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ORIGINAL RESEARCH

Identification of Challenging Diagnostic Factors in Livedoid Vasculopathy: A Retrospective Study

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Background: Livedoid vasculopathy is an uncommon cutaneous ulcerative dermatosis that is challenging to diagnose. Diagnostic delay brought both pain and uncurable atrophied scar to patients.

Purpose: We conducted this study to identify the factors responsible for the initial misdiagnosis of livedoid vasculopathy and to identify possible methods to increase the diagnostic accuracy of livedoid vasculopathy.

Patients and Methods: We conducted a retrospective medical record review to confirm the diagnosis of livedoid vasculopathy in patients who visited the Department of Peking Union Medical College Hospital for the first time. We used the Diagnosis Error Evaluation and Research taxonomy to evaluate missed cases.

Results: Twenty-three patients (85.18%) had an alternate diagnosis, including 10 (43.4%) with two or more diagnoses. The average time from disease onset to the final diagnosis of livedoid vasculopathy was 4.61 ± 0.69 years. The major diagnostic errors were clinician assessment failures and failures in the timely follow-up and rechecking of patients. Allergic vasculitis was the most common misdiagnosis. Other alternate diagnoses include Henoch-Schoenlein purpura, pigmented purpuric dermatosis, eczema, erythema nodosum, and reactive perforating collagenases. Twenty-three patients (65.21%) received systemic corticosteroid therapy before the final diagnosis of livedoid vasculopathy.

Conclusion: It is critical to raise the awareness of clinicians about livedoid vasculopathy, especially when patient present with extensive livedo racemosa or long-lasting purpuric lesions on the lower limbs. Long-term follow-up is necessary, especially for younger patients. Skin biopsy is recommended before systematic therapy.

Keywords: livedoid vasculopathy, atrophie blanche, diagnostic accuracy, vasculitis

Introduction

Livedoid vasculopathy, an uncommon cutaneous ulcerative condition with a chronic course and relapsing exacerbations, was recently described as an occlusive condition of the capillary microcirculation that causes cutaneous ischemia and infarction, which explains the severe pain, paresthesia, and hyperesthesia experienced by those affected.[1–3] Livedoid vasculopathy often affects the legs bilaterally in young to middle-aged individuals, particularly women.[4] Most patients present with livedo racemosa and painful ulceration, followed by healing as porcelain-white atrophic scars, while a few patients demonstrate purpura lesions resembling pigmented purpura dermatosis.[5] The periodic clinical course and great pain of livedoid vasculopathy substantially affect patients' lives, limiting their mobility and reducing their overall quality of life.[6] Meanwhile, the presence of silver atrophic scars causes a certain psychological stigma, especially in younger females.[7]

Early diagnosis and treatment of livedoid vasculopathy before ulcer formation can reduce pain and prevent scar formation and other complications. However, apart from the Delphi consensus expert recommendations, there are no established diagnostic criteria for livedoid vasculopathy or available treatment guidelines.[8] Histopathological results and clinical manifestations are the foundation for the definitive diagnosis of livedoid vasculopathy.[9] Although misdiagnosis

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often occurs and epidemiologic data point to a 5-year delay in receiving a proper diagnosis, systematic research on differential diagnoses and factors contributing to diagnostic delay or failure has not yet been conducted.[10]

In this retrospective study, we reviewed the diagnostic course of patients with livedoid vasculopathy before they obtained their final diagnosis and report the diagnostic errors that contributed to misdiagnosis. The findings of this study should help to raise awareness of the need for accurate diagnosis and provide a possible protocol to improve the diagnostic accuracy of livedoid vasculopathy.

Materials and Methods

This study was approved by the ethics committee of Peking Union Medical College Hospital and the study complies with the Declaration of Helsinki. Written informed consent for publication was obtained from all patients.

Study Design

We conducted a retrospective medical record review of patients who visited the Department of Peking Union Medical College Hospital for the first time between September 2022 and September 2023 to confirm the diagnosis of livedoid vasculopathy. Using the electronic database at our institution, we identified patients with livedoid vasculopathy. We reviewed the paper and computerized medical records of patients who underwent further confirmation of livedoid vasculopathy by both skin biopsy and the recommended diagnostic pathway.[11]

We used the Diagnosis Error Evaluation and Research (DEER) taxonomy to evaluate patients with a final diagnosis of livedoid vasculopathy in whom the diagnosis was missed or delayed before visiting our clinic.[12]

Sample Collection

We included all patients aged ≥12 years who were referred to us with a prior diagnosis of livedoid vasculopathy or who received a diagnosis of livedoid vasculopathy at our institution. The diagnosis of livedoid vasculopathy was determined by two experienced dermatologists (YMG and HZJ) on the basis of history, characteristic clinical symptoms, cutaneous presentation signs, and skin biopsy findings that demonstrated histopathological confirmation, as interpreted by an expert pathologist majoring in dermatology at our institution. Patients with severe systemic disease or a conflicting diagnosis were excluded.

Data Collection

Age, sex, and body mass index (measured as weight in kilograms divided by height in meters squared) were recorded. Relevant data were gathered based on the materials and notes offered by the patients, as well as their medical history, examination results, previous diagnostic test results, initial diagnoses, and therapies. For the missing records, we would first ask the hospital then to contact the local doctors the patients visited to get the missing records. We excluded patients with non-detailed records. The patients' medical records were also searched to identify the duration until final diagnosis and to obtain comprehensive referral information.

Analysis Methods

The Mann–Whitney *U*-test was used to compare continuous variables, while Fisher's exact test was used to compare categorical variables. Statistical analyses were performed using SPSS version 26.0.

Results

We identified 29 patients who visited our clinic for the first time between September 2022 and September 2023 with a final diagnosis of primary livedoid vasculopathy according to the electronic database at our institution. The study flowchart is shown in Figure 1. After excluding two patients with uncertain diagnoses due to atypical presentation, the medical records of 27 patients were reviewed (Table 1). Twenty-seven patients (74.1%) were female, while seven (25.9%) were male. The average age of the patients was 33.7 ± 3.08 years, and the mean age at livedoid vasculopathy onset was 27.68 ± 2.96 years. There was no significant difference in the average age or age at onset between males and females (P = 0.156 and P = 0.296, respectively). The average duration of illness was 5.44 ± 0.77 years.

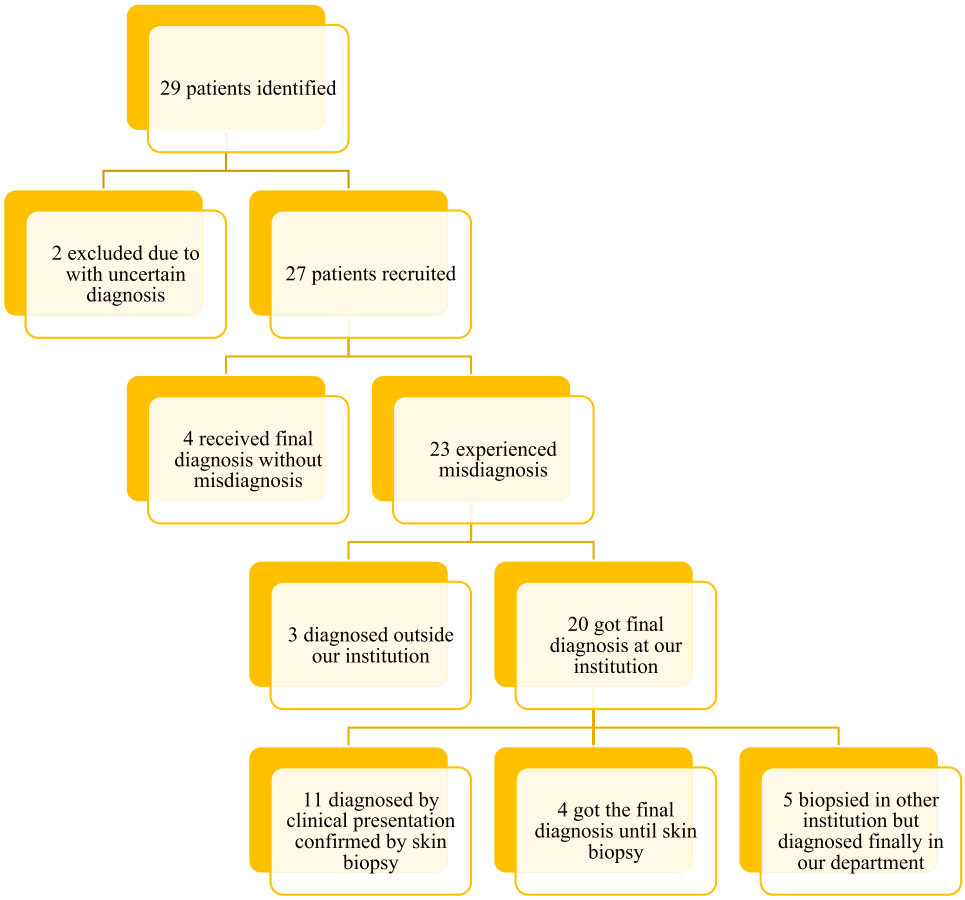

Figure 1 Main study protocol.

Prior to the final diagnosis of livedoid vasculopathy, 23 patients (85.18%) had an alternate diagnosis, including 10 of 23 patients (43.4%) who had two or more diagnoses. The average time from disease onset to the final diagnosis of livedoid vasculopathy was 4.61 ± 0.69 years. Three patients with a final diagnosis were diagnosed before visiting our institution. The remaining 20 patients were diagnosed at our institution. We reviewed the history of these 20 patients,

Table 1 Clinical Characteristics of 27 Patients with Livedoid Vasculopathy

Characteristics	N (%)
Gender	
Female	20 (74.1%)
Male	7 (25.9%)
Age, years	
≤20	6 (22.2%)
21–30	6 (22.2%)
31–40	8 (29.6%)
>40	7 (25.9%)

(*Continued*)

Table 1 (Continued).

Characteristics	N (%)
Age of onset, years	
≤10	3 (11.1%)
10–20	7 (25.9%)
21–30	6 (22.2%)
31–40	7 (25.9%)
>40	4 (14.8%)
Characteristics	Mean ± SD
Age, years	33.7±3.08
Male	40.29±4.62
Female	31.40±4.93
P	0.156*
Onset of age, years	27.68±2.96
Male	36.00±4.48
Female	24.90±3.50
P	0.296*
Duration of illness, years	5.44±0.77
Time from the disease onset to get the final diagnosis, years	4.61±0.69

Note: **t*-test for continuous variables.

including 11 patients (55%) who were diagnosed based on clinical presentation and experience, with further confirmation by skin biopsy; five patients (25%) who underwent skin biopsy outside our institution but with an alternative diagnosis before visiting our institution; and four (20%) who received an alternative initial diagnosis at our department, but in whom further skin biopsy revealed a final diagnosis of livedoid vasculopathy. Most patients were misdiagnosed by a dermatologist, while three patients were referred by the immunology and rheumatology departments for consideration of immune complex-mediated vasculitis. Instead of dermatology clinics, two patients with a delayed diagnosis visited traditional Chinese medicine clinics.

We applied the DEER taxonomy to 23 patients with delayed or missed diagnoses. The major diagnostic errors were clinician assessment failures (errors in hypothesis generation and weighing) and failure in achieving timely follow-up and rechecking of patients. These diagnostic errors were responsible for nearly all patients who received an alternative diagnosis before the final diagnosis of livedoid vasculopathy (23/27 [85.19%]). Nine patients (33.3%) had a delayed or missed diagnosis because of physical examination misinterpretation, and erroneous clinician interpretation occurred in five patients (Table 2).

Among the alternative diagnoses (Table 3), 17 of 23 patients (73.91%) were diagnosed with allergic vasculitis, and two patients were diagnosed with allergic vasculitis twice at two different institutions. One patient was diagnosed with livedoid vasculopathy by pathology. He visited another community clinic 3 years later with recurrent erythema, painful ulcers, and silver-atrophied scars, and allergic vasculitis was diagnosed (Figure 2a). Three patients were diagnosed with pigmented purpuric dermatosis (Figure 2b), and four were treated for Henoch-Schönlein purpura (Figure 2c) until recurrent painful ulcers were noticed by the dermatologist. Eczema (Figure 2d), erythema nodosum (Figure 2e), and reactive perforating collagenases were the other alternative diagnoses received by the patients.

Table 2 Categorization of the Types of Diagnostic Error in Patients with Diagnoses Other Than Livedoid Vasculopathy Evaluated According to the Diagnosis Error Evaluation and Research (DEER) Criteria

Point in the Diagnostic Process	What Went Wrong	No. (%)
1. Access/presentation		
A	Failure/delay in presentation	8 (29.6%)
B	Failure/denied care access	
2. History		
A	Failure/delay in eliciting critical piece of history data	
B	Inaccurate/misinterpretation	23 (85.19%)
C	Failure in weighing	
D	Failure/delay to follow-up	23 (85.19%)
3. Physical examination		
A	Failure/delay in eliciting critical examination finding	9 (33.33%)
B	Inaccurate/misinterpreted	5 (18.5%)
C	Failure in weighing	
D	Failure/delay to follow-up	23 (85.19%)
4. Tests Ordering		
A	Failure/delay in ordering needed test(s)	
B	Failure/delay in performing ordered test(s)	11 (40.7%)
C	Error in test sequencing	
D	Ordering of the wrong test(s)	
E	Test ordered the wrong way	
Performance		
F	Sample mix-up/mislabeled (eg, wrong patient/test)	
G	Technical error/poor processing of specimen/test	
H	Erroneous laboratory/radiology reading of test	5 (18.5%)
I	Failed/delayed reporting of the result to the clinician	
Clinician processing		
J	Failed/delayed follow-up (abnormal) test result	11 (40.7%)
K	Error in clinician interpretation of test	5 (18.5%)
5. Assessment		
Hypothesis generation		
A	Failure/delay in considering the correct diagnosis	23 (85.19%)

(*Continued*)

Table 2 (Continued).

Point in the Diagnostic Process	What Went Wrong	No. (%)
Suboptimal weighing/prioritizing		
B	Too little consideration/weight given to the diagnosis	
C	Too much weight on competing/coexisting diagnosis	
Recognizing urgency/complications		
D	Failure/delay to recognize/weigh urgency	
E	Failure/delay to recognize/weigh complication(s)	
6. Referral/consultation		
A	Failure in ordering referral	3 (11.11%)
B	Inappropriate/unneeded referral	5 (18.5%)
C	Error in diagnostic consultation performance	
D	Failed/delayed communication/follow-up of consultation	23 (85.19%)
7. Follow-up		
A	Failure to refer patient to close/safe setting/monitoring	
B	Failure/delay in timely follow-up/rechecking of patient	23 (85.19%)

Table 3 Alternative Diagnoses Received by the Patients with a Final Diagnosis of Livedoid Vasculopathy

Alternative Diagnosis	N (%, Percent of 23 Patients with Misdiagnosis History[#])
Allergic vasculitis*	17 (73.91%)
Henoch-Schoenlein purpura	4 (17.39%)
Pigmented purpuric dermatosis	3 (13.04%)
Eczema	1 (4.35%)
Erythema nodosum	1 (4.35%)
Reactive perforating collagenases	1 (4.35%)

Notes: *Two patients were diagnosed allergic vasculitis twice in two different institutions. [#]10 patients who had two or more diagnoses.

After the initial diagnosis, 15 of 23 patients (65.21%) received low-to-medium-dose systemic corticosteroid therapy with prednisone, ranging from 15 mg/day to 30 mg/day. Ten patients were unresponsive to oral prednisone, and Cushing's syndrome was found in four patients after long-term systemic corticosteroid exposure.[13] Five patients received immunosuppressants, such as thalidomide, hydroxychloroquine, methotrexate, and cyclophosphamide. Five patients tried traditional Chinese herbal medications, while one received topical corticosteroid cream only as therapy. Two patients were administered systemic antibiotics, among which one stopped owing to allergic drug rashes. Although there was no final diagnosis, only one patient was prescribed an anticoagulant, piperazine ferulate, after the patient showed unresponsiveness to systemic corticosteroids (Table 4).

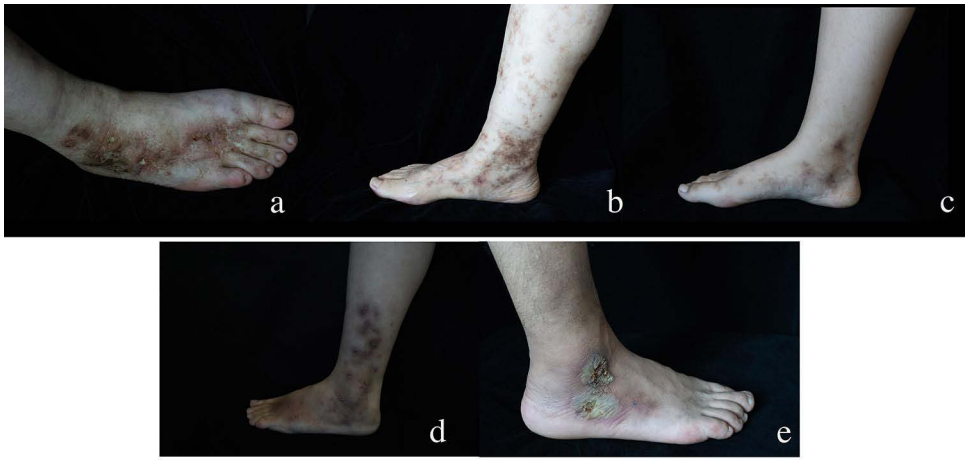

Figure 2 Clinical presentation of patients who were misdiagnosed with allergic vasculitis (**a**), pigmented purpuric dermatosis (**b**), Henoch-Schönlein purpura (**c**), eczema (**d**), and erythema nodosum (**e**).

Discussion

This retrospective, single-center study evaluated the misdiagnosis of patients with livedoid vasculopathy and systematically reviewed alternative diagnoses in patients with this condition before obtaining the final diagnosis and suitable therapy. Of the 27 patients, the ratio of males to females was 1:2.8, illustrating a female predominance, consistent with prior studies in the Chinese population.[5,14,15] The average age of the patients was 27.68 years, with 32.1% first noticing skin lesions before 18 years of age, which is also consistent with a previous report in the Chinese population.[16]

Approximately 85.18% of the recruited patients were misdiagnosed, with nearly half (43.4%) having received more than one diagnosis prior to reaching the final diagnosis of livedoid vasculopathy. The average time from disease onset to the final diagnosis was 4.61 years, which is similar to studies conducted in Germany, while it was longer than the time of 3.4 years reported in a study conducted in France[17] and shorter than the time of 6.25 years reported in a study conducted in Brazil.[10,18,19]

Compared with non-dermatologists, dermatologists are more accurate and quicker at diagnosing skin conditions.[20,21] Among the patients in the present study, five received an alternative diagnosis when they presented to the clinics of other specialties. Three patients who presented to the rheumatology clinic of our institution were not diagnosed with livedoid

Table 4 Treatments Received by the Patients Before the Final Diagnosis of Livedoid Vasculopathy

Treatment	N (%, Percent of 23 Patients with Misdiagnosis History)
Systematic corticosteroid therapy	15 (65.21%)
Immunosuppressant	5 (21.74%)
Thalidomide	4 (17.39%)
Hydroxychloroquine	3 (13.04%)
Methotrexate	1 (4.35%)
Cyclophosphamide	1 (4.35%)
Traditional Chinese herbal medications	5 (21.74%)
Topical corticosteroid cream	1 (4.35%)
Systematic system antibiotics	2 (8.70%)
Anti-coagulant	1 (4.35%)

vasculopathy; rather, they were diagnosed with immune-mediated vasculitis until they were referred to our dermatology clinic for biopsy after showing unresponsiveness to traditional immunosuppressant therapy and systemic steroid therapy. The other two patients who consulted a traditional Chinese medicine clinic outside of our institution were treated for eczema with oral herbs and tropical herbal ointments until the lesions deteriorated.

To confirm the diagnosis of livedoid vasculopathy and exclude other entities as differential diagnoses, biopsy was necessary. In the refractory phase, endothelial proliferation, fibrin deposition in the vessel walls, and intraluminal hyaline thrombi were observed in the upper and middle dermis under a microscope, while scar tissue with negligible microvessels and an atrophic epidermis were noted when the biopsy was taken at the scar site. Twelve of 23 patients (52.2%) did not receive a final diagnosis of livedoid vasculopathy until skin biopsy. Leukocytoclasia and perivascular inflammatory infiltrate may be seen in the acute phase, which pose a diagnostic challenge when differentiating livedoid vasculopathy by pathology, especially when differentiating it from inflammatory vasculitis.[22] Five of the patients in the present study were misdiagnosed with cutaneous small-vessel vasculitis based on skin biopsy performed at another institution. This underscores the importance of raising awareness of livedoid vasculopathy among dermatologists and dermatopathologists.

Knowledge gaps, inexperience, incomplete history gathering, ineffective questioning of cognitive biases, faulty visual processing, and faulty verification (confirmation or test choice) account for the majority of diagnostic errors (>75%).[23] In this study, with the help of the DEER taxonomy, clinician assessment failures (errors in hypothesis generation and weighing) and failure to perform timely follow-up and rechecking of patients were identified as collectively responsible for 89.15% of cases of misdiagnosis. The diagnosis was delayed or missed in one-third of the patients because of misinterpretation of the physical examination until painful ulcers appeared.

At the very early stage of livedoid vasculopathy, only slight livedo racemose or purpura are noticed by both patients and their physicians.[5] In the present study, two patients presented with extensive livedo reticularis, while seven patients who presented with purpura were diagnosed with pigmented purpuric dermatosis and Henoch-Schönlein purpura at a very early stage of the skin lesions. Pigmented purpuric dermatosis-like skin lesions in livedoid vasculopathy were first reported by Zhao et al in 2023. Such lesions may last for many years and predominantly occur in younger patients. In our study, four of seven patients (57.1%) were female and aged <20 years, while two male patients were around 30 years of age when the purpura began (27 and 30 years old). Of note, we also noticed that a female patient first presented with purpura when she was 60 years old.

Anabolic steroids are recognized as the second most commonly used treatment for livedoid vasculopathy, especially in patients with connective tissue diseases. Steroids are beneficial when used alone or in conjunction with other treatment modalities for patients with livedoid vasculopathy and related connective tissue diseases, such as systemic lupus erythematosus. In the present study, steroids may have worked at the initial dose, and the symptoms may have relapsed as soon as the steroid dose was tapered. Furthermore, approximately 65.21% of the patients received systemic corticosteroid therapy before the final diagnosis. They did not undergo skin biopsy or consider the possibility of livedoid vasculopathy until the patients presented little response to corticosteroid therapy, with the development of Cushing's syndrome in two patients. Instead of systemic corticosteroids, anticoagulants are the most widely used therapy for livedoid vasculopathy, while prednisolone is efficacious when used in combination with other therapeutic methods.[24] Most patients respond well to anticoagulants and gradually reduce their daily steroid intake.

This study has some limitations that should be considered. First, this was a retrospective, single-center study with a small sample size, which means that there could be bias in the sample. Second, the history of a few patients was judged based solely on their recall, which may have introduced patient recall bias. Finally, some of the patients came from rural areas where there is limited access to medical specialists, and the initial symptoms at the very early stage of livedoid vasculopathy may have been neglected.

Conclusion

In summary, this single-center retrospective study reviewed the course of 27 patients who were misdiagnosed before obtaining a final diagnosis of livedoid vasculopathy. Livedoid vasculopathy is a diagnostic challenge, especially at the very early stage of the condition, probably due to its rarity and the lack of awareness of its early symptoms. Long-term follow-up should be conducted for those who present with extensive livedo racemosa with negative systemic symptoms

and normal immunological laboratory results, and those with long-lasting purpuric lesions on the lower limbs, especially younger patients. For patients with painful ulcers, skin biopsy is recommended and necessary before systemic steroid therapy. Moreover, for non-dermatologists, especially rheumatologists, when patients are diagnosed with vasculitis only on clinical presentation and medical history, and are unresponsive to systemic corticosteroid therapy or exhibit disease relapse as soon as steroid therapy is tapered, skin biopsy and livedoid vasculopathy should be considered.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author, Prof. Hongzhong Jin, upon reasonable request.

Statement of Ethics

This study was approved by the ethics committee of Peking Union Medical College Hospital. Written informed consent for publication was obtained from all patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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