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Early Hypoxemia Burden is Strongly Associated with Severe Intracranial Hemorrhage in Preterm Infants

Zachary A. Vesoulis[1], **Rachel L. Bank**[1], **Doug Lake**[2], **Aaron Wallman-Stokes**[4], **Rakesh Sahni**[4], **J. Randall Moorman**[2], **Joseph R. Isler**[4], **Karen D. Fairchild**[3], and **Amit M. Mathur**[1]

[1]Department of Pediatrics, Washington University School of Medicine, Division of Newborn Medicine, St. Louis, MO

[2]Department of Medicine, University of Virginia, Charlottesville, VA

[3]Department of Pediatrics, University of Virginia, Charlottesville, VA

[4]Department of Pediatrics, Columbia University, New York, NY

Abstract

Objectives: The objective of this study was to define the association between the burden of severe hypoxemia ($SpO_2 \leq 70\%$) in the first week of life and development of severe ICH (grade III/IV) in preterm infants.

Study Design: Infants born <32 weeks or weighing <1500g underwent prospective SpO_2 recording from birth through 7d. Severe hypoxemia burden was calculated as the percentage of the error-corrected recording where $SpO_2 \leq 70\%$. Binary logistic regression was used to model the relationship between hypoxemia burden and severe ICH.

Results: A total of 163.3 million valid SpO_2 data points were collected from 645 infants with mean EGA=27.7±2.6 weeks, BW=1005±291g; 38/645 (6%) developed severe ICH. There was a greater mean hypoxemia burden for infants with severe ICH (3%) compared to those without (0.1%) and remained significant when controlling for multiple confounding factors.

Conclusion: The severe hypoxemia burden in the first week of life is strongly associated with severe ICH.

INTRODUCTION

Intracranial hemorrhage is the most common form of preterm brain injury, affecting approximately 25% of all infants born before 30 weeks of gestation (1–3), of which approximately 10% have severe (grade III/IV) ICH. Instability of cerebral blood flow is a key mechanism by which ICH occurs (4,5). Pressure-passive cerebral autoregulation, common in infants born before 30 weeks (6–8), leads to significant fluctuations in cerebral

Address correspondence to: Zachary A. Vesoulis, MD, 1 Children's Place, Box 8116, St. Louis, MO 63110, Phone: 314-454-6148, Fax: 314-454-4633, vesoulis_z@wustl.edu.

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perfusion as blood flow to the brain changes with systemic blood pressure. Repeated episodes of ischemia followed by reperfusion generate reactive oxygen species (9) which further damage the fragile blood vessels and alter blood vessel growth (10) within the germinal matrix, increasing the risk of ICH (11).

Oxygenation saturation burden has been the subject of several decades of study, primarily with a focus on hyperoxemia and the risk of retinopathy of prematurity (12,13). A series of successful randomized trials led to the adoption of narrowly defined oxygen saturation guidelines (14–16) and markedly reduced the incidence of ROP. More recently however, concern has risen that chronic exposure to lower oxygen saturations is associated with adverse events, including mortality (17,18) and intracranial hemorrhage (19).

The objective of this study was to address the significant knowledge gap between the theoretical and proven risk of ICH in association with the hypoxemia burden. In this study we attempt to narrow this gap by defining the association between the burden of severe hypoxemia ($SpO_2 \leq 70\%$) in the first week of life and the development of severe ICH (grade III or IV) using high-resolution, error-corrected data prospectively collected in a multi-institution initiative.

METHODS

Patient selection

Infants at risk for the development of ICH who underwent prospective recording of cardiorespiratory monitoring from birth through the first week of life were enrolled at three level IV NICUs (Morgan Stanley Children's Hospital, St. Louis Children's Hospital, UVA Children's Hospital) over a five-year period (2012–2017). Inclusion criteria were GA < 32 weeks at birth and/or birthweight <1500 grams, cranial ultrasound imaging in the first week of life, and availability of continuous pulse oximetry data in the first week of life. We limited our analysis to the first week of life as this is the highest-risk period for the development of ICH (11). Infants were excluded if they did not meet the above requirements or if they were transferred or expired prior to the end of the first week of life. The Institutional Review Board at each center reviewed and approved the study protocol.

Sample characteristics

Comprehensive demographic and outcome data were collected for all included infants, including GA at birth, BW, small for gestational age (defined as BW at < 10^{th} centile), sex, highest grade of ICH, and mortality (after 7d). Other risk factors for ICH were also collected including antenatal steroid exposure, prophylactic indomethacin use, delivery type (Cesarean section or vaginal delivery), and pneumothorax requiring intervention during the first week of life (needle aspiration or thoracostomy tube placement). All infants had cranial ultrasound imaging performed at least once in the first week of life, and the highest noted grade of ICH was used for analysis.

Oxygen saturation data collection

Masimo (UVA and CUMC) and Nellcor (WU) pulse oximeters were utilized in this study. A common averaging time of 8 seconds was used by all centers. During the study period, all three centers used similar target oxygen saturation guidelines, with a goal SpO_2 range between 90–95%. At each center, physiologic data (including SpO_2) from the patient monitor is prospectively archived in a database (BedMasterEx, ExcelMedical, Jupiter, FL) with a sampling rate of 0.5 Hz. The file associated with each infant was then extracted from the database and converted to a MATLAB matrix for further processing.

Data analysis

SpO_2 error correction—All data underwent a two-step error correction process. First, the entire recording was partitioned into 60-second (30 sample) epochs. Each epoch was then examined for completeness; epochs were discarded if more than 50% of the data were missing (e.g. pulse oximeter probe not in contact with the skin, temporarily detached for bath, repositioning, or procedure). Remaining epochs were then examined for motion artifact, identified by sudden, non-physiologic changes in the measured oxygen saturation. Epochs were judged to have motion artifact when they contained segments with sudden change (either increase or decrease) of excessive magnitude, defined as absolute change between serial points exceeding two standard deviations of the normative mean. As normative data of this type do not exist in the literature, they were derived using a subset of the overall cohort (15 million samples from 30 infants judged to have recordings with exemplary signal quality by visual inspection of the time-series). From this data we determined that the mean change in SpO_2 between serial measurements is 0% with a standard deviation of 1.5%, thus epochs with a ΔSpO_2 greater than 3% between serial data points were judged to be contaminated with motion artifact and were discarded.

Hypoxemia burden calculation—After the error-correction was complete, all remaining epochs for each infant were used to calculate the hypoxemia burden, defined as the proportion of measured SpO_2 samples ≤ 70%. This threshold of hypoxemia was chosen as it represents a severe level of desaturation, corresponding to a PaO_2 of 35–40 mmHg (20,21). Although hypoxemia has been conventionally defined as a PaO_2 < 50 mmHg (22,23), pulse oximetry in the neonate has a margin of error of roughly ±6% (24). The SpO_2 threshold of 70% therefore represents a definitive point of desaturation, without risk of accidental classification error (25). A note of caution is warranted however, in that pulse oximetry is a surrogate measure of hypoxemia as it is only a measure of oxygen bound to hemoglobin (HbO_2) and not the total oxygen content of the blood (PaO_2).

As a secondary outcome, a *hyperoxemia* burden, defined as the proportion of measured SpO_2 samples > 95% was also obtained to assess the degree to which infants' SpO2 was above the target range of 90–95%.

Statistical approach

Univariate comparisons of the sample characteristics were made between two groups (those with severe ICH and those without) using the Mann–Whitney U-test for continuous variables and Fisher's Exact Test (two-sided) for categorical variables. For the primary outcome, a

binary logistic regression model for the prediction of high-grade ICH was constructed using the hypoxemia burden as the predictor variable, while also controlling for important confounders including GA, BW, antenatal steroid exposure, prophylactic indomethacin, and pneumothorax requiring intervention during the first week of life. Two secondary outcomes were evaluated: the association between hypoxemia burden and mortality, and the difference in hyperoxemia burden between the two groups.

For all regression models, correlation between predictors was assessed using the variance inflation factor (VIF), a measure of the degree of multicollinearity where VIF > 5 is indicative of highly correlated predictors. P values were considered significant when less than 0.05. All statistical comparisons were made using R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient sample

A total of 1179 infants were admitted during the study window; 231 infants were excluded based on predefined criteria while another 303 infants were excluded as the recording was corrupted or incomplete (missing data). After exclusion, 645 infants remained for further analysis (Figure 1). The group mean GA was 27.7 ± 2.6 weeks, mean BW was 1005 ± 291g, 47% were male, 30/645 (5%) died during the NICU course, and 38/645 (6%) had grade III or IV ICH on cranial ultrasound in the first week of life. Not surprisingly, there were a number of significant differences between the subgroups with and without severe ICH including GA (25.1 vs. 27.9 weeks, $p<0.01$), BW (819 vs. 1017 grams, $p<0.01$), and mortality (42 vs 3%, $p<0.01$). (Table 1)

Data quality metrics

During error correction, the overall mean data rejection rate was 3 ± 7%. Of the rejected epochs, 15% were rejected due to incomplete or missing data and 85% were rejected due to motion artifact. The median length of the error-corrected recording was 5.8 days (interquartile range 5.0–6.2 days) for a total of 163.3 million valid SpO_2 measurements used for the hypoxemia burden calculations. There was no significant difference in the length of recording or data rejection rate between those with and without severe ICH.

Severe hypoxemia burden

There was a significant difference ($p<0.01$) in mean hypoxemia burden between infants with severe ICH (3% of recording) and those without severe ICH (0.1% of recording) (Figure 2). This relationship remained statistically significant ($p<0.01$) when controlling for confounders in the regression model and had good discrimination (AUC=0.854). None of the covariates demonstrated excessive collinearity (all VIF < 5). Complete regression model output is shown in Table 2. Early hypoxemia burden was not a significant predictor of mortality ($p=0.71$) after the first week of life.

Hyperoxemia burden

The mean hyperoxemia burden, defined as the proportion of the recording where SpO_2 was > 95%, was significantly less for infants with severe ICH compared to those without (42% vs. 60%). This difference was also statistically significant ($p<0.01$).

CONCLUSIONS

In this study we demonstrated in a high-resolution, longitudinal, multi-center cohort that severe hypoxemia burden in the first week of life can be quantified and that it is associated with the development of severe intraventricular hemorrhage, even when controlling for a broad range of other factors. The measured burden of severe hypoxemia was nearly thirty times greater in the group of infants with severe ICH compared to those without. While these results do not establish a causal relationship between hypoxemia and ICH, one plausible interpretation is that chronic hypoxemia, at least in part, contributes to the adverse clinical milieu which results in this most common form of brain injury in the preterm infant.

To our knowledge, this is the first clinical study to examine the association between hypoxemia burden and the development of ICH. Intriguingly, a recent paper (26), which used the cross correlation of heart rate and SpO_2 during the first 12 hours after birth and clinical variables, had a similar discriminatory power for predicting severe IVH (AUC = 0.879 vs 0.854) despite the use of a different physiologic measure, suggesting that longitudinal analysis of pulse oximetry measurements provides stable predictive power in the short and long term.

Other studies of pulse oximetry in preterm infants have focused on retinopathy of prematurity and mortality at a much higher threshold of hypoxemia (SpO_2 < 85%). While ROP was not a focus of this study, mortality was a secondary outcome and intriguingly, hypoxemia burden was not a significant predictor of mortality. As noted earlier, the association of hypoxemia and mortality has been the source of active debate in the recent literature. While the authors of the SUPPORT trial reported an increased rate of mortality in the group of infants with intentionally lower saturations, the lower SpO_2 limit of that group was 85%; far above the 70% threshold used in this study. A potential explanation for the lack of association between mortality and hypoxemia burden in this study may come from bias introduced by the inclusion criteria. In this study, infants were only included if they survived past the first 7 days of life (and thus had complete data for analysis). Literature suggests that the majority of preterm infants who die do so in the first 48–72 hours after birth (27,28), a finding mirrored in our study with nearly 75% (88/118) of deaths occurring during the first week of life. This meant that a significant proportion of infants who died prior to discharge were not evaluated in this study. To capture these infants, a similar methodology could be applied to a shorter timeframe for further study of this outcome.

The unexpected results of the SUPPORT trial highlight obvious gaps in the literature, essentially the definition of hypoxemia. Some researchers have suggested that the preterm neonate should be relatively tolerant of hypoxemia, arguing that the *in utero* conditions they might otherwise have experienced are characterized by low arterial oxygen content (29,30). However, the transition to *ex utero* physiology, particularly gas exchange and a shift in the

hemoglobin disassociation curve as the infant transitions from hemoglobin F to A (22), result in a remarkably different physiology than that of the fetus with correspondingly different risks (30). Our understanding of the precise impact that repetitive episodes of hypoxemia have on the development of ICH remains limited, although there are animal models suggesting that hypoxemia induces angiogenesis of immature, poorly supported blood vessels (10) and human data to suggest that intermittent hypoxemia has been associated with poorer neurodevelopmental outcomes (31). The SafeBoosC trial was the first to demonstrate a definitive link between cerebral desaturation and increased rates of brain injury (19).

While not the primary focus of the study, there was a notable difference between the subgroups in the amount of time spent with SpO_2 > 95%, with higher saturations in the group without severe ICH. There are a number of possible explanations for this finding including decreased saturation stability in the setting of hemorrhage or differential compliance with alarm limits. Future studies should focus on developing a standardized model of saturation stability and should include capture of the fraction of inspired oxygen in order to assess the contribution of these factors.

In animal models, the germinal matrix is marked by extensive angiogenesis and high metabolic demand, predominantly mediated through vascular endothelial growth factor (VEGF) and angiopoietin-2 (ANGPT-2) (32). Expression of these factors suggests that the germinal matrix operates in a state of physiologic hypoxemia (33). When there is additional hypoxemia resulting from systemic desaturation, it is reasonable to hypothesize that VEGF and ANGPT-2 expression increases, leading to even more extensive angiogenesis (10). These rapidly expanding blood vessels, which lack the structure and support of pericytes (34,35), decreased endothelial tight junctions (36), and reduced perivascular coverage by astrocyte endfeet (37), are then exposed to the turbulent transitional hemodynamics of the first week of life without a properly functioning cerebrovascular autoregulatory system, resulting in an increased likelihood of vessel rupture, and ultimately leading to intraventricular hemorrhage.

There are a number of important limitations to this study which should be considered when generalizing the results. The foremost limitation is the lack of frequent standardized cranial ultrasound imaging or specific timing of imaging for individual patients. While this study demonstrates an association between severe ICH and hypoxemia, it cannot be definitively established whether hypoxemia is the proximal cause or if severe ICH induces hemodynamic instability manifested as hypoxemia. Future studies should include frequent cranial ultrasound imaging with standardized timing to clearly establish pre- and post-hemorrhage hypoxemia data in order to establish the causal relationship. Other limitations include a lack of respiratory support parameters (e.g. mean airway pressure, fraction of inspired oxygen) captured in the study design. Future studies should include these data in order to better understand differences in respiratory support and oxygen titration between these groups.

The goal of this study was to characterize the association between hypoxemia and development of severe ICH. While there is literature to suggest that the cerebrovascular

autoregulatory system of this cohort of infants is often impaired (8,9), this study does not include a direct measure of autoregulation, thus it remains an unverifiable presumption that severe systemic hypoxemia ($SpO_2 \leq 70\%$) results in simultaneous cerebral desaturation (hypoxia). Future studies should consider using an ancillary measure such as near-infrared spectroscopy to evaluate cerebral saturations.

In conclusion, infants who develop severe ICH have roughly thirty times the severe hypoxemia burden in the first week of life as infants without severe ICH. This hypoxemia burden is strongly associated with severe ICH in a binary logistic regression model, even when correcting for GA and birthweight. Infants with injury also spent significantly less time with high saturations ($SpO_2 > 95\%$) compared to those without severe ICH.

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Acronym expansion:

AUC	area under the curve
BW	birth weight
CUMC	Columbia University Medical Center
GA	gestational age
ICH	intracranial hemorrhage
ROP	retinopathy of prematurity
SGA	small for gestational age
SpO_2	oxygen saturation
UVA	University of Virginia
VIF	variance inflation factor
WU	Washington University

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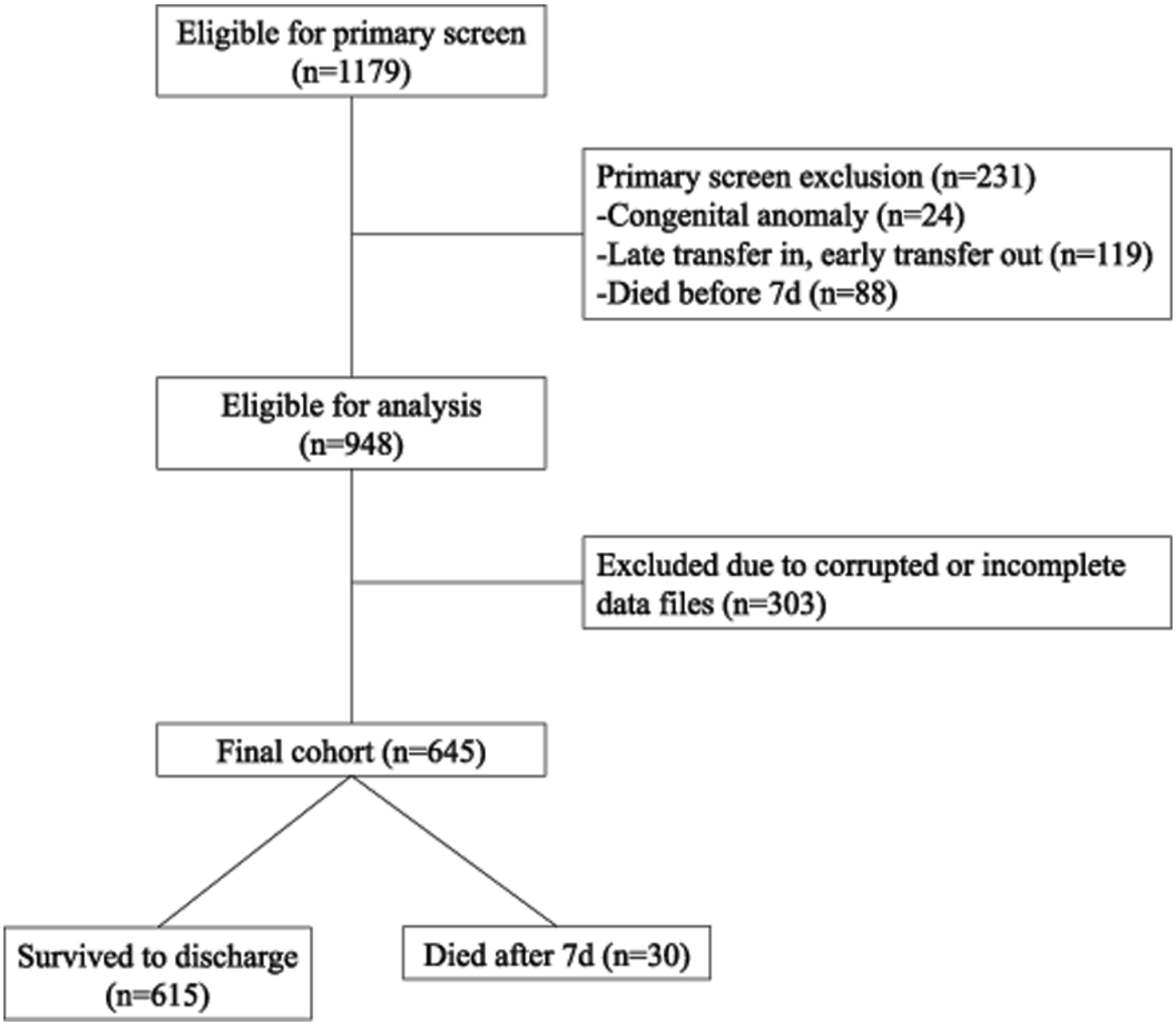

Figure 1-

Patient flow chart demonstrating the number of infants initially available and the number remaining after primary screening and exclusion for corrupt/incomplete files.

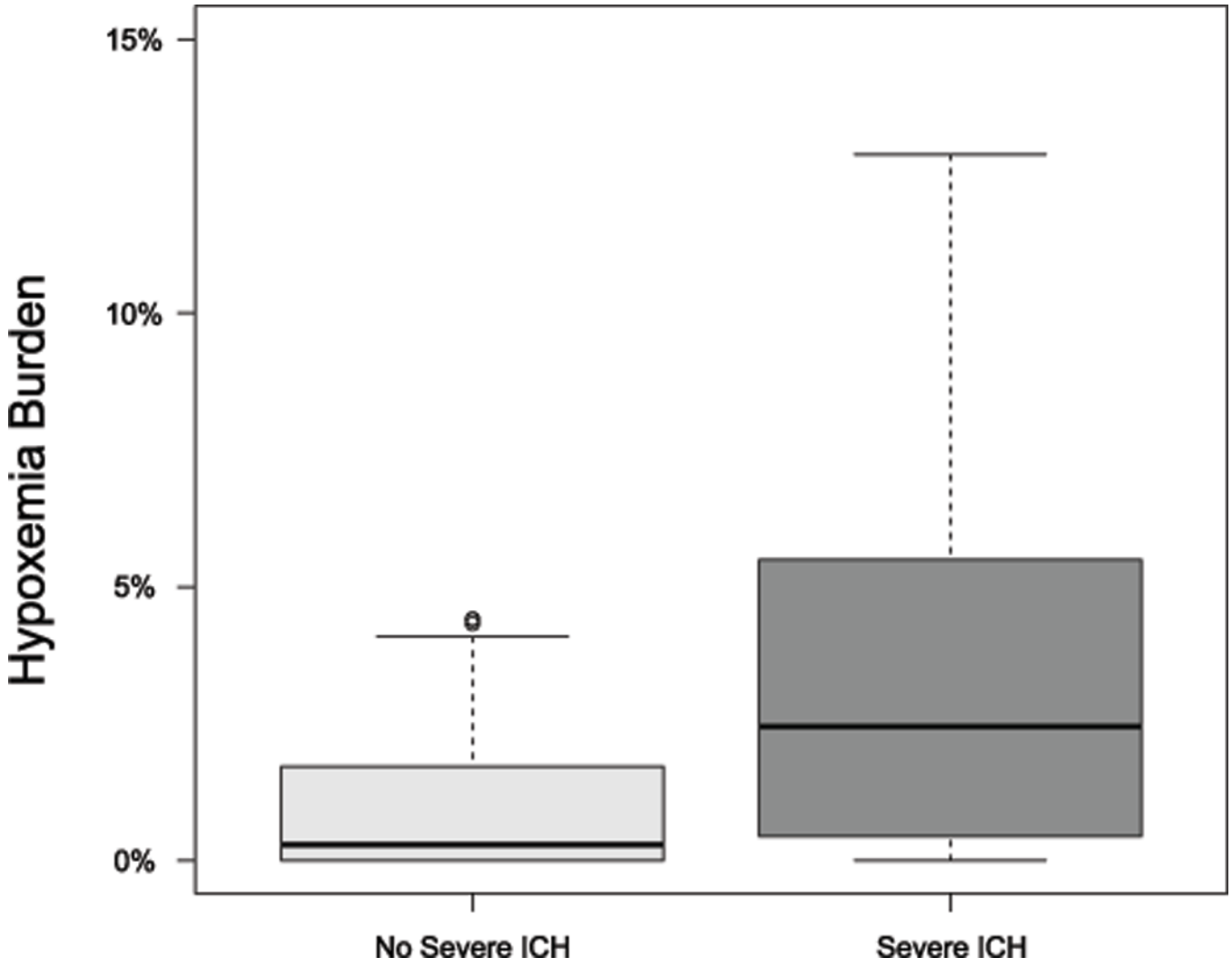

Figure 2-
Whisker and box plot demonstrating the difference in severe hypoxia burden between the no severe ICH and severe ICH groups.

Table 1.

Sample Characteristics

	No Severe ICH (n=607)	Severe ICH (n=38)	P value
EGA, mean (SD), weeks	27.9 (2.5)	25.1 (1.3)	<0.01*
Birthweight, mean (SD), grams	1016.9 (291.59)	818.9 (208.2)	<0.01*
SGA, n (%)	103 (17)	2 (5)	0.07
Male sex, n (%)	275 (45)	20 (53)	0.41
Vaginal delivery, n (%)	381 (63)	13 (34)	0.02*
Antenatal steroids, n (%)	537 (88)	30 (79)	0.11
Pneumothorax in first 7d, n (%)	34 (6)	4 (11)	0.27
Prophylactic indomethacin, n (%)	70 (12)	12 (32)	<0.01*
Died, n (%)	21 (3)	9 (24)	<0.01*
BPD, n (%)	89 (15)	17 (45)	<0.01*

Footnote:

* denotes significance at p<0.05

Table 2.

Logistic regression, hypoxemia burden and ICH

Variable	Beta coefficient	Z statistic	P value	VIF
Gestational age	−0.954	−4.84	<0.01*	3.59
Birthweight	0.004	2.62	<0.01*	3.57
Antenatal steroids	−0.479	−1.02	0.31	1.04
Vaginal delivery	−0.457	−1.15	0.25	1.18
Prophylactic indomethacin	0.242	0.586	0.56	1.11
Pneumothorax in first 7d	0.797	1.25	0.21	1.11
Severe hypoxemia burden	6.56	2.70	<0.01*	1.01

Footnote:

* denotes significance at $p<0.05$