Original Article

Analysis of In-hospital Neonatal Death in the Tertiary Neonatal Intensive Care Unit in China: A Multicenter Retrospective Study

Chen-Hong Wang[1], Li-Zhong Du[1], Xiao-Lu Ma[1], Li-Ping Shi[1], Xiao-Mei Tong[2], Hong Liu[3], Guo-Fang Ding[4], Bin Yi[5], Xin-Nian Pan[6], Dan-Ni Zhong[7], Ling Liu[8], Mei Li[9], Cui-Qing Liu[10], Shi-Wen Xia[11], Hong-Yun Wang[12], Ling He[13], Kun Liang[14], Xiao-Yu Zhou[15], Shu-Ping Han[16], Qin Lyu[17], Yin-Ping Qiu[18], Ruo-Bing Shan[19], De-Zhi Mu[20], Xiao-Hong Liu[21], Si-Qi Zhuang[22], Jing Guo[23], Li Liu[24], Jia-Jun Zhu[25], Hong Xiong[26]

[1]Department of Neonatal Intensive Care Unit, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310051, China
[2]Department of Pediatrics, Peking University Third Hospital, Beijing 100191, China
[3]Department of Neonatology, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China
[4]Department of Pediatrics, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China
[5]Department of Neonatology, Gansu Provincial Maternity and Children-care Hospital, Lanzhou, Gansu 730050, China
[6]Department of Neonatology, Guangxi Maternal and Child Health Hospital, Nanning, Guangxi 530003, China
[7]Department of Neonatology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, China
[8]Department of Neonatology, Guiyang Maternal and Child Health Care Hospital, Guiyang, Guizhou 550003, China
[9]Department of Neonatology, Harbin Children's Hospital, Harbin, Heilongjiang 150010, China
[10]Department of Neonatology, Children's Hospital of Hebei Province, Shijiazhuang, Hebei 050031, China
[11]Department of Neonatology, Hubei Maternity and Child Heath Hospital, Wuhan, Hubei 430070, China
[12]Department of Neonatal Intensive Care Unit, Inner Mongolia Maternal and Child Health Hospital, Huhhot, Inner Mongolia 010030, China
[13]Department of Neonatology, Jiangxi Provincial Children's Hospital, Nanchang, Jiangxi 330006, China
[14]Department of Pediatric, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, China
[15]Department of Neonatology, Nanjing Children's Hospital of Nanjing Medical University, Nanjing, Jiangsu 320100, China
[16]Department of Neonatology, Nanjing Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University, Nanjing, Jiangsu 210004, China
[17]Department of Neonatal Intensive Care Unit, Ningbo Women and Children's Hospital, Ningbo, Zhejiang 315012, China
[18]Department of Neonatology, General Hospital of Ningxia Medical University, Yinchuan, Ningxia 750004, China
[19]Department of Neonatology, Qingdao Women and Children's Hospital, Qingdao, Shandong 266000, China
[20]Department of Neonatology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China
[21]Department of Neonatology, Shenzhen Children's Hospital, Shenzhen, Guangdong 518026, China
[22]Department of Neonatology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510080, China
[23]Department of Neonatology, Tianjin Children's Hospital, Tianjin 300074, China
[24]Department of Neonatology, The First Affiliated Hospital of Medical School, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China
[25]Department of Neonatology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310006, China
[26]Department of Neonatology, Zhengzhou Children's Hospital, Zhengzhou, Henan 450007, China

The 5th to 29th authors' list is not ranked.

Abstract

Background: Globally, the proportion of child deaths that occur in the neonatal period remains a high level of 37–41%. Differences of cause in neonate death exist in different regions as well as in different economic development countries. The specific aim of this study was to investigate the causes, characteristics, and differences of death in neonates during hospitalization in the tertiary Neonatal Intensive Care Unit (NICU) of China.

Methods: All the dead neonates admitted to 26 NICUs were included between January l, 2011, and December 31, 2011. All the data were collected retrospectively from clinical records by a designed questionnaire. Data collected from each NICU were delivered to the leading institution where the results were analyzed.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.193458

Address for correspondence: Dr. Li-Zhong Du, Department of Neonatal Intensive Care Unit, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310051, China
E-Mail: dulizhong@zju.edu.cn

Received: 11-06-2016 **Edited by:** Yi Cui
How to cite this article: Wang CH, Du LZ, Ma XL, Shi LP, Tong XM, Liu H, Ding GF, Yi B, Pan XN, Zhong DN, Liu L, Li M, Liu CQ, Xia SW, Wang HY, He L, Liang K, Zhou XY, Han SP, Lyu Q, Qiu YP, Shan RB, Mu DZ, Liu XH, Zhuang SQ, Guo J, Liu L, Zhu JJ, Xiong H. Analysis of In-hospital Neonatal Death in the Tertiary Neonatal Intensive Care Unit in China: A Multicenter Retrospective Study. Chin Med J 2016;129:2652-8.

Results: A total of 744 newborns died during the 1-year survey, accounting for 1.2% of all the neonates admitted to 26 NICUs and 37.6% of all the deaths in children under 5 years of age in these hospitals. Preterm neonate death accounted for 59.3% of all the death. The leading causes of death in preterm and term infants were pulmonary disease and infection, respectively. In early neonate period, pulmonary diseases (56.5%) occupied the largest proportion of preterm deaths while infection (27%) and neurologic diseases (22%) were the two main causes of term deaths. In late neonate period, infection was the leading cause of both preterm and term neonate deaths. About two-thirds of neonate death occurred after medical care withdrawal. Of the cases who might survive if receiving continuing treatment, parents' concern about the long-term outcomes was the main reason of medical care withdrawal.
Conclusions: Neonate death still accounts for a high proportion of all the deaths in children under 5 years of age. Our study showed the majority of neonate death occurred in preterm infants. Cause of death varied with the age of death and gestational age. Accurate and prompt evaluation of the long-term outcomes should be carried out to guide the critical decision.

Key words: Cause-of-death; Mortality; Newborn; Retrospective Survey

Introduction

A worldwide analysis in 2009 estimated about 3.3 million babies died in the 1st month of life and more than half of all neonatal deaths occurred in five countries of the world. China was one of the countries.[1] Another large research in 2013 reported the proportion of deaths in children below 5 years of age in the neonatal (early and late) period increased from 33.4% in 1970 to 37.4% in 1990 and to 41.6% in 2013.[2] However, in low-income countries, neonatal mortality rates, trends, and causes have attracted relatively little attention compared to maternal deaths or deaths among older children under 5 years, and in international public health policy, neonatal deaths still do not receive attention commensurate with their burden.[3] Since the Millennium Development Goal 4 was set, which calls for a two-thirds reduction in mortality risks of children under 5 years of age between 1990 and 2015,[4] it has raised great concern in prevention of neonate death and promotion of newborn health.

Information on cause of death is lacking for most neonatal deaths that occur in countries with inadequate civil registration.[5] Causes of death in neonate have been estimated worldwide by analyzing the data of vital registration and reports of research studies in 2000.[5] There are variances of causes in neonate death in different regions, as well as in different countries of economic development. Given the considerable variations in health systems and individual countries, national and regional neonatal cause-of-death estimates are needed and should be a target for future estimation exercises and data collection.[6] Only few studies are about the neonate death in China, with most about the overall mortality, geographical disparities in mortality, and main cause of death, but lack of details of causes, perinatal factors, disparities in death based on gestational age (GA) or birth weight (BW), and hospital differentiation.

The specific aim of this study was to investigate the causes, characteristics, and differences of death in neonates during hospitalization in the tertiary Neonatal Intensive Care Unit (NICU) of China to improve the quality of perinatal medicine.

Methods

Study design

A collaborative study group for data collection was established within 26 tertiary hospitals of the Group for Neonatology of the Chinese Medical Association, including ten pediatric hospitals, nine maternal hospitals, and seven general hospitals. The NICUs from these hospitals are located in six Chinese regional areas, which are representatives of health facilities offering newborn intensive care in their respective areas.

The Children's Hospital of Zhejiang University School of Medicine agreed to coordinate this survey where all the data were collected and analyzed with confidence after received from other NICUs. This study was approved by the Ethics Committees of Children's Hospital of Zhejiang University School of Medicine and adopted by all the participating hospitals through local scientific committee approval. Informed consent was waived because this was a retrospective study, in which data were collected from observational parameters and no specific intervention as diagnosis or treatment was applied in the protocol.

Subjects and data collection

The inclusion population included all the newborns who died at the age of 0–27 days during hospitalization in these NICUs between January 1, 2011, and December 31, 2011. Four cases were excluded because their ages were unavailable being abandoned by parents. Data collected from these NICUs were based on a designed questionnaire including neonatal demographics, maternal status, major complications, cause of death, therapy, and cost of hospital stay. Information of this study was collected retrospectively from clinical records and neonatologist by a written survey.

Quality control

To collect data consistently, in each NICU, the same international criteria were followed to determine disease types and stages. To minimize bias among hospitals and investigators, we provided systematic training for the staff committed to the survey to ensure that all the records to be cross-checked by on-site physician and coordinator. Quality control was focused on completeness and accuracy of the contents in records by the on-site investigators, along with visiting, telephone, or email communication, for verification and correction of the data. At the end of the survey, we checked the numbers of neonate death and the total hospitalized neonatal numbers.

Definitions for the cause of neonatal death

Causes of neonatal death were classified among our following cause-of-death categories [Table 1], adapted from

Table 1: Case definitions for neonatal cause of death used for the study data

Cause-of-death category	Case definition accepted in study data
Infection	Sepsis, pneumonia, meningitis, diarrhea, virus infection (cytomegalovirus, herpes simplex virus, enterovirus), tetanus, syphilis
Neurologic diseases	Birth asphyxia, ICH, bilirubin encephalopathy
Pulmonary disease (noninfection)	NRDS, MAS, PPHN, pulmonary hemorrhage
CHD	Ventricular septal defect, coarctation of aorta, transposition of great arteries, hypoplastic left ventricle, patent ductus arteriosus, pulmonary atresia, etc.
GI diseases	GI abnormalities, necrotizing enterocolitis
IEM	Amino acid disorders, urea cycle disorders, organic acidemias, fatty acid oxidation, etc.
Other congenital abnormalities	Chromosomal diseases
Other	Specific cause of neonatal death not included in the above causes, including neonatal jaundice, hemolytic disease of newborn, hemorrhagic disease of the newborn, term baby dying due to in utero growth restriction, etc.

CHD: Congenital heart disease; IEM: Inborn errors of metabolism; NRDS: Neonatal respiratory distress syndrome; MAS: Meconium aspiration syndrome; PPHN: Persistent pulmonary hypertension of newborn; ICH: Intracranial hemorrhage; GI: Gastrointestinal.

Lawn *et al*.[5] using a hierarchical classification approach with each the conditions being sought in the order listed. A fixed hierarchy would be applied if authors applied more than one cause of death per neonate, in which the main disease of death was defined as the cause of death. We also contacted the authors for additional data regarding missing or unclear causes to allow allocation to a standard category.

In brief, for definition of GA, full term is defined as 37–42 complete weeks of gestation using the 1st day of last menstrual period. Preterm is defined as born before 37 weeks of GA. For definition of BW, it should be obtained as immediate measurement record (usually in the 1st h) by the attending caregivers. The diagnosis of infection is based on clinical symptoms and signs, evidence of focal lesions, or laboratory findings including blood cultures. Birth asphyxia is based on Apgar score below 7 at 5 min and severity of neonatal condition at admission, based on the presence of convulsions within the first 24 h. The diagnosis of intracranial hemorrhage was according to cranial ultrasound. Respiratory distress syndrome was diagnosed in infants with the onset of respiratory distress shortly after birth and a compatible chest radiograph appearance.[7] Meconium aspiration syndrome is defined as respiratory distress in newborn infants born through meconium-stained amniotic fluid whose symptoms cannot be otherwise explained.[8] Persistent pulmonary hypertension of the newborn is defined as the failure of the normal circulatory transition that occurs after birth, which is characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood.[9]

The criteria utilized in our survey for the diagnosis of necrotizing enterocolitis and for grading the severity of disease were based on Bell's stage.[10] Congenital malformation, including congenital heart diseases (CHDs), gastrointestinal (GI) abnormalities, inborn errors of metabolism (IEM), and other abnormalities, is based on the child's clinical presentation at admission and screening with the aid of X-ray, ultrasound scan, echocardiography, and computed tomography scan when applicable. Early and late neonatal periods are defined as 0–6 days of age and 7–27 days of age, respectively.

Statistical analysis

Excel database was used for datasheet recordings, and statistical analysis was performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the median and range, or the mean ± standard deviation (SD), depending on whether their distributions were or were not highly skewed. Comparisons of categorical variables were performed using the Pearson Chi-square test. The Mann-Whitney test or independent-samples test was applied for the comparisons of continuous variables. A value of $P < 0.05$ was considered statistically significant in all tests if applied.

Results

Perinatal data and demographics of all dead neonate

A total of 744 newborns died during the 1-year survey, accounting for 1.2% of all the neonates admitted to hospitals and 37.6% of all the deaths in children younger than 5 years in these 26 hospitals. Some missing numbers of the GA or BW were due to home deliveries or those not accessible by the staff of participating hospitals. Eighteen cases (2.4%) were born at home and their BW was unknown. Seventeen cases' GA was unknown, and they were deleted when analyzing the differences between dead infants with different GA. The mean GA of all the deaths was 33.9 ± 5.0 weeks, and mean BW was 2135.1 ± 975.1g with a male:female ratio of 477 (64.1%)/267 (35.9%). Of all the mothers, 319 (42.9%) underwent cesarean section deliveries, 147 (19.8%) multiple pregnancies, and 179 (24.1%) had pregnancy complications, including pregnant hypertension 64 (8.6%), gestational diabetes mellitus 20 (2.7%), intrahepatic cholestasis of pregnancy 7 (0.9%), premature rupture of membranes (PROM) 71 (9.5%), severe infections 13 (1.7%), and thyroid disorders 4 (0.5%). The mean admission age was 3.1 ± 5.7 days. There were 542 (72.8%) cases who died during the early neonatal period, of whom 229 (30.8%) died within 24 h of postnatal life. The average cost of NICU stay for each case was 10413.7 ± 1.8 China Yuan.

Distribution of deaths in neonates

Neonatal death mainly occurred in newborns with low BW, accounting for 58.7% of all the deaths, of which 9.9% cases were <1000 g, 24.6% 1000–1499 g, and 24.2% 1500–2499 g. There were 14 (1.9%) cases of macrosomia. A total of 441 (59.3%) dead neonates were preterm infants.

The percentages of neonate death in different GA were 18.4%, 28.0%, 12.8%, and 38.6% at ≤28, 29–33, 34–36, and >37 weeks GA, respectively [Table 2].

Differences between term and preterm dead infants

The mean GA and BW of all preterm dead infants were 30.5 ± 3.2 weeks and 1537.3 ± 659.6 g, compared to 39.1 ± 1.3 weeks and 3064.3 ± 586.0 g of term dead infants. Term infants had a higher rate of cesarean section than the preterm dead infants. The incidences of pregnancy complications, multiple pregnancy, and PROM were significantly higher in mothers of preterm infant than term infant [Table 3].

Differences among hospitals

NICUs participating in this study were divided into two groups: pediatric hospital, maternal/general hospital. Maternal/general hospital had the majority of deaths, accounting for 73.9% of all cases. The GA and BW of the deaths were lower in maternal/general hospitals than in pediatric hospitals. More very low birth weight (VLBW) and preterm cases died in maternal/general hospitals than pediatric hospitals. The incidences of pregnancy complications and multiple pregnancies in maternal/general hospitals were much higher than in pediatric hospitals [Table 4].

Causes of death in neonates during hospitalization

According to the classification of death, we divided the causes of death into four types. Of the total cases, 67 (9.0%) died within 12 h of admission despite the immediate resuscitation (Type 1), 161 (21.6%) died after aggressive treatment applied (Type 2). A total of 284 cases (38.2%) died after medical care withdrawal because of no improvement after treatment (Type 3), and 232 (31.2%) who might survive if receive continuing treatment died only because their parents worried about the long-term outcomes or some other reasons (Type 4). From the above classification, 512 neonates died from clear cause of death (Types 1–3) while the causes of death were hard to define for the left 232 cases who might survive if receive continuing treatment (Type 4).

Of the total 512 deaths, causes of death were analyzed based on the age of death and GA [Table 5]. In preterm death cases, pulmonary diseases (46.3%) caused the largest proportion of deaths, followed by infection (16.9%), neurologic diseases (16.3%), and GI diseases (10.1%). While in term death cases, infection (33.7%) was the most frequent causes, followed by neurologic diseases (17.3%), pulmonary diseases (15.3%), and CHDs (10.2%). In early neonate period, pulmonary diseases (56.5%) occupied the largest proportion of preterm deaths while infection (27%) and neurologic diseases (22%) were the two main causes of term deaths. In late neonate period, infection was the leading cause of both preterm and term neonate deaths.

Of the 232 cases who might survive if receive continuing treatment, there were 135 preterm infants, and of whom 85 were VLBW infants. For those preterm deaths, 56.3% (76/135) of cases died after medical care withdrawal because their parents worried about the long-term outcomes, and 43.7% because of poor economic status. For the term cases, about 80% (73/91) were given up because of the possible poor prognosis, and the leading disease was congenital abnormalities (40/91).

Table 2: Distribution of deaths in neonates based on birth weight and GA

Birth weight (g)	*n* (%)	GA (weeks)	*n* (%)
<1000	74 (9.9)	≤28	137 (18.4)
1000–1499	183 (24.6)	29–33	208 (28.0)
1500–2499	180 (24.2)	34–36	95 (12.8)
2500–4000	275 (37.0)	≥37	287 (38.6)
>4000	14 (1.9)	Unknown	17 (2.3)
Unknown	18 (2.4)	–	–

GA: Gestational age.

Discussion

With the development of economy and education all over the world, the global child mortality has declined obviously, but the neonatal death accounted for the proportion of deaths in children under 5 years of age rise instead.[5] In this 1-year survey, we found a total of 744 newborns died, accounting for 37.6% of all the deaths in children under 5 years of age in these 26 hospitals, which was close to some other studies.[2]

Table 3: Differences between term and preterm infants died during hospitalization

Variables	Preterm	Term	*P*
Cases	440 (59.1)	287 (38.6)	
Male	280 (63.6)	190 (66.2)	0.48
GA (weeks)	30.5 ± 3.2	39.1 ± 1.3	<0.001
BW (g)	1537.3 ± 659.6	3064.3 ± 586.0	0.076
Cesarean section	161 (36.6)	138 (48.1)	<0.001
Maternal age (years)	28.7 ± 5.6	27.9 ± 5.1	0.067
Multiple pregnancy	146 (33.2)	6 (2.2)	<0.050
Pregnancy complications	147 (33.4)	66 (23.0)	0.003
PROM	128 (29.1)	47 (16.5)	<0.050
Cost of hospitalization median (range) (CNY)	5986.0 (72.0–156200.0)	4055.5 (164.0–77315.0)	<0.001
Give-up	304 (69.1)	204 (71.1)	>0.050

Data were shown as *n* (%) or mean ± SD. GA: Gestational age; PROM: Premature rupture of membranes; BW: Birth weight; CNY: China Yuan.

Table 4: Differences between pediatric and maternal/general hospital

Variables	Pediatric hospital	Maternal/general hospital	*P*
Cases	194 (26.1)	550 (73.9)	
In-hospital mortality (%)	0.8	1.6	<0.001
Male (%)	64.9	63.8	0.778
GA (weeks)	34.6 ± 4.9	33.6 ± 5.0	0.017
BW (g)	2305.2 ± 989.5	2077.1 ± 961.5	0.004
VLBW	55 (28.4)	202 (36.7)	0.035
Preterm	101 (52.1)	339 (61.6)	0.020
Multiple pregnancy	25 (12.9)	122 (22.2)	0.005
Pregnancy complications	37 (19.1)	181 (32.9)	<0.001
PROM	13 (6.7)	58 (10.5)	0.117
Give-up	131 (67.5)	385 (70)	>0.050

Data were shown as *n* (%) or mean ± SD. GA: Gestational age; PROM: Premature rupture of membranes; VLBW: Very low birth weight; BW: Birth weight.

Table 5: Causes of death in neonates based on the death age and GA, *n* (%)

Causes	Preterm (*n* = 307)			Term (*n* = 196)		
	0–6 days	7–27 days	Total	0–6 days	7–27 days	Total
Infection	22 (9.6)	30 (39.0)	52 (16.9)	38 (27.0)	28 (50.9)	66 (33.7)
Neurologic diseases	44 (19.1)	6 (7.8)	50 (16.3)	31 (22.0)	3 (5.5)	34 (17.3)
Birth asphyxia	35 (15.2)	3 (3.9)	38 (12.4)	27 (19.1)	1 (1.8)	28 (14.3)
ICH	9 (3.9)	3 (3.9)	12 (3.9)	1 (0.7)	1 (1.8)	2 (1.0)
Pulmonary disease (noninfection)	130 (56.5)	12 (15.6)	142 (46.3)	27 (19.1)	3 (5.5)	30 (15.3)
NRDS	112 (48.7)	5 (6.5)	117 (38.1)	8 (5.7)	1 (1.8)	9 (4.6)
MAS	0	0	0	7 (5.0)	1 (1.8)	8 (4.1)
PPHN	7 (3.0)	0	7 (2.3)	9 (6.4)	1 (1.8)	10 (5.1)
Pulmonary hemorrhage	9 (3.9)	3 (3.9)	12 (3.9)	3 (2.1)	0	3 (1.5)
Congenital heart diseases	5 (2.2)	3 (3.9)	8 (2.6)	12 (8.5)	8 (14.5)	20 (10.2)
GI diseases	12 (5.2)	19 (24.7)	31 (10.1)	15 (10.7)	4 (7.3)	19 (9.7)
GI abnormalities	6 (2.6)	1 (1.3)	7 (2.3)	7 (5.0)	1 (1.8)	8 (4.1)
NEC	6 (2.6)	18 (23.4)	24 (7.8)	8 (5.7)	3 (5.5)	11 (5.6)
IEM	0	1 (1.3)	1 (0.3)	6 (4.3)	3 (5.5)	9 (4.6)
Other congenital abnormalities	5 (2.2)	0	5 (1.6)	4 (2.8)	1 (1.8)	5 (2.6)
Other	1 (0.4)	0	18 (5.9)	8 (5.7)	5 (9.1)	13 (6.6)

IEM: Inborn errors of metabolism; NEC: Necrotizing enterocolitis; GI: Gastrointestinal; NRDS: Neonatal respiratory distress syndrome; MAS: Meconium aspiration syndrome; PPHN: Persistent pulmonary hypertension of newborn; ICH: Intracranial hemorrhage; GA: Gestational age.

Globally, the proportion of deaths in children under 5 years of age that occurs in the neonatal period remained a high level of 37–44%.[2,11,12] Hence, increased attention on neonatal death is required as the epidemiology, cause-of-death distribution, and health interventions differ in older children.

In this survey, most of the death happened in the early neonatal period, about 72.8% cases died in early neonatal period, and of whom 30.8% died within 24 h of postnatal life. This is consistent with other studies both in China[13] and other countries where the majority of neonatal deaths also occurred during the early neonatal period.[6,14] Multiple analysis indicated that the majority of neonatal early deaths are associated with events surrounding delivery, pregnancy, and neonatal care following birth.[6]

Maternal status including health and education has a close relation to the neonate health.[2] In our study, 147 (19.8%) mothers underwent multiple pregnancies and 179 (24.1%) had pregnancy complications, which is significantly higher than the overall rate of all births. Approximately 10% of pregnancies have complications from a birth population-based regional survey of estimation of high-risk pregnancy contributing to perinatal morbidity and mortality in 2010 in China.[15] Moreover, multivariate logistic regression of this study revealed that pregnancy complications as well as multiple births, birth defects, and mothers' biological and social status were significantly associated with the neonatal outcome, indirectly reflecting the influence of pregnancy complications and other perinatal risks. Home birth with lack of sterilization, warming, resuscitation and other resources is another high-risk factor related to neonate death. Now, it mainly occurred in the relatively underdeveloped region, like in remote of China, Africa.[16,17] However, in our data, about 2.4% deaths were during home delivery, reminding us to pay more attention on the lack of accessibility to health services and knowledge of care-seeking/warning signs among parents.

According to the distribution of neonate death based on GA, the majority occurred in preterm infants, accounting for 59.1% of all the deaths in our study, with 18% of cases' GA <29 weeks. Our result is similar to the global epidemiology of 15 million preterm births, in which preterm birth estimated to be a risk factor in over 50% of all neonatal deaths.[18,19] However, preterm-associated death may be underestimated because infants with GA <28 weeks might be considered as abortion in some regions of China. During the retrospective study from the population-based Maternal and Child Health Surveillance System of China, Liang J[20] found the proportion of preterm births among the causes of neonatal death increased significantly from 33.6% in 2003 to 40.9% in 2008. One possible reason is the annually increased preterm birth rate. One report from the World Health Organization indicated that the preterm birth rate was more than 10% worldwide, and China was one of the top 10 countries that have the highest number of preterm births.[21] Preterm birth, especially the very preterm infant, has raised a high burden both in low- and high-income countries.[19]

Understanding the neonatal cause-of-death distribution plays an important role in identifying appropriate interventions. Preterm birth complications were estimated to be the leading cause of death in all regions of the world.[6] In our results, prematurity complications also remain the most frequent causes of neonatal death; pulmonary diseases, severe infection, and neurologic diseases were the left main causes, which were different to some previous studies in China in which birth asphyxia (24.5–28.6%) was the most frequent cause.[22,23] The relatively lower proportion of birth asphyxia in all causes may be due to the progress of neonatal resuscitation training and improved perinatal care all over the country.[24] However, birth asphyxia still accounts for a relatively higher proportion in our study than the developed countries in which preterm birth complications and congenital disorders are the leading causes of neonatal death.[6]

Congenital disorders including CHD, GI abnormalities, IEM, and other congenital abnormalities are other important reasons, accounting for about 15% of all the neonate deaths. Previous study also reported the proportion of deaths from congenital abnormalities increased from 6% to 11% in the period of 2000–2008.[22] Congenital disorder is becoming an increasing burden on the health-care resources in the developing countries.[25] Studies from developed countries such as the UK and the USA have reported an overall decreasing trend of congenital disorder and have attributed the decline to increasing prenatal diagnosis and termination of pregnancy.[26,27] Thus, importance of antenatal examination and consultation should be attached more for the parents to make proper planning and decision.

The cause-of-death distribution varied with several factors, including the age of death, GA, regions, and hospitals. In early neonate period, pulmonary diseases (56.5%) occupied the largest proportion of preterm deaths while infection (27%) and neurologic diseases (22%) were the two main causes of term deaths. In late neonate period, infection was the leading cause of both preterm and term neonate death. Compared with preterm cases in which pulmonary diseases account for nearly a half of the death, nearly one-third of term cases is due to infections. Hospital disparities in neonatal death distribution and cause of death were also showed in our study. Maternal/general hospital had the majority of deaths, with much higher in-hospital mortality than pediatric hospital (1.6% vs. 0.8%). One possible reason is that maternal/general hospitals have more percentage of preterm or VLBW neonates, which has raised a challenge of reducing neonatal mortality.[1] Our another study about the mortality of extremely low birth weight (ELBW) infants showed that the maternal/general hospitals have a lower survival rate than pediatric hospitals.[28] Another possible reason might be the higher incidence of pregnancy complications and multiple pregnancies in maternal/general hospitals.

Deaths after withdrawal from critical care accounted for a large proportion of total neonate death in our study, about two-thirds of neonates died after medical care withdrawal. Although more than half of all the withdraw decisions were made for infants due to the lethal disease progression, there was still a large proportion because of other reasons. One reason of withdraw decisions is partially related to the socioeconomic status, especially in the undeveloped regions. In a survey of geographical disparities in infant mortality, 10.7% of infant deaths in the untreated group in the remote region were due to financial difficulties.[13] Nevertheless, since the new national and local government-funded health-care insurance system termed "new rural co-operative health care" was launched nationwide in 2003, withdrawal due to parents' inability to afford the high cost of medical treatment was partly reduced.[29] On the contrary, concern about the long-term outcomes becomes another main reason, especially the neurodevelopmental impairment of VLBW or ELBW and those with congenital abnormalities. A nationwide survey in mainland of China showed a significant portion of ELBW infants (26.7%) died after withdrawal of medical care, accounting for more than half of all the deaths. Similarly, in another recent survey of ELBW infants in one province of China, it was reported that 30.3% infants died after medical care withdrawal[30] whereas multiple researches have proved most preterm births (>90%) survive without neurodevelopmental impairment.[31] Accurate and prompt evaluation of the long-term outcomes, and careful explanation of disease progression, though difficult, should be carried out to guide the important decision.

There are some limitations of this study. The study was not based on birth population and all NICUs are in tertiary hospitals, so the results are representative for neonate death in the Level III hospitals in China, but not for all the country. The fundamental criterion to recruit infant subjects was the neonates who were admitted and died at NICUs. Therefore, this study was mainly focused on the live-born neonates

whereas the stillbirth in the delivery room was not enrolled and there might be cases underreported who did not get access to health care, as well as those died after discharge.

In conclusion, neonate death still accounts for a high proportion of all the deaths in children under 5 years of age. Our study shows the majority of neonate death occurred in preterm infants. Cause of death varied with the age of death and GA. Accurate and prompt evaluation of the long-term outcomes should be carried out to guide the critical decision.

Financial support and sponsorship

This work was funded by grants from the National Key Technology Research and Development Program (No. 2012BAI04B04).

Conflicts of interest

There are no conflicts of interest.

References

1. Oestergaard MZ, Inoue M, Yoshida S, Mahanani WR, Gore FM, Cousens S, *et al*. Neonatal mortality levels for 193 countries in 2009 with trends since 1990: A systematic analysis of progress, projections, and priorities. PLoS Med 2011;8:e1001080. doi: 10.1371/journal.pmed.1001080.
2. Wang H, Liddell CA, Coates MM, Mooney MD, Levitz CE, Schumacher AE, *et al.* Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: A systematic analysis for the global burden of disease study 2013. Lancet 2014;384:957-79. doi: 10.1016/S0140-6736(14)60497-9.
3. Shiffman J. Issue attention in global health: The case of newborn survival. Lancet 2010;375:2045-9. doi: 10.1016/S0140-6736(10)60710-6.
4. You D, Wardlaw T, Salama P, Jones G. Levels and trends in under-5 mortality, 1990-2008. Lancet 2010;375:100-3. doi: 10.1016/S0140-6736(09)61601-9.
5. Lawn JE, Wilczynska-Ketende K, Cousens SN. Estimating the causes of 4 million neonatal deaths in the year 2000. Int J Epidemiol 2006;35:706-18. doi: 10.1093/ije/dyl043.
6. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000-2013. Bull World Health Organ 2015;93:19-28. doi: 10.2471/BLT.14.139790.
7. Bhakta KY. Respiratory distress syndrome. In: Cloherty JP, editor. Manual of Neonatal Care. 7th ed. Philadelphia: Little, Brown and Company; 2012. p. 406-16.
8. Fanaroff AA. Meconium aspiration syndrome: Historical aspects. J Perinatol 2008;28 Suppl 3:S3-7. doi: 10.1038/jp.2008.162.
9. Cabral JE, Belik J. Persistent pulmonary hypertension of the newborn: Recent advances in pathophysiology and treatment. J Pediatr (Rio J) 2013;89:226-42. doi: 10.1016/j.jped.2012.11.009.
10. Neu J. Necrotizing enterocolitis: The search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am 1996;43:409-32. doi: 10.1016/S0031-3955(05)70413-2.
11. Wardlaw T, You D, Hug L, Amouzou A, Newby H. UNICEF Report: Enormous progress in child survival but greater focus on newborns urgently needed. Reprod Health 2014;11:82. doi: 10.1186/1742-4755-11-82.
12. Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team 4 million neonatal deaths: When? Where? Why? Lancet 2005;365:891-900. doi: 10.1016/S0140-6736(05)71048-5.
13. Wang Y, Zhu J, He C, Li X, Miao L, Liang J. Geographical disparities of infant mortality in rural China. Arch Dis Child Fetal Neonatal Ed 2012;97:F285-90. doi: 10.1136/archdischild-2011-300412.
14. Gizaw M, Molla M, Mekonnen W. Trends and risk factors for neonatal mortality in Butajira District, South Central Ethiopia, (1987-2008): A prospective cohort study. BMC Pregnancy Childbirth 2014;14:64. doi: 10.1186/1471-2393-14-64.
15. Sun L, Yue H, Sun B, Han L, Tian Z, Qi M, *et al.* Estimation of high risk pregnancy contributing to perinatal morbidity and mortality from a birth population-based regional survey in 2010 in China. BMC Pregnancy Childbirth 2014;14:338. doi: 10.1186/1471-2393-14-338.
16. Li C, Yan H, Zeng L, Dibley MJ, Wang D. Predictors for neonatal death in the rural areas of Shaanxi Province of Northwestern China: A cross-sectional study. BMC Public Health 2015;15:387. doi: 10.1186/s12889-015-1738-x.
17. Debelew GT, Afework MF, Yalew AW. Determinants and causes of neonatal mortality in Jimma Zone, Southwest Ethiopia: A multilevel analysis of prospective follow up study. PLoS One 2014;9:e107184. doi: 10.1371/journal.pone.0107184.
18. Lawn JE, Kerber K, Enweronu-Laryea C, Cousens S. 3.6 million neonatal deaths – What is progressing and what is not? Semin Perinatol 2010;34:371-86. doi: 10.1053/j.semperi.2010.09.011.
19. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, *et al.* Born too soon: The global epidemiology of 15 million preterm births. Reprod Health 2013;10 Suppl 1:S2. doi: 10.1186/1742-4755-10-S1-S2.
20. Liang J, Mao M, Dai L, Li X, Miao L, Li Q, *et al.* Neonatal mortality due to preterm birth at 28-36 weeks' gestation in China, 2003-2008. Paediatr Perinat Epidemiol 2011;25:593-600. doi: 10.1111/j.1365-3016.2011.01232.x.
21. World Health Organization. Born Too Soon: The Global Action Report on Preterm Birth. Geneva: World Health Organization; 2012. Available from: http://www.who.int/maternal_child_adolescent/documents/born_too_soon/en/. [Last accessed on 2012 May 02].
22. Rudan I, Chan KY, Zhang JS, Theodoratou E, Feng XL, Salomon JA, *et al.* Causes of deaths in children younger than 5 years in China in 2008. Lancet 2010;375:1083-9. doi: 10.1016/S0140-6736(10)60060-8.
23. Sun L, Yue H, Sun B, Han L, Qi M, Tian Z, *et al.* Estimation of birth population-based perinatal-neonatal mortality and preterm rate in China from a regional survey in 2010. J Matern Fetal Neonatal Med 2013;26:1641-8. doi: 10.3109/14767058.2013.794208.
24. Xu T, Wang HS, Ye HM, Yu RJ, Huang XH, Wang DH, *et al.* Impact of a nationwide training program for neonatal resuscitation in China. Chin Med J 2012;125:1448-56. doi: 10.3760/cma.j.issn.0366-6999.2012.08.017.
25. Singh K, Krishnamurthy K, Greaves C, Kandamaran L, Nielsen AL, Kumar A. Major congenital malformations in Barbados: The prevalence, the pattern, and the resulting morbidity and mortality. ISRN Obstet Gynecol 2014;2014:651783. doi: 10.1155/2014/651783.
26. Dastgiri S, Stone DH, Le-Ha C, Gilmour WH. Prevalence and secular trend of congenital anomalies in Glasgow, UK. Arch Dis Child 2002;86:257-63. doi: 10.1136/adc.86.4.257.
27. Peller AJ, Westgate MN, Holmes LB. Trends in congenital malformations, 1974-1999: Effect of prenatal diagnosis and elective termination. Obstet Gynecol 2004;104(5 Pt 1):957-64. doi: 10.1097/01.AOG.0000142718.53380.8f.
28. Lin HJ, Du LZ, Ma XL, Shi LP, Pan JH, Tong XM, *et al.* Mortality and morbidity of extremely low birth weight infants in the mainland of China: A multi-center study. Chin Med J 2015;128:2743-50. doi: 10.4103/0366-6999.167312.
29. Meng Q, Xu K. Progress and challenges of the rural cooperative medical scheme in China. Bull World Health Organ 2014;92:447-51. doi: 10.2471/BLT.13.131532.
30. Collaborative Study Group for Extremely Preterm and Extremely Low Birth Weight Infants. Survival and mortality rate of extremely preterm and extremely low birth weight infants admitted to neonatology departments (in Chinese). Chin J Pediatr 2014;52:729-35. doi: 10.3760/cma.j.issn.0578-1310.2014.10.003.
31. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, *et al.* Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatr Res 2013;74 Suppl 1:17-34. doi: 10.1038/pr.2013.204.