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Hematological Parameters at Birth Fail to Predict Intraventricular Hemorrhage in Very Preterm Infants

Mariana Costa Marques

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina clínica

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Hematological Parameters at birth fail to Predict intraventricular hemorrhage in very preterm Infants

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Mariana Costa Marques, abaixo assinado, nº mecanográfico 201906114, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

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Dedicatória:

“Se desejas procurar realmente a verdade, é necessário que duvides pelo menos uma vez na vida, e na medida do possível, de todas as coisas.” – *René Descartes*

“ A gratidão não é apenas a nossa maior virtude, é a mãe de todas as outras” – Cícero

É com uma gratidão imensa que nomeio cada uma das pessoas que decidi incluir nesta dedicatória.

Em primeiro lugar, um obrigada aos meus pais. As minhas conquistas são o resultado, em parte, do vosso trabalho e dedicação. A criação de alguém é realmente o maior ato de amor incondicional que consigo imaginar.

Um enorme obrigada ao Dr. Gustavo Rocha por ter estado presente desde o início deste trabalho e por me ter ajudado durante todas as etapas. Sem ele não teria sido possível a realização desta dissertação.

Um obrigada à Dr.ª Filipa Flor de Lima por ter sido quem me desafiou a fazer este trabalho e me apoiou desde o início, mesmo com todos os precalços.

Um obrigada à Dr.ª Joana Pereira, colega de faculdade e atualmente médica, pela enorme ajuda e presença sobretudo nas fases iniciais onde nenhuma de nós sabia muito bem o que estava a fazer.

Um obrigada Prof.Doutor Rúben Rocha, pelo apoio e disponibilidade para me orientar na realização deste trabalho.

Um enorme obrigada ao Dr. David Rabiço Costa, sem o qual esta dissertação muito provavelmente não teria ficado pronta no tempo que eu queria. Obrigada por me responder sempre, ainda que fora de horas, e às questões mais parvas.

Um obrigada aos meus amigos que posso chamar de família escolhida por ouvirem os desabafos, choros, desesperos, mas sobretudo por festejarem comigo todas as conquistas: Filipa, Francisca e Francisco, Isabel, Joana, Raquel, Inês, Filipe, Sara e Ivo,

Gonçalo e Joana, Sara (prima e amiga) e Sarinha. Não enumerei todos vocês porque são mais do que os dedos de duas mãos, mas vocês sabem quem são e certamente vão-se identificar ao ler esta parte.

Um obrigada à minha família por estar sempre presente e cheia de orgulho em mim, em especial ao meu avô.

Um obrigada especial a todos os médicos-tutores pelos quais passei e que me inspiraram a tentar dar o melhor de mim para me tornar uma excelente profissional, em particular, à Drª Teresa Tavares e à Prof.Doutora Inês Chora – as minhas maiores inspirações.

Termino a minha dedicatória enumerando aquela que é a arma mais poderosa - a esperança:

"O mal é necessário porque sem ele o livre-arbítrio é impossível, e sem livre-arbítrio não pode haver crescimento – nem progresso nem a possibilidade de nos tornarmos o que Deus quis que fossemos. Por muito horrível e todo-poderoso que o mal possa por vezes parecer num mundo como o nosso, no plano geral **o amor é completamente dominante e acabará sempre por triunfar**." *Dr. Eben Alexander*

Article Title: **Hematological Parameters at Birth Fail to Predict Intraventricular Hemorrhage in Very Preterm Infants**

Short running title: **Hematological Parameters and Intraventricular Hemorrhage**

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Abstract

Objective - Recent studies have demonstrated associations between hematological parameters and indices (HPI) obtained from full blood count (FBC) collected on the first day of life (D1) and the occurrence of intraventricular hemorrhage (IVH) in premature infants. Our objective was to evaluate the association between HPI obtained from the FBC of D1 and the occurrence of IVH in premature infants, in order to assess whether these can be used as prognostic markers. **Study Design** - Retrospective study, at an academic tertiary center, including preterm infants with gestational age below 30 weeks. A statistical analysis compared two groups of infants, with and without IVH. **Results** – 206 infants were included, 86 (41.7%) in the IVH group and 120 (58.3%) in the no-IVH groups. The univariate analysis found that red blood cells (p=0.018), hemoglobin (p<0.001), and hematocrit (p=0.001) were significantly lower in the IVH group. The multivariate analysis by logistic regression adjusted to gestational age and birth weight revealed no significant associations between HPI of D1 and the occurrence of IVH. An analysis in the subgroup of patients with IVH-3 (severe IVH) also did not reveal an association between HPI and IVH-3. An association between bronchopulmonary dysplasia and IVH (all grades) was found (p=0.016). Also, periventricular infarction (p=0.002) and cystic periventricular leucomalacia (p < 0.001) were significantly more prevalent in the IVH-3 group. **Conclusions** – Our results demonstrate that HPI from FBC collected on D1 are not associated with the occurrence of IVH, and therefore cannot be used as predictors of IVH in extremely premature infants.

Key words: blood count; hematological parameters; hematological indices; intraventricular hemorrhage; preterm infant

Key points:

- Hematology indices and intraventricular hemorrhage

- Prematures at risk of intraventricular hemorrhage

- Retrospective analysis

- Single terciary center design

- Robust patient sample

Introduction

Intraventricular hemorrhage (IVH) in premature neonates represents a critical neurological concern for neonatologists. It often manifests within the first few days of life and severe cases can lead to mortality or long-term complications such as cerebral palsy and cognitive impairment [1-3]. Its prevalence can be as high as 45% among extremely preterm infants [3]. The pathogenesis of IVH is multifactorial, influenced by rapid fluctuations in cerebral blood flow (CBF) and the inherent fragility of the germinal matrix [4-12].

Recent research by Cucerea M et al. has shown that early hematological parameters are linked to the development of IVH in preterm infants born between 22–28 weeks of gestation, suggesting their potential use as predictive indicators [3]. Additionally, findings from Dekom S et al. indicate that infants with higher hematocrit (HTC) levels may have a reduced risk of IVH compared to those with levels below 45% [13]. Other hematological factors associated with an increased IVH risk include thrombocytopenia [14,15], low HTC, and low hemoglobin (HB) levels at birth [16]. Previous studies have also highlighted elevated bleeding time and INR levels in premature neonates with IVH [17].

The role of hematological parameters in contributing to the occurrence of IVH in premature newborns remains poorly understood and warrants further investigation. This study aimed to evaluate the association between hematological parameters and indices obtained from the initial full blood count on the first day of life (D1) and the occurrence of IVH in premature infants, in order to assess whether these can be used as prognostic markers.

Material and methods

This is a retrospective study conducted at an academic tertiary neonatal intensive care unit (NICU) that admits preterm newborns from 23 weeks of gestation onwards. Our inclusion criteria were preterm neonates with a gestational age between 23 weeks (23 weeks

and 0 days) and 30 weeks (29 weeks and 6 days), born between January 1, 2008, and October 31, 2023. Our exclusion criteria were: preterm infants born in another hospital (outborn); those affected by TORCH infections (Toxoplasmosis, Others, Rubella, Cytomegalovirus, and Herpes); major congenital anomalies; chromosomal abnormalities; asphyxia (Apgar score at 5 minutes ≤ 3 or umbilical cord arterial blood pH < 7.0); twin-to-twin transfusion syndrome; fetal growth discrepancy (a weight difference > 20% compared to the larger fetus); diagnosis of an inborn metabolic error during prenatal consultation or the neonatal period; and diagnosis or suspicion of a neuromuscular disease.

The data collection protocol included information about the mother, gestation, and delivery, as well as demographic details about the neonate, data on the neonate's resuscitation, and neonatal morbidity and mortality experienced in the NICU. Additionally, data from the anatomopathological study of the placenta and the hematological parameters from the full blood count collected on D1 were also evaluated.

In our NICU, on D1 of life, all preterm infants undergo an initial cranial ultrasound examination, which is then repeated weekly. We used Volpe JJ's classification [18] for the classification of IVH and the criteria from de Vries L and Rennie JM [19] for the classification of cystic periventricular leukomalacia (cPVL).

Our center approaches premature infants according to the recommendations of international guidelines according to the latest scientific evidence [20-30]. Detailed protocols are available on supplementary table 1.

We follow the recommendations from the Portuguese Society of Neonatology for the transfusion of red blood cells [31] and platelets [32]. Platelet transfusion is indicated when platelet counts fall below 50,000 per cubic millimeter, or 100,000 per cubic millimeter if bleeding or clinical instability occurs. Regarding red blood cell transfusions, our goal is to maintain an

HB level of 12 g/dL or higher during the first week of life. All data used were collected from hospital registries following approval by the local Institutional Ethics Committee (CE-42-45).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 28 for Windows (IBM SPSS Statistics®, Inc., Chicago, IL, USA). Normality of sample distribution was assessed using the Kolmogorov-Smirnov test. Categorical variables were presented as absolute and relative frequencies, while symmetrically distributed continuous variables were described using the mean (± standard deviation), and asymmetrically distributed continuous variables by the median (minimum-maximum). Chi-square or Fisher's exact test were used to compare categorical variables, and the Independent t-test or Mann-Whitney U test were employed for symmetric and asymmetric continuous variables, respectively. Predictors were evaluated through multivariate analysis using logistic regression. A p-value < 0.05 was considered statistically significant.

Results

From 241 premature newborns with gestational age (GA) between 23 and 29+6 weeks admitted in our NICU, 35 (14.52%) were excluded: 18 outborns, 1 affected by TORCH (Toxoplasmosis, Others, Rubella, Cytomegalovirus and Herpes) infections, 5 with major congenital anomalies, 1 with chromosomal abnormalities, 6 with Apgar score at 5 minutes ≤ 3, 2 with twin-to-twin transfusion syndrome, and 2 with fetal growth discrepancy. Two hundred and six (85.48%) were eligible and therefore included in this study.

Data on mother, gestation and delivery for the total sample and the subgroups IVH and no-IVH newborns are reported in **table 2**. In the IVH group, clinical chorioamnionitis (p=0.004), cervical insufficiency (p=0.035), preeclampsia (p=0.017) and fetal growth

restriction (p=0.028) were significantly more prevalent. There were no other statistically significant associations.

Demographic data of the total sample and of the subgroups IVH and no-IVH newborns are described in **table 3**. For the total sample, the median of the GA was 27 (range: 23-29) completed weeks and the mean birth weight was 933.30 (±266.8 SD) grams. Both of these variables were significantly lower in the IVH group (p<0.001 and p<0.011, respectively). There were no other statistically significant associations.

Data on delivery room management for the total sample and the subgroups IVH and no-IVH newborns are presented in **table 4**. In the IVH group, the use of endotracheal tube (p=0.043), invasive mechanical ventilation (p=0.042) and use of oxygen (p=0.048) were significantly more prevalent. There were no other statistically significant differences between the two groups.

Data on the neonatal morbidity and mortality for the total sample and the subgroups IVH and no-IVH newborns are shown in **table 5**. Use of surfactant (p<0.001) and systemic postnatal steroids (p=0.127), oxygen dependency at 36 weeks of GA (p=0.003) and oxygen at discharge (p=0.008), were significantly higher in the IVH group. Hemodynamically significant patent ductus arteriosus (Hs-PDA) (p=0.015), necrotizing enterocolitis (NEC) ≥2 (p=0.045), total parenteral nutrition (TPN) (p=0.022), red blood cells (p=0.009) and platelet (p=0.007) transfusions, periventricular venous infarction (PVI) (p<0.001), cystic periventricular leukomalacia (cPVL) (p=0.004), early sepsis (p=0.013), nosocomial sepsis (p=0.033), retinopathy of prematurity (ROP) ≥2 (p=0.020), death (p=0.001) were significantly more prevalent in the IVH group. Days of mechanical ventilation (p=0.016), nasal continuous positive airways pressure (nCPAP) (p<0.005), invasive mechanical ventilation (IMV) (p=0.002), high-frequency oscillatory ventilation (HFOV) (p=0.001) were significantly higher

in the IVH group. There were no statistically significant associations between IVH and the other parameters.

Data on the hematological parameters of D1 for the total sample and the subgroups IVH and no-IVH are shown in **table 6**. The univariate analysis found that red blood cells (RBC) (p=0.018), HB (p<0.001), HTC (p=0.001) were significantly lower in the IVH group compared to the no-IVH group. The multivariate analysis by logistic regression adjusted to gestational age and birth weight revealed no significant associations between hematological parameters and indices of D1 and the occurrence of IVH.

The multivariate analysis by logistic regression adjusted to clinical chorioamnionitis, gestational age, birthweight, use of endotracheal tube, mechanical ventilation and oxygen in the delivery room, surfactant, days of invasive mechanical ventilation and nasal continuous positive airways pressure, oxygen dependency at 36 weeks, oxygen at discharge, total parenteral nutrition, transfusion of red blood cells and platelets, Hs-PDA, PVI, cPVL, early and nosocomial sepsis and ROP found an association between oxygen dependency at 36 weeks of GA and IVH [OR=2.41; 95%CI: 1.18-4.90, p=0.016].

An analysis in the subgroup of patients with IVH-3 (severe IVH) was carried out. The univariate analysis showed that RBC (p=0.018), HB (p<0.001), HTC (p=0.001), red cell distribution width coefficient of variation (RDWCV-RDW) (p=0.007) and lymphocyte-to-monocyte ratio (LMR) (p=0.011) were significantly lower in the IVH-3 group. The multivariate analysis by logistic regression adjusted to confounding variables (multiple gestation, clinical and histologic chorioamnionitis, chorionic vasculitis, gestational age, birthweight, use of endotracheal tube and surfactant, Apgar score at 1st minute < 5 in the delivery room, occurrence of pneumothorax, systemic postnatal steroids, inhaled bronchodilator, oxygen at discharge, transfusion of red blood cells and platelets) showed that

occurrence of PVI (p=0.002) and cPVL (p<0.001) were significantly more prevalent in the IVH-3 group, rather than in the no-IVH group.

Discussion

This study, conducted on a cohort of preterm infants with a gestational age of less than 30 weeks, aimed to evaluate the association between hematological parameters and indices on D1 and the occurrence of IVH. Assessing these parameters can help healthcare professionals identify premature newborns at higher risk of developing IVH, allowing for quicker preventive or therapeutic interventions. Monitoring these parameters can guide decisions on ventilatory support, oxygenation optimization, and even the cautious use of blood transfusions, reducing the risk of complications.

The cohort was analysed according to the two subgroups of newborns: those with IVH and those without IVH. Notably, the two groups differed significantly in gestational age, with the IVH group having a significantly lower gestational age and, consequently, a lower birth weight. Our univariate analyses revealed differences in hematological parameters and hematological indices between the two groups of newborns studied.

The values of RBC, HB, and HCT, interrelated indices, were lower in the group of infants with IVH compared to those without IVH. Low HB and HTC may be related to hypoxia and hemodynamic instability, both of which increase the risk of IVH. Hypoxia weakens blood vessels, making brain tissue more susceptible to hemorrhage. Additionally, low HB levels may indicate the need for blood transfusions, which in themselves can increase bleeding risk [33,34].This aspect has been previously described by other researchers. Cucerea M. [3], Dekom S. [13], and Karagol B.S. [35] studied premature infants and found that lower HCT levels on D1, which reflect the volume of circulating blood, were associated with a higher prevalence of IVH. The authors hypothesized that a low HCT level at birth in extremely

premature infants might significantly increase CBF as a compensatory mechanism for cerebral hypoperfusion and low oxygenation, potentially leading to IVH. In this study, although univariate analysis revealed differences in RBC, HB, and HCT, these differences were not significant in the multivariate analysis adjusted for gestational age and birth weight. Indeed, previous research has shown that the degree of prematurity significantly influences blood parameter values at birth. All three blood cell lines increase in proportion to gestational age. Additionally, prenatal factors and perinatal treatments also influence the hematological parameter values of preterm infants after birth [36].

Our results do not support the hypothesis that hematological parameters and indices on D1 differ between patients with and without IVH, and therefore, these measures are not useful for identifying patients at risk of developing IVH.

In this study, bronchopulmonary displasia (BPD) was found to be associated with IVH after multivariate analysis. BPD is a chronic lung disease that commonly affects extremely preterm neonates. Despite recent advances in perinatal care that have significantly reduced neonatal morbidity and mortality, the incidence of BPD has remained unchanged [35]. Risk factors for BPD include gestational age, birth weight, gender, antenatal corticosteroids, maternal chorioamnionitis, surfactant requirement, type and duration of mechanical ventilation, fraction of inspired oxygen (FiO_2), sepsis, HsPDA, NEC and IVH [37-41]. A recent study by Puerta-Martínez AG et al. demonstrated that lower gestational age, birth asphyxia, an Apgar score of less than 6 at minute 1 and 5, and respiratory-related factors are associated with an increased risk of severe IVH [42]. BPD occurs mostly in extremely preterm infants, a population in which the risk of IVH is also high. Additionally, infants with IVH often require prolonged mechanical ventilation, which is a significant risk factor for developing BPD. The use of positive pressure ventilation can lead to lung injury and contribute to the development of this chronic lung disease [41].

This study encompasses a robust patient sample, enabling a comprehensive assessment of the association between hematological parameters and indices collected on D1 and the occurrence of IVH, which reinforces confidence in our findings. Additionally, the single-center design, coupled with a consistent blood collection methodology, significantly enhances the robustness of our results. Given these strengths, we assert that this study has the potential to make a meaningful contribution to future meta-analyses that evaluate the relationship between early hematological parameters and intraventricular hemorrhage in preterm infants.

The retrospective nature is the main limitation of this study. In retrospective studies, it is challenging to control for confounding variables, that can interfere with the association between exposure and outcome, making it difficult to compare the results between different studies.

Despite these limitations, retrospective studies are valuable tools as an initial step in exploring hypotheses that can later be confirmed by more controlled, prospective studies.

Conclusion

In conclusion, this study shows that hematological parameters and indices derived from blood counts collected on D1 are not associated with the occurrence of IVH. Consequently, these parameters cannot serve as reliable predictors of IVH in extremely premature infants. This pivotal finding underscores the need for ongoing research to identify more effective biomarkers and strategies for predicting IVH, ultimately enhancing clinical outcomes for this vulnerable population.

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Table 2 - Data on mother, gestation and delivery for the total sample and the subgroups IVH and no-IVH patients.

	Total (n=206)	**IVH (n=86)**	**no-IVH (n=120)**	***p** value*
Mother's age, mean (SD)	32.35 (±5.8)	31.57 (±6.2)	32.89 (±5.5)	0.239***
1st pregnancy, n (%)	129 (62.60)	52 (60.40)	77 (64.20)	0.943*
Spontaneous pregnancy, n (%)	161 (78.20)	66 (76.70)	95 (79.20)	0.255*
Supervised pregnancy, n (%)	197 (95.60)	82 (95.30)	115 (95.80)	0.994*
Multiple gestation, n (%)	54 (26.20)	24 (27.90)	30 (25.00)	0.493*
Antenatal steroids, n (%)	187 (90.80)	80 (93.00)	107 (89.20)	0.661*
Full cycle, n (%)	118 (57.30)	51 (59.30)	67 (55.80)	0.648*
Neuroprotection ($MgSO_4$), n (%)	73 (35.40)	35 (40.70)	38 (31.70)	0.421*
C-section, n (%)	138 (67,00)	52 (60.50)	86 (71.70)	0.087*
Rupture of membranes >18h, n (%)	31 (15.00)	13 (15.10)	18 (15.00)	0.446*
Clinical chorioamnionitis, n (%)	**49 (23.80)**	**29 (33.70)**	**20 (16.70)**	**0.004***
Cervical insufficiency, n (%)	**30 (14.60)**	**16 (18.60)**	**14 (11.70)**	**0.035***
Abruptio placentae, n (%)	40 (19.40)	18 (20.90)	22 (18.30)	0.170*
Chronic arterial hypertension, n (%)	14 (6.80)	5 (5.80)	9 (7.50)	0.933**
PE, n (%)	**39 (18.90)**	**11 (12.80)**	**28 (23.30)**	**0.017****
HELLP syndrome, n (%)	13 (6.30)	3 (3.50)	10 (8.30)	0.305**
Gestational hypertension, n (%)	6 (2.90)	1 (1.20)	5 (4.20)	0.341**
Type 1 diabetes, n (%)	1 (0.50)	0 (0.00)	1 (0.80)	0.988**
Gestational diabetes, n (%)	17 (8.30)	6 (7.00)	11 (9.20)	0.956**

Insulin, n (%)	4 (1.90)	1 (1.20)	3 (2.50)	0.577**
Tocolysis, n (%)	53 (25.70)	27 (31.40)	26 (21.70)	0.092*
Smoking, n (%)	18 (8.70)	7 (8.10)	11 (9.20)	0.373**
Alcohol, n (%)	2 (1.00)	1 (1.20)	1 (0.80)	0.392**
Drugs of abuse, n (%)	7 (3.30)	6 (7.00)	1 (0.80)	0.650**
Fetal growth restriction, n (%)	**37 (18.00)**	**11 (12.80)**	**26 (21.70)**	**0.028****
Thrombophilia, n (%)	3 (1.50)	2 (2.30)	1 (0.80)	0.533**
Chronic diseases n (%) **a**	47 (22.80)	23 (26.70)	24 (20.00)	0.840*
Autoimmune diseases n (%) **b**	10 (4.90)	5 (5.80)	5 (4.20)	0.987**
Other pregnancy pathologies n (%) **c**	7 (3.30)	3 (3.50)	4 (3.30)	0.675**
Placentae study				
Chorioamnionitis, n (%)	91 (44.20)	37 (43.00)	54 (45.00)	0.231*
Funisitis, n (%)	17 (8.30)	9 (10.50)	8 (6.70)	0.377*
Chorionic vasculitis, n (%)	47 (22.80)	22 (25.60)	25 (20.80)	0.431*
Changes compatible with preeclampsia, n (%)	27 (13.10)	8 (9.30)	19 (15.80)	0.088*

HELLP - hemolysis, elevated liver enzymes and low platelet count; IVH – intraventricular hemorrhage; n – number; PE – preeclampsia; SD – standard deviation

a asthma; renal lithiasis, hypothyroidism, epilepsy, haemophilia B, congenital heart disease, deficiency of protein C, breast cancer, lung cancer, left renal agenesis, bicornuate uterus, renal failure, hypogonadism, polycystic kidney disease, antiphospholipid syndrome, obesity, hypertension, ulcerative colitis, kidney transplant, tuberous sclerosis; **b** autoimmune

hypothyroidism, Chron disease, polyarthritis; **c** Twin-to-twin transfusion syndrome, hepatic haemorrhage, thrombocytopenia, thrombotic disease;

Bold – **statistically significant.** *Chi square test; ** Fisher's exact test; *** Independent T test

Table 3 – Demographics

	Total (n=206)	**IVH (n=86)**	**no-IVH (n=120)**	***p* value**
Gestational age, median (min-max)	**27 (23-29)**	**26 (23-29)**	**28 (23-29)**	**<0.001****
Birthweight, mean (±SD)	**933.33 (± 266.84)**	**877.45 (±253.28)**	**973.38 (±270.11)**	**<0.011*****
Small for gestational age, n (%)	41 (20.00)	11 (12.80)	30 (25.00)	0.211**
Gender				
Male, n (%)	100 (48.50)	43 (50.00)	57 (47.50)	0.912*
Female, n (%)	106 (51.50)	43 (50.00)	63 (52.50)	

IVH – intraventricular hemorrhage; n – number; SD – standard deviation

Bold – s**tatistically significant. ***Chi square test; ** Fisher's exact test; *** Independent T test; **** Mann Whitney-U test

Table 4 - Delivery room management

	Total (n=206)	**IVH (n=86)**	**no-IVH (n=120)**	***p* value**
Positive pressure, n (%)	193 (93.70)	80 (93.00)	113 (94.20)	0.737**
Endotracheal tube, n (%)	**127 (61.70)**	**60 (69.80)**	**67 (55.80)**	**0.043***

Invasive mechanical ventilation, n (%)	**132 (64.10)**	**62 (72.10)**	**70 (58.30)**	**0.042***
Early-NCPAP, n (%)	86 (41.70)	30 (34.90)	56 (46.70)	0.312*
Oxygen, n (%)	**172 (83.50)**	**77 (89.50)**	**95 (79.20)**	**0.048***
Maximum FiO2, median (min-max)	0.43 (0-1.0)	0.4 (0-1.0)	0.31 (0-1.0)	0.103****
Adrenaline, n (%)	9 (4.40)	5 (5.80)	4 (3.30)	0.421**
Apgar score <5				
1st minute, n (%)	68 (33.00)	29 (33.70)	39 (32.50)	0.139*
5th minute, n (%)	18 (8.70)	6 (7.00)	12 (10.00)	0.898**

FiO2 – fraction of inspired oxygen; IVH – intraventricular hemorrhage; n – number; NCPAP – nasal continuous positive airway pressure

Bold – **statistically significant.** * Chi square test; ** Fisher's exact test; ****Mann-Whitney U Test

Table 5 - Neonatal morbidity and mortality.

	Total (n=206)	**IVH (n=86)**	**no-IVH (n=120)**	***p* value**
RDS, n (%)	180 (87.40)	79 (91.90)	101 (84.20)	0.300**
Surfactant, n (%)	167 (81.20)	79 (91.90)	88 (73.30)	**<0.001****
MV (invasive and NCPAP), n (%)	192 (93.20)	82 (95.30)	110 (91.70)	0.988**
Total days of MV, median (min-max)	35 (1-143)	34 (2-143)	35 (1-90)	**0.016****
Days of NCPAP, median (min-max)	31 (1-85)	30.5 (1-85)	32 (1-70)	**<0.005****
Days of IMV, median (min-max)	7 (1-88)	8 (1-88)	6 (1-61)	**0.002****
Days of HFOV, median (min-max)	5 (1-19)	5 (1-18)	4 (1-19)	**0.001****

Pneumothorax, n (%)	23 (11.20)	12 (14.00)	11 (9.20)	0.089*
Oxygen dependency at 36 weeks of GA, n (%)	**68 (33.00)**	**38 (44.20)**	**30 (25.00)**	**0.003***
Systemic postnatal steroids, n (%)	28 (13.60)	16 (18.60)	12 (10.00)	0.127*
Inhaled postnatal steroids, n (%)	52 (25.20)	25 (29.10)	27 (22.50)	0.192*
Inhaled bronchodilator, n (%)	40 (19.40)	21 (24.20)	19 (15.80)	0.136*
Diuretics, n (%)	25 (12.10)	14 (16.30)	11 (9.20)	0.468*
Oxygen at discharge, n (%)	**41 (19.90)**	**24 (27.90)**	**17 (14.20)**	**0.008***
Days of oxygen, median (min-max)	38 (1-191)	43.5 (1-191)	35 (1-121)	0.758****
HS-PDA, n (%)	**111 (53.90)**	**53 (61.60)**	**58 (48.30)**	**0.015***
Surgical closure, n (%)	23 (11.20)	12 (14.00)	11 (9.20)	0.646*
NEC≥2, n (%)	**17 (8.30)**	**11 (12.80)**	**6 (5.00)**	**0.045***
TPN, n (%)	**197 (95.60)**	**85 (98.80)**	**112 (93.30)**	**0.022****
Days of TPN, median (min-max)	22 (1-210)	23 (2-210)	21 (1-85)	0.619****
Transfusions				
Red blood cells, n (%)	**156 (75.70)**	**73 (84.90)**	**83 (69.20)**	**0.009****
Platelets, n (%)	**54 (26.20)**	**31 (36.00)**	**23 (19.20)**	**0.007***
PVI, n (%)	**17 (8.30)**	**17 (19.80)**	**0 (0.00)**	**<0.001****
cLPV, n (%)	**64 (31.10)**	**28 (32.60)**	**36 (30.00)**	**0.004***
Early sepsis, n (%)	**19 (9.20)**	**13 (15.10)**	**6 (5.00)**	**0.013***
Nosocomial sepsis, n (%)	**86 (41.70)**	**37 (43.00)**	**49 (40.80)**	**0.033***
Pneumonia, n (%)	11 (5.30)	7 (8.10)	4 (3.30)	0.269**
Meningitis, n (%)	2 (1.00)	1 (1.20)	1 (1.20)	0.398**
ROP≥2, n (%)	**17 (8.30)**	**10 (11.60)**	**7 (5.80)**	**0.020***

Deceased, n (%)	**55 (26.70)**	**33 (38.40)**	**22 (18.30)**	**0.001***
Length of stay of survivors, median (min-max)	61 (1-255)	60.5 (2-255)	61 (1-136)	0.074****

cLPV - cystic periventricular leukomalacia; GA - gestational age; HFOV – high frequency oscillatory ventilation; HS-PDA - hemodynamically significant patent ductus arteriosus; IMV – invasive mechanical ventilation; IVH – intraventricular hemorrhage; MV - mechanical ventilation; n – number; NCPAP - nasal continuous positive airways pressure; NEC - necrotizing enterocolitis; PVI - periventricular venous infarction; ROP - retinopathy of prematurity; RDS - respiratory distress syndrome; TPN – total parenteral nutrition

Bold – statistically significant. * Chi square test; ** Fisher´s exact test; **** Mann-Whitney U Test.

Table 6 - Hematological parameters provided by blood count collected on the first day of life.

	Total (n=206)	**IVH (n=86)**	**no-IVH (n=120)**	***p* value**	**Adjusted *p* value@**
RBC (x1012/L), mean (±SD)	**3.95 (±0.70)**	**3.85 (±0.58)**	**4.03 (±0.77)**	**0.018*****	0.365
Hb (g/dL), mean (±SD)	**15.45 (±2.73)**	**15.04 (±2.30)**	**15.74 (±2.98)**	**<0.001*****	0.824
Hematocrit (%), mean (±SD)	**44.67 (±6.99)**	**43.58 (±6.02)**	**45.45 (±7.54)**	**0.001*****	0.842

MCV (fL), mean (±SD)	114.52 (±10.73)	114.52 (±10.80)	114.52 (±10.72)	0.436***	0.067
MCH (pg), mean (±SD)	39.25 (±3.00)	39.18 (±2.95)	39.31 (±3.05)	0.142***	0.092
MCHC (g/dL), mean (±SD)	34.58 (±1.77)	34.61 (±1.94)	34.56 (±1.64)	0.465***	0.847
RDWCV (%), mean (±SD)	16.86 (±2.07)	16.55 (±1.93)	17.09 (±2.14)	0.307***	0.707
RDWSD (fL), mean (±SD)	69.62 (±13.58)	68.58 (±12.22)	70.37 (±14.48)	0.054***	0.979
WBC (x109/L), mean (±SD)	10.05 (±8.15)	11.34 (±11.01)	9.12 (±5.07)	0.452***	0.487
Neutrophils (x109/L), mean (±SD)	2.57 (± 4.66)	4.04 (±4.26)	3.90 (±4.95)	0.436***	0.649
Eosinophils (x109/L), mean (±SD)	0.26 (±1.01)	0.20 (±0.23)	0.29 (±1.31)	0.774***	0.708
Basophils (x109/L), mean (±SD)	0.03 (±0.06)	0.04 (±0.06)	0.03 (±0.06)	0.988***	0.306
Lymphocytes (x109/L), mean (±SD)	4.86 (±3.12)	4.93 (±3.28)	4.81 (±3.01)	0.623***	0.151
Monocytes (x109/L), mean (±SD)	1.30 (±4.24)	1.75 (±6.37)	0.98 (±1.33)	0.244***	0.261
Immature granulocytes (x109/L), mean (±SD)	0.38 (±1.13)	0.45 (±1.08)	0.33 (±1.17)	0.216***	0.824

Erythroblasts, mean (±SD)	65.30 (±140.53)	82.48 (±190.73)	51.91 (±81.30)	0.650***	0.771
Platelets (x109/L), mean (±SD)	184.04 (±66.09)	183.85 (±73.28)	183.38 (±61.06)	0.536***	0.667
Platelet Volume (%), mean (±SD)	0.22 (±0.08)	0.22 (±0.07)	0.22 (±0.09)	0.989***	0.961
MPV (fL), mean (±SD)	10.82 (±0.86)	10.79 (±0.73)	10.84 (±0.95)	0.624***	0.718
PDW, mean (±SD)	12.03 (±1.91)	11.79 (±1.59)	12.21(±2.10)	0.598***	0.811
PLCR, mean (±SD)	29.94 (±6.51)	29.61 (±5.46)	30.18 (±7.19)	0.679***	0.756
PLR, mean (±SD)	46.63 (±30.55)	46.94 (±32.15)	46.41 (±29.49)	0.251***	0.063
NLR, mean (±SD)	1.04 (±1.86)	0.95 (±0.93)	1.11 (±2.31)	0.905***	0.377
LMR, mean (±SD)	8.03 (±9.82)	6.72 (±6.46)	8.96 (±11.58)	0.211***	0.154

Hb – haemoglobin; IVH – intraventricular hemorrhage; LMR - lymphocyte-to-monocyte ratio; MCH - mean corpuscular haemoglobin; MCHC - mean corpuscular haemoglobin concentration; MCV - mean corpuscular volume; MPV - mean platelet volume; n – number; NLR -neutrophil-to-lymphocyte ratio; PDW - platelet distribution width; PLCR - platelet-large cell ratio; PLR - platelet-to-lymphocyte ratio; RBC - red blood cells; RDWCV- red cell destribution width coefficient of variation; RDWSD- RDW standard deviation; SD – standard deviation; WBC - White blood cell

Bold – statistically significant. *** Independent t test. @ Multivariate analysis by logistic regression adjusted to gestational age and birth weight.

Supplementary Table 1- Diagnosis, approach and management of the premature newborn

Diagnosis / Approach	**Definition/Management**	**Reference**
Cranial ultrasound	In our center, on D1 of life, all preterm infants undergo an initial cranial ultrasound examination, which is then repeated weekly. We used Volpe JJ's classification for the classification of IVH and the criteria from de Vries L and Rennie JM for the classification of cPVL.	18,19
Hypertension and PE	Defined according to the American College of Obstetricians and Gynaecologists. We considered the diagnosis of PE as blood pressure values over 140/90 mmHg along with proteinuria higher than 300 mg in 24 hours, detected after 20 weeks of gestation in previously normotensive women. HELLP syndrome was considered as a complication of PE when occurring in association to it.	20
Gestational diabetes Cervical incompetence Placental abruption Fetal growth restriction	Definitions followed the American College of Obstetricians and Gynecologists guidelines, aligned with our institutional terminology.	20
Prenatal corticosteroid	Women at risk of preterm delivery receive prenatal corticosteroids, particularly dexamethasone, up to 34	21

	weeks of gestation, in accordance with the guidelines from the National Institutes of Health (NIH) Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. An additional course of steroids is administered if there is a threat of preterm birth before the 32nd week of gestation, assuming that the previous course was administered 1-2 weeks earlier.	
Antenatal magnesium sulfate	For fetal neuroprotection, prenatal magnesium sulfate was administered to all women. This included an initial intravenous dose of 4g over 30 minutes, followed by a continuous infusion of 1g per hour until delivery, in accordance with established guidelines.	22
Chorioamnionitis	Maternal fever and two or more symptoms such as maternal or fetal tachycardia, uterine tenderness, foul-smelling amniotic fluid, leukocytosis, or elevated CRP were the criteria used to define clinical chorioamnionitis. The presence of polymorphonuclear leukocytes in fetal membranes and chorionic plate was used to define histological chorioamnionitis. Chorionic vasculitis was considered in the presence of infiltration in chorionic vessels, and funisitis was noted	23, 24

	with infiltration in the umbilical cord blood vessel wall and Wharton's jelly.	
Resuscitation in the delivery room	Preterm infants with adequate respiratory drive received polyethylene bag and early nCPAP. In our center, we aim to maintain a FiO2 below 0.30 for supplemental oxygenation.	
Small for gestational age	SGA was defined as a birth weight below the 3rd percentile according to Fenton's fetal growth charts.	25
Protocol-driven assessments	Protocol-driven assessments of all premature infants are conducted within the first hour of life, including collection of a complete blood count, blood culture and CRP measurement following peripheral vein puncture. The blood count is analyzed in the hospital's central laboratory. Additional hematological indices (PLR, NLR and LMR) were calculated from the blood count.	
Respiratory support	Our center primarily uses non-invasive ventilation such as nCPAP, with or without assisted pressure. If ineffective, we employ CV with SIPPV. HFOV is used for rescue ventilation. We target SpO2 ideally between 90% and 94%.	
Caffeine citrate	Caffeine citrate is administered to all preterm neonates in our center, from birth until 34 weeks corrected age, regardless of the presence of apnea episodes.	

Surfactant	When a FiO2 above 0.30 is required to maintain the SpO2 within the target range, preterm infants with RDS receive early rescue surfactant, starting with 200 mg/kg of poractant alpha, with an additional dose of 100 mg/kg if necessary.	
BPD	In accordance with National Institutes of Health criteria, dependence on oxygen supplementation at 36 weeks of corrected age was considered BPD.	26
Pneumonia	Pneumonia was diagnosed based on signs of respiratory distress, abnormal white blood cell count and elevated CRP, positive cultures from urine, blood, or broncho-tracheal samples, and evidence of lung infection on radiography.	27
Sepsis	The assessment of sepsis followed our National Programme of Infection Control Guidelines, differentiating between proven cases of sepsis (confirmed by positive blood culture for bacterial or fungal infection) and clinically diagnosed cases based on symptoms such as fever, hypothermia, lethargy, tachypnea, apnea/bradycardia, cyanosis, hypoglycemia not attributed to other diagnoses, and thrombocytopenia, leukopenia, or elevated CRP. The time limit to classify early and late sepsis was set at 72 hours.	27

Meningitis	Meningitis was diagnosed in clinically ill premature infants based on elevated polymorphonuclear counts and abnormal cerebrospinal fluid biochemistry, regardless of the isolation of a microbiological agent.	27
ROP	Ophthalmological examinations and screening for ROP were conducted according to the criteria of the Portuguese Society of Neonatology. The classification of ROP was determined using the International Classification of Retinopathy of Prematurity published in 2005.	28, 29
Ductus arteriosus patency	All preterm infants underwent echocardiography between 48 and 72 hours of life to screen for HsPDA. Ibuprofen was used as the first-line treatment when HsPDA was present.	
Parenteral nutrition	In stable cases, infants ideally began total parenteral nutrition on D1 of life. Starting with a volume of 70-90 ml/kg/day, the volume was increased by 10-20 ml/kg/day up to 150 ml/kg/day by the seventh day.	
Incubator humidity	Maintained at 70% during the first week.	
NEC	We utilized the modified Bell criteria to diagnose and stage NEC.	30
Hemoderivatives transfusion	We follow the recommendations from the Portuguese Society of Neonatology for the transfusion of red blood cells and platelets. Platelet transfusion is indicated when	31, 32

	platelet counts fall below 50,000 per cubic millimeter, or 100,000 per cubic millimeter if bleeding or clinical instability occurs.	

D1 – first day of life; IVH – intraventricular hemorrhage; cPVL- cystic periventricular leukomalacia; PE – preeclampsia; HELLP - hemolysis, elevated liver enzyme levels, and low platelet levels; CRP - C-reactive protein; nCPAP - nasal continuous positive airway pressure; FiO2 - fraction of inspired oxygen; SGA – Small for gestational age; PLR - platelet-to-lymphocyte ratio; NLR - neutrophil-to-lymphocyte ratio; LMR - lymphocyte-to-monocyte ratio; CV - conventional ventilation; SIPVV - synchronized intermittent positive pressure ventilation; HFOV - high frequency oscillatory ventilation; SpO2 - peripheral oxygen saturation; RDS - respiratory distress syndrome; BPD - bronchopulmonary dysplasia; ROP - retinopathy of prematurity; HsPDA - hemodynamically significant patent ductus arteriosus; NEC - Necrotizing enterocolitis

STROBE Statement - Checklist of items that should be included in reports of *cohort studies*

	Item Nº	**Recommendation**	**Page No**
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract **"Retrospective study, at an academic tertiary center"**	Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **" Retrospective study, at an academic tertiary center, including preterm infants with gestational age below 30 weeks. A statistical analysis compared two groups of infants, with and without IVH."** **"Our results demonstrate that hematological parameters and indices (HPI) from blood count (BC) collected on first day of life (D1) are not associated with the occurrence of intraventricular hemorrhage (IVH), and therefore cannot be used as predictors of IVH in extremely premature infants."**	Page 2
Introduction			
Background / Rationale	2	Explain the scientific background and rationale for the investigation being reported **"Intraventricular hemorrhage (IVH) in premature neonates represents a critical neurological concern for**	Page 4

		neonatologists (…) Its prevalence can be as high as 45% among extremely preterm infants. (…) Recent research by Cucerea M et al. has shown that early hematological parameters are linked to the development of IVH (…) The role of hematological parameters in contributing to the occurrence of IVH in premature newborns remains poorly understood and warrants further investigation"	
Objectives	3	State specific objectives, including any prespecified hypotheses **"This study aimed to evaluate the association between hematological parameters and indices obtained from the initial blood count on the first day of life (D1) and the occurrence of IVH in premature infants, in order to assess whether these can be used as prognostic markers."**	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper **"This is a retrospective study conducted at an academic tertiary neonatal intensive care unit (NICU) that admits preterm newborns from 23 weeks of gestation onwards. Our inclusion criteria were (…) Our exclusion criteria were (…)"**	Page 4-5

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **"at an academic tertiary neonatal intensive care unit (NICU) that admits preterm newborns from 23 weeks of gestation onwards (…) our inclusion criteria were preterm neonates with a gestational age between 23 weeks (23 weeks and 0 days) and 30 weeks (29 weeks and 6 days), born between January 1, 2008, and October 31, 2023 (…)The data collection protocol included information about (…)"**	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **"inclusion criteria were preterm neonates with a gestational age between 23 weeks (23 weeks and 0 days) and 30 weeks (29 weeks and 6 days), born between January 1, 2008, and October 31, 2023. (…) In our NICU, ideally, on D1 of life, all preterm infants undergo an initial cranial ultrasound examination, which is then repeated weekly."**	Page 4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Our study wasn't matched.**	Not applicable

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Supplementary Table 1**	Page 25-30
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **" In our NICU, ideally, on D1 of life, all preterm infants undergo an initial cranial ultrasound examination, which is then repeated weekly. We used Volpe JJ's classification (18) for the classification of IVH (…) Additional hematological indices, including the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR), were calculated from the blood count." Supplementary Table 1**	Page 5, 25-30
Bias	9	Describe any efforts to address potential sources of bias **" The multivariate analysis by logistic regression adjusted to gestational age and birth weight revealed no significant associations between hematological parameters and indices of D1 and the occurrence of IVH. (…) The multivariate analysis by logistic regression adjusted to clinical chorioamnionitis, gestational age, birthweight, use of endotracheal tube,**	Pages 7-8

		mechanical ventilation and oxygen in the delivery room, surfactant, days of invasive mechanical ventilation and nCPAP, oxygen dependency at 36 weeks, oxygen at discharge, total parenteral nutrition, transfusion of red blood cells and platelets, Hs-PDA, PVI, LPVc, early and nosocomial sepsis and ROP found an (…) The multivariate analysis by logistic regression adjusted to confounding variables (multiple gestation, clinical and histologic chorioamnionitis, chorionic vasculitis, gestational age, birthweight, use of endotracheal tube and surfactant, Apgar score at 1st minute < 5 in the delivery room, occurrence of pneumothorax, systemic postnatal steroids, inhaled bronchodilator, oxygen at discharge, transfusion of red blood cells and platelets) showed"	
Study size	10	Explain how the study size was arrived at **A convenience sample was used to obtain at least thirty patients with each of the three degrees of intraventricular hemorrhage (I-III), in a minimum of ninety patients.**	Not applicable:
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. **" symmetrically distributed continuous variables were described using the mean (± standard deviation), and**	Pages 6

		asymmetrically distributed continuous variables by the median (minimum-maximum). (…) the Independent t-test or Mann-Whitney U test were employed for symmetric and asymmetric continuous variables, respectively."	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **"Statistical analysis was performed using IBM SPSS Statistics version 28 for Windows (IBM SPSS Statistics®, Inc., Chicago, IL, USA). (…) Chi-square or Fisher's exact test were used to compare categorical variables, and the Independent t-test or Mann-Whitney U test were employed for symmetric and asymmetric continuous variables, respectively. Predictors were evaluated through multivariate analysis using logistic regression. A p-value < 0.05 was considered statistically significant. (…) The multivariate analysis by logistic regression (…)"**	Page 6
		(*b*) Describe any methods used to examine subgroups and interactions **"An analysis in the subgroup of patients with IVH-3 (severe IVH) was carried out. The univariate analysis showed (…)The multivariate analysis by logistic regression adjusted to confounding variables (multiple**	Page 8

		gestation, clinical and histologic chorioamnionitis, chorionic vasculitis (…)"	
		(*c*) Explain how missing data were addressed **All the variables selected for the study were detailed in the clinical file of each patient, therefore, there wasn't any missing data.**	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed **We didn't have any follow up time.**	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **" From 241 premature newborns with gestational age between 23 and 29+6 weeks admitted in our NICU, 35 (14.52%) were excluded (…) Two hundred and six (85.48%) were eligible and therefore included in this study."**	Page 6
		(b) Give reasons for non-participation at each stage **" 35 (14.52%) were excluded: 18 outborns, 1 affected by TORCH infection, 5 with major congenital anomalies, 1 with chromosomal abnormalities, 6 with Apgar score at 5 minutes ≤ 3, 2 with twin-to-twin**	Page 6

		transfusion syndrome, and 2 with fetal growth discrepancy"	
		(c) Consider use of a flow diagram **In this study, there weren't any patients excluded because of loss of follow-up or loss of interest in participation. Therefore, we considered there was no necessity of doing flow diagrams.**	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **" In the IVH group, clinical chorioamnionitis (p=0.004) was significantly more prevalent. (…) For the total sample, the median of the gestational age was 27 (range: 23-29) completed weeks and the mean birth weight was 933.30 (±266.8 SD) grams. Both of these variables were significantly lower in the IVH group (p<0.001 and p<0.011, respectively). (…) Data on delivery room management for the total sample and the subgroups IVH and no-IVH newborns are presented in table 3. In the IVH group, the use of endotracheal tube (p=0.043), invasive mechanical ventilation (p=0.042) and use of oxygen (p=0.048) were significantly more prevalent. Data on the neonatal morbidity and mortality for the total sample and the**	Page 6-7

		subgroups IVH and no-IVH newborns are shown in table 4." (b) Indicate number of participants with missing data for each variable of interest **All the variables selected for the study were detailed in the clinical file of each patient, therefore, there wasn't any missing data.** (c) Summarise follow-up time (eg, average and total amount) **The patient sample was assessed until hospital discharge. There wasn't any necessity to collect follow-up data after discharge.**	Not applicable Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time **"From two hundred and six preterm neonates eligible included in this study, 120 developed intraventricular hemmorhage (IVH)" Tables 2-6**	Page 17-24

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Table 5. "The multivariate analysis by logistic regression adjusted to gestational age and birth weight revealed no significant associations between hematological parameters and indices of D1 and the occurrence of IVH. The multivariate analysis by logistic regression adjusted to clinical chorioamnionitis, gestational age, birthweight, use of endotracheal tube, mechanical ventilation and oxygen in the delivery room, surfactant, days of invasive mechanical ventilation and nCPAP, oxygen dependency at 36 weeks, oxygen at discharge, total parenteral nutrition, transfusion of red blood cells and platelets, Hs-PDA, PVI, LPVc, early and nosocomial sepsis and ROP found an association between oxygen dependency at 36 weeks of GA and IVH [OR=2.41; 95%CI: 1.18-4.90, p = 0.016]. The multivariate analysis by logistic regression adjusted to confounding variables (multiple gestation, clinical and histologic chorioamnionitis, chorionic vasculitis, gestational**	Pages 8, 20-22

		age, birthweight, use of endotracheal tube and surfactant, Apgar score at 1st minute < 5 in the delivery room, occurrence of pneumothorax, systemic postnatal steroids, inhaled bronchodilator, oxygen at discharge, transfusion of red blood cells and platelets) showed that occurrence of PVI (*p*=0.002) and LPVc (p < 0.001) were significantly more prevalent in the IVH-3 group "	
		(*b*) Report category boundaries when continuous variables were categorized **We didn't categorize any continuous variable**	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **"An analysis in the subgroup of patients with IVH-3 (severe IVH) was carried out."**	Page 8
Discussion			
Key results	18	Summarise key results with reference to study objectives **" the two groups differed significantly in gestational age, with the IVH group having a significantly lower gestational age and, consequently, a lower birth weight. (…) Our results**	Page 9-10

		do not support the hypothesis that hematological parameters and indices on D1 differ between patients with and without IVH (…) In this study, BPD was found to be associated with IVH after multivariate analysis (…) “	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **“The retrospective nature is the main limitation of this study. (…) data may be incomplete, inaccurate, or collected inconsistently, (…) confounding variables (…) retrospective nature limits the ability to infer causal relationships”**	Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **“we assert that this study has the potential to make a meaningful contribution to future meta-analyses that evaluate the relationship between early hematological parameters and intraventricular hemorrhage in preterm infants.”**	Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11

		“ This study encompasses a robust patient sample, enabling a comprehensive assessment of the association between hematological parameters and indices collected on D1 and the occurrence of IVH, which reinforces confidence in our findings. Additionally, the single-center design, coupled with a consistent blood collection methodology and rigorous laboratory analysis, significantly enhances the robustness of our results. Given these strengths, we assert that this study has the potential to make a meaningful contribution”	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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MANUSCRIPT FORMAT

Article Types

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Article Type	Main Text	Abstract Limit	Keywords Limit	Title Limit
Original Manuscript	No limit	Up to 300 words	4 to 9 keywords	Up to 25 words
Clinical Opinion	No limit	Up to 300 words	4 to 9 keywords	Up to 25 words
Short Communication	No limit	Up to 300 words	4 to 9 keywords	Up to 25 words
Reviews	No limit	Up to 300 words	4 to 9 keywords	Up to 25 words
Editorials	No limit	Up to 300 words	4 to 9 keywords	Up to 25 words
Letters	No limit	-	4 to 9 keywords	Up to 25 words
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MANUSCRIPT FORMAT *continued*

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See the section Article Types for word limits.

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Last Updated: August 2024

Declaração

Para os devidos efeitos declaro que o estudo 'Hematological Parameters of Birth Fail to Predict Intraventricular Hemorrhage in Very Preterm Infants', apresentado a esta Comissão de Ética por Mariana Costa Marques, foi submetido com a referência CE-42-25, e que o mesmo foi avaliado e aprovado na reunião de 28 de fevereiro de 2025.

Porto e Unidade Local de Saúde de São João, 14 de março de 2025

Pedro Brito, Secretário da CE da ULS de São João

NIF/Registo Comercial n.º 509 821 197 Capital Estatutário 112.000.000,00 Euros