Pediatrics and Neonatology 63 (2022) 590—598

Available online at www.sciencedirect.com

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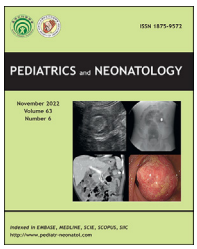

Original Article

Factors influencing extrauterine growth retardation in singleton-non-small for gestational age infants in China: A prospective multicenter study

Ya-Sen Wang [a,b,1], Wei Shen [a,b,1], Fan Wu [c], Jian Mao [d], Ling Liu [e], Yan-Mei Chang [f], Rong Zhang [g], Xiu-Zhen Ye [h], Yin-Ping Qiu [i], Li Ma [j], Rui Cheng [k], Hui Wu [l], Dong-Mei Chen [m], Zhi Zheng [a,b], Xin-Zhu Lin [a,b,**], Xiao-Mei Tong [f,*], the National Multi-centre Eugr Collaborative Group

[a] *Department of Neonatology, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, China*
[b] *Xiamen Key Laboratory of Perinatal-Neonatal Infection, Xiamen, China*
[c] *Department of Neonatology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*
[d] *Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, China*
[e] *Department of Neonatology, Guiyang Maternal and Child Health Hospital·Guiyang Children' s Hospital, Guiyang, China*
[f] *Department of Pediatrics, Peking University Third Hospital, Beijing, China*
[g] *Department of Neonatology, Children's Hospital of Fudan University, Shanghai, China*
[h] *Department of Neonatology, Guangdong Province Maternal and Children's Hospital, Guangzhou, China*
[i] *Department of Neonatology, General Hospital of Ningxia Medical University, Yinchuan, China*
[j] *Department of Neonatology, Children's Hospital of Hebei Province, Shijiazhuang, China*
[k] *Department of Neonatology, Children' Hospital of Nanjing Medical University, Nanjing, China*
[l] *Department of Neonatology, The First Hospital of Jilin University, Changchun, China*
[m] *Department of Neonatology, Quanzhou Maternity and Children's Hospital, Quanzhou, China*

Received Dec 24, 2021; received in revised form Mar 23, 2022; accepted Apr 12, 2022
Available online 1 August 2022

* Corresponding author.
** Corresponding author. Department of Neonatology, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, China.
E-mail addresses: xinzhufj@163.com (X.-Z. Lin), tongxm2007@126.com (X.-M. Tong).
[1] Ya-Sen Wang and Wei Shen contributed equally to this work.

https://doi.org/10.1016/j.pedneo.2022.04.013

Key Words
extrauterine growth retardation;
nutrition;
risk factors;
singleton;
small for gestational age;
very preterm infants

Abstract *Background:* The incidence of extrauterine growth retardation (EUGR) varies considerably in different countries due to the distinct definitions and inclusion criteria of individual studies. Most studies included small for gestational age (SGA) very preterm infants (VPIs), resulting in a higher incidence of EUGR. Experts have suggested the accurate definition of "EUGR" in SGA infants is not "true EUGR". The postnatal growth curve of multiple premature births also differs from that of singletons. As far as we know, there is no study about relationship between singleton-non-SGA preterm infants and EUGR.
Objectives: To analyze the factors influencing EUGR among VPIs who were singleton-non-SGA in China.
Methods: A prospective-multicenter study was conducted in 28 hospitals distributed through China from September 2019 to December 2020. The clinical data on singleton-non-SGA among VPIs were divided into EUGR group (n = 692) and non-EUGR group (n = 912).
Results: Compared to non-EUGR group, the mean gestational age (GA), mean birth weight (BW) and percentage of BW in Fenton curve in EUGR group were lower ($P < 0.001$ for all). The incidence of EUGR among distinct GA groups (classifications of GA < 28weeks, 28—28^{+6} weeks, 29—29^{+6} weeks, 30—30^{+6} weeks and 31—31^{+6} weeks) and distinct BW groups (classifications of BW<1000 g, 1000—1249 g, 1250—1499 g, 1500—1999g and 2000—2500 g) were statistically significant ($P = 0.004$ and $P < .001$). Logistic regression analysis indicated that later addition of human milk fortifier (HMF), later attainment of HMF sufficient fortification, later return to BW, more accumulative days of fasting, longer duration of parenteral nutrition, total duration of oxygen support and moderate/severe bronchopulmonary dysplasia (BPD) were risk factors for the development of EUGR in singleton-non-SGA VPIs ($P < 0.001$, $P = 0.002$, $P < 0.001$, $P = 0.002$, $P = 0.017$, $P = 0.003$ and $P = 0.002$, respectively). The use of full-course antenatal steroids, greater BW as a percentile of the Fenton curve, breastfeeding initiation and faster average velocity of weight growth effectively protected against EUGR ($P = 0.008$, $P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively).
Conclusions: The overall incidence of EUGR was 43.1% among singleton-non-SGA VPIs in China. Raising the full-course antenatal steroids usage, reducing the incidence of moderate and severe BPD, attaching importance to the management of enteral nutrition in VPIs and increasing the weight growth velocity can reduce the incidence of EUGR.

1. Introduction

As the survival rate of preterm infants has improved over the past decade, their life quality has elicited the concern of researchers. Studies have reported the concept of intact survival (or survival without morbidity), which emphasizes survival without significant neuromotor, visual and auditory impairment during follow-up during postmenstrual age of 18—24 months. One study from the Chinese Neonatal Network showed that the survival rate in very preterm infants (VPIs) who received complete care in China was 95.4%. However, the rate of survival without major morbidity was 57.2% for all VPIs with complete care, which is lower than that in developed countries.[1] A recent multicenter study from China showed that the incidence of extrauterine growth retardation (EUGR) of VPI was 47.3%.[2] However, the incidence of EUGR among surviving VPIs in China is higher than that in other developed countries. It influences physical development, causing early complications of preterm infants and potentially damaging long-term health, specifically neurocognitive function. As a result, it increases the risk of cardiovascular diseases and chronic metabolic syndrome in adulthood.[3,4] The incidence of EUGR varies considerably in different countries due to the distinct definitions and inclusion criteria in individual studies. Experts have suggested the accurate definition of "EUGR" in small for gestational age (SGA) infants is a continuation of intrauterine growth retardation (IUGR) rather than cause by postnatal factors. The postnatal growth curve of multiple premature births differs from that of singletons.[5,6] Therefore, this prospective multicenter study analyzed the clinical data of singleton-non-SGA among VPIs and sought to determine the factors influencing EUGR in China. We aim to provide a scientific foundation for preventing EUGR and optimizing nutritional management of VPIs.

2. Methods

2.1. Study population and design

The study population was sourced from the neonatal intensive care units (NICU) of 28 Grade III hospitals located in seven regions of Northeast, North, East, Central, South, Northwest, and Southwest China during the period from September 2019 to December 2020. Clinical information of VPIs was collected from these hospitals.

Inclusion criteria: (1) singleton non-SGA VPIs; (2) birth gestational age (GA) <32 weeks; (3) hospital stay > 2w; and (4) admission within 24 h of birth.

Exclusion criteria: (1) multiple births; (2) SGA; (3) congenital malformation or genetic metabolic disease; (4) surgical treatments in the neonatal period except for necrotizing enterocolitis (NEC); and (5) death, discontinuation of therapy, or left hospital against medical advise.

Of the 2600 VPIs, apart from 86 cases with incomplete maternal/infant information, 130 cases of SGA and 780 cases of non-SGA multiple births were excluded, while 1604 singleton non-SGA VPIs were enrolled in this study (Fig. 1). Based on whether weight fell below the 10th percentile on the growth curve at the corrected GA of 36 weeks or at discharge, infants were divided into EUGR group (n = 692) and non-EUGR group (n = 912).

2.2. Data collection

A questionnaire was designed to collect data including general information, maternal pregnancy complications (diabetes, hypertension, thyroid disease, etc.), clinical data, early-related complications [respiratory distress syndrome (RDS), early-onset sepsis (EOS), NEC, intraventricular hemorrhage (IVH), etc.], time of milk initiation, breastfeeding, the duration of fasting, feeding intolerance (FI), parenteral nutrition time, accumulative amino acid and fat milk intake, and so on.

2.3. Study definitions/Diagnostic criteria

EUGR. EUGR was defined as the weight below the 10th percentile of the 2013 Fenton curve of premature infants of the same GA and sex at postmenstrual age of 36 weeks or at discharge.[7] Infants' weight was measured before feeding, and the weight of clothes and diapers were removed at the same time; weight was measured at least twice each time and the average taken. The measurement result is accurate to 1 g.

Relevant definition of intestinal nutrition. (1) Time of first-time milk feeding: initiation time of oral/nasal breast milk or formula after birth (excluding oral care of colostrum); (2) breastfeeding: the breastfeeding accounts for more than 80% of total enteral feeding; (3) total enteral feeding time in the days: the period from the beginning of feeding to the total feeding up to 150 ml/kg/day; (4) days to reach the target total calorie intake and oral calorie intake: time required to reach 110 kcal/kg/day; (5) FI is defined as preterm infants inability to digest intestinal feeding, and gastric retention exceeding 50% of the previous feed, development of abdominal distension and (or) vomiting, causing interrupted feeding schedules.[8]

Definition of early-related complications. For diagnostic criteria of EOS and late-onset sepsis (LOS) refer to Expert Consensus on the Diagnosis and Management of Neonatal Sepsis (version 2019)[9]; for diagnostic criteria of other diseases [including bronchopulmonary dysplasia (BPD), hemodynamically significant patent ductus arteriosus (hsPDA), parenteral nutrition-associated cholestasis (PNAC), RDS, NEC, IVH, etc.] refer to Practice of Neonatology (5th Edition).[10]

2.4. Calculation formula of weight growth velocity

The average velocity of weight growth g/kg/day = [1000 × ln (Wn/W1)]/(Dn-D1). Wn: The weight of the infant at the day of discharge (g); W1: The weight of the

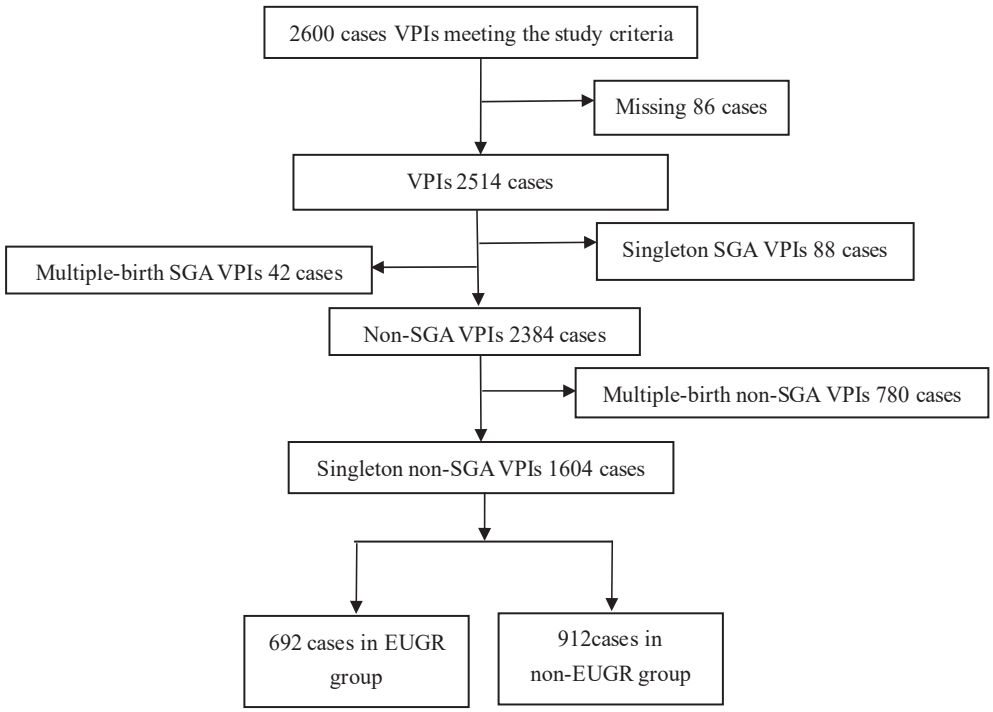

Fig. 1 Flow chart of study participants. VPI: very preterm infants,SGA: small for gestational age, EUGR: extrauterine growth retardation.

infant after delivery at the first day (g); Dn: Length of hospitalization in days (d); D1: the length of regaining birth weight (BW) in days (d).[11]

2.5. Statistical analysis

Statistical analyses were performed using the SPSS 22.0 software. The enumeration data were expressed by a percent sign (%) and the differences were detected using chi-square test or Fisher's exact test. Chi-square correlation coefficient (r) was used to describe the relationship between BW, gestational age and EUGR. Distribution of the data was assessed for normality using the Kolmogorov-Smirnov test. The Independent Samples t-test was used to analyze the mean comparison of two independent groups. The measurement data of abnormal distribution was shown as median, interquartile range, and their differences were analyzed using the rank-sum test. Multivariate analysis was performed using binary logistic regression analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Incidence of EUGR in singleton-non-SGA VPIs at different GAs and BWs

The overall incidence of EUGR was 43.1% among singleton-non-SGA VPIs. The incidence of EUGR with the classifications of GA < 28weeks, 28–28^{+6}weeks, 29–29^{+6}weeks, 30–30^{+6}weeks and 31–31^{+6}weeks in singleton non-SGA VPIs was 51.6% (99/192), 49.4% (118/239), 44.7% (130/291), 39.1% (157/402), and 39.2% (188/480), respectively. The differences among distinct GA groups were statistically significant ($P = 0.004$) and our findings showed that lower GA had higher incidence of EUGR ($r = 0.094$). The incidence of EUGR with the classifications of BW < 1000 g, 1000–1249 g, 1250–1499 g, 1500–1999g, and 2000–2500 g was 77.8% (119/153), 61.4% (251/409), 46.3% (235/508), 17.2% (86/501), and 3.0% (1/33), respectively. Remarkable differences were noted in distinct BW groups ($P < 0.001$), indicating that lower BW resulted in increased incidence rate of EUGR ($r = 0.420$) (Table 1).

Table 1 Incidence of EUGR among singleton non-SGA VPIs at different GAs and BWs.

	Non-EUGR ($n = 912$)	EUGR ($n = 692$)	χ^2	P
GA at birth (n, %)			15.440	0.004*
<28weeks	93 (48.4)	99 (51.6)		
28–28^{+6}weeks	121 (50.6)	118 (49.4)		
29–29^{+6}weeks	161 (55.3)	130 (44.7)		
30–30^{+6}weeks	245 (60.9)	157 (39.1)		
31–31^{+6}weeks	292 (60.8)	188 (39.2)		
BW (n, %)			291.695	<0.001*
<1000 g	34 (22.2)	119 (77.8)		
1000–1249 g	158 (38.6)	251 (61.4)		
1250–1499 g	273 (53.7)	235 (46.3)		
1500–1999g	415 (82.8)	86 (17.2)		
2000–2500 g	32 (97.0)	1 (3.0)		

EUGR, extrauterine growth retardation; non-SGA, non-small for gestational age; VPIs, very preterm infants; GA, gestational age; BW, birth weight.
*Values are significantly different between non-EUGR and EUGR groups (P < 0.05).

3.2. General information and clinical features in singleton-non-SGA VPIs between EUGR group and non-EUGR group

The EUGR group (n = 692) included 368 (53.2%) male babies and 441 cases (63.7%) delivered by cesarean section, with mean GA at birth of 29.9 (28.6, 31.0) weeks, mean BW of 1220.0 (1060.0, 1380.0) grams and BW at the mean percentile of the Fenton curve of 38.1 (21.9, 55.5). The non-EUGR group (n = 912) included 521 (57.1%) male babies and 458 cases (50.2%) of cesarean section, with a mean GA at birth of 30.2 (29.0, 31.1) weeks; mean BW of 1485.0 (1285.0, 1662.5) grams and the BW at the mean percentile of the Fenton curve of 64.1 (49.4, 78.7). Compared to non-EUGR group, EUGR group had comparatively lower average GA at birth, average weight at birth, and lower mean percentile of Fenton curve of BW ($P < 0.001$ for all), yet the number of cesarean sections was greater ($P < 0.001$) (Table 2). No statistically significant difference was noted between the two groups in terms of gender.

In contrast with non-EUGR group, EUGR group contained more cases of 1-min Apgar score ≤7 and postpartum steroids exposure (both $P < 0.001$); fewer cases of full-course antenatal steroids treatment ($P = 0.015$); and longer duration of (non-)invasive mechanical ventilation, total oxygen consumption and accumulated application of antibiotic ($P < 0.001$ for all) (Table 2).

3.3. The complication profile of mothers and preterm infants between groups in singleton non-SGA VPIs

In contrast with the non-EUGR group, a higher proportion of mothers suffered from hypertension in the EUGR group ($P < 0.001$). The higher incidence of early-related complications was detected in the EUGR group including RDS ($P = 0.005$), NEC ≥2 stage ($P < 0.001$), hsPDA ($P < 0.001$), LOS ($P < 0.001$), PNAC ($P < 0.001$), retinopathy of prematurity (ROP) with intervention ($P = 0.010$) and moderate/severe BPD ($P < 0.001$) compared to the non-EUGA group. We found no remarkable differences in EOS, IVH of Grade III/IV, or periventricular leukomalacia (PVL) (Table 3) ($P > 0.05$ for all).

3.4. In-hospital nutrition status among singleton-non-SGA VPIs between groups

Compared to the non-EUGR group, the EUGR group had more accumulated days of fasting, enteral nutrition

Table 2 Clinical features in singleton-non-SGA VPIs between EUGR and non-EUGR groups.

	Non-EUGR (n = 912)	EUGR (n = 692)	Z/χ^2	P
Male (n, %)	521 (57.1%)	368 (53.2%)	2.482	0.115
Cesarean section (n, %)	458 (50.2%)	441 (63.7%)	29.148	<0.001*
Mean gestational age at birth (g) (median, IQR)	30.2 (29.0,31.1)	29.9 (28.6,31.0)	−3.813	<0.001*
Mean birth weight (g) (median, IQR)	1485.0 (1285.0,1662.5)	1220.0 (1060.0,1380.0)	−17.459	<0.001*
Birth weight at the mean percentile of the Fenton curve (%) (median, IQR)	64.1 (49.4, 78.7)	38.1 (21.9, 55.5)	−19.486	<0.001*
One-minute Apgar scores ≤7 (n, %)	280 (30.7)	304 (43.9)	29.740	<0.001*
Full-course antenatal steroids (n, %)	711 (78.0)	503 (72.7)	5.944	0.015*
Invasive mechanical ventilation (days) (median, IQR)	0.0 (0.0,2.0)	2.0 (0.0,6.0)	−10.221	<0.001*
Non-invasive mechanical ventilation (days) (median, IQR)	10.0 (5.0,23.0)	19.0 (8.0,31.0)	−8.352	<0.001*
The total duration of oxygen support (days) (median, IQR)	25.0 (11.0,39.0)	36.0 (21.0,54.6)	−9.919	<0.001*
Antibiotic duration (days) (median, IQR)	10.0 (7.0,17.0)	14.0 (7.0,23.0)	−6.150	<0.001*
Postnatal steroids (n, %)	83 (9.1)	122 (17.6)	25.677	<0.001*

EUGR, extrauterine growth retardation; singleton-non-SGA, singleton-non-small for gestational age; VPIs, very preterm infants; IOR, interquartile range.
*Values are significantly different between non-EUGR and EUGR groups (P < 0.05).

initiation, parenteral nutrition, total enteral nutrition, 110 kcal/kg/day of total calories, 110 kcal/kg/day of oral calories ($P < 0.001$ for all), lower proportion of breastfeeding initiation ($P = 0.030$), later initiation of breastfeeding fortification ($P < 0.001$) and achievement of human milk fortifier (HMF) adequate fortification ($P < 0.001$), more FI cases ($P < 0.001$), longer duration of regaining BW ($P = 0.015$) and hospital stay ($P < 0.001$) as well as a slower velocity of weight growth ($P < 0.001$) and higher cumulative doses of amino acids and fat emulsion during hospitalization ($P < 0.001$). No statistically significant differences were noted regarding maximum weight loss and breastfeeding between the two groups (Table 4).

3.5. Risk factors for EUGR in singleton-non-SGA VPIs

Screening for risk factors indicated that mothers suffer from hypertension; caesarean delivery; mean percentile of Fenton curve of BW; NEC ≥2 stage; hsPDA; LOS; ROP with intervention; moderate/severe BPD; 1-min Apgar scores ≤7; full-course antenatal steroids; (non-)invasive mechanical ventilation; the total duration of oxygen support; antibiotic duration; postnatal steroids; days to regain BW; average velocity of weight growth; time to initiate enteral feeding; breastfeeding initiation; total enteral feeding time in the days; accumulative days of parenteral nutrition; fasting; 110 kcal/kg/day of total calories, and 110 kcal/kg/day of oral calories; FI; accumulative dose of amino acids;

Table 3 Complications of mothers and infants between groups among singleton non-SGA VPIs.

	Non-EUGR (n = 912)	EUGR (n = 692)	χ^2	P
Maternal complications (n, %)				
Diabetes	158 (17.3)	95 (13.7)	3.830	0.050
Hypertension	114 (12.5)	232 (33.5)	102.816	<0.001*
Thyroid disease	43 (4.7)	33 (4.8)	0.003	0.960
Connective tissue disease	12 (1.3)	12 (1.7)	0.467	0.494
Premature complications (n, %)				
RDS	585 (64.1)	490 (70.8)	7.906	0.005*
EOS	129 (14.1)	108 (15.6)	0.668	0.414
NEC> = 2 Stage	54 (5.9)	85 (12.3)	20.122	<0.001*
IVH of Grade III/IV	15 (1.6)	14 (2.0)	0.317	0.573
hsPDA	234 (25.7)	242 (35.0)	16.353	<0.001*
LOS	85 (9.3)	130 (18.8)	30.373	<0.001*
PNAC	55 (6.0)	102 (14.7)	33.798	<0.001*
ROP with intervention	20 (2.2)	31 (4.5)	6.684	0.010*
moderate/severe BPD	82 (9.0)	147 (21.2)	48.256	<0.001*
PVL	33 (3.6)	29 (4.2)	0.347	0.556

SGA, small for gestational age; VPIs, very preterm infants; EUGR, extrauterine growth retardation; RDS, respiratory distress syndrome; EOS, early-onset sepsis; NEC, necrotizing Enterocolitis; IVH, Intraventricular hemorrhage; hsPDA, hemodynamically significant patent ductus arteriosus; LOS, late-onset sepsis; PNAC, parenteral nutrition associated cholestasis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia; IOR, interquartile range.
*Values are significantly different between non-EUGR and EUGR groups ($P < 0.05$).

Table 4 Comparison of in-hospital nutrition between groups among singleton non-SGA VPIs.

	NON-EUGR (N = 912)	EUGR (n = 692)	Z/χ^2	*P*
Maximum weight loss (%) (median, IQR)	6.3 (3.7,9.0)	6.8 (3.7,10.0)	−1.482	0.138
Days to regain birth weight (days) (median, IQR)	9.0 (7.0,11.0)	9.0 (7.0,12.0)	−2.425	0.015*
Average velocity of weight growth (g/kg/day) (median, IQR)	15.8 (13.5,19.3)	13.9 (11.6,16,6)	−9.851	<0.001*
Time to initiate enteral feeding (hours) (median, IQR)	20.0 (7.0,30.5)	24.0 (12.0,48.0)	−5.924	<0.001*
Breastfeeding for first time (n, %)	153 (16.8)	89 (12.9)	4.707	0.030*
Total enteral nutrition (days) (median, IQR)	21.0 (15.0,30.0)	30.0 (21.0,40.0)	−11.431	<0.001*
Breast feeding (n, %)	398 (43.6)	294 (42.5)	0.214	0.644
Days of parenteral nutrition (days) (median, IQR)	17.0 (11.0,26.0)	24.0 (17.0,36.0)	−11.833	<0.001*
Accumulative days of fasting (days) (median, IQR)	1.0 (0.5,3.0)	3.0 (1.0,7.0)	−10.357	<0.001*
Feeding intolerance (n, %)	260 (28.5)	317 (45.8)	51.130	<0.001*
Days of total calories up to standard 110 kcal/kg/day (days) (median, IQR)	8.0 (6.0,12.0)	11.0 (7.0,18.0)	−9.597	<0.001*
Days of oral calories up to standard 110 kcal/kg/day (days) (median, IQR)	19.0 (13.0,28.0)	28.0 (20.0,39.0)	−12.617	<0.001*
Accumulative dose of amino acids during hospitalization (g/kg) (median, IQR)	36.5 (20.5,58.3)	52.0 (34.2,84.1)	−10.748	<0.001*
Accumulative dose of fat emulsion during hospitalization (g/kg) (median, IQR)	31.0 (15.8,50.5)	45.3 (28.5,73.0)	−10.579	<0.001*
Amount of breast milk to start adding HMF (ml/kg/day) (median, IQR)	100.0 (87.6120.0)	107.9 (93.0.128.0)	−3.590	<0.001*
Days of reaching HMF sufficient fortification (days) (median, IQR)	6.0 (4.0,17.0)	11.0 (5.0,20.0)	−5.012	<0.001*
Days in hospital (days) (median, IQR)	39.0 (30.0,51.0)	52.0 (41.0,66.0)	−14.092	<0.001

EUGR, extrauterine growth retardation; VPIs, very preterm infants; SGA, small for gestational age; HMF, human milk fortifier; IOR, interquartile range.
*Values are significantly different between non-EUGR and EUGR groups ($P < 0.05$).

fat emulsion during hospitalization; initiation of breastfeeding fortification and days of achievement of HMF adequate fortification correlated with EUGR. Logistic regression analysis revealed that late addition of HMF (*OR* = 1.022, 95% *CI*:1.012–1.032), late attainment of HMF sufficient fortification (*OR* = 1.042, 95% *CI*: 1.015–1.070), late return to BW (*OR* = 1.192, 95% *CI*:1.115–1.274), more accumulative days of fasting (*OR* = 1.104, 95% *CI*:1.036–1.177), longer duration of parenteral nutrition (*OR* = 1.022, 95% *CI*:1.004–1.041) and total oxygen consumption (*OR* = 1.018, 95% *CI*:1.006–1.031) and moderate/severe BPD (*OR* = 3.111, 95% *CI*:1.520–6.368) were the independent risk factors for EUGR development in singleton non-SGA VPIs. Usage of full-course antenatal steroids (*OR* = 0.439, 95% *CI*:0.239–0.805), greater BW as a percentile of the Fenton curve (*OR* = 0.911, 95% *CI*:0.896–0.926), breastfeeding initiation (*OR* = 0.189, 95% *CI*:0.107–0.334) and faster average velocity of weight growth (*OR* = 0.794, 95% *CI*:0.745–0.847) were the protective factors (Table 5).

4. Discussion

Notably, VPIs had the highest mortality and morbidity among preterm infants, accounting for up to 50% of all neonatal deaths.[12] VPIs also represent a high-risk group for EUGR occurrence. The incidence of EUGR among 479 VPIs cases in Spain between 2003 and 2014 was 50.7%[5] while those among non-small for gestational age of VPIs and small for gestational age of VPIs were 42.7% and 98.5%, respectively. This study found that the incidence rates of EUGR in singleton-non-small for gestational age of VPIs and singleton-small for gestational age of VPIs were 43.1% and 97.7%, respectively, which was in line with previous reports.[5] Moreover, the incidence of EUGR with SGA was remarkably higher than that of non-SGA. The "true EUGR" occurs in infants with no evidence of IUGR, i.e., infants with non-SGA'.[5] Furthermore, the weight of multiple births was lower than that of singletons[13] and infant growth is affected by multiple genetic and intrauterine environmental factors.[6] Thus, we performed this study and attempted to provide a scientific basis for optimizing the management of VPIs.

4.1. Relationship among GA, BW, and EUGR

In line with previous research,[14] we found that younger GA or lower BW in singleton-non-SGA VPIs resulted in higher incidence of EUGR. Unlike GA, BW had a stronger relationship with the EUGR occurrence ($r = 0.420$). Premature infants with lower BW and younger GA had poor growth, less mature organs, and a low accumulation of nutrients in utero. They were more inclined to complications related to premature infants with greater nutritional demands and higher energy consumption.[15] This increased their susceptibility to nutritional deficiency, potentially resulting in EUGR. We found that a significant number of mothers in the EUGR group were complicated with hypertension. Hypertensive disorders in

Table 5 Multivariate logistic regression of the factors for EUGR occurrence.

	B	SE	P	*OR (95%CI)*
Full-course antenatal steroids	−0.824	0.310	0.008*	0.439 (0.239−0.805)
Percentage of birth weight in Fenton curve	−0.094	0.008	<0.001*	0.911 (0.896−0.926)
Breastfeeding initiation	−1.665	0.290	<0.001*	0.189 (0.107−0.334)
Amount of breast milk to start adding HMF	0.022	0.005	<0.001*	1.022 (1.012−1.032)
Days of reaching HMF sufficient fortification	0.041	0.013	0.002*	1.042 (1.015−1.070)
Days to regain birth weight	0.175	0.034	<0.001*	1.192 (1.115−1.274)
Average velocity of weight growth	−0.230	0.033	<0.001*	0.794 (0.745−0.847)
Accumulative days of fasting in hospital	0.099	0.032	0.002*	1.104 (1.036−1.177)
Days of parenteral nutrition	0.022	0.009	0.017*	1.022 (1.004−1.041)
The total duration of oxygen support	0.018	0.006	0.003*	1.018 (1.006−1.031)
moderate/severe BPD	1.135	0.365	0.002*	3.111 (1.520−6.368)
Constants	3.370			

EUGR, extrauterine growth retardation; BPD, bronchopulmonary dysplasia; HMF, human milk fortifier.
*$P < 0.05$ was considered statistically significant.

pregnancy (particularly pre-eclampsia and eclampsia) caused the remodeling barrier of uterine spiral artery trophoblast, placental ischemia, and hypoxia. Furthermore, attenuation of placental perfusion function potentially affects nutritional supply, resulting in IUGR and fetal distress, thereby lowering the percentage of BW in the Fenton curve along with increasing the rate of EUGR.[16,17] Our study revealed that BW at the higher percentile of the Fenton curve was a protective factor against EUGR. This was in agreement with an earlier report that BW at the percentile of the Fenton curve is a vital predictor of EUGR occurrence.[18]

4.2. Premature infants with severe complications increases the risk of EUGR

Previous studies indicated that moderate/severe BPD was an independent risk factor for EUGR in non-SGA preterm infants.[5,16] The long duration of total oxygen consumption in infants with EUGR indicated that they were in serious condition and required more medical interventions including more postnatal steroids exposure, and longer duration of (non-)invasive mechanical ventilation, ultimately causing higher incidence of EUGR. Rutkowska et al.[19] reported that mechanical ventilation time >7 days was an independent risk factor for severe BPD. Our study further confirmed that a longer time of total oxygen consumption and moderate/severe BPD were independent risk factors for the development of EUGR in singleton-non-SGA VPIs.

In 2019, the European Consensus Guidelines on the Management of RDS reported that to reduce the incidence of RDS, a single course of antenatal steroids therapy should be administered 24 h before VPIs delivery.[20] Moreover, a sufficient course of antenatal steroids usage can promote the maturation of the gastrointestinal tract and other organs,[21] and the early establishment of enteral feeding of preterm infants, decreasing the incidence of EUGR. This study confirmed that adequate antenatal treatment with steroids was a protective factor consistent with that reported by Clark et al.[22] The application rate of antenatal steroids in the full course of treatment was 72.7% in the EUGR group, which was lower than that of 78.0% in the non-EUGR group. As report goes, the application rate of antenatal steroids among infants of GA < 30 weeks or BW ≤ 1500 g was 86.9% at Italy.[23]There is still a large disparity between usage of antenatal steroids in China and other developed countries.

4.3. Nutritional status in singleton non-SGA VPIs

This study observed that late addition of HMF, late attainment of HMF adequacy fortification, late return to BW, longer cumulative days of fasting, and longer duration of parenteral nutrition were risk factors for EUGR in singleton-non-SGA VPIs. Additionally, breastfeeding for the first time and a faster average velocity of weight growth were considered as protective factors. A cohort study by Izquierdo Renau et al.[24] on the relationship between nutrition and growth among VPIs revealed that the rate of weight growth in the EUGR group was slower than that in the non-EUGR group (14.2 g/kg/day vs. 15.9 g/kg/day). Another study shows that slower velocity of weight growth was an independent risk factor for EUGR,[14] which was consistent with our results. Regain BW slower indicates insufficient nutritional intake during the early postnatal period, resulting in excessively slow weight growth. Klevebro et al.[25] showed that a higher level of energy intake in the early postnatal period can promote weight growth and reduce the risk of BPD. The enteral feeding was initiated at 23.0 (9.0, 40.0) hours for all infants in our study when the breast milk was colostrum. Colostrum initiation reduced the risk of NEC, LOS, BPD, and it improved long-term neurocognitive and motor function.[26−28] Nevertheless, a consensus exists among peers that HMF needs timely addition since the protein of breast milk gradually decreased over time until it was insufficient for the normal growth of VPIs.[29] Unlike the non-EUGR group, infants in the EUGR group added late HMF (107.9 ml/kg/day vs. 100.0 ml/kg/day), reaching the comprehensive fortification of HMF (11.0 days vs. 6.0 days). In both the EUGR and non-EUGR groups, the amount of breast milk for HMF initiation and the time of full fortification lagged behind the recommendations of the Chinese Expert Consensus on the Application of Breast Milk Fortification in Preterm Infants.[30] We found that the EUGR group had more accumulated days of enteral nutrition initiation (30 days vs. 21 days) and total enteral nutrition (24 h vs. 20 h). This may indicate that they were in serious condition. Starding enteral feeding soon

after birth has been resisted due to severity of the condition and concern about early enteral feeding leading to NEC, resulting in longer duration of fasting time, duration of parenteral nutrition, and untimely addition of HMF in EUGR group.[31] It was suggested that the management of enteral nutrition in VPIs with EUGR was poor. A retrospective study by Wemhöner et al.[32] showed that enteral nutrition played an irreplaceable role in the prevention and treatment of BPD, and Alshaikh et al.[33] also confirmed that delayed total enteral nutrition increased the incidence of moderate and severe BPD, thus increasing the risk of EUGR. Therefore, clinicians should pay attention to the enteral nutrition management of singleton-non-SGA VPIs.

This study has compelling limitations. First, an information bias was inevitable due to the lack of uniformity among measuring tools. However, all surveyors received unified and standardized training including the methods of measurement and application of measuring devices to minimize information bias. Secondly, although we conducted standardized nutrition management training for clinicians, variations in nutritional management were still inevitable between infants because our data were obtained from hospitals located in different regions of China.

5. Conclusion

In summary, the incidence of EUGR was 43.1% in singleton-non-SGA VPIs in China. In addition, lower gestational age and weight at birth can lead to higher incidence of EUGR. The incidence of EUGR can be reduced by raising the full-course antenatal steroids usage; reducing the incidence of moderate and severe BPD; reducing the incidence of moderate and severe BPD; attaching importance to the management of enteral nutrition and increasing the weight growth velocity of VPIs.

Ethics and clinical registration

This study was organized by the Nutrition Professional Committee of Neonatologists Branch of Chinese Medical Doctor Association and registered in the Chinese Clinical Trial Registry (Registration No: ChiCTR1900023418). The research protocol was approved by the Ethics Committee of Women and Children's Hospital affiliated to Xiamen University/Xiamen Maternal and Child Health Hospital (Batch number kY-2019-016).

Declaration of competing interests

None.

Acknowledgments

We thank the infants and their parents or guardians who participated in the study. We thank all selected hospitals for their participation and great cooperation. This study was supported by grants from Guidance Project of Xiamen Medical and Health in 2019 (3502Z20199139) and Guidance Project of Xiamen Medical and Health in 2021 (3502Z 20214ZD1225).

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Abbreviations

EUGR	extrauterine growth retardation
VPIs	very preterm infants
SGA	small for gestational age
GA	gestational age
BW	birth weight
RDS	respiratory distress syndrome
NEC	necrotizing enterocolitis
BPD	bronchopulmonary dysplasia
HMF	human milk fortifier
FI	feeding intolerance
IUGR	intrauterine growth retardation
NICU	neonatal intensive care units
EOS	early-onset sepsis
IVH	intraventricular hemorrhage
hsPDA	hemodynamically significant patent ductus arteriosus
LOS	late-onset sepsis
PNAC	parenteral nutrition-associated cholestasis
ROP	retinopathy of prematurity
PVL	periventricular leukomalacia