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RESEARCH REPORT

Perioperative critical events and morbidity associated with anesthesia in early life: Subgroup analysis of United Kingdom participation in the NEonate and Children audiT of Anaesthesia pRactice IN Europe (NECTARINE) prospective multicenter observational study

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Abstract

Background: The NEonate and Children audiT of Anaesthesia pRactice IN Europe (NECTARINE) prospective observational study reported critical events requiring intervention during 35.2% of 6542 anesthetic episodes in 5609 infants up to 60 weeks postmenstrual age. The United Kingdom (UK) was one of 31 participating countries.

Methods: Subgroup analysis of UK NECTARINE cases (12.8% of cohort) to identify perioperative critical events that triggered medical interventions. Secondary aims were to describe UK practice, identify factors more commonly associated with critical events, and compare 30-day morbidity and mortality between participating UK and nonUK centers.

Results: Seventeen UK centers recruited 722 patients (68.7% male, 36.1% born preterm, and 48.1% congenital anomalies) undergoing anesthesia for 876 surgical or diagnostic procedures at 25–60 weeks postmenstrual age. Repeat anesthesia/surgery was common: 17.6% patients prior to and 14.4% during the recruitment period. Perioperative critical events triggered interventions in 300/876 (34.3%) cases. Cardiovascular instability (16.9% of cases) and/or reduced oxygenation (11.4%) were more common in younger patients and those with co-morbidities or requiring preoperative intensive support. A higher proportion of UK than nonUK cases were graded as ASA-Physical Status scores >2 or requiring urgent or emergency procedures, and 39% required postoperative intensive care. Thirty-day morbidity (complications in 17.2%) and mortality (8/715, 1.1%) did not differ from nonUK participants.

Conclusions: Perioperative critical events and co-morbidities are common in neonates and young infants. Thirty-day morbidity and mortality data did not demonstrate national differences in outcome. Identifying factors associated with increased

*The members of "UK Collaborators and NECTARINE Group Steering Committee" is in Appendix section

risk informs preoperative assessment, resource allocation, and discussions between clinicians and families.

KEYWORDS
anesthesia, adverse effects, anesthesia, mortality, infant, newborn, patient-relevant outcome

1 | INTRODUCTION

Postoperative mortality is higher in neonates than in older children,[1–3] with additional risk factors including co-morbidities, preoperative instability requiring intensive support, sepsis, emergency surgery, birth at younger gestational ages, and complications of prematurity.[1,3,4] Severe perioperative critical events are also more common in neonates than in older children.[5] Reported perioperative outcomes frequently relate to clinical indicators (i.e., adverse cardiorespiratory events, changes in vital signs, or laboratory measures) in neonates, whereas patient-centered and comfort measures (i.e., pain, analgesia, nausea and vomiting, and behavior) are common for older ages.[6]

The APRICOT study recruited over 30 000 children across 33 European countries and identified a higher incidence of critical events in 361 neonates.[5] The subsequent NEonate and Children audiT of Anaesthesia pRactice IN Europe (NECTARINE) prospective multicenter observational study focused on patients up to 60 weeks postmenstrual age requiring anesthesia for surgical or diagnostic procedures, and reported perioperative critical events, morbidity and mortality for 5609 infants undergoing 6542 procedures.[7] Severe critical events requiring interventions occurred in 35.2% of cases, and the triad of hypotension, hypoxemia, and anemia had a major impact on morbidity and mortality.[7]

Differences in the incidence and management of severe perioperative critical events across countries participating in the APRICOT cohort highlighted variability in pediatric and neonatal anesthesia practice, and raised issues related to training, resources, clinical experience, workload, and infrastructure.[8,9] As a result, the Trial Steering Committee agreed that secondary analyses for nations contributing large numbers of patients to NECTARINE could test the hypothesis that primary outcome measures were not different from the remaining cohort.

This manuscript relates to UK recruitment of neonates and infants (</=60 weeks postmenstrual age) requiring general anesthesia for surgery or nonsurgical procedures in the NECTARINE prospective cohort study. The primary aim of this subgroup analysis was to report the incidence of severe critical perioperative events in UK centers, with particular emphasis on cardiovascular, respiratory events, and management of difficult airways. Secondary aims were to compare 30-day morbidity and mortality between UK and participating nonUK centers and explore potential differences in anesthesia practice.

What is known

The incidence of critical perioperative events and morbidity and mortality is higher in neonates and young infants than in older children.

What this study adds

A high proportion of neonates/young infants undergoing anesthesia have clinically important co-morbidities, with many requiring perioperative intensive care management and/or repeated surgical or procedural interventions.
Despite some differences in recruited patient population and service delivery, incidences of critical perioperative events, morbidity and mortality were comparable for UK and nonUK participants in the NECTARINE study.

2 | MATERIALS AND METHODS

2.1 | Study design and approvals

The NEonate-Children sTudy of Anaesthesia pRactice IN Europe (NECTARINE) is a European prospective multicenter observational cohort study (ClinicalTrials.gov NCT02350348) with participating centers in 31 countries. The study protocol, standardized case report form (CRF) and additional documents are available online (European Society of Anaesthesiology and Intensive Care - Clinical Trial Network; https://www.esaic.org/research/clinical-trial-network/completed-trials/nectarine/).[7] The Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) endorsed the study, coordinated a call for UK participating centers, and provided funding for centralized follow-up in the UK. Ethics approvals (National Health Service [NHS] National Research Ethics Service, 16/LO/0238, 16-3-2016; NHS Health Research Authority, 21-3-2016) for parental consent prior to, or within 24 h of anesthesia, and for follow-up were obtained. Thirty-day follow-up was performed via medical records. Standardized follow-up at 90 days was performed by the Great Ormond Street Hospital Somers Clinical Research Facility, following secure transfer of recruited subject information. The recruiting hospital and/or family doctor was contacted initially to confirm the patient's status. Parents had the option to agree to access of the child's medical records but decline direct

telephone contact at 90 days. Recruitment commenced at 4 centers on 1-4-2016, an additional 13 centers on 1-5-2016, and ceased on 5-7-2016.

Data were collected by the anesthesia team onto a standardized CRF, that included details of the following: patient demographics and medical history, preanesthesia assessment, baseline parameters, surgery/procedure, anesthesia management, and perioperative critical events. CRF data was entered into a secure internet-based electronic case record form (OpenClinica, Boston, MA, USA).[7] Following data cleaning and resolution of queries, the final NECTARINE dataset was exported for analysis in October 2019,[7] and national datasets were subsequently available to Lead Investigators.

2.2 | Participants

Eligibility and data collection for the study are as previously described.[7] In brief, neonates and infants up to 60 weeks postmenstrual age (PMA: gestational age at birth plus chronological age) undergoing anesthesia for surgical or nonsurgical procedures were eligible for inclusion.

2.3 | Critical event variables

Eight predetermined critical events that required intervention by the anesthesia team related to: oxygenation; carbon dioxide (CO_2) and alveolar ventilation; blood pressure; heart rate and electrocardiogram (ECG) rhythm; cerebral oxygenation (if monitoring with near-infrared spectroscopy was available); blood glucose and plasma sodium; hemoglobin levels; and body temperature. The physiological parameter threshold that triggered an intervention(s), and the type and timing of intervention(s) were recorded. Perioperative data collection continued until the patient was discharged from the postanesthesia care unit (maximum 120 min) and/or transferred to a neonatal or pediatric intensive care unit. Thirty-day data included patient status (i.e., at home or in hospital), time in intensive care and morbidity/complications. Mortality data were collected at 30- and 90-day follow-up.

2.4 | Statistical analysis

Quantitative variables are reported as median [25, 75 interquartile range] and compared with Mann–Whitney, or if normally distributed as mean ± standard deviation and compared with Student's *t*-test. All tests were two-sided. *p* values are reported to a minimum of $p < 0.001$, and $p < 0.05$ was considered statistically significant. Patient categorical data are summarized as absolute numbers and percentages, and comparisons performed with chi-squared test with *p* values and odds ratio [95% CI] reported. Throughout, group values and analyses are based on available data, and any missing data are reflected by the reduced sample size (*n*). The statistical analysis plan for the full NECTARINE cohort was based on an expected percentage of severe perioperative critical events of 11% and estimated a sample of 4941 patients for a logistic regression analysis with more than one covariate.[10] Therefore, analyses for the current subgroup data are restricted to descriptive comparisons. Analysis was performed with SPPS Statistics V27 (IBM, Portsmouth, UK; June 2020).

3 | RESULTS

3.1 | Participants

Perioperative data for 876 procedures in 722 patients in the UK represents 13.4% of the 6542 procedures and 12.9% of the 5609 patients reported in the NECTARINE cohort.[10] Nineteen UK centers expressed interest, two were subsequently unable to participate, and 17 centers contributed data for between two and 114 patients (Figure S1). Seventeen patients were excluded following recruitment due to incomplete consent, a large amount of missing data despite queries, or subsequent withdrawal of parent/carer consent.

Comparing UK data with nonUK cohort data reveals no statistically significant difference in the proportion of participants born preterm (<37 weeks gestational age 261/722 vs. 1739/5609 patients) but a slightly higher incidence of congenital anomalies (OR 1.2 [1.0, 1.4]; odds ratio [95% CI]) (Table 1). At the time of anesthesia, a higher proportion of UK neonates had undergone previous surgery (OR 1.4 [1.2, 1.6]); ASA scores of III–IV were more common (OR 1.9 [1.7, 2.2]); and a higher proportion were graded as urgent or emergency rather than elective cases (OR 4.2 [3.6, 4.9]) (Table 2).

The majority of UK cases was recruited at major pediatric centers with neonatal and/or pediatric intensive care wards, and 26.7% of cases required intensive care preoperatively. Postoperatively, 39% of cases (341/875) were transferred to intensive care; this was unplanned in four (0.46%) and related to the perioperative critical event in one. The majority of patients remained intubated for transfer to intensive care (238/341; 70%), and intubation was unplanned and related to the critical event in seven (0.8%) cases. Thirty days following the last anesthesia episode, 19/715 (2.7%) patients were still in intensive care, a further 29/716 (4.1%) had been readmitted to intensive care as a separate event, and total intensive care days for these patients ranged from 1–36 (median 7 [3, 21]).

3.2 | Procedures

Anesthesia was required for surgical procedures in 79.8% (gastrointestinal/abdominal surgery most common) and for procedural or diagnostic interventions in 20.2% (see Table S1 for details).

TABLE 1 Study population characteristics for UK cohort and comparison with Full NECTARINE cohort

	<28 weeks n = 66 (9.1%)	28–32 weeks n = 79 (10.9%)	33–36 weeks n = 116 (16.1%)	>/= 37 weeks n = 461 (63.9%)	UK cohort[a] n = 722 (100%)	NECTARINE Full cohort n = 5609 (100%)
Gestational age at birth (weeks)	25.14 (1.39) [23–27]	30.14 (1.57) [28–32]	34.87 (1.08) [33–36]	38.8 (1.13) [37–41]	35.98 (4.61) [23–41]	36.2 (4.4)[b]
Birth weight (g)	800 (190) [408–1500] *n* = 66	1460 (560) [650–3800] *n* = 76	2240 (506) [1050–3820] *n* = 114	3280 (580) [600–4805] *n* = 439	2800 (1030) [480–4850] *n* = 695	2730 (984)
APGAR score at 5 min	7.13 (2.0) [2–10] *n* = 38	7.34 (2.11) [2–10] *n* = 41	8.71 (1.67) [1–10] *n* = 65	9.04 (1.45) [0–10] *n* = 169	8.52 (1.82) [0–10] *n* = 313	8.8 (1.7)
					UK cohort[c] *n* = 722 (100%)	**NonUK cohort *n* = 4887 (100%)**
Sex: M/F (% M)	43/23 (65.2)	53/26 (67.1)	82/34 (70.7)	318/143 (69.0)	496/226 (68.7)	3174/1713 (64.9)
Delivery: vaginal/ cesarean/NA (%)	34/28/4 (51.5/42.4/6.1)	22/51/6 (27.8/64.6/7.6)	49/67/0 (42.2/57.8/0)	306/141/13 (66.4/30.6/3.0)	411/287/24 (56.9/39.8/3.3)	2461/1966/460 (50.3/40.2/9.4)
Congenital anomalies, *n* (%)	13 (19.7)	32 (40.5)	65 (56.0)	189 (49.6)	347 (48.1)	2109 (43.1)
Cong. heart disease	11	13	15	61	100 (13.9)	614 (12.7)
Other (noncardiac)[d]	3	24	66	201	296 (41.0)	1418 (29.0)

Note: Data represented as mean (SD) [range]. For variables with missing data, *n* = number with available data.

Abbreviations: cong., congenital; F, female; g, grams; M, male; NA, data not available.

[a]Summary data for the UK cohort is compared to the Full NECTARINE cohort (*n* = 5609).

[b]% in each gestational age range in full cohort: <28wks 8.2%, 28–32 weeks 9.9%, 33–36 weeks 17.6%, >/=37 weeks 64.3%.

[c]Incidence data is compared between UK cohort and the remainder of the nonUK NECTARINE cohort (*n* = 4887).

[d]Some patients had more than one congenital abnormality.

UK anesthesia team members included a postfellowship consultant anesthetist plus anesthetist in training for 413/876 cases (47.1%) or consultant only for 303 cases (34.6%). Two or more consultants were involved in 149 cases (17%); this included a senior (>5 years post certification) and junior consultant for 105 cases, plus an anesthetist in training for 34 cases. Only 11 cases (1.3%) were undertaken by anesthesia trainees alone (age range 36.1–57 weeks PMA, ASA-PS >2 in 3 cases).

Repeated episodes of anesthesia were frequent in UK (269/876, 30.7%) and nonUK participants (2037/5934, 34.3%). At the time of initial recruitment, 138/722 UK participants had required previous anesthesia (≥3 in 22). Throughout the 9–13 weeks of UK recruitment, 104 patients underwent an additional surgery or procedure (1 in 77, 2 in 15, ≥3 in 12).

Anesthesia techniques included general anesthesia in 65.9%, combined general and regional anesthesia in 33.4%, or regional anesthesia alone in 6 cases (0.7%) (Table S2). Airway management included tracheal intubation for the majority of episodes (90.2%), with the oral route (708/788) and uncuffed (607/787) endotracheal tubes most commonly used (Table S3).

Standard monitoring (ECG, SpO2, capnography, anesthetic agent, and temperature) was reported for all cases. An arterial line was used in 138 (15.8%), central venous catheter in 85 (9.7%), and both in 76 cases. Near-infrared spectroscopy was used in 42 surgical cases (4.8%) at 6 centers.

3.3 | Primary outcome: incidence of critical events

3.3.1 | Incidence and type of critical events

Perioperative critical events requiring 455 interventions were reported in 300/876 (34.3%) anesthesia cases, and this incidence is comparable with the full cohort (35.3% [95% CI 34.1–36.4])[7]. Interventions were most commonly for cardiovascular instability (49.3% interventions) and/or hypoxemia (33%) in UK cases, and in the full cohort (60.7% and 36%, respectively).[7] Additional interventions related to the following: alterations in body temperature (*n* = 49; trigger range 34–39°C); red cell transfusion for anemia (*n* = 36; hemoglobin trigger range 4.0–11.5 g dL^{-1}); or disturbances in blood glucose (*n* = 32; trigger reported as </=4 mMol L^{-1} in 19 and >/=9 mMol L^{-1} in 10) and/or plasma sodium (*n* = 3; trigger value 124–138 mMol L^{-1}). In 6 cases, changes in NIRS rSO_2 led to an intervention (triggered by absolute value in the range 10–50; or 15–20% decrease).

3.3.2 | Cardiovascular critical events

Perioperative cardiovascular instability was reported in 130 patients during 148 episodes of anesthesia (Table 3). These patients were born at younger gestational ages, and were more likely to have congenital

TABLE 2 Medical history and status at time of anesthesia episodes

Anesthesia episodes	UK cohort	UK %	Remainder cohort[b]	Remainder Cohort, %
Sex. male/female, % male	575/301 *n* = 876	65.6 male	3661/2005 *n* = 5666	64.6 male
Past history[a]				
Apnea/respiratory support	389/876	44.4	3626/5666	64.0
Intraventricular hemorrhage	76/875	8.7	387/5666	6.8
ECMO	5/871	0.6	57/5666	1.0
PDA	192/875	21.9	1027/5666	18.2
Previous surgery	269/876	30.7	1362/5666	24.0
Admission from				
Home/ward	528/876	60.3	3698/5666	65.2
ICU	234/876	26.7	1578/5666	27.9
Other hospital	114/876	13.0	390/5666	6.9
Respiratory status at time of anesthesia				
No additional support	629/876	71.8	4979/5666	87.8
On oxygen	82/876	9.4	327/5666	5.8
Noninvasive vent. or CPAP	36/876	4.1	137/5666	2.4
Intubated and ventilated	128[c]/876	14.6	745/5666	13.1
ECMO	1/876	0.1	18/5666	0.3
Preoperative assessment[a]				
Respiratory problems	231/872	26.4	963/5666	17.0
Cardiovascular problems	211/871	24.1	1193/5666	21.1
Metabolic problems	103/874	11.8	563/5666	9.9
Neurological problems	143/869	16.3	670/5666	11.8
Renal problems	57/872	6.5	405/5666	7.1
ASA-PS score[a]				
I	155/871	17.7	602/5665	10.6
II	289/871	33.0	2859/5665	50.5
III	332/871	37.9	1591/5665	28.1
IV	92/871	10.5	578/5665	10.2
V	3/871	0.3	35/5665	0.6
Urgency				
Elective	305/876	34.8	1876/5664	64.7
Urgent or emergency	571/876	65.2	1735/5664	30.6
Surgery	699/876	79.8	4501/5666	79.4
Nonsurgical procedure	177/876	20.2	1164/5666	20.5

Note: Data presented as number reported/total available data.

Abbreviations: ASA-PS, American Society of Anesthesiologists - Physical Status score; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PDA, patent ductus arteriosus; vent., ventilation.

[a]Data not reported for *n* = 2–7 episodes per category.

[b]UK data subtracted from full NECTARINE Cohort (*n* = 6542 episodes in 5609 patients; Disma et al. Br J Anesth 2021 Supplementary Table A; https://doi.org/10.1016/j.bja.2021.02.016).

[c]Conventional ventilation *n* = 126; high frequency oscillatory ventilation *n* = 2.

anomalies, a previous requirement for respiratory support, or patent ductus arteriosus. By 30-day follow-up, a higher proportion of patients with perioperative cardiovascular instability had experienced complications, required intensive care, and remained in hospital (Table 4).

Inotrope/vasopressor infusions were required preoperatively in 25 cases and were part of anesthesia management from the beginning in an additional 18 cases. Subsequent intraoperative cardiovascular instability requiring intervention was reported in 148/876

TABLE 3 Episodes of anesthesia associated with or without interventions for cardiovascular instability or hypoxemia

Episodes (n = 876)	CVS instability	No CVS instability	Comparison, p[a]	Hypoxemia event	No hypoxemia event	Comparison, p[a]
Number, *n* (%)	**148 (16.9%)**	**728 (83.1%)**		**100 (11.4%)**	**776 (88.6%)**	
Postmenstrual age at anesthesia (weeks)	41.4 [36.8, 45.5] range 27–60	44.6 [40.4, 51.4] range 25–61	<0.001 −4.0 [−5.3, −2.6]	41.8 [38.3, 47.6] range 27–61	44.0 [40.1, 51.0] range 5–61	0.004 −2.3 [−3.9, −0.7]
Chronological age at anesthesia (days)	4.4 [0.9, 10.8] range 0–33	9.6 [4.0, 14.6] range 0–34	<0.001 −3.3 [−4.4, −2.0]	7.1 [2.3, 12.9] range 0–34	9.1 [3.5, 14.4] range 0–34	0.10 −1.1 [−2.7, 0.2]
Weight at anesthesia (kg)	3.1 [2.3, 4.1] range 0.84–8.3	3.9 [3.0, 5.3] range 0.53–9.60	<0.001 −0.8 [−1.1, −0.6]	3.1 [2.4, 4.1] range 0.82–7.45	3.8 [3.0, 5.2] range 0.53–9.60	<0.001 −0.7 [−1.0, −0.4]
Sex, male/female (% male)	97/51 (65.5)	478/250 (65.7)	0.98	61/39 (61%)	514/262 (66.2%)	0.30
Admit from						
Home	27 (18.2%)	281 (38.6%)	<0.001; OR 0.4 [0.2, 0.6]	22 (22%)	286 (36.9%)	0.003; OR 0.5 [0.3, 0.8]
Ward	33 (22.3%)	187 (25.7%)	-	23 (23%)	197 (25.4%)	-
Other hospital	20 (13.5%)	94 (12.9%)	-	8 (8%)	106 (13.7%)	-
ICU	68 (45.9%)	166 (22.8%)	<0.001; OR 2.9 [2.0, 4.2]	47 (47%)	187 (24.1%)	< 0.001; OR 2.8 [1.8, 4.3]
Preoperative intensive support						
CVS support/inotropes	14 (9.5%)	11 (1.5%)	<0.001; OR 6.8 [3.0, 15.3]	8 (8%)	17 (2.2%)	0.001; OR 3.9 [1.6, 9.2]
Respiratory support	48 (32.4%)	117 (16.1%)	<0.001; OR 2.5 [1.7, 3.7]	37 (37%)	128 (16.5%)	<0.001; OR 3.0 [1.9, 4.7]
Admission from ICU	68 (45.9%)	166 (22.8%)	<0.001; OR 2.9 [2.0, 4.2]	47 (47%)	187 (24.0%)	<0.001; OR 2.8 [1.8, 4.3]
ASA-PS III-IV	107/147, (72.8%)	320/724 (44.2%)	<0.001; OR 3.4 [2.3, 5.0]	68 (68%)	359/775 (46.3%)	<0.001; OR 2.4 [1.6, 3.8]
Current co-morbidities						
Respiratory problems	44 (29.7%)	187 (25.7%)	0.31	50/99 (50.5%)	181/773 (23.4%)	<0.001; OR 3.3 [2.2, 5.1]
CVS problems	63 (42.5%)	149 (20.5%)	<0.001; OR 2.9 [1.9, 4.2]	42 (42%)	169/771 (21.9%)	<0.001; OR 2.3 [1.7, 4.0]
Metabolic problems	38 (25.7%)	65 (8.9%)	<0.001; OR 3.5 [2.3, 5.5]	12 (12%)	91/774 (11.8%)	0.94
Neurological problems	22 (14.9%)	121 (16.6%)	0.19	16 (16%)	127/769 (16.5%)	0.90
Renal problems	9/146 (6.1%)	48/726 (6.6%)	0.20	5 (5%)	52/772 (6.7%)	0.51
Urgent/emergency	122 (82.4%)	449 (61.6%)	<0.001; OR 2.9 [1.9, 4.6]	78 (78%)	493 (63.5%)	0.004; OR 2.0 [1.2, 3.3]
Surgery						
Surgery vs. other procedure	122/148 (82.4%)	577/728 (79.3%)	0.43	73/100 (73%)	626/776 (80.7%)	0.07
Length of surgery/ Procedure (min)	91.50 [50.00, 170.75] range 15–1600	50.00 [30.00, 95.00] range 2–1595	<0.001	64.50 [36.25, 135.75] range 8–384	54.00, [30, 105.00] range 0–1600	0.08
Type of surgery (GI/thor/ Cardiac/GU/neuro/ophth%)	91/2/15/3/5 (74.6/1.6/12.3/2.5/4.1%)	338/6/33/40/57 (58.6/1.0/5.7/6.9/9.9%)	-	41/4/7/3/8 (56.2/5.5/9.6/4.1/11%)	388/4/41/40/54 (61.9/0.6/6.5/6.4/54%)	-
Anesthesia management						
Induction, IV vs. inhalation	26/146 (17.8%)	56/722 (7.8%)	<0.001; OR 2.6 [1.6, 4.3]	14/97 (14.4%)	68/771 (8.8%)	0.08

TABLE 3 (Continued)

Episodes (n = 876)	CVS instability	No CVS instability	Comparison, p[a]	Hypoxemia event	No hypoxemia event	Comparison, p[a]
Muscle relaxant	140/148 (94.6%)	556/722 (77.0%)	<.001; OR 5.2 [2.5, 10.9]	77/99 (77.8%)	619/771 (80.3%)	0.56
RA + GA vs. GA alone	32/148 (21.6%)	261/721 (36.2%)	<0.001; OR 0.5 [0.3, 0.7]	24/99 (24.2%)	269/770 (34.9%)	0.034; OR 0.6 [0.37, 0.97]
Face Mask vs. ETT	1/146 (0.07%)	19/663 (28.7%)	0.124	2/94 (2.1%)	18/715 (2.5%)	0.82
ETT vs. SGA	145/146 (99.3%)	644/675 (95.4%)	0.027; OR 0.14 [0.02, 0.06]	92/93 (98.9%)	697/728 (95.7%)	0.14
Vasopressor/inotrope	20/145 (13.8%)	21/714 (2.9%)	<.001; OR 5.3 [2.8, 10.0]	8/99 (8.1%)	33/760 (4.3%)	0.10
Baseline parameters[b]						
Systolic BP[c]	69 (20); *n* = 135	76 (17); *n* = 632	<0.001; −6.6 [−9.8, −3.3]	74 (18); *n* = 89	75 (17); *n* = 678	0.82
Mean BP	44 (14); *n* = 83	43 (12); *n* = 370	0.02; −4.1 [−7.4, −0.8]	49 (17); *n* = 54	47 (12); *n* = 399	0.19
Diastolic BP	38 (15); *n* = 128	40 (14); *n* = 610	0.21	39 (15); *n* = 84	40 (14); *n* = 654	0.98
Heart rate	142 (21); *n* = 146	141 (19); *n* = 718	0.34	142 (19); *n* = 98	141 (19); *n* = 766	0.42
Hb	13.1 (3.5); *n* = 117	12.1 (3.2); *n* = 382	0.16	12.8 (3.2); *n* = 65	12.3 (3.3); *n* = 434	0.21
SpO_2	97 [94, 100]; *n* = 61	99 [97, 100]; *n* = 233	-	97 [91, 100]; *n* = 37	99 [97, 100]; *n* = 257	-
PCO_2	45 [39, 52]; *n* = 55	51 [44, 60]; *n* = 27	-	47 [40, 60]; *n* = 22	46 [40, 53]; *n* = 130	-

Abbreviations: ASA-PS, American Society of Anesthesiology - Physical Status score; BP, blood pressure; CVS, cardiovascular; ETT, endotracheal tube; GA, general anesthesia; GI, gastro-intestinal; GU, genitourinary; Hb, hemoglobin; ICU, intensive care unit; IV, intravenous; neuro, neurological; ophth, ophthalmological; RA regional anesthesia; SGA, supraglottic airway; thor, thoracic.

[a]Continuous data presented as median [IQR], with *p* values calculated with Mann–Whitney and difference between median [95% CI] reported. Categorical data presented as number/total episodes with available data (%) and *p* values calculated with two-tailed Chi-squared; odds ratio OR [95% CI]. Normally distributed continuous data presented as mean (SD) and comparison *p* values calculated with 2-tailed Student's *t*-test; mean difference [95% CI].

[b]Available data for baseline parameters is presented (*n* = no. of cases); no statistical comparison for SpO_2 and PCO_2 as limited available data.

[c]See Figure 2 in Supplementary File for plots of individual BP data points.

Bold values represent subsection headings and main findings.

TABLE 4 Demographics and outcomes in patients with or without interventions for perioperative cardiovascular instability or hypoxemia

Patients ($n = 722$)	CVS instability	No CVS instability	Comparison, p #	Hypoxemia	No hypoxemia	Comparison, p #
Demographics						
Number, n (%)	130 (18%)	592 (82%)		93 (12.9%)	629 (87.1%)	
Birth age (weeks)	37 [32, 39]	38 [35, 40]	0.08	37.0 [32, 39]	38.0 [35, 39]	0.52
Birth weight (kg), $n = 695$	2.6 [1.8, 3.4]	2.9 [2.0, 3.5]	0.03	2.6 [1.2, 3.2]	2.9 [2.1, 3.5]	0.21
Sex, male/female (% male)	86/44 (66.2%)	409/183 (69.1%)	0.51	57/36 (61.3%)	439/190 (69.8%)	0.10
Apgar score (5 mins), $n = 313$	9 [7, 10]	9 [8, 10]		8 [7, 9]	9 [8, 10]	
Congenital anomalies, n (%)	**75/130 (58%)**	**272/592 (46%)**	**0.015; OR 1.6 [1.1, 2.3]**	**58.0%, 54/93**	**40.6%, 293/722**	**0.039; OR 1.6 [1.0, 2.5]**
CHD	32 (24.6%)	69 (11.7%)		26 (28.0%)	74 (11.8%)	
Other (noncardiac)	55 (42.3%)	235 (39.7%)		42 (45.2%)	248 (39.4%)	
History, Y/total (%)						
Respiratory support	75/130 (57.7%)	215/592 (36.3%)	<0.001; OR 2.4 [1.6, 3.5]	58/93 (62.3%)	231/629 (36.7%)	<0.001; OR 2.9 [1.8, 4.5]
IVH	11/129 (8.5%)	42/592 (7.1%)	0.57	11/93 (11.8%)	42/629 (6.7%)	0.08
PDA	44/129 (34.1%)	102/592 (17.2%)	<0.001; OR 2.5 [1.6, 3.8]	30/93 (38.7%)	114/629 (17.3%)	0.002; OR 2.2 [1.3, 3.5]
Previous surgery	31/130 (23.8%)	116/592 (19.6%)	0.28	15/93 (16.1%)	123/629 (19.6%)	0.43
ECMO	-	5/592		-	5/629	
Intensive care admission						
Postop transfer to ICU, Y/total (%)	79/130 (60.8%)	170/586 (29%)	<0.001; OR 3.6 [2.4, 5.3]	51/93, 54.8%	209/629, 33.2%	<0.001; OR 2.4 [1.6, 3.8]
Subsequent ICU admission to D30, Y/total (%)	13/117 (10%)	16/586 (2.7%)	<0.001; OR 4.0 [1.9, 8.3]	8/93 (8.6%)	21/629 (3.4%)	0.017; OR 2.3 [1.2, 6.3]
ICU total days (from D0 to D30)	8 [4, 27]	7 [3, 18]	0.09	9.0 [4, 29]	7.5 [3, 19]	0.39
Day 30 status[a]						
Discharged home	77/130 (59.2%)	467/592 (78.9%)	<0.001; OR 0.2 [0.1, 0.3]	61/93 (65.6%)	482/622[b] (77.5%)	0.01; OR 0.5 [1.1, 2.8]
Still in hospital	11/130 (8.5%)	8/592 (1.4%)		8/93 (8.6%)	58/622 (9.3%)	
Discharge to other hospital	20/130 (15.4%)	45/592 (7.6%)		15/93 (16.1%)	64/622 (10.3%)	
Still in ICU	19/130 (14.6%)	60/592 (10.1%)		4/93 (4.3%)	15/622 (2.4%)	
Death	3/130 (2.3%)	5/592 (0.8%)		5/93 (5.4%)	3/622 (0.4%)	

TABLE 4 (Continued)

Patients (n = 722)	CVS instability	No CVS instability	Comparison, p #	Hypoxemia	No hypoxemia	Comparison, p #
Morbidity 30 days, n (%)[c]	**48/130 (36.9%)**	**71/592 (12%)**	**<0.001; OR 4.1 [2.6, 6.4]**	**28/88 (31.8%)**	**91/604 (15.1%)**	**<0.001; OR 2.6 [1.6, 4.3]**
Cardiovascular	20 (15.4%)	15 (2.5%)		10 (10.8%)	25 (4.0%)	
Respiratory	25 (19.2%)	33 (5.6%)		18 (19.4%)	40 (6.4%)	
Surgical	21 (16.2%)	23 (3.9%)		12 (12.9%)	32 (5.1%)	
Neurologic	8	13		5	16	
Renal insufficiency/Liver failure	7/2	7/5		3/2	11/5	

Note: Total, cases with available data. Continuous variables are presented as median[IQR] and compared with Mann–Whitney. Categorical data presented as number of patients/total in group, and odds ratio and 95% confidence intervals (OR [95% CI]) calculated with Chi-squared test.

Abbreviations: CHD, congenital heart disease; CVS, cardiovascular system; D, day; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; Y, yes.

[a]Comparisons restricted to the outcome with the largest sample.

[b]Data not available n = 7.

[c]30-day morbidity data details N/A for 30 patients: includes 3 died before 30 days; 12 still in ICU; 10 at home; 5 with no 30-day follow-up.

Bold values represent subsection headings and main findings.

(16.9%) cases. Perioperative cardiovascular instability was more commonly associated with the following: younger postmenstrual and chronological age at the time of anesthesia; preoperative intensive support; ASA-PS score III-IV; current cardiovascular and metabolic co-morbidities; and the need for urgent or emergency surgery (Table 3).

Critical changes in blood pressure triggered interventions in 142 cases, of which 65 cases required a single intervention and 46 cases required multiple (3 or more) interventions. Baseline systolic blood pressure increased with postmenstrual age at the time of anesthesia (Spearman's $\rho = 0.41$ [95% CI 0.34, 0.47]) was variable across all ages (Figure S2A) but lower in patients who subsequently developed cardiovascular instability (Table 3; Figure S2B). Management of hypotension included administration of intravenous fluid in 134 cases, pharmacological interventions in 57 cases, or both (Table S4). The change in blood pressure that triggered an intervention was variable (average decrease for fluids $41 \pm 22\%$, and for drugs $42 \pm 24\%$) (Figure S2C). Heart rate disturbances triggered 11 interventions (Table S2). Successful treatment was reported in 135 cases, but cardiovascular instability persisted in 4 (3 admitted from intensive care and all transferred to intensive care postoperatively). Thirty cases required interventions for both hypotension and hypoxia and included 7 cases (0.8%) with the composite event of hypotension, hypoxia, and anemia requiring red blood cell transfusion.

3.3.3 | Respiratory events

Interventions were required for hypoxemia (11.4%, $n = 100$) altered CO_2 (9.1%, $n = 80$) or difficult airway management (3.3%, $n = 29$).

Hypoxemia triggered interventions in 100 cases (93 patients, 7 patients with hypoxemia in 2 episodes), with 54/100 triggered by $SpO_2 < 85\%$. Hypoxemia interventions were more common when anesthesia episodes were required at younger postmenstrual age for urgent/emergency procedures. A higher proportion were requiring preoperative respiratory or intensive care support, and baseline SpO_2 was lower (Table 3). Episodes of hypoxemia were more common during maintenance (72%) than induction (24%) or awakening (12%) with ≥3 interventions required during 31 cases. Oxygenation improved in 95 cases, but persistent decreases despite intervention were reported in 5 cases.

Patients requiring intervention(s) for hypoxemia were more likely to have congenital abnormalities or preexisting medical conditions. Thirty-day morbidity was higher, and a lower proportion had been discharged home (Table 4).

Changes in ventilation in response to altered pCO_2 were more commonly triggered by hypercapnia (61/876, 7.0%) than hypocapnia (11/876, 1.3%). Across 80 episodes, a single intervention was required in 38 episodes, with ≥3 interventions in 20 cases, and persistent difficulties despite interventions were noted in 10% (8/80) of cases.

Unplanned intraoperative intubation was reported in 4/876 (0.46%) to improve oxygenation (2 cases) or alveolar ventilation (2 cases).

3.3.4 | Difficult airway

Cormack–Lehane scores were graded as 1–2 in 678/787 (77.4%) and 3–4 in 6/787 (0.7%) (Table S3). Interventions for difficult airways were reported in 29 episodes (1 patient during 2 episodes), were unplanned in 20/29, and were associated with difficulty with face-mask ventilation in 2, hypoxemia in 6, and bradycardia in 1 of 29 cases. Successful intubation was achieved in 28 cases, and the most frequent interventions included changing laryngoscope blades (15/29) and/or using a stylet or bougie (13/29). Advanced interventions included video-assisted intubation in 4 and fiber-optic bronchoscopy in 1 case. One patient who was unable to be intubated despite multiple attempts was woken up, but successfully intubated with video-assisted intubation on a subsequent occasion (Table S5).

3.4 | Morbidity and mortality

Thirty-day morbidity and mortality data were comparable in UK and nonUK NECTARINE participants (Table 5). At 30 days, complications were reported in 17.2% of UK patients. Causes for mortality by 30-day follow-up (8/715, 1.1%) included sepsis, multiorgan failure, congenital, or acquired brain abnormality, and respiratory failure.

By 30 days, fewer UK neonates (75.9%) had been discharged home compared with the remainder of the cohort (OR 0.76 [95% CI 0.63, 0.92]) as a higher proportion remained in the treating hospital or had been transferred to another hospital (Table 5). Ninety-day follow-up data was obtained for 303/722 patients (42%), with 8/303 still in hospital and additional mortality (3/303) between 30–90 days (Table S6).

3.5 | UK practice compared with nonUK practice

Inhalation rather than intravenous induction was much more common in UK vs. nonUK cases (786/868, 90.5% vs. 3016/5452, 55.3%; OR 7.7 [95% CI 6.1–9.7]).

Opioid administration at induction and/or during maintenance was reported in 21.6% and 46.3% of UK cases, respectively. Fentanyl was the commonest opioid used in UK and nonUK cases, but remifentanil was given less frequently in the UK (1.4% at induction, 4.4% during maintenance vs. 5.2% induction, 8.8% maintenance), and sufentanil was not utilized in the UK but was reported in other countries (12.7% induction, 10.5% maintenance).

Baseline hemoglobin for 499/876 UK cases was 11.6 [9.9, 14.4] g dl^{-1} (median[IQR]) and comparable to the full cohort (11.1 [9.5, 12.9][11]). Transfusion for anemia and/or cardiovascular instability was reported in 48 (5.4%) cases with a trigger of 8.2 [7.2, 9.3] g dl^{-1} (6.9% of cases in full cohort with trigger 8.4 [7.5, 9.6][11]).

Anesthesia teams frequently included at least one senior anesthetist for both UK (730/875, 83.4%) and nonUK (4771/5664, 84.2%) cases. However, some aspects of service delivery differed. Eleven urgent/emergency procedures (0.11%; 8 surgery, 2 IV access, 1 bronchoscopy) at 7 different UK centers were performed in ICU, which represents a smaller proportion than nonUK cases (252/5414, 4.4%). Inter-hospital transfers were more frequent in the UK, with a higher proportion of patients admitted from another hospital preoperatively (114/876, 13% vs. 390/5666, 6.9%) and discharged to another hospital by 30 days (79/715, 11.1% vs. 178/4505, 4%).

4 | DISCUSSION

In this UK subgroup analysis of the NECTARINE study, perioperative critical events occurred in just over a third of neonatal/infant anesthetics before 60 weeks PMA (875 anesthetics in 722 patients). The overall incidence and the predominance of events triggered by cardiovascular or respiratory parameters are consistent with data from nonUK centers. Within the constraints of the UK sample size, patient factors associated with critical events and subsequent 30-day morbidity and mortality were comparable with full cohort data.[7]

Serious perioperative clinical events requiring medical intervention were reported in one third of cases. Interventions for cardiovascular instability or hypoxemia were more often required in younger patients born at earlier gestational ages, those with current co-morbidities and requirements for intensive preoperative support (reflected by higher ASA-PS scores), and during urgent/emergency or more prolonged procedures. This is consistent with NECTARINE[7] and previous studies,[5] and reflects parameters included in risk assessment tools for pediatric surgery.[4,12] These data also highlight the need for enhanced reporting of critical events[13–15] and quality improvement initiatives.[15,16] Triggers for intervention were variable, but single data points do not reflect the speed of change that may have occurred, or the degree of change which may be tolerated in neonates with differing co-morbidities.

The incidence of difficult tracheal intubation in 3.7% of UK cases was lower than 5.8% reported for the full NECTARINE cohort,[10] but the pattern of interventions was similar. Direct laryngoscopy remains the primary choice for endotracheal intubation in neonates with a change of blade or the addition of a stylet or bougie and calling for assistance as the first line for difficult airways. The use of videolaryngoscopy or fiberoptic techniques was rare at the time of recruitment, but evidence of higher success rates with videolaryngoscopy has now been documented.[17] The need for ongoing teaching, training, and frequent practice of difficult airway scenarios, while addressing nonhuman factors, has also been highlighted.[18] Changes to the systematic and continuous use of oxygen during endotracheal intubation while ensuring appropriate and effective use of new technologies may be required. Guidelines for the management of difficult airways in older children are available (e.g., https://www.

TABLE 5 Morbidity, status, and mortality at 30 days

	UK	NonUK cohort
30-day morbidity, *n*/total patients (%)	**119/692**[a] **(17.2%)**	**731/4523**[b] **(16.2%)**
Respiratory complications[e], *n* (% of complications)	**58/119 (48.7%)**	**399/731 (54.6%)**
ECMO	2	12
Failure wean/prolonged ventilatory support	17	212
Re-intubation after extubation	27	44
Pleural effusion	9	37
Pneumonia	15	29
Pneumothorax	8	45
Surgical complications, *n* (% of complications)	**44 (36.9%)**	**285 (39.0%)**
Re-operation as unsuccessful or complicated 1st surgery	27	151
Severe surgical site infection with new onset antibiotics	13	85
Prolonged parenteral nutrition due to surgical complication.	12	31
Cardiovascular complications[f], *n* (% of complications)	**35 (29.4%)**	**280 (38.3%)**
Arrhythmia	9	61
Episode(s) of cardiac arrest	8	42
Cardiac ischemia (elevated troponin)	0	5
ECMO	2	15
Arterial/venous embolism	1	8
Inotropes/vasopressors needed	17	206
Venous thrombosis on central line	6	16
Neurological complications, *n* (% of complications)	**21 (17.6%)**	**125 (17.1%)**
New onset hypertonia	3	10
New onset hypotonia	2	18
Intracranial bleeding (confirmed by imaging)	10	36
Intracranial ischemia (confirmed by imaging)	2	24
Seizures (clinically or EEG)	9	50
Renal insufficiency, *n* (% of complications)	**14 (11.8%)**	**84 (11.5%)**
Continuous renal replacement therapy	9	15
Increase creatinine requiring adjustment of doses	4	63
Peritoneal dialysis	2	15
Liver failure, *n* (% of complications)	**7 (5.9%)**	**44 (6.0%)**
Coagulation disorder (INR >2)	2	25
Increase serum bilirubin (>300 μmol L^{-1} or 10 mg dL^{-1})	6	26
Status at 30 days	***n* = 715**[c]	***n* = 4505**[d]
Discharged home	543 (75.9%)	3629 (80.6%)
Still in hospital	66 (9.2%)	341 (7.6%)
Discharge to another hospital	79 (11%)	178 (4.0%)
Still in ICU	19 (2.7%)	260 (5.8%)
Death	8 (1.1%)	97 (2.2%)

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; INR, international normalized ratio.

[a]UK morbidity data available for 692/722 patients; *n* = 23 unknown and *n* = 7 missing 30-day follow-up.

[b]Remaining cohort morbidity data = UK numbers subtracted from available Full Cohort data (850/5215;16.3%) as reported in Disma et al. Br J Anaesth 2021, Supplementary Table D.

[c]UK 30-day status available for 715of 722 patients (*n* = 7 missing).

[d]Remaining cohort 30-day status = UK numbers subtracted from available Full Cohort data (*n* = 5220 of 5609) as reported in Supplementary Table E, Disma et al. Br J Anaesth 2021.

[e]78 complications in 58 pts (1 patient, complication type NR).

[f]43 complications in 35 patients (2 patients, complication type NR).

Bold values represent subsection headings and main findings.

das.uk.com/guidelines/paediatric-difficult-airway-guidelines), and there are current plans to develop an international, evidence-based consensus for the management of the difficult airway in neonates.

Thirty-day morbidity was increased in patients with perioperative cardiorespiratory critical events, the proportion requiring intensive care management postoperatively was increased, and fewer patients had been discharged home. Many factors resulting in physiological instability are inter-related, with both hypotension and hypoxia occurring in 30 cases, and in 7 cases, there was co-occurrence of hypoxia, hypotension, and anemia, which was associated with increased morbidity (RR 3.56 [95% CI 1.64–7.71]) and mortality (RR 19.80 [95% CI 5.87–66.7]) in the full cohort.[7] While the UK sample is too small to reliably calculate relative risk, proportions are consistent with analyses derived from NECTARINE[7] and previous studies from major pediatric centers.[2,3] However, reported rates of anesthesia-related mortality and 30-day hospital mortality can be influenced by definitions, inclusion criteria, methods of reporting, and case-mix (e.g., academic vs. general hospitals).[19] While the proportion of surgical vs. nonsurgical cases (80% and 20%, respectively) and surgical disciplines (e.g., 49% gastro-intestinal surgery) did not differ between UK and nonUK cases, a higher proportion of UK infants had ASA-PS scores of III-IV were requiring respiratory support at the time of anesthesia and underwent urgent/emergency cases. Despite this apparent higher risk case-mix, 30-day morbidity and mortality were not increased for UK cases. However, differences in reporting criteria or preoperative management, variability in interpreting criteria and assigning ASA-PS scores, and the relatively small UK sample size may also be contributory factors. The relative and inter-related contributions of preoperative status, perioperative instability, and postoperative complications to mortality cannot be determined, but data highlight risk factors that can inform discussions with medical care teams and parents/caregivers. There is an ongoing need to understand the impact of postmenstrual age on "normal ranges" for physiological parameters (e.g., blood pressure[20] and hemoglobin[11]) and to know when and how to intervene to optimize physiological homeostasis and improve outcome.

Younger age at birth and at time of anesthesia were associated with increased morbidity and mortality, particularly in those born extremely preterm (<28 weeks PMA)[7] who continue to be at risk for early mortality.[21] The need for surgery following preterm birth has been associated with increased surgical morbidity and 30-day mortality,[22] and also adverse effects on long-term neurodevelopmental outcome.[23] The type of surgery and duration of anesthesia and hospital stay also requires consideration, with adverse neurodevelopmental outcome also reported following single or repeated neonatal surgery for major noncardiac anomalies.[24,25] Impaired tissue perfusion associated with hypotension, hypoxia, and anemia may contribute to brain injury. Interventions based primarily on NIRS values were uncommon in the NECTARINE study,[7] and further prospective trials have been recommended to establish the specificity and benefit of perioperative neuromonitoring in neonates.[26] As a relatively high proportion of UK patients required pre and/or postoperative intensive care admission, data related to surgery and perioperative critical events should be considered when evaluating long-term outcome following NICU.[23]

The current data highlight resource requirements for delivery of surgical, anesthetic, and intensive care for neonatal patients. Early recognition of "high risk" patients and procedures, and timely transfer to specialized centers with experienced staff may minimize adverse outcomes.[27] The UK National Health Service (NHS) has service specifications for neonatal surgery (E02/S/c Paediatric Surgery: Neonates; www.england.nhs.uk/wp-content/uploads/2013/06/e02-paedi-surg-neon.pdf) and neonatal intensive care (E08/S/a Neonatal Critical Care; www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/e08-serv-spec-neonatal-critical.pdf). Services are organized into clinical networks within geographical catchment areas, and specifications for neonatal intensive care transport (E08/S/b; https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/e08-serv-spec-neonatal-critical-transp.pdf) facilitate transfer for specialist care. This service model includes recommendations for clinical care pathways, staffing, capacity, and response times. As a result, UK recruitment included a high proportion of cases from major pediatric centers, and the higher rate of inter-hospital transfers reflects the NHS organizational structure. Alongside UK studies reporting surgical and anesthetic considerations for specific neonatal conditions (e.g., esophageal atresia[28,29]), the current data highlight issues related to preoperative assessment and co-morbidities that will inform best practice.

Provision of neonatal anesthesia requires specialist expertise that may take several years to acquire, and a high proportion of NECTARINE cases were performed by senior anesthesia staff. Anesthesia training and standards in the UK are overseen by the Royal College of Anaesthetists, with specific guidelines for the provision of pediatric anesthesia services (www.rcoa.ac.uk/gpas/chapter-10). Training requirements for anesthesia are among the longest in Europe with additional advanced fellowships (e.g., additional specialist pediatric training) frequently undertaken during the "trainee" or "residency" period. A harmonized European approach to pediatric and neonatal training is required to identify generalizable effects of experience and team cohesion.

This subgroup analysis has several limitations. As with previous NECTARINE analyses, the effects of preventive measures in the preoperative period, and variability in self-reporting and paper-based data entries remain unquantified. There is potential for under-reporting of events that were tolerated or considered acceptable by some practitioners or in some clinical contexts. The current data relates predominantly to tertiary care of high-risk neonates in the UK and may not reflect rates of complications for healthy neonates/infants undergoing more minor procedures. In addition, due to the proportionally small UK sample size, multivariable analyses were not performed, but descriptive analyses are comparable with the remainder of the NECTARINE cohort.

Morbidity and mortality following anesthesia is higher in neonates and young infants than older children. Severe critical events requiring medical interventions are common, particularly when anesthesia is required in those with prior or current co-morbidities,

at younger postmenstrual ages, or for urgent/emergency surgery. National data can inform discussions of risk with parents/caregivers, highlight ongoing training needs and resource requirements, and identify areas requiring ongoing study or standardization of practice to improve outcome for neonates and young infants.

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CONFLICT OF INTEREST

The authors report no financial conflict of interest relevant to this manuscript. Suellen Walker and Thomas Engelhardt are Section Editors for *Pediatric Anesthesia*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the manuscript and accompanying Supplementary Information. Additional data for the full NECTARINE cohort are available in the original manuscript (Disma et al. *Br J Anaesth*. 2021;126[6]:1157–1172) and the related Supplementary Information (https://doi.org/10.1016/j.bja.2021.02.016). Reasonable requests for additional data will be considered by the study sponsor (European Society of Anaesthesiology and Intensive Care - Clinical Trials Network; ESAIC-CTN) and NECTARINE Steering Committee.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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