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ORIGINAL PAPER

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Clinical Manifestations of European Borreliosis on the Skin in Acute, Subacute and Chronic Disease

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ABSTRACT

Background: Lyme borreliosis is a multisystemic infection caused by the spirochete *Borrelia burgdorferi*. Erythema migrans is the main clinical marker of the disease. **Objective:** This study aimed to investigate the frequency and clinical manifestations of European borreliosis on the skin, and to determine the significance of these findings for diagnosis and therapy. **Methods:** A retrospective-prospective clinical study of outpatients treated and monitored in a private clinic of an infectologist was conducted over nine years from 2013-2021. The study was clinical, descriptive and analytical in nature. **Results:** In the investigated period, 509 (30.8%) patients with borreliosis symptoms were treated. EM in our patients occurred under the following conditions: a) ringed redness, b) redness of target cells and d) continuous round or oval redness of different sizes of individual redness, or multiple occurrences with primary dissemination. Skin changes with multiorgan chronic symptoms of borreliosis occurred in 67.7% of cases including: walking redness of different shapes and sizes, pink borreliosis stretch marks, white borreliosis stretch marks, borreliosis palms and soles, psoriatic changes, Acrodermatitis chronica atrophicans, Scleroderma circumscripta-morphae, Erythema nodosum, Granuloma anulare and Lichen striatus et atrophicans. Of the 509 patients treated for borreliosis, 32.3% with multi-organ symptomatology had no skin changes. **Conclusion:** The skin manifestations of European borreliosis are multi-layered and Erythema migrans are basic, but not the only markers of the disease. 'Pink borreliose stretch

marks, "white borreliosis striae", "borreliosis palms or soles", and intermittent redness accompanied by itching are unique markers for the diagnosis of chronic borreliosis, if they are manifested.

Keywords: Borreliosis, white stretch marks, pink stretch marks, Europe, Erythema nodosum.

1. BACKGROUND

Lyme borreliosis (LB) is the most common form of infection in Europe (1). Global climate change has widened the range of tick vectors, and LB remains an important health problem for decades. Lyme disease is the most commonly transmitted infection by ticks and among is the most commonly diagnosed tick-borne infections worldwide.

In countries where Lyme disease is common, its incidence is approximately 40 per 100,000 people (1). Infection occurs in late spring, summer and early autumn. Only approximate estimates of the incidence of LB in Europe are possible. A major problem in assessing the prevalence of borreliosis is the unreported newly discovered tick bite or the existence of registries in epidemiological and infectious institutions. The average population incidence rate for regional cargo LB in Western Europe was calculated as 22.05 cases per 100,000 persons per year (2). For example, in France the annual incidence rate was 53/100,000 between 2009 and 2017 (3). In northern Italy (Lombardy), there were only 1.24 new cases per million inhabitants

between 2000 and 2015 (4). The annual incidence in the UK is 12.1/100,000 (5), in Finland 61/100,000 (6) and in Lithuania 99.9 cases per 100,000 inhabitants, one of the highest rates on the continent.

Presentation on the skin is very frequent in Bosnia and Herzegovina, and there are no published results. The disease is caused by the bacterial spirochete *Borrelia burgdorferi* and is transmitted by tick bites from the genus *Ixodes*, most commonly *Ixodes scapularis*. In Eurasia, the dominant pathogens are *B. burgdorferi*, *Borrelia afzelii* and *Borrelia garinii* (3, 4). Depending on the genus, *B. burgdorferi* has special affinity for joints. *B. garinii* is found exclusively in Europe and has selectivity for causing encephalitis in the white matter of the brain. *B. afzelii* has an affinity for the skin and is present at the site of infection. However, in endemic areas, patients with a typical rash may begin treatment without waiting for serological testing.

The main clinical syndromes are: neuroborreliosis (mainly in Europe (*B. afzelii* and *B. garinii*)), Lyme arthritis (mainly in the United States (*B. burgdorferi*)), Lyme carditis, skin changes, erythema migrans and Borelian lymphocytes (7).

Erythema migrans are a diagnostic markers and there is no need for additional laboratory tests. The diagnosis is dependent on clinical judgment and supported by laboratory tests. Enzyme-linked immunosorbent assay (ELISA) is typically used to detect immunoglobulin in Lyme disease, followed by immunoblotting (8). The risk of infection depends on the geographical area, ecological factors and increase in outdoor human activity (9).

The disease is multisystemic, and can affect every organ, most often the skin, nerve tissue, joints, heart, muscles, urinary system, eye, ear and other organs (10-13). It occurs in three stages: primary stage-localized infection, secondary stage-early dissemination and tertiary stage-late dissemination-persistent infection (13)

The skin form of Erythema migrans (EM) is considered to be the basic clinical marker of Lyme disease that originates in the acute or subacute form. Serologic confirmation of the diagnosis is not required for initiation of therapy. Delayed clinical manifestations of chronic course borreliosis have been described, such as Acrodermatitis chronica atrophicans (ACA), Lymphadenitis benigna cutis (Lymphocytoma cutis), Scleroderma cirkumskripta (Morphae), Lichen sclerosis et atrophicans, and Granuloma anulare (14).

Diagnosis of LB is confirmed by serological and microbiological isolation and/or detection of DNA-organisms by PCR-method from tissue, body fluids, or ex yuvantibus, based on the treatment effect (14).

Classical rashes occurs in 70% of patients and can develop between 5-7 days after a tick bite. A uniform rash usually occurs at the site of a tick bite, can burn, itch or be asymptomatic. Rashes tend to spread over several days and concentric rings may be visible. If not treated, the rashes lasts for 2-3 weeks. Approximately 20% of patients may experience recurrent episodes of rash, and multiple lesions are not unusual. Flu-like symptoms may be co-existing. Fever is low and may be associated with

myalgia, neck stiffness, and headache. Vision problems include redness of the eyes and tearing. Approximately 30% of patients experiencing rash do not show further progression of symptoms (14-16).

2. OBJECTIVE

The aim of this study was to clarify the basic characteristics and clinical manifestations of European borreliosis on the skin in the Bosnian and Herzegovinian population, and to determine how much they mean for the diagnosis and therapy of LB.

3. MATERIAL AND METHODS

Study area

This research was conducted in Bosnia and Herzegovina, a country located in Southeastern Europe, in order to investigate the progress of knowledge and practice in diagnosing and managing *Borrelia* skin infections.

Study design

This is a retrospective-prospective clinical study in which duration of study was nine years, from 2013 to 2021.

Inclusion criteria

Patients with borreliosis who had a clinical picture during 2021 were included in this study. The criteria included were a) Clear clinical picture of migran erythema (EM) as solitary or disseminated on first arrival with normal routine results; b) Positive results of white and/or pink stretch marks at predictive sites (groin, armpits, L-S and gluteal area, lower third/half back, lateral chest area, back and front shoulder) with data on chronic intermittent problems of multiple organs for more than eight months, with regular laboratory findings; and c) Positive results of ELISA/WB/Immunoblot on borelia, with multi-organ intermittent symptoms or negative results of the same tests at patient's arrival, which after antibiotic therapy became positive 4-6 months.

Exclusion criteria

Exclusion criteria were: a) Patients with evidence of malignancy or blood disease and patients who refused treatment because they had received several months/years of biologic, corticosteroid or homeopathic therapy; and b) To reduce the risk of hematological abnormalities, pregnancy and malignancies were excluded from the study.

Data collection

Patient data including clinical presentations, laboratory results, and medical history were collected. Routine blood tests (CBC, DCS, SHOCK, urea, creatinine, CRP, fibrinogen, hepatogram, transaminases, gamma-GT) were conducted in all patients. Additional tests for immune-related diseases, serology for *Borrelia* (ELISA, WB, Immunoblot), and thyroid hormone tests were performed as necessary. Data was maintained in Microsoft excel. All patients signed informed consent forms to participate in the study.

Data analysis

Data collected from patients were analyzed using SPSS and GraphPad prism was used to get better visualization of results. Descriptive statistics, such as means, percent-

Characteristics	Retrospective study (2013-2017)	Prospective study (2018-2021)	Total
Number of patients	958	696	1654
Symptomatic LD patients	76 (7.9%)	443 (62.2%)	509 (30.8%)
Patients with EM	14 (18.4%)	62 (14.3%)	76 (14.9%)
Patients with EM dys-seminata	10 (13.2%)	7 (11.3%)	17 (22.4%)
Patients with MOS and whitish skin changes	24 (31.6%)	269 (62.1%)	293 (67.7%)
Patients with MOS and without skin changes	38 (50%)	102 (23.6%)	140 (32.3%)

Table 1. Retrospective and Prospective Study on Distribution of LD patients on the basis of skin changes in acute, subacute and chronic phases of disease. LD: Lyme disease; EM: Erythema migrans; MOS: multiorgan symptoms

Characteristics	Total number of patients	Adults	Children
Patients	509	445	64
Age	28.7(1.8-77.)	39.6(18-77)	9.9(1.8-17)
Sex (M:Ž)	189:320	149:296	40:24
Duration of illness	8.3. (9 days.-45. years)	-	-

Table 2. Distribution of Lyme disease patients according to age, gender and duration of the disease

Skin changes	Percentage
EM of round or oval continuous red shape	46.10%
Multiple annular round or oval continuous redness	22.40%
EM as target cells	17%
Ring-shaped EM	14.50%

Table 3 Skin changes in the acute/subacute phase of the disease in patients during a 9-year study

ages, and standard deviations, were used to summarize the data.

Ethical approval

This study was approved by the Ethical Committee of the General Hospital “Prim. Dr Abdulah Nakas,” Sarajevo, Bosnia and Herzegovina (No. 26-35/23).

4. RESULTS

Retrospective study and Prospective study on Distribution of LD patients on the basis of appearance of Skin changes in Acute, Subacute and Chronic phases

Table 1 shows summarized data from both a retrospective study (conducted from 2013 to 2017) and a prospective study (conducted from 2018 to 2021), providing insights into the characteristics of patients with Lyme disease.

A total of 1,654 patients were included in both studies. In the retrospective study, 7.9% (76 patients) were found to be symptomatic Lyme disease patients. In the prospective study, a higher percentage of 62.2% (443 patients) fell into this category.

Skin changes	Percentage
Walking point redness or beach redness	92.10%
White borreliosis stretch marks	72.20%
Bluish-red irregular striped changes - pink borreliosis stretch marks	24.60%
White borreliosis stretch marks on the palms and soles	5.60%
Urticarial generalized changes with pronounced exudation	4.80%
Stamped psoriatic changes with scaly peeling and often with secondary infection	7.10%
Acrodermatitis chr.atrofikans with white borreliosis striae	2.50%
Erythema nodosum on both lower legs	2.50%
Granuloma annulare	2.50%
Scleroderma circumscripta (Morpheae)	2.50%
Lichen striatus et atrophicans extrem. inf.l.dex.	0.80%

Table 4 Skin changes in patients with chronic relapsing symptoms

Characteristics	Research group	Control group
EM + white borreliosis striae	92.10%	5%
Pink borreliosis stretch marks	24.60%	10%
White borreliosis stretch marks	72.20%	70.50%

Table 5. Relationship between recurrent EM, white Lyme striae and pink Lyme striae

In the retrospective study, 13.2% (10 patients) had disseminated EM, while in the prospective study, 11.3% (7 patients) exhibited this condition. Combined, 32.3% (140 patients) had MOS without skin changes. For better understanding of retrospective and prospective study on distribution of LD patients based on skin changes in acute, subacute and chronic phases of disease (Figure 1).

Distribution of Lyme disease patients according to Age, Gender and Duration of the disease

The average duration of illness was 8.3 years, with a range from 9 days to 45 years as shown in Table 2.

Skin changes in the acute/subacute phase of the disease in patients

Table 3 shows skin changes in the acute/subacute phase of the disease in patients during a 9-year study. In a significant portion of cases (46.10%), EM manifested as round or oval continuous red shapes on the skin. Another substantial group (22.40% of cases) exhibited multiple annular (ring-shaped) round or oval continuous red areas on their skin. Skin changes in the acute/subacute phase of the disease in patients in a 9-year study are presented in Figure 2.

Skin changes in Lyme disease patients with chronic relapsing symptoms

The most prevalent skin change observed, occurring in approximately 92.10% of cases, is characterized by redness in the form of small, point-like or beach-like patches on the skin. White stretch marks associated with borreliosis were present in a significant proportion of cases, affecting approximately 72.20% of individuals. Urticarial changes with pronounced exudation, char-

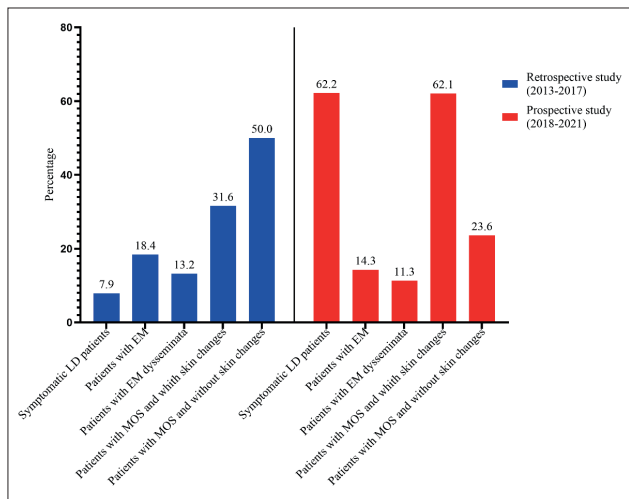


Figure 1. Relationship between the number of LD patients with skin changes and without skin changes with multiorgan symptomatology

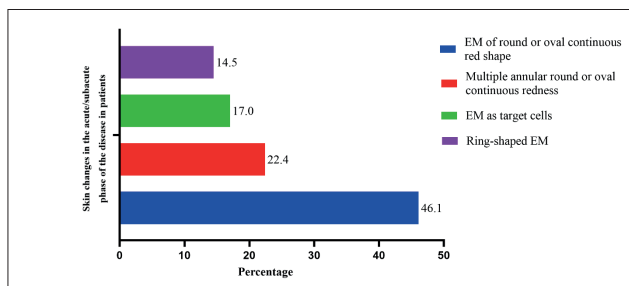


Figure 2. Skin changes in the acute/subacute phase of the disease in patients during a 9-year study

acterized by itchy, raised, and inflamed skin, were observed in 4.80% of cases. Psoriatic changes, marked by scaly peeling and sometimes associated with secondary infections, were present in 7.10% of cases. Acrodermatitis chronica atrophicans, accompanied by white striae associated with borreliosis, was seen in 2.50% of cases. Erythema nodosum, a condition characterized by painful red nodules, appeared on both lower legs in 2.50% of cases. Scleroderma circumscripita, also known as Morphea, was seen in 2.50% of cases, leading to localized skin thickening and discoloration. A less common presentation, lichen striatus et atrophicans, appeared on the extremities, affecting only 0.80% of cases. All above data is presented in Table 4 and depicted in Figure 3.

Relationship between recurrent EM, white Lyme striae and pink Lyme striae

Table 5 shows relationship between recurrent EM, white Lyme striae and pink Lyme striae. Walking redness with white borreliosis stretch marks was found in the investigated group significantly more often than in the control group (92.1% vs5%; p<0.05) cases. Also, pink borreliosis stretch marks were found in the investigated group significantly more often than in the control group (24.6% vs. 10%; p<0.1). Figure 4 shows relationship between recurrent EM, white Lyme striae and pink Lyme striae.

5. DISCUSSION

In our study women were affected more frequently than men. Gender distribution is the same as reported in other European countries: Finland (15, 16) and Nor-

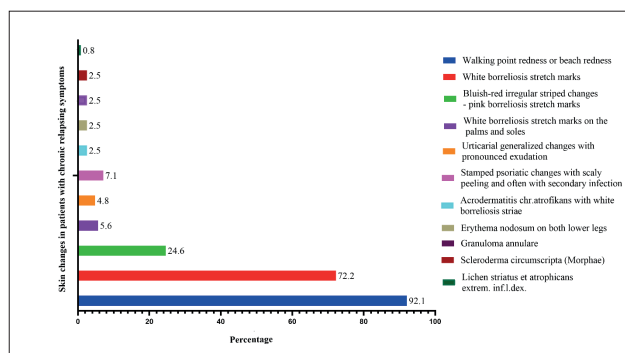


Figure 3. Skin changes in patients with chronic relapsing symptoms

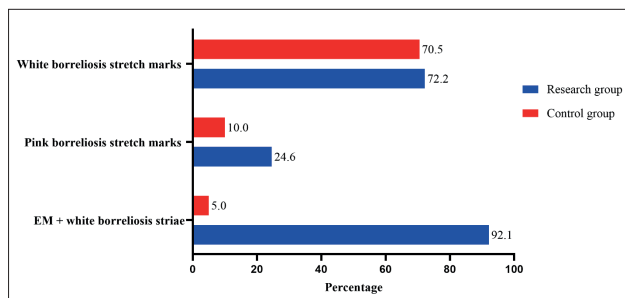


Figure 4. Relationship between recurrent EM, white Lyme striae and pink Lyme striae

way (17) This may be because women pay more attention to their skin changes and turn to healthcare when they are in the erythema migrans stage of the disease. In our study the most affected were adults, but we recorded 9.9 (1.8-17) years in childhood.

In our patients with symptoms of chronic borreliosis, with multi-organ involvement and recurrent skin lesions, migrating erythema has been monitored several years, although in some previously conducted antibiotic therapy of primary EM for 7-15 days. The appearance of walking erythema with itching of the skin has always meant the reactivation of chronic persistent borreliosis, which is consistent with the results of the available literature (16-18).

In our patients we especially emphasize irregular, partially flat or twisted bluish red (pink) and white borrelioid stretch marks, and hard scaly skin on the soles and palms, which lamellar peeling with cracking of the skin under the skin, and the appearance of traces on the side of the wrist and fingers of the hands. Bluish skin cartoon changes (pink borreliosis striae) in women and men persisted for months and years, without any local skin sensations, also spread to the environment. Under intermittent antibiotic therapy, after months and years, they turned into old white stretch marks. Some patients could not remember exactly when these pink skin changes occurred, they thought they were ordinary “stretch marks” due to rapid growth and thickness, although in most patients they had normal weight for height and age. No patients had a positive history for taking corticosteroids or oral antibiotics before the onset of stria, nor had Cushing’s or Marphan’s syndrome (19).

Borreliosis stretch marks have been very little researched, and the available literature is very deficient (20). Pink boreliosis stretch marks occurred in the ingui-



Picture 1. Walking spot redness or beach redness of different size and distribution with moderate to severe itching of the skin in 116 patients of the study group (A: Walking continuous borreliosis redness; B (Walking chronically disseminated spot redness)).



Picture 2. (A: EM chronica II disseminata, B: EM- Round Continuous Redness)

nal regions or in the upper third of the inner or back of the thigh, in the skin of the cruciate part and the gluteal region, laterally in the thorax just below the armpits, in the lower half or lower third of the back skin, or in the upper part of the inner arm, on the front of the shoulders, in the breasts of girls and women, and on the back of the lower legs.

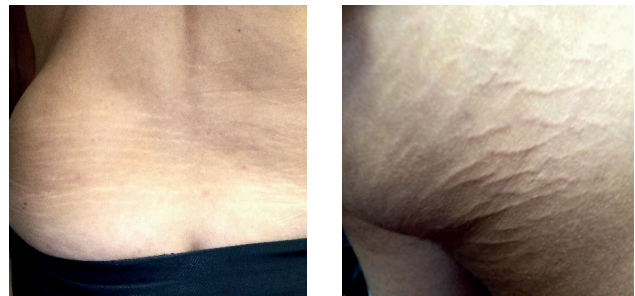
The pink borreliose stretch marks on the front and side of the abdomen, on the side of the thorax or on the inside of the arms and legs are vertically placed, those in the lumbo-sacral part and on the front and back of the shoulder skin are horizontal. On the skin, the gluteal regions are obliquely placed, and on the breasts longitudinally from the base to the mamilla. On the back they are more often on the right than on the left half, and have the appearance of zigzag lines, or are similar to commas.

Since we have received positive serological findings for borrelia in almost all cases, whenever we discovered these irregular pink stretch marks at the first examination of the patient with a positive history for possible borreliosis, these changes are considered predictive for active chronic relapsing borreliosis. Two isolated cases, with striking pink skin lesions and negative initial findings of ELISA and Borrelia Immunoblot, had a typical history of chronic borreliosis and became seropositive after four and six months of intermittent dual antibiotherapy.

In most of our patients, white, often short, stretch marks were found in the gluteal and slightly longer in the lumbosacral region, straight or oblique, and sideways on the thighs and abdomen longitudinally positioned, and on the shoulders horizontal. In our study, white borrelio-



Picture 3. Changes in the soles of the feet and/or palms in terms of dry, hard, cracking skin that scatters from scaly to lamellar waste with heel cracks and finger cracks or the lateral aspect of the upper arm and white borreliose stretch marks was seen in seven (5.6%) patients.



Picture 4. White borreliose stretch marks (short longitudinal stretch marks on the inner or outer side of the thigh, short hair in the gluteus area, and long horizontal old borrelian stretch marks in the upper part of the cruciferous region and the lower back, and longitudinal ones on the back of the knee, horizontal ones on the front of the shoulder) were found at 91 (72.2%) out of 126 patients. Pink borreliose stretch marks- in the groin area, armpits, side of the abdomen, on the inner and back sides of the upper and lower legs, in the L-S region and on the lower and middle back, without any local sensations, in 31 (24.6%) of 126 patients of the investigational group.

sis stretch marks showed a high prevalence and spread in the general population, which on the other hand speaks of a very widespread persistent infection with borrelia. These white stretch marks are considered an indicator of the presence of a persistent infection with borrelia from childhood, which for many years, they did not have pronounced other clinical manifestations, but they were activated by some of the triggers; stress psycho-physical, new tick bite, dietary errors, extreme heat, direct sun and cold. In the available literature we did not find this type of presentation of irregular bluish-red and drastic skin changes (pink borreliose stretch marks) that are associated with borreliosis of this presentation (21).

Based on 10 years of experience, we could at the first examination of the patient diagnose active borreliosis if they had intermittent problems of several organs, and found bluish-red or pink stretch marks, or that it was a chronic long-term persistent and/or relapsing borreliosis, if they had white sedative stretch marks with walking problems of several organs.

Our patients had complex occasionally walking symptoms of the disease lasting from 8 months to 20 years, and included fatigue, headache, dizziness, occasional blurred vision, double vision, pressure on eyeballs or stabbing pains, intermittent ptosis or strabismus, swallowing disturbances, walking joint pain, occasional heart palpitations or extrasystole, insomnia, frequent wak-

ing up, frequent night urination, intermittent tinnitus, itchy skin, redness of various shapes and sizes, disorder speech, altered handwriting, panic attacks, anxiety, or depression. In the literature, striae are mentioned as stretch marks of skin that occur during pregnancy, then with prolonged use of corticosteroids, in Cushing and Marphan syndrome. The pathogenesis of stretch marks alone is not sufficiently understood (22-25).

Limitation of the study

There are limitations of the study because the literature data are scarce. And we did not find an association of infection with borelia with the appearance of skin changes on the palms and soles in the form of hard, scaly skin that is lamellar peeling (borreliosis palms and soles), and painful ragadas especially on the soles of the feet. We also found no support in the literature for the scaly-colored psoriatic lesions, from reddish to brownish, round or oval in skin on extremities, with secondary staphylococcal infections in some of them, which were reversible to long-term intermittent antibiotherapy. In our patients, these changes on the palms and soles of the hands and soles of the feet occurred previously before other symptoms and lasted for several months or years before the onset of symptoms for chronic LB. Antibiotics completely resolved, and their exacerbation meant exacerbation of relapsed-chronic borreliosis disease.

6. CONCLUSION

Our study of Lyme borreliosis (LB) in patients reveals a diverse spectrum of clinical manifestations and the existence of acute, subacute, and chronic relapsing courses of the disease. While Erythema migrans (EM) remains a fundamental marker of LB, it is not the sole indicator. The presence of EM, with its various forms such as ringed redness, target-shaped lesions, and round/oval ringed or continuous redness, is a crucial diagnostic feature, especially during primary dissemination.

Furthermore, our research highlights the significance of specific skin manifestations as unique markers for LB diagnosis and therapy. Pink and white borreliosis stretch marks, along with borreliosis on palms and soles, intermittent walking redness with skin itching, are distinct indicators of LB, particularly in cases of persistent and relapsing chronic borreliosis. In summary, the varied skin manifestations observed in LB patients underscore the complexity of the disease and the importance of considering multiple clinical markers and diagnostic signs for its timely identification and appropriate management.

- **Patient Consent Form:** All participants were informed about subject of the study.
- **Author's Contribution:** S.DK. and E.D. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. H.A, D.D., and T.D. had a part in article preparing for drafting or revising it critically for important intellectual content. N.M., R.G., J.B. and V.M., gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** None.

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