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Clinical characteristics, and outcomes of severe neonatal thrombocytopenia: a retrospective cohort study in China

Yuanyuan Shan[1†], Ting Peng[2†], Peng Zhang[2] and Guoqiang Cheng[2,3*]

Abstract

Background Severe neonatal thrombocytopenia, as a rare but life-threatening disease with multiple etiologies, has limited relevant reports in China. The single-center study was performed in a severe thrombocytopenic cohort to improve the prognosis of this disease.

Methods We included all the patients diagnosed with severe thrombocytopenia (platelet counts ≤ 50×10^3/μL) in our institution between October 2016 and February 2021, and retrospectively reviewed their electronic records. Comparisons were made according to etiology and outcome.

Results Among the 5819 inpatients, 194 with severe thrombocytopenia were included in this study, with 64.4% of the cases manifesting thrombocytopenia within 72 h of life. The highest incidence was recorded among extremely low birth weight neonates (6.5%). The main etiologies included sepsis (22.2%), genetic syndromes (14.4%), perinatal asphyxia (9.8%), necrotizing enterocolitis (NEC; 8.8%), and cytomegalovirus infection (6.7%). The median platelet nadir was 5.0×10^3/μL [IQR:2.0×10^3/μL-16.0×10^3/μL], and 112 patients developed very severe thrombocytopenia (platelet counts ≤ 30×10^3/μL), of which 21.4% were associated with late-onset sepsis. In 45 culture-positive cases, the gram-negative group had a lower level of platelets (mean [SD]: 28 [11]×10^3/μL) as compared to the gram-positive group (mean [SD]: 39 [12]×10^3/μL). A total of 120 cases (61.9%) exhibited evidence of hemorrhage, with patients diagnosed with NEC demonstrating the highest incidence of hemorrhage at 58.8%. The platelet counts took a median of 10 days to recover: 11 and 7 days for early and late-onset cases; 15 days without and 21 days with platelet transfusions, respectively. The overall mortality rate was 26.8%. The causes of severe thrombocytopenia in 32.7%, 19.2%, and 17.3% of patients who died were identified as sepsis, birth asphyxia, and NEC, respectively. The levels of PT ($P=0.025$), APTT ($P=0.046$), and lactate ($P=0.028$) were lower among surviving patients.

Conclusions Sepsis, genetic syndromes, and perinatal asphyxia are the predominant etiologies of severe neonatal thrombocytopenia in China. The overall prognosis of severe neonatal thrombocytopenia is poor, but its severity and outcome were related to laboratory results (PT, APTT, and lactate) and the underlying etiology.

Keywords Thrombocytopenia, Neonates, Platelet transfusion, Hemorrhage

†Yuanyuan Shan and Ting Peng contributed equally to this work.

*Correspondence:
Guoqiang Cheng
gqcheng_cm@fudan.edu.cn

[1]Department of Pediatric Intensive Care Unit, National Children's Medical Center, Children's Hospital of Fudan University, Shanghai, China
[2]Department of Neonatology, National Children's Medical Center, Children's Hospital of Fudan University, Shanghai, China
[3]Fujian Key Laboratory of Neonatal Diseases, Xiamen Children's Hospital, 92 Yibin Road, Xiamen, Fujian 361000, China

Introduction

Thrombocytopenia, defined as a platelet count < 150×10^3/μL, occurs in 20 to 35% of patients admitted to the neonatal intensive care unit (NICU) [1]. A small minority (2.1–10%) developed severe neonatal thrombocytopenia (platelet count ≤ 50×10^3/μL), but such patients are at increased risks of severe consequences, such as intraventricular hemorrhage (IVH) and death, compared to those with mild or moderate thrombocytopenia, making it a common concern for neonatologists [2, 3]. Additionally, the severity of neonatal thrombocytopenia significantly influences platelet transfusion decisions. However, most of the published reports of neonatal thrombocytopenia include mild to severe patients, with limited data for severe thrombocytopenic neonates.

The objective of this study was to provide a comprehensive description of the etiological spectrum, clinical features and outcomes of severe neonatal thrombocytopenia in a monocentric cohort. Additionally, we explored risk factors for prolonged thrombocytopenia and death. Our findings may help clinicians to understand the causes of severe neonatal thrombocytopenia and develop personalised treatment plans based on the causes, thereby enhancing efficacy and improving prognosis.

Methods

All neonates with a diagnosis of severe thrombocytopenia admitted to the NICU of the Children's Hospital of Fudan University, a tertiary care center in China, from October 2016 to the end of February 2021 were included retrospectively for analysis. Local ethical approval for the study was obtained.

Patients

Neonates with at least one episode of severe thrombocytopenia (defined as a platelet count ≤ 50×10^3/μL, confirmed by a peripheral blood smear) during their hospital stay were incorporated into the cohort. We excluded inpatients: (i) undergoing exchange transfusion; (ii) whose clinical data were missing.

Data collection

Onset of thrombocytopenia and the date on which severe thrombocytopenia was diagnosed were collected. Maternal data included mode of delivery, aids in delivery, and maternal diseases such as diabetes mellitus, pre-eclampsia, immune thrombocytopenic purpura, and systemic lupus erythematosus. The following perinatal and neonatal characteristics were collected: multiple births; Apgar score at 1 and 5 min; history of premature rupture of the membrane; sex; GA in weeks, categorized as term (≥ 37 weeks), moderate to late preterm (32-37 weeks), very preterm (< 32 weeks); and BW in grams, categorized as normal (≥ 2500 g), low (1500–2499 g), very low (VLBW; 1000–1499 g), and extremely low (ELBW; < 1000 g). In addition, various types of hemorrhage, coagulation disorders, sepsis, chromosomal disorders, NEC, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, patent ductus arteriosus, platelet counts, time of onset, treatment (platelet transfusions and mechanical ventilation), durations of hospital stay and thrombocytopenia, and outcomes were collected. The primary outcome was death at discharge. Secondary outcomes were hemorrhage, the number of platelet-transfusion episodes per participant, receipt of at least one platelet transfusion, the rate of thrombocytopenia recovery before discharge, and the duration of thrombocytopenia. Data from all patients were collected until they were transferred to other hospitals, discharged, or deceased.

Definitions

Thrombocytopenic cases (platelet count < 150×10^3/μL) were classified as either early-onset (manifesting within the first 72 h of life) and late-onset (after 72 h of life). The severity of thrombocytopenia was further categorized into severe (platelet count $31–50 \times 10^3$/μL) and very severe (platelet count ≤ 30×10^3/μL) subgroups based on the platelet nadir. PMI (platelet mass index) is the product of platelet count and mean platelet volume. Neonatal sepsis was defined as (I) positive blood culture; (II) clinical signs of infection with the presence of two or more non-specific test indicators, including: (a) decreased white blood cell (WBC) count (< 5×10^3/μL) or increased WBC (> 25×10^3/μL for ≤ 3 d; > 20×10^3/μL for > 3 d); (b) the ratio of rod-shaped nucleated cells to neutrophils (I/T) > 0.16; (c) serum C-reactive protein (CRP) level ≥ 8 mg/L; (d) platelet count ≤ 100×10^3/μL; (e) erythrocyte sedimentation ≥ 15 mm/h. Sepsis was divided into early-onset sepsis (EOS; onset within the first 72 h of life) and late-onset sepsis (LOS; onset after 72 h of life). An Apgar score < 7 at 1 and 5 min was considered a low Apgar score. Neonatal asphyxia was diagnosed with an Apgar score < 7 at 1 and 5 min without establishing spontaneous respiration and an umbilical artery pH < 7.2. Severe neonatal asphyxia was diagnosed with an Apgar score ≤ 3 at 1 min or an Apgar score ≤ 5 at 5 min and an umbilical artery pH < 7.0. IVH was detected using cranial ultrasonography or magnetic resonance imaging and graded according to Papile et al. [4]. Genetic testing was implemented in cases of severe thrombocytopenia that were refractory to treatment (platelet transfusions, adrenocortical hormone, etc.) or accompanied by a family history of thrombocytopenia. The criteria for platelet transfusion in our unit were as follows: (I) platelet count < 50×10^3/μL, unstable (mechanical ventilation or vasopressors), and (or) overt bleeding; (II) platelet count < 30×10^3/μL, preterm or unstable (mechanical

ventilation or vasopressors); (III) platelet count < 20×10^3/μL. Normalization of thrombocytopenia was defined as two episodes of platelet count > 150×10^3/μL with an interval of 24 h.

Statistical analysis

Data were analyzed using SPSS Statistics (version 20.0; SPSS, Chicago, Illinois, USA). Quantitative data are represented as mean and standard deviation (SD), or median and interquartile range (IQR, P_{25}-P_{75}). Data were compared using Student's t-test or one-way ANOVA. Qualitative data are presented as numbers and percentages and were compared using either the chi-square test or Fisher's exact test. The Mann-Whitney test and Fisher's exact test were used to compare outcomes. A *P*-value < 0.05 in all statistical tests was judged to be significant.

Patient and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Total patient population

In total, 5819 neonates were admitted to our NICU during the study period and 194 (3.3%) neonates with severe thrombocytopenia were ultimately enrolled in this study (Fig. 1), of whom 69 (35.6%) presented thrombocytopenia within the first 72 h of life and 125 (64.4%) after 72 h. Very severe thrombocytopenia was found in 82 (42.3%) cases. As shown in Table 1, of the 194 included neonates, 95 (49.0%), 44 (22.7%) and 21 (10.8%) weighed < 2500, < 1500 and < 1000 g, respectively. The median birth weight (BW) was 2560 (IQR: 1610–3200) g, and the median gestational age (GA) of life was 37.1 (IQR: 35.4–39.0) weeks. In total, 93 (47.9%) patients were born preterm, among which 45 (23.2%) and 13 (6.7%) were born at less than 32 and 28 weeks of gestational age, respectively. Severe thrombocytopenia was observed in 21 (point estimate: 6.5%, 95% CI: 3.6–9.4%) and 173 (point estimate: 3.1%, 95% CI: 1.8–4.4%) neonates with BW < 1000 g and ≥ 1000 g, respectively. By doing comparative analysis by applying ANOVA, it was noted that the lower the birth weight, the lower the platelet level ($P = 0.018$). However, the other parameters were not statistically significant: gender, $P = 0.255$; gestational age, $P = 0.068$; and mode of delivery, $P = 0.501$.

Etiologies

The etiology of severe neonatal thrombocytopenia was identified in 190 (98.0%) patients. Sepsis was the most commonly identified etiology, occurring in 37.6% (73/194, [43 EOS, 30 LOS]) of the patients, followed by genetic defects (28/194, 14.4%) and neonatal asphyxia (19/194, 9.8%) (Table 2). The sepsis group included 45 (45/73, 61.6%) neonates with positive blood culture. The top three organisms in the culture-positive cases were E.coli ($n = 8$), Klebsiella ($n = 6$), and Enterobacter cloacae ($n = 5$). In the cases of gram-negative organisms, the level of platelets (mean: 28×10^3/μL, SD: 11×10^3/μL) was lower as compared to gram-positive organisms (mean: 39×10^3/μL, SD: 12×10^3/μL), with a *p* value of 0.030. Very severe neonatal thrombocytopenia was significantly associated with sepsis and predominantly with LOS ($P = 0.006$). Wiskott-Aldrich syndrome (WAS) accounted for 25.0% (7/28) of the genetic defect group, and other gene mutations related with thrombocytopenia included GATA1 ($n = 3$, 10.7%), PTPN11 ($n = 3$, 10.7%), UNC13D ($n = 2$, 7.1%), TUBB1 ($n = 2$, 7.1%), ANKRD26 ($n = 2$, 7.1%), PCCB ($n = 2$, 7.1%), SLFN14 ($n = 1$, 3.6%) and ITGA2B ($n = 1$, 3.6%). The asphyxia group in our series included nineteen patients, of whom fifteen had severe neonatal asphyxia and underwent therapeutic hypothermia. NEC ($n = 17$) and congenital cytomegalovirus (CMV) infection ($n = 13$) accounted for 8.8% and 6.7% of the patients, respectively. In addition, the etiology could not be determined in 2.1% (4/194) of the patients, and they did not undergo trio whole exome sequencing (trio-WES) or bone marrow puncture due to critical condition or family member refusal.

Clinical features and laboratory data

Figure2 shows the day of life on which severe thrombocytopenia was recognized. Severe thrombocytopenia was first recognized at a median age of 5 (IQR: 2–16) days, with 50% detected by day 5, 75% by day 16, and 95% by day 40 after birth. Patients with birth asphyxia were diagnosed at the youngest age (median: 1 day, IQR: 1–3.5 days). In contrast, patients with NEC were diagnosed at the oldest age (median: 6 days, IQR: 4–15 days). Family history of repeated miscarriages, neonatal death was most common among the genetic defect group (35.7%, 10/28); and maternal diabetes was most common among the sepsis group (27.4%, 20/73).

Table 3 shows hematological parameters, C-reactive protein (CRP) and lactate levels in neonates with severe thrombocytopenia. The mean (SD) platelet nadir in this cohort was 26.0 (14.0) × 10^3/μL. The platelet level was lower in the sepsis-associated group [mean (SD) 21.5 (18.6) × 10^3/μL], and the LOS subgroup had lower platelet nadir than the EOS subgroup [mean (SD) 23.3 (13.4)×10^3/μL vs. 27.7 (13.5)×10^3/μL; $P = 0.032$]. By doing comparative analysis, it was found that the higher the CRP level, the lower the platelet level ($F = 4.545$, $P = 0.010$). Lactate levels negatively correlated with platelet counts with a *p* value of 0.184.

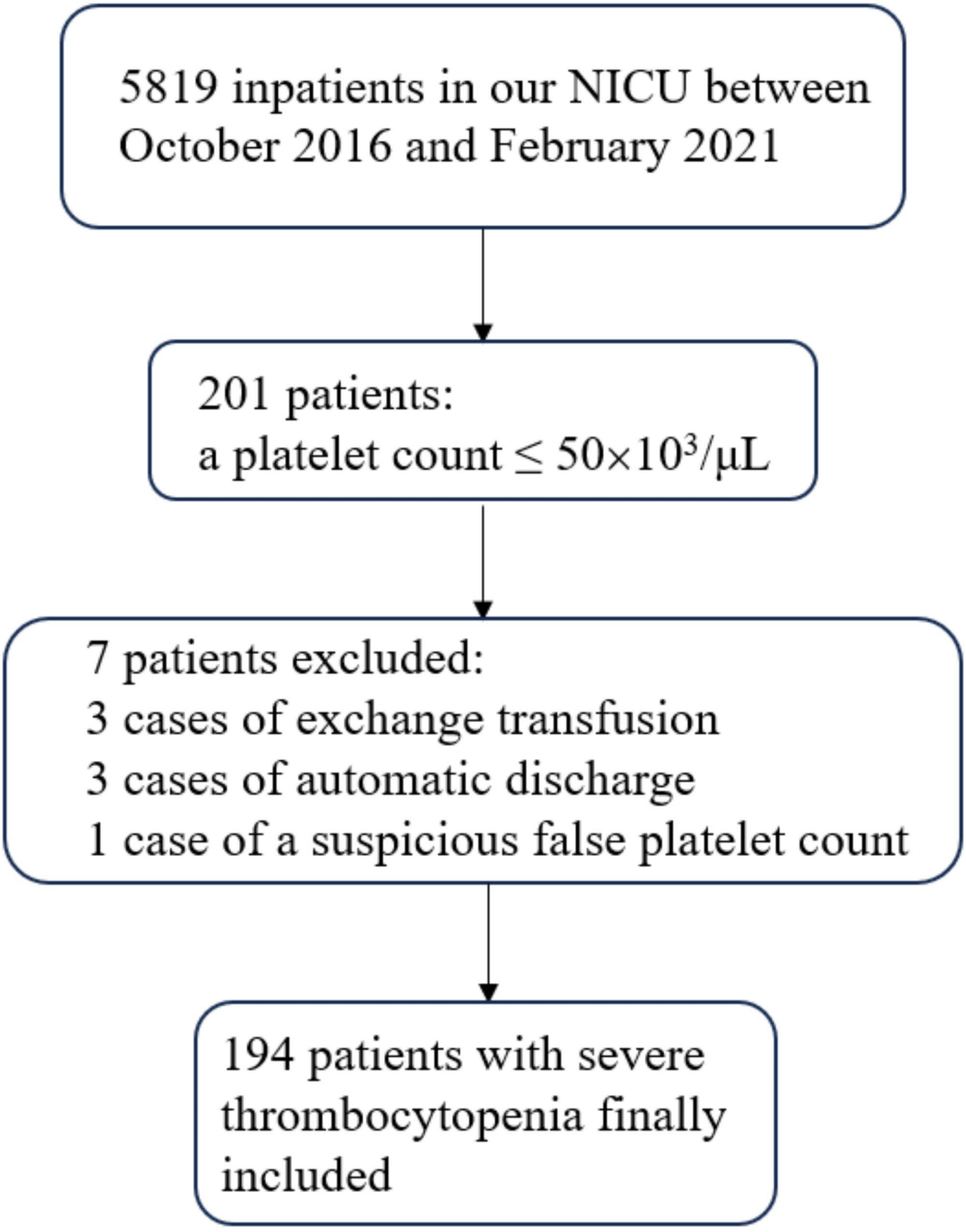

Fig. 1 Case ascertainment in the severe neonatal thrombocytopenia group

Table 1 Baseline maternal and neonatal characteristics

Variables	Summary
Mother's age(years)	30.4 ± 4.9
Multifetation	35 (18.0%)
Caesarean section	118 (60.8%)
PROM > 24 h	22 (11.3%)
Maternal diabetes	33 (17.0%)
Maternal preeclampsia	18 (9.3%)
Maternal ITP or SLE	9 (4.6%)
Birth weight(gram)	2560 (1610–3200)
VLBW	44 (22.7%)
ELBW	21 (10.8%)
Gestational age(weeks)	37.1 (35.4–39.0)
< 32	45 (23.2%)
< 28	13 (6.7%)
Male	128 (66.0%)
5 min Apgar score	8 (6–9)

PROM premature rupture of membrane; *ITP* immune thrombocytopenic purpura; *SLE* systemic lupus erythematosus; *VLBW* very low birth weight; *ELBW* extremely low birth weight.

Platelet transfusions and outcomes

As illustrated in Table4, the results concerning platelet transfusion treatment and outcomes are presented. Over one third ($n=69$, 35.6%) of the 194 patients received more than one platelet transfusion (median: 1 [range: 1–10]). Among those with platelet nadir between 30 and 50×10^3/ μL, only 6 (5.4%) neonates received platelet transfusions due to critical conditions. Very severe thrombocytopenia was signifcantly associated with a higher rate of platelet transfusions (point estimates with 95% CI: 76.8% [54.6–99.0%] vs. 5.4% [1.1–9.7%]). Neonates with NEC received the highest number of platelet transfusions (IQR: 1–3 [range: 0–10].

The platelet counts took a median (IQR) of 10 (4.5–30.5) days to recover; 11 (6–25.5) days for early-onset and 7 (5–16) days for late-onset cases ($P=0.046$). The median duration of thrombocytopenia was 15 days without platelet transfusions versus 21 days with platelet transfusions, respectively (Table 4). However, the decreased platelet nadir did not increase the duration of thrombocytopenia ($P=0.187$). Thrombocytopenia persisted in 50 patients at discharge and 45 patients at death. Of the 95 unrecovered patients, 42 (44.2%), 37 (38.9%), and 16 (16.8%) still had mild, moderate, and severe thrombocytopenia, respectively.

Hemorrhage was detected in 120 (61.9%) cases, including the skin (62.5%, 75/120), gastrointestinal tract (20.0%, 24/120), lungs (15.0%, 18/120), intracranial space (45.0%, 54/120), and umbilicus (9.2%, 11/120). Neonates with very severe thrombocytopenia had a higher incidence rate of hemorrhage (77.8%) than those with the platelet nadir between 30 and 50×10^3/μL (53.5%). Among neonates with different etiologies, the rate of hemorrhage was highest in patients with NEC ($n=10$, 58.8%) and

Table 2 Etiologies in different subgroups categorized by onset time of thrombocytopenia and platelet nadir

Diagnosis	Summary ($n=194$)	Onset of thrombocytopenia		*P* value	Platelet nadir($\times10^9$/L)		*P* value
		≤ 72 h ($n=125$)	> 72 h ($n=69$)		< 30 ($n=112$)	30–50 ($n=82$)	
Early onset sepsis	43 (22.2)	30 (24.0)	13 (18.8)	0.408	25 (22.3)	18 (22.0)	0.951
Late onset sepsis	30 (15.5)	12 (9.6)	18 (26.1)	0.003	24 (21.4)	6 (7.3)	0.007
CMV infection	13 (6.7)	9 (7.2)	4 (5.8)	0.941	7 (6.3)	6 (7.3)	0.769
Asphyxia	19 (9.8)	17 (13.6)	2 (2.9)	0.016	10 (8.9)	9 (11.0)	0.636
NEC	17 (8.8)	3 (2.4)	14 (20.3)	0.000	11 (9.8)	6 (7.3)	0.542
Post-surgery	2 (1.0)	2 (1.6)	0 (0)	0.539	0 (0)	2 (2.4)	0.346
Hemolytic disease	6 (3.1)	5 (4.0)	1 (1.4)	0.425	1 (0.9)	5 (6.1)	0.099
Genetic	28 (14.4)	21 (16.8)	7 (10.1)	0.207	21 (18.8)	7 (8.5)	0.046
Chromosomal anomalies	3 (1.5)	2 (1.6)	1 (1.4)	1.000	1 (0.9)	2 (2.4)	0.785
Metabolic disorders	9 (4.6)	4 (3.2)	5 (7.2)	0.354	4 (3.1)	5 (6.1)	0.631
KMP	8 (4.1)	6 (4.8)	2 (2.9)	0.714	3 (2.7)	5 (6.1)	0.414
NAT	12 (6.2)	10 (8.0)	2 (2.9)	0.219	4 (3.6)	8 (9.8)	0.077
Idiopathic	4 (2.1)	4 (3.2)	0 (0)	0.299	1 (0.9)	3 (3.7)	0.408

CMV cytomegalovirus, *NEC* necrotizing enterocolitis, *KMP* Kasabach-Merritt phenomenon, *NAT* neonatal alloimmune thrombocytopenia.

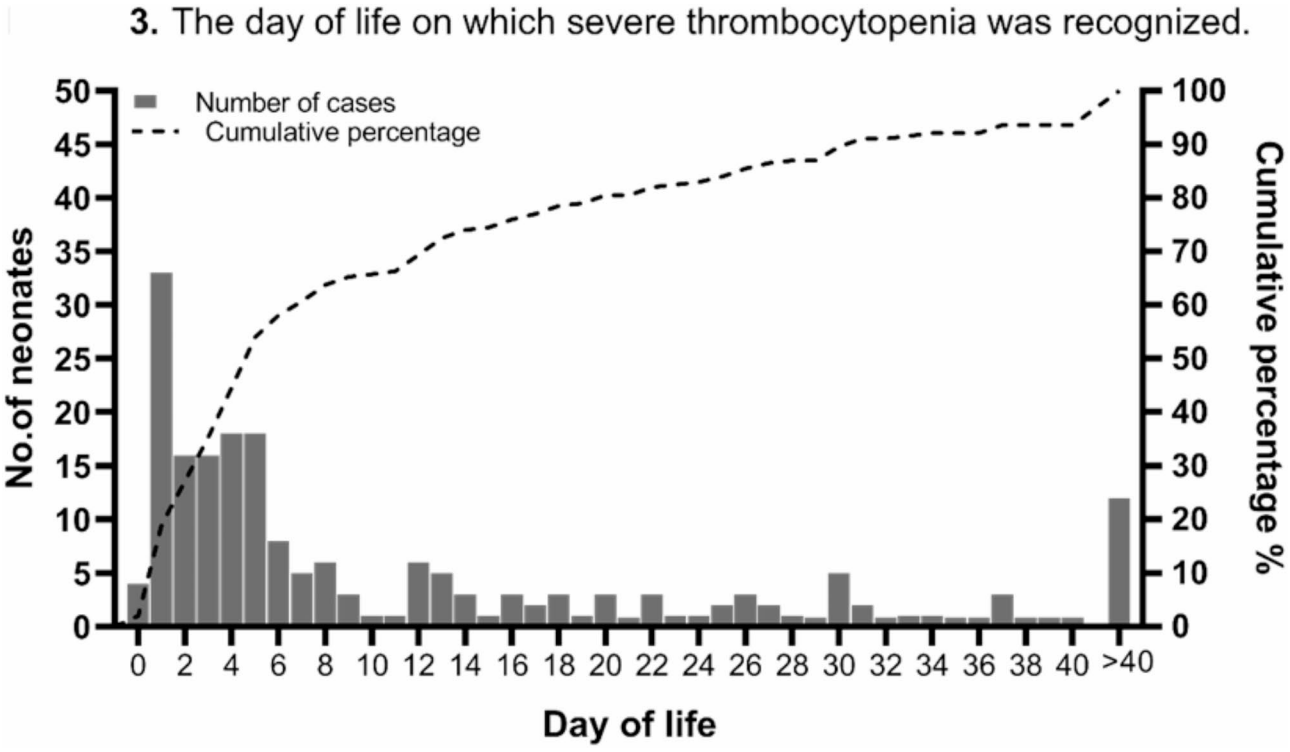

Fig. 2 The day of life on which severe thrombocytopenia was recognized

Table 3 Hematological parameters, CRP and lactate levels in neonates with severe thrombocytopenia

Parameters	PLT ($\times 10^3$/μL)	Hemoglobin (g/dL)	MPV (fL)	PT (s)	APTT (s)	CRP (mg/dL)	Lac (mmol/L)
Mean	26	12.3	11.8	21.4	55.1	13.5	2.1
SD	14	2.1	4.5	13.2	34.6	8.7	1.4

SD Standard deviation, *PLT* platelet, *MPV* mean platelet volume, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *CRP* C-reactive protein, *lac* lactate.

Table 4 Outcomes of 194 neonates with severe thrombocytopenia

Variables	Summary statistics
Receipt of platelet transfusion	69 (35.6%)
Number of platelet transfusion (per patient)	1 (1–10)
Recovery from thrombocytopenia	99 (51.0%)
Duration of thrombocytopenia (days)	10 (4.5–30.5)
Hemorrhage	120 (61.9%)
Intraventricular hemorrhage	30 (15.5%)
Death	52 (26.8%)

Data are given as n (%) or median (IQR).

lowest in those with congenital CMV infection ($n = 2$, 15.4%). Patients with LOS had the most IVH of all grades (30.0%, 9/30). In eighteen cases (60.0%, 18/30) of neonates with IVH, thrombocytopenia developed during the subsequent course of hemorrhage.

The overall mortality rate was 26.8% (52/194) at the last follow-up: 14 and 38 with early- and late-onset thrombocytopenia, respectively. Most of the deaths were from sepsis (32.7%, 17/52), birth asphyxia (19.2%, 10/52) and NEC (17.3%, 9/52) groups (Fig. 3). And the mortality rate was found to be greater than 50% in the NEC group (52.9%, 9/17) and the asphyxia group (52.6%, 10/19). The survival group received significantly fewer episodes of platelet transfusion when compared with the death group ($P = 0.032$). Coagulation data were also collected from both groups. The values of prothrombin time (PT), activated partial thromboplastin time (APTT) and lactate in the deceased patients were significantly higher than those in the patients who survived. Other characteristics were not significantly different between patients who survived and died (all p values < 0.05) (Table 5).

Discussion

Severe neonatal thrombocytopenia is a rare but highly fatal disease in NICU, however, it is rarely reported and examined in detail, particularly in the Chinese population. This study was conducted at a large tertiary pediatric hospital in China. Our data indicated that the overall incidence rate of severe neonatal thrombocytopenia was 3.3% in our NICU over the 5-year study period, which was comparable to the rates reported in the literature. We

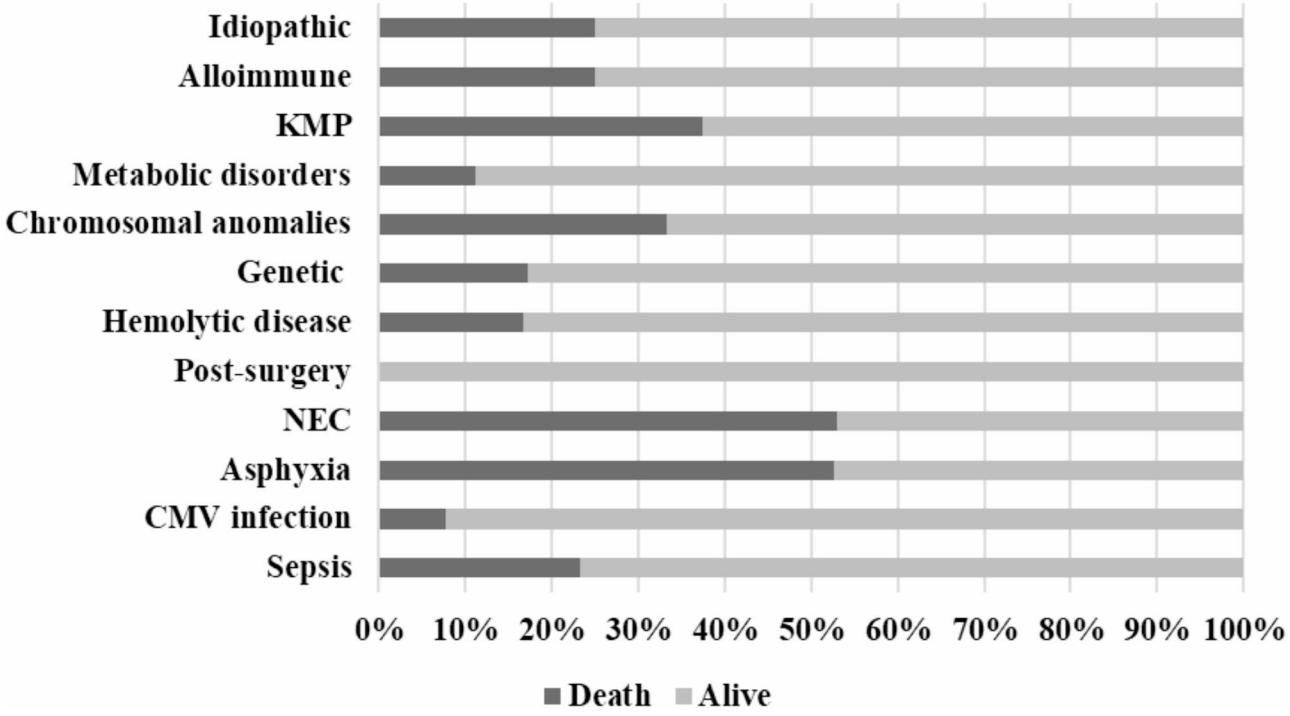

Fig. 3 Death and survival in neonates with severe thrombocytopenia of different etiologies

Table 5 Patients and laboratory features of different outcomes

	Survival	Death	*P* value
Birth weight (gram)	2860(2310–3350)	2350 (1520–3100)	0.564
Gestational age (weeks)	37.8 (35.4–39.1)	35.9 (33.4–38.1)	0.134
Age at diagnosis (days)	3 (2-9.5)	4 (2-11.5)	0.728
PLT ($\times 10^3$/μL)	32 (25.7–40.1)	29 (22.9–37.3)	0.124
PT (s)	24.5 (12.4–31.4)	34.2 (24.6–48.9)	0.025
APTT (s)	51.2 (36.8–53.6)	61.3 (49.6–86.7)	0.046
CRP (mg/dL)	9 (5.6–12.4)	12 (6.2–15.8)	0.164
Lac (mmol/L)	0.9 (0.2–1.8)	2.5 (1.1–4.5)	0.028

PLT platelet, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *CRP* C-reactive protein, *Lac* lactate.

discovered that lower birth weight was correlated with lower platelet counts in this cohort. Furthermore, the prevalence of severe thrombocytopenia in ELBW neonates was more than twice as high as in patients weighing over 1,000 g at birth. Biological differences observed between fetal, neonatal, and adult megakaryocytes are likely involved in the marked susceptibility of ELBW neonates to develop thrombocytopenia [5].

Our data demonstrated that sepsis, particularly early-onset sepsis, was the predominant cause of severe neonatal thrombocytopenia, which was consistent with the findings of Ree et al. [6]. The increased incidence of severe thrombocytopenia may be attributable to a partial response in terms of platelet and thrombopoietin production during sepsis with diminished energy reserves in the host [7]. Furthermore, we explore the pathogenic organisms in culture-positive cases, indicating that gram-negative bacteria were the most common pathogen isolated from blood culture samples and was shown to be associated with a lower nadir platelet count. Arabdin et al. [8] reported that neonatal thrombocytopenia was independently associated with gram-negative sepsis. In animal models, the likely mechanisms of thrombocytopenia associated with gram-negative sepsis include cell-free extracts comprising lipopolysaccharide and a constituent of gram-negative bacteria's cell wall [9]. Furthermore, it was discovered that an elevated CRP level was associated with decreased platelet counts. This finding was also supported by Rabindran et al. [10] and Arabdin et al. [8].

Genetic defect was the second most common etiology in our series. Trio-WES was performed for neonates with a suspected genetic disease or an unknown cause of severe thrombocytopenia, resulting in the diagnosis of 28 patients, including seven cases caused by WAS gene mutation, which has been highlighted in previous studies. We analyzed the records of these patients to look for any commonality of features among this group and found that congenital thrombocytopenia needs to be considered when unexplained severe or very severe thrombocytopenia occurs in term or normal birth weight neonates within three days after birth, especially in those with congenital malformations or a family history of thrombocytopenia.

In our study, perinatal asphyxia, especially severe asphyxia, also played an important role in severe neonatal thrombocytopenia. In neonates with severe

thrombocytopenia associated with perinatal asphyxia, a greater proportion of the thrombocyopenia began within 72 h of birth than after 72 h. The mechanism by which perinatal asphyxia is associated with early-onset thrombocytopenia remains unclear. Several studies have shown that acute severe hypoxia may play a role in the pathogenesis of neonatal thrombocytopenia: reducing platelet survival time and impairing platelet production by altering the structural and functional characteristics of megakaryocytes [11, 12].

The prevalence of hemorrhage in thrombocytopenic neonates was approximately 20-30% [13]. The higher incidence of hemorrhage in neonates with very severe thrombocytopenia discovered in our study (61.9%) was similar to that reported in the literature [4]. This study established a link between the risk of hemorrhage and etiologies of severe thrombocytopenia. NEC and sepsis have been identified as the most common etiologies in the hemorrhage and IVH group, respectively, as shown in our data. And a similar result was observed in Robert et al.'s study [14]. However, pathological hemorrhage in neonates is multifactorial and unlikely to be attributable solely to a lower platelet count. We recorded over half of the neonates who developed IVH subsequently exhibited thrombocytopenia, as opposed to thrombocytopenia being the cause of IVH, which was in line with several studies [13, 15, 16], and whether there was a causal link between severe thrombocytopenia and IVH requires a deeper inquiry.

In line with previous reports, platelet transfusion was not significantly associated with shorter duration of thrombocytopenia, which may be explained, in part, by the fact that severely ill patients receive more platelet transfusions; but may also be explained by adverse effects of platelet transfusions [17]. We recorded a overall mortality rate of 26.8%, which was positively correlated with the number of platelet transfusions, but not with the platelet nadir. This finding was in line with several studies [16, 18, 19]. Platelet transfusions do raise the platelet count in the majority of neonates with severe thrombocytopenia and can be considered an effective therapy. However, should all neonates with severe thrombocytopenia be given platelet transfusions? We considered platelet counts together with clinical conditions before giving a platelet transfusion. The proportion of severely thrombocytopenic neonates receiving platelet transfusions and the incidence of intracranial hemorrhage, including intraventricular hemorrhage, were lower in this study than in the PlaNeT-2 trial, in which neonates born at less than 34 weeks of gestation received a platelet transfusion at a platelet-count threshold of either $25 \times 10^3/\mu L$ or $50 \times 10^3/\mu L$ [20]. However, the mortality rate in this study was similar to the group with liberal platelet transfusion strategy in PlaNeT-2. Further research is needed to explain whether the outcome was related to the platelet transfusion strategy or to the poor general condition of these patients due to their original disease.

Severe thrombocytopenia was related to a high mortality rate. Neonates with late-onset thrombocytopenia had a higher mortality rate than those with early-onset thrombocytopenia (26.1% vs. 11.2%), and the highest mortality rate was attributable to severe thrombocytopenia secondary to NEC. We speculate that this increase in mortality rate can be explained by the fact that severe thrombocytopenia secondary to NEC occurs more commonly after 72 h of life and has more serious and life-threatening conditions. The great majority (62.3%) of deaths were ascribed to cardiopulmonary failure and 10 (5.2%) cases eventually progressed to multiple organ dysfunction syndrome. DIC was recorded in 10 (5.2%) episodes of discharge diagnosis and coagulopathy in 56 (28.9%). The prolongation of both PT and APTT in deceased patients may suggest a correlation between death from severe thrombocytopenia and coagulation disorders [21]. The production and accumulation of lactate in blood occur after asphyxia due to poor tissue perfusion following anaerobic metabolism [22]. Given the elevated lactate levels observed in deceased patients, it is plausible that perinatal asphyxia was more prevalent and severe in this cohort compared to those who survived.

A limitation of this study is that it was conducted at a single center with a relatively small sample size due to the rarity of the disease and the diversity of its etiologies. Multicenter studies are required to address the limitations of the sample size and the discrepancies in the results due to regional specificity. In addition, intrauterine growth restriction and antenatal steroid administration were not included in the analysis, as several patients were initially treated in the outer court and subsequently transferred to our specialized children's hospital.

Conclusions

In summary, this study reported an incidence rate of 3.3% and a mortality rate of 26.8% among the study population. Sepsis, genetic syndromes, and birth asphyxia were the predominant factors related to severe neonatal thrombocytopenia in this Chinese population. And the severity and outcome of severe neonatal thrombocytopenia were associated with the underlying etiology. Further research is needed to improve the accuracy and accessibility of diagnostic tests, such as trio-WES, bone marrow aspiration and blood culture, in order to achieve accurate and timely diagnoses and improve outcomes.

The primary etiological factors contributing to severe neonatal thrombocytopenia in the Chinese cohort were identified as sepsis, genetic syndromes, and birth asphyxia. The clinical severity and short-term prognostic outcomes of severe thrombocytopenia were found to

be significantly correlated with the underlying etiological factors. To enhance diagnostic precision and clinical management, future research should focus on optimizing the accuracy and clinical utility of diagnostic modalities, including trio whole-exome sequencing (trio-WES), bone marrow aspiration, and blood culture analysis. Such advancements are crucial for facilitating timely and accurate diagnoses, thereby improving patient outcomes.

Abbreviations

BW	Birth weight
ELBW	Extremely low birth weight
VLBW	Very low birth weight
GA	Gestational age
LOS	Late-onset sepsis
EOS	Early-onset sepsis
CMV	Cytomegalovirus
PT	Prothrombin time
APTT	Activated partial thromboplastin time
IQR	Interquartile range
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NRDS	Neonatal respiratory distress syndrome
PDA	Patent ductus arteriosus
DIC	Disseminated intravascular coagulation

Supplementary Information

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Supplementary Material 1

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Author contributions

YY Shan, P Zhang, and GQ Cheng designed the study. YY Shan and T Peng collected the data. YY Shan was involved in data cleaning, mortality follow-up, and verification. YY Shan, T Peng, and P Zhang analyzed the data. YY Shan interpreted the results and drafted the manuscript. GQ Cheng contributed to critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). This study obtained ethical approval from the Ethics Committee of the Children's Hospital of Fudan University [No.(2022) 125]. Informed consent was not applicable because the data were anonymized. Ethics Committee of the Children's Hospital of Fudan University waived the need for patient informed consent due to retrospective analysis of medical records.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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