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Immunotherapeutic Potential of *Echinococcus granulosus* Hydatid Cyst Antigens in Autoimmune Disease and Allergy

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ABSTRACT

This study explores recent advances in harnessing the immunotherapeutic potential of hydatid cyst antigens for the treatment of allergies and autoimmunity. The aim is to elucidate the immunotherapeutic mechanisms employed by these parasite antigens. The hydatid cyst is considered the larval stage of *Echinococcus granulosus*, a parasitic helminth with life cycles involving a carnivorous definitive host (usually dogs) and an intermediate herbivore host (human, ungulate, or rodent). The two major species of this parasite with human public health importance are *E granulosus* and *E multilocularis*. *E granulosus* is a highly immunogenic organism that stimulates proinflammatory responses, significant antibody production, and T cell-mediated responses. Host adaptive immune responses to the parasite are T_H2 dominant, but responses are absent in one-fifth of patients. Diagnostic antigens from cyst fluid are well-known, and the high abundance of hydatid cysts in the lungs and livers of slaughtered farm animals has made it easy to access the source of cyst antigens. Emerging from current preclinical studies, antigens derived from hydatid cyst cells and fluid show potential for suppressing and regulating immune responses associated with allergic and autoimmune conditions, disorders which increase with Western-type human development.

Keywords: Allergy; Autoimmunity; Echinococcosis; Immunotherapy

INTRODUCTION

Echinococcosis is a zoonotic disease caused by *Echinococcus granulosus*, a cestode belonging to the genus *Echinococcus* in the family Taeniidae.[1] The larval infection of *Echinococcus* in intermediate hosts, such as humans or sheep, leads to hydatid disease or hydatidosis. The life cycle steps and etiology of *Echinococcus* have been extensively reviewed in previous studies.[2,3]

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Hydatid cysts are fluid-filled structures surrounded by a hydatid wall consisting of 2 layers: a thin continuous layer of parasite cells, called the germinal layer, and a thick acellular coat called the laminated layer (LL). The interaction between host tissues and the parasite leads to the formation of an adventitia layer, typically a fibrous layer.[4,5] The LL secreted by germinal layer cells is approximately up to 3 mm in thickness. Due to its direct contact with host cells, particularly immune components, the LL can play an immune regulatory function. The LL is composed of a fibrillar meshwork and electron-dense granules individually or in clusters naturally.[4] The LL meshwork is formed by highly glycosylated O-linked glycoprotein, with a

composition compatible with mucin glycoproteins. The monosaccharide composition of the LL includes galactose, N-acetyl galactosamine, and N-acetylglucosamine.[6]

Immune Responses to *E granulosus* Antigens

The immunology and immunodiagnostic of *E granulosus* infection have been reviewed elsewhere.[1,5,7,8,9] *E granulosus* eggs stimulate the immune response in the intermediate host, initiating between 2 and 4 weeks after infection. Among assayed antibodies, high levels of systemic immunoglobulin (Ig) G1 and local peritoneal IgM and IgG3 were detected.[10,11] The earliest IgG antibodies specific for *E granulosus* are detectable within 2 to 11 weeks after infection.[1] Approximately 30–40% of *E granulosus*-infected patients are antibody-negative, however, circulating antigens of *E granulosus* and circulating immune complexes are detectable in patients. A lipoprotein antigen from hydatid cyst fluid, known as Ag5 appears as arc 5 in immunoelectrophoresis and shows significant immunoprecipitates with the serum of most patients infected with *E granulosus*. However, this antigen precipitates nonspecifically with the serum of patients infected with *E multilocularis* or unknown parasitic diseases.[12]

Antibodies such as IgM, IgG, and IgE are elevated in humans with established cysts. IgG1 specific for antigen 5 (Ag5) and IgG4 for antigen B (AgB) are observed to be the predominant classes in seropositive individuals.[1]

In previous studies, the regular cellular and molecular events regarding the first human inflammatory response to organ-resident oncospheres were not reported. However, the recruitment of neutrophils, macrophages, and then eosinophils and lymphocytes within the early phase of infection was reported as the initial cellular response.[13,14] Cellular infiltration of eosinophils, neutrophils, macrophages, and fibrocytes without a severe inflammatory response occurs in the established phase of infection. Host cells in the adventitial layer organize into three layers, including mononuclear leukocytes in the inner layer near the LL, a middle layer with the infiltration of inflammatory cells, mainly eosinophils, plasma cells, neutrophils, lymphocytes, and fibroblasts, and finally, the outer loose connective tissue.[13]

There was limited information regarding cytokine release in the early phases of oral challenge with *E granulosus* eggs. The production of interleukin (IL) 10, IL-4, and IL-5 was stimulated as early as week 1 post-inoculation in mice inoculated with live *E granulosus* protoscoleces. Studies have reported that in vitro hydatid cyst fluid antigens stimulate peripheral blood mononuclear cells isolated from infected human subjects, to produce elevated levels of IL-4, IL-5, IL-6, and interferon-gamma IFN-γ.[15,16] Along with cyst development, T helper (T_H)1-produced cytokines that mediate killing of the meta cestode at the initial stages tend to convert to T_H2 cytokines in the chronic stage.[11,17] Therefore, the hallmark of chronic *Echinococcus* infection is a high level of IL-10 cytokine. IL-10 modulates both innate and adaptive immunity, first by exploiting anti-inflammatory effects. Though this cytokine belongs to the type 2 immune response, it is worth noting that T_H1 cells are also an important source of IL-10, which acts as a negative feedback loop in T cell responses.[18] Both T_H1 and T_H2 cytokines are elevated at least in cysts that survive from the immune response with an unknown mechanism.[1]

There is a correlation between IL-4 and IL-10 cytokines and high levels of IgE and IgG4 in cystic echinococcosis[19] as well as IL-5 production correlated significantly with IgG4 and IgE expression.[16] Although the Th2 response and IgE production are key defense mechanisms of the body against worm parasites, studies have shown that this response is elevated in individuals who do not respond to anthelminthic drug therapy.[19] Additionally, among diagnostic serological tests based on specific antibodies, the most sensitive is the specific IgG enzyme-linked immunosorbent assay (ELISA), while the least sensitive is the specific IgE ELISA.[20]

The fact that the parasite can survive for many years in mammalian hosts suggests that effective immune modulation mechanisms are used by the parasite to evade immune responses. Shielding cells of GL and protoscolex by LL was considered the major immune resistance mechanism employed by *E granulosus.*[5] In addition, there are several minor immune evasion mechanisms reviewed in another study,[11] including shedding and masking of surface antigens, antigenic diversity, deviation of T_H1/T_H2 responses, inhibition of immune cell recruitment, molecular mimicry, and interfering with antigen presentation using mitogenic components of the parasite. AgB, a 140-kDa multimeric lipoprotein isolated from hydatid cysts, is considered another immune evasion factor of *E granulosus*. This antigen impacts both innate and adaptive immune responses, modulating activities such as inhibiting

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elastase activity and neutrophil chemotaxis, and interfering with dendritic cell maturation and monocyte differentiation.[21,22]

Previous studies have focused on the relationship between *E granulosus* and immune-mediated diseases such as allergies and autoimmunity to identify immune-stimulatory and immune-regulatory antigens. While no study has detected a higher prevalence of allergic diseases in *E granulosus*-endemic areas compared to non-endemic areas, the Hygiene Hypothesis supports the correlation between the prevalence of helminthic infections and allergic diseases.[23] These concepts of the hypothesis have led to studies on the therapeutic potential of *E granulosus* antigens in animal models of allergies.

This review aims to extract and evaluate studies that have used *E granulosus*-derived components in allergies and autoimmunity, focusing on their immunotherapeutic aspects. The list of diseases targeted for immunotherapy using different *E granulosus* antigens is presented in Table 1.

Allergic Diseases

According to the Hygiene Hypothesis, the increased prevalence of allergic diseases in Western industrialized countries is related to low levels of exposure to infectious agents.[31] The activation of T_H2 cells and the production of IgE are the main hallmarks of allergic disorders. However, there is limited data showing how helminth infections may have protective effects on allergic diseases. As mentioned before, T_H1 and IFN-γ are dominant immune responses in the primary phase of *E granulosus* infection and in the chronic status, T_H2 and IL-4 are dominant as well. However, no report shows a high rate of susceptibility and risk of allergic disease for inhabitants living in the endemic areas of *E granulosus* infection. Studies have reported that chronic exposure to *Schistosoma mansoni* down regulates the onset of T_H1-mediated hypersensitivities, such as Crohn's disease, multiple sclerosis, and diabetes mellitus, as well as T_H2-mediated hypersensitivities like atopic diseases.[32] Given that the T_H2 response is a crucial element in the survival of *E granulosus*, allergic disorders characterized by T_H2-mediated hypersensitivity are predicted to be enhanced in patients with echinococcosis. In contrast, animal studies indicate that *E granulosus* infection significantly reduces the severity of airway inflammation in a mouse ovalbumin (OVA)-induced asthma model.[24] Similarly, *Toxascaris leonina* inhibited allergic-specific T_H2 responses in the OVA-induced asthma model.[33]

Cytokine analysis in patients with cystic echinococcosis showed that T_H1 cytokine responses were associated with disease resistance. While, T_H2 cytokine responses were associated with disease susceptibility and chronicity. In vitro and in vivo studies have shown that a good response to chemotherapy was associated with high levels of T_H1, while high levels of T_H2 cytokines (IL-4 and IL-10) were observed in patients with refractory disease. These types of responses suggest that T_H2 cytokines impair the therapeutic response and allow *E granulosus* to survive in the body.[8]

E granulosus employs various immunomodulatory mechanisms to attenuate the inflammatory response associated with T_H2-mediated allergy (Figure 1A). However, the precise modulatory role of different parasite components in allergic reactions remains unspecified. For instance, Jeong et al reported that extracellular vesicles derived from *E granulosus* diminish airway resident immune cells and cytokines, including eosinophils and T_H2- and T_H17-related cytokines.[25] Similar outcomes were reported in a study by Kim et al, where hydatid cyst fluid was employed in an OVA-induced airway inflammation model.[27] Research indicates that the excretory-secretory products released by adult Echinococcus prompt the generation of $CD4^+CD25^+Foxp3^+$ T cells, recognized as the prototypic phenotype of regulatory T cells (Treg), exhibiting immune-suppressive activities.[34] Tregs produce 2 principal immunosuppressive cytokines, namely IL-10 and transforming growth factor beta (TGF-β), with elevated production levels observed in patients with cystic echinococcosis.[35] In addition, the production of IL-10 and TGF-β is increased by M_2 macrophages activated by cyst antigens.[36,37]

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Table1. List of Immuno-regulatory Diseases Targeted for Immunotherapy Using *E Granulosus* Antigens.

Disease	Antigen	Selected results	Cases	References
Asthma	*E granulosus* infection	Reduced the severity of the inflammation in the airways.	Mouse, OVA-induced asthma	[24]
Asthma	*E granulosus*-derived extracellular vesicles	Ameliorated the T_H2 allergic airway inflammation through Tregs.	Mouse, OVA-induced asthma	[25]
Asthma	Somatic antigens of protoscoleces	The levels of T_H2 cytokine and the recruitment of eosinophils into the bronchoalveolar lavage fluid were increased.	Mouse, OVA-induced asthma	[26]
Asthma	Hydatid cystic fluid	The number of eosinophils and other immune cells in the bronchoalveolar lavage fluid, as well as levels of T_H2 and T_H17-related cytokines were decreased.	Mouse, OVA-induced asthma	[27]
Rheumatoid arthritis	Antigen B	The levels of main pro-inflammatory cytokines such as IL-6 and TNF-α were reduced. However, this reduction had no effect on nociception and clinical score in chronic arthritis.	Mouse, experimental arthritis	[28]
IBD	Antigen B	The symptoms of DSS-induced IBD were reduced.	Mouse, DDS-induced colitis	[29]
Sepsis	Antigen B	The survival rate of mice with CLP-induced sepsis was increased, proinflammatory cytokine levels were reduced, regulatory cytokines were increased, and there was a promotion of macrophage polarization from classically activated macrophage (M_1) to regulatory M_2-like.	Mouse, CLP-induced Sepsis	[30]

CLP: cecal ligation and puncture; DDS: dextran sodium sulphate; IBD: inflammatory bowel disease; OVA: ovalbumin.

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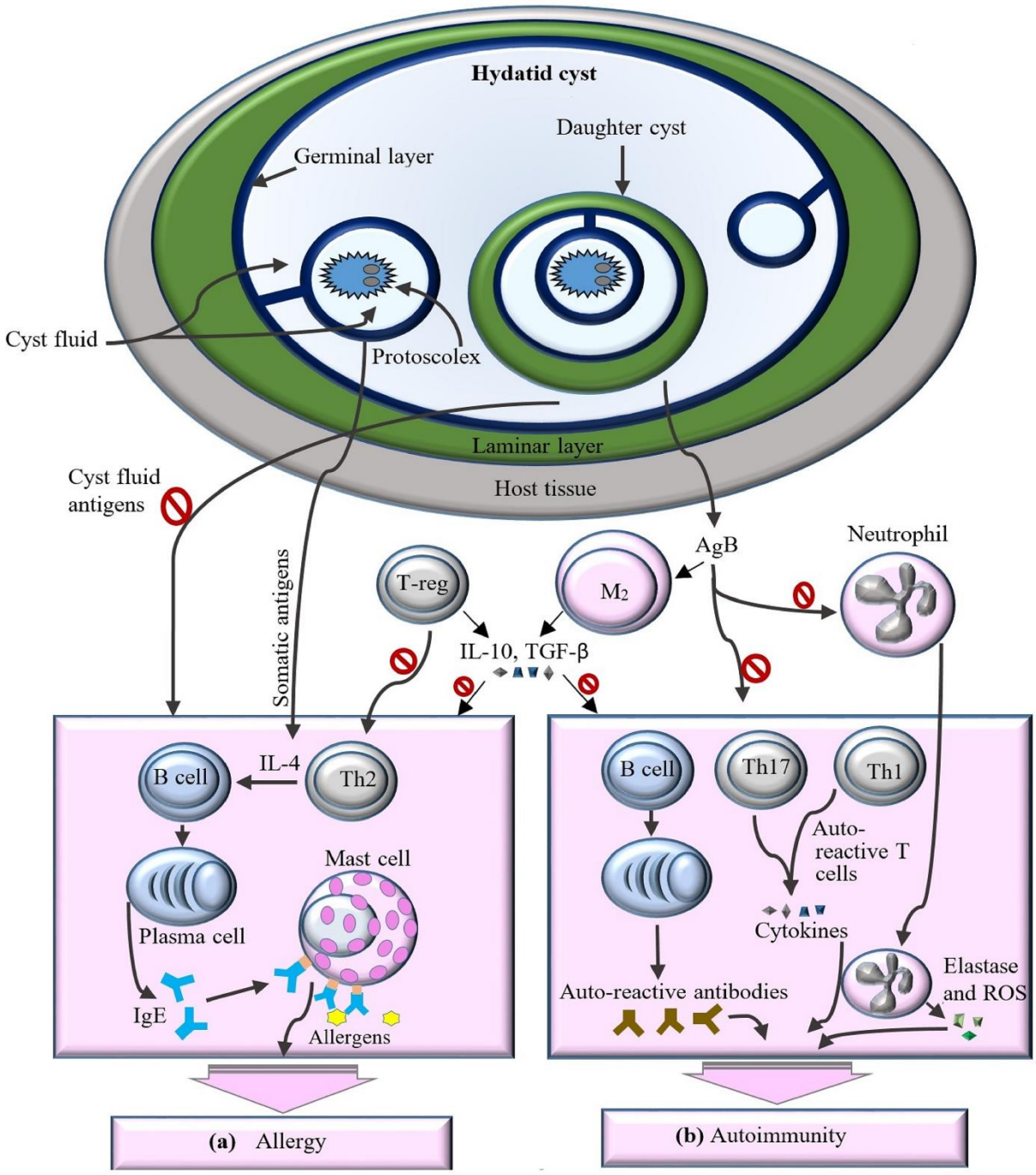

Figure 1. Antigens derived from *E granulosus* cysts modulate allergy and autoimmunity through direct and immune-mediated mechanisms. A. *E granulosus*-induced regulatory T cells (Tregs) and cyst fluid antigens have an antiallergic function, while protoscolex-derived somatic antigens stimulate T_H2 cells and allergic reactions. Antigen B (AgB) and the laminated layer (LL) cyst antigens and induce the production of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) through the activation of M_2 macrophages. These cytokines can inhibit allergic and autoimmune reactions by suppressing T lymphocytes. B. Immunomodulation of autoimmune disorders can be mediated by AgB and Tregs during *E granulosus* infection.

In contrast, somatic antigens of the protoscolex are considered potential modulating antigens for allergies, as demonstrated in studies. Administration of these antigens to mice challenged with OVA-induced asthma resulted in an exacerbation of allergic airway inflammation, characterized by increased T_H2 cytokine levels in lung homogenates and the recruitment of eosinophils into bronchoalveolar lavage fluids.[26]

The raises the question of whether protoscolex antigens, distinct from antigens derived from adult parasites and cyst fluid, may have a different impact on allergy prevention. This difference could be attributed to the amount and type of antigen exposure to the host immune system. Since cyst-surrounded protoscolex somatic antigens are less exposed to the host immune system, they may stimulate and regulate immune responses to a lesser extent compared to excretory-secretory antigens and LL antigens.

Although preclinical studies show that some components of cysts have allergy-suppressing effects, one of the life-threatening complications of hydatid cysts is the anaphylactic reaction in some affected individuals. There are several case reports of anaphylactic shock due to a ruptured hydatid cyst in patients with echinococcosis.[38,39,40,41,42,43] The most common cause of anaphylaxis in echinococcosis is the rupture of the patients' pulmonary cysts. Anaphylactic shock occurs when a large amount of the antigenic contents of the cyst fluid enters the bloodstream, causing IgE secretion and histamine release. In patients with anaphylactic shock, symptoms such as skin rash, edema, bronchospasm, and hemodynamic and respiratory disorders may be observed.[20]

Despite the considerable time that has elapsed since the introduction of the Hygiene Hypothesis and numerous studies conducted to elucidate its complexity, this hypothesis has yet to address all pertinent challenges. For noncommunicable diseases, such as asthma, which have exhibited an increased prevalence in recent years, evaluating the correlation between fundamental lifestyle changes and physical/mental conditions can be instrumental in managing associated issues.

Autoimmune Diseases

Recent studies suggest that molecules produced by helminths in the host body play a role in regulating or modulating the host immune response as a survival strategy for the helminths themselves.[44] Studies have demonstrated that proteins derived from helminths can increase the number of Tregs and anti-inflammatory factors like TGF-β and IL-10.[45] Helminth infection or its proteins have also been shown to transform monocytes into M_2-like macrophages, which are a type of anti-inflammatory and repairing macrophage.[46,47] As a result, helminthic infection or helminth-derived proteins have been experimentally used in the treatment of inflammatory or autoimmune diseases.

Studies in animal models suggest that helminthic infections mitigate the severity of autoimmune diseases by decreasing the T_H17 response.[48] Immunomodulatory antigens of *E granulosus* are crucial for the development of cystic echinococcosis (CE), as they inhibit basic immune responses and modulate immune function. Conversely, elevated levels of anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA) and anti-mitochondrial antibody (AMA) are observed in operated patients with hydatid cysts compared to cyst-free individuals.[49] Notably, the homology between a protein from *E granulosus* protoscoleces and a human immunoregulator protein called cyclophilin directs attention toward potential immunoregulatory compounds in protoscoleces.[50] Evidences also suggest that the parasite can suppress autoimmune diseases through helminth-induced Tregs and TGF-β production.[48,51]

Three studies explored the immune-regulatory function of AgB in animal models of autoimmune diseases and sepsis.[28,29,30] Farinon et al reported that AgB reduced the clinical score of arthritis immediately after disease induction but had no effect on chronic arthritis. AgB administration inhibited neutrophil migration into knee joints. AgB and Kunitz type protease inhibitor (EgKI-1), both components derived from *E granulosus*, significantly reduce neutrophil recruitment and neutrophil protease activity, respectively.[52] In another study, Bao et al found that AgB significantly reduced symptoms of inflammatory bowel disease induced by DSS. The immunotherapeutic potential of AgB was associated with its inhibitory effect on M_1 macrophages.

T_H2 and T_H17 cells play crucial roles in immune responses against helminthic parasite and fungal infections. They also serve as cellular mediators in the immune-pathogenesis of allergy and autoimmunity. Although 2 studies did not explicitly define the direct

immunotherapeutic effects of TGF-β and Tregs, it appears that the immune suppression induced by parasite-related Tregs and their produced cytokines, particularly TGF-β, inhibits T_H2 and T_H17 cell function and their consequent pathogenesis (Figure 1B).

In addition to studying the suppressive effects of hydatid cyst antigens on autoimmune diseases, some research has focused on the presence of autoimmune disease markers, particularly autoreactive antibodies, in patients with hydatid cysts. One study compared autoreactive antibodies, such as ANA, ASMA and AMA in patients with hydatid cysts, operated patients with hydatid cysts and healthy individuals with no known chronic diseases.[49] Although the results were not presented separately for each antibody, they indicated higher antibody titers in operated patients with hydatid cysts compared to the other 2 groups. In another study, Anti-neutrophil cytoplasmic antibodies (ANCA) were analyzed in patients with active and inactive cysts, and the results revealed higher antibody titers in active cysts than in inactive cysts.[53]

CONCLUSION

This study collected and evaluated research associated with the application of *E granulosus* cyst antigens in the treatment of disorders such as allergy and autoimmunity. *E granulosus* cysts contain several immunoregulatory and highly immunogenic antigens produced in response to host immune reactions. As previously discussed, conflicting reports exist regarding the therapeutic effects of *E granulosus* antigens in allergy diseases. Therefore, it is suggested to distinctly isolate, identify, and separately evaluate parasite molecules to obtain homogeneous responses.

Immune responses to helminth parasites are primarily classified as the second type of responses, involving Th2 cells, which are also implicated in allergic reactions. Typically, allergic responses occur without strong innate immune responses, activating mast cells and eosinophils, a response observed in worm infections as well. Most parasites' immunoregulatory functions are believed to be mediated by parasite-induced Tregs and TGF-β, though detailed studies in this field are limited. Identifying Treg-inducer molecules can help find therapeutic molecules for treating allergies and autoimmunity. In general, an important strategy for immunotherapy studies of cyst antigens is to investigate the effect of antigens from different cyst stages separately on the induction of T-reg, Th1 and Th2 cells.

STATEMENT OF ETHICS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data presented in this study are available upon request from the corresponding author.

AI ASSISTANCE DISCLOSURE

AI-assisted tools, including OpenAI's language model, were used to review and enhance the grammatical accuracy and clarity of this manuscript.

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