

CLINICAL PRESENTATION OF WILSON'S DISEASE: A CROSS-SECTIONAL STUDY AT ABBASI SHAHEED HOSPITAL, KARACHI

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ABSTRACT

Wilson's disease (WD), referred to as hepatolenticular degeneration, involves the progressive degeneration of the basal ganglia alongside chronic liver disease, potentially leading to cirrhosis. This uncommon autosomal recessive genetic disorder impacts around 30 individuals per million, making it a rare condition. The clinical symptoms associated with Wilson's disease are numerous and intricate. The current study aims to evaluate the clinical manifestations and laboratory findings to highlight the various presentation patterns and enhance understanding for early diagnosis. Study Design cross sectional study. Twenty five patients with confirmed diagnosis of Wilson's disease invited to participate in this research after satisfying the inclusion and exclusion criteria. Patients were assessed through history, clinical examination and laboratory investigations. Data was collected using a pre-established structured format and subsequently analyzed statistically. A total of 25 patients meeting the specified inclusion and exclusion criteria were part of this study. The average age recorded was 42.39 years, with a standard deviation of ± 14.38 . The cohort comprised 18 males (72%) and 7 females (28%). Out of 25 patients, 09 (36%), 09 (36%), 07 (28%), 11 (44%), 09 (36%), 18 (72%), 13 (52%), 11 (44%) had most common clinical features tremor, rigidity, gait abnormality, facial abnormality, seizure, anger depression and insomnia. This informative data illustrates the clinical challenges and variability associated with Wilson's Disease (WD), highlighting the importance of improved education on diagnostic testing and the need for multidisciplinary support.

Key-words: Wilson's disease, hepatic, neurologic, psychiatric, copper, Kayser Fleischer rings.

INTRODUCTION

In 1912, Kinnier Wilson first detailed Wilson's disease (WD), also referred to as hepatolenticular degeneration, as a progressive degeneration of the lenticular area, which is associated with chronic liver disease that can culminate in cirrhosis (Abdel-Ghaffar *et al.*, 2011). This rare genetic disorder, inherited in an autosomal recessive manner, affects approximately 30 individuals per million due to copper metabolism issues (Ala *et al.*, 2007). The occurrence rate ranges from 1 in 30,000 to 1 in 100,000, particularly among Chinese and other Asian populations (Ala *et al.*, 2007). Wilson's disease can manifest at any age, but most cases are observed between the ages of 5 and 35, with approximately 3% of patients presenting after the age of 40, either with liver or neurological complications (Borjigin *et al.*, 1999). The presence of mutations in the ATP7B gene, encoding a copper-transporting P-type ATPase, are associated with Wilson's disease, enabling the transport of copper for its integration into apoceruloplasmin and its elimination via bile (Cuthbert, 1998; De Bie *et al.*, 2007). Impaired function of ATP7B causes excessive copper to accumulate in liver, brain, cornea, kidneys and other tissues, thereby leading to the hepatic and neurological symptoms associated with Wilson's disease (Czlonkowska *et al.*, 2012). Currently, more than 400 mutations have been documented, and it is expected that further mutations will be identified, which may help to elucidate the clinical variability of the disease (Janczyk *et al.*, 2012; Ferenci *et al.*, 2007). The diagnostic challenge arises from the non-specific nature of the symptoms and the involvement of multiple organ systems, leading to potential confusion with other disorders (Gow *et al.*, 2000). Furthermore, significant progress has been made in the last twenty years regarding our comprehension of the disease's pathogenesis, cellular biology, and molecular genetics (Li *et al.*, 2011). This disorder is most frequently seen in children and young adults, with patients showing a range of clinical manifestations based on the organ that is most severely impacted, including acute liver failure, cirrhosis, and neurological or psychiatric syndromes (Merle *et al.*, 2007; Parkash *et al.*, 2013). The disease will inevitably result in death if not properly managed with chelating agents (Roberts and Schilsky, 2008). The diagnostic test showed that Ceruloplasmin level was reduced in 86.6%, serum copper reduced in 68.1% and 24 hours urinary copper excretion was raised in 47.6% (Taly *et al.*, 2009). However, the study conducted in India reported reduced hepatic symptoms (14.9%), neurological (69.2%), psychiatric (2.48%) and others as around

14%, while the diagnostic test showed that Ceruloplasmin level was reduced in 88% and 24 hours' urinary copper excretion was raised in 96% (Tao and Gitlin, 2003). Wilson disease (WD) is a genetic disorder characterized by autosomal recessive inheritance, resulting from mutations in the ATP7B gene that disrupt copper metabolism. Historically, the prevalence of this condition was estimated at 1 in 30,000 individuals; however, recent studies indicate a potentially higher genetic prevalence of 1 in 7,000. The process of copper absorption begins in the stomach and duodenum, after which it is taken up by the liver and released into the bloodstream in conjunction with ceruloplasmin. Copper must be transported via the trans-Golgi network in liver cells by the ATP 7B transporter in order for it to be incorporated into apoceruloplasmin. Furthermore, when cytoplasmic concentrations of copper are high, ATP7B plays a crucial role in the biliary excretion of copper. Copper buildup in the liver due to ATP7B dysfunction results in non-ceruloplasmin in the bloodstream as well as cellular damage and illness. Additionally, copper deposits in various organs, particularly the brain, where it is linked to cellular injury and disease. It is still unknown how precisely brain disorders are linked to elevated levels of free circulating copper or the deficiency of neurons expressing ATP7B (Tao and Gitlin, 2003; Walshe, 1986; Wilson, 1912; Hahn, 2014; Bandmann *et al.*, 2015; Cheng, 1932; Li *et al.*, 2013; Xie and Wu, 2017; Hedera, 2017; Dong *et al.*, 2016; Roberts and Schilsky, 2008; Zheng *et al.*, 2022; Brewer *et al.*, 1998; Sterlieh and Scheinberg, 1968). In 1912, Samuel Alexander Kinnier Wilson characterized this condition as progressive lenticular degeneration, establishing a connection between neurological disorders and cirrhosis. He acknowledged the prevalence of psychiatric symptoms but indicated that cirrhosis was seldom symptomatic throughout life. In 1925, Barnes and Hurst reported that Wilson's disease can manifest as symptomatic liver disease without accompanying neurological symptoms. It is now recognized that liver or brain involvement may present either independently or concurrently (Tao and Gitlin, 2003; Walshe, 1986; Wilson, 1912; Hahn, 2014; Bandmann *et al.*, 2015; Cheng, 1932; Li *et al.*, 2013; Xie and Wu, 2017; Hedera, 2017; Dong *et al.*, 2016; Roberts and Schilsky, 2008; Zheng *et al.*, 2022; Brewer *et al.*, 1998; Sterlieh and Scheinberg, 1968). A significant ophthalmological characteristic of Wilson's disease is the presence of the Kayser-Fleischer (KF) ring. This ring develops due to the accumulation of copper in Descemet's membrane of the cornea. Although not every patient displays this characteristic, its occurrence is almost definitive for Wilson's Disease. Furthermore, clinical symptoms in other systems, including the musculoskeletal, renal, endocrine, and cardiovascular systems, have been observed, although these are rarely the primary symptoms (Bachmann *et al.*, 1979; Saito, 1981; Park *et al.*, 1991; Reilly *et al.*, 1993; Lo and Bandmann, 2017; Coffey *et al.*, 2013; Shribman *et al.*, 2021; EASL, 2025).

MATERIALS AND METHODS

Study Setting: Department of Neurology, Abbassi Shaheed Hospital; Karachi. Abbassi Shaheed Hospital is a tertiary care teaching hospital affiliated with Karachi Medical and Dental College. The patients with suspected diagnosis of Wilson's disease will be recruited from the outpatient department of Neuromedicine department of Abbassi Shaheed Hospital; Karachi.

Sample Size: A total of one hundred patients diagnosed with Wilson's disease who are visiting the outpatient Department of Neurology at Abbassi Shaheed Hospital in Karachi will be invited to take part in this descriptive cross-sectional study, provided they meet the eligibility criteria. Participants will be enrolled after giving their informed consent.

Sampling Technique: Non-probability consecutive sampling.

Data Analysis Plan: Data was documented using a pre-established structured form that will undergo statistical analysis. Prior to the analysis, the data collection form was reviewed twice to confirm the accuracy of the entries. Descriptive statistics were conducted, with categorical variables represented as frequencies or percentages, while quantitative variables were expressed as Mean \pm SD.

Ethical Consideration: This research was performed according to the ethical guidelines established by the Helsinki Declaration and the Pakistan Medical and Research Council (PMRC). Participants were fully briefed on the research's aims, the data collection methods, and any associated risks and benefits.

RESULTS

The study included 100 patients admitted to the Department of Neurology at Abbassi Shaheed Hospital in Karachi, all of whom satisfied the inclusion and exclusion criteria. The demographic breakdown revealed 72 males and 28 females (Fig. 1). The age frequency distribution demonstrated that 52 patients were aged between 20 and 40

years, while 48 patients were aged between 41 and 60 years (Fig. 2). The analysis of ethnicity distribution revealed that among 100 patients, 48 were Urdu Speaking, 24 were Pathan, 8 were Sindhi, 8 were Balochi, 8 were Punjabi, and 4 were Seraiki (Fig. 3). The educational status distribution indicated that out of 100 patients, 4 were illiterate, 36 had primary education, 8 had secondary education, 38 completed matric, 8 had intermediate qualifications, 8 held bachelor's degrees, and 4 were postgraduate (Fig. 4). The frequency distribution regarding family history of Wilson's disease revealed that 88 patients had a family history of the condition, while 12 did not show any history of disease (Fig. 5). Furthermore, the frequency distribution concerning the presence of KF rings demonstrated that 68 patients had KF rings, whereas 32 were free of KF ring (Fig. 6). The frequency distribution of hepatic presentation indicated that among 100 patients, 12 exhibited hepatic presentation while 88 did not show any hepatic presentation (Fig. 7)

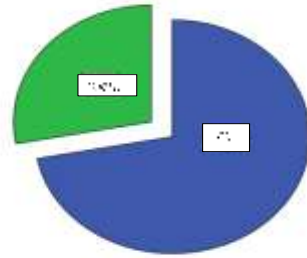


Fig.1. Gender Distribution n=100

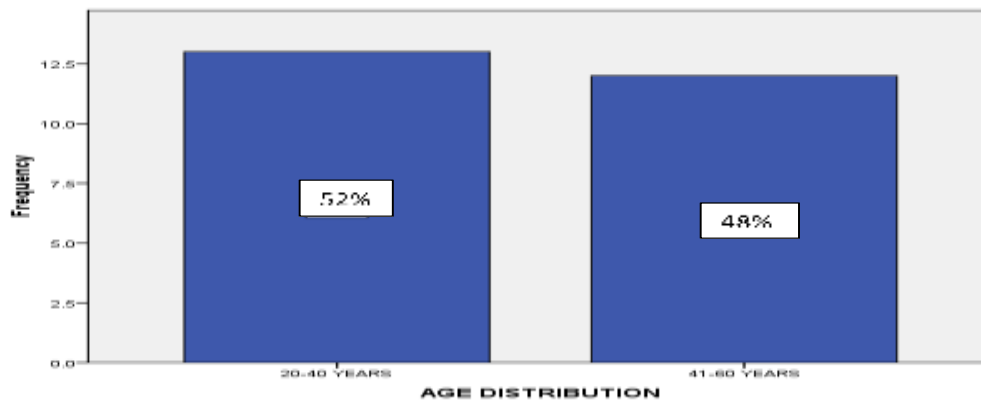


Fig. 2. Age Distribution (n=100)

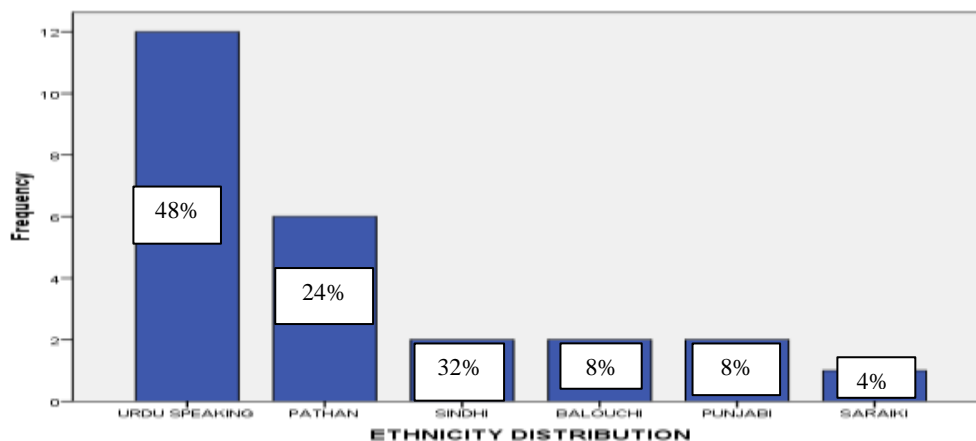


Fig.3. Ethnicity Distribution (n=100)

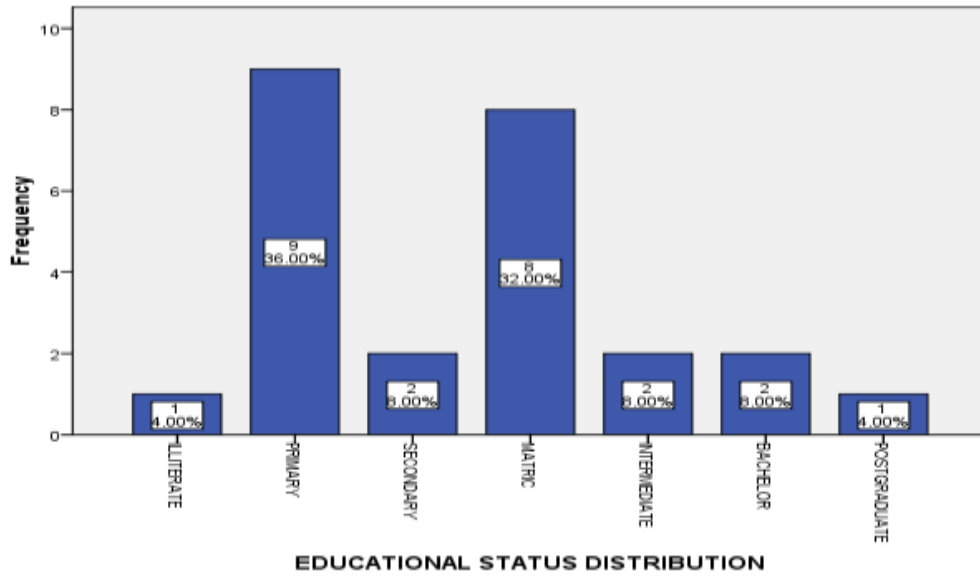


Fig.4. Educational Status Distribution (n=100)

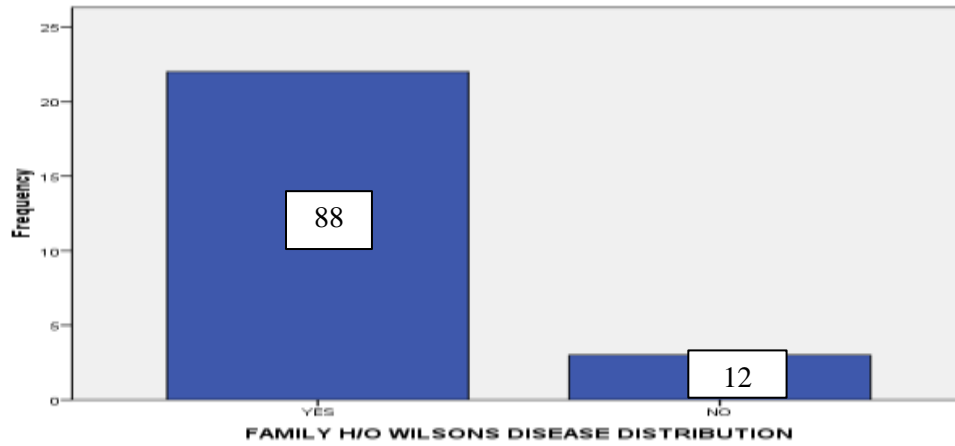


Fig.5. History of Wilson's Disease Distribution (n=100)

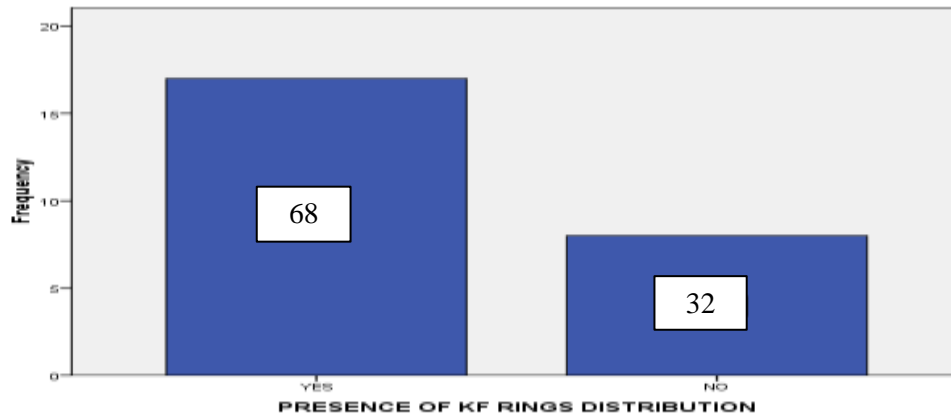


Fig.6. Presence of KF Ring Distribution (n=100)

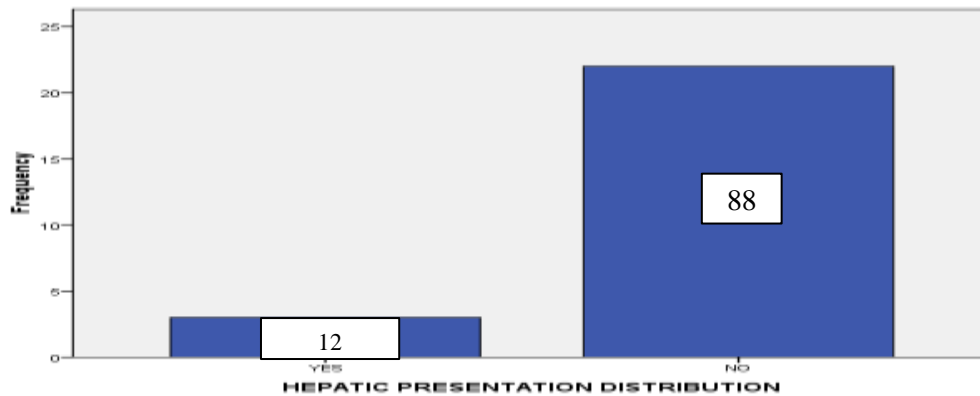


Fig. 7. Hepatic Presentation Distribution (n=100)

DISCUSSION

This study included a total of 25 patients, all of whom met the inclusion and exclusion criteria. Mean age in our study was 42.39 years with the standard deviation of ± 14.38 . 18 (72%) and 07 (28%) were male and female. Out of 25 patients, 09 (36%), 09 (36%), 07 (28%), 11 (44%), 09 (36%), 18 (72%), 13 (52%), 11 (44%) had most common clinical features tremor, rigidity, gait abnormality, facial abnormality, seizure, anger depression and insomnia.

In this research, a total of 25 patients suffering from Wilson's disease (WD) were examined. The average age at which they were diagnosed was 24 years, accompanied by a standard deviation of 9.8 years, with 65.3% of the cohort being male. The median follow-up period after diagnosis was 39.5 months, with a range of 33.8 to 60.4 months. The disease was chiefly identified at diagnosis through a combination of neurological, psychiatric, and hepatic symptomatology, accounting for 52.9% of cases, followed by neurological/psychiatric symptoms alone at 20.0%, hepatic symptoms at 16.9%, and asymptomatic cases at 10.2%. The most frequently observed clinical features at diagnosis included Kayser-Fleischer rings in 77.2% of patients, low ceruloplasmin levels in 95.2%, high hepatic copper levels in 97.8%, elevated 24-hour urinary copper excretion in 90.2%, and abnormal liver function tests ranging from 38.7% to 85.1%. At the time of diagnosis, the key biochemical indicators or hepatic signs and symptoms were characterized by elevated liver enzymes (50.5%), abdominal discomfort (16.8%), and fatigue (15.9%). The neurologic signs and symptoms that were most commonly observed included headaches (18.4%), dysarthria (17.6%), and ataxia (17.1%). The prevalent psychiatric manifestations comprised anxiety, depression, and various mood changes (36.0%), emotional instability (13.0%), and a rise in irritability or anger outbursts (9.3%). The rates of biochemical abnormalities or clinical manifestations at diagnosis and after roughly one year of follow-up were neurologic (60.0% and 44.0%), hepatic (69.7% and 37.8%), and psychiatric (53.8% and 37.8%), respectively. Important new symptoms detected around one year subsequent to the diagnosis of WD included atypical liver enzyme readings (5.7%), headaches (6.3%), and mood fluctuations such as anxiety and depression (7.4%).

An investigation into the continental origins of the patients revealed that 75.0% had European ancestry. The average age at which initial symptoms were first noted was 24 ± 9.0 years, with a diagnostic delay averaging 28 ± 42.0 months. At the time of presentation, hepatic symptoms were the most common, observed in 39.0% of patients, followed by mixed symptoms (both hepatic and neuropsychiatric) at 30.6%, and neuropsychiatric symptoms alone at 25%. KF rings were present in 56.0% of the patients, particularly with neuropsychiatric symptoms (78.0%). Eighteen (18) patients exhibited neuropsychiatric features, with cerebellar syndrome being the most prevalent. Neuroradiological imaging irregularities were observed in 72.0% of these individuals. Chronic liver disease was detected in 68% of patients exhibiting hepatic symptoms. A total of 94.2% of patients were treated with D-penicillamine for an average duration of 130.0 ± 108.5 months. Other treatment modalities included zinc salts, combination therapy, and liver transplantation. Following the initiation of treatment, 79.0% of patients experienced stable or improved outcomes, with an overall survival rate of 90.0%.

An investigation of a cross-sectional nature was performed at A. K. University Hospital in Karachi, involving all patients who were admitted with either primary or secondary diagnoses of Wilson's disease (Prakas *et al.*, 2013). The study comprised 47 patients, of whom 68% (n = 32) were male. The mean age of the cohort was 26.6 ± 9.97 years. The majority of patients presented with hepatic symptoms (n = 22, 46.8%), followed by neurological

symptoms (n = 17, 36.2%) and psychiatric symptoms (n = 8, 17%). The average ceruloplasmin level was 0.17 ± 0.13 g/dl, with 39 patients (86.6%) having levels below 0.25 g/dl. Serum copper levels were diminished in 32 patients (68.1%), while 24-hour urinary copper levels were elevated in 22 patients (47.6%). A slit lamp examination was conducted to assess for Kayser-Fleischer rings in 15 patients, representing 31.9% of the total cohort, with 9 patients, or 60%, exhibiting the presence of these rings. The mean serum AST to ALT ratio was recorded at 1.92, and the median ratio of ALP to total bilirubin was noted as 79.30 (The Interquartile Range (IQR) 35.05; 166.50). In this study, there were 05 male and 06 female patients presenting a range of symptoms: (i) isolated liver dysfunction, (ii) both liver and neurological involvement, and (iii) neurological symptoms alone. The mean age at which symptoms appeared was 8.7 ± 3.92 years, spanning from 4 to 19 years, with 45% of the cohort being male. All patients exhibited low serum ceruloplasmin, increased urinary copper excretion over 24 hours, and signs of chronic liver injury, while Kayser-Fleischer rings were identified in 72% of the individuals. Among those with severe Wilson's disease (WD), serum prothrombin activity was recorded at less than 50%, with low serum ceruloplasmin and elevated serum copper levels compared to patients with non-severe WD. Maintaining a high index of suspicion is crucial for initiating timely treatment, which leads to positive outcomes.

Conclusion

This empirical study offers detailed insights into the signs and symptoms experienced by patients diagnosed with Wilson's Disease (WD). The variety of symptoms documented in this analysis emphasizes the intricate and diverse nature of WD. Furthermore, the study highlights the necessity for ongoing monitoring, laboratory evaluations, and access to a multidisciplinary support system. The neurologic, psychiatric, and hepatic manifestations, along with laboratory irregularities associated with WD, pose a significant challenge for both patients and healthcare providers. There is a pressing need for enhanced education for healthcare professionals regarding WD, as well as the development of resources to assist in the identification of signs, symptoms, and laboratory abnormalities that require a systematic approach to diagnosis and treatment.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was taken from healthcare institute; Informed consent in the language of understanding was signed by parents/guardian.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration and Good Clinical Practice.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

None.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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(Accepted for publication June 2025)