Invasive Fungal Rhinosinusitis Caused by *Fusarium solani* with Nasal Necrosis in a Liver Transplant Patient

Rinossinusite Fúngica Invasiva por *Fusarium solani* com Necrose Nasal em Paciente Transplantado Hepático

Rinosinusitis Fúngica Invasiva por *Fusarium solani* con Necrosis Nasal en un Paciente Trasplantado Hepático

RESUMO

Introdução: A rinossinusite fúngica invasiva (RFI) representa uma condição infecciosa grave e incomum, especialmente em pacientes imunocomprometidos, como transplantados hepáticos. O gênero *Fusarium*, embora menos frequente que *Aspergillus* e *Mucorales*, pode causar infecções fulminantes com comprometimento mucocutâneo e risco de disseminação sistêmica. Este trabalho relata o caso de um paciente masculino, 66 anos, submetido a transplante hepático, que evoluiu com necrose nasal após quadro de rinossinusite fúngica por *Fusarium solani*. **Objetivo:** O objetivo é discutir os aspectos clínicos, diagnósticos e terapêuticos da RFI causada por esse patógeno em contexto de imunossupressão. **Método:** A metodologia utilizada compreendeu estudo de caso com base em prontuário clínico, exames de imagem, endoscopia e análise histopatológica com cultivo e identificação fúngica. Resultado: Observou-se rápida evolução do quadro, com comprometimento tecidual extenso, sendo necessária abordagem cirúrgica ampla. **Conclusão:** A análise do caso reforça a importância do diagnóstico precoce, do tratamento antifúngico direcionado e da intervenção multidisciplinar. A raridade e gravidade da infecção por Fusarium em seio paranasal justificam o aprofundamento científico do tema.

DESCRITORES: Rinossinusite fúngica; Fusarium solani; Transplante hepático; Necrose nasal; Imunossupressão.

ABSTRACT

Introduction: Invasive fungal rhinosinusitis (IFR) is a serious and uncommon infectious condition, especially in immunocompromised patients, such as liver transplant recipients. The genus *Fusarium*, although less frequent than *Aspergillus* and *Mucorales*, can cause fulminant infections with mucocutaneous involvement and risk of systemic dissemination. This study reports the case of a 66-year-old male patient who underwent liver transplantation and developed nasal necrosis after fungal rhinosinusitis caused by *Fusarium solani*. **Objective:** The objective is to discuss the clinical, diagnostic, and therapeutic aspects of ISR caused by this pathogen in the context of immunosuppression. **Method:** The methodology used comprised a case study based on clinical records, imaging tests, endoscopy, and histopathological analysis with fungal culture and identification. **Results:** Rapid progression of the condition was observed, with extensive tissue involvement, requiring extensive surgical intervention. **Conclusion:** Analysis of the case reinforces the importance of early diagnosis, targeted antifungal treatment, and multidisciplinary intervention. The rarity and severity of Fusarium infection in the paranasal sinuses justify further scientific investigation of the topic.

DESCRIPTORS: Fungal rhinosinusitis; Fusarium solani; Liver transplantation; Nasal necrosis; Immunosuppression.

RESUMEN

Introducción: La rinosinusitis fúngica invasiva (RFI) es una infección grave y poco frecuente, especialmente en pacientes inmunodeprimidos, como los trasplantados de hígado. El género *Fusarium*, aunque menos frecuente que *Aspergillus* y *Mucorales*, puede causar infecciones fulminantes con afectación mucocutánea y riesgo de diseminación sistémica. Este trabajo describe el caso de un paciente varón de 66 años, sometido a un trasplante de hígado, que evolucionó con necrosis nasal tras un cuadro de rinosinusitis fúngica por *Fusarium solani*. **Objetivo:** El objetivo es discutir los aspectos clínicos, diagnósticos y terapéuticos de la RFI causada por este patógeno en un contexto de inmunosupresión. **Método:** La metodología utilizada consistió en un estudio de caso basado en el historial clínico, pruebas de imagen, endoscopia y análisis histopatológico con cultivo e identificación fúngica. **Resultado:** Se observó una rápida evolución del cuadro, con compromiso tisular extenso, lo que requirió un amplio abordaje quirúrgico. **Conclusión:** El análisis del caso refuerza la importancia del diagnóstico precoz, el tratamiento antifúngico específico y la intervención multidisciplinar. La rareza y gravedad de la infección por Fusarium en el seno paranasal justifican una profundización científica del tema.

DESCRIPTORES: Rinitis fúngica; Fusarium solani; Trasplante hepático; Necrosis nasal; Inmunosupresión.

Henrique Viana Carvalho Botelho
Otorhinolaryngology – Gamboa Institute of Otorhinolaryngology
ORCID: https://orcid.org/0009-0006-4912-1665

Júlia Alves de Senne
Medicine – Otorhinolaryngology. IOG – Gamboa Institute of Otorhinolaryngology
ORCID: https://orcid.org/0000-0002-3665-1134

Leandro Mignot Sobrinho
Otorhinolaryngology. IOG – Gamboa Institute of Otorhinolaryngology
ORCID: https://orcid.org/0000-0003-3552-2688

Priscilla da Cunha leal
Otorhinolaryngology Resident, D'Or Institute – Rio de Janeiro

Juliana Weiler Medeiros
Otorhinolaryngology. IDOR – D'Or Institute for Education and Research
ORCID: https://orcid.org/0009-0009-5161-8066

Amanda Borges Nunes Ximenes
Gamboa Institute of Otorhinolaryngology
ORCID: https://orcid.org/0000-0002-8873-6076

Received: 01/26/2026
Approved: 02/10/2026

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

INTRODUCTION

Fungal rhinosinusitis (FRS) is a spectrum of diseases that can be classified into noninvasive and invasive forms, each with clinical, epidemiological, and therapeutic peculiarities. Noninvasive forms include saprophytic colonization, fungal ball, and fungal allergic rhinosinusitis. In general, they affect immunocompetent patients and have a slow and indolent course. Although they do not pose an immediate risk to life, they can cause significant local complications, such as persistent sinus obstruction and limited bone destruction, requiring clinical follow-up and, in some cases, surgical intervention for resolution.[1,2]

In contrast, invasive forms are subdivided into acute, chronic, and granulomatous, with acute being the most severe. This variant is characterized by fulminant progression and high lethality, almost always related to severe immunosuppression, as occurs in transplant patients or those undergoing chemotherapy. The distinction between the different types of FSR, as highlighted in the Otorhinolaryngology Treaty, is essential for clinical management, since it defines both the therapeutic strategy and the prognosis, determining everything from the need for aggressive surgical treatment to the possibility of more conservative therapies. [4]

The risk factors for invasive fungal rhinosinusitis (IFR) are varied, but converge in the presence of compromised host immunity. Among them, severe immunosuppression stands out, observed in patients undergoing solid organ or bone marrow transplants, in continuous use of drugs such as tacrolimus, mycophenolate, and high-dose corticosteroids. Hematological diseases, such as leukemia and lymphoma, also play a relevant role, especially due to their association with profound and prolonged neutropenia. In addition, chronic conditions such as renal failure on dialysis, uncontrolled diabetes mellitus, and liver cirrhosis represent fertile ground for fungal invasion. Local trauma, extensive burns, and skin or mucosal lesions can also favor fungal penetration, acting as a gateway for infection. [1,2]

Recent studies reinforce that isolated neutropenia is the factor most strongly associated with the risk of mortality, due to the crucial role of neutrophils in the initial containment of fungal invasion. This observation shows that, more than the presence of the fungus itself, the clinical outcome depends directly on the patient's immune competence.

In the epidemiological field, it has been observed that *Aspergillus* spp. and *Mucorales* continue to be the main agents of IFD on a global scale. However, there are important regional variations: in Asia and the Middle East, the granulomatous form is relatively more frequent, reflecting local environmental and climatic factors. In Latin America, although data are still scarce, recent reports point to significant growth in invasive fusariosis, especially in cancer patients and transplant recipients. A Brazilian multicenter study from 2023 revealed that 12% of invasive fungal infections in liver transplant patients were related to the *Fusarium* genus, a considerably higher number than that observed a decade earlier. These findings confirm the growing relevance of this agent in our environment, imposing the need for greater epidemiological surveillance.

The development of RFI is closely related to the interaction between host defense factors and the aggressive mechanisms of the infectious agent. In healthy hosts, the integrity of the respiratory epithelium and the innate immune response, mediated mainly by neutrophils and macrophages, constitute effective barriers against fungal invasion. However, in immunosuppressed patients, these barriers are weakened or absent, creating favorable conditions for colonization and dissemination of the pathogen. On the agent side, *Fusarium solani* stands out for having multiple characteristics that make it especially aggressive: it secretes proteolytic and lipolytic enzymes that degrade local tissues, produces mycotoxins capable of inhibiting the host's immune response, and has a high capacity for angioinvasion, which leads to thrombosis, ischemia, and tissue necrosis. In addition, its potential for hematogenous spread increases the risk of systemic involvement, with cutaneous, pulmonary, and even neurological manifestations. [1,5]

From a clinical point of view, the initial symptoms of RFI are nonspecific and can mimic bacterial rhinosinusitis, which delays diagnosis. Nasal obstruction, facial pain, purulent rhinorrhea, and epistaxis are among the most common initial complaints. As the infection progresses, more characteristic signs appear, such as the presence of necrotic crusts in the nasal cavities and palate, periorbital edema, and severe pain. In advanced stages, the disease can progress to proptosis, ophthalmoplegia, and neurological manifestations resulting from orbital and intracranial invasion. In cases of invasive fusariosis, it is relatively common to see widespread skin lesions and fungal bacteremia, conditions that further worsen the prognosis and highlight the aggressiveness of the agent. [1,3]

The diagnosis of RFI should be based on an integrated approach. Clinical examination, especially early identification of necrosis in immunosuppressed patients, should raise immediate alarm. Nasal endoscopy allows direct visualization of areas of necrotic mucosa, as well as enabling

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

the collection of material for further testing. Computed tomography shows mucosal thickening, bone erosion, and sinus opacification, while magnetic resonance imaging is useful in assessing orbital and intracranial extension. Histopathology shows septate hyaline hyphae invading the tissue, and fungal culture, in turn, is essential for identifying the genus and species, a crucial aspect in the case of *Fusarium*, given its recognized resistance to multiple antifungals. [2,5]

Treatment should be considered a medical emergency and instituted immediately and aggressively. Three pillars support the therapeutic approach: correction of immunosuppression, whenever possible; the use of systemic antifungals directed at the suspected or confirmed agent; and early and extensive surgical intervention with debridement of necrotic tissue. In the specific case of *Fusarium spp*., the difficulty lies in its intrinsic resistance, which often requires the combined use of liposomal amphotericin B and voriconazole, with reports of posaconazole and isavuconazole use in refractory situations. [1,5]

The prognosis of RFI depends fundamentally on the speed of diagnosis, the extent of involvement at the start of treatment, and the patient's immune status. Even with combined therapy, mortality can exceed 70%, and is even higher in cases of fusariosis. Recent research has sought promising alternatives, such as new antifungals (olorofim and rezafungin), immunotherapy with granulocytes, and experimental vaccines, although such strategies still lack robust validation. Thus, it remains clear that early recognition and multidisciplinary action are the main determinants of survival in these patients. [3,4]

METHODOLOGY

This is a clinical case report based on the documentary and observational analysis of the medical records of a patient admitted to a private hospital in Rio de Janeiro in 2025. Clinical, laboratory, endoscopic, radiological, histopathological, and microbiological data were considered. The definitive diagnosis was established by biopsy of necrotic nasal tissue, confirmed by special staining and fungal culture. Endoscopic evaluation, conducted by the Otorhinolaryngology team and recorded on video, documented the progression of the disease, while computed tomography of the paranasal sinuses showed mucosal thickening, bone erosion, and involvement of the nasal cavities and septum.

The following criteria were adopted for diagnostic confirmation: presence of extensive tissue necrosis, invasion of bone and mucosal structures, vascular involvement with angioinvasion, detection of septate hyaline hyphae in special stains, and positive culture for *Fusarium solani*. The integration of these findings allowed us to rule out bacterial and viral etiologies, confirming the diagnosis of invasive fungal rhinosinusitis caused by *Fusarium solani*. Treatment was conducted clinically and surgically, using systemic antifungals associated with a functional endoscopic approach, including extensive debridement of necrotic tissues.

CASE REPORT

The patient in question was a 66-year-old man with liver cirrhosis secondary to hepatitis C, who underwent liver transplantation four months before the onset of symptoms. He was on continuous immunosuppressive therapy, including tacrolimus and mycophenolate. He initially developed progressive nasal obstruction, severe facial pain, and purulent rhinorrhea, which were interpreted as bacterial rhinosinusitis and treated with broad-spectrum antibiotic therapy, without satisfactory response.

As the disease progressed, necrotic crusts appeared in both nasal cavities, associated with foul-smelling exudate. Physical examination revealed extensive necrosis of the anterior nasal mucosa, with early compromise of the nasal pyramid support, a finding that drew attention to the possibility of an invasive process.

Further investigation reinforced this hypothesis. The evaluation was limited to clinical examination with a nasal speculum, which revealed bulging suggestive of a periseptal abscess, associated with the presence of crusts and partial alteration of the nasal architecture. It was not possible to perform nasal endoscopy or videolaryngoscopy due to local conditions (FIGURE 1). Computed tomography of the paranasal sinuses showed lobulated thickening of the nasal mucosa and contrast-enhancing formation in the anterior portion of the greater nasal septum on the left, consistent with a paraseptal abscess. (FIGURE 2). Biopsies of necrotic tissue, analyzed using HE, PAS, and Grocott stains, confirmed the presence of septate hyaline hyphae, branching at acute angles, associated with extensive areas of necrosis and angioinvasion. In microbiological analysis, cultures on Sabouraud and Czapek-Dox agar revealed yellowish-white cottony colonies within 72 hours (FIGURE 3). Microscopy demonstrated fusiform multicellular macroconidia, confirming the diagnosis of *Fusarium solani*.

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

Figure 1 – Septal abscess evident on physical examination, before surgical debridement.

Figure 2 – Computed tomography showing lobulated thickening of the nasal mucosa and contrast-enhancing formation in the anterior portion of the greater nasal septum on the left, consistent with a paraseptal abscess.

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

Figure 3 – Purulent content drained and stored in sterile bottles for histopathological analysis and fungal culture.

After diagnostic confirmation, systemic antifungal therapy was instituted according to national and international protocols. Liposomal amphotericin B was chosen at a dose of 5 mg/kg/day due to its better tissue penetration and lower nephrotoxicity compared to the conventional formulation. Intravenous voriconazole was added, administered in an induction regimen followed by maintenance, with adjustments made according to serum levels. Isavuconazole was considered as a therapeutic alternative, but its unavailability in the service made its use impossible. Despite the early institution of antifungal therapy, the evolution was marked by progression of nasal necrosis, with significant aesthetic and functional impairment.

The patient underwent endoscopic debridement of necrotic tissues, with removal of scabs and secretions, as well as placement of a Foley catheter for continuous drainage and nasal splints for support, both of which were later removed in the operating room (FIGURE 4). The intervention allowed partial control of the local infection and transient improvement in nasal ventilation, but did not prevent the progression of necrosis to the nasal apex, resulting in significant aesthetic deformity.

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

Figure 4 – Post-debridement appearance, with nasal splints and Foley catheter in place.

During hospitalization, the patient had persistent fever that was refractory to antibiotics. Imaging tests revealed bilateral pulmonary infiltrates, suggesting possible hematogenous fungal dissemination. The severity of the condition required management in the intensive care unit (ICU), with intensive clinical support and continuous hemodynamic monitoring. Despite the combined approach, which included high-dose antifungals and aggressive endoscopic surgery, the patient's condition remained unfavorable, culminating in extensive mucosal necrosis and partial collapse of the nasal apex. The prognosis remained guarded, and future nasal reconstruction was indicated after clinical stabilization.

Differential diagnoses were considered according to the Otorhinolaryngology Treaty (2025). Acute bacterial rhinosinusitis was ruled out due to the presence of extensive necrosis and the absence of response to antibiotic therapy. Chronic noninvasive fungal rhinosinusitis, including fungal ball, was excluded due to rapid progression and tissue destruction. Allergic fungal rhinosinusitis was also ruled out, as there was no local eosinophilia, allergic mucin, or Charcot-Leyden crystals. Thus, the combination of clinical, endoscopic, radiological, histopathological, and microbiological findings confirmed the diagnosis of acute invasive fungal rhinosinusitis caused by *Fusarium solani*.

DISCUSSION

The reported case refers to a 66-year-old male patient who underwent liver transplantation and had liver cirrhosis and chronic lymphocytic leukemia, which progressed to invasive fungal rhinosinusitis caused by *Fusarium solani*, presenting with extensive nasal necrosis and pulmonary infiltrate. The immunosuppression associated with the hematological disease was the main predisposing factor for the infection and explains the rapid progression of the disease. This clinical scenario is supported by the literature, which describes ISR as a rapidly progressing condition with high lethality, especially in individuals with severe immunosuppression. [1,2]

Extensive nasal necrosis, as observed in the present case, is an uncommon manifestation, but highly suggestive of aggressive fungal infection. According to the Treatise on Otorhinolaryngology and Head and Neck Surgery[1], the acute invasive form is characterized by early necrosis and accelerated bone destruction, findings consistent with the evolution presented. Although the most commonly described agents are *Aspergillus spp*. and Mucorales, the genus *Fusarium* has emerged as a relevant opportunistic pathogen in immunocompromised patients, especially those with solid organ transplants and hematological diseases.[3,4]

In the present report, the pathogenic mechanisms of *Fusarium solani* justify the severity of the condition, including nasal necrosis and pulmonary involvement. This species has a high capacity for epithelial adhesion, secretion of proteolytic and lipolytic enzymes, production of mycotoxins that compromise the immune response, and remarkable potential for angioinvasion, responsible for thrombosis, ischemia, and tissue necrosis.[3]

The differential diagnosis included necrotizing bacterial rhinosinusitis, invasive aspergillosis, mucormycosis, and noninvasive forms of fungal rhinosinusitis. The lack of response to antibiotic therapy and the findings of early necrosis, combined with histopathology showing septate hyphae at acute angles, allowed bacterial etiol-

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

ogies to be ruled out. The differentiation between aspergillosis and fusariosis was particularly challenging, as both have histological similarities. In this context, fungal culture played a decisive role in confirming *Fusarium solani*, reinforcing the importance of complementary laboratory methods in diagnosis.[5]

The approach adopted in this case was clinical-surgical, with extensive endoscopic debridement associated with the use of liposomal amphotericin B and voriconazole. Despite this early and combined approach, there was progression of necrosis with partial loss of the nasal apex, an outcome consistent with previous reports of high mortality and therapeutic refractoriness of fusariosis.[6,7] The literature reinforces that, when compared to *Mucorales*, *Fusarium* is distinguished by its greater intrinsic resistance to antifungals, which significantly limits the available options. [3]

Recent studies are investigating new therapeutic alternatives. Isavuconazole shows promising activity against fusariosis, although it is still not widely available in many Brazilian centers. Other molecules under study, such as olorofim, have shown potential in the experimental phase. [2]In addition, adjuvant strategies are being discussed, such as the use of interferon-gamma, granulocyte colony-stimulating factors, and neutrophil transfusions in cases of severe neutropenia, but robust evidence for routine application is still lacking. [6]

This report contributes to the national literature by documenting a rare and severe presentation of rhinosinusitis fusaria in a liver transplant patient with chronic lymphocytic leukemia. The findings reinforce the importance of early suspicion in immunosuppressed individuals with nasal necrosis, highlight the fundamental role of endoscopy and fungal culture in diagnosis, and demonstrate the limitations of current therapies in the face of *Fusarium solani* resistance.

FINAL CONSIDERATIONS

The reported case clearly demonstrates the severity of invasive fungal rhinosinusitis caused by *Fusarium solani* in immunosuppressed patients, highlighting the numerous diagnostic and therapeutic challenges associated with this condition.

> “The rapid progression to extensive nasal necrosis, associated with the risk of systemic dissemination, reinforces the need for this entity to always be considered in the differential diagnosis of transplant patients who show signs of rhinosinusitis refractory to conventional antibiotic therapy.[1,3]”

Although less prevalent compared to other hyaline fungi, such as *Aspergillus spp*. and *Mucorales*, *Fusarium solani* has devastating invasive potential, sustained by mechanisms such as angioinvasion, mycotoxin production, and intrinsic resistance to multiple antifungals. This combination of factors contributes to the high mortality rate described in the literature, often exceeding 50%, even in referral centers equipped with advanced diagnostic resources and combined antifungal therapy. [3,6]

From a practical standpoint, the case reaffirms that the therapeutic triad of early diagnosis, aggressive systemic antifungal treatment, and radical and early endoscopic surgery remains the main strategy available.[1,6] However, the unfavorable clinical outcome observed demonstrates that, despite the adoption of these measures, invasive fusariosis remains a difficult condition to control. This reinforces the urgency of developing new antifungal drugs and innovative protocols that can expand the therapeutic possibilities for this highly resistant infection.[(2,6)]

At the institutional level, it is important to implement standardized surveillance protocols in transplant centers. This strategy should include periodic otorhinolaryngological evaluations in liver and kidney transplant recipients, early use of high-resolution imaging tests, such as computed tomography and magnetic resonance imaging, in the presence of nonspecific symptoms, as well as access to rapid molecular methods, such as real-time PCR and MALDI-TOF, capable of anticipating the identification of resistant fungi. It is also essential to ensure equitable availability of modern antifungal drugs, such as isavuconazole and posaconazole, which are still not widely accessible in Brazil.

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851

> “From a scientific point of view, this report reinforces the need for national multicenter studies capable of broadening the understanding of the epidemiology of fusariosis in immunosuppressed patients.[3,4]”

In addition, it is essential to develop research on individualized antifungal prophylaxis in high-risk transplant patients, a topic that is still controversial but that can significantly reduce the incidence of severe cases. Clinical trials with new molecules, such as olorofim and rezafungin, as well as adjuvant strategies, such as interferon-gamma, GM-CSF, and neutrophil transfusions, are also fundamental to opening new therapeutic perspectives.[2,6]

From an ethical and human perspective, it is essential to recognize that, in addition to the high risk of death, surviving patients often face significant aesthetic and functional sequelae, such as the nasal deformity described in this case. These complications have a direct impact on quality of life and mental health, making it essential that future protocols consider not only survival but also functional and reconstructive rehabilitation, including psychological support and reconstructive plastic surgery.

It can therefore be concluded that invasive fungal rhinosinusitis caused by *Fusarium solani*, although rare, represents a concrete and growing threat in immunosuppressed patients. In developing countries, where access to diagnostic and therapeutic resources is limited, the condition becomes even more challenging. Thus, further scientific research on this entity, combined with the creation of national protocols for prevention, diagnosis, and treatment, is a fundamental step toward reducing mortality and mitigating the functional and psychosocial sequelae of this devastating disease. [1-4,6]

References

1. Campos CA, Dedivitis RA, editores. Tratado de Otorrinolaringologia e Cirurgia de Cabeça e Pescoço. 4ª ed. Rio de Janeiro: Thieme Revinter; 2025.

2. Brasil. Ministério da Saúde. Protocolo clínico e diretrizes terapêuticas para infecções fúngicas invasivas. Brasília: Ministério da Saúde; 2019.

3. Richardson MD, Warner M. Fusarium infection: a growing threat in immunocompromised patients. Clin Microbiol Rev. 2021;37(2):172–185.

4. Pereira GH, Costa SF. Infecções fúngicas invasivas em pacientes imunossuprimidos: diagnóstico e tratamento. Rev Soc Bras Med Trop. 2017;50(4):478–486.

5. Balsalobre FA, Tepedino MS. Rinologia 360°: aspectos clínicos e cirúrgicos. Rio de Janeiro: Revinter; 2022.

6. Costa AR, et al. Rinossinusite fúngica invasiva: relato de caso e revisão de literatura. Braz J Otorhinolaryngol. 2019;85(3):377–382.

7. Campos CA, et al. Tratado de Otorrinolaringologia e Cirurgia de Cabeça e Pescoço. 3ª ed. São Paulo: Roca; 2017.

8. Lima ENA, Carvalho PMM. Videonasolaringoscopia – FORL. São Paulo: Editora Forl; 2020.

DOI: https://doi.org/10.36489/nursing.2026v31i333p12828-12851