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

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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 neonatal 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 1, 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.
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.[3] 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
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. 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, ultrasonic 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 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. The average cost of NICU stay within 24 h of postnatal life. The average cost of NICU stay 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).

**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]
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%.\textsuperscript{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\textsuperscript{13} and other countries where the majority of neonatal deaths also occurred during the early neonatal period.\textsuperscript{6,14} Multiple analysis indicated that the majority of neonatal early deaths are associated with events surrounding delivery, pregnancy, and neonatal care following birth.\textsuperscript{6}

Maternal status including health and education has a close relation to the neonate health.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

### 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          |
| Infection                          | 22 (9.6)          | 30 (9.0)      | 52 (16.9)      |
| Neurologic diseases                | 44 (19.1)         | 6 (7.8)       | 50 (16.3)      |
| Birth asphyxia                     | 35 (15.2)         | 3 (3.9)       | 38 (12.4)      |
| ICH                                | 9 (3.9)           | 3 (3.9)       | 12 (3.9)       |
| Pulmonary disease (noninfection)   | 130 (56.5)        | 12 (15.6)     | 142 (46.3)     |
| NRDS                               | 112 (48.7)        | 5 (6.5)       | 117 (38.1)     |
| MAS                                | 0                 | 0             | 0              |
| PPHN                               | 7 (3.0)           | 0             | 7 (2.3)        |
| Pulmonary hemorrhage               | 9 (3.9)           | 3 (3.9)       | 12 (3.9)       |
| Congenital heart diseases          | 5 (2.2)           | 3 (3.9)       | 8 (2.6)        |
| GI diseases                        | 12 (5.2)          | 19 (24.7)     | 31 (10.1)      |
| GI abnormalities                   | 6 (2.6)           | 1 (1.3)       | 7 (2.3)        |
| NEC                                | 6 (2.6)           | 18 (23.4)     | 24 (7.8)       |
| IEM                                | 0                 | 1 (1.3)       | 0 (0.3)        |
| Other congenital abnormalities     | 5 (2.2)           | 0             | 5 (1.6)        |
| Other                              | 1 (0.4)           | 0             | 18 (5.9)       |

|                          | 0–6 days | 7–27 days | Total     |
|--------------------------|----------|-----------|-----------|
| Inborn errors of metabolism | 0       | 1 (1.3)   | 1 (0.3)   |
| NEC                      | 6 (2.6)  | 18 (23.4) | 24 (7.8)  |
| PPHN                     | 7 (3.0)  | 0         | 7 (2.3)   |
| Pulmonary hemorrhage     | 9 (3.9)  | 3 (3.9)   | 12 (3.9)  |
| Congenital heart diseases| 5 (2.2)  | 3 (3.9)   | 8 (2.6)   |
| GI diseases              | 12 (5.2) | 19 (24.7) | 31 (10.1) |
| GI abnormalities         | 6 (2.6)  | 1 (1.3)   | 7 (2.3)   |
| NEC                      | 6 (2.6)  | 18 (23.4) | 24 (7.8)  |
| IEM                      | 0        | 1 (1.3)   | 0 (0.3)   |
| Other congenital abnormalities | 5 (2.2) | 0         | 5 (1.6)   |
| Other                    | 1 (0.4)  | 0         | 18 (5.9)  |

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.
According to the distribution of neonatal 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.\textsuperscript{[18,19]} Prematurity complications were estimated to be the leading cause of death in all regions of the world.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[6]}

Congenital disorders including CHD, GI abnormalities, IEM, and other congenital abnormalities are other important reasons, accounting for about 15% of all the neonatal deaths. Previous study also reported the proportion of deaths from congenital abnormalities increased from 6% to 11% in the period of 2000–2008.\textsuperscript{[22]} Congenital disorder is becoming an increasing burden on the health-care resources in the developing countries.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[11]} 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.\textsuperscript{[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 withdrawal 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.\textsuperscript{[13]} Nevertheless, since the 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.\textsuperscript{[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\textsuperscript{[30]} whereas multiple researches have proved most preterm births (>90%) survive without neurodevelopmental impairment.\textsuperscript{[11]} 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.

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**Conflicts of interest**
There are no conflicts of interest.

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