Real-world evidence regarding the growth of very premature infants with small for gestational age after birth: A multi-center survey in China

Xue Rong Huang
Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen,
Wei Shen
Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen,
Fan Wu
the Third Affiliated Hospital of Guangzhou Medical University
Jian Mao
Shengjing Hospital of China Medical University
Ling Liu
Guiyang maternal and Child Health Hospital·Guiyang Children's Hospital
Yan-Mei Chang
Peking University Third Hospital
Rong Zhang
Pediatric Hospital of Fudan University
Xiu-Zhen Ye
Guangdong Province Maternal and Children's Hospital
Yin-Ping Qiu
General hospital of Ningxia Medical University
Li Ma
Children's Hospital of Hebei Province
Rui Cheng
Children' hospital of Nanjing Medical University
Hui Wu
the first hospital of Jilin university
Dong-Mei Chen
Quanzhou maternity and Children's Hospital
Ling Chen
Huazhong University of Science and Technology
Ping Xu
Liaocheng people's hospital
Hua Mei

the Affiliate Hospital of Inner Mongolia Medical University

San-Nan Wang

Suzhou Municipal Hospital

Fa-Lin Xu

The Third Affiliated Hospital of Zhengzhou University

Rong Ju

University of Electronic Science and Technology of China

Zhi Zheng

Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen,

Xin-Zhu Lin (xinzhufj@163.com)

Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen,

Xiao-Mei Tong

Peking University Third Hospital

Research Article

Keywords: extrauterine growth retardation, extremely premature infants, Nutrition, small for gestational age, Z score, GV

Posted Date: May 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1641245/v1

Abstract

Objective: To analyze the real-world growth pattern of very premature infants (VPI) with small for gestational age (SGA) after birth by using the ΔZ value of weight at discharge and evaluate the occurrence and risk factors of extrauterine growth retardation (EUGR). Methods: The clinical data of VPI with SGA were prospectively collected from 28 hospitals in seven different regions of China from September 2019 to December 2020. They were divided into the EUGR group and the non-EUGR group according to the criterion of ΔZ value of weight at discharge < −1.28.

Results: This study included 133 eligible VPI with SGA. Following the criterion for the weight at discharge as the 10^{th} percentile of the Fenton curve, the incidence of EUGR was found to be 98.50% (131/133), and following the criterion of ΔZ value of weight at discharge < −1.28, the incidence of EUGR was 36.84% (49/133). The birth weight, the 5-minute Apgar score, and the proportion of male infants in the EUGR group were lower than those in the non-EUGR group ($P < 0.05$). The average invasive ventilation time, cumulative duration of the administration of antibiotics, blood transfusion time, blood transfusion ratio, and total days of hospitalization were significantly higher in the EUGR group than those in the non-EUGR group ($P < 0.05$). The time to start enteral feeding, the quantity of milk added with human milk fortifier (HMF), the time to reach full fortification, the cumulative fasting time, the time to reach full enteral feeding, the duration of parenteral nutrition (PN), days to reach the target total calorie intake and oral calorie intake (both 110 kcal/kg/d), and the age of recovering birth weight in the EUGR group were significantly higher than that in the non-EUGR group ($P < 0.05$). The average weight gain velocity (GV) was significantly lower in the EUGR group than that in the non-EUGR group ($P < 0.001$). The incidences of patent ductus arteriosus with hemodynamic changes (hsPDA), neonatal necrotizing enterocolitis (NEC) ³ stage 2, late-onset sepsis (LOS), and feeding intolerance (FI) in the EUGR group were significantly higher than that in the non-EUGR group ($P < 0.05$). Multivariate logistic regression analysis showed that birth weight, sex (male), and GV were the protective factors for EUGR, while a long time to achieve full-dose fortification, slow recovery of birth weight, and NEC ³ stage 2 were the independent risk factors.

Conclusion: SGA in VPI can reflect the occurrence of EUGR more accurately by using the ΔZ value of weight at discharge than using the p-value of weight. Strengthening enteral nutrition support, achieving full breast milk fortification more earlier increasing GV, shortening the recovery time of birth weight, and avoiding NEC can effectively reduce the incidence of EUGR.

What Is Known

- SGA is an independent risk factor for EUGR, the incidence of extrauterine growth retardation (EUGR) in SGA children is significantly higher than the incidence of EUGR in non-SGA children.

What is New:

- We conducted a national prospective multi-center study in China to analyze the real-world incidence of EUGR and risk factors that affect very premature infants (VPI) in SGA, based on the ΔZ value of

weight.

- SGA in VPI can reflect the occurrence of EUGR more accurately by using the ΔZ value of weight at discharge than using the p-value of weight.

Introduction

With an increase in the understanding of short-term and long-term health-influencing factors that affect small for gestational age (SGA), the perinatal medical community has focused on the prevention and the management of nutrition of SGA infants. Regarding the incidence of SGA, China (6.5% incidence) ranks fifth globally (16% incidence) [1]. In 2016, the WHO defined SGA as a newborn whose birth weight is below the 10th percentile of the birth weight for infants of the same sex of the same gestational age or whose Z-value of birth weight is < − 1.28. The Fenton growth curve (2013) [1] is used for the diagnosis of SGA. SGA can be divided into premature SGA, full-term SGA, and overdue SGA, among which premature SGA is affected by intrauterine growth retardation and immature gestational age. The risk of early complications after birth and perinatal death increases, and it can also lead to many long-term complications such as adult cardiovascular diseases, insulin resistance, and neurocognitive dysfunction, which increases the burden on society and families.

Appropriate catch-up growth in the early stage is beneficial to the physical growth and the development of the nervous system of SGA infants, and adequate nutrition is the key to ensuring catch-up growth [2, 3]. However, due to intrauterine growth retardation, the growth and development of SGA infants are slow, and it is difficult for the growth and development indicators of SGA children to reach the 10th percentile value for the same gestational age at the time of discharge. Thus, it takes a long time to complete the catch-up growth [4]. Therefore, the incidence of extrauterine growth retardation (EUGR) in SGA children is significantly higher than the incidence of EUGR in non-SGA children. Many studies have reported that SGA is an independent risk factor for EUGR [5, 6].

EUGR is related to intrauterine growth retardation (IUGR). Studies generally refer to the Fenton growth curve (2013) and define the 10th percentile of the weight, height, and head circumference at the corrected gestational age of 36 weeks or at discharge as EUGR and the 3rd percentile below the growth curve as severe EUGR. By this standard, the incidence of EUGR in SGA is 87.6%~98.5% [5, 7], which is significantly higher than 44.44% in non-SGA [5]. Some researchers have suggested that the occurrence of EUGR in SGA is a continuation of intrauterine growth retardation but not “real EUGR” [8]. Therefore, the percentile (P-value) of the Fenton growth curve cannot reflect the growth pattern of SGA after birth. To better reflect the growth status of premature infants after birth, Simon et al. [9] suggested that the change in the Z scores between the weight at discharge and birth weight (ΔZ value) should be used to evaluate EUGR. The Z-score indicates how far the infant’s weight and height are from the 50th percentile or the median of the reference growth charts for infants of the same age and sex, i.e., Z value = (measured value-average value of the same gestational age and gender)/standard deviation of this gestational age and gender). Therefore, the ΔZ value might be more suitable for analyzing the extrauterine growth of individuals after birth [9]. We conducted a national prospective multi-center study in China to analyze the real-world

incidence of EUGR and risk factors that affect very premature infants (VPI) in SGA, based on the ΔZ value of weight.

Objective And Methods

Study population

This study was a multi-center prospective survey conducted from September 2019 to December 2020. The data were obtained from 28 tertiary hospitals in seven regions of China. The protocol was approved by the Ethics Committee of Women and Children's Hospital affiliated with Xiamen University/Xiamen Maternity and Child Health Care Hospital (KY-2019–016), and the study was registered in the Chinese Clinical Trials Registry (http://www. chictr.org.cn) with the registration number ChiCTR1900023418.

We collected the clinical data of VPI with SGA hospitalized in the abovementioned multi-centers. Inclusion criteria: ① SGA; ② Birth gestational age < 32 weeks; ③ Hospitalization time > 2 weeks; ④ Admission within 24 h after birth. Exclusion criteria: ① Congenital malformation or genetic metabolic disease; ② Death, interruption of treatment, or automatic discharge during hospitalization; ③ Incomplete data.

The VPI with SGA were divided into the EUGR and non-EUGR groups

A change in the Z-score (△Z value) of weight by more than 1.28 between two points (discharge and birth) was considered to be EUGR, and a change in the Z-score (△Z value) of weight by less than 1.28 was considered to be non-EUGR [10].

Methods

Using a unified questionnaire, perinatal data of VPI with SGA were collected (gestational age at birth, Z value of physical indices at birth, sex, delivery mode, multiple births, prenatal glucocorticoid administration, and the 5-minute Apgar score), maternal and pregnancy complications (gestational hypertension and gestational diabetes), growth and nutritional status during hospitalization [maximum weight loss, the age of recovering birth weight, the average weight gain velocity (GV), the ΔZ-value of physical indices at discharge, start time of enteral feeding, the age of reaching total enteral nutrition, cumulative fasting days, breast milk volume after the addition of human milk fortifier (HMF) and days needed for full fortification, the age of reaching the standard of oral calorie, cumulative calorie intake in the first week of hospitalization, cumulative dose of amino acids and fat milk in the first week of hospitalization, the duration of parenteral nutrition (PN)],main treatment conditions (invasive mechanical ventilation time, total oxygen consumption time, the use rate of postnatal hormones, cumulative duration of antibiotics used, hospitalization time) and main complications during hospitalization [neonatal respiratory distress syndrome (NRDS), early-onset sepsis (EOS), feeding intolerance (FI), patent ductus arteriosus with hemodynamic changes (hsPDA), neonatal necrotizing enterocolitis (NEC) ≥ stage 2, bronchopulmonary dysplasia (BPD), late-onset sepsis (LOS), grade III-IV intraventricular hemorrhage

(IVH), periventricular leukomalacia (PVL), parenteral nutrition-associated cholestasis (PNAC), retinopathy of prematurity (ROP) requiring intervention, metabolic bone disease of prematurity (MBDP), EUGR], and other clinical data were also collected.

Definition or diagnostic criteria of related diseases

(1) SGA is a newborn whose birth weight is lower than the 10th percentile of the birth weight of a newborn of the same sex, and gestational age or whose birth weight Z value is < − 1.28; (2) The EUGR evaluation criteria refer to the Fenton growth curve [11] published in 2013. ▯ Percentile (P value) evaluation criteria: VPI with weight lower than the 10th percentile weight, as per the 2013 Fenton growth curve, at 36 weeks of corrected gestational age or during discharge;▯ ΔZ value evaluation criteria: △Z value of weight = (Z value of birth weight-Z value of weight at 36 weeks of corrected gestational age or during discharge); EUGR is defined as weight ΔZ value < − 1.28 [10]; (3) BPD is defined as a newborn with persistent oxygen dependence for ≥ 28 days after birth [12]; (4) EOS and LOS diagnostic criteria [13] refer to the consensus of experts on the diagnosis and treatment of neonatal sepsis (2019 edition); (5) FI diagnostic criteria [14]: the stomach residue exceeds 50% of the previous feeding amount, accompanied by vomiting and/or abdominal distension; the feeding plan fails, including reduced, delayed, or interrupted enteral feeding; (6) Diagnostic criteria of MBDP: refers to the consensus of clinical management experts of metabolic bone disease in premature infants (2021) [15]; (7) NEC ≥ stage 2: diagnostic criteria of Papile et al. [16]; (8) Diagnostic criteria of hsPDA: PDA catheter diameter > 1.5 mm, accompanied by heart murmur, tachycardia, rapid respiration, increased pulse pressure, hypotension; (9) The complications such as NRDS, IVH ≥ stage 3, PVL, PNAC, and ROP need intervention; refer to the diagnostic criteria [17] in *Practical Neonatology (5th Edition).*

Definition of enteral nutrition

(1) Start time of enteral feeding (h): the time to start oral feeding/nasal feeding of breast milk or formula milk after birth (excluding colostrum oral care); (2) Total enteral feeding time (d): the time required for oral milk intake to reach 150 mL/kg/d; (3) Time for total and oral calorie intake to reach the target: the recommended calorie intake standard was 110 kcal/(kg·d). (4) Mean GV [g/(kg·d)]: [1,000 × ln (Wn/W1)]/(Dn-D1) after regaining birth weight. In this formula, Wn indicates weight (g) at discharge, W1 indicates birth weight (g), Dn indicates the length of hospital stay (day), and D1 indicates the time to regain birth weight (day) [18].

Statistical analysis

The SPSS 22.0 statistical software was used for statistical analysis. Normally distributed measurement data were presented as the mean ± SD, and two independent-samples t-tests were performed for comparison between groups. Non-normally distributed quantitative data were presented as the median and interquartile ranges, and the Mann-Whitney U test was conducted for comparison between groups. The count data were presented as the number and rate of cases, and the Chi-squared test or Fisher's exact test was conducted for comparison between groups. The variables with $P < 0.05$ in the single-factor analysis were included in a multivariate analysis, and the variables were screened using a stepwise

method by constructing a multivariate logistic regression model, with inspection level α = 0.05. All differences among and between groups were considered to be statistically significant at $P < 0.05$.

Results

The incidence of EUGR

During the study period, data on 2,600 VPI were collected. Of these, 86 cases were excluded due to incomplete information about the mother and the baby, 2,381 cases of non-SGA in VPI were excluded, and finally, 133 VPI with SGA were included in the study, who were evaluated based on the Fenton curve. The birth weight between the EUGR and the non-EUGR groups was not significantly different ($P = 0.881$), but the weight of the EUGR group at discharge was significantly lower (0.31 vs. 16.32, $P = 0.012$). According to the weight of the infants at 36 weeks of corrected gestational age or during discharge as the 10th percentile of the 2013 Fenton growth curve, the incidence of EUGR in VPI with SGA was 98.50% (131/133 cases). According to the standard ΔZ value of the weight, the Z scores of the birth and discharge weights of the EUGR group were lower than those in the non-EUGR group (-1.58 vs. − 1.49, $P = 0.017$; − 3.54 vs. − 2.21, $P < 0.001$). For ΔZ value of weight at discharge < − 1.28, there were 49 cases in the EUGR group and 84 cases in the non-EUGR group, and the incidence of EUGR was 36.84% (49/133 cases); see Table 1.

Table 1
Comparison of the incidence of EUGR evaluated by the p-value and the ΔZ value of weight at discharge between the EUGR and the non-EUGR groups

EUGR standard	Non-EUGR	EUGR	*t/Z*	*P*
Evaluate with < P10				
Discharge weight [n (%)]	2(1.50)	131(98.50)		
birth weight P-value [M (Q1, Q3)]	6.62(4.65,8.25)	6.36(5.85,06.87)	-1.49	0.881
Discharge weight P-value [M (Q1, Q3)]	16.32(12.57,20.08)	0.31(0.06,0.98)	-2.42	0.012
Evaluate with Δ z <-1.28				
Discharge weight [n (%)]	84(63.16)	49(36.84)		
Z value of birth weight [M (Q1, Q3)]	-1.49(-1.61, -1.37)	-1.58(-1.85, -1.43)	-2.394	0.017
Discharge weight Z value [$\bar{x} \pm s$]	-2.21 ±0.55	-3.54 ±0.69	12.17	< 0.001
Note: EUGR is extrauterine growth retardation; SGA is smaller than gestational age; VPI is extremely premature.				

General information and main treatment of VPI with SGA during the perinatal period

Following the criterion of ΔZ of weight < − 1.28, the birth weight, the 5-minute Apgar score, and the incidence of male infants in the EUGR group were lower than those in the non-EUGR group ($P < 0.05$ for all parameters). The average invasive ventilation time, the cumulative duration of antibiotic use, blood transfusion times, blood transfusion ratio, and total hospitalization days were significantly higher in the EUGR group than those in the non-EUGR group ($P < 0.05$ for all parameters). The gestational age, gestational hypertension, gestational diabetes, delivery mode, multiple births, the rate of administration of postnatal hormones, noninvasive mechanical ventilation time, and nasal catheter oxygen supply time were not significantly different between the EUGR and the non-EUGR groups ($P > 0.05$); see Table 2.

Table 2
Comparison of the general perinatal information and main treatment of VPI with SGA between the EUGR and non-EUGR groups

Variable	Non-EUGR n = 84	EUGR n = 49	*t/Z/χ2*	*P*
Male [n (%)]	46(75.41)	30(41.67)	15.353	< 0.001
Birth age Week [$\bar{x} \pm s$]	30.58 ± 1.40	30.23 ± 1.43	1.372	0.172
birth weight g [$\bar{x} \pm s$]	976.50 ± 176.35	854.92 ± 170	3.886	< 0.001
Cesarean section [n (%)]	78(92.86)	46(93.88)	/	> 0.999
use rate of postnatal hormones [n (%)]	68(80.95)	44(89.8)	2.087	0.352
Pregnancy hypertension [n (%)]	47(55.95)	34(69.39)	2.346	0.126
gestational diabetes [n (%)]	8(9.52)	4(8.16)	/	> 0.999
multiple births [n (%)]	23(27.38)	20(40.82)	2.553	0.111
5 min Apgar [M (Q1, Q3)]	9(8,10)	8(7,9)	-2.52	0.012
Invasive ventilation time d [M (Q1, Q3)]	0(0,2.50)	2(0,7)	2.934	0.003
Noninvasive ventilation time d [M (Q1, Q3)]	18.5(7.5,29)	19(9,32)	0.74	0.459
Oxygen use time of nasal catheter d [M (Q1, Q3)]	9.65(4,19)	13(4,25)	1.508	0.132
cumulative duration of antibiotics use d [M (Q1, Q3)]	12.5(6.50,17.50)	16(10,25)	2.54	0.011
Frequency of blood transfusion d [M (Q1, Q3)]	1(0.5,20)	3(1,6)	3.656	< 0.001
Blood transfusion ratio [n (%)]	61(72.62)	43(87.76)	4.158	0.041
Total hospitalization days d [$\bar{x} \pm s$]	53.82 ± 17.39	69.08 ± 16.92	-4.929	< 0.001
Remarks:/: Fisher's accurate test, no such value.				

Nutritional status of VPI with SGA in the hospital Following the criterion of ΔZ of weight < − 1.28, the start time of enteral feeding, the amount of milk added with HMF, the time to reach full fortification, the cumulative fasting time, the time to reach total intestinal feeding, the duration of PN, the number of days to reach the target total calorie intake and oral calorie intake (both 110 kcal/kg/d), and the date of recovery of birth weight in the EUGR group were significantly more than those in the non-EUGR group (*P*<

0.05). GV was significantly lower in the EUGR group than that in the non-EUGR group ($P < 0.001$). In the first week of hospitalization, the accumulated amino acids, fat emulsion, accumulated calories, and the maximum physiological weight loss between the EUGR and the non-EUGR groups were not significantly different ($P > 0.05$); see Table 3.

Table 3
Comparison of the nutritional status of VPI with SGA between the EUGR and the non-EUGR groups in the hospital

Variable	Non-EUGR n = 84	EUGR n = 49	$t/Z/\chi^2$	P
start time of enteral feeding h [M (Q1, Q3)]	21.75(3,38)	36(16,90)	2.403	0.016
the amount of milk added with HMF ml [M (Q1, Q3)]	88(60.50,91.50)	100(78,109.60)	2.348	0.019
time needed to reach the full amount of fortification d [M (Q1, Q3)]	3(3,4.5)	9(3,10)	3.927	< 0.001
Fasting days during hospitalization d [M (Q1, Q3)]	2(0.95,6)	5.9(2,8.10)	3.882	< 0.001
age of reaching total enteral nutrition d [M (Q1, Q3)]	27(21,35.50)	33(28,50)	3.542	< 0.001
Parenteral nutrition days d [M (Q1, Q3)]	25(16.50,31)	32(23,47)	3.739	< 0.001
Accumulation of amino acids in the first week (g/kg) [M (Q1, Q3)]	17.4(15.20,19.45)	17(14.10,19.60)	0.795	0.426
accumulation of fat emulsion in the first week g/kg [$\bar{x} \pm s$]	13.62 ± 3.94	12.91 ± 5.17	0.827	0.413
Accumulated calories in the first week kcal/kg [$\bar{x} \pm s$]	494.78 ± 105.62	461.65 ± 113.63	1.696	0.092
time for the total calorie to reach 110 kcal/(kg d) d [M (Q1, Q3)]	9.5(7,14)	14(10,22)	3.255	0.001
time for oral calorie to reach 110 kcal/(kg.) d [M (Q1, Q3)]	27(18.50,33.50)	32(26,45)	3.416	0.001
Maximum physiological weight loss % [M (Q1, Q3)]	5(0.40,7.80)	6(2,8.70)	1.191	0.234
the date of recovery of birth weight d [M (Q1, Q3)]	7(3,9.5)	9(7,12)	2.904	0.004
GV g/kg·d [$\bar{x} \pm s$]	18.97 ± 4.77	14.58 ± 2.26	7.16	< 0.001

Note: EUGR is extrauterine growth retardation; SGA is smaller than gestational age; VPI is extremely premature. GV: Average weight growth rate

In-hospital complications of VPI with SGA Following the criterion of ΔZ of weight at discharge < − 1.28, the incidences of hsPDA, NEC ≥ stage 2, LOS, and FI in the EUGR group were significantly higher than that in the non-EUGR group ($P < 0.05$). The incidences of complications such as NRDS, EOS, BPD, NEC ≥ stage 3, PVL, ROP, PNAC, and MBDP were not significantly different between the groups ($P > 0.05$); see Table 4.

Table 4
Comparison of the complications related to the hospitalization of VPI with SGA between the EUGR and the non-EUGR groups

Variable	Non-EUGR n = 84	EUGR n = 49	$\chi 2$	*P*
NRDS [n (%)]	68(80.95)	37(75.51)	0.551	0.458
hsPDA [n (%)]	37(44.05)	32(65.31)	5.602	0.018
EOS [n (%)]	14(16.67)	6(12.24)	0.474	0.491
FI [n (%)]	35(41.67)	30(61.22)	4.737	0.031
LOS [n (%)]	7(8.33)	11(22.45)	5.269	0.022
NEC ≥ stage 2 [n (%)]	4(4.76)	10(20.41)	8.044	0.005
Operation NEC [n (%)]	2(2.38)	2(4.08)	/	0.625
BPD [n (%)]	45(53.57)	33(67.35)	2.422	0.122
NEC ≥ grade 3 [n (%)]	0(0.00)	2(4.08)	/	0.134
PVL [n (%)]	3(3.57)	0(0.00)	/	0.297
ROP requiring intervention [n (%)]	32(38.10)	17(34.69)	0.154	0.695
MBDP [n (%)]	4(4.76)	4(8.16)	/	0.466
PNAC [n (%)]	13(15.48)	10(20.41)	0.526	0.468
Note:/Fisher's accurate test, no such value.				

Multivariate logistic regression analysis of EUGR in VPI with SGA

Multivariate logistic regression analysis showed that birth weight, high GV, and the male sex were the protective factors for EUGR, while a long time to reach complete fortification, slow recovery of birth weight, and NEC ≥ stage 2 were the independent risk factors for EUGR; see Table 5.

Table 5
Multivariate logistic regression analysis of EUGR in VPI with SGA

Variable	β	Standard error	Wald χ^2	*P*	*OR* (*95%CI*)
birth weight	-0.003	0.001	5.091	0.024	0.997(0.994,0.999)
male	-2.085	0.661	9.944	0.002	0.124(0.034,0.454)
time to reach the full amount of fortification	0.12	0.043	7.93	0.005	1.127(1.037,1.225)
the date of recovery of birth weight	0.135	0.061	4.949	0.026	1.144(1.016,1.289)
GV	-0.706	0.157	20.27	< 0.001	0.494(0.363,0.671)
NEC ≥ stage 2	1.764	0.874	4.069	0.044	5.835(1.051,32.384)

Note: SGA is small for gestational age; VPI is extremely premature; EUGR is extrauterine growth retardation; GV: average weight growth rate; NEC is necrotizing enterocolitis.

Discussion

Clark [19] first proposed the concept of EUGR in 2003. He plotted a growth curve to evaluate the incidence of EUGR. However, there are still many controversies about the timing and standard of EUGR evaluation which leads to differences in clinical recommendations and practice [20]. The revised Fenton growth curve of different sexes published in 2013 (hereinafter referred to as the Fenton curve) was based on the data of four million premature infants. Data from developed countries, including Germany, Italy, the United States, Australia, Canada, and Scotland, from 1991 to 2007, were used to monitor and evaluate the growth and development of premature infants. According to the data on the gestational age, weight, height, and head circumference of newborns, the accurate p-value and the standardized Z value [11] associated with the growth curve of the current growth of newborns can be calculated. This is the most commonly used method to evaluate the intrauterine and extrauterine growth of premature infants. Birth weight is the most commonly used index for the clinical monitoring of newborn growth and nutritional status because of its simple and accurate measurement and good repeatability. Clinically, the presence of EUGR is often evaluated according to the weight of premature infants after correction for gestational age of 36 weeks or when they are discharged from the hospital. For the same study population, a big difference in the evaluation was found depending on whether the p-value or the $\triangle Z$ value on the curve was considered as the criterion. Griffin et al. [20] used two methods to evaluate the incidence of EUGR in 25,899 VPI with a birth weight of 500 ~ 1500 g and gestational age of 22 ~ 32 weeks in California, USA. The incidence of EUGR was 53.3% with the p-value of weight at discharge < 10 and 41.4% with $\triangle Z$ value < − 1. Premature infants with gestational age ≤ 32 weeks at Mount Sinai Medical Center in the United States were evaluated by Lin et al. [10]. When the discharge weight Z score < − 1.28 (i.e., p-value < 10th percentile) was used as the diagnosis criterion, the incidence of EUGR at discharge was 35.3%, for $\triangle Z$ <

− 1.28, the EUGR incidence was 25.5%, and for △Z < − 2, the EUGR incidence was 4.5%. There were considerable differences among the three evaluation methods. The incidence of SGA in this cohort was 5.30%, which was slightly lower than the national average [1] and slightly higher than that reported in an American study (4.12%) [21]. In our evaluation of 133 VPI with SGA cases, the incidence of EUGR was 98.50% following the p-value criterion and 36.84% following the criterion of △Z < − 1.28; there was a discrepancy of 61.66% in this study due to the difference between the evaluated population and the △Z value. The incidence of EUGR differed considerably with different evaluation methods. The p-value evaluation method was based on the horizontal evaluation of group data, while the △Z value was based on the vertical evaluation and objective analysis of individual data. Longitudinal evaluation can better reflect the actual growth pattern of neonates [22, 23]. Therefore, the △Z value was used in this study to evaluate the real-world incidence of EUGR in VPI with SGA to provide a scientific standard for optimizing the nutritional strategy for this special group of infants.

The results of the univariate analysis showed that the non-EUGR group had a higher birth weight ($P < 0.001$) and a larger Z-value of birth weight ($P = 0.017$). The results of the multivariate analysis showed that high birth weight was a protective factor related to the occurrence of EUGR in VPI with SGA (OR = 0.997, 95% CI: 0.994 ~ 0.999, $P = 0.024$). Our results were similar to those of previous studies [24]. The results showed that the birth weight of children in the EUGR group was lower, the intrauterine growth was more restricted, and the organs and tissues were relatively underdeveloped. EUGR is caused by scarcity of nutrients in the uterus, greater nutritional demand, and higher energy metabolism, which is more likely to lead to nutritional deficiency and premature infant-related complications after birth [25]. The nutritional status of VPI with SGA after birth was also closely related to the occurrence of EUGR. The results of the multivariate analysis showed that the requirement of a long time for breast milk fortification and the slow recovery of birth weight were independent risk factors for EUGR in VPI with SGA, and the high GV was a protective factor. Breast milk is the best source of nutrition for babies, especially premature infants. However, the energy and nutrients in breast milk cannot meet the growth-related needs of premature infants at the early stages after birth, especially of premature SGA infants. Therefore, HMF containing multiple nutrients is commonly added to breast milk [26].

Our results showed that the quantity of HMF added to milk was more in the EUGR group than that in the non-EUGR group (100 mL vs. 88 mL), and it took longer (9 d vs. 3 d) to reach full fortification in the EUGR group. Experts in China recommended that premature infants should start the use of HMF when the breastfeeding volume reaches 50–80 mL/(kg·d), the standard adequate fortification should be achieved within 3–5 days In a study, the addition of HMF when the breastfeeding volume reaches was shown to be the best way to reduce the incidence of EUGR [27].

A prospective randomized controlled study by Bozkurt et al. [28] showed that when full-dose intensive breastfeeding occurred sooner, the GV in VPI was higher, which reduced the recovery time of birth weight. The GV was higher during hospitalization, which was a significant independent protective factor to avoid EUGR and promote the development of the nervous system [29]. Jeffrey et al. [30] reported that GV increased from 11.8 to 12.9 g/kg d, and the incidence of EUGR in very low birth weight

infants(VLBWI)decreased from 64.5–50.3%, which was consistent with the results of this study. These results suggested that more attention should be paid to enteral nutrition support for VPI with SGA. By following the recommendations of HMF experts, full breast milk fortification can be achieved at the earliest, the growth rate can be increased, and the recovery time of birth weight can be shortened. These factors play an important role in reducing the incidence of EUGR.

Early postnatal complications directly affect the nutritional supply and extrauterine growth and development of VPI with SGA. The results of the univariate analysis showed that the 5-minute Apgar score in the EUGR group was lower ($P = 0.012$), and the invasive ventilation time was longer (P = 0.003) than that in the non-EUGR group. Because of the severity of the illness after birth, the early enteral nutrition measures recommended by the clinicians could not be implemented effectively, resulting in delayed initiation of enteral feeding. The average starting time of enteral feeding of the EUGR group in this study was later that that in the non-EUGR group (36.00 h vs. 21.75 h). A delay in enteral feeding might cause gastrointestinal mucosa atrophy and delayed functional maturity and also increase the incidence of FI ($P = 0.031$) and NEC [31, 32]. The incidence of LOS among children in the EUGR group was higher than that among children in the non-EUGR group ($P = 0.022$), which led to longer administration of antibiotics ($P = 0.011$), greater extent of intestinal microecology disorder, and a higher incidence of NEC among children in the EUGR group [33]. The incidence of hsPDA in the EUGR group was higher ($P = 0.018$), the proportion of blood transfusion was higher ($P = 0.01$), and the frequency of blood transfusion was higher ($P < 0.001$) than that in the non-EUGR group. These factors might increase the risk of NEC [34]. In a study, the incidence rate of NEC in premature infants was 2%~5%, among which the incidence rate of very low birth weight infants was 4.5%~8.7% [35]. Our study found that the incidence rate of NEC ≥ stage 2 in the EUGR group was 20.4%, but there was no significant difference in NEC requiring surgery between the EUGR and the non-EUGR groups ($P = 0.625$). The results of the multivariate analysis confirmed that NEC ≥ stage 2 was an independent risk factor for EUGR (OR = 5.835, 95% CI: 1.051–32.384, $P = 0.044$), which showed that the risk of EUGR increased by 5.8 times after NEC occurred in VPI with SGA. These results were similar to those of previous studies [36]. In this study, most children with NEC ≥ stage 2 were treated conservatively in internal medicine, and clinicians were often very cautious about the fasting time and the indications for re-starting milk, which might lead to a decrease in the nutrient intake [7]. A comprehensive assessment of the risk balance between FI and NEC should be performed to avoid unnecessary fasting and prevent NEC from worsening.

The results of the multivariate analysis also showed that male sex was a protective factor of EUGR in VPI with SGA. Male infants with premature SGA were reported to have a faster physical catch-up growth in the early postnatal period than female infants [37]. This might be related to the differences in the effects of gender on the physical growth of premature SGA, although it needs to be confirmed in future studies.

Advantages and limitations

This was the first prospective multi-center study in China to analyze the factors related to the growth pattern of VPI with SGA after birth based on the △Z score. Data were collected from 28 tertiary hospitals

in seven regions of China, including general hospitals, children's hospitals, and women's and children's hospitals. Hence, this study accurately and objectively showed the occurrence of EUGR in VPI with SGA in China. Our study had some limitations. First, as China is a big country and the data were collected from different hospitals in different regions, the nutrition management strategies among hospitals may differ, which can lead to differences in the results. Second, as the inclusion criteria excluded cases of death, the correlation between EUGR and the risk of death could not be evaluated. Third, data on VPI with SGA follow-up was lacking, and we aim to conduct a follow-up study on this cohort.

To summarize, using the $\triangle Z$ value to evaluate the occurrence of EUGR in VPI with SGA can more accurately reflect the growth pattern of this special group of infants after birth. The incidence of EUGR following the criterion of $\triangle Z$ value of weight < − 1.28 was 36.8%. Regarding VPI with SGA, more attention should be paid to enteral nutrition support. Strengthening enteral nutrition support, achieving full breast milk fortification at the earliest, increasing GV, shortening the recovery time of birth weight, and avoiding NEC can effectively reduce the incidence of EUGR.

Declarations

Acknowledgments

The authors thank the neonatal units in the following hospitals and centres for providing data for this survey (Information of the Chinese Multi-center EUGR Collaborative Group).

Department of Neonatology, Women's and Children's Hospital Affiliated to Xiamen University/Xiamen maternal and Child Health Hospital, Xiamen, Fujian 361003, China (WS, ZZ, XL). Department of Neonatology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510150, China (FW, Qianxin Tian, and Qiliang Cui). Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110000, China (JM, Yuan Yuan and Ling Ren). Department of Neonatology, Guiyang maternal and Child Health Hospital·Guiyang Children's Hospital, Guiyang, Guizhou 550002, China (LL, Bizhen Shi, and Yumei Wang). Department of Pediatrics, Peking University Third Hospital, Beijing 100191, China (YC, Jinghui Zhang, and XT). Department of Neonatology, Pediatric Hospital of Fudan University, Shanghai 201102, China (Yan Zhu, WS, RZ and CC). Department of Neonatology, Guangdong Province Maternal and Children's Hospital, Guangzhou, Guangdong 510030, China ((Jingjing Zou and XY). Department of Neonatology, General hospital of Ningxia Medical University, Yinchuan, Ningxia 750001, China (Yuhuai Li, Baoyin Zhao, and YQ). Department of Neonatology, Children's Hospital of Hebei Province, Shijiazhuang, Hebei 050031, China (Shuhua Liu and LM). Department of Neonatology, Children' hospital of Nanjing Medical University, Nanjing, Jiangsu 210000, China (Ying Xu and RC). Department of neonatology, The first hospital of Jilin university, Changchun, Jilin 130000, China (Wenli Zhou and HW). Department of Neonatology, Quanzhou maternity and Children's Hospital, Quanzhou, Fujian 362000, China (Zhiyong Liu and DC). Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430000, China (Jinzhi Gao, Jing Liu, and Ling Chen). Department of Neonatology, Liaocheng people's hospital,

Liaocheng, Shandong 252000, China (Cong Li, Chunyan Yang, and Ping Xu). Department of Neonatology, the Affiliate Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia 010010, China (Yayu Zhang, Sile Hu, and Hua Mei). Department of Neonatology, Suzhou Municipal Hospital, Suzhou, Jiangsu 215002, China (Zuming Yang, Zongtai Feng, and Sannan Wang). Department of Neonatology, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China ((Er-Yan Meng, Li-Hong Shang, and Falin Xu). Department of Neonatology, Chengdu Women' and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan 611731, China (Shaoping Ou and Rong Ju). Department of Neonatology, Hunan children's Hospital, Changsha, Hunan 410000, China (Gui-Nan Li). Department of Neonatology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang 830001, China (Long Li). Department of Neonatology, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong 510150, China (Zhe Zhang). Department of Neonatology, Shanghai Children's Medical Center, Shanghai, 200120, China (Fei Bei). Department of Neonatology, Children's Hospital of Chongqing Medical University, Chongqing, 400014, China (Chun Deng). Department of Neonatology, The First People's Hospital of Yulin, Yulin, Guangxi 537000, China (Ping Su). Department of Neonatology, the People's Hospital of Baoji, Baoji, Shanxi 721000, China (Ling-Ying Luo). Department of Pediatrics, Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China (Xiao-Hong Liu). Departments of Neonatology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250021, China (Li-Jun Wang). Departments of Neonatology, Xi'an Children's Hospital, Xi'an, Shanxi 710003, China (Shu-Qun Yu).

Authors Contributions Conceptualization, X.Z.L., X.M.T. and C.C.; methodology, W.S., Y.M.C., R.Z., Z.Z.; software, X.R.H..W.S., X.Z.Y., Y.P.Q.; validation, L.M., R.C., H.W., D.M.C.; formal analysis, W.S., F.Wu. ,L.C., P.X., H.M., S.N.W., F.L.X., R.J.; investigation and resources, F.Wu., J.M., L.L., Y.M.C., R.Z., Z.Z., X.Z.Y., Y.P.Q., L.M., R.C., H.W., D.M.C.; data curation, X.R.H..W.S., Y.M.C., R.Z., Z.Z.; writing-original draft preparation, X.R.H.. W.S.; writing-review and editing, X.Z.L., X.M.T. and C.C.; visualization; supervision, F.Wu., J.M., L.L.; project administration, X.Z.L., X.M.T. and C.C.. All authors have read and agreed to the published version of the manuscript.

Funding This research was funded by Guidance Project of Xiamen Science and Technology Plan (grant number 3502Z20199139); and Guidance Project of Xiamen Science and Technology Plan (grant number 3502Z20214ZD1225).

Availability of data and material All raw data is available from the authors.

Code availability Not applicable.

Ethics approval The protocol was approved by the Ethics Committee of Women and Children's Hospital affiliated with Xiamen University/Xiamen Maternity and Child Health Care Hospital (No: KY-2019–016).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publication Not applicable.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

References

1. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, Adair L, Baqui AH, Bhutta ZA, Caulfield LE (2013) National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global Health 1:e26-e36
2. Liu M, Chen J (2020) Progress in feeding recommendations for small for gestational age infants. International Journal of Pediatrics:394–397
3. Lei X, Chen Y, Ye J, Ouyang F, Jiang F, Zhang J (2015) The optimal postnatal growth trajectory for term small for gestational age babies: a prospective cohort study. The Journal of pediatrics 166:54–58. e53
4. Crispi F, Rodríguez-López M, Bernardino G, Sepúlveda-Martínez Á, Prat-González S, Pajuelo C, Perea RJ, Caralt MT, Casu G, Vellvé K (2021) Exercise capacity in young adults born small for gestational age. JAMA cardiology 6:1308–1316
5. Shen W, Zheng Z, Lin X-Z, Wu F, Tian Q-X, Cui Q-L, Yuan Y, Ren L, Mao J, Shi B-Z et al (2020) Incidence of extrauterine growth retardation and its risk factors in very preterm infants during hospitalization:a multicenter prospective study. Chinese Journal of Contemporary Pediatrics 24:132–140
6. Gidi NW, Goldenberg RL, Nigussie AK, McClure E, Mekasha A, Worku B, Siebeck M, Genzel-Boroviczeny O, Muhe LM (2020) Incidence and associated factors of extrauterine growth restriction (EUGR) in preterm infants, a cross-sectional study in selected NICUs in Ethiopia. BMJ paediatrics open 4
7. Yu Y (2020) Risk factors for extrauterine growth retardation in very low birth weight infants:a multicenter study. Chinese Journal of Pediatrics 58:653–660
8. Figueras-Aloy J, Palet-Trujols C, Matas-Barceló I, Botet-Mussons F, Carbonell-Estrany X (2020) Extrauterine growth restriction in very preterm infant: etiology, diagnosis, and 2-year follow-up. European Journal of Pediatrics 179:1469–1479
9. Simon L, Hanf M, Frondas-Chauty A, Darmaun D, Rouger V, Gascoin G, Flamant C, Nusinovici S, Rozé J-C (2019) Neonatal growth velocity of preterm infants: the weight Z-score change versus Patel exponential model. PLoS One 14:e0218746
10. Lin Z, Green RS, Chen S, Wu H, Liu T, Li J, Wei J, Lin J (2015) Quantification of EUGR as a measure of the quality of nutritional care of premature infants. PLoS One 10:e0132584
11. Fenton TR, Kim JH (2013) A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC pediatrics 13:1–13
12. Jobe AH, Bancalari E (2001) Bronchopulmonary dysplasia. American journal of respiratory and critical care medicine 163:1723–1729

13. Neonatology Group of Pediatric Branch of Chinese Medical Association, Association IPCoNBoCM (2019) Expert consensus on the diagnosis and management of neonatal sepsis (version 2019). Chinese journal of pediatrics 57:252–257
14. Moore TA, Wilson ME (2011) Feeding intolerance: a concept analysis. Advances in Neonatal Care 11:149–154
15. Chang Y-M, Lin X-Z, Zhang R, Liu X-H, Tong X-M, Chen P-Y, Feng Z-C, Nutritional Committee of Neonatology Branch of Chinese Medical Doctor Association, Neonatal Nutrition and Health Management Group, Professional Committee of Child Health et al (2021) Expert consensus on clinical management of metabolic bone disease of prematurity(2021). Chinese Journal of Contemporary Pediatrics 23:761–772
16. Papile L-A, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. The Journal of pediatrics 92:529–534
17. Qiu X, Ye H, Shao X (2018) Practical Neonatology, 5th edition edn. People's Medical Publishing House, Beijing
18. Patel AL, Engstrom JL, Meier PP, Kimura RE (2005) Accuracy of methods for calculating postnatal growth velocity for extremely low birth weight infants. Pediatrics 116:1466–1473
19. Clark RH, Thomas P, Peabody J (2003) Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 111:986–990
20. Bonnar K, Fraser D (2019) Extrauterine growth restriction in low birth weight infants. Neonatal Network 38:27–33
21. Makker K, Ji Y, Hong X, Wang X (2021) Antenatal and neonatal factors contributing to extra uterine growth failure (EUGR) among preterm infants in Boston Birth Cohort (BBC). Journal of Perinatology 41:1025–1032
22. Editorial Board of Chinese Journal of Pediatrics, Child Health Group of Pediatrics Branch of Chinese Medical Association, Neonatal Group of Pediatrics Branch of Chinese Medical Association (2016) Suggestions on feeding premature and low birth weight infants after discharge. Chinese Journal of Pediatrics 54:6–12
23. KoletzkoB P (2014) Nutritioncareof preterminfants, scientificbasisandpracticalguidelines. sKargerPub, Germany
24. Zhao T, Feng H-M, Caicike B, Zhu Y-P (2021) Investigation Into the Current Situation and Analysis of the Factors Influencing Extrauterine Growth Retardation in Preterm Infants. Frontiers in Pediatrics 9:301
25. Izquierdo Renau M, Aldecoa-Bilbao V, Balcells Esponera C, del Rey Hurtado de Mendoza B, Iriondo Sanz M, Iglesias-Platas I (2019) Applying methods for postnatal growth assessment in the clinical setting: evaluation in a longitudinal cohort of very preterm infants. Nutrients 11:2772
26. Lin R, Shen W, Wu F, Mao J, Liu L, Chang Y, Zhang R, Ye X, Qiu Y, Ma L (2022) Human Milk Fortification in Very Preterm Infants in China: A Multicentre Survey. Frontiers in Pediatrics:42

27. Expert consensus working group on the use of breast milk fortifier for premature infants, Editorial board of Chinese Journal of Neonatology (2019) Consensus on the use of human milk fortifier for preterm infants. Chinese Journal of Neonatology (Chinese and English) 34:321–328
28. Bozkurt O, Alyamac Dizdar E, Bidev D, Sari FN, Uras N, Oguz SS (2022) Prolonged minimal enteral nutrition versus early feeding advancements in preterm infants with birth weight ≤ 1250 g: a prospective randomized trial. The Journal of Maternal-Fetal & Neonatal Medicine 35:341–347
29. William Jr W (2017) Optimizing nutrition of the preterm infant. Chinese Journal of Contemporary Pediatrics 19:1–21
30. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, Buzas JS, Bertino E, Gagliardi L, Bellù R (2015) Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000–2013. Pediatrics 136:e84-e92
31. Ramaswamy VV, Bandyopadhyay T, Ahmed J, Bandiya P, Zivanovic S, Roehr CC (2021) Enteral feeding strategies in preterm neonates ≤ 32 weeks gestational age: A Systematic review and network meta-analysis. Annals of Nutrition and Metabolism:1–17
32. Dorling J, Gale C (2019) Early enteral feeding in preterm infants. Seminars in Perinatology 43:151159
33. Duchon J, Barbian ME, Denning PW (2021) Necrotizing enterocolitis. Clinics in Perinatology 48:229–250
34. Evidence-based Professional Committee of Neonatology Branch of Chinese Medical Doctor Association, Tang J, Feng Z, Mu D, Huang L, Xiong T (2021) Clinical guidelines for the diagnosis and treatment of neonatal necrotizing enterocolitis (2020). Chinese Journal of Contemporary Pediatrics 23:1–11
35. Hansson L, Lind T, Wiklund U, Öhlund I, Rydberg A (2019) Fluid restriction negatively affects energy intake and growth in very low birthweight infants with haemodynamically significant patent ductus arteriosus. Acta Paediatrica 108:1985–1992
36. Hong CR, Fullerton BS, Mercier CE, Morrow KA, Edwards EM, Ferrelli KR, Soll RF, Modi BP, Horbar JD, Jaksic T (2018) Growth morbidity in extremely low birth weight survivors of necrotizing enterocolitis at discharge and two-year follow-up. Journal of Pediatric Surgery 53:1197–1202
37. Shan C, Feng Q, Wang Y, Li X, Zhang X, Sang T, Ru X, Song X (2018) Early catch-up growth status and its influencing factors in small for gestational age preterm infants. Chinese Journal of Neonatology (Chinese and English) 33:175–181