



Original Research

Evaluation of the Clinical, Laboratory and Radiology Findings and Treatment Methods of Children with Acute Bronchiolitis: Experience of a Tertiary Center

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Abstract

Objectives: The aim of this study is to determine the factors affecting the duration of hospitalization and causing the initiation of antibiotics in children with acute bronchiolitis.

Methods: This study was conducted retrospectively in Konya Training and Research Hospital. Demographic data, clinical features, laboratory and radiological findings, treatment methods and duration of hospitalization of 102 patients followed up in the pediatric service between September 2017 and April 2019 (in autumn, winter and spring seasons) were recorded from patient files.

Results: 67 (65.7%) of 102 patients were male, and 35 (34.3%) were female. Median age was 6.5 (11.0) months. According to Wang bronchiolitis clinical scoring, 36 (35.3%) of the patients were mild, 51 (50.0%) were moderate, 15 (14.7%) were severe bronchiolitis. The most common agents in polymerase chain reaction (PCR) were respiratory syncytial virus 60 (58.8%), influenza virus 20 (19.6%), rhinovirus 15 (14.7%), bocavirus 15 (14.7%) and parainfluenza virus 12 (11.7%). The median duration of hospitalization was 7.0 (4.0) days. Forty-two (41.2%) of the patients were hospitalized for ≤ 5 days, and 60 (58.8%) were hospitalized for > 5 days. Duration of hospitalization was significantly and positively correlated with crepitant crackles, leukocytosis, neutrophilia, and coinfection with influenza virus ($p=0.036$, $p=0.034$, $p=0.028$, $p=0.036$, respectively). Duration of hospitalization was significantly and negatively correlated with pH and increased aeration ($p=0.002$, $p=0.003$, respectively). Antibiotic initiation was significantly and positively correlated with wheezing, crepitant crackles, leukocytosis, and neutrophilia ($p=0.033$, $p=0.013$, $p=0.028$, $p=0.002$, respectively).

Conclusion: A significant relationship was found between crepitant crackles in physical examination, respiratory acidosis in laboratory, co-infection with influenza virus detected by PCR and hospitalization for more than 5 days. A significant relationship was determined between wheezing or crepitant crackles in physical examination, leukocytosis or neutrophilia in laboratory and the initiation of antibiotic.

Keywords: Antibiotic, bronchiolitis, children, hospitalization, respiratory syncytial virus

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Acute bronchiolitis is a clinical condition caused primarily by viral agents, characterized by inflammatory obstruction of the bronchioles, chest retraction, wheezing, and rapid breathing. Although the incidence varies according to the seasons, its frequency increases in winter and early spring.^[1] It causes an increase in morbidity and mortality rates in underdeveloped and developing countries, especially in the infantile period.^[2,3] Therefore, it is important to determine the etiology in infants with bronchiolitis.^[4] Respiratory syncytial virus (RSV) is the predominant agent detected by polymerase chain reaction (PCR) in patients diagnosed with acute bronchiolitis. Other common agents include influenza virus, parainfluenza virus, rhinovirus, bocavirus, adenovirus, and enterovirus.^[4,5]

The hospitalization rate of infants with acute bronchiolitis is 2-3% worldwide.^[1,4] The presence of an underlying disease such as chronic lung disease, bronchopulmonary dysplasia, congenital heart disease, neuromuscular disease, and immune deficiency are risk factors for the development of acute bronchiolitis. Major complications of acute bronchiolitis are acute respiratory failure and bacterial co-infection.^[4,6] Acute bronchiolitis is one of the common reasons for admission to primary health care centers. Therefore, early diagnosis by physicians working in these centers and identification of patients to be referred to higher centers will reduce disease-related morbidity and mortality.

In this study, our objective is to identify factors influencing hospitalization duration and antibiotic initiation in pediatric acute bronchiolitis patients. Through these findings, we aim to improve patient care, reduce unnecessary hospital stays, and prevent unnecessary use of antibiotics.

Methods

Study Population

This retrospective descriptive study was conducted in Konya Training and Research Hospital. Medical files of 697 patients who were followed up with the diagnosis of acute bronchiolitis in the pediatric ward between September 2017 and April 2019 were reviewed. Demographic data, clinical features, laboratory and radiological findings, treatment methods and duration of hospitalization of 102 patients meeting the study criteria were recorded. A total of 595 patients were not recorded in the study because 503 patients did not meet the inclusion criteria, and 92 patients met the exclusion criteria.

Inclusion and Exclusion Criteria

Patients meeting the following criteria were included in the study;

1. Patients with ages between 1 and 36 months,

2. Patients who had symptoms of viral respiratory tract infections such as fever, cough, coryza,
3. Who had clinical findings of bronchiolitis like chest retraction, respiratory distress, rapid breathing, wheezing, rhoncus and/or crepitant crackles at the time of admission,
4. Who was hospitalized in autumn, winter and spring seasons,
5. Who had an examination of complete blood count, C-reactive protein (CRP), posterior-anterior chest (PAC) radiography, and nasopharyngeal swab after admission.

The exclusion criteria were; the patient who was hospitalized in the pediatric intensive care unit after admission to the hospital; the patient who had a chronic illness, such as congenital heart disease, asthma and immunodeficiency, that could explain chest retraction, respiratory distress, rapid breathing, and wheezing.

Clinical, Laboratory and Radiological Evaluation

Patients were classified based on the Wang bronchiolitis clinical scoring system^[7], which evaluates patients' general condition, respiratory rate per minute, wheezing, and retraction. Patients were classified clinically according to Wang bronchiolitis clinical scoring as mild (1-3 points), moderate (4-8 points), and severe (9-12 points) bronchiolitis.

Serum CRP value, ≤ 3 mg/L was considered as negative, >3 mg/L as positive, 4-10 mg/L as slightly high, and >10 mg/L as significantly high.^[8] In blood gas, pH 7.35-7.45, PaCO₂ 35-45 mmHg and HCO₃ 22-26 mmol/L were accepted as normal values.^[9]

In the nasopharyngeal swab samples of the patients, viral agents (adenovirus, metapneumovirus A-B, parainfluenza virus 1-2-3-4a-4b, rhinovirus, RSV A-B, bocavirus, coronavirus, enterovirus, influenza A-B-C virus) were studied using the multiplex PCR (CG1-96, Corbett Research Company, Australia) method.

The findings on the PAC radiographs taken during the hospitalization of patients were evaluated by the same pediatrician, and radiological classification was made. Increased aeration (increased aeration at more than seven ribs on inspiratory radiography, flattening of the diaphragm, parallelization of the ribs, mediastinum and heart area shrinkage), minimal infiltration (perihilar changes), infiltration (parenchymal and lobar infiltrations) and viral pneumonia (bilateral peribronchial thickening and small atelectatic areas) were evaluated.^[10]

Ethical Approval

This study was performed with the approval of the 'Necmettin Erbakan University Faculty of Medicine Ethics Committee (Approval date: October 4, 2019, and Approval number: 2019/2104). The study was carried out in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Windows software (ver. 22; IBM SPSS, Chicago, USA) was used for all statistical analyses. The normality analysis of the data was analyzed using the Kolmogorov-Smirnov test. Numerical data not normally distributed was given as median (interquartile range). Categorical variables were shown as numbers (n) and percentages (%). The Chi-square test was used in the comparison of categorical variables. Spearman correlation analysis was used to detect relationships between data. Statistical significance was accepted as $p < 0.05$.

Results

While 67 (65.7%) of 102 patients were male, and 35 (34.3%) were female. Median age was 6.5 (11.0) months. Distribution of the demographic and clinical characteristics of patients with acute bronchiolitis is shown in Table 1.

As the application complaint, 100 (98.0%) patients had a cough, 68 (66.7%) wheezing and 52 (51.0%) had a high fever. As per physical examination findings, 91 (89.2%) patients had rhoncus, 63 (61.8%) wheezing, 51 (52.0%) tachypnea, 45 (44.1%) dyspnea, 39 (38.2%) crepitant crackles and 39 (38.2%) had retraction.

As the laboratory findings, 22 (21.6%) patients had anemia, 12 (11.8%) leukopenia, 8 (7.8%) leukocytosis, 39 (38.2%) lymphopenia, 2 (2.0%) lymphocytosis, 12 (11.8%) neutrophilia, 6 (5.9%) neutropenia, 25 (24.5%) thrombocytosis and 3 (2.9%) had thrombocytopenia. CRP value of 69

(67.6%) patients was positive, and it was significantly high at 39 (38.2%) of them. Venous blood gas analysis was done in 52 (51.0%) patients, and 36 (69.2%) patients had normal results, 13 (25.0%) had respiratory acidosis, and 3 (5.8%) had respiratory alkalosis.

While no agent was determined at nasopharyngeal swab PCR of 15 (14.7%) of the patients, 54 (52.9%) had a single virus, and 77 (75.5%) had co-infection. The distribution of viruses according to the PCR results is shown in Table 2.

Distribution of patients' PAC radiography findings, 28 (27.5%) patients had increased aeration, 36 (35.3%) minimal infiltration, 21 (20.6%) infiltration and 17 (16.6%) had viral pneumonia.

Salbutamol treatment was given for all patients, and steroid treatment was started for 63 (61.8%). Antibiotic treatment was started for 63 (61.8%) patients, and 29 (46.0%) of these antibiotics were ampicillin-sulbactam, 22 (34.9%) clarithromycin, 7 (11.1%) cefotaxime + teicoplanin and 5 (8.0%) were cefotaxime.

The median duration of hospitalization was 7.0 (4.0) days. Forty-two (41.2%) of the patients were hospitalized for ≤ 5 days, and 60 (58.8%) were hospitalized for > 5 days.

There was no statistically significant relationship between gender, age range, seasons and duration of hospitalization (≤ 5 days/ > 5 days) ($p > 0.05$ for all).

There was no significant relationship between each of the application complaints (yes/no), bronchiolitis clinical score and duration of hospitalization ($p > 0.05$ for all).

Among the physical examination findings; a statistically significant relationship was found between the presence of crepitant crackles and duration of hospitalization ($p = 0.036$). Of the patients with crepitant crackles, 11 (28.2%) were hospitalized for ≤ 5 days, and 28 (71.8%) for more than five days. There was no significant relationship between other physical examination findings and duration of hospitalization ($p > 0.05$ for all).

Table 1. Distribution of the demographic and clinical characteristics of patients with acute bronchiolitis

Parameters	Acute bronchiolitis (n=102)
Gender	
Female	35 (34.3)
Male	67 (65.7)
Age range (month)	
1-6	51 (50.0)
7-12	21 (20.6)
13-24	14 (13.7)
25-36	16 (15.7)
Seasons	
Winter	68 (66.7)
Spring	21 (20.6)
Autumn	13 (12.7)
Bronchiolitis clinical scoring	
Mild	36 (35.3)
Moderate	51 (50.0)
Severe	15 (14.7)

Data are presented as n (%).

Table 2. Distribution of viruses according to the polymerase chain reaction results

Agents	Single virus	Co-infection	Total
Respiratory syncytial virus	31 (30.4)	29 (28.4)	60 (58.8)
Influenza virus	7 (6.9)	13 (12.7)	20 (19.6)
Rhinovirus	5 (4.9)	10 (9.8)	15 (14.7)
Bocavirus	4 (3.9)	11 (10.8)	15 (14.7)
Parainfluenza virus	5 (4.9)	7 (6.9)	12 (11.8)
Metapneumovirus	1 (1.0)	3 (2.9)	4 (3.9)
Adenovirus	1 (1.0)	3 (2.9)	4 (3.9)
Enterovirus	0 (0.0)	1 (1.0)	1 (1.0)

Data are presented as n (%).

Among the laboratory findings, a significant relationship was found between the presence of respiratory acidosis and duration of hospitalization ($p=0.013$). All patients with respiratory acidosis were hospitalized >5 days. There was no significant relationship between other laboratory findings and the duration of hospitalization ($p>0.05$ for all). The comparison of duration of hospitalization and laboratory and radiological findings is shown in Table 3.

Table 3. Comparison of duration of hospitalization and laboratory and radiological findings

	Duration of hospitalization		p
	≤ 5 days (n=42)	>5 days (n=60)	
Hemoglobin			0.700
Anemia	9 (21.4)	13 (21.7)	
Normal	33 (78.6)	46 (76.7)	
Polycythemia	0 (0.0)	1 (1.6)	
White blood count			0.051
Leukopenia	8 (19.0)	4 (6.6)	
Normal	33 (78.6)	49 (81.7)	
Leukocytosis	1 (2.4)	7 (11.7)	
Absolute neutrophil count			0.096
Neutropenia	4 (9.5)	2 (3.3)	
Normal	36 (85.7)	48 (80.0)	
Neutrophilia	2 (4.8)	10 (16.7)	
Absolute lymphocyte count			0.474
Lymphopenia	17 (40.5)	22 (36.7)	
Normal	25 (59.5)	36 (60.0)	
Lymphocytosis	0 (0.0)	2 (3.3)	
Platelet			0.785
Thrombocytopenia	1 (2.4)	2 (3.3)	
Normal	32 (76.2)	42 (70.0)	
Thrombocytosis	9 (21.4)	16 (26.7)	
C-reactive protein			0.311
Normal	17 (40.5)	16 (26.7)	
Slightly high	10 (23.8)	20 (33.3)	
Significantly high	15 (35.7)	24 (40.0)	
Increased aeration			0.004
Presence	18 (42.9)	10 (16.7)	
Absence	24 (57.1)	50 (83.3)	
Minimal infiltration			0.107
Presence	11 (26.2)	25 (41.7)	
Absence	31 (73.8)	35 (58.3)	
Infiltration			0.861
Presence	9 (21.4)	12 (20.0)	
Absence	33 (78.6)	48 (80.0)	
Viral pneumonia			0.105
Presence	4 (9.5)	13 (21.7)	
Absence	38 (90.5)	47 (78.3)	

Data are presented as n (%); Chi-square test.

There was a significant relationship between the presence of the influenza virus and duration of hospitalization ($p=0.035$). Ten (77.0%) of 13 patients co-infected with influenza virus were hospitalized for >5 days. There was no significant relationship between other causative viruses and duration of hospitalization ($p>0.05$ for all). The comparison of duration of hospitalization and viral agents is shown in Table 4.

Among the PAC radiography findings, there was a significant relationship between the presence of increased aeration and duration of hospitalization ($p=0.040$). Eighteen of 28 patients with increased aeration had ≤ 5 days hospital stay. There was no significant relationship between other radiography findings and duration of hospitalization ($p>0.05$ for all) (Table 3).

There was no significant relationship between gender, age range, seasons and antibiotic initiation (yes/no) ($p>0.05$ for all). No significant relationship was found between each of the application complaints, bronchiolitis clinical score and antibiotic initiation ($p>0.05$ for all).

As physical examination findings, a significant relationship was determined between the presence of wheezing, crepitant crackles and antibiotic initiation ($p=0.033$, $p=0.013$).

Table 4. Comparison of duration of hospitalization and viral agents

Viral agents	Duration of hospitalization		p
	≤ 5 days (n=42)	> 5 days (n=60)	
Respiratory syncytial virus			0.381
Single virus	13 (31.0)	18 (30.0)	
Co-infection	9 (21.4)	20 (33.3)	
Absent	20 (47.6)	22 (36.7)	
Rhinovirus			0.464
Single virus	3 (7.2)	2 (3.3)	
Co-infection	4 (9.5)	6 (10.0)	
Absent	35 (83.3)	52 (86.7)	
Influenza virus			0.035
Single virus	5 (11.9)	2 (3.3)	
Co-infection	3 (7.1)	10 (16.7)	
Absent	34 (81.0)	48 (80.0)	
Bocavirus			0.218
Single virus	2 (4.8)	2 (3.3)	
Co-infection	2 (4.8)	9 (15.0)	
Absent	38 (90.4)	49 (81.7)	
Parainfluenza virus			0.558
Single virus	3 (7.1)	2 (3.3)	
Co-infection	2 (4.8)	5 (8.3)	
Absent	37 (88.1)	53 (88.4)	

Data are presented as n (%); Chi-square test.

Forty-four of the 63 patients with wheezing and 30 of the 39 patients with crepitant crackles were initiated antibiotic therapy. There was no significant relationship between other physical examination findings and antibiotic initiation. The comparison of antibiotic initiation and physical examination findings is shown in Table 5.

Among the laboratory findings, a significant relationship was found between the presence of leukocytosis, neutrophilia and antibiotic initiation ($p=0.04$, $p=0.001$). Antibiotic treatment was started in 7 (87.5%) of 8 patients with leukocytosis and 11(91.7%) of 12 patients with neutrophilia.

Table 5. Comparison of antibiotic initiation and physical examination findings

Physical examination findings	Antibiotic initiation		p
	Yes (n=63)	No (n=39)	
Wheezing			0.033
Presence	44 (69.8)	19 (48.7)	
Absence	19 (30.2)	20 (51.3)	
Dyspnea			0.084
Presence	32 (50.8)	13 (33.3)	
Absence	31 (49.2)	26 (66.7)	
Tachypnea			0.356
Presence	35 (55.6)	18 (46.2)	
Absence	28 (44.4)	21 (53.8)	
Rhoncus			0.239
Presence	58 (92.1)	33 (84.6)	
Absence	5 (7.9)	6 (15.4)	
Crepitant crackles			0.013
Presence	30 (47.6)	9 (23.1)	
Absence	33 (52.4)	30 (76.9)	
Retraction			0.222
Presence	27 (42.9)	12 (30.8)	
Absence	36 (57.1)	27 (69.2)	

Data are presented as n (%). Chi-square test.

There was no significant relationship between other laboratory findings and antibiotic initiation ($p>0.05$ for all).

No significant relationship was found between the virus type, radiological findings and antibiotic initiation ($p>0.05$ for all).

Duration of hospitalization was significantly and positively correlated with crepitant crackles, leukocytosis, neutrophilia, and coinfection with influenza viruses ($p=0.036$, $p=0.034$, $p=0.028$, $p=0.036$, respectively). Duration of hospitalization was significantly and negatively correlated with pH and increased aeration ($p=0.002$, $p=0.003$, respectively). Antibiotic initiation was significantly and positively correlated with wheezing, crepitant crackles, leukocytosis, and neutrophilia ($p=0.033$, $p=0.013$, $p=0.028$, $p=0.002$, respectively). Correlation analysis of the acute bronchiolitis patients is shown in Table 6.

Discussion

In this study, the most common agent was RSV (58.8%), followed by the influenza virus (19.6%). Most of the patients co-infected with influenza virus were hospitalized for >5 days. The median duration of hospitalization was 7.0 (4.0) days. Most of the patients with increased aeration on PAC radiography had ≤ 5 days hospital stay. Antibiotic therapy was initiated for most of the patients with leukocytosis and neutrophilia. The main reasons for prolonging hospital stay are the presence of an underlying risk factor and/or severe clinical condition. The treatment of acute bronchiolitis is symptomatic and antibiotics can be initiated in the presence of secondary bacterial infection.^[11,12]

In lung auscultation, sibilant rhoncus and crepitant crackles may be heard at the end of inspiration, and the expiration. In general, the expiration is prolonged.^[13-15] In this study, it was found that most of the patients with crepitant crackles had hospital stay of more than 5 days. In addition, it was determined that most of the patients with wheezing and crepitant crackles were initiated antibiotic therapy. Antibiotic initiation in the presence of crepitant crackles

Table 6. Correlation analysis of the acute bronchiolitis patients

	Wheezing	Crepitant crackles	Leukocytosis	Neutrophilia	pH	Influenza virus	Increased aeration	Viral pneumonia
Duration of hospitalization								
r	0.080	0.207*	0.210*	0.218*	-0.419**	0.471*	-0.289**	0.160
p	0.427	0.036	0.034	0.028	0.002	0.036	0.003	0.107
Antibiotic initiation								
r	0.211*	0.245*	0.217*	0.301**	-0.174	0.105	-0.194	0.189
p	0.033	0.013	0.028	0.002	0.219	0.660	0.051	0.056

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level. Spearman correlation analysis.

was attributed that clinicians might have thought crepitant crackles as a symptom of bacterial pneumonia.

Wang bronchiolitis clinical scoring system is used to determine the severity of the disease and the effectiveness of the treatment.^[2,7] While it was expected that patients with high respiratory scores had longer hospital stay and increased frequency of antibiotic initiation, in this study no significant relationship was determined between bronchiolitis clinical scoring, and hospital stay and antibiotic initiation.

In patients with acute bronchiolitis, the leukocyte count is usually within normal limits and lymphocyte is dominant.^[1,4] In this study, leukocyte count was within normal limits in 80.4% of the patients. In addition, it was determined that antibiotic therapy was initiated to most of the patients with leukocytosis or neutrophilia. The reason for starting antibiotic in the presence of leukocytosis or neutrophilia may be that clinicians see these findings as an indication of secondary bacterial infection.

There are publications stating that PAC radiography findings do not reflect the clinical severity of the disease and do not significantly direct the treatment of patients.^[15,16] There are also opinions arguing that chest radiography is necessary for the differential diagnosis of diseases such as foreign body aspiration, gastroesophageal reflux, pneumonia, cystic fibrosis and congenital heart disease, especially in patients presenting with the first wheezing attack.^[17,18] In this study, on PAC radiography, most of patients with increased aeration had a hospital stay ≤ 5 days.

The PCR method using a nasopharyngeal swab sample allows to detect of many viruses simultaneously.^[19,20] It is important to investigate the viral etiology in order to prevent the unnecessary use of antibiotics and to initiate antiviral therapy for some viruses.^[21] In a study conducted by Petrarca et al.^[22] the PCR results of patients hospitalized due to acute bronchiolitis were examined, and it was reported that the two most common agents were RSV (75.1%) and rhinovirus (18.3%). In a study conducted by Kanik et al.^[21] the most frequently determined agents were RSV (57.1%), rhinovirus (27.1%), influenza virus (13.0%) and bocavirus (9.0%). In this study, the most frequently detected agent was RSV (58.8%), followed by influenza virus (19.6%), rhinovirus (14.7%) and bocavirus (14.7%). All these studies indicate that the most common cause of acute bronchiolitis is RSV, followed by rhinovirus, influenza virus and bocavirus, and the order of their frequency varies according to countries and regions.

In various studies, it was reported that approximately 25.0% of patients hospitalized with the diagnosis of acute bronchiolitis were hospitalized for more than 5 days.^[23,24] In a study conducted in a tertiary hospital, it was reported that the mean duration of hospitalization was found to

be 8.16 ± 5.10 days.^[21] In this study, the median duration of hospitalization was 7.0 (4.0) days, and 58.8% of the patients were hospitalized for more than 5 days. We think that the reason for the longer hospital stay of our patients is that patients with mild bronchiolitis frequently apply to primary and secondary health care centers, patients with moderate-severe bronchiolitis are referred to us, and secondary bacterial infections develop in some hospitalized patients.

In a survey study on the use of antibiotics for acute bronchiolitis, it was reported that 10.0% of pediatricians working in the secondary care hospitals used it routinely and 58.0% used sometimes, and 6.0% of pediatricians working in the tertiary hospitals used it routinely and 66.0% used sometimes. In addition, it was stated that the most common used antibiotics were amoxicillin-clavunate (26.0%), ampicillin-sulbactam (26.0%), and macrolide group (23.0%).^[25] Antibiotics were started in 61.8% of the patients in our study. The initiated antibiotics were ampicillin-sulbactam (46.0%), clarithromycin (34.9%), cefotaxime + teicoplanin (11.1%), and cefotaxime (8.0%). Our high antibiotic initiation rate was attributed to a higher rate of cases with moderate and severe bronchiolitis.

Retrospective, single-center and relatively few patients can be considered as limitations of our study. Prospective, multicenter studies with larger samples may contribute more to the determination of the factors affecting the length of hospital stay and initiation of antibiotic. Thus, the duration of hospital stay may be reduced and unnecessary antibiotic use may be reduced.

Conclusion

A significant relationship was found between crepitant crackles in physical examination, respiratory acidosis in laboratory, co-infection with influenza virus detected by PCR and hospitalization for more than 5 days. A significant relationship was determined between wheezing or crepitant crackles in physical examination, leukocytosis or neutrophilia in laboratory and initiation of antibiotic.

Disclosures

Ethics Committee Approval: This study was performed with the approval of the Necmettin Erbakan University Faculty of Medicine Ethics Committee (Approval date: October 4, 2019, and Approval number: 2019/2104).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.U., E.S.; Design – C.U., E.S.; Supervision – C.U., T.D.; Materials – E.S., T.D.; Data collection and/or processing – E.S., T.D.; Analysis and/or interpretation – C.U., E.S.; Literature search – C.U., E.S.; Writing – C.U., E.S.; Critical review – C.U., E.S., T.D.

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