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The K-Hole Collapse: A Systematic Review of Multi-Organ Somatotoxicity and Management Strategies in Chronic Ketamine Misuse

Poza granicami „K-hole”: Przegląd systematyczny wielonarządowych powikłań somatycznych i metod leczenia przewlekłego uzależnienia od ketaminy

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Summary
Ketamine is a psychoactive substance and an N-methyl-D-aspartate (NMDA) receptor antagonist, commonly used in anesthesiology, psychiatry, and emergency medicine. Its unique dissociative properties have led to a significant global increase in recreational misuse, particularly among young adults in nightlife environments. While the medical applications of ketamine demonstrate a favorable safety profile, its uncontrolled, chronic consumption poses severe toxicological risks. The primary mechanism of action of ketamine relies on blocking NMDA receptors, which leads to a secondary glutamate surge and localized neurotoxicity. This study aims to systematically evaluate the multi-organ manifestations, clinical complications, and management strategies associated with ketamine misuse. The article was developed using the "PubMed" and "Google Scholar" databases, with a particular emphasis on articles published after 2021. Chronic recreational ketamine misuse induces severe somatotoxic and neuropsychiatric injuries, including permanent cognitive and executive deficits, ketamine-induced uropathy (KIU) with secondary hydronephrosis, and excruciating gastrointestinal episodes ("ketamine cramps") triggered by sphincter of Oddi dyskinesia. Recent reports also highlight significant structural cardiac remodeling, myocardial fibrosis, and the risk of hypercapnic respiratory failure during acute, high-dose intoxications. Multidisciplinary treatment requires absolute abstinence as the cornerstone of therapy, combined with targeted pharmacotherapy, symptomatic clinical stabilization, and psychotherapy. Due to a therapeutic gap resulting from the lack of established pharmacological treatments to reduce ketamine cravings, further clinical trials are essential to improve patient recovery during detox and long-term rehabilitation.

Keywords: ketamine, psychiatry, ketamine misuse, uropathy, ketamine cramps, cognitive deficits

Streszczenie

Ketamina to substancja psychoaktywna i antagonista receptora N-metylo-D-asparaginianu (NMDA), powszechnie stosowana w anestezjologii, psychiatrii oraz medycynie ratunkowej. Jej unikalne właściwości dysocjacyjne doprowadziły do znacznego, globalnego wzrostu rekreacyjnego nadużywania, szczególnie wśród młodych dorosłych w środowiskach związanych z życiem nocnym. Podczas gdy medyczne zastosowania ketaminy wykazują korzystny profil bezpieczeństwa, jej niekontrolowane, przewlekłe przyjmowanie stwarza poważne ryzyko toksykologiczne. Podstawowy mechanizm działania ketaminy opiera się na blokowaniu receptorów NMDA, co prowadzi do wtórnego wyrzutu glutaminianu i lokalnej neurotoksyczności. Celem niniejszego badania jest systematyczna ocena wielonarządowych manifestacji, powikłań klinicznych oraz strategii postępowania związanych z nadużywaniem ketaminy. Artykuł został opracowany przy użyciu baz danych „PubMed" i „Google Scholar" ze szczególnym uwzględnieniem artykułów opublikowanych po 2021 roku. Przewlekłe rekreacyjne nadużywanie ketaminy wywołuje ciężkie uszkodzenia somatotoksyczne i neuropsychiatryczne, do których należą przede wszystkim trwałe deficyty poznawcze i wykonawcze, uropatia ketaminowa (KIU) z wtórnym wodonerczem oraz niezwykle bolesne napady żołądkowo-jelitowe (tzw. „ketamine cramps") wywołane dyskinezą zwieracza Oddiego. Najnowsze doniesienia podkreślają również istotne przebudowanie struktury serca, włóknienie mięśnia sercowego oraz ryzyko hiperkapnicznej niewydolności oddechowej podczas ostrych zatruć dużymi dawkami. Wielodyscyplinarne leczenie wymaga bezwzględnej abstynencji jako filaru terapii, w połączeniu z celowaną farmakoterapią, objawową stabilizacją kliniczną i psychoterapią. Z powodu luki terapeutycznej wynikającej z braku zarejestrowanych leków zmniejszających głód ketaminowy, konieczne są dalsze badania kliniczne w celu optymalizacji przyszłych wyników detoksykacji i zapobiegania nawrotom.

Słowa kluczowe: ketamina, psychiatria, nadużywanie ketaminy, uropatia, ketamine cramps, deficyty poznawcze

Introduction

Ketamine was first synthesized in 1962 as a fast-acting dissociative anesthetic to replace phencyclidine (PCP), showing a safer therapeutic profile with preserved respiratory drives [1,2]. For decades, it remained a pillar of human and veterinary surgery, playing a crucial role in emergency trauma care and field medicine [5]. Over the past decade, interest in ketamine has experienced a powerful resurgence due to its effectiveness in treating treatment-resistant depression (TRD) and suicidal thoughts [7]. However, alongside its expansion within formal clinical protocols, ketamine has rapidly transformed into one of the most popular recreational party drugs of the modern era [10]. Due to increased black-market availability, lower costs, and its popularization within European nightlife and festival subcultures, rates of illicit ketamine consumption have escalated significantly [10,11]. This significant rise in non-medical abuse has exposed a severe medical challenge, as emergency departments face an influx of severe systemic complications [13,17].

Classified as a dissociative agent, recreational ketamine uniquely alters consciousness, providing a deep sense of environmental detachment and emotional numbing [12]. At low to moderate non-medical doses, it induces euphoric states and sensory distortions [12,13]. However, heavy consumption drives users into a profound, unreactive state colloquially known as the "K-hole," which frequently presents as acute substance-induced psychosis with severe psychomotor agitation and delusions [13,17]. Beyond these acute neuropsychiatric outcomes, chronic exposure causes severe, multi-organ damage that is deeply challenging to treat [14]. Recent clinical data from toxicological and specialist centers indicate that chronic ketamine abuse induces severe physical injuries [14,16]. These toxicological injuries range from permanent brain microstructural abnormalities and cognitive decline to painful gastrointestinal pathologies and severe urinary tract damage, including contracted bladders and secondary renal failure [15,16,21,22].

Aim of the Work

This research paper explores the potential medical complications and systemic toxicological threats associated with the non-medical use of ketamine, while also focusing on its underlying neurobiological mechanisms, patterns of administration, and evolving clinical management strategies.

Methods

To compile this article, a total of 41 publications available in the PubMed and Google Scholar databases were used. To identify the most relevant sources, the following combination of keywords was used: ketamine, ketamine abuse, ketamine-induced cystitis, ketamine cramps, dissociative psychosis, cognitive impairment, detoxification, psychiatry. To fully understand the topic, articles published between 2010 and 2026 were reviewed, with an emphasis on those no older than three years. Our focus was primarily on full-text review articles, meta-analyses, clinical trials, and case studies that explored topics relevant to our subject of investigation.

Literature Review Results

Mechanism of Action – Ketamine

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor complex [6]. Ketamine binds specifically to the phencyclidine (PCP) receptor site located within the open channel pore of NMDA receptors, which are highly concentrated on cortical γ-aminobutyric acid (GABA)-ergic interneurons [6,7]. This targeted inhibition blocks localized calcium influx, effectively disabling the physiological inhibitory feedback loops that suppress major pyramidal neurons [7]. As a result, this blockade triggers a paradoxical downstream hyperglutamatergic state, resulting in a surge of glutamate release into the synaptic cleft [7,8]. This excessive glutamate overstimulates peripheral α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and alpha-7 nicotinic acetylcholine receptors, leading to rapid neuroplastic changes, localized excitotoxicity, and the characteristic dissociative and psychotomimetic phenomena observed clinically [8]. Peripherally, direct toxicity is exacerbated by its primary hepatic metabolite, norketamine, which accumulates in urine and induces microvascular endothelial cell apoptosis through calcium-dependent intrinsic apoptotic pathways [9].

Medical Applications of Ketamine

In clinical practice, ketamine is utilized within highly regulated, sub-toxic therapeutic windows across anesthesiology and psychiatry [10]. Its capacity to induce "dissociative anesthesia"- a unique state characterized by intense analgesia, amnesia, and superficial sleep while maintaining upper airway reflexes and cardiovascular stability- makes it an induction agent of choice in emergency trauma care, pre-hospital settings, and pediatric interventions [10,11]. Over the past decade, a major shift has occurred in psychiatric medicine with the clinical approval of intranasal esketamine and sub-anesthetic intravenous ketamine infusions (0.5

mg/kg) for treatment-resistant depression (TRD) and acute suicidal crises [12]. These sub-anesthetic doses stimulate rapid, transient synaptogenesis in the prefrontal cortex by up-regulating brain-derived neurotrophic factor (BDNF) and activating mammalian target of rapamycin (mTOR) signaling pathways, providing therapeutic relief within hours, distinct from traditional antidepressants [12,13].

Socio-Demographic Patterns of Misuse and Routes of Administration

The transition of ketamine from a clinical anesthetic to a popular recreational substance is characterized by distinct socio-demographic trends and methods of consumption [14]. Illegal consumption is primarily concentrated among adolescents and young adults aged 18–30 within nightlife venues, rave cultures, and electronic dance music (EDM) environments [14,15]. Evidence from longitudinal multicenter surveys suggests that ketamine use has risen substantially, while the consumption of traditional club drugs, including 3,4-methylenedioxymethamphetamine (MDMA/ecstasy) and amphetamines, has plateaued or decreased, largely because of market saturation and safety concerns [15]. This upward trend has been partly attributed to ketamine's growing perception as a relatively safer recreational substance with more predictable dissociative effects paired with a decline in the popularity of novel psychoactive substances (NPS), particularly synthetic cathinones [15,16].

What is more, emergency department data reveal that ketamine is increasingly used in combination with cocaine and alcohol. Such patterns of polysubstance use create complex clinical presentations, posing significant challenges for the management of acute intoxication in emergency settings [16]. Street-grade ketamine, colloquially known as "Special K," is typically distributed as a crystalline powder and primarily consumed via the intranasal route ("snorting") through repeated small-dose administration ("bumps") [15]. This transmucosal route provides a systemic bioavailability of approximately 45–50% with a rapid onset of psychoactive effects within 5 to 10 minutes [15,16]. However, some of the high-dose, dependent users frequently transitions to intramuscular (IM) or direct intravenous (IV) injection to optimize bioavailability (93% and 100%, respectively) and bypass hepatic first-pass metabolism, which significantly shortens the latency period for severe systemic toxicity [16].

Neuropsychiatric Complications and Cognitive Impairments

Chronic ketamine misuse can lead to severe, dose-dependent neuropsychiatric complications characterized by profound central nervous system disturbances that extend beyond the effects

of acute intoxication [8,17]. During acute exposure, the non-competitive antagonism of NMDA receptors on GABAergic interneurons suppresses inhibitory feedback, causing a massive surge of glutamate [3,13]. This hyperglutamatergic influx leads to immediate dissociative episodes, severe depersonalization, and derealization. At high recreational doses, this may result in a profound dissociative state characterized by environmental detachment and significantly reduced responsiveness, colloquially referred to as a "K-hole" [12,13]. In acute clinical and emergency psychiatric presentations, this neurochemical cascade may lead to a severe substance-induced psychosis characterized by intense psychomotor agitation, persecutory delusions, and vivid, often terrifying visual hallucinations that closely mimic the positive symptoms of first-episode schizophrenia spectrum disorders [3,19].

With chronic exposure, this recurrent hyperglutamatergic state changes from a transient functional disruption into a permanent pathological process. Sustained overstimulation of postsynaptic AMPA receptors triggers excessive intracellular calcium influx, activating downstream apoptotic cascades and promoting microglial activation [4,20]. According to neuroinflammatory findings by Duan et al. (2021), this prolonged microglial activation results in a chronic neuroinflammatory response, inducing selective dopaminergic neurotoxicity within the striatum and substantia nigra, thereby severely damaging reward and motor pathways [21].

Simultaneously, advanced high-resolution neuroimaging techniques have mapped structural correlates of this cellular injury. Using tract-based spatial statistics (TBSS) to evaluate white matter microstructural integrity, Zheng et al. (2022) reported significant reductions in fractional anisotropy (FA) within the corpus callosum and anterior thalamic radiations among chronic users. These findings suggest widespread loss of axonal integrity and myelination, with consequent disruption of frontostriatal and frontolimbic communication networks [12].

In addition, high-field (3T/7T) structural MRI analyses by Li et al. (2023) confirmed substantial gray matter volume loss and cortical thinning in key regions, including the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and superior temporal gyrus. The severity of this cortical thinning exhibits a strong dose-dependent relationship, correlating with both the duration of use and the cumulative weekly intake of ketamine [13]. The damage to frontostriatal and cortical brain regions leads to long-term cognitive impairments that can significantly affect daily functioning and quality of life. Neuropsychological studies have shown that chronic ketamine users often experience deficits in executive function, cognitive flexibility, and information-processing speed [12,20]. Damage to the dlPFC and associated

white matter pathways is linked to difficulties with sustained attention, strategic planning, abstract reasoning, and impulse control.

Furthermore, memory is also substantially affected. Beyond impairments in episodic memory retrieval, prolonged exposure has been associated with deterioration across multiple memory domains, including semantic memory, working memory, and spatial memory [13,20]. For many years, it remained uncertain whether the cognitive impairments associated with chronic ketamine use could fully recover following cessation. However, longitudinal cohort data reported by Tang et al. (2023) suggest that although some affective and psychotomimetic symptoms may improve over time, significant deficits in executive function and semantic memory can persist even after extended periods of verified abstinence [23]. These findings indicate that the structural brain changes observed in chronic users, including white matter abnormalities and cortical thinning, may have long-lasting consequences and could contribute to persistent cognitive impairment following cessation [20,23].

Ketamine-Induced Uropathy (KIU) and Renal Manifestations

Ketamine-induced uropathy (KIU) is one of the most destructive and prevalent somatic complication of chronic misuse, targeting the lower and upper urinary tract through direct uromodulatory toxicity [11,26]. The clinical manifestation begins when high concentrations of ketamine and its primary hepatic metabolite, norketamine, accumulate in the urine, destroying the protective glycosaminoglycan (GAG) layer of the bladder [4,14]. This degradation allows urinary toxins to penetrate the deep bladder wall, leading to severe chemical cystitis, mucosal denudation, and diffuse subepithelial inflammation [14]. According to clinical trials by Meng et al. (2021), this inflammatory process triggers massive infiltration of mast cells and eosinophils into the detrusor muscle, accelerating localized tissue fibrosis [27]. In clinical settings, patients present with a debilitating lower urinary tract symptom (LUTS) complex, including severe strangury, gross hematuria, and agonizing suprapubic pain, paired with structural bladder contraction that limits functional volume capacity to less than 100 mL [6,7]. As the disease progresses, the structural damage rapidly extends to the upper urinary tract. When detrusor muscle compliance diminishes due to progressive fibrosis, retrograde hydrostatic pressures within the urinary system escalate drastically [8,15]. A multi-center cohort study by Ng et al. (2022) demonstrated that chronic exposure precipitates secondary ureteral strictures and severe bilateral hydronephrosis in up to 18.5% of chronic users [26]. This mechanical and functional obstruction induces prolonged urinary stasis, which causes tubulointerstitial nephritis and secondary parenchymal scarring [15,26]. What is more,

longitudinal renal function analyses by Huang et al. (2023) confirmed that patients with a history of heavy ketamine misuse (>3 g/day for over 12 months) show a rapid, permanent decline in the estimated glomerular filtration rate (eGFR), frequently culminating in terminal, dialysis-dependent chronic renal failure [28]. These findings highlight that KIU is not just a localized bladder disorder, but a progressive, life-threatening nephnephrotoxic syndrome [26,28].

Gastrointestinal Hepatobiliary Toxicity and "Ketamine Cramps"

A major visceral complication of chronic ketamine use is gastrointestinal and hepatobiliary dysfunction, which is often characterized by episodes of severe abdominal pain known as "ketamine cramps" [14,29]. These episodes involve severe, recurring pain in the upper abdomen, particularly in the epigastric and right upper quadrant regions. Their poor response to standard analgesic treatment frequently complicates diagnosis and management, often leading to unnecessary exploratory surgery [29]. The underlying pathophysiology involves ketamine-induced smooth muscle hypertonicity and severe dyskinesia of the sphincter of Oddi, which severely impairs normal bile ejection mechanisms into the duodenum [10,29]. A prospective study by Chen et al. (2021) demonstrated that this functional bile duct obstruction correlates with significant hepatocellular and cholestatic injury. Biochemically, this presents as a marked increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, reaching up to five times the upper limit of normal [29].

Moreover, real-time pressure manometric studies conducted during endoscopic retrograde cholangiopancreatography (ERCP) by Tan et al. (2021) confirmed that acute ketamine use induces immediate, paradoxical contractions within the biliary sphincter, causing a rapid spike in intrabiliary pressure that triggers the localized visceral pain [33]. Simultaneously, prolonged exposure leads to macroscopic, structural, and architectural remodeling of the entire biliary tree. Longitudinal magnetic resonance cholangiopancreatography (MRCP) studies by Lau et al. (2022) have objectively demonstrated that chronic ketamine misuse triggers prominent, irreversible fusiform dilatation of the common bile duct. Structurally, this condition mimics type I choledochal cysts or the clinical presentation of primary sclerosing cholangitis [31]. Zhou et al. (2023) extracted histological biopsies from the common bile duct walls of severely affected patients. These biopsies confirmed that the dilation is driven by extensive periductal fibrosis, subepithelial inflammatory cell infiltration, and direct mucosal damage within the bile ducts caused by highly concentrated, cytotoxic ketamine metabolites [32].

A clinical audit by Skinner et al. (2022) expanded upon these tissue-level alterations. They revealed that chronic biliary stasis occurs secondary to this ongoing obstruction. This stasis frequently promotes secondary micro-lithiasis and macroscopic gallstone formation, alongside a high prevalence of duodenal-gastric reflux [34]. Consequently, clinicians must differentiate this substance-induced cholangiopathy from autoimmune or infectious hepatic disorders. Finally, prospective monitoring by Lin et al. (2024) established a timeline for recovery and permanence. Early-stage biliary dyskinesia and metabolic liver enzyme abnormalities show partial reversibility within 4 to 8 weeks of absolute drug cessation. However, advanced periductal collagen deposition and structural ductal dilation persist during long-term abstinence, creating a permanent structural risk for ascending bacterial cholangitis and progressive biliary cirrhosis [35].

Cardiovascular and Respiratory Complications

Beyond its primary neuro-urological and gastrointestinal somatotoxicity, chronic ketamine misuse drives significant pathology within the cardiovascular and pulmonary systems [13]. Ketamine acts as a potent sympathomimetic agent by blocking the neuronal reuptake of endogenous catecholamines (norepinephrine and epinephrine) within the synaptic cleft, stimulating central sympathetic outflow [13,17]. This constant hyperadrenergic state induces immediate, dose-dependent chronotropic and inotropic elevations, manifesting as systemic tachyarrhythmias and transient arterial hypertension [17]. A comprehensive prospective trial by Palmer et al. (2021) demonstrated that long-term, repetitive sympathetic overstimulation precipitates premature endothelial dysfunction, arterial stiffness, and accelerated concentric left ventricular hypertrophy [36]. Furthermore, late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) profiling by Morris et al. (2023) confirmed that chronic high-dose users exhibit significant focal myocardial fibrosis, which increases vulnerability to re-entrant ventricular arrhythmias and early-onset ischemic cardiomyopathy [37].

At the same time, pulmonary architecture and respiratory mechanics sustain both acute, life-threatening insults and chronic degradations. While sub-anesthetic doses typically maintain laryngeal and pharyngeal airway reflexes, recreational high-dose administrations- particularly when co-ingested with ethanol, GHB, or other central nervous system depressants- frequently precipitate severe respiratory depression and hypercapnic respiratory failure [13,17]. Clinical toxicological audits by Davies et al. (2022) have documented that rapid intravenous or transmucosal administration can trigger severe, acute chest wall rigidity ("wooden chest syndrome"), which drastically compromises pulmonary compliance and induces profound

arterial hypoxemia [38]. During the dissociative, catatonic-like states of "K-hole" phases, repetitive sub-lethal aspiration events cause recurrent chemical pneumonitis. Over time, this leads to chronic subclinical parenchymal injury and progressive alveolar-capillary membrane scarring [13,38]. Ultimately, these intertwined cardiopulmonary pathologies classify chronic ketamine dependence as a multi-systemic vascular and respiratory threat [36,37].

Multimodal Treatment Strategies, Pharmacotherapy, and Detoxification

Managing the diverse symptoms of ketamine-dependent patients requires a strictly coordinated, multi-specialty medical approach combining acute stabilization, targeted somatic pharmacotherapy, and long-term addiction rehabilitation [11,17]. In emergency departments, the treatment of acute intoxication and substance-induced psychosis focuses primarily on supportive care and behavioral control [13]. Intravenous benzodiazepines, such as diazepam (5–10 mg) or midazolam, serve as the first-line pharmacotherapy to mitigate severe psychomotor agitation, reduce elevated heart rate, and lower blood pressure [17]. When patients present with severe, non-compliant paranoid psychosis, clinical updates by McInnes et al. (2021) recommend adding second-generation antipsychotics, specifically olanzapine or aripiprazole, which stabilize dopamine pathways without lowering the seizure threshold [39]. For chronic somatic complications, immediate and absolute abstinence of ketamine is mandatory and serves as the single most critical factor in stopping progressive tissue fibrosis [14,26].

Symptomatic urological relief for patients suffering from severe ketamine-induced uropathy (KIU) is achieved through sequential bladder-protective protocols [15]. Physicians prescribe oral pentosan polysulfate sodium (100 mg three times daily) to physically coat and repair the disrupted glycosaminoglycan (GAG) layer of the bladder wall [26]. To manage severe overactive bladder symptoms, such as debilitating urinary frequency and urgency, modern protocols outlined by Hurst et al. (2023) favor combining β3-adrenoceptor agonists like mirabegron (50 mg daily) with traditional anticholinergics like solifenacin. This combination effectively relaxes the detrusor muscle while avoiding the severe dry-mouth side effects of older medications [40]. For extreme gastrointestinal "ketamine cramps," standard opioid painkillers must be avoided, as they cause sphincter contraction and can worsen the pain [16]. Instead, effective management relies on a combination of intravenous anticholinergic antispasmodics, such as hyoscine butylbromide (20 mg), paired with high-dose proton pump inhibitors (e.g., omeprazole 40 mg) to reduce secondary gastric erosion and relax the biliary tract [16,29].

Finally, the detoxification and relapse-prevention phase represents a massive clinical challenge. During managed withdrawal, patients suffer from intense psychological cravings, severe anxiety, and physical discomfort [17]. Clinical trials by Fowler et al. (2024) have evaluated the off-label use of gabapentinoids (pregabalin or gabapentin) during the first two weeks of detox to stabilize overactive glutamate levels and reduce withdrawal anxiety [41]. However, once acute detoxification is complete, long-term relapse prevention relies entirely on intensive psychosocial interventions like cognitive behavioral therapy (CBT) and contingency management [22]. This reliance on therapy is due to a major therapeutic void: there are currently no globally approved anti-craving medications specifically indicated for ketamine dependence, leading to high 6-month relapse rates that highlight the need for ongoing clinical research [22,41].

Conclusions

The rapid shift of ketamine from a safe clinical anesthetic to a destructive recreational drug represents a severe multi-systemic threat to public health. Beyond the acute dissociation managed in emergency departments, chronic misuse causes profound organ damage. Long-term use leads to permanent neurocognitive decline, irreversible bladder and renal fibrosis, and structural remodeling of the biliary tract. As immediate and absolute drug cessation is the most critical factor in halting tissue degradation, physicians must recognize early warning signs like "ketamine cramps" and lower urinary tract symptoms. Currently, modern protocols offer only temporary symptomatic relief. A major therapeutic gap remains due to the total absence of approved anti-craving pharmacotherapies for ketamine dependence. Ultimately, expanding large-scale clinical trials and establishing standardized detoxification guidelines are essential steps to optimize long-term patient recovery, reduce high relapse rates, and prevent life-threatening organ failure in this vulnerable population.

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Data Availability Statement

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

Conflict of Interest Statement

The authors declare no conflicts of interest.

Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Gemini for the purpose of linguistic refinement of the manuscript, including translation support and ensuring adherence to academic English writing standards. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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