Peer Review File

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Reviewer A

Comment 1: Introduction Section, lines 96-98: Authors mention that most of the existing studies related to SIP are single-center and smaller sample size studies. However, large, multi-site SIP-epidemiology and outcome studies have been published from the NICHD NRN network and the Canadian neonatal network.
Reply 1: We have modified our text as advised.
Changes in the text: Page 3, line 96-98.

Comment 2: Method Section; Study setting and population: Why was the analysis called secondary analysis? What was the primary objective/primary research question? Please elaborate.
Reply 2: The primary objective of the CHNN database is to monitor outcomes and clinical practices of all preterm infants born with GA < 32 weeks or birth weight < 1,500g and admitted to participating hospitals. Our study was a retrospective cohort study based on this database. Therefore, we have modified our text to reduce ambiguity.
Changes in the text: Page 4, line 111.

Comment 3: The authors need to elaborate on what radiological features of intestinal ischemia were used to differentiate between surgical NEC and SIP.
Reply 3: Radiological features of intestinal ischemia, such as fixed dilated bowel loops and pneumatosis intestinalis, were used to differentiate between surgical NEC and SIP.
Changes in the text: We have modified our text as advised (see Page 5, line 138-139).

Comment 4: Why were the preterm neonates receiving Mechanical Ventilation, TPN, or inotropic support discharged? Were they all left against medical advice? Please clarify.
Reply 4: If the infants' caregivers chose to terminate treatment and have them leave the hospital before the attending physicians recommended discharge, they were considered to be discharged against medical advice. In this case, the infants might still require mechanical ventilation, TPN, or inotropic support when discharged.
Changes in the text: We have clarified it as advised (see Page 5, line 154-155).

Comment 5: Statistical analysis: How were the co-variates for multivariable logistic regression models selected?
Reply 5: The covariates were selected based on previous evidence, suggesting these covariates may be associated with SIP.
Changes in the text: We have modified our text as advised (see Page 6, line 197-198).
1. Fisher JG, Jones BA, Gutierrez IM, et al. Mortality associated with laparotomy-confirmed neonatal spontaneous intestinal perforation: a prospective 5-year multicenter analysis. J Pediatr Surg 2014;49:1215-9.
2. Shah J, Singhal N, da Silva O, et al. Intestinal perforation in very preterm neonates: risk factors and outcomes. J Perinatol 2015;35:595-600.
3. Culbreath K, Keefe G, Edwards E M, et al. Morbidity associated with laparotomy-confirmed spontaneous intestinal perforation: A prospective multicenter analysis. J Pediatr Surg 2022;57:981-5.

Comment 6: Result section: Authors state that a total of 28 infants with SIP received conservative medical management. Please clarify if any of them have received needle aspiration of free intraperitoneal air.
Reply 6: Needle aspiration was not recorded in our database. Whether the 28 SIP infants without surgical management received needle aspiration of free intraperitoneal air remained unknown.
Changes in the text: We have modified our text (see Page 7, line 225-226).

Comment 7: Result section: What criteria were used to determine the need for a secondary lap or rescue lap for those who had undergone primary drain placement?
Reply 7: The criteria to determine the need for secondary laparotomy after peritoneal drainage were not

collected in our database. Generally, whether to perform secondary laparotomy depends on signs and symptoms of clinical deterioration after peritoneal drainage. We have included this as a limitation in the Discussion section.
Changes in the text: Page 11, line 368-369.

Reviewer B

Comment 1: However, I am wondering why this study is defined as a prospective study, while actually its look like a retrospective one - following data that where exist?
Reply 1: We agree with your comment. We have revised it as a retrospective cohort study using the existing CHNN database.
Changes in the text: We have modified our text as advised (see Page 4, line 111).

Comment 2: On the end of the row 97-98 you wrote understand better the epidemiology - the epidemiology is already known, and you actually mentioned it in table 3.
Reply 2: Though some studies have reported the epidemiology of SIP, data on the burden of SIP in China were lacking. This large multicenter cohort study was meaningful as it presented a detailed epidemiology of SIP among very preterm infants in China, as shown in Table 1 and Table 3. We have modified our text to reduce ambiguity.
Changes in the text: Page 3, line 96-98.

Comment 3: The interesting finding that you had in this table - less babies got caffeine treatment, if you matched your study group to a control group, how come you got less caffeine in the study group - unless as you mentioned the majority of the study group were not extremely low birth weight.
Reply 3: Vongbhavit et al. reported similar results in a case-control study of preterm infants with birth weight < 2000g and GA < 34 weeks, indicating that caffeine might play a protective role in the development of SIP (Vongbhavit K, Underwood MA. Intestinal perforation in the premature infant. J Neonatal Perinatal Med 2017;10:281-9). However, further studies were needed to clarify its causality and mechanisms.
Changes in the text: We have added this in the Results (see Page 8, line 253-254) and Discussion section (see Page 9, line 299-303).

Comment 4: I think that is better to refer the groups in the context of very low birth weight and extremely low birth weight rather than very preterm infant.
Reply 4: All infants included in this study were born at 24^{+0} – 31^{+6} weeks' gestation and some of them had a birth weight of more than 1,500g, so we used "very preterm infant" rather than "very low birth weight infant" to refer to them.

Reviewer C

Comment 1: Regarding Major morbidities, the authors included LOS, BPD, PVL and Severe ROP. I think including severe Intraventricular hemorrhage (IVH) would also be important if they have that data available, as it significantly affects long term outcomes.
Reply 1: IVH usually occurs within three days after birth. However, our study showed the median age of SIP onset was four (IQR 2 – 6) days in very preterm infants. It is not appropriate to consider IVH as a consequence of SIP.

Comment 2: Page 3, Introduction 1st Paragraph- The author mention "Most existing studies, however, were conducted in a single center, and the sample sizes were small. More large-scale studies are needed to understand better the epidemiology, current treatment practices, and outcomes of SIP."
- This statement may not be true completely, as there are a few multi center studies reporting long term outcomes, although they are not with huge sample size. Please revise accordingly. Some studies are:
o 1. Hospital and neurodevelopmental outcomes of extremely low-birth-weight infants with necrotizing enterocolitis and spontaneous intestinal perforation; PMID: 22157625, J Perinatol. 2012 Jul; 32(7): 552–558.
o 2. Long-Term Outcome of Necrotizing Enterocolitis and Spontaneous Intestinal Perforation. PMID: 36200375, Pediatrics, 2022 Nov 1;150(5):e2022056445. doi: 10.1542/peds.2022-056445.

o 3. Outcomes of surgery for necrotizing enterocolitis and spontaneous intestinal perforation in Finland during 1986–2014; PMID: 30122449, DOI: 10.1016/j.jpedsurg.2018.07.020
o 4. Risk factors and epidemiology of spontaneous intestinal perforation among infants born at 22–24 weeks' gestational age, Journal of Perinatology volume 44, pages94–99 (2024)
Reply 2: We have modified our text as advised and added the references mentioned above.
Changes in the text: Page 3, line 96-98.

Comment 3: Page 7, section 3.2. Please change the wording of "with the duration of fasting as long as 10 (IQR 8 – 13) days" to "with the median duration of fasting of 10 (IQR 8 – 13) days" for ease of reading.
Reply 3: We have modified our text as advised.
Changes in the text: Page 7, line 219.

Comment 4: Section 3.3. The author mention "Of all infants with SIP…….the remaining eight received complete care". Suggesting 8 infants received non-surgical intervention based on the choice of the treating physician. If this is true, please include in discussion what might be the rationale for no surgical intervention, as this would not be considered standard of care.
Reply 4: If infants with SIP were too unstable to tolerate surgery, or if they could be relieved by less invasive options such as needle aspiration of free intraperitoneal air, then surgical intervention might not be performed.
Changes in the text: We have added this in the Discussion section (see Page 10, line 322-327).

Comment 5: A recent large study reported: "Antenatal magnesium exposure, antenatal indomethacin exposure, postnatal hydrocortisone exposure, postnatal indomethacin exposure, and weight loss ≥15% were associated with SIP". Risk factors and epidemiology of spontaneous intestinal perforation among infants born at 22–24 weeks' gestational age, Journal of Perinatology volume 44, pages94–99 (2024)
- Hydrocortisone and Indomethacin use have been reported in many studies to be associated with SIP.
- The authors have not evaluated for medication use and association with SIP in their population. Please review for availability of medication use data if possible. If not please include this as a limitation of the study.
- If no data available, they can also discuss what is the standard practice in China regarding these medications.
Reply 5: The data on medication use and association with SIP were not available, and we have included this as a limitation in the Discussion section.
Changes in the text: Page 12, line 372-375.