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ORIGINAL ARTICLE

Lymphocyte-C-reactive protein ratio as a predictor of severity in acute lower respiratory infections due to respiratory syncytial]virus in hospitalized infants

Indice linfocito-proteína C reactiva como predictor de gravedad en infecciones respiratorias agudas bajas por Virus Sincicial Respiratorio en lactantes hospitalizados

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

Acute lower respiratory infections (ALRI) are a common cause of pediatric consultations and hospitalizations. Having tools to identify their severity facilitates proper patient categorization and guides more accurate and timely clinical decisions.

What does this study contribute to what is already known?

This study contributes to evaluating the effectiveness of the lymphocyte-to-C-reactive protein (LCRP) ratio, which has been studied in oncological and infectious diseases and even in newborn patients with severe sepsis. This tool could be predictive of the course and/or severity of ALRI caused by respiratory syncytial virus (RSV) in hospitalized patients under 2 years of age. In this experience in infants hospitalized with ALRI due to RSV, the LCRP ratio was not useful in predicting the severity of the disease.

Abstract

Respiratory Syncytial Virus (RSV) is a common cause of acute lower respiratory tract infection (LRTI) in pediatrics. The lymphocyte-to-C-reactive protein ratio (LCR) has been studied as a predictor of inflammation, sepsis, and severity in viral respiratory infections. **Objectives**: To estimate the LCR in hospitalized infants with RSV-associated acute LRTI and assess its ability to identify disease severity. **Patients and Method**: A cross-sectional study including infants hospitalized with a diagnosis of RSV-associated acute LRTI over 12 months. Absolute lymphocyte count (cells/mm³), C-reactive protein (CRP) level (mg/L), and the Argentine Respiratory Distress Assessment Scale (EDRAR) score at admission were recorded. The LCR was calculated and categorized into two groups: LCR < 100 and ≥ 100, and its relationship with EDRAR was analyzed. **Results:** A total of 209 patients were included, with a mean age of 7.4 ± 6.3 months. According to the EDRAR, only 6.7% (n = 14) were classified as severe. The median LCR was 305.7 (IQR 109.3–1201.5), with no significant difference between severe and non-severe patients (p = 0.9). In 23.4% of patients, LCR was < 100, with a sensitivity of 70.3% (95% CI: 63.2–76.4) and specificity of 28.57% (95% CI: 9.58–58) for predicting severity. **Conclusion:** In infants hospitalized with RSV-associated acute LRTI, the LCR was not useful in predicting disease severity.

Keywords:
Acute Respiratory Infection;
Respiratory Syncytial Virus;
Diagnostic Test;
Lymphocyte-to-C-Reactive Protein Ratio

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Introduction

Acute lower respiratory infections (ALRI) are one of the main health problems, with an impact on infant mortality and health costs[1]. Viruses are the main cause, with respiratory syncytial virus (RSV) not only being the most frequently detected, but also presenting a 10-fold increased risk of severe disease[2,3]. In Argentina, in 2019, RSV was identified in 59% of patients. RSV is the main virus detected (62%) and is associated with a 10-fold increased risk of severity compared to other viruses[4]. Although RSV disease is usually mild and can be managed on an outpatient basis, a limited number of patients (1-4%) may require hospitalization[5], and of these, approximately 2% require intensive care[1].

Evidence shows that the presence of certain biological factors (age < 3 months, prematurity/low birth weight, comorbidities, etc.) and socio-environmental factors (smoking, overcrowding, among others) are associated with a higher rate of complications, hospitalization, and death (many of them at home)[1].

Respiratory infections are one of the most frequent causes of visits to pediatric emergency departments, where the decision on how to manage them depends mainly on the severity of the obstruction. Several scales have been designed for this assessment, such as the Wood-Downes-Ferrés scale and the Ellis scale, the Scarfone pulmonary index, the pulmonary score[6], and the Argentine respiratory distress scale (EDRAR) of the Ministry of Health[7]. Some scales use only clinical variables, but others are based on oxygen saturation, peak expiratory flow, pulmonary function tests, respiratory rate, heart rate, PaO2, and PaCO2, or combinations of them. These scales classify bronchial obstructive syndrome (BOS) as mild, moderate, or severe[6].

The EDRAR, a modification of the Tal score, assesses respiratory rate, heart rate, wheezing auscultation, and chest wall retractions. This tool was validated by showing that a score ≥ 5 was the best predictor of hypoxemia (sensitivity = 100%, specificity = 54.3%). The EDRAR allows obstructive symptoms to be classified as mild (score ≤ 4), moderate (score 5-8), or severe (score ≥ 9) (Table 1)[7].

Despite being based on elements that can be considered objective, the importance of the observer and the timing of these instruments' administration means that their accuracy, and that of other clinical scales for assessing severity, has been questioned[8].

Therefore, having prediction tools based on more objective elements (laboratory tests) allows for greater accuracy when making decisions about the management of these patients. CRP is an acute-phase protein produced by the liver in response to inflammation, infection, or tissue damage. During sepsis, CRP levels typically increase due to the body's immune response to infection. CRP is a sensitive but non-specific acute-phase reactant. Its interpretation should always be done in conjunction with clinical findings and other laboratory results[9].

The LCRP ratio is a specific indicator used to measure the ratio of lymphocyte count to plasma CRP levels. In sepsis, the lymphocyte count decreases, and CRP levels increase[10]. The LCRP ratio was associated with a lower risk of cardiovascular mortality and overall mortality in a study by the National Health and Nutrition Examination Survey (2017). This ratio was a stronger predictor of mortality compared to absolute lymphocyte count and C-reactive protein levels[11].

Respiratory viral infections, such as influenza or RSV, are often associated with transient leukopenia and lymphopenia, due to the inhibition of hematopoiesis by inflammatory cytokines and the migration of leukocytes to infected tissues[12].

The objective of this study is to evaluate the diagnostic capacity of the LCRP ratio to identify critically ill patients in infants hospitalized due to RSV-associated ALRI[13-15].

Patients and Method

Design

Cross-sectional study evaluating a diagnostic test.

Objectives

To estimate the LCRP ratio in infants hospitalized due to RSV-associated ALRI and evaluate its ability to identify severity.

Population

All infants (aged 1 month to 2 years) hospitalized with a diagnosis of ALRI (bronchiolitis and pneumonia) and microbiological identification of RSV at the *Hospital General de Niños Pedro de Elizalde* from January 1, 2023, to December 31, 2023, were included in the study. Those with other associated viral or bacterial microbiological identification were not excluded. As these were hospitalized patients, all had chest X-rays, although these were not considered for this study.

Patients with oncohematological disease, immunodeficiencies, congenital or acquired heart disease, chronic obstructive pulmonary disease, bronchopulmonary dysplasia, and neurodevelopmental disorders (cerebral palsy, neuromuscular diseases) were excluded since all these conditions are considered to increase the risk of developing severe forms of ALRI[4].

Table 1. Argentine respiratory distress scale (EDRAR) to assess the severity of broncho-obstructive syndrome

Score	Heart Rate	Respiratory Rate < 6 months	Frecuencia Respiratory Rate > 6 months	Wheezing	Chest retractions
0	< 120	< 40	< 30	None	No
1	120-140	40-55	30-45	End of expiration	Mild intercostal
2	140-160	55-70	45-60	Inspiration and expiration	Generalized retractions
3	> 160	> 70	> 60	Audible without a stethoscope	Retractions and nasal flaring

Variables

In all cases, absolute lymphocyte counts (absolute number/mm^3) and CRP (mg/l) were recorded for the calculation of the LCRP ratio. Once this ratio was calculated, two groups were established according to whether it was below or above 100 (LCRP < 100 or ≥ 100)[10,16].

The severity of the disease was categorized according to the Argentine Respiratory Distress Scale (EDRAR), classifying it as mild (score 1-4), moderate (score 5-8), and severe (score > 9)[7].

Results analysis

The recorded variables were described using proportions with a 95% confidence interval (95% CI) for categorical and ordinal variables, and mean with standard deviation or median with interquartile range for continuous variables (according to normality or non-normality as assessed by the Kolmogorov-Smirnov test). To compare continuous variables, the t-test or the Mann-Whitney test was used, as appropriate.

The best cut-off point of the LCRPP ratio for predicting severity was estimated using an ROC curve (including the calculation of AUC and its 95% CI). Cut-off values for diagnostic testing are reported with their 95% CI. A p-value < 0.05 was considered significant. The analysis was performed using the SPSS 20.0 software.

Sample size calculation

Considering that, in the only pediatric experience, this test has shown a sensitivity of 45% (neonates with sepsis)[13], and expecting that in the study population it would perform at least similarly (50% sensitivity), a total of 638 patients would be required (5% precision) (StatCalc, Epi Info 7.2). The study was conducted during 2021, and data on hospitalizations due to RSV from years before the pandemic were used to calculate the sample size, expecting to have the required cases[17]. However, as is well known, non-pharmacological mitigation measures for the COVID-19 pandemic significantly affected the circulation of RSV, preventing the initially calculated sample size from being reached. An interim analysis of the data obtained during the study period calculated that if the observed distribution were to continue, the results obtained up to that point would not be modified by an increase in the sample size. Given this finding and considering the high likelihood of the introduction of universal RSV vaccination in Argentina in the very near future, as indeed occurred, it was decided not to extend the study.

Results

During the study period, 269 patients were included, and 60 patients were excluded because they did not have complete laboratory data or they had heart disease and chronic lung disease as the most frequent causes, resulting in a sample of 209 patients. The age was 7.4 (IIC 2.7-10.9). 57.4% were male (n = 120). 95.7% (n = 200) were admitted during the winter season. The lymphocyte count was 3,605/mm³ (95% CI 2,504-5,229), and the median CRP value was 13 mg/L (95% CI 3.2-34.1). (Table 2).

According to the EDRAR score, 93.3% (n = 195) of patients were non-severe, and 6.7% (n = 14) were severe. The EDRAR score was 6 (IIC 1-11). The LCRP ratio was 305.7 (IIC 109.3-1201.5). 23.4% of patients had an LCRP ratio below 100 (severe). Initially, 2.4% (n = 5) were admitted to the Pediatric Intensive Care Unit (PICU), and 97.6% were admitted to the general ward (n = 204); of the latter, 17 required intensive care during their stay. The length of stay in the general ward was 8.7 ± 13.5 days and in the PICU 15.2 ± 14.3 days (Table 2).

The LCRP ratio in severe cases was 324.9 (95% CI 106.4-1024.2) and in non-severe cases 305.7 (95% CI 108.4-1250.3) (p = 0.9).

A ROC curve was used to predict severe cases using the LCRP ratio (AucROC = 0.5; 95% CI 0.3-0.6), with a cut-off point of 120 for the LCRP ratio. The %LCRP was analyzed (AucROC = 0.5; 95% CI 0.4-0.7). (Figure 1) The LCRP ratio showed a sensitivity of 70.3% (95% CI 63.2-76.4); a specificity of 28.57% (95% CI 9.58-58); positive predictive value 93.2% (95% CI 87.5-

96.5); negative predictive value 6.45% (95% CI 2.1-16.5), positive likelihood ratio 0.9 (95% CI 0.7-1.4), and negative likelihood ratio 1.1 (95% CI: 0.4-2.4).

The most commonly used method of oxygen administration was nasal cannula/mask (59.1%) (Table 2). Following local treatment guidelines for these cases[4], all patients received at least one dose of salbutamol but did not receive ipratropium bromide. 62.2% of patients received corticosteroid therapy during hospitalization for 3.7 ± 4.5 days.

Discussion

In our study, 23.4% of patients had an LCRP ratio < 100, which is categorized as severe. The LCRP ratio showed a sensitivity of 70.3% and a specificity of 28.6% in patients with RSV-associated ALRI. Li Xiaojuan et al., in 2023, evaluated the clinical importance of the LCRP ratio as an early indicator of sepsis in neonates, with a sensitivity of 88% and a specificity of 55%, higher than those obtained in our study[13].

The cut-off point of the LCRP ratio as a predictive capacity for severity used in adults described in the literature is not useful for the pediatric population, as it does not correlate with the EDRAR severity ratio in patients with RSV-associated ALRI younger than 2 years of age. A ROC curve was used to predict severe cases using the LCRP ratio, obtaining a cut-off point of 120. However, the LCRP ratio value is lower in more severe patients. Gandino et al. evaluated 730 adult patients with positive nasopharyngeal swabs for SARS-CoV-2 during the COVID-19 pandemic. The group with an LCRP < 100 had a higher proportion of deaths (7.7% vs. 2%; p = 0.001) compared to those with a ratio > 100[16].

Table 2. Clinical and laboratory characteristics according to the severity attributed by the Argentine Respiratory Distress Scale (EDRAR

Variable		All (n = 209)	Mild/Moderate (n= 195)	Severe (n = 14)	Value p
Age (moths, mean ± SD)		7.4 ± 6.3	7.5 ± 6.4	5.3 ± 3.6	NS
Peso (kg, mean ± SD)		7.5 ± 2.5	7.4 ± 2.5	7.8 ± 1.9	NS
Eutropic/Malnutrition		205 / 4	191 / 4	14 / 0	NS
Bronchiolitis (Yes/No)		208 / 1	194 / 1	14 / 0	NS
Pneumonia (Yes/No)		41 / 168	37 / 160	4 / 10	NS
Viral Co-infection (Yes/No)		1 / 208	1 / 194	0 / 14	NS
Bacterial Co-infection (Yes/No)		4 / 205	3 / 192	1 /13	NS
Hyperinflation (Yes/No)		151 / 58	140 / 55	11 / 3	NS
Consolidation (Yes/No)		21 / 188	19 / 176	2 / 12	NS
Bronchoalveolar infiltrate (Yes/No)		104 / 105	95 / 100	9 / 5	NS
Leukocytes (cells/µL, mean ± SD)		11637.7 ± 5139.9	11615.1 ± 5120.9	12089 ± 5779.1	NS
Lymphocytes (cell/µL, mean ± SD)		4082.9 ± 2101.8	4097.2 ± 2089.3	3784.7 ± 2441.6	NS
CRP (mg/L, mean ± SD)		25.7 ± 40.4	25.7 ± 40.8	23.9 ± 31.9	NS
L/CRP ratio (mean ± SD)		1717.1 ± 5266.1	1762.6 ± 5388.4	813.3 ± 1156.2	NS
Oxygen therapy[1]	Nasal cannula/mask	120	115	5	
	High flow nasal cannula	71	64	7	
	Non-invasive ventilation	2	2	0	
	Invasive mechanical ventilation	10	8	2	
	No oxygen therapy required	6	6	0	
Antibiotics (Yes/No)		60 / 149	55 / 140	5 / 9	NS
Corticosteroids (Yes/No)		130 / 79	120 / 75	10/ 4	NS
PICU (Yes/No)		22 / 187	20 / 175	2 / 12	NS
Days of hospitalization (mean ± SD)		8.2 ± 5.4	8.2 ± 5.5	8.7 ± 4.2	NS

[1]SThe most complex oxygen delivery device used in each patient is reported. [2]All patients who required PICU are considered, either direct admission or transfer during their clinical course

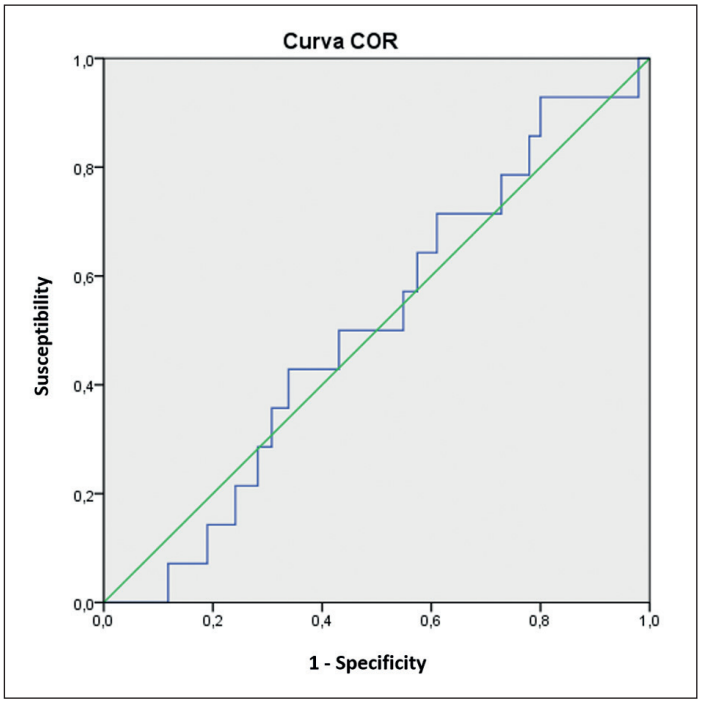

Figure 1. ROC curve of the Lymphocyte/C-Reactive Protein (LCRP) ratio.

Recent studies found that the LCRP was closely related to SARS-CoV-2 disease (COVID-19). Yang et al. found that the LCRP was more beneficial than CRP or lymphocytes alone in the evaluation of severe COVID-19 in adults. In the timely identification and anticipation of the severity and lethality of COVID-19, the LCRP can be a useful prognostic indicator, with a sensitivity of 95.8%[18].

There is little bibliographic evidence of the use of this ratio in pediatrics, but some studies have been described in neonatology and adult development in both oncological and infectious pathologies.

Although our report focuses on infants with RSV infection, without excluding co-infections, these types of patients can be considered fairly homogeneous for the study.

Even with the potential limitation of not having reached the calculated sample size given the COVID-19 pandemic, this study provides evidence on this diagnostic tool in a setting where it had not been tested, and which continues to be one of the most common in pediatrics.

Finally, it is important to highlight the importance of always presenting research results, even if they can be considered "negative", as in our study. This not only increases knowledge and avoids wasting resources but also complies with an important ethical premise of clinical research.

The main limitations of the study were not reaching the planned sample size and the low number of severe cases.

Conclusion

In our study, the LCRP ratio did not allow us to predict the severity of the clinical picture in infants hospitalized with RSV-associated ALRI.

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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