Role and targeting of the AGC kinase family in pulmonary fibrosis (Review)

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Abstract. Pulmonary fibrosis (PF) is a progressive and irreversible pulmonary disease with a high mortality rate and limited treatment options. The cAMP-dependent protein kinase A, cGMP-dependent protein kinase G and phospholipid-dependent protein kinase C, collectively known as AGC kinases, are evolutionarily conserved protein kinases that are widely distributed among eukaryotes. AGC kinases serve a crucial role in a variety of cellular functions and pathological processes, including cancer, diabetes, inflammation and viral infections, where they have been implicated the pathogenesis of PF. The present review summarizes the evidence for the involvement of specific AGC kinases in the pathogenesis of PF, and provides a theoretical basis for the development of targeted AGC kinase small molecule inhibitors or targeted drugs, offering more effective treatment options and strategies for patients with PF.

Contents

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1. Introduction

Pulmonary fibrosis (PF) is a respiratory disease that is characterized by scarring in the lungs and subsequent breathing difficulties (1). There are various types of PF including asbestosis, hypersensitivity pneumonitis and idiopathic pulmonary fibrosis (IPF), with IPF being one of the most common and severe forms (2). IPF is an interstitial lung disease of unknown etiology that is chronic, progressive, and irreversible (3). It is distinguished by epithelial cell activation and injury, fibroblast proliferation and differentiation, extracellular matrix (ECM) deposition, irreversible destruction of the alveolar structure and respiratory insufficiency (Fig. 1) (4). IPF primarily occurs among the middle-aged and elderly populations, where it is limited to the lungs (5,6). The treatment of IPF typically involves a combination of medications, pulmonary rehabilitation and, in some cases, lung transplantation (7). IPF is a chronic and progressive disease, and existing treatments, including antifibrotic medications, aim to slow down the progression rather than cure the condition (7). However, the antifibrotic medications may have side effects, and not all individuals with IPF can tolerate these drugs (8). The causes and pathogenesis of IPF remain unclear and the effects conferred by currently available therapeutic methods are limited (9,10). The survival rate after IPF diagnosis is typically only 2-5 years, where the prognosis of which is even worse compared with that of several types of cancer including uterine, breast and colon cancer (5).

Epithelial cell dysfunction and senescence has emerged as a central component of the IPF pathophysiology (11,12). The alveolar epithelium consists of alveolar epithelial type 1 (AT1) and alveolar epithelial type 2 cells (AT2). The alveolar surface is mostly covered by AT1 cells, whose thin squamous morphology and intimate contact with the adjacent capillary plexus permit efficient gas exchange (13). Although loss of AT1 cells is considered to be a cardinal feature of the IPF histology, accumulating evidence has revealed AT2 cells to also serve an important role in IPF (14,15). This is in part due to its function in alveolar niche homeostasis through the production of pulmonary surfactants and as a progenitor cell for both self-renewal and transdifferentiation into AT1 cells if needed (13). In particular, single-cell RNA sequencing has previously identified a cell population expressing both AT2 (SOX4, SOX9, COL1A1 and FN1) and AT1 (COL1A1, FN1

and SCGB1A1) markers in IPF lungs, suggesting a subset of epithelial cells transitioning between the AT1 and AT2 phenotype (16).

In eukaryotic cells, a substantial proportion of signal transduction activity is facilitated by protein kinases, which is achieved through phosphorylation of target substrates (17,18). This process serves pivotal roles in the regulation of a wide variety of cellular functions, including proliferation, differentiation, metabolism and programmed cell death (19,20). In humans, protein kinases can be categorized into nine groups based on the evolutionary relationships of their catalytic domains (17,18,21). One such group is one consisting of cAMP-dependent protein kinase A, cGMP-dependent protein kinase G and phospholipid-dependent protein kinase C (AGC), collectively known as AGC kinases (21).

AGC kinases form a highly conserved group of kinases that are ubiquitously distributed across different orders of eukaryotic organisms (21). Members of the AGC kinases group have been reported to regulate different cellular processes, where their targets may have therapeutic implications for various human diseases, including but not limited to cancer, diabetes, obesity, immunological disorders, inflammation, neurological disorders, viral infections and muscular dystrophies (21-24). Therefore, targeting members of the AGC kinases may prove to be a potential method of treatment for PF.

The present review summarizes the reported significant effects of AGC kinases on the pathological procession of PF, before discussing their potential as molecular targets for the treatment of this disease. In addition, focus will be placed on the role of different families of AGC kinases in PF.

2. AGC kinases

The AGC kinase group is comprised of 63 serine/threonine protein kinases that are evolutionarily related. This group includes the protein kinase G and protein kinase C families of kinases, Akt/protein kinase B, Aurora kinases, ribosomal protein S6 kinases and the phosphoinositide-dependent kinases (17,22,24). In addition, the majority of AGC kinases each have multiple isoforms and splice variants, increasing the complexity of this family of kinases (25).

AGC kinases typically exhibit a conserved fold that is characterized by a catalytic domain consisting of a small N-terminal lobe and a large C-terminal lobe (21). The predominant secondary structure of the large C-terminal lobe is α-helical, whereas the small N-terminal lobe is comprised of a single helix (α-C) and a 5-stranded β-sheet (22). An ATP-binding site is located between the two lobes (21,26), where the bound ATP serves as the phosphate donor during phosphorylation (25). The activation loop originating from an Aspartate-Phenylalanine-Glycine motif is also situated amidst the large and the small lobe (21). In addition. the majority of AGC kinases contain a conserved catalytic core with a C-terminal hydrophobic motif (HM) sequence (21). This HM sequence is known to bind to a co-evolved hydrophobic site in the small lobe of the catalytic core, which is referred to as the 3-phosphoinositide-dependent protein kinase-1-interacting fragment (PIF)-pocket (Fig. 2) (27,28). According to a previous study, the PIF-pocket is proposed to be a central and common on-off switch in the AGC kinases (22). Apart from the conserved catalytic domain, the AGC kinases group contains various functional domains. The AGC kinases can be classified into 14 families and 21 subfamilies based on homology outside the catalytic domain (17,25).

AGC kinases serve a crucial role in regulating a multitude of cellular functions, including but not limited to cell cycle progression, cellular differentiation, cell survival and apoptosis (21). In both animals and yeast, AGC kinases have been documented to serve as key mediators that are capable of transducing signaling cascades initiated by secondary messengers through substrate phosphorylation (29,30). In plants, AGC kinases have been demonstrated to serve indispensable roles in diverse cellular and developmental processes including growth, immunity, cell death and defense responses (31-33).

3. AGC kinases in PF

Pyruvate dehydrogenase kinase 1 (PDK1). PDK1 is a serine/threonine kinase that was initially discovered in previous studies on insulin-activated Akt signaling in the presence of phosphatidylinositol-3,4,5-triphosphate (PIP3) (34-36). PDK1 is a conserved protein kinase that is expressed in eukaryotes (37). PDK1 is mainly located in the cytoplasm, but under certain conditions it can be induced to translocate into the nucleus (38). PDK1 was originally considered to be a regulator of glycolysis in the cytoplasm (39-41). Subsequent studies have revealed that PDK1 can regulate a number of physiological processes, such as blood vessel formation, metabolism and development (42,43). In addition, the pathological processes of Alzheimer's disease (44), diabetes (45) and cancer (46,47) have all been reported to be caused at least in part by PDK1 activity (39).

Previous studies have revealed that PDK1 serves a role in the regulation of PF. The *PDK1* gene was previously shown to be a direct target gene of hypoxia-inducible factor-1 (HIF-1) (48,49). Glycolytic metabolism, which is mediated by PDK-1, serves a crucial role in the progression of PF (50-52). Goodwin *et al* (53) previously reported that hypoxia markedly enhanced transforming growth factor-β (TGF-β)-induced myofibroblast differentiation in fibrotic lesions via HIF-1α. However, overexpression of PDK1 was sufficient in activating glycolysis and potentiate myofibroblast differentiation regardless of the existence of HIF-1α. Additionally, bleomycin (BLM)-induced PF can be significantly attenuated by using dichloroacetate, a potent PDK inhibitor (54,55). Yang *et al* (56) revealed that PDK1 knockdown can attenuate PF by inhibiting the NF-κB/p65 signaling pathway. Mannan-binding lectin (MBL) can interact with and ubiquitinate PDK1 to inhibit epithelial-mesenchymal transition (EMT) in PF by attenuating store-operated calcium entry (SOCE) signaling (57). However, the specific mechanism of PDK1 in IPF remains unclear.

Rho-associated coiled-coil-forming protein kinase (ROCK). ROCK is a downstream target protein of Rho and has been implicated in a wide range of cell functions, such as proliferation, migration, adhesion, apoptosis and differentiation (58-60). ROCK has two isoforms, namely ROCK-I and ROCK-II, which regulate cytoskeletal reorganization by phosphorylating myosin phosphatase to increase the phosphorylation level of myosin light chain (61). In addition to brain and muscle tissues, the

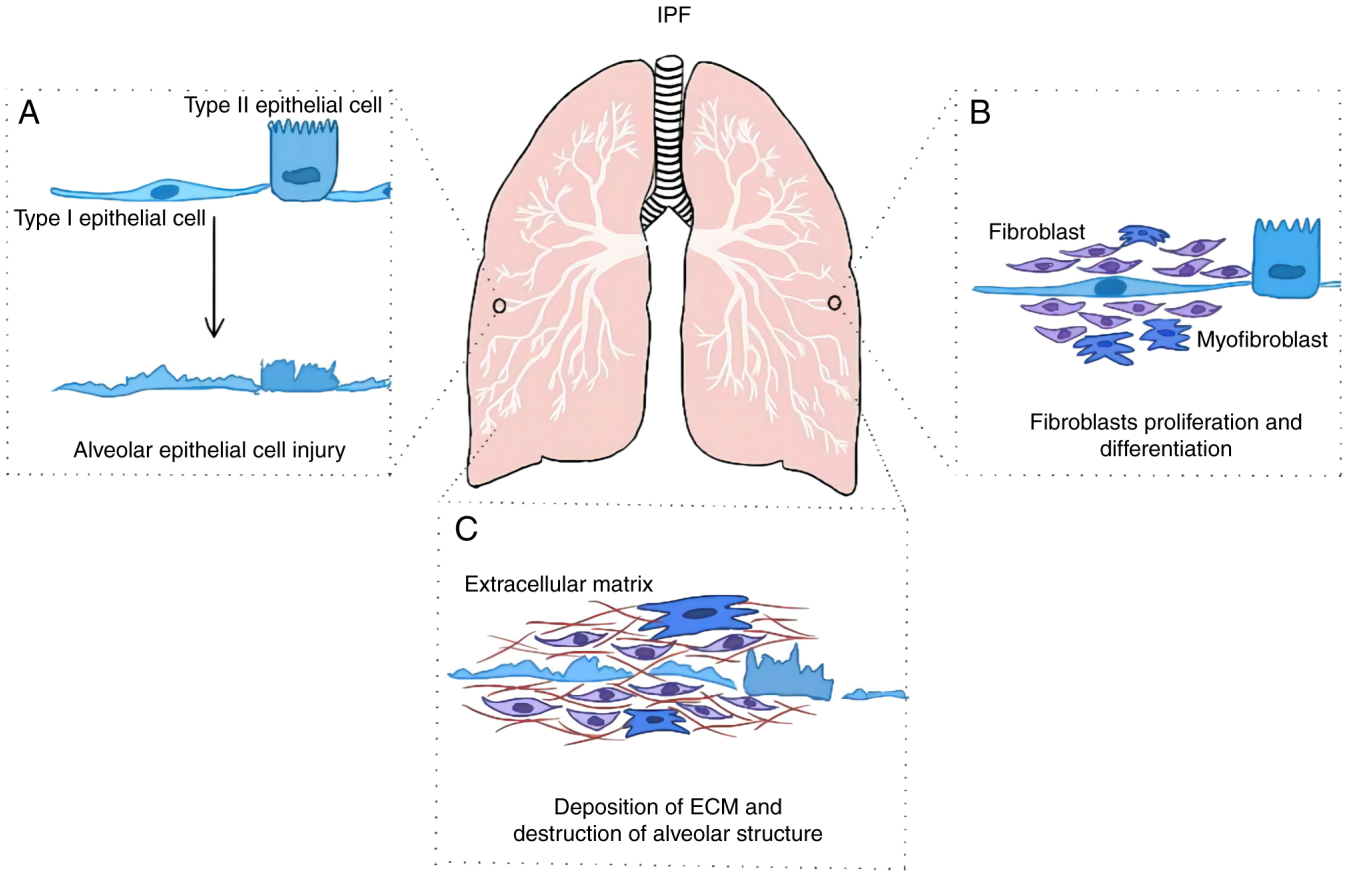

Figure 1. Characteristic manifestations of IPF. (A) Injury of alveolar epithelial cells. (B) Fibroblasts are activated, and proliferate and differentiate into myofibroblasts. (C) Deposition of ECM and irreversible destruction of alveolar structure. ECM, extracellular matrix; IPF, idiopathic pulmonary fibrosis.

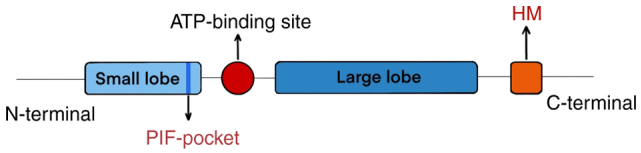

Figure 2. Conserved catalytic domain and specific features of most AGC kinases. HM, hydrophobic motif; PIF, PDK-interacting fragment.

expression of ROCK-I is widespread, whilst ROCK-II expression tends to be limited to the brain and muscle, especially in the smooth muscle (62). However, the functional differences between ROCK-I and ROCK-II remain unclear (59).

ROCK-II mRNA expression has been previously revealed to be increased in a murine model of lung fibrosis induced by BLM (59). The Rho/ROCK signaling pathway can be inhibited to prevent fibrosis by decreasing the levels of inflammatory cells (macrophages, neutrophils and lymphocytes) and cytokine (TGF-β1, connective tissue growth factor (CTGF) and plasminogen activator inhibitor (PAI)-1 levels (59,63). Shimizu *et al* (64) demonstrated that the expression and activity of ROCK-II was increased in several types of lung cells in patients with IPF, including bronchial epithelial cells, airway smooth muscle cells, vascular smooth muscle cells and fibroblasts (64). The RhoA/ROCK-I signaling pathway has also been demonstrated to promote the migration of lung fibroblasts and synthesis of collagen by myofibroblasts, both of which can exacerbate PF (65). Rho/ROCK inhibitors, such as Fasudil, have been shown to attenuate BLM-induced lung fibrosis by suppressing the recruitment of inflammatory cells such as neutrophils and reducing the production of TGF-β1, CTGF, α-smooth muscle actin (α-SMA) and PAI-1 in BLM-induced mouse lungs (63). Recently, compound 9b, a novel selective inhibitor of ROCK-II, has demonstrated marked anti-PF effects by suppressing the expression of α-SMA and collagen I in BLM-induced IPF mice model (66). Notably, dual pharmacological inhibition of ROCK-I and -II was found to counteract TGF-β-induced PF in an organoid assay, which included freshly isolated $EpCAM^+$ mouse lung cells co-cultured with human lung fibroblasts (67). However, it should be emphasized that although the main role of ROCK in PF has been established, the precise regulatory mechanisms mediated by Rho/ROCK signaling require further clarification.

Large tumor suppressor 1/2 (LATS1/2). LATS1 and 2 are important components of the kinase cascades in the Hippo signal pathway in mammalian cells (68-70). A number of studies have demonstrated that LATS2 and its downstream signaling pathway have a vital impact on the proliferation, migration, differentiation and immunomodulation of mesenchymal stem cells (MSCs) (71,72). Dong and Li (71) previously revealed that LATS2-underexpressing bone marrow-derived MSCs (transfected with LATS2-interfering lentivirus vector) can repair the alveolar epithelium damaged by lipopolysaccharide in a mouse model of acute lung injury (ALI).

Table I. Mechanisms of AGC kinases in IPF.

First author(s), year	AGC kinases	Isoforms	Mechanisms	(Refs.)
Yang *et al*, 2021	PDK1		NF-κB/p65 pathway	(56)
Goodwin *et al*, 2018			Hypoxia-inducible factor-1a/3-phosphoinositide-dependent protein kinase-1-mediated glycolytic reprogramming	(53)
Jiang *et al*, 2012	ROCK		Rho/ROCK signaling pathway	(63)
Shimizu *et al*, 2014			Rho/ROCK signaling pathway	(64)
Dong and Li, 2019	Large tumor suppressor		Hippo signaling pathway	(71)
Wang *et al*, 2022	AKT		PI3K/AKT signaling pathway	(81)
Nie *et al*, 2019		AKT1	Modulating IL-13 expression in macrophages	(89)
Nie *et al*, 2017		AKT2	AKT2/Forkhead box O3a signaling pathway	(87)
Song *et al*, 2013	PKC		Protease-activated receptor-1/PKC/ERK pathways	(99)
Wang *et al*, 2020		PKC-δ	NF-κB/A20 signaling	(97)
Kim *et al*, 2020	p90 ribosomal S6 kinase		TGF-β1/smad3 signaling	(112)
Madala *et al*, 2016	S6K		S6K signaling	(109)

ROCK, Rho-associated coiled-coil-forming protein kinase; PKC, protein kinase C; S6K, p70 ribosomal S6 kinase.

Lung injury has been reported to trigger the fibrotic process (73). Previous studies have demonstrated that MSCs can reduce collagen fiber deposition and alleviate early-stage PF in mice with ALI (74,75). Dong and Li (71) revealed that this effect is amplified in bone marrow-derived mesenchymal stem cells with low expression levels of LATS2 (due to transfection with LATS2-interfering lentivirus vector). However, further studies are required to investigate the specific mechanisms of LATS in PF.

AKT. AKT, also known as PKB, has three isoforms in mammals, namely AKT1, AKT2 and AKT3. It can regulate numerous cellular processes, such as cell survival, proliferation, differentiation and intermediary metabolism (76-81). Specifically, it has been previously revealed that both AKT1 and AKT2 can modulate the migration and invasion of cancer cells. AKT1 can stimulate prostate cancer cell motility, whereas AKT2 inhibits motility and migration in breast cancer and ovarian cancer cells (82,83). Since AKT3 is primarily expressed in the brain tissue and has only been reported to serve a role in neuronal development (84), research on the role of AKT in PF has mainly concentrated on AKT1 and AKT2 (81).

Previous studies have demonstrated that TGF-β1 can regulate the activation of AKT in myofibroblasts and that inhibiting the function of AKT can alleviate TGF-β1-induced PF (85,86). It has been found that AKT1 and AKT2 can mediate significant roles in regulating the function of alveolar macrophages in IPF (87,88). Specifically, AKT1 can promote macrophage mitochondrial reactive oxygen species (ROS) and mitophagy, as well as increase TGF-β1 expression, resulting in the development of fibrosis (88). In addition, the pro-fibrotic cytokine IL-13, can be upregulated by AKT1 in macrophages in PF (89). Nie *et al* (87) revealed that AKT2 phosphorylation is upregulated in the tissues of patients with PF. AKT2 deficiency protects against BLM-induced PF and inflammation (87). In conclusion, AKT may serve an important role in the development of IPF, suggesting that it can be a potential molecular target for its therapeutic intervention.

Protein kinase C (PKC). PKC is a type of phospholipid-dependent serine/threonine kinase for which 12 isozymes have been identified (90). PKCs are classified into three subfamilies, based on structural and activation characteristics: conventional or classic PKCs (cPKCs: α, βI, βII and γ), novel or non-classic PKCs (nPKCs: δ, ε, η and θ), and atypical PKCs (aPKC: ζ, ι and λ) (91). PKC isozymes participate in signal transduction by either directly or indirectly activating or inactivating target proteins through phosphorylation (92). PKC has been documented to mediate various cellular processes, including proliferation, migration, apoptosis, adhesion and differentiation (93-96).

The role of PKC-δ in IPF remains controversial, despite its reported involvement in the progression of PF (97). PKC-δ has been reported to inhibit NF-κB signaling by enhancing the activity and stability of A20, which is an endogenous negative regulator of NF-κB (97). In addition, the deficiency of PKC-δ has been reported to increase the expression of proinflammatory cytokines to exacerbate inflammation and PF induced by BLM (97), suggesting that PKC-δ may serve a protective role in IPF. Previous studies have demonstrated that the inhibitor of PKC-δ rottlerin can downregulate the expression of type I and type III collagen gene, and suppress the type I collagen production in cultured dermal fibroblasts derived from patients with systemic sclerosis (98). Additionally, Song *et al* (99) revealed that thrombin induces EMT and collagen I secretion by activating protease-activated receptor (PAR-1), PKC (α/β, δ and ε) and ERK1/2 in A549 cells. A549 is an adenocarcinomic human alveolar basal epithelial cell line, that is widely used as a model of alveolar epithelial-like behavior in IPF study (100). Therefore, targeting PAR-1 or specific PKC isoforms (α, β, δ and ε) may halt the fibrotic process in human IPF by preventing

thrombin-induced EMT. Results reported by the aforementioned studies suggest that PKC-δ may promote IPF. However, the possible link between PKC and IPF require further studies.

Ribosome protein S6 kinase (RPS6K). RPS6Ks can be divided into two subfamilies, p90 ribosomal S6 kinase (RSK) and p70 ribosomal S6 kinase (p70S6K). The p70S6K subfamily has two members of the p70S6K (S6K1 and S6K2), whilst the RSK subfamily has four members (RSK1-4) (101,102). RSK is activated by the ERK signaling pathway. p70S6K is activated through a complex network of signaling molecules, and mTOR serine/threonine kinase is necessary for its full activation (103). These kinases are involved in various signaling pathways and can regulate multiple cellular processes, such as cell proliferation, differentiation, growth, transformation and apoptosis (104-108).

Madala *et al* (109) previously revealed an increase in S6 phosphorylation in the airway and alveolar epithelium and in the mesenchyme of advanced subpleural fibrotic regions of TGF-α-induced PF mice. The specific targeted inhibition of the S6K with the small molecule inhibitor LY-2584702 attenuates TGF-α and platelet-derived growth factor-β-induced proliferation of pulmonary fibroblasts (109). In another study, Han *et al* (110) revealed that rapamycin, an mTOR inhibitor, can attenuate BLM-induced PF and EMT by decreasing S6K- and TGF-β1-induced Smad2/3 phosphorylation. In addition, S6K was also found to enhance proliferation and fibroblast-to-myofibroblast transition in human embryonic lung fibroblasts (111). Kim *et al* (112) revealed that inhibition of RSK suppressed TGF-β1-induced ECM accumulation and EMT in lung epithelial cells and fibroblasts. These findings suggest that RPS6K may also have a role in the development of IPF. However, the specific mechanism underlying IPF progression requires further elucidation.

4. Conclusions

The AGC kinases form a widely conserved family of protein kinases that have been implicated in various pathologies, including cancer, metabolic disorders, cardiovascular disease, immunological disorders and neurological disorders. Accumulating evidence has shown that AGC kinases can exert important roles in IPF through distinct mechanistic pathways (Table I). Several inhibitors of AGC kinases such as RSK-inhibitor peptide (112), dichloroacetate (53), BX795 and BX912 (113) have been found to attenuate PF. However, additional research is required to fully comprehend the contribution of AGC kinases towards IPF. Identification of AGC kinases with the potential to serve as therapeutic targets of IPF may facilitate the discovery of novel drugs for IPF treatment.

At present, to the best of our knowledge, only a small number of AGC kinases have been found to be involved in regulating the pathological process of PF. To further explore the key role of AGC kinases comprehensively in the pathogenesis of PF, more functions of AGC kinases in PF need to be explored. As single-cell sequencing and spatial proteomics technology advance, the distinct functions mediated by AGC kinase in various cell types during different stages of PF will be elucidated (114-116). In addition, continuous advancements in organoid technology are expected to facilitate studies into the microenvironment of lung tissues in the pathological process of PF in the future, where the role of AGC kinases should also be investigated. Understanding the specific substrates and associated signaling pathways by AGC kinases in the regulation of PF will also be a focus of future attention. Based on the results and findings of existing studies, it would be of benefit to screen small molecule inhibitors or targeted drugs for AGC kinase and conduct relevant clinical trials, providing more effective treatment options and strategies for patients with IPF.

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Availability of data and materials

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Authors' contribution

YL conceived the study and revised the manuscript. CM prepared the figures and wrote the manuscript. TC, XH and CX participated in the writing of the manuscript. SC reviewed the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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