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ORIGINAL ARTICLE

Intrahospital costs in very low birth weight premature infants with bronchopulmonary dysplasia

Costos intrahospitalarios de prematuros de muy bajo peso al nacer con displasia broncopulmonar

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

Worldwide, the healthcare cost of patients with bronchopulmonary dysplasia (BPD) is considerably higher than the cost of patients without this condition. According to international reports, the cost of patients with BPD could be up to 2.3 times higher than the cost of preterm patients without BPD.

What does this study contribute to what is already known?

In Chile, and similar to the international literature, the costs of BPD are higher compared to patients without BPD. This study quantifies how costs decrease with increasing gestational age and rise with greater severity of BPD.

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Abstract

Worldwide, the cost of patients with bronchopulmonary dysplasia (BPD) is higher than that of patients without BPD. However, the magnitude of this cost difference in Chile is unknown. **Objective:** To determine the difference in in-hospital cost among very low birth weight (VLBW) preterm newborns with BPD (mild, moderate, severe) or without it in Chile. **Subjects and Method:** Retrospective, bottom-up cost analysis study, carried out based on data collected from the NEOCOSUR Network**.** The study included VLBW neonates born in the 14 centers in Chile of the network, between 2006 and 2021, who survived beyond 28 days, with a birth weight between 400 and 1,500 grams, and 24 to 33 weeks of gestational age, categorized according to whether or not they had BPD in its three levels. VLBW newborns with congenital malformations and major comorbidities were excluded. Linear regression analysis was performed in order to determine those variables with the highest influence on costs. **Results:** The average cost of patients with BPD is 1.78 times higher than that of patients without it. The cost increases as BPD severity increases and decreases as the gestational age increases. **Conclusions:** The average cost of patients with BPD is 78% higher than the cost of those without BPD. The length of hospital stay is the variable that contributes the most to the increase in costs, where for each additional day of hospitalization the costs increase by USD 46.82.

Keywords:
Bronchopulmonary Dysplasia;
Preterm;
Health Care Costs;
Cost Analysis

Introduction

In recent years, cost analysis has been a central part of evaluation and is a constant concern for evaluators and decision-makers in healthcare and has been a topic of great interest[1,2].

The increase in healthcare spending and demand potentially leads to lower efficiency in service delivery, highlighting the need for a change in how cost information is understood[2]. Therefore, it is necessary to develop economic information systems that allow us to know not only how much is spent, but also how resources are invested. In this sense, cost analysis offers great possibilities for hospital management, becoming an important tool for decision-making[2].

Bronchopulmonary dysplasia (BPD) is a disease whose etiology is not yet fully understood and is associated with multiple risk factors that can damage the immature lung. It is also the most frequent morbidity and cause of mortality in very low birth weight (VLBW) preterm newborns (NBs)[3-5]. Worldwide, the healthcare costs of patients with BPD are considerably higher than those of patients without this condition. One study showed that although VLBW preterm NBs (weight < 1,500 gr.) account for only 1.5% of live births in the United States, the cost of this group is among the highest in the neonatal population, reaching nearly 13.4 billion dollars per year[6]. According to international reports, the cost of patients with BPD could be up to 2.3 times higher than the cost of preterm patients without BPD[6]. In addition, a retrospective study of 7,988 preterm NBs published in 2020 showed that the average cost in patients with BPD during the first year of life was USD 377,871 compared to USD 175,836 for children without BPD, with an adjusted cost index of 1.54 (95%CI 1.49-1.59), where patients with BPD have a longer hospital stay and are at higher risk of readmission[7].

Regarding the epidemiology of BPD, in the United States, BPD affects between 10,000 to 15,000 NBs annually[8]. In countries such as Canada and Japan, between 2006 and 2008, the prevalence of BPD in VLBW preterm NBs was 12.3% and 14.6%, respectively[8]. In Chile, it is estimated that approximately 350 new cases of BPD should be diagnosed each year[9]. Specifically, in the *Hospital Clínico UC-Christus*, the incidence of BPD between 2005 and 2014 in VLBW NBs was 23.9%, with a moderate or severe presentation of 13.3%[9]. Although in Chile the cost of patients with BPD is also expected to be higher than that of patients without this condition, the extent of this cost difference is unknown.

To date, we are not aware of any published studies in Chile that comparatively analyze the economic costs associated with the care of patients with and without BPD. This study will help determine the magnitude of BPD-related healthcare costs, contributing to a better understanding of its economic impact, increasing the visibility of the issue, and positioning it on the public agenda. It will also allow for future comparisons with other diseases during this stage of life.

The objective of this study was to determine the difference in in-hospital costs between patients with and without BPD among VLBW NBs in 14 neonatal intensive care units (NICUs) in Chile.

Subjects and Method

Population and sample

Retrospective study using prospectively recorded data, of bottom-up construction of direct disease costs based on clinical data extracted from the NEOCOSUR Neonatal Network database of VLBW NBs. Direct costs are those that can be easily attributed to a particular product, activity, or service.

NEOCOSUR is a not-for-profit collaborative network of 32 South American neonatal intensive care units distributed in Argentina, Chile, Peru, Paraguay, and Uruguay that continuously monitors the outcomes of VLBW NBs. Data are recorded prospectively, using predefined diagnostic criteria and an anonymous online data entry system (www.neocosur.org).

This study included all NBs born in the 14 centers in Chile part of the network, between 2006 and 2021, who survived beyond 28 days, with birth weight between 400 grams and 1,500 grams and gestational age (GA) between 24 and 33 weeks, categorized based on the presence or absence of BPD, and, if present, further classified as mild, moderate, or severe.

VLBW NBs with congenital malformations, major comorbidities such as necrotizing enterocolitis, grade III and IV intracranial hemorrhage, periventricular leukomalacia, late-onset sepsis, congenital heart disease, central nervous system defects, gastrointestinal, genitourinary, and chromosomal anomalies, and other defects were excluded from the study (Supplementary Table 1, available online). In addition, those NBs without sufficient data to perform the bottom-up cost analysis were excluded.

Definition of BPD severity

Those NBs requiring oxygen for more than 28 days but less than 36 weeks post-conceptional age or at discharge, were considered with mild BPD; those requiring less than 30% oxygen at 36 weeks post-conceptional age or discharge were considered with moderate BPD; finally, those NBs requiring more than 30% oxygen and/or ventilatory support at 36 weeks post-conceptional age or discharge were considered with severe BPD[10].

Cost estimation

A bottom-up model was used to estimate the costs of patients with and without BPD based on the National Health Fund's (FONASA) official fee schedule (11) in order to determine the cost of a day of hospitalization in the NICU during the study period (for a detailed breakdown of what the FONASA hospitalization day includes, see Appendix 1). The bottom-up cost model is an estimate of the cost by adding up the individual components to finally obtain the total cost. FONASA is a public, decentralized, and inclusive access health fund that collects, manages, and distributes resources for the general health benefits system in Chile.

In addition, data on supply prices (medications and devices) were obtained from the National Supply Center (CENABAST) and from economic valuation studies[12-15] to determine changes in costs of drugs between 2006 and 2021 (adrenaline, indomethacin, theophylline, postnatal corticosteroid, and surfactant). This allowed the construction of per-patient cost models based on days of hospitalization in the NICU, surfactant doses, and the use of adrenaline, indomethacin, theophylline, and postnatal corticosteroids.

Statistical analysis

The mean cost difference between patients with and without BPD was determined using the Student t-test. A stratified analysis was performed to evaluate costs according to the clinical severity of BPD, reporting the cost ratio for each severity level with respect to the cost of patients without BPD with their 95% confidence intervals (95%CI). An ANOVA test, with Bonferroni correction, was used to quantify the difference in means. A second stratified analysis was performed to evaluate the costs at the different GAs using the Student t-test (for groups > 30 subjects) and the Mann-Whitney test (for groups < 30 subjects).

A multiple linear regression analysis was performed to assess the extent to which each cost component affected the total in-hospital cost in patients with BPD.

A constant semi-elasticity model relates an explanatory variable in its original scale to a response variable previously transformed using the natural logarithm. This allows the evaluation of how absolute changes in the explanatory variable affect the response variable in percentage terms. This model was applied using total hospitalization costs as the response variable and the cost components as explanatory variables.

Given the high number of subjects participating in the study, normality will be assumed in the distribution of values based on the central limit theorem[16]. Statistical analysis was performed with STATA 14.0 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Ethics

The protocol of this study was approved by the Scientific Ethical Committee of the *Pontificia Universidad Católica de Chile* on October 6, 2022.

There is no conflict of interest for this study.

Results

Of the 9,183 patients initially included in the database, 3,928 were included in the analysis (42.77%)

(Figure 1). Of the 5,255 patients excluded, 3,463 (37.7% of the total initial patients, 65.9% of the excluded patients) were because of presenting congenital malformations or major comorbidities, and 704 (7.66% of the total patients, 13.4% of those excluded) due to not having data on days in NICU or number of surfactant doses to estimate direct in-hospital costs (Figure 1). Only these two cost variables were chosen because of their relevance within the total cost of hospitalization. Finally, 1,088 patients (11.85% of the total, 20.70% of those excluded) were excluded because they died before 28 days. Of the patients included in the analysis, 1,523 (28.98%) had BPD.

Patients with BPD were significantly younger in GA, had lower birth weight, were more likely to be female, and had more days of hospitalization, mechanical ventilation, and oxygen therapy compared to those without BPD (Table 1). In addition, 80.7% of patients with BPD received pulmonary surfactant, while only 37.6% of patients without BPD did ($p < 0.001$). Furthermore, 47.8% of patients with BPD were discharged with oxygen and had lower Apgar scores at one minute.

The average in-hospital direct costs of patients with BPD during their hospitalization was \$3,798,230 ± 1,424,661, while the average costs of patients without BPD was \$2,138,245 ± 959,434 ($p < 0.001$), which indicates that the average in-hospital costs in patients with BPD are 1.78 (95%CI 1.73-1.82) times higher than the in-hospital cost of patients without BPD.

In patients with BPD, the in-hospital cost, expressed in thousands of Chilean pesos and U.S. dollars, decreases as GA increases and the duration of hospitalization decreases (Table 2).

Table 3 shows that as the severity of the disease increases, in-hospital costs increase, which on average are 1.51 (95%CI 1.46-1.57), 1.82 (95%CI 1.76-1.87), and 2.25 (95%CI 2.14-2.37) more expensive for a patient with mild, moderate, and severe BPD, respectively, compared to one without it, this variation statistically significant.

In addition, it is observed that the cost of BPD has increased 1.8 times from 2006 with an average cost of \$2,954,528 ± 1,053,005 to 2021 with an average cost of \$5.299,209 ± 1,556,893. This increase is mainly associated with the rise in the cost of a NICU bed-day in the FONASA fee schedule, which went from \$33,560 in 2006 to \$55,000 in 2021. In Supplementary Table 2 (available online), annual data are presented in thousands of Chilean pesos. Supplementary Table 3 (available online) shows the changes over time in the variables associated with BPD-related costs. It includes the annual cost (based on FONASA rates) of a day of hospitalization in the NICU, as well as variations in NICU days, days on mechanical ventilation, days on oxygen therapy, and the number of surfactant doses per year, according to data from the NEOCOSUR Network database.

The joint analysis of the variables determined that only days in NICU and the number of surfactant doses significantly influence in-hospital costs of BPD patients, while the variables "adrenaline", "indomethacin", "corticosteroid", and "aminophylline" do not contribute significantly to in-hospital costs of BPD patients. For each day hospitalized in the NICU, the costs increase to \$46,445 (95%CI 45,061.23-47,829.05; $p < 0.001$), while for each dose of surfactant, the in-hospital cost increases on average \$89,485 (95%CI 36,710.35-142,261.1; $p = 0.001$) (Table 4) in the presence of the variables "adrenaline" and "indomethacin". We can observe that for each day NICU stay the costs increase by 1%, for the use of indomethacin the cost increases by 2.3%, and for each dose of surfactant + use of aminophylline the cost increases by 2.2% in the presence of the variables "adrenaline" and "corticosteroid". The variable "number of doses of surfactant + aminophylline" is expressed as a combined variable by collinearity, i.e., all patients who used surfactant also received aminophylline (Table 5).

Of the total number of eligible patients, 704 (7.67%) were excluded because they did not have data on days in the NICU or the number of surfactant doses to estimate direct in-hospital costs. Importantly, days in the NICU, days on mechanical ventilation, and even days of oxygen therapy were significantly higher in the excluded patients. Supplementary Table 1 (available online) describes these data.

Discussion

This study of VLBW NBs who survived beyond 28 days found that the average in-hospital cost for those with BPD was 78% higher than for those without it, totaling \$3,798,230 compared to \$2,138,245, respectively.

The results show that preterm NBs with BPD are born at a lower GA and with lower birth weight than those without BPD and undergo a more demanding hospitalization in terms of clinical requirements.

The results found agree with the available evidence on the costs of BPD worldwide. Although our study does not compare the direct costs of BPD with other pathologies of the VLBW NB, it did show that the in-hospital costs of patients with BPD are 1.78 times higher compared to those without BPD ($p < 0.001$). This agrees with that reported by Russel et al, who showed that BPD increases in-hospital costs 2.3 times, being the most expensive of the diseases evaluated (brain damage increases 1.6, necrotizing enterocolitis 1.4, and sepsis 1.4 times in-hospital costs)[17].

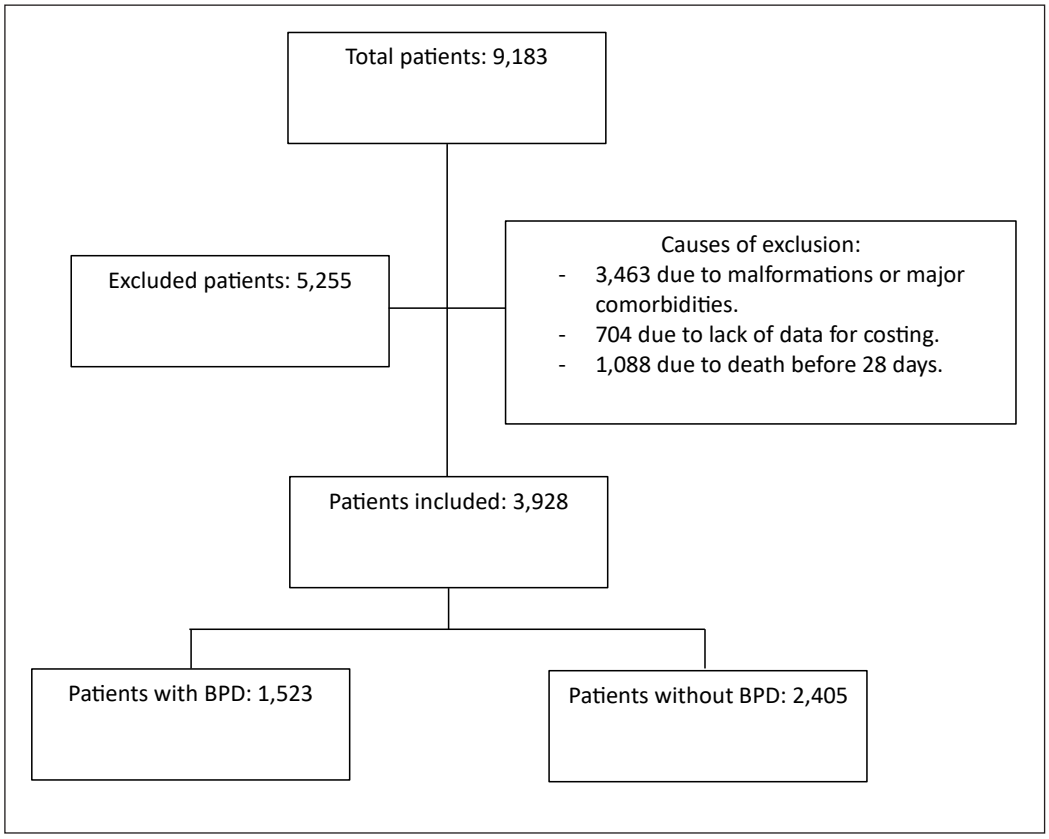

Figure 1. Flowchart for the selection of the study sample of patients from the NEO-COSUR Network database in Chile between 2006 and 2021.

Table 1. Demographic characteristics of low birth weight newborns. Neocosur Network of centers in Chile, 2006-2021

	With BPD (n = 1523)	Without BPD (n = 2405)	
GA (wk), mean (SD)	27,4 (1,86)	29,9 (1,86)	< 0,001
Born weight (gr), mean (SD)	931 (234)	1.173 (194)	< 0,001
Hospitalization days, mean (SD)	86 (28)	49 (17)	< 0,001
Female sex, %	42,8	51,4	< 0,001
Prenatal corticosteroids, %	89,9	90,4	0,99
Type of delivery, cesarean section, %	75,5	82,6	< 0,001
Apgar 1 < 3, (%)	19,8	16,7	< 0,001
Use of surfactant, %	80,7	37,6	< 0,001
MV days, mean (SD)	14,1 (17,38)	3,2 (5,09)	< 0,001
O2 days, mean (SD)	69,8 (30,64)	9,17 (13,12)	< 0,001
Discharged with O2 use, %	47,8	0,8	< 0,001

BPD: bronchopulmonary dysplasia; GA: Gestational age; Wk: weeks; SD: Standard deviation. Gr: grams; MV: Mechanical ventilation; O2: Oxygen. For the statistical significance evaluation of numerical and categorical variables, Student´s T test and Chi square test were used, respectively.

Table 2. Direct in-hospital cost of patients with and without BPD according to GA, expressed in thousands of pesos ($) and dollars (USD). Neocosur Network of centers in Chile, 2006-2021

	With BPD			Without BPD		
GA (wk)	Subjects with BPD	Hospital days (BPD)	(n = 1523) Mean ± SD	Subjects without BPD	Hospital days (No BPD)	(n = 2405) Mean ± SD
24	77	118	$5.399 ± 1.983 USD 5,536 ± 2,033	22	64	$1.174 ± 2.017 USD 1,203 ± 2,068
25	160	106	$4.716 ± 1.478 USD 4,836± 1,515	26	80	$2.083 ± 2.171 USD 2,135 ± 2,225
26	238	93	$4.061 ± 1.320 USD 4,164 ± 1,353	47	72	$3.227 ± 1.639 USD 3,308 ± 1,680
27	322	88	$3.898 ± 1.272 USD 3,996 ± 1,303	104	68	$2.980 ± 1.313 USD 3,055 ± 1,346
28	296	80	$3.563 ± 1.223 USD 3,653 ± 1,254	275	59	$2.548 ± 933 USD 2,612 ± 9,56
29	228	72	$3.245 ± 1.027 USD 3,326 ± 1,053	440	53	$2.326 ± 812 USD 2,384 ± 832
30	125	69	$3.067 ± 1.094 USD 3,145 ± 1,121	530	47	$2.122 ± 831 USD 2,175 ± 852
31	40	65	$2.857 ± 1.011 USD 2,929 ± 1,037	414	43	$1.898 ± 737 USD 1,945 ± 755
32	27	63	$2.864. ± 839 USD 2,937 ± 859	380	41	$1.818 ± 760 USD 1,864 ± 778
33	10	69	$2.321 ± 2.049 USD 2,379 ± 2101	167	38	$1.651 ± 589 USD 1,693 ± 604
Average total cost			$3.798 ± 1.425 USD 3,894 ± 1460.85			$2.138 ± 959 USD 2,192 ± 983

GA: Gestational age; BPD: Bronchopulmonary dysplasia; SD: Standard deviation. The cost in dollars was calculated with the value of this as of 4-12-2024. The comparison between BPD and No BPD cost was done with the Student's T test (in groups with sample size over 30) and the Mann-Whitney test (in groups with sample size less than 30). All values $p < 0.001$.

Table 3. Estimated direct cost according to BPD severity, expressed in thousands of pesos ($) and dollars (USD). Neocosur Network of centers in Chile, 2006-2021

BPD severity	Average hospital days	Average cost ± SD	Subjects
Without BPD	47	$2.138 ± 959 USD 2,202 ± 988	2.408
Mild	72	$3.192 ± 1.047 USD 3,273 ± 1,073	359
Moderate	86	$3.834 ± 1.253 USD 3,931 ± 1,284	879
Severe	105	$4.742 ± 1.807 USD 4,862 ± 1,852	266

BPD: bronchopulmonary dysplasia; SD: Standard deviation. The cost in dollars was calculated with the value of this as of 4-12-2024. P-value < 0.001for the ANOVA test and Bonferroni´s correction.

Besides, a systematic review showed that there is an increase in costs as the GA is lower, which is consistent with our findings where as GA increases, costs decrease significantly[18].

As expected, there was evidence of an increase in cost as BPD became more severe. This information is new and also adds to the magnitude of the cost increase.

Among the variables used to estimate the direct in-hospital costs of BPD patients, the number of NICU stay days has the greatest impact on overall costs. Although each additional day of hospitalization results in a smaller percentage change than surfactant, aminophylline, or indomethacin, it should be noted that the latter two are administered only once or a few times during the hospital stay. Regarding the cost of the drugs included in the analysis, data from the economic valuation studies of 2012, 2015, and 2018 were used, in addition to the data provided by CENABAST. No adjustments were made per year for these prices given that the variation of them is insignificant, considering that these variables are categorical (uses or does not use the drug), so it is only counted once for each patient in case of having used it.

Another study showed that the cost of patients with BPD during the first year of life was significantly higher compared to patients without BPD. Although this study does not compare costs during the first year of life, it did show that BPD patients had a higher proportion of oxygen use at discharge (47.8% vs 0.8%), which partially reflects an increase in out-of-hospital costs[19]. For decision-makers, such as hospital administrators, it is important to understand the sample selection criteria in order to determine whether these results can be extrapolated to their specific context.

BPD often occurs alongside other relevant diseas-

Table 4. Association between the hospitalization total cost and its determining variables. Multiple lineal regression model. Neocosur Network of centers in Chile, 2006-2021

BPD cost	Coefficient	SE	P-value	CI95%
Adrenaline	-36.206	81.045	0,655	-195.401 - 122.988
N° surfactant dose + Aminophylline	89.485	26.867	0,001	36.710 - 142.261
Indomethacin	56.310	38.896	0,148	-20.092 - 132.713
Corticosteriods	86.407	51.670	0,095	-15.087 - 18.7902
NICU days	46.445	704	<0,001	45.061 - 47829
Constant	-47.293	78.535	0,547	-201.558 - 106.971

BPD: Bronchopulmonary dysplasia; SE: Standard error; CI95%: 95% Confidence Interval; NICU: Neonatal intensive care unit; Number of observations:557. The low number of observations is due to the fact that the model included patients who presented all the variables. R2: 0.9076.

Table 5. Constant semi-elasticiy model to estimate the percentage of change in in-hospital cost in relation to modifications in the covariates determining them. Neocosur Network in centers from Chile, 2006-2021

BPD cost	Coefficient	SE	P-value	CI95%
Adrenaline	-0,025	0,021	0,229	-0,066 – 0,016
N° surfactant dose + Aminophylline	0,022	0,006	0,002	0,008 – 0,035
Indomethacin	0,023	0,010	0,024	0,003 – 0,043
Corticosteroids	-0,01	0,013	0,583	-0,034 – 0,019
NICU days	0,010	0,0002	<0,001	0,010 – 0,011
Constant	14,25	0,020	<0,001	14,214 – 14,294

BPD: Bronchopulmonary dysplasia; NICU: Neonatal intensive care unit; SE: Standard error; CI95%: 95% confidence interval. Number of observations: 565. R2: 0,7891.

es[8]. In order to isolate the effect of dysplasia, the sample selection was performed only with subjects who had BPD as the sole disease or had no relevant diseases. This avoids the confounding bias that could be generated by the inclusion of other diseases that also contribute significantly to hospital costs.

This study stands out for the rigor of the NEOCOSUR Network in its records related to clinical processes and outcomes, as well as for the involvement of experts in both healthcare cost analysis and the care of patients with BPD.

Additionally, it has a large sample size, including 3,928 patients (compared to the 425 patients in the study by Johnson et al.[6]). Furthermore, we estimate that the inclusion of 14 centers in Chile, 4 private and 10 public, could be considered representative of the country's reality.

Besides, given that cost in patients with BPD in Chile have not been evaluated, this publication provides new information for the decision-maker when allocating health resources, considering that by presenting the costs per year (Supplementary Table 2, available online), more accurate projections can be made on the variation of costs of the disease.

This study is not without limitations. Although the data recorded by the NEOCOSUR Network collaborators is rigorous and has a large sample size, the database is not designed for cost-analysis studies. As a result, some cost-related variables (such as certain medications) are recorded as dichotomous variables (use/no use), which prevents determining the exact number of times the medication was used. The study does not provide a comprehensive account of supplies, services, procedures, or other cost-related aspects such as complementary tests or specialist consultations. Therefore, certain variables, such as the use of adrenaline, indomethacin, theophylline, and corticosteroids, were used to make the most accurate estimate possible.

Future studies should also include other variables associated with direct costs in order to obtain a cost estimate closer to reality, given that the estimated cost of patients with BPD in this study is necessarily underestimated due to the lack of variables and the low rates of FONASA[20], where bed-day costs can be more than 10 times higher in the private healthcare system compared to the public one (Appendix 2). Alternatively, each patient could be assigned to a Diagnosis-Related Group (DRG), which relates the complexity of a hospital to its resource consumption[21]. Although it was initially created to measure hospital activities, its potential as a hospital payment mechanism was later realized[21]. Finally, variables that allow for the estimation of the magnitude and significance of the indirect costs associated with BPD could also be included.

Conclusion

The direct in-hospital costs of VLBW NBs attributable to BPD are 1.78 times higher than those of NBs without the disease. Costs increase when the GA at birth is lower and as the severity of the condition increases.

Length of stay in the NICU is the variable that contributes most to the increase in in-hospital costs.

Ethical Responsibilities

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

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

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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