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Systematic review

Factors to predict the risk ofProgression to severity in children with bronchiolitis. Systematic review with meta-analysis

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ABSTRACT

Acute bronchiolitis is the most frequent cause of lower respiratory tract infection in infants. To synthesize the available scientific evidence on factors capable of predicting the risk of progression to severity in children with acute bronchiolitis, a systematic review with meta-analysis was conducted. This review included case-control, cohort, cross-sectional observational, prospective, and retrospective studies. The digital scientific literature search was conducted

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between April 1 and May 31, 2024, in the search engines PUBMED, Cochrane, MEDLINE, ENFISPO, Scopus, SciELO, and Google Scholar. A total of 407 studies were examined; After the elimination of duplicates and abstract filtering, 32 were ultimately included. The factors with the highest statistical significance were: low fluid intake (OR 11.3; CI 2.29–54.45), lung consolidation on ultrasound (OR 9.67; CI 4.98–18.77), oxygen saturation less than 92% (n: 1313; OR 4.45; CI 2.98–6.66), and apnea at admission (n: 1649; OR 4.44; IQ 2.93–6.73). The utility of the included factors for predicting the progression to severe acute bronchiolitis was demonstrated. The results highlight the necessity of developing novel tools to optimize the prediction of disease progression to severity, based on the factors examined.

Keywords: Acute Bronchiolitis, Severity, Prognostic factor.

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Introduction

Acute bronchiolitis (AB), from a global perspective, has one of the highest rates of morbidity and mortality in children under 2 years of age. The prevalence of the disease and the associated costs make it one of the most impactful in childhood, and in fact, it constitutes an active area of research. (1-4)

In this regard, acute bronchiolitis is the most frequent cause of lower respiratory tract infection in infants and is also the leading cause of hospital admission in children under 2 years of age. It refers to inflammation and obstruction of the lower respiratory tract, particularly the small airways such as the bronchioles, causing distal air trapping accompanied by mild, moderate, or severe respiratory distress. (2,3,5)

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Globally, it is the second leading cause of death in children aged 1 to 12 months, with a death rate of 66,000 to 199,000 children per year. In the United States, it is responsible for more than 100,000 hospitalizations per year in patients under 12 months of age. Furthermore, a study conducted in Spain showed that 2% to 6% of pediatric patients required treatment in the intensive care unit due to this disease. (4, 6)[-9)]

The severity of bronchiolitis is characterized by a persistent increase in respiratory effort (evidenced by tachypnea, nasal flaring, and retractions), hypoxemia, apnea, and acute respiratory failure, with the use of accessory muscles. Factors associated with greater disease severity include a toxic or ill appearance, oxygen saturation < 90% by pulse oximetry while breathing room air, and a respiratory rate ≥ 70 breaths/minute. (10)

In general, disease severity is determined through clinical assessment; it is a dynamic process and can range from mild to severe respiratory failure. However, objective indicators for predicting progression to severity from an integrated perspective are not yet sufficiently accurate.

Scientific literature shows multiple investigations carried out at the international and national level, (8) but there is no consensus to evaluate the evolution to the severity of bronchiolitis, considering that not only clinical evaluation predicts severity, but there are other humoral and radiological factors that must be considered, based on the physiological basis of the disease.

In this sense, further study of the aforementioned factors favors a better evaluation and monitoring of the patient and enables the development of new scales that allow predicting the evolution to severity, in order to initiate early therapy, which reduces complications and their sequelae.

The importance of the topic, the high morbidity in pediatric intensive care units, and the diversity of criteria for evaluating the progression to severity of bronchiolitis, support the present research, which was oriented to answer the following question: What factors allow estimating the progression to severity in children with bronchiolitis and can be useful for constructing a predictive scale in the evaluation of these patients?

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To answer the question posed, a systematic review with meta-analysis was conceived with the objective of synthesizingthe available scientific evidenceon factors that can predict the progression to severity in children with acute bronchiolitis.

Methods

A systematic review with meta-analysis was conducted, considering case-control, cohort, cross-sectional observational, prospective, and retrospective studies. An electronic search of the scientific literature related to the topic was performed between May 1 and 31, 2024, using the search engines PubMed, Cochrane, MEDLINE, ENFISPO, Scopus, SciELO, and Google Scholar.

No limits were set based on language, country of origin, or publication date. Reference lists of previous systematic reviews and relevant original research articles were searched to identify studies not found in the initial database search. Inclusion criteria included studies that reported updated theoretical aspects—clinical-epidemiological, historical, procedural, evaluative, and conceptual—related to predictors of disease progression to severity in children under two years of age.

Non-original studies, those that were not directly related to the title of the systematic review, and those that did not list an author or Digital Object Identifier System (DOI) were excluded.

Selection of studies: The authors independently screened the titles and abstracts identified by the planned search strategies. For research eligible based on the title or abstract, the full article was retrieved. Studies potentially eligible based on at least one author were assessed in full-text versions. Articles meeting the inclusion criteria were independently evaluated by the researchers, and discrepancies were resolved through discussion of the inclusion or exclusion criteria.

To increase the reliability and safety of the process, the degree of agreement between reviewers was measured by calculating the kappa statistic for each item on the selection sheet. This

statistic, simply put, measures the degree of agreement between reviewers that exceeds what would be expected by chance. In cases where there were discrepancies between the two reviewers regarding the decision to include or exclude an article, a third researcher (a subject matter expert) was appointed to arbitrate the discrepancies and make the final decision.

The Cochrane Collaboration standardized data extraction form was used to independently extract the following data: study name (along with the first author's name and year of publication), country where the study was conducted, study design, number of participants, exposure, outcome, and notification of bias. When the data were insufficient or incomplete, this information was obtained from the text, tables, or by calculating the utilization of the data included in the study.

Bias analysis: The risk of bias in the included studies was assessed using the Newcastle Ottawa Scale (NOS).

Information analysis: The meta-analysis was carried out using Epidat software version 3.1 to evaluate the Odds Ratio (OR) of the risk factors involved in the study.

Heterogeneity was assessed using the I^2 statistical test (which indicates the proportion of variability observed in the intervention effect between studies that is due to heterogeneity between studies and not to chance). For this purpose, a value of 25% was considered low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity, as measured by the Chi-square test.

Strategy for searching for the most relevant articles

407 studies were selected, 398 from databases and 9 from other sources. Of these, 26 duplicates were excluded. Filtered based on title and abstract, 381 were selected, of which 78 were excluded. Using eligibility criteria, 78 studies were selected, of which 46 were excluded. Finally, 32 studies were included.

Ethical considerations

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This is a review of articles; no contact was made with patients during the research. The ethical considerations of the World Medical Association regarding health databases and biobanks were taken into account.

Results

Qualitative analysis of the systematic review revealed an association between the identified risk factors and the progression to severe bronchiolitis. In order of prevalence, low water intake was the greatest risk factor, followed by the presence of pulmonary consolidation, oxygen saturation (O2) below 92%, apnea on admission, and prematurity. The neutrophil-to-lymphocyte ratio was found to be a contributing factor to severity in some studies, while in others it acted as a protective factor.

Result of the qualitative analysis according to selected factors

Comorbidity

• Author, year of publication, country: Esquivel-Suman R(11), 2016, Panama. Study: case and control, population: 167; OR: 2.68; 95% confidence interval (95% CI) lower limit: 11.51; upper limit: 6.27; level: 95.

• Author, year of publication, country: Rodríguez-Martínez CE.(12), 2018, Colombia. Study: cases and control, population: 303;OR: 7.77; 95% confidence interval (95% CI) lower limit: 0.82; upper limit: 12.54; level 95.

• Author, year of publication, country: Niranjan-Lal J(13), 2021, Saudi Arabia. Study: case and control, population: 684; OR: 3.24; 95% confidence interval (95% CI) lower limit: 1.79; upper limit: 5.86; level 95.

Age under 6 months

• Author, year of publication, country: Dorothy Damore MD(14), 2008, United States of America. Study: cohort, population: 1459; OR: 4.14; 95% confidence interval (95% CI) lower limit: 2.05; upper limit: 8.34; level: 95.

• Author, year of publication, country: De los Ríos-Herrera A (15), 2018, Peru. Study: cases and controls, population: 174; OR: 7.54; 95% confidence interval (95% CI) lower limit: 2.72; upper limit: 20.86; level: 95.

• Author, year of publication, country: WeiCai (16), 2019, Germany. 95% confidence interval (95% CI)

• Author, year of publication, country: Niranjan-Lal J (13), 2021, Saudi Arabia. Study: cases and controls, population: 684, OR: 1.84; 95% confidence interval (95% CI); lower limit: 1.45; upper limit: 1.12; level: 95.

• Author, year of publication, country: Mondragón-García A(17)2024, Peru. Study: cases and controls, population: 222; OR: 5.02; 95% confidence interval (95% CI) lower limit: 2.55; upper limit: 99.01; level: 95.

Prematurity

• Author, year of publication, country: De los Ríos-Herrera A(15), 2018, Peru. Study: cases and controls, population: 174, OR: 2.97; 95% confidence interval (95% CI) lower limit: 1.26; upper limit: 7.02; level: 95.

• Author, year of publication, country: Rodríguez-Martínez CE (12) ,2018, Colombia. Study: cases and controls, population: 303;OR: 2.97; 95% confidence interval (95% CI) lower limit: 1.10; upper limit: 36.46; level: 95.

• Author, year of publication, country: WeiCai (16), 2019, Germany. Study: cohort, population: 438; OR: 6.71; 95% confidence interval (95% CI) lower limit: 2.19; upper limit: 20.61; level: 95.

• Author, year of publication, country Pérez Delgado JC (18), 2020, Peru. Study: cases and controls, population: 225; OR: 3.12; lower limit: 1.00; upper limit: 10.79; level: 95.

Apnea on admission

• Author, year of publication, country: Pérez Delgado JC (18), 2020, Peru. Study: cases and controls, population: 225; OR: 6.28; 95% confidence interval (95% CI) lower limit: 1.72; upper limit: 23.00; level: 95.

• Author, year of publication, country: Ramos-Fernández JM (19), 2018, Spain. Confidence interval 95% (95% CI).

• Author, year of publication, country: Martínez Aimelis. (20)2018, Cuba. Study: cases and controls, population: 47; OR: 3.30; 95% confidence interval (95% CI) lower limit: 1.87; upper limit: 5.83; level: 95.

• Author, year of publication, country, García-Común EA. (21)2023, Peru. Study: cases and controls, population: 180, OR: 7.08; 95% confidence interval (95% CI) lower limit: 1.97; upper limit: 25.33; level: 95.

Low water intake

• Author, year of publication, country: Dorothy Damore MD.(14), 2008, United States of America. Study: cohort, population: 1459, OR: 3.31; 95% confidence interval (95% CI) lower limit: 1.55; upper limit: 7.07; level: 95.

• Author, year of publication, country: Ramos-Fernández J M.(19), 2017, Spain. Study: cases and controls, population: 695; OR: 12.40; 95% confidence interval (95% CI) lower limit: 3.12; upper limit: 49.35; level: 95.

• Author, year of publication, country: Esquivel-Suman R (11),2022, Cuba. Study: cases and controls, population: 654; OR: 47.0; 95% confidence interval (95% CI) lower limit: 11.12; upper limit: 200.45; level: 95.

Oxygen saturation less than 92%

•Author, year of publication, country: Pérez Delgado JC (18), 2020, Peru. Study: cases and controls, population: 225; OR: 6.44; lower limit: 2.17; upper limit: 19.11 level: 95.

• Author, year of publication, country: Gjengstø-Hunder JO.(22)2020, Norway. Study: Clinical trial, population: 404; OR: 4.65; lower limit: 1.52; upper limit: 14.24 level: 95.

• Author, year of publication, country: Niranja-Lal J.(13)2020, Arabia. Study: Clinical trial, population: 684; OR: 4.12; lower limit: 2.57; upper limit: 6.60 level: 95.

Neutrophil-lymphocyte ratio

• Author, year of publication, country: Beltrán et al (23)2016, Peru. Study: cohort, population: 83, OR: 3.96; 95% confidence interval (95% CI) lower limit: 1.92; upper limit: 8.17; level: 95.

• Author, year of publication, country: Wang et al (24)2017, Asia. Study: meta-analysis, population: 2297; OR: 1.84; 95% confidence interval (95% CI) lower limit: 1.52; upper limit: 2.22; level: 95.

• Author, year of publication, country: Mu et al (25)2018, Asia. Study: meta-analysis, population: 2515, OR: 1.83; 95% confidence interval (95% CI) lower limit: 1.24; upper limit: 2.69; level: 95.

• Author, year of publication, country: Moisa, E(26)2021, Romania Study: cohort, population: 272; OR: 2.25; 95% confidence interval (95% CI) lower limit: 1.31; upper limit: 3.86; level: 95.

Consolidation pattern on lung ultrasound

•Author, year of publication, country: Dorothy Damore MD. (14) 2008, USA. Study: cohort, population: 1459, OR: 1.55; 95% confidence interval (95% CI) lower limit: 3.31; upper limit: 7.07; level: 95.

• Author, year of publication, country: Ramos JM (19)2018, Spain. Study: cases and controls, population: 695; OR: 12.40; 95% confidence interval (95% CI) lower limit: 3.12; upper limit: 49.36; level: 95.

• Author, year of publication, country: Ezquivel-Suman R(11) 2022, Spain. Study: cases and controls, population: 654; OR: 47.79; 95% confidence interval (95% CI) lower limit: 11.12; upper limit: 205.45; level: 95.

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• Author, year of publication, country: Pérez Delgado JC. (18) 2020, Peru. Study: cases and controls, population: 225; OR: 7.24; 95% confidence interval (95% CI) lower limit: 3.15; upper limit: 16.67; level: 95.

- Author, year of publication, country: Gori L. (27) 2022; Italy. Study: cohort; population: 233; OR: 4.22; 95% confidence interval (95% CI) lower limit: 1.59; upper limit: 11.22; level: 95

• Author, year of publication, country: Uriarte-Méndez AE. (28) 2022, Peru. Study: cases and controls, population: 654; OR: 9.55; 95% confidence interval (95% CI) lower limit: 3.94; upper limit: 23.13; level: 95.

Quantitative analysis of risk factors from the systematic review. Meta-analysis

Low water intake increased the probability of progressing to severe illness by 11 times [OR: 11.37; confidence interval (CI) 2.2924-56.4465].variance between studies: 0.0000, variance within studies: 0.1808, the RI coefficient: 0.000, coefficient of variation between studies: 0.0000 and theI2 0%This issue showed homogeneity among the studies. (Fig. 1)

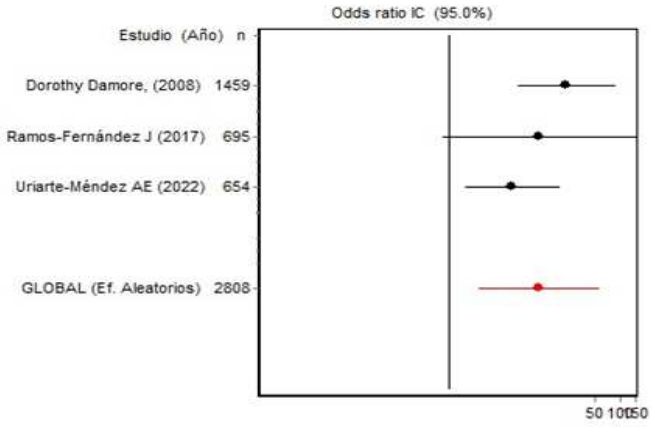

Fig. 1 Meta-analysis. Association between low water intake and progression to severe illness in children with acute bronchiolitis

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LThe presence of the pulmonary consolidation pattern (b) increased the probability of developing severe bronchiolitis by 9 times (OR: 9.67; CI: 4.98-18.77), variance between studies: 0.2726, variance within studies: 0.2732, RI coefficient: 0.2994, coefficient of variation between studies: 0.2394; I2 30%, with slight heterogeneity between studies (Fig. 2).

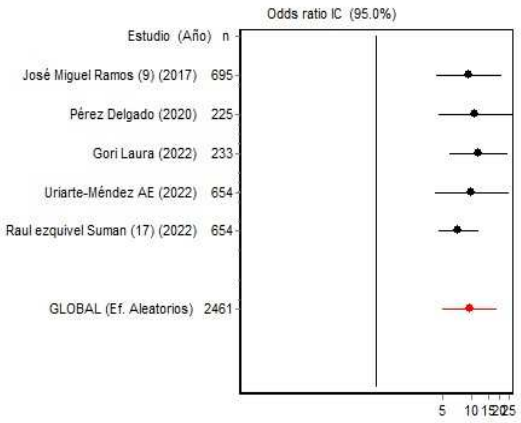

Fig. 2 Pulmonary consolidation pattern and progression to severity in children with acute bronchiolitis.

Oxygen saturation less than 92% (a) by pulse oximetry was a factor favoring the severity of bronchiolitis, after including homogeneous studies in a meta-analysis (OR: 4.45; CI: 2.98-6.66), variance between studies: 0.0000, variance within studies: 0.1273; RI coefficient: 0.0000; coefficient of variation between studies: 0.0000 and I2 0%. (Fig. 3)

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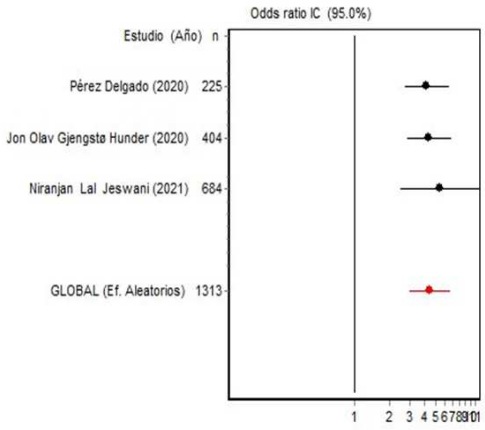

Fig. 3. Meta-analysis. Association between oxygen saturation of 92%, and progression to severity in children with acute bronchiolitis.

The presence of apnea on admission (b) within the clinical picture of bronchiolitis quadrupled the progression to severity. The selected studies were homogeneous (OR: 4.44; CI: 2.93-6.73), variance between studies: 0.0000; variance within studies: 0.808; RI coefficient: 0.0000; coefficient of variation between studies: 0.0000 and I2 00% (Fig 4).

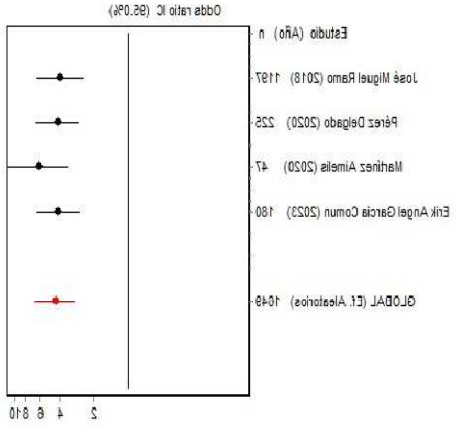

Fig. 4. Meta-analysis. Association between apnea on admission and progression to severity in children with acute bronchiolitis.

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The influence of prematurity was evident, increasing the probability of progressing to severe bronchiolitis by 3 times (OR: 3.54; CI: 2.14-5.86; variance between studies: 0.0000; variance within studies: 0.2648; RI coefficient: 0.0000; the coefficient of variation between studies was 0.0000 and the I200%). (Fig. 5)

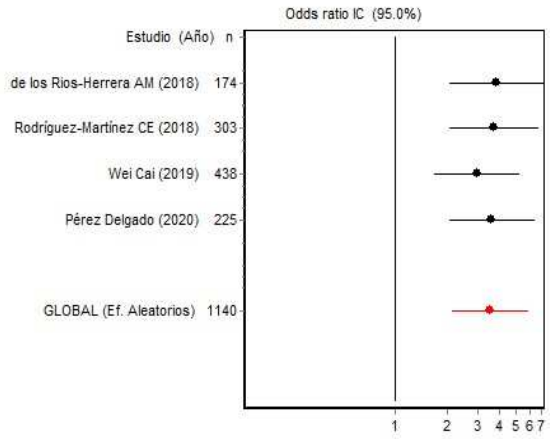

Fig 5. Meta-analysis. Association between prematurity and progression to severity in children with acute bronchiolitis.

Discussion

It is acknowledged that children may experience feeding difficulties. Maintaining adequate hydration is challenging due to circumstances such as increased insensible losses from tachypnea and fever, or decreased intake due to respiratory effort or congestion. In this regard, the increased respiratory distress attributable to bronchiolitis serves as a guide for fluid replacement recommendations. (14,11)

Several studies indicate that poor food intake in the previous 24 hours can be a predictor of oxygen saturation, associated with a pulse oximetry value <95%. When the respiratory rate exceeds 60 to 70 breaths per minute, feeding may be compromised, particularly if nasal

secretions are abundant. Difficulty maintaining adequate intake is related to the severity of bronchiolitis in patients. Research shows that poor intake (less than 50% of basal requirements), often interpreted as food refusal, increases the need for mechanical ventilation and is therefore considered an important predictor of severity. (11, 14, 18)

Lung ultrasound is a very useful tool in the diagnosis and monitoring of various diseases, including bronchiolitis; consequently, many researchers include diagnostic and prognostic instruments in it. (14,15,29) A review of the evidence shows that the appearance of a consolidation pattern on lung ultrasound was one of the most significant risk factors, increasing the probability of progressing to severe bronchiolitis by more than 9 times in studies with slight heterogeneity.

Bronchiolitis causes structural alterations in the pulmonary periphery due to impaired ventilation related to bronchiolar inflammation, air trapping, dysventilation, or atelectasis. Ultrasound allows for the evaluation of the subpleural lung in terms of density, and therefore, the absolute or relative reduction in the quantitative ratio of air space to interstitium. Accordingly, it is reasonable to opt for a combination of clinical and ultrasound parameters in clinical practice. (29,30)

Currently, there is increasing agreement between white lung and small consolidation (generally surrounded by white lung). Studies have shown that patients with an ultrasound pattern consistent with bronchiolitis have a significant correlation with the consolidation pattern, progressing to severity. In this sense, lung ultrasound is demonstrated to be a useful tool for predicting hospitalization and severity. (14,15, 30)

Inflammation causes narrowing of the bronchial lumen, leading to uneven airflow resistance in the various airways. This unequal ventilation-perfusion ratio results in early hypoxemia, which occurs because oxygenated blood from ventilated alveoli is insufficient to compensate for the low oxygen tension in non-ventilated or hypoventilated alveoli. Hypoxemia is the most frequently reported blood gas abnormality in the literature. Its indirect determination, through

oxyhemoglobin saturation, is easily detected with a pulse oximeter, which is currently used to monitor hospitalized patients. Oxygen saturation is closely related to the intensity of tachypnea and, especially, to retractions.

The studies consulted suggest that low oxygen saturation is an associated factor for the development of severe bronchiolitis and show that patients under two years of age with an oxygen saturation ≤ 92% have a 4.1 times greater risk of progressing to a severe form of the disease. Other authors refer to oxygen saturation below 90%. In the present systematic review, oxygen saturation ≤ 92% was a statistically significant prognostic factor. (13, 21)

It is noted that obstructive apneas in young infants are clearly related to the pathophysiology of bronchiolitis, due to increased secretions and airway inflammation. Undoubtedly, apnea episodes can worsen bronchiolitis, especially in children with a history of prematurity and those under 8 weeks of age. While not specific to any particular virus, these episodes predispose infants to developing respiratory failure and requiring mechanical ventilation.

Pérez-Delgado, (18) reports that apnea episodes on admission occurred in 10.0% of all patients evaluated with this diagnosis, and of these, 80% had an unfavorable evolution by presenting severe acute bronchiolitis, with statistically significant evidence.

Other authors associate apnea episodes with prematurity and low birth weight. (15,16) Ramos Fernández (19) suggests that knowing which infants are more likely to experience apnea helps clinicians anticipate complications or severity. In his study, the incidence of apnea during hospital admission for bronchiolitis was 4.4%.

Preterm infants are themselves a risk factor for bronchiolitis because they did not receive transplacental immunoglobulins and antibodies against respiratory syncytial virus (RSV) transmitted by the mother during the last trimester of pregnancy, which passively protect them. It is accepted that premature infants often have a weak capacity to control the pulmonary inflammation observed in this pathology, in addition to the abnormal baseline oxygenation present in these children, which leads to a greater risk of severe illness. Similarly, an association

between these two variables is argued, with studies finding that children born before 37 weeks have a seven times greater risk of developing severe acute bronchiolitis. (16)

Esquivel-Suman (11) concluded in his study that prematurity is a risk factor for developing severe bronchiolitis through two fundamental mechanisms: an inadequate immune response, unable to neutralize the infection, and pulmonary immaturity. Pérez-Delgado, for his part, also noted in his research that 75.0% of patients with severe bronchiolitis had a history of prematurity. (18)

In accordance with the above, the younger the child, the greater the risk of developing more severe conditions, due to the immaturity, anatomical characteristics of the airways, and their defensive mechanisms, which predispose them to respiratory failure. Therefore, infants tolerate bronchiolar edema, bronchospasm, and the accumulation of excessive secretions less well, with lower initial respiratory conductance.

In children under 6 months of age, respiratory infections are more severe because their defense mechanisms are insufficient, they have a poor response to the cough reflex, little mucociliary development, insufficient alveolar macrophages, hypofunction of the complement system and lymphocytes, and an increased predisposition to infections due to a tendency towards diaphragmatic fatigue because they have obligatory nasal breathing; the central airways are larger than the peripheral ones. (13-15)

The reviewed studies suggest that the most affected children are those under 6 months of age, and especially those under three months of age. This is related to a decrease in lung compliance and increased airway resistance with impaired innate immunity, which predisposes them to suffer serious illnesses in the first months of life. (13-15)

Underlying diseases, such as alterations in the immune system, affect both humoral and cellular immunity, but it is in the cellular response where a marked deterioration occurs, with a decrease in T lymphocytes, causing anergy to various antigens. Complement is also affected, and CH50 values are decreased, which plays an important role in defense mechanisms. Ozuna et al. (31) showed in their study an association between the presence of comorbidities and severe

bronchiolitis, increasing the risk of illness sixfold. Regarding comorbidities, Andrea Ayala, in her research, found that 22% of patients presented with some underlying pathology, with congenital heart disease being the most frequent (12%). (32) This demonstrates that children hospitalized in the PICU with bronchiolitis require careful screening to detect underlying cardiac, pulmonary, or neurological diseases.

The neutrophil-to-lymphocyte ratio, for its part, is an acute-phase reactant of undeniable diagnostic and prognostic value, indicating a state of inflammation in the body. The pathogenesis of the disease is characterized by inflammation of the bronchioles, and neutrophil accumulation is reportedly dominant in bronchiolitis. The expression of various pro-inflammatory cytokines and chemokines increases, and these mediators attract inflammatory leukocytes. Although many different molecules can play a role in the inflammatory response, the complete blood count (CBC) is the first parameter evaluated in pediatric clinics because it is readily available and inexpensive. (23,26)

In recent years, the neutrophil-to-lymphocyte ratio (NLR) has been used as a systemic inflammatory marker to predict the prognosis of infectious diseases. The literature reviewed shows that this biomarker has good discriminatory power for diagnosing severity in bronchiolitis, with a sensitivity of 84.4% and a specificity of 82.2%. Other authors associate a neutrophil-to-lymphocyte ratio greater than 4 with a worse prognosis and report that this elevated ratio more than doubles the likelihood of a poor outcome. Furthermore, they report that patients with this elevated ratio have lower survival rates.(76% vs 48%). (1, 23, 26)

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Conclusions

The usefulness of the included factors in predicting the progression to severity in children with acute bronchiolitis was demonstrated.The results highlight the need to develop new tools that take into account the factors discussed in order to optimize severity prediction.

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Conflict of interest

The authors declare no conflicts of interest.

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