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Original Article

Association between Neonatal Outcomes and Admission Hypothermia among Very Preterm Infants in Chinese Neonatal Intensive Care Units: A Multicenter Cohort Study

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Abstract

Objective We aimed to investigate the relationship between admission hypothermia and outcomes among very preterm infants (VPIs) in neonatal intensive care units (NICUs) in China. We also investigated the frequency of hypothermia in VPIs in China and the variation in hypothermia across Chinese Neonatal Network (CHNN) sites.

Study Design This retrospective cohort study enrolled infants with $24^{0/7}$ to $31^{6/7}$ weeks of gestation with an admission body temperature $\leq$37.5 °C who were admitted to CHNN-participating NICUs between January 1 and December 31, 2019.

Results A total of 5,913 VPIs were included in this study, of which 4,075 (68.9%) had hypothermia (<36.5 °C) at admission. The incidence of admission hypothermia varied widely across CHNN sites (9–100%). Lower gestational age (GA), lower birth weight, antenatal steroid administration, multiple births, small for GA, Apgar scores <7 at the 5th minute, and intensive resuscitation were significantly associated with admission hypothermia. Compared with infants with normothermia (36.5–37.5 °C), the adjusted odds ratios (ORs) for composite outcome among infants with admission hypothermia

Keywords
- admission hypothermia
- very preterm infants
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- outcomes
- risk factors

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<35.5 °C increased to 1.47 (95% confidence interval [CI], 1.15–1.88). The adjusted ORs for mortality among infants with admission hypothermia (36.0–36.4 and <35.5 °C) increased to 1.41 (95% CI, 1.09–1.83) and 1.93 (95% CI, 1.31–2.85), respectively. Admission hypothermia was associated with a higher likelihood of bronchopulmonary dysplasia, but was not associated with necrotizing enterocolitis ≥stage II, severe intraventricular hemorrhage, cystic periventricular leukomalacia, severe retinopathy of prematurity, or sepsis.

Conclusion Admission hypothermia remains a common problem for VPIs in a large cohort in China and is associated with adverse outcomes. Continuous quality improvement of admission hypothermia in the future may result in a substantial improvement in the outcomes of VPIs in China.

Key Points

- Admission hypothermia is common in VPIs.
- The incidence of admission hypothermia in VPIs remains high in China.
- Admission hypothermia is associated with adverse outcomes in VPIs.

One of the first challenges newborns face at birth is adapting to the ambient temperature. Very preterm infants (VPIs) with gestational age (GA) $<32^{0/7}$ weeks are more susceptible to hypothermia because of their relatively large body surface area, low subcutaneous fat, thin skin, environmental factors in the delivery room (DR), and DR-to-neonatal intensive care unit (NICU) transfer after birth, all of which can cause a rapid drop in body temperature.[1,2] Several studies have shown that admission hypothermia is significantly associated with increased mortality and morbidity in preterm infants.[3–5] However, the relationship between neonatal outcomes (such as mortality and morbidity) and admission hypothermia among VPIs in China has not been established, and data on the incidence of hypothermia and related risk factors among neonates in Chinese NICUs are lacking in the literature. Therefore, we aimed to determine the incidence of admission hypothermia and investigate its relationship with outcomes among VPIs in NICUs in China.

Materials and Methods

Settings

The Chinese Neonatal Network (CHNN) hospitals are tertiary referral facilities with extensive neonatal services and recognized expertise in caring for high-risk neonates. A total of 57 hospitals from 25 provinces throughout China collected annual data in 2019 using the CHNN database. These 57 hospitals included 4 national children's medical centers, 4 regional children's medical centers, and 30 provincial perinatal or children's medical centers. The other 19 hospitals were major referral centers in large cities across China. Forty-three hospitals were perinatal centers with birthing facilities, and 14 were freestanding children's hospitals. Detailed hospital characteristics have been described in previous publications.[6,7]

Study Population

This retrospective cohort study used data from the CHNN. Since January 1, 2019, the CHNN has established and maintained a standardized clinical database of VPIs in participating NICUs throughout China to monitor outcomes and care practices. This study was approved by the Ethics Committee of the Children's Hospital of Fudan University and recognized by all participating hospitals. This study enrolled inborn infants with a GA at birth ranging from $24^{0/7}$ to $31^{6/7}$ weeks who were admitted to NICUs participating in the CHNN less than 24 hours after birth, spanning from January 1 to December 31, 2019. Infants with major congenital anomalies, missing admission temperatures, or hyperthermia (admission temperature >37.5 °C) were excluded from the study. Infants transferred to nonparticipating hospitals within 24 hours of birth were also excluded.

Data Collection

Data were extracted from the medical records of each CHNN hospital using the standard manual of definitions and then entered into a standardized database with built-in error checking. De-identified data were transmitted to the coordinating center at the Children's Hospital of Fudan University. Periodic data audits with appropriate data corrections were conducted at each CHNN site.[8]

Exposure

The first measurement of rectal and axillary temperatures were recorded within 2 hours of birth. Admission temperature was stratified into four groups: normothermia (36.5–37.5 °C), mild hypothermia (36–36.4 °C), moderate hypothermia (35.5–35.9 °C), and severe hypothermia (<35.5 °C).

Outcomes

The primary outcome included a composite outcome defined as mortality and at least one of the following major

outcomes: necrotizing enterocolitis (NEC) ≥stage II, bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age or discharge, severe intraventricular hemorrhage (IVH) ≥degree 3, severe retinopathy of prematurity (ROP) ≥stage 3, cystic periventricular leukomalacia (cPVL), or sepsis.

The secondary outcomes were a short-term composite outcome (defined as confirmed respiratory distress syndrome [RDS] or early death [mortality <7 d]), length of stay, and length of ventilation.

Definitions

Severe IVH was defined as grade 3 or higher, according to Papile et al's criteria.[9] cPVL was defined as the presence of periventricular cysts on cranial ultrasonography or magnetic resonance imaging. We defined brain damage as grade III or IV IVH or periventricular echogenicity.[9,10] NEC was defined as stage II or higher according to Bell et al's criteria.[11,12] Sepsis was defined as a positive blood or cerebrospinal fluid culture and antibiotic therapy or intent of antibiotic therapy for ≥5 days.[13] Severe ROP was defined as stage 3 or higher according to the International Classification of ROP.[14] Severe BPD was defined as oxygen (O_2) treatment for at least 28 days and receiving ≥30% O_2 or nasal CPAP/High-flow nasal cannula (HFNC) or mechanical ventilation for ≥36 weeks' postmenstrual age.[15] Small for gestational age (SGA) was defined as birth weight <10th percentile for the GA according to the Chinese neonatal birth weight values.[16] Intensive resuscitation was defined as the need for invasive ventilation, epinephrine administration, or chest compressions in the DR.

Statistical Analysis

The admission temperature was initially categorized into four groups: normothermia, mild hypothermia, moderate hypothermia, and severe hypothermia. The baseline characteristics were then summarized. To compare the baseline characteristics of the four groups, we employed the chi-square test for categorical baseline variables, analysis of variance for normally distributed variables, and the Kruskal–Wallis test for highly skewed variables, as appropriate. To evaluate the association between hypothermia and infant outcomes, the neonatal outcomes of the four different groups were compared using the same methods as those employed for the baseline characteristics. Trend analyses were conducted using the Cochran–Armitage trend test for categorical variables and the Jonckheere–Terpstra test for continuous variables.

Furthermore, multivariable logistic regression was employed to calculate the adjusted odds ratio (OR) of binary outcomes, with adjustment for potential confounders, using normothermia as the reference group. Additionally, the two continuous outcomes (length of NICU stay and duration of invasive ventilation) were log-transformed to ensure normality. Subsequently, multivariable linear regression, with adjustment for potential confounders, was utilized to estimate the mean ratios of these continuous outcomes with normothermia as the reference group. The mean ratio of length of stay was calculated among those who survived until discharge, while the mean ratio for the duration of invasive ventilation was calculated among those who required invasive ventilation. The potential confounders included GA, SGA, sex, maternal age, maternal hypertension, maternal diabetes, mode of delivery, use of antenatal steroids, an Apgar score <7 at the 5th minute, multiple births, and maternal primigravida status. Model parameters were estimated using a generalized estimating equation approach with a symmetric covariance matrix in the multivariable regressions to account for cluster effects of the hospitals. The variance inflation factor of each independent variable was tested to assess multicollinearity before modeling.

All statistical analyses and data management were conducted using SAS version 9.4 (SAS Institute, Inc.). A two-sided p-value ≤0.05 was considered statistically significant.

Results

Baseline Characteristics across Admission Temperature Groups

A total of 5,960 infants born at $24^{0/7}$ to $31^{6/7}$ weeks' GA at 57 CHNN centers were enrolled within 24 hours after birth. Among them, 30 infants with major congenital anomalies, 7 with missing admission temperatures, and 10 with hyperthermia were excluded (►Fig. 1). The remaining 5,913 infants were included in the study. Maternal and infant characteristics are shown in ►Table 1. The baseline characteristics of the infants with different admission temperatures are shown in ►Table 1. VPIs with normothermia were more often born to mothers who were primigravida, had cesarean section deliveries, or had premature prolonged rupture of membranes when compared with infants who were hypothermic on admission. Maternal antenatal steroid administration, multiple births, infant SGA status, an Apgar score <7 at the 5th minute, and the need for intensive DR resuscitation were all associated with hypothermia on admission.

Distribution of Admission Temperature

The median GA was 30.00 (interquartile range [IQR], 28.57–31.00) weeks, and the median birth weight was 1,320 (IQR, 1,100–1,550) g. The median temperature at admission was 35.9 °C (IQR, 35.2–36.4 °C). Over two-thirds (68.9%) of VPIs were admitted to the hospital with a body temperature of less than 36.5 °C, including 2,787 infants (47.1%) in the mild hypothermia group and 1,288 infants (21.8%) in the moderate or severe hypothermia group (►Fig. 1). There was an inverse relationship between the GA at birth and the incidence of admission hypothermia, with 81% of the infants born at 24 weeks of gestation improving to 67% born at 31 weeks of gestation (►Fig. 2). A wide variation in the incidence of hypothermia at admission was observed across the 57 centers, ranging from 9 to 100% (►Fig. 3).

Association of Admission Temperature and Neonatal Outcomes

The univariate analysis of the primary outcomes revealed that admission hypothermia was associated with mortality, NEC, severe BPD, severe ROP, sepsis ($p \leq 0.05$), but not with severe IVH and cPVL (►Table 2). Compared with infants with normothermia (36.5–37.5 °C), the adjusted ORs for

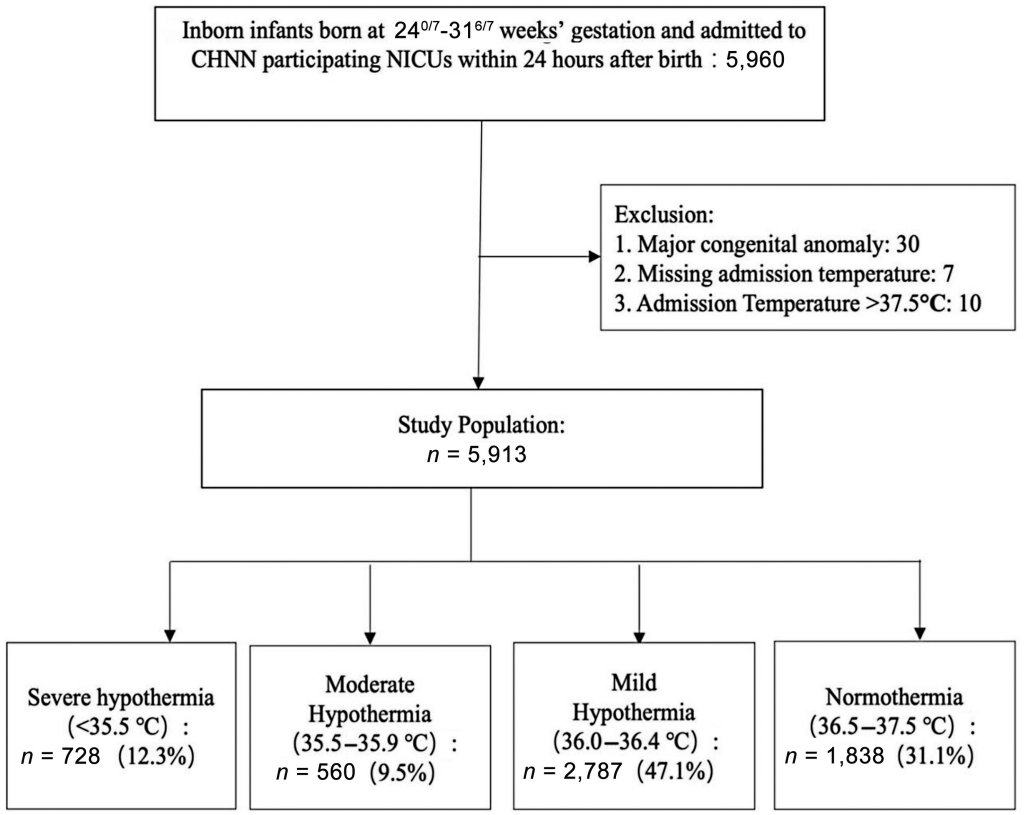

Fig. 1 Diagram of the study population. CHNN, Chinese Neonatal Network; NICU, neonatal intensive care unit.

composite outcome among infants with admission hypothermia <35.5 °C increased to 1.47 (95% confidence interval [CI], 1.15–1.88). Compared with infants with normothermia (36.5–37.5 °C), the adjusted ORs for mortality among infants with admission hypothermia (36.0–36.4 and <35.5 °C) increased to 1.41 (95% CI, 1.09–1.83) and 1.93 (95% CI, 1.31–2.85), respectively. Compared with normothermic infants, the adjusted OR for BPD increased to 1.25 (95% CI, 1.09–1.43) for infants with admission temperatures of 36–36.4 °C, to 1.41 (95% CI, 1.11–1.79) for infants with admission temperatures of 35.5–35.9°C, and to 1.99 (95% CI, 1.60–2.47) for infants with admission temperatures of <35.5 °C.

The adjusted OR of sepsis decreased to 0.65 (95% CI, 0.45–0.95) for infants with admission temperatures of 35.5–35.9 °C. NEC ≥stage II, severe IVH, cPVL, and severe ROP were not significantly correlated with admission hypothermia in the multivariate analysis (►Table 3).

The univariate analysis of the secondary outcomes showed that admission hypothermia was associated with early death, RDS, length of stay, and length of invasive ventilation ($p \leq 0.05$; ►Table 2). Compared with infants with normothermia (36.5–37.5 °C), the adjusted ORs for early deaths in infants with admission hypothermia (36.0–36.4 and <35.5 °C) increased to 1.53 (95% CI, 1.11–2.11) and 2.21 (95% CI, 1.35–3.60), respectively. The adjusted mean ratios for length of stay in infants with admission hypothermia (35.5–35.9 and <35.5 °C) increased to 1.03 (95% CI, 1.00–1.06) and 1.07 (95% CI, 1.04–1.11), respectively. The adjusted mean ratio for duration of invasive ventilation decreased to 0.77 (95% CI, 0.64–0.92) for infants with admission temperatures of 35.5–35.9 °C (►Table 4).

Discussion

To the best of our knowledge, this is the first comprehensive nationwide cohort study to examine admission hypothermia in VPIs. We confirmed the high prevalence of admission hypothermia in China and its association with increased mortality and poor outcomes.

In our study, the prevalence of hypothermia on admission was 68.9%, while the incidence of moderate or severe hypothermia (<36 °C) was 21.8%. Our results suggest a decrease in the incidence of hypothermia compared with previous reports from China. Yu et al[17] reported an admission hypothermia rate of 88.2% among 1,247 infants with birth weights <1,500 g admitted to NICUs in Shandong province. However, similar to a single-center study from Sichuan province that reported a 97.6% incidence of admission hypothermia in 2015 to 2016, several hospitals (20%) in our current cohort reported hypothermia in ≥90% of the VPI admissions. While our current incidence of admission hypothermia is comparable to that of the Korean Neonatal Network in 2013 to 2015,[18] our results lag behind those of the Effective Perinatal Intensive Care in Europe in 2011 to 2012.[19] This discrepancy indicates a considerable scope for improvement.

The incidence of admission hypothermia in VPIs is inversely related to the GA and birth weight, as previously described.[3] We found that admission hypothermia was

Table 1 Basic characteristics of the study population

Characteristics	Normothermia	Mild hypothermia	Moderate hypothermia	Severe hypothermia	*p*-Value	*p*-Value for trend
N	1,838	2,787	560	728		
Maternal information						
Maternal age, mean (Std)	31.21 (4.80)	31.27 (4.84)	31.26 (4.67)	30.65 (4.95)	0.02	0.07
Antenatal steroid administration, *N* (%)	1,450/1,831 (79.2%)	2,279/2,774 (82.2%)	457/558 (81.9%)	618/725 (85.2%)	<0.01	<0.01
Hypertension, *N* (%)	350/1,836 (19.1%)	596/2,787 (21.4%)	110/560 (19.6%)	135/726 (18.6%)	0.16	0.85
Diabetes, *N* (%)	351/1,835 (19.1%)	499/2,786 (17.9%)	110/559 (19.7%)	155/726 (21.3%)	0.18	0.21
C-section, *N* (%)	1,102/1,836 (60.0%)	1,623/2,783 (58.3%)	284/560 (50.7%)	395/727 (54.3%)	<0.01	<0.01
Multiple births, *N* (%)	534/1,838 (29.1%)	856/2,787 (30.7%)	200/560 (35.7%)	265/728 (36.4%)	<0.01	<0.01
Primigravida, *N* (%)	1,023/1,829 (55.9%)	1,440/2,765 (52.1%)	266/560 (47.5%)	359/721 (49.8%)	<0.01	<0.01
Rupture of membranes, *N* (%)	1,289/1,831 (70.4%)	1,860/2,775 (67.0%)	343/554 (61.9%)	484/722 (67.0%)	<0.01	<0.01
Infant information						
Gestational age, Median (P25, P75)	30.00 (28.71, 31.00)	29.86 (28.57, 31.00)	29.86 (28.14, 31.00)	29.71 (28.14, 30.86)	<0.01	<0.01
<26 wk	45/1,838 (2.4%)	91/2,787 (3.3%)	33/560 (5.9%)	46/728 (6.3%)	<0.01	<0.01
26–27 wk	207/1,838 (11.3%)	336/2,787 (12.1%)	78/560 (13.9%)	116/728 (15.9%)		
28–29 wk	600/1,838 (32.6%)	968/2,787 (34.7%)	172/560 (30.7%)	227/728 (31.2%)		
30–31 wk	986/1,838 (53.6%)	1,392/2,787 (49.9%)	277/560 (49.5%)	339/728 (46.6%)		
Birth weight, mean (Std)	1,372.20 (310.02)	1,330.89 (318.98)	1,268.65 (320.70)	1,246.43 (328.88)	<0.01	<0.01
Male, *N* (%)	1,038/1,832 (56.7%)	1,551/2,785 (55.7%)	318/558 (57.0%)	401/728 (55.1%)	0.82	0.58
Small for gestational age, *N* (%)	66/1,832 (3.6%)	129/2,785 (4.6%)	46/558 (8.2%)	52/728 (7.1%)	<0.01	<0.01
Z score of birth weight, Mean (Std)	0.16 (0.78)	0.10 (0.81)	0.00 (0.83)	−0.07 (0.81)	<0.01	<0.01
Apgar score <7 at 5 minutes, *N* (%)	54/1,791 (3.0%)	130/2,763 (4.7%)	22/527 (4.2%)	69/699 (9.9%)	<0.01	<0.01
Intensive resuscitation, *N* (%)	402/1,827 (22.0%)	663/2,777 (23.9%)	111/560 (19.8%)	232/718 (32.3%)	<0.01	<0.01

Abbreviation: wk, weeks.
Values are presented as number (%) or median (interquartile range). Differences were considered statistically significant at a two-sided *p*-value of ≤0.05.

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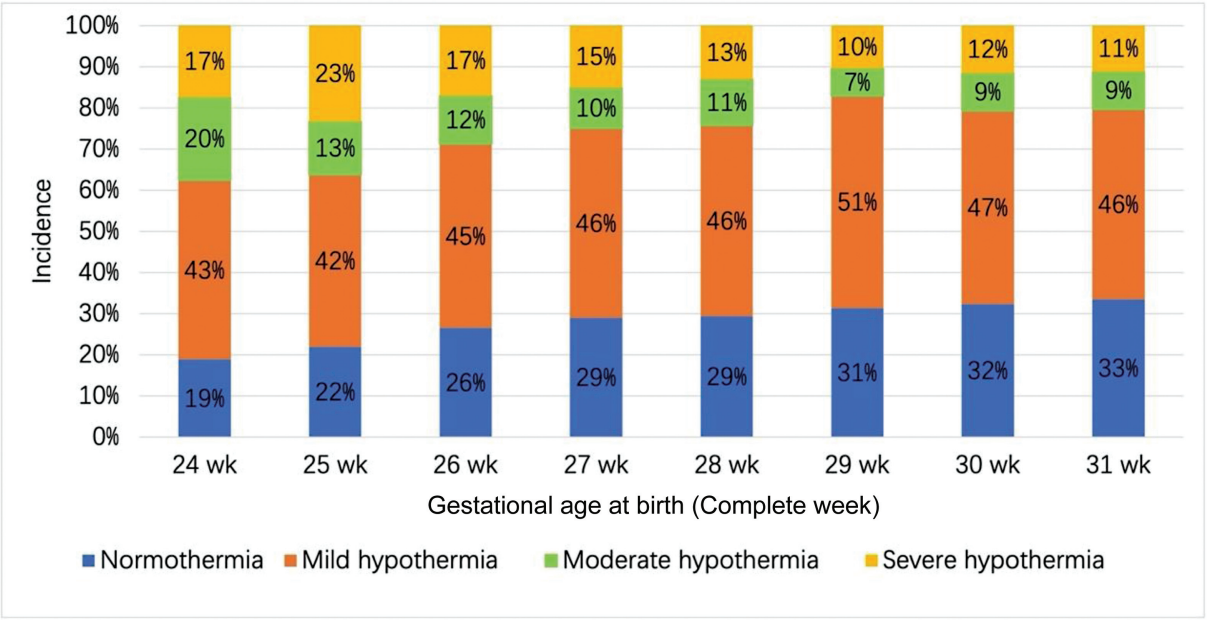

Fig. 2 Temperature distribution based on gestational age. wk, weeks.

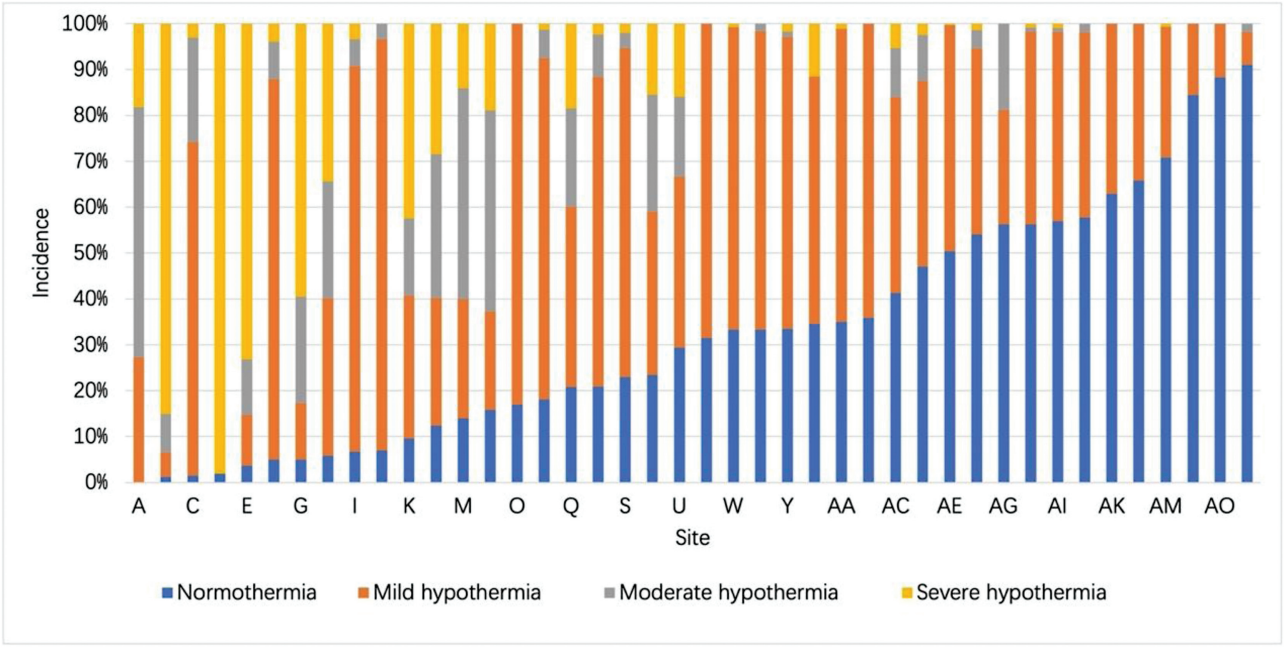

Fig. 3 Distribution of infant body temperature at admission to neonatal intensive care by centers.

associated with SGA, intensive resuscitation, and an Apgar score of <7 at the 5th minute. SGA is a risk factor for admission hypothermia due to increased heat loss due to decreased subcutaneous fat, decreased heat production due to in utero stress, depletion of energy stores, and a relatively large surface area-to-volume ratio.[20] Admission hypothermia was more frequently observed in infants with Apgar scores <7 at the 5th minute and intensive resuscitation, as infants who do not require resuscitation are usually healthier and better able to maintain their core body temperature.[21,22] Warming measures during resuscitation tend to be overlooked when the establishment of ventilation and circulation are prioritized.[4]

The incidence of hypothermia on admission varies considerably among CHNN centers, reflecting the wide variation in temperature management within different centers. China is a vast country with inequalities in terms of economic development, medical technology, and quality of care. Delineation of specific practices for the maintenance of temperature in the DR at each center was beyond the scope of this study. Therefore, we were unable to perform a rigorous analysis of the causes of this variation. However,

Table 2 Univariate analysis for association of hypothermia with neonatal outcomes

Outcome	Normothermia	Mild hypothermia	Moderate hypothermia	Severe hypothermia	Overall	*p*-Value	*p*-Value for trend
N	**1838**	**2,787**	**560**	**728**	**5,913**		
Composite outcome, *N* (%)	762/1,838 (41.5%)	1,190/2,787 (42.7%)	242/560 (43.2%)	349/728 (47.9%)	2,543/5,913 (43.0%)	0.03	<0.01
Mortality, *N* (%)	179/1,838 (9.7%)	324/2,787 (11.6%)	65/560 (11.6%)	115/728 (15.8%)	683/5,913 (11.6%)	<0.01	<0.01
NEC ≥stage II, *N* (%)	77/1,838 (4.2%)	104/2,787 (3.7%)	34/560 (6.1%)	41/728 (5.6%)	256/5,913 (4.3%)	0.02	0.03
Severe BPD, *N* (%)	521/1,838 (28.3%)	840/2,787 (30.1%)	184/560 (32.9%)	276/728 (37.9%)	1821/5,913 (30.8%)	<0.01	<0.01
Brain damage, *N* (%)[a]	150/1,535 (9.8%)	225/2,356 (9.6%)	38/494 (7.7%)	67/607 (11.0%)	480/4,992 (9.6%)	0.31	0.79
Severe IVH, *N* (%)[a]	105/1,526 (6.9%)	153/2,341 (6.5%)	25/494 (5.1%)	41/606 (6.8%)	324/4,967 (6.5%)	0.54	0.55
cPVL, *N* (%)[a]	64/1,581 (4.0%)	103/2,431 (4.2%)	24/507 (4.7%)	33/618 (5.3%)	224/5,137 (4.4%)	0.56	0.17
Severe ROP, *N* (%)[b]	36/1,348 (2.7%)	53/2,079 (2.5%)	22/439 (5.0%)	27/559 (4.8%)	138/4,425 (3.1%)	<0.01	<0.01
Sepsis, *N* (%)	173/1,838 (9.4%)	292/2,787 (10.5%)	34/560 (6.1%)	50/728 (6.9%)	549/5,913 (9.3%)	<0.01	<0.01
Short-term composite outcome, *N* (%)	1,351/1,838 (73.5%)	2,068/2,787 (74.2%)	397/560 (70.9%)	569/728 (78.2%)	4,385/5,913 (74.2%)	0.02	0.1
Early death, *N* (%)	105/1,838 (5.7%)	204/2,787 (7.3%)	43/560 (7.7%)	77/728 (10.6%)	429/5,913 (7.3%)	<0.01	<0.01
RDS, *N* (%)	1,320/1,832 (72.1%)	2,006/2,781 (72.1%)	386/560 (68.9%)	560/726 (77.1%)	4,272/5,899 (72.4%)	<0.01	0.09
Length of stay[c]	43 (32, 56)	45 (34, 59)	46 (35, 59)	53 (38, 69)	45 (34, 59)	<0.01	<0.01
Length of invasive ventilation[d]	4 (2, 9)	4 (2, 9)	4 (2, 7)	4.5 (2, 11)	4 (2, 9)	0.03	0.4

Abbreviations: BPD, bronchopulmonary dysplasia; cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

Values are presented as numbers (%) or medians (interquartile ranges).

Differences were considered statistically significant at a two-sided *p*-value ≤0.05.

[a]Incidences of brain damage, severe IVH, and PVL were calculated among infants with neuroimaging results.

[b]Incidence of severe ROP was calculated among infants who underwent eye examinations in the neonatal intensive care unit.

[c]Median length of stay was calculated for infants who survived until discharge.

[d]Median length of invasive ventilation was calculated for infants with invasive ventilation.

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Table 3 Adjusted odds ratios with 95% confidence interval of neonatal outcomes associated with different grades of admission temperature

Outcomes[a]	Normothermia	Mild hypothermia	Moderate hypothermia	Severe hypothermia
Composite/primary outcome	Reference	1.08 (0.95, 1.23)	1.15 (0.94, 1.39)	1.47 (1.15, 1.88)
Mortality	Reference	1.41 (1.09, 1.83)	1.35 (0.92, 1.97)	1.93 (1.31, 2.85)
NEC ≥stage II	Reference	0.93 (0.73, 1.20)	1.49 (0.91, 2.44)	1.22 (0.67, 2.19)
Severe BPD	Reference	1.25 (1.09, 1.43)	1.41 (1.11, 1.79)	1.99 (1.60, 2.47)
Brain damage[b]	Reference	0.85 (0.72, 1.02)	0.75 (0.50, 1.13)	1.26 (0.82, 1.94)
Severe IVH[b]	Reference	0.87 (0.70, 1.08)	0.78 (0.51, 1.19)	1.22 (0.78, 1.91)
cPVL[b]	Reference	0.84 (0.61, 1.15)	0.97 (0.62, 1.52)	1.24 (0.79, 1.96)
Severe ROP[c]	Reference	0.87 (0.60, 1.25)	1.56 (0.98, 2.47)	1.53 (0.89, 2.61)
Sepsis	Reference	0.86 (0.65, 1.14)	0.65 (0.45, 0.95)	0.75 (0.47, 1.21)
Short-term composite outcome	Reference	0.97 (0.83, 1.12)	1.23 (0.95, 1.59)	1.45 (1.04, 2.02)
Early death	Reference	1.53 (1.11, 2.11)	1.45 (0.92, 2.28)	2.21 (1.35, 3.60)
RDS	Reference	0.92 (0.80, 1.06)	1.18 (0.90, 1.54)	1.44 (1.03, 2.00)

Abbreviations: BPD, bronchopulmonary dysplasia; cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

[a]Adjusted odds ratios of neonatal binary outcomes estimated by the multivariable logistic regression were reported after control for maternal age, maternal hypertension, maternal diabetes, C-section, usage of antenatal corticosteroid, 5-minute Apgar score <7, multiple births, primigravida, gestational age, infant sex, and small for gestational age.

[b]Incidence of brain damage, severe IVH, and periventricular leukomalacia was calculated among infants with neuroimaging results.

[c]Incidence of severe ROP was calculated among infants who underwent eye examinations in the neonatal intensive care unit.

Table 4 Adjusted mean ratios with 95% confidence interval of length of stay and duration of invasive ventilation associated with different grades of admission temperature

Outcome[a]	Normothermia	Mild hypothermia	Moderate hypothermia	Severe hypothermia
Length of stay[b]	Reference	1.00 (0.98, 1.02)	1.03 (1.00, 1.06)	1.07 (1.04, 1.11)
Length of invasive ventilation[c]	Reference	0.94 (0.84, 1.05)	0.77 (0.64, 0.92)	1.04 (0.82, 1.32)

[a]Adjusted mean ratios of two neonatal continuous outcomes estimated by the multivariable linear regression were reported after control for maternal age, maternal hypertension, maternal diabetes, C-section, usage of antenatal corticosteroid, 5-minute Apgar score <7, multiple births, Primigravida, gestational age, infant sex, and small for gestational age.

[b]Length of stay was initially log-transformed before entering multivariable linear regression. Mean ratios for the length of stay were calculated for infants who survived until discharge.

[c]The duration of invasive ventilation was initially log-transformed before entering multivariable linear regression. Mean ratios for the duration of invasive ventilation by were calculated for infants receiving invasive ventilation.

implementing a standardized approach to DR resuscitation of VPIs, such as the "Golden Hour Protocol," has been shown to reduce rates of admission hypothermia and may be beneficial to individual centers seeking to improve outcomes.[23,24]

The results of this study are similar to those of previous studies, which reported a significant correlation between admission hypothermia and mortality. A cohort study conducted in Guinea-Bissau found that a body temperature below 34.5 °C significantly increased the risk of infant death by about five times in the first 7 days of life and was associated with an increased mortality rate between 8 and 56 days after birth.[25] In another multicenter prospective study, hypothermia on admission to the NICU increased the odds of early neonatal death by 1.64-fold (95% CI, 1.03–2.61).[26] In our study, the adjusted OR for mortality in infants with a temperature below 35.5 °C was 1.93 (95% CI, 1.31–2.85). Among these infants, the OR for early death (<7 d) was higher than that for mortality, with an OR of 2.21 (95% CI, 1.35–3.60). Even with mild hypothermia, the ORs for mortality and early death increased to 1.41 (95% CI, 1.09–1.83) and 1.53 (95% CI, 1.11–2.11), respectively. In contrast, moderate admission hypothermia was not associated with mortality; these results may be related to sample size. One meta-analysis showed that the lower the temperature of a preterm infant, the higher the risk of mortality.[27] Consequently, 11 European countries adopted measures to prevent admission temperatures <36 °C to improve survival and minimize complications in preterm infants <32 weeks of GA.[28]

Many studies have shown that admission hypothermia is associated with an increased risk of one or more adverse outcomes in preterm infants.[21,29–31] However, after adjusting for neonatal baseline and maternal variables, our study found that admission hypothermia was not associated with

an increased risk of NEC ≥stage II, severe IVH, cPVL, severe ROP, and sepsis. Some studies have found no association between admission hypothermia and IVH.[21,32,33] The results of one meta-analysis showed that the risk of NEC among very low birth weight infants with and without hypothermia was not significantly different between the two groups.[34] de Siqueira Caldas et al[35] showed that mildly induced therapeutic admission hypothermia may have a protective effect against NEC in preterm infants. Another study reported that admission hypothermia can protect against ROP.[36] Several confounding factors have been identified as contributing to the development of sepsis, including the length of hospital stay and the degree of prematurity of the infant. Our study design did not evaluate these risk factors separately.[37]

Our study has several limitations. First, it is a retrospective observational study and did not use a uniform method to collect admission temperature data. Moreover, maternal temperature data at the time of delivery were not available, which may have been a confounding factor affecting initial infant temperature. Furthermore, our data were not all measured within 1 hour of birth, which may affect our findings on the impact of hypothermia on outcomes. Finally, given the small sample size, we were unable to get a narrower CI by analyzing the exposure variable as a continuous function. Therefore, we believe the relatively small sample size is a limitation of this study, which may bias the conclusions drawn from our findings. More specifically, as shown in ►**Table 3**, the adjusted ORs for the primary composite outcome among infants with mild and moderate hypothermia were 1.08 (95% CI: 0.95–1.23) and 1.15 (95% CI: 0.94–1.39), respectively. These findings suggest that there is "no significant association" between mild and moderate hypothermia and the primary outcome. However, it is important to note that with an increase in sample size, the lower limit of these two CIs may exceed 1. This implies that mild and moderate hypothermia could be associated with an increased risk of the primary neonatal composite outcome, aligning with the direction of the findings for severe hypothermia.

Conclusion

The prevalence of hypothermia in VPIs remains high in Chinese hospitals. Prior to our study, there was a lack of baseline data on the incidence of admission hypothermia in a large multicenter sample of preterm infants. Our study suggests that the management of thermoregulation of VPIs has not received sufficient attention and that there are opportunities to improve thermal protection in our hospitals. We confirmed the association between admission hypothermia and a composite of adverse outcomes, including mortality and morbidity, further highlighting the urgent need to address the thermal stability of VPIs at both the institutional and national levels.

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Conflict of Interest

None declared.

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