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ORIGINAL ARTICLE

Circumstances, causes and timing of death in extremely preterm infants admitted to NICU: The EPIPAGE-2 study

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Abstract

Aim: To describe the circumstances, causes and timing of death in extremely preterm infants.

Methods: We included from the EPIPAGE-2 study infants born at 24–26 weeks in 2011 admitted to neonatal intensive care units (NICU). Vital status and circumstances of death were used to define three groups of infants: alive at discharge, death with or without withholding or withdrawing life-sustaining treatment (WWLST). The main cause of death was classified as respiratory disease, necrotizing enterocolitis, infection, central nervous system (CNS) injury, other or unknown.

Results: Among 768 infants admitted to NICU, 224 died among which 89 died without WWLST and 135 with WWLST. The main causes of death were respiratory disease (38%), CNS injury (30%) and infection (12%). Among the infants who died with

Abbreviations: CNS, central nervous system; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; WWLST, withholding or withdrawing life-sustaining treatment.

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WWLST, CNS injury was the main cause of death (47%), whereas respiratory disease (56%) and infection (20%) were the main causes in case of death without WWLST. Half (51%) of all deaths occurred within the first 7 days of life, and 35% occurred within 8 and 28 days.

Conclusion: The death of extremely preterm infants in NICU is a complex phenomenon in which the circumstances and causes of death are intertwined.

KEYWORDS

cause of death, extremely preterm infants, end of life decision, preterm birth, withdrawal

1 | INTRODUCTION

Among liveborn extremely preterm infants (i.e. born between 22 and 28 completed weeks of gestation), reported survival rates at discharge vary substantially across countries. For instance, in extremely low gestational age neonates (ELGAN), survival rates in low-income countries were reported to be as low as 28%.¹ Whereas survival rates for infants born at 22–26 weeks in high-income countries reached 51% in England in 2006,² 77% in Japan in 2005,³ 52% in France in 2011⁴ and 65% in the United States of America (USA) between 2008 and 2012.⁵ These differences observed between survival rates in high-income countries could be partly explained by national attitudes to management in both the delivery room and the neonatal intensive care unit (NICU).⁶ We previously reported a mortality rate of 76% in the delivery room for infants liveborn at 22–24 weeks of gestation in France, that was mainly related to deaths following withholding or withdrawing life-sustaining treatment (WWLST).⁷ Conversely, only 10% of liveborn neonates born at 25–26 weeks died in the delivery room. Therefore, WWLST in the delivery room cannot explain the differences in survival rates at discharge for preterm infants born at 25 and 26 weeks of gestation for infants born in France (68%)⁷ compared to Japan (88%)³ and the USA (81%).⁵ Studies reporting survival rates of extremely preterm infants at discharge typically do not report the causes, timing or circumstances of death (e.g. following WWLST) making comparisons between studies rather challenging.^{2–5}

A study published in 2015 in the USA reported a decline in overall death rates for infants born at 22–28 weeks of gestation between 2000 and 2011.⁸ A notable feature of this study was its 'proportionate mortality' analysis showing how the cause of death varied according to gestational age at birth and also to postnatal age. Within 12 h of life, the primary cause of death was immaturity, since comfort care was provided in the delivery room for the most extremely premature infants.⁹ By contrast, during the first week of life, respiratory distress syndrome (RDS) was the main cause of death, whereas necrotizing enterocolitis and infection became the predominant causes after 2 weeks of age.⁸ Data on whether intensive care was voluntarily withdrawn or withheld were not available and therefore their impact on mortality was not analysed. Thus, an accurate analysis of extremely preterm infants mortality across studies and countries would require to consider not only the causes and timing but also

Key Notes

- In extremely preterm infants born at 24–26 weeks of gestation, the majority of deaths occurred with withholding or withdrawing life-sustaining treatment in France in 2011.
- The main cause of death differed depending on the circumstances of death (with or without withholding or withdrawing life-sustaining treatment).
- The analysis of survival rates in extremely preterm infants should consider not only the causes of death but also the circumstances of death.

the circumstances leading to death. We suggest that some countries may have a higher mortality rate due to decisions of active discontinuation of life-sustaining treatment in NICU. Assuming this, we would expect differences in the main cause of death in extremely preterm infants with WWLST compared to those without WWLST. Our objective was to describe the circumstances, the causes and timing of death in extremely preterm infants admitted to NICU which were included in the EPIPAGE-2 national cohort study.

2 | PATIENTS AND METHODS

2.1 | Study population

Our study sample was selected from the EPIPAGE-2 population-based cohort. EPIPAGE-2 is a prospective national study of preterm infants born between 22 and 34 completed weeks in France in 2011, including terminations of pregnancy, stillbirths and live births.^{10,11} Families received information and agreed to participate in the study before any data collection began. Maternal, obstetric and neonatal data were collected prospectively at birth and during the neonatal hospitalisation, from medical records. All infants live born between 24 and 26 weeks of gestation enrolled in the EPIPAGE-2 without severe congenital malformations and subsequently admitted to NICU were included in this secondary analysis. Infants born at 22 ($n=2$) and 23 ($n=7$) weeks of gestation were not included in the analysis

because of their small number. Among them, five died before day 2 and only one was discharged alive. For these infants, death mainly occurred with WWLST, consistent with French practices in 2011 to provide comfort care to infants born at 22–23 weeks of gestation.

2.2 | Outcomes

To categorise the circumstances of death, we classified deaths according to whether or not there had been active discontinuation of life-sustaining treatment according to the answer to the specific item 'Did the death occur following withdrawal or withholding of life-sustaining treatment?' Vital status and circumstances of death were used to define three groups of infants: alive at discharge, death with WWLST and death without WWLST.

The primary cause of death was defined as the single underlying proximate disease leading to death. Three neonatologists (P.B., M.L. and L.F.-L.) independently determined the proximal cause of death after a detailed analysis of the questionnaires. The main cause of death was classified as respiratory disease, necrotizing enterocolitis (NEC), infection, central nervous system (CNS) injury, other or unknown using the same definitions as Patel et al.⁸ Respiratory disease was defined as severe respiratory insufficiency during the first 28 days of life (i.e. increasing oxygen and ventilatory pressure requirements, pneumothorax, pneumopericardium) or as progressive respiratory insufficiency for infants with chronic lung disease requiring oxygen for greater than 28 days.⁸ NEC was defined as stages II and III according to Bell staging¹² or as spontaneous perforation. Infection was defined as proven sepsis with positive blood or cerebrospinal fluid culture results for pathogenic bacteria.⁸ CNS injury was defined by the occurrence of severe intraventricular haemorrhage defined as grade III or IV intraventricular haemorrhage.¹³ The 'other' category included infants with other causes of death such as severe asphyxia with multi-system failure, severe metabolic disease and severe trauma. Cardio-respiratory arrest was not used as a cause of death. For the 'unknown' category, the cause of death was investigated but could not be established.⁸ Given the design of our study where infants with death in the delivery room or provided comfort care initially were not included, we cannot consider the first category of Patel classification, so we removed 'immaturity' as a cause of death.

Postnatal age at death was defined as age at death, within four categories: 0–2, 3–7, 8–28 and 29 or more days of life.

2.3 | Other variables

We collected maternal and obstetrical characteristics: maternal age, maternal place of birth, parity and type of pregnancy (single or multiple). The cause of preterm birth was classified as spontaneous (preterm labour or preterm premature rupture of membranes [PPROM]) or induced (maternal hypertensive disorders with or without foetal growth restriction [FGR], placental abruption or FGR without

hypertensive disorders) according to a previously defined classification.¹⁴ We also collected data on antenatal corticosteroid administration (at least one injection before birth), mode of delivery (vaginal or caesarean) and inborn/outborn status. Neonatal characteristics collected were sex, birth weight (<600, 600–749, ≥750g) and gestational age at birth in completed weeks (defined as the best obstetric estimate combining the last menstrual period and ultrasonogram assessment). We also collected neonatal morbidities.

2.4 | Statistical analysis

First, maternal and neonatal characteristics were compared across the three groups: alive at discharge, death with WWLST and death without WWLST. Second, we described the distribution of causes, circumstances and postnatal age at death according to gestational age. Finally, we also described proportionate mortality for causes of death according to postnatal age in all deaths and separately in each of the two sub-groups of death with and without WWLST to specifically address the causes of death according to the circumstances. Categorical variables were compared using χ^2 or Fisher's exact tests. All tests were two-sided with $p < 0.05$ considered statistically significant. Statistical analyses were performed using SAS (version 9.3, SAS Institute, Inc, Cary, NC).

2.5 | Ethics

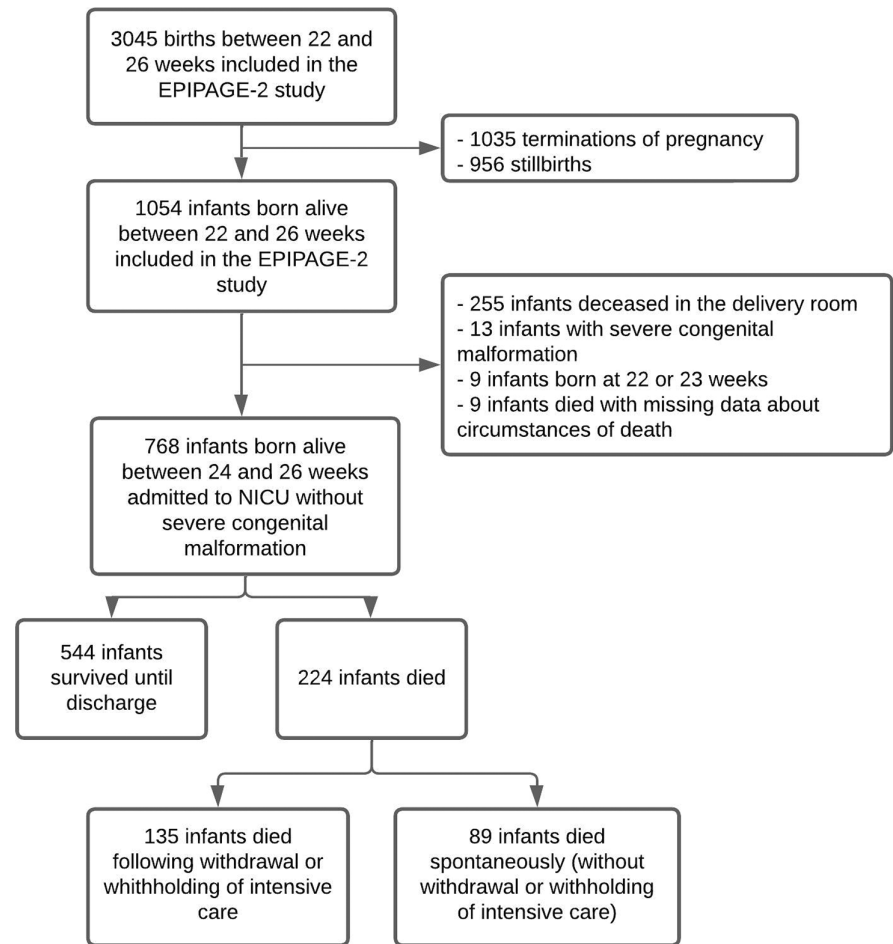
Non-opposition for participation was provided by mothers at delivery. EPIPAGE-2 was approved by the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL n°911009) and by appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes [reference 10.626] and the Committee for the Protection of People participating in biomedical research [reference CPP SC-2873]).

3 | RESULTS

Of the 3045 infants born between 22 and 26 weeks of gestation included in the EPIPAGE-2 study, 768 were born alive between 24 and 26 weeks, admitted to NICU and presented no severe congenital malformations (Figure 1). Among the 768 infants included, 544 survived until NICU discharge while 224 died. Among the 224 deaths, 135 died with WWLST and 89 died without WWLST.

Table 1 shows the characteristics of the three groups (alive at discharge, death with and without WWLST). Maternal characteristics such as multiple gestation and the cause of preterm birth were not statistically different between the three groups. The frequencies of antenatal corticosteroids administration, caesarean section and inborn status were higher in the group alive at discharge. Gestational age and weight at birth were significantly different between the

FIGURE 1 Flowchart. Among infants who died before discharge, 9 had missing information on circumstances of death and were therefore excluded from the analysis: 2 were born at 24 weeks of gestation, while 4 and 3 were, respectively, born at 25 and 26 weeks. Death occurred between day 0 and 2 for 3, between day 3 and 7 for 2 and between day 8 and 28 for the last 4. The cause of death was central nervous system injury ($n=3$), infection ($n=2$), respiratory distress syndrome ($n=2$) and unknown ($n=2$).



three groups, with a higher proportion of infants born at 26 weeks or with a birthweight ≥ 750 g in the group alive at discharge. Neonatal morbidity was different between the three groups. The frequency of CNS injury was markedly higher in the group of death with WWLST with 70% versus 10% and 21% in the groups alive at discharge and death without WWLST, respectively.

The main causes of death were respiratory disease (85 infants, 38% of all deaths) and CNS injury (68 infants, 30% of all deaths) (Table 2). Infection was identified as the main cause of death for 27 infants (12% of all deaths) and NEC for only 7 (3% of all deaths). Most deaths occurred within the first 7 days of life (51%) and within 8 and 28 days (35%) (Table 2). The causes and timing of death were similarly distributed for births at 24, 25 or 26 weeks of gestation. In contrast, the circumstances of death differed according to gestational age. Death with WWLST was more frequent when birth occurred at 24 versus 26 weeks of gestation (65% vs 54%) (Table 2). The proportion of each cause differed markedly depending on whether or not life-sustaining treatment was withdrawn or withheld (Figure 2). The distributions of causes of death according to postnatal age at death for all deaths and separately for deaths with or without WWLST are presented in Table S1. CNS injury was the main cause of death in infants who died with WWLST (47%), whereas respiratory disease (56%) and infection (20%) were the major causes of death in infants who died without WWLST. Finally, CNS injury was identified as the main cause of death for only 4/89 patients who died without WWLST (5%) (Table S1).

4 | DISCUSSION

In this French prospective cohort of extremely preterm infants, we showed that the distribution of causes of death varied markedly according to the circumstances of death (i.e. with or without WWLST). CNS injury was the main cause of death with WWLST, whereas respiratory disease was the main cause of death without WWLST. These results underline that mortality in extremely preterm infants depends not only on the primary cause of death but also on its circumstances.

These findings are in line with Ryvasy et al.'s suggestion that survival rates in extremely preterm infants should take into account the actual number of infants with initiation of active treatment.¹⁵ Survival rate analyses including infants who did not receive active treatments resulted in 'self-fulfilling' prognoses. Thus, we suggest that survival rates in extremely preterm infants admitted to NICU should not only take into account the number of infants who received initiation of life-sustaining treatment but also the circumstances surrounding the death of these infants. Indeed, not considering the circumstances of death could also induce a 'self-fulfilling' prognosis since the higher death rates due to the withdrawal or withholding of life-sustaining treatment led to lower survival rates.

We have previously shown that the lower survival rates at 25 and 26 weeks of gestation in France compared to other countries were not related to the withholding or withdrawal of life-sustaining

TABLE 1 Maternal and neonatal characteristics of the 768 extremely preterm infants admitted to the neonatal intensive care unit.

	Total N = 768	Alive at discharge N = 544	Death with WWLST N = 135	Death without WWLST N = 89	p value
	n (%)	n (%)	n (%)	n (%)	
Maternal and obstetrical characteristics					
Maternal age (years) (N = 768)					
<25	162 (21.1)	106 (19.5)	35 (25.9)	21 (23.6)	0.45
25–34	453 (59.0)	324 (59.5)	76 (56.3)	53 (59.5)	
≥35	153 (19.9)	114 (21.0)	24 (17.8)	15 (16.9)	
Mother born in France (N = 737)	549 (74.5)	394 (73.5)	93 (76.9)	62 (77.5)	0.60
Primiparous (N = 759)	418 (55.1)	299 (55.7)	79 (59.0)	40 (45.5)	0.10
Multiple gestation (N = 768)	257 (33.5)	177 (32.4)	48 (35.6)	33 (37.1)	0.60
Antenatal corticosteroids (N = 755)	594 (78.7)	441 (82.1)	89 (68.5)	64 (72.7)	0.001
Magnesium sulfate (N = 749)	49 (6.5)	39 (7.3)	5 (3.8)	5 (5.9)	0.34
Cause of preterm birth (N = 717)					
Spontaneous	626 (87.3)	447 (87.8)	112 (88.9)	67 (81.7)	0.26
Induced	91 (12.7)	62 (12.2)	14 (11.1)	15 (18.3)	
Caesarean delivery (N = 759)	341 (44.9)	258 (48.0)	44 (32.8)	39 (44.3)	0.007
Inborn status (N = 768)	643 (83.7)	468 (86.0)	100 (74.1)	75 (84.3)	0.003
Neonatal characteristics					
Gestational age at birth (weeks) (n = 768)					
24	110 (14.3)	58 (10.7)	34 (25.2)	18 (20.2)	<0.001
25	272 (35.4)	179 (32.9)	58 (43.0)	35 (39.3)	
26	386 (50.3)	307 (56.4)	43 (31.8)	36 (40.5)	
Birth weight (g) (n = 768)					
<600	61 (7.9)	28 (5.1)	18 (13.3)	15 (16.8)	<0.001
600–749	248 (32.3)	161 (29.6)	51 (37.8)	36 (40.5)	
≥750	459 (59.8)	355 (65.3)	66 (48.9)	38 (42.7)	
Female sex (n = 768)	365 (47.5)	269 (49.5)	59 (43.7)	37 (41.6)	0.24
Neonatal morbidities ^a					
Severe RDS (N = 755)	274 (36.3)	162 (30.3)	75 (56.4)	37 (42.5)	<0.001
Early onset sepsis (N = 723)	23 (3.2)	8 (1.5)	10 (8.3)	5 (6.3)	<0.001
Late-onset sepsis (N = 699)	321 (45.9)	265 (50.1)	28 (24.8)	28 (49.1)	<0.001
NEC (N = 743)	38 (5.1)	26 (4.8)	4 (3.1)	8 (10.7)	0.05
CNS injury (N = 747)	163 (21.8)	56 (10.3)	91 (70.0)	16 (21.3)	<0.001
BPD (N = 527)	213 (40.4)	205 (39.6)	3 (100)	5 (83.3)	0.01
Severe neonatal morbidity (N = 672)	321 (47.7)	202 (39.6)	96 (85.7)	23 (46.0)	<0.001

Note: WWLST withholding or withdrawing life-sustaining treatment. For each variable, percentages might not sum up to 100%, owing to rounding. Bronchopulmonary dysplasia (BPD): administration of oxygen for at least 28 days together with the need for 21% or more oxygen and/or mechanical ventilatory support or continuous positive airway pressure among infants alive at 36 weeks' postmenstrual age. NEC: stages II and III according to Bell staging. Early onset sepsis: positive blood or cerebrospinal fluid culture result for pathogenic bacteria within 3 days of birth. Late-onset sepsis: positive blood culture occurring after 72 h of life, associated with antibiotic administration for 5 days or more or death within 5 days following positive blood culture. Severe neonatal morbidity: any of the following outcomes: CNS injury; NEC; stage 3 or higher retinopathy of prematurity and/or BPD.

^aSevere respiratory distress syndrome (RDS): two or more surfactant doses administered within the first 2 days of life.

treatment in the delivery room.⁷ Another hypothesis for the lower survival rates at 25–26 weeks in France could be an absence of national resuscitation guidelines for lower gestational ages.^{4,6} In

the Netherlands, survival improved also for 26-week infants after lowering the gestational age threshold for active intervention from 26 weeks to 25 weeks.¹⁶ The discrepancy in survival rates between

TABLE 2 Distribution of circumstances, main cause and postnatal age at death in NICU according to gestational age at birth.

Weeks of gestation	24	25	26	Total
Deaths in NICU (n/N)	52/110 (47.2)	93/272 (43.9)	79/386 (20.5)	224/768 (29.2)
Circumstances of death				
With WWLST	34 (65.4)	58 (62.4)	43 (54.4)	135 (60.3)
Without WWLST	18 (34.6)	35 (37.6)	36 (45.6)	89 (39.7)
Main cause of death				
Respiratory disease	19 (36.5)	37 (39.8)	29 (36.7)	85 (38.0)
NEC	1 (1.9)	3 (3.2)	3 (3.8)	7 (3.1)
Infection	5 (9.6)	7 (7.5)	15 (19.0)	27 (12.0)
CNS injury	18 (34.6)	26 (28.0)	24 (30.4)	68 (30.4)
Other	6 (11.5)	11 (11.8)	6 (8.0)	23 (10.3)
Unknown	3 (5.8)	9 (9.7)	2 (2.5)	14 (6.3)
Postnatal age at death				
0–2 days	13 (25.0)	19 (20.4)	21 (26.6)	53 (23.7)
3–7 days	15 (28.9)	23 (24.7)	23 (29.1)	61 (27.2)
8–28 days	17 (32.7)	37 (39.8)	25 (31.7)	79 (35.3)
≥29 days	7 (13.4)	14 (15.1)	10 (12.7)	31 (13.8)

Note: Data are presented as the number (percentage) of patients.

Abbreviations: CNS central nervous system; NEC necrotizing enterocolitis; NICU neonatal intensive care unit; WWLST withholding or withdrawing life-sustaining treatment.

The 'other' category included infants with other causes of death such as severe asphyxia with multi-system failure, severe metabolic disease and severe trauma. Cardio-respiratory arrest was not used as a cause of death. For the 'unknown' category, the cause of death was investigated but could not be established.

EPIPAGE-2 and other cohorts might be due to similar reasons: actively resuscitating 23-weekers might lead to more competence and experience also when caring for 24–26 weekers.

Alternately, the present results could suggest that the lower survival rate at discharge observed in France⁴ compared with those observed in other countries^{3,5} could be related to the withdrawal of life-sustaining interventions in the NICU, ultimately leading to death. Such decisions are possibly based on the medical team's view that severe cerebral lesions (severe intracranial haemorrhage and/or cPVL) are associated with a high risk of neurodevelopmental impairment and subsequently a poor quality of life.¹⁷ Ethical questions remain regarding the care of these infants in NICU across countries. For example, redirection of care in case of severe cerebral lesions is frequent in France, Australia and New Zealand while rare in Sweden.¹⁸ Such a 'paternalistic' approach should logically lead to a lower rate of cerebral palsy. However, the rates of cerebral palsy at 2 years in infants born before 27 weeks of gestation in Sweden and France (7% in both countries).^{19,20}

The main strength of our study relies on the EPIPAGE-2 cohort, one of the largest population-based cohorts with a prospective enrolment of preterm infants. Standardised definitions of outcomes following international recommendations were used and prospective collection of all information available for a sample of 768 extremely preterm infants admitted to NICU allowed comparisons with other international cohorts.

A limitation of our study comes from the assessment of the variable of interest 'death with or without WWLST', which was based

on the answer provided to the question 'Did death occur following withdrawal or withholding of life-sustaining treatment?' Therefore, we were unable to identify two categories of infants: first, those discharged alive despite WWLST and second, among those deceased following WWLST, those who could have died spontaneously later. The first category does not modify the mortality rate before discharge, whereas, with the second category, we may have overestimated the death rate following WWLST by including infants that could have died later without WWLST. However, the survival rate at discharge at 25–26 weeks (68%) is lower in France⁷ compared to other countries (around 80%).^{3,5} Therefore, it seems therefore unlikely that many infants in the group of those deceased following WWLST would have died anyway, and even if they would have, the overwhelming main cause of death would not have been CNS injury as we have observed.

Finally, the main causes of death were classified using the definitions described by Patel et al.⁸ We cannot exclude a risk of misclassification of the main cause of death since identifying one single cause of death can be difficult for some extremely preterm infants as previously suggested.⁸ Nevertheless, potential misclassifications should be distributed similarly between the two groups.

The American Academy of Pediatrics recommends an accurate reporting of perinatal deaths using standardised terminology.²¹ We fully agree and further suggest that, in future studies, identifying whether or not the deaths of extremely preterm infants followed WWLST may contribute to improve such studies aiming to reduce death rates in this high-risk population. We also believe that for

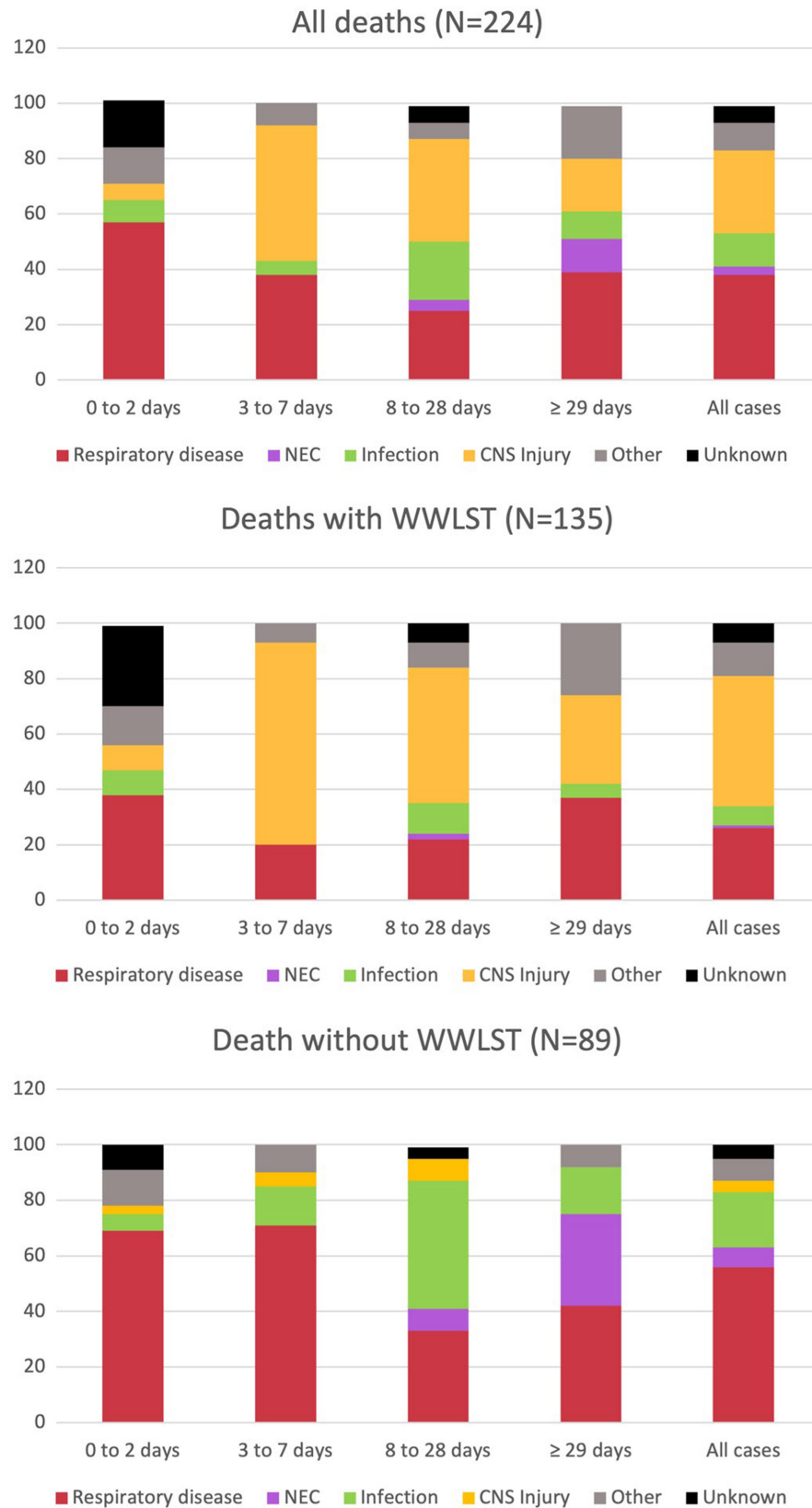


FIGURE 2 Proportionate mortality for causes of death according to postnatal age. CNS, central nervous system; NEC, necrotizing enterocolitis.

the sake of transparency, the analysis of survival rates in extremely preterm infants should also consider the circumstances of death (i.e. whether or not death followed WWLST) and not only the causes of death.

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CONFLICT OF INTEREST STATEMENT

The authors have no potential conflict of interest, real or perceived, to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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