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The Chinese adverse prognosis of very preterm infants (CARE-Preterm) cohort: study design and baseline characteristics for a prospective multicenter cohort study

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Abstract

Background As the increasing survival of preterm infants bearing lower gestational age (GA) and birth weight (BW), new challenges have emerged regarding their management and prognosis. In low- and middle-income countries, there is notable absence of prospective multicenter cohorts to accurately reflect their real treatment capacity for these preterm infants. This cohort study aims to fill this gap by investigating the impact of perinatal management on the prognosis of preterm infants in Northern China.

Methods The Chinese Adverse Prognosis of Very Preterm infants (CARE-Preterm) cohort study is a prospective, multicenter, longitudinal, and open cohort study based on the Sino-northern Neonatal Network (SNN) since 2018, covering 60 neonatal intensive care units from 8 densely-populated provinces and autonomous regions in Northern China. All very preterm infants (VPIs) born with GA < 32 weeks or very low birth weight infants (VLBWI) born with BW < 1500 g admitted alive to the participating units are continuously enrolled from January 1, 2018. Baseline clinical data and biological samples are longitudinally collected from the perinatal period to discharge.

Results From January 1, 2018, to December 31, 2022, approximately 10,447 infants were included and 9325 infants were discharged alive. Notably,1472 (14.09%) were born with GA < 28 weeks, and 1566 (14.99%) with BW < 1000 g. Among the 9325 survivors, the smallest GA and BW were 23^{+3} weeks and 450 g, respectively. The main findings of this cohort study highlight substantial improvements in perinatal medicine treatment capabilities and current treatment bottlenecks.

Conclusion This cohort study provides crucial insight into updated real-world data from low- and middle-income countries, helping to identify treatment bottlenecks and improve both the survival rate and life quality for preterm infants. Furthermore, it is expected to serve as a reference for establishing population-based cohort studies in other low and middle-income countries.

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Trial registration The current projects based on this cohort study have been registered in the Chinese Clinical Trial Registration Center (Registration number: ChiCTR1900025234, ChiCTR1900020861, ChiCTR2000037918, ChiCTR2000029162, ChiCTR2100053780 and ChiCTR2200066764).

Keywords Cohort study, Prospective, Very preterm infant, Very low birth weight infant, Adverse prognosis

Introduction

Globally, preterm birth rates have gradually increased over recent decades, now representing approximately 10% of all newborns [1]. With advanced treatment options, an escalating number of very preterm infants (VPIs) and very low birth weight infants (VLBWIs) with lower gestational age (GA) and birth weight (BW) are surviving. However, this increased survival has subsequently led to a rise in preterm-related complications and deficits amongst survivors, presenting a significant global health concern. Correspondingly, the demand for medical decision-making and perinatal management has undergone substantial changes [2]. In high-income countries such as the United States and France, national or regional neonatal networks and preterm birth cohorts have been established to evaluate their treatment capabilities for preterm infants using population-based data. These resources provide reliable evidence for the adjustment of healthcare practices and policies [3–6]. In contrast, in China and other low- and middle-income countries with a larger population base of preterm birth, neonatal birth cohorts primarily focus on investigating birth defects or maternal-child outcomes [7, 8]. There is lack of large, updated population-based datasets that accurately reflect the survival rates, prognosis and real treatment capacities for preterm infants, which highlights the pressing need for comprehensive data to guide healthcare practices in these regions.

As China undergoes rapid industrialization and adjusts its birth policies, the number of preterm births has experienced a significant surge, reaching approximately 1,172, 259 preterm births (7.8%) in 2010, ranking the second-highest globally. Consequently, preterm-related complications and deaths caused by preterm birth are expected to become the leading cause of child mortality [9–13]. Concurrently, the swift advancement of perinatal medicine presents unique challenges for the management of preterm infants in low- and middle-income countries. Due to imperfections in healthcare systems, deaths resulting from withdrawal of care according to social-economic factors are still very common in these countries [13]. Our single-center study showed that among all live-born extremely preterm infants (EPIs) with GA < 28 weeks in the delivery room (DR) from 2010 to 2019, over 73% of deaths occurred due to care withdrawal, either in the DR or neonatal intensive care unit (NICU), thereby denying these infants the opportunity for active treatment [14]. Additionally, among the infants who received active treatment but subsequently died, the primary causes of death were sepsis, respiratory distress syndrome (RDS), and severe asphyxia. The proportion of RDS-associated deaths was notably higher compared to high-income countries, indicating a lag in the medical staff's treatment concept and constraints in the implementing international guidelines. Furthermore, as other studies have shown, preterm-related complications continue to threaten the quality of life of surviving preterm infants [15].

However, in China and other low- and middle-income countries, the lack of large population-based data on deaths, preterm-related complications and prognosis of preterm infants hinders an accurate assessment of treatment abilities and identifies bottlenecks. This underlines the urgent need for a prospective, multicenter, longitudinal, open, and continually updated cohort study to address these challenges and provide effective care for preterm infants in these countries. Such a cohort would provide reliable baseline data to investigate the causes and risk factors of death and preterm-related complications, and evaluate the demand for medical practices within NICUs, which is expected to gradually enhance treatment confidence, reduce the occurrence of care withdrawal, and ultimately improve the survival rate and life quality for preterm infants in these regions.

Methods

Cohort study design

The Chinese Adverse Prognosis of Very Preterm infants (CARE-Preterm) cohort is a regional, prospective, multicenter, longitudinal, open and continuously updated preterm cohort established based on a clinical research database, the Sino-northern Neonatal Network (SNN, www.snn-med.com), in 2018. The SNN is a data platform initiated on January 1, 2018, by Shandong Provincial Hospital affiliated to Shandong First Medical University, with authorization from the Shandong Health Committee and the National Institute of Health Data Science of China. In 2019, the data platform was established as an online database, managed by the National Health Medical Data North Center, and it is connected with the Child Health Care System and the Education system of Shandong Province.

This cohort currently encompasses 60 neonatal intensive care units (NICUs) across perinatal medical centers and comprehensive medical institutions in 8 densely-populated provinces and autonomous regions, including

Shandong Province, Beijing City, Hebei Province, Henan Province, Shanxi Province, Shaanxi Province, Ningxia Hui autonomous Region and Inner Mongolia Autonomous Region, covering approximately 120 million people and most parts of the Northern China (Fig. 1).

Eligibility and enrollment

The inclusion criteria for CARE-Preterm cohort comprise all VPIs with birth GA less than 32 weeks or VLBWIs with BW less than 1500 g, who are born alive or transferred alive to the participating units within 28 days after birth since January 1, 2018. A live birth is defined as any infant showing signs of life, such as breathing, heartbeat, or voluntary muscle movement at the time of birth. Infants who are withdrawn of care or died in the DR before admission to the units, including stillbirths that showed no signs of life or infants who lost signs of life after active resuscitation, as well as infants whose guardians refused to participate, are excluded from the cohort.

Longitudinal and continuous data collection strategies

Data collection is conducted longitudinally at various time points, spanning from the perinatal period to hospitalization and outpatient visit. This enables the tracking of the occurrence, development and outcomes of death and preterm-related complications in these preterm infants. By outpatient visit and connecting with the Child Health Care System and the Education System of Shandong Province, all participants are expected to be followed up until school age (Fig. 2). Furthermore, this cohort is an open cohort, and preterm infants are enrolled continuously since January 1, 2018.

Perinatal management within the first week after birth

To evaluate the impact of maternal diseases and their management during pregnancy on adverse outcomes in preterm infants, detailed data on the diagnosis and management of maternal diseases before delivery are obtained from obstetric records and through parental interviews during admission to NICU. To investigate the effect of early treatment strategies during delivery on the initial stability of vital signs and early infant mortality,

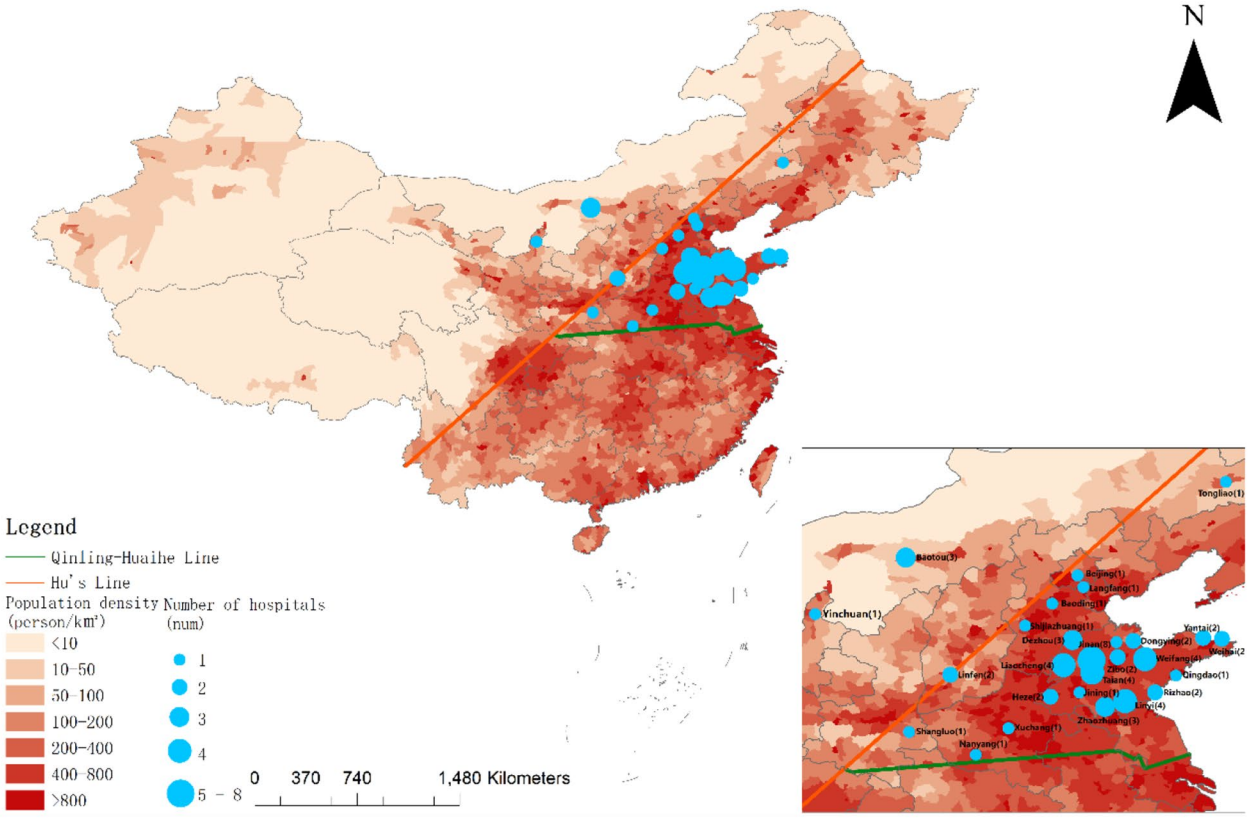

Fig. 1 Geographical distribution and population coverage of CARE-Preterm cohort. Shading represents the population density of each district (person/km^2), and the blue dots represent the location of participating hospitals and the diameter of the circle represent the numbers of participating hospitals in each city. The Qinling-Huaihe Line is the dividing line between East and West China, about 94% of the total populations in China resides east of the Qinling-Huaihe Line and only 6% resides west of the line. The Hu's Line is the dividing line between Northern and Southern China. All participating NICUs are located in Northern China

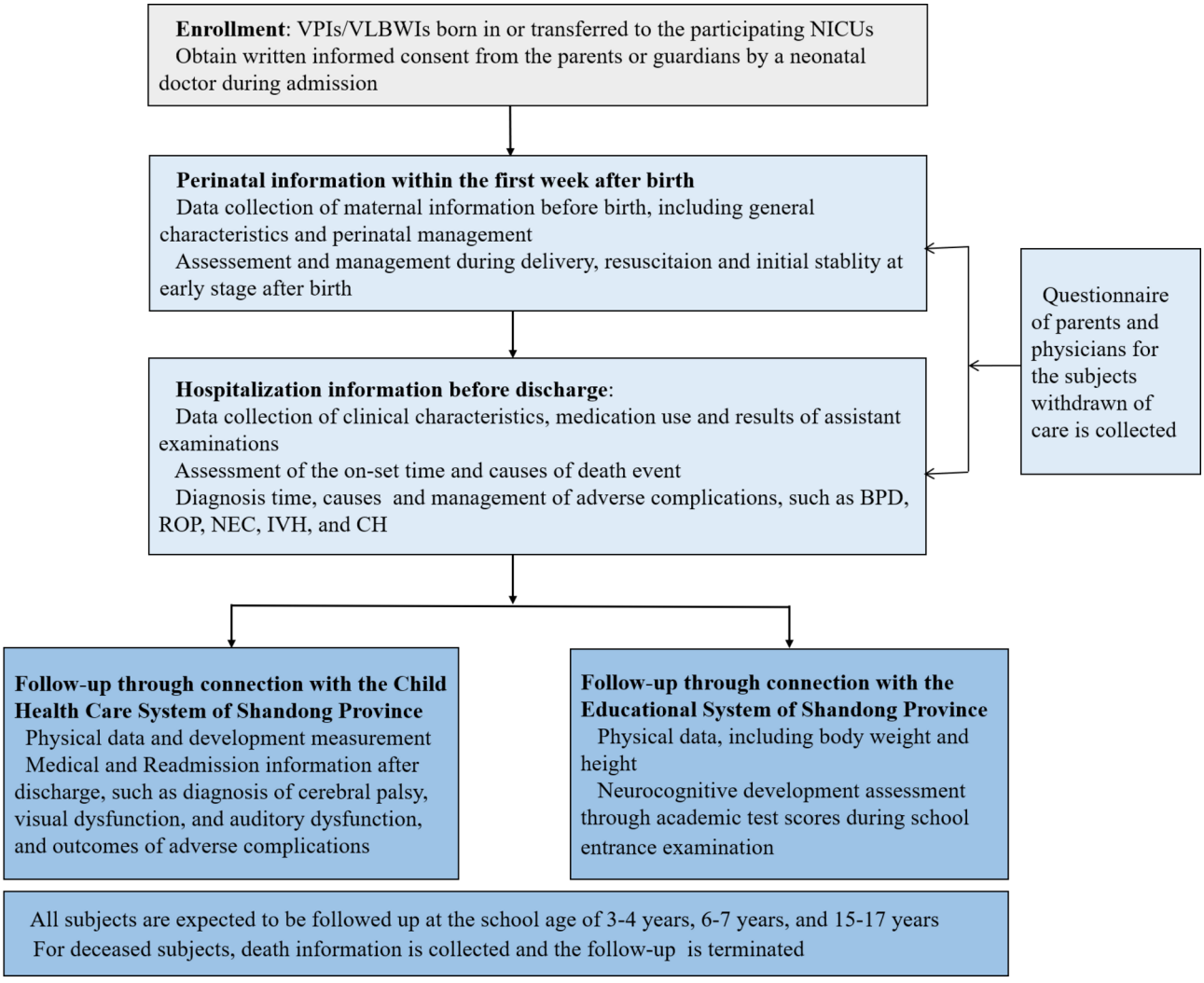

Fig. 2 Subject enrollment, data collection and adverse prognosis evaluation at each follow-up time point. VPI: Very preterm infant, VLBWI: Very low birth weight infant, BPD: Bronchopulmonary dysplasia, ROP: Retinopathy, NEC: Necrotizing enterocolitis, IVH: Intraventricular hemorrhage, CH: Congenital hypothyroidism

information regarding the delivery process, primary resuscitation, and treatment strategies implemented in the DR is obtained from DR records. Furthermore, detailed clinical management information within the first week after admission to the NICU is obtained from neonatal medical records, enabling the assessment of early mortality and occurrences of complications in preterm infants.

Hospitalization management and assessment before discharge

During the hospitalization period, comprehensive neonatal interventions and outcomes are extracted from medical records before discharge. These data are collected to evaluate the incidence, causes, development, and medical management of adverse complications in preterm infants, including death, early-onset sepsis (EOS), late-onset sepsis (LOS), necrotizing enterocolitis (NEC), pulmonary hemorrhage, intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and other preterm-related complications. For infants who unfortunately passed away in the NICU, detailed information is also collected to accurately define the types of death, such as death after withdrawal of care or death after active treatment, so as to explore the reason for care withdrawal and the identification of potential bottlenecks in medical management. Additionally, questionnaires are collected from both parents and physicians to investigate the reasons for care withdrawal. By conducting a thorough analysis of this collected hospitalization data, this model aims to gain insights into the management and outcomes of preterm infants during hospitalization, including the occurrence and progression

of adverse complications, as well as the factors influencing care withdrawal decisions.

Outpatient visits

Following hospital discharge, outpatient visits are initiated to track the long-term outcomes of complications. A detailed follow-up schedule is provided to the parents or guardians by a dedicated nurse at the participating center. Each infant is scheduled for a follow-up visit at postmenstrual age (PMA) 40 weeks if discharged before that time. Follow-up visits are then scheduled every 1 to 3 months between PMA 40 weeks and 12 months, and every 3 to 6 months from PMA 13 months to 36 months. Follow-up information on growth, development, and neurological function is collected from the outpatient medical records. If an infant misses a scheduled visit, the nurse will contact the guardians by phone to ensure compliance. If the infant passes away during follow-up, the cause of death will be recorded, and follow-up will be terminated.

To facilitate the outpatient visits, a connection between the SNN database and the Child Health Care System of Shandong Province has been established. Through the connection, medical information and rehospitalization data of the participants can be retrieved and collected using their unique identification numbers of Chinese citizens, which were registered at the time of discharge. In addition to medical information, the growth and neurocognitive development of the participants during their school-age years can be assessed by connecting with the Educational System of Shandong Province. These outpatient visits, along with the comprehensive data collection from both the healthcare and educational system, enable a thorough assessment of the long-term outcomes, growth and neurodevelopmental process of preterm infants. This information plays a crucial role in understanding the impact of perinatal management and preterm birth on their lives and informing future healthcare interventions.

Modules and key variables

For all enrolled infants, the data collection is divided into three modules, including the maternal module, hospitalization module and outpatient follow-up module.

The maternal module primarily focuses on gathering information related to general sociodemographic characteristics, maternal health, complications during pregnancy, management strategies, and the composition of the family members. The hospitalization module encompasses data related to delivery, resuscitation, transportation, early stability after birth, integrated management in NICU, diagnosis and management of complications, as well as information at the time of death and discharge. The outpatient follow-up module is dedicated to assessing the development, measurement and outcome of the adverse complications at different corrected ages during the follow-up visits. The main categories and key variables collected in this cohort are listed in supplementary Table 1. Besides, questionnaires are collected from both parents and physicians to investigate the reasons for withdrawal of care.

Additionally, data regarding re-admission and medical care received at other healthcare institutions after discharge can be collected by connection with the Child Health Care System of Shandong Province. Moreover, the physical data, such as body weight and height, and academic test scores during the school entrance examination can also be extracted by connecting with the Educational System of Shandong Province. All survivors are expected to be followed up at the school age of 3–4 years, 6–7 years, and 15–17 years prior to college. For those who died or cannot be contacted by telephone calls, the follow-up will be terminated.

Data management and quality control

To ensure smooth cohort operation, implementation and data quality, a mature study management organization has been established, including an executive chairman, a principal investigator (PI) association, a clinical research multidisciplinary team (MDT), a data quality control team and data entry coordinators. The PI association is composed of the executive chairman and 60 PIs from the participating units, and is responsible for the study design, implementation, and data quality control. This association plays a crucial role in overseeing the overall progress of the study. The clinical research MDT is established to ensure the rigor and accuracy of the study protocols and data analysis, including experts from clinical medicine, informatics, epidemiology, statistics, pharmacy, and evidence-based medicines.

The data entry coordinators are well trained and are responsible for the data collection in each participating unit. They receive training from the PI association and the data quality control team on data entry procedures, including the modules, categories and variables in the database, as well as how to collect and input these variables accurately into the database. To ensure consistent and clear definitions of each clinical variable, a detailed manual of operation for data entry has been developed by the PI association. The coding strategies for these clinical variables are based on the International Classification of Diseases 10th Revision (ICD-10). Additionally, objective variables and diagnostic criteria are managed within the online registration system according to these strategies. For example, BPD was defined as the requirement for supplemental oxygen for more than 28 days of life, and moderate-to-severe BPD was defined as any infant requiring supplemental oxygen and/or respiratory

support at 36 weeks postmenstrual age or at hospital discharge, whichever occurred earlier [16]. In the variable settings for BPD in preterm infants, the system includes information on respiratory support conditions at 28 days after birth and at 36 weeks postmenstrual age, making it convenient for the data quality administrator to check and verify the diagnosis of BPD.

During data entry, small errors will be checked and revised by the database automatically. Additionally, a data quality control team has been established by the PI association to monitor and ensure the accuracy and completeness of data from each center. After data upload, the administrators of the data quality control team conduct a second round of data quality control and feedback the queries to the data entry coordinators each week, ensuring data accuracy and consistency. Each month, the PI association organizes online meetings with the participating centers to report and feedback the data quality of the last month, and conducts site visits to 3–4 participating hospitals every month to verify the completeness of the enrolled data at each center, ensuring the integrity of the included population.

To guarantee the privacy of the data and information of the subjects, the data of the study can only be obtained by the team leader, and an experienced software administrator is appointed for the management of the data extraction. All researchers have to sign the data confidentiality agreements to ensure the safety and privacy of the data.

Biological samples collection and storage

In addition to clinical data, biological samples from the infants are collected at various time points, ranging from birth to outpatient visits, including cord blood, amniotic fluid, peripheral blood, stool, urine and so on. Furthermore, for infants whose mothers have been diagnosed with preterm premature rupture of membranes, chorioamnionitis or cervical incompetence, maternal vaginal secretions are collected during antenatal examination for pathogen detection. This allows for a homology analysis to be conducted with pathogens detection in preterm with early-onset sepsis after birth, with the aim of exploring the causes of early-onset sepsis. By combining comprehensive clinical data with biological sample collection, the study aims to further explore the factors contributing to preterm birth, complications, and adverse outcomes, thereby advancing our understanding of preterm infant health and providing opportunities for further mechanical researches and interventions.

To manage the biological samples, a biological bank has been established in Shandong Provincial Hospital Affiliated to Shandong First Medical University. All samples are stored in refrigerators at a temperature of -80 °C. Samples from participating units are sent to Shandong Provincial Hospital Affiliated to Shandong First Medical University through thermostats at the end of each month using thermally insulated containers with ice packs. A well-trained staff member is designated for the registration, storage and extraction of these samples, ensuring proper sample handling and maintaining their integrity.

Results and key findings

As of December 31, 2022, a total of 10,447 preterm infants have been enrolled in this cohort. On average, more than 2000 subjects are enrolled annually. Among these participants, the mortality rate is 10.74%. And the rates of moderate and severe BPD, ROP greater than stage II, and IVH greater than grade II is 7.16%, 3.28%, and 3.21%, respectively. The incidence of maternal hypertension during pregnancy (HDP) in the entire cohort is 26.44%, with a gradual increase from 2018 to 2021(Table 1). From the cohort, a total of 9325 subjects were discharged alive and subsequently entered the outpatient follow-up phase. Table 2 showed the general characteristics and primary complication rates of these survivors upon discharge. The lowest GA and BW recorded among the survivors were 23^{+3} weeks and 450 g, respectively. Notably, moderate and severe BPD emerged as the most prevalent preterm-related complication, affecting 7.52% of the survivors (Table 2).

Based on the CARE-Preterm cohort, a methodological system of clinical research has been conducted using epidemiological design and evidence-based medical research methods. As of 2022, a series of clinical research articles based on this cohort have been published, revealing significant findings. The main findings are summarized below.

Accurate classification of death types in VPI/VLBWIs

A key contribution of the cohort study has been the accurate classification of death types among VPI/VLBWIs. Based on the actual treatment received in the NICUs, deaths have been categorized into three types: death after redirection of care (ROC), death due to socio-economic considerations (SEC), and death after maximal intensive care (MIC). Among these, ROC and MIC are categorized as active treatment, while SEC is classified as withdrawal of care [14]. This classification enables accurate calculation of mortality rates among preterm infants, as well as the examination of the timing and causes of death, facilitating further analysis of independent risk factors associated with mortality.

Scientific definition of treatment ability for extremely preterm infants

The CARE-Preterm cohort study has played a pivotal role in scientifically defining the treatment ability for extremely preterm infants (EPIs) in China. In the current Chinese textbook, the definition of preterm birth

Table 1 Baseline characteristics of the preterm infants enrolled by year in CARE-Preterm cohort study

Variables	2018 (*N* = 2160)	2019 (*N* = 2469)	2020 (*N* = 2367)	2021 (*N* = 1841)	2022(*N* = 1610)	Total (*N* = 10447)
BW, n (%)	480–2590 g	400–2880 g	320–2700 g	420–2600 g	340–2980 g	320–2980 g
Range	1 (0.05)	7 (0.28)	4 (0.17)	5 (0.27)	6 (0.37)	23 (0.22)
<500 g	46 (2.13)	65 (2.63)	67 (2.83)	57 (3.10)	57 (3.54)	292 (2.80)
500–749 g	209 (9.68)	275 (11.14)	279 (11.79)	252 (13.69)	236 (14.66)	1251 (11.97)
750–999 g	529 (24.49)	599 (24.26)	527 (22.26)	456 (24.77)	392 (24.35)	2503 (23.96)
1000–1249 g	748 (34.63)	777 (31.47)	780 (32.95)	580 (31.50)	488 (30.31)	3373 (32.29)
1250–1500 g	627 (29.03)	746 (30.22)	710 (30.00)	491 (26.67)	431 (26.77)	3005 (28.76)
> 1500 g						
GA, n (%)	23^{+4}w -36^{+6}w	23^{+1}w -36^{+6}w	23^{+0}w -36^{+6}w	22^{+2}w -36^{+5}w	23^{+4}w-37^{+1}w	22^{+2}w -37^{+1}w
Range	1 (0.05)	4 (0.16)	2 (0.08)	10 (0.54)	2 (0.12)	19 (0.18)
<24w	31 (1.44)	46 (1.86)	55 (2.32)	65 (3.53)	62 (3.85)	259 (2.48)
24^{+0}-25^{+6}w	211 (9.77)	285 (11.54)	279 (11.79)	222 (12.06)	197 (12.24)	1194 (11.43)
26^{+0}-27^{+6}w	627 (29.03)	733 (29.69)	616 (26.02)	520 (28.25)	437 (27.14)	2933 (28.08)
28^{+0}-29^{+6}w	1022 (47.31)	1132 (45.85)	1097 (46.35)	803 (43.62)	689 (42.80)	4743 (45.40)
30^{+0}-31^{+6}w	268 (12.41)	269 (10.90)	318 (13.44)	221 (12.00)	223 (13.85)	1299 (12.43)
> 32^{+0}w						
Gender, n (%)	1159 (53.66)	1346 (54.52)	1254 (52.98)	1041 (56.55)	911 (56.58)	5711 (54.67)
Male	1001 (46.34)	1123 (45.48)	1113 (47.02)	800 (43.45)	699 (43.42)	4736 (45.33)
Female						
Singleton or Multiples, n (%)	1646 (76.20)	1870 (75.74)	1807 (76.34)	1327 (72.08)	1129 (70.12)	7779 (74.46)
Singleton	514 (23.80)	599 (24.26)	560 (23.66)	514 (27.92)	481 (29.88)	2668 (25.54)
Multiples						
Mortality, n (%)	296 (13.70)	273 (11.06)	213 (9.00)	194 (10.54)	146 (9.07)	1122 (10.74)
Withdrawal of care	126 (42.57)	126 (46.15)	113 (53.05)	96 (49.48)	95 (65.07)	556 (49.55)
Treatment failure	170 (57.43)	147 (53.85)	100 (46.95)	98 (50.52)	51 (34.93)	566 (50.45)
PS, n (%)	702 (32.50)	834 (33.78)	768 (32.45)	693 (37.64)	894 (55.53)	3891 (37.25)
Severe Complications, n (%)	158 (7.31)	163 (6.60)	165 (6.97)	172 (9.34)	90 (5.59)	748 (7.16)
BPD (moderate and severe)	98 (4.54)	101 (4.09)	66 (2.79)	41 (2.22)	37 (2.30)	343 (3.28)
ROP (> stage II)	79 (3.66)	81 (3.28)	85 (3.59)	50 (2.72)	40 (2.48)	335 (3.21)
IVH (> grade II)						
Maternal information						
Maternal age, years, *n* (%)	15 to 45 years	15 to 52 years	13 to 51 years	16 to 53 years	16 to 56 years	13 to 56 years
Range	566 (26.20)	576 (23.33)	522 (22.05)	346 (18.79)	323 (20.06)	2333 (22.33)
>35	1575 (72.92)	1865 (75.54)	1826 (77.14)	1478 (80.28)	1274 (79.13)	8018 (76.75)
20 to 35	19 (0.88)	28 (1.13)	19 (0.80)	17 (0.93)	13 (0.81)	96 (0.92)
<20						
Pregnancy complications, *n* (%)	515 (23.84)	641 (25.96)	636 (26.87)	562 (30.53)	408 (25.34)	2762 (26.44)
Maternal HDP	237 (10.97)	332 (13.45)	426 (18.00)	376 (20.42)	310 (19.25)	1681 (16.09)
Maternal diabetes	56 (2.59)	90 (3.65)	128 (5.41)	94 (5.11)	73 (4.53)	441 (4.22)
Chorioamnionitis						
PPROM, n (%)	669 (32.36)	650 (26.33)	663(28.01)	465 (25.26)	379 (23.54)	2826 (27.05)
< 24 h	251 (37.52)	230 (35.38)	260 (39.22)	202 (43.44)	124 (32.72)	1067 (37.76)
24 h to 1w	336 (50.22)	353 (54.31)	337 (50.83)	224 (48.17)	221 (58.31)	1471 (52.05)
> 1w	82 (12.26)	67 (10.31)	66 (9.95)	39 (8.39)	34 (8.97)	288 (10.19)
Antenatal steroids, n (%)	1597 (73.94)	1540 (62.37)	1570 (66.33)	1365 (74.14)	1142 (70.93)	7214 (69.05)
Incomplete course	711 (44.52)	556 (36.10)	612 (38.98)	448 (32.82)	379 (33.19)	2706 (37.51)
Complete course	886 (55.48)	984 (63.90)	958 (61.02)	917 (67.18)	763 (66.81)	4508 (62.49)
Cesarean section	1490 (68.98)	1654 (66.99)	1575 (66.54)	1313 (71.31)	1092 (67.83)	7124 (68.19)
Assisted pregnancy, n (%)	268 (12.41)	272 (11.02)	267 (11.28)	277 (15.05)	246 (15.28)	1330 (12.73)

BW: Birth weight, GA: Gestational age, w: Weeks, PS: Pulmonary surfactant, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, ROP: Retinopathy of prematurity, NEC: Necrotizing enterocolitis, HDP: Hypertension during pregnancy, PPROM: Preterm premature rupture of membranes

has been updated from GA 28w-37w to GA < 37w. However, the lower GA cut-off for active treatment is still unclear. In light of this, based on our previous single-center study, we conducted a multicenter study utilizing the CARE-Preterm cohort to assess the treatment ability of EPIs [17]. By assessing the survival rates without severe neurological injury (SNI) at different GA, the study indicated that infants born with GA 25w – 28w have comparable survival rates without severe complications to those born with GA > 28w. Thus, it suggested that the lower cut-off for the active treatment of preterm infants should be redefined based on the reliable treatment capacity in

Table 2 General characteristics and complications of the infants discharged alive from 2018 to 2022 in the CARE-Preterm cohort

Variables	Total (*N* = 9325) *n* (%)
Birth weight, g	450–2980 g
Range	1143 (12.26)
<1000 g	5541 (59.42)
1000–1500 g	2641 (28.32)
> 1500 g	
Gestational age, weeks	23^{+3}w – 37^{+1}w
Range	968 (10.38)
≤ 27^{+6}w	7102 (76.16)
28^{+0}-31^{+6}w	1255 (13.46)
> 32^{+0}w	
Male	5089 (54.57)
Singleton	7179 (76.99)
BPD	2415 (25.90)
Moderate and severe	701 (7.52)
ROP	1450 (15.55)
> stage II	274 (2.94)
IVH	1548 (16.60)
> grade II	183 (1.96)
NEC	480 (5.15)
> grade II	77 (0.83)
CH	193 (2.07)
EUGR	2863 (30.70)
Maternal age ≥ 35years	2590 (27.78)
Antenatal steroids	6466 (69.34)
Cesarean section	6456 (69.23)
Assisted pregnancy	1088 (11.67)

w: Weeks, BPD: Bronchopulmonary dysplasia, ROP: Retinopathy, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, CH: Congenital hypothyroidism, EUGR: Extrauterine growth retardation

China. The results of our study had been cited for the formulation of expert suggestions regarding the GA cut-off for EPIs to receive intensive care in China in 2022 [18]. The suggestion advanced the limit of treatment viability to GA 24w, which could greatly improve treatment confidence, reduce withdrawal of care, and promote the revision and optimization of perinatal policies in China.

Analysis of causes and risk factors of preterm death

We also analyzed the real mortality rate, main causes and risk factors of preterm birth based on the CARE-Preterm cohort [19]. The findings showed that the overall mortality rate among EPIs and extremely low birth weight infants (ELBWIs) was 39.1%. Among the deaths, 48.3% occurred after care withdrawal, while 51.7% were attributed to treatment failure. Our data showed that the GA and BW of infants who died after care withdrawal were larger compared to those who died after active treatment and treatment failure, indicating that they might have had a greater chance of survival if provided with more active treatment opportunities. Among the infants who died due to treatment failure, 25.8% passed away within the first week after birth. The top three causes of death in this group were sepsis, RDS, and severe asphyxia. Notably, sepsis was the main cause of death, highlighting the significance of addressing infection-related complications in preterm infants. Furthermore, the analysis of risk factors showed that admission hypothermia was an independent risk factor associated with treatment failure [18]. These findings emphasized the critical importance of perinatal management and early stabilization after birth as crucial periods for the treatment of preterm infants. They also underscored the urgent need for evidence-based practice for improving quality (EPIQ) projects to enhance the outcomes of preterm infants.

Conducting EPIQ projects on admission hypothermia

The management of moderate and severe admission hypothermia has a significant impact on the mortality and adverse prognosis of preterm infants [20]. Through a retrospective multicenter survey of admission hypothermia in VLBWIs, we found that the incidence of admission hypothermia was alarming high, reaching 89.3% in 2017. Moreover, the incidence of moderate and severe hypothermia was 43.8%, considerably higher than that observed in developed countries [20, 21]. To address this issue, an EPIQ project targeting admission hypothermia in VLBWIs was established in 2019 [22]. Through the project, the incidence of admission hypothermia in VLBWIs was reduced to 71.3% in 2021 among the participating NICUs, accompanied by a significant decrease of moderate and severe hypothermia (38.5%) [23, 24].

Intrauterine infection, hospital-acquired infection and use of antibiotics in NICU

Another major contribution of CARE-Preterm cohort study is to standardize the diagnosis of sepsis and the use of antibiotics in the participating NICUs [25–29]. Based on the cohort, we found that Escherichia coli (27.2%) and Klebsiella pneumonia (27.9%) were the main pathogenic bacteria of EOS and LOS, respectively, in VPIs with positive blood culture. Additionally, hospital-acquired LOS pathogens exhibited significant drug resistance (60.7%), raising concerns regarding this issue [30]. To address these challenges, we established a population pharmacokinetics (PPK) model-based dosing regimen for piperacillin/tazobactam to guide the standardized and effective use of antibiotics [31]. However, in VLBWIs without culture-proven sepsis or NEC, the overall antibiotic use rate (AUR) was 55%, significantly higher than that reported by the Canadian neonatal network (CNN) [32, 33], highlighting the issue of excessive antibiotics exposure among preterm infants in China (17%). Consequently, we plan to establish an antibiotic EPIQ project to formulate quality improvement measures with Chinese characteristics in the participating NICUs, so as to standardize the application of antibiotics among preterm infants.

Relationship between maternal HDP and prognosis of VPIs

By analyzing the causes of preterm birth in VPIs based on the CARE-Preterm cohort, we found that maternal HDP was the leading cause of preterm birth, with a prevalence of approximately 24.4%. Furthermore, we observed a close association between maternal HDP and the occurrence of several complications, such as CH [34–37]. Therefore, it is crucial to further investigate the impact of maternal diseases during pregnancy and perinatal management on the occurrence and outcomes of preterm birth and associated complications in future studies [38–41].

Discussion

CARE-Preterm cohort is a prospective, population-based, longitudinal, open, and real-time updated preterm birth cohort, which has a wide coverage and huge population base in Northern China, with 60 participating NICUs across eight densely-populated provinces. Until 2022, more than 10,000 preterm infants have been enrolled, and several researches have been conducted based on this cohort. The main results highlight substantial improvements in perinatal treatment capacities, and are expected to aid in enhancing the survival rate and life quality for preterm infants.

Since the 1980s, several developed countries have gradually established neonatal networks, such as the Vermont-Oxford Network (VON), the Canadian Neonatal Network (CNN), and the Spanish Neonatal Network [6, 42]. VON is an international network that includes over 1000 NICUs worldwide, with data on more than 20 million preterm infants. In 2014, the mortality rate for VLBWI within the VON is approximately 10.9% [43]. In our cohort, the mortality rate is 10.07%, slightly lower than that reported by VON. Besides, the proportion of EPI with GA < 28 weeks is only 14.9%, lower than in developed countries. It is important to note that our cohort included only preterm infants who are born alive or transferred alive to a NICU. These findings are due to the exclusion on non-referred infants who died in the delivery room or at non-NICU hospitals in the participating regions.

Our previous study has found that over 73% of death among EPI are related to care withdrawal, either in the delivery room or during NICU hospitalization, which is a common phenomenon in low- and middle-income countries influenced by socioeconomic factors [14]. This may explain the relatively lower proportion of EPI and lower mortality rate among VLBWIs in our cohort compared to the VON. To better understand the reasons behind care withdrawal, we have been collecting questionnaires from both parents and physicians when the decisions of care withdrawal are made, so as to reduce the rate of care withdrawal in our participating NICUs.

Despite this, the mortality rate for preterm infants with GA of 22 to 28 weeks is 17.8% in our cohort, which is significantly higher than the 12.4% reported by VON, indicating a significant gap compared to developed countries. In the following study, subjects are expected to be enrolled continuously. The mortality and outcomes of the preterm infants will be explored through more data analysis. Baseline characteristics of Chinese preterm infants will be provided based on the large population and geographical coverage, so as to optimize the diagnosis and treatment of various preterm-related diseases. At the same time, a long-term follow-up is planned to be conducted by connecting with the Child Health Care System and the Educational System of Shandong Province, and all participants are expected to be followed up until school age, so as to investigate the effect of perinatal management on the long-term prognosis of these preterm infants longitudinally.

The wide coverage of the CARE-Preterm cohort study enhances the representativeness of the cohort and increases the generalizability of the findings. Moreover, the prospective and longitudinal study design allows for the collection of data at multiple time points and enabling the examination of the long-term outcomes of preterm infants, which is expected to provide real-world evidence for improving the survival and prognosis of preterm infants by focusing on the management strategies related to the perinatal period, especially the implementation of international evidence-based guidelines. In addition, the study has a well-established study management organization, including a clinical research MDT and quality control team, which ensures the quality and rigor of the research protocol and data analysis.

There are also limitations in this study. Firstly, variations in medical resources and healthcare practices across the participating NICUs may introduce heterogeneity in the study population. To address this shortcoming, efforts have been made to formulate standardize diagnostic criteria and treatment processes, as well as to evaluate the medical resources and practices of each participating unit to mitigate this bias. Secondly, most studies based on this cohort are observational studies, and there might be missing data for some variables due to the nature of observational design. However, the cohort's open design and continuous data collection, along with its large population base, helps mitigate the potential bias caused by data missing. Additionally, although this cohort includes preterm infants from 60 NICUs across 8 provinces in Northern China, not all NICUs in these regions are included, which may introduce selection bias. Regional differences in medical conditions, geography, and socio-economic status may influence the results, limiting their generalizability to other regions or countries. Further research using government-level vital statistics

data could provide a more accurate assessment of birth and mortality rates in Northern China.

Conclusion

In conclusion, CARE-Preterm cohort allows innovative investigation of the impact of perinatal management on the adverse outcomes of preterm infants in Northern China. by sharing the study design and research methods, this cohort study aims to serve as a valuable reference for researchers in other low- and middle-income countries undergoing rapid industrialization, facilitating the conduction of population-based cohort study.

Supplementary Information

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Supplementary Material 1

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Author contributions
All authors contributed to the study conception and design. Ranran Shi analyzed the data and drafted the manuscript. Yonghui Yu designed the study and revised the manuscript. Simmy Reddy revised the grammar of the manuscript. Xiaoyu Dong, Li Wang and Wenwen Zhang collected and analyzed data of this manuscript.

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Data availability
The datasets generated and analyzed in this study are not publicly available before the publication of the related research. Researchers from other institutions can contact the corresponding author (YHY, alice20402@126.com) by email to apply for cooperation and obtain data by submitting detailed research protocols and ethical approval.

Declarations

Ethical approval and consent to participate
These projects have been authorized by the ethics committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (Approval number: (LCYJ: NO.2019 – 132) and registered in the Chinese Clinical Trial Registration Center (Registration number: ChiCTR1900025234, ChiCTR1900020861, ChiCTR2000037918, ChiCTR2000029162, ChiCTR2100053780 and ChiCTR2200066764). These studies are completed in accordance with the Declaration of Helsinki as revised in 2013.All researchers have signed the written informed consent and approved the submission of this manuscript and take full responsibility for the manuscript. All the parents or guardians of the participants have signed informed consent form to confirm that their data could be used for various studies.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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