Association between hypothermia in the first day of life and survival in the preterm infant

Short title: Hypothermia and mortality in the preterm infant

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Abbreviations:

NICU: neonatal intensive care unit

WG: weeks of gestation

HR: hazard ratio

RH: relative humidity

RR: risk ratio

OR: odds ratio

CI: confidence interval

$T_{Body\ Nadir\ 24h}$: lowest temperature during the first 24 h of life

Abstract:

Objective: Hypothermia is associated with elevated mortality in the preterm infant. The preterm infant's thermoregulatory capacity is limited, and the thermal environment in an incubator is often perturbed by nursing procedures. We evaluated the incidence of a postnatal low body temperature and hypothermia in preterm infants and its association with mortality.

Methods: We measured the lowest body temperature during the first 24 h of life ($T_{Body\ Nadir\ 24h}$) and hypothermia ($T_{Body\ Nadir\ 24h}$ <36.0°C) in preterm infants (gestational age: 23^0–31^6 weeks) in a neonatal intensive care unit. Prenatal and neonatal characteristics associated with mortality were identified in univariate and multivariable analyses.

Results: A total of 102 preterm infants were included, with a mean gestational age at birth of 28.4±2.3 weeks. The incidence of hypothermia during the first 24 h was 53%. A Cox multivariate regression model indicated that $T_{Body\ Nadir\ 24h}$ (hazard ratio (HR) [95% confidence interval]: 0.57 [0.36–0.90]; p=0.017), gestational age (0.62 [0.50–0.76]; p<0.001), and amine use (4.55 [2.01–10.28]; p=0.001) were significantly associated with mortality. When considering a threshold for $T_{Body\ Nadir\ 24h}$, a value of 35.0°C had the highest HR (3.30 [1.42-7.68]; p<0.01).

Conclusion: In preterm infants, the incidence of hypothermia during the first 24 h of life was 53%. $T_{Body\ Nadir\ 24h}$ had an influence on mortality, independently of other factors (notably birth weight and amine use). Within the framework of a quality improvement strategy, the implementation of a thermoregulation bundle is required to prevent hypothermia and decrease mortality in preterm infants.

Keywords: care provision; preterm infant; temperature; outcome

1. Introduction

Neonatal hypothermia (often defined as a body temperature [T_{Body}] <36.0°C on admission to the neonatal intensive care unit [NICU]) has been linked to an elevated mortality rate among preterm infants [1–3]. The literature data also highlight an inverse relationship between neonatal hypothermia and major neonatal morbidities, such as intraventricular hemorrhage [4], late-onset sepsis (with an 11% increase per 1°C decrement in admission temperature) [2], severe retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia [5], and severe neurodevelopmental impairment [6]. A number of studies have also identified interactions between thermal stress and certain physiological functions, such as sleep [7,8], heart rate control [9], ventilation, and the incidence of apneic events [8]. Very-low-birth-weight infants are especially at risk: The admission temperature is 0.04°C lower for each 100-g decrement in birth weight [3].

Several measures are known to prevent hypothermia in the preterm infant in the delivery room [10–12]. The use of a polyethylene bag decreases the incidence of hypothermia [11], as does a high (26°C) ambient temperature, the use of a polyethylene cap [12], the use of heated, humidified air during resuscitation at birth [13], and a reduction in the opening of closed incubators [14]. Most of these measures have been included in the guidelines on resuscitation of newborns [15]. Nevertheless, over 40% of preterm infants experience hypothermia upon admission to the NICU [2,16]. Recent studies have shown that an admission temperature <35.5°C was associated with increased mortality in the first 28 days of life but not after that time point [16]. Phoya et al. used hypothermia within the first 24 h of life as a marker of thermal control [17]; this might correspond to (a) thermal management in the delivery room, (b) the preterm infant's early thermoregulatory capacity [7,8], and/or (c) disturbance of the thermal environment during nursing procedures [18]. The last parameter is a partial guide to the newborn's frailty and may indicate the quality of nursing procedures [18].

The primary objective of the present study was to evaluate the putative association between the lowest body temperature during the first 24 h of life ($T_{Body\ Nadir\ 24h}$) and survival in preterm infants before a corrected gestational age of 40 weeks. The secondary objective was to determine whether or not $T_{Body\ Nadir\ 24h}$ was an independent risk factor for mortality.

2. Materials and Methods

We performed a retrospective cohort study in the NICU at Amiens University Hospital (Amiens, France). All parents provided their written informed consent. The study protocol was approved on September 16, 2019, by the local independent ethics committee (Amiens, France; reference: PI2019_843_0073).

2.1 Population

The inclusion criteria were as follows: preterm delivery (gestational age between 23^0 and 31^6 weeks of gestation [WG]) in Amiens University Hospital, and direct admission to the NICU from the delivery room. The exclusion criteria included congenital brain malformations, malformations resulting in an open lesion (e.g., myelomeningocele or abdominal wall defects), or a prenatal diagnosis prompting a decision to withdraw or limit intensive care. The inclusion period was from September 1, 2018, to September 31, 2019, to ensure that 100 neonates could be included. In view of this epidemiological study's observational design, a sample size could not be prespecified.

2.2 Protocol

In the delivery room, preventive actions were taken to reduce body heat loss and/or provide warmth via external heat sources, in accordance with the 2015 guidelines on resuscitation in the delivery room [15,19]. The measures taken to reduce body heat loss included the use of occlusive wrapping (Heltis Line, Heltis Diffusion, Bourges, France) and a cotton cap, a target delivery room temperature of 25°C, and protection from draughts [19]. The preterm infant was not dried before being wrapped in the polyethylene bag. Warmed, humidified air was not used during respiratory support, since the NICU was only 20 m from the delivery room. After the preterm infants had stabilized, they were taken to the NICU in a transport incubator (NITE, Mediprema, Tauxigny, France) set to 36°C.

The nursery temperature was set at 25.0°C, and the mean relative humidity (RH) in the

NICU was 50% [20]. During the first hours of life, umbilical lines were put in place and transfontanellar and transthoracic ultrasound scans were performed. All preterm neonates were nursed naked in the supine position in an incubator with an abdominal skin servo-control mode (Caleo®, Dräger, Lübeck, Germany), in line with the standard procedures of our NICU. The target incubator air temperature was set to 37.0°C [21].

2.3 Data recording and analysis

The primary study outcome was the lowest temperature recorded during the first 24 h of life ($T_{Body\ Nadir\ 24h,}$ °C). An incubator thermal probe was attached to the preterm infant's abdomen with a reflective foil patch, in order to measure the body temperature according to the zero heat flow theory [22]. The axillary temperature was recorded every 3 h. If the axillary temperature was <36.0°C, the rectal temperature was recorded. Hence, $T_{Body\ Nadir\ 24h}$ was defined as the lowest of the eight temperatures recorded during the first 24 h of the preterm infant's life. Hypothermia was defined as $T_{Body\ Nadir\ 24h}$ <36.0°C, according to the World Health Organization guidelines [23]. Data on maternal and neonatal characteristics were extracted from medical records. The secondary study outcome was survival up until hospital discharge or death before a corrected gestational age of 40 WG. The following variables were explored for associations with mortality before 40 WG: (a) prenatal variables, including antenatal steroids (a partial or complete course), maternal temperature (the highest value between admission to the delivery room and 2 h after birth), maternal hypertensive disease (essential hypertension, preeclampsia, and eclampsia), chorioamnionitis (clinically and histologically confirmed chorioamnionitis), single birth vs. multiple births; (b) the infant's characteristics, including gestational age (obstetric estimate), birth weight, and sex; (c) delivery room events, including the delivery mode, the 5-min Apgar score, the ventilation strategy, and whether or not the infant was admitted to the NICU during the hospital's main

working hours (8 a.m. to 7 p.m., Monday to Friday); and (d) clinical data within the first 24 h of life, including $T_{Body\ Nadir\ 24h}$, amine use, the temperature and RH inside the incubator upon admission to the NICU, the immediate postnatal blood gas analysis results (within 2 h of birth), umbilical lines, and number of procedures with prolonged opening of the incubator (defined as an opening lasting 15 min or more, as defined by Deguines et al. [18] for catheter insertion, an ultrasound scan, etc.).

2.4 Statistical analysis

Outcome parameters were compared using Student's *t* test or (with non-normally distributed data), a Mann–Whitney U test for continuous variables, and Fisher's exact test for categorical variables. In the survival analysis, the main dependent variable was the date of death. The data were censored after 20 weeks of follow-up. The association between the independent variables recorded during the study and the time to event (mortality) in the premature infants was assessed using a Cox proportional hazards regression model [23]. The survival function was represented according to the Kaplan–Meier method.

Firstly, the associations between survival and the independent variables were assessed in a univariate analysis. The independent variables analyzed were: $T_{Body\ Nadir\ 24h}$, gestational age, birth weight, amine use, ventilation strategy, the 5-min Apgar score, antenatal steroids, incubator opening, delivery mode, maternal temperature, umbilical lines, maternal hypertensive disease, multiple births, day of the working week, and sex (female). The Holm–Sidak correction for multiple testing was applied, with k=16, p<0.05, and α<0.05. In a second step, we performed a multivariate analysis of survival and adjusted for the independent variables with p<0.2 in the univariate analysis [23]. The best Cox regression model was determined by backward stepwise elimination, based on minimization of the Akaike

information criterion. The proportional hazards assumption in the best Cox regression model was confirmed by testing the change over time in the Schoenfeld residuals.

In order to determine a clinically relevant body temperature cut-off (in addition to the continuous value of $T_{Body\ Nadir\ 24h}$), we performed additional multivariate analyses of survival with a binarized $T_{Body\ Nadir\ 24h}$. The $T_{Body\ Nadir\ 24h}$ was transformed into a binary variable as follows: 1 if $T_{Body\ Nadir\ 24h}$ was below a given temperature threshold and 0 if it was equal to or above the threshold. $T_{Body\ Nadir\ 24h} \geq$ thresholds from 34.0°C to 37.0°C (with a 0.5°C increment) were tested. The variables selected after backward stepwise elimination in the main statistical analysis were introduced as covariables for $T_{Body\ Nadir\ 24h}$ thresholds in the Cox regression model. The statistical significance of $T_{Body\ Nadir\ 24h}$ thresholds was corrected for multiple comparisons, using the Holm–Sidak test.

Survival function analysis, representations, and backward stepwise elimination according to the Akaike information criterion were performed with the *survival*, *survminer*, *forestmodel*, *GGally,* and *MASS* packages in R software (R Core Team, 2013; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

3. Results

Of the 106 infants included in the study, four were excluded for congenital anomalies. Hence, 102 infants were included in our analysis. The incidence of hypothermia ($T_{Body\ Nadir\ 24h}$ < 36.0°C) during the first 24 h of life was 53% (54 of the 102 infants). The $T_{Body\ Nadir\ 24h}$ was achieved on admission for 27 (50%) of the neonates with hypothermia and later in the first 24 h of life for the 27 (50%) others.

The survival rate was 55.6% (30 out of the 54) among the preterm infants with hypothermia and 91.2% (44 out of 48) among the infants without hypothermia (p<0.001). The incidence of grade III and/or IV intraventricular hemorrhage was 25.9% (14 out of 54) among the preterm infants with hypothermia and 8.3% (4 out of 48) among those without hypothermia (p<0.001). Of the 28 infants who died during the follow-up period, 23 (82.1%) died within 5 weeks of birth (Figure 1) and 13 (46.4%) had a grade III and/or IV intraventricular hemorrhage (vs. 4 [5.4%] in the control group; p<0.001).

In a univariate analysis, the factors associated with mortality before 40 GA for antenatal and delivery room events (Table 1) and clinical data within the first 24 h of life (Table 2) included: $T_{Body\ Nadir\ 24h}$ (HR: 0.33; 95% CI: [0.22–0.48]; p<0.001), gestational age (HR: 0.55; 95% CI: [0.46–0.67]; p<0.001), birth weight (HR: 0.996; 95% CI: [0.994–0.997]; p<0.001), amine use (HR: 7.78; 95% CI: [3.55–17.1]; p<0.001), ventilation strategy (HR: 10.5; 95% CI: [2.50–44.4]; p=0.0014), the 5-min Apgar score (HR: 0.84; 95% CI: [0.75–0.95]; p=0.0046), antenatal steroids (OR: 0.61; 95% CI: [0.4-0.91]; p=0.015), and incubator opening (HR: 2.42; 95% CI: [1.06–5.50]; p=0.035) (Figure 2). The other factors were not significantly associated with mortality (Table 3, column A).

The adjusted proportional hazard ratio (HR) obtained in the multivariate analysis showed that $T_{Body\ Nadir\ 24h}$ (HR: 0.59; 95% CI: [0.34–0.99], p=0.049), gestational age (HR: 0.65; 95% CI: [0.45–0.94], p=0.024) and amine use (HR: 4.79; 95% CI: [1.88–12.2], p=0.0011) were

significantly and independently associated with mortality (Table 3, column B). The other variables included in the multivariate model were not significantly associated with mortality. The parsimonious Cox regression model (Table 3, column C) obtained with backward stepwise selection confirmed that the $T_{Body\ Nadir\ 24h}$ (HR: 0.57; 95% CI: [0.36–0.90], p=0.017), gestational age (HR: 0.62; 95% CI: [0.50–0.76], p<0.001) and amine use (HR: 4.55; 95% CI: [2.01–10.28], p=0.001) were significantly associated with mortality among the preterm infants (Appendix 2). The change over time in the Schoenfeld residuals (Appendix 1) confirmed the proportional hazards assumption for the three variables ($T_{Body\ Nadir\ 24h}$, gestational age, and amine use), which therefore constituted the most parsimonious multivariate Cox model.

Of the $T_{Body\ Nadir\ 24h}$ thresholds (33.0°C to 37.0°C) tested, the highest HRs were found for values of 35.0°C (HR: 3.30; 95% CI: [1.42–7.68]; p=0.0056) and 34.5°C (HR: 2.81; 95% CI: [1.10–7.00]; p=0.027). Cox regressions were not applicable for threshold values of 33.0°C, 33.5°C, and 37.0°C (Figure 3). The $T_{Body\ Nadir\ 24h}$ < 35.0°C threshold remained statistically significant after correction for multiple comparisons (k= 6, p<0.05). With a $T_{Body\ Nadir\ 24h}$ < 35.0°C, the covariables gestational age (HR: 0.61; 95% CI: [0.49–0.76], p<0.001) and amine use (HR: 6.74; 95% CI: [2.86–15.87], p=0.001) were significantly associated with mortality among the preterm infants (Appendix 3). The Schoenfeld residuals indicated that proportional hazard assumption was met for the full model and for $T_{Body\ Nadir\ 24h}$ < 35.0°C, gestational age and amine use.

4. Discussion

The incidence of hypothermia within the first 24 h of life was 53% for preterm infants. The lowest body temperature within the first 24 h of life occurred on admission for half the preterm infants but occurred later during this period for the other 50%. The lowest body

temperature within the first 24 h of life was significantly associated with mortality during the first 5 weeks of life ($p<0.001$), independently of the other factors (notably, gestational age and amine use).

Although the NICU complied with the guidelines on preventing hypothermia [11–15], the incidence of hypothermia within the first 24 hours of life (53%) was high. However, this incidence was similar to the values reported in previous studies of the body temperature on admission to the NICU (ranging from 40.9% to 46.9%) [2,3]. Many studies have focused on the association between mortality and the admission temperature [2,3,24]. Among 5277 preterm infants <1500 g born in 2002 and 2003, the mortality rate increased by 28% per degree decrement in the temperature on admission to the NICU (OR: 1.28, 95% CI: [1.16–1.41]) [2].

The Kaplan–Meier survival analysis yielded an inverted exponential curve; this confirmed the report by Wilson et al. that hypothermia was a risk factor for early mortality [16]. In an adjusted model, an admission temperature <35.5°C was associated with increased mortality at postnatal ages of 1 to 6 days (risk ratio [RR]: 2.41; 95% CI: [1.45–4.00]) and 7–28 days (RR: 1.79; 95% CI: [1.15–2.78]) but not after 28 days [16]. To the best of our knowledge, hypothermia during the first 24 h of life has not previously been clearly identified as an independent risk factor for mortality. Phoay et al. studied the incidence of hypothermia during the first 24 h of life but did not find any significant relationships, probably because the population was different (preterm infants >1000 g) [17]. In the present study, the mean $T_{Body\ Nadir\ 24h}$ in the non-survivor group was low (34.9±0.9°C) and had a wide range; this may explain why it was statistically significant in our multivariate analysis but not in earlier studies of the admission temperature [2,3].

Our search for a potential $T_{Body\ Nadir\ 24h}$ threshold revealed that a value below 35.0°C was strongly associated with mortality after adjustment for gestational age and amine use. The

$T_{Body\ Nadir\ 24h}$ threshold of 35.0°C was very close to that reported by Wilson et al.: An admission temperature < 35.5°C was associated with elevated mortality at a postnatal age of 1–6 days (RR: 2.41; 95% CI [1.45–4.00]) [16]. Nevertheless, the question of whether the temperature is causally related to mortality or is only a marker of the risk of death requires further investigation [3]. Although we considered many confounding parameters, the prognosis of the preterm infant also depends on many other factors, such as birth weight, gestational age, and perinatal factors (e.g., prenatal steroid use), which were previously observed in the multivariable analysis [25].

Furthermore, the preterm infant's thermal environment is perturbed during nursing procedures – especially during the first 24 h of life [18].

Our study had a number of limitations, which restrict comparisons with the literature data. The mortality rate in the present study was 27.5%, versus 6.3%–14.3% in the literature on the relationship between the admission temperature and mortality [2,3,5]. However, the study populations differed with regard to factors influencing mortality (e.g., the incidence of prenatal steroid administration in the present study was only 75%). However, the mortality was not very different from the value for France as a whole reported in the EPIPAGE-2 study (85.4% at 28 WG) [26]. Furthermore, our study population was very similar to other French cohorts [26]. Nevertheless, all the other parameters analyzed in this study were very close to those in previous works [2,3,5].

Caregivers should take precautions to prevent hypothermia both in the delivery room and during the first few hours after admission to the NICU [7,8,18]. Efforts to limit heat loss are important for stabilizing newborns immediately after birth and have been incorporated in the World Health Organization guidelines on thermal control of newborns [27] and the guidelines for neonates in the delivery room [15,19]. Measures that can prevent hypothermia include wrapping the infant in plastic (without drying), covering the head with a cap, and

using radiant warmers and exothermic mattresses [10,19]. Minimizing heat loss in low-birth-weight and premature infants is difficult because of (a) the high evaporative heat losses due to the large temperature gradient from the skin to the ambient air, and (b) the premature infant's physical characteristics (high surface area to weight ratio, an immature epidermal barrier, and limited amounts of vernix caseosa and subcutaneous fat) [28]. Furthermore, the preterm infant's thermal environment is perturbed during nursing procedures, especially during the first 24 h of life [18]. In the present study, we analyzed the relationship between a low body temperature during the first 24 h of life and mortality. Further research should focus on factors related to the occurrence of hypothermia not only in the delivery room but also in the NICU. Prevention of hypothermia in the preterm infant should be evidence-based [29] and implemented in the NICU as part of a quality improvement strategy with regular assessments [30].

5. Conclusion

In preterm infants in the NICU, the incidence of hypothermia during the first 24 h of life was 53%. Along with gestational age and amine use, hypothermia during the first 24 h of life was independently associated with elevated mortality within the first 5 weeks of life. Quality improvement strategies for preventing hypothermia and decreasing mortality among preterm infants are urgently required.

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Table 1: Antenatal characteristics and characteristics in the delivery room.

		Non-survivors (*n* =28)	**Survivors (*n* = 74)**	***p***
Antenatal variables				
Antenatal steroid use	2 doses	**19 (67.9%)**	**62 (83.8%)**	**<0.01**
	1 dose	**2 (7.1%)**	**9 (12.2%)**	
	0 dose	**7 (25.0%)**	**3 (4.0%)**	
Maternal temperature (°C)		37.1±0.7	36,9±0.7	ns
MHD		5 (17.9%)	24 (32.4%)	ns
Chorioamnionitis		8 (28.6%)	21 (28.4%)	0.90
Multiple births		8 (28.6%)	15 (20.3%)	ns
Infant characteristics				
Gestational age (WG)		**25.9±1.7**	**29.3±1.8**	**<0.001**
Birth weight (g)		**743±217**	**1175±378**	**<0.001**
Sex	Male	15 (53.6%)	36 (48.6%)	ns
	Female	13 (46.4%)	38 (51.4%)	
Delivery room events				
Delivery mode	Caesarean	13 (46.4%)	48 (64.9%)	ns
	Vaginal	15 (53.6%)	26 (35.1%)	
5-min Apgar score		**7.3±3.3**	**8.6±1.9**	**<0.01**
Ventilation strategy	**CPAP**	**2 (7.1%)**	**38 (51.4%)**	**<0.001**
	IMV	**26 (92.9%)**	**36 (48.6%)**	
Working period	Working week[$]	6 (21.4%)	23 (31.1%)	ns
	Weekend[$$]	22 (78.6%)	51 (68.9%)	

MHD: maternal hypertensive disease; CPAP: continuous positive airflow pressure; IMV: invasive mechanical ventilation; [$] main working week: 8 a.m. to 7 p.m., Monday to Friday; [$$] Saturday, Sunday, and 7 p.m. to 8 a.m. Monday to Friday.

Table 2: Clinical data within the first 24 h of life.

	Non-survivors (*n* = 28)	**Survivors (*n* = 74)**	***p***
$T_{Body\ Nadir\ 24h}$ (°C) *	**34.9±0.9**	**35.9±0.6**	**<0.001**
$T_{Body\ Nadir\ 24h}$ < 36°C	**24 (85.7%)**	**30 (40.5%)**	**<0.001**
Amine use	**10 (35.7%)**	**3 (4.1%)**	**<0.001**
Incubator opening	**27 (96.4%)**	**62 (83.7%)**	**<0.05**
Umbilical lines	26 (92.8%)	63 (85.1%)	ns
Incubator temperature	36.5±1.0	35.8±1.9	0.08
Incubator relative humidity (missing data = 2)	65±16%	60±15%	0.14
Blood pH on admission (missing data = 7)	7.22±0.11	7.24±0.19	0.54
Blood lactate on admission (missing data = 10)	5.4±3.5	3.9±3.4	0.30

* $T_{BodyNadir\ 24h}$: lowest temperature during the first 24 h of life.

Table 3: Proportional hazard ratios (HRs), 95% CI, and *p* values for the Cox model of postnatal survival in a univariate analysis [A]; a multivariate analysis including independent variables with $p<0.2$ in the univariate analysis [B]; multivariate analysis with backward stepwise elimination based on minimization of the Akaike information criterion [C]..

Independent variables	**[A] Univariate analysis** HR [95% CI]	*p*	**[B] Multivariate analysis** Adj. HR [95% CI]	*p*	**[C] Multivariate analysis, PM** Adj. HR [95% CI]	*p*
$T_{Body\ Nadir\ 24h}$	**0.33 [0.22-0.48]**	**<0.001^{HS}**	**0.59 [0.34-0.99]**	**0.049**	**0.57 [0.36-0.90]**	**0.017**
Gestational age	**0.55 [0.46-0.67]**	**<0.001^{HS}**	**0.65 [0.45-0.94]**	**0.024**	**0.62 [0.50-0.76]**	**<0.001**
Amine use	**7.78 [3.55-17.1]**	**<0.001^{HS}**	**4.79 [1.88-12.2]**	**0.001**	**4.55 [2.01-10.28]**	**0.001**
Birth weight	**0.996 [0.994-0.997]**	**<0.001^{HS}**	**0.65 [0.45-0.94]**	**0.024**	Backward stepwise elimination	
Ventilation strategy	**10.5 [2.50-44.4]**	**0.0014^{HS}**	2.66 [0.50-14.2]	0.26	Backward stepwise elimination	
5-minute Apgar score	**0.84 [0.75-0.95]**	**0.0046^{HS}**	1.06 [0.90-1.25]	0.45	Backward stepwise elimination	
Antenatal steroids	**0.61 [0.4-0.91]**	**0.015**	0.99 [0.62-1.57]	0.96	Backward stepwise elimination	
Incubator opening	**2.42 [1.06-5.50]**	**0.035**	1.43 [0.54-3.80]	0.47	Backward stepwise elimination	
Caesarean delivery	0.52 [0.25-1.10]	0.089	1.51 [0.57-4.00]	0.41	Backward stepwise elimination	
Maternal temperature	1.49 [0.91-2.45]	0.12	1.18 [0.58-2.42]	0.64	Backward stepwise elimination	
Umbilical lines	4.53 [0.62-33.3]	0.14	0.40 [0.04-4.01]	0.44	Backward stepwise elimination	
MHD	0.52 [0.20-1.36]	0.21	Not included		Not included	
Multiple births	1.49 [0.65-3.38]	0.35	Not included		Not included	
Working period	1.26 [0.54-2.97]	0.60	Not included		Not included	
Sex (female)	0.83 [0.39-1.74]	0.62	Not included		Not included	

Adj. HR: adjusted hazard ratio; [HS]: significant after Holm–Sidak correction for multiple testing (k=16, p and $\alpha < 0.05$); PM: most parsimonious model, MHD: maternal hypertensive disease.

Figures:

Figure 1: Postnatal survival time in preterm children with a $T_{Body\ Nadir\ 24h}$ below 36.0°C and in those with a $T_{Body\ Nadir\ 24h}$ of 36.0°C or more.

Figure 2: Adjusted hazard ratios [95% CI] in the complete multivariate Cox model of postnatal survival. Only independent variables with $p<0.2$ in the univariate analysis were included in the multivariate model.

Figure 3: Adjusted hazard ratios [95% CI] in the Cox multivariate model of postnatal survival for stratified $T_{Body\ Nadir\ 24h}$ thresholds, with gestational age, and amine use as covariables (left part). Death ratio and sample ratio as a function of different values of stratified $T_{Body\ Nadir\ 24h}$ (right part).

[a]: summary of the HR [95% CI] for a stratified $T_{Body\ Nadir\ 24h}$ of 34.0°C to 36.5°C; the black rectangle shows the range of HRs for a stratified $T_{Body\ Nadir\ 24h}$ of 34.0°C to 36.5°C; horizontal bars show the upper and lower boundaries of the 95% CI for a stratified $T_{Body\ Nadir\ 24h}$ of 34.0°C to 36.5°C. All *p* values were below 0.001 for gestational age and amine use for a stratified $T_{Body\ Nadir\ 24h}$ of 34.0°C to 36.5°C.

Matériels complémentaires (e-component):

Appendix 1: In the parsimonious multivariate model, the change over time in the Schoenfeld residuals confirmed the proportional hazard assumption for the variables $T_{Body\ Nadir\ 24h}$, gestational age, and amine use.

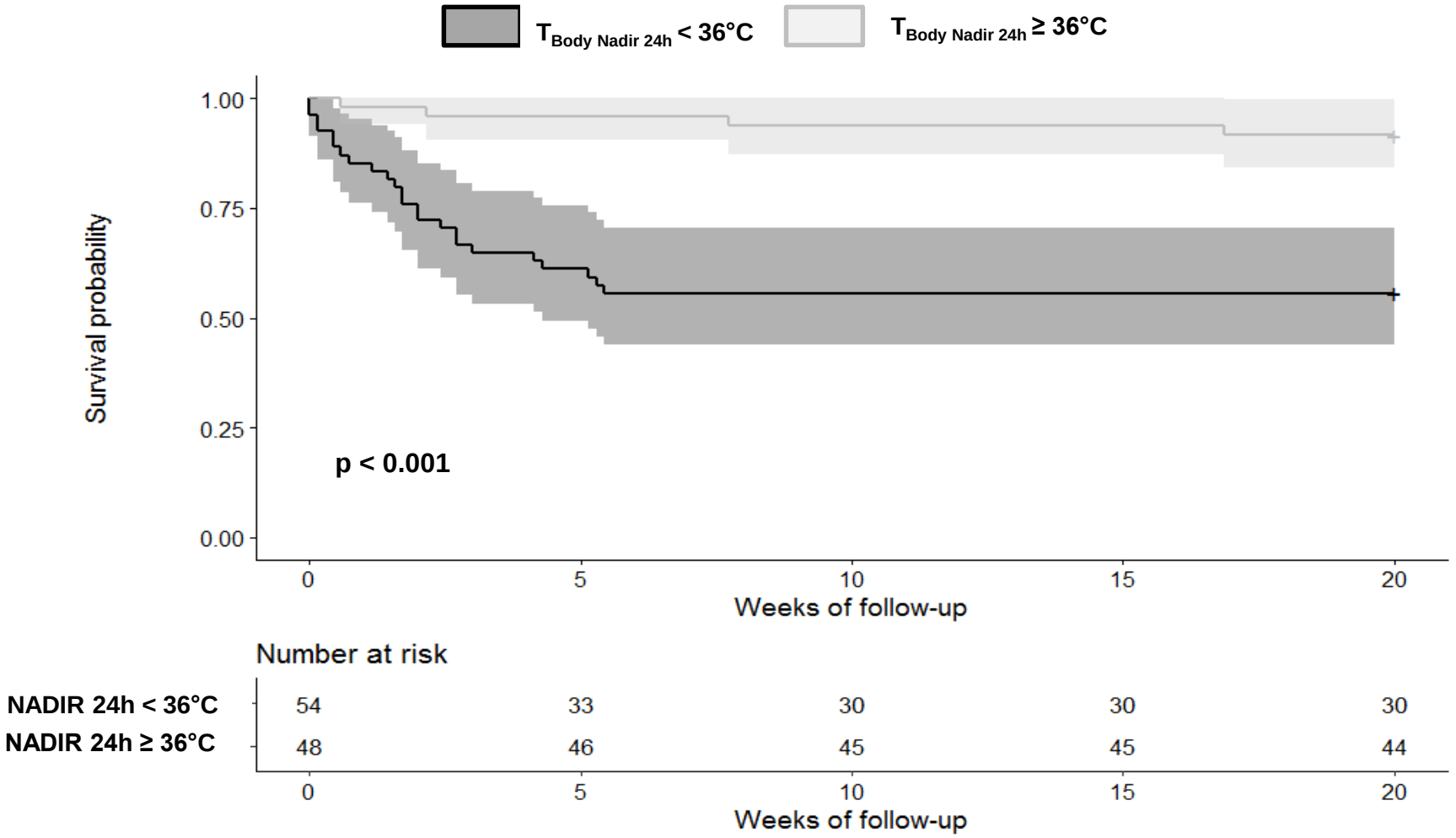
http://www.sciencedirect.com,doi...

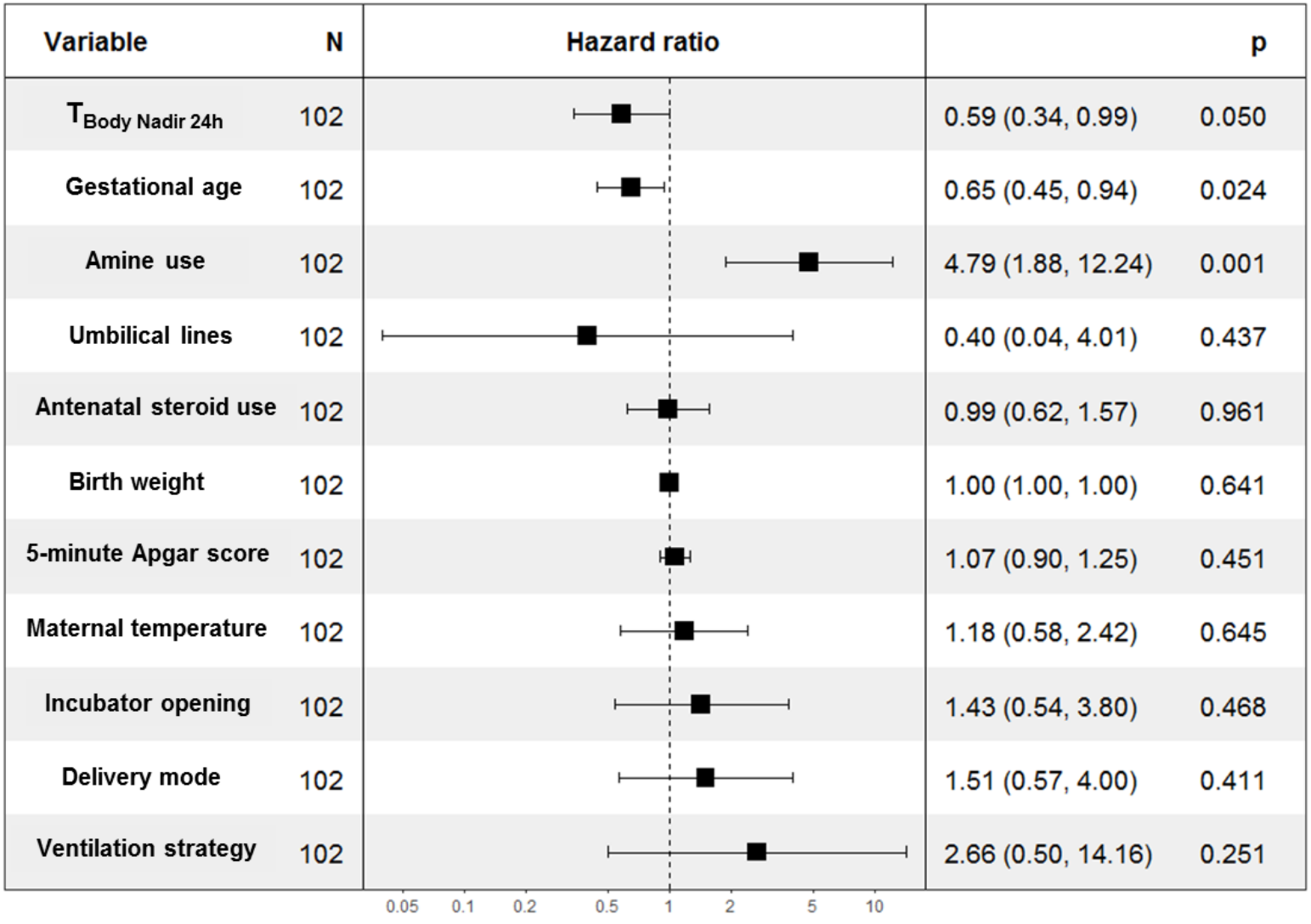
Appendix 2: Hazard ratios [95% CI] from the parsimonious multivariate Cox model of postnatal survival, based on backward stepwise selection with minimization of the Akaike information criterion. GA: gestational age.

http://www.sciencedirect.com,doi...

Appendix 3: Postnatal survival time in preterm children with a Stratification for $T_{Body\ Nadir\ 24h}$ adjusted for gestational age and amine use

http://www.sciencedirect.com,doi...


$T_{Body\ Nadir\ 24h}$ < 36°C
$T_{Body\ Nadir\ 24h}$ ≥ 36°C
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.001
0
5
10
15
20
Weeks of follow-up
Number at risk
NADIR 24h < 36°C
NADIR 24h ≥ 36°C
54
33
30
30
30
48
46
45
45
44
0
5
10
15
20
Weeks of follow-up


Variable
N
Hazard ratio
p
$T_{Body\ Nadir\ 24h}$ 102 0.59 (0.34, 0.99) 0.050
Gestational age 102 0.65 (0.45, 0.94) 0.024
Amine use 102 4.79 (1.88, 12.24) 0.001
Umbilical lines 102 0.40 (0.04, 4.01) 0.437
Antenatal steroid use 102 0.99 (0.62, 1.57) 0.961
Birth weight 102 1.00 (1.00, 1.00) 0.641
5-minute Apgar score 102 1.07 (0.90, 1.25) 0.451
Maternal temperature 102 1.18 (0.58, 2.42) 0.645
Incubator opening 102 1.43 (0.54, 3.80) 0.468
Delivery mode 102 1.51 (0.57, 4.00) 0.411
Ventilation strategy 102 2.66 (0.50, 14.16) 0.251
0.05
0.1
0.2
0.5
1
2
5
10

Variable	N	Hazard ratio	p
NADIR< 33°	102	*no applicable*	
NADIR< 33.5°	102	*no applicable*	
NADIR< 34°	102	1.91 *(0.53 – 6.90)*	*0.3*
NADIR< 34.5°	102	2.81 *(1.10 – 7.00)*	***0.027*** *
NADIR< 35°	102	3.30 *(1.42 – 7.68)*	***0.006*** **
NADIR< 35.5°	102	1.98 *(0.88 – 4.48)*	*0.1*
NADIR< 36°	102	2.60 *(0.84 – 8.09)*	*0.1*
NADIR< 36.5°	102	1.58 *(0.21 – 11.9)*	*0.7*
NADIR< 37°	102	*no applicable*	
Gestational-age[a]	102	0.59 *(0.47 – 0.75)*	***<0.001*** **
Amine-use[a]	102	5.17 *(1.75 – 15.87)*	***<0.001*** **