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Feeding Status, Inflammatory Biomarkers, Clinical Severity, and Six-Month Recurrence in RSV-Predominant Bronchiolitis Among Infants Younger than Six Months

Soumia Boucif [1,*], Mohammed Chems Eddine Smahi [1,2,3,*], El Hadi Seninet [4] and Souheila Amal Benmansour [1,2,3]

[1] Laboratory of Applied Molecular Biology and Immunology, W0414100, University of Tlemcen, Tlemcen 13000, Algeria
[2] Department of Neonatology, Specialized Mother-Child Hospital of Tlemcen, Tlemcen 13000, Algeria
[3] Faculty of Medicine, University of Tlemcen, Tlemcen 13000, Algeria
[4] Biology Department, Faculty of Natural and Life Sciences, Blida 1 University, Blida 09000, Algeria
* Correspondence: soumia.boucif@univ-tlemcen.dz (S.B.); mohammedchemseddine.smahi@univ-tlemcen.dz (M.C.E.S.)

Highlights

What are the main findings?

- In a prospective cohort of 192 infants, exclusive breastfeeding was associated with lower bronchiolitis severity and a more favourable systemic inflammatory profile, including among RSV antigen-positive infants.
- The CRP-to-albumin ratio (CAR) showed strong discrimination of moderate-to-severe bronchiolitis (AUC 0.981) and six-month recurrence (AUC 0.906), with performance comparable to CRP and albumin.

What are the implications of the main findings?

- Feeding status remained associated with acute disease severity after multivariable adjustment, whereas its association with six-month recurrence did not persist, highlighting differences between acute and longer-term outcomes.
- Routinely available inflammatory biomarkers, including CRP, albumin, and CAR, offer promising candidates for further research into bronchiolitis severity assessment, although external validation is essential before clinical application.

Abstract

Background/Objectives: Respiratory syncytial virus (RSV) bronchiolitis is a major cause of morbidity in early infancy. This study evaluated associations between feeding status, systemic inflammatory profiles, clinical severity, and six-month recurrence in infants with RSV-predominant bronchiolitis. **Methods:** In this prospective observational cohort, 192 infants younger than six months with acute bronchiolitis were enrolled in Mascara, Algeria, and followed for six months. Feeding status, RSV antigen status, Wang Clinical Severity Score, clinical outcomes, and routinely available inflammatory biomarkers were analyzed using univariable and multivariable methods. **Results:** RSV antigen positivity was detected in 149 infants (77.6%). Exclusive breastfeeding was associated with lower clinical severity, hospitalization, oxygen therapy, and unadjusted recurrence, together with lower CRP, CAR, NLR, PLR, SII, and SIRI and higher albumin and LMR. Biomarker differences remained significant after false discovery rate correction and persisted among RSV antigen-positive infants. After adjustment, feeding status remained associated with moderate-to-severe bronchiolitis (wang score ≥4), whereas its association with six-month

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recurrence did not persist. CAR showed strong discrimination for moderate-to-severe bronchiolitis (AUC 0.981) and recurrence (AUC 0.906), with performance comparable to CRP and albumin**. Conclusions:** Feeding status was associated with distinct inflammatory profiles and clinical outcomes, particularly acute disease severity. Routinely available biomarkers may help characterize acute severity and short-term recurrence.

Keywords: respiratory syncytial virus; bronchiolitis; infant feeding; breastfeeding; inflammatory biomarkers; C-reactive protein/albumin ratio; serum albumin; leukocyte-derived inflammatory indices; clinical severity; recurrence

1. Introduction

Bronchiolitis is one of the most common lower respiratory tract infections in infancy and a major cause of pediatric consultations and hospitalizations worldwide. Respiratory syncytial virus (RSV) is the leading viral cause, although other respiratory viruses may also be involved. Young infants are particularly vulnerable because of their developing airways and immune systems [1,2]. Although bronchiolitis is usually self-limiting, it may progress to clinically significant respiratory distress, especially in infants with risk factors such as prematurity or underlying comorbidities [2,3]. Management remains predominantly supportive, including oxygen supplementation and hydration when required [4,5], and severe bronchiolitis has also been associated with an increased risk of recurrent wheezing and asthma-related outcomes later in childhood [6].

The clinical expression of RSV bronchiolitis reflects not only viral infection but also the host immune–inflammatory response [7,8]. Innate immune activation contributes to viral control but may also promote airway obstruction and tissue injury when excessive [9], while dysregulated adaptive immune responses may contribute to greater disease severity [7,10,11]. Routinely available blood-based biomarkers may therefore provide insight into systemic inflammatory activation [10]. Leukocyte-derived indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), reflect complementary aspects of neutrophil, lymphocyte, platelet, and monocyte responses [12] and have increasingly been explored in pediatric respiratory infections and bronchiolitis [10,13,14]. C-reactive protein (CRP) is a widely used acute-phase marker, whereas serum albumin is a negative acute-phase reactant influenced by inflammation and physiological stress [15,16]. The CRP/albumin ratio (CAR) combines these two complementary signals into a readily available integrated index [15,16]. Infant feeding practices may also influence immune development and responses to respiratory infection. Human milk contains secretory antibodies, lactoferrin, cytokines, human milk oligosaccharides, antimicrobial peptides, and other bioactive components that support mucosal immunity and modulate inflammatory responses [17–20]. Previous studies suggest that breastfed infants may experience milder respiratory infections and improved outcomes compared with non-breastfed or formula-fed infants [17,19,21,22]. This question is particularly relevant during the first six months of life, when infants are at increased risk of clinically significant bronchiolitis and milk feeding remains the predominant dietary exposure [2,3,23,24].

Although inflammatory biomarkers have been investigated in bronchiolitis and RSV infection, previous studies have largely focused on viral diagnosis, individual biomarkers, or acute disease severity [10,12,14,15]. Limited information is available on how feeding status relates simultaneously to systemic inflammatory and albumin-related profiles, RSV status, acute clinical severity, and subsequent recurrence, particularly in infants younger than six months. This study therefore aimed to determine whether feeding status is

associated with distinct clinical, inflammatory, and albumin-related profiles in infants younger than six months with RSV-predominant acute bronchiolitis, and to examine how these profiles relate to acute clinical severity and six-month recurrence. Particular attention was given to routinely available biomarkers, including CRP, albumin, CAR, NLR, PLR, LMR, SII, and SIRI.

2. Materials and Methods

2.1. Study Design and Participants

This prospective observational cohort study was conducted in a hospital facility in Mascara, Algeria, during the bronchiolitis epidemic season, from October 2025 to January 2026. Infants were followed for six months after the index episode. All eligible infants presenting to the participating hospital facility during the study period were screened, and those meeting the inclusion criteria with complete clinical, virological, laboratory, and follow-up data were included.

Eligible participants were infants younger than six months evaluated for acute bronchiolitis. Bronchiolitis was diagnosed clinically based on acute respiratory symptoms, including cough, wheezing, increased respiratory effort, and/or signs of lower respiratory tract infection. Infants with major underlying comorbidities, including chronic respiratory disease, congenital heart disease, primary or secondary immunodeficiency, major congenital anomalies, or other severe chronic conditions, were excluded. Infants with incomplete clinical, virological, laboratory, or follow-up data were also excluded.

A flow diagram summarizing participant screening, exclusions, and final inclusion in the analytical cohort is presented in Figure 1.

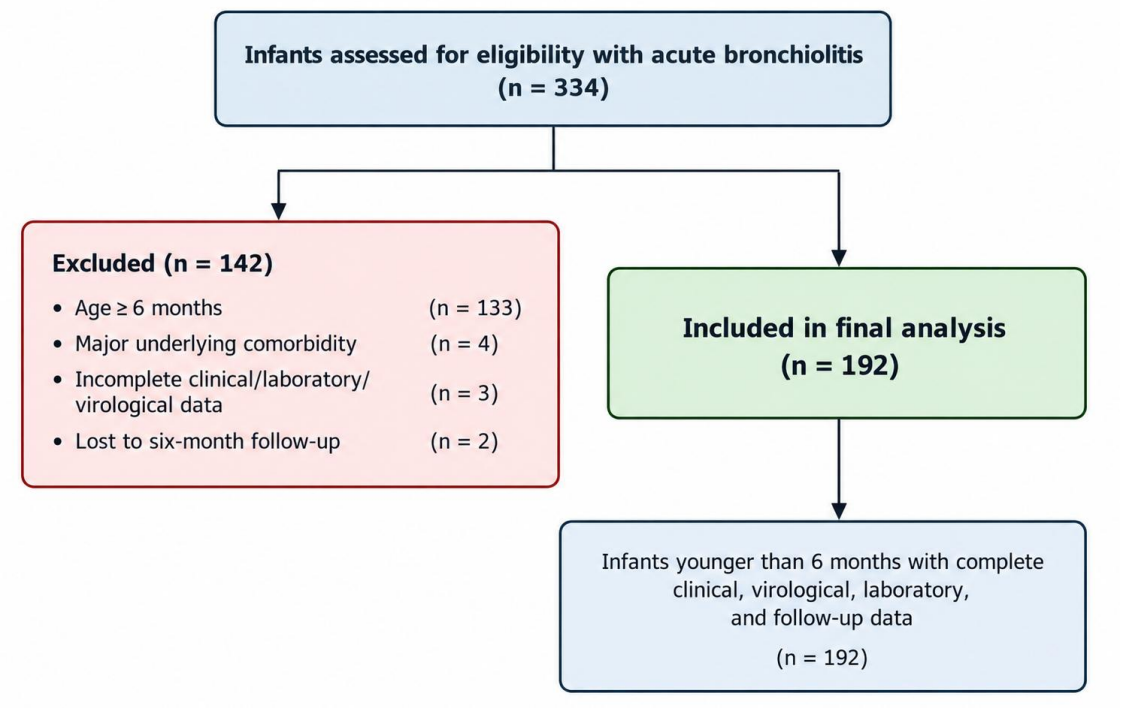


Figure 1. Study flow diagram.

2.2. Clinical Data, Feeding Classification, Anthropometry, and Outcomes

Demographic, environmental, clinical, virological, and laboratory data were collected using a standardized form during the initial consultation. Recorded variables included age, sex, gestational age, family history of atopy, personal history of atopic disease, passive smoking exposure, feeding type, RSV antigen status, Wang clinical severity score,

oxygen saturation, respiratory rate, chest retractions, hospitalization, oxygen therapy, complications, and bronchiolitis recurrence during the six-month follow-up period.

No infant had documented exposure to maternal RSV vaccination during pregnancy or infant RSV monoclonal antibody prophylaxis. Feeding status was classified according to the infant's usual feeding pattern before the onset of the index bronchiolitis episode, based on parental/legal guardian report and World Health Organization definitions [25]. Changes in feeding introduced after symptom onset because of reduced intake or feeding difficulties were not used to determine the feeding category. Exclusive breastfeeding was defined as breast milk feeding without formula milk, mixed feeding as combined breast milk and formula feeding, and formula feeding as formula milk without breastfeeding. The precise duration of each feeding pattern before the index episode was not systematically recorded.

Weight and recumbent length recorded at the initial consultation were used to calculate sex-specific weight-for-length z-scores (WLZ) according to the WHO Child Growth Standards [26]. WLZ was included as an anthropometric indicator to characterize the cohort and to examine whether anthropometric status differed according to feeding type.

Disease severity was assessed during the initial consultation using the Wang Clinical Severity Score, which evaluates respiratory rate, wheezing, chest retractions, and general condition [27,28]. The Wang Clinical Severity Score ranges from 0 to 12. Severity was classified as mild (0–3), moderate (4–8), and severe (9–12); the minimum observed score in the present cohort was 1. For binary analyses, moderate-to-severe bronchiolitis was defined as Wang score ≥4.

The primary outcomes were moderate-to-severe bronchiolitis and bronchiolitis recurrence during six-month follow-up. Secondary outcomes included oxygen therapy and hospitalization.

Parents/legal guardians were contacted at 1, 3, and 6 months after the index episode and were provided with a dedicated telephone number to report new respiratory symptoms between scheduled contacts. Families could also seek clinical assessment if respiratory symptoms recurred. Resolution of the index episode was determined clinically by the disappearance of acute bronchiolitis symptoms and return to the infant's usual respiratory condition. Recurrence was defined as at least one new episode of clinically diagnosed bronchiolitis occurring after complete resolution of the index episode [29]. No fixed minimum symptom-free interval was required. Parental reports alone were not sufficient; suspected recurrent episodes were clinically assessed and confirmed by the treating pediatrician. Persistent symptoms from the initial episode or isolated wheezing without a new diagnosis of bronchiolitis were not classified as recurrence.

Bacterial superinfection was diagnosed by the treating pediatrician based on a combination of concordant clinical and paraclinical findings. Clinical indicators included persistent or secondary fever, clinical deterioration, and signs suggestive of a focal bacterial infection. Supporting evidence included laboratory abnormalities, radiological findings such as pulmonary consolidation, and microbiological results when available. The final diagnosis was based on the pediatrician's clinical judgment, taking into account the overall clinical presentation and available investigations. Routine bacterial cultures are not recommended in typical bronchiolitis [30], and microbiological diagnosis of childhood pneumonia can be challenging [31]. Cultures were not systematically performed in this cohort. Given the potential influence of bacterial superinfection on inflammatory biomarkers, this variable was included in the multivariable analyses, and a sensitivity analysis excluding affected infants was performed.

2.3. Virological, Laboratory and Biomarker Assessment

Nasopharyngeal swabs were collected during the initial consultation for RSV detection using the TES-H107 Triplex COVID-19/Influenza A-B/RSV rapid immunochromatographic antigen test (Qingdao Hightop Biotech Co., Ltd., Qingdao, China), according to the manufacturer's instructions. Infants were classified as RSV antigen-positive or RSV antigen-negative. No RT-PCR-based multiplex respiratory viral testing was performed, and systematic testing for other respiratory viruses was not available.

Clinical assessment, Wang scoring, and venous blood sampling were performed during the initial consultation. For infants who were subsequently hospitalized, baseline clinical assessment and blood sampling were completed before inpatient admission and initiation of respiratory support. The exact interval between symptom onset and blood sampling was not systematically recorded.

Venous blood for complete blood count and leukocyte differential was collected into EDTA tubes and analyzed using a Zybio Z50 automated hematology analyzer (Zybio Inc., Chongqing, China) with an automated five-part leukocyte differential. Blood for CRP and albumin measurements was collected in plain tubes, with serum used for biochemical analysis on a Mindray BS-240 Pro automated biochemistry analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). CRP was measured using a latex-enhanced immunoturbidimetric method, whereas serum albumin was measured using a colorimetric bromocresol green method. The reagents used for both CRP and albumin measurements were supplied by Shenzhen Mindray Bio-Medical Electronics Co., Ltd. (Shenzhen, China). Samples were analyzed immediately or within a few hours of collection.

Leukocyte-derived inflammatory indices were calculated from the source laboratory values before presentation rounding. These included the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), calculated as follows:

NLR = neutrophils/lymphocytes;
PLR = platelets/lymphocytes;
LMR = lymphocytes/monocytes;
SII = platelets × neutrophils/lymphocytes;
SIRI = neutrophils × monocytes/lymphocytes.

The CRP/albumin ratio (CAR) was calculated as CRP divided by serum albumin. All derived inflammatory indices were calculated using the original laboratory measurements at their recorded analytical precision, with rounding applied only for presentation.

2.4. Statistical Analysis

Analyses were performed using Python 3.11 with pandas 3.0.5, NumPy 2.3.5, SciPy 1.17.1, scikit-learn 1.9.0, statsmodels 0.15.0, and Matplotlib 3.11.1. Because of the exploratory observational design, no formal a priori sample size calculation was performed, and all eligible infants were included.

Continuous variables were summarized as medians with interquartile ranges, and categorical variables as frequencies and percentages. Between-group comparisons were performed using the Mann–Whitney U test for two groups and the Kruskal–Wallis test for three groups. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Univariable analyses were performed according to feeding type, RSV antigen status, Wang severity category, and recurrence status. Additional analyses restricted to RSV antigen-positive infants were performed to assess whether feeding-associated clinical and biomarker patterns persisted within the RSV-positive subgroup.

Spearman rank correlation was used to evaluate associations between Wang score, oxygen saturation, and inflammatory biomarkers.

Multivariable logistic regression models were used to examine the independent association of feeding status with (1) moderate-to-severe bronchiolitis, defined as Wang score ≥4, and (2) six-month recurrence. Exclusive breastfeeding was the reference feeding category. The severity model was adjusted for age, gestational age, RSV antigen status, passive smoking exposure, family history of atopy, and bacterial superinfection. The recurrence model included the same covariates with additional adjustment for baseline Wang score. Adjusted odds ratios (aORs) with 95% confidence intervals were reported, and the overall contribution of feeding status was assessed using likelihood-ratio testing.

Associations between individual biomarkers and the two outcomes were evaluated in separate multivariable models because of the strong biological and mathematical correlations between the biomarkers. These models additionally adjusted for feeding status. CRP, CAR, NLR, PLR, LMR, SII, and SIRI were log2-transformed and expressed as the odds ratio associated with a doubling of the biomarker value; albumin was expressed per 5 g/L increase. Benjamini–Hochberg false-discovery-rate correction was applied across biomarker models [32]. Because several severity models showed evidence of quasi-separation, Firth bias-reduced logistic regression was performed as a sensitivity analysis.

Receiver operating characteristic (ROC) analyses were used to assess biomarker discrimination of concurrent Wang-defined moderate-to-severe bronchiolitis and six-month recurrence. AUC values, 95% confidence intervals, Youden-optimal thresholds, sensitivity, and specificity were estimated. For albumin, ROC analyses were performed in the inverse direction because lower values were associated with greater severity and recurrence. No formal statistical comparison of AUCs was performed.

To assess potential optimism from deriving and evaluating ROC thresholds in the same cohort, internal validation was performed using 2000 bootstrap resamples with out-of-bag evaluation. For each bootstrap resample, the Youden-optimal threshold was derived in the bootstrap training sample and evaluated in observations not selected into that resample. Out-of-bag AUC, sensitivity, and specificity were summarized across resamples. ROC thresholds were considered exploratory and not externally validated.

A sensitivity analysis excluding infants with bacterial superinfection was performed to determine whether biomarker discrimination was materially influenced by bacterial inflammatory confounding.

For multiple biomarker comparisons, the Benjamini–Hochberg procedure was used to calculate FDR-adjusted q-values [32]. No imputation was performed for missing data. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

2.5. Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the University of Tlemcen on 2 July 2025. No separate approval/reference number was issued by the Ethics Committee. Regulatory authorization to conduct the study was granted by the Directorate of Health and Population of Mascara Province, Algeria, on 20 July 2025, in accordance with applicable local authorization procedures. Institutional authorization to conduct the study and use the relevant clinical and laboratory data was obtained from the Director of the hospital facility on 20 September 2025.

Written informed consent was obtained from the parents or legal guardians of all participating infants before enrollment. The clinical and laboratory examinations included in the study were performed as part of routine patient care and were not undertaken solely for research purposes. All data were anonymized before analysis, and the

confidentiality of participants' personal and medical information was maintained throughout the study.

3. Results

3.1. Study Population and Baseline Characteristics

A total of 192 infants were included in the final analysis (Figure 1). Median age was 4 months [IQR: 3–5], and 149 infants (77.6%) were RSV antigen-positive. The median Wang Clinical Severity Score was 6 [IQR: 2–8]. Using the conventional Wang severity categories, 70 infants (36.5%) had mild bronchiolitis (0–3), 102 (53.1%) had moderate disease (4–8), and 20 (10.4%) had severe disease (9–12). During the index episode, 70 infants (36.5%) were hospitalized, of whom 60 required oxygen therapy (31.2% of the total cohort); 69 infants (35.9%) experienced a recurrent bronchiolitis episode during six-month follow-up (Table 1).

Table 1. Baseline characteristics of the study population (N = 192).

Variable	Value
Age, months, median [IQR]	4 [3–5]
Male sex, *n* (%)	101 (52.6%)
Gestational age, weeks, median [IQR]	38 [37–40]
Weight-for-length z-score, median [IQR]	−0.02 [−0.75–0.55]
Family history of atopy, *n* (%)	63 (32.8%)
Passive smoking exposure, *n* (%)	32 (16.7%)
Feeding status, *n* (%)	
Exclusive breastfeeding	75 (39.1%)
Mixed feeding	51 (26.6%)
Formula feeding	66 (34.4%)
RSV antigen-positive, *n* (%)	149 (77.6%)
Wang score, median [IQR]	6 [2–8]
Wang severity category, *n* (%)	
Mild (0–3)	70 (36.5%)
Moderate (4–8)	102 (53.1)
Severe (9–12)	20 (10.4%)
Oxygen saturation, %, mean ± SD	94.21 ± 3.61
Hospitalization, *n* (%)	70 (36.5%)
Oxygen therapy, *n* (%)	60 (31.2%)
Bacterial superinfection, *n* (%)	39 (20.3%)
Six-month recurrence, *n* (%)	69 (35.9%)

IQR = interquartile range; RSV = respiratory syncytial virus; SD = standard deviation; SpO_2 = peripheral oxygen saturation; WLZ was calculated using sex-specific WHO Child Growth Standards.

Median weight-for-length z-score (WLZ) was −0.02 [IQR: −0.75 to 0.55], with 185/192 infants (96.4%) having values between −2 and +2 SD. Bacterial superinfection was documented in 39 infants (20.3%) and was considered in the adjusted and sensitivity analyses.

3.2. Feeding Status, Clinical Outcomes, and Biomarker Profiles

Clinical severity and inflammatory and albumin-related profiles differed according to feeding status (Table 2 and Figure 2). Exclusively breastfed infants had lower Wang scores and lower hospitalization and oxygen-therapy requirements than infants receiving mixed or formula feeding. Six-month recurrence also differed between feeding groups in the unadjusted analysis ($p = 0.015$).

Table 2. Clinical Outcomes and Biomarkers by Feeding Type.

Variable	Exclusive Breastfeeding (*n* = 75)	Mixed Feeding (*n* = 51)	Formula Feeding (*n* = 66)	*p*-Value
Wang score, median [IQR]	3 [1–6]	7 [3–8]	6 [4.25–8]	<0.001
Hospitalization, *n* (%)	13 (17.3%)	28 (54.9%)	29 (43.9%)	<0.001
Oxygen therapy, *n* (%)	12 (16.0%)	26 (51.0%)	22 (33.3%)	<0.001
Six-month recurrence, *n* (%)	18 (24.0%)	20 (39.2%)	31 (47%)	0.015
WLZ, median [IQR]	0.13 [−0.53–0.54]	−0.31 [−0.98–0.54]	0.08 [−0.61–0.63]	0.386
CRP, mg/L, median [IQR]	6 [5–22]	26 [10–28]	38 [18–75.75]	<0.001
Albumin, g/L, median [IQR]	43 [40–44]	40 [39–42.5]	39 [35–41]	<0.001
CAR, median [IQR]	0.14 [0.11–0.54]	0.67 [0.23–0.72]	0.97 [0.43–2.20]	<0.001
SII, median [IQR]	328 [265–437]	472 [352–615]	701 [375–2098]	<0.001

Continuous variables were compared using the Kruskal–Wallis test and categorical variables using chi-square or Fisher's exact test, as appropriate. For the four biomarkers shown, Benjamini–Hochberg FDR-adjusted q-values were <0.001. Full biomarker comparisons are provided in Supplementary Table S1. CAR = CRP/albumin ratio; CRP = C-reactive protein; SII = systemic immune-inflammation index; WLZ = weight-for-length z-score.

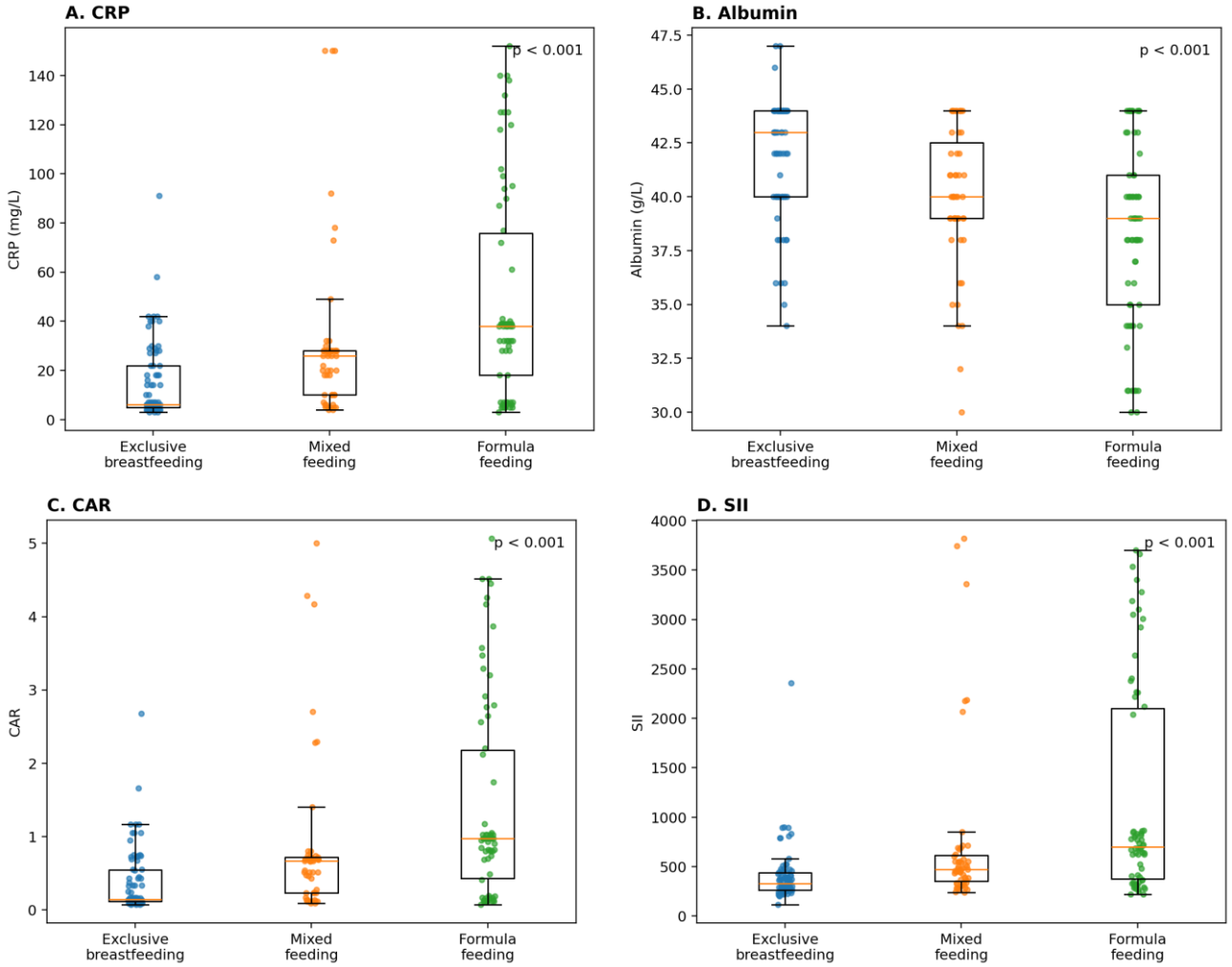


Figure 2. Feeding-associated clinical/biomarker profiles. (**A**) CRP; (**B**) albumin; (**C**) CAR; (**D**) SII. Blue, orange, and green represent exclusive breastfeeding, mixed feeding, and formula feeding, respectively. Dots represent individual observations; boxes indicate interquartile ranges, horizontal lines indicate medians, and whiskers show data dispersion.

CRP, CAR, and SII were lower, and serum albumin was higher among exclusively breastfed infants, with significant differences across feeding groups (all $p < 0.001$). In contrast, WLZ did not differ significantly according to feeding status ($p = 0.386$), indicating no evident anthropometric difference between the feeding groups.

Feeding distribution did not differ significantly according to RSV antigen status ($p = 0.394$). Feeding-associated clinical and biomarker differences were also observed when the analysis was restricted to RSV antigen-positive infants. Full clinical and biomarker comparisons according to RSV antigen status are presented in Table S2, while feeding-associated profiles restricted to RSV antigen-positive infants are provided in Table S3.

3.3. Multivariable Analyses of Acute Severity and Six-Month Recurrence

After adjustment for age, gestational age, RSV antigen status, passive smoking exposure, family history of atopy, and bacterial superinfection, feeding status remained associated overall with Wang-defined moderate-to-severe bronchiolitis (global $p < 0.001$). Compared with exclusive breastfeeding, formula feeding was associated with greater odds of moderate-to-severe disease (aOR 6.51, 95% CI 2.43–17.42), whereas the association with mixed feeding was not statistically significant. RSV antigen positivity, family history of atopy, and bacterial superinfection were also independently associated with greater acute severity (Table 3).

In contrast, feeding status was not independently associated with six-month recurrence after adjustment for the same covariates and baseline Wang score (global $p = 0.217$). Recurrence was independently associated with passive smoking exposure, family history of atopy, bacterial superinfection, and greater baseline Wang severity (aOR per point 1.63, 95% CI 1.33–2.00; $p < 0.001$) (Table 3).

Table 3. Multivariable logistic regression analyses of moderate-to-severe bronchiolitis and six-month recurrence.

Predictor	Wang ≥4, aOR (95% CI)	*p*-Value	Six-Month Recurrence, aOR (95% CI)	*p*-Value
Mixed vs. exclusive breastfeeding	2.09 (0.79–5.54)	0.137	0.36 (0.11–1.17)	0.089
Formula vs. exclusive breastfeeding	6.51 (2.43–17.42)	<0.001	0.52 (0.16–1.71)	0.284
Age, per month	0.74 (0.56–0.98)	0.036	1.30 (0.89–1.91)	0.177
Gestational age, per week	0.97 (0.74–1.26)	0.801	0.99 (0.73–1.35)	0.974
RSV antigen-positive	10.43 (3.67–29.63)	<0.001	0.93 (0.25–3.46)	0.908
Passive smoking	1.19 (0.37–3.86)	0.773	7.13 (2.23–22.79)	<0.001
Family history of atopy	3.88 (1.44–10.46)	0.007	2.89 (1.18–7.06)	0.020
Bacterial superinfection	7.97 (1.95–32.59)	0.004	8.55 (2.69–27.17)	<0.001
Baseline Wang score, per point	—	—	1.63 (1.33–2.00)	<0.001

Moderate-to-severe bronchiolitis was defined as Wang score ≥ 4. Exclusive breastfeeding was the reference feeding category. The severity model adjusted for age, gestational age, RSV antigen status, passive smoking, family history of atopy, and bacterial superinfection. The recurrence model included the same covariates plus baseline Wang score. Overall feeding-status likelihood-ratio *p*-values were 0.00032 for acute severity and 0.217 for recurrence. aOR = adjusted odds ratio; CI = confidence interval; RSV = respiratory syncytial virus.

3.4. Biomarkers in Relation to Severity and Recurrence

Inflammatory and albumin-related biomarker profiles showed clear gradients across Wang severity categories (Figure 3 and Table S4). CRP, CAR, SII, and the other leukocyte-derived inflammatory indices increased with greater clinical severity, whereas albumin and LMR decreased. Similar biomarker differences were observed according to six-month

recurrence status (Table S5). Associations between Wang score, oxygen saturation, and inflammatory biomarkers are illustrated in the Spearman correlation matrix (Figure S1).

Among the biomarkers evaluated, CAR, CRP, and albumin showed the strongest discrimination of concurrent moderate-to-severe bronchiolitis (apparent AUCs 0.981, 0.978, and 0.966, respectively). They also showed strong discrimination of six-month recurrence (AUCs 0.906, 0.900, and 0.900, respectively). Complete ROC results and corresponding curves are presented in Table S6 and Figure S2. The sensitivity analysis excluding infants with bacterial superinfection showed that biomarker discrimination remained strong (Table S7). Separate adjusted biomarker models and Firth bias-reduced sensitivity analyses are reported in Tables S8 and S9, respectively. Bootstrap out-of-bag internal validation showed little deterioration in discrimination (Table S10A,B).

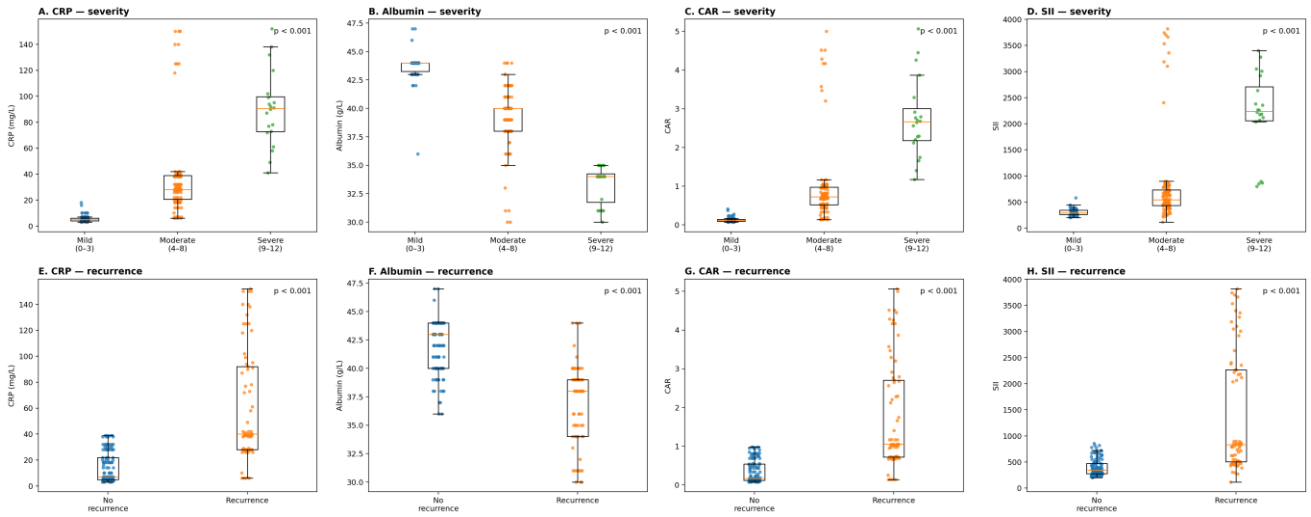


Figure 3. Severity and recurrence biomarker profiles. (**A**–**D**) CRP, albumin, CAR, and SII by disease severity, respectively; (**E**–**H**) the same biomarkers by six-month recurrence status, respectively. Blue, orange, and green indicate mild, moderate, and severe bronchiolitis in panels A–D; blue and orange indicate no recurrence and recurrence in panels E–H. Boxplot elements are defined as in Figure 2.

4. Discussion

4.1. Principal Findings and Contribution of the Study

In this prospective cohort of infants younger than six months with RSV-predominant acute bronchiolitis, feeding status was associated with a coherent pattern of clinical severity and systemic biomarker expression. Exclusively breastfed infants generally presented with lower Wang Clinical Severity Scores, lower hospitalization and oxygen-therapy requirements, lower CRP, CAR, and leukocyte-derived inflammatory indices, and higher serum albumin. Importantly, these differences were not restricted to the overall cohort but remained evident among RSV antigen-positive infants.

The main contribution of this study therefore extends beyond the observation that breastfeeding is associated with a milder clinical course of bronchiolitis, an association already supported by previous clinical literature [17,19,21,22,33]. By examining feeding status together with RSV antigen status, conventional inflammatory markers, leukocyte-derived indices, serum albumin, CAR, clinical severity, and six-month recurrence within the same cohort, the present study adds a biological dimension to this established clinical association and identifies a broader feeding-associated clinical and inflammatory phenotype.

The consistency of this pattern across complementary analyses is particularly noteworthy. The biomarkers that differed according to feeding status were also closely related to Wang severity, oxygenation, and recurrence status. Moreover, after adjustment for age, gestational age, RSV status, passive smoking, family history of atopy, and bacterial superinfection, feeding status remained associated overall with moderate-to-severe bronchiolitis, with formula feeding showing the clearest association compared with exclusive breastfeeding. This strengthens the interpretation that the observed feeding-related pattern was not explained solely by differences in the measured clinical risk factors.

The recurrence analysis provides an important additional perspective. Recurrence was more frequent among mixed- and formula-fed infants in unadjusted analyses, but feeding status was no longer independently associated with recurrence after adjustment for baseline severity and other covariates. Thus, feeding status appears more clearly related to the expression of the acute episode, whereas subsequent recurrence likely reflects a broader interaction between initial disease severity, environmental exposures, host predisposition, and inflammatory response.

4.2. Feeding Practices and Systemic Inflammatory Profiles

The less inflammatory clinical and biological profile observed among exclusively breastfed infants is biologically plausible. Human milk contains secretory antibodies, lactoferrin, cytokines, antimicrobial peptides, human milk oligosaccharides, immune cells, microbiota-related factors, and microRNAs that may contribute to mucosal immune defense, immune maturation, and regulation of inflammatory responses during early infancy [34]. These mechanisms provide a plausible biological context for the differences observed between feeding groups.

The present findings support this concept at the systemic level. Exclusive breastfeeding was associated with lower CRP, NLR, SII, SIRI, and CAR and higher albumin. These markers represent different components of the host response: NLR reflects the balance between neutrophil-mediated innate inflammation and lymphocyte-related regulation, while SII and SIRI integrate neutrophils with platelet or monocyte populations [12]. Their broadly concordant behavior suggests that the feeding-associated differences were not confined to one isolated laboratory marker.

The mixed-feeding group deserves particular consideration because it did not consistently behave as a simple intermediate category. Mixed-fed infants had particularly high hospitalization and oxygen-therapy rates, whereas formula-fed infants generally showed the strongest inflammatory profiles and formula feeding had the clearest adjusted association with moderate-to-severe disease. Mixed feeding may represent a heterogeneous exposure, including different proportions and durations of breast milk and formula feeding and different reasons for supplementation. This heterogeneity may partly explain why its clinical pattern was not simply intermediate between exclusive breastfeeding and formula feeding.

These findings are particularly relevant in infants younger than six months, when exclusive breastfeeding is internationally recommended, and complementary feeding is generally absent or limited [23]. Feeding practices during this period therefore represent a major nutritional and immunological exposure. Anthropometric status was broadly comparable across feeding groups, with no significant difference in weight-for-length z-scores, providing additional context for the observed feeding-associated differences in systemic inflammatory markers and serum albumin.

4.3. RSV-Predominant Bronchiolitis and Virological Relevance

The RSV-predominant nature of the cohort is central to the interpretation of the findings. More than three-quarters of infants were RSV antigen-positive, and RSV antigen

positivity was associated with greater clinical severity and systemic inflammatory activation, consistent with the established importance of RSV in clinically significant lower respiratory tract disease during infancy [6,35,36]. Importantly, feeding distribution did not differ significantly according to RSV antigen status. Furthermore, when the analysis was restricted to RSV antigen-positive infants, feeding-associated differences in clinical severity, oxygenation, hospitalization, oxygen-therapy requirements, and inflammatory biomarkers remained evident. This subgroup analysis strengthens the interpretation that the feeding-associated clinical and biological pattern is relevant within RSV-associated bronchiolitis itself rather than being explained simply by a greater proportion of RSV-positive cases in one feeding group.

RSV was identified using rapid antigen testing rather than systematic RT-PCR. Rapid antigen assays generally have high specificity but lower sensitivity than molecular testing [37], meaning that some RSV antigen-negative infants may have had undetected RSV infection or bronchiolitis caused by other respiratory viruses. The term RSV-predominant bronchiolitis therefore remains the most appropriate description of this cohort.

4.4. CAR, Albumin, and Biomarkers in Relation to Acute Severity

One of the most striking findings was the close alignment between routinely available biomarkers and clinical severity. CRP, CAR, NLR, PLR, SII, and SIRI increased with greater Wang severity, whereas albumin and LMR decreased. These patterns were also reflected in their relationships with oxygen saturation. The fact that the same biological profile distinguished feeding groups and tracked clinical severity supports the clinical relevance of the biomarker findings.

CAR was particularly informative because it combines two complementary acute-phase signals: increased CRP and decreased albumin. In this cohort, CAR increased markedly across severity categories and showed strong discrimination of concurrent moderate-to-severe bronchiolitis. Its performance was comparable to CRP and albumin individually. The overlapping confidence intervals do not support claiming that CAR is superior; rather, its interest lies in providing a simple integrated index of inflammatory activation and albumin-related physiological response.

Albumin itself also emerged as an informative marker. It was higher among exclusively breastfed infants, decreased with increasing disease severity, and was lower among infants who subsequently experienced recurrence. Albumin is not solely a nutritional marker; as a negative acute-phase reactant, it may decrease during systemic inflammation through altered hepatic metabolism, vascular permeability, redistribution, and catabolism [15]. Previous work has also suggested clinical relevance for serum albumin and albumin-based inflammatory ratios in bronchiolitis and RSV infection [38,39]. The present findings therefore position albumin as part of the broader biological response accompanying bronchiolitis severity rather than as an isolated nutritional measure.

The ROC analyses further illustrate the strength of these relationships. CAR, CRP, and albumin showed particularly strong discrimination of concurrent moderate-to-severe bronchiolitis, while leukocyte-derived indices also performed well. Internal bootstrap validation showed little deterioration in discrimination. These findings support further investigation of readily available biomarkers as adjuncts to clinical severity assessment.

4.5. Biomarkers and Six-Month Recurrence

The recurrence findings add a longitudinal dimension to the study. Infants who experienced a new bronchiolitis episode during follow-up already showed higher CRP, CAR, NLR, PLR, SII, and SIRI and lower albumin and LMR during the index episode. Several biomarker associations with recurrence also persisted after multivariable

adjustment, suggesting that the biological response during the acute episode may contain information about subsequent short-term respiratory vulnerability.

Previous studies have linked RSV bronchiolitis with later recurrent wheezing and asthma-related outcomes [6,35]. The present study addresses a shorter and more specific outcome, clinically confirmed bronchiolitis recurrence within six months, and should not be interpreted as demonstrating later asthma susceptibility. Nevertheless, the association between the acute biomarker profile and subsequent recurrence provides a rationale for longer-term follow-up studies.

Recurrence is likely to be multifactorial. Airway development, viral re-exposure, environmental exposures, family atopy, passive smoking, genetic susceptibility, immune maturation, and other clinical or social factors may contribute [40,41]. This is consistent with the adjusted analysis, in which passive smoking, family history of atopy, bacterial superinfection, and greater baseline Wang severity were independently associated with recurrence, whereas feeding status was not. The findings therefore suggest that the acute inflammatory profile represents one component of a broader susceptibility to recurrent respiratory illness.

4.6. CRP, Bacterial Superinfection, and Robustness of the Biomarker Findings

CRP was strongly related to feeding status, clinical severity, and recurrence. However, CRP is a nonspecific acute-phase reactant and may increase during viral inflammation as well as bacterial infection, pneumonia, fever, and other inflammatory conditions [15,42,43]. This is particularly relevant because bacterial superinfection was present in a subset of the cohort.

The sensitivity analysis excluding infants with bacterial superinfection therefore provides an important robustness check. The principal biomarker discrimination patterns remained strong after these infants were removed, including those for CAR, CRP, albumin, SII, SIRI, and NLR. This indicates that the associations observed in the overall cohort were not driven solely by infants with bacterial superinfection.

4.7. Clinical and Regional Relevance

The use of routinely available biomarkers is an important practical aspect of this study. CRP, serum albumin, and complete blood count-derived inflammatory indices are relatively accessible and inexpensive. They may therefore provide useful complementary information on inflammatory burden and disease severity, particularly in clinical environments where advanced molecular or immunological testing is not readily available.

This does not imply that biomarker testing should replace clinical assessment or be performed routinely in every infant with bronchiolitis. Bronchiolitis remains primarily a clinical diagnosis, and current recommendations do not support routine laboratory testing in typical uncomplicated disease [3,30,44]. Rather, the present findings suggest that in clinically significant or hospitalized cases, or in settings where additional characterization of inflammatory burden is relevant, routinely available biomarkers merit further investigation as adjuncts to established clinical assessment.

The study also contributes data from a North African setting, where pediatric RSV disease remains less represented in the literature than in many high-income settings [45]. This regional dimension is important because RSV burden, breastfeeding practices, access to viral diagnostics, and availability of specialized laboratory testing may differ between healthcare systems. The use of simple, widely available biomarkers may therefore have particular relevance in resource-limited and intermediate-resource settings.

From a public-health perspective, the findings also add biological context to the established benefits of breastfeeding during early infancy. The study cannot establish that breastfeeding itself caused the observed differences, but the combination of a more

favorable clinical course and a less inflammatory systemic profile among exclusively breastfed infants supports continued investigation of how early feeding exposures interact with host responses to respiratory infection.

4.8. Strengths and Limitations

This study has several strengths. First, it focused on infants younger than six months, an age group in which bronchiolitis severity is clinically important and milk-feeding practices remain the dominant nutritional exposure [2,3,23]. Its prospective design and six-month follow-up allowed both acute severity and subsequent recurrence to be examined in the same cohort. The high proportion of RSV antigen-positive infants and the persistence of feeding-associated differences in the RSV-positive subgroup strengthened the virological relevance of the findings.

A further strength is the integrated analytical approach. Feeding type, RSV status, clinical severity, hospitalization, oxygen requirement, anthropometry, conventional inflammatory markers, leukocyte-derived indices, albumin, CAR, and recurrence were evaluated together rather than as isolated outcomes. The robustness of the findings was further examined through multivariable adjustment, false-discovery-rate correction, sensitivity analysis excluding bacterial superinfection, and bootstrap internal validation.

Some limitations should nevertheless be considered. This was a single-center observational study, and residual confounding cannot be excluded; causal effects of feeding practices therefore cannot be established. Although weight-for-length z-scores provided an anthropometric assessment, they do not capture all aspects of nutritional status. Therefore, the observed albumin-related differences should not be interpreted as direct evidence of differences in nutritional status between feeding groups.

RSV classification relied on rapid antigen testing rather than systematic RT-PCR, and comprehensive testing for other respiratory viruses was not performed [37]. The exact interval from symptom onset to blood sampling was not systematically recorded, although clinical assessment, Wang scoring, and blood sampling were performed during the initial consultation and, in subsequently hospitalized infants, before inpatient admission and initiation of respiratory support.

The severe subgroup was relatively small, and data-derived ROC thresholds require validation in independent populations before clinical application. Follow-up was limited to six months, and recurrence should be interpreted as short-term recurrent bronchiolitis rather than long-term recurrent wheezing or asthma. These limitations define the scope of the study but do not detract from the consistency of the clinical and biological associations observed across complementary analyses.

5. Conclusions

In this prospective cohort of infants younger than six months with RSV-predominant bronchiolitis, feeding status was associated with acute clinical severity and systemic inflammatory profiles. Formula feeding showed higher adjusted odds of moderate-to-severe bronchiolitis than exclusive breastfeeding, whereas the association between feeding status and six-month recurrence did not persist after adjustment.

CRP, albumin, CAR, and several leukocyte-derived inflammatory indices were associated with clinical severity and subsequent recurrence. Further multicenter studies with external validation are warranted to establish their clinical utility.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children13121644/s1: Table S1: Full clinical, anthropometric, and biomarker comparisons according to feeding status; Table S2: Clinical and biomarker profiles according to RSV antigen status; Table S3: Feeding-associated profiles among RSV antigen-positive

infants; Table S4: Biomarkers according to Wang severity categories (0–3, 4–8, 9–12); Table S5: Clinical and biomarker profiles according to six-month recurrence; Table S6: Complete ROC performance for Wang ≥4 and six-month recurrence; Table S7: Sensitivity analysis excluding infants with bacterial superinfection; Table S8: Adjusted biomarker associations with severity and recurrence; Table S9: Firth bias-reduced logistic-regression sensitivity analysis; Table S10A: Bootstrap out-of-bag validation, discrimination and thresholds; Table S10B: Bootstrap out-of-bag validation, sensitivity and specificity; Figure S1: Spearman correlation matrix; Figure S2: Receiver operating characteristic (ROC) curves for biomarkers discriminating concurrent moderate-to-severe bronchiolitis (Wang score ≥ 4) and six-month recurrence.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Tlemcen on 2 July 2025. No separate approval/reference number or protocol code was issued by the Ethics Committee. Regulatory authorization to conduct the study was granted by the Directorate of Health and Population of Mascara Province, Algeria, on 20 July 2025, in accordance with applicable local authorization procedures. Institutional authorization to conduct the study and use the relevant clinical and laboratory data was obtained from the Director of the hospital facility on 20 September 2025. The clinical and laboratory examinations included in the study were performed as part of routine patient care and were not undertaken solely for research purposes. All data were anonymized before analysis, and the confidentiality of participants' personal and medical information was maintained throughout the study.

Informed Consent Statement: Written informed consent was obtained from the parents or legal guardians of all participating infants before enrollment. Written informed consent for publication was not applicable because the manuscript does not contain any identifiable individual-level information, images, or case details.

Data Availability Statement: Due to the sensitive nature of pediatric clinical data, the dataset is not publicly available but may be obtained from the corresponding authors upon reasonable request, subject to applicable ethical and institutional requirements.

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Abbreviations

The following abbreviations are used in this manuscript:

AUC	Area under the curve
BF	Breastfeeding
CAR	C-reactive protein/albumin ratio
CI	Confidence interval

CRP	C-reactive protein
IQR	Interquartile range
LMR	Lymphocyte-to-monocyte ratio
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
ROC	Receiver operating characteristic
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
SII	Systemic immune-inflammation index
SIRI	Systemic inflammation response index
SpO_2	Peripheral oxygen saturation
WHO	World Health Organization

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