**Supplementary material**

Table A.1. Systemic damage score in the cohort of infants with hypoxic-ischemic encephalopathy

|  |  |  |
| --- | --- | --- |
| Systemic damage | Score | Definition |
| Cardiovascular | 1 | Need for inotropes |
| Pulmonary  | 3 | Use of nitric oxide for pulmonary hypertension |
|  | 1 | Pulmonary hypertension and/or use of supplementary oxygen |
| Renal | 3 | Creatinine levels > 1.5 mg/dl and/or use of dialysis |
|  | 1 | Use of diuretics |
| Hepatic | 3 | alanine and/or aspartate aminotransferase transaminases > 500 UI/L |
|  | 1 | alanine and/or aspartate aminotransferase transaminases > 100 UI/L |
| Coagulopathy | 3 | Need for fresh frozen plasma and coagulation factors |
|  | 1 | Need for fresh frozen plasma |
| Hemorrhage | 3 | Need for platelet and/or red blood transfusion  |
|  | 1 | Presence of hemorrhage but no need for transfusion |
| Gastrointestinal | 3 | Necrotizing enterocolitis  |
|  | 1 | Gastrointestinal bleeding |

Table A.2. and Figure A.2. Temporal trends of using overlapping periods of time

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Period | Births (n) | Total HIE | Moderate HIE (n) | Severe HIE (n) | Global rate (95% CI) | Moderate HIE rate (95% CI) | Severe HIE rate (95% CI) |
| July 2010-Dec 2012 | 50,036 | 44 | 27 | 17 | 0.880.62-1.14 | 0.540.34-0.74 | 0.340.18-0.5 |
| Jan 2011- Dec 2013  | 57,044 | 55 | 36 | 19 | 0.960.71-1.22 | 0.630.43-0.84 | 0.330.18-0.48 |
| Jan 2012- Dec 2014  | 55,269 | 53 | 36 | 17 | 0.960.70-1.22 | 0.650.44-0.86 | 0.310.16-0.45 |
| Jan 2013- Dec 2015  | 53,586 | 49 | 34 | 15 | 0.910.66-1.17 | 0.630.42-0.85 | 0.280.14-0.42 |
| Jan 2014- Dec 2016  | 52,367 | 42 | 29 | 13 | 0.800.56-1.04 | 0.550.35-0.76 | 0.250.11-0.38 |
| Jan 2015-Dec 2017 | 50,064 | 35 | 23 | 12 | 0.700.47-0.93 | 0.460.27-0.65 | 0.240.10-0.38 |
| Jan 2016-Dec 2018 | 47,736 | 43 | 33 | 10 | 0.900.63-1.17 | 0.690.46-0.93 | 0.210.08-0.34 |
| Jan 2017-July 2019 | 39,237 | 41 | 33 | 8 | 1.040.73-1.36 | 0.840.55-1.13 | 0.200.06-0.35 |

HIE incidence rates are expressed as number per 1,000 births; HIE = hypoxic-ischemic encephalopathy; n = number; CI = confidence interval.



Cumulative incidence rate expressed as number of infants with HIE per 1,000 births for moderate-to-severe HIE (black line) (χ2 for trend, p=0.8), moderate HIE only (grey dashed line) (χ2 for trend, p=0.3), and severe HIE only (grey dotted line) (χ2 for trend, p=0.06).