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CLINICAL SERIE

Lupus nephritis in children

Nefropatía lúpica en pacientes pediátricos

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

Although systemic lupus erythematosus (SLE) is more frequently diagnosed in adulthood, 20% of cases occur in patients under 18 years old. Presentation of SLE in childhood differs from that in adults, including a higher proportion of males and greater severity.

What does this study contribute to what is already known?

SLE onset varies in children, presenting clinically as frequent and significant renal involvement, even in cases with scant analytical manifestations, thus highlighting the importance of renal biopsy. New treatments have improved the survival of these patients.

Abstract

Lupus nephritis is an early manifestation in the development of systemic lupus erythematosus that worsens the morbidity and mortality of these patients. **Objective:** To study the form of presentation in patients with lupus nephritis, the clinical and immunological characteristics, and their relationship with renal histology. **Patients and Method:** Retrospective study in children under 18 years of age, with lupus nephritis, in follow-up in a third level children's hospital in Madrid, between January 2012 and May 2020. We recorded demographic, clinical, and laboratory data (blood count, renal function, liver function, protein, ionogram, blood glucose, uric acid, lactate dehydrogenase, coagulation, and urine analysis), as well as immunological data (immunoglobulins, antinuclear antibodies, complement, and lupus anticoagulant), and histological classification data. Descriptive analysis and analysis of associations between variables was performed, with a significant $p < 0.05$. **Results:** 16 patients (11 women) were included, the median age at presentation was 10.6 ± 2.3 years (5.7-15.3). The median time between symptoms onset and renal involvement was 6.3 months ± 10.5 (range 0 - 33.6). Renal involvement was the initial manifestation in 37.5% of patients. 50% had arthralgias or arthritis prior to diagnosis, and 25% had fever and constitutional symptoms (asthenia, anorexia, and/or weight loss). The most frequent form of renal involvement was microhematuria associated with proteinuria in non-nephrotic range. In the renal anatomo-pathological study, according to the ISN/RPS 2003

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classification, grades III (46.6%) and IV (33.3%) predominated. **Conclusions:** Six patients presented renal involvement at baseline with musculoskeletal involvement being more frequent. Most patients (86.6%) presented advanced lupus nephritis in the histological study at diagnosis. Immunologic involvement was the only marker that correlated with systemic involvement.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that presents chronically with exacerbations and can affect any organ or system. Although the disease is more frequently diagnosed in adulthood, up to 20% of cases occur in patients younger than 18 years of age[1], among whom the worldwide incidence is between 0.3 and 0.9 cases per 100,000 child-years[2]. Sixty percent of pediatric cases occur in patients over age 10 years, with less than 5% occurring in children under 5 years of age[3]. Among the adult population, SLE most commonly affects women (9:1 ratio), though in the first decade of life the female/male ratio is 4:3, increasing to 4:1 in the second decade[4].

Lupus nephritis (LN), one of the primary factors affecting morbidity and mortality in lupus disease, is associated with a more unfavorable prognosis[5]. Renal involvement is more frequent in children than in adults[4]. Between 50% and 75% of children with SLE present renal involvement, compared to 34% to 48% of adults[4]; over 90% of pediatric cases develop renal involvement within the first 2 years of diagnosis[6]. In the United States, renal involvement has been found to be more common in Asians, African Americans, and Hispanics[1,7-9].

Symptoms of LN include macroscopic or microscopic hematuria, proteinuria, high blood pressure, and kidney failure. Disease course ranges from asymptomatic forms with mild urinary findings (microhematuria) to rapidly progressive glomerulonephritis with severe kidney failure in the acute phase. Early diagnosis of renal involvement is essential, as proper treatment improves prognosis and reduces morbidity and mortality[10].

Histopathologic study by renal biopsy defines the degree of renal involvement and the therapeutic strategy to be followed, given that clinical and laboratory findings alone do not accurately reflect the severity of renal disease. Currently, histologic classification is based on the criteria of the International Society of Nephrology/Renal Pathology Society (ISN/RPS 2003)[11], which make no distinction between histologic involvement in adults and children[12].

New therapeutic strategies have improved renal survival by between 77% and 93% at 5 years; however, treatment is complex, is associated with adverse effects, and treatment adherence is difficult. The mortality rate in patients requiring renal replacement therapy is 22%[2].

The objective of this study is to analyze the presentation of LN in a pediatric population in order to refine clinical suspicion and initiate early treatment.

Patients and Method

A retrospective, observational study was performed of patients under 18 years of age with a diagnosis of LN undergoing follow-up in the nephrology and rheumatology departments of a tertiary children's hospital in Madrid, Spain between January 2012 and May 2020.

Medical records were reviewed and demographic characteristics (age, sex, race), clinical findings (clinical presentation, renal involvement, extrarenal symptoms at baseline and during follow-up), laboratory results (blood count, renal function, liver function, protein, electrolytes, blood glucose, uric acid, lactate dehydrogenase, coagulation, and urine analysis), and immunological data (immunoglobulins, antinuclear antibodies, complement factors, and lupus anticoagulant) were collected, in addition to histological classification.

SLE diagnosis and assessment of organ damage were performed based on the criteria of Systemic Lupus International Collaborating Clinics (SLICC)[13].

Dermatologic involvement was defined by the presence of acute and/or chronic cutaneous lupus, nonscarring alopecia, or the presence of mouth and/or nasopharyngeal ulcers. Musculoskeletal involvement was established as the presence of synovitis, arthritis, or arthralgias affecting 2 or more joints. Neuropsychiatric manifestations were classified according to the American College of Rheumatology 1991 criteria[14]. Hematologic involvement was indicated by the presence of one of the following criteria: hemolytic anemia, thrombocytopenia (platelets < 100,000 mm^3), leukopenia (leukocytes < 4,000/mm^3), or lymphopenia (lymphocytes < 1,000/mm^3). Renal manifestations included micro- or macroscopic hematuria, proteinuria in the pathological range, kidney failure (according to KDIGO classification)[15], or high blood pressure (HBP). All

patients with analytic alterations compatible with renal involvement underwent ultrasound-guided percutaneous core needle biopsy. Biopsy specimens were studied by light microscopy, immunofluorescence, and electron microscopy. The ISN/RPS 2003 criteria were used for the histopathologic classification[11].

Statistical analysis

Descriptive analysis was performed for all the variables collected. Quantitative variables were expressed as mean or median values with standard deviation depending on whether the variable followed a normal distribution or not. Qualitative variables were described as frequencies and percentages. Statistical associations were calculated using the Chi-square test or Fisher's exact test and the Mann-Whitney test. Statistical analysis was performed with the IBM SPSS 22.0 software for Windows. In all tests, a $p < 0.05$ was the minimum limit for statistical significance.

Ethical considerations

Following Spanish law 15/1999 on the protection of personal data, confidentiality of all files was maintained. Written informed consent was not requested from the patients included, since the medical data were coded to preserve anonymity. The ethical soundness of this study is determined by the societal value of the study's findings given the rarity of the disease.

Results

Sixteen patients were included, 11 of whom were females. The median age at symptom onset was 10.9 years ± 2.3 (range 5.7-15.3) and median age at LN diagnosis was 12 years ± 2.3 (range 7.2-15.4). Six patients (37.5%) were younger than 10 years of age. Most were Caucasian (62.5%), followed by Hispanic (18.8%), Asian (12.5%), and Arab (6.3%).

1. Initial manifestations

Regarding the first symptoms of the disease, 8 patients (50%) presented musculoskeletal manifestations, 6 (37.5%) renal involvement, 5 (31.2%) dermatologic symptoms, and 4 (25%) hematologic symptoms. Four patients (25%) presented fever and constitutional symptoms (asthenia, loss of appetite, and/or weight loss).

Musculoskeletal manifestations

Eight patients (50%) initially consulted due to arthralgias and/or arthritis. One patient was initially diagnosed with juvenile arthritis according to the ACR criteria[16]. Patients with musculoskeletal involvement at baseline were older (median 11.9 years vs. 10.1 years) than those presenting with other symptoms, though this difference did not reach statistical significance.

Renal involvement

Of the 6 patients with renal involvement at the onset of the disease, 2 (12.5%) presented isolated proteinuria and 2 (12.5%) kidney failure. One patient presented with recurrent macrohematuria and persistent proteinuria, with an initial diagnosis of IgA nephropathy. One patient presented isolated microhematuria. Five of these patients (83%) had extrarenal symptoms at this time.

Dermatologic manifestations

Five patients (31.25%) presented skin lesions as the first manifestation. In 2 of them, this was the only initial symptom, manifesting as discoid lupus and urticarial vasculitis. One patient presented purpura and arthralgias which was initially diagnosed as Henöch-Schonlein purpura. Two patients presented malar rash associated with arthralgias and polyarthritis.

Hematologic symptoms

Autoimmune thrombocytopenia was the initial manifestation in 2 patients, with one year of evolution before the diagnosis of SLE. Two patients presented acute thrombotic microangiopathy, one thrombotic thrombocytopenic purpura, and one atypical hemolytic uremic syndrome. One patient presented mild-to-moderate pancytopenia on laboratory tests performed as the first stage of the diagnosis workup.

2. Disease course

Nephrology

The most frequent form of renal involvement involved presence of microhematuria associated with proteinuria in the non-nephrotic range, which was observed in 10 patients (62.5%). Two of these patients had associated kidney failure and one patient had HBP.

Four patients presented proteinuria in the nephrotic range: 2 in the context of thrombotic microangiopathy, another related to a nephrotic syndrome, and another with associated microhematuria. One patient developed recurrent outbreaks of macroscopic hematuria with proteinuria and an additional patient experienced a hypertensive crisis with kidney injury.

LN was an early finding. The median time between the onset of SLE symptoms and renal involvement was 6.3 months ± 10.5 (range 0-33.6).

All patients underwent a biopsy at the onset of renal symptoms except the patient with a previous hypertensive crisis and kidney failure; in this case, biopsy was declined by parental decision. The median age at the time of biopsy was 11.9 years ± 2.1 (range 8.3-15.4)

and the median time between the first symptoms and biopsy was 7.5 months ± 10.4 (range 1.4-35) (figure 1).

Using the ISN/RPS 2003 classification[11], class III (46.6%) and IV (33.3%) were the most common histology findings (figure 2). One patient underwent a second renal biopsy due to an unfavorable disease course, during which the patient deteriorated from histological class I-II to IIIa-V.

There was no significant statistical relationship between histologic findings and renal or systemic involvement.

Immunology

All patients had positive antinuclear antibodies at diagnosis. The median titer was 1/640 (range 1/80-1/2560). C3 and C4 levels were decreased at diagnosis in 14 patients (87.5%). Median complement factor C3 was 43.9 ± 25.9 mg/dl (range 12.8-101) and 6.5 ± 6.2 mg/dl for complement factor C4 (range 2-24.4). Eight patients (50%) had a positive test for lupus anticoagulant (table 1).

There was no correlation between immunological alterations and the degree of renal or histological involvement.

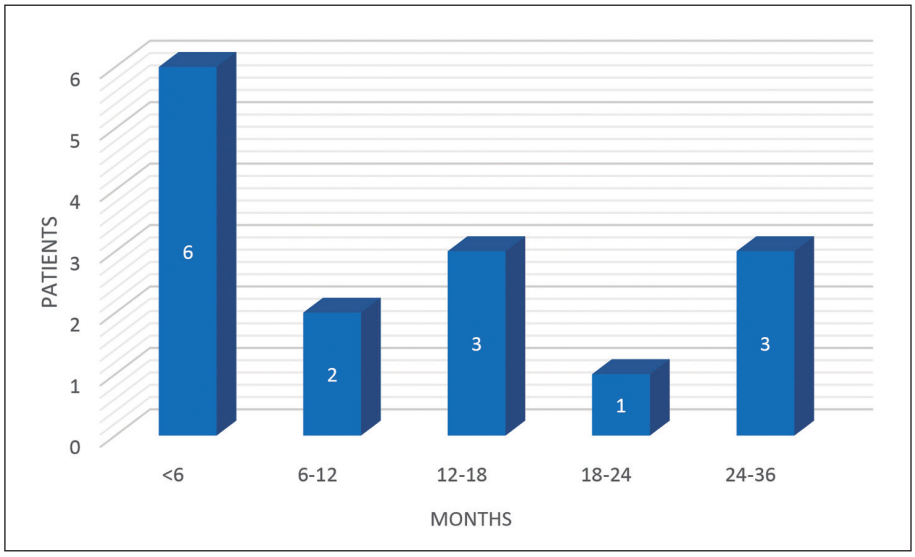

Figure 1. Time (months) between onset of SLE symptoms and kidney biopsy. SLE: Systemic lupus erythematosus.

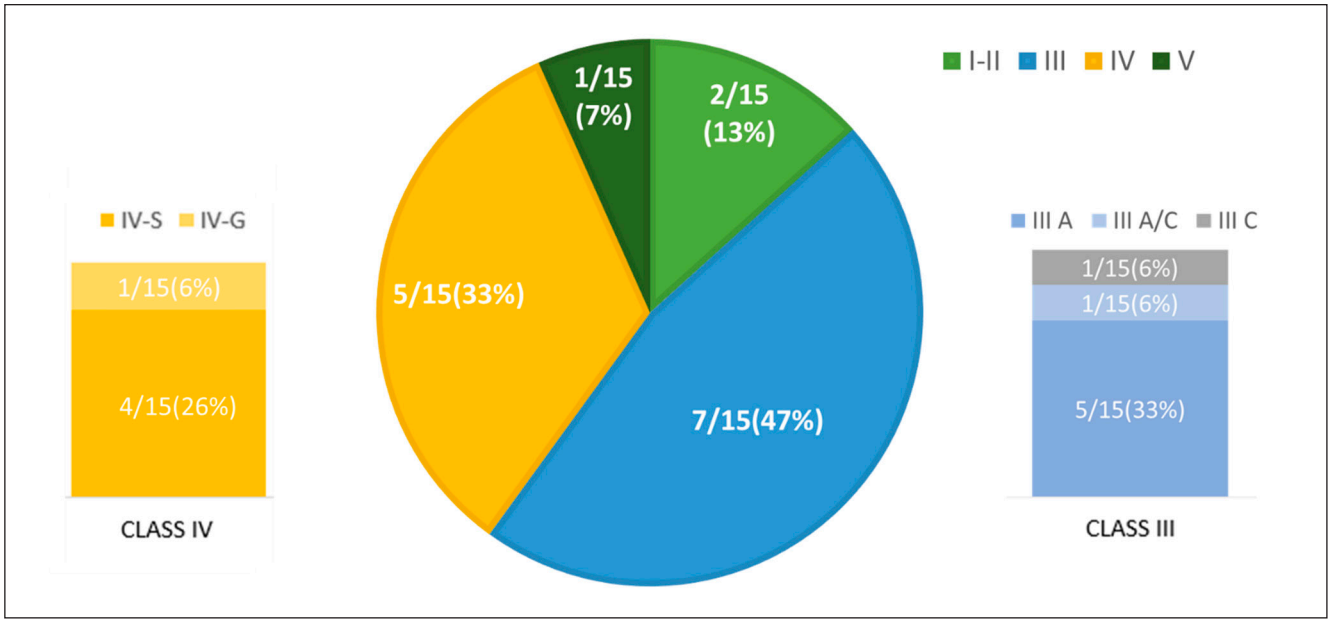

Figure 2. Tissue injury on renal biopsy. Classification of lupus nephritis (ISN/RPS 2003): I (minimal mesangial lupus nephritis), II (mesangial proliferative lupus nephritis), III A (active lesions-focal proliferative lupus nephritis), III A/C (active and chronic lesions-focal proliferative and sclerosing lupus nephritis), III C (chronic inactive lesions-focal sclerosing lupus nephritis), IV-S (diffuse segmental proliferative lupus nephritis), IV-G (diffuse global proliferative lupus nephritis), and V (membranous lupus nephritis).

Table 1. Immunological disorders

Immunological marker	n (%)
Positive Antinuclear antibodies	16 (100%)
- Positive Anti-dsDNA antibodies	14 (87,5%)
- Positive Anti ENA antibodies	
• Anti Ro	6 (38 %)
• Anti La	3 (19 %)
• Anti Sm	4 (25 %)
• Anti RNP	4 (25 %)
• Anti SCL-70	1 (6 %)
• Anti Jo-1	1 (6 %)
Low C3 levels	14 (88%)
Low C4 levels	14 (88%)
Positive lupus anticoagulant	8 (50%)

Other systems

The mean follow-up time was 4.6 years ± 3.3 (range 0.13-12.4). No patient required renal replacement therapy and none died. During the course of the disease, all patients presented involvement of other organs or systems in addition to the renal system (table 2). The musculoskeletal (81%) and dermatological (68.7%) systems were the most frequent.

Eleven patients (68.7%) presented constitutional symptoms. Hematologic alterations were observed in 68.7% of patients. Half of the patients presented neuropsychiatric symptoms. Five patients (31.2%) showed digestive manifestations and 4 (31.2%) ophthalmologic or otorhinolaryngologic alterations. Cardiac involvement was an uncommon finding. In addition to renal involvement, 11 patients (69%) presented involvement of ≥ 3 systems throughout the course of the disease. On statistical analysis, a statistically significant relationship ($p < 0.05$) was observed between the number of affected systems and the decrease in C3 and C4, as well as the increase in anti-dsDNA antibodies at diagnosis. No relationship was observed between the number of systems affected and the degree of renal or histological involvement.

Discussion

The initial presentation of LN is variable, erratic, and insidious. The median age of presentation of our patients was 10.9 years, with a minimum age of 5.7 years. These data are consistent with those appearing in the literature, where the diagnosis in children younger than 5 years of age was very infrequent and the median age at presentation was 11-12 years[3,17-19].

Regarding sex, the female:male ratio was 2.2:1, thus resembling other pediatric series of LN such as the series by Caggiani M., with a ratio of 2.3:1[20], or that of George J., with a ratio of 3.5:1[21].

Previous studies have observed a higher incidence of LN in non-Caucasian patients, with higher prevalence among black, Asian, and Hispanic populations[1,7,8] as well as a higher severity of disease in African American patients[4]. In our study, where more than half of the patients were Caucasian, no greater severity of disease was observed in non-Caucasian patients.

The complaints that led patients to seek consultation varied widely and were unspecific, though the most common were musculoskeletal manifestations and constitutional symptoms. These 2 initial presentations have not always been studied, as described in the Chilean cohort of 31 patients by Gonzalez et al.[22]. Four patients had intermittent skin lesions. Three patients consulted due to more specific symptoms mimicking other diseases: 2 were initially diagnosed with autoimmune thrombocytopenia and one with IgA nephropathy.

LN is usually an early manifestation of SLE. In our patients, renal involvement was observed at baseline in slightly more than one-third of patients, a somewhat lower percentage than the 82.6% prevalence described in the series of patients from India published by Samanta M.[18]. Only 23% of the patients in our study had renal involvement 2 years after diagnosis, which is in line with other authors[23,24]. When compared to adult series, the presentation is early, as most patients were diagnosed during the first year of diagnosis, and only 10.5% of LN cases were detected between the 1st and 5th years and fewer than 5% after the 5th year of diagnosis[8,9].

In our study, the most frequent form of presentation of LN was microhematuria with or without associated proteinuria. In the largest Spanish series, which included 79 patients with LN[17], the initial alterations caused by nephropathy were hematuria (82%), usually associated with proteinuria (75%), and to a lesser extent, nephrotic syndrome (49%). Twenty-eight percent of the children in that study were hypertensive and the same proportion had kidney failure.

According to reports in the literature, nephritis class III and IV are the most frequent forms of nephritis, accounting for 50% to 80% of all biopsies[1] in both Spanish children's series[17,25] and studies of American child patients[26,27]. Coinciding with the literature 80% of renal biopsies in our series were categorized as class III and IV.

In adult patients with LN, serum creatinine levels at diagnosis are positively correlated with the histological type found on renal biopsy[28]. In our study, there

Table 2. Organ and systemic damage during the disease course

Patient number	Constitutional symptoms	Musculo-skeletal	Renal	Dermatolo-gical	Neuro-psychiatric	HEM	Cardiologic	Digestive	ORL-OPH
1		Arthritis	Microhematuria Non-nephrotic proteinuria	Malar rash	Psychosis	Leukopenia Anemia	Pericarditis	Hypertransa-minasemia	Senso-rineural hearing loss
2	Asthenia Anorexia Weight loss Int. fever	Arthralgias	Microhematuria Non-nephrotic proteinuria AKI	Urticaria Angioede-ma Oral aphthous	Depressed mood	Anemia			
3		Arthralgias	Microhematuria Non-nephrotic proteinuria		Headache Depressed mood				
4	Asthenia	Arthralgias Arthritis	Microhematuria Nephrotic proteinuria	Malar rash Oral aphthae					
5		Arthralgias	Microhematuria Non-nephrotic proteinuria HTN	Edema Purpuric rash					
6	Asthenia Anorexia Weight loss	Arthralgias	Microhematuria, Non-nephrotic proteinuria	Malar rash Genital aphthae	Headache	Leukopenia Anemia			
7	Int. fever	Arthralgias	Microhematuria, Non-nephrotic proteinuria	Malar rash		Leukopenia			
8	Asthenia Anorexia Weight loss Persistent fever	Arthralgias	Microhematuria Non-nephrotic proteinuria	Oral aphthae Malar rash					
9	Persistent fever	Arthralgias Myalgia	Microhematuria Non-nephrotic proteinuria AKI	Discoid lupus					
10	Asthenia Anorexia Int. fever	Arthralgias	Hypertensive crisis	Hemato-mas	Hemichorea	Thrombo-cytopenia			
11	Asthenia Anorexia Low-grade fever	Arthralgias	Microhematuria Non-nephrotic proteinuria			Leukopenia Thrombo-cytopenia Anemia			Retinal vasculitis
12			Microhematuria Nephrotic proteinuria HTN			TMA		Vomiting	
13	Asthenia Anorexia Int. fever		Microhematuria Nephrotic proteinuria HTN AKI		Seizure	Leukopenia TMA			
14	Asthenia Anorexia Weight loss Low-grade fever	Arthralgias Myalgia	Microhematuria Nephrotic proteinuria HTN AKI	Malar rash Hair loss Edema Oral aphthous	Seizure Psychosis	Anemia		Vomiting Hypertransa-minasemia	Photopsia
15	Asthenia	Arthralgias	Microhematuria Non-nephrotic proteinuria AKI			Leukopenia Thrombo-cytopenia			
16			Macrohematuria Non-nephrotic proteinuria		Tremor	Anemia			Tinnitus

Abbreviations: HEM (hematologic), ORL (otorhinolaryngologic), OPH (ophthalmologic), HTN (hypertension), AKI (acute kidney injury), TMA (thrombotic microangiopathy), Int (intermittent)

was no significant statistical relationship between the degree of kidney failure and histological involvement.

All In addition to renal manifestations, all patients presented involvement of several organs or systems throughout the course of the disease. Some presented severe symptoms such as thrombotic microangiopathy, central nervous system involvement (hemichorea, leukoencephalopathy, seizures, psychosis), retinal vasculitis, or pericarditis. In the cohort studied by Groot et al.[29], comprising 111 patients with pediatric SLE with a mean time of evolution of 20 years, the authors observed that most patients had multi-organ damage during the course of the disease (62%), mainly musculoskeletal, neuropsychiatric, and renal. The time of disease evolution was the main variable associated with the degree of organ damage, followed by the presence of antiphospholipid antibodies and HBP. In our study, the decrease in C3 and C4, as well as the increase in anti-dsDNA antibodies at diagnosis, were the only variables associated with greater systemic involvement.

Anti-dsDNA antibodies are very sensitive in SLE and their titer is used as a serological marker of LN severity. In the group of adult patients with LN published by Ali et al.[28], all patients in classes III and IV had positive anti-dsDNA antibodies, and most of them with titers higher than 50 UI/ml. In our study, the percentage of patients with positive anti-dsDNA was 80%, similar to other series (60%-82.1%)[18,20]. However, neither the levels of anti-dsDNA nor any of the other immunologic alterations analyzed in our patients correlated with a greater degree of renal or histologic involvement.

Conclusion

LN is an early manifestation in patients with pediatric SLE. In our study, only 6 patients had renal involvement at baseline, where the onset of nonspecific symptoms such as musculoskeletal, dermatologic, or constitutional symptoms was more frequent.

At the time of histologic diagnosis, most of our patients had advanced LN (class III or IV), which did not correlate with major renal or systemic involvement.

An immunocompromised state was the only marker that correlated significantly with major systemic damage.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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