Extrauterine growth restriction in very low birth weight infants according to different growth charts: a retrospective 10 years observational study

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Research Article

Keywords: extrauterine growth restriction, very low birth weight, growth charts, Fenton, Intergrowth 21, INeS charts

Posted Date: July 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1769169/v1

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Abstract

Background

Extrauterine growth restriction (EUGR) is common among very low birth weight (VLBW) infants and associated with poor neurodevelopmental outcomes. Prevalence of EUGR is a basic indicator of ‘nutritional care’ and an important health outcome measure. There are two types of EUGR definitions (cross-sectional and longitudinal) and many growth charts for monitoring postnatal growth. Aims of our study were 1) to compare the rate of small for gestational rate (SGA) and EUGR in a population of VLBW infants, both according to different growth charts (Fenton, INeS charts and Intergrowth-21) and according to different definitions; 2) to identify risk factors for EUGR.

Methods

this is a single centre retrospective observational study, including all VLBW infants born between 1st of January 2009 and 31st of December 2018. Anthropometric measures were obtained at birth and at discharge and presented as z-scores according to three growth charts (Fenton, INeS charts, Intergrowth-21). Maternal, clinical and nutritional data were retrieved from clinical records.

Results

228 VLBW were included. Percentage of SGA did not change significantly according to the three different growth charts (Fenton 22.4%, INeS charts 22.8%, Intergrowth 28.2%, p 0.27). Prevalence of EUGR was significatively higher when INeS and Fenton charts were used, compared to Intergrowth charts regardless of EUGR-definition (cross sectional-EUGR: Fenton 33.5%, INeS charts 40.9%, Intergrowth-21 23.8%, p 0.001; longitudinal-EUGR (loss of 1SDS): Fenton 15%, INeS charts 20.4%, Intergrowth 4%, p < 0.001). In our population late-onset-sepsis increased the risk of longitudinal EUGR (OR: 2.69, 95%CI: 0.79–9.17), similarly as a longer time to reach 100 ml/kg of feeds (OR: 1.12, 95%CI: 0.97–1.29). On the contrary, preeclampsia was a protective factor for longitudinal EUGR.

Conclusions

We confirmed a wide variability of EUGR rates when using different charts and definitions, highlighting that Intergrowth-21 charts identify less EUGR when compared to INeS and Fenton charts. Standardized criteria for defining EUGR are warranted in order to facilitate comparisons between studies and to improve the nutritional management of VLBW infants.

What Is Known?

The rate of EUGR depends both on the growth chart and definition used
What Is New?

When using cross-sectional growth charts such as Fenton and INeS charts, the prevalence of EUGR was higher, regardless of the longitudinal or cross-sectional definition of EUGR.

In our historical cohort LOS more than doubled the risk of EUGR.

Background

Adequate growth of preterm infants remains a challenge for neonatologists. Extrauterine growth restriction (EUGR), defined as poor growth during hospitalization, is common both in preterm and very low birth weight babies (VLBW). Many factors are known to influence EUGR such as periods of inadequate nutrition, feeding intolerance and a range of morbidities associated with preterm birth (respiratory distress, patent ductus arteriosus, anaemia, late onset sepsis, bronchopulmonary dysplasia) [1]. Moreover, EUGR has been associated with later impaired neurodevelopment [2]. Optimizing nutrition and postnatal growth is, therefore, a fundamental component of the management of preterm infants and an important health outcome measure in Neonatal Intensive Care Units (NICUs) [3]. However, results of existing studies on EUGR are difficult to compare, as there is a wide variability in the charts used for growth assessment and a lack of a consistent definition of EUGR.

Current EUGR definitions can be classified in (1) cross-sectional as weight at a given time < 10th centile, independently of birthweight or (2) longitudinal as weight loss between birth and a given time with different standard deviation thresholds (ΔSDS) [4]. Moreover, growth charts have been developed with different approaches: (1) cross-sectional, based on the size at birth of premature infants in population-based surveys, (2) longitudinal studies of postnatal growth of cohorts of preterm infants, and (3) estimates of fetal weight from ultrasonography scans. [5]

In cross-sectional charts, assessment is based on intrauterine growth standards and does not reflect the adaptation of premature infants to extrauterine life. The most used cross-sectional growth chart is Fenton's, [6] derived from a meta-analysis of 6 large population-based surveys from developed countries including almost four million births. The cross-sectional Italian Neonatal Study (INeS) charts were developed between 2005 and 2007 with a nationwide prospective study involving 22,087 girls and 23,375 boys with both parents of Italian origin, born between 23 and 42 gestational weeks [7]. This study is part of the Fenton metanalysis [6].

The most recently developed charts with a longitudinal approach are the Intergrowth-21 [8]. The Intergrowth 21st Project was a prospective, longitudinal, multicentre, multi-ethnic study with strict selection criteria and it describes optimal rather than average growth of preterm infants.

Previous studies showed that the rate of neonates either classified as small for gestational age (SGA) or as having EUGR changes remarkably when assessed with different charts [9–12], and the prevalence of EUGR is strongly influenced by its different definitions [11].
The primary aim of the present study was to describe the differences of prevalence of SGA and EUGR among very low birth weight (VLBW) infants born in an Italian referral hospital, according to the three growth charts most commonly used in Italy (Fenton, INeS and Intergrowth) and according to EUGR different definitions (cross-sectional versus longitudinal). Secondary aim was to identify maternal, neonatal and nutritional factors associated with EUGR in our VLBW population.

Methods

Ours is a retrospective observational cross-sectional time-series study conducted at the Institute of Maternal and Child Health, IRCCS Burlo Garofolo, Trieste (Italy), a public tertiary level university hospital with approximately 1600 births annually. The study was approved by our Institutional Board Review (CR 09/2020). Our study population included infants with a birthweight ≤ 1500 g born between the 1st of January 2009 and the 31st December 2018 and admitted within 72 hours of birth to our NICU. Infants who were transferred to other hospitals before 34 weeks of postmenstrual age, with chromosomal abnormalities and/or major congenital abnormalities were excluded. In the study period there were no changes in the NICU nutritional protocols.

Clinical and growth data were retrospectively collected from hospital records. The anthropometric measures of VLBW infants were captured at birth and discharge. Birth and growth data were presented as centiles (Standard Deviation Score or z-score) according to the three reference standards (Fenton, INeS charts and Intergrowth-21). For the Intergrowth 21st Project growth standards, the Intergrowth 21st Project newborn charts were used to derive the birth weight z-scores and the Intergrowth 21st Project postnatal growth charts were used to derive the z-scores at discharge.

Neonates were defined as SGA if their birthweight was below the 10th percentile of the chart used. EUGR was defined as cross-sectional-EUGR if the weight was below the 10th percentile at discharge, whereas longitudinal-EUGR if the weight loss was more than respectively 1 SDS (moderate) and 2 SDS (severe) between birth and discharge.

Pregnancy complications (intra-uterine growth restriction (IUGR), gestational diabetes, preeclampsia), antenatal steroid administration (complete prophylaxis-2 doses), and delivery mode; gender, gestational age at birth, Apgar score, morbidities related to prematurity (bronchopulmonary dysplasia, retinopathy of prematurity (ROP), late-onset sepsis (LOS), necrotizing enterocolitis), time (days) to regain birthweight, duration of parenteral nutrition (PN), days for achieving 100 ml/kg/die of enteral feeding and feeding with maternal milk were all recorded.

Bronchopulmonary dysplasia or chronic lung disease (BPD/CLD) was defined as moderate/severe according to Jobe's classification [13] if there was need for oxygen at week 36 post menstrual age (PMA) if born gestational age (GA) < 32 week and at > 28 days postnatal age if born at GA ≥ 32 week (moderate CLD < 30% oxygen, severe CLD ≥ 30% oxygen and/or positive pressure). Necrotizing enterocolitis ( NEC) was defined as grade 2 or 3 according to modified Bell's staging [14]; ROP was defined according to the
international classification of ROP: any stage and severe ROP including stage 3 or more and/or plus disease were considered. [15] LOS was defined by a positive blood culture associated with clinical signs.

For the analysis of EUGR risk factors in our population, we used the *longitudinal-EUGR* definition since it seems to better predict the auxological long-term outcome [4] and psychomotor development at 18–24 months [16, 17]. Moreover, it limits the impact of IUGR on EUGR diagnosis, since SGA babies have a high probability to be discharged < 10°centile, despite of an adequate postnatal growth [11]. Weight loss of 1 SD was chosen as a cut-off, as the prevalence of 2 SD loss was low in our group. For this secondary analysis, INeS charts were chosen as reference, as they are the ones commonly used in our NICU clinical practice.

**Statistical analysis:**

Descriptive analysis was conducted calculating frequency and percentage for categorical variables and median and Interquartile Range (IQR) for continuous variables.

We evaluated the percentage of SGA as the ratio between the number of children whose birthweight was below the 10th percentile of the chart used and the total of newborns. We calculated, also, the EUGR percentage using the three definitions above mentioned: number of children with 1) weight below the 10th percentile on discharge (*cross-sectional-EUGR*), 2) weight loss > 1 SDS (*longitudinal-EUGR-1*), and 3) weight loss > 2 SDS between birth and discharge (*longitudinal-EUGR-2*), on the total of newborns, for all charts used.

Chi square test or exact Fisher test were used to evaluate the association between two categorical variables while Wilcoxon Mann Whitney non parametric test was applied to verify the difference in the distribution of a continuous variable between the categories of a dichotomous variable.

To identify EUGR risk factors, we used a backward selection logistic model adjusted for SGA at birth, sex and weeks of hospitalization. Clinical data and anthropometric measures, both maternal and neonatal, were included as independent variables. A *p*-value < 0.05 was considered as statistically significant. All statistical analysis was performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Considering α = 0.05 and presuming EUGR prevalence at discharge of 72%, according to longitudinal EUGR definition and using INeS charts [4], with a margin of error of 6%, the sample size should be 216 infants.

**Results**

Between 2009 and 2018, 266 VLBW infant were admitted to our NICU. Thirty-eight newborns were excluded for the following reasons: 24 died, 4 were transferred to other hospitals before 34 weeks of postmenstrual age, 9 had chromosomal abnormalities or major congenital abnormalities and 1 had no available data.
Hence, 228 VLBW were included in the study.

Table 1 shows that percentage of SGA in our population did not change significantly according to the three different growth charts used. When assessing EUGR according to *cross-sectional-EUGR* and *longitudinal-EUGR-1* definitions, both INeS and Fenton charts estimated a statistically significantly higher prevalence of EUGR when compared to Intergrowth charts. (Table 1) On the contrary, EUGR prevalence when defined as *longitudinal-EUGR-2* did not significantly change according to reference growth chart.

Table 1. Distribution of SGA and EUGR according to different reference growth charts in our VLBW population

<table>
<thead>
<tr>
<th></th>
<th>Fenton</th>
<th>INeS</th>
<th>Intergrowth-21</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA (%)</td>
<td>22.4</td>
<td>22.8</td>
<td>28.2</td>
<td>0.27</td>
</tr>
<tr>
<td>EUGR (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional EUGR (weight at discharge &lt;10°ct)</td>
<td>33.5&lt;sup&gt;+&lt;/sup&gt;</td>
<td>40.9&lt;sup&gt; ▲ ▲&lt;/sup&gt;</td>
<td>23.8&lt;sup&gt; ▲ ▲ ▲&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td>Longitudinal-EUGR-1 (Loss of z-score &gt; 1 )</td>
<td>15&lt;sup&gt;△ △&lt;/sup&gt;</td>
<td>20.4&lt;sup&gt; ▲ ▲ ▲&lt;/sup&gt;</td>
<td>4&lt;sup&gt; ▲ ▲ ▲ ▲&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Longitudinal-EUGR-2 (Loss of z-score &gt; 2 )</td>
<td>0.9&lt;sup&gt; ▲ ▲ ▲ ▲ ▲&lt;/sup&gt;</td>
<td>1.3&lt;sup&gt; ▲ ▲ ▲ ▲ ▲ ▲&lt;/sup&gt;</td>
<td>0.4&lt;sup&gt; ▲ ▲ ▲ ▲ ▲ ▲ ▲&lt;/sup&gt;</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Chi -square test

<sup>+</sup> 1 case not analysed

<sup>▲ ▲</sup> 2 cases not analysed

<sup> ▲ ▲ ▲</sup> 3 cases not analysed

Abbreviations: SGA: small for gestational age EUGR: extrauterine growth restriction

As shown in table 2, EUGR infants were more likely to be male, and to have a significatively lower median birth weight and gestational age compared to their non-EUGR counterparts. Moreover, they had lower median APGAR score at 5-minute, they experienced a higher duration of parenteral nutrition PN (24 vs 16 days), took as well as a higher median time to reach 100 ml/kg/die of enteral feeds and to regain birthweight. Some morbidities were significantly higher in the EUGR VLBW including LOS and ROP, while there were no differences regarding NEC and BPD (Table 2).

Table 2. Study population characteristics according to EUGR status (defined as loss of z-score > 1 and according to INeS charts)
<table>
<thead>
<tr>
<th></th>
<th>Total sample (n=228)**</th>
<th>non-EUGR (n=179)</th>
<th>EUGR* (n=46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid coverage - n (%)</td>
<td>188 (82.8)</td>
<td>149 (83.7)</td>
<td>37 (80.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Gestational DM - n (%)</td>
<td>23 (10.1)</td>
<td>18 (10.1)</td>
<td>4 (8.7)</td>
<td>0.77</td>
</tr>
<tr>
<td>IUGR - n (%)</td>
<td>72 (31.7)</td>
<td>64 (36.0)</td>
<td>8 (17.4)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Preeclampsia - n (%)</td>
<td>36 (15.9)</td>
<td>34 (19.1)</td>
<td>2 (4.3)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td><strong>Delivery mode - n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vaginal delivery</td>
<td>51 (22.4)</td>
<td>33 (18.4)</td>
<td>17 (37.0)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>- Caesarean section</td>
<td>177 (77.6)</td>
<td>146 (81.6)</td>
<td>29 (63.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Newborn characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex - n (%)</td>
<td>111 (48.7)</td>
<td>79 (44.1)</td>
<td>29 (63.0)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Singletons - n (%)</td>
<td>93 (40.8)</td>
<td>74 (41.3)</td>
<td>17 (37.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Gestational age (weeks) – median (IQR)</td>
<td>29 (28 - 31)</td>
<td>30 (28 - 31)</td>
<td>28 (26 - 29)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Birthweight (g) – median (IQR)</td>
<td>1169 (919 - 1371)</td>
<td>1198 (968 - 1388)</td>
<td>940 (795 - 1368)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Weeks of hospitalization</td>
<td>8 (6 – 10)</td>
<td>7 (5 – 9)</td>
<td>10 (8 – 12)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PMA at discharge (weeks) – median (IQR)</td>
<td>37 (36 - 38)</td>
<td>37 (36 - 38)</td>
<td>38 (37 - 39)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Weight at discharge (g) – median (IQR)</td>
<td>2615 (2280 - 2880)</td>
<td>2580 (2240 - 2880)</td>
<td>2665 (2350 - 2760)</td>
<td>0.52</td>
</tr>
<tr>
<td>APGAR score at 5 min – median (IQR)</td>
<td>8 (8 - 9)</td>
<td>9 (8 - 9)</td>
<td>8 (6 - 9)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>LOS - n (%)</td>
<td>22 (9.7)</td>
<td>11 (6.1)</td>
<td>9 (19.6)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>BPD - n (%)</td>
<td>22 (9.7)</td>
<td>14 (7.8)</td>
<td>6 (13.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>NEC - n (%)</td>
<td>4 (1.8)</td>
<td>3 (1.7)</td>
<td>1 (2.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>ROP - n (%)</td>
<td>47 (20.6)</td>
<td>29 (16.2)</td>
<td>16 (34.8)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>- Severe ROP</td>
<td>14 (6.2)</td>
<td>7 (3.9)</td>
<td>6 (13.0)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Duration of PN – median (IQR)</td>
<td>16.5 (12 - 24)</td>
<td>16 (12 - 20)</td>
<td>24 (16 - 36)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Time to reach 100 ml/kg per os – median (IQR)</td>
<td>12 (9 - 17)</td>
<td>12 (9 - 16)</td>
<td>16 (12-27)</td>
<td><strong>0.0002</strong></td>
</tr>
</tbody>
</table>
Time to reach birthweight (days) – median (IQR)

<p>| | | | |</p>
<table>
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<tr>
<td></td>
<td>median</td>
<td>IQR</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(8 - 10)</td>
<td>8 (7 - 10)</td>
<td>10 (8 - 11)</td>
</tr>
<tr>
<td></td>
<td>0.003</td>
<td></td>
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</tr>
</tbody>
</table>

Mother's own milk during hospitalization - n (%)

<table>
<thead>
<tr>
<th></th>
<th>0% - 50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>(31.6)</td>
<td>145 (68.4)</td>
</tr>
<tr>
<td>54</td>
<td>(32.3)</td>
<td>113 (67.7)</td>
</tr>
<tr>
<td>13</td>
<td>(28.9)</td>
<td>32 (71.1)</td>
</tr>
<tr>
<td>0.66</td>
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</tbody>
</table>

* EUGR defined as loss of > 1 SDS according to INeS charts

** 3 infants were excluded from the analysis, because discharged after week 42

In the multivariate analysis, independently of birthweight, gender and duration of hospitalization, the risk of being EUGR was higher, if VLBW experienced a LOS (OR: 2.69 – 95%CI: 0.79-9.17), 0.74-5.76) and a higher time to reach 100 ml/kg of enteral feeds (OR: 1.12 – 95%CI: 0.97-1.29). (Table 3). On the contrary, in our study having a mother who suffered from preeclampsia significantly reduced the risk of EUGR at discharge (Table 3).

Table 3. Odds Ratio (OR) and relative 95% Confidence interval (95%CI) of univariate and multivariate logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>EUGR (Loss of &gt; 1 SDS – INeS)</th>
<th>Univariate*</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AIC</td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>YES vs NO</td>
<td>201.14</td>
<td>0.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Late onset sepsis</td>
<td>YES vs NO</td>
<td>203.44</td>
<td>3.18</td>
<td>1.10</td>
</tr>
<tr>
<td>Time to reach 100 ml/kg per os</td>
<td>Units = 2</td>
<td>195.02</td>
<td>1.16</td>
<td>1.02</td>
</tr>
</tbody>
</table>

* The models were adjusted by SGA at birth, sex and weeks of hospitalization.

**Discussion**

In our study we found that rates of EUGR varied significantly according to charts and definitions used, resulting higher when using INeS charts both when applying a cross-sectional and a longitudinal-EUGR-1 definition. At multivariate analyses, LOS and a longer time for reaching 100 ml/kg enteral feeding were associated with a higher risk of EUGR at discharge, while maternal preeclampsia reduced this risk.

In line with other studies, in our population frequency of SGA was higher, though not significantly so, when using the Intergrowth-21st growth charts [9, 10, 18]. This result is expected, as Intergrowth-21 charts were plotted with a standard population, with the lowest risk factors known to affect prenatal and
postnatal growth (low-risk women, non-smokers, with a normal pregnancy history with normal growing fetuses) and this may explain a tendency to overestimate SGA newborns.

On the contrary, when using Intergrowth-21th charts, EUGR prevalence was lower when compared to Fenton and INeS charts, both with the cross-sectional and the longitudinal definition. This result is consistent with previous studies [9, 10, 18-20] and this difference may be expected, as the Intergrowth charts are based on longitudinal growth of preterm babies, who grow in a completely different environment and with different metabolic responses compared to fetuses in the intrauterine environment. The difference between Intergrowth-21 and INeS charts is even more significant than between Intergrowth and Fenton and this could reflect the more homogeneous population that were used to design them.

Ideal growth for preterm babies is far from being clearly defined. One of the widely accepted goals of neonatal nutritional care is to try to replicate the intrauterine growth as close as possible [21]- and, for this reason, the most commonly used growth charts have been the cross-sectional charts based on in utero growth. However, it is still debated whether it is appropriate to expect preterm babies to grow at the same rate as those in utero [22]. Benefits of improved growth on neurodevelopmental outcomes and chronic lung disease are well known, but the optimal pattern of growth in preterm infants to achieve good long-term health should also take into account the potential impact of excessive growth, associated with the risk of metabolic and cardiovascular disease in later life. The Intergrowth 21th Project therefore developed new growth standards from a cohort of uncomplicated pregnancies with normal growing fetuses, uncomplicated postnatal period and up-to-date nutritional support [8], and explain why EUGR prevalence – regardless of its cross-sectional or longitudinal definition – turns to be lower when compared to other reference charts.

These trends to lower rates of EUGR when using Intergrowth-21 charts have been reported by several other studies, both for cross sectional EUGR definition [9, 10] and longitudinal EUGR [18]. In a European multicountry cohort, cross-sectional EUGR rates were reduced from 24% (Sweden) and 60% (Portugal) when using Fenton charts to 13% (Sweden) and 43% (Portugal), when using Intergrowth-21 [23].

Our study was done because knowing and monitoring the prevalence of EUGR in our Unit, is considered to be a quality measure of care for preterm infants [3]. In our population EUGR prevalence ranged from 40.9% using cross-sectional definition with INeS charts to 4% using longitudinal-1 definition with Intergrowth-21 standards. However, to draw comparisons between different centers is difficult not only because definition of EUGR and reference growth charts differ, but also because maternal and clinical characteristics of the study population, time at EUGR evaluation (36 weeks, 40 weeks PMA, discharge) and choice of ΔSDS threshold when applying the longitudinal-EUGR definition (> 1, >2 SDS), changes. EUGR rates from NICUs of high-income countries similar to ours, evaluated at discharge, varied from 17% to 77.2% for the cross-sectional EUGR [4, 25-29], from 29.8-39.1% for longitudinal-1 definition [30,31] and from 5.2-13% for longitudinal-2 EUGR [30-32].

When looking for risk factors, we confirmed that the characteristics of the study population are determinant to EUGR at discharge. Other studies demonstrated that the degree of longitudinal EUGR is
influenced by birth weight z score and gestational age: the lower the birthweight centile, the lower the probability to lose 1 or 2 SDS; on the other hand, the lower the gestational age, the higher the probability to lose z-score [18, 24, 31]. In our series we found a significant role of lower gestational age and, consequently, longer duration of hospitalization on EUGR. Male sex was also significatively related with poor growth, as reported in other studies [18, 33, 34]. Therefore, we decided to adjust our logistic regression for low z-score at birth (SGA), male sex and duration of hospitalization.

Independently of the above factors, in our population we found that LOS more than doubled the risk for EUGR, although not statistically significant. In other studies [18, 24, 34, 35] other comorbidities associated with prematurity had a significant effect on the incidence of growth restriction: patent ductus arteriosus, broncopulmonary dysplasia, necrotizing enterocolitis and late-onset sepsis, need for assisted ventilation, exposure to postnatal steroids and major brain lesions. These risk factors may only be markers for severity of illness: sick infants are often fed less than healthier infants, have increased metabolic demands, and their nutritional needs are rarely met, all of which result in malnutrition and poor growth. However, the presence of LOS as an independent risk factor underlines the necessity for implementing interventions targeted to reduce the incidence of neonatal sepsis [36, 37].

In our analyses longer time to reach 100 ml/kg/die of enteral feeding was found to be a potential risk factor even though only with a borderline statistical significance. Again, this may be an indirect sign of severity of illness, as increasing oral nutrition may be harder in sick infants. Intervention studies showed that optimising nutrition (such as introducing guidelines for increasing feeds and weaning PN) reduced the incidence of EUGR [38-40]

In our study it was surprising to find that preeclampsia was protective for EUGR, reducing it of 83%. As far as we know, no other study found preeclampsia as a protective factor for EUGR. However, IUGR, which is frequently associated with preeclampsia, was found to be protective on longitudinal EUGR in a Spanish cohort of preterm babies [11]. This finding may be explained by the fact that having both a low z-score at birth and losing >1 SD may be difficult to occur. Risk factors for EUGR may vary according to the definition used with a low z-score at birth as a possible risk factor for cross-sectional-EUGR, while higher z-score at birth for longitudinal-EUGR [10, 11,18].

Limitations of our study are inherent to the retrospective observational nature of the study. Moreover, our cohort is small and includes a wide range of gestational ages. Another limitation may lie in the choice of discharge as a time point for assessing EUGR, as there is a wide range of time of evaluation. However this was taken into account in the multivariate analysis by correcting for duration of hospitalization. Moreover, as this study was conducted in a single medical centre, generalization of the data is limited.

In conclusion, our study confirms a wide variability of EUGR rates when using different charts and definitions. It highlights the need to standardize criteria and the evaluation method for EUGR, which would facilitate comparisons between studies and help to improve nutrition in neonatal units and to perform studies on its long term implication.
Abbreviations

BPD/CLD Bronchopulmonary dysplasia or chronic lung disease

EUGR: extrauterine growth restriction

GA gestational age

IUGR intrauterine growth restriction

LOS late-onset sepsis

NEC necrotizing enterocolitis

NICU neonatal intensive care unit

PN parenteral nutrition

ROP retinopathy of prematurity

SGA small for gestational age

VLBW: very low birth weight

Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript

Competing Interests: The authors declare that they have no competing interests.

Availability of data and material: The datasets used during the current study are available from the corresponding author on request

Authors' contributions: M.S. and J.B. Conceived and designed the study, supervised data collection and wrote the paper, G.C. Collected data for analysis, M.G. analysed the data, L.T. and J.B. revised the manuscript. All authors approved the final manuscript.

Ethics approval: The study was approved by our Institutional Board Review (RC 09/2020). This was a retrospective study, the need for consent to participate was waived.

Consent to participate: N/A

Consent for publication: N/A

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