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The Role of Cytokines and Pattern Recognition Receptors in Inflammation Caused by *Helicobacter pylori* Infection in Gastric Cancer

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Abstract

One of the most common and most critical mortality causes in modern society is gastrointestinal (GI) cancer. *Helicobacter pylori* is one of the most potent risk factors of gastric cancer. This bacterium can suppress the immune system by various pathogenic factors and mechanisms, lead to chronic inflammatory responses, and play a critical role in the induction of cancer. The first part of this article begins with a description of *H. pylori* carcinogenicity and in the next part, the roles of innate immunity pattern recognition receptors (PRRs), Toll-like receptors (TLRs), cytokines, and inflammatory regulatory mechanisms in *H. pylori* infection are discussed. According to our current knowledge, screening and on-time diagnosis of the disease, timely treatment, and immediate eradication of *H. pylori* are the most critical ways to barricade gastric cancer progression. In the end, it is suggested that, considering the expensive costs of gastric cancer treatment, *H. pylori* diagnostic screening tests be done at least annually in middle-aged and at-risk people.

Keywords: Cytokine, Gastric cancer, *Helicobacter pylori*, Inflammation, Pattern recognition receptors

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Introduction

Currently, cancers have a major impact on societies. Gastrointestinal (GI) cancers are considered among the most important causes of mortality and morbidity.[1] Gastric cancer (GC) is the second major cause of mortality across the world.[2] The most common form of GC is adenocarcinoma, originating from the innermost layer of the gastric wall or mucosal layer. The second most frequent cause of cancer mortality around the world is gastric adenocarcinoma, and infection with the bacterial pathogen *Helicobacter pylori* is the most substantial recognized risk factor for this malignancy.[3] Gastric adenocarcinoma is a major type of cancer due to its high death rate, high prevalence, fast prognosis, and late diagnosis.[4] Its prevalence is high in East Asia, Eastern Europe, and parts of Central and South America. Although *H. pylori* plays a key role in GC, its pathogenesis involves several bacterial, host, and environmental factors.[5] The Nobel Prize in medicine in 2005 was awarded to Robin Warren and Barry Marshall for separating *H. pylori* from the human stomach and discovering its association with stomach diseases.[6] The global incidence of GC is more than 1 million cases[7], which is more common in less-developed countries than developed ones.[8] Chronic infection with *H. pylori* is the leading cause of GC, accounting for almost 89% of distal GC cases worldwide.[7] In Iran, cancer is reported as the third major cause of mortality and claims more than 30 000 lives annually. Maddah et al reported the

prevalence rates of 92% and 60% for *H. pylori* in the group with gastric adenocarcinoma (based on pathology and urea test) and noncancerous cases, respectively. Maddah et al also reported a direct relationship between gastric adenocarcinoma and *H. pylori*, as well as the increased risk of gastric adenocarcinoma due to *H. pylori*.[9]

There is an association between inflammation and infections with 15%-20% of the malignancies worldwide, and these two are contributing factors to GC.[10] First, the relationship between inflammation and cancer was suggested by Virchow in 1863, which has been proven by epidemiological investigations. A long-term inflammatory response against *H. pylori* in the gastric mucosa may cause prolonged tissue damage, leading to distal GC. Host genetic factors might affect the nature and severity of the immune response to *H. pylori*.[11] Shacter and Weitzman emphasized the association between inflammation and cancer.[12] Several studies emphasized the association between inflammation and cancer. In addition, the sixth chapter of Khandia and Munjal's book also mentioned this issue.[13] Genetic variation in genes associated with inflammation, especially cytokines and their receptors, plays a role in tumor initiation and progression. The perception of the molecular mechanisms and changes that occur before the onset and progression of gastric tumorigenesis is highly important for the early diagnosis of the disease and identification of new therapeutic and clinical targets for GC. However, decoding the mechanisms of GC is of vital importance, as the molecular pathogenesis of GC has not been fully perceived.[2] According to what was mentioned above and since numerous studies have emphasized the destructive impact of *H. pylori* on human health, the current study discussed the association and mechanism of *H. pylori* inflammation and its role in GC.

Carcinogenicity of *Helicobacter pylori*

Helicobacter pylori infection, genetic differences in individuals, and environmental factors, such as nutrition and health status, are all risk factors for GC, but each of these factors affects other factors. As poor nutrition increases the inflammatory effect of bacteria, and on the other hand, the presence of genetic background in the individual will affect the development of mild inflammation of the wound, atrophy, and eventually malignancy and cancer.[14] *H. pylori* is a small gram-negative bacilli bacterium with high mobility, causing infection in the mucosal layer of the human stomach.[14] The clinical course of this infection can be within a range of lifelong asymptomatic infection to severe diseases, such as a peptic ulcer or GC.[16] Exposure to vomiting and fecal-oral ways are among the main transmission ways of *H. pylori*.[15] *H. pylori* is catalase- and oxidase-positive and a potent producer of urease enzyme, which converts urea into ammonia and bicarbonate and produces an alkaline condition in the acidic environment of the stomach.[10] *H. pylori* causes cancer through different mechanisms and pathogenic factors, such as urease, flagellum, BabA, vacuolating cytotoxin A (VacA), cytotoxin-associated gene A (CagA), HpaA, OipA, lipopolysaccharides (LPS), DupA, IceA, AlpA/AlpB, SabA, and HP-NAP.[16]

Important Pathogens of *Helicobacter pylori*

According to the latest studies, *H. pylori* pathogenic genes are classified into three groups[17]:

1. The first group is specific genes that have been identified only in *H. pylori* strains. In this group, the most well-known genes belong to the island of cag (cag PAI) pathogenesis.[18,19] The *cagA* gene is the main factor involved in the pathogenicity of genes belonging to the island of cag pathogenicity. One of the important functions of cagA pathogenic elements is to activate and stimulate immune responses, including the activation of transcription factors. Activation of these transcription factors leads to the expression of several genes, including carcinogenic genes, genes encoding chemokines, and genes that activate the anti-apoptotic cycle.[20]
2. The second group of *H. pylori* genes includes variable phase genes. The six major genes in this group are *oipA*, *sabA*, *babC*, *babB*, *sabB*, and *hopZ*.[21]
3. The third group are genes that have the structure of variable genotypes in each strain, the most important of which is *vacA*.[22]

Helicobacter pylori has a wide variety of pathogenic factors, the most important of which are cytotoxins CagA and VacA that are found in 60%-70% of *H. pylori* strains (Table 1).[3] In a study conducted on pediatric gastric biopsy in the United States, Podzorski et al reported that 64% of *H. pylori* strains carried the *CagA* gene, and

Table 1. Important Pathogenic Factors of *Helicobacter pylori*

Name	Characteristics	Function	Ref.
cagA: Cytotoxin-associated gene A	Bacterial oncoprotein 120-140 kDa, the most severe pathogenic factor, cytoplasmic vacuolation, the presence of five repeated amino acid sequences at the end of the terminal carboxyl protein, and extensive variation at the end of carboxylic regions, including EPIYA motifs.	Suppressing T-cell function by directly affecting calcium signaling, activating and stimulating immune reactions, high ability to induce tissue inflammation and inhibit cytokine production, and stimulating a variety of transcription factors involved in essential functions (e.g., cell proliferation).	20,25-28
vacA: Vacuolating cytotoxin A	A cytotoxin associated with gene A and a 120 kDa protein available in 60%-70% of *H. pylori* strains.	Spindle tuber viroid playing an important role in cell messaging; induction of apoptosis, ability to destroy gastric epithelial cells and gastric mucosal ulceration, and disrupting the function of intracellular membrane proteins.	27,29-31

44% of the strains had two genes together.[23] In another study, Palframan et al showed that the *VacA* pathogenic gene causes the secretion of a key toxin in tissue damage, which leads to damage to gastric epithelial cells and peptic ulcers.[24] *H. pylori* infection causes the activation of nuclear factor-kappa B (NF-κB) in gastric epithelial cells and releases pro-inflammatory agents, such as interleukin 8 (IL-8).[25] Animal models provide important experiences regarding carcinogenic mechanisms caused by *H. pylori*. Ohnishi et al showed that the expression of *CagA* in mice brings about numerous malignancies, such as GI cancers, gastric epithelial hyperplasia, hyperplastic polyps, and hematologic malignancies, such as myeloid leukemia and B-cell lymphoma.[26]

Main Mechanisms of *Helicobacter pylori* Infection in GC

Several studies showed that the carcinogenic effect of *H. pylori* infection could occur through different mechanisms. *H. pylori* causes GC by directly affecting the epithelial cells of the stomach.[32] In other words, *H. pylori* mainly causes the infection of the epithelial cells in the gastric mucosa and can continue to live in the human body for decades through the inhibition of immune system response and induction of chronic inflammatory responses. During the previous three decades, inflammation was considered to have caused deoxyribonucleic acid (DNA) damage, leading to stomach ulcer disease and making cells susceptible to malignant neoplasms.[33] In general, *H. pylori* contributes to GC through two mechanisms. The first mechanism is the presence of pathogens that have interactions with host epithelium and result in neoplastic deformity; the second mechanism is the permanent presence of a pathogen in the stomach resulting in an effective immune response of neutrophils and lymphocytes and the production of pro-inflammatory cytokines, which result in chronic inflammation.[28] In 2021, researchers presented a mechanism that *H. pylori* might cause stomach cancer through the repeated contact of gastric epithelial cells with *CagA* pathogenic factors over the years.[34] Despite the evidence regarding the relationship between *H. pylori* and severe human diseases, the precise mechanisms of *H. pylori* involvement in these processes are still unknown.[15]

Genetic Variations and *Helicobacter pylori*

The first genome sequence of *H. pylori* (strain 26695) has a size of 1.67 million base pairs and contains 1590 predicted coding sequences.[35] *H. pylori* has extraordinary genetic diversity in human populations, both in terms of gene content and sequencing,[36] which is higher than all other bacteria. The most unusual feature of this variation is numerous unique nucleotide sequences for each gene that has been studied up to now.[37] The early stages of *H. pylori* gastritis are associated with infection and inflammation, leading to epithelial cell mutations, genetic changes, microRNA and gene expression alterations, genomic instability, altered cellular signaling, and unbalanced proliferation and apoptosis of gastric epithelial cells.[38] During the last years, molecular oncology studies have identified several genes that contribute to gastric carcinogenicity.[3] DNA hypermethylation in the CpG promoter islands causes the shutdown of tumor-suppressing genes and therefore contributes to GC. In addition, various molecular deviations, including misplaced chromatin structures, gene mutations, structural types, and changes in the number of somatic copies, are involved in GC.[39]

How the Body Reacts to Bacterial Antigen

Helicobacter pylori induces damage to the entire epithelium of the stomach and can produce urea through a particular process that leads to ammonia production for the protection of itself against stomach acidity. Additionally, *H. pylori* brings about the production of enzymes, such as phospholipase A2, C, and glycosulphatase, which are involved in causing gastric mucosa damage. *H. pylori* produces inflammatory responses through gastric epithelium by the production of pro-inflammatory cytokines, such as IL-1β and IL-8.[40] The first line of immunological defense against microbial pathogens activating innate immune signaling is their identification by pattern recognition receptors (PRRs). Among the most important PRRs are Toll-like receptors (TLRs) that identify a wide range of bacterial, viral fungal, and parasitic pathogen-associated molecular patterns (PAMPs).[41]

Role of TLRs in *Helicobacter pylori* Infection

Several PRR classes have been described in detail, including TLRs, retinoic acid-inducible gene I-like receptors, nucleotide-binding oligomerization domain leucine-rich repeat-containing receptors, absent in melanoma 2 receptors, C-type lectin receptors, and a family of enzymes acting as intracellular sensors of nucleic acids, such as oligoadenylate synthase and cyclic GMP-AMP synthase proteins.[42] Among these receptors, TLRs are of particular importance. To date, a total of 11 TLR homologous have been discovered in the Human Genes Database.[43] TLRs are membrane glycoproteins expressed both on the cell surface and within intracellular vesicles,[44] 10 of which are functional (TLR1-10), and their ligands have been identified; however, TLR-11 is inactive in humans (Table 2).[45] All TLRs have a common structure of three zones, namely a transmembrane region, an N-terminal, and a C-terminal cytoplasmic tail.[43]

The respective ligands of TLR1, TLR2, TLR4, TLR5, and TLR6 are bound on the cell surface. Moreover, microbial membrane components (e.g., lipids, lipoproteins, and proteins) are recognized by TLR1, TLR2, TLR4, TLR5, and TLR6. Furthermore, TLR3, TLR7, TLR8, and TLR9 are observed in intracellular vesicles (e.g., the endosome or

Table 2. The Role of TLRS in *Helicobacter pylori* Infection

PRRs	Position	Ligand	Gene Position	*H. pylori* Component Recognized by the Receptor[a]	Function	Ref.
TLR1	Cell membrane	Triacyl lipoprotein	4p14	-	Helps TRL2 detect bacterial LPS	45,46
TLR2	Cell membrane, Phagosomes	LPS, glycolipids,	4q32	HSP60, NAP	Diagnosis of *H. pylori* bacterial LPS	47-49
TLR3	Endolysosomal, plasma membrane and endoplasmic reticulum	dsRNA	4q35	-	Plays a major role in the identification of microbial nucleic acids, which are detected in intracellular vesicles.	45,47, 49
TLR4	Cell membrane phagosomes	LPS	9q32-33	LPS, HP0175	Similar to TLR2, it detects bacterial LPS, but it requires other molecules such as MD-2, the LPS-binding protein, and CD14.	49,53
TLR5	Cell membrane	Flagellin	1q33.3	Flagellin	Detection of *H. pylori* by TLR5 is achieved through p38 MAP kinase signaling	52,54
TLR6	Cell membrane	Diacyl lipoprotein, Cell membrane	4p14	-	TLR 6 could also be binding partners for TLR2, aiding in its ability to recognize different ligands.	48,50,51,55
TLR7	Cell membrane, endolysosomal, plasma membrane, and endoplasmic reticulum	ssRNA	Xp22.3	*H. pylori* RNA	Pure RNA detects *H. pylori* and induces proinflammatory cytokines in a MyD88-dependent manner.	49
TLR8	Endolysosomal, plasma membrane and endoplasmic reticulum	ssRNA	Xp22	*H. pylori* RNA	Pure RNA of *H. pylori* is detected by this receptor, inducing proinflammatory cytokines in a MyD88-dependent manner.	47,49,50
TLR9	Endosomes, Endolysosomes, Lysosomes, and Phagosomes	CpG-DNA	3p21.3	*H. pylori* DNA	Identification of *H. pylori* DNA.	48,55,56
TLR10	Endolysosomal, plasma membrane and endoplasmic reticulum	Diacyl lipoprotein, triacyl lipoprotein, viral glycoproteins, double-stranded (ds)RNA	4p14	-	It can be considered a functional receptor that is produced in response to innate immune induction by *H. pylori*.	45,46,49,50
TLR11	Cell membrane, endolysosomal, plasma membrane, and endoplasmic reticulum	Profilin-like molecule	19q13.42	-	This receptor is inactive in humans.	45,50

Abbreviations: PRRs, Pattern recognition receptors; TLR, Toll-like receptor; LPS, lipopolysaccharide.
[a] Toll-like receptors involved in response to distinct *H. pylori* components.

lysosome and the endoplasmic reticulum) and primarily involved in the identification of microbial nucleic acids.[55]

TLRs are horseshoe-shaped proteins with extracellular tailings consisting of 18-25 leucine-rich copies. TLR-4 is one of the most important PRRs in the innate immune system,[57] which is involved in recognizing PAMPs.[53] Most clinical studies performed on the diagnosis of intrinsic patterns have focused on TLR4 due to its role in immune-mediated pathologies and the fact that this receptor is located at the cellular level and can detect microbial components and LPS outside the cell. In addition, it is the only TLR that activates both signaling pathways in response to infection.[58] Accordingly, the identification of LPS requires the heterodimerization of TLR4 using its auxiliary protein (i.e., myeloid differentiation factor-2), followed by the dimerization of the receptor intracellular demine that results in an intracellular signaling cascade, possibly providing the activation of the myeloid differentiation primary response 88 and TIR-domain-containing adapter-inducing interferon-β-dependent pathways.[59] This, in turn, leads to the activation of several innate safety signaling pathways by transcription factors, such as activator protein 1, NF-κB, and interferon regulatory factor 3, which is vital in regulating responses,[50] and ultimately activates some innate immune cells (e.g., macrophages and DCs). Moreover, the production of inflammatory cytokines caused by LPS initiates host defense system activity against injury and infection.[60]

The Role of Inflammatory Responses

As a defense mechanism, inflammatory responses are activated upon tissue damage in infections and cancers, providing a link between chronic inflammation and the tumorigenesis process. Inflammatory responses have a decisive role in various stages of tumor growth.[61] Generally, redness, swelling, heat, pain, and loss of tissue function are considered five characteristic symptoms of inflammation. The aforementioned macroscopic symptoms increase vascular endothelium permeability, inflammatory response completion, and tissue repair. Noninfectious diseases, such as graft-versus-host disease can also be the cause of cytokine production. Inflammatory responses are also of great importance for the pathogenesis of autoimmune diseases.[47] The onset and persistence of the inflammatory response are considered the primary pathophysiological event in *H.*

pylori infection. This inflammatory process is caused by bacteria or their products, and cytokines are the primary mediators in this regard.[62]

Role of Cytokines in Regulating Inflammation and Immune Responses

In 1974, Stanley Cohen first introduced the term cytokine.[63] Cytokines are proteins or glycoproteins with low molecular weight. In lexical terms, the cytokine is composed of two words "sato", meaning cell, and "quinine", meaning hormone.[64] Cytokines have a critical role in causing inflammation and its regulation. Pro-inflammatory and anti-inflammatory cytokines are two groups of these compounds; a dynamic balance between these two groups is highly important for maintaining a stable body state.[64] In general, cytokines can also be categorized into five groups as follows:

1. ILs are cytokines made by a leukocyte that can affect other leukocytes, which have been identified and named from IL-1 to 35, respectively.
2. Tumor necrotizing factors (TNF) also act as necrotizing mediators induced by LPS in cancer cells.
3. Chemokines are another subgroup of cytokines that play a role in the chemotaxis (i.e., chemical absorption) of other cells and immune system mediators.
4. Interferons are compounds that cause cell resistance to viral contamination.
5. Lymphokines are another subgroup of cytokines produced by lymphocytes.

In another category of cytokines, it is composed of proteins-interleukins, lymphokines, monokines (i.e., cytokines made by monocytes), interferons, and chemokines (i.e., cytokines with chemotactic activities).[65] More than any other cytokine family, the ligand family and IL-1 receptors are primarily associated with acute and chronic inflammation.[66] Additionally, IL-8, IL-10, and IL-1β are key cytokines and are effective in inflammation.[67] The evidence collected over the years suggests that IL-1β plays a pre-tumorigenic role in all types of cancers. Solid tumors, including breast, lung, head, and neck, and melanoma, which have high expression of this cytokine, show a weaker prognosis.[67] Furthermore, the messaging of this cytokine is highly associated with inflammation, and the latter has a crucial role in cancer progression. Numerous chemotherapy drugs produce pro-inflammatory cytokines in cancer, thereby reducing the patient's immunity.[68] White blood cells and other types of cells (e.g., epithelial cells, fibroblasts, and endothelial cells) cause the secretion of cytokines in the body in response to stimulations. Furthermore, cytokines are not fundamentally expressed.[63] The latest development in cytokinesis is cytokine gene therapy for different cancers; however, the actual effectiveness of this approach requires further investigations.[63]

Most Important Pro-inflammatory Cytokines

Pro-inflammatory cytokines are mostly produced by active macrophages and play a role in regulating inflammatory reactions. There is ample evidence to suggest that some of the most important pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, are involved in this process as follows (Table 3):[65]

1. IL-1β increases the synthesis of endothelium-binding molecules on inflammatory cells (e.g., neutrophils, monocytes, and fibroblasts), which causes vascular dilation, chemotaxis, and inflammation in the region.[69]
2. IL-6 plays the main role in neural reaction to nerve damage.
3. TNF-α, also known as cachectin, via two cell surface receptors (i.e., TNF receptor-1 and TNF receptor-2), acts on several different messaging pathways to regulate apoptosis pathways, activation of NF-κB inflammation, and activation of stress-activated protein kinases. The TNF-α receptors are α in both neurons and glia.[70] Based on similarity to the TNF-α sequence, 19 different proteins have been identified,

Table 3. The Role of Pro-inflammatory and Anti-inflammatory Cytokines in *Helicobacter pylori* infection

Name	Category	Role	Effect	Ref.
Interleukin 1 beta	Interleukin	After infection with *H. pylori,* interleukin-1 causes inflammation and secretion of other cytokines. Gastritis in patients with *H. pylori* is characterized by the production of Interleukin 1 beta.	Pro-inflammatory cytokines	44,67,72,73
Tumor necrosis factor-alpha	Tumor necrotizing factors	It activates leukocytes during *H. pylori* infection	Pro-inflammatory cytokines	63,66
Interleukin 6	Interleukin	Interleukin 6 is secreted by monocytes and macrophages in chronic gastritis and is associated with *H. pylori* in the gastric and duodenal mucosa.	Pro-inflammatory and anti-inflammatory cytokines	64,62,72
Interleukin 4	Lymphokine	Interleukin-4, plays a key role in humoral and cell-mediated immunity.	Anti-inflammatory cytokines	67,68,74
Interleukin 10	Interleukin	Increased expression of interleukin 10 is directly related to *H. pylori* infection.	Anti-inflammatory cytokines	70,75
Interleukin 13	Lymphokine	Until now, no data concerning IL-13 expression in gastric mucosa has been reported.	Anti-inflammatory cytokines	44,70,76,77
Interferon gamma	Interferon	Pro-inflammatory, especially cellular immunity. Play an important role in gastritis caused by *H. pylori* infection.	Anti-inflammatory cytokines	64,70,78

classified as TNF superfamily. In addition, 29 proteins have been identified as TNF superfamily receptors.

Concluding Remarks

The etiology of GC is complex and multifactorial, including environmental factors and host, genetic, and epigenetic changes. The infection with *H. pylori* is a necessary but insufficient source of stomach cancer.[79] The onset and persistence of the inflammatory response are considered the main pathophysiological event in *H. pylori* infection. This inflammatory process is caused by bacteria or their products, and cytokines are the major mediators in this regard.[62] In addition, cytokine and inflammation are strongly associated, and inflammation has a crucial role in cancer progression.[70]

Among the infectious and bacterial agents causing cancer, *H. pylori* is the most important bacterium involved in carcinogenesis. *H. pylori* has two potentials. It is a pathogen, and on the other hand, by the strategy and techniques of genetic engineering and biotechnology, this pathogen can be used as a tool to treat cancer. The pathogenicity of *H. pylori* is because, on the one hand, by having a series of factors, it induces apoptosis, and on the other hand, it has factors that induce cell proliferation. In these cases, the factors that induce apoptosis can be used directly to kill cancer cells, and the factors that stimulate the immune system can be used to activate the immune system to attack cancer cells through the system.[16] In a study conducted by Chang et al, *H. pylori* infection having specific virulence factors was related to an increased risk of serious clinical consequences, which was also cited in this study.[80]

Altogether, 120 *H. pylori* strains were isolated in another study conducted by Heidari et al. The frequencies of cagA were 67.5%, 60%, and 45% in patients with GC, peptic ulcer, and without ulcer and GC, respectively, which confirms the results of the present study.[20]

In summary, the role of *H. pylori* in GC development depends on pathogens and the host immune response. Therefore, the timely evaluation of the aforementioned factors would be helpful for the management and prevention of the further progression of GC.[28] As previously mentioned, *H. pylori* has a major role in GC development. Therefore, the best strategy to prevent the progression of GC is to eradicate *H. pylori*.[81] On the other hand, TLRs are a group of membrane receptors belonging to PRRs that are involved in identifying PAMPs, thereby causing an immune response.[82]

The TLRs are the first line of defense against pathogens.[38] Therefore, targeting TLR and pathogenic factors of *H. pylori* to induce apoptosis and stimulate the immune system will be a promising, attractive, and helpful method for cancer prevention. Cytokine gene therapy for different cancers is the latest advancement in cytokines; however, the efficacy of this method would be apparent only through performing further studies in the future.[63] Finally, considering the high cost of GC treatment, it is recommended to perform screening and tests associated with the diagnosis of *H. pylori* before the presentation of symptoms at middle age.

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Authors' contributions

All authors contributed equally in literature search, qualification of studies, and preparing and editing the manuscript.

Competing Interests

The authors have no conflict of interest to declare.

Ethical Approval

Not applicable.

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