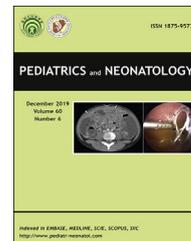




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Original Article

# Risk factors for postdischarge growth retardation among very-low-birth-weight infants: A nationwide registry study in Taiwan



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## Key Words

growth disorders;  
infant;  
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risk factors;  
very low birth weight

**Background:** Very-low-birth-weight (VLBW) infants have a high risk of postdischarge growth retardation (GR). Continued GR might exert negative long-term effects on their health. This study examined the prevalence and the risk factors for postdischarge GR among VLBW infants in Taiwan.

**Methods:** Nationwide data from the Taiwan Premature Infant Follow-up Network between 2007 and 2011 were analyzed. Infants with a gestational age (GA) < 37 weeks and birth body weight (BBW) < 1500 g were enrolled. They were followed up after discharge at the corrected ages of 6, 12, and 24 months. Associations between postdischarge GR at the follow-ups and possible risk factors were analyzed.

**Results:** The prevalence of postdischarge GR among 2124 VLBW infants was 17.3%, 19.4%, and 13.8% at the corrected age (CA) of 6, 12, and 24 months, respectively. The significant perinatal factors of postdischarge GR were being small for gestational age (SGA) and extremely low birth weight (ELBW). ELBW infant with extra-uterine growth retardation (EUGR) at discharge or longer length of hospital stay (LOS) had poorer growth outcomes. Among non-ELBW infants, EUGR at discharge and surgical necrotizing enterocolitis (NEC) were the main influencing factors of unfavorable growth outcomes. RDS with surfactant therapy had a positive effect of

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postdischarge growth outcomes in ELBW infants.

**Conclusion:** Postdischarge GR is still a serious problem in Taiwan. Being SGA and ELBW and EUGR were significant risk factors for postdischarge GR throughout the first two years of life in VLBW infants. An integrated and organized team for postdischarge care as well as scheduled follow-ups, detailed nutritional education, and thorough inspection are necessary.

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## 1. Introduction

The survival rates of very-low-birth-weight (VLBW) preterm infants have increased over the past few decades owing to the introduction of antenatal steroids, surfactants, and advanced ventilation techniques.<sup>1,2</sup> In the past decade, the survival rate of VLBW infants has significantly increased in Taiwan.<sup>3</sup> Although the overall survival rates of VLBW infants have increased, these infants remain at risk of growth and neurodevelopmental problems.<sup>4,5</sup>

VLBW preterm infants are deprived of intrauterine nutrition during the third trimester because of preterm birth. After birth, they have to exhibit high consumption of energy to achieve adequate body weight gain and subsequent catch-up growth. Therefore, extrauterine growth retardation (EUGR, growth value below the 10th percentile of intrauterine growth expectation based on estimated postmenstrual age) is a crucial problem encountered by surviving VLBW preterm infants.<sup>6,7</sup> In addition, these infants were also reported to have higher risk of postdischarge growth retardation (GR).<sup>8,9</sup> Continued GR among VLBW infants has been shown to cause a reduction in cognitive performance and result in behavior problems and learning difficulties in school, which exert significant negative long-term effects.<sup>8,10–14</sup>

Therefore, investigating growth outcomes in VLBW infants after discharge and examining the potential risk factors of postdischarge GR are necessary for improving the quality of medical care in VLBW premature infants.

Previous studies have examined potential risk factors associated with postdischarge GR among preterm infants. Power et al. reported that a gestational age (GA) of <26 weeks was associated with postdischarge growth failure.<sup>8</sup> Another study demonstrated that intrauterine growth failure was a common problem in VLBW preterm infants, which caused an additional growth lag.<sup>13</sup> Wang et al. also described that birth weight, birth height, intraventricular hemorrhage, and birth outside the referral hospital were factors affecting the growth of VLBW infants in a previous study in Taiwan.<sup>15</sup> Furthermore, the growth of VLBW infants may be affected by perinatal, cultural, ethnic, or environmental factors.<sup>5,8,10,13,14,16</sup>

The present study described the prevalence of postdischarge GR among VLBW infants in Taiwan and identified possible risk factors for postdischarge GR from nationwide registry data.

## 2. Method

We collected data of preterm infants born between 2007 and 2011 from the data bank of Taiwan Premature Infant Follow-up Network funded by Premature Baby Foundation of Taiwan. The study protocol was reviewed and approved by Institutional Review Board of Taichung Veterans General Hospital.

Premature infants born in these 5 years were enrolled if their birth body weight (BBW) was less than 1500 g. Infants were excluded if they expired before discharge or they had chromosome anomalies or did not complete all follow-ups at the corrected age (CA) of 6, 12, and 24 months. The infants included in this study were followed up at outpatient departments (OPD) of hospitals of the network after discharge. Body weight (BW) was measured at the CA of 6, 12, and 24 months by trained nurses. Postdischarge GR was defined as a BW below the 3rd percentile of the standard growth curve for Taiwanese children by the corrected age.<sup>17</sup>

In addition, perinatal and postnatal factors, including maternal education level, maternal age, parity, multiple birth, small-for-gestational-age (SGA), respiratory distress syndrome (RDS) with surfactant therapy, surgical necrotizing enterocolitis (NEC, Bell's stage IIIB), patent ductus arteriosus (PDA) with intervention (surgical or medical), chronic lung disease (CLD) with steroid treatment (including systemic and inhaled steroid), severe intraventricular hemorrhage (IVH, grade III and IV), retinopathy of prematurity (ROP), extrauterine growth retardation (EUGR) at discharge, and length of hospital stay (LOS), were used for the analysis of postdischarge growth outcomes.

All data were presented as mean  $\pm$  standard deviation (SD). The chi-square test was used for non-continuous data, and the student t test was used for continuous data. We used multivariate logistic regression to evaluate possible perinatal and postnatal risk factors for postdischarge GR in VLBW preterm infants. The level of statistical significance was set at  $P < 0.05$ .

## 3. Results

In total, 4636 preterm infants with BBW less than 1500 g were born between 2007 and 2011 in Taiwan and registered in the data bank of Taiwan Premature Infant Follow-up Network. Among these cases, 731 infants were excluded

due to chromosome anomalies (n = 24) or death (n = 707). The follow-up rates of these infants were 90.7% at the CA 6-month-old visit, 60.4% at the CA 12-month-old visit, and 54.4% at the CA 24-month-old visit. An additional 1781 infants did not complete the follow-up and measurement at all the 3-age visits. Finally, a total of 2124 VLBW preterm infants were enrolled in our study (Fig. 1). The mean gestational age was 29.2 ± 2.7 weeks (range: 22–36 weeks) and the mean BBW was 1142 ± 249 g (range: 422–1500 g). The demographic data of the included infants are presented in Table 1.

Up to 70.7% (1479/2092) of the enrolled infants were EUGR at discharge, and there was no significant difference in prevalence of EUGR between male and female. The overall prevalence of postdischarge GR was 17.3% (368/

2124) at the CA of 6 months, 19.4% (413/2124) at the CA of 12 months, and 13.8% (294/2124) at the CA of 24 months. Fig. 2 shows the proportions of growth outcomes of the 2124 enrolled infants at the CA of 6, 12, and 24 months.

In the analysis of postdischarge GR in SGA and non-SGA infants, 88.5% of SGA infants were diagnosed as EUGR at discharge; 31.5%, 33.8% and 23.4% were GR at the CA of 6, 12, 24 months, respectively. The prevalence of postdischarge GR for SGA infants was higher than that for non-SGA infants (CA 6 months: 31.5% vs. 9.8%; CA 12 months: 33.8% vs. 11.8%; CA 24 months: 23.4% vs. 8.8%, all P < 0.001).

### 3.1. Growth retardation at 6, 12, 24 months CA in relation to perinatal factors

Multivariate regression analysis showed that both SGA and extremely low birth weight (ELBW) affected postdischarge GR significantly at the CA of 6 months, 12 months, and 24 months (Table 2). Male gender was associated with postdischarge GR only at the CA of 12 months (OR = 1.37, CI: 1.08–1.73). Infants with higher maternal education level (more than high school) had lower risk of postdischarge GR at the CA of 24 months (OR = 0.71; CI: 0.53–0.94).

### 3.2. Growth retardation at 6, 12, 24 months CA in relation to postnatal morbidities

ELBW was a significant perinatal risk factor in our study. Thus, we divided enrolled infants into ELBW group (BBW <1000 g) and non-ELBW group (BBW: 1001–1500 g) and investigated postnatal factors independently (Table 3).

Among ELBW group (BBW <1000 g), infants who were EUGR at discharge or had longer LOS were at higher risk of postdischarge GR at three-age visits. In addition, infants who were diagnosed as RDS and received surfactant therapy seemed to have lower prevalence of postdischarge GR throughout the two years after birth.

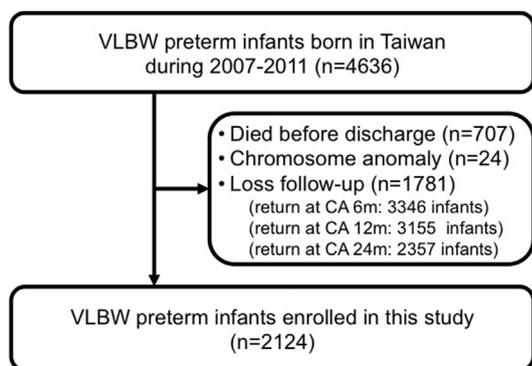


Figure 1 Flow chart of the procedure to enroll infants in the study.

Table 1 Demographic data of 2124 enrolled infants in our study.

Gestational age, wk <sup>a</sup>	29.2 ± 2.7
Birth body weight, gm <sup>a</sup>	1141.6 ± 249.1
Birth body height, cm <sup>a</sup>	36.8 ± 3.6
ELBW	29.7% (631/2124)
Small for gestation age <sup>b</sup>	34.2% (727/2124)
Male gender <sup>b</sup>	51.9% (1104/2124)
Primiparity <sup>b</sup>	58.0% (1232/2124)
Cesarean section <sup>b</sup>	73.4% (1559/2122)
Maternal age, year-old <sup>a</sup>	32 ± 5 (18 missing data)
Multiple birth <sup>b</sup>	32.0% (680/2123)
RDS with surfactant therapy <sup>b</sup>	35.0% (743/2124)
PDA with intervention <sup>b</sup>	38.4% (803/2093)
Surgical NEC <sup>b</sup>	0.5% (11/2120)
Severe IVH <sup>b</sup>	3.8% (79/2076)
CLD with steroid treatment <sup>b</sup>	4.9% (103/2094)
ROP <sup>b</sup>	48.9% (1037/2122)
LOS, day <sup>a</sup>	70.3 ± 32.0
EUGR at discharge <sup>b</sup>	70.7% (1479/2092)

Abbreviations: CLD = chronic lung disease; ELBW = extremely low birth weight; EUGR = extrauterine growth retardation; IVH = intraventricular hemorrhage; LOS = length of hospital stay; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; SD = standard deviation.

<sup>a</sup> Mean ± SD.

<sup>b</sup> Percentage (case number/total number).

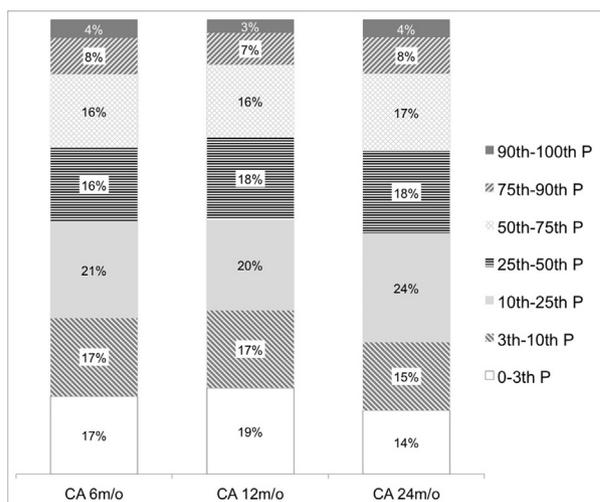


Figure 2 The proportions of growth outcomes at the corrected age (CA) of 6, 12, and 24 months.

**Table 2** Perinatal risk factors for postdischarge growth retardation.

Factors	CA 6-month-old OR (95% CI)	CA 12-month-old OR (95% CI)	CA 24-month-old OR (95% CI)
Small GA (<29wks)	0.85 (0.59–1.22)	0.85 (0.60–1.19)	0.76 (0.52–1.09)
ELBW	3.33 (2.39–4.63)***	2.63 (1.93–3.59)***	2.48 (1.76–3.49)***
Gender	0.99 (0.77–1.27)	1.37 (1.08–1.73)**	1.20 (0.92–1.56)
SGA	3.82 (2.87–5.08)***	3.35 (2.57–4.38)***	2.67 (1.98–3.58)***
Advanced maternal age (>35-year-old)	0.89 (0.68–1.17)	1.15 (0.89–1.47)	1.15 (0.87–1.52)
High maternal education level <sup>a</sup>	1.01 (0.78–1.31)	0.88 (0.69–1.13)	0.71 (0.53–0.94)*
Primiparity	1.12 (0.86–1.45)	1.19 (0.93–1.52)	1.26 (0.95–1.66)
Multiple birth	1.37 (1.06–1.77)	1.22 (0.95–1.55)	1.00 (0.76–1.32)

\*P ≤ .05, \*\*P ≤ .01, \*\*\*P ≤ .001.

Abbreviations: CA = corrected age; ELBW = extremely low birth weight; GA = gestational age; SGA = small for gestational age.

<sup>a</sup> Maternal education level was more than high school.

In the group of non-ELBW infants, EUGR remained the main factor affecting postdischarge unfavorable growth condition. LOS was only associated with postdischarge BW gain at the CA of 6 months in non-ELBW infants. Surgical NEC (Bell's stage IIIB) correlated to postdischarge GR at the CA of 12 and 24 months. Compared to infants with non-surgical NEC, infants who had surgical NEC were still at higher risk to develop postdischarge GR at the CA of 12 and 24 months (CA 12 months: 83.3% vs. 14.3%,  $P < 0.001$ ; CA 24 months: 50.0% vs. 5.7%,  $P = 0.002$ ).

#### 4. Discussion

Following the improvement of VLBW prematurity survival rates, growth retardation has become a common and serious problem. Premature infants with unfavorable growth outcomes may have higher risk of cognitive dysfunction, behavioral problems, and academic difficulties in later childhood.<sup>8,10–14</sup> In our study, the prevalence of postdischarge GR in VLBW preterm infants decreased as they grew up. Of the 2124 VLBW infants, up to 13.8% of the infants remained postdischarge GR at the CA of 24 months. The major perinatal factors affecting postdischarge GR until the CA of 24 months were SGA and ELBW. Among postnatal morbidities, EUGR at discharge and LOS were significant factors in the ELBW group; EUGR at discharge and advanced NEC were significant factors in the non-ELBW group.

Compared to one previous study in Taiwan conducted from 1995 to 1996, the prevalence of postdischarge GR was slightly higher in our study.<sup>15</sup> The survival rates of VLBW infants have improved.<sup>3</sup> VLBW infants in our study had smaller gestational age and lower BBW than those infants in that previous study.<sup>15</sup> Our study also enrolled more ELBW infants (29.7% vs. 21.8%). In addition, Wang defined "below normal growth" of VLBW infants as growth below the average value of full-term infants of less than 2 standard deviations, which was different from our definition. These variations could explain the differences in the prevalence of GR.

Being SGA was the strongest predictor of postdischarge GR at the CA of 24 months in our study. Up to 34.2% of the enrolled infants in our study were SGA at birth. Being SGA

has been considered as a crucial factor associated with unfavorable postnatal growth outcomes, higher mortality rates and neonatal morbidities.<sup>18,19</sup> Other studies have reported SGA infants had lower rates of catch-up growth.<sup>20</sup> Hsu et al. also found that SGA was a significant factor for postdischarge failure to thrive in another nationwide cohort study in Taiwan.<sup>14</sup> Since postdischarge GR correlated to poorer neurodevelopmental outcomes, it is important to give adequate nutrition support for catch-up growth in SGA VLBW infants.<sup>14</sup> However, postnatal rapid weight gain in SGA infants seemed to be associated with increased fat mass and cardiovascular disease in later life.<sup>21–23</sup> The ideal growth pattern in SGA infants remains undefined and needs further study to be established.

ELBW was an important risk factor for postdischarge GR among the VLBW preterm infants in our study, which was the same as in a previous study.<sup>15</sup> ELBW infants suffered from more nutritional deficits of the third trimester, and they faced more energy consumption and more environmental stress after birth.<sup>24</sup> Our study also suggested that EUGR at discharge was related to poorer postdischarge growth outcomes in both ELBW and non-ELBW infants. Another study noted a similar finding that EUGR at discharge was important for body weight in early childhood.<sup>12</sup> Reduced growth during hospitalization significantly impacted postdischarge outcomes in the preterm infants.<sup>25,26</sup> Early and aggressive nutritional intervention for adequate BW gain during hospitalization may mitigate further risk of postdischarge growth retardation.

Kent et al. reported that male preterm infants had higher mortality, poorer long-term neurologic outcomes and that they were prone to sepsis, major surgery and IVH.<sup>27</sup> Other studies also noted that male infants were more likely to have non-optimal growth outcomes and adverse neurologic outcomes.<sup>7,28</sup> In our study, male gender was related to postdischarge GR only at the CA of 12 months. The possible mechanism between gender and growth retardation is unclear. A previous study described the sex-specific alterations of pro-oxidant/antioxidant balance with a predominantly pro-oxidant status in placenta of male infants.<sup>29</sup> Early sex-dependent differences in response to environmental stress caused by sex chromosomes or hormones was suggested by several human and animal

**Table 3** Postnatal risk factors for postdischarge growth retardation in ELBW and non-ELBW group.

	ELBW infants				Non-ELBW infants				
	CA 6-month-old, OR (95% CI)	CA 12-month-old, OR (95% CI)	CA 24-month-old, OR (95% CI)	CA 6-month-old, OR (95% CI)	CA 12-month-old, OR (95% CI)	CA 24-month-old, OR (95% CI)	CA 6-month-old, OR (95% CI)	CA 12-month-old, OR (95% CI)	CA 24-month-old, OR (95% CI)
	RDS with surfactant	0.62 (0.41–0.93)*	0.58 (0.39–0.87)**	0.53 (0.34–0.84)**	0.71 (0.46–1.11)	0.63 (0.41–0.95)*	0.61 (0.38–0.99)*	0.71 (0.46–1.11)	0.63 (0.41–0.95)*
PDA with intervention	0.70 (0.47–1.04)	0.73 (0.50–1.08)	1.00 (0.64–1.56)	0.57 (0.37–0.86)**	0.88 (0.61–1.27)	1.33 (0.88–2.00)	0.57 (0.37–0.86)**	0.88 (0.61–1.27)	1.33 (0.88–2.00)
Surgical NEC	1.25 (0.10–15.09)	1.41 (0.12–16.32)	2.13 (0.18–24.82)	4.49 (0.85–23.78)	23.53 (2.67–207.87)**	8.97 (1.74–46.34)**	4.49 (0.85–23.78)	23.53 (2.67–207.87)**	8.97 (1.74–46.34)**
Severe IVH	0.80 (0.37–1.71)	1.06 (0.52–2.18)	0.77 (0.32–1.83)	0.81 (0.24–2.76)	0.77 (0.23–2.61)	0.75 (0.17–3.30)	0.81 (0.24–2.76)	0.77 (0.23–2.61)	0.75 (0.17–3.30)
CLD with steroid	0.64 (0.34–1.20)	1.21 (0.68–2.15)	1.07 (0.55–2.09)	1.89 (0.52–6.92)	0.53 (0.07–4.16)	0.84 (0.11–6.66)	1.89 (0.52–6.92)	0.53 (0.07–4.16)	0.84 (0.11–6.66)
ROP	1.04 (0.67–1.62)	1.11 (0.73–1.70)	0.99 (0.61–1.59)	0.82 (0.58–1.17)	1.18 (0.86–1.62)	1.43 (0.99–2.05)	0.82 (0.58–1.17)	1.18 (0.86–1.62)	1.43 (0.99–2.05)
EUGR at discharge	2.10 (1.27–3.45)**	1.68 (1.05–2.70)*	1.84 (1.05–3.20)*	2.25 (1.47–3.46)***	2.36 (1.58–3.54)***	2.00 (1.26–3.18)**	2.25 (1.47–3.46)***	2.36 (1.58–3.54)***	2.00 (1.26–3.18)**
LOS, day	1.03 (1.02–1.04)***	1.02 (1.01–1.02)***	1.02 (1.01–1.03)***	1.02 (1.01–1.02)***	1.00 (0.99–1.01)	0.99 (0.98–1.00)	1.02 (1.01–1.02)***	1.00 (0.99–1.01)	0.99 (0.98–1.00)

\*P ≤ .05, \*\*P ≤ .01, \*\*\*P ≤ .001.

Abbreviations: CA = corrected age; EUGR = extrauterine growth retardation; IVH = intraventricular hemorrhage; LOS = length of hospital stay; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity.

studies.<sup>30</sup> Nutrition could affect male infants more dramatically than female infants.<sup>28</sup> Hack et al. also reported female VLBW infants had greater catch-up growth than male infants by 20 years old.<sup>31</sup> The gender differences in catch-up growth are probably multifactorial, including genetic potential. More information of postdischarge nutrition strategy and lifestyle are needed for further analysis and interpretation.

Among non-ELBW infants, we found that surgical NEC played a role in postdischarge GR at the CA of 12 and 24 months. Similar to our study, Griffin et al. reported that NEC exerted a significant negative effect on postnatal growth in VLBW preterm infants.<sup>32</sup> Complications of NEC, such as intestinal stenosis, malabsorption, and short bowel syndrome (SBS) may interfere with BW gain after discharge.<sup>33,34</sup> Longer time to achieve full enteral feeding was reported to be a significant risk factor for postnatal growth failure (PGF) both in SGA and AGA VLBW infants.<sup>35</sup> Infants suffering from surgical NEC may have needed prolonged parenteral nutrition support, which delayed the commencement of complete enteral feeding. However, we did not have detailed parenteral nutrition data to validate this in our study. The number of surgical NEC was relatively low in ELBW group, which might be the reason that it did not become a significant factor for postdischarge GR. For better long-term growth outcome, nutritional investigation and practice are important for VLBW infants who had surgical NEC.

Interestingly, our study suggested that RDS with surfactant therapy was a protective factor of postdischarge GR among ELBW infants. Lee et al. had reported RDS was the predictor of PGF among VLBW SGA infants.<sup>35</sup> Severe RDS can contribute to additional energy consumption by more requirement of respiratory work. Administration of surfactant in preterm infants with RDS can reduce mortality and decrease incidence of air leak syndrome and need for mechanical ventilation.<sup>36</sup> It is possible that surfactant therapy reduces energy expenditure among ELBW infants by effectively improving respiration and alleviating lung injury and subsequent complications of RDS. PDA with intervention was also a protective factor among non-ELBW infants only at the CA of 6 months. Timely management of significant PDA among VLBW infants might also reduce energy expenditure in the early postnatal period.

Our retrospective study design had some limitations. First, all growth data were recorded by trained nurses at each hospital and the recording methods were site-specific. This might have caused some measurement errors. Second, body height and head circumference were incompletely recorded, which may create selection bias. Third, postdischarge nutritional management was non-uniform and was not documented in the record of follow-up visits. However, the large size of our study population facilitated bias reduction and provided the overall condition in this study.

In conclusion, the prevalence of postdischarge GR among VLBW infants in Taiwan decreased as they grew up, but it remains a serious problem. VLBW infants still face a higher risk of postdischarge GR until the CA of 24 months. Being SGA, ELBW, and EUGR at discharge were the most significant risk factors for postdischarge GR throughout the first two years of life in this study. For further comprehensive

investigation of postdischarge condition, more information concerning nutrition strategy and lifestyle at home is needed. Owing to concerns regarding the long-term growth of VLBW preterm infants in Taiwan, an integrated and organized team for postdischarge care together with scheduled follow-ups, detailed nutritional education, and thorough inspection are necessary.

### Conflicts of interest statement

The authors declare no financial or nonfinancial conflicts of interest related to the subject matter or materials presented in the manuscript.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pedneo.2019.03.004>.