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Mechanisms of endothelial dysfunction and tubulointerstitial fibrosis in radiation-induced kidney injury

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ABSTRACT

Radiation-induced kidney injury embodies a convergent process in which endothelial dysfunction initiates and perpetuates tubulointerstitial fibrosis through oxidative stress, inflammatory cell recruitment, microvascular collapse, and disturbed cellular plasticity. The sequence begins with endothelial apoptosis and barrier breakdown, evolves through chronic hypoxia and fibrosis-promoting signaling, and culminates in irreversible architectural remodeling that compromises renal filtration and oxygen delivery. The hallmark mechanisms include reactive oxygen species-mediated eNOS uncoupling, sustained nuclear factor-kappa B (NF-κB) and transforming growth factor-beta (TGF-β) activation, endothelial-to-mesenchymal (EndMT) and epithelial-to-mesenchymal (EMT) transitions, microvascular rarefaction, and senescent secretory phenotypes – all contributing to a feed-forward loop that defines radiation nephropathy as a progressive, self-amplifying vascular-fibrotic syndrome.

Keywords: Endothelial dysfunction, Radiation nephropathy, Tubulointerstitial fibrosis, Oxidative stress, Ionizing radiation, Chronic kidney disease, Reactive oxygen species

Review

Implication for health policy/practice/research/medical education:

Radiation-induced kidney injury, known as radiation nephropathy, is a progressive vascular-fibrotic syndrome. It starts with endothelial dysfunction, leading to tubulointerstitial fibrosis. This process involves a sequence of events beginning with endothelial cell death and barrier disruption. The injury progresses through chronic hypoxia and signaling that promotes fibrosis, eventually resulting in irreversible structural changes in the kidney. These changes impair the organ's ability to filter blood and deliver oxygen effectively. Key mechanisms driving this injury include oxidative stress from reactive oxygen species-mediated eNOS uncoupling, persistent activation of inflammatory and fibrotic pathways, endothelial-to-mesenchymal (EndMT) and epithelial-to-mesenchymal (EMT) transitions, and the loss of small blood vessels. These factors create a self-amplifying cycle, worsening the condition over time.

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Introduction

Radiation nephropathy is a form of kidney injury resulting from exposure to ionizing radiation, which is commonly employed in radiotherapy. The use and intensity of radiotherapy are often limited by potential damage to normal tissues, including the kidneys (1). Histopathologic examination of radiation nephropathy reveals damage to vascular, glomerular, and tubulointerstitial structures. The

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precise molecular and cellular mechanisms underpinning radiation nephropathy are not yet fully understood (1). Ionizing radiation instigates double-stranded DNA breaks, leading to cell death by apoptosis and necrosis in renal endothelial, tubular, and glomerular cells (2). In addition, oxidative stress and inflammation have been suggested as pathogenic mechanisms during the latent phase of radiation nephropathy (1). Similarly, cellular senescence, activation of the renin-angiotensin-aldosterone system, and vascular dysfunction may also contribute to this disease. Epidemiological data indicated that high doses of ionizing radiation could lead to cardiovascular disease over time too (1). We therefore aimed to consider mechanisms of endothelial dysfunction and tubulointerstitial fibrosis in radiation-induced kidney injury.

Method of the search

To identify relevant literature for this narrative review, we conducted a comprehensive search across multiple databases, including PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar. The search strategy incorporated keywords and related terms such as 'endothelial dysfunction', 'radiation nephropathy', 'tubulointerstitial fibrosis', 'oxidative stress', 'ionizing radiation', 'chronic kidney disease', and 'reactive oxygen species'.

Endothelial dysfunction following ionizing radiation

The endothelium, a single layer of cells lining various organs and cavities such as the heart and blood vessels, plays a crucial role in vascular homeostasis and is involved in pathophysiological processes like thrombosis, inflammation, and hypertension (3). Ionizing radiation can damage the endothelium, leading to endothelial dysfunction. This endothelial damage is a central feature preceding the development of cardiovascular diseases. Radiation can impair both endothelium-dependent and endothelium-independent vasomotor responses (4). Specifically, studies have shown that increases in renal blood flow induced by endothelium-dependent vasodilators are significantly impaired in irradiated kidneys (5). This condition suggests that renal irradiation causes endothelial dysfunction even before the onset of hypertension, while sparing vascular smooth muscle cells (5,6). Then blocking nitric oxide synthesis (NOS) can mimic the blunted responsiveness seen in irradiated rats, indicating a role for NO in radiation-induced endothelial dysfunction (7). Meanwhile, radiation exposure causes the release of oxygen radicals and proteases, leading to a loss of endothelial barrier function (8). The molecular mechanisms of radiation-induced endothelial dysfunction consisted of an impaired energy metabolism, perturbation of the insulin/IGF-PI3K-Akt signaling pathway, premature endothelial senescence, increased oxidative stress, decreased NO availability, and enhanced inflammation, which are strongly implicated as main causes of long-term radiation-induced vascular dysfunction (9). Likewise, basic fibroblast growth factor has been shown to ameliorate radiation-induced endothelial dysfunction in the urinary bladder and preserve bladder histology in early and delayed phases of radiation-induced bladder injury (10). Radiation can cause injury to endothelial cells, and thrombomodulin may serve as a marker for this injury. An increase in thrombomodulin release and activity on the cell surface is observed 24 hours after irradiation, in a dose-dependent manner (11). However, the capacity of cells to produce and release thrombomodulin decreases two to six days post-exposure (11). Given that, the renal microvasculature, particularly the peritubular capillaries and glomerular endothelial cells, is exquisitely sensitive to radiation due to its high proliferative turnover and metabolic activity (1). Upon exposure to ionizing radiation, endothelial cells undergo acute DNA damage, primarily in the form of double-strand breaks, which activate the DNA damage response pathways involving ataxia-telangiectasia mutated (ATM) and ATM- and Rad3-related kinases (12). Persistent DNA damage response signaling, especially when repair mechanisms are overwhelmed or defective, can lead to cellular senescence or apoptosis (13). In the kidney, endothelial cell loss disrupts the integrity of the microvascular network, leading to capillary rarefaction as a hallmark of chronic radiation nephropathy. This structural loss reduces perfusion and oxygen delivery to tubular epithelial cells, creating a state of chronic hypoxia that further exacerbates tissue injury (14). Beyond direct cytotoxicity, radiation induces a pro-inflammatory and pro-thrombotic endothelial phenotype (15). Ionizing radiation upregulates the expression of adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin on endothelial surfaces, promoting the adhesion and transmigration of leukocytes, particularly monocytes and T lymphocytes, into the renal interstitium. This inflammatory infiltration contributes to ongoing tissue damage through the release of reactive oxygen species (ROS), proteases, and pro-fibrotic cytokines (8). Concurrently, radiation impairs the production and bioavailability of NO, a critical vasodilator and anti-inflammatory mediator synthesized by endothelial NOS (eNOS) (16). The reduction in NO is multifactorial: radiation directly oxidizes tetrahydrobiopterin (BH4), an essential eNOS cofactor, leading to eNOS uncoupling; uncoupled eNOS generates superoxide rather than NO, further amplifying oxidative stress (17). Additionally, radiation increases the expression of asymmetric dimethylarginine, an endogenous inhibitor of eNOS, thereby suppressing NO synthesis (18). The resultant vasoconstriction, platelet aggregation, and leukocyte adhesion collectively foster a microenvironment conducive to thrombosis and ischemia (19). Oxidative stress is a critical driver of endothelial dysfunction in radiation-induced kidney toxicity (1). Ionizing radiation generates ROS both directly through water radiolysis and indirectly by mitochondrial dysfunction and activation of NADPH oxidases, which is highly expressed in renal endothelial and tubular cells (20). Excessive ROS production overwhelms endogenous antioxidant defenses such as superoxide dismutase, catalase, and glutathione peroxidase, leading to oxidative damage of lipids, proteins, and DNA (21). Lipid peroxidation products like 4-hydroxynonenal and malondialdehyde further impair endothelial function by modifying signaling proteins and inducing pro-apoptotic pathways (22). Besides, reactive oxygen species activate redox-sensitive transcription factors such as nuclear factor-kappa B (NF-κB) and activator protein-1, which orchestrate the expression of numerous pro-inflammatory and pro-fibrotic genes, thereby linking endothelial injury to downstream fibrotic responses (23). In fact, the transition from endothelial dysfunction to tubulointerstitial fibrosis involves a cascade of cellular and molecular events centered on maladaptive repair and chronic inflammation (24). Tubulointerstitial fibrosis as the pathological accumulation of extracellular matrix (ECM) proteins such as collagen I, III, and fibronectin in the renal interstitium is the final common pathway leading to end-stage renal disease in radiation-induced kidney injury (25). Although initially viewed as a passive scar, fibrosis is now recognized as a dynamic process driven by activated fibroblasts and myofibroblasts, which are the primary ECM-producing cells in the injured kidney (26). The origin of these myofibroblasts has been a subject of extensive investigation; while a minor contribution may arise from epithelial-to-mesenchymal transition (EMT) or endothelial-to-mesenchymal transition (EndMT), lineage-tracing studies strongly support resident fibroblasts and pericytes as the predominant sources in radiation nephropathy (27, 28). It should remember that, Radiation-induced tubular epithelial cell injury is a key initiating event in fibrogenesis (29). Direct DNA damage, oxidative stress, and loss of microvascular support lead to tubular cell apoptosis, necrosis, or senescence (30). Senescent tubular cells adopt a senescence-associated secretory phenotype (SASP), characterized by the sustained secretion of pro-inflammatory cytokines (like interleukin 6 and TNF-α), chemokines and matrix metalloproteinases, which recruit immune cells and activate fibroblasts (31). Moreover, damaged tubular cells release damage-associated molecular patterns such as high-mobility group box 1 and ATP, which engage pattern recognition receptors on macrophages and dendritic cells, perpetuating innate immune activation (32). Moreover, infiltrating immune cells, particularly macrophages, play a dual role in radiation-induced kidney injury. In the acute phase, classically activated (M1) macrophages contribute to tissue clearance and inflammation (33). However, in the chronic phase, a shift toward alternatively activated (M2) macrophages promotes fibrosis through the secretion of transforming growth factor-beta (TGF-β), platelet-derived growth factor, and insulin-like growth factor-1 (IGF-1) (33). Notably, TGF-β is arguably the most potent pro-fibrotic cytokine in radiation-induced renal damage. Radiation upregulates TGF-β expression in multiple renal cell types, including tubular epithelial cells, endothelial cells, and macrophages (34,35). Once activated, TGF-β signals through canonical Smad-dependent pathways (Smad2/3 phosphorylation and nuclear translocation) and non-canonical pathways (e.g., MAPK, PI3K/Akt), leading to the transcription of genes encoding ECM proteins and inhibitors of matrix degradation such as tissue inhibitors of metalloproteinases (36). Accordingly, TGF-β induces the differentiation of fibroblasts into α-smooth muscle actin (α-SMA)-positive myofibroblasts, which exhibit enhanced contractility and ECM synthesis (37). In addition to TGF-β, other signaling pathways contribute to fibrogenesis in radiation-induced renal toxicity (38). The renin-angiotensin-aldosterone system (RAAS) is frequently activated following radiation exposure (1). Angiotensin II, as the primary effector of RAAS, promotes vasoconstriction, oxidative stress, inflammation, and fibrosis via the angiotensin type 1 receptor (AT1R). Angiotensin II stimulates NADPH oxidase activity, further amplifying ROS production, and enhances TGF-β expression, creating a feed-forward loop that accelerates fibrosis (39). Aldosterone, another RAAS component, independently induces collagen synthesis and fibroblast proliferation. Consequently, RAAS inhibitors such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have shown efficacy in attenuating radiation nephropathy in preclinical models and some clinical settings (1). Hypoxia, resulting from capillary rarefaction and microvascular dysfunction, is another critical driver of fibrosis. Hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α, accumulate under low oxygen conditions and regulate the expression of genes involved in angiogenesis, metabolism, and fibrosis (40). Paradoxically, chronic HIF activation in radiation-induced renal injury contributes to fibrogenesis by upregulating connective tissue growth factor, lysyl oxidase, and other pro-fibrotic mediators (41,42). Furthermore, hypoxia impairs the resolution of fibrosis by suppressing the activity of matrix-degrading enzymes and promoting fibroblast survival (43). Several studies found that, the dysregulation of ECM homeostasis is central to the development of tubulointerstitial fibrosis. Under physiological conditions, the synthesis and degradation of ECM components are tightly balanced by matrix metalloproteinases and their inhibitors (44). In radiation-induced kidney injury, this equilibrium is disrupted. On one hand, MMP activity is often reduced due to oxidative inactivation or transcriptional down-regulation. On the other hand, TIMP expression is increased, particularly TIMP-1, under the influence of TGF-β and other cytokines (45-47). The net result is excessive accumulation of collagen and other matrix proteins, leading to interstitial expansion, tubular atrophy, and loss of nephron function (48). Moreover, cross-linking of collagen fibers by enzymes such as lysyl oxidase renders the fibrotic matrix resistant to degradation, contributing to the irreversibility of advanced fibrosis (49). Consequently, cellular senescence extends beyond tubular epithelial cells to include endothelial cells and fibroblasts in radiation-induced kidney damage (50). Senescent fibroblasts exhibit a pro-fibrotic SASP that sustains local inflammation and ECM production, even in the absence of ongoing radiation exposure. The accumulation of senescent cells over time may explain the progressive nature of radiation nephropathy long after the initial insult (51). Interestingly, emerging therapeutic strategies, such as senolytics (drugs that selectively eliminate senescent cells), have shown promise in preclinical models of kidney fibrosis, including radiation-induced kidney toxicity, by reducing SASP-mediated inflammation and fibrosis (52). The interplay between endothelial dysfunction and tubulointerstitial fibrosis is bidirectional and self-reinforcing. Endothelial injury leads to hypoxia and inflammation, which activate fibroblasts and promote fibrosis (53). In turn, fibrotic expansion compresses peritubular capillaries, further reducing perfusion and exacerbating endothelial stress. This vicious cycle underscores the importance of targeting both vascular and fibrotic pathways in therapeutic interventions (54). For instance, strategies aimed at preserving endothelial integrity, such as administration of antioxidants, NO donors, or agents that enhance endothelial progenitor cell mobilization, may mitigate the downstream development of fibrosis (55). Similarly, anti-fibrotic approaches targeting TGF-β, connective tissue growth factor, or RAAS may indirectly improve microvascular health by reducing interstitial pressure and inflammation (56).

Kidney pathology of radiation-induced kidney injury

The kidney is a radiosensitive organ, and although modern radiotherapy techniques have improved targeting precision and reduced off-target exposure, radiation-induced kidney toxicity remains a clinically relevant entity due to its insidious onset, progressive nature, and potential for irreversible renal dysfunction (1). The pathological changes in radiation-induced renal toxicity reflect a complex interplay of direct cellular injury, microvascular damage, chronic inflammation, and fibrotic remodeling, finally culminating in glomerulosclerosis, tubular atrophy, and interstitial fibrosis as the hallmarks of chronic kidney disease (1). The initial insult in radiation-induced kidney damage arises from ionizing radiation causing direct DNA damage and generating reactive oxygen species that overwhelm endogenous antioxidant defenses (1). Endothelial cells of the renal microvasculature are particularly vulnerable due to their high mitotic rate and limited regenerative capacity (57). Early pathological changes, often evident within weeks to months post-irradiation, include endothelial cell swelling, detachment, and apoptosis, leading to capillary rarefaction and micro-thrombosis. This vascular injury disrupts the delicate hemodynamic balance within the glomerulus and peritubular capillary network, resulting in localized ischemia (1). Concurrently, podocytes and tubular epithelial cells experience direct radiation damage, manifesting as nuclear enlargement, cytoplasmic vacuolization, and loss of brush border in proximal tubules. These early histological features may be subtle and are often overlooked in routine biopsies unless there is a high index of suspicion for radiation injury (1,58). As the injury progresses beyond the acute phase, the pathological picture evolves toward a chronic sclerosing phenotype. Glomerular changes become more prominent, characterized by global or segmental glomerulosclerosis, often with collapse of capillary loops and thickening of the glomerular basement membrane (59); which reflects a response to chronic hypoxia and loss of capillary integrity (1,60,61). Mesangial expansion may occur but is usually mild compared to diabetic nephropathy (62). Notably, immune complex deposition is absent on immunofluorescence, and electron microscopy typically which differentiates radiation-induced kidney toxicity from other causes of proteinuric kidney disease (1,63). The tubulointerstitial compartment bears the brunt of chronic radiation injury (59). Tubular atrophy is widespread, with simplification of tubular architecture, loss of epithelial cell height, and flattening of nuclei. Regenerative attempts may be seen in the form of tubular epithelial cell hyperplasia, but these are often inadequate to restore normal function (64). Interstitial fibrosis is a defining feature of advanced radiation-induced nephrotoxicity and correlates strongly with the degree of renal functional impairment (1). This fibrosis is driven by persistent activation of pro-fibrotic signaling pathways, notably the TGF-β axis, which promotes the differentiation of fibroblasts into myofibroblasts and excessive deposition of ECM proteins such as collagen I and III (26). Inflammatory infiltrates, though typically sparse compared to autoimmune or infectious interstitial nephritides, may include lymphocytes and macrophages that perpetuate tissue injury through cytokine release and ROS production (65). Given that, vascular pathology remains central to the progression of radiation-induced renal toxicity (1). Arterioles and small arteries exhibit hyalinization, intimal fibrosis, and medial hypertrophy changes reminiscent of hypertensive nephrosclerosis; however, occurring independently of systemic blood pressure elevation. These vascular alterations further compromise renal perfusion, creating a vicious cycle of ischemia, tubular injury, and fibrosis (66). In severe cases, obliterative endarteritis may develop, characterized by concentric intimal proliferation that occludes the vessel lumen (1). The timeline of pathological evolution in radiation-induced nephrotoxicity is highly variable and influenced by multiple factors, including total radiation dose, fractionation schedule, volume of kidney irradiated, and individual susceptibility (1). Classical radiation-induced nephrotoxicity typically manifests 6–12 months after exposure, but late-onset forms can appear years or even decades later, especially following low-dose protracted exposure (59). In contrast, accelerated radiation-induced nephrotoxicity may develop within weeks when radiation is combined with other nephrotoxic insults (2). Histologically, early biopsies may show minimal changes despite functional decline, underscoring the importance of clinical correlation. Over time, however, the constellation of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and vascular sclerosis becomes increasingly apparent and often indistinguishable from other forms of chronic kidney disease, necessitating a careful history of radiation exposure for accurate diagnosis (67). From a molecular standpoint, radiation-induced renal injury involves dysregulation of multiple cellular pathways (1). Persistent DNA damage triggers sustained activation of p53 and other stress-response genes, leading to cellular senescence as a state of irreversible cell cycle arrest that promotes a pro-inflammatory and pro-fibrotic microenvironment by the SASP (68). Senescent endothelial and tubular cells secrete interleukin-6, monocyte chemoattractant protein-1, and matrix metalloproteinases, which recruit immune cells and remodel the ECM (69). Additionally, dysregulation of the renin-angiotensin-aldosterone system contributes to vasoconstriction, sodium retention, and fibrosis, explaining why angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are often used empirically in radiation-induced nephrotoxicity despite limited high-quality evidence (70). It should remember that the pathological features of radiation-induced nephrotoxicity are not pathognomonic and must be interpreted in the appropriate clinical context. Renal biopsy findings alone cannot definitively confirm radiation etiology without corroborating history (71). Moreover, coexisting conditions such as diabetes, hypertension, or recurrent malignancy can confound the histological picture. Nevertheless, certain patterns such as the combination of karyomegaly in tubular nuclei, obliterative arteriopathy, and the absence of immune deposits strongly support a diagnosis of radiation-induced nephrotoxicity when radiation exposure is documented (1,72).

Detection of radiation nephropathy

Diagnosing radiation nephropathy is challenging due to the latent interval between radiation exposure and clinical manifestations, as well as confounding factors. Contrast-enhanced computed tomography is often used, showing little contrast enhancement in injured renal tissues (59). In one case, a radiation therapy dose of 60 Gy combined with chemotherapy for cervical cancer led to worsening renal function and proteinuria nine months post-treatment, aligning with the onset of acute radiation nephropathy (59). The kidney is a late-responding tissue with slow cell turnover, explaining the delayed manifestation of renal injury after radiation exposure. While radiation can induce cell death by apoptosis, it is more likely delayed until cell division occurs, as a result of the low- mitotic activity of normal renal tissue, delayed injury manifestation is expected (59).

Therapeutic options for radiation-induced kidney injury

Currently, effective treatments for radiation-induced kidney injury are limited. Research is exploring options such as betulinic acid as a radiosensitizer, traditional Chinese medicine compounds, and small molecule drugs like astragaloside IV to inhibit inflammasome activation (73). Recently, CpG-ODNs have shown promise in preventing DNA damage and oxidative stress by blocking the PARP1/XRCC1 axis. However, these findings are primarily in laboratory settings and have not yet been clinically translated (73). Investigating the role of intestinal lectin ITLN1 in radiation-induced kidney injury is also underway, as it may regulate renal function and physiological homeostasis (73). Recently, He et al, found ITLN1 (intelectin-1) overexpression has been found to inhibit oxidative stress, cell apoptosis, inflammatory responses, cellular senescence, and fibrosis by activating the Akt/GSK-3β/Nrf2 signaling pathway, thereby improving renal dysfunction in rats with radiation-induced kidney injury. This study offers theoretical foundations for identification of radiation necrosis pathogenesis and developing new therapeutic strategies, as well as providing evidence for the safety and efficacy of radiotherapy in clinical practice (73). Management of radiation nephropathy includes blood pressure control and the use of angiotensin-converting-enzyme inhibitors (ACE inhibitors) or angiotensin (AII) receptor blockers (74). Statins have also been shown to protect endothelial cells from radiation-induced injury by preventing the loss of endothelium-dependent relaxation, preserving NO production, and suppressing cytosolic reactive oxidative stress (75). Pravastatin, a hydrophilic statin, additionally inhibits mitochondrial superoxide production, mitochondrial DNA damage, loss of electron transport chain activity, and inflammatory marker expression (75).

Conclusion

Radiation-induced kidney injury represents a complex pathological process driven primarily by endothelial dysfunction and tubulointerstitial fibrosis. Ionizing radiation triggers oxidative stress, DNA damage, and chronic inflammation, which collectively impair endothelial cell integrity and function. This endothelial dysfunction disrupts microvascular perfusion, promotes leukocyte adhesion, and compromises the glomerular filtration barrier, ultimately contributing to ischemia and hypoxia within the renal parenchyma. Concurrently, persistent inflammatory signaling and activation of pro-fibrotic pathways, particularly the TGF-β/Smad axis stimulate fibroblast proliferation and excessive ECM deposition in the tubulointerstitial compartment. The loss of peritubular capillaries further exacerbates tissue hypoxia, creating a vicious cycle that accelerates fibrosis and progressive renal dysfunction. Notably, crosstalk between damaged endothelial cells, tubular epithelial cells, and immune cells amplifies the fibrotic response, underscoring the interdependence of vascular and interstitial pathology in radiation-induced kidney injury. Recent therapeutic strategies aim to mitigate these mechanisms by targeting oxidative stress, preserving endothelial health, or inhibiting key fibrotic mediators. Identification of the intricate interplay between endothelial injury and fibrogenesis not only clarifies the pathophysiology of radiation-induced kidney injury but also highlights potential biomarkers and intervention points for early detection and treatment, eventually aiming to preserve renal function in patients exposed to therapeutic or accidental radiation.

Authors' contribution

Conceptualization: Maktuba Mirrakhimova, Muhtorali Umarkulov, and Qaxramon O'rinboyev.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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