Factors associated with long stay in hospital for preterm newborns

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Abstract

Objectives: to identify factors associated with long hospital stays among preterm newborns.

Methods: this is a retrospective cohort study, conducted in an outpatient clinic monitoring high-risk newborns in Northern Minas Gerais. All morbidities in the group were recorded according to the prematurity classification. Long stay was defined based on the last quartile of times, in days of stay, for the group evaluated. The variables associated with long hospital stay were defined using bivariate analysis followed by binary logistic regression, with only variables with a significance level of 5% remaining in the final model.

Results: 293 newborns participated in this study, 56.6% of whom were male. The gestational age of the group ranged from 24 to 36 weeks, and 25.3% were extremely preterm. The main morbidities were related to respiratory and infectious disorders. Long stays were recorded for 25.9% of preterm newborns and the associated factors were gestational age ($p<0.001$), birth weight ($p<0.001$), late-onset sepsis ($p<0.001$) and necrotizing enterocolitis ($p=0.036$).

Conclusion: the factors associated with long stays highlight the need for greater vigilance in prenatal care, with safe monitoring of pregnancy and prevention of prematurity, and post-natal care, with strict surveillance in the prevention of nosocomial infections.

Key words *Infant premature, Morbidity, Length of stay, Neonatal intensive care units*

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Introduction

Prematurity is the leading cause of infant mortality in various parts of the world, including Brazil, and therefore requires constant surveillance. The risk of mortality for preterm newborns (NB) varies according to several factors, including the classification.[1] Based on gestational age, the NB can be classified as extreme preterm (less than 28 weeks), very preterm (28 to 31 weeks) and moderate to late preterm (32 to 36 weeks).[2,3]

The first weeks of life for preterm NBs, particularly those with very low birth weight and/or who are more premature, are characterized by a heightened risk of complications due to the significant fragility of this group. They require specialized care during this critical stage, as it can have lifelong implications.[3] The most prevalent complications and intercurrent conditions for low-birth-weight newborns include respiratory, cardiac, neurological, and infectious issues. [1-4] In this context, Neonatal Intensive Care Units (NICUs) have played an increasingly significant role in reducing infant morbimortality, and their absence may lead to harmful implications.[5] In NICUs, the aim is to provide appropriate surveillance, treatment, and care for high-risk newborns, especially preterm infants who present with special care needs or require highly complex treatments.

The limit of viability has been observed for newborn situations with increasingly lower gestational ages. This translates to higher risks for this group and a prolonged hospital stay in the NICU.[1-3] It is not uncommon for complications or morbidities arising in NICUs to result in sequelae or necessitate follow-up after hospital discharge.[5-7] Specialized outpatient clinics, staffed by multidisciplinary teams, provided ongoing follow-up for NBs after NICU discharge. The results observed from these high-risk NB follow-up outpatient clinics can provide appropriate and timely feedback to both the professionals and services within the NICUs. However, there is a scarcity of studies on this topic within the national literature.[8]

The length of hospital stay in NICUs is a relevant aspect in the care provided after discharge and a poorly studied variable.[5,9,10] A prolonged hospitalization in NICUs leads to several impacts. These include the direct consequences of a neonate's exposure to a noisy environment, with intense light and the risk of acquiring infections,[11] as well as interferences in parental relationships, such as long family distancing, compromised breastfeeding and increased hospital costs.[12]

Some actors argue that fundamental aspects of preterm infant care can influence the length of hospital stay beyond what would be expected in cases of prematurity.[5,9,10,13] This study aimed to characterize the hospital morbidity profile and identify factors associated with prolonged NICU stay for preterm infants receiving care in a high-risk outpatient clinic in northern Minas Gerais.

Methods

This is a retrospective cohort study conducted at a high-risk newborn outpatient clinic that serves infants discharged from NICUs in Montes Claros, a hub city in northern Minas Gerais. The region, with a territorial extension larger than several Brazilian states and encompassing over 80 municipalities, has a sole outpatient clinic for the follow-up of high-risk newborns, who occasionally experience prolonged stays in NICUs. Children are sent to the outpatient clinic after NICU discharge through a referral process that details birth conditions and hospital stay history, and are then followed-up by a multidisciplinary team.

The study population was composed of preterm newborns followed-up in the outpatient clinic from March 2014 to July 2018, regardless of their birthweight. Inclusion criteria were: a recorded gestational age of less than 37 weeks. Children with severe malformations or residing in other cities were excluded. For the sample calculation, following statistical models,[14] we considered a 95% confidence level, an 80% statistical power, a 1:3 ratio of exposed to unexposed and risk ratio of two, which defined a minimum number of 290 neonates for follow-up.

Data collection was conducted by medical students, supervised by a neonatologist and the data collection form, a structured, paper-based one, which was specially developed for this study, containing information on pregnancy and birth conditions (maternal hypertension, diabetes and urinary tract infections, prenatal corticosteroid, use gestational age, newborn sex, birthweight according to the classification that establishes extreme low weight as below 1000 grams, very low weight between 1000 and 1499 grams and low weight from 1500 to 2499 grams[15] and delivery room resuscitation), complications/morbidities observed during NICU stay (apneas, bronchopulmonary dysplasia, early and late-onset sepsis, intracranial hemorrhage (ICH), necrotizing enterocolitis (NEC) and hemodynamic instability).

Apneas were defined as respiratory pauses affecting in heart rate or oxygen saturation, as recorded by the healthcare team.[16] Bronchopulmonary dysplasia was defined for neonates as the need for supplemental oxygen therapy for a period equal to or greater than 28 days or 36 weeks of corrected gestational age.[17] Early-onset sepsis

was defined based on diagnosis recorded in the chart for a compatible clinical picture with an onset occurred in the first 72 hours of life; and late-onset sepsis for a diagnosis recorded after 72 hours of life.[18] Sepsis was defined based on the medical diagnosis and the treatment used, regardless of the results of blood cultures. Intracranial hemorrhages were recorded based on the diagnosis and imaging findings. Necrotizing enterocolitis was assessed based on the records in charts, and hemodynamic instability was considered for cases requiring vasoactive amines.

The response variable was long stay. This is a poorly explored variable in the literature, and lacks a standardized definition. For the purpose of this study, the length of stay in the NICU for all evaluated newborns was distributed into quartiles, with a long stay being defined as the length of stay within the last quartile.[9,10]

After data collection, the IBM-SPSS for Windows version 22.0 software was used for data entry, processing and analysis. Frequency distributions of the main variables and morbidities were performed according to gestational age. Distribution analysis was conducted using Pearson's chi-square test, assuming a 5% significance level (p<0.05). The variables associated with long stay were defined using bivariate analysis, followed by binary logistic regression analysis. For the multiple analysis, variables with an association up to a 20% significance level (p<0.20) in the bivariate analyses were considered. In the final model, only variables with a 5% significance level (p<0.05) were maintained, with their respective odds ratios and 95% confidence intervals recorded.

The research project, which forms the basis of the information presented here, was approved by the Research Ethics Committee of the State University of Montes Claros (Unimontes – Portuguese acronym), under opinion number 1.800.915.

Results

A total of 293 newborns participated in the study. The majority of the group was male (n=163, 55.5%), and were moderate or late preterm, with a gestational age of 32 to 36 weeks (n=148; 50.5%). Regarding pregnancy and birth conditions, prenatal corticosteroids were used in 134 mothers (45.7%), the most frequent type of delivery was cesarean section (64.3%) and 56 neonates (19.1%) required resuscitation at birth.

The most frequent morbidities and complications during stays in NICUs were: Respiratory Distress Syndrome – RDS (93.9%), early-onset sepsis (48.1%), apnea (39.2%), late-onset sepsis (21.5%), bronchopulmonary dysplasia (21.2%) and hemodynamic instability (20.5%). The distribution of the main clinical conditions and complications are exposed in Table 1, according to gestational age, which also records the most common conditions or complications that were statistically associated with gestational age.

The stay in the NICUs varied from three to 347 days for the assessed group, with a median of 37 days. Of the NB's total, 76 (25.9%) had a period of stay equal to or greater than 63 days (final quartile for the total of days hospitalized), which defines long NICU stay. Table 2 shows the results of bivariate analyses between newborns' characteristics and pregnancy and birth conditions and long stay.

In this stage, variables that were statistically associated were: gestational age <28 weeks (OR=205.92; 95%CI = 56.55-749,82; p<0.001); gestational age of 28 to 31 weeks (OR = 14.19; 95%CI =5.12-39.36; p<0.001); birthweight <1000g (OR=84.01; 95%CI=31.33-225.28; p<0.001); birthweight of 1000 to 1499g (OR=5.86; 95%CI = 2.47-13.94; p<0.001); resuscitation at birth (OR=2.67; 95%CI=1.45-4.92; p=0.001) and mother's use of corticosteroid (OR=3.05; 95%CI=1.76-5.26; p<0.001).

Table 3 shows the association of the most frequent morbidities and complications among the newborns observed, with long stay. On this stage of bivariate analyses, all morbidities and complications were associated with long stay = Use of surfactants (OR=6.03; 95%CI = 3.42-10.63; p<0.001); Seizures (OR=8.07; 95%CI = 2.45-26.57; p<0.001); Apneas (OR=4.15; 95%CI= 2.39-7.21; p<0.001); Bronchopulmonary Dysplasia (OR=8.89; 95%CI = 4.75-16.59; p<0.001); Early-onset sepsis (OR=2.87; 95%CI = 1.55-4.98; p<0.001); Late-onset sepsis (OR=6.33; 95%CI = 3.46-11.59; p<0.001) ICH (OR=4.19; 95%CI = 2.02-8.66; p<0.001); NE (OR=4.77; 95%CI = 1.95-11.68; p<0.001) and Hemodynamic Instability (OR=3.70; 95%CI = 2.03-6.74; p<0.001)

After multiple analysis, the variables gestational age, including that of under 28 weeks (OR=56.88; 95%CI = 11.27-286-97; p<0.001), as well as that of 28 to 31 weeks (OR=7.67; 95%CI = 2.35-25.021; p=0.001); the birthweight, including that under 1000g (OR=10.21; 95%CI= 2.84-36.63; p<0.001) as well as that of 1000 to 1499g (OR=9.61; 95%CI = 3.38-27.32; p<0.001); early-onset sepsis ((OR=6.10; 95%CI =2.45-15.19; p<0.001) and necrotizing enterocolitis (OR=3.97; 95%CI =1.09 -14.04; p=0.036) had statistically significant association with long stay (Table 4).

Table 1

Main morbidities and complications in the neonatal intensive care unit in preterm neonates attended in a follow-up outpatient clinic. Montes Claros/MG, 2014-2018 (N=293).

Morbidities and complications	Total	Gestational age							*p**
		<28 weeks (n=41)		28-31 weeks (n=104)		32-36 weeks (n=148)			
	n	%	n	%	n	%	n	(%)	
RDS	275	93.9	41	100.0	101	97.1	133	89.9	0.013
Early-onset sepsis	141	48.1	29	70.7	59	56.7	53	35.8	<0.001
Apnea	115	39.2	28	68.3	60	57.7	27	18.2	<0.001
Late-onset sepsis	63	21.5	16	39.0	27	26.0	20	13.5	0.001
Bronchopulmonary Dysplasia	62	21.2	27	65.9	28	26.9	7	4.7	<0.001
Hemodynamic Instability	60	20.5	19	46.3	27	26.0	14	9.5	<0.001
ICH	35	11.9	18	43.9	14	13.5	3	2.0	<0.001
Necrotizing enterocolitis	22	7.5	5	12.2	12	11.5	5	3.4	0.025
Hypoglycemia	15	5.1	4	9.8	5	4.8	6	4.1	0.336
Seizures	14	4.8	6	14.6	7	6.7	1	0.7	0.001

RDS=Respiratory Distress Syndrome; ICH=Intracranial Hemorrhage; *Pearson's chi-square test.

Table 2

Association between neonate's characteristics, pregnancy and birth conditions and prolonged stay in neonatal intensive care unit. Bivariate Analysis. Montes Claros/MG, 2014-2018 (n=293).

Variables	N	%	Prolonged stay*				OR (95% CI) crude	*p***
			Yes		No			
			n	%	n	%		
Gestational age (weeks)								
< 28	41	14.0	36	87.8	5	12.2	205.92 (56.55-749.82)	<0.001
28 - 31	104	35.5	35	33.7	69	66.3	14.19 (5.12-39.36)	<0.001
32 - 36	148	50.5	5	3.4	143	96.6	1.00	
Sex								
Male	163	55.6	36	22.1	127	77.9	0.64 (0.38-1.08)	0.092
Female	130	44.4	40	30.8	90	69.2	1.0	
Birthweight(g)								
<1.000	57	19.5	47	82.5	10	17.5	84.01 (31.33-225.28)	<0.001
1.000 - 1.499	85	29.0	21	24.7	64	75.3	5.86 (2.47-13.94)	<0.001
1.500 - 2499	151	51.5	8	5.3	143	94.7	1.00	
Resuscitation at birth								
Yes	56	19.1	24	42.9	32	57.1	2.67 (1.45-4.92)	0.001
No	237	80.9	52	21.9	185	78.1	1.00	
Mother's use of corticosteroid								
Yes	134	45.7	50	37.3	84	62.7	3.05 (1.76-5.26)	<0.001
No	159	54.3	26	16.4	133	83.6	1.0	
Maternal hypertension								
Yes	81	27.6	21	25.9	60	74.1	0.99 (0.56-1.79)	0.998
No	212	72.4	55	25.9	157	74.1	1.0	
Gestational diabetes								
Yes	23	7.8	5	21.7	18	78.3	0.78 (0.28-2.17)	0.632
No	270	92.2	71	26.3	199	73.7	1.0	
Urinary tract infection								
Yes	46	15.7	8	17.4	38	82.6	0.55 (0.25-1.25)	0.150
No	247	84.3	68	27.5	197	72.5	1.0	

* Prolonged stay defined as a length of stay equal to or greater than 63 days; **Pearson's chi-square test.

Table 3

Associations between morbidities and complications of neonates and prolonged stay in neonatal intensive care unit. Bivariate analysis Montes Claros/MG, 2014-2018 n=293).

Variables	N	%	Prolonged stay*				OR (95%CI) crude	*p***
			Yes		No			
			n	%	n	%		
Surfactants use								
Yes	90	30.7	46	51.1	44	48.9	6.03 (3.42-10.63)	<0.001
No	203	69.3	30	15.4	173	85.2	1.00	
Seizures								
Yes	14	4.8	10	71.4	4	28.6	8.07 (2.45-26.57)	<0.001
No	279	95.2	66	23.7	213	76.3	1.00	
Apneas								
Yes	115	39.2	49	42.6	66	57.4	4.15 (2.39-7.21)	<0.001
No	178	60.8	27	15.2	151	84.8	1.00	
Bronchopulmonary Dysplasia								
Yes	62	21.2	39	62.9	23	37.1	8.89 (4.76-16.59)	<0.001
No	231	78.8	37	16.0	194	84.0	1.00	
Early-onset sepsis								
Yes	141	48.1	51	36.2	90	63.8	2.87 (1.66-4.98)	<0.001
No	152	51.9	25	16.4	127	83.6	1.00	
Late-onset sepsis								
Yes	63	21.5	36	57.1	27	42.9	6.33 (3.46-11.59)	<0.001
No	230	78.5	40	17.4	190	82.6	1.00	
Occurrence of hemorrhage (ICH)								
Yes	35	11.9	19	54.3	16	45.7	4.19 (2.02-8.66)	<0.001
No	258	88.1	57	22.1	201	77.9	1.00	
Necrotizing enterocolitis								
Yes	22	7.5	13	59.1	9	40.9	4.77 (1.95-11.68)	<0.001
No	271	92.5	63	23.2	208	76.8	1.00	
Hemodynamic instability								
Yes	60	20.5	29	48.3	31	51.7	3.70 (2.03-6.74)	<0.001
No	233	79.5	47	20.2	186	79.8	1.00	

ICH=Intracranial Hemorrhage; *Prolonged stay defined as a length of stay equal to or greater than 63 days; **Pearson's chi-square test.

Table 4

Factors associated with prolonged stay in neonatal intensive care units between preterm neonates attended in a follow-up outpatient clinic. Multiple analysis (Binary logistic regression*). Montes Claros/MG, 2014-2018 (n=293).

Independent variables	Prolonged stay**		
	OR adjusted	95%CI	*p*
Gestational age (weeks)			
<28	56.88	11.27-286.97	<0.001
28-31	7.67	2.35-25.01	0.001
32-36	1.00		
Birthweight (g)			
<1.000	10.21	2.84-36.63	<0.001
1.000-1.499	9.61	3.38-27.32	<0.001
1.500-2.499	1.00		
Late-onset sepsis			<0.001
Yes	6.10	2.45-15.19	
No	1.00		
Necrotizing enterocolitis			
Yes	3.97	1.09-14.40	0.036
No	1.00		

*Hosmer-Lemeshow test: chi-square: 3.117 (5gl); *p*=0.682; ** Prolonged stay defined as a length of stay equal to or greater than 63 days.

Discussion

This study allowed us to characterize the morbidity profile in preterm infants in NICUs in Northern Minas Gerais, revealing that respiratory and infectious conditions comprise the most common complications. It was also observed that there is still a significant association between frequency of these problems and gestational age, in an inverse relationship. These findings are consistent with the literature.[4,7,13,19,20]

Both national and international literature report that respiratory disorders are the main morbidity in NICUs, followed by infectious conditions. They also point to the occurrence of cardiac and metabolic problems.[4,7,11] Bronchopulmonary dysplasia, intracranial hemorrhage and necrotizing enterocolitis,[7] are also highlighted and were likewise observed in this study. The results of this study point to a statistically significant association between the main morbidities observed and the classification of gestational age. Distinct data were recorded in China,[7] where the authors observed a higher occurrence of some complications in moderate preterm infants (between 29 and 32 weeks). In that study, this finding is justified by the high number of preterm infants discharged without medical authorization, within few days after birth, at the request of the families – a situation that is not recorded in Brazil.

In a cohort study conducted across 25 hospitals in the United States, the authors highlighted the occurrence of complications such as ICH, seizures, necrotizing enterocolitis, bronchopulmonary dysplasia, and respiratory distress. They also stated that the frequency of all morbidities reduces significantly after 32 weeks of gestational age.[21]

The identification and recognition of the main morbidities that affect preterm neonates is significant, considering that some of those are avoidable and adequate and timely treatment may favorably interfere in the future life of these children. In a study conducted in Israel, the authors assessed the impact of the most frequent neonatal morbidities related to postnatal growth, recording that respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus and intraventricular hemorrhage are common conditions for neonates with birthweight under 1500g and interfere significantly with the extrauterine growth.[20] A follow-up study conducted in the United States concluded that preterm neonates that survived conditions such as necrotizing enterocolitis, sepsis, ICH and bronchopulmonary dysplasia had high rates of readmissions and neuropsychomotor delays.[19]

Regarding the factors associated with long NICU stays, this study revealed that lower gestational age, lower birthweight, late-onset sepsis and necrotizing enterocolitis are intimately associated with longer hospital stay, highlighting that the aspects related to the care provided to preterm infants interfere with the length of NICU stay, besides prematurity itself. In light of these findings, it is worth highlighting that the literature does not define a maximum length for NICU stay, nor does it define what constitutes a long stay for preterm neonates. In Brazil, particularly, few studies approach the length of hospitalization in the neonatal period.[4,22,23]

In two systematic reviews on the subject,[9,10] the authors highlight the significance of standardizing concepts, especially given the increase of neonatal survival in the last years. This factor implies a broader usage of neonatal care in the long term, and consequently an increase in the total number of days of healthcare. In some of the studies identified, the length of hospitalization was measured since the postmenstrual age, and the researchers define it as late discharge when it occurs after 42 weeks of gestational age. In other studies, long hospital stay is defined as 21 days or more, in yet other studies, after the final quartile of the hospitalization period.[9,10] In this study, we opted to use the last quartile, assuming it as a condition that establishes the comparison between the care and the local conditions for all preterm infants.

A study that assessed perinatal and postnatal factors that influence the length of hospitalization in preterm NBs (25-33 weeks of pregnancy) admitted in NICUs in India, concluded that the length of hospitalization was increased in nine days per each week of pregnancy below the common period for pregnancy, as well as the increase of the length of hospitalization due to the presence of morbidities such as respiratory distress syndrome, bronchopulmonary dysplasia and sepsis.[24] A study from the United States concluded that the length of neonatal hospitalization decreased significantly with each entire week of pregnancy. For infants born between 26 and 32 weeks of gestation, each additional week in the womb reduced the subsequent length of neonatal hospitalization by at least eight days.[21]

In the present study, both gestational age and birthweight were independently associated with higher length of hospitalization. Although birthweight is a more objective measure than gestational age, it is influenced by factors that result in intrauterine growth restriction, with significant influence of the social conditions.[25] The prolonged hospital stay due to low birthweight is related to the dynamics of weight gaining itself. This

is characterized by an initial weight loss, followed by the recovery of the birthweight, the intensity and length of these two stages inversely related to gestational age, birthweight and complications experienced by the neonate. This characteristic prevents the preterm NB from quickly reaching the necessary parameters for hospital discharge, thus resulting in prolonged hospital stay.

It is worth emphasizing that preterm NBs and/or those with low weight has determined conditions and are more vulnerable to determined morbidities, and accordingly, will require treatments and assistance with invasive or non-invasive techniques, the use of medication for the control of frequent homeostasis and phlebotomy and, all of these aspects will result in prolonged hospital stay. A study conducted in Minas Gerais also reported that the combination of lower birthweight and gestational age was associated with higher risk of prolonged hospital stay compared to other profiles of associated complications.[26]

In this study, although all clinical complications assessed were associated with a prolonged stay in the bivariate analyses, only two conditions remained statistically associated with a prolonged stay in the final model: late-onset sepsis and necrotizing enterocolitis. Both are severe and common clinical conditions for preterm infants, carrying a high risk of mortality.[27] The role of infection and feeding disorders (which may indicate necrotizing enterocolitis), was previously observed in other studies.[4,28] In that regard, the prevention of perinatal and nosocomial infection and the adoption of adequate and tolerable feeding strategies may be highly effective in the reduction of the length of NICU stay for low birthweight preterm infants.

NEC, in spite of the improvements in neonatal care, is still affecting approximately 7% of preterm infants with a birthweight lower than 1500 grams.[29] Its occurrence is associated with hypoxia and mesenteric ischemia, as a correlation of factors related to enteral feeding, gut microbiota and inflammation. One of the first events that leads to NEC is an abnormal response of the premature intestine to colonizing microorganisms. The inflammatory response, with mucosal lesions and bacterial translocation, defines a severe condition that requires prolonged care, thereby justifying a longer NICU stay.[29]

Neonatal sepsis is a frequent case of neonatal morbidity and mortality, mainly in developing countries. It is hard to diagnose, since its clinical signs are unspecific and supplementary exams have low accuracy.[30] The association of late-onset sepsis and BPD is particularly present in those cases in which sepsis is related to the need for mechanical ventilation for a prolonged period.

The variables related to neonatal morbidities that increase the length of stay highlight the need for constant surveillance in relation to care and management of preterm neonates in the NICUs. The possibility of treatment and repeated treatments for the recovery of preterm neonates with late-onset sepsis or NEC inherently leads to a prolonged hospital stay. This is initially due to the period necessary for antimicrobial administration and observation for potential resistance, and subsequently, to the time required for the health condition to evolve in response to the adopted treatment.[30] In that regard, the management of neonatal infectious processes remains a challenge that requires continuous surveillance of their risk factors and etiologic agents, which in turn facilitates improved care.

The findings of this study should be considered in the light of some limitations. It should be considered that the data refer to surviving neonates receiving care in a follow-up outpatient clinic. In that regard, data collected longitudinally, since the birth, would be more adequate for the definition of prolonged stays and its associated factors. It should be also considered the lack of standardization of the definition of prolonged stay in the literature. Demographic and social data related to the mothers and pregnancy conditions were not assessed as well, and they could add significant information to the results. It is also applied to the classification of severity for the clinical conditions assessed, which were not defined during data collection. In spite of its limitations, this study provides a panorama of hospital morbidity for neonates discharged from NICUs in Northern Minas Gerais, offering previously unknown data, and novel insights into prolonged hospital stay for the group evaluated. This highlights the need for broader surveillance and improved prenatal and postnatal care.

In conclusion, the factors associated with prolonged stay are primarily linked to the early interruption of gestations and neonatal care. This highlights the need for greater attention to prenatal care, including comprehensive follow-up prematurity prevention, as well as to postnatal care, with a greater focus on preventing nosocomial infections.

Authors' contribution

Menezes MSD and Caldeira AP: idealization and coordination of the research project. Rodrighes JES and Mendonça IP: data analysis and collection. All authors equally contributed to the data analysis, writing and critical review of the manuscript. They approved the final version of the article and declared no conflicts of interest.

Data availability

All datasets supporting the results of this study are included in the article.

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