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ORIGINAL ARTICLE

Factors associated with Periventricular Leukomalacia in very low birth weight infants. A multicenter study in the NEOCOSUR Network

Factores asociados a Leucomalacia Periventricular en recién nacidos prematuros de muy bajo peso. Estudio multicéntrico en la Red NEOCOSUR

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What do we know about the subject matter of this study?

Periventricular leukomalacia (PVL) is an ischemic lesion of cerebral white matter, of greater morbidity in the preterm newborn, with great long-term impact, associated with neurodevelopmental disorders and cerebral palsy. Its associated factors seem to be multiple.

What does this study contribute to what is already known?

This is a multicenter analysis of the PVL incidence and its associated factors in our region. Bronchopulmonary dysplasia, necrotizing enterocolitis, late-onset sepsis, severe intraventricular hemorrhage, patent ductus arteriosus, and use of mechanical ventilation were found to be factors associated with a higher likelihood of PVL. These results could be used for comparison and implementation of initiatives to reduce the incidence of this entity and its sequelae.

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Abstract

The global prevalence of Periventricular Leukomalacia (PVL) has remained stable (~4%) in very low birth weight (VLBW) infants in the NEOCOSUR Neonatal Network for 16 years. **Objective:** To determine the factors associated with the presence of PVL in surviving VLBW infants at discharge, its overall incidence, and gestational age (GA). **Patients and Method:** Observational, multicenter, retrospective study with prospectively recorded data (period 2012 - 2021). Newborns with birth weight between 400 to 1500 g and 23 to 31+6 weeks of GA surviving at discharge were included. A bivariate analysis was performed using Pearson's chi-square test to contrast the percentage of PVL for categorical variables and the student's t-test to contrast averages for numerical variables. To explore the independent effect of each explanatory variable, a multivariate logistic regression analysis was performed. **Results:** In 6,825 surviving VLBW newborns, the global incidence of PVL was 8.5%. Factors associated with increased likelihood of PVL were bronchopulmonary dysplasia (BPD) [OR 2.27; 95% CI 1.80-2.87], necrotizing enterocolitis (NEC) [OR 1.78; 95% CI 1.35-2.34], late-onset sepsis (LOS) [OR 1.71; 95% CI 1.34-2.19], severe intraventricular hemorrhage (IVH) [OR 4.64; 95% CI 3.51-6.14], patent ductus arteriosus (PDA) [OR 1.32; 95% 1.06-1.64], and mechanical ventilation (MV) [OR 2.03; 95% CI 1.54-2.67]. **Conclusion:** In surviving VLBW infants at discharge, a higher probability of PVL was associated with the presence of BPD, NEC, LOS, severe IVH, and PDA and the use of MV.

Keywords:
Periventricular Leukomalacia;
Premature Newborn;
Very Low Birth Weight Newborn;
Brain Injury

Introduction

During the last decades, neonatology has advanced significantly in the care of extremely preterm infants[1]. This has reduced mortality in this population; however, it has come with a significant burden of increased morbidity and disability, with the associated support and rehabilitation requirements for each patient, their family, and the health care system[2-7].

Among the factors that influence the long-term neurological prognosis of these patients are their birth weight and gestational age (GA)[8], as well as the presence of the so-called "major morbidities", which include the presence of brain lesions such as severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL)[8-10].

PVL is an intraparenchymal lesion involving cerebral white matter because of hypoxic-ischemic events leading to necrosis and vacuolization of this area. It has a characteristic distribution involving the anterior horns of the lateral ventricles and atrium in the occipital horns[7-11].

Diagnosis is often made by serial cranial ultrasound, with lesions usually appearing after the first 2 weeks of life in preterm newborns[12,13]. In a high percentage of cases, it is associated in the long term with neuropsychiatric and neurodevelopmental complications (language, social and emotional, hyperactivity and attention disorders, cognitive and motor deficits, spastic diplegia, epilepsy, and visual and auditory alterations)[11,14,15]. This generates major healthcare and economic burdens for the healthcare system and affected families. Therefore, the prevention and management of PVL are of great relevance for improving the prognosis of these patients[8].

Besides, it has been observed that despite advances in neonatal care in recent years, the incidence of PVL has not decreased significantly worldwide[16,17]. Available data show a global incidence ranging from 4 to 10%, for example, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network reports a 4% incidence between 1993 and 2012[18], a multicenter study in China reported 5% incidence between 2005 and 2006[19], and the NEOCOSUR Network reported an incidence of 3.8% until 2016[20].

In our region, the NEOCOSUR Neonatal Network has described between 2001 and 2016 an incidence of PVL that has remained constant over time, at around 4% of the overall population of very low birth weight newborns (VLBWNB)[20].

Due to the significant burden of morbidity that this pathology may have, the standstill in its incidence over time despite improvements in obstetric and neonatal care, associated with the limited prevention and treatment measures currently available, it is important to evaluate the associated factors in order to generate possible strategies to reduce its incidence.

The objective of this study is to evaluate the factors associated with the presence of PVL in surviving VLBWNB at discharge, born between 23 and 31+6 weeks of GA, in the NEOCOSUR Neonatal Network. In addition, to determine its overall incidence and stratified by GA over 10 years.

Patients and Method

Observational retrospective cohort study, multicenter, with prospective data collection using the NEOCOSUR Neonatal Network database.

Population

All newborns born in centers of the NEOCOSUR Neonatal Network surviving at discharge, with birth weight between 400 to 1500 grams and GA between 23 and 31+6 weeks, born between January 2012 and December 2021 were included. All patients with major congenital malformations were excluded. We established 31+6 weeks of GA as the upper limit since the incidence of PVL above that GA is very low.

The clinical data analyzed in this study were extracted from the NEOCOSUR Neonatal Network database. This is a non-profit collaborative network of 32 South American neonatal intensive care units (NICUs) distributed in Argentina, Chile, Paraguay, Peru, and Uruguay that continuously monitors the outcomes of VLBWNB. Data are recorded prospectively, using predefined diagnostic criteria and an anonymous online data entry system (www.neocosur.org). Supplementary material shows the variables recorded in the NEOCOSUR Network (available in the online version).

For the analysis of this study, 21 of 32 units of the NEOCOSUR Network were included. The centers that did not have data recorded during the entire period were excluded. Of the 21 centers, 9 are from Argentina, 8 from Chile, 1 from Paraguay, 2 from Peru, and 1 from Uruguay.

Variables

The event of interest was defined as the diagnosis of PVL, which was established by the presence of any intraparenchymal necrotic lesion in the white matter identified by cranial ultrasound during hospitalization. This was compared to patients who did not have this diagnosis. All patients included in the analysis underwent at least one cranial ultrasound during their hospital stay.

The independent variables studied were grouped into maternal and perinatal characteristics and morbidities, neonatal morbidities, and interventions.

The maternal characteristics and morbidities considered were multiple pregnancy, gestational diabetes, maternal hypertension, intrauterine growth restriction, use of prenatal corticosteroids (at least one dose), presence of chorioamnionitis, and route of delivery. The perinatal characteristics considered were GA calculated by date of last menstrual period (LMP) or early ultrasound (1st trimester), sex, birth weight, diagnosis of small for gestational age (defined according to Fenton curves)[21], and Apgar score at 1 and 5 minutes of life (3 points or less).

The neonatal morbidities studied were the presence of respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), defined as the need for oxygen supplementation for >28 days and oxygen requirement at 36 weeks of corrected GA; necrotizing enterocolitis (NEC) diagnosed according to Bell's criteria (22) and confirmed by abdominal X-ray with the presence of pneumatosis and/or bowel perforation (or surgical findings); early sepsis (positive blood culture or CSF in NB < 72 hours of life), late sepsis (positive blood culture or CSF in NB > 72 hours of life), IVH diagnosed by cranial ultrasound and classified according to Papile and Burstein criteria (23) and the presence of hemodynamically significant patent ductus arteriosus (PDA) (with or without treatment).

The following interventions were evaluated as independent variables: use of continuous positive airway pressure (CPAP), and use of mechanical ventilation (MV) (conventional and/or high frequency).

As this was a multicenter study, the factor center was added as an adjustment variable.

Statistical Analysis

The analysis was separated according to the group, defining as a group those patients with a diagnosis of PVL and compared with the group without a diagnosis of PVL at the time of discharge.

A bivariate analysis was performed using Pearson's chi-square test to compare the percentage of PVL according to categorical variables and the t-Student test to compare averages of numerical variables in NBs with and without PVL; in addition, the incidence of PVL according to GA and center was described.

To evaluate the existence of a trend in the percentage of leukomalacia according to GA, a simple linear regression was fitted where the response variable was the percentage of PVL, and the p-value of the Wald statistic of the coefficient for GA was reported.

To explore the independent effect of different morbidities and therapies for PVL, multivariate logistic regressions were fitted and adjusted for center and perinatal variables. The selection of perinatal variables is based on those known to be confounders when analyzing outcomes in VLBWNB mentioned in other publications as possible risk factors for PVL. The perinatal adjustment variables were center, GA (weeks), sex, delivery route, maternal hypertension, antenatal corticosteroids (at least one dose), chorioamnionitis, SGA (according to Fenton), APGAR at 1 minute ≤ 3 points, APGAR at 5 minutes ≤ 3 points, and multiple pregnancy. Odds Ratios (OR) with their 95% confidence intervals (95%CI) are reported.

The significance level was set at p-< 0.05. The STATA 14.0 software was used for statistical analyses.

Ethical Considerations

This study was approved by the Scientific Committee of the NEOCOSUR Network and the Scientific Ethical Committee of Health Sciences of the *Pontificia Universidad Católica de Chile* (ID 220922001).

Results

During the period analyzed, there were 11,056 newborns with birth weights between 400 and 1,500 grams. Of these, 10,026 had a GA between 23 and 31+6 weeks and no major congenital malformations. A total of 6,825 NBs survived at discharge and had PVL diagnosis. In this study, 27 variables were analyzed, including maternal and newborn conditions and interventions performed on the newborns.

Figure 1 shows the incidence of PVL by GA, with an overall incidence of 8.5%. PVL decreases by two percentage points for each week of increase in GA (beta = -2.05; 95%CI= -2.48 - -1.62; p-value= 0.01). At 23 weeks of GA, the incidence is 19.2% and decreases to 4.7% at 31 weeks of GA.

Table 1 summarizes the maternal and perinatal characteristics and morbidities, neonatal morbidities, and interventions used for the groups included in the analysis. The mean GA and standard deviation (SD) for the PVL group was 27.5 ± 1.9 weeks, while the mean GA for the non-PVL group was 28.5± 1.8 weeks ($p < 0.001$). The average birth weight for the PVL patients was 1,008 ± 242 grams, while for the non-PVL group, it was 1,115 g± 244 grams ($p < 0.001$). Additionally, the PVL population had a higher incidence of vaginal delivery and low APGAR at 1 minute and 5 minutes of life. Likewise, the population without PVL had a higher incidence of multiple deliveries (23.1% vs. 16.4%; $p < 0.001$) and maternal hypertension (31.5% vs. 26.9%; $p = 0.023$).

Table 2 summarizes the multivariate analysis. The factors associated with a higher incidence of PVL were BPD, NEC, severe IVH, and the presence of PDA, adjusted for the variables defined. The chance of having PVL in NBs with BPD is 2.27 times that of having PVL in patients without BPD (OR = 2.27; 95% CI = 1.80 - 2.87); the chance of having PVL in NBs with NEC is 1.78 times that of subjects without NEC (OR = 1.78; 95% CI = 1.35 - 2.34). The chance of having PVL in NB with late sepsis is 1.71 times that of subjects without late sepsis (OR = 1.71; 95% CI = 1.34 - 2.19). The chance of PVL in subjects with severe IVH is 4.64 times that of subjects without IVH (OR = 4.64; 95% CI = 3.51 - 6.14). The chance of PVL in subjects with PDA is 1.32 times that of subjects without PDA (OR = 1.32; 95% CI = 1.06 - 1.64) and the chance of PVL is 2.03 times higher in subjects with mechanical ventilation than in subjects without it (OR = 2.03; 95% CI = 1.54 - 2.67).

It was observed that RDS (OR 1.39; 95% CI 0.92 - 2.09), early sepsis (OR 1.36; 95% CI 0.79 - 2.33), and CPAP use (OR 1.14; 95% CI 0.79 - 1.63) were not associated with PVL.

Other variables such as labor room intubation, surfactant administration, postnatal corticosteroid administration, erythropoietin administration, and treatment of apnea of prematurity were analyzed without representing a significant contribution to the analysis.

Discussion

In this study, factors associated with a higher incidence of PVL diagnosed by ultrasound were BPD, NEC, late sepsis, severe IVH, the presence of PDA, and the use of mechanical ventilation; with an overall incidence of PVL of 8.5% in the population studied.

The pathogenesis of PVL has been linked to three main interacting factors: an incomplete state of development of vascular supply to the cerebral white matter, a maturation-dependent impairment in cerebral blood flow regulation leading to a propensity for ischemic injury to cerebral white matter, and maturation-dependent vulnerability of the oligodendrocyte precursor cells 24.

Several studies have shown that many factors, such as chorioamnionitis, perinatal asphyxia, and hypocapnia increase the risk of PVL [25,26] in extremely low birth weight NBs (ELBWNB) versus VLBWNB[27]. In this study, it was not associated with chorioamnionitis, although it was associated with BPD and late sepsis.

The association between late sepsis and PVL has been reported in other studies and may be related to the inflammatory effects associated with it[16,28]. The association between BPD and PVL should not be surprising since both morbidities are related to oxidative stress[29,30].

Regarding the association observed in our analysis between severe IVH and PVL, there is strong evidence in the literature that agrees with this result. A systematic review that included newborns of 36 weeks of GA or less found that only the presence of IVH would increase the risk of developing PVL with moderate evidence according to GRADE, while the other studied risk factors showed low or very low evidence when adjusted for confounding factors[16].

The evidence linking the presence of PDA with PVL is still controversial[31,32]. The presence of PDA with hemodynamic involvement would imply prolonged exposure to increased flow causing cerebral vascular remodeling with consequent tissue ischemia[33], so the association between both pathologies found in our analysis is to be expected.

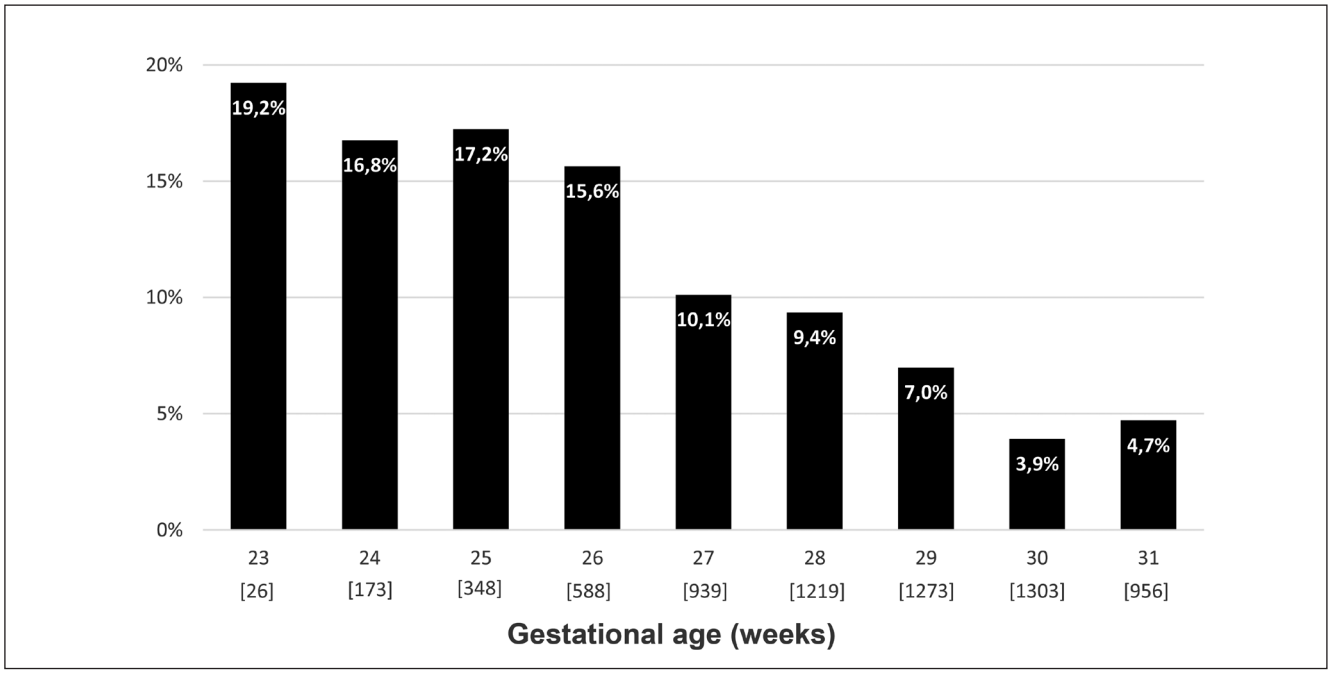

Figure 1. Incidence of periventricular leukomalacia according to gestational age in very low birth weight infants surviving at discharge. NEOCOSUR, 2012-2021. (n=6825; [n by gestational age]) As gestational age increases, the incidence of periventricular leukomalacia decreases. p-value for trends = 0.01.

Table 1. Maternal and perinatal characteristics and morbidities, neonatal morbidities and interventions of the population of very low birth weight infants surviving at discharge with and without periventricular leukomalacia. (NEOCOSUR, 2012-2021)

	PVL (+) (n = 580)	PVL (-) (n = 6245)	p-value
Maternal/perinatal characteristics and morbidities			
Gestational Age (wk); mean (SD)	27.5 (1.9)	28.5 (1.8)	< 0.001
Male; %	55.5	51.9	0.099
Birth weight (g); mean (SD)	1008 (242)	1115 (244)	< 0.001
Small for gestational age (Fenton); %.	6.7	7.0	0.790
Multiple gestation; %	16.4	23.1	< 0.001
Maternal Diabetes; %	8.6	7.6	0.422
Maternal Arterial Hypertension; %	26.9	31.5	0.023
Intrauterine growth restriction; %	23.8	22.9	0.607
Antenatal steroids (at least one dose); %	87.8	87.4	0.828
Chorioamnionitis; %	12.6	12.6	0.987
Spontaneous labor; %	28.3	21.7	< 0.001
Apgar at 1 minute 3 o less; %	24.0	14.9	< 0.001
Apgar at 5 minutes 3 o less; %	4.3	2.4	0.004
Neonatal morbidities and Interventions			
Respiratory distress syndrome	94.5	87.4	< 0.001
BPD (oxygen at 36 weeks)	59.5	23.5	< 0.001
Necrotizing enterocolitis	19.1	7.4	< 0.001
Early onset sepsis	3.3	2.5	0.282
Late onset sepsis	30.1	20.3	< 0.001
Severe Intracranial Hemorrhage	21.8	4.8	< 0.001
Patent Ductus Arteriosus	67.9	48.7	< 0.001
Use of CPAP	91.5	85.2	< 0.001
Mechanical Ventilation	79.1	63.6	< 0.001

CPAP: continuous positive airway pressure; BPD: bronchopulmonary dysplasia; SD: standard deviation; PVL: periventricular leukomalacia.

Table 2. Multivariate analysis of the relation between periventricular leukomalacia and main neonatal morbidities and interventions in very low birth weight infants surviving at discharge. NEOCOSUR, 2012-2021

Neonatal morbidities / Interventions	ORa (95%CI)
Respiratory distress syndrome	1.39 (0.92 - 2.09)
BPD (Oxygen at 36 weeks)	2.27 (1.80 - 2.87)
Necrotizing enterocolitis	1.78 (1.35 - 2.34)
Early Onset Sepsis	1.36 (0.79 - 2.33)
Late Onset Sepsis	1.71 (1.34 - 2.19)
Severe Intracranial Hemorrhage	4.64 (3.51 - 6.14)
Patent Ductus Arteriosus	1.32 (1.06 - 1.64)
Use of CPAP	1.14 (0.79 - 1.63)
Mechanical Ventilation	2.03 (1.54 - 2.67)

Each logistic regression considered periventricular leukomalacia as a response variable, morbidity or therapies as an explanatory variable and perinatal variables (gestational age, sex, route of delivery, maternal arterial hypertension, antenatal steroids, chorioamnionitis, small for gestational age, Apgar at minute 1 <=3, Apgar at 5 minutes <=3 and multiple gestation) and center as adjustment variables. CPAP: continuous positive airway pressure; BPD: bronchopulmonary dysplasia; 95% CI: 95% confidence interval; ORa: adjusted odds ratio.

Regarding the association with NEC, the systemic inflammation that is generated would play a fundamental role in the generation of PVL[34,35]. In a multicenter study conducted in the Spanish Neonatal Network (SEN1500) between 2005 and 2017 where newborns of less than 1500 grams and 24 to 31+6 weeks of GA were analyzed, an association was found between NEC with PVL, both in NEC with surgical treatment and in those without it, with an ORa of 2.50 (1.98 - 3.16) and ORa of 1.70 (1.21 - 2.40), respectively[36].

The use of MV showed a statistically significant association with the development of PVL. It has been postulated that PVL would occur in these patients due to oxidative stress, hypoxemia, and the release of proinflammatory cytokines[30,37].

As we can see, the factors associated with this pathology are situations in which we can intervene with measures such as the prevention of preterm delivery and severe IVH, as well as the prevention and timely diagnosis and treatment of late sepsis, NEC, and PDA. Therefore, it would be relevant to develop strategies to prevent and optimize the management of these pathologies, which could reduce the incidence of PVL.

Regarding the incidence of PVL in this network, an overall incidence of PVL of 8.5% was found in NBs with birth weights between 400 and 1500 grams and GA between 23 and 31+6 weeks surviving at discharge. The incidence increased with lower GA, which is to be expected since this morbidity is associated with greater immaturity[7,38]. It should be considered that in patients with higher GA, the incidence may be even lower since only patients under 1,500 grams are included in this analysis. In comparison with other neonatology centers and networks, we found similar incidences in some of these. A study conducted in the network of neonatology units in Brazil between 2012 and 2013, reported an incidence of 8.5% in NBs from 400 to 1,499 grams[39]. Another study conducted in two centers in Germany with an *n* of 280 patients with less than 30 weeks of GA described an incidence of 3%[40]. However, an enormous variability in the incidence of PVL has also been described in various studies, which has been explained in the literature as differences in the populations studied, the design of the studies, the diagnostic technique, and the classifications used to categorize it[26].

In this study, only patients surviving at discharge are analyzed. The rationale for this criterion is that PVL is precisely a morbidity that occurs in survivors. This allows us to better visualize its impact as a negative burden on the future prognosis of this group of patients[41]. In contrast, severe IVH is a major cause of death during the first days of life[42]. Therefore, it is very challenging to determine the factors associated with PVL and eventually try to decrease its incidence.

Limitations and Strengths

This study has limitations. Cranial ultrasound is limited and may underestimate the diagnosis of PVL[43]. However, all international neonatal networks define the diagnosis of PVL based on ultrasound or MRI[13]. This is due to the high cost of performing MRI on thousands of ELBWNB.

We were also unable to identify the exact time of hospitalization at which the diagnosis of PVL was made. However, the Network's operating manual requests that we record whether the patient underwent ultrasound at three points in time: < 7 days, 7-21 days, and > 21 days.

Another limitation is that the literature describes other risk factors for developing PVL, such as hypocarbia[44,45], which are not recorded in our database.

The strength of the study lies in the fact that it includes a large number of VLBWNBs from a South American network, with numerous centers that reflect a variety of realities.

Conclusions

In this study of a South American network, it was found that the factors associated with a higher incidence of PVL diagnosed by ultrasound in surviving VLBWNBs were the presence of BPD, NEC, late sep-

sis, severe IVH, PDA, and the use of MV. The overall incidence of PVL was 8.5%, being higher at lower GA.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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