room intubation; however, significance varied by gestational age. Variation by gestational age was also present in the complete multivariable analysis results (**Table IV**; available at www.jpeds.com). Antenatal steroid exposure was the only factor associated with a decreased odds of severe IVH across all gestational age subgroups. These results were similar when we included infants without imaging who survived to day of life 7 as infants without IVH.

There was marked variation in the incidence of severe IVH across the CPQCC, with a median crude rate of 7.7% (IQR 6.0%-10.2%) and median adjusted rate of 5.4% (IQR 4.2%-7.0%). There was a significant decrease in the incidence of IVH, both less severe and severe IVH, over the study period. The incidence of severe IVH decreased from 9.7% to 5.9%, a relative reduction of 39%. The incidence of grade I and II IVH decreased from 18.3% to 14.1%, a relative reduction of 23%. When evaluating the incidence of severe IVH across the gestational age subgroups over time, the 24-25$^{6/7}$, 26-27$^{6/7}$, and 28-29$^{6/7}$ subgroups had statistically significant decreases in severe IVH over the study period (**Figure 1**).

Changes in the rates of significant, potentially modifiable factors identified in the multivariable analysis, specifically antenatal steroids, mode of delivery, and delivery room intubation, were assessed over time. In infants with severe IVH, rates of antenatal steroid exposure increased from 71.7% to 81.3% over the study period, a significant increase of 1.0% per year, (95% CI 0.4%-1.6%). This increase was seen across the cohort as a whole (1.2%, 95% CI 1.1%-1.3%), in infants without IVH (1.1%, 95% CI 1.0%-1.2%), and those with grade I or II IVH (1.2%, 95% CI 0.9%-1.6%) (**Figure 2**, A). There was no significant change in rates of cesarean delivery for infants with severe IVH (annual rate change of 0.32, 95% CI -0.17 to 0.81).

Rates of delivery room intubation significantly decreased in infants with severe IVH from 86.6% to 70.7%, a decrease of 1.5% per year (95% CI 0.9%-2.2%) over the study period. This significant decrease was also seen across the whole cohort (2.4%, 95% CI 1.7%-3.2%), in those without IVH (2.2%, 95% CI 1.4%-3.0%), and those with grade I or II IVH (2.6%, 95% CI 1.6%-3.6%) (**Figure 2**, B). Before 2010, rates of delivery room intubation remained stable (a change of -0.8% per year, 95% CI -1.9%-0.2%). After 2010, there was a significant decrease in the rate of delivery room intubation of 3.3% (95% CI 1.4%-5.2%) for the cohort as a whole. During part of the study period, a collaborative quality improvement project across the CPQCC implemented a delivery room bundle of 5 practices, one of which was the optimization of respiratory support in the delivery room. This specified early use of continuous positive airflow pressure (within the first 60 seconds of life), avoiding intubation when possible, and avoiding prophylactic surfactant administration when possible.[17]

The statistically significant decrease in the incidence of severe IVH for the whole cohort, the 24-25 $^{6/7}$ gestational age group, 26-27$^{6/7}$ gestational age group, 28-29$^{6/7}$ gestational age group, and key variables from the multivariable analysis were considered in the mediation analysis. **Table V** reports the contribution of mediating factors on the decrease in severe IVH. The percentage reported in the top row reflects the contribution explained by year, sex, gestational age, and multiple gestation, with the individual addition of antenatal steroids, cesarean delivery, and delivery room intubation. The bottom row reflects the contribution of all factors. In the whole cohort, 45.6% (95% CI 38.7%-71.8%) of the decrease in severe IVH

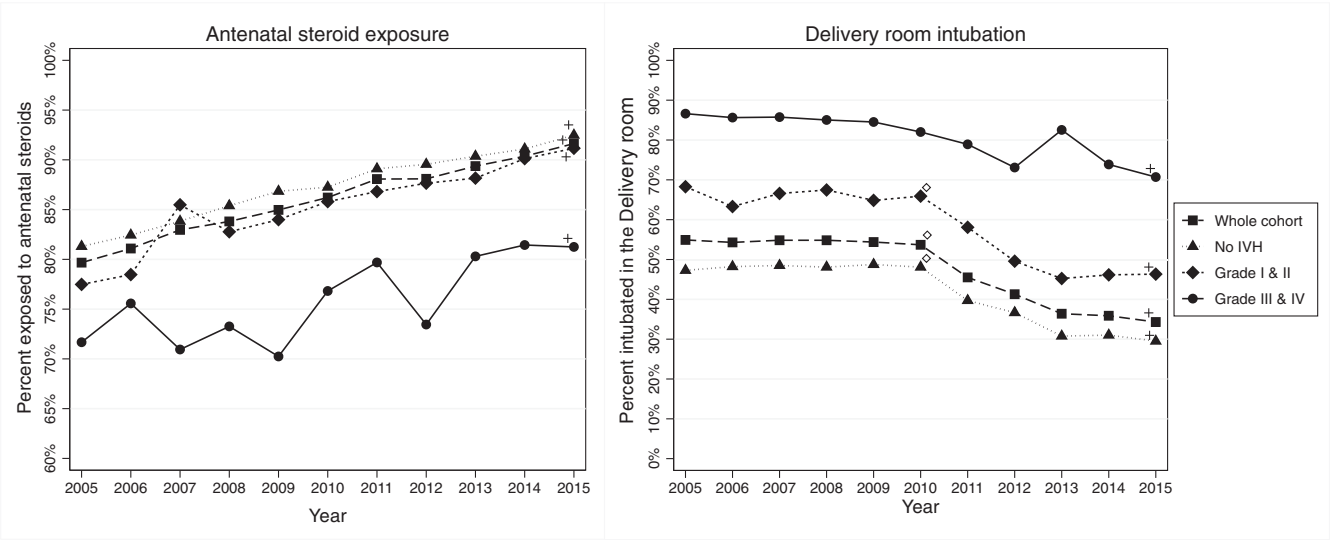

Figure 2. Rates of antenatal steroid exposure and delivery room intubation over time by IVH status. + Indicates significant decrease over 11-year period; ◊ Indicates significant change in rate of decrease.

was mediated by patient factors; this contribution varied by gestational age. Antenatal steroid exposure and delivery room intubation made the largest contributions to the reduction in severe IVH, ranging from 12.9% to 24.1% and 13.4% to 43.7%, respectively, though the impact varied by gestational age.

Discussion

Severe IVH remains a significant morbidity for preterm infants. In this large population-based cohort, we saw a significant decrease in the incidence of severe IVH between 2005 and 2015, a decrease driven by infants born at 24-29$^{6/7}$ gestational age weeks. Significant risk factors for severe IVH were similar to those previously reported, including younger gestational age, male sex, lack of antenatal steroid exposure, and delivery room CPR.[5-7,9] However, we found that gestational age had differential impact on the significance of explanatory variables (**Table III**). Only antenatal steroid exposure was significantly protective across all gestational age strata. Of note, we found that patient and delivery room factors had variable impact on the burden of severe IVH by gestational age strata with antenatal steroids and delivery room intubation explaining the greatest amount of variation. These detailed data identifying significant, mediating, and potentially modifiable, IVH risk factors in the context of gestational age have the potential to inform targeted study and collaborative changes to improve care for very preterm infants. However, given that maternal, patient and delivery room factors accounted for less than one-half of the decrease in severe IVH reported, additional study of other factors, specifically unit and hospital level factors, may lead to further reduction of severe IVH.

The only factor that was associated with decreased IVH across all gestational age groups was antenatal steroids. The CPQCC has worked to increase antenatal steroid awareness and specifically worked to identify groups at risk for not receiving steroids.[18] This effort is evident in the steady and significant increase in antenatal steroids reported here. Previous data from the CPQCC reported a decrease in severe IVH in infants 22-29 weeks with antenatal steroid exposure.[19] The results of this study confirm those findings, but are slightly different as we found that antenatal steroids were associated with less IVH up to 31$^{6/7}$ weeks, which could be due to the current study including more time (2005-2015 vs 2007-2013). Unlike previously studies of severe IVH, this study quantifies the differential impact of antenatal steroids on the decrease in IVH across dif-

Table V. Contribution of mediating factors in severe IVH reduction

	24-25 gestational age wk (%, 95% CI)	26-27 gestational age wk (%, 95% CI)	28-29 gestational age wk (%, 95% CI)	Whole cohort (%, 95% CI)
Birth year, sex, gestational age , multiple gestation	–1.9% (–11.8%, 6.4%)	–2.3% (–7.3%,1.4%)	–5.2% (–13.6%, –1.4%)	13.2% (4.1%, 22.6%)
Antenatal steroids	16.1% (8.8%, 37.3%)	12.9% (6.2%, 24.0%)	24.1% (11.9%, 49.6%)	19.4% (13.9%, 27.5%)
Cesarean delivery	0.3% (–1.7%, 3.4%)	1.1% (–0.8%,1.2%)	1.1% (–2.5%, 0.8%)	1.1% (–0.2%, 1.6%)
Delivery room intubation	13.4% (5.8%, 33.8%)	31.0% (19.6%, 63.9%)	43.7% (26.1%, 92.1%)	27.3% (20.3%, 39.2%)
Antenatal steroids, Cesarean delivery, delivery room intubation	31.0% (14.6%, 66.7%)	41.0% (25.0%, 82.8%)	64.1% (34.8%, 100.0%)	45.6% (38.7%, 71.8%)

ferent gestational age strata. Antenatal steroids accounted for 16.1% of the decrease in the 24-25$^{6/7}$ gestational age infants, 12.9% in the 26-27$^{6/7}$ gestational age infants, 24.1% in the 28-29$^{6/7}$ gestational age infants, and 19.4% across the whole cohort. These data highlight the importance of ongoing vigilance in antenatal steroid administration efforts.

The change in delivery room intubation practices and the attributable impact on the decrease in IVH in a key finding of this study and demonstrate how a widespread change in practice can impact outcomes. In all but the 24-25$^{6/7}$ gestational age subgroup, the impact of decreased intubation was more significant than antenatal steroids, accounting for as much as 43.7% of the decrease in severe IVH seen in the 28-29$^{6/7}$ gestational age subgroup. Previous publication of the CPQCC delivery room bundle quality improvement project reported a reduction in any IVH after the intervention, but no significant decrease in severe IVH in the collaborative quality improvement group.[20] In the current study, we examined the whole state of California including NICUs that did not participate in that collaborative. The ongoing decrease in rates of delivery room intubation and significant decrease in the incidence of severe IVH may have been influenced by the collaborative project, as well as ongoing efforts outside the official collaborative to improve delivery room management. Of note, there is increasing literature on the association between the number of intubation attempts, severe IVH and neurodevelopmental impairment in very low birth weight infants.[11,21] Thus, these data, in concert with other literature highlight the need for ongoing efforts to optimize delivery room practices and management for very low birth weight infants.

Strengths of this study include the large, diverse, population-based cohort it describes over an 11-year period. In addition, the gestational age stratified analyses and mediation analysis of modifiable factors are unique features that have not previously been reported. The quantification of the contribution of relevant factors, specifically antenatal steroid exposure and delivery room intubation on the incidence of severe IVH, provides new insights into IVH development and prevention.

However, it is important to note limitations of this study, which are related to the gestational age of infants captured in the cohort, availability of cranial imaging data, and the granularity of available data regarding cranial imaging, antenatal steroids, and indomethacin. For gestational age, particularly for the 22-23$^{6/7}$-week infants, although antenatal steroid exposure was protective, there were limited variables of significance. The limited findings for this subgroup are likely multifactorial, but may be related to the relatively small number (n = 1516) of 22-23$^{6/7}$-week infants captured in the study cohort and may reflect variation in counseling and resuscitation practices for 22-23$^{6/7}$-gestational age week infants. Older infants, 30-31$^{6/7}$ weeks, may have been less consistently captured by the CPQCC, and, thus, those included could either be more ill and at higher risk for adverse outcomes or less likely to have cranial imaging obtained secondary to their stable clinical status, the latter of which was accounted for in the sensitivity analysis. Another source of missing cranial imaging data is infants who died prior to obtaining imaging. The available details regarding cranial imaging are a limitation of this study, as the exact timing of cranial imaging, and, therefore, diagnosis of IVH is unknown as well as any involvement of the cerebellum. Similarly, a dose dependent protective relationship with antenatal steroids and IVH has been reported in the literature; however, details about antenatal exposure are not available for this cohort.[7] Information about administration of prophylactic indomethacin also was not available. Finally, we restricted this study to include infants born within the CPQCC, thus, excluding outborn infants who, if transferred, are at increased risk for severe IVH; this limits the generalizability of these findings in that subpopulation.

This study highlights a clinically important reduction in severe IVH across the CPQCC between 2005 and 2015 and identification of mediating factors. Interventions have differential risks and benefits for infants at varying degrees of prematurity. Ongoing attention to increase antenatal steroid exposure and optimize delivery room respiratory management may continue to reduce the burden of severe IVH. However, the factors studied accounted for only a portion of the change as shown in the mediation analysis and varied by gestational age, as little as 31.0% in the 24-25$^{6/7}$-gestational age infants and as much as 64.1% in the 28-29$^{6/7}$-gestational age infants. This suggests there are other factors mediating the reduction, or development of severe IVH, especially in the youngest, highest risk infants, some of which may be identifiable and others unmeasurable.

Although in our study, gestational age was a major driver in the development of severe IVH, the impact of IVH-associated risk factors varied significantly by gestational age. Potentially modifiable variables, including antenatal steroid administration and avoidance of delivery room intubation when possible, accounted for the greatest amount of variation in the burden of severe IVH across gestational age strata. Less than one-half of the decrease in severe IVH was mediated by patient-related factors; thus, exploration of other factors, such as unit-level processes, practices, and hospital-level characteristics, is required to provide additional insights into opportunities to improve care and optimize outcomes for these vulnerable patients. ■

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Table I. Cohort characteristics

	No IVH, No. (%) n = 33 388	Grade I or II IVH, no. (%) n = 7269	Severe IVH, no. (%) n = 3371	*P* value
Birth weight, g, mean (SD)	1177.0 (346.1)	1043.5 (356.1)	850.0 (291.7)	<.0001
Gestational age, wk, mean (SD)	28.4 (2.2)	27.2 (2.4)	25.5 (2.1)	<.0001
SGA	2233 (6.7%)	420 (5.8%)	138 (4.1%)	<.0001
Male	17 357 (52.0%)	3972 (54.7%)	1970 (58.4%)	<.0001
Multiple gestation	9469 (28.4%)	1804 (24.8%)	936 (27.8%)	<.0001
Antenatal steroids	29 194 (87.4%)	6184 (85.1%)	2542 (75.4%)	<.0001
Maternal hypertension	9011 (27.4%)	1468 (20.6%)	395 (12.0%)	<.0001
Chorioamnionitis	1835 (7.4%)	586 (11.5%)	301 (13.1%)	<.0001
Maternal bleed	6016 (18.3%)	1429 (19.9%)	704 (21.2%)	<.0001
Prenatal care	32 376 (97.0%)	7023 (96.6%)	3186 (94.5%)	<.0001
Race/ethnicity				<.0001
Non-Hispanic white	9316 (27.9%)	1973 (27.1%)	783 (23.2%)	
Hispanic	15 003 (44.9%)	3178 (43.7%)	1699 (50.4%)	
Non-Hispanic black	4182 (12.5%)	1013 (13.9%)	526 (15.6%)	
Asian/Pacific Islander	3918 (11.7%)	924 (12.7%)	279 (8.3%)	
Native American	109 (0.3%)	19 (0.3%)	6 (0.2%)	
Other	860 (2.6%)	162 (2.2%)	78 (2.3%)	
Cesarean delivery	25 120 (75.2%)	4669 (64.3%)	2188 (64.9%)	<.0001
1-min Apgar, median (IQR)	6 (4-8)	5 (3-7)	4 (2-6)	<.0001
5-min Apgar, median (IQR)	8 (7-9)	8 (6-9)	7 (5-8)	<.0001
Delivery room intubation	13 692 (41.0%)	4265 (58.7%)	2743 (81.4%)	<.0001
Delivery room CPR*	454 (1.4%)	218 (3.0%)	248 (7.4%)	<.0001
Surfactant administration	20 223 (60.6%)	5422 (74.6%)	3171 (94.1%)	<.0001
Death prior to discharge	1142 (3.4%)	559 (7.7%)	1319 (39.1%)	<.0001

SGA, small for gestational age.
*Delivery room CPR receipt of chest compressions or administration of epinephrine.

Table II. Cohort characteristics by gestational age subgroup

	22-23$^{6/7}$ gestational age wk				24-25$^{6/7}$ gestational age wk				26-27$^{6/7}$ gestational age wk			
	No IVH n = 560	Grade I or II n = 409	Grade III or IV n = 547	*P* value	No IVH n = 3566	Grade I or II n = 1662	Grade III or IV n = 1377	*P* value	No IVH n = 6411	Grade I or II n = 1783	Grade III or IV n = 858	*P* value
Birth weight, mean (SD), g	588.4 (94.3)	591.1 (91.6)	585.9 (90.5)	.69	725.6 (137.4)	718.7 (128.1)	713.3 (121.8)	.009	933.6 (184.6)	934.5 (190.9)	944.4 (180.1)	.27
Gestational age, wk, mean (SD)	22.8 (0.3)	22.9 (0.3)	22.9 (0.4)	.28	24.6 (0.5)	24.5 (0.5)	24.4 (0.5)	<.0001	26.6 (0.5)	26.5 (0.5)	26.5 (0.5)	<.0001
SGA	15 (2.7%)	6 (1.5%)	9 (1.7%)	.32	180 (5.1%)	73 (4.4%)	50 (3.6%)	.09	284 (4.4%)	82 (4.6%)	30 (3.5%)	.40
Male	285 (50.9%)	201 (49.1%)	301 (55.0%)	.16	1823 (51.1%)	866 (52.1%)	790 (57.4%)	.0004	3267 (51.0%)	1011 (56.7%)	500 (58.3%)	<.0001
Multiple gestation	136 (24.3%)	85 (20.8%)	171 (31.3%)	.001	772 (21.7%)	403 (24.3%)	393 (28.5%)	<.0001	1510 (23.6%)	436 (24.5%)	237 (27.6%)	.03
Antenatal steroids	436 (77.9%)	289 (70.7%)	340 (62.2%)	<.0001	3197 (89.7%)	1451 (87.3%)	1096 (79.6%)	<.0001	5697 (88.9%)	1524 (85.5%)	681 (79.4%)	<.0001
Maternal hypertension	47 (8.6%)	27 (6.8%)	34 (6.4%)	.36	554 (15.8%)	202 (12.4%)	120 (9.0%)	<.0001	1496 (23.8%)	340 (19.5%)	115 (13.6%)	<.0001
Chorioamnionitis	60 (14.4%)	49 (16.4%)	52 (13.8%)	.62	356 (13.5%)	184 (15.7%)	140 (15.0%)	.16	468 (10.1%)	157 (12.7%)	65 (11.1%)	.03
Maternal bleed	145 (26.3%)	113 (28.2%)	105 (19.4%)	.003	812 (23.0%)	404 (24.6%)	296 (22.0%)	.22	1278 (20.3%)	356 (20.3%)	180 (21.3%)	.80
Prenatal care	546 (97.5%)	382 (93.4%)	503 (92.0%)	.0002	3425 (96.1%)	1603 (96.5%)	1306 (94.8%)	.07	6181 (96.4%)	1725 (96.8%)	824 (96.0%)	.63
Race/ethnicity				.08				.007				.08
Non-Hispanic white	104 (18.6%)	59 (14.4%)	118 (21.6%)		822 (23.1%)	412 (24.8%)	281 (20.4%)		1669 (26.0%)	436 (24.5%)	215 (25.1%)	
Hispanic	306 (54.6%)	226 (55.3%)	283 (51.7%)		1681 (47.1%)	766 (46.1%)	685 (49.8%)		2985 (46.6%)	843 (47.3%)	437 (50.9%)	
Non-Hispanic black	87 (15.5%)	82 (20.1%)	101 (18.5%)		584 (16.4%)	240 (14.4%)	247 (17.9%)		850 (13.3%)	246 (13.8%)	113 (13.2%)	
Asian/Pacific Islander	48 (8.6%)	33 (8.1%)	36 (6.6%)		376 (10.5%)	201 (12.1%)	124 (9.0%)		726 (11.3%)	218 (12.2%)	71 (8.3%)	
Native American	0 (0%)	2 (0.5%)	1 (0.2%)		12 (0.3%)	2 (0.1%)	2 (0.2%)		26 (0.4%)	5 (0.3%)	1 (0.1%)	
Other	15 (2.7%)	7 (1.7%)	8 (1.5%)		91 (2.6%)	41 (2.5%)	38 (2.8%)		155 (2.4%)	35 (12.0%)	21 (2.5%)	
Cesarean delivery	313 (55.9%)	181 (44.3%)	260 (47.5%)	.003	2529 (70.9%)	1080 (65.1%)	911 (66.2%)	.0001	4744 (74.0%)	1184 (66.4%)	621 (72.4%)	<.0001
1-min Apgar, median (IQR)	3 (2-5)	3 (1-5)	3 (2-5)	.024	4 (2-6)	4 (2-6)	3 (2-5)	<.0001	6 (4-7)	5 (3-7)	4 (2-6)	<.0001
5-min Apgar, median (IQR)	6 (4-7)	6 (4-7)	6 (4-7)	.006	7 (6-8)	7 (5-8)	6 (5-8)	<.0001	8 (7-9)	8 (6-8)	7 (5-8)	<.0001
Delivery room intubation	515 (92.0%)	382 (93.4%)	509 (93.1%)	.66	3010 (84.5%)	1432 (86.2%)	1229 (89.3%)	<.0001	3927 (61.3%)	1220 (68.4%)	663 (77.4%)	<.0001
Delivery room CPR*	41 (7.3%)	43 (10.5%)	56 (10.2%)	.14	130 (3.7%)	89 (5.4%)	112 (8.1%)	<.0001	115 (1.8%)	35 (2.0%)	44 (5.1%)	<.0001
Surfactant administration	540 (96.43%)	403 (98.5%)	545 (98.4%)	.0003	3262 (91.6%)	1558 (93.8)	1341 (97.5%)	<.0001	4997 (78%)	1514 (84.9%)	811 (94.5%)	<.0001
Death prior to discharge	194 (34.6%)	144 (35.2%)	360 (65.8%)	<.0001	420 (11.8%)	230 (13.8%)	638 (46.3%)	<.0001	282 (4.4%)	105 (5.9%)	234 (27.3%)	<.0001

	28-29$^{6/7}$ gestational age wk				30-31 + $^{6/7}$ gestational agewk			
	No IVH n = 10333	Grade I or II n = 1837	Grade III or IV n = 416	*P* value	No IVH n = 12518	Grade I or II n = 1578	Grade III or IV n = 173	*P* value
Birth weight, mean (SD), g	1195.9 (231.3)	1193.6 (237.1)	1201.1 (256.0)	.83	1441.0 (279.5)	1451.2 (297.0)	1459.2 (340.1)	.29
Gestational age, wk, mean (SD)	28.6 (0.5)	28.5 (0.5)	28.5 (0.5)	<.0001	30.5 (0.5)	30.5 (0.5)	30.4 (0.5)	.02
SGA	514 (5.0%)	100 (5.4%)	25 (6.0%)	.47	1240 (9.9%)	159 (10.1%)	24 (13.9%)	.22
Male	5423 (52.5%)	1023 (55.7%)	268 (64.4%)	<.0001	6559 (52.4%)	871 (55.2%)	111 (64.2%)	.001
Multiple gestation	2969 (28.7%)	483 (26.3%)	99 (23.8%)	.01	4082 (32.6%)	397 (25.2%)	36 (20.8%)	<.0001
Antenatal steroids	9101 (88.1%)	1586 (86.3%)	305 (73.3%)	<.0001	10 763 (86.0%)	1334 (84.5%)	120 (69.4%)	<.0001
Maternal hypertension	2732 (26.9%)	400 (22.1%)	79 (19.4%)	<.0001	4182 (33.8%)	499 (32.1%)	47 (27.5%)	.09
Chorioamnionitis	519 (6.9%)	118 (9.6%)	31 (11.0%)	.0003	432 (4.6%)	78 (6.8%)	13 (10.9%)	<.0001
Maternal bleed	1919 (18.8%)	317 (17.5%)	90 (22.0%)	.09	1862 (15.1%)	239 (15.3%)	33 (19.3%)	.30
Prenatal care	10 019 (97.0%)	1788 (97.3%)	393 (94.5%)	.009	12 205 (97.5%)	1525 (96.6%)	160 (92.5%)	<.0001
Race/ethnicity				.02				<.0001
Non-Hispanic white	2944 (28.5%)	567 (30.9%)	106 (25.5%)		3777 (30.2%)	499 (31.6%)	63 (36.4%)	
Hispanic	4616 (44.7%)	765 (41.6%)	219 (52.6%)		5415 (43.3%)	578 (36.6%)	75 (43.4%)	
Non-Hispanic black	1281 (12.4%)	222 (12.1%)	45 (10.8%)		1380 (11.0%)	223 (14.1%)	20 (11.6%)	
Asian/Pacific Islander	1216 (11.8%)	237 (12.9%)	37 (8.9%)		1552 (12.4%)	235 (14.9%)	11 (6.4%)	
Native American	29 (0.3%)	5 (0.3%)	0 (0%)		42 (0.3%)	5 (0.3%)	2 (1.2%)	
Other	247 (2.4%)	41 (2.2%)	9 (2.2%)		352 (2.8%)	38 (2.4%)	2 (1.2%)	
Cesarean delivery	7830 (75.8%)	1181 (64.3%)	285 (68.5%)	<.0001	9704 (77.5%)	1043 (66.2%)	111 (64.2%)	<.0001
1-min Apgar, median (IQR)	7 (5-8)	6 (4-8)	5 (3-7)	<.0001	7 (5-8)	7 (5-8)	5 (2-7)	<.0001
5-min Apgar, median (IQR)	8 (7-9)	8 (7-9)	7 (6-8)	<.0001	8 (8-9)	8 (7-9)	8 (6-9)	<.0001
Delivery room intubation	3817 (37.0%)	840 (45.8%)	261 (62.9%)	<.0001	2423 (19.4%)	391 (24.8%)	81 (46.8%)	<.0001
Delivery room CPR*	108 (1.1%)	32 (1.7%)	21 (5.1%)	<.0001	60 (0.5%)	19 (1.2%)	15 (8.7%)	<.0001
Surfactant administration	6155 (59.6%)	1215 (66.2%)	351 (84.4%)	<.0001	5269 (42.1%)	732 (46.4%)	123 (71.1%)	<.0001
Death prior to discharge	156 (1.5%)	54 (2.9%)	69 (16.6%)	<.0001	90 (0.7%)	26 (1.7%)	18 (10.4%)	<.0001

*Delivery room CPR receipt of chest compressions or administration of epinephrine.

Table III. Multivariate analysis of significant risk factors for severe IVH

	22-23 gestational age wk		24-25 gestational age wk		26-27 gestational age wk		28-29 gestational age wk		30-31 gestational age wk	
Risk factors	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Sex (Male)	1.22	0.98, 1.53	1.28	1.13, 1.45	1.17	1.01, 1.36	1.55	1.25, 1.91	1.47	1.07, 2.03
Multiple gestation	1.57	1.23, 2.01	1.58	1.37, 1.83	1.37	1.15, 1.63	0.96	0.75, 1.24	0.78	0.53, 1.16
Antenatal steroids	0.61	0.48, 0.78	0.55	0.46, 0.65	0.62	0.51, 0.75	0.50	0.39, 0.63	0.54	0.38, 0.78
Maternal hypertension	0.88	0.57, 1.37	0.61	0.49, 0.76	0.63	0.50, 0.79	0.77	0.58, 1.01	0.92	0.63, 1.35
Cesarean delivery	0.88	0.70, 1.10	0.85	0.74, 0.98	0.95	0.79, 1.13	0.73	0.58, 0.92	0.48	0.34, 0.68
Delivery room intubation	1.02	0.66, 1.57	1.20	0.98, 1.47	1.40	1.16, 1.69	1.77	1.39, 2.24	1.54	1.05, 2.26
Delivery room CPR*	1.09	0.74, 1.63	1.09	0.83, 1.43	1.41	0.94, 2.07	1.13	0.64, 2.01	3.79	1.85, 7.76

*Delivery room CPR-receipt of chest compressions or administration of epinephrine.

Table IV. Complete results of multivariate analysis for the whole cohort and gestational age subgroups

	22-31 gestational age wk			22-23 gestational age wk			24-25 gestational age wk			26-27 gestational age wk			28-29 gestational age wk			30-31 gestational age wk		
Risk factors	**aOR**	**95% CI**		**aOR**	**95% CI**		**aOR**	**95% CI**		**aOR**	**95% CI**		**aOR**	**95% CI**		**aOR**	**95% CI**	
Sex (male)	**1.29**	**1.19**	**1.40**	1.22	0.98	1.53	**1.28**	**1.13**	**1.45**	**1.17**	**1.01**	**1.36**	**1.55**	**1.25**	**1.91**	**1.47**	**1.07**	**2.03**
Birth weight	1.15	0.89	1.48	0.86	0.24	3.04	0.71	0.40	1.24	**1.83**	**1.14**	**2.92**	1.06	0.65	1.73	0.82	0.45	1.49
Gestational age wk																		
22 Gestational age wk	**26.34**	**16.50**	**42.03**	1.00	0.72	1.39												
23 Gestational age wk	**26.22**	**18.15**	**37.88**	ref	ref	ref												
24 Gestational age wk	**20.10**	**14.26**	**28.32**				**1.49**	**1.30**	**1.71**									
25 Gestational age wk	**13.25**	**9.54**	**18.40**				ref	ref	ref									
26 Gestational age wk	**9.10**	**6.65**	**12.43**							**1.42**	**1.21**	**1.67**						
27 Gestational age wk	**6.72**	**4.99**	**9.05**							ref	ref	ref						
28 Gestational age wk	**3.46**	**2.57**	**4.64**										**1.28**	**1.03**	**1.57**			
29 Gestational age wk	**2.60**	**1.95**	**3.46**										ref	ref	ref			
30 Gestational age wk	**1.43**	**1.05**	**1.95**													1.32	0.96	1.83
31 Gestational age wk	ref	ref	ref													ref	ref	ref
Multiple gestation	**1.36**	**1.24**	**1.49**	**1.57**	**1.23**	**2.02**	**1.58**	**1.37**	**1.83**	**1.37**	**1.15**	**1.63**	0.96	0.75	1.24	0.78	0.53	1.16
Antenatal steroids	**0.57**	**0.51**	**0.63**	**0.61**	**0.48**	**0.78**	**0.55**	**0.46**	**0.65**	**0.62**	**0.51**	**0.75**	**0.50**	**0.39**	**0.63**	**0.54**	**0.38**	**0.78**
Maternal hypertension	**0.69**	**0.61**	**0.78**	0.88	0.57	1.37	**0.61**	**0.49**	**0.76**	**0.63**	**0.50**	**0.79**	0.77	0.58	1.01	0.92	0.63	1.35
Chorio-amnionitis	1.03	0.90	1.19	0.80	0.56	1.16	1.00	0.81	1.23	0.92	0.69	1.21	1.38	0.94	2.04	1.81	0.99	3.29
Prenatal care	0.89	0.74	1.06	0.63	0.40	1.01	0.94	0.69	1.26	1.18	0.80	1.73	0.78	0.49	1.23	0.75	0.40	1.40
Race																		
Hispanic	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Non-Hispanic White	0.94	0.85	1.04	1.30	0.97	1.75	0.84	0.71	1.00	0.91	0.75	1.09	0.80	0.62	1.03	1.35	0.95	1.92
Non-Hispanic Black	0.95	0.86	1.07	1.04	0.77	1.41	1.06	0.89	1.27	0.90	0.71	1.13	**0.69**	**0.49**	**0.97**	0.84	0.50	1.39
Other	**0.78**	**0.69**	**0.89**	0.79	0.53	1.18	0.85	0.69	1.04	**0.75**	**0.58**	**0.95**	**0.68**	**0.48**	**0.94**	0.60	0.34	1.06
Cesarean delivery	**0.84**	**0.77**	**0.92**	0.88	0.70	1.10	**0.85**	**0.74**	**0.98**	0.95	0.79	1.13	**0.73**	**0.58**	**0.92**	**0.48**	**0.34**	**0.68**
1-min Apgar <3	**1.23**	**1.11**	**1.37**	0.98	0.75	1.27	**1.19**	**1.02**	**1.40**	**1.44**	**1.18**	**1.76**	1.23	0.91	1.67	**1.87**	**1.17**	**2.97**
1-min Apgar <7	**1.52**	**1.36**	**1.71**	1.26	0.82	1.94	**1.24**	**1.02**	**1.50**	**1.50**	**1.23**	**1.83**	**1.72**	**1.33**	**2.22**	**1.80**	**1.22**	**2.66**
5-min Apgar <3	**1.32**	**1.12**	**1.57**	0.84	0.58	1.22	**1.78**	**1.39**	**2.29**	1.04	0.72	1.50	**1.79**	**1.07**	**3.01**	1.00	0.48	2.10
5-min Apgar <7	**1.36**	**1.23**	**1.50**	**1.40**	**1.07**	**1.84**	**1.21**	**1.04**	**1.42**	**1.50**	**1.25**	**1.82**	**1.50**	**1.13**	**1.98**	1.56	0.98	2.46
Delivery room intubation	**1.51**	**1.35**	**1.69**	1.02	0.66	1.57	1.20	0.98	1.47	**1.40**	**1.16**	**1.69**	**1.77**	**1.39**	**2.24**	**1.54**	**1.05**	**2.26**
Delivery room CPR*	1.20	1.00	1.43	1.09	0.74	1.63	1.09	0.83	1.43	1.40	0.94	2.07	1.13	0.64	2.01	**3.79**	**1.85**	**7.76**

Values in bold are significant aORs.
*Delivery room CPR-receipt of chest compressions or epinephrine administration.