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ORIGINAL RESEARCH

Non-Tuberculous Mycobacterial Infections of the Skin and Soft Tissue in a Chinese Population: A Retrospective Analysis of 15 Cases

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Background: Non-tuberculous mycobacteria (NTM) skin and soft tissue infections (SSTIs) are increasingly recognized but underdiagnosed in China.

Methods: This retrospective study analyzed 15 confirmed cases of NTM SSTIs treated at a southern Chinese hospital from 2012 to 2022. Clinical data, including demographics, clinical presentations, comorbidities, diagnostic methods, treatment regimens, and outcomes, were collected and analyzed. Diagnostic efficacy of conventional culture and metagenomic next-generation sequencing (mNGS) was compared.

Results: The median age of patients was 57 years, and 66.7% were farmers. Pathogens identified included *Mycobacterium abscessus* (20.0%), *M. marinum* (13.3%), and rapidly growing mycobacteria (13.3%). Immunocompromised states, such as anti-interferon-gamma autoantibody positivity, were present in 40.0%. mNGS demonstrated superior diagnostic performance, achieving a detection rate of 86.7% (13/15 cases), compared to 26.7% for culture. Treatment regimens, including clarithromycin, rifampin, ethambutol, and moxifloxacin, lasted 1–24 months. Outcomes showed cure in 8 patients (53.3%), improvement in 6 (40.0%), and 1 lost to follow-up.

Conclusion: NTM SSTIs present significant diagnostic and therapeutic challenges, with clinical variability and frequent association with immunocompromised states. *M. abscessus, M. marinum*, and *M. avium* were the predominant pathogens. mNGS improves detection but still should complement culture. Precise pathogen identification and tailored therapy are essential for achieving optimal outcomes, and further studies are needed to refine diagnostics and treatment strategies.

Keywords: non-tuberculous mycobacteria, skin and soft tissue infections, China, metagenomic next-generation sequencing, antibiotic therapy

Introduction

Non-tuberculous mycobacteria (NTM) are environmental pathogens that are widely distributed in water and soil.[1] Approximately 90% of NTM infections involve the pulmonary system, although infections can also affect lymph nodes, skin, soft tissues, and bones.[2] NTM skin and soft tissue infections (SSTIs) often arise following penetrating injuries, trauma, injections, or surgical procedures, making them challenging to diagnose.[3] Due to the variable and sometimes subtle clinical presentations, NTM SSTIs are frequently misdiagnosed as sporotrichosis or other fungal infections, highlighting a potential gap in clinical awareness and understanding of these infections among healthcare providers.

In recent years, the incidence of NTM infections has increased, attributed to a higher prevalence of immunosuppressive therapies and the growing popularity of dermatological and surgical procedures. This trend underscores the importance of timely recognition and accurate diagnosis of NTM SSTIs in clinical practice.[4] However, despite global recognition of NTM infections, there remains a lack of case summary analysis of NTM SSTIs in the Chinese population, leading to potential diagnostic delays and challenges in clinical management.

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This study aims to address these challenges by retrospectively analyzing the clinical characteristics, disease progression, treatment approaches, and outcomes of patients with NTM SSTIs treated at a general hospital in southern China over a 10-year period. By providing detailed, real-world observations from this cohort, the study seeks to fill the national data gap, thereby informing diagnostic and therapeutic strategies.

Materials and Methods

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. It included a total of 15 patients diagnosed with NTM skin and soft tissue infections in the Department of Dermatology and Venereology of the First Affiliated Hospital of Guangxi Medical University from January 1, 2012, to December 31, 2022. Clinical data collected from medical records encompassed demographic information (sex, age, occupation), clinical characteristics, laboratory findings, treatment regimens, and patient outcomes.

Patient Selection Criteria

Patients were diagnosed based on the following criteria:[1] A history and clinical presentation consistent with NTM skin and soft tissue infections.[2] Isolation of one or more NTM strains from skin or soft tissue samples (including wounds, abscesses, tissues, or catheters) through culture and/or molecular biology methods.[3] Histopathological evidence suggestive of infectious granulomas with positive acid-fast bacilli staining. Only cases of NTM SST infection were included in this analysis if they met all three of the above criteria.

Diagnostic Methods

Diagnostic methods for pathogen identification included acid-fast staining of tissue homogenates or tissue sections, bacterial culture, biochemical phenotyping, and molecular biology methods. All samples followed strict protocols for microbiological culture and next-generation macrogenomic sequencing (mNGS).

mNGS Sample Processing and Bioinformatics

Fresh tissue or abscess material was processed for DNA extraction using mechanical/enzymatic lysis followed by silica-membrane-based methods. DNA libraries were prepared via enzymatic fragmentation and indexed adapters, followed by paired-end sequencing on an Illumina platform. Human reads were removed, and remaining sequences were classified using a curated microbial database with a k-mer and alignment-based pipeline. Negative controls were processed in parallel. A sample was considered positive for NTM if taxon-specific reads exceeded background and met pre-defined thresholds. Results were provided to the clinical team for management guidance alongside culture and histopathology.

Data Collection

Demographic and clinical data were extracted from patient records, covering information on the patient's sex, age, occupation, clinical presentation, laboratory results, treatment plans, and clinical outcomes. Special attention was given to factors such as immunological status and trauma history.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, clinical features, treatments, and outcomes. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Statistical analyses were conducted using SPSS version 24.0.

Results

Demographics of Patients

Among the 15 patients confirmed with NTM skin and soft tissue infections, occupations were primarily farmers (n=10), with the remaining employed as office workers or in other roles. Ages ranged from 39 to 79 years, with a median age of 56. Common comorbidities included hypertension (n=3), diabetes (n=3), and tuberculosis history (n=2), while one patient

was HIV-positive. Six patients reported a history of trauma or surgical intervention at the infection site, such as hand injuries or breast prosthesis implantation. The median time from symptom onset to confirmed diagnosis was approximately 15 months, with two cases initially misdiagnosed as lymphoma (Table 1).

Clinical Manifestations and Infection Sites

The clinical appearances of the 15 cases predominantly include nodules (12/15, 80%), ulcers (10/15, 67%), and purulent discharges (9/15, 60%), often accompanied by erythema or edematous erythema, plaques, papules, and crusts (Figure 1). Common patterns include nodules and ulcers with purulent discharge, observed in 7 cases (47%), affecting areas such as the hands, face, neck, and limbs. Additionally, more complex features, such as plaques with erosion or crusting with sinus tract formation, were noted in 3 cases (20%), indicating a spectrum of infectious and inflammatory dermatological conditions. In terms of self-reported symptoms, spontaneous pain was reported by 7 patients (46.7%), itching by 3 patients (20.0%), and burning sensations by 2 patients (13.3%). Infection sites varied, with upper limbs affected in 6 patients (40.0%) and lower limbs in 5 patients (33.3%). Other infection locations included the head, neck (20.0%), and trunk (13.3%). Disseminated infection was noted in 5 cases (33.3%), often accompanied by systemic symptoms such as fever and lymphadenopathy. Immune status varied: 5 patients (33.3%) tested positive for anti-interferon-gamma autoantibodies (AIGA), suggesting an immune predisposition, while one patient (6.7%) was HIV-positive. Other comorbidities included hypertension (20.0%), diabetes (20.0%), and tuberculosis history (13.3%) (Table 1).

Histopathological Findings

Histopathological analysis was conducted for all 15 cases, revealing three main patterns. Infectious granulomas were the most prevalent histopathological finding, seen in 8 patients (53.3%) and characterized by dense infiltration of lymphocytes, histiocytes, and neutrophils, with occasional multinucleated giant cells (Figure 2). Five patients (33.3%) exhibited nonspecific inflammatory changes, primarily showing perivascular lymphocyte infiltration in the superficial dermis, and in some cases, eosinophilic infiltration was noted. Additionally, one patient (6.7%) presented with superficial dermal vasculitis, marked by notable vascular changes with minimal inflammatory cell infiltration. These findings suggest that infectious granulomas are the predominant histopathological response in NTM SSTIs, especially in chronic or recurrent infections.

Pathogen Identification

Pathogen identification was achieved through both conventional and molecular methods. The primary pathogens isolated were *Mycobacterium abscessus, M. avium*, and *M. marinum*. Distribution of these species varied according to immune status, with *M. abscessus* and *M. fortuitum* more frequently observed in AIGA-positive patients, while *M. marinum* was more common in immunocompetent individuals. mNGS identified NTM species in 13/15 cases tested (86.7%), enabling detection of rare strains such as *Mycobacterium shigaense*, which are difficult to culture.

Diagnostic Method Effectiveness

The diagnostic effectiveness of mNGS was notable compared to traditional methods. Although bacterial smears and cultures were performed for all patients, positive results were obtained in only 4 cases (26.7%). In contrast, mNGS identified NTM species in 13 of the 15 cases tested (86.7%), demonstrating a higher sensitivity and shorter turnaround time. The use of mNGS was particularly beneficial for cases with atypical presentations or rare NTM strains that conventional culture methods struggled to detect.

Treatment and Outcomes

The treatment regimens for the 15 cases varied, predominantly involving combinations of antibiotics such as clarithromycin (CLA), rifampin (RFP), ethambutol (EMB), and moxifloxacin (MXF), with therapy durations ranging from 1 to 24 months. Most cases (8/15, 53%) achieved a cured outcome, while 6 cases (40%) showed improvement, and 1 case (7%) was lost to follow-up. Shorter regimens, such as Levofloxacin + CLA + RFP + EMB (4 months) or EMB + CLA + MXF

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Table 1 Clinical and Microbiological Characteristics of the 15 Cases

Case	Sex/Age	Occupation	Past History	Immune Condition	Time to Diagnosis	Symptoms	Sites	Clinical Appearance	Disseminated Infection	Systemic Symptoms	Bacterial Species	Therapy/ Duration (Months)	Outcome
1	M/79	Farmer	Healthy History	Good	222 days	Burning sensation, Pain	Dorsum of right hand	Edematous erythema, Nodule, Ulcer, Purulent discharge	No	None	Mycobacterium marinum	Levofloxacin, CLA, RFP, EMB/4	Cured
2	M/64	Employee	Healthy History	Anti–IFN-γ autoantibodies positive	1 year 3 months	Itching, Pain	Nose, Left face	Edematous erythema, Erosion, Crust, Purulent discharge, Papule, Plaque	No	Fever, Discharge, Epistaxis	Mycobacterium shigaense	EMB, INH, AMK, LZD/ 12	Cured
3	F/39	Other	Diabetes	Suffered from multiple lung abscesses 1 year ago	More than 2 years	Burning sensation, Pain	Face, Limbs	Nodule	No	None	Mycobacterium marinum	EMB, CLA, MXF, RFP/6	Cured
4	F/47	Farmer	Tuberculosis	Good	11 months	None	Face, Neck	Edematous erythema, Ulcer, Sinus tract, Crust	Yes	Fever	Mycobacterium avium complex	RFP, MXF, CLA/24	Improved
5	M/67	Farmer	Hypertension; Diabetes	Good	71 days	Burning sensation	Buttocks, Both lower limbs	Edematous erythema, Ulcer, Purulent discharge	No	High fever	Rapidly growing mycobacteria	MXF, CLA, EMB/5	Cured
6	F/57	Farmer	Previously healthy	Anti–IFN-γ autoantibodies positive	1 year 1 month	Traction pain	Chest wall	Nodule	Yes	Fever, Chills, Bone pain	Mycobacterium intracellulare complex	EMB, CLA, MXF, INH/12	Improved
7	M/39	Farmer	Hypertension	Good	More than 1 year	Pain	Third finger of the left hand	Plaque, Erosion, Ulcer	No	None	Mycobacterium haemophilum	CLA, MXF/1	Cured
8	M/66	Farmer	Hypertension; HIV	HIV+	1 year	Itching, Pain	Left forearm	Nodule, Ulcer	No	None	Mycobacterium massiliense	MXF, CLA, RFP, EMB/6	Cured
9	F/56	Farmer	Tuberculosis; Diabetes	Good	1 year 5 months 24 days	Pain	Hands	Edematous erythema	No	None	Mycobacterium abscessus	RFP, CLA, DOX/3	Cured
10	M/53	Farmer	Healthy History	Anti–IFN-γ autoantibodies positive	8 months	None	Face, Neck, Upper arm	Nodule, Ulcer, Purulent discharge	Yes	None	Mycobacterium colombiense	MXF, AZM	Lost to follow-up
11	F/48	Employee	Previously healthy	Good	More than 8 months	Pain	Right thigh, Buttocks	Nodule	No	None	Mycobacterium abscessus	CLA, LZD/1	Improved
12	F/65	Other	Previously healthy	Good	More than 3 months	None	Index finger, Middle finger of the left hand	Edematous erythema, Nodule	No	None	Mycobacterium abscessus	CLA, AMK, EMB/24	Improved

13	F/42	Farmer	Tuberculosis; Talaromyces marneffei infection	Anti–IFN-γ autoantibodies positive	20 days	None	Below left breast	Erythema, Papule, Nodule, Ulcer, Purulent discharge	No	None	Mycobacterium avium	MXF, CLA, EMB, AMK/2	Cured
14	M/58	Other	Diabetes	Good	1 month	Pain	Surgical site on the left foot	Erythema, Purulent discharge	No	None	Rapidly growing mycobacteria	MXF, CLA/24	Improved
15	F/66	Farmer	Healthy History	Anti–IFN-γ autoantibodies positive	10 months	None	Elbow, Back, Neck, Armpit, Thigh, Groin	Erythema, Nodule, Ulcer, Purulent discharge	Yes	Fever, Lymphadenopathy, Bone pain	Mycobacterium colombien	CLA, EMB, MXF, INH/12	Improved

Abbreviations: CLA, Clarithromycin; RFP, Rifampin; EMB, Ethambutol; MXF, Moxifloxacin; INH, Isoniazid; AMK, Amikacin; LZD, linezolid; CLA, Clarithromycin.

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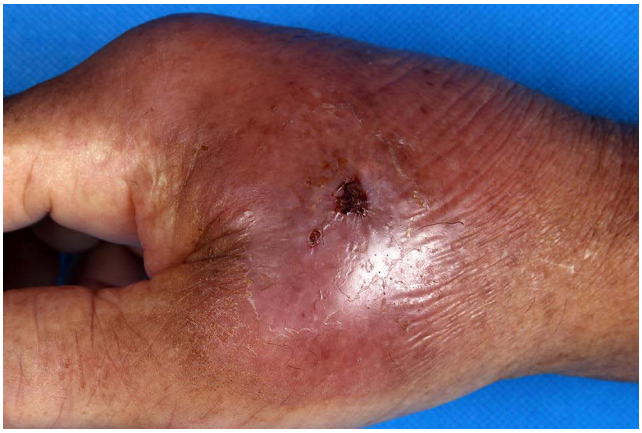

Figure 1 Patchy dark-red macules with multiple nodules and ulcers of varying sizes on the dorsum of the right hand, accompanied by localized swelling and warmth, with light-yellow exudate oozing from the lesions (Case 1).

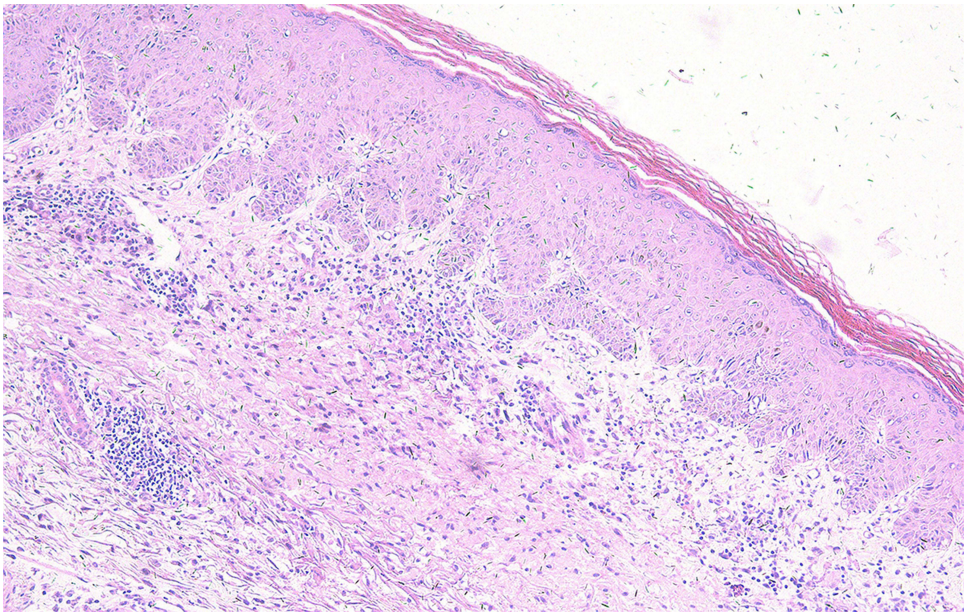

Figure 2 Irregular thickening of the epidermis with diffuse lymphohistiocytic and neutrophilic infiltration in the superficial and deep dermis, accompanied by multinucleated giant cells and clumped fibrinoid necrosis, consistent with infectious granulomatous changes (hematoxylin–eosin [HE], original magnification ×100) (Case 1).

+ RFP (6 months), were more frequently associated with cured outcomes. In contrast, prolonged regimens, such as CLA + EMB + MXF + INH (12 months) or RFP + MXF + CLA (24 months), were linked to partial improvement in several cases (Table 1).

The outcomes varied across bacterial species. *Mycobacterium marinum* cases both achieved cure following combination antibiotic therapy. *Mycobacterium abscessus* was associated with one cure and two improvements, while *Mycobacterium colombiense* had one improvement and one loss to follow-up. *Rapidly growing mycobacteria* cases showed one cure and one improvement. *Mycobacterium avium* complex and *Mycobacterium intracellulare* complex each had a single case, both improving after prolonged treatment. In contrast, single cases of *Mycobacterium shigaense, Mycobacterium haemophilum*, and *Mycobacterium massiliense* each resulted in cure. These patterns reflect notable variability in treatment responses among species, with some, such as *M. marinum* and *M. massiliense*, responding well to therapy, whereas others, including *M. colombiense* and *M. avium* complex, often required extended or tailored regimens (Table 1).

Discussion

This study provides significant insights into the clinical characteristics, pathogen distribution, diagnostic challenges, and treatment outcomes of NTM skin and soft tissue infections (SSTIs) in a cohort from southern China. Major findings include a predominance of *Mycobacterium abscessus, M. marinum*, and *M. avium* as causative pathogens, a notable association of infections with immunocompromised states (such as AIGA positivity), and the effectiveness of metagenomic next-generation sequencing (mNGS) in facilitating prompt and accurate pathogen identification. These findings underscore the importance of early and precise diagnosis, particularly in cases requiring prolonged antibiotic therapy or surgical interventions for optimal outcomes.

Our data showed that *M. abscessus, M. marinum*, and *M. avium* were the primary pathogens, in line with other reports on NTM SSTIs.[3] *M. abscessus* and *M. fortuitum* were prevalent among patients with compromised immune states, particularly those with AIGA positivity, supporting prior findings on the role of immune suppression in NTM susceptibility. In our study, six cases of NTM SSTI were secondary to disseminated infections, and three initially localized SSTIs progressed to disseminated infections. Five of these patients were AIGA-positive, aligning with Hase's study that identified skin and soft tissue involvement in 18% of AIGA-positive NTM cases.[4–6] These findings emphasize that clinicians should consider NTM SSTIs in patients with risk factors such as recent surgery, trauma, or immunosuppression, especially when they exhibit poor responses to conventional antibiotics.

Given the diversity of over 170 Mycobacterium species capable of causing SSTIs,[3] empirical use of broad-spectrum antibiotics is common, potentially exacerbating drug resistance. Accurate species identification is essential to select appropriate antibiotics. In this study, 13 of 15 patients were diagnosed through mNGS, while only 4 had positive cultures, underscoring the time-consuming and labor-intensive nature of culture and its low yield. Molecular techniques such as DNA sequencing provide rapid and accurate pathogen identification, improving clinical outcomes by guiding precise drug selection.[7] Wang's study on 96 patients with NTM SSTIs found that mNGS doubled detection rates compared to culture, especially for Mycobacterium species, consistent with our findings.[8] For instance, *M. shigaense*, a rare strain challenging to culture, was identified only by mNGS, reflecting the advantage of advanced molecular diagnostics for detecting atypical NTM pathogens.[9]

Our findings highlight the diagnostic challenges of NTM SSTIs, which often mimic other infections, leading to potential misdiagnoses. mNGS demonstrated higher sensitivity than traditional culture, facilitating early detection of rare or atypical strains. Routine mNGS could therefore serve as a frontline diagnostic tool for suspected NTM infections, especially in complex cases. Additionally, most patients in this study presented with elevated inflammatory markers (eg, white blood cell counts, CRP, ESR), with disseminated infections linked to systemic symptoms and higher inflammatory markers compared to localized infections. Although histopathology offered valuable insights—granulomas were the most common finding, along with nonspecific inflammation and vasculitis—it lacks strain specificity, underscoring the need for pathogen identification to confirm diagnosis and tailor treatment.

Treatment of NTM SSTIs is complex, reflecting differences in drug susceptibility among species and the frequent need for prolonged therapy. In this small cohort, multidrug regimens were used across all species, with agent selection influenced by prior experience and clinical judgment rather than standardized protocols. *M. abscessus* cases received combinations such as clarithromycin, amikacin, or linezolid, with outcomes including one cure and two improvements. *M. colombiense* was observed in two patients, one improving and one lost to follow-up, both involving prolonged courses; disseminated infections in this group posed particular challenges for adherence and response. *M. marinum* cases both achieved cure with regimens containing rifampin, ethambutol, and clarithromycin, but the small number precludes firm conclusions on optimal regimen length. Other single-species cases—*M. shigaense, M. haemophilum*, and *M. massiliense*—each resulted in cure, while *M. avium* complex and *M. intracellulare* complex cases improved following extended treatment. These observations, though limited by sample size, illustrate variability in clinical response across NTM species. Empirical therapy, guided by general recommendations, case reports, and expert input, was the mainstay in this study due to limited availability of drug susceptibility results.[10] Surgical interventions, including debridement, were particularly valuable in chronic or recurrent cases and may be enhanced by local antibiotic delivery or negative pressure wound therapy, as supported by existing literature.[11]

This study has certain limitations. This single-center retrospective study has a small sample (n=15) due to the rarity of NTM SSTIs, and our findings may not generalize widely. Nonetheless, the work helps address national data scarcity and may inform future multicenter studies in China. Additionally, mNGS has only recently become widely adopted in clinical practice, so data from patients prior to its implementation were primarily derived from traditional methods, potentially affecting the comprehensiveness of pathogen identification. Future research should prioritize multicenter studies to confirm the diagnostic and therapeutic advantages of mNGS and explore other advanced diagnostic tools across diverse populations. Further investigations focusing on new therapeutic agents and optimized treatment combinations tailored to specific NTM resistance profiles will also be valuable in reducing recurrence rates and improving outcomes, particularly for high-risk groups with complicated or refractory infections.

Conclusions

This study highlights that NTM SSTIs present significant diagnostic and therapeutic challenges, with clinical variability and frequent association with immunocompromised states. The findings underscore the predominance of *M. abscessus, M. marinum*, and *M. avium* as causative agents. Precise pathogen identification and tailored therapy are essential for achieving optimal outcomes, and further studies are needed to refine diagnostics and treatment strategies.

Significance

This study emphasizes the challenges of diagnosing and managing non-tuberculous mycobacterial (NTM) skin and soft tissue infections (SSTIs). It highlights the superior sensitivity of metagenomic next-generation sequencing (mNGS) over traditional culture methods and the necessity of tailored, prolonged antibiotic regimens for effective treatment. The frequent association with immunocompromised states underscores the need for early diagnosis and personalized management to improve patient outcomes.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2025-E0061), and written informed consent was obtained from all participates. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate Declarations

Consent to publish were obtained from all the participants.

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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 declare that they have no conflicts of interest for this work.

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