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ORIGINAL ARTICLE

New morbidity following critical illness in Latin American children under 18 years old with lower respiratory tract infection

Nueva Morbilidad tras Enfermedad Crítica en Niños Latinoamericanos menores de 18 años con infección severa del tracto respiratorio inferior

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

The development of residual functional morbidity at discharge from pediatric intensive care has become an essential healthcare outcome. The Functional Status Scale (FSS) is a validated tool in pediatrics to detect the development of new morbidity after critical illness. Residual functional morbidity is frequent after severe acute respiratory failure in cohorts from developed countries.

What does this study contribute to what is already known?

We present one of the first multicenter reports describing the acquisition of new morbidity in children with severe respiratory infections treated in pediatric intensive care units in Latin America. We identified that the development of residual morbidity in these children is infrequent and detected its main risk factors, some of which are modifiable. Invasive mechanical ventilation, pediatric mortality rate at admission, previous comorbidities, sepsis, development of Acute Respiratory Distress Syndrome, healthcare-associated infections, and certain infectious agents were associated with the acquisition of new morbidity.

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Abstract

Acquisition of new morbidity (NM) has become a key clinical outcome measure after pediatric critical illness. Data on Latin American children are still scarce. **Objective:** to analyze the development of new morbidities acquired after hospitalization due to lower respiratory tract infection (LRTI) in pediatric intensive care units (PICU). **Patients and Method:** we included patients from 35 PICUs from 8 countries, aged 0 to 18 years with a diagnosis of LRTI, discharged alive, registered between April 2018 and September 2019, and who required some type of ventilatory support (high-flow system, noninvasive ventilation or invasive ventilation), included in the LARed Network registry, which includes the Functional Status Scale (FSS) validated in the pediatric population, which assesses functional status in six domains: mental status, sensory, communication, motor skills, feeding, and respiratory status. NM considered LRTI after hospitalization and was defined as an increase of ≥ 3 points in the FSS. **Results:** Of 3280 children with LRTI, 85 (2.6%) developed NM, associated with diagnoses of sepsis and acute respiratory distress syndrome (ARDS), pneumococcal or adenovirus infection, healthcare-associated infections (HAIs), and invasive mechanical ventilation. Adenovirus infection, ARDS, and HAIs were independently associated with NM. **Conclusions:** We observed that the development of NM at PICU discharge is infrequent but is associated with modifiable risk factors. These data define certain risk groups for future interventions and initiatives to improve the quality of care.

Keywords:
Functional Status; Morbidity; Critical Care Outcomes; Intensive Care Units; Pediatric

Introduction

In recent decades, the decrease in mortality observed in children admitted to pediatric intensive care units (PICUs) has led to a shift in the focus on the critically ill child, from simply improving survival, to avoiding morbidity related to critical illness[1]. Many validated tools are available to assess the occurrence of new functional morbidity in children admitted to PICU, with the Functional Status Scale (FSS) being one of the most widely used[2,3].

The FSS is a tool validated for the pediatric population in different regions of the world, pending validation throughout Latin America, which assesses functional status in six domains: mental status, sensory, communication, motor functioning, feeding, and respiratory status. Each domain is graded from normal (score 1) to severe (score 5), resulting in a score ranging from 6 to 30[2] (Supplementary Table 1).

Correlation between the FSS and the Pediatric Cerebral Performance Category (PCPC) and the Pediatric Overall Performance Category (POPC) functional scales has been demonstrated. A change from baseline FSS versus FSS at discharge between 2 and 3 points correlates with a change from mild to moderate disability in the POPC/PCPC score[4].

There is growing evidence that serious illness can lead to acquired morbidity in children, resulting in a health burden that extends well beyond hospital discharge[5]. However, these data come from studies conducted in developed countries, whereas data from resource-limited settings, such as Latin America, are still lacking. The objective of this study was to describe the incidence and risk factors for the development of functional morbidity in children admitted due to lower respiratory tract infections (LRTI) in PICUs participating in a Latin American multinational collaborative network.

Patients and Method

Design

We analyzed the LARed Network registry, which includes demographic and epidemiological data on children admitted due to acute respiratory failure to one of 40 PICUs in eight Latin American countries. Data were recorded using a secure web-based electronic data collection platform.

The registry is composed of patients aged 0 to 18 years (17 years 11 months and 29 days), with a primary respiratory diagnosis, who required admission to a PICU for advanced respiratory support (i.e., high-flow nasal cannula oxygen therapy, noninvasive mechanical ventilation at two levels of continuous positive airway pressure, mechanical ventilation) or monitoring. A detailed description of this registry has been published previously[6].

Patients

For this study, we included children aged 0-18 years with a diagnosis of LRTI, discharged alive, admitted between April 2018 and September 2019, and who required some type of ventilatory support (high-flow system, noninvasive ventilation, or invasive ventilation). To reduce bias, we only included patients from

centers that applied the FSS in more than 90% of patients discharged during the study period.

The baseline FSS score was calculated using the child's health status immediately prior to the illness leading to hospitalization and PICU discharge, both obtained from the medical records and physical examination. The primary outcome was the development of new morbidity, defined as an increase in FSS score at discharge ≥ 3 points from the initial FSS score[4,7].

Statistical analysis

We compared cases with and without new morbidity by bivariate analysis with a Pearson or Fisher Chi^2 test or a nonparametric Kruskal Wallis test. We then constructed a mixed-effects logistic regression model with random effect by center for the independent factors associated with the primary outcome in the bivariate analysis. Statistical analyses were performed with Stata 13.1. A p-value ≤ 0.05 was considered statistically significant.

Ethical approval

Each institution approved the LARed Network database. This study was reviewed and approved by the institutional review board of *Hospital de San José* (IRB00011307, CEISH 0023-2022), Bogotá, Colombia.

Results

A total of 3,316 patients from 35 PICUs in 8 countries were included, of whom 36 (1.1%) were excluded due to death. Finally, 3,280 met the inclusion criteria for the study, 80% of the children were less than 24 months old. 85 children (2.6%) met the definition of new morbidity (an increase in FSS score ≥ 3 points from baseline) during their PICU stay (Tables 1 and 2). Patients who developed new morbidity had a significant increase in FSS score from a baseline median of 6 (IQR 6-6; 81.2 % in 6) to a median of 9 (IQR 9-12; 57.7 % in 9) at PICU discharge.

Patients with new morbidity had higher PIM-3 scores and were more likely to have pneumonia, ARDS, sepsis, or adenovirus infection than patients without new morbidity. Noninvasive ventilation or invasive mechanical ventilation was used in 2,310 (70.4%) and 892 (27.2%) patients, respectively. New morbidity was found in 13 of 2,310 (0.6%) patients treated with noninvasive ventilation and in 69 of 892 (7.7%) patients treated with invasive mechanical ventilation ($p < 0.01$) (Figure 1). Patients with new morbidity also had a longer duration of invasive mechanical ventilation, longer duration of PICU stay, and more hospital-acquired infections.

After multivariate analysis, adenovirus infection (OR 5.8, 95% CI 2.2-14.9), development of ARDS (OR 2.0, 95% CI 1.1-3.5), and healthcare-associated infections (HAIs) (OR 2.7, 95% CI 1.3-5.5) were independently associated with the development of new morbidity. Neurological comorbidity was not shown to be independently associated with the development of new morbidity (OR 1.7; 95% CI 0.8-3.7). In contrast, treatment with noninvasive ventilation was associated with a lower probability of developing new morbidity (OR 0.2; 95% CI 0.0-0.6).

Discussion

In this large Latin American cohort, we found that 2.6% of critically ill children treated for LRTI developed new morbidity following admission to the PICU. This occurrence is three times greater among children treated with invasive mechanical ventilation. The development of new morbidity was directly associated with a diagnosis of ARDS, sepsis, adenovirus infection, and HAIs, and was also associated with a longer duration of invasive mechanical ventilation and PICU length of stay.

Our study is one of the first multicenter studies to describe the development of a new functional morbidity associated with critical respiratory illness in Latin American children. Recent regional single center reports have used the FSS at PICU discharge. In Argentina, Alvarez et al.[8] showed a 3.6% acquisition of new morbidity at PICU discharge in a single center. Eulmesekian et al.[9] found that 0.7% of patients who had an adverse event during their PICU stay also acquired new morbidity measured by FSS. One difference with our cohort is the fact that these studies analyzed more heterogeneous infant populations than ours. In Brazil, Souza Bastos et al.[10] have translated and cross-culturally adapted the FSS into Portuguese, and Dannenberg et al.[11] analyzed 128 children at PICU discharge, finding a drop in the FSS score in 79 cases (62%). However, 33% still had an altered FSS one year after discharge. They demonstrated that the deterioration of the FSS score at PICU discharge was independently associated with the persistence of this deterioration (drop in FSS) at one-year follow-up [RR 7.5 (2.4-23.0)].

We found a lower rate of new residual morbidity in comparison with studies from developed countries focusing on respiratory disease. In the United States, using the FSS scale, Yagiela et al.[5] observed the acquisition of new morbidity in 8.6% of children admitted to PICU due to respiratory failure. This could be explained by population differences, such as the disease severity as marked by the PIM-3 value at PICU admission, which were strikingly lower in our cohort. Also, the cohort reported by Yagiela et al. had a higher median age. Our cohort was composed of children under 18 years of

Table 1. Basal Characteristics and bivariate analysis of patients with Lower Respiratory Tract Infection admitted to the PICU

		All patients	No New Morbidity	Newly-Acquired Morbidity	*p*
Total, n (%)		3280 (100%)	3195 (97.4%)	85 (2.6%)	
Age (months), median (IQR)		8 (3-21)	8 (3-22)	6 (2-19)	0.45
0-24 months		2516 (76.8%)	2449 (76.7%)	67 (78.8%)	0.651
25-215 months		761 (23.2%)	743 (23.3%)	18 (21.2%)	
Male sex, n (%)		1941 (59.2%)	1884 (59%)	57 (67%)	0.32
FSS score (Points) median	Baseline	6 (6-6)	6 (6-6)	6 (6-6)	0.733
	PICU discharge	7 (6-7)	7 (6-7)	9 (9-12)	< 0.001
PIM3%	Median (IQR)	0.4 (0.2-1.2)	0.4 (0.2-1.2)	0.60 (0.4-3.8)	< 0.001
	No data (%)	197 (6%)	196 (6.1%)	1 (1.2%)	n/a
Pre-existing comorbidity, n (%)	None	1737 (53%)	1695 (53%)	42 (49%)	0.507
	Any respiratory	1140 (34.8%)	1113 (35%)	27 (32%)	0.557
	Prematurity	414 (12.6%)	400 (13%)	14 (17%)	0.279
	Any neurologic	173 (5.3%)	163 (5%)	10 (12%)	0.007
	Any cardiovascular	137 (4.2%)	131 (4%)	6 (7%)	0.178
	Any genetic	112 (3.4%)	107 (3%)	5 (6%)	0.204
	Undernutrition	79 (2.4%)	75 (2%)	4 (5%)	0.162

Values are counts (n) and percentages (%), or medians and interquartile ranges (IQR). PIM3%, Pediatric Index of Mortality-3 (percent), PICU, Pediatric Intensive Care Unit n/a: not aplicable.

age, but 80% of them were younger than 2 years, with a median age of 8 months. Respiratory infections have different etiologies and clinical courses depending on age group, with viral infections being more frequent in children under 2 years of age, especially RSV[12-14]. The latter was not shown in our analysis to be independently related to the acquisition of new morbidity.

Senna et al.[15] demonstrated the correlation between PIM-3 and the probability of acquiring new morbidity measured by FSS, which was higher in their study due to greater severity of illness on admission to the PICU in that cohort. In our sample, the children presented a PIM-3 value at admission lower than those reported by Yagiela.

It is striking that, despite not meeting our definition for the acquisition of a new morbidity *per se*, 55% of patients in our study had an increase in baseline FSS by at least one point. This indicates that more than half of the children did not leave the PICU in the same condition in which they entered. It would be interesting to further investigate this finding in future qualitative research, especially its impact on the quality of life of the child and on their environment.

The fact that most children treated in the PICU are now expected to survive hospital discharge has led to a paradigm shift in defining success and failure in our specialty. Survival alone no longer serves as the principal outcome; we must also consider the medium- and

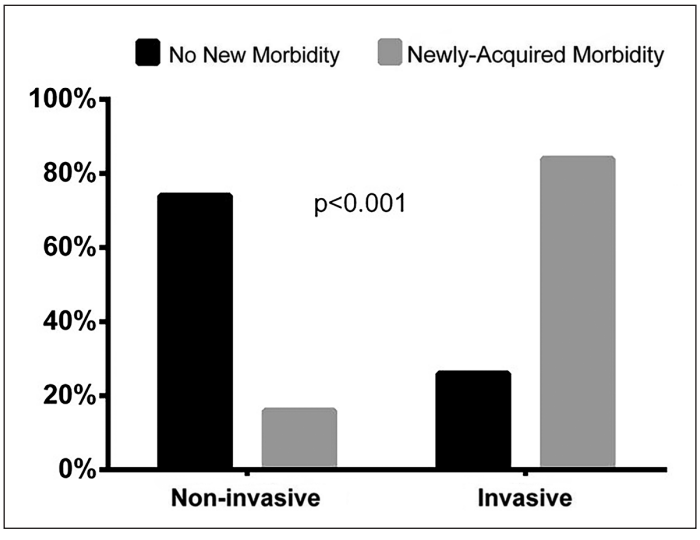

Figure 1. Proportion of patients without morbidity and new morbidity with non-invasive ventilation (n = 2,310) or invasive mechanical ventilation (n = 892).

Table 2. Clinical characteristics, clinical course, and treatment of patients with Lower Respiratory Tract Infection. Bivariate analysis

		Total pacientes	Sin nueva morbilidad	Con nueva morbilidad	*p*
Admission diagnosis, n (%)	Wheezing	2351 (71.7%)	1731 (54%)	41 (48.2%)	< 0.001
	Pneumonia	771 (23.5%)	735 (23%)	36 (42.4%)	< 0.001
	Others	158 (4.8%)	150 (4.7%)	8 (9.4%)	0.127
ARDS, n (%)		361 (11%)	238 (7%)	32 (38%)	< 0.001
Sepsis n (%)		330 (10.1%)	299 (9.4%)	31 (36.5%)	< 0.001
Initial respiratory support, n (%)	Any high flow system	200 (6.1%)	187 (5.9%)	13 (15.3%)	0.058
	Non-invasive ventilation	2454 (74.8%)	2428 (76.0%)	26 (30.6%)	0.002
	Invasive mechanical ventilation	626 (19.1%)	580 (18.2%)	46 (54.1%)	0.004
Maximal respiratory support, n (%)	Any high flow system	78 (2.4%)	75 (2%)	3 (4%)	0.455
	Non-invasive ventilation	2310 (70.4%)	2297 (72%)	13 (15%)	< 0.001
	Invasive mechanical ventilation	892 (27.2%)	823 (26%)	69 (81%)	< 0.001
Viral isolates, n (%)	RSV	1409 (43%)	1379 (43%)	30 (35%)	0.148
	Influenza	115 (3.5%)	109 (3%)	6 (7%)	0.122
	Adenovirus	83 (2.5%)	76 (2%)	7 (8%)	0.001
	HRV/EV	83 (2.5%)	79 (2.5%)	4 (4.7%)	0.167
	HMPV	74 (2.3%)	71 (2%)	2 (2%)	0.714
	Parainfluenza	62 (1.9%)	61 (2%)	1 (1%)	1.000
Bacterial isolates, n (%)	Pneumococcus	40 (1.2%)	36 (1.1%)	4 (4.7%)	0.003
	Pertussis	13 (0.4%)	12 (0.4%)	1 (1.%)	0.290
	Mycoplasma	20 (0.6%)	19 (0.6%)	1 (1.2%)	0.409
	Other bacteria	175 (5.3%)	163 (5.1%)	12 (14.1%)	< 0.001
Hospital acquired infections, n (%)	Any	85 (2.6%)	70 (2.2%)	15 (17.6%)	< 0.001
	CLABSI	31 (0.9%)	25 (0.8%)	6 (7.1%)	< 0.001
	CAUTI	19 (0.6%)	13 (0.4%)	6 (7.1%)	< 0.001
	VAP	26 (0.8%)	20 (0.6%)	6 (7.1%)	0.003
Duration of IMV, hours (IQR)		99 (41-189)	98 (41-186)	154 (46-286)	0.019
PICU LOS, days (IQR)		4.7 (3.1-7.8)	4.6 (3-7.5)	9.5 (5.6-20.4)	< 0.001

Values are counts (n) and percentages (%), or medians and interquartile ranges (IQR). ARDS, acute respiratory distress syndrome; HMPV, human metapneumovirus, HRV/EV, human rhinovirus/enterovirus; CLABSI, central line-associated bloodstream infection; CAUTI, catheter-associated urinary tract infection; VAP, ventilator-associated pneumonia; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation; PICU, pediatric intensive care unit; LOS, length of stay.

long-term consequences that critical care has on children and their families[16]. Functional status assessments the PICU and at discharge can better guide a plan to address their needs in the post-hospital setting and justifies continued follow-up of these vulnerable subjects. Identifying these affected children at the time of hospital discharge may allow for interventions designed to help them reach their full potential[17].

Emphasizing the need for follow-up and defining children with PICU-acquired morbidity as a high-risk group, Pollack et al.[18] reported that, although most of these patients recovered during the first six months after discharge, one-third of them died at long-term follow-up. In addition, FSS at PICU discharge is associated with odds of readmission[5], and multiple PICU admissions are associated with lower survival. From a

broader perspective, these children meet the criteria for Post Intensive Care Syndrome in pediatrics (PICS-p)[19], an entity described in recent years that denotes the observed alteration in the well-being of children and their families after PICU discharge. While the reason for establishing a longitudinal assessment of children recovering from a critical illness beyond PICU discharge may seem fairly obvious, building a robust interdisciplinary follow-up clinic or healthcare center for PICU patients can be challenging.

Our study has several limitations. First, as is characteristic of studies involving retrospective analyses of observational data, we cannot establish causality, only associations between clinical variables and the primary outcome. Second, our observations on the acquisition of new morbidity are limited to the period of PICU stay. This period is crucial in determining new critical illness morbidity, but the clinical course may have different trajectories after PICU discharge (i.e., improvement, worsening, or stability). Therefore, our results may over- or underestimate morbidity at discharge or mid- and long-term follow-up. Third, to date, the FSS has not been translated or validated into Spanish, which could affect its reliability and overall performance. However, we believe that this concern is mitigated by its simplicity, ease of application, and lack of culturally specific items. Finally, as in any study involving database analysis, there is the possibility of inaccurate data entry. The LARed Network registry has quality control measures to reduce the likelihood of missing or erroneous data. Our study also has important strengths, such as a robust sample size, a diverse group of centers contributing data to the registry, and a dedicated collaborative network with experience in collecting data for research purposes.

In conclusion, we identified an important group of critically ill children with LRTI who developed new morbidity during their PICU stay. Newly acquired morbidity was associated with the severity of illness, sepsis, diagnosis of ARDS, and treatment with invasive mechanical ventilation, thus defining a high-risk group that should be the focus of future research. In addition, new morbidity was associated with PICU length of stay and the development of nosocomial infections. These data may guide the design of prospective functional outcome studies in children and quality-improvement initiatives to address modifiable risk factors related to morbidity among PICU survivors.

The implementation of protocols aimed at decreasing days on mechanical ventilation, the proper administration of measures to reduce HAIs, and the deepening of public health programs to fight immunopreventable diseases that lead to severe respiratory infections and sepsis, such as pneumococcal infection, could not only have a direct impact on pediatric mortality both in and out of the hospital, but could also positively impact the quality of life of those children who survive the disease. Functional disabilities following critical illness affect not only the child but the entire family and the community in which the child lives; therefore, the study of factors that contribute both to its prevention and development are mandatory in this new era of critical care.

Latin American Pediatric Collaborative Network (LARed Network)

Collaborators

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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.

Financial Disclosure

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