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ANÁLISE DO MANEJO DO DESMAME DE OXIGÊNIO EM PREMATUROS, INFLUÊNCIA NA DISPLASIA BRONCOPULMONAR, PERFIL DEMOGRÁFICO E EPIDEMIOLÓGICO DE DOENÇAS NEONATAIS

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“Educação não
transforma o mundo.

Educação muda as
pessoas.

Pessoas mudam o
mundo.”

Paulo Freire

RESUMO

O uso do oxigênio (O2) é comum em doenças neonatais, principalmente pela necessidade de suporte ventilatório devido à imaturidade pulmonar. No entanto, a descrição do uso de O2 e os fatores que levam à displasia broncopulmonar são pouco conhecidos. Desta forma, o objetivo do estudo foi avaliar a redução do O2, buscando associar este marcador com o desenvolvimento da displasia broncopulmonar. Concomitantemente, foi realizada análise epidemiológica das doenças que frequentemente necessitam do uso de O2 em recém-nascidos (RNs) [hipóxia intrauterina (HIU), síndrome de aspiração do mecônio (SAM) e desconforto respiratório neonatal (DRN)], e foi descrito o perfil dos pacientes da Unidade de Terapia Intensiva neonatal (UTIN) local para identificar os fatores de risco ao óbito. A análise do suplemento do O2 foi um estudo observacional/prospectivo pela análise de prontuários e do controle de enfermagem de prematuros com suporte ventilatório/oxigenoterapia. O perfil epidemiológico dos pacientes da UTIN foi um estudo retrospectivo no período de 5 anos pela análise das características maternas e do RN, diagnóstico, seguimento e desfecho. O perfil epidemiológico da HIU, SAM e DRN foi um estudo observacional/retrospectivo entre 1998-2018, contabilizando o ano de óbito na Unidade de Federação pelo CID-10, sexo, etnia e índice de desenvolvimento humano (IDH). No uso do O2 foram descritas 1.436 avaliações de 128 RNs. Na análise univariada a maior chance de evoluir para a displasia broncopulmonar foi associada a: extremo/muito baixo peso (46,2%/30,8%), ventilação mecânica invasiva/não-invasiva (70,6%/23,5%), bucal (52,9%), cateter nasal (47,7%), idade gestacional, peso e ganho de peso, % de taxa de sucesso em 24hs para a redução de O2, idade no desmame, quantidade de reduções de O2, tempo de uso de O2/internação. Na multivariada, apenas o choque séptico e a % de taxa de sucesso foram significativos em predizer a displasia broncopulmonar. Na análise do perfil epidemiológico foram incluídos 846 RNs, sendo observado 140 (16,5%) óbitos; a análise multivariada foi significativa para predizer a chance de óbito (P- value<0,001) pelos seguintes preditores: gestação prévia ≤2 (OR=2.639; 95%IC=1.256-5.544), asfixia moderada/grave (OR=2,188; 95%IC=1,083-4,420; OR=3,543; 95%IC=1,405-8,931), prematuridade (OR=5,463; 95%IC=1,415-21,096), apneia da prematuridade (OR=0,253; 94%IC=0,077-0,831), choque séptico (OR=8,468; 95%IC=3,386-21,178), forame oval pérvio (OR=0,256; 95%IC=0,071-0,920), idade gestacional (OR=0,946; 95%IC=0,926-0,967), e tempo de internação (OR=0,952, 95%CI=0,933-0,973). O número de óbitos para a HIU (N=17.209), SAM (N=25.015), e DRN (N=89.785) reduziu ao longo do tempo e foi mais frequente no sexo masculino. O implemento do IDH foi associado a redução do número de óbitos com intensidade variável para a HIU, DRN e SAM. Os principais preditores para displasia broncopulmonar foram o choque séptico e a % da taxa de sucesso da redução de O2. Dessa forma, a avaliação do manejo de O2, evitando fatores associados à displasia broncopulmonar, pode minimizar a ocorrência dela. Na UTIN houve uma prevalência de óbitos de 16.5% que foi associada a fatores como a asfixia, prematuridade e choque séptico. Nacionalmente houve redução ao longo de 20 anos da taxa de mortalidade por HIU, SAM e DRN com o aumento do IDH.

Palavras-chaves: Displasia Broncopulmonar. Epidemiologia. Oxigênio. Prematuros. Unidades de Terapia Intensiva Neonatal.

ABSTRACT

The treatment using oxygen (O_2) is common in neonatal diseases, mainly due to the need for ventilatory support due to pulmonary immaturity. However, the description of the use of O_2 and the factors that lead to bronchopulmonary dysplasia are poorly understood yet. Thus, the aim of the study was to evaluate the reduction of O_2 and to associate this marker with the developmentof bronchopulmonary dysplasia. Concomitantly, an epidemiological analysis of diseases that frequently require the use of O_2 in newborns [neonatal intrauterine hypoxia (NIU), meconium aspiration syndrome (MAS) and neonatal respiratory distress (NRD)] was performed, and the profile of patients in the local neonatal intensive care unit (NICU) to identify risk factors for death. The analysis of the O_2 supplement was an observational/prospective study through the analysis of medical records and the nursing control of preterm infants with ventilatory support/oxygen therapy. The epidemiological profile of NICU patients was a retrospective study over a 5-year period using maternal-infant analysis: maternal and newborns characteristics, diagnosis, follow-up and outcome. The epidemiological profile of NIU, MAS and NRD was an observational/retrospective study between 1998-2018, counting the year of death in the Federation Unit by ICD-10, gender, ethnicity and human development index (HDI). In the use of O_2, 1,436 evaluations of 128 newborns were described. In the univariate analysis, the greatest chance of developing bronchopulmonary dysplasia was associated with: extreme/very low weight (46.2%/30.8%), invasive/non-invasive mechanical ventilation (70.6%/23.5%), O_2 oral (52.9%), O_2 nasal catheter (47.7%), gestational age, weight and weight gain, % success rate in 24 hours for O_2 reduction, age at weaning, number of O_2 reductions, time of O_2 use/hospitalization. In the multivariate, only septic shock and the % success rate were significant in predicting bronchopulmonary dysplasia. In the analysis of the epidemiological profile, 846 newborns were included, with 140 (16.5%) deaths being observed; multivariate analysis was significant to predict the chance for death (P-value<0.001) by the following predictors: previous pregnancy ≤2 (OR=2.639; 95%CI=1.256-5.544), presence of moderate/severe asphyxia (OR=2.188; 95%CI=1.083-4.420; OR=3.543; 95%CI=1.405-8.931), prematurity (OR=5.463; 95%CI=1.415-21.096), septic shock (OR=8.468; 95%CI=3.386-21.178), patent foramen ovale (OR=0.256; 95%CI=0.071-0.920), gestational age (OR=0.946; 95%CI=0.926-0.967), and length of hospital stay (OR=0.952, 95% CI=0.933-0.973). The number of deaths for NIU (N=17,209), MAS (N=25,015), and NRD (N=89,785) decreased over time and was more frequent in males. The implementation of the HDI was associated with a reduction in the number of deaths due to NIU, NRD, and MAS. The main predictors for bronchopulmonary dysplasia were septic shock and the % O_2 reduction success rate. Thus, the assessment of O_2 management, avoiding factors associated with bronchopulmonary dysplasia, can minimize the occurrence of this disease. In the NICU there was a prevalence of deaths of 16.5% which was associated with factors such as asphyxia, prematurity, and septic shock. Nationally, there was a reduction over 20 years in the mortality rate due to NIU, MAS and NRD with the increase in the HDI.

Keywords: *Oxygen. Bronchopulmonary Dysplasia. Prematures. Neonatal Intensive Care Units. Epidemiology*.

Lista de Símbolos e Abreviações

FC	Frequência cardíaca
FR	Frequência respiratória
HUSF	Hospital Universitário São Francisco
IDHM	Índice de Desenvolvimento Humano Municipal
OMS	Organização Mundial de Saúde
O_2	Oxigênio
PA	Pressão arterial
RN	Recém-nascido
RNPT	Recém-nascido pré-termo
SpO_2	Saturação periférica de oxigênio
SUS	Sistema Único de Saúde
UBR	Unidade de baixo risco
UCI	Unidade de cuidados intermediários
UTIN	Unidade de terapia intensiva neonatal

SUMÁRIO

1. INTRODUÇÃO

De acordo com a Organização Mundial da Saúde (OMS) define-se recém-nascido (RN) os bebês com até 28 dias de vida pós-natal, sendo considerado o RN como pré-termo (RNPT) se nascido vivo antes de 37 semanas de idade gestacional não concluída. O RNPT, por sua vez, podeser classificado em: (i) extremamente prematuro (≤28 semanas de gestação); (ii) pré-termo moderado (entre 28 e 32 semanas de gestação); e por último, (iii) pré-termo limítrofe (entre 32 e 37semanas de gestação) (1).

O número de nascidos vivos no estado de São Paulo, em 2017, foi de 611.803 nascimentos, destes, 2.224 nascimentos ocorreram em Bragança Paulista/SP (2). No mesmo ano, em aspecto mundial, 2,5 milhões de RNs foram a óbito nos primeiros 28 dias de vida, destes, dois terços eram prematuros, considerando este um problema mundial de saúde pública (3).

No Brasil, os RNPT e suas mães, são amparados no Sistema único de Saúde (SUS) que implementa numerosos programas para reduzir a mortalidade e aprimorar a saúde materna, neonatal e infantil – principais indicadores sociais de um país. Dessa forma, háa possibilidade de acesso para reduzir a taxa de fecundidade, universalizar o pré-natal e garantir o direito hospitalar ao parto. Além do que, a assistência pré-natal adequada às mães de risco e os avanços da terapia intensiva neonatal com uso de tecnologia sofisticada, permite a maior sobrevida aos RNs (4,5).

A atenção multidisciplinar e humanizada ao prematuro ou RN com baixo peso e à sua família no âmbito hospitalar é primordial, uma vez que, existe a necessidade de maior cuidado noperíodo de internação, incluindo ações e manejos diferenciados para o correto acolhimento do paciente e de sua família (6). Na maternidade, os RNs, devem ser avaliados ainda na sala de parto [peso ao nascimento, idade gestacional e condutas clínicas] para que o direcionamento ao correto setor de referência hospitalar seja realizado. Desta forma, a classificação de risco neonataldireciona o cuidado hospitalar de acordo com o risco aferido (7).

Na rotina de atendimento são indicativos para a internação em unidade de cuidados intermediários (UCI): (i) RNPT; (ii) presença de asfixia perinatal; (iii) filho de mãe com diabetes mellitus; (iv) necessidade de uso de fototerapia para adequar os níveis de bilirrubina; (v) diagnóstico de malformação congênita; (vi) presença de distúrbio hidroeletrolítico; (vii) presença

de infecção perinatal; (viii) necessidade de nutrição paraenteral; (ix) diagnóstico de cardiopatias compensadas; (x) transferência da unidade de terapia intensiva neonatal (UTIN). A alta do UCI é indicada para os RNs estáveis, com a necessidade de ganho de peso ou para finalizar a antibioticoterapia, sendo estes transferidos para a unidade de baixo risco (UBR) (8).

Os RNs com maiores riscos [(i) presença de peso ao nascimento inferior a 1.500 g ou idade gestacional inferior a 34 semanas; (ii) presença de desconforto respiratório com a necessidade de ventilação mecânica; (iii) presença de apneia neonatal; (iv) presença de anóxia grave; (v) presença de insuficiência circulatória; (vi) diagnóstico de sepse neonatal; (vii) pós-operatório; (viii) diagnóstico de exsanguineo transfusão; (ix) diagnóstico de distúrbio cardiovascular; (x) diagnóstico de enterocolite necrosante; (xi) presença de instabilidade nos parâmetros vitais] parao óbito devem permanecer na UTIN (8).

Os RNPTs encaminhados para a UTIN estão em situação de vulnerabilidade por inúmeros fatores, uma vez que, ao nascimento, o prematuro interrompe o desenvolvimento normal do sistema respiratório e gera uma imaturidade dos sistemas corporais, sendo necessária a administração de fármacos, suplemento de oxigênio (O_2) e/ou suporte ventilatório com o uso, muitas vezes, prolongado da ventilação mecânica. Na via aerífera, o uso do O_2, acarreta o aumento de radicais livres, gerando áreas inflamatórias e, posteriormente, regiões de fibrose no epitélio dessas vias, com repercussão em longo prazo, inclusive durante a infância (9). Devido a esses fatores, além da imaturidade pulmonar, frequentemente há a necessidade de suporte de O_2 suplementar dos prematuros após a alta hospitalar, com o tempo médio estimado de desmame total do O_2 ofertado de aproximadamente dez meses após a alta hospitalar (10).

Realizar a dosagem correta da administração de O_2 é necessário para o sucesso terapêutico. O uso indiscriminado do O_2 pode ser maléfico aos sistemas corporais, porém evitar a administração de O_2 quando necessário, ou seja, quando não alcançar a saturação periférica de oxigênio (SpO_2) alvo (valores entre 91-95%), pode gerar eventos como a hipóxia (valores inferiores a 91%) e quando a oferta for além do necessário, causar a hiperóxia (valores superiores a 95%), sendo que ambos os fatores (hipóxia e hiperóxia) podem cursar com sequelas como a displasia broncopulmonar, impacto negativo no desenvolvimento neurológico, perda auditiva e retinopatia da prematuridade (11). A hipóxia concomitantemente aumenta o risco de enterocolite necrosante, com aumento da mortalidade antes da alta hospitalar em comparação

com pacientes com hiperóxia (11,12).

Para reduzir riscos de sequelas, o manejo da ventilação, da oxigenação e dos parâmetros utilizados devem ser adaptados de acordo com protocolos específicos, otimizando o desmame do O_2. Porém, há escassez de diretrizes baseadas em evidências para direcionar no desmame gradual e correto dos pacientes prematuros com o suporte ventilatório (12,14). No Brasil, a maioria das unidades de terapias intensivas neonatais utilizam protocolos não padronizados para o desmame e evolução ventilatória, baseando-se na redução do suporte respiratório e julgamento clínico, demonstrando a necessidade de evidência científica para a padronização de protocolos no desmame em neonatologia em cenário nacional (15). O desmame rápido sem correto manejo, pode aumentar o desconforto respiratório, retornando ao princípio do tratamento e, o desmame lento, pode aumentar o risco de infecção hospitalar ou de desenvolver doenças pulmonares e sistêmicas (16).

Recomenda-se para o desmame de O_2 a avaliação da estabilidade clínica, sendo que o peso e a idade dos RNs não devem ser considerados. Dentre os marcadores para avaliar a alteração fisiológica no RN, incluem-se a influência dos sinais vitais, comoa frequência cardíaca (FC), a frequência respiratória (FR), a SpO_2 e a pressão arterial de oxigênio (PA). A FC é denominada como a quantidade de batimentos cardíacos por minuto e, quando estiver aumentada para faixa etária é denominada taquicardia e se estiver diminuída, é considerada bradicardia. A FR refere-se à quantidade de incursão respiratória por um minuto, considerada eupneica quando opadrão respiratório estiver normal, bradipneica quando estiver diminuída e taquipneica quando estiver com um esforço maior do que o limítrofe/idade para que se respire (17). A PA é avaliada por meio de manguito de tamanho adequado para a criança, cerca de 1 ou 2 centímetros acima da área antecubital ou poplítea (16,18).

Com a assistência dos profissionais da saúde para o desmame de O_2, dentre os benefícios gerados, pode-se elencar a redução do custo hospitalar, já que em 2015 o custo do O_2 medicinal comprimido foi de R$ 5,60 m^3 (19). Já para o paciente, o benefício seria observado com o menor dano em seus sistemas corporais, pois exposições curtas de O_2 com elevadas pressões acarretam a toxicidade do sistema nervoso central e a maior exposição com níveis elevados de O_2, acarretam a toxicidade pulmonar (20).

Em vista disso, o ambiente hospitalar se torna necessário, mas distante de ser o lugar

adequado para o RN que sofre influências de agentes estressores, podendo refletir nos sinais vitais, consequentemente, em seu estado de saúde. A labilidade do RN internado retrata a necessidade de atenção a esses pacientes, como melhora da ação humanizada da equipe multidisciplinar. Assim, a aplicação correta do desmame de O_2, podem refletir de forma positiva no tratamento, minimizando sequelas, como a evolução com a retinopatia e a displasia broncopulmonar e, consequentemente, otimizar a alta hospitalar em conjunto com outras ações multidisciplinares deve uma meta a ser atingida pelos pacientes.

Nesse cenário, este trabalho teve como objetivo avaliar o desmame de O_2 em prematuros internados na UTIN, com intuito de demonstrar a eficiência e importância do desmame de O_2, além de analisar concomitantemente fatores que influenciam a displasia broncopulmonar. Adicionalmente, foi realizada uma análise epidemiológica retrospectiva sobre características sociais e clínicas das puérperas e dos RNs internados em UTIN e uma análise epidemiológica sobre as principais doenças [a saber: i. Hipóxia intrauterina; ii. Síndrome de Aspiração do Mecônio; iii. Desconforto Respiratório] que acometem o RN, além da prematuridade, culminando na necessidade de suplemento de O_2, associados com a sua prevalência e gravidade nacional em um estudo com o levantamento de dados de um período de 20 anos.

2. OBJETIVOS

2.1 Objetivo geral

Avaliar o manejo do desmame de O_2 dos RNPT internados no Hospital Universitário São Francisco de Assis na Providência de Deus (HUSF), Bragança Paulista – SP, bem como analisar os fatores que influenciam na displasia broncopulmonar desses prematuros; classificar o perfil sócio demográfico e clínico dos RNs internados no HUSF retrospectivamente e analisar epidemiologicamente o perfil das doenças neonatais que influenciam na necessidade de O_2 [hipóxia intrauterina, síndrome de aspiração do mecônio e desconforto respiratório] em um estudo retrospectivo que contempla um período de 20 anos.

2.2 Objetivos específicos

Avaliar o manejo/desmame de O_2 em prematuros na UTIN correlacionando com as características que influenciam para evolução da displasia broncopulmonar.

Analisar o perfil epidemiológico materno-infantil dos pacientes internados na UTIN durante o período de cinco anos, correlacionando com fatores relacionados ao óbito desses RNs.

Avaliar a prevalência de óbito por Unidade de Federação de três doenças neonatais, a saber: i. Hipóxia intra-uterina, ii. Síndrome de aspiração, iii. Desconforto respiratório, correlacionando com o Índice de Desenvolvimento Humano (IDHM – geral, renda e longevidade), em um período de 20 anos.

3. CAPÍTULO 1 – Artigo I

Title: Supplemental Oxygen Use in Preterm Infants up to Hospital Discharge: Influence of Weight, Gestational age, and the Impact on Bronchopulmonary Dysplasia

Running title: Oxygen Management and Bronchopulmonary Dysplasia in Preterm Infants

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ABSTRACT

Introduction: Prematurity is characterized by pulmonary immaturity, which usually requires treatment by using supplemental oxygen (O_2) with consequent evolution into a bronchopulmonary dysplasia diagnosis. However, efficient O_2 in preterm infants and the factors that influence bronchopulmonary dysplasia are still under investigation.

Methods: This is an observational prospective study carried out through the analysis of medical records and nursing control of preterm infants in hospital treatment requiring ventilatory support/oxygen therapy. The neonatal characteristics and the O_2 management were evaluated during the period from the hospital admission and the discharge.

Results: The total number of evaluations was 1,436 and comprised 128 preterm infants. The univariate analysis associated the factors listed below with the patients' evolution into a bronchopulmonary dysplasia diagnosis: extremely/very low weight (46.2%; 30.8%), invasive/non-invasive ventilation (70.6%; 23.5%), O_2 mouthpiece (52.9%), O_2 nasal catheter (47.7%), lower gestational age, older age at weaning, lower weight at admission, lower weight gain during hospitalization, greater O_2 reduction, lower success rate % in 24h for O_2 reduction, longer time of O_2 use/hospitalization. The success rate % in 24h as of the O_2 reduction correlated with higher gestational age (CC=0.375), lower O_2 reduction (CC=(–)0.493), shorter hospitalization time (CC=(–)0.480), and O_2 use (CC=(–)0.488). When the multivariate model was used for the chance of evolution into bronchopulmonary dysplasia, only septic shock and the success rate % in 24h of the O_2 reduction were significant and considered predictors of that disease.

Conclusions: Several preterm infants' characteristics might contribute to a bronchopulmonary dysplasia diagnosis. However, in our study, the main predictors were septic shock and the success rate % in 24h as of the O_2 reduction. Therefore, the O_2 management multidisciplinary assessment preventing factors associated with bronchopulmonary dysplasia might minimize the occurrence of this disease.

Keywords: *Septic shock. Oxygen therapy. Prematurity. Neonatal Intensive Care Units. Mechanical ventilation.*

INTRODUCTION

Prematurity reaches around 135 million newborns worldwide and, approximately, 11% newborns in Brazil are characterized as preterm. This condition is characterized by the early interruption in the development of organs and body systems, with hospital admission for maturation or rehabilitation from specific neonatal diseases[1,2]. Due to pulmonary immaturity, around 1:10 newborns require ventilatory support after birth and approximately 300 thousand infants require ventilatory support to cater for the ventilation/perfusion demand in Brazil. The type of treatment employed is oxygen (O_2) delivery, which can be carried out through invasive or non-invasive ventilation by the inspired O_2 fraction (FiO_2), or O_2 therapy using devices that provide supplemental O_2 gas with values higher than those found in the ambient air (>21%)[3,4].

Supplemental O_2 is a therapeutic gas that causes systemic vasodilation reversing the hypoxemia. However, high levels of this gas might trigger a rebound effect resulting in hyperoxemia[5]. This condition might generate events as harmful as the hypoxemia, due to the toxic effect provoked by the oxidative stress that leads to an increase in free radicals and O_2 reactive species in the body. These events favor the development of illnesses such as retinopathy of prematurity, atelectasis, seizures, neurological damage, and in prolonged use (>28 days) they might lead to bronchopulmonary dysplasia[6,7], which is a chronic inflammatory lung disease resulting from prenatal factors and postnatal injuries[8,9].

Although bronchopulmonary dysplasia affects around 10,000 preterm infants in the United States annually, different classifications of this disease might result in underdiagnosis and alterations in the numbers of this disease incidence[10,11]. However, a new classification was recently introduced that stratifies the disease into three stages according to the amount of O_2 supplied and the gestational age. The classification in each stage requires the following characteristics: (i) use of nasal cannula larger than 2 L/min, or the use of continuous positive pressure in the airways, or non-invasive positive pressure; and (iii) use of invasive mechanical ventilation[12]. The new bronchopulmonary classification allowed the identification of important associations in preterm infants with bronchopulmonary dysplasia stage III and the neonatal death rate in relation to other stages, which might be a sensitive marker in the short and medium terms, signaling the severity of the disease and pointing out the need for the hospital team action to improve the clinical procedures[13].

For the supplemental O_2 delivery with reduced risk of developing bronchopulmonary dysplasia, the O_2 peripheral saturation (SpO_2) target values indicated to preterm infants are around 91-95%, thus preventing undesirable effects and reducing mortality as a result of this disease[14]. However, to reach the SpO_2 target, the correct use of O_2 therapy limit values, correct management, and patient monitoring by thehospital multidisciplinary team are necessary[15,16].

Although O_2 is a widely used gas to reverse unsuitable respiratory conditions, its ideal management is still uncertain and depends on individual responses to the O_2 therapy and the base illness[15,17]. The American Heart Association issued a guideline addressing the correct use of O_2 during cardiorespiratory arrest (PCR) in newborns and children. However, supplemental O_2 management during hospitalization remains empirical, and factors such as the relation between O_2 reduction and gestational age, weight, devices used, O_2 weaning, and the bronchopulmonary dysplasia remain scarce in the literature[18].

Taking that into consideration, this study aimed to analyze the use of O_2 in preterm infants during hospitalization in the Neonatal Intensive Care Unit (NICU) of a university hospital up to O_2 weaning, and associate it with neonatal features (sex, gestational age, weight, and Apgar score). We also addressed predictor factors of the evolution into a bronchopulmonary dysplasia diagnosis.

METHODS

An observational prospective study was carried out through the analysis of medical records and nursing control of preterm infants admitted to the NICU of the São Francisco na Providência de Deus University Hospital (HUSF), in Bragança Paulista – SP, Brazil, in the period from January 2020 and July 2021. The study was approved by the Ethics and Research Committee [C.A.A.E #29719020.6.0000.5514] of that institution and is in accordance with the Helsinki Declaration.

Preterm infants (<37 gestational weeks) that required O_2 therapy and/or ventilatory support were included randomly according to their admission to the intensive care unit. Only cases that presented fully completed nursing control and medical records were included. Newborns that were transferred to another hospital unit, or discharged with O_2 use, or died

were considered as discontinuity criteria. In addition, full term newborns, those with congenital abnormalities or incompatible with life were excluded.

The variables selected from the medical records included sex (female/male), gestational age at birth and current (days), gestational growth (small for the gestational age: <p10; suitable for the gestational age: between p10 and p90; big for the gestational age: >p90), weight at birth and current (extremely low weight: <1,000g; very low weight: between >1,001g and <1,500g; low weight: between >1,501g and <2,500g; normal: between 2,501g and <4,000g), weight gain during O_2 therapy (grams), Apgar at 1 and 5 minutes (severe asphyxia: between 0 and 3 points; moderate asphyxia: between 4 and 6 points; and good vitality: between 7 and 10 points), hospitalization diagnosis, devices used to deliver initial and final O_2 (mouth piece, nasal catheter, and halo mask), initial and final ventilatory support (invasive and non-invasive mechanical ventilation), hospitalization time, time using O_2, and evolution into a bronchopulmonary dysplasia.

The O_2 management was evaluated from the nursing control protocol up to the O_2 weaning. The protocol described the patients' evolution in periods of 24h each during hospital stay (from 7:00h am to 07:00h am on the following day), with new evaluations until the patient evolved to ambient air. The nursing control is carried out to identify more broadly the patient's hemodynamic stability from the notes filled in by the nursing team such as vital signs and temperature. The number of times O_2 was reduced and the times O_2 was not increased after a reduction during the evaluation period (reduction success rate) were the variables selected from the nursing control. The relative percentage between both markers (successes/reductions) was also calculated and described as success rate %.

The descriptive analysis was based on two approaches: (i) categorical markers – N (%): sample size (percentage); (ii) numerical markers – mean (standard deviation). The normality of the numerical data was evaluated using the descriptive measurement of central tendency analysis; graphic method, and the Kolmorov-Smirnov and Shapiro-Wilk statistical tests. When associating categorial data groups, the chi- square tests and the Fisher's Exact test were used. Numerical and categorical data were compared by employing the T test, and in the numerical data comparison, Pearson's correlation was carried out. The correlations considered the following cut off points: (i) ±0.90-1.0 very high correlation index; (ii) ±0.70-0.90 high

correlation index; (iii) ±0.50-0.70 moderate correlation index; (iv) ±0.30-0.50 low correlation index; and (v) ±0.00-0.30 insignificant correlation index.

The multivariate binary logistic regression following the backward stepwise method included the markers that presented association one to another and represented a multicollinearity effect. Bronchopulmonary dysplasia was the dependent variable, and the other markers were considered risk predictors for the disease evolution.

A 0.05 alpha was considered in the statistical analyses. The statistical analyses were aided by the software Statistical Package for the Social Sciences version 24.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp) and the MedCalc 15.0 (MedCalc for Windows, version 15.0; MedCalc Software, Ostend, Belgium).

RESULTS

There were 1,436 initial evaluations from a total of 150 preterm infants selected in the period under analysis. Out of those, 22 participants were excluded for the following reasons: death (n=19), hospital discharge using O_2 (n=1), and hospital transfer using O_2 (n=2), totaling 128 preterm infants that evolved into ambient air and were included in the study.

Out of the 128 preterm infants that took part in the analysis, 113 (88.3%) presented an early respiratory distress diagnosis, 61 (47.7%) had neonatal jaundice, and 43 (33.6%) were affected byneonatal sepsis (**Table 1**).

TABLE 1. Characterization of the diagnosis profile of preterm infants admitted to the Neonatal Intensive Care Unit.

To be continued

Diagnosis*	N (%)
Early respiratory distress	113 (88.3%)
Neonatal jaundice	61 (47.7%)
Neonatal sepsis	43 (33.6%)
Septic shock	23 (18.0%)
Twin birth	20 (15.6%)

Anemia	10 (7.8%)
Neonatal anoxia	7 (5.5%)
Birth injury	6 (4.7%)
Pelvic delivery	6 (4.7%)
Hyaline membrane	6 (4.7%)
Seizure	6 (4.7%)
Persistent arterial duct	5 (3.9%)
Pulmonary hypertension	4 (3.1%)
Perinatal depression	4 (3.1%)
Hypoglycemia	3 (2.3%)
Fetal birth restriction	2 (1.6%)
Pneumothorax	2 (1.6%)
Enterocolitis	2 (1.6%)
Meconium aspiration syndrome	2 (1.6%)
Cardiorespiratory arrest	2 (1.6%)
Hyponatremia	2 (1.6%)
Atelectasis	2 (1.6%)
Atrial thrombus	2 (1.6%)
Hypomagnesia	2 (1.6%)
Postoperative of exploratory laparotomy, bridle lysis, and tactic appendectomy	2 (1.6%)
Therapeutical hypothermia	2 (1.6%)

*Diagnosis present in a single patient: hyperkalemia, oligohydramnio, septic delivery, oral moniliasis,congenital toxoplasmosis, suspected hydrocephaly, congenital syphilis, transient tachypnea of the newborn, left foot amniotic band, foot malformation, polycythemia, bradycardia, post-extubation laryngitis, interatrial communication, scrotum hernia, herniorrhaphy postoperative, orchidopexy postoperative, vomit, pneumonia, pneumatocele, coagulation disorder, paralytic ileum, gastroparesis, pneumoperitoneum, transfusion reaction, pneumomediastinum, hypothermia.

Data presented as N (number of patients) and % (percentage).

Male infants prevailed (n=76; 59.4%), as well as good vitality in the 1st and 5th-minute Apgar (n=87, 69.6%, and n=118, 94.4%, respectively), suitable growth for the gestational age (n=102, 84.3%), and low weight at birth (n=56, 56%). The mean number of O_2 reductions carried out was 11.67±14.75 and the mean O_2 therapy time was 13.34±16.6 days, which was similar to the hospitalization time 13.83±16.25 days (**Table 2**).

TABLE 2. Characteristics of the 128 preterm infants admitted to the Neonatal Intensive Care Unit and included in the study.

Preterm infants' characteristics	**Group**	**N (%)**
Sex	Female	52 (40.6%)
	Male	76 (59.4%)
Gestational age at birth (days)		226.26±19.40
Gestational age at O_2 weaning (days)		239.01±16.93
Gestational growth	Small for the gestational age	15 (12.4%)
	Suitable for the gestational age	102 (84.3%)
	Big for the gestational age	4 (3.3%)
Classification of the infants' weight at Birth (Kg)	Low weight	56 (56%)
	Very low weight	34 (34%)
	Extremely low weight	10 (10%)
Infants' gross weight (Kg)	At admission	1,745.16±542.86
	At O_2 weaning	1,832.30±490.89
	Weight gain during oxygen therapy	83.11±357.91
Apgar at 1 min		7.34±1.92
	Good vitality	87 (69.6%)
	Moderate asphyxia	33 (26.4%)
	Severe asphyxia	5 (4.0%)
Apgar at 5 min		8.88±1.53
	Good vitality	118 (94.4%)
	Moderate asphyxia	5 (4.0%)
	Severe asphyxia	2 (1.6%)
Device supporting the O_2 delivery (initial)	O_2 mouthpiece	6 (4.7%)
	O_2 halo mask	25 (19.5%)
	Non-invasive mechanical ventilation	54 (42.2%)
	Invasive mechanical ventilation	43 (33.6%)
Device supporting the O_2 delivery (final)	O_2 mouthpiece	89 (69.5%)
	O_2 halo mask	17 (13.3%)
	O_2 nasal catheter	18 (14.1%)

	Non-invasive mechanical ventilation	2 (1.6%)
	Invasive mechanical ventilation	2 (1.6%)
Number of O_2 reductions		11.67±14.75
Time without O_2 increase in 24h (success)		9.09±9.82
% of time without O_2 increase in 24h (success)		87.02±14.84
O_2 time (days)		13.34±16.16
Hospitalization time (days)		13.83±16.25
Bronchopulmonary dysplasia	Yes	17 (13.3%)
	No	111 (86.7%)

Categorical data is presented as N (number of patients) and % (percentage); Numerical data is presented as mean ± standard deviation

When analyzing the comparison between initial O_2 delivery devices and the ventilatory support used during the infants' admission in relation to weaning, non-invasive mechanical ventilation was the most frequent choice (n=54, 41.2%), with later change to the O_2 mouthpiece (n=36, 40.4%), O_2 nasal catheter O_2 (n=9, 50.0%), and O_2 halo mask (n=7, 41.2%). However, 2 (100.0%) infants were directly exposed to ambient air after removal of the non-invasive mechanical ventilation (**Table 3**).

TABLE 3. Comparison between the O_2 delivery devices at admission and throughout the O_2 weaning of preterm infants admitted to theNeonatal Intensive Care Unit.

Initial device	Final device					Total	P-value
	O_2 mouthpiece	**Nasal catheter**	**O_2 Halo mask**	**Non-invasive mechanical ventilation**	**Invasive mechanical ventilation**		
O_2 mouthpiece	6 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (4.7%)	0.113
O_2 halo mask	19 (21.3%)	0 (0.0%)	6 (35.3%)	0 (0.0%)	0 (0.0%)	25 (19.5%)	
Non-invasive mechanical ventilation	36 (40.4%)	9 (50.0%)	7 (41.2%)	2 (100.0%)	0 (0.0%)	54 (42.2%)	
Invasive mechanical ventilation	28 (31.5%)	9 (50.0%)	4 (23.5%)	0 (0.0%)	2 (100.0%)	43 (33.6%)	
Total	89 (100.0%)	18 (100.0%)	17 (100.0%)	2 (100.0%)	2 (100.0%)	128 (100.0%)	

Data presented as N (number of patients) and % (percentage). Statistical analysis carried out using the Fisher Exact test, 0.05 alpha.

When associating the bronchopulmonary dysplasia diagnosis with the preterm infants' characteristics (gestational growth, weight, O_2 delivery devices, ventilatory support, and Apgar score), weight at birth and the initial and final O_2 delivery devices were seen to be related with the evolution into bronchopulmonary dysplasia. Extremely low weight (n=6, 46.2%), very low weight (n=4, 30.8%), invasive mechanical ventilation (n=12, 70.6%), and non-invasive mechanicalventilation at admission (n=4, 23.5%), O_2 mouthpiece (n=9, 52.9%), and the O_2 nasal catheter (n=8, 47.7%) were related to the disease diagnosis (**Table 4**).

TABLE 4. Association between the evolution into a bronchopulmonary dysplasia diagnosis and sex with the characteristics of preterm infants (gestational growth, weight, O_2 delivery device, and Apgar score) admitted to the Neonatal Intensive care unit.

Preterm infants' characteristics	**Data**	**Bronchopulmonary Dysplasia**		**Total**	**P-value**
		Yes	**No**		
Sex	Female	10 (58.8%)	42 (37.8%)	52 (40.6%)	0.117
	Male	7 (41.2%)	69 (62.2%)	76 (59.4%)	
Gestational growth (gestacional age)	Small	4 (28.6%)	11 (10.3%)	15 (12.4%)	0.135
	Big	0 (0.0%)	4 (3.7%)	4 (3.3%)	
	Suitable	10 (71.4%)	92 (86.0%)	102 (84.3%)	
Classification of the infants' weight at birth	Low weight	3 (23.1%)	53 (60.9%)	56 (56.0%)	<0.001
	Very low weight	4 (30.8%)	30 (34.5%)	34 (34.0%)	
	Extremely low weight	6 (46.2%)	4 (4.6%)	10 (10.0%)	
O_2 delivery device (initial)	O_2 mouthpiece	0 (0.0%)	6 (5.4%)	6 (4.7%)	0.012
	O_2 halo mask	1 (5.9%)	24 (21.6%)	25 (19.5%)	
	Non-invasive mechanical ventilation	4 (23.5%)	50 (45.0%)	54 (42.2%)	
	Invasive mechanical ventilation	12 (70.6%)	31 (27.9%)	43 (33.6%)	
O_2 delivery device (final)	O_2 mouthpiece	9 (52.9%)	80 (72.1%)	89 (69.5%)	0.002
	O_2 Nasal catheter	8 (47.1%)	10 (9.0%)	18 (14.1%)	
	O_2 halo mask	0 (0.0%)	17 (15.3%)	17 (13.3%)	
	Non-invasive mechanical ventilation	0 (0.0%)	2 (1.8%)	2 (1.6%)	
	Invasive mechanical ventilation	0 (0.0%)	2 (1.8%)	2 (1.6%)	
Apgar at 1 min	Severe asphyxia	2 (12.5%)	3 (2.8%)	5 (4.0%)	0.130
	Moderate asphyxia	5 (31.3%)	28 (25.7%)	33 (26.4%)	
	Normal	9 (56.3%)	78 (71.6%)	87 (69.6%)	
Apgar at 5 min	Severe asphyxia	0 (0.0%)	2 (1.8%)	2 (1.6%)	0.220

	Moderate asphyxia	2 (12.5%)	3 (2.8%)	5 (4.0%)	
	Normal	14 (87.5%)	104 (95.4%)	118 (94.4%)	
Preterm infants' characteristics	**Data**	**Sex**		**Total**	**P-value**
		Male	**Female**		
Gestational growth	Small	5 (6.8%)	10 (20.8%)	15 (12.4%)	0.080
	Big	3 (4.1%)	1 (2.1%)	4 (3.3%)	
	Suitable	65 (89.0%)	37 (77.1%)	102 (84.3%)	
Classification of the infants' weight at birth	Low weight	31 (51.7%)	25 (62.5%)	56 (56.0%)	0.281
	Very low weight	24 (40.0%)	10 (25.0%)	34 (34.0%)	
	Extremely low weight	5 (8.3%)	5 (12.5%)	10 (10.0%)	
O_2 delivery device (initial)	O_2 mouthpiece	4 (5.3%)	2 (3.8%)	6 (4.7%)	0.583
	O_2 halo mask	12 (15.8%)	13 (25.0%)	25 (19.5%)	
	Non-invasive mechanical ventilation	32 (42.1%)	22 (42.3%)	54 (42.2%)	
	Invasive mechanical ventilation	28 (36.8%)	15 (28.8%)	43 (33.6%)	
O_2 delivery device (final)	O_2 mouthpiece	52 (68.4%)	37 (71.2%)	89 (69.5%)	0.629
	O_2 Nasal catheter	9 (11.8%)	9 (17.3%)	18 (14.1%)	
	O_2 halo mask	11 (14.5%)	6 (11.5%)	17 (13.3%)	
	Non-invasive mechanical ventilation	2 (2.6%)	0 (0.0%)	2 (1.6%)	
	Invasive mechanical ventilation	2 (2.6%)	0 (0.0%)	2 (1.6%)	
Apgar at 1 min	Severe asphyxia	4 (5.3%)	1 (2.0%)	5 (4.0%)	0.247
	Moderate asphyxia	16 (21.1%)	17 (34.7%)	33 (26.4%)	
	Normal	56 (73.7%)	31 (63.3%)	87 (69.6%)	
Apgar at 5 min	Severe asphyxia	1 (1.3%)	1 (2.0%)	2 (1.6%)	0.831
	Moderate asphyxia	4 (5.3%)	1 (2.0%)	5 (4.0%)	
	Normal	71 (93.4%)	47 (95.9%)	118 (94.4%)	

Data presented as N (number of patients) and % (percentage). Statistical analysis carried out using the Fisher Exact test, 0.05 alpha.

When analyzing the bronchopulmonary dysplasia diagnosis and the other preterm infants' characteristics (gestational age, gross weight, Apgar score, O_2 delivery mode, and hospitalizationtime), gestational age at birth and gestational age at weaning, weight at admission, weight gain, number of O_2 reductions, time without O_2 increase in 24h, % of time without O_2 increase in 24h, O_2 therapy time, and time of hospitalization were observed to present association with the evolution into bronchopulmonary dysplasia. Lower gestational age at birth (207.94±23.02 days), older gestational age at O_2 weaning (251.76±21.51 days), lower weight at admission (1,284.41±530.28 Kg), lower weight gain during the O_2 therapy (663.53±611.30 Kg), higher number of O_2 reductions (37.58±25.61), lower time % without O_2 increase in 24h (69.07±12.28),longer O_2 therapy time (44.18±23.25 days), and hospitalization time (43.82±23.47 days) were all related to the disease diagnosis (**Table 5**).

TABLE 5. Association between the evolution into a bronchopulmonary dysplasia diagnosis and sex with the preterm infants' characteristics (gestational age, weight, Apgar score, O_2 delivery mode, and hospitalization time) admitted to the Neonatal Intensive Care Unit.

Preterm infants' characteristics	**Bronchopulmonary dysplasia**		**P-value**
	Yes (n=17)	**No (n=110)**	
Gestational age at birth (days)	207.94±23.02	229.09±17.24	<0.001
Gestational age at O_2 weaning (days)	251.76±21.51	237.04±15.30	0.001
Infants' gross weight at admission (Kg)	1,284.41±530.28	1,816.36±511.03	<0.001
Infants' gross weight at O_2 weaning (Kg)	1,947.94±639.70	1,814.59±465.08	0.419
Weight gain during oxygen therapy (Kg)	663.53±611.30	-6.59±180.44	<0.001
Apgar at 1 min	6.63±2.391	7.44±1.82	0.113
Apgar at 5 min	8.38±1.74	8.95±1.49	0.159
Number of O_2 reductions (n)	37.58±25.61	7.70±6.01	<0.001
Time without O_2 increase in 24h (success) (days)	25.88±16.48	6.5±4.63	<0.001
% of time without O_2 increase in 24h (success)	69.07±12.28	89.77±13.22	<0.001
O_2 time (days)	44.18±23.25	8.61±7.32	<0.001
Hospitalization time (days)	43.82±23.47	9.23±8.01	<0.001
Preterm infants' characteristics	**Male (n=75)**	**Female (n=52)**	
Gestational age at birth (days)	225.25±18.71	227.71±20.47	0.485
Gestational age at O_2 weaning (days)	236.91±15.83	242.01±18.13	0.093

Infants' gross weight at admission (Kg)	1758.73±546.90	1725.58±541.68	0.736
Infants' gross weight at O_2 weaning (Kg)	1835.72±488.59	1827.31±498.96	0.925
Weight gain during oxygen therapy (Kg)	70.20±327.61	101.73±400.179	0.627
Apgar at 1 min	7.43±2.07	7.18±1.65	0.478
Apgar at 5 min	8.95±1.57	8.78±1.49	0.543
Number of O_2 reductions (n)	10.00±9.29	14.12±20.12	0.173
Time without O_2 increase in 24h (success) (days)	8.09±6.49	10.54±13.21	0.220
% of time without O_2 increase in 24h (success)	89.08±13.64	84.01±16.11	0.580
O_2 time (days)	12.51±13.99	14.54±18.98	0.488
Hospitalization time (days)	12.96±14.09	15.10±19.05	0.467

Data presented as mean ± standard deviation. Statistical analysis carried out using the T test, 0.05 alpha.

The associations carried out between gestational growth, weight, and Apgar with the O_2 delivery devices did not present significant difference, except for weight and the final O_2 delivery device (before weaning). Preterm infants that presented low weight (n=42, 75%), very low weight (n=21, 61.8%), and extremely low weight (n=5, 50%) at birth used, mainly, the O2 mouthpiece just before weaning. However, some low weight patients used the O2 halo mask (n=10, 17.9%), while the remaining very low weight (n=9, 26.5%) and extremely low weight (n=3, 30%) patients used the O_2 nasal catheter (**Table 6**).

TABLE 6. Association between gestational growth, weight at admission and Apgar one with the otherand with the O_2 delivery devices to preterm infants admitted to the Neonatal Intensive Care Unit.

Preterm infants' characteristics	**Data**	**Gestational growth**			**Total**	**P-value**
		Small	**Suitable**	**Big**		
Classification of the infants' weight at birth	Low weight (LW)	5 (38.5%)	51 (58.6%)	0 (0.0%)	56 (56.0%)	0.144
	Very low weight (VLW)	5 (38.5%)	29 (33.3%)	0 (0.0%)	34 (34.0%)	
	Extremely low weight (ELW)	3 (23.1%)	7 (8.0%)	0 (0.0%)	10 (10.0%)	
O_2 delivery device (initial)	O_2 mouthpiece	1 (6.7%)	5 (4.9%)	0 (0.0%)	6 (5.0%)	0.773
	O_2 halo mask	3	20	2	25	

		(20.0%)	(19.6%)	(50.0%)	(20.7%)	
	Non-invasive mechanical ventilation	5 (33.3%)	44 (43.1%)	1 (25.0%)	50 (41.3%)	
	Invasive mechanical ventilation	6 (40.0%)	33 (32.4%)	1 (25.0%)	40 (33.1%)	
O_2 delivery device (final)	O_2 mouthpiece	10 (66.7%)	70 (68.6%)	3 (75.0%)	8 (68.6%)	0.934
	O_2 Nasal catheter	3 (20.0%)	14 (13.7%)	0 (0.0%)	17 (14.0%)	
	O_2 halo mask	2 (13.3%)	14 (13.7%)	1 (25.0%)	17 (14.0%)	
	Non-invasive mechanical ventilation	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (1.7%)	
	Invasive mechanical ventilation	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (1.7%)	
Apgar at 1 min	Severe asphyxia	1 (7.1%)	4 (4.0%)	0 (0.0%)	5 (4.2%)	0.419
	Moderate asphyxia	8 (57.1%)	24 (24.0%)	2 (50.0%)	82 (69.5%)	
	Normal	8 (57.1%)	72 (72.0%)	2 (50.0%)	82 (69.5%)	
Apgar at 5 min	Severe asphyxia	1 (7.1%)	1 (1.0%)	0 (0.0%)	2 (1.7%)	0.074
	Moderate asphyxia	1 (7.1%)	3 (3.0%)	1 (25.0%)	5 (4.2%)	
	Normal	12 (85.7%)	96 (96.0%)	3 (75.0%)	111 (94.1%)	
Preterm infants' characteristics	**Data**	**LW**	**VLW**	**ELW**	**Total**	**P-value**
O_2 delivery device (initial)	O_2 mouthpiece	3 (5.4%)	1 (2.9%)	0 (0.0%)	4 (4.0%)	0.113
	O_2 halo mask	14 (25.0%)	3 (8.8%)	1 (10.0%)	18 (18.0%)	
	Non-invasive mechanical ventilation	24 (42.9%)	18 (52.9%)	2 (20.0%)	34 (34.0%)	
	Invasive mechanical ventilation	15 (36.8%)	12 (35.3%)	7 (70.0%)	44 (44.0%)	

O_2 delivery device (final)	O_2 mouthpiece	42 (75.0%)	21 (61.8%)	5 (50.0%)	68 (68.0%)	0.002
	O_2 nasal catheter	3 (5.4%)	9 (26.5%)	3 (30.0%)	15 (15.0%)	
	O_2 halo mask	10 (17.9%)	4 (11.8%)	0 (0.0%)	14 (14.0%)	
	Non-invasive mechanical ventilation	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	
	Invasive mechanical ventilation	0 (0.0%)	0 (0.0%)	2 (20.0%)	2 (2.0%)	
Apgar at 1 min	Severe asphyxia	3 (5.5%)	1 (2.9%)	1 (11.1%)	5 (5.1%)	0.754
	Moderate asphyxia	15 (27.3%)	9 (26.5%)	3 (33.3%)	27 (27.6%)	
	Normal	37 (67.3%)	24 (70.6%)	5 (55.6%)	66 (67.3%)	
Apgar at 5 min	Severe asphyxia	1 (1.8%)	1 (2.9%)	0 (0.0%)	2 (2.0%)	0.666
	Moderate asphyxia	2 (3.6%)	1 (2.9%)	1 (11.1%)	4 (4.1%)	
	Normal	52 (94.5%)	32 (94.1%)	8 (88.9%)	92 (93.9%)	

Preterm infants' characteristics	**Data**	**Apgar at 1 min**			**Total**	**P-value**
		Normal	**Moderate asphyxia**	**Severe asphyxia**		
O_2 delivery device (initial)	O_2 mouthpiece	4 (4.6%)	1 (3.0%)	0 (0.0%)	5 (4.0%)	0.003
	O_2 halo mask	22 (25.3%)	3 (9.1%)	0 (0.0%)	25 (20.0%)	
	Non-invasive mechanical ventilation	41 (47.1%)	12 (36.5%)	0 (0.0%)	42 (33.6%)	
	Invasive mechanical ventilation	20 (23.0%)	17 (51.5%)	5 (100.0%)	53 (42.4%)	
O_2 delivery device (final)	O_2 mouthpiece	60 (69.0%)	24 (72.7%)	3 (60.0%)	87 (69.6%)	0.665

	O_2 nasal catheter	11 (12.6%)	4 (12.1%)	2 (40.0%)	17 (13.6%)	
	O_2 halo mask	13 (14.9%)	4 (12.1%)	0 (0.0%)	17 (13.6%)	
	Non-invasive mechanical ventilation	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	
	Invasive mechanical ventilation	1 (1.1%)	1 (3.0%)	0 (0.0%)	2 (1.6%)	
Preterm infants' characteristics	**Data**	**Apgar at 5 min**			**Total**	**P-value**
		Normal	**Moderate asphyxia**	**Severe asphyxia**		
O_2 delivery device (initial)	O_2 mouthpiece	5 (4.2%)	0 (0.0%)	0 (0.0%)	5 (4.0%)	0.180
	O_2 halo mask	25 (21.2%)	0 (0.0%)	0 (0.0%)	25 (20.0%)	
	Non-invasive mechanical ventilation	52 (44.1%)	1 (20.0%)	0 (0.0%)	53 (42.4%)	
	Invasive mechanical ventilation	36 (30.5%)	4 (80.0%)	2 (100.0%)	42 (33.6%)	
O_2 delivery device (final)	O_2 mouthpiece	81 (68.6%)	4 (80.0%)	2 (100.0%)	87 (69.6%)	1.000
	O_2 nasal catheter	16 (13.6%)	1 (20.0%)	0 (0.0%)	17 (13.6%)	
	O_2 halo mask	17 (14.4%)	0 (0.0%)	0 (0.0%)	17 (13.6%)	
	Non-invasive mechanical ventilation	2 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	
	Invasive mechanical ventilation	2 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	

Data presented as N (number of individuals) and % (percentage). Statistical analysis carried out using the Fisher Exact test, 0.05 alpha.

The Pearson correlation between the patients' characteristics (gestational age and weight), O_2 delivery mode, and hospitalization time showed that the higher the patient's gestational age atbirth, the lower the number of O_2 reductions (CC=(-)0.499) is, the higher the % of time without O_2 increase in 24h (higher success rate), the lower the hospitalization time (CC=(-)0.574), and the O_2 use (CC=(-)0.564) are. Gross weight at admission was correlated to the higher the weight, the lower the number of O_2 reductions (CC=(-)0.412), the lower the hospitalization time (CC=(-)0.466), and the lower the O_2 (CC=(-)0.461). Regarding the number of reductions carried out, we could observe that the higher the number of reductions was, the lower the gestational age at birth was (CC=(-)0.499), the lower the gross weight at admission (CC=(-)0.412), and the lower the % of time without O_2 increase in 24h were (lower success rate) (CC=(-)0.493) (**Table 7**). The % of time without O_2 increase in 24h presented positive correlation to the gestational age at birth (CC=0.375), and negative correlation with the number of O_2 reductions (CC=(-)0.493), hospitalization time (CC=(-)0.480), and O_2 use (CC=(-)0.488) (**Table 7**).

TABLE 7. Pearson Correlation between preterm infants' characteristics (gestational age and weight), O_2 delivery mode, and hospitalization time.

Preterm infants' characteristics		Gestational age at birth (days)	Gestational age at O_2 weaning (days)	Preterm infants' gross weight at admission	gross weight at O_2 weaning	Weight gain during oxygen therapy	Number of O_2 reductions	- increase in 24h success	O_2 increase in 24h (success)	Hospitalization time	O_2 time
Gestational age at birth (days)	CC	1	0.575**	0.777**	0.491**	-0.506**	-0.499**	-0.493**	0.375**	-0.574**	-0.564**
	P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Gestational age at O_2 weaning (days)	CC	0.575**	1	0.419**	0.691**	0.312**	0.326**	0.333**	-0.025	0.319**	0.322**
	P-value	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	0.781	<0.001	<0.001

Preterm infants' gross weight at admission	CC	0.777**	0.419**	1	0.765**	-0.468**	-0.412**	-0.407**	0.343**	-0.466**	-0.461**
	P-value	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Preterm infants' gross weight at O_2 weaning	CC	0.491**	0.691**	0.765**	1	0.211*	0.161	0.156	0.079	0.148	0.149
	P-value	<0.001	<0.001	<0.001		0.017	0.069	0.080	0.373	0.096	0.093
Weight gain during oxygen therapy	CC	-0.506**	0.312**	-0.468**	0.211*	1	0.848**	0.835**	-0.404**	0.910**	0.904**
	P-value	<0.001	<0.001	<0.001	0.017		<0.001	<0.001	<0.001	<0.001	<0.001
Number of O_2 reductions	CC	-0.499**	0.326**	-0.412**	0.161	0.848**	1	0.988**	-0.493**	0.929**	0.933**
	P-value	<0.001	<0.001	<0.001	0.069	<0.001		<0.001	<0.001	<0.001	<0.001
Time without O_2 increase in 24h (success)	CC	-0.493**	0.333**	-0.407**	0.156	0.835**	0.988**	1	-0.421**	0.928**	0.928**
	P-value	<0.001	<0.001	<0.001	0.080	<0.001	<0.001		<0.001	<0.001	<0.001
% of time without O_2 increase in 24h	CC	0.375**	-0.025	0.343**	0.079	-0.404**	-0.493**	-0.421**	1	-0.480**	-0.488**

(success)	P-value	<0.001	0.781	<0.001	0.373	<0.001	<0.001	<0.001		<0.001	<0.001
Hospitalization time	CC	-0.574**	0.319**	-0.466**	0.148	0.910**	0.929**	0.928**	-0.480**	1	0.989**
	P-value	<0.001	<0.001	<0.001	0.096	<0.001	<0.001	<0.001	<0.001		<0.001
O_2 time	CC	-0.564**	0.322**	-0.461**	0.149	0.904**	0.933**	0.928**	-0.488**	0.989**	1
	P-value	<0.001	<0.001	<0.001	0.093	<0.001	<0.001	<0.001	<0.001	<0.001	

*. The correlation is significant at the 0.05 level (bilateral).

**. The correlation is significant at the 0.01 level (bilateral).

CC, correlation coefficient.

The multivariate model proposed was able to predict the evolution into bronchopulmonary dysplasia in 90.2% cases (X^2=36.435; P-value<0.001; R^2 of Nagelkerke=0.476). Among the predictors used in the multivariate analysis of neonatal characteristics for bronchopulmonary dysplasia development, the presence of septic shock (P-value=0.023) and % of time without O_2 increase in 24h (success rate %) (P-value=0.001), were the two factors identified as significant predictors for the bronchopulmonary dysplasia development in preterm infants (**Table 8**).

TABLE 8. Multivariate[a,b,c,d] analysis with the preterm infants' characteristics as predictor factors for bronchopulmonary dysplasia.

Patient's characteristics	**B**	**E.P.**	**Wald**	**gl**	**Sig.**	**Exp(B)**	**95% C.I. para EXP(B)**	
							Lower	**Higher**
Septic shock (present)	1.614	0.711	5.161	1	0.023	5.025	1.248	20.229
Initial weight (Kg)	-0.001	0.001	3.494	1	0.062	0.999	0.997	1.000
% of time without O_2 increase in 24h (success)	-0.086	0.024	12.932	1	0.001	0.918	0.876	.962
Constant	6.657	2.039	10.656	1	0.001	778.481		

a. Variables inserted in step 1 of 9: sex, early respiratory distress, neonatal jaundice, septic shock, prematurity apnea, twin birth, O_2 delivery device (initial), gestational age at birth (days), preterm infants' gross weight at admission, Apgar at 1 min, % of time without O_2 increase in 24h (success).

b. Factors that were not included due to the multi-collinearity effect: gestational growth (suitable for the gestational age, small for the gestational age, and big for the gestational age), preterm infants' weight classification at birth (low weight, very low weight, and extremely low weight), and sepsis diagnosis.

c. Factors such as time in oxygen therapy and hospitalization time were not included due to their association with the natural diagnosis of bronchopulmonary dysplasia. In addition, the O_2 delivery device (final) was not included due to its correlation with diagnosis and follow-up time.

d. The number of O_2 reductions and the time without O_2 increase in 24h (success) were used to calculate the % of time without O_2 increase in 24h (success).

DISCUSSION

This study showed greater prevalence of male infants with good 1st and 5th-minute Apgar score, with suitable growth for the gestational age and low weight at birth. They presented an average of 13.34±16.6 days of O_2 use. The factors identified were neonatal features that influence the evolution into bronchopulmonary dysplasia, association between neonatal features and O_2 delivery devices, correlation between neonatal variables and the O_2 delivery mode. The study also showed that the septic shock diagnosis and the % of time without O_2 increase in 24h (success rate) were considered as predictor factors for the diagnosis of bronchopulmonary dysplasia.

Among the neonatal characteristics for association of the bronchopulmonary dysplasia evolution, weight at birth (extremely low weight and very low weight), initial O_2 delivery device (invasive and non- invasive mechanical ventilation), and final O_2 delivery device (O_2 mouthpiece and O_2 nasal catheter) were classified as indicators for the bronchopulmonary dysplasia evolution. Extremely low weight and very low weight at birth were related to extreme prematurity, consequently, with higher lung immaturity and nutritional deficiency, thus requiring longer O_2 use[19]. A study carried out with 233 preterm infants with bronchopulmonary dysplasia and very low weight at birth identified that the capillary carbon partial pressure ($PaCO_2$), weight gain, cannula flow rate, pulmonary acuity score and persistent arterial duct ligation are associatedwith success factors for the discontinuation of supplemental O_2 use[20].

Invasive and non-invasive mechanical ventilation are used in more severe conditions, where the time of use depends on clinical rehabilitation of the ventilatory support indication, which might prolong O_2 use and influence the development of bronchopulmonary dysplasia[21]. The mechanical ventilation used in this study in 43 infants (33.6%) is identified in the literature as a common risk factor for the development of bronchopulmonary dysplasia, ventricular leukomalacia and retinopathy of prematurity, and its avoidance might reduce the risk of developing such diseases[22]. In addition, the relation between mechanical ventilation and alteration of the resident stromal and mesenchymal cells, that is, those cells involved in tissue development, repair and growth, might impact preterm infants' lung maturation, delaying their growth and repair processes and leading to the development of lung diseases such as

bronchopulmonary dysplasia[23].

Ventilatory support using non-invasive mechanical ventilation was the most used option to provide initial support in this study. The literature also reports that non-invasive mechanical ventilation is indicated as the ideal support for preterm infants, for being less invasive and providing lung repair parameters faster than invasive mechanical ventilation[21].

FiO_2 adjustment in invasive and non-invasive mechanical ventilation, preventing the occurrence of hypoxia and hyperoxia, might be key for an efficient weaning. However, the reduction decision depends on a multidisciplinary evaluation. The literature reports the creation ofa closed-circuit automated control of inspired O_2 concentration, which allows the FiO_2 control using a closed circuit and monitoring O_2 (oximeter) and the gas support (ventilator or nasal cannula), with an algorithm that determines the FiO_2 sizeand adjustments, providing information about the oxygenation status continuously throughout the durationof the ventilatory support and O_2 therapy[24]. However, this reality is far from that in developing countries such as Brazil.

The O_2 mouthpiece and the O_2 nasal catheter were described as final devices in the evolution into bronchopulmonary dysplasia for being devices that couple efficiently to the infant and provide and O_2 low flow, indicated for the weaning transition and are frequently used in preterm infants in prolonged O_2 therapy[25]. In addition, our study described the association between low weight at birth, very low weight at birth and extremely low weight at birth with the device used immediately before weaning, O_2 mouthpiece and O_2 nasal catheter, exactly for the fact that weight influences longer O_2 time, and consequently, the bronchopulmonary dysplasia diagnosis. However, the SpO_2 evaluation and the O_2 flow must be constantly assessed and, according to the literature, SpO_2 higher or equal to 92% after 40 minutes of evaluation and a 20 mL/minute flow in preterm infants with bronchopulmonary dysplasia might predict readiness for O_2 weaning[26].

Another relevant piece of data in our study is that the chance of evolving into bronchopulmonary dysplasia increases with lower gestational age at birth, lower weight at admission, higher gestational age at O_2 weaning, lower weight gain during O_2 therapy, higher number of O_2 reductions, lower success rate % in 24h after reduction, longer hospitalization time and longer O_2 use. That is, the lower the gestational age and the weight are, the higher the chances of prolonged O_2 use and association with bronchopulmonary dysplasia diagnosis in

advanced gestational age are. This might hamper the O_2 reduction and weaning processes, possibly reducing the success rate % after reduction. According to the literature, the supplemental O_2 use impact after the infants' stabilization also influences genomic alterations that in excessdoses might cause DNA hyper or hypomethylation, being considered a facilitator factor for the development of cancer in the childhood when supplied soon after birth[27]. In addition, O_2 therapy in low weight preterminfants was associated with increased capillary rarefaction, favoring the increase in arterialpressure during adjusted age after 40 weeks with long term effects when compared to low weight preterm infants that did not use O_2 therapy[28].

The % of time without O_2 increase in 24h (success rate) identified in our study, showed positive correlation with the patients' increased gestational age, lower gestational age at weaning, lower number of O_2 reductions required, shorter hospitalization time and O_2 use, being also considered a predictor factor for bronchopulmonary dysplasia. Therefore, the lower the success rate % is, the greater the chance of developing bronchopulmonary dysplasia is. Thus, a thorough and efficient evaluation by the multidisciplinary team is highly relevant to decide the correct O_2 reduction and lower the chances of developing bronchopulmonary dysplasia, since the supplemental O_2 use in a restricted way is related to a reduction in retinopathy of prematurity and bronchopulmonary dysplasia. However, its unrestricted use presents significant potential damage[29].

The literature reports a multicentric clinical study [SUPPORT (surfactant, positive pressure, and oxygen)] evaluating prematurity and O_2 therapy. However, the ideal O_2 therapy for extreme and vulnerable preterm infants is still uncertain[30]. The results obtained in this study, taking into consideration the gestational age at birth, weight, and devices used might help a better clinical conduct, observing the need for caloric support, weight gain during O_2 therapy, ventilatory support transition, and hypoxemia and hyperoxemia evaluation, which might increase the O_2 weaning success rate %. For the O_2 weaning in the post-hospital environment, facilitating and evaluation factors were identified such as growth (96%), vital signs (85%), hospitalization frequency (68%), echocardiogram (59%), and thorax x-ray analysis (21%). However, only 8% pulmonologists used protocols for the weaning management[31].

Regarding the patients' diagnoses, septic shock was considered one of the predicting factors for bronchopulmonary dysplasia. The evolution from the sepsis to the septic shock was reported in the literature as a frequent consequence of pneumonia associated with mechanical

ventilation (PAV) and a risk factor for the PAV clinical treatment failure, with effects on the time of exposure to the ventilation. Thus, the mechanical ventilation time increases the PAV risk, also generating greater risk of septic shock and influencing the bronchopulmonary dysplasia[32].

In addition to the factors influencing the bronchopulmonary dysplasia and the O_2 management found in this study, other extrinsic factors are also associated with the occurrence of bronchopulmonary dysplasia. According to the literature, maternal previous history such as smoking habits and hypertension might be related to the risk of developing respiratory problems in childhood and bronchopulmonary dysplasia in preterm infants, suggesting that control of maternal addiction and comorbidities might help to prevent the occurrence of bronchopulmonary dysplasia[33].

It seems relevant to emphasize that this study was carried out using information found in the medical records and the nursing control of the patients during hospitalization time. Those records might present mistakes made and gaps left by multidisciplinary team professionals.

CONCLUSION

Several characteristics of preterm infants might contribute to the bronchopulmonary dysplasia diagnosis. However, the main predictors in our study were septic shock and the O_2 reduction success rate %. Therefore, the O_2 management multidisciplinary evaluation preventing bronchopulmonary dysplasia might favor the treatment and minimize this disease occurrence.

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4. CAPÍTULO 2 – Artigo II

Title: Risk Factors Associated with Newborn Infant Death in a Neonatal Intensive Care unit: a Retrospective and Epidemiological study

Running title: Neonatal Death Risk: Hospital Scenery

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ABSTRACT

Introduction: The knowledge of maternal and infant characteristics can be used to devise health conducts and reduce neonatal death, mainly in the neonatal intensive care unit (NICU). Therefore, this study aimed to carry out an epidemiological analysis of newborn infant death risk factors in a NICU in Brazil.

Methods: A 5-year epidemiological and retrospective study was carried out on the analysis of maternal and infant characteristics, including data referring to the mothers' demographic profile and gestational background, and the infants' features, including diagnosis, follow-up, and outcome. A multivariate binary logistic regression analysis following the forward stepwise method was performed to identify death predictors, with a 0.05 alpha error.

Results: Out of the 846 infants included, 140 (16.5%) died. The multivariate analysis was significant in predicting the infants' death rate [$X^2(12)=215.494$; P-value<0.001], with a 92.4% global prediction percentage. Significant predictors in this study were: previous pregnancy ≤2 (OR=2.639; 95%CI=1.256- 5.544); moderate asphyxia (OR=2.188; 95%CI=1.083-4.420) or severe asphyxia (OR=3.543; 95%CI=1.405-8.931) in the 1st minute; prematurity (OR=5.463; 95%CI=1.415-21.096); septic shock (OR=8.468; 95%CI=3.386-21.178) and/or patent foramen ovale (OR=0.256; 95%CI=0.071-0.920); gestational age (OR=0.946; 95%CI=0.926-0.967), and time of hospitalization (OR=0.952; 95%CI=0.933-0.973).

Conclusion: A 16.5% prevalence of infant death was observed in the NICU. The main death predictors such as asphyxia, prematurity and septic shock can be easily identified and, in some cases, prevented, which should result in decreased death prevalence.

Keywords*:* *Infant mortality. Prematurity. Infants. Neonatal Intensive Care Units*

INTRODUCTION

Admission to the neonatal intensive care unit (NICU) is related to an increased preterm birth rate, which requires very specific hospital care due to the maturation of the infants' body systems, which many times lead to prolonged hospital stay (1). In addition, full-term infants might present some factors that require hospitalization such as unstable temperature, hypoglycemia, respiratory distress, hyperbilirubinemia, jaundice, dehydration, eating difficulties, urinary tract infection, diarrhea, meningitis, perinatal asphyxia, and sepsis (2,3).

The NICU treatment focuses on life preservation, regardless of the aftereffects of illnesses appearing at the time of admission or due to clinical complications occurred during the NICU treatment (4). These aftereffects might appear in different body systems. However, neurological consequences cause greater impact during the NICU follow-up period, since they might favor the development of other diseases such as chronic encephalopathy of the childhood. This condition results in increased time of hospitalization and motor and cognitive impairment in the long term (5,6). Curiously, hospitalization time is an important factor for the infant's prognosis (7,8), since it is related to the presence of unfavorable outcomes, with increased morbimortality and hospital readmission (9). In addition to the hospitalization time, the presence of comorbidities, diagnosis and physiological abnormalities are characterized as risk factors for hospital readmissions (9,10).

Some factors related to family health background might influence the infants' diagnosis andthe time of hospitalization. The literature reports that maternal comorbidities such as chronic arterial hypertension, gestational diabetes mellitus, eclampsia, premature membrane rupture, and the presence of maternal older age (>40 years old) are considered risk factors for admission to the NICU. Curiously, among infants whose mothers were >40 years old, 5% required NICU admission (11). Concomitantly, lower gestational age, low weight at birth, prematurity, sepsis, kernicterus, and respiratory distress are associated with higher neonatal mortality rates (12).

Although neonatal and infant death have reduced recently, around 16,000 children under 5 years old still dye daily. According to the United Nations (UN), neonatal mortality must be reduced to 12 per 1,000 live births, while child's death must be reduced to 25 per 1,000 live birthsup to 2030 (13). Countries of low and medium income present around 99% of the cases of neonatal mortality worldwide, with causes varying according to the neonatal period and

location of the infants treated in NICU (14,15).

In such context, tracking maternal and infant information aiming to identify the health system flaws might result in efficient conducts of the public health action based on the identification of neonatal death risk factors. Such informed actions should minimize unfavorable clinical situations, reduce the need for hospital admission for modulating the instability conditionsand mainly reducing neonatal morbimortality, which would reduce health costs.

Taking all that into consideration, this study aimed to carry out an epidemiological analysisof infant death risk factors in a NICU in the interior of the state of São Paulo, Brazil.

METHODS

This epidemiological and retrospective study was developed in the period from 2015 to 2019 by surveying the medical records of patients admitted to the mixed ICU (NICU and pediatric ICU - PICU) of the São Francisco de Assis na Providência de Deus University Hospital (HUSF), in Bragança Paulista, interior of the state of São Paulo. The period under analysis excluded the COVID-19 pandemic period, since this disease caused great impact on the admission to the NICU investigated. The HUSF is a charity institution and a referral hospital in the region where Bragança Paulista is situated, and assists around 500,000 people from 11 municipalities, its main focus is the Brazilian Unified Health System (SUS) and partner agencies. The HUSF has a mixed neonatal and pediatric ICU with 10 beds and multiprofessional assistance.

The data collection was carried out by surveying the medical records that were filed in the hospital, which were made available after the presentation of inclusion criteria (newborns from HUSF or referred by other services that required hospital care at the NICU in the period 2015- 2019). The records excluded were those that did not present relevant information or could not be accessed, the ones belonging to patients in the pediatrics age range, or admitted to other sectors (pediatric ward, maternity, or low risk unit).

The maternal variables evaluated were: marital status (married, divorced, single, or stable union), age (years), ethnic group (self-declared), number of previous pregnancies (≤ 2 or >2), previous normal delivery (none or ≥ 1), presence of previous cesarian section, previous abortion (none or

≥1), number of prenatal consultations (<6 or ≥6), and the presence of maternal complications. The neonatal evaluation considered the following data: sex (female/male), cephalic perimeter (cm), gestational age at birth (days), gestational growth (small for the gestational age: <p10; proper for the gestational age: between p10 and p90; big for the gestational age: >p90), weight at birth (extremely low weight: <1,000g; very low weight: between >1,001g and <1,500g; low weight: between >1,501g and <2,500g; normal: between 2,501g and <4,000g), transferred from another unit (yes/no), type of delivery (cesarean section/normal), time of birth (preterm <37 gestational weeks; full-term >37 gestational weeks), apgar at 1 and 5 minutes (severe asphyxia: between 0 and 3 points; moderate asphyxia: between 4 and 6 points; and good vitality: between 7 and 10 points), diagnosis at the time of admission, need for oxygen supplementation (O2), devices used to provide O2 (mouthpiece, face tent, nasal cannula, and halo mask), ventilatory support (invasive and non-invasive mechanical ventilation), evolution into bronchopulmonary displasia and/or retinopathy (degrees I, II and III), and final outcome (discharge/death).

The descriptive analysis followed two approaches: (i) categorical markers – N (%): sample size (percentage); (ii) numeric markers – mean (standard deviation) or median (interquartile interval), according to the data distribution, either parametric or non-parametric, respectively. The numeric data normality was evaluated employing the central tendency descriptive measure analysis; graphic method (Normal Q-Q plot, Q-Q plot without tendency, and boxplot), and the Kolmorov-Smirnov and Shapiro-Wilk statistical tests.

When death risk was associated with other markers, the Fisher Exact or Chi-square tests were used for independent variables classified as categorical; while the T test or Mann-Whitney test were used for data with numerical distribution. Regarding categorical data, relative risk (RR) and 95% confidence interval (95%CI) values were calculated, using the group of patients that were discharged as reference.

The multivariate binary logistic regression following the forward stepwise method included markers that presented p-value below 0.05 in the univariate analysis. However, markers that were associated one to another and represented a multicollinearity effect were excluded. In addition, our proposed model excluded cephalic perimeter due to the high occurrence of missing data. Death was considered a dependent variable and the remaining markers were allocated as death risk predictors.

The statistical analysis considered a 0.05 alpha and no technique was employed to stipulate missing data values. The statistical analysis was carried out using the software Statistical Package for the Social Sciences version 24.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp) and the MedCalc 15.0 (MedCalc for Windows, version 15.0; MedCalc Software, Ostend, Belgium). Graphs were built using the software GraphPad Prism version 8.0.0 for Mac, GraphPadSoftware, San Diego, California USA,www.graphpad.com.

The study was approved by the institution Research Ethics Committee [C.A.A.E #29719020.6.0000.5514] for being in accordance with the Helsinki Declaration and respecting the Health National Council Resolution (CNS) nº 466, of 12th December 2012 for the use of hospital data available without providing access information or identification of the individuals related to the research.

RESULTS

The medical records of 948 patients treated between 2015 and 2019 were evaluated in the period 2020-2021. Out of those, 846 patients were included in the analysis for meeting the inclusion criteria, while102 were excluded [55 without described outcome due to loss of follow-upor transfer; 43 due to admission to the pediatrics age range (>28 days after birth); 3 cases of absence of diagnosis description; and 2 cases without admission data]. In addition, 4 medical records were not available for evaluation at the time of the data collection.

Epidemiological profile of the newborns' maternal-infant characteristics

According to the sample characterization, the maternal profile resulted in mean age of 27±7.45 years, and higher prevalence of the white ethnic group (535; 63.4%). Regarding obstetric background, curiously the highest prevalence of previous pregnancies was ≤2 pregnancies (449; 62.9%) and most of the mothers had ≥6 prenatal consultations (351; 55.9%). Previous normal delivery showed higher prevalence when compared to previous cesarean sections [411 (40.2%) vs. 182 (27.0%)], and most mothers reported no previous abortion (519; 76.5%). Concomitantly, 674 (94.7%) mothers reported some type of maternal complication

during the current pregnancy such as premature membrane rupture, gestational diabetes mellitus, and arterial pressure alteration (**Table 1; Supplementary Material – Table 1**).

TABLE 1. Maternal characterization of the mothers of newborns admitted to the Neonatal Intensive CareUnit of a university hospital in the period 2015-2019.

Maternal characteristic	**Group**	**Distribution**
Mother's age		27.17±7.45; 27 (21-33)
Mother's marital status	Married	113/825 (13.7)
	Divorced	9/825 (1.1)
	Single	697/825 (84.5)
	Stable union	6/825 (0.7)
Ethnic group	Pardo (mixed Black and White)	152/844(18.0)
	White	535/844 (63.4)
	Black	20/844 (2.4)
	Not informed	134/844(15.9)
Number of previous pregnancies (number)	≤2	449/714 (62.9)
	>2	265/714 (37.1)
Previous normal deliveries (number)	None	411/687 (59.8)
	≥1	276/687 (40.2)
Previous cesarean deliveries (number)	Yes	182/673 (27.0)
	No	491/673 (73.0)
Previous abortion (number)	None	519/678 (76.5)
	≥1	159/678 (23.5)
Prenatal (number)	<6	277/628 (44.1)
	≥6	351/628 (55.9)
Maternal complication	Present	674/712 (94.7)
	Preterm labor	216/712 (30.3)
	Membrane rupture	186/712 (26.1)
	Arterial pressure alteration	177/712 (24.9)
	Urinary tract infection	63/712 (8.8)
	Gestational diabetes mellitus	52/712 (7.3)
	Streptoccus Infection	50/712 (7.0)
	Addiction	49/712 (6.9)
	Amniotic fluid alteration	46/712 (6.5)

	Vaginal delivery	39/712 (5.5)
	Fetal centralization	35/712 (4.9)
	Early placental abruption	33/712 (4.6)
	Physiometry	31/712 (4.4)
	Thyroidopathy	28/712 (3.9)
	Fetal growth restriction	25/712 (3.5)
	Amniorrhexis	15/712 (2.1)
	Sepsis	12/712 (1.7)
	Other maternal complications	153/712 (21.5)

Data presented by absolute and relative frequency or the mean ± standard deviation, median (percentile 25and percentile 75).

The sample comprising the newborns admitted was formed mostly by male (498; 58.9%) and premature (604; 72.1%) patients. However, most of the patients presented suitable growth for the gestational age (650; 82.2%), and the expected weight for the birth conditions (353; 41.7%). Unlike the maternal previous data, in the choice of type of delivery, prevalence of cesarean sections (521; 65%) was observed, and most newborns presented good vitality in the 1-min (506; 63.7%) and 5-min (719; 90.3%) Apgar (**Table 2**).

TABLE 2. Characterization of newborns admitted to the Neonatal Intensive Care Unit of a university hospital in the period 2015-2019.

Newborns' characteristic	**Group**	**Distribution**
Sex	Male	498/846 (58.9)
	Female	348/846 (41.1)
Age at the time of admission (days)		1.17±4.36; 0 (0-0)
Cephalic perimeter (cm)		30.96±3.71; 31 (29-33)
Gestational age (days)		213.13±30.84; 237 (214.50-237.0)
Gestational growth	Small for the gestational age	94/791 (11.9)
	Normal for the gestational age	650/791 (82.2)
	Big for the gestational age	47/791 (5.9)
Weight at birth (Kg)		2,079±910.22; 1,935 (1,357-2,805)
	Low weight	223/846 (26.4)
	Extremely low weight	88/846 (10.4)

	Very low weight	182/846 (21.5)
	Normal	353/846 (41.7)
Transferred from another unit	No	665/846 (78.6)
	Yes	181/846 (21.4)
Type of delivery	Cesarean	521/802 (65.0)
	Normal	281/802 (34.0)
Time of birth	Preterm	604/838 (72.1)
	Full-term	234/838 (27.9)
1-minute apgar		6.85±2.22; 7 (6-9)
	Severe asphyxia	87/794 (11.0)
	Moderate asphyxia	201/794 (25.3)
	Good vitality	506/794 (63.7)
5-minute apgar		8.74±1.61; 9 (8-10)
	Severe asphyxia	9/796 (1.1)
	Moderate asphyxia	68/796 (8.5)
	Good vitality	719/796 (90.3)

Data presented by absolute and relative frequency or the mean ± standard deviation, median (p25and p75).

The most common risk factors associated with NICU admission were the presence of early respiratory distress (570; 67.4%), sepsis (293; 34.6%), and neonatal jaundice (268; 31.7%). During the hospitalization period, 771 (91.1%) patients required ventilatory support and oxygen therapy that lasted around 12±20.43 days. The most used ventilatory support was non-invasive mechanical ventilation (431; 50.9%), and the oxygen therapy devices used were O2 halo mask (558; 66%) followed by O2 mouthpiece (313; 37%). The hospital stay mean time was 21±25.56 days, evolving into bronchopulmonary displasia in 91 (10.8%) newborns and prematurity retinopathy in 13 (1.5%) patients. Finally, death of 140 (16.5%) newborns was recorded (**Table 3**).

TABLE 3. Characterization of the hospitalization period and description of the newborns' diagnoses associated with referral to admission to the Neonatal Intensive Care Unit of a university hospital in the period 2015-2019.

Risk factors at the time of admission	**Group**	**Distribution**
Diagnosis	Early respiratory distress	570/846 (67.4)
	Sepsis	293/846 (34.6)
	Neonatal jaundice	268/846 (31.7)
	Apnea of prematurity	131/846 (15.5)
	Cardiopathy	129/846 (15.2)
	Anemia	108/846 (12.8)
	Patent foramen ovale	99/846 (11.7)
	Glycemic alteration	79/846 (9.3)
	Septic shock	74/846 (8.7)
	Convulsive crisis	60/846 (7.1)
	Hemorrhage/intracranialhypertension	56/846 (6.6)
	Anoxia-hypoxia	55/846 (6.5)
	Meconium aspiration syndrome	45/846 (5.3)
	Hyponatremia	42/846 (5.0)
	Reversed cardiorespiratory arrest	30/846 (3.5)
	Other diagnoses	467/846 (55.2)
Multiple pregnancy (twin)	Twin birth	77/846 (9.1)
Characterization of hospitalization time	**Group**	**Distribution**
Hospitalization time (days)		21.65±25.56; 13 (7-28)
Oxygen therapy (days)		12.09±20.43; 6 (6-12)
Need for oxygen		
Oxygen offer device		771/846 (91.1)
	Mouthpiece	313/846 (37.0)
	Face tent	3/846 (0.4)
	Nasal catheter	63/846 (7.4)
	Halo mask	558/846 (66.0)
Invasive mechanical ventilation		426/846 (50.4)
Non-invasive mechanical ventilation		431/846 (50.9)

Outcomes	Group	Distribution
Bronchopulmonary dysplasia		91/846 (10.8)
Retinophaty	No	833/846 (98.5)
	Yes – Degree I	7/846 (0.8)
	Yes – Degree II	5/846 (0.6)
	Yes – Degree III	1/846 (0.1)
Final outcome	Hospital discharge	706/846 (83.5)
	Death	140/846 (16.5)

Data presented by absolute and relative frequency or the mean ± standard deviation, median (percentile 25and percentile 75).

Risk association between maternal-infant characteristics and infant death

The infant death risk factors according to the maternal profile were: number of pregnancies ≤2 (RR=1.632; 95%CI=1.137-2.343); <6 prenatal consultations (RR=2.500; 95%CI=1.739-3.593); placental abruption (RR=2.205; 95%CI=1.361-3.570), fetal centralization (RR=2.072; 95%CI=1.271-3.379), and amniotic fluid alteration (RR=1.992; 95%CI=1.271-3.123) (**Figure 1**; **Supplementary Material – Table 2**).

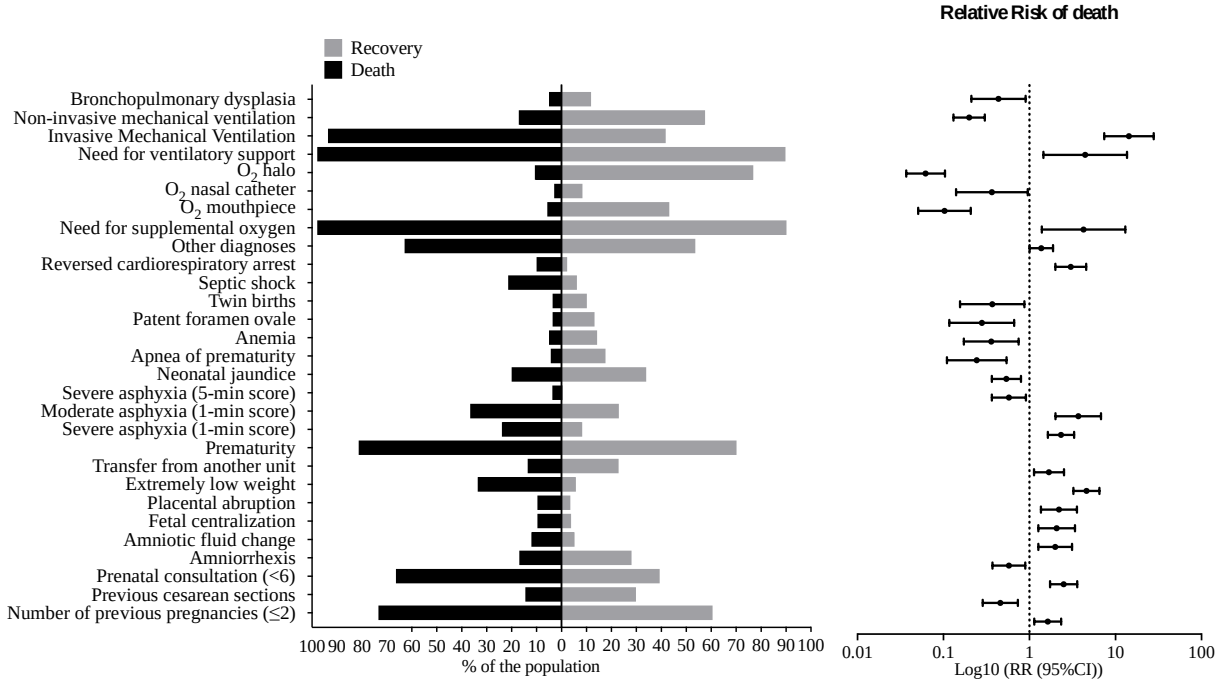

FIGURE 1. Associated maternal-infant characteristics as risk factors for the death of

newborns admitted to the Neonatal Intensive Care Unit of a university hospital in the period 2015-2019. The figure shows the percentage of cases for each characteristic according to the outcome (death or hospital discharge). The data presented represent relative risk (RR) and the 95% confidence interval (95%CI). The Log10 scale was chosen to present the data due to the high amplitude of confidence intervals for some of the data. All data presented showed a P-value≤0.05. The complete data presentation is found in Tables 2 to 4 in the Supplementary Material.

Regarding neonatal characteristics, the factors that increased death risk were: 1-min and 5- min apgar classified as severe asphyxia (respectively, RR=3.515; 95%CI=2.413-5.110 and RR=3.699; 95%CI=2.010-6.804); and 1-minute apgar classified as moderate asphyxia (RR=2.372; 95%CI=1.636-3.311); presence of other diagnosis at the time of admission (RR=1.371; 95%CI=1.002-1.882), preterm birth (RR=1.684; 95%CI=1.130-2.529) along with either very low weight (RR=1.419; 95%CI=0.918-2.194) or extremely low weight (RR=4.598; 95%CI=3.248-6.510) (**Figure 1**; **Supplementary Material – Table 3**).

Other death risk factors observed were: the presence of septic shock (RR=2.845; 95%CI=2.054- 3.941), reverse cardiorespiratory arrest (RR=3.022; 95%CI=1.996-4.576), need for O2 (RR=4.248; 95%CI=1.389-12.99) and/or ventilatory support (RR=4.442; 95%CI=1.451-13.60), mainly with invasive mechanical ventilation (RR=14.35; 95%CI=7.404-27.81) (**Figure 1**; **Table 4**).

TABLE 4. Multivarate binary logistic regression analysis to predict death of newborns admitted to a Neonatal Intensive Care Unit of a university hospital in the period 2015-2019.

Predictor	B	S.E.	Wald	df	Sig.	Exp (B)	95%CI	
							Lower limit	Upper limit
Pregnancies (<2)	0.970	0.379	6.560	1	0.010	2.639	1.256	5.544
Apgar								
Good vitality			9.267	2	0.010			
Moderate asphyxia	0.783	0.359	4.765	1	0.029	2.188	1.083	4.420
Severe asphyxia	1.265	0.472	7.188	1	0.007	3.543	1.405	8.931
Birth time (preterm)	1.698	0.689	6.067	1	0.014	5.463	1.415	21.096
Weight								
Normal			6.214	3	0.102			
Low weight	-0.147	0.523	0.079	1	0.778	0.863	0.310	2.405
Very low weight	0.832	0.573	2.111	1	0.146	2.298	0.748	7.062
Extremely low weight	1.258	0.703	3.202	1	0.074	3.517	0.887	13.944
Apnea of prematurity (Present)	-1.376	0.607	5.127	1	0.024	0.253	0.077	0.831
Septic shock (Present)	2.136	0.468	20.862	1	<0.001	8.468	3.386	21.178
Patent foramen ovale (Present)	-1.365	0.654	4.356	1	0.037	0.256	0.071	0.920
Gestational age (days)	-0.055	0.011	25.929	1	<0.001	0.946	0.926	0.967
Hospitalization time (days)	-0.049	0.011	20.819	1	<0.001	0.952	0.933	0.973
Constant	10.123	2.577	15.426	1	<0.001	24,901.654		

Variables not inserted in the equation due to the use of the forward stepwise method: cesarean delivery; prenatal; membrane rupture; early placental abruption; fetal centralization; amniotic fluid alteration; 5- minute apgar; twin birth; anemia; cardiorespiratory arrest; need for ventilatory support. B, regression coefficient estimated for the predictor; SE, regression coefficient standard error; df, degrees of freedom; Exp(B), predictor odds ratio; CI, confidence interval.

Simultaneously, patients that died presented lower absolute values of 1st and 5-minute apgar (**Figure 2**), hospitalization time, oxygen therapy time (**Figure 3**), gestational age, weight at the time of admission in the NICU, and cephalic perimeter (**Figure 4**).

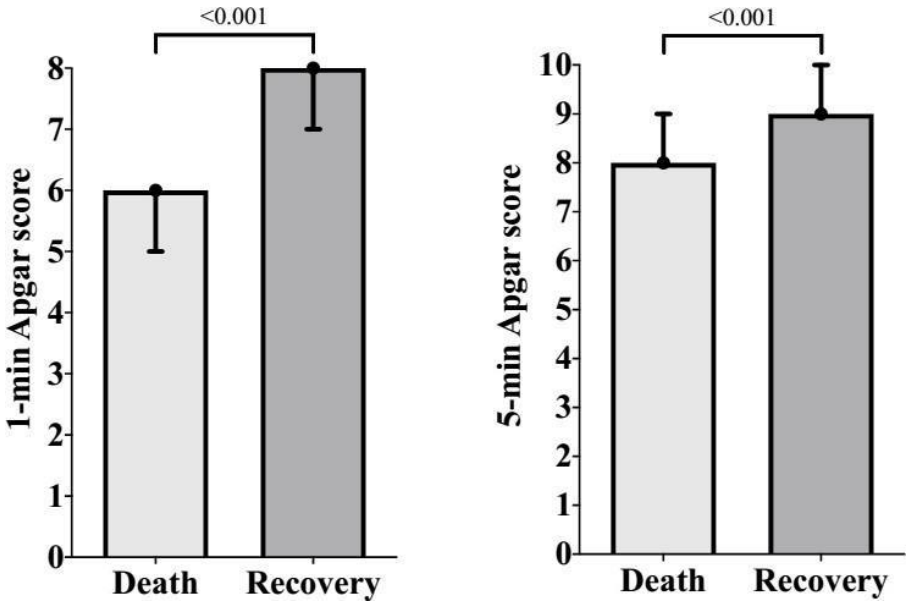

FIGURE 2. Association of 1-min and 5-min apgar in the group of newborn patients according to the outcome (death or hospital discharge). The Mann-Whitney test was used in the statistical analysis with a 0.05 alpha.

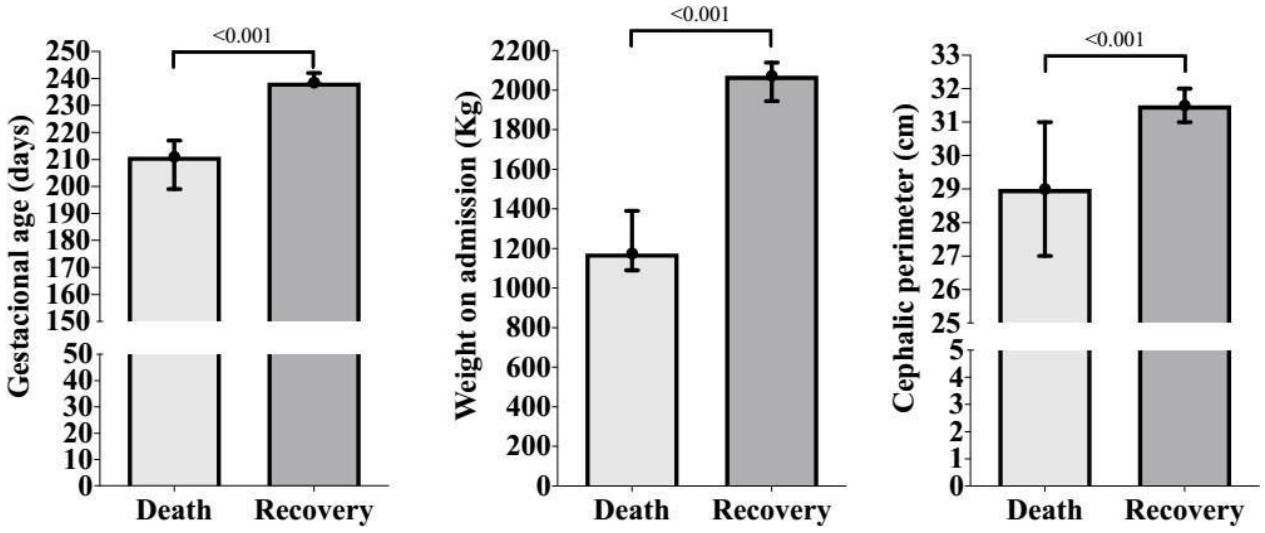

FIGURE 3. Association of gestational age, newborn's weight and cephalic perimeter at the time of admission according to the outcome (death or hospital discharge). The Mann-Whitney test was used in the statistical analysis with a 0.05 alpha.

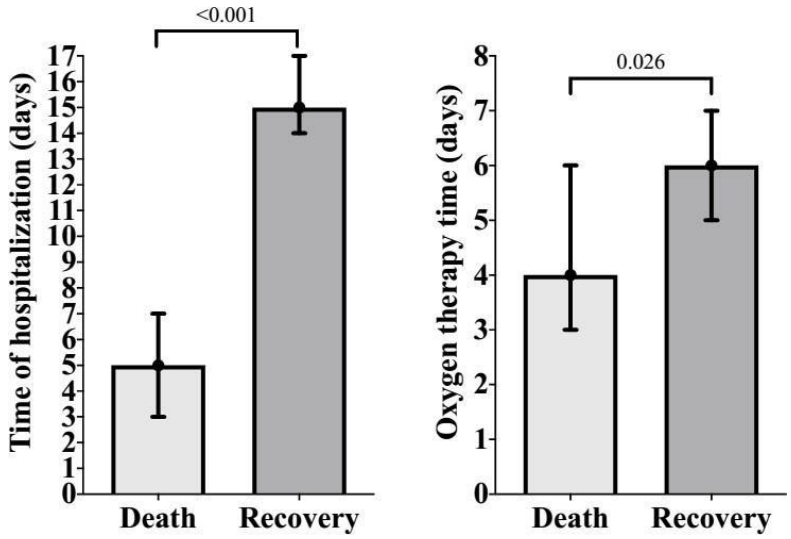

FIGURE 4. Association of the newborns' hospitalization time and oxygen therapy timeaccording to the outcome (death or hospital discharge). The Mann-Whitney test was used in the statistical analysis with a 0.05 alpha.

However, some maternal and neonatal characteristics were associated with lower death risk. These include: cesarean section delivery (RR=0.458; 95%CI=0.286-0.733); membrane rupture (RR=0.577; 95%CI=0.372-0.894); low weight at birth (RR=0.894; 95%CI=0.520-1.387); apnea of prematurity (RR=0.244; 95%CI=0.110-0.542); anemia (RR=0.360; 95%CI=0.173-0.748); neonatal jaundice (RR=0.539; 95%CI=0.366-0.795); patent foramen ovale (RR=0.280; 95%CI=0.117-0.665); twin birth (RR=0.370; 95%CI=0.156-0.875); oxygen therapy with mouthpiece devices (RR=0.103; 95%CI=0.051- 0.208), O2 catheter (RR=0.366; 95%CI=0.140-0.955), O2 halo mask (RR=0.062; 95%CI=0.037-0.104); non-invasive mechanical ventilation (RR=0.199; 95%CI=0.131-0.303), bronchopulmonary dysplasia (RR=0.437; 95%CI=0.211-0.905), and newborns transferred from another unit (RR=0.577; 95%CI=0.366-0.909) (**Figure 1**; **Supplementary Material – Tables 2-4**).

Multivariate binary logistic regression as a newborn death predictor

The multivariate binary logistic regression following the forward stepwise method was significant in predicting newborns' chance of death [$X^2(12)=215.494$; P-value<0.001; Nagelkerke's $R^2=0.558$], with a 92.4% prediction global percentage. The significant predictors included: previous pregnancy ≤2 (OR=2.639; 95%CI=1.256-5.544); 1-minute apgar classified as

moderate asphyxia (OR=2.188; 95%CI=1.083-4.420) or severe asphyxia (OR=3.543; 95%CI=1.405-8.931); preterm delivery (OR=5.463; 95%CI=1.415-21.096); septic shock (OR=8.468; 95%CI=3.386-21.178) and/or patent foramen ovale (OR=0.256; 95%CI=0.071-0.920); gestational age (OR=0.946; 95%CI=0.926-0.967), and time of hospitalization (OR=0.952, 95%CI=0.933- 0.973). Conversely, the newborns' weight, grouped in low weight, very low weight and extremely low weight, was not significant in the prediction of a bronchopulmonary dysplasia in the multivariate analysis carried out (**Table 4** and **Figure 5**).

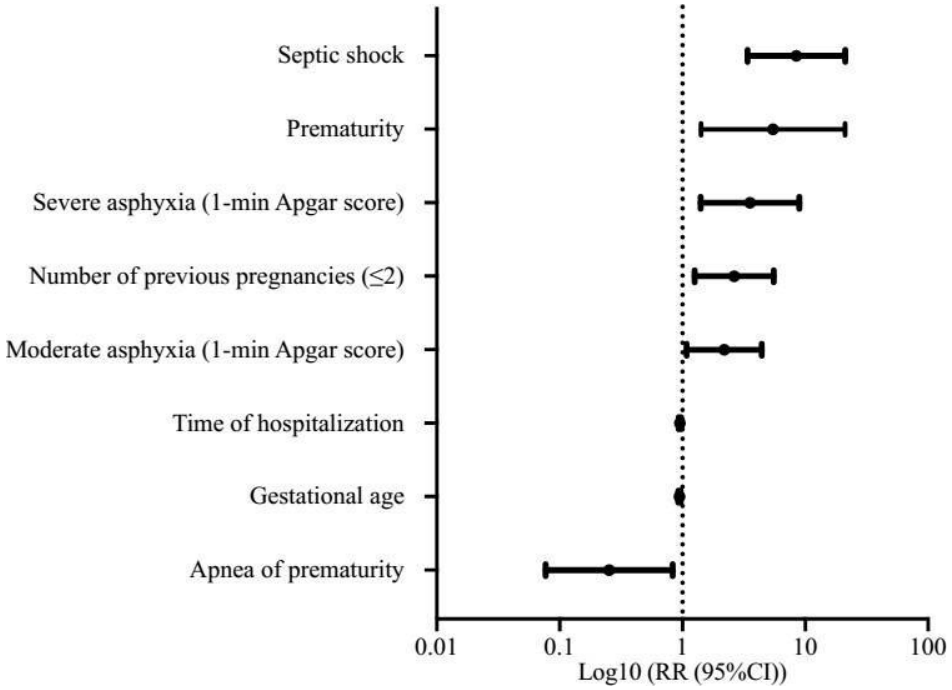

FIGURE 5. Predictors that contributed to the prediction of death of newborns admitted to the Neonatal Intensive Care Unit of a university hospital in the period 2015-2019 in the multivariate binary logistic regression analysis. The data presented showed relative risk (RR) and a 95% confidence interval (95%CI). The Log10 scale was chosen to present the data due to high amplitude of confidence intervals for some of the data.

DISCUSSION

Throughout the period evaluated in this study, 846 NICU admissions were recorded with a 21-dayhospitalization mean time, prevalence of premature newborns (RNPTs), male, with proper growth for the gestational age, normal weight, cesarean section delivery, and with good vitality in the 1-min and 5-minute apgar. Among these hospitalizations, death occurred in 16.5%

of the patients and was associated with maternal-infant characteristics, mainly, number of deliveries below 2, prematurity, presence of moderate or severe asphyxia, and septic shock.

Considering the characteristics that are associated with hospital health care, the hospitalization mean time varies according to the place and admission diagnosis. In Europe, in 2012/2013, the hospitalization mean time in a health center was around 63.1 days and mortality reached 27.7% in the whole continent, while in the same period in Brazil the mortality rate reached10.6%, which shows early recovery in our study, with a 21-day hospitalization mean time and 16.5% death rate in five years (16-18). As observed, the percentage of deaths in NICU is also varied, and according to the literature, this is due to unequal health actions provided and the municipality economic level. In the state of São Paulo, a study carried out to evaluate mortality ina 10-year period revealed 48,309 (8%) death of newborns. Curiously, the variables associated with neonatal deaths were distinct in different municipalities. This fact shows the uneven health management, as well as epidemiological differences regarding maternal-infant characteristics, even within the same State Federative Unit (19).

In the Brazilian scenery according to geographical region, the highest mortality rate was observed in the North region with 11.45% deaths, followed by the Northeast (10.65%), Midwest (9.21%), Southeast (7.97%), while the South region presented the lowest rate of neonatal death, 7.23% (18). This shows that the variation in the neonatal death rate in relation to the geographicalregion is related to the local human development index, in which income, education and health areevaluated. This triad is directly proportional to the neonatal mortality in the place. For example, the North and Northeast regions present the worst indices in Brazil with the lowest *per capita* income in 2017 (Acre – 497 and Ceará – 538), while the Southeast and South regions presented the best indices, with the highest *per capita* income (São Paulo – 1,130 and Rio Grande do Sul – 1,070) (20).

This study showed that some maternal characteristics are related to neonatal death risk. Thenumber of prenatal consultations, for example, can be one of the most important maternal variables related to death risk since it is related to other death risk predictors. The suitable number of prenatal consultations (recommended as >6 consultations by the Brazilian Health Ministry) might reduce delayed fetal growth, prematurity rates, and the frequency of low weight at birth.

Thus, the factors listed as responsive to prenatal care were previously described as death risk factors (21), and in our study, both prematurity and low weight at birth were related to death.

The number of previous pregnancies below two was also considered as a maternal risk factor contributing to the newborns' death. This condition might be related to the mothers' profile in our study, since they are mostly young (27±7.45 years), with little gestational experience, poor prenatal preparation, and receiving inefficient primary health care (22), since around 94.7% of the mothers evaluated presented associated comorbidities, even if in the absence of previous abortion in most cases. Due to the faulty primary care, other factors might be associated with neonatal death risk and the number of previous pregnancies, in the state of Rio de Janeiro, for instance, single pregnancies are related to low schooling, adolescent mothers, and low weight at birth (23).

Among the high index of maternal comorbidities described in our study, early placental abruption, fetal centralization, and alteration of amniotic fluid are some of the maternal risk factors associated with neonatal death. The three comorbidities are associated with chances of neonatal complications such as prematurity, fetal growth restriction, low weight at birth, and sepsis. That is, they might influence the newborn profile found in the study in addition to presenting high indication for cesarean section (24,25). Curiously, septic shock was one of the main characteristics associated with death, and this factor is associated with other comorbidities, as described. Our maternal findings are similar to the results obtained in a University hospital in Finland that in a 5-year period (between 2007 and 2011) demonstrated factors such as nulliparity, multiple pregnancy, and maternal complications [hypertensive crises (58%) and obstetric hemorrhage (25.1%)] as risk factors for the need for NICU support and newborns' death (eightfold higher than in mothers without comorbidities) showing that the mother's obstetric background might be a risk factor for adverse perinatal results (26). However, the literature reports advanced maternal age and the presence of previous abortion as neonatal risk predictive factors, which should call our attention to the health care of young mothers as the ones in our study (27,28).

Concomitantly, neonatal gestational age was inversely proportional to the increased death risk in our study, which indicates that preterm newborns have higher chances of death than full-term infants. In addition to being influenced by maternal factors, prematurity favors the birth of

newborns presenting very low and extremely low weight. Since weight at birth is considered a sensitive variable to be used in screenings in neonatal death surveillance programs, as a result of body immaturity and nutrient intake, it draws attention to maternal comorbidities or poor maternal nutrition (29).

The Apgar score is another variable considered a predictor of neonatal mortality, and severe and moderate asphyxia at 1 minute and 5 minutes was related to higher risk of neonatal death (29) in our findings. Perinatal factors such as prolonged birth time and incorrect indication of type of delivery might influence the Apgar. In addition, the newborn's hypotonic appearance in comparison to full-term newborns might result in a mistaken neonatal asphyxia score, favoring greater prevalence of asphyxia in preterm newborns (30). Therefore, despite its importance, Apgar must be evaluated thoroughly and the subjectivity of this score should be taken into consideration.

The literature and our results show prevalence of NICU admission of male newborns. This fact might be due to their delayed growth when compared to female infants, as a result of the genetic determination of certain diseases. In addition, prematurity and elective cesarean section also prevailed in NICU admissions, possibly as a result of maternal complications (19,31). In the literature, factors associated with neonatal hospitalization predominantly involve respiratory complications (25.2%), resuscitation post maneuver observation (24.1%), and hypoglicemia (9.1%) (32). However, at our center, the main factors associated with hospital admission besides respiratory causes were sepsis (34.6%) and neonatal jaundice (31.7%), while in Eritrea, the first cause of hospital admission is sepsis (35.5%), followed by neonatal asphyxia (10%). These are alarming data and draw attention to the importance of septic delivery prevention and maternal instruction to reduce neonatal jaundice in our service. This fact also points out that the causes of NICU admission, different from respiratory distress, vary according to the place, availability of primary health care (33).

Development of septic shock, reversed cardiorespiratory arrest, need for O2 or ventilatory support, mainly in invasive mechanical ventilation, are related to the neonatal death risk, as consequences of worsened conditions after admission, low response to the treatment, and pulmonary disorder (34). Regarding invasive mechanical ventilation, it is a respiratory insufficiency recovery strategy and is associated with severe clinical conditions and, possibly,

higher death risk and risk of posthospitalization sequelae (34).

Neonatal death risk factors in low-income countries include adverse perinatal events, prematurity, asphyxia, and infections. These conditions are usually preventable by the use of contraception, vaccination, hygienic delivery, and healthcare team training. In high income countries, neonatal death factors usually include prematurity and congenital disorders, which might be reduced by the referral of risk deliveries to specialized centers and immediate resuscitation (36). The death-related factors in our study are similar to those found in low-income countries, due to the fact that Brazil is a developing country. Such factors are relevant and contribute to neonatal mortality in Africa, Southeast Asia, and Latin America, indicating the needfor health managers to specifically coordinate primary care (36).

The factors considered to have lower relation to death in our study such as cesarean delivery, presence of membrane rupture, low weight at birth, apnea of prematurity, anemia, neonatal jaundice, patent foramen ovale, twin birth, oxygen therapy (O2 mouthpiece, nasal catheter, halo mask), non-invasive mechanical ventilation, bronchopulmonary dysplasia, and transfer from another unit must be thoroughly evaluated, since their lower relation to death might be associated to the patients' condition lower severity in some types of oxygen therapy and in non-invasive mechanical ventilation. Another explanation could be the lower severity of some characteristics in detriment of others that were pointed out as risk factors such as the presence of anemia and septic shock. Additionally, some factors might be associated with lower death risk forbeing related to better prepartum monitoring, and better preparation for the intrapartum and postpartum periods, for instance.

It seems relevant to emphasize that this study was carried out from professional data found in the medical records of hospitalization, which might present mistakes, underreporting, and lack of information.

CONCLUSION

A 16.5% prevalence of death was observed in the NICU and the main death predictors foundwere the presence of asphyxia, prematurity and septic shock, which can be easily identified and in some cases even prevented resulting in a reduced death rate. Thus, approaching

modifiable factors related to death, mainly maternal aspects such as incentivizing prenatal and primary care, and promoting mothers' health with special attention to comorbidities, might determine the newborns' health condition with consequent reduction in the number of neonatal deaths.

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SUPPLEMENTARY MATERIAL

TABLE 1. Maternal description of newborns admitted to the Neonatal Intensive Care of auniversity hospital.

Number of previous pregnancies		**Distribution [N (%)]**
	0	1/715 (0.1)
	1	284/715 (39.7)
	2	164/715 (22.9)
	3	129/715 (18.0)
	4	74/715 (10.3)
	5	31/715 (4.3)
	6	16/715 (2.2)
	7	9/715 (1.3)
	8	7/715 (1.0)
Number of previous deliveries		
	0	411/687 (59.8)
	1	136/687 (19.8)
	2	68/687 (9.9)
	3	37/687 (5.4)
	4	15/687 (2.2)
	5	12/687 (1.7)
	6	7/687 (1.0)
	7	1/687 (0.1)
Number of cesarean deliveries		
	0	491/673 (73.0)
	1	122/673 (18.1)
	2	46/673 (6.8)
	3	11/673 (1.6)
	4	3/673 (0.4)
Number of previous abortions		
	0	519/678 (76.5)
	1	132/678 (19.5)
	2	21/678 (3.1)
	3	4/678 (0.6)

	4	2/678 (0.3)
Presence of prenatal care		
	1	14/628 (2.2)
	2	24/628 (3.8)
	3	48/628 (7.6)
	4	67/628 (10.7)
	5	91/628 (14.5)
	6	92/628 (14.6)
	7	76/628 (12.1)
	8	64/628 (10.2)
	9	58/628 (9.2)
	10	28/628 (4.5)
	11	14/628 (2.2)
	12	5/628 (0.8)
	13	8/628 (1.3)
	14	3/628 (0.5)
	18	1/628 (0.2)
	19	2/628 (0.3)
	None	33/628 (5.3)

N, number of patients; %, percentage.

TABLE 2. Associated maternal characteristics as risk factors for death of newborns admitted to the Neonatal Intensive Care Unit of a university hospital in the period 2015-2019.

Group	**Category**	**Death**	**Hospital discharge**	**Total**	**P-value**	**RR**	**95%CI**
Mother's marital status	Married	16 (11.9%)	97 (14.1%)	113 (13.7%)	0.915#	0.847	0.523-1.373
	Stable union	1 (0.7%)	5 (0.7%)	6 (0.7%)		1.019	0.169-6.137
	Divorced	1 (0.7%)	8 (1.2%)	9 (1.1%)		0.677	0.106-4.321
	Single	117 (86.7%)	580 (84.1%)	697 (84.5%)		1.194	0.754-1.889
Ethnic group	Asian	1 (0.7%)	2 (0.3%)	3 (0.4%)	0.482#	2.164	0.433-10.81
	White	93 (66.9%)	442 (62.7%)	535 (63.4%)		1.444	1.010-2.065
	Pardo	24 (17.3%)	128 (18.2%)	152 (18.0%)		1.026	0.683-1.541
	Black	4 (2.9%)	16 (2.3%)	20 (2.4%)		1.302	0.534-3.175
	Not informed	17 (12.2%)	117 (16.6%)	134 (15.9%)		0.329	0.157-0.687
Number of previous pregnancies	≤2	94 (73.4%)	355 (60.6%)	449 (62.9%)	**0.006***	**1.632**	**1.137-2.343**
	>2	34 (26.6%)	231 (39.4%)	265 (37.1%)		1	Reference
Number of previous deliveries	None	85 (66.4%)	326 (58.3%)	411 (59.8%)	0.110*	1.327	0.951-1.853
	≥1	43 (33.6%)	233 (41.7%)	276 (40.2%)		1	Reference
Number of previous	Yes	18 (14.5%)	164 (29.9%)	182 (27.0%)	**<0.001***	**0.458**	**0.286-0.733**

cesarean deliveries	No	106 (85.5%)	385 (70.1%)	491 (73.0%)		1	Reference
Previous abortions	Yes	26 (20.5%)	133 (24.1%)	159 (23.5%)	0.418*	0.840	0.567-1.244
	No	101 (79.5%)	418 (75.9%)	519 (76.5%)		1	Reference
Prenatal care	<6	73 (66.4%)	204 (39.4%)	277 (44.1%)	**<0.001***	**2.500**	**1.739-3.593**
	≥6	37 (33.6%)	314 (60.6%)	351 (55.9%)		1	Reference
Maternal complication	Present	116 (93.5%)	558 (94.9%)	674 (94.7%)	0.660*	0.818	0.432-1.547
	Absent	8 (6.5%)	30 (5.1%)	38 (5.3%)		1	Reference
Preterm labor without cause	Present	39 (31.5%)	177 (30.1%)	216 (30.3%)	0.830*	1.054	0.747-1.486
	Absent	85 (68.5%)	411 (69.9%)	496 (69.7%)		1	Reference
Membrane rupture	Present	21 (16.9%)	165 (28.1%)	186 (26.1%)	**0.013***	**0.577**	**0.372-0.894**
	Absent	103 (83.1%)	423 (71.9%)	526 (73.9%)		1	Reference
Arterial pressure alteration	Present	25 (20.2%)	152 (25.9%)	177 (24.9%)	0.209*	0.763	0.509-1.144
	Absent	99 (79.8%)	436 (74.1%)	535 (75.1%)		1	Reference
Urinary tract infection	Present	10 (8.1%)	53 (9.0%)	63 (8.8%)	0.862*	0.904	0.500-1.634
	Absent	114 (91.9%)	535 (91.0%)	649 (91.2%)		1	Reference
Gestational diabetes mellitus	Present	7 (5.6%)	45 (7.7%)	52 (7.3%)	0.461*	0.759	0.374-1.542
	Absent	117 (94.4%)	543 (92.3%)	660		1	Reference

				(92.7%)			
Streptococcus sp. infection	Present	8 (6.5%)	42 (7.1%)	50 (7.0%)	0.850*	0.913	0.474-1.760
	Absent	116 (93.5%)	546 (92.9%)	662 (93.0%)		1	Reference
Addiction	Present	11 (8.9%)	38 (6.5%)	49 (6.9%)	0.435*	1.317	0.762-2.276
	Absent	113 (91.1%)	550 (93.5%)	663 (93.1%)		1	Reference
Amniotic fluid alteration	Present	15 (12.1%)	31 (5.3%)	46 (6.5%)	**0.008***	**1.992**	**1.271-3.123**
	Absent	109 (87.9%)	557 (94.7%)	666 (93.5%)		1	Reference
Vaginal delivery	Present	5 (4.0%)	34 (5.8%)	39 (5.5%)	0.521*	0.725	0.315-1.670
	Absent	119 (96.0%)	554 (94.2%)	673 (94.5%)		1	Reference
Fetal centralization	Present	12 (9.7%)	23 (3.9%)	35 (4.9%)	**0.011***	**2.072**	**1.271-3.379**
	Absent	112 (90.3%)	565 (96.1%)	677 (95.1%)		1	Reference
Early placental abruption	Present	12 (9.7%)	21 (3.6%)	33 (4.6%)	**0.006***	**2.205**	**1.361-3.570**
	Absent	112 (90.3%)	567 (96.4%)	679 (95.4%)		1	Reference
Physiometry	Present	5 (4.0%)	26 (4.4%)	31(4.4%)	1.000*	0.923	0.407-2.094
	Absent	119 (96.0%)	562 (95.5%)	681 (95.6%)		1	Reference
Thyroidopathy	Present	4 (3.2%)	24 (4.1%)	28 (3.9%)	0.803[#]	0.814	0.324-2.017
	Absent	120 (96.8%)	564 (95.9%)	684 (96.1%)		1	Reference

Fetal growth restriction	Present	4 (3.2%)	21 (3.6%)	25 (3.5%)	1.000[#]	0.916	0.368-2.282
	Absent	120 (96.8%)	567 (96.4%)	687 (96.5%)		1	Reference
Amniorrhexis	Present	0 (0.0%)	15 (2.6%)	15 (2.1%)	0.087[#]	NA	NA
	Absent	124 (100%)	573 (97.4%)	697 (97.9%)		NA	NA
Sepsis	Present	1 (0.8%)	11 (1.9%)	12 (1.7%)	0.702[#]	0.474	0.072-3.118
	Absent	123 (99.2%)	577 (98.1%)	700 (98.3%)		1	Reference
Other maternal complications	Yes	31(25.0%)	122 (20.7%)	153 (21.5%)	0.336*	1.218	0.845-1.754
	No	93 (75.0%)	466 (79.3%)	559 (78.5%)		1	Reference

RR, relative risk; 95%CI, 95% confidence interval (lower and upper limits); O_2, oxygen; NA, not applicable. *, statistical analysis carried out using the chi-square test; [#], statistical analysis carried out using the Fisher's Exact test. Statistically significant data were presented in bold, 0.05 alpha.

TABLE 3. Associated newborns' characteristics as risk factors for death of patients admitted to the NeonatalIntensive Care Unit of a university hospital in the period 2015-2019.

Group	Category	Death	Hospital discharge	Total	P-value	RR	95%CI
Sex	Female	58 (41.4%)	290 (41.1%)	348 (41.1%)	1.000*	1.014	0.746-1.379
	Male	82 (58.6%)	416 (58.9%)	498 (58.9%)		1	Reference
Gestational age	Suitable	106 (79.7%)	544 (82.7%)	650 (82.2%)	0.116*	1	Reference
	Small	22 (16.5%)	72 (10.9%)	94 (11.9%)		1.435	0.957-2.152
	Big	5 (3.8%)	42 (6.4%)	47 (5.9%)		0.652	0.280-1.521
Weight	Low	22 (15.7%)	201 (28.5%)	223 (26.4%)	**<0.001***	**0.849**	**0.520-1.387**
	Very low	30 (21.4%)	152 (21.5%)	182 (21.5%)		**1.419**	**0.918-2.194**
	Extremely low	47 (33.6%)	41 (5.8%)	88 (10.4%)		**4.598**	**3.248-6.510**
	Normal	41 (29.3%)	312 (44.2%)	353 (41.7%)		1	Reference
Transfer from another unit	Yes	19 (13.6%)	162 (22.9%)	181 (21.4%)	**0.017***	**0.577**	**0.366-0.909**
	No	121 (86.4%)	544 (77.1%)	665 (78.6%)		1	Reference
Type of delivery	Cesarean delivery	83 (63.8%)	438 (65.2%)	521 (65.0%)	0.834*	0.914	0.662-1.261
	Normal delivery	49 (36.5%)	232 (34.5%)	279 (34.8%)		1	Reference
Birth time	Preterm	113 (81.3%)	491 (70.2%)	604 (72.1%)	**0.009***	**1.684**	**1.130-2.529**
	Full-term	26	208 (29.8%)	234		1	Reference

		(18.7%)		(27.9%)			
1-minute Apgar score	Severe asphyxia	32 (23.9%)	55 (8.3%)	87 (11.0%)	**<0.001***	**3.512**	**2.413-5.110**
	Moderate asphyxia	49 (36.6%)	152 (23.0%)	201 (25.3%)		**2.327**	**1.636-3.311**
	Good vitality	53 (39.6%)	453 (68.6%)	506 (63.7%)		1	Reference
5-minute Apgar score	Severe asphyxia	5 (3.7%)	4 (0.6%)	9 (1.1%)	**<0.001#**	**3.699**	**2.010-6.804**
	Moderate asphyxia	21 (15.7%)	47 (7.1%)	68 (8.5%)		2.056	1.384-3.054
	Good vitality	108 (80.6%)	611 (92.3%)	719 (90.3%)		1	Reference

RR, relative risk; 95%IC, 95% confidence interval (lower and upper limits); *, statistical analysis carried out using the chi-square test; #, statistical analysis carried out using the Fisher's Exact test. Statistically significant data were presented in bold, 0.05 alpha

TABLE 4. Diagnosis and management of newborns as risk factors for death of patients admitted to the Neonatal Intensive Care Unit of a university hospital in the period 2015-2019.

Group	**Category**	**Death**	**Hospital discharge**	**Total**	**P-value**	**RR**	**95%CI**
Early respiratory distress	Present	90 (64.3%)	480 (68.0%)	570 (67.4%)	0.430*	0.872	0.637-1.194
	Absent	50 (35.7%)	226 (32.0%)	276 (32.6%)		1	Reference
Sepsis	Present	49 (35.0%)	244 (34.6%)	293 (34.6%)	0.923*	1.016	0.740-1.395
	Absent	91 (35.0%)	462 (65.4%)	553 (65.4%)		1	Reference
Neonatal jaundice	Present	28 (20.0%)	240 (34.0%)	268 (31.7%)	**0.001***	**0.539**	**0.366-0.795**
	Absent	112 (80.0%)	466 (66.0%)	578 (68.3%)		1	Reference
Apnea of prematurity	Present	6 (4.3%)	125 (17.7%)	131 (15.5%)	**<0.001***	**0.244**	**0.110-0.542**
	Absent	134 (95.7%)	581 (82.3%)	715 (84.5%)		1	Reference
Cardiopathy	Present	26 (18.6%)	103 (14.6%)	129 (15.2%)	0.247*	1.268	0.865-1.858
	Absent	114 (81.4%)	603 (85.4%)	717 (84.8%)		1	Reference
Anemia	Present	7 (5.0%)	101 (14.3%)	108 (12.8%)	**0.003***	**0.360**	**0.173-0.748**
	Absent	133 (95.0%)	605 (85.7%)	738 (87.2%)		1	Reference
Patent foramen ovale	Present	5 (3.6%)	94 (13.3%)	99 (11.7%)	**0.001***	**0.280**	**0.117-0.665**
	Absent	135 (96.4%)	612 (86.7%)	747 (88.3%)		1	Reference
Glycemic alteration	Present	17	62 (8.8%)	79 (9.3%)	0.264*	1.342	0.855-

		(12.1%)					2.107
	Absent	123 (87.9%)	644 (91.2%)	767 (90.7%)		1	Reference
Twin birth	Present	5 (3.6%)	72 (10.2%)	77 (9.1%)	**0.015***	**0.370**	**0.156-0.875**
	Absent	135 (96.4%)	634 (89.8%)	769 (90.9%)		1	Reference
Septic shock	Present	30 (21.4%)	44 (6.2%)	74 (8.7%)	**<0.001***	**2.845**	**2.054-3.941**
	Absent	110 (78.6%)	662 (93.8 %)	772 (91.3%)		1	Reference
Convulsive crisis	Present	10 (7.1%)	50 (7.1%)	60 (7.1%)	1.000*	1.008	0.560-1.813
	Absent	130 (92.9%)	656 (92.9%)	786 (92.9%)		1	Reference
Hemorrhage/intracranial hypertension	Present	6 (4.3%)	50 (7.1%)	56 (6.6%)	0.267*	0.632	0.292-1.366
	Absent	134 (95.7%)	656 (92.9%)	790 (93.4%)		1	Reference
Anoxia/hypoxia	Present	10 (7.1%)	45 (6.4%)	55 (6.5%)	0.851*	1.106	0.618-1.980
	Absent	130 (92.9%)	661 (93.6%)	791 (93.5%)		1	Reference
Meconium aspiration syndrome	Present	5 (3.6%)	40 (5.7%)	45 (5.3%)	0.411*	0.659	0.285-1.528
	Absent	135 (96.4%)	666 (94.3%)	801 (94.7%)		1	Reference
Hyponatremia	Present	6 (4.3%)	36 (5.1%)	42 (5.0%)	0.833*	0.857	0.402-1.827
	Absent	134 (95.7%)	670 (94.9%)	804 (95.0%)		1	Reference
Reversed cardiorespiratory arrest	Present	14 (10.0%)	16 (2.3%)	30 (3.5%)	**<0.001***	**3.022**	**1.996-4.576**

	Absent	126 (90.0%)	690 (97.7%)	816 (96.5%)		1	Reference
Other diagnoses	Yes	88 (62.9%)	379 (53.7%)	467 (55.2%)	**0.051***	**1.373**	**1.002-1.882**
	No	52 (37.1%)	327 (46.3%)	379 (44.8%)		1	Reference
Need for oxygen	Yes	137 (97.9%)	637 (90.2%)	774 (91.5%)	**0.001#**	**4.248**	**1.389-12.99**
	No	3 (2.1%)	69 (9.8%)	72 (8.5%)		1	Reference
O_2 Mouthpiece	Yes	8 (5.7%)	305 (43.2%)	313 (37.0%)	**<0.001***	**0.103**	**0.051-0.208**
	No	132 (94.3%)	401 (56.8%)	533 (63.0%)		1	Reference
O_2 Face tent	Yes	0 (0.0%)	3 (0.4%)	3 (0.4%)	1.000#	NA	NA
	No	140 (100%)	703 (99.6%)	843 (99.6%)		NA	NA
O_2 Nasal Catheter	Yes	4 (2.9%)	59 (8.4%)	63 (7.4%)	**0.021#**	**0.366**	**0.140-0.955**
	No	136 (97.1%)	647 (91.6%)	783 (92.6%)		1	Reference
O_2 Halo mask	Yes	15 (10.7%)	543 (76.9%)	558 (66.0%)	**<0.001***	**0.062**	**0.037-0.104**
	No	125 (89.3%)	163 (23.1%)	288 (34.0%)		1	Reference
Ventilatory support	Yes	137 (97.9%)	634 (89.8%)	771 (91.1%)	**0.001#**	**4.442**	**1.451-13.60**
	No	3 (2.1%)	72 (10.2%)	75 (8.9%)		1	Reference
Invasive mechanical ventilation	Yes	131 (93.6%)	295 (41.8%)	426 (50.4%)	**<0.001***	**14.35**	**7.404-27.81**
	No	9 (6.4%)	411 (58.2%)	420 (49.6%)		1	Reference
Non-invasive	Yes	24	407	431	**<0.001***	**0.199**	**0.131-**

mechanical ventilation		(17.1%)	(57.6%)	(50.9%)			**0.303**
	No	116 (82.9%)	299 (42.4%)	415 (49.1%)		1	Reference
Bronchopulmonary dysplasia	Yes	7 (5.0%)	84 (11.9%)	91 (10.8%)	**0.016***	**0.437**	**0.211-0.905**
	No	133 (95.0%)	622 (88.1%)	755 (89.2%)		1	Reference
Retinopathy	Yes	1 (0.7%)	12 (1.7%)	13 (1.5%)	0.706#	0.461	0.070-3.049
	No	139 (99.3%)	694 (98.3%)	833 (98.5%)		1	Reference

R, relative risk; 95%CI, 95% confidence interval (lower and upper limits); O2, oxygen; NA, not applicable. *, statistical analysis carried out using the chi-square test; #, statistical analysis carried out using the Fisher's Exact test.Statistically significant data were presented in bold, 0.05 alpha.

5. CAPÍTULO 3 – Artigo III

Title: Infant mortality due to intrauterine hypoxia, aspiration syndrome and neonatal respiratory distress in children under one year old in Brazil within a 20-year period

Running title: Overview of Neonatal Diseases in Brazil

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Declarations

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Authors' contributions: TAC and IAR performed the data collection. FALM performed the statistical analysis. The authors have written and approved the manuscript and agreed with its submission.

Ethics approval: The study was approved by the Research Ethics Committee [C.A.A.E #29719020.6.0000.5514] for being in accordance with the Helsinki Statement on Health and respecting the Health National Council Resolution (CNS) nº 466, of 12th December 2012.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

ABSTRACT

Introduction: Neonatal intrauterine hypoxia (NIH), meconium aspiration syndrome (MAS), and neonatal respiratory distress (NRD) are diseases that present high incidence in the neonatal period and that might affect mortality rates and, thus, impact the Human Development Index (HDI). This study aimed to analyze the number of deaths due to these diseases in Brazil in children under one year old and correlate this data with the country's HDI.

Methods: This is an observational, retrospective study comprising the period between 1998 and 2018, considering the year of death per occurrence in the Federative Unit recorded with CID-10. The data was adjusted by the number of live birth children. Sex, ethnic group and HDI (general index, GNI per capita, education and life expectancy) were evaluated. The Spearman correlation was carried out between death frequency and HDI.

Results: A reduction was observed in the number of deaths due to the three diseases in the period investigated, mainly for NRD. The numbers of deaths found were 17,209, 25,015, and 89,785 due to NIH, MAS, and NRD, respectively. The highest frequency of deaths occurred in themale group (NIH, N=9,709; MAS, N=13,414; NRD, N=51,339), in the brown ethnic group for NIH (N=6,819), and in the white ethnic group for MAS (N=9,943) and NRD (N=34,605). The significant and negative correlation between death and HDI was moderate when analyzing the correlation between HDI (general, GNI per capita, education, and life expectancy) and NIH (CC=-0.68, CC=-0.66, CC=-0.62, and CC=-0.68); moderate or low between HDI (general, GNI per capita, education and life expectancy) and NRD (CC=-0.69, CC=-0.67, CC=-0.69, and CC=-0.49); and low between general HDI and death due to MAS (CC=-0.37).

Conclusions: In Brazil, a reduction in the mortality rate of the three diseases evaluated was observed with the increase in HDI over 20 years.

Keywords: *Ethnicity. Infant mortality. Neonatal Diseases. Sex*

INTRODUCTION

Newborns are susceptible to the development of diseases caused by the birth condition, immaturity of organs and systems of preterm infants (PTI), and the treatment cytotoxic effect [1]. The diseases affecting newborns (NB) include neonatal intrauterine hypoxia (NIH), meconium aspiration syndrome (MAS), and the neonatal respiratory distress (NRD), which are the most incident in the neonatal intensive care unit (NICU) [2].

Neonatal hypoxia might be primary or secondary to an intrapartum pre-existing medical condition and occurs due to the reduction or interruption of oxygen supply to the NB. It can be an acute or chronic event of intrauterine or extrauterine occurrence [3]. During labor, when there is a sudden reduction in the mother-fetus gas exchanges, due to a long labor, resistance to the birth canal, or pelvic delivery, a reduction in the oxygen supply to the infant occurs, resulting in intrauterine hypoxia (NIH), with consequent fetal distress and intrapartum asphyxia. This condition might be modulated by therapeutic hypothermia, which provides neuroprotection against brain injury [4]. Another factor contributing to the NIH development is the presence of other diseases such as MAS and fetal growth restriction. Fetal growth restriction affects ~5-10% NB and is the second most common cause of perinatal death [5,6].

Oxygen deprivation due to the reduction in the provision of repeated oxygen therapy duringthe extrauterine neonatal period might threaten the NB survival and cause life quality loss due to brain injuries [7]. Another condition triggered by the neonatal hypoxia is the perinatal brain injury. For example, intra- ventricular hemorrhage, with long term effects and damage to the neurological development due to the oxygen restriction that provokes neuronal excitotoxicity, cellapoptosis and microglial activation, resulting in hypoxic-ischemic encephalopathy [8-10].

MAS is associated to oxygen deprivation during delivery and is the main cause of term and post term infants' morbidity and mortality, with repercussions such as brain lesion and respiratory changes [11-13]. This disease occurs after meconium aspiration during the first respiratory movements, and this neonatal exposure might result in chemical pneumonia with consequent lung damage such as pulmonary hypertension, chorionic plate and umbilical vessel inflammation,and neurological system injuries that contribute to the neonatal morbidity [14,15]. The MAS risk factors include c-section delivery, asphyxia and fetal distress, intrauterine growth restriction, incomplete or abnormal cardiotocography, mother's intrapartum temperature, Apgar

score below seven in the first minute, and the need for endotracheal intubation at birth [16-18]. To minimize its deleterious effects, the use of antibiotics, pulmonary surfactant, inhaling nitric acid, therapeutic hypothermia, and support therapies such as oxygen therapy, mechanical ventilation, extracorporeal membrane oxygenation, and high frequency oscillatory ventilation are included in the treatment and rescue of MAS patients [17-19]. Additionally, a thorough prenatal care must be provided, enabling the identification of risk factors and indicating the most efficient postnatal procedures for this disease management [18,20].

MAS, NIH and other neonatal diseases such as congenital pulmonary malformation provoke NRD, which presents a heterogeneity of risk factors that include low weight at birth, cesarean delivery and certain characteristics of the male fetus [21,22]. NRD is most frequent in preterm infants, presenting high levels of mortality and morbidity and its main clinical manifestations are the neonatal tachypnea and alteration of vital signs. The NRD treatment includes prenatal corticosteroids, postnatal surfactant, oxygen therapy, and invasive mechanic ventilation, requiring long term hospital support [23,24].

The incidence of neonatal diseases causes a negative impact on the population's life expectancy, since these diseases might generate comorbidities and mortality, which also impact the human development index (HDI) [25]. Around 2.8 million pregnant women and NB die every year worldwide, many times, due to preventable causes [25]. The mortality rates in these groups vary in different regions of the world and are mainly related to the access to health services and better socio-economic conditions. For instance, in Europe, the estimate is one in 196 children dying before reaching the age of five, while in the Subsaarian Africa, this figure is 15 times higher than in Europe, that is, one in 13 children dies before reaching that age [26].

The situations experienced from the prenatal period to the start of labor and the postnatal conception require attention and specialized medical care to minimize the deleterious effects on the NB. Distinct neonatal diseases, which present similarities regarding their seriousness, could be prevented with the efficient action of public health teams during the prenatal appointments, which would minimize aftereffects to the NB and reduce hospital costs. Taking that into consideration, this study aims to analyze retrospectively the epidemiological scenery of NIH, MAS and NRD in Brazil in a 20-year period according to the demographic markers described by the Brazilian Health Ministry and correlate the country's HDI of that

period with the prevalence of deaths due to the three diseases in each Federation Unit.

METHODS

An observational and retrospective study on the prevalence of deaths of infants under one year old due to NIH, MAS and NRD in the period from 1998 to 2018 was carried out. The data was obtained from the Information Technology Department of the Brazilian Unified Health System (SUS) – Data-SUS [http://www2.datasus.gov.br/DATASUS]. In addition, the HDI of Brazilian states and the Federal District in 2000, 2010, 2016 and 2017 was analyzed. These years were selected due to the availability of data from the Human Development Atlas in Brazil in 2021, developed in collaboration with the Applied Research Institute, the United Nations Development Program, and the João Pinheiro Foundation [http://www.atlasbrasil.org.br/ranking].

To analyze the three diseases, the year of death per occurrence in the Federative Unit recorded with CID-10 (namely, NIH, MAS and NRD) in the under one-year-old group was considered. The number of deaths was described per sex (female, male, and ignored) and ethnic group (white, black, brown, yellow, indigenous, and ignored). The data was adjusted by the number of live birth infants per occurrence in the Federative Units.

To verify the HDI in the Brazilian federative units in 2000, 2010, 2016, and 2017, the following factors were evaluated: HDI general (HDI), HDI GNI per capita (HDI-GNI), HDI education (HDI-E), and HDI life expectancy (HDI-LE).

The HDI values were correlated to the number of cases of the three diseases per live birth infants using the Spearman correlation. The statistical analysis was carried out using the software Statistical Package for the Social Sciences (IBM SPSS Statistics for Macintosh, Version 27.0). The following cut-off points were considered in the Spearman Correlation: (i) ±0.90-1.0 very high correlation index; (ii) ±0.70-0.90 high correlation index; (iii) ±0.50-0.70 moderate correlation index; (iv) ±0.30-0.50 low correlation index; and (v) 0.00-0.30 insignificant correlation index.

The study was approved by the Research Ethics Committee [C.A.A.E #29719020.6.0000.5514] for being in accordance with the Helsinki Statement on Health and

respecting the Health National Council Resolution (CNS) nº 466, of 12th December 2012, obtaining data made available by the SUS and Atlas Brazil, without disclosing access informationor identification of the individuals related to this research.

RESULTS

Table 1 presents the prevalence of deaths of infants under one year old due to NIH, MAS, and NRD according to sex and ethnic group in the period of 20 years in Brazil. The data is presented as gross value and the value adjusted by the number of live birth infants. Curiously, the three diseases showed higher prevalence of deaths in male infants. As for ethnic groups, the data varied for the three diseases. Regarding NIH, the highest number of deaths was observed in the brown group, followed by the groups described as ignored, white, black, indigenous, and yellow. MAS and NRD showed the highest number of cases in the white group, with different values in the other ethnic groups.

TABLE 1. Deaths of children under one year old due to neonatal intrauterine hypoxia (NIH), Meconium aspiration syndrome (MAS), and neonatal respiratory distress (NRD) in a 20-year period in Brazil.

NIH	**Group**	**N (%)**	**% related to live birth (10^{-3})**
Total		17,209 (100)	
Sex	Female	7,305 (42.45)	0.12
	Male	9,709 (56.42)	0.15
	Ignored	195 (1.13)	<0.01
Ethnicity	White	5,050 (29.35)	0.08
	Black	348 (2.02)	<0.01
	Brown	6,819 (39.62)	0.11
	Yellow	60 (0.35)	<0.01
	Indigenous	124 (0.72)	<0.01
	Ignored	4,808 (27.94)	0.08
MAS	**Group**	**N (%)**	**% related to live birth (10^{-3})**
Total		25,015 (100)	
Sex	Female	11,522 (46.06)	0.18
	Male	13,414 (53.62)	0.21

	Ignored	79 (0.32)	<0.01
Ethnicity	White	9,943 (39.75)	0.16
	Black	582 (2.33)	<0.01
	Brown	9,322 (37.27)	0.05
	Yellow	84 (0.34)	<0.01
	Indigenous	322 (1.29)	<0.01
	Ignored	4,762 (19.04)	0.08
NRD	**Group**	**N (%)**	**% related to live birth (10^{-3})**
Total		89,785 (100)	
Sex	Female	38,066 (42.40)	0.61
	Male	51,339 (57.18)	0.82
	Ignored	380 (0.42)	<0.01
Ethnicity	White	34,605 (38.54)	0.55
	Black	1,795 (2.00)	0.03
	Brown	31,260 (34.82)	0.50
	Yellow	360 (0.40)	<0.01
	Indigenous	371 (0.41)	<0.01
	Ignored	21,394 (23.82)	0.34

The live birth related values were calculated according to the total number of live birthchildren per category, considering sex and ethnicity.

In the Spearman correlation between prevalence of death due to NIH, MAS, and NRD per live birth infants and HDI, a reduction in the number of cases was observed when the HDI increased. To sum up, a correlation index with moderate value was observed between HDI, HDI-GNI, HDI-E and HDI-LE with NIH (CC=-0.68, CC=-0.66, CC=-0.62, and CC=-0.68, respectively) and NRD; however, the latter (NRD), showed a low correlation index with HDI-LE (CC=-0.69, CC=-0.67, CC=-0.69, and CC=-0.49, respectively) (**Table 2**; **Figure 5**). Finally, when MAS was investigated, the Spearman correlation resulted in a low value between HDI and the prevalence of death due to this disease (CC=-0.37).

TABLE 2. Spearman correlation between the prevalence of deaths of children under one year old due to neonatal intrauterine hypoxia, meconium aspiration syndrome, and neonatal respiratory distress per live birth children in Brazil and the human development index (HDI) in the federative units in 2000, 2010, 2016, and 2017.

Marker	Data	HDI	HDI-GNI per capita	HDI Education	HDI Life Expectancy
Neonatal intrauterine hypoxia (%)	CC	-0.682	-0.653	-0.617	-0.680
	P-value	<0.001	<0.001	<0.001	<0.001
Meconium aspiration syndrome (%)	CC	-0.495	-0.526	-0.436	-0.373
	P-value	<0.001	<0.001	<0.001	<0.001
Neonatal respiratory distress (%)	CC	-0.692	-0.663	-0.687	-0.495
	P-value	<0.001	<0.001	<0.001	<0.001

CC, correlation coefficient. The following cut-off points were considered in the correlations: (i) ±0.90-1.0 very high correlation index; (ii) ±0.70-0.90 high correlation index; (iii) ±0.50-0.70 moderate correlation index; (iv) ±0.30-0.50 low correlation index; and (v) 0.00-0.30 insignificant correlation index. A 0.05 was adopted in all analyses carried out.

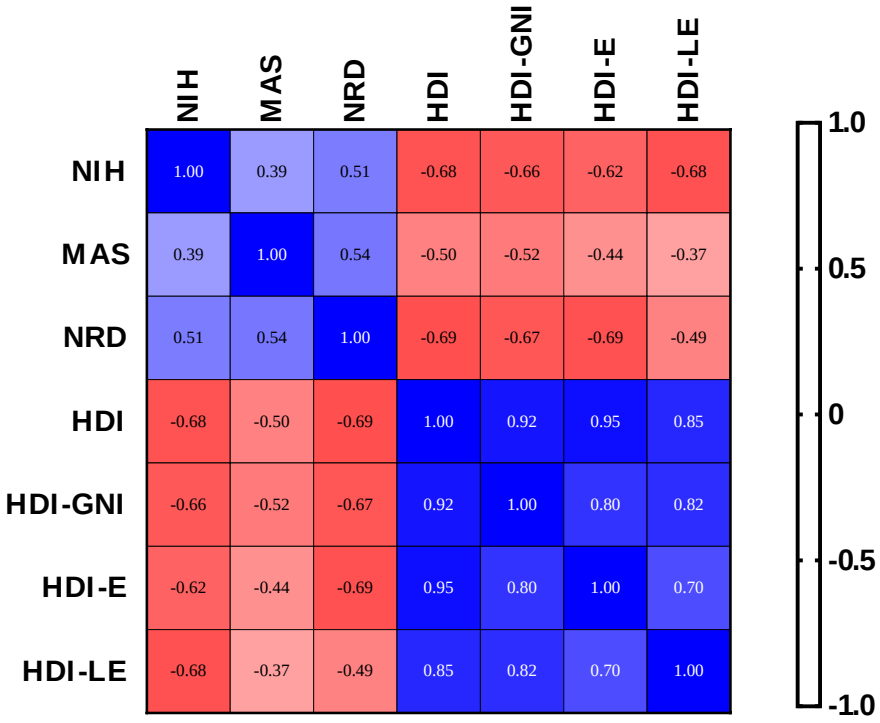

FIGURE 1. Matrix of the Spearman correlation between the human development index [HDI general (HDI), HDI GNI per capita (HDI-GNI), HDI education (HDI-E), HDI life expectancy (HDI-

LE)]. With prevalence of deaths due to neonatal intrauterine hypoxia (NIH), meconium aspiration syndrome (MAS), and neonatal respiratory distress (NRD), per live birth children in Brazil in the period 1998-2018. The following cut-off points were considered in the correlations: (i) ±0.90-1.0 very high correlation index; (ii) ±0.70-0.90 high correlation index; (iii) ±0.50-0.70 moderate correlation index; (iv) ±0.30-0.50 low correlation index; and (v) 0.00-0.30 insignificant correlation index. All p values were significant and below 0.01. A 0.05 was used in all analyses carried out.

Throughout the period under evaluation, a great reduction in the number of death cases due to NRD occurred. The decrease in the number of deaths due to MAS was also evident in the first year, keeping a descending pattern in the following years. NIH was the only disease to present increase in the number of deaths in the first year of analysis, with a reducing trend over time and an epidemiological curve similar to that of the MAS deaths (**Figure 2**).

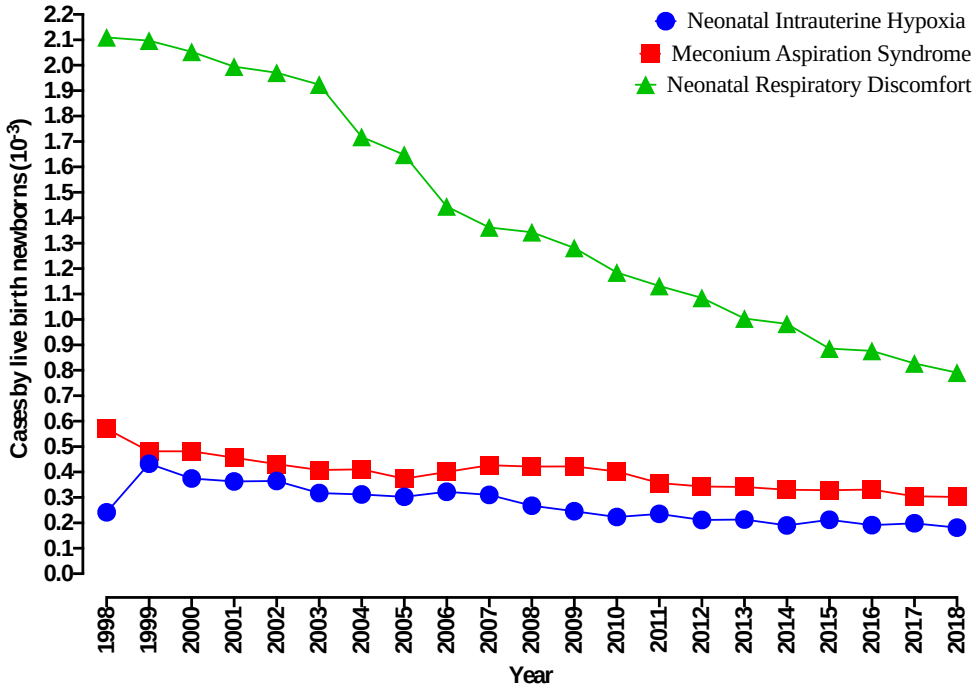

FIGURE 2. Evolution of the prevalence of deaths of children. To neonatal intrauterine hypoxia, meconium aspiration syndrome, and neonatal respiratory distress, per live birth children in Brazil in the period 1998-2018.

When analyzing the occurrence of number of deaths due to NIH in relation to sex, both male and female infants showed an increase in the number of deaths in the first year, but kept a decreasing trend after that period, with prevalence of deaths in male infants. When ethnic groups and NIH were evaluated, the white and brown groups presented the highest numbers of death

cases; however, the white group showed a decrease in the number of cases over time, this trend was not observed in the brown group though. The remaining ethnic groups presented the same linear trend in the number of death cases throughout the study period (**Figure 3)**.

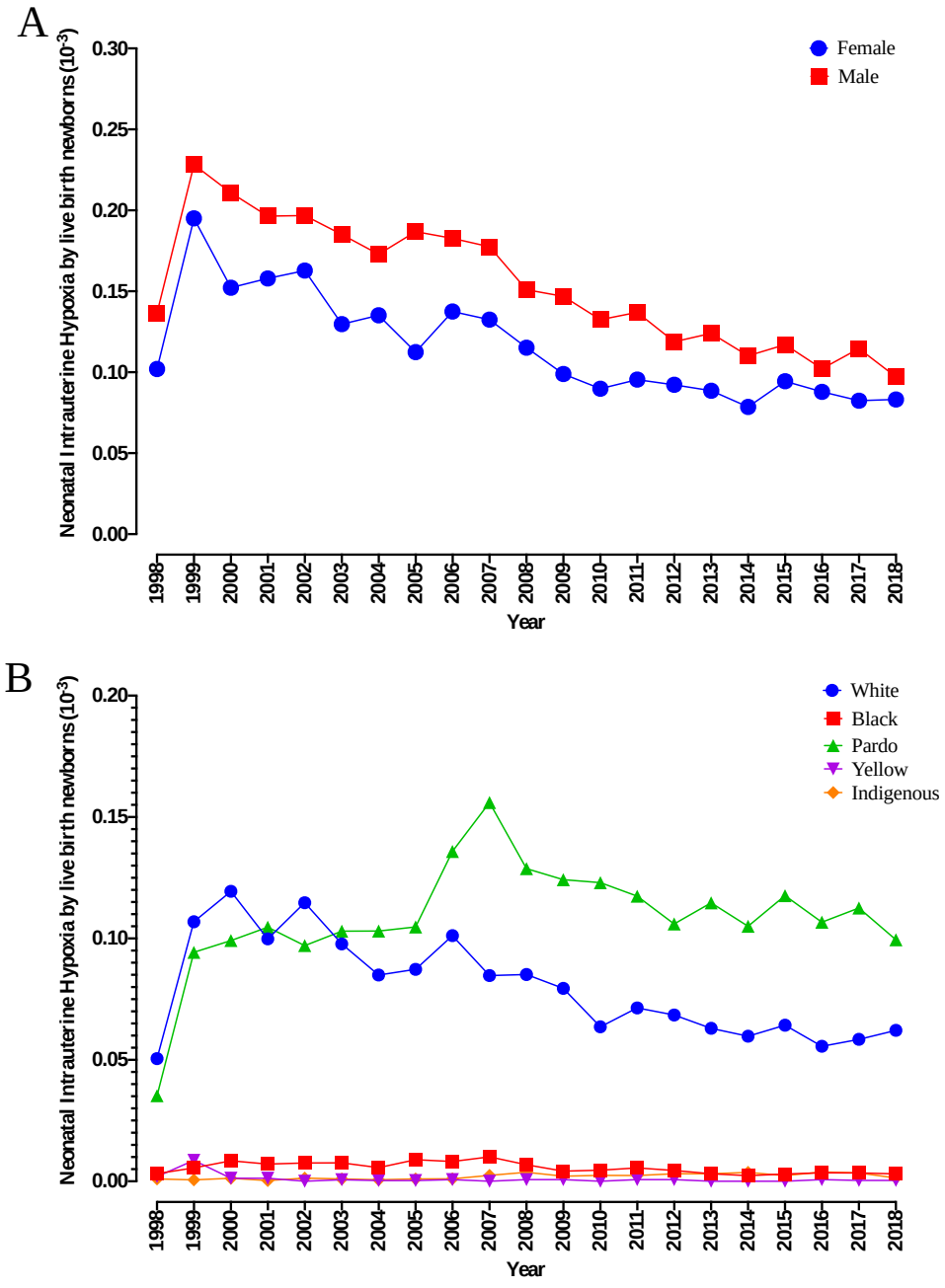

FIGURE 3. Evolution of the prevalence of deaths of children. To neonatal intrauterine hypoxia (NIH) per live birth children in Brazil in the period 1998-2018 related to sex. **B.** Evolution of the prevalence of deaths of children under one year old due to NIH per live birth children in Brazil in the period 1998-2018 related to ethnicity.

The number of death cases due to MAS related to sex presented a decreasing trend in the period analyzed, with an increasing trend only between 2006 and 2011, reducing the number of deaths after this period for both sexes. However, the highest prevalence of male infant deaths was kept throughout the whole period. When evaluating death due to MAS related to ethnic groups in the 20 years, an inversion was seen in the number of cases between the white and brown groups, with an evident increase in the prevalence of cases in the brown group over time and the simultaneous reduction in the number of cases in the white group. The other ethnic groups kept the same prevalence of deaths due to MAS throughout the period (**Figure 4**).

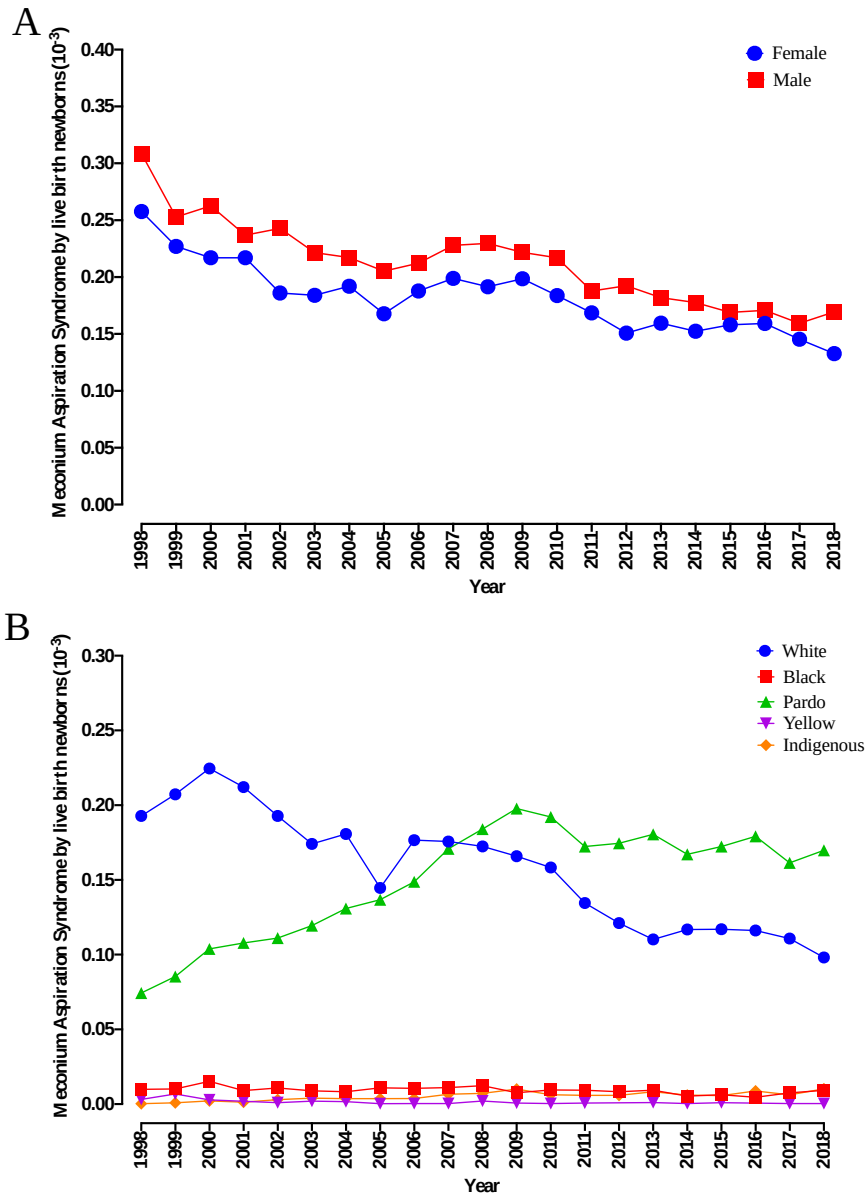

FIGURE 4.A. Evolution of the prevalence of deaths of children. To meconium aspiration syndrome (MAS) per live birth children in Brazil in the period 1998-2018 related to sex. **B.** Evolution of the prevalence of deaths of children under one year old due to MAS per live birth children in Brazil in the period 1998-2018 related to ethnicity.

The number of deaths due to NRD showed a similar profile to that of the other diseases (NIH and MAS) in relation to sex, with reduction in the number of deaths over time and prevalence of deaths of male infants. Following the same trend as MAS, the white and brown ethnic groups inverted the prevalence of number of deaths from 2005 onwards, showing an increase in the number of deaths in the brown group with simultaneous reduction in the number of deaths in the white group, unlike the results of the first few years. The other ethnic groups evaluated kept the same pattern as those in NIH and MAS (**Figure 5**). Also, the complete data is shown as **Supplementary Table**.

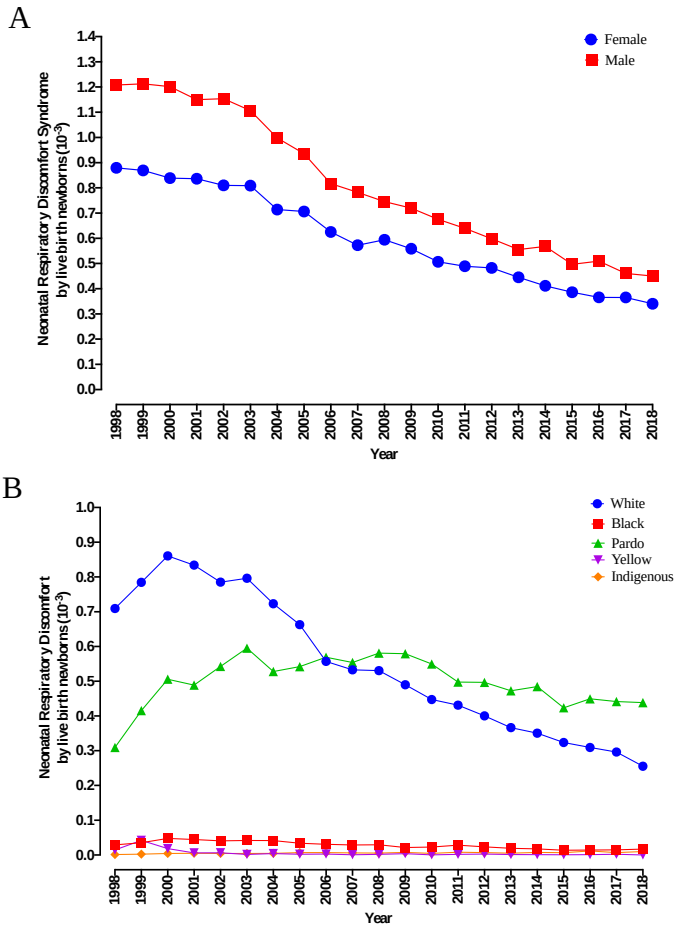

FIGURE 5.A. Evolution of the prevalence of deaths of children under one year old due to neonatal respiratory distress (NRD) per live birth children in Brazil in the period 1998-2018 related to sex. **B.** Evolution of theprevalence of deaths of children under one year old due to NRD per live birth children in Brazil in the period 1998- 2018 related to ethnicity.

DISCUSSION

In the study period, there was a reduction in the death rate of infants under one year old due to NIH, MAS, and NRD in Brazil. At the same time, throughout the period, the highest prevalence of death occurred in male infants in the white and brown ethnic groups. The infant mortality rate (IMR) results from the deaths up to one year of age divided by the number of live birth infants and multiplied by 1,000. This impacts neonatal mortality (from 0 to 27 days old) andpostnatal (28 days to one year old) and represents the effects of the public health conditions in thecountry, differentiating the HDI between states and the Federal District [27].

A similar study analyzed neonatal deaths in the municipality of Londrina, state of Paraná (PR/Brazil), in 1994, 1999, and 2002. That study presented similar findings to the ones in this study by demonstrating a mortality rate reduction over time. The justification presented for the mortality reduction included, mainly, improvements in the health basic actions and the presence of specialized neonatal care. However, the authors of that study concluded that most of the neonatal deaths could have been prevented, since they resulted from maternal causes, pregnancy

complications and/or flaws in the health system [28]. According to Rêgo et al. (2018), preventable perinatal deaths due to the SUS intervention in Recife, state of Pernambuco (PE/Brazil), are related to possible flaws in the perinatal assistance provided to the mother during pregnancy and at labor, justifying the high percentage of asphyxia and/or hypoxia (82.5%), although historically, a reduction in the perinatal mortality coefficient was observed between 2010 and 2014 in that region [29]. Conversely, another study developed in Recife (PE/Brazil) in 1998, reported the problematic discrepancy between the basic cause of deaths and the death statement provided by neonatologists, which might indicate the need for improvement of the epidemiological data collection and for devising a better protocol to evaluate the real cause of death, which would better inform and guide health public policies [30].

In southeastern Brazil, in the municipality of São Paulo (SP/Brazil), from 2001 to 2003,

thepredominance of mortality associated to perinatal asphyxia was observed, while 18% deaths due to MAS occurred, with a higher mortality rate in the interior of that state. Perinatal asphyxia contributes to the preventable mortality rate, and therefore, requires a specific approach to the mothers' pre and postpartum assistance, minimizing morbidity and mortality related to preventable events [31]. In the same municipality (SP), a transversal retrospective study in a hospital center, indicated that the presence of meconium in the amniotic liquid during delivery was observed more frequently in cesarian sections, associated to primiparous women, and gestational age over 41 weeks, the use of oxytocin and apgar below seven in the 5^{th} min. In that center, 50% of the neonatal deaths were associated to a MAS diagnosis, confirming the need for assuring fetal assistance during the delivery, with the need for the creation of protocols to minimize neonatal mortality [32].

The several factors that might trigger MAS can explain the results obtained in this study, where a decrease in the number of cases of the diseases investigated was observed with increased HDI, with a more noticeable correlation with NRD followed by NIH, and low correlation with MAS due to its multiple causes. A study that evaluated the period between 1997 and 2005 reportedthat the IMR followed a decreasing trend, with epidemiological relevance, and that it is mainly associated to neonatal mortality. However, curiously, infant mortality is also related to several risk factors and might be associated to markers such as mother's schooling and age, social inequality, low weight at birth, prematurity, presence of multiple pregnancy, prenatal assistance, and intrapartum care. Among these markers, many can be managed aiming to optimize the pregnant woman and NB care, with optimization of the postpartum treatment and, thus, death rate reduction. Therefore, health policies and actions present a direct impact on the neonatal mortality, focusing on the care regionalization/hierarchysation, suitable transport, immediate accommodation, holistic care, qualified assistance, and incentivizing the best practices in the neonatal period [33].

In addition to the general factors observed to influence IMR, biological and genetic interferences might occur that result in neonatal and infant diseases in certain groups, as observed in this study, with higher rate of cases in male infants, and in the white and brown ethnic groups. The male sex, for presenting a slower pulmonary development process when compared to the female sex, and due to the specific hormones of this gender, might provoke over mortality in neonatal diseases [34]. The white and brown ethnic groups presented higher number

of cases when compared to the other ethnic groups evaluated, probably due to a biological predisposition and also the ethnic contribution to the general population of these individuals in Brazil. However,the inversion in the number of cases over time between these two ethnic groups (white and brown) might have occurred due to improvements in the care provided to the white group along with socioeconomic factors such as schooling, income, and longevity. This data reveals social inequalities still existing between the different ethnic groups and shows that ethnicity is a relevant social determiner disclosing the disparity of the health management in Brazil [35].

Our study shows a reduction in neonatal and infant mortality in Brazil resulting from the three (NIH, MAS, and NRD) main causes of newborns' death throughout the period evaluated, which were related to higher number of cases in male NB and in the white and brown ethnic groups. However, even with the neonatal and infant mortality reduction, the evaluation and complementarity of the public health care is still necessary, since most of the deaths, mainly due toNIH, MAS, and NRD are still considered preventable. At the same time, the ethnic/social issue must also be addressed, so that real equality is achieved in the health care.

Finally, our study presents some limitations, which include: the differences found in relationto the death statement by the neonatologists and the reliability of the official statistical data, whichmight generate biased data related to the numbers made available, and the access to data only recorded per year, rather than including the patients' gross data, so that more elaborated statistical analysis could be carried out.

CONCLUSION

The most common neonatal complications, which frequently present a high mortality index are NIH, MAS, and NRD. However, in the 20-year period investigated, a reduction in infant mortality of children under a year old due to these three diseases was observed in Brazil. The decrease in the number of deaths was correlated to increased HDI, with higher mortality of male infants, in the white and brown ethnic groups. Neonatal and infant mortality is a consequence of events usually considered preventable, with focus on the public health care and management process, and epidemiological relevance for impacting the population's health and development. Therefore, the importance of optimizing prenatal and intrapartum care becomes evident as a way

to develop strategies to achieve greater reduction in the number of neonatal and infant deaths, mainly of children under one year old, due to these diseases in Brazil.

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6. CONCLUSÃO

Numerosas características do paciente RN prematuro podem contribuir para o diagnóstico de displasia broncopulmonar; no entanto, em nosso estudo sobre análise do uso do O_2 e influência da displasia broncopulmonar, os principais preditores foram o choque séptico e a % da taxa de sucesso da redução de O_2. Dessa forma, a avaliação multidisciplinar para o manejo do O_2, evitando fatores associados à displasia broncopulmonar, pode favorecer o tratamento, minimizando a ocorrência da doença.

No estudo sobre o perfil dos pacientes da UTIN, observou-se que houve umaprevalência deóbitos de 16.5%, e os principais preditores de óbito foram a presença de asfixia, prematuridade e de choque séptico, que podem ser facilmente identificados, e, em alguns casos evitados, proporcionando na redução da taxa de óbito.

Observamos no estudo sobre as principais doenças (HIU, SAM e DRN) que necessitam do uso de O_2 em RNs, que no Brasil houve redução ao longo de 20 anos da taxa de mortalidade com o aumento do IDH para as doenças avaliadas, e dessa maneira, a mortalidade infantil é consequência, principalmente de eventos evitáveis.

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8. ANEXOS E APÊNDICES

ANEXO I: Aprovação do Comitê de Ética e Pesquisa

UNIVERSIDADE SÃO FRANCISCO-SP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Quantificação do cortisol, nível de dor e sinais vitais em recém-nascidos com e sem embrulho modificado durante a realização de técnicas de fisioterapia respiratória

Pesquisador: Fernando Augusto de Lima Marson
Área Temática:
Versão: 1
CAAE: 29719020.6.0000.5514
Instituição Proponente: Universidade São Francisco-SP
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.939.775

Apresentação do Projeto:
Quantificação do cortisol, nível de dor e sinais vitais em recém-nascidos com e sem embrulho modificado durante a realização de técnicas de fisioterapia respiratória. A população alvo irá incluir os recém-nascidos (RNs) até 28 dias de vida, internados nos setores hospitalares da unidade de terapia intensiva neonatal (UTIN), unidade de cuidados intermediários (UCI), unidade de baixo risco (UBR), com número amostral de ~160 RNs; será realizado o protocolo de fisioterapia respiratória nos participantes do grupo intervenção e controle; como a terapia ativa de intervenção será realizado o embrulho modificado nos participantes antes da avaliação. No grupo controle será realizado o protocolo de fisioterapia respiratória sem o uso do embrulho modificado; o desfecho será analisado entre o momento pré-intervenção e pós-intervenção pela análise do nível de cortisol. Concomitantemente, serão mensurados os marcadores frequência cardíaca (FC), frequência respiratória (FR), saturação de oxigênio da hemoglobina (SpO2), sessão arterial (PA) e escala de dor antes de 5 min, a cada 4 min e depois de 5 min da realização da manobra fisioterápica; (Time) o tempo para realizar a intervenção do estudo será de 15 min de atendimento fisioterapêutico, no total de um ano e meio para a coleta, análise e publicação dos dados. Será realizado um estudo clínico de intervenção, não cego e não randomizado com o intuito de validar a segurança e tolerância ao embrulho modificado e verificar sua eficácia tendo como parâmetros o nível de cortisol, nível de dor e a análise dos sinais vitais pela comparação entre grupos com

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(anos); etnia (autodeclarada); pessoas que residem na casa (n); número de gestações (n); estado civil (solteira, casada, divorciada); escolaridade (ensino fundamental, médio, superior ou pós-graduação – completo ou incompleto); ocupação (empregada e desempregada)] avaliados nos setores hospitalares (UTIN, UCI, UBR) do HUSF nos últimos 10 anos de atendimento;(ix) avaliar o tempo de oxigenioterapia e relacionar o dado com a prevalência de retinopatia nos RNs avaliados nos setores hospitalares (UTIN, UCI, UBR) do HUSF nos últimos 10 anos de atendimento;(x) avaliar a taxa de sucesso de desmame de oxigênio e fração inspirada de oxigênio após o atendimento fisioterapêutico dos prematuros pela anotação em prontuário ou anotação de enfermagem, e correlacionar com a presença de broncodisplasia e, dessa forma, identificar as principais dificuldades no desmame.

Avaliação dos Riscos e Benefícios:

RISCOS:

Não haverá riscos eminentes ao protocolo a ser testado, uma vez que, um estudo prévio e piloto identificou que nenhum participantes apresentou problemas relacionados ao procedimento. Adicionalmente, as demais técnicas realizadas no estudo fazem parte da rotina do atendimento da unidade hospitalar

BENEFÍCIOS:

No grupo com embrulho (intervenção) espera-se encontrar menor nível de cortisol e de pontuação na escala de dor, com concomitante aumento da SpO2, redução da frequência cardíaca e aumento da frequência respiratória. Adicionalmente, com o estudo, será possível descrever o perfil epidemiológico dos RNs da população avaliada.

Comentários e Considerações sobre a Pesquisa:

Todos os documentos foram apresentados sendo que o TCLE foi elaborado para o representante legal dos participantes de pesquisa.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados e estão de acordo.

Recomendações:

Por se tratar de pesquisa a ser realizada em ambiente hospitalar, considera-se que todas as medicas preventivas contra o novo COVID-19 sejam tomadas.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado, não foram encontrados óbices éticos.

UNIVERSIDADE SÃO FRANCISCO-SP

Continuação do Parecer: 3.939.775

Considerações Finais a critério do CEP:

APÓS DISCUSSÃO EM REUNIÃO DO DIA 26/03/2020, O COLEGIADO DELIBEROU PELA APROVAÇÃO DO PROJETO DE PESQUISAS. APÓS A CONCLUSÃO DO PROJETO É OBRIGATÓRIO O ENVIO DO RELATÓRIO FINAL PARA ENCERRAMENTO DO PROJETO.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇOES_BASICAS_DO_PROJETO_1515410.pdf	04/03/2020 14:04:17		Aceito
Projeto Detalhado / Brochura Investigador	ProjetoEmbrulho.pdf	04/03/2020 14:03:51	Fernando Augusto de Lima Marson	Aceito
Declaração de Instituição e Infraestrutura	ConcordanciaInstitucional.PDF	04/03/2020 13:58:41	Fernando Augusto de Lima Marson	Aceito
Folha de Rosto	TatianaFolhaRosto.pdf	04/03/2020 13:57:12	Fernando Augusto de Lima Marson	Aceito
Outros	ConfidencialidadeTatiana.PDF	21/02/2020 12:36:53	Fernando Augusto de Lima Marson	Aceito
Cronograma	CronogramaTati.pdf	21/02/2020 12:10:38	Fernando Augusto de Lima Marson	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TermoConsentimentoTati.pdf	21/02/2020 12:09:29	Fernando Augusto de Lima Marson	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

BRAGANCA PAULISTA, 27 de Março de 2020

Assinado por:
CARLOS EDUARDO PULZ ARAUJO
(Coordenador(a))

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