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Neurodevelopmental Outcomes of Extremely Low Birth Weight Infants with Spontaneous Intestinal Perforation or Surgical Necrotizing Enterocolitis

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Abstract

Objective—To determine if extremely low birth weight infants with surgical necrotizing enterocolitis have a higher risk of death or neurodevelopmental impairment and neurodevelopmental impairment among survivors (secondary outcome) at 18–22 months corrected age compared to infants with spontaneous intestinal perforation and infants without necrotizing enterocolitis or spontaneous intestinal perforation.

Study Design—Retrospective analysis of the Neonatal Research Network very low birth weight registry, evaluating extremely low birth weight infants born between 2000–2005. The study infants were designated into 3 groups: 1) Spontaneous intestinal perforation without necrotizing enterocolitis; 2) Surgical necrotizing enterocolitis (Bell's stage III); and 3) Neither spontaneous intestinal perforation nor necrotizing enterocolitis. Multivariate logistic regression analysis was performed to evaluate the association between the clinical group and death or neurodevelopmental impairment, controlling for multiple confounding factors including center.

Results—Infants with surgical necrotizing enterocolitis had the highest rate of death prior to hospital discharge (53.5%) and death or neurodevelopmental impairment (82.3%) compared to infants in the spontaneous intestinal perforation group (39.1% and 79.3%) and no necrotizing enterocolitis/no spontaneous intestinal perforation group (22.1% and 53.3%; $p<0.001$). Similar results were observed for neurodevelopmental impairment among survivors. On logistic regression analysis, both spontaneous intestinal perforation and surgical necrotizing enterocolitis were associated with increased risk of death or neurodevelopmental impairment (adjusted OR 2.21, 95% CI: 1.5, 3.2 and adjusted OR 2.11, 95% CI: 1.5, 2.9 respectively) and neurodevelopmental impairment among survivors (adjusted OR 2.17, 95% CI: 1.4, 3.2 and adjusted OR 1.70, 95% CI: 1.2, 2.4 respectively).

Conclusions—Spontaneous intestinal perforation and surgical necrotizing enterocolitis are associated with a similar increase in the risk of death or neurodevelopmental impairment and neurodevelopmental impairment among extremely low birth weight survivors at 18–22 months corrected age.

Keywords

spontaneous intestinal perforation; necrotizing enterocolitis; extremely low birth weight; neurodevelopmental impairment

INTRODUCTION

Spontaneous intestinal perforation (SIP) and necrotizing enterocolitis (NEC) are serious morbidities affecting extremely low birth weight (ELBW) infants.[1,2] The incidence of SIP ranges from 3–8 % in ELBW infants,[2, 3] with that of NEC being similarly high (7%), with as many as 30% receiving surgical intervention.[4] Although SIP and NEC have been recognized as distinct entities,[5–7] they are both associated with significant morbidities.[8] Since SIP is a localized disease, it is often assumed that SIP is less likely to be associated

with a systemic inflammatory reaction than NEC, with lower risk of adverse outcomes. Although mortality and in-hospital morbidity of infants with SIP have been shown to be lower than infants with surgical NEC,[9] we previously found an increased risk of poor neurodevelopmental outcomes in ELBW infants with SIP.[10] Similarly, ELBW infants with surgical NEC have been shown to be at increased risk of poor neurodevelopmental outcome.[11]

While it is plausible that longer-term outcomes for infants with SIP may be better than infants with surgical NEC, comparative neurodevelopmental outcomes for ELBW infants with these two conditions have not been studied in a large cohort of infants.

The objective of this study was to compare the composite outcome of death or neurodevelopmental impairment in ELBW infants with SIP and surgical NEC.

METHODS

This is a retrospective cohort study of ELBW infants (birth weight between 401 g and 1000 g) admitted to the participating centers of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) during calendar years 2000–2005. Infants who died before 12 hours of age were excluded from the study. This cohort also included 156 ELBW infants admitted to these participating centers between February, 2001 and August, 2002, who developed intestinal perforation, whose outcomes have previously been reported [9]. Unlike the present study, the primary focus of that study, however, was to report on the comparative outcomes of these infants based on the surgical approach, rather than the underlying disease state.

Infants were categorized into three groups: 1) SIP (intestinal perforation without NEC), 2) SurgNEC (Bell's stage III), and 3) neither SIP nor any NEC (No NEC/No SIP). Infants coded as having both SIP and SurgNEC were excluded due to the possibility that they may have been misclassified.

Prospectively collected data in the NRN generic database (GDB) included maternal and neonatal information, treatment and clinical outcomes. Trained research coordinators obtained the data based on the definitions listed in the Manual of Operations. SIP was defined as evidence of intestinal perforation without evidence of pneumatosis intestinalis, and SurgNEC was defined as NEC needing an operation. All centers participating in the Neonatal Research Network received local IRB approval for data collection.

At 18–22 months corrected age, the survivors underwent follow-up assessment consisting of neurologic evaluation and hearing, vision and developmental testing, the latter by a certified examiner. The neurological examination administered was based on the Amiel-Tison assessment, including an evaluation of tone, strength, reflexes, angles, and posture. Cerebral palsy was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture. Hearing and visual status was obtained by parental history; deafness was confirmed by audiologic testing; and a standard vision assessment was completed. Deafness was defined as hearing loss needing bilateral amplification. Blindness was defined as bilateral

corrected vision of less than 20/200. The Bayley Scales of Infant Development–II [BSID-II] were administered, and a Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were derived. An MDI or PDI < 70 (≥ 2 standard deviations below the mean) indicated significant delay. Children who could not be assessed due to severe developmental delay were assigned MDI and PDI scores of 49.

Neurodevelopmental impairment (NDI) was defined as the presence of one or more of the following: moderate or severe cerebral palsy, bilateral blindness, bilateral hearing loss needing amplification, Bayley MDI or Bayley PDI less than 70. Death occurring after 12 hours of age and before 18–22 months follow-up was included in our composite primary outcome measure of death or NDI because death is a competing outcome for NDI.

Data Analysis

Outcomes at 18–22 months corrected age were compared among infants with SIP, SurgNEC and those with no NEC/no SIP. The primary outcome was death or neurodevelopmental impairment (NDI) at 18–22 months corrected age. Secondary outcome included NDI among survivors. Adjusted analysis was performed for the primary and secondary outcome, using multivariate logistic regression analysis to determine the independent association of diagnostic group with outcomes, controlling for potential confounding factors. In addition to SIP and SurgNEC, the variables included in the regression analyses for NDI/ death and NDI were those that have previously been shown to affect neurodevelopmental outcomes, including maternal education, birth weight, male sex, small for gestation (SGA) status, inborn, antenatal antibiotic and corticosteroid therapy, postnatal corticosteroid therapy, bronchopulmonary dysplasia, severe intraventricular hemorrhage, periventricular leukomalacia, late onset sepsis and center.[12

RESULTS

A total of 9,507 ELBW infants were admitted to NICHD NRN study centers between 2000 and 2005 and survived beyond 12 hours of age. Among these, 437 ELBW infants were diagnosed with medical NEC (Bell's stage 2 or lower), 472 with SurgNEC, and 282 with SIP; 8,184 infants were in the no SIP/no NEC group. The following infants were excluded from analysis: 128 infants coded as having both SIP and NEC and four infants with missing perforation data. Of the 6,772 infants who survived to discharge, 132 infants died after hospital discharge. Of the 6,640 surviving infants, who were eligible for follow up, 5,786 ELBW infants completed the 18–22 month follow up visit (follow up rate of 87.1%) (Figure 1).

Maternal characteristics of the three groups are shown in Table 1. A greater proportion of mothers of infants in the SIP group received prenatal antibiotics (a possible surrogate for maternal chorioamnionits). Mothers of infants in the SIP group were less likely to have hypertension as compared to the other two groups.

Infant characteristics of the three groups are shown in Table 2. Infants in the SIP and SurgNEC group were more likely to be male than those in the no SIP/no NEC group. Infants in the SIP group were more likely to be of lower gestation and have lower mean birth weight

than infants in the other two groups. They were also less likely to be small for gestation or to be inborn, as compared to the other two groups.

A greater proportion of infants in the SIP and SurgNEC group had been exposed to indomethacin postnatally and required PDA ligation as compared to infants in the No SIP/No NEC group. Similarly, these infants were more likely to have received postnatal steroids and had a longer duration of parenteral nutrition.

Both SIP and SurgNEC groups had a higher proportion of infants with significant morbidities (Table 3) and had a longer length of stay and a greater postmenstrual age at discharge as compared to the no NEC/no SIP group. These two groups also had a higher proportion of infants who died or developed NDI. The proportion of surviving infants with various components of NDI was also higher in these two groups for each of the components (Table 4). On logistic regression analysis, both SIP (odds ratio: 2.2, 95% CI: 1.5, 3.2) and SurgNEC (odds ratio: 2.1, 95% CI: 1.5, 2.9) were associated with an increased risk of death or NDI (Figure 2) when compared to infants in the no SIP/no NEC group. When SIP and SurgNEC were compared, the risk of death or NDI was similarly increased in both groups (odds ratio: 0.9, 95% CI: 0.6, 1.5). An increased risk was also seen for NDI among survivors (Figure 3).

DISCUSSION

In this retrospective study, we demonstrate that both SIP and SurgNEC are associated with an increased risk of death or adverse neurodevelopmental outcomes at 18–22 months of age when compared with infants without SIP or NEC. The risk for these outcomes is increased in a similar fashion for ELBW infants with SIP or SurgNEC.

ELBW infants who develop SIP or NEC needing surgery represent a group of infants with extremely high morbidity and mortality, regardless of the surgical approach employed.[13, 14] Attridge et al. showed a higher risk of death and periventricular leukomalacia among infants with SIP as compared to infants without this morbidity.[3] However, they did not include infants with SurgNEC in their analysis. Blakely et al. showed a higher postoperative risk of mortality with prospectively collected data in infants with SurgNEC as compared to SIP.[13] Others have also reported similar results.[15] Our study cohort also had a higher mortality prior to discharge for ELBW infants with SurgNEC as compared to SIP infants and no SurgNEC/no SIP infants. The reasons for the difference in survival between SurgNEC and SIP are not clear but may involve a multitude of factors, including the extent of disease,[13] the varying pathogenesis[16] and different organisms implicated in the etiology of peritonitis accompanying the disease process.[17

Several retrospective studies have examined the association of NEC with growth and other outcomes. While some of the initial reports suggested no difference in outcomes of infants with surgical NEC,[18,19] larger studies have shown an increased risk of poor growth and neurodevelopmental outcome in infants with SurgNEC in comparison to infants without SurgNEC.[20–22] Hintz et al. studied an NICHD NRN cohort of 2,948 ELBW infants and showed that infants with SurgNEC had a substantially higher risk of postnatal growth failure

and adverse neurodevelopmental outcomes at 18–22 months of age as compared to infants with medical NEC or no NEC.[11] Pike et al. reported follow up outcomes of survivors with NEC at seven years of age, showing a higher risk of impairment as compared to infants without NEC.[23] Similar results were found on systematic review of observational studies of outcomes of infants with NEC.[24] There is, however, a paucity of information on the comparative post discharge outcomes of ELBW infants with SurgNEC compared to those with SIP.

Blakely et al. reported 18–22 month neurodevelopmental outcomes in ELBW infants with NEC and SIP needing surgery and suggested poorer outcomes in infants undergoing laparotomy as compared to those receiving peritoneal drains as an initial therapy.[9] They studied a cohort of only 156 ELBW infants; and unlike our study, the purpose of their study was not to evaluate the comparative outcomes of infants with SurgNEC and SIP. As mentioned above in methods, the infants in the Blakely study are also included in our present cohort. More recently, Shah et al.[25] reported on comparative outcomes in 50 ELBW survivors with surgical NEC and 26 ELBW survivors with SIP using data from a single center. They reported neurodevelopmental impairment to be similar amongst infants with SIP and surgical NEC. Our study confirms their finding using a larger cohort of ELBW infants.

Adesnya et al.[26] studied 62 VLBW infants with intestinal perforation and compared growth and 1-year neurodevelopmental outcomes among infants with SIP and intestinal perforation secondary to NEC. While their study showed no difference in growth parameters between the two groups, they showed lower Bayley MDI and PDI scores in survivors with NEC as compared to SIP infants. Our study showed that the proportion of infants with growth failure in both groups was similar, although substantially higher than it was for the infants with no SIP/no NEC. Our results also showed that the risk of NDI or death was higher among infants with SIP and SurgNEC as compared to ELBW infants without these morbidities. We found that the risk was similarly increased in both groups. In addition, the proportion of infants with each component of NDI amongst survivors was higher in these two groups as compared to ELBW infants with no SIP/no NEC. Although the infants in the SurgNEC and SIP group had a higher incidence of co-morbidities as compared to infants in the no NEC/no SIP group, this increased risk of adverse neurodevelopmental outcomes persisted even after controlling for those factors. This supports the notion that SurgNEC and SIP independently increase the risk of adverse outcomes. The mechanism of mediation of this increased risk is unclear. We speculate that adverse outcomes may be mediated through an inflammatory cascade or through exposure to anesthesia for infants undergoing surgical management. Although exposure to neonatal anesthesia has been associated with adverse neurodevelopmental outcomes in infants,[27] we did not collect information on anesthesia exposure and thus cannot explore exposure to anesthesia as a possible factor. In addition, other factors like hypoperfusion, associated sepsis and nutritional issues may also play a role in mediating these adverse outcomes.

An interesting observation about our study cohort was that mothers of infants with SIP were more likely to have received antibiotics prior to delivery (as a surrogate for chorioamnionitis). This observation is in agreement with previous reports hypothesizing a

role of prenatal placental inflammation in the pathogenesis of SIP in ELBW infants.[28,29] A strength of our study is the large cohort of ELBW infants. Although this is a retrospective analysis, trained research nurses prospectively collected the data. Our study has several important limitations. The diagnosis of SIP and SurgNEC were made on clinical grounds. This raises the possibility of misclassification of the underlying condition, although it has been shown that the careful clinical diagnosis of these conditions can have an accuracy of up to 95%.[13] We also did not have information on the timing of onset of SIP and SurgNEC. There were also 128 infants with a diagnosis of both SIP and NEC, who were excluded from the data analysis. Although our follow up rates overall were good (87.1 %), we had infants with missing follow-up data. The incidence of key morbidities prior to discharge (BPD, severe IVH, PVL and late onset sepsis) was however, similar among infants who were followed up and those who were lost to follow up. Despite this, it is possible that infants with missing follow-up data may have influenced our results. BSID-II was used for evaluation of infants during the time period for this cohort study. All of the centers have switched to BSID-III since that time period. We believe that although the MDI and PDI scores on BSID-III overall may be higher, these findings will still hold true. Despite these limitations, these results are a valuable addition to the literature on neurodevelopmental outcomes of ELBW infants with SIP and SurgNEC, by showing an increased risk of death or NDI with both these morbidities.

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Abbreviations

ELBW	extremely low birth weight
GDB	generic database
MDI	Mental Developmental Index
NEC	necrotizing enterocolitis
NDI	neurodevelopmental impairment
NRN	Neonatal Research Network
PDA	patent ductus arteriosus
PDI	Psychomotor Developmental Index
SIP	spontaneous intestinal perforation
SurgNEC	surgical necrotizing enterocolitis

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What is known on this subject

SIP and surgical NEC are serious neonatal morbidities affecting ELBW infants. Both of these conditions are associated with an increased risk of adverse neurodevelopmental outcomes in these infants.

What this study adds

This study explores the comparative risk of death or neurodevelopmental impairment at 18–22 months of corrected age in ELBW infants with SIP and surgical NEC. The results show that these risks are equally increased in ELBW infants with either condition.

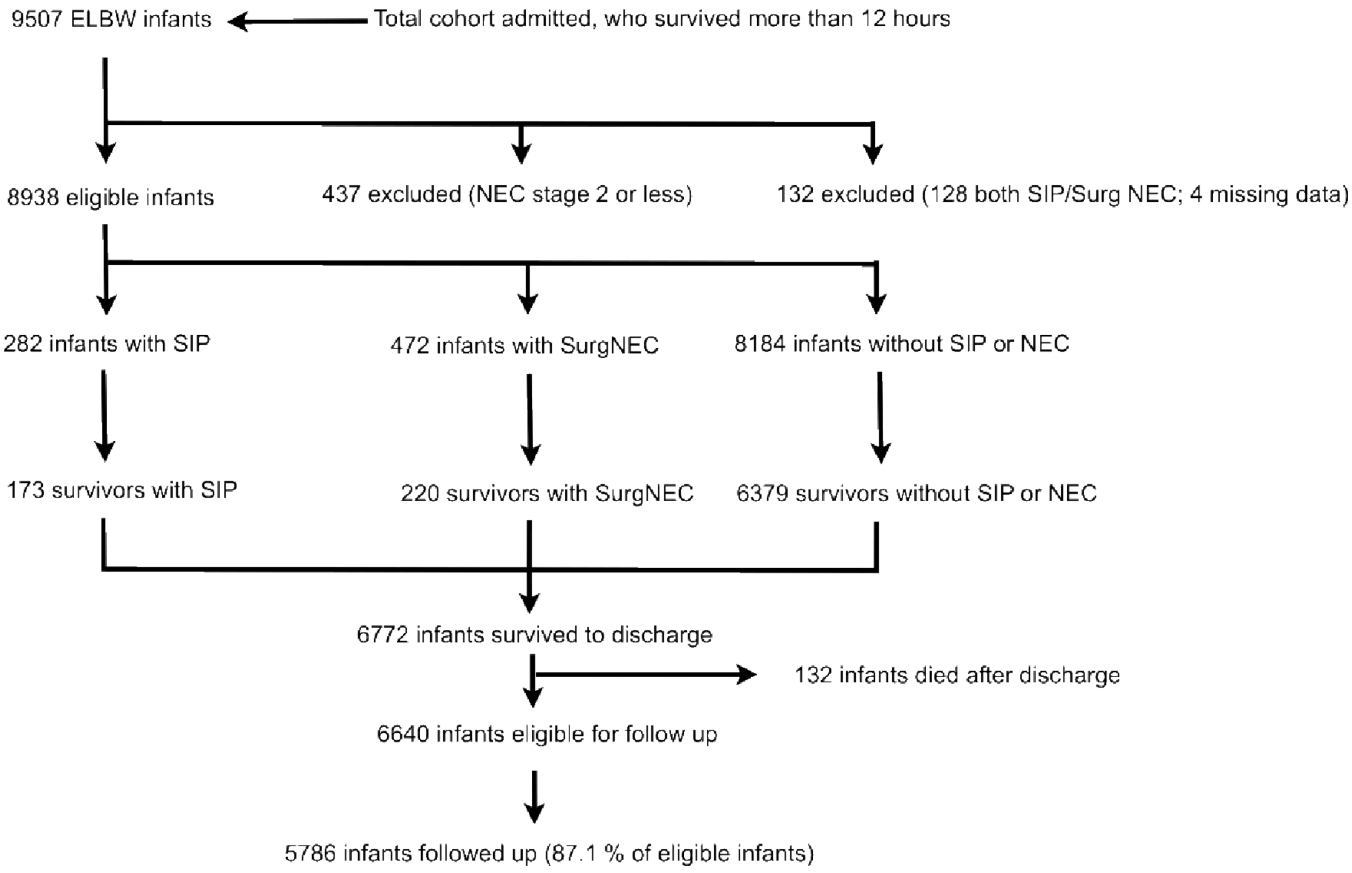

Figure 1.
Number of study subjects

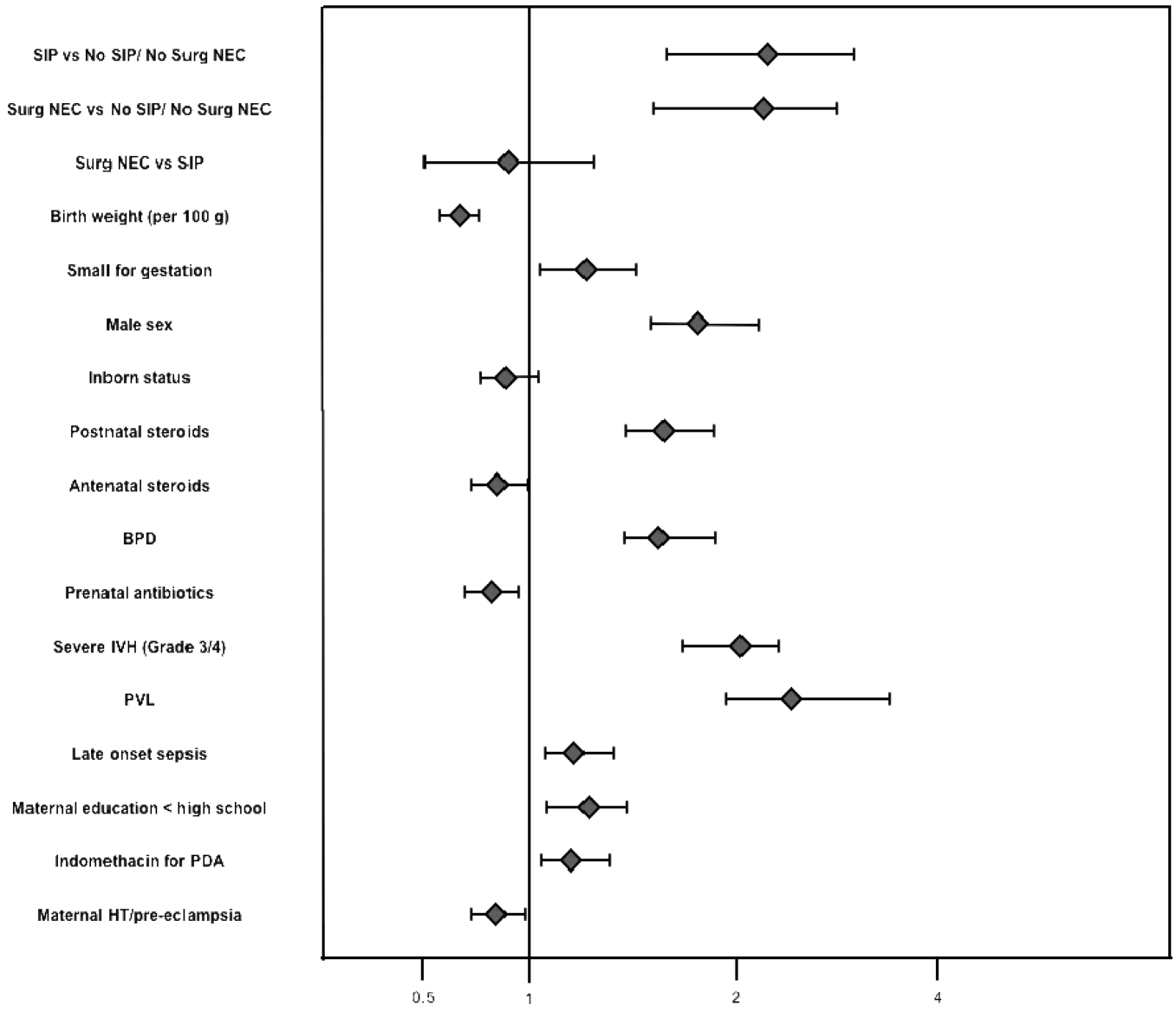

Figure 2.

Logistic regression analysis: Odds ratio and 95% confidence interval for NDI or death. In addition to the variables shown, center was also included in the model.

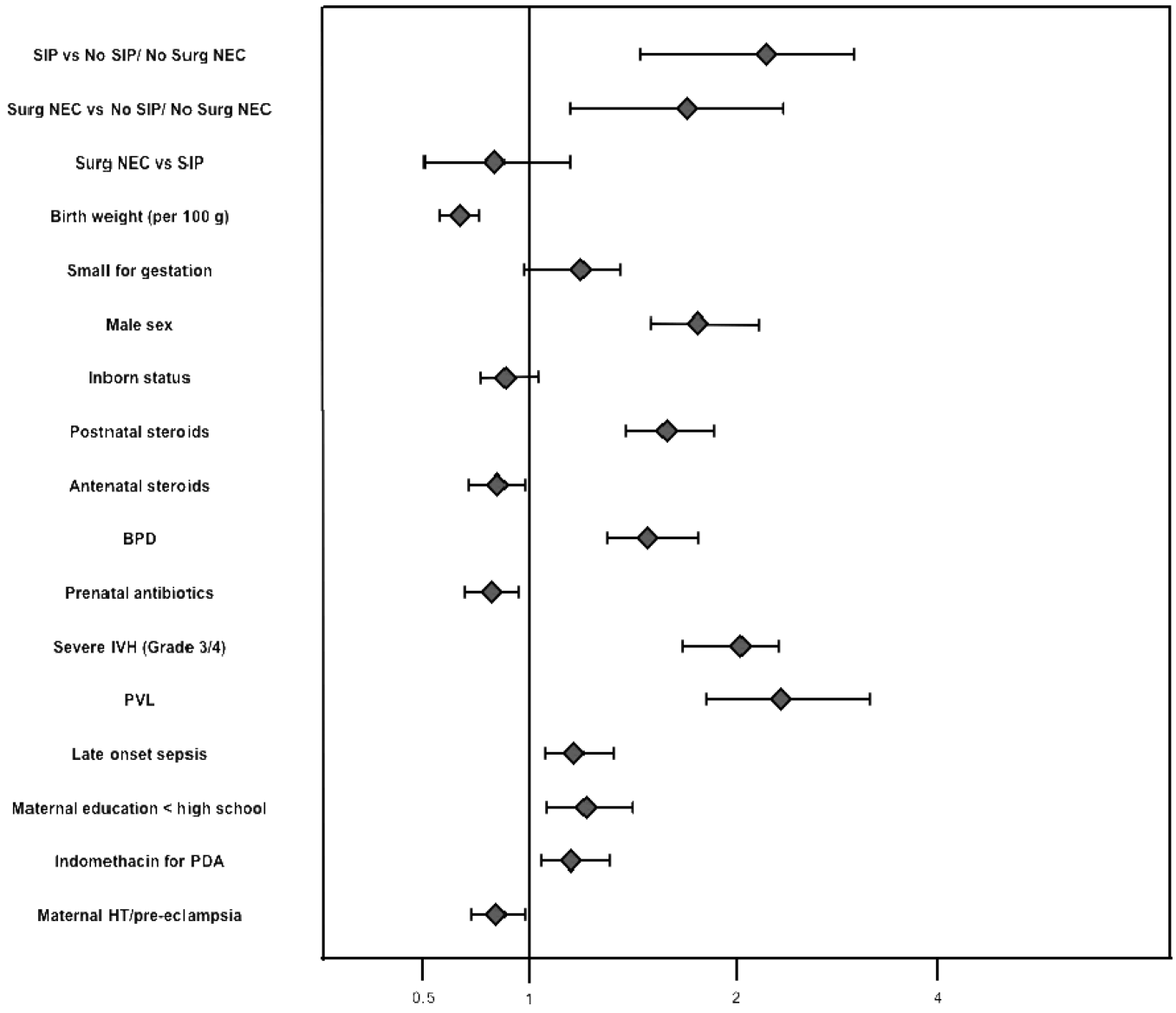

Figure 3.

Logistic regression analysis: Odds ratio and 95% confidence interval for NDI among survivors. In addition to the variables shown, center was also included in the model.

Table 1

Maternal characteristics

Maternal characteristics	No NEC and No SIP n = 8184	SIP only n = 282	Surgical NEC n = 472	*P*
Mean age (in years)	26.9 (*SD* = 6.7)	26.4 (*SD* = 6.5)	26.7 (*SD* = 6.4)	.36
Race - White	54.1%	57.1%	50.2%	.09
Married	46.1%	50.4%	44.3%	.26
Education < 12th grade	24.3%	27.1%	22.9%	.47
Prenatal care	93.2%	94.0%	93.4%	.85
Hypertension	26.9%	14.5%	23.4%	<.001
Antibiotic therapy	63.7%	75.4%	67.2%	.001
ROM>18 hrs	22.2%	22.1%	27.4%	.04
Antenatal steroids (at least 1 dose)	77.7%	77.4%	81.0%	.25

Table 2

Infant characteristics

Clinical Characteristics	**No NEC and No SIP n = 8184**	**SIP only n = 282**	**Surgical NEC n = 472**	***P***
Male	48.6%	63.8%	58.3%	<.001
Mean gestational age (in weeks)	25.9 (*SD* = 2.1)	24.8 (*SD* = 1.5)	25.6 (*SD* = 1.9)	<.001
Multiple births	23.5%	27.0%	23.9%	.40
Mean birth weight (in grams)	765 (*SD* = 147)	715 (*SD* = 138)	736 (*SD* = 142)	<.001
Small for gestational age	17.4%	9.9%	16.3%	.004
Inborn	87.5%	71.3%	83.5%	<.001
Prophylactic Indomethacin	36.3%	42.9%	46.6%	<.001
Indomethacin for PDA	36.4%	50.7%	41.5%	<.001
Surgery for PDA	12.9%	30.9%	18.2%	<.001
Postnatal Steroids	17.9%	28.4%	20.4%	<.001
Mean age at first postnatal steroids (in days)	n = 1461 31.8 (*SD* = 22.3)	n = 80 37.5 (*SD* = 28.4)	n = 97 38.6 (*SD* = 29.5)	.003
Mean days of parenteral alimentation	n = 7825 26.8 (*SD* = 19.4)	n = 276 52.6 (*SD* = 33.5)	n = 468 57.4 (*SD* = 36.5)	<.001

Table 3

Clinical outcomes among study infants

Morbidity	**No NEC and No SIP n = 8184**	**SIP only n = 282**	**Surgical NEC n = 472**	***P***
Motality prior to discharge	22.1%	39.1%	53.5%	<.001
Late onset sepsis	36.0%	61.7%	63.7%	<.001
BPD	48.1%	73.3%	67.0%	<.001
Severe IVH	17.8%	32.3%	22.9%	<.001
Cystic PVL	4.6%	10.0%	11.3%	<.001
Mean length of stay in hospital for survivors (days)	80.78 (*SD* = 52.71)	103.06 (*SD* = 69.75)	101.18 (*SD* = 79.79)	<.001
Mean postmenstrual age at discharge (weeks)	39.81 (*SD* = 5.12)	44.00 (*SD* = 6.43)	47.48 (*SD* = 8.16)	<.001
Growth failure at 18–22 months	48.4%	64.2%	61.8%	<.001
NDI among survivors at 18–22 months	36.0%	63.2%	56.7%	<.001
NDI or death at 18–22 months	53.3%	79.3%	82.3%	<.001

Table 4

Components of NDI among survivors

Morbidity	No NEC and No SIP	SIP only	Surgical NEC	*P*
MDI < 70 at 18–22 months	1548/5095(30.4%)	74/140(52.9%)	88/174(50.6%)	<.0001
PDI < 70 at 18–22 months	1010/5043(20.0%)	69/139(49.6%)	81/175(46.3%)	<.0001
Cerebral Palsy at 18–22 months	300/5433(5.52%)	25/147(17.0%)	43/191(22.5%)	<.0001
Deaf at 18–22 months	91/5418(1.68%)	7/147(4.76%)	16/190(8.42%)	<.0001
Blind at 18–22 months	31/5433(0.57%)	5/147(3.40%)	10/191(5.24%)	<.0001