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Bacterial infection in patients with juvenile systemic lupus erythematosus and fever

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Abstract

Background Juvenile Systemic Lupus Erythematosus (JSLE) is a chronic, systemic autoimmune disease characterized by an increased susceptibility to infections. Fever in these patients can result from infection, heightened lupus activity, or a combination of both. Various clinical factors and biomarkers have been proposed to differentiate between infection and disease activity, but the results remain inconclusive. The Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2 k) is used to assess lupus activity in the presence or absence of infection. This study aimed to identify factors associated with bacterial infections in JSLE patients presenting with fever.

Methods A case–control study, approved by the institutional ethics committee, was conducted.

Results Bacterial infection was identified in 17% of 116 patients. Factors evaluated included immunomodulator use, high-dose steroids, renal replacement therapy, erythrocyte sedimentation rate (ESR) > 20, C-reactive protein (CRP) > 60 and > 90 mg/L, ferritin > 500 ng/mL, neutrophil-to-lymphocyte ratio (NLR) > 6, platelet-to-lymphocyte ratio (PLR) > 133, procalcitonin (PCT) > 0.9 ng/mL, lymphocyte-to-C4 ratio (LC4R) > 66.7, and ESR/CRP ratio < 2. In the adjusted model, PCT > 0.9 ng/mL retained significance with $p < 0.01$. Nagelkerke's R^2 was 0.65, and the Hosmer–Lemeshow test indicated good internal validity.

Conclusions Bacterial infection was detected in 17% of JSLE patients with fever. Procalcitonin > 0.9 ng/mL is a critical marker for identifying bacterial infection. NLR, PLR, ESR/CRP ratio, LC4R, and ferritin require further investigation to establish definitive cut-off values for differentiating bacterial infections from other infections or disease activity. Individual patient evaluation remains the recommended approach for diagnosis.

Keywords Bacteria, Biomarkers, Fever, Systemic lupus erythematosus

Background

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by the presence of autoantibodies caused by immune system dysregulation. Its prevalence ranges from 3.2 to 300 cases per 100,000 people, with an incidence of 1.4 to 8.7 per 100,000 people [1]. SLE exhibits extensive phenotypic variability, with juvenile-onset SLE (JSLE) being the most common, accounting for 55.7% of cases. JSLE typically manifests between the ages of 7 and 13 [2] and is associated with a higher susceptibility to infections, increased disease activity, greater tissue and organ damage [3], and

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the need for more intensive immunosuppressive therapy [4]. The disease alternates between potentially life-threatening periods of immune activity and phases of remission [5–7].

In JSLE, infections contribute to morbidity and mortality in 44% of cases and increase healthcare costs by 30% due to prolonged hospitalizations and admissions to pediatric intensive care units. Infections can be bacterial, viral, or fungal in nature [8–10]. Approximately 50% of adults with SLE experience severe infectious episodes requiring extended hospitalization, and early identification of infected patients significantly improves outcomes [11]. Fever is a common symptom of both infection and heightened lupus activity, and these conditions often coexist. Fever is reported in 36–96% of adults with SLE, with 60% of cases attributed to disease activity, 23% to infection, and 12% to both conditions [12, 13].

Several clinical features and biomarkers have been investigated to assist clinicians in differentiating between disease activity and infection in SLE patients with fever. Evidence regarding the utility of biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), ferritin, and procalcitonin (PCT) remains inconclusive [14–20]. Ju-Yang et al. (2019) identified serositis, hematologic involvement, and high-dose glucocorticoids (>7.5 mg/day of prednisolone) as factors associated with severe infections, such as those requiring Intensive Care Unit (ICU) hospitalization or intravenous antibiotic use [21].

Zhai et al. (2021) reported a scoring system for identifying bacterial infections in adults with SLE, achieving an area under the curve (AUC) of 0.842 and a 95% confidence interval (CI) of 0.794–0.891. Variables such as white blood cell count, neutrophil count, ESR, CRP, PCT, interleukin-6, interleukin-10, interferon-gamma, and tumor necrosis factor-alpha were significantly elevated in patients with bacterial infections [22].

In pediatrics, Luo et al. reported that the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), fever, CRP, PCT, lymphocyte percentage, NLR, hemoglobin, and the SLE Disease Activity Index 2000 (SLEDAI-2 K) are predictive of infection, with an area under the curve (AUC) of 0.7886, sensitivity of 63.5%, and specificity of 89.2%. The authors recommend individualized clinical analysis for decision-making [23].

Sari et al. identified urinary tract infections (41%), skin and soft tissue infections (20.5%), and pneumonia (20.5%) as the most common infections, with methylprednisolone pulse therapy being a predictor of infection [24].

Disease activity indices, such as SLEDAI, are designed to classify disease activity regardless of the triggering cause [25–27]. Biomarkers like NLR, ESR/CRP ratio, platelet-to-lymphocyte ratio (PLR), and lymphocyte/C4 index (L/C4) have been studied in adult Colombian populations to differentiate infection from disease activity. The optimal cutoff values for infection detection were NLR > 6, ESR/CRP ratio < 2, PLR > 132, and L/C4 index > 66.7 [28].

The objective of this study is to identify factors associated with bacterial infections in JSLE patients with fever.

Ethical considerations

The study protocol was approved by the Pediatric Research Group (GRINPED) under record 072 on August 12, 2023; the Ethics and Bioethics Research Committee of Fundación Clínica Infantil Club Noel under registration 268 on October 20, 2023; and the Ethics Committee of Universidad Libre Seccional Cali, Colombia (Resolution CEB-10–2024, dated March 28, 2024), in accordance with the Declaration of Helsinki of the World Medical Association.

Methods

An observational, analytical case–control study with retrospective data collection was conducted at a pediatric referral institution in Cali, Colombia (Fundación Clínica Infantil Club Noel). The study was self-funded.

Patient selection

The study included 116 febrile patients with juvenile systemic lupus erythematosus (JSLE) who were admitted between January 2015 and December 2023.

Cases were defined as JSLE patients diagnosed according to the American College of Rheumatology 2017 criteria, the SLICC 2012 criteria, or diagnostic confirmation by a pediatric rheumatology expert, who experienced at least one febrile episode exceeding 38 °C of non-hospital onset, with bacterial infection confirmed by culture isolation or detection using staining, antigenic tests, serological, or molecular methods.

Controls included febrile JSLE patients, as defined above, in whom bacterial pathogens could not be detected or isolated.

Patients were excluded if they:

- Had more than 20% of their data missing.
- Received initial stabilization care and were referred to another institution.
- Presented with severe trauma, burns, or underwent major surgery.
- Had malignant neoplasms, coexisting inflammatory bowel disease, chronic liver disease, or pre-existing and known chronic infections (e.g., osteomyelitis, endocarditis, active HIV, or hepatitis B).
- Experienced macrophage activation syndrome.

The calculated sample size (Epi Info 7.10) of 18 cases and 78 controls (Fleiss method) was achieved. Figure 1 shows the patient selection flowchart.

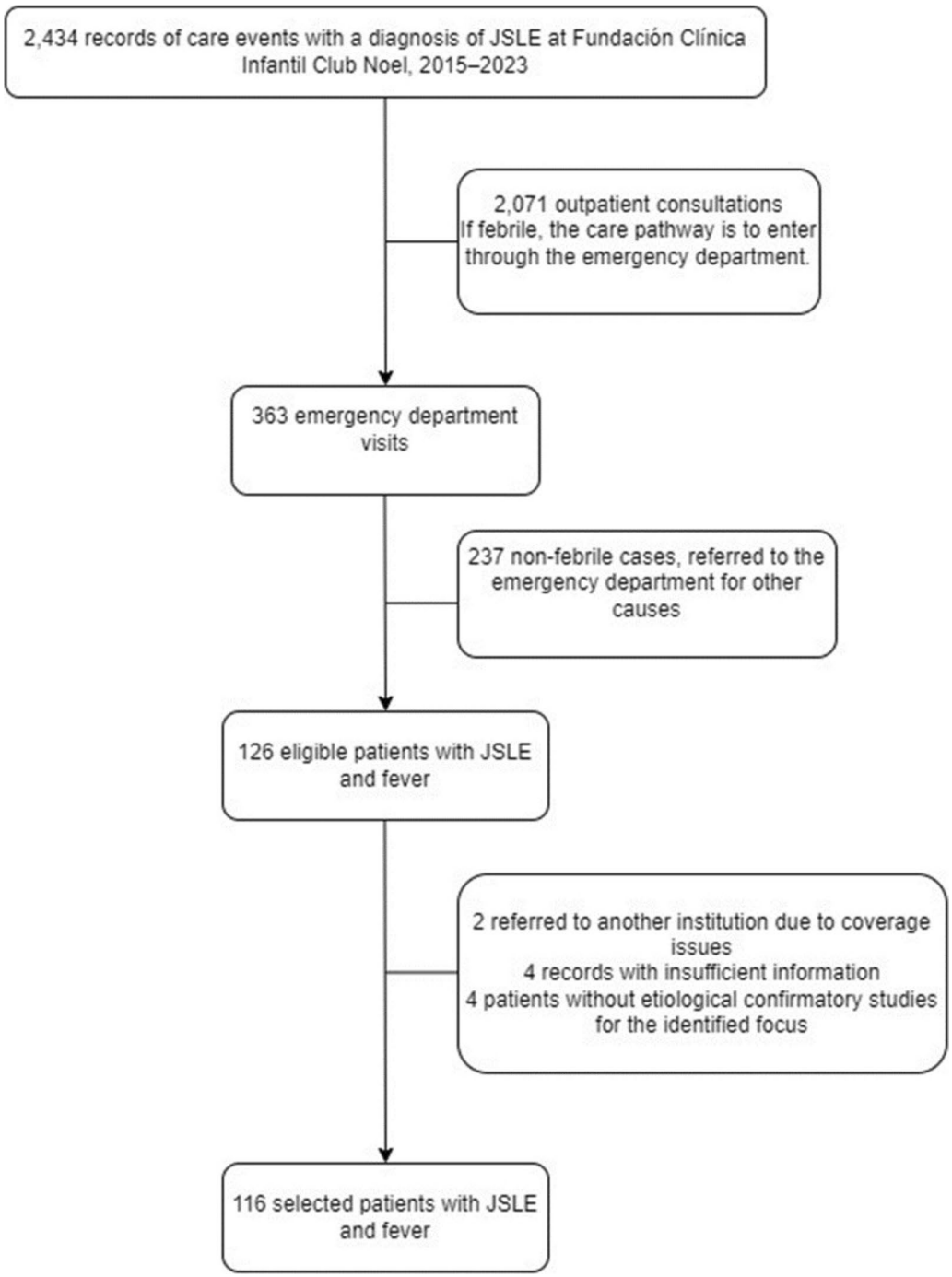

Fig. 1 Flowchart of patient selection for the study

Measures

The data were sourced from medical records. Disease activity was classified using the SLEDAI-2 K scale [25–27]. Sociodemographic variables included age, sex, place of residence, and social security coverage. Clinical variables analyzed included duration of fever (in days), temperature at admission, disease onset, nutritional status, use of immunosuppressants, use of high-dose steroids (>7.5 mg/day of prednisolone), renal replacement therapy, and the SLEDAI-2 K score.

Laboratory tests analyzed were those performed upon patient admission and included hematological

parameters and biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), ferritin (FERRI), complement C3 (C3), and complement C4 (C4). Ratios such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), ESR/CRP ratio, and lymphocyte/C4 ratio were also calculated. Immunological tests included rheumatoid factor (RF), antinuclear antibodies (ANA), anti-dsDNA antibodies, anti-RNP antibodies, anti-Sm antibodies, anti-SS-A/Ro antibodies, and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), as well as C3 and C4 levels.

The dependent variable was bacterial infection, defined as isolation by culture or detection through molecular tests, staining, or antigen tests. Clinical bacterial infections without microbiological confirmation were not classified as cases to minimize investigator bias.

Data collection

Data were collected in Microsoft Office Excel® and processed using IBM SPSS Statistics version 29.0.2.0 (2020) © International Business Machines Corporation.

Statistical analysis

The distribution of quantitative variables was determined using the Kolmogorov–Smirnov test, and in the case of non-normality, they were summarized by median and interquartile range. Qualitative variables were summarized using frequencies and percentages. Associations were established through bivariate and multivariate analyses, assessing the goodness of fit of the resulting model. To assess how well the regression model explains the observed data, Nagelkerke's R-squared and the Hosmer–Lemeshow test were used.

Results

Sociodemographic characteristics

A total of 116 febrile JSLE patients were included in the study, of which 20 patients with confirmed bacterial detection or isolation formed the case group, and 96 patients without bacterial detection or isolation comprised the control group, yielding a case-to-control ratio of 1:4. The cohort consisted of 16 males and 100 females, with 70 patients residing in Cali and 46 from other municipalities.

Regarding social security coverage, 37 patients were under the contributory scheme, 78 under the subsidized scheme, and one under a special scheme.

Diagnosis and clinical characteristics

Twenty-eight patients were unaware of their disease status, and 19 were undergoing renal replacement therapy (RRT). The proportion of confirmed bacterial infection was 17%.

All 116 study patients had a positive SLEDAI-2 K score indicating disease activity, with 22 patients classified as having mild activity and 94 as having moderate to severe activity.

Table 1 provides a detailed description of the sociodemographic and clinical characteristics of the study population, stratified by case and control groups.

Table 2 presents the quantitative clinical and laboratory characteristics of interest. The distribution of all quantitative variables, except for the SLEDAI-2 K score, was non-parametric as determined by the Kolmogorov–Smirnov test. All variables, including the SLEDAI-2 K score, are summarized using the median and interquartile range (IQR).

Laboratory studies

Regarding immunological tests for juvenile systemic lupus erythematosus (JSLE), the most commonly observed antinuclear antibody (ANA) pattern was homogeneous, found in 21 patients, followed by a speckled pattern in 17 patients and a fine granular pattern in 7 of the 59 patients tested.

The most frequently reported ANA titers were 1:1280, observed in 22 cases, followed by 1:640 in 14 patients and 1:2560 in 8, out of a total of 58 patients tested.

Anti-dsDNA antibodies were tested in 64 patients and were positive in 16. Anti-RNP was positive in 4 of 48 patients, anti-Sm in 4 of 47, anti-SS-A/Ro in 10 of 47, and rheumatoid factor in 12 of 36 patients tested.

Table 3 presents the studies conducted on the 116 patients to identify the etiology of the infection, while Table 4 provides details of patients with bacterial isolations or detections and their associated non-bacterial co-infections.

Bivariate analysis

Bivariate analysis in Tables 5, 6 and 7 describes the relationships between sociodemographic and clinical characteristics, biomarkers and indicators, and immunological tests with confirmed bacterial infection in patients with Juvenile Systemic Lupus Erythematosus (SLEJ) and fever.

Multivariate analysis

For the multivariate analysis, variables with a significant crude odds ratio (OR) and those with a crude OR < 0.25 were included in the explanatory model for bacterial infection. These variables included the use of immunomodulators, high-dose steroids, renal replacement therapy, erythrocyte sedimentation rate (ESR) > 20, C-reactive protein (CRP) > 60, CRP > 90, ferritin > 500, interleukin

Table 1 Sociodemographic and clinical characteristics of the study population, stratified by case and control groups

Characteristic	Total (n, %)	Confirmed Bacterial Infection (Cases $n=20$)	No Bacterial Confirmation (Controls $n=96$)
Sex: male	16 (13%)	2 (10%)	14 (15%)
Sex female	100 (86%)	18 (90%)	82 (85%)
Origin: Cali	70 (60%)	11 (55%)	59 (61%)
Social Security			
Contributive	37 (32%)	6 (30%)	31 (32%)
Subsidized	78 (67%)	14 (70%)	64 (67%)
Special	1	0	1
Exception	0	0	0
Uninsured	0	0	0
Main Complaint Symptom			
Respiratory	11 (9%)	2 (10%)	9 (9%)
Gastrointestinal	14 (12%)	2 (10%)	12 (13%)
Urinary	2 (2%)	0	2 (2%)
Systemics	32 (28%)	4 (20%)	28 (29%)
Musculoskeletal	25 (22%)	4 (20%)	21 (22%)
Skin, Soft Tissues, Neurological	5 (4%)	1 (5%)	4 (4%)
	6 (5%)	0	6 (6%)
Fever	2 (2%)	0	2 (2%)
Hematological	19 (16%)	7 (35%)	12 (13%)
Use of Immunomodulators	63 (54%)	16 (80%)	47 (49%)
Type of Immunomodulator			
Steroid alone	7 (6%)	1 (5%)	6 (6%)
Azathioprine	3 (3%)	0	3 (3%)
Methotrexate	1 (1%)	0	1 (1%)
Mycophenolate	2 (2%)	0	2 (2%)
Cyclophosphamide	1 (1%)	0	1 (1%)
Biologics	1 (1%)	0	1 (1%)
Combined Therapy	52 (45%)	14 (70%)	38 (40%)
High-dose Steroids	24 (21%)	6 (30%)	18 (19%)
SLE Onset	28 (24%)	2 (10%)	26 (27%)
Renal Replacement Therapy	19 (16%)	7 (35%)	12 (13%)
Nutritional Status			
Eutrophic	60 (52%)	9 (45%)	51 (53%)
Depleted	43 (37%)	6 (30%)	37 (39%)
Severe Malnutrition	5 (4%)	1 (5%)	4 (4%)
Obesity	8 (7%)	4 (20%)	4 (4%)

(IL) > 6, platelets > 133, procalcitonin (PCT) > 0.9, and, based on researcher interest, the indices ILC4 > 66.7 and ESR/CRP < 2. The variable PCT > 0.9 retained significance with a p-value < 0.01. The other variables were not included in the final model (Table 8). The Nagelkerke R-squared was 0.65. The Hosmer–Lemeshow test demonstrated adequate internal validity, with a chi-squared value of 0.000, indicating perfect concordance between the observed and expected frequencies.

Discussion

In the studied population of patients with SLEJ and fever, the confirmed bacterial infection rate was 17%, which is lower than the 35% reported in Colombia for adult SLE patients by Beltrán et al. and the 32% found in Medellín, Colombia, as reported by Santamaría-Alza et al. in adult populations [13, 28]. The most common infection identified was urinary tract infection, consistent with the findings of Sari et al., who reported a rate of 41% [24].

Table 2 Clinical and laboratory characteristics at admission of febrile JSLE patients, stratified by confirmed bacterial infection

Characteristic (n)	Median (IQR) (n)			*p*-value
	***n* = 116**	**Confirmed Infection (cases) (*n* = 20)**	**No infection confirmation (controls) (*n* = 96)**	
Age in years	116	14,5 (12 – 16)	15 (13–16)	0,64
Fever duration in days	115	2 (1 – 7)	4 (1 – 15)	0,48
Temperature (°C)	116	38 (38 – 39)	38 (38 – 39)	0,82
PCT (ng/mL)	26	0,57 (0,16 – 4,51)	0,14 (0,06 – 0,30)	0,20
CRP (mg/L)	111	42,5 (2,70 – 115)	14,6 (3,06 – 45,6)	0,77
ESR (mm/hra)	97	90 (49 – 103)	80 (35 – 108)	0,56
Ferritin (ng/mL)	66	428 (199 – 640)	220 (118 – 639)	0,07
Leukocytes (/ml^3)	115	5515 (3860 – 10192)	6700 (4800 – 9390)	0,48
Lymphocytes (/ml^3)	115	1030 (722–1412)	1400 (920–2050)	0,03
Neutrophils (/ml^3)	115	3940 (2135 – 8625)	4530 (3070 – 6700)	0,83
Hemoglobin (gr/dl)	115	10,0 (8,3 – 11,8)	10,1 (8,6 – 11,8)	0,6
Platelets ($\times 10^3$/ml^3)	115	217,5 (160,25 – 30825)	277 (210 – 396)	0,23
NLR	115	5,75 (1,46 – 9,81)	3,19 (1,85 – 5,97)	0,43
VES/PCR	94	2,4 (0,71 – 28,6)	4,9 (1,6 – 17,6)	0,28
IPL	115	242 (154 – 334)	200 (134 – 310)	0,20
ILC4	96	110 (42,5 – 153)	171 (70 – 440)	0.01
C3 (mg/dl)	97	58,3 (40 – 89,9)	52,5 (32,2 – 111)	0,96
C4 (mg/dl)	97	11,9 (6 – 20)	6,9 (3,2 – 20)	0,28
SLEDAI-2 k	116	23 (3—41)	19 (11—28)	0,74

PCT Procalcitonin, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *NLR* Neutrophil-to-lymphocyte ratio, *ESR/PCR* Erythrocyte sedimentation rate-C-reactive protein index, *PLR* Platelet-to-lymphocyte ratio, *LC4* Lymphocyte-C4 index, *SLEDAI-2 k* Systemic Lupus Erythematosus Disease Activity Index 2000

Table 3 Studies performed on JSLE patients with fever to identify the etiology of the infection (*n* = 116)

Study	Number of patients who underwent the study	Isolation or microbiological detection
Blood culture	73 (63%)	10 (9%)
Urine culture	18 (16%)	11 (9%)
Stool culture	20 (17%)	3 (3%)
Peritoneal culture	5 (4%)	1 (1%)
Bronchoalveolar lavage (BAL) culture	8 (7%)	3 (3%)
Molecular panel		
Respiratory	16 (14%)	10 (9%)
Pneumonia	2 (2%)	1 (1%)
Central Nervous System (CNS)	1 (1%)	0
Sepsis	3 (3%)	1 (1%)
Gastrointestinal	4 (4%)	2 (2%)
Other studies		
Ziehl–Neelsen stain	3 (3%)	1 (1%)
Galactomannan antigen	4 (4%)	2 (2%)
Dengue serology	13 (11%)	6 (5%)
CMV viral load	6 (5%)	4 (4%)
Respiratory virus antigens	60 (52%)	35 (30%)

Table 4 Bacterial isolations or detections in JSLE patients with fever and confirmed bacterial infection

Patient[a]	Sex	Age	Isolation or detection
12	F	17	Urine culture: *E. coli*
13	F	15	Urine culture: *E. coli*
14	F	13	Blood Culture: *Pasteurella multocida* Peritoneal Fluid Culture: *Pasteurella multocida*
17	F	16	Blood Culture: *S. aureus* + *Leuconostoc lactis* Molecular Panel Pneumonia: *S. aureus* + *Streptococcus pneumoniae* Sputum Culture: *S. aureus* Dengue Virus Serology Positive
19	F	12	Molecular Sepsis Panel: *E. coli* + *S. aureus* Blood Culture: *E. coli* + *S. aureus* Urine Culture: *E. coli* + *S. aureus* Stool Culture: *E. coli* Gastrointestinal Molecular Panel: *E. coli*
34	F	17	Blood Culture: *S. aureus* Urine Culture: *Proteus mirabilis*
35	F	11	Urine Culture: *E. coli*
44	F	15	Urine Culture: *E. coli*
47	F	15	Blood Culture: *S. aureus* Stool Culture: *E. coli* Dengue Virus Serology: positive
48	F	17	Blood Culture *Acinetobacter baumannii* + *Klebsiella pneumoniae*
51	F	14	Urine Culture: Escherichia coli Bronchoalveolar Lavage (BAL): *Aspergillus fumigatus* with positive galactomannan Positive Bacilloscopy
54	M	15	Blood Culture: *S,aureus* Urocultivo: *Leclercia adecarboxylata*
62	F	14	Hemocultivo: *E. coli* Urine Culture: *E. coli*
68	F	11	Blood Culture *Burkholderia cepacia* Positive Viral Load CMV Positive Viral Load Epstein-Barr Virus
70	F	16	Urine Culture: *Proteus mirabilis*
81	F	17	Stool Culture: *E. coli*
92	F	13	Urine Culture*: E. coli*
93	M	11	Gastrointestinal Molecular Panel: *Brucella abortus* Positive Serology for SARS-CoV-2/COVID-19
97	F	14	Blood Culture: *S. aureus* + *S. hominis* Superficial Fungal Culture: *Candida spp*
116	F	10	Bronchoalveolar lavage (BAL) culture: *Staphylococcus aureus*

[a] Patient data registration row in the database

The clinical presentation of patients with bacterial infections did not significantly differ from those without bacterial infections. In both groups, the primary reason for consultation was systemic or musculoskeletal symptoms, observed in 40% and 51% of cases, respectively. Neither the duration of fever nor the onset of SLEJ were associated with the presence of bacterial infection. The use of immunomodulators in SLEJ initially suggested a higher likelihood of bacterial infection, as reported by Ju-Yang et al. in adult SLE patients. However, this factor did not remain significant in the final model. Other factors, such as hematological involvement and high-dose steroid use—factors previously suggested in adult populations—did not show significant differences between the groups in this study of SLEJ patients [21].

Direct biomarkers such as procalcitonin, CRP, and ESR did not show significant differences between the groups when using the cut-off values suggested for healthy individuals. A recent study in an adult population by Abdel-Magied et al. used a procalcitonin cut-off value of 0.9 ng/mL, which is higher than the 0.25–0.50 ng/mL range typically suggested for healthy subjects.This study confirmed a significant association between elevated procalcitonin levels and bacterial infection [29]. Similarly, the

Table 5 Bivariate analysis of sociodemographic and clinical factors and their relationship with bacterial infection in patients with SLEJ and fever ($n = 116$, Ca = 20, Co = 96)

Characteristic and Description	N	Cases ($n = 20$)	Controls ($n = 96$)	ORc	95% CI	*p*-value
Sex						
Male	16	2	14	0,65	0,13 – 3,11	0,73
Female	100	18	82			
Origin Cali						
YES	70	11	59	0,76	0,29 – 2,02	0,59
NO	46	9	37			
Fever for 3 or more days						
YES	63	9	54	0,62	0,23 – 1,63	0,33
NO	52	11	41			
Fever for 7 or more days						
YES	41	5	36	0,54	0,18 – 1,63	0,31
NO	64	15	59			
Immunomodulators						
YES	63	16	47	*4,17*	*1,29–13,38*	*0.01*
NO	53	4	49			
High-dose Steroids						
YES	24	6	18	1,85	0,62—5,49	0,25
NO	92	14	78			
JSLE Onset						
YES	28	2	26	0,29	0,65 – 1,38	0,15
NO	88	18	70			
Renal Replacement Therapy						
YES	19	7	12	*3,76*	*1,25 – 11,3*	*0,01*
NO	97	13	84			
SLEDAI 2 k						
Mild	22	5	17	1,54	0,49 – 4,84	0,53
Moderate to Severe	94	15	79			

JSLE Juvenile Systemic Lupus Erythematosus, *SLEDAI-2 k* Systemic Lupus Erythematosus Disease Activity Index 2000

present study found that a procalcitonin level of 0.9 ng/mL was the only variable retained in the final explanatory model for bacterial infection in SLEJ patients with fever. Other variables, such as CRP > 60 mg/L, CRP > 90 mg/L, ESR > 20 mm/h, and ferritin > 500 ng/mL, although significant in the bivariate analysis, were excluded from the final model.

Regarding biomarker indicators, Santamaría-Alza's study in Medellín, Colombia, used a neutrophil-to-lymphocyte ratio (NLR) cut-off of 6.3 in an adult population, significantly higher than the 2.0 cut-off proposed by Abdel-Magied. For other indices, Santamaría-Alza set the platelet-to-lymphocyte ratio (PLR) cut-off at 132.9, suggested a value of < 2 for the ESR/CRP ratio as indicative of infection, and used a lymphocyte-C4 ratio of 66.7. In that study, the lymphocyte-C4 ratio emerged as the best-performing index.

In the present study, bivariate analysis suggested potential associations with IL > 6, PLR > 133, and, for research purposes, we included ILC4 > 66.7 and ESR/CRP < 2 in the multivariate analysis. However, these indices were not retained in the final binary logistic regression model for bacterial infection.

Immunological tests are widely used in adults as markers of disease activity and are incorporated into the SLEDAI-2 K scale. However, their usage in the study population was low, ranging from 17 to 55% depending on the specific marker. This may be attributed to the clinicians' primary focus on identifying the source of fever, leading to an initial treatment for infection. It's important to note that disease activity may increase in the presence of infection. The present study specifically focuses on patients with juvenile systemic lupus erythematosus, also known as childhood-onset systemic lupus erythematosus (cSLE) [30].

Table 6 Bivariate analysis of biomarkers and their relationship with bacterial infection in patients with SLEJ and fever ($n = 116$, Ca = 20, Co = 96)

Characteristic and Description	N	Cases	Controls	ORc	95% CI	*p*-value
PCT > 0.90 ng/mL						
YES	5	4	1	17	1,47 – 1,96	0,02
NO	21	4	17			
ESR > 20 mm/hr						
YES	83	17	66	0,79	0,71 – 0,88	0,12
NO	14	0	14			
CRP > 6 mg/L						
YES	67	13	54	1,27	0,46 – 3,49	0,63
NO	44	7	37			
CRP > 60 mg/L						
YES	25	10	15	*5,06*	*1,79–14,28*	*0,001*
NO	86	10	76			
CRP > 90 mg/L						
YES	13	6	7	*5,14*	*1,50–17,56*	*0,005*
NO	98	14	84			
Ferritin > 500 ng/mL						
YES	22	7	15	2,10	0,64—6,83	0,21
NO	44	8	36			
Consumed C3 (< 88 mg/dl)						
YES	65	14	51	1,48	0,48 – 4,55	0,59
NO	32	5	27			
Consumed C4 (< 15 mg/dl)						
YES	63	12	51	0,90	0,32 – 2,57	0,85
NO	34	7	27			
NLR > 2.0						
YES	77	14	63	1,18	0,41—3,37	0,75
NO	38	6	32			
NLR > 6.0						
YES	30	9	21	*2,28*	*1,05 – 7,88*	*0,03*
NO	95	21	74			
PLR > 132.9						
YES	93	18	75	2,40	0,51–11,21	0,35
NO	22	2	20			
ESR/CRP Index < 2						
YES	60	9	51	0,57	0,19 – 1,66	0,30
NO	34	8	26			
LC4 > 66.7						
YES	73	13	60	0,64	0,20 – 1,85	0,38
NO	23	6	17			

PCT Procalcitonin, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *NLR* Neutrophil-to-lymphocyte ratio, *ESR/PCR* Erythrocyte sedimentation rate-C-reactive protein index, *PLR* Platelet-to-lymphocyte ratio, *LC4* Lymphocyte-C4 index, *SLEDAI-2 k* Systemic Lupus Erythematosus Disease Activity Index 2000

Limitations and biases

Our results must be interpreted in light of several limitations inherent to the chosen study style.

A strategy was implemented to minimize selection bias by clearly defining the study population (patients with SLE and fever) and selecting all eligible patients. The controls were drawn from the database of febrile SLE patients, which is a strength of the study. This design allowed for a focused investigation into bacterial infection in patients with SLEJ and fever, rather

Table 7 Bivariate analysis of immunological disease activity markers and their relationship with bacterial infection in patients with SLEJ and fever ($n = 116$, Ca = 20, Co = 96)

Characteristic and Description	N	Cases	Controls	ORc	95% CI	*p*-value
SLEDAI 2 k						
Mild	22	5	17	1,54	0,49 – 4,84	0,53
Moderate to Severe	94	15	79			
p-ANCAS						
Positive	12	2	10	0,33	0,04 – 2,68	0,34
Negative	8	3	5			
Anti-dsDNA						
Positive	14	3	11	0,77	0,18 – 3,22	1,00
Negative	50	13	37			
Anti-RNP						
Positive	4	1	3	1,29	0,12–13,98	1,00
Negative	44	9	35			
Anti-Sm						
Positive	4	1	3	1,45	0,13–15,90	1,00
Negative	43	8	35			
Anti-SS-A/Ro						
Positive	10	3	7	2,24	0,44–11,08	0,37
Negative	37	6	31			

SLEDAI-2 k Systemic Lupus Erythematosus Disease Activity Index 2000, *p-ANCAs* Perinuclear anti-neutrophil cytoplasmic antibodies, *Anti-dsDNA* Anti-double stranded DNA antibodies, *Anti-RNP* Anti-ribonucleoprotein U1 antibodies, *Anti-Sm* Anti-Smith antigen antibodies, *Anti-SS-A/Ro* Anti-Sjögren's syndrome-related antigen A

than in healthy individuals or those with SLEJ who were not febrile.

To further control for bias, patients with a clinical diagnosis of bacterial infection, but without microbiological confirmation, were included as controls, regardless of whether they were receiving antimicrobial treatment. This helped minimize the possibility of biases that could arise from treatment-induced differences.

Information bias was mitigated by establishing operational definitions and using quantitatively measured exposures, which helped ensure the validity of the recorded data. The only reconstructed variables in the study were nutritional status and the SLEDAI-2 K score. Furthermore, the multivariate analysis was adjusted for potential confounding variables, strengthening the model's reliability.

Conclusions

The detection of bacterial infection in patients with SLEJ and fever continues to be a challenging clinical issue. In our study, the bacterial infection rate was 17%. Procalcitonin, with a cut-off of 0.9 ng/mL, proved to be a valuable decision-making tool, although it is not definitive on its own. Other biomarkers such as interleukin (IL), platelet-to-lymphocyte ratio (PLR), ESR/CRP ratio, lymphocyte-C4 ratio (ILC4), and ferritin levels warrant further investigation. The optimal cut-off values for these biomarkers in distinguishing bacterial infection from other types of infections or disease activity in febrile SLEJ patients are yet to be established. Ultimately, individualized patient assessment remains the cornerstone of clinical practice.

Table 8 Binary logistic regression of factors associated with bacterial infection in patients with SLE and fever

Characteristic	*p*-value	Inclusion in the explanatory model
PCT > 0.9	0.000	YES
Use of immunomodulators	0,360	No
High-dose steroids	0,685	No
Renal replacement therapy	0,255	No
ESR > 20	0,551	No
CRP > 60	0,423	No
CRP > 90	0,448	No
FERRI > 500	0,756	No
NLR > 6	0,756	No
PLI > 133	0,255	No
LC4I > 66.7	0,283	No
ESR/CRP < 2	0.91	No

PCT Procalcitonin, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *FERRI* Ferritin, *NLR* Neutrophil–lymphocyte index, *PLI* Platelet-lymphocyte index, *LC4I* Lymphocyte-complement C4 index, *ESR/CRP* Erythrocyte sedimentation rate-C-reactive protein index

Nagelkerke R-squared = 0.654

Abbreviations

GRINPED	Pediatric Research Group
SLE	Systemic Lupus Erythematosus also known as Childhood-onset systemic lupus erythematosus (cSLE) (30)
JSLE	Juvenile Systemic Lupus Erythematosus
SLEDAI-2k	Systemic Lupus Erythematosus Disease Activity Index-2000
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
PCT	Procalcitonin
LC4R	Lymphocyte-to-C4 ratio
ESR/CRP ratio	Erythrocyte sedimentation rate - C-reactive protein ratio
SLE	Systemic lupus erythematosus
ICU	Intensive Care Unit
CI	Confidence interval
AUC	Area under the curve
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SLICC	Systemic Lupus Collaborating Clinics
HIV	Human Immunodeficiency Virus
RF	Rheumatoid factor
ANA	Antinuclear antibodies
Anti-dsDNA	Anti-double stranded DNA antibodies
Anti-RNP	Anti- ribonucleoprotein antibodies
Anti-Sm	Anti-Smith antibodies
anti-SS-A/Ro	Anti-Sjögren's syndrome related antigen A antibodies
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
IQR	Interquartile range

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Authors' contributions
Each author contributed to the redaction, proofreading, and correction of the manuscript. JFGU and NYM contributed to the research, data recollection, analysis, writing, and proofreading, while MAGA, MPGM, LFMR, JPRH and RPL contributed in analysis data, corrected and adding relevant medical changes to the case. All authors read and approved the final manuscript. All authors participated in the acquisition, analysis, and interpretation of the data. Each author has agreed both to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, (even ones in which the author was not personally involved), are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
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Consent for publication
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Competing interests
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