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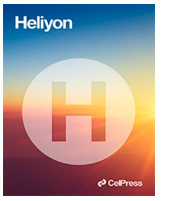

Review article

Unraveling the gut-Lung axis: Exploring complex mechanisms in disease interplay

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ABSTRACT

The link between gut and lung starts as early as during organogenesis. Even though they are anatomically distinct, essential bidirectional crosstalk via complex mechanisms supports GLA. Emerging studies have demonstrated the association of gut and lung diseases via multifaceted mechanisms. Advancements in omics and metagenomics technologies revealed a potential link between gut and lung microbiota, adding further complexity to GLA. Despite substantial studies on GLA in various disease models, mechanisms beyond microbial dysbiosis regulating the interplay between gut and lung tissues during disease conditions are not thoroughly reviewed. This review outlines disease specific GLA mechanisms, emphasizing research gaps with a focus on gut-to-lung direction based on current GLA literature. Moreover, the review discusses potential gut microbiota and their products like metabolites, immune modulators, and non-bacterial contributions as a basis for developing treatment strategies for lung diseases. Advanced experimental methods, modern diagnostic tools, and technological advancements are also highlighted as crucial areas for improvement in developing novel therapeutic approaches for GLA-related diseases. In conclusion, this review underscores the importance of exploring additional mechanisms within the GLA to gain a deeper understanding that could aid in preventing and treating a wide spectrum of lung diseases.

1. Introduction

Gut and lungs have structural and functional similarities in their developmental stages, exposure to the external environment, protective mucous layer, and colonized microbes [1]. Emerging evidence highlights the associations of gut and lung diseases. The link between the gut and lung starts as early as during organogenesis and outlines several common signaling pathways [2]. The earliest evidence of gut-lung interactions was delineated based on the diagnosis of chronic bronchopulmonary disease in patients previously reported with inflammatory bowel disease [3]. Thereafter, many studies have focused on the GLA, although limited studies have focused on the lung-gut axis. Therefore, the vast part of this review will be elaborating the GLA axis in disease conditions.

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List of abbreviations

APC	Antigen presenting cells
AEC	Alveolar epithelial cells
COPD	Chronic obstructive pulmonary disease
CRP	C reactive protein
CCL	Chemokine ligand
CXCL	CX-C motif chemokine
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
F/B	Firmicutes/Bacteroidetes
GLA	Gut-Lung axis
GPCR	G-protein coupled receptor
IBD	Inflammatory bowel disease
IFABP	Intestinal fatty acid binding protein
ILC	Innate lymphoid cell
LPS	lipopolysaccharides
LBP	LPS binding protein
mLN	mesenteric lymph node
NAD	Nicotinamide adenine dinucleotide
nILC2	natural innate lymphoid cell 2
PAMPs	Pathogen-associated molecular patterns
PNAd	P nicotinamide adenine dinucleotide
ROS	Reactive oxygen species
SCFA	Short chain fatty acid
TBI	Traumatic brain injury
T_{CM}	Central memory T cells
T_{EM}	Effector memory T cells
Th2	T helper type 2
TLR	Toll like receptor
TMAO	Trimethylamine-N-oxide
ZOT	Zonula occludens toxin

Advancement in omics and metagenomics technologies has revealed a vital bidirectional crosstalk between the composition of inter-organ microbiota since birth and throughout the lifetime [4]. These mechanisms have added further complexity to the GLA. There were 2172 species identified via MetaHit and Human Microbiome Project and classified into 12 different phyla, of which 93.5 % belonged to *Actinobacteria*, *Bacteroidetes*, *Proteobacteria*, and *Firmicutes*. Among these species, 386 were commonly found in mucosal compartments, including the oral cavity, lungs, and the gut [5]. Gut is colonized with more than 40 trillion microbiota with rich species diversity [6], while the lung microbiota constitutes approximately 3600 bacterial species [7]. It is now evident that microbial communities in the gut, as well as other epithelial layers significantly influence distinct organ function and immune regulations [8,9].

The significance of early life microbial colonization in regulating and maturation of the immune system is well accepted. There is no universal healthy gut microbiota composition that fits all. Every individual's healthy gut microbiota composition varies, depending on several factors including their gestational birthday, mode of delivery, feeding practices, and weaning period in neonatal stage [10]. The acquired host specific native core microbiota is stable throughout adulthood. This acquired composition of microbiota is considered to be healthy microbiota of that specific host, and any disturbances in the composition, can affect largely the immune homeostasis and drive the disease pathogenesis. Moreover, association of dysbiosis with the pathogenesis of various diseases, including lung diseases such as asthma and COPD [11].

Based on the current understanding, the lung microbiome may have a potential influence by translocated microbes from other tissues into the lung [12] leading to lung microbiota dysbiosis. However, the factors that influence both gut and lung microbiome and their relevance in diseases are yet to be addressed. Even though the GLA in different disease models are studied and reviewed substantially, the mechanisms other than microbiota-mediated process are less explored.

This review aims to provide insights on the intricate mechanisms that are orchestrating the GLA and highlights the importance of exploring additional mechanisms that could help in preventing and treating a wide spectrum of lung diseases. Therefore, the different mechanisms regulating GLA, including gut and lung microbial dysbiosis, breaching of epithelial barriers, microbes' crosstalk, immune cell mis-homing, and mucosal compartment inter-talk, will be discussed in this review. In addition, potential factors involved in the GLA, such as metabolites immune modulators and vitamin D deficiency with a focus on gut to lung direction, will also be summarized. This review would further facilitate more precise understanding of the mechanisms within GLA and help to tailor the appropriate experimental studies to better unravel additional novel mechanisms of GLA.

2. Gut-lung axis

Despite the distinct anatomic locations, the gut and lungs influence each other bi-directionally in health and disease, generally termed GLA (Fig. 1). Although different gut and lung diseases have differential spectrums of immune response, they share certain pathologic mechanisms that regulate the GLA [13]. Several gut diseases, including IBD, ulcerative colitis, and Crohn's disease, were reported to be linked with lung diseases, like asthma, COPD, and cystic fibrosis [14,15]. In disease conditions, the gut and lungs communicate via various mechanisms (Fig. 2). However, dysbiosis-triggered GLA is widely studied. Gut microbial dysbiosis is mediated by various factors, including antibiotic use, stress, diet, and metabolic diseases (Fig. 1), which are believed to impact immune responses and initiate an exaggerated inflammation [16]. Although different bacterial species are altered in specific disease conditions, F/B ratio is the widely accepted measure for gut dysbiosis. The low F/B ratio with increased *Bacteroidetes* and reduced *Firmicutes* in the gut denotes an inflammation in the intestinal tissues. This imbalance in the F/B ratio results in disruption of the epithelial tight junction barrier, mucous layer erosion, dysregulation of Paneth cell functions, and increased intestinal permeability.

Enhanced systemic exposure to the microbes from a dysbiotic gut and their metabolites induce inflammatory cytokines, including TNF-α, TGF- β, IL-5, IL-6, IL-1β, IL-13, IL-17, IL-18 and IL-33, chemokines like IL-8, CCL 2, 3, 4, 7, 20, CXCL 5, CXCL8, CXCL10 [17]. This further recruits pro-inflammatory immune cells like neutrophils and T cells into the mucosal epithelial layer and forms a lymphoid aggregate. These primed cells subsequently enter the blood circulation and infiltrate other distinct organs, including the lung parenchyma [18]. In addition to systemic blood circulation, mesenteric lymphatics may also transport gut-derived pro-inflammatory factors, leading to the activation of pulmonary endothelial cells and immune cells, resulting in alveolar barrier damage as observed in

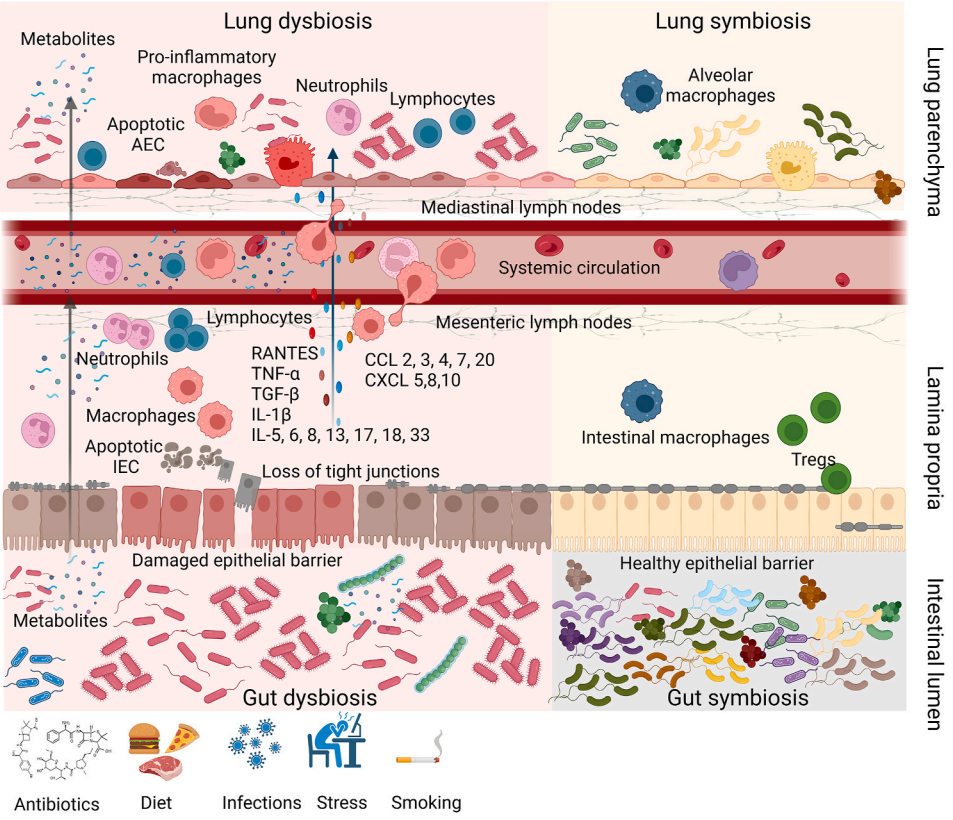

Fig. 1. Overview of GLA In Symbiosis gut and lungs observed with intact epithelial membrane barriers with diverse microbial populations and predominantly tissue protective macrophages in lungs and along with regulatory T cells in gut lamina propia together maintains homeostasis. Several factors including antibiotics, drugs, diet, infections, stress, and smoking can lead to gut dysbiosis. Gut microbial dysbiosis drives exaggerated inflammation resulting in intestinal epithelial cells (IEC) apoptosis, epithelial tight junction barrier damage and increased intestinal permeability. This facilitates the enhanced systemic exposure to commensal bacteria, their metabolites, inflammatory cytokines including TNF-α, TGF- β, IL-1β, IL-5, IL-6, IL-13, IL-17, IL-18 and IL-33, chemokines like IL-8, CCL 2, 3, 4, 7, 20, CXCL 5, CXCL8, CXCL10 and RANTES into blood circulation. This further recruits the pro-inflammatory immune cells like neutrophils and T cells into the mucosal epithelial layer and forms a lymphoid aggregate. These primed cells subsequently enter the blood circulation and infiltrate other distinct organs, including lung parenchyma. In addition to systemic blood circulation, mesenteric lymphatics may also transport gut-derived pro-inflammatory factors via mediastinal lymphatics leading to activation of alveolar macrophages and pro-inflammatory milieu results in AEC apoptosis and alveolar barrier damage. In addition, microbial metabolites are absorbed into gut mucosal tissue and enter lung via systemic blood circulation and modulate the function of lung epithelial cell, innate and adaptive immune cells. Thus, the inflammatory process can translocate from gut to lungs. Created with BioRender.com.

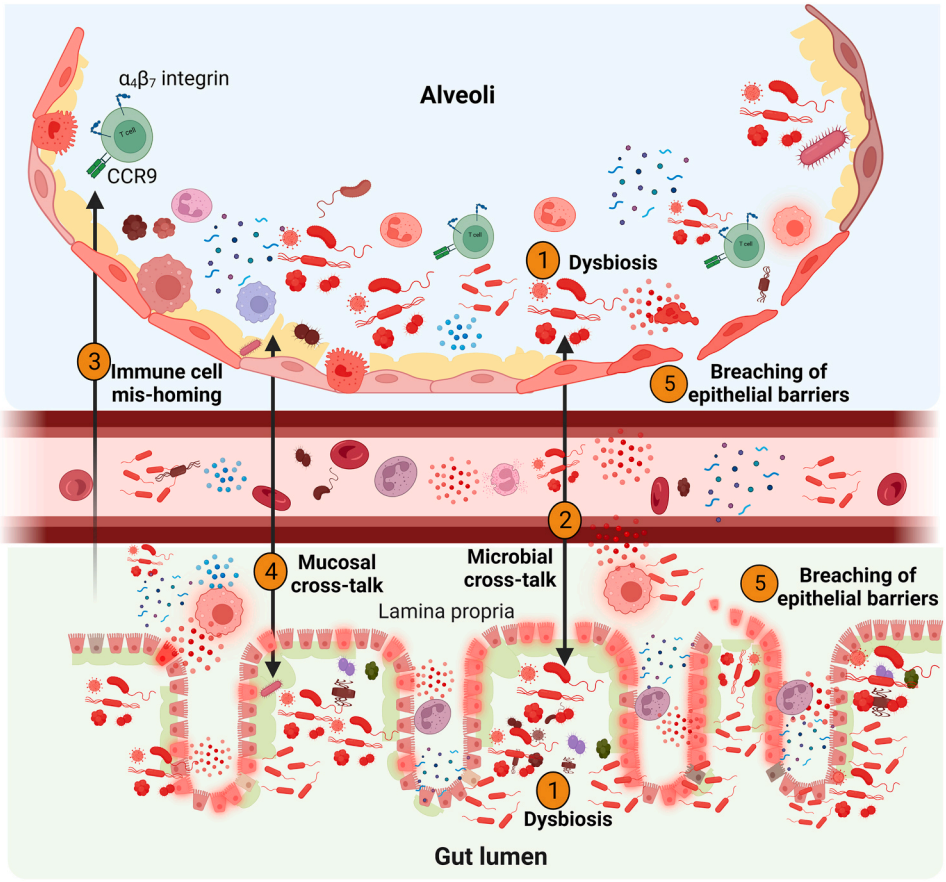

Fig. 2. Mechanisms regulating GLA Different potential mechanisms are proposed based on the current available literature on GLA. 1) Dysbiosis-imbalance in the composition of native symbiosis can affect the anatomy, physiology and immune responses in the gut that can mirror in lungs, 2) Microbial cross talk-gut native microbes translocate into lungs via systemic circulation and modulate immune responses, 3) Mis-homing of immune cells-gut homing (α4β7 integrin and CCR9) T lymphocytes can mis-home in lungs and mediate inflammatory responses. 4) Mucosal inter-talk- the mucosal layer in both gut and lung can serve as bridge for translocation of various inflammatory mediators including microbes, their contents, activated immune cells and their products and 5) Breaching epithelial barrier-inflammatory milieu in intestine can lead to epithelial apoptosis and results in gut epithelial barrier damage leading to dissemination of gut contents including microbes, their products, immune cells and pro-inflammatory mediators can translocate into lungs and promote adverse effects. Created with BioRender.com.

acute respiratory distress syndrome [19]. However, the role and mechanisms of pro-inflammatory mediators that migrate via mesenteric lymphatics and induce tissue injury are incompletely understood.

In addition, microbial metabolites are absorbed into gut mucosal tissue and may enter the lungs via systemic blood circulation. These metabolites bind to the GPCRs to modulate the function of lung epithelial cells and innate and adaptive immune cells [20]. Thus, the inflammatory process could shift from the gut to the lungs (Fig. 1).

3. Mechanisms regulating GLA

Due to the complexity observed in understanding the GLA, it is clear that GLA consists of other complex mechanisms that involve not only the host microbiota but also, their metabolites, host immune cells, their immune mediators, and their interactions [21] (Fig. 2). These interactions within GLA are key for maintaining the host homeostasis and immune modulations during an insult.

3.1. Dysbiosis

Gut microbiota is essential in the formation and maturation of the immune responses, and the immune system has a vital role in modulating the composition and function of microbiota (eubiosis) [22]. Disruption of such a balanced, healthy microbiome promotes immune dysfunction and systemic inflammation. An imbalance between the species of organisms presents in an individual's natural microflora, especially that of the gut of a healthy individual, that can contribute to a range of diseases. Gut microbiota composition is vulnerable to several factors like antibiotics, stress, drugs, diet, etc., and lead to gut dysbiosis (Fig. 1), which in turn can affect other distinct organs, including lung functions (Table 1).

However, antibiotics are the major cause that has been studied and observed to be associated with lung diseases like allergic asthma [23]. According to the human microbiome project and other reports, most of the amplified genes from human feces are from bacteria, particularly, phyla *Bacteroidetes* and *Firmicutes* [24]. The phyla, *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Fusobacteria* [25] and the genus *Bacteroides*, *Clostridium*, *Faecalibacterium*, *Eubacterium*, *Ruminococcus*, *Peptococcus*, *Pepto-streptococcus*, and *Bifidobacterium* are majorly observed in healthy human gut [26]. The dysbiotic gut differentially associates with increase of different species in different inflammatory and infectious lung diseases (Table 1). Moreover, it has been observed that different antibiotic treatments could affect the gut microbiota differently [27]. Therefore, antibiotics must be prescribed considering their potential deleterious effects on healthy gut microbiota. Recently, pulmonary infections like influenza virus, respiratory syncytial virus are found to influence the gut microbiota (Table 2) [28]. However, further studies are required for detailed evaluation of these specific infections that would significantly affect the gut microbiota composition and functions.

3.2. Breaching of epithelial barrier

Gut dysbiosis promotes gut inflammation and epithelial barrier damage, leading to gut including asthma and COPD [29,30]. The epithelial cells are arranged tightly with via junctional complexes including junctional proteins (tight, adherent and gap junctions) and desmosomes. These tight junction mediated intestinal barrier integrity can be modulated by other factors including PAMPs and DAMPs induced epithelial apoptosis [31] (Fig. 2). However, they were also observed to be modulated in the dysbiotic gut [32]. For example, an increased expansion of pathobiont *Bilophila wadsworthia* (a member *Proteobacteria*), impaired intestinal barrier integrity was observed [33]. *Salmonella typhimurium* shown to up-regulate the claudin expression, which plays a role in intestinal permeability [34]. In another study, *Vibrio cholerae* observed to target the intestinal epithelial barrier by producing the ZOT [35]. Similarly, an enterotoxin Zonulin is secreted by human intestinal epithelium following stimuli from antibiotics, diets and dysbiosis that can affect the intestinal epithelial barrier [32,33]. The breached epithelial barrier results in the dissemination of intestinal microbial contents like LPS and their metabolites like SCFA in the systemic circulation; however, there is no substantial evidence [36]. In addition, host-released factors including pro-inflammatory cytokines [37] due to inflamed gut epithelium, might enter circulation and modulate distant organ functions. For example, IL-4 and IL-13 are type-2 cytokines majorly involved in the pathogenesis of asthma. However, they also play a major role in ulcerative colitis [38]. These cytokines can be released into the systemic circulation to have their effects on the lungs and promote development of airway allergic diseases. However, this mechanism of GLA is in its nascent stage and must be largely explored.

3.3. Microbes' crosstalk

Microbes' communications within a host are multi-dimensional, bi-directional, and complex (Fig. 2). Emerging studies suggest a possible mechanism of microbial crosstalk between the gut and lungs. This mechanism is supported by clinical studies, where the gut associated bacteria like *Firmicutes*, *Bacteroidetes*, *Lachnospiraceace* and *Enterobacteriaceae* families were detected in the lungs of acute respiratory distress syndrome, sepsis, asthma, tuberculosis, cystic fibrosis patients [39,40]. An in vivo study demonstrated the effect of

Table 1
Factors involved in gut dysbiosis and associated lung diseases.

Mediators of Gut dysbiosis	Dysbiosis in gut	Associated lung diseases	References
Age	• Increased Firmicutes, *Enterobacteria, C. perfringens and C. difficile.* • Decreased Prevotella, *Veillonella*, Leptotrichia, Staphylococcus, Propionibacterium, Moraxella, *Bacteroides, Bifidobacteria and Lactobacilli.*	COPD, IPF, Lung cancer and Asthma	[109]
Antibiotics	• Increased *Candida* species, *Firmicutes*, *Verrucomicrobia (Akkermansia muciniphila)*, *Burkholderiaceae*, *Clostridiales and* Proteobacteria. • Decreased *Muribaculaceae, Prevotellaceae, Lachnospiraceae, Actinobacteria, Bacteroidetes, and Clostridium.*	Pneumonia, COPD, and Asthma	[27,110, 111]
Drugs	• Proton pump inhibitors increased *C. difficile, S. pneumonia.* • Steroid treatment increased *Proteobacteria, Pseudomonas, Neisseria, Haemophilus, Moraxella, Bifidobacterium, and Lactobacillus.* • Decrease in *abundance* of *Prevotella, Bacteroidetes, and Fusobacteria*	Asthma, Pneumonia, and COPD	[112,113],
Diet	• Increased *Proteobacteria, Burkholderiaceae, Firmicutes and* Erysipelotrichaceae (low fiber diet). • Decreased *Bacteroidetes, Bifidobacteriaceae and Actinobacteria* (low fiber diet), *Bifidobacteria and Eubacterium species* (saturated fat and low carbohydrate diet)	Asthma	[97,114, 115]
Diseases (Obesity)	• Increase in taxa *belonging* to *Prevotellaceae*, *Mycoplasmataceae*, *Lachnospiraceae,* and *Spirochaetaceae*	Asthma	[116,117]
Mode of Delivery (C-section delivery)	• Increased *abundance* of *Veillonella, and* Clostridium *difficile*. • Decreased *Lactobacillus*, *Bacteroides*, *Prevotella*, *Roseburia, Ruminococcus, Akkermansia, Alistipes, Dialister, Faecalibacterium, and Bifidobacteria*	Childhood Asthma and Atopy	[118–120]
Pets	• Increase of *Clostridiaceae*, *Veillonella* (dogs), *C. difficile* and *Coprococcus*. • Decreased *Bifidobacteria*		[120,121]
Smoking	• *Increased Proteobacteria,* and *Enterobacteria.* • *Decreased Bifidobacteria.*	COPD	[122]

Table 2
Lung diseases and its associated gut and lung dysbiosis.

Lung diseases	Lung dysbiosis	Gut dysbiosis	References
Asthma	• Increase in *Firmicutes (streptococcus), Proteobacteria (Moraxella, Hemophilus and Neisseria)*. • Decreased *Bacteroidetes (Prevotella), Proteobacteria (Acinetobacter), Actinobacteria (Corynebacterium)*.	• Increase in *Firmicutes (Clostridium difficile and Enterococcus)*. • Decrease in *Firmicutes (Lachnospira, Veillonella, Faecalibacterium, Actinobacteria (Rothia) and Faecalibacterium*.	[12,120, 123]
COPD	• Increase in *Streptococcus parasanguinis*.	• Increase in *Streptococcus parasanguinis, Streptococcus salivarius* and *Firmicutes*. • *Decrease* in *Acidobacteria* and *Cyanobacteria*.	[124,125]
Cystic fibrosis	• Increase in *Pseudomonas aeruginosa, Haemophilus influenzae, Staphylococcus aureus* and *Burkholderiacepacia complex*. • *Decrease* in genus *Parabacteroides*.	• Increase in *Enterobacteriaceae*, *Enterococcus* and *Streptococcus*. • *Decrease* in *Bacteroides, Bifidobacterium and Faecalibacterium*.	[14,126, 127]
Lung infections	TB: • Increase in *Pseudomonas, Streptococcus, Gramulicatella, Streptococcus pneumonia*. • Decrease *Catonella, Prevotella, Leptotrichia, Coprococcus and Treponema*. Pneumonia: • *Klebsiella pneumonia, Hemophilus influenzae, Legionella pneumophilia, Chlamydophila psittaci, Staphylococcus aureus and Mycoplasma pneumonia*. SARS-CoV-2: • Increased *Acinetobacter, Chryseobacterium, Burkholderia, Brevundimonas, Sphingobium, and Enterobacteriaceae*.	TB: • Increase in *Actinobacteria, Proteobacteria, Proteobacteria, Enterobacteriaceae*. • Decrease in *Clostridiales (Lachnospiraceae, Ruminococcaceae) and Bacteroidetes (Provetella)*. Influenza A: •Increase in *Proteobacteria (Escherichia), Firmicutes (Lactobacillus), Clostridiales (Ruminococcus), Mogibacteriacecea (Coprococcus)*. • Decrease in *Bacteroidetes, Betaproteobacteria (Sutterella)* and *Segmented Filamentous Bacteria*. SARS-CoV-2: • Increase in *Bacteroides nordii, Rothia, Clostridium hathewayi, Streptococcus, Actinomyces viscosus, Veillonella, and Actinomyces*. • Decrease in *Faecalibacterium prausnitzii, Eubacterium ventriosum, Roseburia and Lachnospiraceae*.	[28, 128–135]
Lung Cancer	• Increase in *Firmicutes and TM7 (Streptococcus, Veillonella, Megasphaera), Enterobacter, Haemophilus influenzae and Staphylococcus*.	• Increase in *Firmicutes (Streptococcus, Veillonella), Bacteroidetes, and Proteobacteria (Enterobacteriaceae, Rikenellaceae, Prevotella, Streptococcus, Lactobacillus)*. • Decrease in *Escherichia-Shigella, Verrucomicrobia, Kluyvera, Fecalibacterium, Enterobacter, and Dialister*.	[136–138]

fecal microbiota transfer in rats on changing lung microbiota composition [41]. Similarly, modifications in the infant's diet were found to influence the microbiota of the respiratory tract [42]. A recent investigation of patients with *Schistosoma mansoni* (an intestinal pathogen) induced pulmonary arterial hypertension, has observed the translocation of *Schistosoma* eggs to lungs via mesenteric veins leading to the damage in the endothelial lining of the capillary walls resulting in chronic pulmonary vascular diseases [43]. This study suggested a possible mechanism of translocation through the mesenteric system. Moreover, a transient recolonization [44] of lung microbiome by a constant seeding from oral and gut might help filling the microbiota niches in the lung was speculated [45]. However, these findings need further validation.

Advanced sequencing technologies such as NGS, and shotgun metagenomics enabled comprehensive analysis of microbial communities in the GLA, providing information on their diversity and functions. Microbiome analysis helps to understand the modulation of the gut-lung axis during different diseases, shedding light on microbial and immune interactions. In a recent study, investigators proposed the possible crosstalk and translocation of gut bacteria to the lung after TBI by sequencing both fecal and lung tissues in mice models of TBI, followed by SourceTracker; a bioinformatics tool to trace the origin of bacteria [46]. These studies suggest the direct transfer of gut microbiota into the lungs; however, the involved regulating mechanisms are yet to be explored. Sencio V et al. suggested that the gut resident bacteria can remotely support the lungs during viral infections [28]. Therefore, understanding the mechanism by which the intestinal microbiome affects the lung microbiota or vice versa would facilitate further knowledge of the microbe's translocation within the GLA [9]. In addition, it is intriguing to investigate if there are specific microbes that might patrol between the gut and lungs in a specific disease. This would provide added knowledge and help to target the specific microbe or the related signaling pathway in a particular disease for therapeutic approaches.

One possible mechanism could be the migration of microbes from unfavorable to favorable microenvironments. The other mechanism might be hijacking the host immune cell machinery to migrate interorgan. Moreover, similar to immune cells that express homing receptors to infiltrate target tissues [47], gut microbes could migrate to the lung or vice versa; however, the pathways involved and the trigger for migration from native tissue to foreign tissues need to be better understood.

3.4. Mis-homing of immune cells

Specific homing receptors are expressed on activated immune cells that use ligand-receptor interactions to direct them to the site of inflammation [48]. However, an undesired microenvironment can alter these mechanisms, resulting in mis-targeted homing of the activated immune cells into distinct organs (Fig. 2), where they exert their pro-inflammatory effects, disturbing the local tissue homeostasis [49]. T lymphocytes expressing $\alpha_4\beta_7$ integrin recruited to the inflamed gut may infiltrate the lungs and exhibit bronchiectasis and chronic bronchitis. In a clinical study with IBD patients, activated neutrophils were shown to enter lung parenchyma and release various pro-inflammatory mediators [50]. Similarly, the primed lung marginated neutrophils produced excessive myeloperoxidase, elastase, and lactotransferrin, leading to lung tissue injury, which mimics the pathologic features of COPD characterized by bronchiectasis and chronic bronchitis [51]. This undesirable flooding of pro-inflammatory mediators by neutrophils bypasses the endogenous safety mechanisms and results in tissue damage [52]. These altered homing mechanisms of neutrophils and lymphocytes induce tissue injury and resemble the key pathological features of chronic bronchitis and bronchiectasis. This mechanism of immune cell mis-homing was observed in Crohn's disease patients who were found to have neutrophilic and lymphocytic alveolitis and alveolar leakage [53]. Moreover, it was recently reported that activation of memory lymphocytes in the gut circulate and reach the liver in primary sclerosing cholangitis patients [54]. This further adds evidence to the mis-homing of immune cells from the gut to other organs; similar speculations can be made within the GLA axis.

Moreover, activated DCs in mLN also can induce plasma cells to produce IgA and IgG antibodies [55,56], which then translocate to draining lymph nodes and mucosal tissues, including lungs, to improve immunological response against respiratory pathogens. In a recent study, gut microbiota (*Proteobacteria*) facilitates nILC2 migration via IL-33-CXCL-16 signaling, that can increase IL-33 and nILC2 accumulation in the lungs [57]. Similarly, effector and CCR9 + T cells from lung are found infiltrated to the intestine, then secrete IFN-I and alter the gut microbiota [58].

Mis-targeted homing of the activated immune cells also occurs within the GLA [59]. Anatomically distinct gut and lung tissues are part of a common mucosa and its associated lymph system where lung homing by lymphocytes occurs through non-tissue specific mechanisms mediated by P nicotinamide adenine dinucleotide (PNAd) and l-selectin or VCAM-1 and α4β1 integrin [60]. Moreover, the miss-homing of memory T_{CM} and T_{EM} generated at one site and mis-homed to another tissue [61,62] are interesting targets for investigation within GLA. For example, CCR9+ and $\alpha_4\beta_7$ integrin + T_{EM} cells primed in gut, via CD62L/PNAd interaction on the lung endothelium can home to secondary lymphoid tissue near lungs [62,63]. Similarly, a certain mis-homed T_{CM} might enter systemic circulation and recognize antigens in both gut and lungs. These cells can sense a common antigen in both tissues and promote an inflammatory response that may be mirrored in both organs independent on active inflammation in both tissues. These studies insist on an intense need to further explore immune-cell mis-homing studies within GLA.

3.5. Mucosal compartment inter-talk

Mucosal tissues are interconnected, where activation of immune cells of one site of the mucosal compartment can influence the other site [64], through bi-directional mechanisms (Fig. 2). In addition, exposure to antigens in the gastrointestinal tract has shown to induce specific antibodies in the other mucosal sites [65]. These data demonstrate a dynamic interaction between the microbiota and the mucosa. Mucosal inter-talk is achieved by mesenteric lymph node cells distributed in most mucosal tissue. As a result of this connection, vaccination in one mucosal site confers protection in another [66].

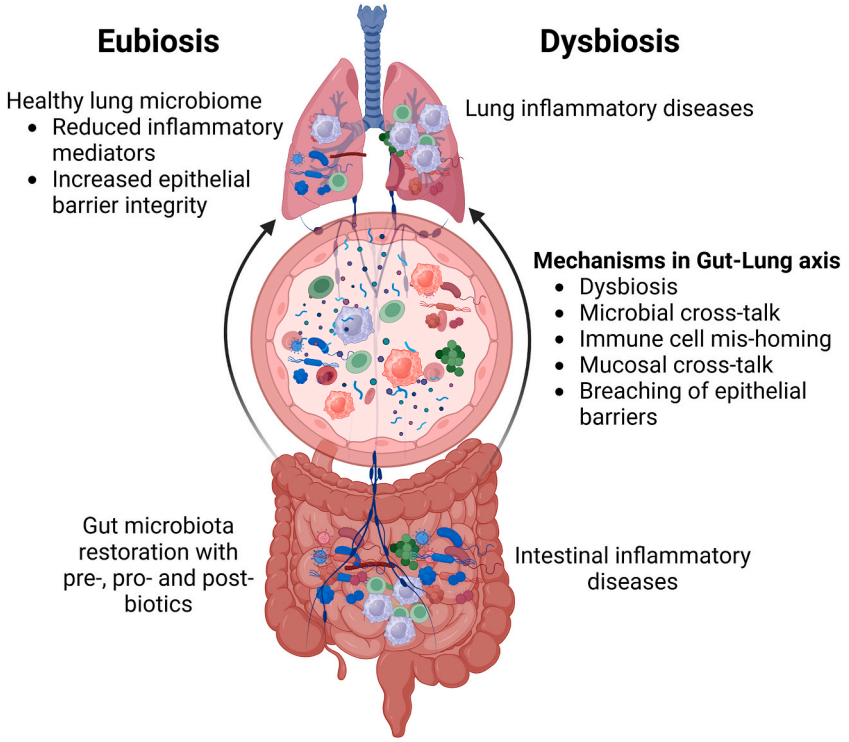

Fig. 3. Summary:
This review discusses potential mechanisms of GLA that contribute to lung inflammatory diseases in gut to lung direction. In addition, the possible impact of gut microbiota and their products like pre-, pro- and post-biotics for developing a treatment strategy for lung diseases are also discussed. Created with BioRender.com.

The mucosal arm of the adaptive immune system develops in Peyer's patches of small intestine via an endocytic machinery that can process antigens of gut lumen microbiota and provides humoral and cell-mediated immunity [67]. The molecular phylotypic analysis has revealed a complex and diverse collection of organisms in the intestinal mucosal membrane that could affect the functional state of other mucosal sites in health and diseases [68]. Based on multiple signals derived from the microbiota, gut and lung may have bidirectional interactions. However, the outcomes are still incompletely understood [69]. Exploring these possibilities is an exciting and vital task for future research.

4. Factors involved in GLA

The mechanisms within GLA are orchestrated by several factors like microbial and host cellular products, released effector mediators, etc., that further need to be investigated and explored for better understanding. In addition, several other factors that can influence GLA, like diet, nutrition, Vitamin D deficiency, and non-bacterial microbiota, still remain majorly unattended within GLA mechanisms. These factors influence the GLA axis via two major routes that connect the gut and lung, which are the lymphatic and circulatory systems (Fig. 1).

4.1. Metabolites

Microbiota-produced metabolites play a crucial role in regulating host homeostasis by promoting metabolic functions and regulating the immune system [70]. These metabolites can reach the lung by blood or lymphatics to modulate immune responses [71]. Mounting evidence showed the influence of gut microbiota on lung homeostasis and immunity, through metabolic by-products. Such products are derived from dietary fibers fermentation [51]. Metabolites derived from microbes can also be transferred within the lamina propria to the mesenteric lymph nodes by APC and eventually activate naïve B and T cells [71]. SCFAs, the most well-studied metabolites, are absorbed by gut mucosal tissue and enter the lung via systemic blood circulation. They bind to their receptors in the lungs and activate the immune cells [64]. SCFA, including butyrate and propionate, are the most abundant and beneficial metabolites of the intestinal flora, interact with immune cells via GPCRs or TLR to modulate epithelial and immune cells functions [20,72].

While SCFAs demonstrate considerable benefits, other microbiota-derived metabolites can impose negative effects on the host. For instance, the metabolite TMAO has been associated with COPD adverse outcomes, exacerbation, and survival. In COPD patients with shorter lifetimes, TMAO levels were observed to be significantly increased [73]. Further studies are required to better understand the

molecular and cellular mechanisms of gut metabolites mediated immune modulation in order to develop therapeutic strategies [70]. Further, there are specific metabolites of bacterial, host, and co-metabolites. However, no study has reported on their specific role in GLA.

4.2. Immune modulators

Immune modulators can be broadly of two different origins in GLA; the major one is microbes and their products, and secondly, the host cells released factors that might translocate between the gut and lungs. Microbes and their products that enter gut mucosa are recognized by APC and are transferred to mLN. These APCs later facilitate the priming of the T and B cells by expression of specific activation and homing receptors. These cells or their released immune effector molecules then migrate back to the gut mucosa or distant tissues like pulmonary epithelium and lymph nodes via lymph and systemic blood circulation [16,71,74]. The type of immune modulators released is majorly dependent on the nature of gut microbes present in eubiosis or dysbiosis and determines the type of immune response in local and distinct tissues, including the lungs. These immune modulators can migrate from the gut to the lungs to exert their long-reaching immune impact on lung function [74].

Many studies referred to the interaction between microbiota and tissue-resident DCs, APCs that affect immune responses [45]. DCs extend their dendrites through the gut epithelium to sample the bacterial antigens [75]. These sensitized DCs, using their Syk kinase-coupled signaling pathway, drive the differentiation of CD4 T cells into Th17-producing IL-17 and IL-22 cells [76], which are largely involved in lung diseases, including asthma, COPD, lung infections, and autoimmune diseases [77]. Additionally, IL-25 produced by inflamed gut epithelial cells can trigger the migration of ILCs from gut tissue to the lungs [78]. Moreover, the increased production of prostaglandin E2 levels in the inflamed gut due to infection with candida species can reach the lungs and drive alveolar macrophage differentiation to M2 phenotype that enhances the development of asthma [79]. Moreover, immune mediators such as IL-6, TNF-a, IFNγ, IL-10, TGF-β, CCR9, and CCR4 were shown to migrate from gut to lung via mLN [80].

In addition, bacterial products like flagellin, LPS, peptidoglycan, Lipoteichoic acid, phospholipids, etc., can enter the systemic circulation and elicit immune responses in distinct organs. However, these bacterial factors within GLA are largely unexplored and need consideration. The increase in inflammatory mediators, including CRP, complement factors, and transport proteins like haptoglobin, in addition to pro-inflammatory cytokines are detected in the serum of patients with gut disorders, have been observed to influence the immune responses in lung [81]. This suggests the communication of gut and lung via gut-derived immune mediators that transfer via systemic blood circulation and mesenteric system (Fig. 1).

4.3. Vitamin D deficiency

Vitamin D deficiency is reported in gut and lung diseases, such as IBD, asthma, COPD, tuberculosis, and COVID-19 [82–84]. However, the bridging mechanisms are not well understood. In a mouse model of DSS-induced colitis, intestinal dysbiosis with an abundance of *Proteobacteria* and a reduced *Firmicutes* phyla showed a reduced active Vitamin D and its VDR receptor [85]. In vivo IBD model and in cystic fibrosis patients, deficiency of VDR or Vitamin D resulted in dysbiosis linked to the abundance of *Bacteroides* in the gut and lung, respectively [86,87]. Interestingly, an improved outcome has been noted when Crohn's disease and COVID-19 patients are supplemented with Vitamin D [88,89]. These studies indicate how vitamin D deficiency could influence the balance of microbiota and reduce inflammation in the gut and lungs. However, the mechanisms involved and the role of Vitamin D in lung microbiota are yet to be explored [90]. Therefore, exploring further possibilities in this direction within GLA would open complementary applications for treating GLA associated diseases.

4.4. Non-bacterial microbiota

In addition to bacteria, the intestine has a community of commensal fungi whose role in the microbiota is unclear. Overusing antibiotics not only results in bacterial dysbiosis but also in fungal dysbiosis [91]. Gut fungal dysbiosis has been shown to enhance the severity of asthma and COPD with frequent exacerbations. An orally supplemented mixture of *Wallemia Sebi*, *Aspergillus Amsterdam* and *Epicoccum nigrum* fungal species reduced the exacerbations in fungal dysbiosis observed with allergic airway disease. Moreover, pro-asthmatic airborne respiratory fungus such as *Aspergillus*, *Penicillium* or *Alternaria* were shown to be present within the human intestinal mycobiota [92]. In vivo, gut expansion of *Wallemia mellicola* created intestinal mycobiota dysbiosis and enhanced the severity of asthma without any detectable fungus in the lungs. Despite these experimental studies of gut mycobiome dysbiosis, human studies are lacking and drawing attention for future research. Moreover, the emerging studies on virome and archaea have also shown an association with lung diseases, particularly in asthma exacerbations [93]. These studies highlight the need to understand the contribution of non-bacterial dysbiosis to lung inflammatory diseases.

5. Potential gut microbiota derived mediators to treat lung diseases

Therapeutic speculations in mechanisms other than dysbiosis within GLA are too early due to a lack of better understanding. However, a relatively well-studied gut dysbiosis can be targeted using gut microbiota and their products as potential candidates for developing future treatment of lung diseases. In a placebo-controlled clinical trial, lactobacillus species showed a beneficial effect on asthmatic school children [94]. In an in-vivo study, treatment with *Lactobacillus rhamnosus* GG showed promising results in *Pseudomonas aeruginosa* induced pneumonia by improving the barrier permeability and claudin expression [95], however, clinical trials are

not satisfactory. A combination of low abundant eleven fecal bacterial species isolated from healthy humans proved effective in treating tumors by enhancing antitumor CD8 T cells [96]. Gut microbiota derived metabolites are also an interesting candidate for the treatment of lung diseases (Fig. 3). Dietary fibers can modulate gut microbiota and vice versa. Increased abundance of *Firmicutes*, reduced abundance of *Bacteroides*, and an increase in the concentration of intestinal SCFAs are observed with a high-fiber diet. Microbiota metabolizes dietary fibers into SCFAs that can prevent inflammation and allergic reactions by modulating the functions of phagocytes and T regulatory cells and protecting intestinal epithelial barrier integrity [16]. In an in-vivo study, enhanced circulating SCFA levels attained by feeding mice with a high fiber diet showed a protective effect against lung inflammatory diseases [9]. In addition, a direct treatment with propionate ameliorated inflammatory lung disease by dampening the Th2 activity [9]. Similarly, in another study, butyrate was found to induce cytokines like IL-10 as well as preventing proinflammatory cytokine secretion [96]. Moreover, a clinical study highlighted the significance of SCFAs, particularly butyrate, acetate, and propionate, in protecting against asthma development [9].

In addition to SCFA, indole-3-acetate produced from gut microbiota is proven to regulate Treg generation and participate in the protection against asthma pathogenesis and COPD exacerbation [97]. Furthermore, metabolites of gut microbiota can drive the hematopoietic pattern of DC and attenuate Th2 immunity in allergic asthma models [8]. In addition to SCFA, niacin, tryptophan, polyamines, urolithin, pyruvate, and lactate can modulate inflammatory responses in the lungs via entering systemic circulation [98].

An in-vivo study in allergic airway inflammation demonstrated that dietary fibers significantly reduced inflammatory responses by effectively balancing the type 1 and type 2 immune reactions [97]. Moreover, studies with pre-biotics, probiotics, post-biotics, and oral supplementation of crude bacterial lysates to treat allergic lung diseases are underway and awaiting clinical validation [98]. Even though the precise mechanisms are not clearly understood, these studies provide significant evidence that in the future, gut microbiota and their products can be developed to treat various lung diseases.

6. Future perspectives

The alteration in gut and lung microbiota is one of the major spokes of the wheel regulated by GLA. Yet, considering the complexity of understanding GLA, other spokes in the wheel remain less explored. This implies a complex multi-dimensional mechanism involved in GLA (Fig. 2). However, extensive studies on microbiota have outstripped the other mechanisms. The complex host microbe interactions at early stages of modern life result in detrimental immunological responses that lead to increased incidence of diseases like allergies, obesity, asthma and other autoimmune disorders [99]. Therefore, understanding the host immune-microbe relationships and their evolutionary perspective would be beneficial to overcome the rise of modern diseases.

Currently, the dysbiosis mechanism within GLA is investigated on manipulated gut microbiota mainly by antibiotics cocktail. There is no well-defined dysbiosis model that closely resembles the dysbiosis observed in human diseases. The use of gnotobiotic mice models still need to be improved to at least mimic the dysbiosis observed in human diseases. Therefore, there is a rising demand for well-defined animal models to study GLA mechanisms. In addition, the current therapeutic treatments like prebiotics, probiotics, and fecal microbiota transplantations that are intended to shape the microbiota and to improve health, have shown limited success due to lack of achieving the desired microbial composition and their stability over time [100]. This limitation is majorly due to consistent exposure of gut bacteria to other microbial species, human physiology, diet, medications, etc. Therefore, tailoring microbiota composition during disease, considering the influences of various factors especially antibiotics, adds crucial understanding and are essential to derive novel therapeutic approaches [101].

Evolving approaches like synthetic microbiome design might overcome these disadvantages [102], however detailed evaluations are demanding. Recently CRISPR-Cas based gene editing technology on gut microbes propose a promising tool for microbiota manipulation [103]. Additionally, commensal bacterial species were proposed to be the mucosal vaccine vectors [104,105] and purified encapsulated microbiota of a "healthy donors" are already considered [106], though further validation for translation is required for these studies. Although the DNA content from fecal samples can determine the ecological and evolutionary changes mediated by different factors on microbes, the real time adaptation to evolving environmental changes at their gene expression level is not reflected in DNA [107]. In a recent study, RNA-based profiling using CRISPR-Cas technology, introduced as a "Record-seq system," could record real-time microbial responses in vivo based on their responsive gene expressions [108]. Suggesting a promising cutting-edge invasive technique that can reveal further in-depth knowledge about how gut microbiota could affect host immunity.

In the future, microbial diversity studies within the GLA are anticipated to undergo remarkable advancements driven by cutting-edge technologies and refined methodologies. For example, integrating multi-omics techniques such as genomics, transcriptomics, proteomics, and metabolomics to comprehensively profile the microbial composition and its functional dynamics within the GLA may provide deeper insights into the intricate interplay between microbial communities and their impact on health and disease. Higher-resolution mapping of microbiota in gut and lungs facilitates the identification of rare, unexplored microbial species, their interactions, functional roles, and their influence on local and systemic health. Furthermore, innovations in imaging technologies might enable real-time visualization and tracking of microbial dynamics within the gut and lung tissues, which could provide insights into spatial organization, interactions with host cells, and the impact of microbial localization on disease pathogenesis.

In addition, futuristic studies may pinpoint specific microbial signatures or metabolites serving as diagnostic or prognostic biomarkers for various lung and gut-related disorders, enabling early detection and personalized treatment strategies. Moreover, personalized microbiota-based therapies targeting the GLA can be developed to treat specific disease conditions [44]. Finally, it is also very important to consider the use of antibiotics and other microbiota influencing factors while choosing the cohort for the microbiota studies in patients, which would help to better understand the specific association of dysbiosis and disease and facilitate appropriate experimental models.

GLA involves major organ systems, microbiota, and conducting mediators like metabolites and microbial products, as well as bridging systems like systemic circulation, mucosal compartment, and lymphatic system (Fig. 1). These mechanisms involved within GLA are not yet satisfactorily understood. Furthermore, there are still several reported mechanisms in GLA that possess significant gaps in knowledge. For example, breaching of the intestinal barrier leads to the release of various mediators that are usually impermeable into the systemic circulation. LPS, a predominant bacterial product, Zonulin, LBP and IFABP are gut specific leakage markers [30]. However, their specific role in inflammatory responses in distinct organs after leaking into the systemic circulation is not well understood. In addition, a wide range of host cellular components like apoptotic cells and their contents, food contents, functional immune cells, macrovesicles of both microbiota and host cellular components, etc., might affect the systemic organs, including lungs. However, this mechanism of GLA is in its nascent stage and must be largely explored. In addition, it can be speculated that a transient recolonization of lung microbiome by constant seeding from oral and gut microbiome. Tissue mis-homing lymphocytes are studied, but the mononuclear phagocytes, including macrophages mis-homing, are also interesting to study, as they have key role in immune response in both gut and lungs.

Therefore, there is still a huge gap of knowledge in the currently explored mechanisms and further possibility of identifying novel mechanisms in GLA. In addition, the potential microbes or their derived mediators with promising immunomodulatory effects are intriguing to further investigate, validate, and develop into treatable therapeutics (Fig. 3).

In summary, the connection between gut microbiota and respiratory tract can influence the development of respiratory diseases. Specific gut microbial species can play a crucial role in this process by modulation of systemic immune responses (Fig. 3). Further research will assist in presenting the complete layout of GLA and to identify novel and effective therapeutics. Understanding micro-environmental changes, complex host-microbe crosstalk, and exploring additional mechanisms within GLA could aid in preventing and treating a spectrum of human diseases. However, further developments in technologies and strategies are yet to be shaped up to achieve tailored treatment strategies in GLA.

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Mariam Wed Eladham: Conceptualization, Writing - review & editing, Writing - original draft. **Balachandar Selvakumar:** Writing - review & editing, Writing - original draft, Conceptualization. **Narjes Saheb Sharif-Askari:** Writing - review & editing, Project administration. **Fatemeh Saheb Sharif-Askari:** Writing - review & editing. **Saleh Mohamed Ibrahim:** Writing - review & editing. **Rabih Halwani:** Writing - review & editing, Conceptualization.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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