Birth Time and Early Outcomes in Very Preterm Infants in China: A Cohort Study

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Abstract

Background Previous studies suggest that birth timing may impact the prognosis of extremely premature infants, increasing early mortality and the risk of intensive resuscitation, asphyxia, or sIVH. The aim of this study was to investigate the relationship between birth timing and outcomes of very preterm infants (VPIs) in China.

Methods This multicenter retrospective study used CHNN 2019–2021 data on preterm infants born at 24^0 to 31^6 weeks' GA. Exposure included birth timing (daytime, evening, night) on weekdays and non-weekdays. The primary outcome was in-hospital mortality rate. Secondary outcomes included delivery room outcomes and morbidities.

Results The study included 17,670 VPIs and found increased mortality during both daytime-evening shifts and night shifts on weekdays, primarily affecting infants born at 24^0 to 27^6 weeks' GA. Among weekday births, evening shifts were associated with 5-minute Apgar scores ≤7 (aOR 1.22, 95% CI 1.07–1.39) and sIVH (aOR 1.30, 95% CI 1.08–1.57), while nighttime shifts were linked to hypothermia (aOR 1.13, 95% CI 1.02–1.24). In infants born at 28^0 to 29^6 weeks' GA, night shifts were associated with intensive resuscitation (aOR 1.23, 95% CI 1.02–1.48), and evening shifts with 5-minute Apgar scores ≤7 (aOR 1.38, 95% CI 1.11–1.71). For infants born at 30^0 to 31^6 weeks' GA, the evening shift significantly increased the risk of sIVH (aOR 1.78, 95% CI 1.27–2.48).

Conclusion Mortality increased for infants born during daytime handovers and nighttime, especially at 24^0 to 27^6 weeks' GA. Infants at 28^0 to 31^6 weeks' GA faced higher risks of asphyxia, hypothermia, or sIVH during off-peak hours.

Background

Very Preterm Infants (VPIs), defined as infants born less than 32 weeks' gestational age (GA) or birth weight less than 1500 grams, are regarded as the most vulnerable population among newborns. In the past two decades, outcomes of VPIs have been obviously improved, but substantial differences across centers still exist[1]. Compared to developed countries, the survival rate of infants born less than 28 weeks GA is still lower in China[2], however significant improvements among this population have been found, especially between 26 and 27 weeks GA, reaching 89.1% in 2019[3].

The association between mortality rates and the timing of birth has been extensively investigated within various multinational neonatal networks worldwide. Notably, a phenomenon referred to as the "weekend effect" has been consistently observed, indicating higher mortality rates for VPIs born on weekends compared to weekdays[4]. Furthermore, additional studies have reported an increased odds ratio (OR) for the need for delivery room chest compressions and lower 5-minute Apgar scores in VPIs born during weekends[5]. While the precise mechanisms underlying the "weekend effect" remain incompletely understood, weekends may potentially coincide with suboptimal staffing levels, potentially impacting medical response times, nursing coordination, and neonatal outcomes[6].

Beyond the "weekend effect", research has also indicated that delivering during off-peak hours is associated with an elevated risk of mortality rates in extremely low birth weight infants[7] and adverse composite outcomes such as death or severe intraventricular hemorrhage (sIVH) in very low birth weight infants[8]. It has also been associated with an increased likelihood of requiring intubation, pulmonary surfactant usage, and anemia necessitating transfusion[9]. Notably, there is a paucity of multicenter cohort studies on this subject conducted in China. Therefore, this study was to investigate the influence of birth timing on neonatal mortality and morbidity in Chinese NICUs (neonatal intensive care unit). Our hypothesis is that unfavorable outcomes may occur among VPIs born on non-weekdays and during off-peak hours.

Methods

Data source

This was a retrospective cohort study using the database of the Chinese Neonatal Network (CHNN), prospectively collecting data of very preterm or very low birth weight infants (GA <32 weeks or birth weight <1500g) admitted to tertiary NICUs during January 1, 2019 to December 31, 2021. The CHNN initially comprised 57 NICUs in 2019, expanded to 70 NICUs in 2020, and 79 in 2021. All participating NICUs are tertiary referral facilities representing neonatal care in different regions of the country. Clinical data were collected from patient medical records according to the abstractor's manuals by trained data abstractors.[3, 10, 11]. All data were transmitted electronically to the CHNN coordinating centre at Children's Hospital of Fudan University, with patient identity kept confidential for quality and integrity checking.

Participants

Infants who were stillborn, experienced delivery room deaths, or were transferred to non-participating hospitals within 24 hours of birth were not included in the database. Instances of readmissions and transfers between participating hospitals were tracked as data related to the same infants. Infants born outside the participating hospitals, those with major congenital anomalies, or those with missing birth time data were excluded from the study.

Exposure

Infants were categorized as having weekday deliveries if their date of birth occurred between Monday and Friday, inclusive of overtime hours following holidays (from 00:00 on Monday to 23:59 on Friday). Non-weekday deliveries were defined when the date of birth fell on Saturday or Sunday, including national holidays in the People's Republic of China (from 00:00 on Saturday to 23:59 on Sunday). The timing of birth was extracted from medical records and classified as follows: daytime birth (from 08:00 to 16:59), evening birth (from 17:00 to 23:59), and night birth (from 00:00 to 7:59).

Outcomes

Primary outcome is in-hospital death. Secondary outcomes included delivery room intensive resuscitation, 5-minute Apgar score ≤7, admission hypothermia, surfactant therapy, invasive ventilation ≤24h after admission, use of inotropes ≤24h after admission, severe intraventricular hemorrhage (sIVH), cystic periventricular leukomalacia (cPVL), necrotizing enterocolitis (NEC) at stage ≥2, late sepsis, bronchopulmonary dysplasia (BPD), and severe retinopathy of prematurity (sROP) at stage ≥3.

Intensive resuscitation was defined as any delivery room resuscitation procedure, including intubation, chest compressions, or epinephrine administration[12]. An additional measure of resuscitation quality was a 5-minute Apgar score ≤7. Asphyxia strongly correlates with mortality and morbidity[13], and reflects the effectiveness of resuscitation. Hypothermia was defined as a temperature below 36.5°C. sIVH was categorized as grade ≥3 based on the Papile criteria[14]. cPVL was defined as the presence of periventricular cysts identified on cranial ultrasonography or magnetic resonance imaging[15]. NEC was defined according to the Bell criteria[16], and late-onset sepsis was characterized as positive blood or cerebrospinal fluid culture along with antibiotic therapy for 5 days or longer[17]. BPD was defined as ventilation or oxygen requirement at 36 weeks post-menstrual age or at the time of discharge, transfer, or death before 36 weeks' corrected age[18].

Covariates

Maternal characteristics included maternal age, diabetes, hypertensive disorders, antenatal corticosteroid administration, magnesium sulfate ($MgSO_4$) treatment, placental abruption, placenta previa, chorioamnionitis, premature rupture of membranes (PROM) lasting ≥ 24 hours, cervical incompetence, and delivery method. Infant characteristics included GA, birth weight, sex, small for gestational age (sGA), single or multiple births, and the Apgar score at 1 minute after birth, with a score of ≤3 indicating a critical condition.

Statistical analysis

The study population was divided into three groups based on birth time (daytime, evening, and night), stratified by weekday or non-weekday births. Infant characteristics and outcomes were reported as frequencies (proportions) for categorical variables and as means (SD) for continuous variables. Comparisons among groups were conducted using Pearson Chi-square or one-way ANOVA for categorical or continuous variables, respectively. Logistic regression models evaluated the relationship between outcomes and birth time for weekday births. Adjusted Odds ratios (aOR) and 95% confidence intervals (CI) were estimated, adjusting for confounding variables. In model A, we adjusted for diabetics, hypertension, placental previa, placental abruption, cervical incompetence, chorioamnionitis, premature rupture of membranes>24h, sGA, and gestational age. In model B, we further adjusted for MgSO4 and antenatal steroids. These confounders, identified from previous literature and clinical experience, were confirmed by a directed acyclic graph (Online Resource Supplementary Figure 1). Adjusted OR and 95% CI were estimated. We also performed GA subgroup analysis (GA 24^0-27^6 weeks, GA 28^0-29^6 weeks, and GA 30^0-31^6 weeks) and delivery type subgroup analysis (vaginal delivery and Cesarean section) to test whether GA and delivery type modified the effect of birth time on outcomes.

Furthermore, the probability of death (with 95% CI) was plotted for weekday and non-weekday birth by birth time with generalized additive models, using Empower (R) (www.empowerstats.com, X&Y solutions, inc. Boston MA). And then with the plot of death by time stratified by GA and delivery type for weekday birth infants. Statistical analysis was conducted using R software (version 4.2.3. http://www.R-project.org) with two sided significance level 0.05.

Results

Demographic characteristics of study population

Between 2019 and 2021, a total of 28,264 infants with GA between 24^0 to 31^6 weeks were born within the CHNN hospitals. Of these, 17,670 infants were included in the study (see Figure 1). The characteristics of the study population born on weekdays and non-weekdays were shown in Online Resource Supplementary Table 1.

The characteristics of the study population born at daytime, evening and night on weekdays or non-weekdays were shown in Table 1. On weekdays, mothers with infants born during the daytime shift were more likely to have hypertension, receive antenatal corticosteroids and $MgSO_4$, and undergo cesarean deliveries. These mothers were less likely to undergo placental abruption, placenta previa, chorioamnionitis, PROM ≥ 24 hours, and cervical incompetence. Infants born at daytime shift on weekdays were more likely to be sGA and have a lower rate of 1-minute Apgar≤3. Similar characteristics were observed among infants born on non-weekdays.

Table 1 Maternal and neonatal characteristics among very preterm infants born at Different Times on weekdays and non-weekdays

Characteristics, n/N (%)	Weekday birth				Non-weekday birth		
	Daytime, N = 6,911	Evening, N = 3,531	Night, N = 2,602	p-value	Daytime, N = 2,055	Evening, N = 1,405	Night, N =
Maternal characteristics							
Maternal Age, Mean(SD), y	31.2(4.9)	31.0(4.8)	30.8(4.8)	0.005	31.0(5.0)	31.0(4.7)	30.7(5.0)
Maternal Diabetics	1,439/6,904(20.8%)	685/3,526(19.4%)	597/2,596(23.0%)	0.003	428/2,053(20.8%)	314/1,405(22.3%)	246/1,15
Hypertensive disorders	1,888/6,903(27.4%)	742/3,527(21.0%)	238/2,600(9.2%)	<0.001	417/2,054(20.3%)	244/1,405(17.4%)	116/1,16
Antenatal steroids	5,878/6,880(85.4%)	2,892/3,520(82.2%)	2,069/2,592(79.8%)	<0.001	1,709/2,047(83.5%)	1,192/1,396(85.4%)	895/1,16
Receive MgSO4	4,366/6,853(63.7%)	2,012/3,515(57.2%)	1,424/2,587(55.0%)	<0.001	1,248/2,041(61.1%)	835/1,397(59.8%)	621/1,16
Placental Abruption	344/6,910(5.0%)	232/3,531(6.6%)	205/2,602(7.9%)	<0.001	150/2,055(7.3%)	93/1,404(6.6%)	91/1,165
Placental Previa	501/6,910(7.3%)	278/3,531(7.9%)	245/2,602(9.4%)	0.002	180/2,055(8.8%)	109/1,404(7.8%)	111/1,16
Chorioamnionitis,	1,314/6,911(19.0%)	728/3,531(20.6%)	550/2,602(21.1%)	0.029	460/2,055(22.4%)	299/1,405(21.3%)	210/1,16
Premature rupture of membranes>24h	4,113/6,853(60.0%)	2,168/3,510(61.8%)	1,683/2,579(65.2%)	<0.001	1,296/2,041(63.5%)	885/1,392(63.6%)	761/1,15
Cervical incompetence	523/6,911(7.6%)	390/3,531(11.0%)	283/2,602(10.9%)	<0.001	183/2,055(8.9%)	164/1,405(11.7%)	125/1,16
Cesarean section	4,993/6,908(72.3%)	2,073/3,529(58.7%)	1,094/2,601(42.1%)	<0.001	1,250/2,052(60.9%)	786/1,404(56.0%)	504/1,16
Neonatal charactristics							
Male	3,816/6,911(55.2%)	1,925/3,531(54.5%)	1,511/2,602(58.0%)	0.014	1,134/2,055(55.2%)	793/1,405(56.4%)	676/1,16
sGA	688/6,911(10.0%)	281/3,531(8.0%)	109/2,602(4.2%)	<0.001	182/2,055(8.9%)	87/1,405(6.2%)	49/1,166
Gestational age, wks				<0.001			
24^0~27^6	1,010/6,911(14.6%)	666/3,531(18.9%)	527/2,602(20.3%)		345/2,055(16.8%)	261/1,405(18.6%)	209/1,16
28^0~29^6	2,217/6,911(32%)	1,200/3,531(34%)	846/2,602(33%)		672/2,055(33%)	488/1,405(35%)	378/1,16
30^0~31^6	3,684/6,911(53%)	1,665/3,531(47%)	1,229/2,602(47%)		1,038/2,055(51%)	656/1,405(47%)	579/1,16
Birth weight, Mean(SD)	1,309.5(316.3)	1,296.9(321.3)	1,334.0(323.8)	<0.001	1,309.3(323.3)	1,304.9(315.4)	1,358.7(3
Single birth	4,784/6,911(69.2%)	2,416/3,531(68.4%)	1,750/2,602(67.3%)	0.2	1,451/2,055(70.6%)	974/1,405(69.3%)	789/1,16
1-min Apgar score≤3	314/6,893(4.6%)	199/3,529(5.6%)	142/2,584(5.5%)	0.028	113/2,051(5.5%)	83/1,399(5.9%)	71/1,161

SD: standard deviation; **s**GA: small for gestational age

Association between birth time and neonatal outcomes

There were no significant differences in mortalities and adverse outcomes among infants born on non-weekdays and those born on weekdays (Online Resource Supplementary Table 2).

In the subgroups born on weekdays (Table 2), compared with daytime, infants born during evening or night had higher rates in intensive resuscitation (23.8% in the daytime vs. 26.3% in the evening vs. 24.3% at night, p = 0.017; aOR for model A: 1.08(0.97, 1.19) for evening, 1.01(0.90, 1.13) for night; aOR for model B: 1.11(1.00, 1.23) for evening, 1.10(0.97, 1.23) for night), 5-minute Apgar scores ≤7 (10.3% vs. 13.1% vs. 11.0%, p < 0.001; aOR for model A: 1.22(1.07, 1.39) for evening, 1.00(0.85, 1.17) for night; aOR for model B: 1.23(1.07, 1.40) for evening, 1.02(0.87, 1.20) for night) and sIVH (5.0% vs. 6.8% vs. 5.4%, p = 0.001; aOR for model A: 1.30(1.08, 1.57) for evening, 1.04(0.83, 1.29) for night; aOR for model B: 1.27(1.05, 1.53) for evening, 1.00(0.80, 1.25) for night). Infants born at night were more likely to experience hypothermia (aOR for model A: 1.13(1.02,1.24)) and less likely to receive surfactant (aOR for model A: 0.90(0.81,0.99)), although the latter was no longer statistically significant in adjusted model B.

Table 2 Association between birth time and neonatal outcomes on weekdays

Outcomes, n/N(%)	Weekday birth				Crude model		Adjusted Model A[b]	
	Daytime, N = 6,911	Evening, N = 3,531	Night, N = 2,602	p-value	Unadjusted OR(95%CI)[a] for evening	Unadjusted OR(95%CI) [a] for Night	aOR(95%CI) [a] for Evening	aOR(95 for Nigl
Primary outcome								
Mortality in hospital	710/6,911(10.3%)	376/3,531(10.6%)	309/2,602(11.9%)	0.078	1.04(0.91, 1.19)	**1.18(1.02, 1.36)**	0.91(0.78, 1.04)	1.06(0. 1.24)
Delivery room resuscitation								
Intensive resuscitation	1,643/6,902(23.8%)	927/3,520(26.3%)	631/2,597(24.3%)	0.017	**1.14(1.04, 1.26)**	1.03(0.92, 1.14)	1.08(0.97, 1.19)	1.01(0. 1.13)
5-min Apgar score ≤7	702/6,845(10.3%)	458/3,494(13.1%)	282/2,560(11.0%)	<0.001	**1.32(1.16, 1.50)**	1.08(0.93, 1.25)	**1.22(1.07, 1.39)**	1.00(0. 1.17)
Early outcomes in NICU								
Hypothermia	4,462/6,874(64.9%)	2,324/3,509(66.2%)	1,728/2,585(66.8%)	0.15	1.06(0.97, 1.16)	1.09(0.99, 1.20)	1.06(0.97, 1.16)	**1.13(1. 1.24)**
Iurfactant	4,009/6,911(58.0%)	2,091/3,531(59.2%)	1,458/2,602(56.0%)	0.044	1.05(0.97, 1.14)	0.92(0.84, 1.01)	0.99(0.91, 1.08)	**0.90(0. 0.99)**
Start mechanical ventilation within 1st day	2,211/6,911(32.0%)	1,206/3,531(34.2%)	881/2,602(33.9%)	0.046	**1.10(1.01, 1.20)**	1.09(0.99, 1.20)	1.03(0.94, 1.13)	1.03(0. 1.14)
Use vasoactive drug within 1st day	1,138/6,911(16.5%)	579/3,531(16.4%)	417/2,602(16.0%)	0.9	1.00(0.89, 1.11)	0.97(0.86, 1.09)	0.94(0.84, 1.05)	0.91(0. 1.03)
NICU complications								
sIVH	305/6,161(5.0%)	212/3,125(6.8%)	127/2,331(5.4%)	0.001	**1.40(1.17, 1.67)**	1.11(0.89, 1.37)	**1.30(1.08, 1.57)**	1.04(0. 1.29)
cPVL	243/6,143(4.0%)	144/3,113(4.6%)	104/2,323(4.5%)	0.3	1.18(0.95, 1.45)	1.14(0.90, 1.43)	1.13(0.91, 1.40)	1.10(0. 1.39)
NEC(stage≥2)	345/6,911(5.0%)	187/3,531(5.3%)	124/2,602(4.8%)	0.6	1.06(0.89, 1.28)	0.95(0.77, 1.17)	1.04(0.86, 1.25)	0.93(0. 1.15)
late-onset sepsis	518/6,911(7.5%)	239/3,531(6.8%)	179/2,602(6.9%)	0.3	0.90(0.76, 1.05)	0.91(0.76, 1.09)	0.87(0.74, 1.02)	0.90(0. 1.08)
BPD	2,303/6,911(33.3%)	1,233/3,531(34.9%)	905/2,602(34.8%)	0.2	1.07(0.99, 1.17)	1.07(0.97, 1.17)	1.00(0.91, 1.09)	1.05(0. 1.17)
ROP(stage≥3)	167/5,354(3.1%)	90/2,772(3.2%)	55/2,007(2.7%)	0.6	1.04(0.80, 1.35)	0.88(0.64, 1.18)	0.90(0.69, 1.18)	0.73(0. 1.00)

NICU: neonatal intensive care unit; Intensive resuscitation: including intubation, chest compressions, or epinephrine administration; sIVH: severe intraventricular hemorrhage; cPVL: cystic periventricular leukomalacia; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity

[a] Daytime as reference

[b] Model A adjusted for Diabetics, Hypertension, Placental Previa, Placental Abruption, Cervical incompetence, Chorioamnionitis, ROM, sGA, gestational age

[c] Model B adjusted for model A+ receive MgSO4 + receive antenatal steroids

There were no differences in the above outcomes for infants born during off-peak hours compared to daytime on non-weekdays (see Online Resource Supplementary Table 3).

Subgroup analysis

The study population born on weekdays was stratified by GA and delivery mode. Maternal and neonatal characteristics across different shifts were detailed in Supplementary Table 4 for each GA group and in Supplementary Table 5 for each delivery mode. The subgroup analysis (Table 3) showed that the in-hospital mortality decreased significantly during the evening births with GA between 24^0-27^6 weeks (aOR 0.77, 95% CI 0.62 to 0.96). Similar trend was found in vaginal delivery subgroup (Table 3). Additionally, within the subgroup of infants born with 28^0-29^6 weeks GA, the association between the night shift and the likelihood of requiring intensive resuscitation (aOR 1.23, 95% CI 1.02 to 1.48) or the evening shift and 5-minute Apgar scores ≤7 (aOR 1.38, 95% CI 1.11 to 1.71) remained statistically significant. Among VPIs with GA ranging from 30^0-31^6 weeks, there was a statistically significant increase in the risk of sIVH during the evening shift (aOR 1.78, 95% CI 1.27 to 2.48). Similar trends in morbidities found in the two GA subgroups were also found in cesarean delivery subgroup (Table 3).

Table 3 Subgroups analysis for the association between birth time and neonatal outcomes on weekdays stratified by GA and delivery type

	Primary outcomes, n/N(%)	Daytime	Evening	Night	p-value	aOR(95%CI)[a] for evening	aOR(95%CI)[a] for night
Stratified by GA	**GA 24^0-27^6 weeks**	N = 1,010	N = 666	N = 527			
	Mortality in hospital	325/1,010(32%)	186/666(28%)	160/527(30%)	0.2	**0.77(0.62, 0.96)**	0.90(0.71, 1.14)
	Intensive resuscitation	513/1,008(51%)	337/662(51%)	247/524(47%)	0.3	1.03(0.84, 1.25)	0.90(0.73, 1.12)
	5-min Apgar score ≤7	265/998(27%)	195/655(30%)	125/507(25%)	0.13	1.17(0.94, 1.47)	0.92(0.72, 1.18)
	Hypothermia	661/1,001(66%)	438/663(66%)	370/523(71%)	0.14	1.02(0.82, 1.26)	1.25(0.99, 1.58)
	sIVH	99/825(12%)	76/558(14%)	53/445(12%)	0.6	1.16(0.84, 1.61)	1.03(0.72, 1.48)
	GA 28^0-29^6 weeks	N = 2,217	N = 1,200	N = 846			
	Mortality in hospital	228/2,217(10%)	101/1,200(8.4%)	97/846(11%)	0.062	0.83(0.64, 1.06)	1.25(0.96, 1.61)
	Intensive resuscitation	597/2,211(27%)	329/1,198(27%)	236/844(28%)	0.9	1.07(0.91, 1.26)	**1.23(1.02, 1.48)**
	5-min Apgar score ≤7	235/2,198(11%)	163/1,192(14%)	100/837(12%)	0.036	**1.38(1.11, 1.71)**	1.25(0.96, 1.61)
	Hypothermia	1,449/2,203(66%)	800/1,193(67%)	573/840(68%)	0.4	1.08(0.93, 1.26)	1.17(0.98, 1.39)
	sIVH	124/2,004(6.2%)	72/1,072(6.7%)	39/762(5.1%)	0.4	1.10(0.81, 1.49)	0.86(0.58, 1.25)
	GA 30^0-31^6 weeks	N = 3,684	N = 1,665	N = 1,229			
	Mortality in hospital	157/3,684(4.3%)	89/1,665(5.3%)	52/1,229(4.2%)	0.2	1.30(0.99, 1.70)	1.14(0.81, 1.58)
	Intensive resuscitation	533/3,683(14%)	261/1,660(16%)	148/1,229(12%)	0.019	1.13(0.96, 1.33)	0.88(0.72, 1.08)
	5-min Apgar score ≤7	202/3,649(5.5%)	100/1,647(6.1%)	57/1,216(4.7%)	0.3	1.09(0.85, 1.40)	0.85(0.61, 1.15)
	Hypothermia	2,352/3,670(64%)	1,086/1,653(66%)	785/1,222(64%)	0.5	1.07(0.95, 1.22)	1.06(0.92, 1.21)
	sIVH	82/3,332(2.5%)	64/1,495(4.3%)	35/1,124(3.1%)	0.003	**1.78(1.27, 2.48)**	1.31(0.86, 1.96)
Stratified by delivery type	**Vaginal delivery**	N = 1,915	N = 1,456	N = 1,507			
	Mortality in hospital	314/1,915(16%)	201/1,456(14%)	218/1,507(14%)	0.087	**0.75(0.60, 0.92)**	0.89(0.72, 1.10)
	Intensive resuscitation	482/1,909(25%)	357/1,448(25%)	344/1,502(23%)	0.3	0.91(0.76, 1.08)	0.92(0.77, 1.09)
	5-min Apgar score ≤7	249/1,884(13%)	199/1,437(14%)	166/1,475(11%)	0.088	1.03(0.83, 1.28)	0.85(0.68, 1.07)
	Hypothermia	1,308/1,902(69%)	989/1,446(68%)	1,030/1,501(69%)	>0.9	1.00(0.86, 1.16)	1.01(0.87, 1.17)
	sIVH	109/1,668(6.5%)	104/1,277(8.1%)	86/1,345(6.4%)	0.14	1.22(0.92, 1.63)	1.00(0.74, 1.35)
	Cesarean section	N = 4,993	N = 2,073	N = 1,094			
	Mortality in hospital	396/4,993(7.9%)	175/2,073(8.4%)	91/1,094(8.3%)	0.7	1.03(0.85, 1.25)	1.15(0.89, 1.48)
	Intensive resuscitation	1,159/4,990(23%)	568/2,070(27%)	287/1,094(26%)	<0.001	**1.24(1.10, 1.40)**	**1.29(1.10, 1.51)**
	5-min Apgar score ≤7	453/4,958(9.1%)	259/2,055(13%)	116/1,084(11%)	<0.001	**1.39(1.17, 1.64)**	1.24(0.98, 1.54)
	Hypothermia	3,151/4,969(63%)	1,334/2,062(65%)	697/1,083(64%)	0.6	1.04(0.94, 1.16)	1.09(0.95, 1.26)

	sIVH	195/4,490(4.3%)	108/1,848(5.8%)	41/985(4.2%)	0.026	**1.36(1.06, 1.74)**	1.00(0.69, 1.42)

GA: gestational age, sGA: small for gestational age, sIVH: severe intraventricular hemorrhage

[a]Daytime as reference, Model was adjusted for Diabetics, Hypertension, PreclampsiaEAnte, Placental Abruption, Placental Previa, Chorioamnionitis, Cervical incompetence, ROM, sGA

Smooth curve fitting

The curve fitting in generalized additive models revealed two prominent peaks (Figure 2). The initial peak corresponded to the "handover effect," observed during the day-evening shift between 15:00 and 17:00. The second peak occurred during the night shift, particularly for infants born on weekdays. Subsequent analysis, stratified by GA, indicated that infants with a GA of 24^0-27^6 weeks were notably influenced by the "handover effect." In a further analysis stratified by delivery type for weekday births, the population significantly impacted by the "handover effect" was infants delivered vaginally, accompanied by a slight leftward shift in the peak mortality rate.

Discussion

In our nationwide multi-center cohort study, we observed two major facts. First, there's a bimodal pattern of mortaliy on weekday birth. The first peak appeared between 3:00 PM and 5:00 PM on weekdays, with the second peak raising at night. Upon subgroup analysis, we identified infants with a gestational age of 24^0-27^6 weeks as a pivotal cohort contributing to this bimodal pattern. At the same time, similar trend was presented in subgroup of vaginal delivery. Second, heightened risks were noted for asphyxia, hypothermia, and sIVH in the population of GA 28^0-31^6 born during non-working hours on weekdays.

Just like other countries[19], day-evening handover shift in our country happened between 3:00 PM and 5:00 PM. We know that the day shift is characterized by optimal staffing levels, efficient resource allocation, and well-structured organizational arrangements. The evening and night shift tends to have a relatively lower staffing complement. Handover effect highlights concerns related to the staff handover process, particularly in situations where there may be vulnerabilities concerning patient care, emergency response, and the allocation of human resources. The adjustment period required to attain stability following the redistribution of human resources should not be underestimated. It is therefore reasonable to hypothesize that the weekday handover shift may have implications such as increased workload, diminished nursing quality, abrupt reductions in staffing levels, and a decline in professionalism. The overall survival of very preterm infants born between 24 and 29 weeks' gestation and weighing <1500 g ranged from 78% to 93% among international networks[20-22]. Among them, infants with GA ranging from 24^0 to 27^6 weeks are considered the most vulnerable population, whose first 24 hours after birth hold critical significance for their survival[23, 24]. So infants with GA 24^0 to 27^6 weeks are particularly susceptible to handover effects. However, specific data for comparative analysis is currently lacking. Hence, it is imperative to conduct further research regarding the distribution, variances in diagnosis, and treatment disparities among healthcare professionals during handovers in various regions, facilitating the identification of potential remedies. Additionally, careful consideration should also be given to the characteristics of key populations that contribute to the handover effect and impact nursing quality. Furthermore, the phenomenon of night hours effect is consistent with the findings of Rizzolo et al[19], who reported an increased mortality rate among infants with a gestational age of 22^0-27^6 weeks born during nighttime.

A study found that extremely premature infants born during regular working hours were more likely to result from planned deliveriese[25], increasing the likelihood of receiving comprehensive tocolytic therapy, including antepartum corticosteroids and magnesium sulfate, and proactive care at birth. In contrast, cesarean sections during non-weekday hours are linked to maternal complications such as placental abruption, placenta previa, and cervical incompetence. We conducted subgroup analysis based on delivery mode. Compared to cesarean sections, the proportion of infants with GA 24^0-27^6 weeks was much higher in vaginal delivery (29.2%:9.5%). Among infants with GA 24^0-27^6 weeks, 64.7% were delivered vaginally. This stratification confirms that infants with GA 24^0-27^6 weeks are most affected by these effects and highlights the potential risks of vaginal delivery. Studies suggest vaginal delivery is associated with higher odds of perinatal death[26], while cesarean section reduces brain damage risks [27, 28] and improves outcomes for extremely premature infants. [29-31]. Further research is needed to understand the role of delivery mode in the prognosis of extremely premature infants in our population.

Several studies have reported that extremely premature infants born on weekends exhibit an increased likelihood of receiving intensive resuscitation and asphyxia when compared to those born on weekdays[5, 9, 32]. One possible explanation may be the physiological condition of VPIs delivered on working hours may vary from those born on off-peak hours. Despite our efforts to control for numerous risk factors, such as maternal and fetal variables, there may still exist some unmodifiable high-risk factors contributing to these disparities. For instance, the incidence of 1-minute Apgar scores ≤3 in infants born during off-peak hours on weekdays was notably elevated compared to those born during regular working hours. This observation implies the potential existence of intrauterine distress. An alternate explanation could be attributed to variations in the distribution of healthcare personnel resources, as previously discussed, leading to suboptimal implementation of neonatal resuscitation and thermal management interventions.

Extremely low birth weight infants are particularly susceptible to hypoxia and severe intraventricular hemorrhage (sIVH) due to their underdeveloped central nervous system and fragile hemodynamic stability, leading to profound neurological impairments[33-35]. Additionally, hypothermia is linked to an increased risk of intraventricular hemorrhage[36, 37] and mortality[38, 39]. Subgroup analysis indicates this phenomenon is most evident in infants born between 28^0 and 31^6 weeks GA or those delivered via cesarean section. These findings support the notion that infants in the 28^0-31^6 weeks GA range are the primary group requiring advanced resuscitative measures in the delivery room.

We have implemented proactive measures at the national level to enhance the support for delivery room resuscitation. These measures include inpatient policies and backup systems designed to address challenges with neonates born between 24^0-27^6 weeks GA. However, we have identified a concerning trend in the management of infants born within the 28^0-31^6 weeks GA, where there may be a tendency to underestimate the need for and be less vigilant in delivery room resuscitation. Currently, infants born in this range account for 82.9% of the study population. Although our survival rate for these infants has reached 97.3%[3], nearing standards seen in developed countries, it is crucial to maintain focus on the quality of delivery room resuscitation. Strengthening collaboration within neonatology, particularly in less-developed regions, is essential.

Our study boasts several key strengths, including a substantial sample size, a nationwide multi-center approach, and a comprehensive dataset with detailed maternal and neonatal factors. These attributes allow for a rigorous and comprehensive investigation. However, our study also has several limitations. Firstly, as a retrospective cohort study, the level of evidence is constrained. Secondly, we did not gather additional information on staffing patterns, such as physician-to-patient ratios, staff workload, shift handovers, and nursing levels, limiting our ability to analyze the potential factors contributing to the handover effect. Additionally, China is a vast country with a large number of participating centers, and regional disparities exist in their development. These disparities may be less pronounced in more advanced regions. Thus, a nationwide comparison of hospitals at different levels through a continuous quality improvement platform is essential.

Conclusions

In conclusion, the day-evening handover effect and nighttime peak effect on weekdays are particularly pronounced in infants born between 24^0 and 27^6 weeks GA. Additionally, birth during non-working hours on weekdays is associated with an increased risk of asphyxia, hypothermia, and sIVH in infants born between 28^0 and 31^6 weeks GA. It is essential to investigate healthcare personnel distribution during different time periods, with emphasis on the day-evening handover shift. Research should also focus on early management strategies for infants born between 24^0 and 27^6 weeks GA and resuscitation protocols for those born between 28^0 and 31^6 weeks GA.

Abbreviations

bronchopulmonary dysplasia (BPD)

Chinese Neonatal Network (CHNN)

cystic periventricular leukomalacia (cPVL)

magnesium sulfate ($MgSO_4$)

necrotizing enterocolitis (NEC)

NICUs (neonatal intensive care unit)

odds ratio (OR)

premature rupture of membranes (PROM)

severe intraventricular hemorrhage (sIVH)

severe retinopathy of prematurity (sROP)

small for gestational age (sGA)

very preterm infants (VPIs)

Declarations

Supplementary Information

The online version contains supplementary material available at ……

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Data availability statement The data supporting the findings of this study are stored in the database of the Chinese Neonatal Network (CHNN). Access to the data is restricted to authorized personnel to ensure the confidentiality and security of patient information. Researchers interested in accessing the data can submit a formal request to the CHNN, subject to approval and compliance with relevant ethical and data-sharing policies.

Ethics Approval The study was approved by the ethics review board of Children's Hospital of Fudan University (2018-296) and was endorsed by all participating centers. The research was conducted in accordance with the Declaration of Helsinki. Waiver of consent was granted at all sites owing to the use of deidentified patient data.

Consent for publication

Not applicable.

Competing Interests No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Data sharing statement

Requests for access to these data will be made according to Chinese Neonatal Network's (CHNN) data sharing policy. After the publication of the article, the corresponding author may offer de-identified data, but this requires the provision of scientific rationale and sound methods.

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Figures

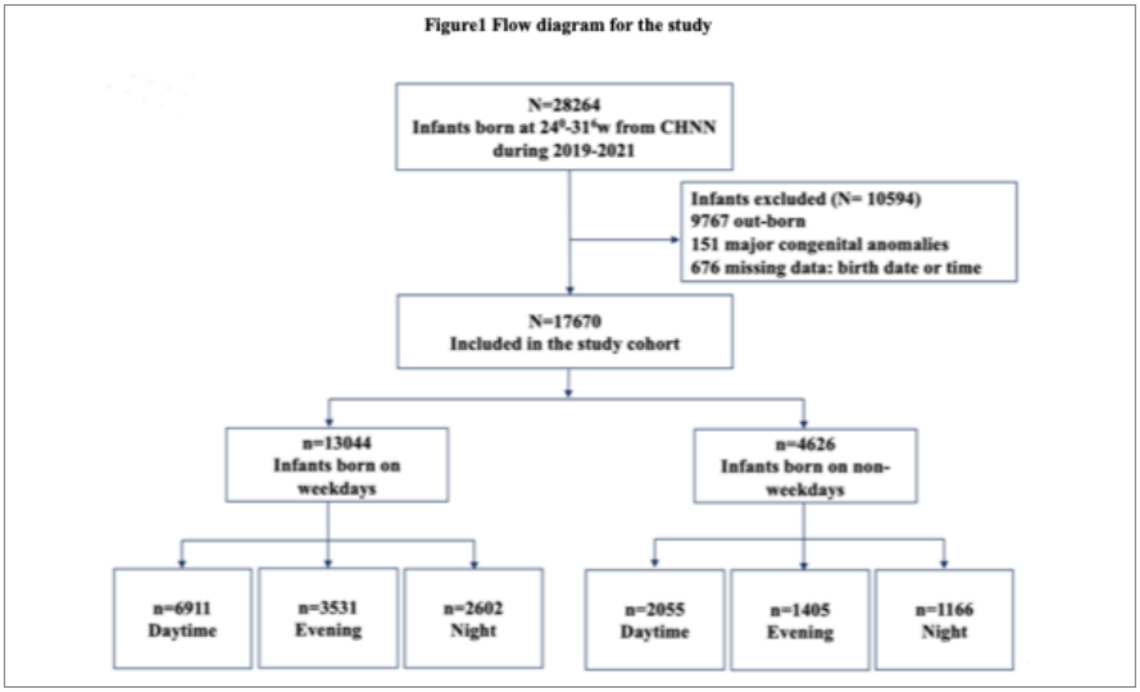
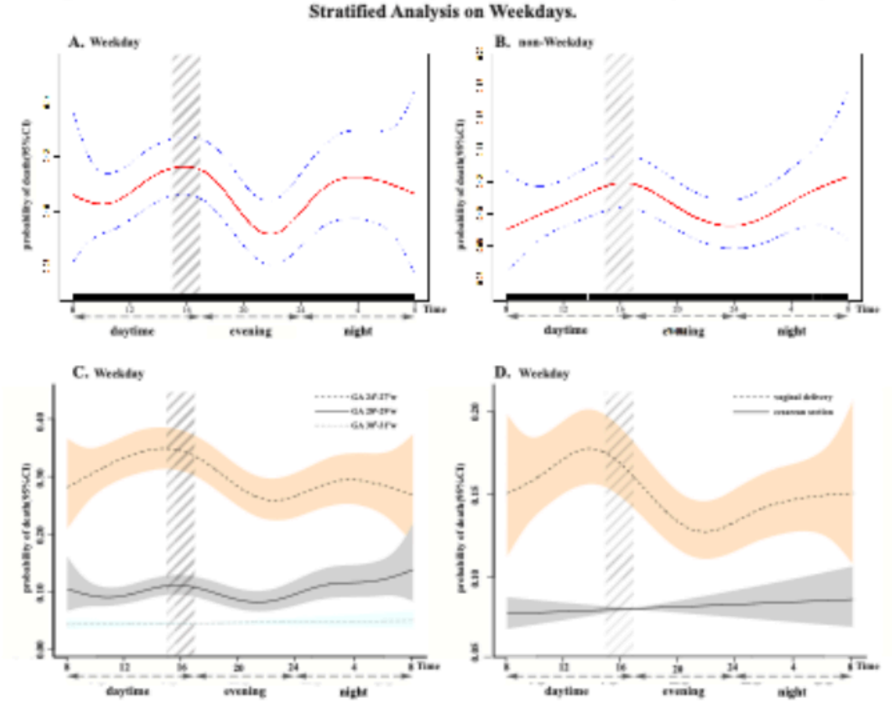


Figure 1

See image above for figure legend.

Figure 2 Association of Total Neonatal Mortality with Birth Time on Weekdays or non-Weekdays and Stratified Analysis on Weekdays.



The probability of death (with 95% CI) was plotted for both weekday and non-weekday birth by birth time with generalized additive models. A and B, The solid red line represents rates as smooth curve fit between the birth time and probability of death. Blue bands represent the 95%CI of rates. The shadow represents the handover period from 15:00 to 17:00. The data were adjusted for the maternal and infant characteristics by adjusted model A. C and D, smooth curve stratified analysis on Weekdays, by GA or delivery type.

Figure 2

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarytable.docx
- supplementaryFigure1DAGmap.pdf