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Synergistic effects of sepsis and prematurity on neonatal postoperative mortality

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Abstract

Introduction: Compared with term neonates, preterm babies are more likely to die from sepsis. However, the combined effects of sepsis and prematurity on neonatal postoperative mortality are largely unknown. Our objective was to quantify the proportion of neonatal postoperative mortality that is attributable to the synergistic effects of preoperative sepsis and prematurity.

Methods: We performed a multicentre, propensity-score-weighted, retrospective, cohort study of neonates who underwent inpatient surgery across hospitals participating in the United States National Surgical Quality Improvement Program-Pediatric (2012–2017). We assessed the proportion of the observed hazard ratio of mortality and complications that is attributable to the synergistic effect of prematurity and sepsis by estimating the attributable proportion (AP) and its 95% confidence interval (CI).

Results: We identified 19 312 neonates who realised a total of 321 321 person-days of postsurgical observations, during which 683 died (mortality rate: 2.1 per 1000 person-days). The proportion of mortality risk that is attributable to the synergistic effect of prematurity and sepsis was 50.5% (AP=50.5%; 95% CI, 28.8–72.3%; $P < 0.001$). About half of mortality events among preterm neonates with sepsis occurred within 24 h after surgery. Just over 45% of postoperative complications were attributable to the synergistic effect of prematurity and sepsis when both conditions were present (AP=45.8; 95% CI, 13.4–78.1%; $P<0.001$).

Conclusion: Approximately half of postsurgical mortality and complications were attributable to the combined effect of sepsis and prematurity among neonates with both exposures. These neonates typically died within a few days after surgery, indicating a very narrow window of opportunity to predict and prevent mortality.

Clinical trial number and registry: Not applicable.

Keywords: complications; mortality; neonatal; postoperative outcome; prematurity; preoperative sepsis; synergistic effect

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Editor's key points

- There is little information on perioperative risk in premature neonates, especially with co-existing sepsis.
- This large, multicentre, retrospective study sought to estimate the risks for postoperative mortality conferred by prematurity and by sepsis, and to ascertain whether the combination was associated with a synergistic increase in death risk.
- The findings suggest that premature babies with sepsis are nine times more likely to die after surgery than term babies without sepsis; this markedly increased risk is higher than would be expected by summating the risks conferred by each factor.
- Proactive diagnosis and treatment of sepsis is warranted in premature babies. Delaying elective surgery in premature babies might be worthwhile, especially where risk of sepsis is high.

Despite ongoing improvements in neonatal surgical care,[1,2] preterm babies still face a substantially higher risk of postoperative mortality compared with full-term neonates.[3–6] Although the mechanisms explaining this excess risk of mortality have not been fully elucidated, neonates are in a transition phase from intrauterine to extrauterine life during which they are vulnerable to life-threatening perioperative comorbidities.[7] Neonatal sepsis is a major cause of morbidity and mortality and approximately 1 million neonates die each year from sepsis-related complications.[8] The co-existence of prematurity and sepsis among neonates who require surgery can create a therapeutic dilemma for surgeons and anaesthetists, especially during the decisions to proceed with surgery and preoperative discussions with parents of these patients.

To date, no study has evaluated the interaction and joint effects of prematurity and sepsis in relation to the risk and timing of neonatal postoperative mortality. Such data would inform on the burden of neonatal surgical mortality that is attributable to the individual and combined effects of prematurity and sepsis.[9] Such data would also inform on whether redesigning current management of preoperative sepsis would have the biggest impact on neonates at risk of sepsis.[9] Recent studies approached these goals by evaluating the risk of neonatal postoperative mortality as a result of sepsis.[10,11] However, these studies only included a sample of preterm neonates, suggesting that only variation in sepsis status was accounted for in the estimated risk of mortality. The risk of mortality estimated in this way may not discriminate between the individual and synergistic implications of prematurity and sepsis.

To overcome these limitations, we evaluated a large cohort that included both preterm and full-term neonates and evaluated the combined effects of prematurity and sepsis in relation to surgical mortality. Our objective was to quantify the proportion of neonatal postoperative mortality that is attributable to the synergistic effects of preoperative sepsis and prematurity.

Methods

Study design and population

We performed a propensity-score-weighted, retrospective, cohort study of neonates who underwent inpatient surgery across hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program-Pediatric (NSQIP-P). Previous manuscripts have described the NSQIP-P pertaining to sampling design, data management protocols and collection.[12–14] Briefly, the NSQIP-P program was developed to prospectively collect nationally representative, systematically sampled, perioperative data among children (<18 years) undergoing surgical procedures at hundreds of hospitals across the USA. These data are collected by trained onsite staff, who undergo routine audit by the NSQIP oversight committee.[13] Our institutional review board has determined this study to be exempt from formal review, because the NSQIP database is completely deidentified. We selected in our analytical sample all inpatient surgical cases between 2012 and 2017 among children who were <28 days old at the time of their surgical procedure. Neonatal sepsis was defined as the presence of sepsis, septic shock, or systemic inflammatory response syndrome within 48 h before surgery.[15]

Outcome measures

Our primary outcome was time to postoperative mortality, considered as inpatient, all-cause mortality occurring within 30 days of the index procedure. Our secondary outcome was time to serious postoperative complication, which we considered as the occurrence of grade II, III, or IV postoperative morbidity event per the Clavien-Dindo classification system.[16]

Statistical analyses

We evaluated the excess protection against mortality, among children without sepsis, that is attributable to a weekly increment in the gestational age (coded as continuous variable and centred around the median). We used Cox proportional hazards models that included preoperative sepsis, gestational age, and a two-way product term 'preoperative sepsis×gestational age'. To adjust for confounders, we used the propensity score weighting, to correct for potential imbalance between babies with and without sepsis. We estimated the propensity of having preoperative sepsis by using a multivariable logistic model, that included the following baseline variables: binary 'yes *vs* no' variables (Central Nervous System[CNS] abnormality, congenital malformation, presence of a cardiac risk factor, gastrointestinal disease, and haematologic disorder), case type (emergent/urgent *vs* elective), sex (male *vs* female), race (White, African American, Other/unknown), year of operation (2012, 2013, 2014, 2015, 2016, 2017), and complexity of operation (low, intermediate, high). We derived the complexity of operation by using principal component analysis of operation time and work relative value unit. The first component explained 75.4% of the variability in the dataset and was categorised into tertiles (low, intermediate, and high).[17]

We also estimated the proportion of the instantaneous risk of postoperative mortality that was attributable to the

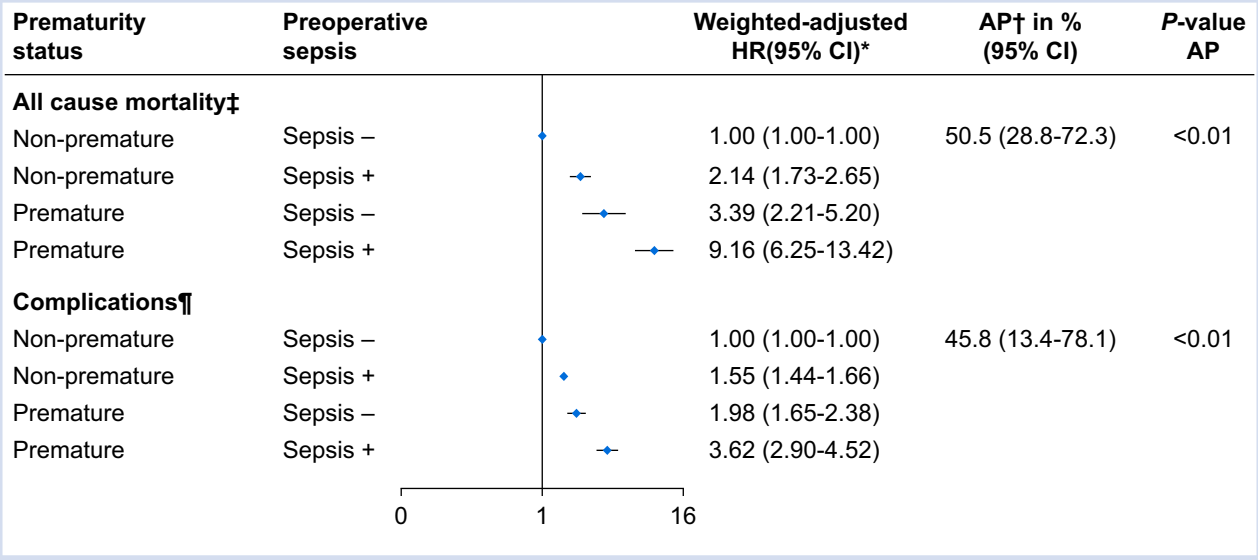

Fig 1. Quantification of synergism between preoperative sepsis and prematurity, NSQIP-P 2012–2017. *Estimated using propensity-weighted Cox proportional hazards models that included, as covariates, variables that remained unbalanced across levels of prematurity-sepsis status (sex, congenital malformation, and year of operation). †AP=(HR_{11}-HR_{10}-HR_{01}+1)/HR_{11} where: HR_{11}: hazard ratio of mortality comparing preterm with sepsis (*considered as doubly exposed*) **vs** full-term without sepsis (*considered as doubly unexposed*); HR_{10}: hazard ratio of mortality comparing preterm without sepsis *vs* full-term without sepsis (*considered as doubly unexposed*); HR_{01}: hazard ratio of mortality comparing full-term with sepsis *vs* full-term without sepsis (*considered as doubly unexposed*).‡Inpatient mortality occurring within 30 days of the index procedure. ¶Occurrence of grade II, III or IV postoperative morbidity event per the Clavien-Dindo classification system. Abbreviations: AP, Attributable proportion; CI, confidence interval; CIF, cumulative incidence function; HR, hazard ratio, NSQIP-P, National Surgical Quality Improvement Program-Pediatrics.

synergistic effect of prematurity and preoperative sepsis. For this analysis, we considered babies born at <37 completed weeks of gestation as premature, as defined by the NSQIP[15] and used in previous studies.[18–20] We began by classifying neonates into four mutually exclusive groups according to prematurity and sepsis status: (1) full-term without sepsis (*considered as doubly unexposed*), preterm without sepsis, full-term with sepsis, and preterm with sepsis (*considered as doubly exposed*). We then estimated the joint effect hazard ratios (HRs) of prematurity and sepsis on postoperative mortality. Using the propensity-adjusted joint effect HRs, we estimated the attributable proportion (AP) that corresponds to the proportion of the observed HR of mortality that was attributable to the synergism between prematurity and sepsis. This should be equal to zero in the absence of synergism.[21] We derived the inverse probability weight from generalised propensity scores to control for confounding because of factors that may systematically affect the distribution of neonates across the four categories of prematurity-sepsis status. We calculated the generalised propensity scores from four propensity scores, each corresponding to a level of prematurity-sepsis status and estimated via multivariable logistic regression.[22] Selection of covariates into the propensity score model was based on prior knowledge regarding which factors may be associated with belonging to both categories of prematurity and sepsis status. We checked the balancing of covariates by estimating the absolute standardised difference in proportions (ASD), where an ASD value lower than 10% was considered acceptable balance.[23,24] We included into the weighted models, as covariates, factors that remained unbalanced. We checked and found no gross violations of the proportional hazards assumption, indicating that our HRs represent valid estimates of the instantaneous risk of death at any point in time during the study period. We performed all analyses using Stata, version 15 (StataCorp, College Station, TX, USA), for which a *P*-value <0.05 was considered as statistically significant.

Results

Study cohort

A total of 483 098 children underwent inpatient surgical procedures between 2012 and 2017 across the NSQIP-P participating hospitals. After applying the inclusion criteria, we identified 19 446 neonates who underwent inpatient surgical procedures and excluded 134 who were missing information on prematurity status (Fig. 1) This left us with 19 312 neonates who were retained in our analytical cohort and accrued a total of 321 321 person-days of postsurgical observations, during which 683 neonates died (mortality rate: 2.1 per 1000 person-days). Of the unweighted cohort of 19 312 neonates, there were 773 (4.0%) preterm babies with sepsis (*doubly exposed*), 362 (1.9%) preterm babies without sepsis, 5545 (28.7%) full-term neonates with sepsis, and 12 632 (65.4%) full-term neonates without sepsis (*doubly unexposed*). Patients' distribution across the four categories of prematurity-sepsis status differed in their baseline characteristics with regards to sex, race, case type, complexity of surgery, year of operation, structural CNS abnormality, congenital malformation, presence of a cardiac

Table 1 Characteristics of neonates (<28 days) who underwent inpatient surgical procedure, before and after weighting using the inverse probability of being premature and having preoperative sepsis (doubly exposed).*

Characteristics	Cohort before inverse probability of exposure weighting			Cohort after inverse probability of exposure weighting		
	Premature + sepsis		Standardised difference‡	Premature + sepsis		Standardised difference‡
	No	Yes		No	Yes	
	No. of neonates (%)†			No. of neonates (%)†		
No. of children (%)	18673 (96.0)	773 (4.0)		14352 (74.3)	4959 (25.7)	
Male sex	11576 (62.0)	461 (59.6)	0.05	8801 (61.3)	3394 (68.4)	0.15
Race						
White	12185 (65.3)	368 (47.6)	0.36	9286 (64.7)	3214 (64.8)	0.00
African American	2466 (13.2)	235 (30.4)	0.43	1985 (13.8)	531 (10.7)	0.08
Other/unknown	4022 (21.5)	170 (22.0)	0.01	3081 (21.5)	1215 (24.5)	0.07
Case type						
Elective	7840 (42.0)	76 (9.8)	0.79	5996 (41.8)	2001 (40.3)	0.04
Emergent/urgent	10833 (58.0)	697 (90.2)	0.79	8355 (58.2)	2959 (59.7)	0.04
Complexity of operation						
Low	5516 (29.5)	232 (30.0)	0.01	4108 (28.6)	1398 (28.2)	0.01
Intermediate	4491 (24.1)	301 (38.9)	0.32	3612 (25.2)	1156 (23.3)	0.04
High	8665 (46.4)	240 (31.0)	0.32	6632 (46.2)	2405 (48.5)	0.05
Structural CNS abnormality	2961 (15.9)	82 (10.6)	0.16	2289 (15.9)	871 (17.6)	0.05
Congenital malformation	10898 (58.4)	194 (25.1)	0.72	8376 (58.4)	3210 (64.7)	0.14
Cardiac risk factors	6508 (34.9)	368 (47.6)	0.26	5263 (36.7)	1631 (32.9)	0.08
Gastrointestinal disease	10934 (58.6)	636 (82.3)	0.54	8484 (59.1)	2904 (58.5)	0.01
Haematologic disorder	1427 (7.6)	331 (42.8)	0.89	1325 (9.2)	482 (9.7)	0.01
Year of operation						
2012	2175 (11.6)	73 (9.4)	0.07	1627 (11.3)	557 (11.2)	0.00
2013	2501 (13.4)	101 (13.1)	0.01	1823 (12.7)	772 (15.6)	0.09
2014	2537 (13.6)	110 (14.2)	0.02	1949 (13.6)	558 (11.3)	0.07
2015	3476 (18.6)	146 (18.9)	0.01	2612 (18.2)	1165 (23.5)	0.14
2016	3828 (20.5)	169 (21.9)	0.03	3105 (21.6)	934 (18.8)	0.07
2017	4156 (22.3)	174 (22.5)	0.01	3235 (22.5)	973 (19.6)	0.07

NSQIP-P, National Surgical Quality Improvement Program-Pediatrics.

* We retained in our sample neonates (age <28 days old) who underwent inpatient surgical procedures between 2012 and 2017 among US hospitals participating in the NSQIP-Peds program. Standardised difference <0.10 was considered acceptable balance.

† Percentages are for column.

‡ Absolute standardised difference in proportions, where a value lower than 10% was considered acceptable balance.

risk factors, gastrointestinal disease, and haematological disorders. Premature babies with preoperative sepsis were more likely to be of African American race (30.4% *vs* 13.2%), have emergent or urgent surgical procedure (90.2% *vs* 58.0%), have cardiac risk factors (47.6% *vs* 34.9%), have gastrointestinal diseases (82.35% *vs* 58.6%), and have haematologic disorders (42.8% *vs* 7.6%); but were less likely to have structural CNS abnormality (10.6% *vs* 15.9%), congenital malformations (25.1% *vs* 58.4%), or complex surgical cases (31.0% *vs* 46.4%) (Table 1).

Moderation, by gestational age of association between preoperative sepsis and mortality

A weekly increment in gestational age was associated with a 9% relative reduction in the risk of surgical mortality among children who did not have sepsis (HR: 0.91; 95% confidence interval [CI] 0.87–0.95; *P*<0.001) (Table 2). This risk reduction, as a result of increase in gestational age, was also observed for complications after surgery (HR: 0.91; CI 0.89–0.94; *P*<0.001). In addition, each additional week of gestational age resulted in a 7% relative excess protection against mortality, from not having sepsis (relative to having sepsis) (HR: 0.93; 95% CI: 0.89–0.97; *P*-value <0.001) A similar trend was observed for postoperative complications, although it was not statistically significant at the alpha level of 0.05. On average, babies without sepsis were 76% less likely to die compared with their peers who had sepsis (HR: 0.23; 95% CI: 0.16–0.34; *P*-value <0.001). Compared with babies who had sepsis, those who did not have sepsis were 43% less likely to develop complications after surgery (HR: 0.57; 95% CI: 0.46–0.71; *P*-value <0.001).

Proportion of mortality that is attributable to the synergistic effect of prematurity and sepsis

The HRs of mortality, considering full-term neonates without sepsis as the reference group, among preterm neonates with sepsis and preterm neonates without sepsis were 9.16 (95% CI: 6.26–13.42) and 3.39 (95% CI: 2.21–5.20), respectively (Fig. 1). This means that preoperative sepsis tripled the risk of mortality among preterm neonates. The proportion of mortality risk that is attributable to the synergistic effect of prematurity and sepsis was 50.5% (AP=50.5%, 95% CI: 28.8–72.3%; *P* < 0.001).

Table 2 Moderation by gestational age of the association between preoperative sepsis and mortality, NSQIP-peds 2012–2017.*

Outcomes	Parameters	†Hazard ratio (95% CI)	P-value
Mortality	Gestational age at birth (weeks)	0.91 (0.87–0.95)	<0.001
	Preoperative sepsis		
	Yes	Reference	–
	No	0.23 (0.16–0.34)	<0.001
	Gestational age at birth (weeks)×preoperative sepsis	0.93 (0.89–0.97)	<0.001
Complication	Gestational age at birth (weeks)	0.91 (0.89–0.94)	<0.001
	Preoperative sepsis		
	Yes	Reference	–
	No	0.57 (0.46–0.71)	<0.001
	Gestational age at birth (weeks)×preoperative sepsis	0.98 (0.96–1.01)	0.33

CI, confidence interval; NSQIP-P, National Surgical Quality Improvement Program-Pediatrics.
* We retained in our sample neonates (age <28 days old) who underwent inpatient surgical procedures between 2012 and 2017 among US hospitals participating in the NSQIP-Peds program.
† Estimated from propensity score weighted Cox proportional hazards regression models and including as covariates the following variables that remained imbalanced after propensity score weighting: congenital malformation, surgical complexity index, and year of operation.

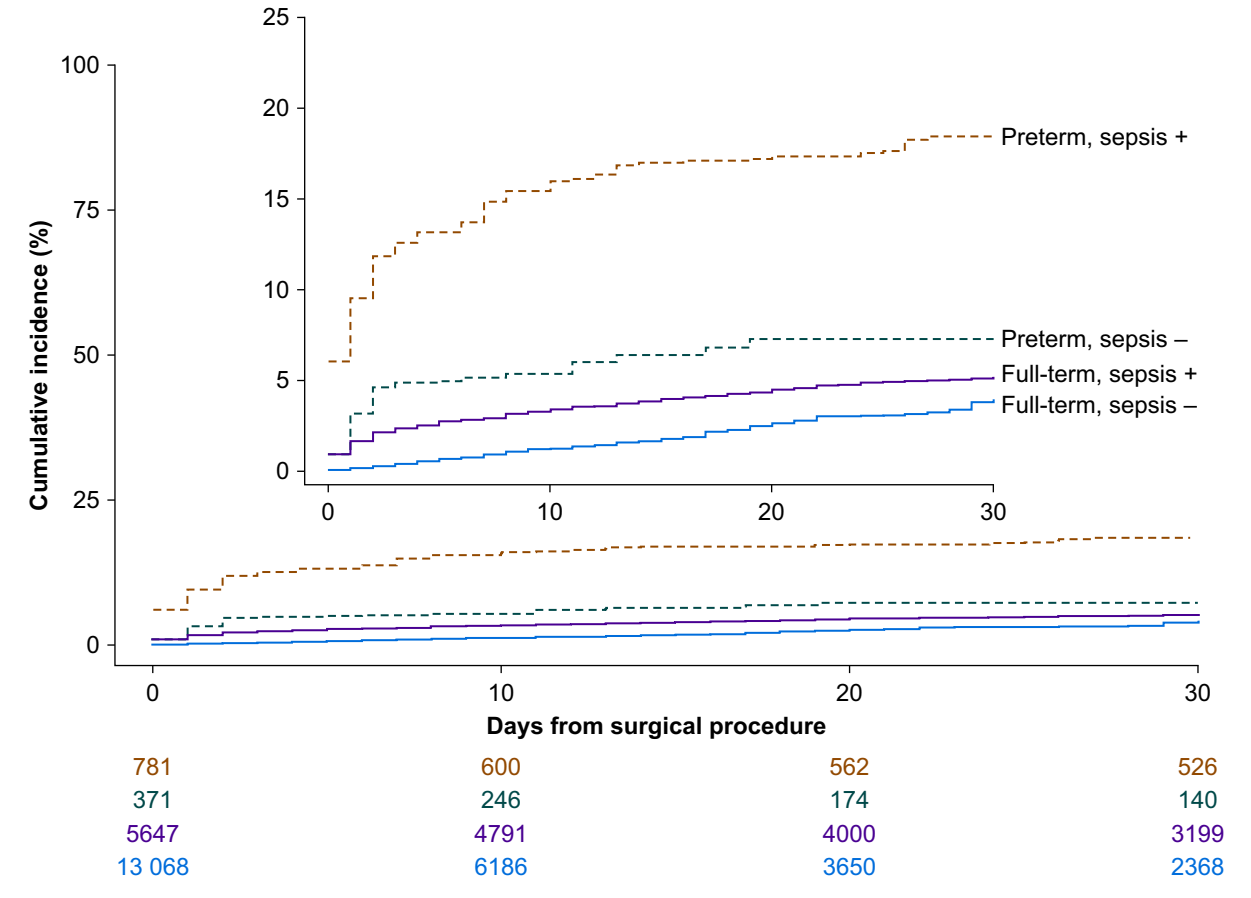

Fig 2. Inverse probability of exposure-weighted cumulative incidence functions (CIF) curves of mortality, according to prematurity-sepsis status. The risk table shows actual number of neonates. The inset graph represents the same data, but with enhanced Y axis.

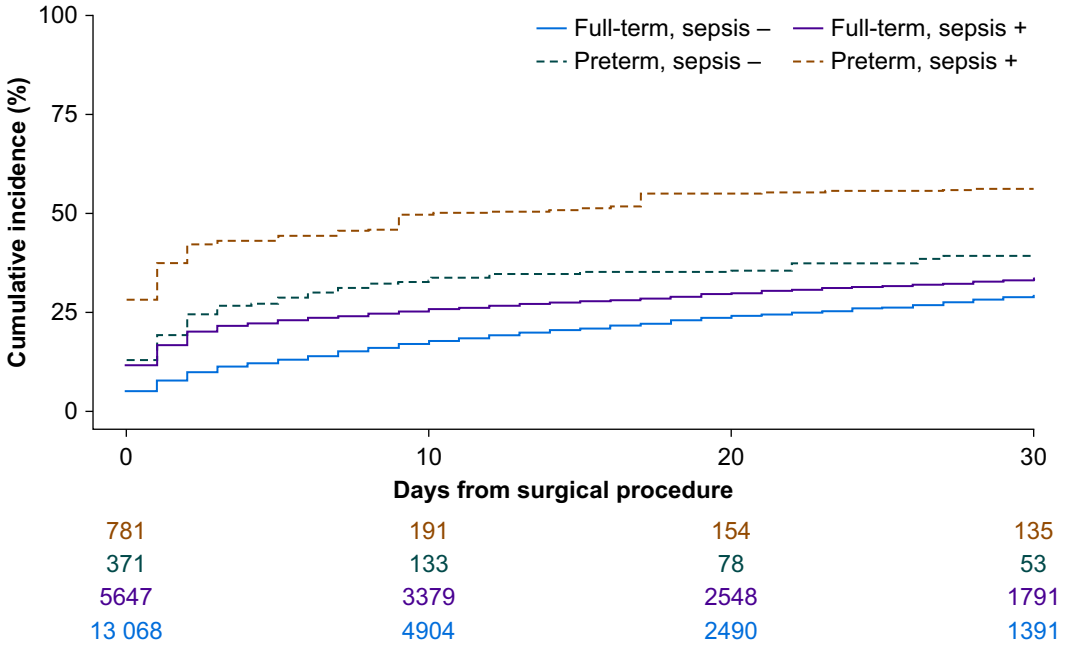

Fig 3. Inverse probability of exposure-weighted cumulative incidence functions (CIF) curves of postoperative complications, according to prematurity-sepsis status. The risk table shows actual number of neonates. The inset graph represents the same data, but with enhanced Y axis.

Half of mortality events among preterm neonates with sepsis occurred within 24 h after surgery (Fig. 2). By the fifth day after surgery, 80% of mortality events among preterm neonates with sepsis occurred. Comparatively, about 10 days elapsed before 80% of mortality among preterm neonates without sepsis occurred. Of note, the instantaneous risk of mortality was two times higher among full-term neonates with preoperative sepsis relative to full-term neonates without sepsis (HR: 2.14, 95% CI: 1.73–2.65) (Fig. 1).

Proportion of complication events that is attributable to the synergistic effect of prematurity and sepsis

Among preterm babies, preoperative sepsis almost doubled the risk of postoperative complications (HR: 3.62 *vs* HR: 1.98) (Fig. 1). Just over 45% of postoperative complications were attributable to the synergistic effect of prematurity and sepsis when both conditions were present (AP=45.8%, 95% CI: 13.4–78.1%; $P<0.001$). These complications typically occurred within the first 24 h after surgery (Fig. 3).

Discussion

To our knowledge, this is the first study to confirm and quantify the synergistic effects of preoperative sepsis and prematurity on the risk of neonatal postoperative mortality and complications. We found that about half of postsurgical mortality and complications were attributable to the synergistic effect of sepsis and prematurity among neonates with both exposures. Focusing efforts on improving the management protocol or earlier identification of preoperative sepsis is likely to have the biggest impact on reducing postsurgical death among preterm neonates. This is further supported by the timing of death, which typically occurred within a few days after surgery, and indicating a very narrow window of opportunity to prevent mortality during the postoperative period. Although there are no directly comparable data, our study is consistent with studies emphasising the physiologic immaturity of a newborn and the resulting immunosuppression.[25] Such physiologic immaturity could increase the likelihood for sepsis to become rapidly fulminant and result in mortality, especially in the context of perioperative stress.[25,26]

Despite the unique physiology of neonates, current guidelines for the management of paediatric sepsis were mostly informed by studies performed among adults.[27] In addition, there is a lack of consensus on the perioperative management of children with sepsis, which may be needed to improve their postoperative survival. Given that the preterm neonate is a relatively immunocompromised host with increased susceptibility to bacteraemia and sepsis,[28–30] specific perioperative management protocols targeting this at-risk group are needed.

Although the majority of procedures in neonates with sepsis were urgent or emergent, approximately one out of 10 of preterm neonates with sepsis underwent surgical procedures designated as elective. Given that the risk of surgical mortality is nine-fold higher in the context of prematurity and sepsis, we recommend further investigation into the potential benefit of deferring elective procedures among preterm neonates with sepsis. Such improvements could be pivotal because of the high incidence of preterm births (<37 weeks gestation), and the resulting surge in neonatal surgical cases.[31] Furthermore, the identification of sepsis early on in the preoperative course may allow the institution of adequate treatment before to non-elective procedures.

Some limitations should be accounted for when interpreting the results of the current study. First, the NSQIP-P database does not collect information on participating hospitals, precluding us from accounting for potential clustering of survival times. However, the existence of within-hospital correlation of survival times does not usually bias the effect size, but only their standard errors. In addition, previous studies have shown that higher performing hospitals do not systematically have lower mortality rates.[32] Therefore, it is unlikely that the statistical significance of our findings would be the result of a substantial within-hospital correlation of survival times. Second, our study might be limited by its observational design, with the potential for misclassification and information biases. In addition, because of the retrospective design, we had no control over variable definitions, coding, and granularity of patients' characteristics. However, our sample was derived from one of the most complete and reliable databases of paediatric surgical procedures in the USA.[33] This not only improves the internal validity, but also the external validity in that our findings may be generalisable to neonatal surgical patients across the USA. Finally, we used an unambiguous categorical outcome (mortality), which would greatly reduce the potential for differential or non-differential misclassification of the outcome.

In conclusion, we confirmed and quantified the synergy between sepsis and prematurity on the risk of neonatal postoperative mortality. Specifically, about half of postsurgical mortality and complications were attributable to the synergistic effect of sepsis and prematurity among neonates with both exposures. Mortality among these neonates typically occurred within a few days after surgery, indicating a very narrow window of opportunity for clinicians to predict and prevent mortality. Improving the management protocol of preoperative sepsis would have the biggest impact on optimising postoperative survival of preterm neonates.

Authors' contributions

Idea conception, study design, and data acquisition: CM, OON, JTD
Critical review of literature, data analyses, draft of the initial manuscript: CM, OON
Study design, interpretation of the data, review and revision of the manuscript for critical intellectual contents: EGS, RKT, OOD, JDT.
Oversaw the acquisition and analyses of the data and the review of literature, and critically reviewed and revised the manuscript: JDT
Approved the final version of the manuscript: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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